Journal of
Clinical Medicine

Special Issue Reprint

Clinical Features of COVID-19 in Elderly Patients

Edited by
Riccardo Giorgino and Filippo Migliorini

mdpi.com/journal/jcm

MDPI

Clinical Features of COVID-19 in Elderly Patients

Clinical Features of COVID-19 in Elderly Patients

Editors

Riccardo Giorgino
Filippo Migliorini

MDPI

Basel • Beijing • Wuhan • Barcelona • Belgrade • Novi Sad • Cluj • Manchester

Editors
Riccardo Giorgino
University of Milan
Milan, Italy

Filippo Migliorini
RWTH University Hospital Aachen
Aachen, Germany

Editorial Office
MDPI
St. Alban-Anlage 66
4052 Basel, Switzerland

This is a reprint of articles from the Special Issue published online in the open access journal *Journal of Clinical Medicine* (ISSN 2077-0383) (available at: https://www.mdpi.com/journal/jcm/special_issues/COVID-Elderly).

For citation purposes, cite each article independently as indicated on the article page online and as indicated below:

Lastname, A.A.; Lastname, B.B. Article Title. *Journal Name* **Year**, *Volume Number*, Page Range.

ISBN 978-3-0365-9304-3 (Hbk)
ISBN 978-3-0365-9305-0 (PDF)
doi.org/10.3390/books978-3-0365-9305-0

Contents

Journal of
Clinical Medicine

MDPI

Editorial

Clinical Features of COVID-19 in Elderly Patients: Tools for Predicting Outcomes Are Needed

Riccardo Giorgino [1,2,*] and Filippo Migliorini [3]

[1] Residency Program in Orthopedics and Traumatology, University of Milan, 20122 Milan, Italy
[2] IRCCS Istituto Ortopedico Galeazzi, 20157 Milan, Italy
[3] Department of Orthopaedic, Trauma, and Reconstructive Surgery, RWTH University Hospital, 52074 Aachen, Germany
* Correspondence: riccardo.giorgino@unimi.it; Tel.: +39-02-5032-5032

Citation: Giorgino, R.; Migliorini, F. Clinical Features of COVID-19 in Elderly Patients: Tools for Predicting Outcomes Are Needed. *J. Clin. Med.* **2022**, *11*, 7505. https://doi.org/10.3390/jcm11247505

Received: 13 December 2022
Accepted: 14 December 2022
Published: 18 December 2022

The COVID-19 pandemic faced the healthcare landscape with new challenges, impacting work dynamics across all medical disciplines [1–4]. A prompt and dynamic hospital reorganization was necessary to tackle the pandemic [5,6]. Alongside the management of the COVID-19 pandemic, this reorganization was associated with an improvement in the quality and efficacy of hospital care and services [7]. Hence, the time interval between diagnosis, treatment, and discharge was reduced in several disciplines [8,9]. Following the improvement in hygiene standards, the rate of nosocomial infections was also reduced [9].

Given the intrinsic characteristics of COVID-19, elderly patients are particularly at risk, especially those with comorbidities [10–13]. The limited reserve capacity, fragility and age-related global immune system dysfunction of elderlies, influence the severity and progression of COVID-19 [14–20]. The identification of patients who are most at risk of complications is essential. Among hospitalized patients, multimorbidity and frailty were highly prevalent [21]. In the geriatric population, acute decompensation of pre-existent comorbidities was the main reason for progression in severity of COVID-19 and longer hospitalization [21]. Multimorbidity also significantly reduced the survival rate of patients infected with COVID-19 [21]. The cause of death in patients infected with COVID-19 was investigated post mortem using clinical chart review and autopsy [22]. Along with hypoxemic respiratory failure, acute decompensation of pre-existent comorbidities within the first week of infection was the most common cause of death [22]. Several studies investigated prognostic factors in elderlies with COVID-19 infections [23–27]. Scheffler et al. investigated the prognostic role of subcutaneous and visceral adipose tissue using a quantification fat area on 64 patients with a mean age of 86.4 ± 6.0 years [23]. There was evidence of a positive association with the subcutaneous and visceral adipose tissue and in-hospital mortality and severe COVID-19 pneumonia [23]. The prognostic value of fever, chest X-ray (CXR), and clinical frailty (CFS) scores were investigated in 122 elderlies aged 65 or older, resulting in these being considered the main predictors of in-hospital mortality [24]. Fever, CXR, and CFS might predict outcomes more accurately than other individual risk factors, confirming the importance of multidimensional assessment of elderlies with COVID-19 [24]. The C_2HEST has been proposed as a possible tool to evaluate outcomes in elderly patients with active or previous COVID-19 infection. The C_2HEST is a stratification scoring system to assesses the risk of developing atrial fibrillation. Rola et al. [25] demonstrated that the C_2HEST was effective in predicting six-month and in-hospital mortality in 1047 elderlies with COVID-19. Moreover, the C_2HEST was also valid in predicting the risk of non-fatal events, including cardiogenic shock and acute kidney and heart failure in elderlies affected by COVID-19 [25]. COVID-19 negatively impacted the outcomes of elderlies who underwent surgery for lower limb fractures in terms of biochemical parameters (e.g. monocytes, calcium levels, C-reactive protein, creatine phosphokinase, aspartate aminotransferase) and survival [28]. Infection sequelae, including disorientation, fatigue, and dyspnea, might

impair postoperative rehabilitation and recovery [28]. Moreover, infected elderlies who underwent surgery for lower limb fractures demonstrated reduced patient-reported outcome measures (PROMs) compared to an age-matched control group of healthy patients [7]. Fericean et al. [29] evaluated whether differences exist in severity progression of infected elderlies between pandemic waves. Among 360 inpatients (60 eligible elderly patients over six consecutive waves) admitted at the Infectious Diseases and Pulmonology Hospital, dyspnea, disorientation, gastrointestinal symptoms, lymphocytosis, and high levels of interleukin-6 were common [29]. Though no significant between waves difference in mortality was reported, a more severe progression of COVID-19 during the third and fourth pandemic waves was observed [29].

In conclusion, given their intrinsic frailty and comorbidities, elderlies are more at risk of a severe COVID-19 progression. The identification of prognostic factors, risk stratification and a tailored management are recommended in this population.

Author Contributions: R.G., writing; F.M., revision. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Albano, D.; Bruno, A.; Bruno, F.; Calandri, M.; Caruso, D.; Clemente, A.; Coppolino, P.; Cozzi, D.; De Robertis, R.; Gentili, F.; et al. Impact of coronavirus disease 2019 (COVID-19) emergency on Italian radiologists: A national survey. *Eur. Radiol.* **2020**, *30*, 6635–6644. [CrossRef] [PubMed]
2. Migliorini, F.; Weber, C.D.; Pappalardo, G.; Schenker, H.; Hofmann, U.K.; Eschweiler, J.; Hildebrand, F. Orthopaedic, trauma surgery, and Covid-2019 pandemic: Clinical panorama and future prospective in Europe. *Eur. J. Trauma Emerg. Surg.* **2022**, *48*, 4385–4402. [CrossRef] [PubMed]
3. Giorgino, R.; Maggioni, D.M.; Viganò, M.; Verdoni, F.; Pandini, E.; Balbino, C.; Manta, N.; D'Anchise, R.; Mangiavini, L. Knee Pathology before and after SARS-CoV-2 Pandemic: An Analysis of 1139 Patients. *Healthcare* **2021**, *9*, 1311. [CrossRef]
4. Aiello, F.; Genzano Besso, F.; Pocobelli, G.; Gallo Afflitto, G.; Colabelli Gisoldi, R.A.M.; Nucci, C.; Ponzin, D.; Italian Society Eye Bank Group (SIBO). Corneal transplant during COVID-19 pandemic: The Italian Eye Bank national report. *Cell Tissue Bank* **2021**, *22*, 697–702. [CrossRef]
5. Zagra, L.; Faraldi, M.; Pregliasco, F.; Vinci, A.; Lombardi, G.; Ottaiano, I.; Accetta, R.; Perazzo, P.; D'Apolito, R. Changes of clinical activities in an orthopaedic institute in North Italy during the spread of COVID-19 pandemic: A seven-week observational analysis. *Int. Orthop.* **2020**, *44*, 1591–1598. [CrossRef] [PubMed]
6. Luceri, F.; Morelli, I.; Accetta, R.; Mangiavini, L.; Maffulli, N.; Peretti, G.M. Italy and COVID-19: The changing patient flow in an orthopedic trauma center emergency department. *J. Orthop. Surg. Res.* **2020**, *15*, 323. [CrossRef]
7. Faggiani, M.; Risitano, S.; Aprato, A.; Conforti, L.; Massè, A. Management of Femur Fractures during COVID-19 Pandemic Period: The Influence of Vaccination and Nosocomial COVID-19 Infection. *J. Clin. Med.* **2022**, *11*, 6605. [CrossRef]
8. Obamiro, E.; Trivedi, R.; Ahmed, N. Changes in trends of orthopedic services due to the COVID-19 pandemic: A review. *World J. Orthop.* **2022**, *13*, 955–968. [CrossRef]
9. Brayda-Bruno, M.; Giorgino, R.; Gallazzi, E.; Morelli, I.; Manfroni, F.; Briguglio, M.; Accetta, R.; Mangiavini, L.; Peretti, G.M. How SARS-CoV-2 Pandemic Changed Traumatology and Hospital Setting: An Analysis of 498 Fractured Patients. *J. Clin. Med.* **2021**, *10*, 2585. [CrossRef]
10. Perazzo, P.; Giorgino, R.; Briguglio, M.; Zuffada, M.; Accetta, R.; Mangiavini, L.; Peretti, G.M. From Standard to Escalated Anticoagulant Prophylaxis in Fractured Older Adults with SARS-CoV-2 Undergoing Accelerated Orthopedic Surgery. *Front. Med.* **2020**, *7*, 566770. [CrossRef]
11. Morelli, I.; Luceri, F.; Giorgino, R.; Accetta, R.; Perazzo, P.; Mangiavini, L.; Maffulli, N.; Peretti, G.M. COVID-19: Not a contraindication for surgery in patients with proximal femur fragility fractures. *J. Orthop. Surg. Res.* **2020**, *15*, 285. [CrossRef] [PubMed]
12. Giorgino, R.; Soroush, E.; Soroush, S.; Malakouti, S.; Salari, H.; Vismara, V.; Migliorini, F.; Accetta, R.; Mangiavini, L. COVID-19 Elderly Patients Treated for Proximal Femoral Fractures during the Second Wave of Pandemic in Italy and Iran: A Comparison between Two Countries. *Medicina* **2022**, *58*, 781. [CrossRef] [PubMed]
13. Migliorini, F.; Giorgino, R.; Hildebrand, F.; Spiezia, F.; Peretti, G.M.; Alessandri-Bonetti, M.; Eschweiler, J.; Maffulli, N. Fragility Fractures: Risk Factors and Management in the Elderly. *Medicina* **2021**, *57*, 1119. [CrossRef] [PubMed]
14. Gilis, M.; Chagrot, N.; Koeberle, S.; Tannou, T.; Brunel, A.-S.; Chirouze, C.; Bouiller, K. Older adults with SARS-CoV-2 infection: Utility of the clinical frailty scale to predict mortality. *J. Med. Virol.* **2021**, *93*, 2453–2460. [CrossRef] [PubMed]

15. Briguglio, M.; Porta, M.; Zuffada, F.; Bona, A.R.; Crespi, T.; Pino, F.; Perazzo, P.; Mazzocchi, M.; Giorgino, R.; De Angelis, G.; et al. SARS-CoV-2 Aiming for the Heart: A Multicenter Italian Perspective About Cardiovascular Issues in COVID-19. *Front. Physiol.* **2020**, *11*, 571367. [CrossRef] [PubMed]
16. Kokkoris, S.; Gkoufa, A.; Maneta, E.; Doumas, G.; Mizi, E.; Georgakopoulou, V.E.; Sigala, I.; Dima, E.; Papachatzakis, I.; Ntaidou, T.K.; et al. Older adults with severe coronavirus disease 2019 admitted to intensive care unit: Prevalence, characteristics and risk factors for mortality. *Minerva Anestesiol.* **2022**, *88*, 803–814. [CrossRef]
17. Briguglio, M.; Giorgino, R.; Dell'Osso, B.; Cesari, M.; Porta, M.; Lattanzio, F.; Banfi, G.; Peretti, G.M. Consequences for the Elderly After COVID-19 Isolation: FEaR (Frail Elderly amid Restrictions). *Front. Psychol.* **2020**, *11*, 565052. [CrossRef]
18. Pietrobon, A.J.; Teixeira, F.M.E.; Sato, M.N. I mmunosenescence and Inflammaging: Risk Factors of Severe COVID-19 in Older People. *Front. Immunol.* **2020**, *11*, 579220. [CrossRef]
19. Gabrielli, M. COVID-19 in Older Adults at the Time of the Omicron Variant. *J. Clin. Med.* **2022**, *11*, 5273. [CrossRef]
20. Chen, Y.; Klein, S.L.; Garibaldi, B.T.; Li, H.; Wu, C.; Osevala, N.M.; Li, T.; Margolick, J.B.; Pawelec, G.; Leng, S.X. Aging in COVID-19: Vulnerability, immunity and intervention. *Ageing Res. Rev.* **2021**, *65*, 101205. [CrossRef]
21. Ticinesi, A.; Parise, A.; Cerundolo, N.; Nouvenne, A.; Prati, B.; Chiussi, G.; Guerra, A.; Meschi, T. Multimorbidity and Frailty Are the Key Characteristics of Patients Hospitalized with COVID-19 Breakthrough Infection during Delta Variant Predominance in Italy: A Retrospective Study. *J. Clin. Med.* **2022**, *11*, 5442. [CrossRef] [PubMed]
22. Malézieux-Picard, A.; Ferrer Soler, C.; De Macedo Ferreira, D.; Gaud-Luethi, E.; Serratrice, C.; Mendes, A.; Zekry, D.; Gold, G.; Lobrinus, J.A.; Arnoux, G.; et al. Undetected Causes of Death in Hospitalized Elderly with COVID-19: Lessons from Autopsy. *J. Clin. Med.* **2021**, *10*, 1337. [CrossRef] [PubMed]
23. Scheffler, M.; Genton, L.; Graf, C.E.; Remuinan, J.; Gold, G.; Zekry, D.; Serratrice, C.; Herrmann, F.R.; Mendes, A. Prognostic Role of Subcutaneous and Visceral Adiposity in Hospitalized Octogenarians with COVID-19. *J. Clin. Med.* **2021**, *10*, 5500. [CrossRef]
24. Cecchini, S.; Di Rosa, M.; Soraci, L.; Fumagalli, A.; Misuraca, C.; Colombo, D.; Piomboni, I.; Carnevali, F.; Paci, E.; Galeazzi, R.; et al. Chest X-ray Score and Frailty as Predictors of In-Hospital Mortality in Older Adults with COVID-19. *J. Clin. Med.* **2021**, *10*, 2965. [CrossRef] [PubMed]
25. Rola, P.; Doroszko, A.; Trocha, M.; Giniewicz, K.; Kujawa, K.; Skarupski, M.; Gawryś, J.; Matys, T.; Szahidewicz-Krupska, E.; Gajecki, D.; et al. Mortality Predictive Value of the C2HEST Score in Elderly Subjects with COVID-19-A Subanalysis of the COLOS Study. *J. Clin. Med.* **2022**, *11*, 992. [CrossRef] [PubMed]
26. Migliorini, F.; Torsiello, E.; Spiezia, F.; Oliva, F.; Tingart, M.; Maffulli, N. Association between HLA genotypes and COVID-19 susceptibility, severity and progression: A comprehensive review of the literature. *Eur. J. Med. Res.* **2021**, *3*, 84. [CrossRef]
27. Migliorini, F.; Vaishya, R.; Eschweiler, J.; Oliva, F.; Hildebrand, F.; Maffulli, N. Vitamins C and D and COVID-19 Susceptibility, Severity and Progression: An Evidence Based Systematic Review. *Medicina* **2022**, *15*, 941. [CrossRef]
28. Colombini, A.; Lombardo, M.D.M.; de Girolamo, L.; De Vecchi, E.; Giorgino, R.; Peretti, G.M.; Banfi, G.; Mangiavini, L. COVID-19 in Elderly Patients Surgically Treated for Lower Limbs Fracture. *J. Clin. Med.* **2021**, *11*, 168. [CrossRef]
29. Fericean, R.M.; Rosca, O.; Citu, C.; Manolescu, D.; Bloanca, V.; Toma, A.-O.; Boeriu, E.; Dumitru, C.; Ravulapalli, M.; Barbos, V.; et al. COVID-19 Clinical Features and Outcomes in Elderly Patients during Six Pandemic Waves. *J. Clin. Med.* **2022**, *11*, 6803. [CrossRef]

Journal of
Clinical Medicine

MDPI

Article

Undetected Causes of Death in Hospitalized Elderly with COVID-19: Lessons from Autopsy

Astrid Malézieux-Picard [1,*,†], Cecilia Ferrer Soler [2,†], David De Macedo Ferreira [1], Emilie Gaud-Luethi [2], Christine Serratrice [1], Aline Mendes [2], Dina Zekry [1], Gabriel Gold [2], Johannes Alexander Lobrinus [3], Grégoire Arnoux [3], Fulvia Serra [3,‡] and Virginie Prendki [1,4,‡]

[1] Division of Internal Medicine for the Aged, Department of Rehabilitation and Geriatrics, University Hospitals of Geneva, Hôpital des Trois-Chêne, 1226 Thônex-Genève, Switzerland; davidjose.demacedoferreira@hcuge.ch (D.D.M.F.); christine.serratrice@hcuge.ch (C.S.); dina.zekry@hcuge.ch (D.Z.); virginie.prendki@hcuge.ch (V.P.)
[2] Division of Geriatrics, Department of Rehabilitation and Geriatrics, University Hospitals of Geneva, Hôpital des Trois-Chêne, 1226 Thônex-Genève, Switzerland; Cecilia.ferrersoler@hcuge.ch (C.F.S.); Emilie.luethi@hcuge.ch (E.G.-L.); aline.mendes@hcuge.ch (A.M.); Gabriel.gold@hcuge.ch (G.G.)
[3] Division of Pathology, University Hospitals of Geneva, 1205 Geneva, Switzerland; Johannes.a.lobrinus@hcuge.ch (J.A.L.); gregoire.arnoux@unige.ch (G.A.); fulvia.serra@hcuge.ch (F.S.)
[4] Division of Infectious Disease, University Hospitals of Geneva, 1205 Geneva, Switzerland
* Correspondence: astrid-marie.malezieux@hcuge.ch
† These authors contributed equally to this work.
‡ These authors share last authorship.

Citation: Malézieux-Picard, A.; Ferrer Soler, C.; De Macedo Ferreira, D.; Gaud-Luethi, E.; Serratrice, C.; Mendes, A.; Zekry, D.; Gold, G.; Lobrinus, J.A.; Arnoux, G.; et al. Undetected Causes of Death in Hospitalized Elderly with COVID-19: Lessons from Autopsy. *J. Clin. Med.* **2021**, *10*, 1337. https://doi.org/10.3390/jcm10071337

Academic Editor: Riccardo Giorgino

Received: 8 March 2021
Accepted: 20 March 2021
Published: 24 March 2021

Abstract: Background: Mechanisms and causes of death in older patients with SARS-CoV-2 infection are still poorly understood. Methods: We conducted in a retrospective monocentric study, a clinical chart review and post-mortem examination of patients aged 75 years and older hospitalized in acute care and positive for SARS-CoV-2. Full body autopsy and correlation with clinical findings and suspected causes of death were done. Results: Autopsies were performed in 12 patients (median age 85 years; median of 4 comorbidities, mainly hypertension and cardiovascular disease). All cases showed exudative or proliferative phases of alveolar damage and/or a pattern of organizing pneumonia. Causes of death were concordant in 6 cases (50%), and undetected diagnoses were found in 6. Five patients died from hypoxemic respiratory failure due to coronavirus disease 2019 (COVID-19), five had another associated diagnosis and two died from alternative causes. Deaths that occurred in the second week were related to SARS-CoV-2 pneumonia whereas those occurring earlier were related mainly to heart failure and those occurring later to complications. Conclusions: Although COVID-19 hypoxemic respiratory failure was the most common cause of death, post-mortem pathological examination revealed that acute decompensation from chronic comorbidities during the first week of COVID-19 and complications in the third week contributed to mortality.

Keywords: elderly patients; COVID-19; autopsy

1. Introduction

The new coronavirus, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has caused to date close to 2 million deaths worldwide. Older patients, who present the highest prevalence of multiple chronic diseases, are the hardest hit among the population and advanced age is the strongest predictor of mortality [1–3]. Although several autopsy studies of coronavirus disease 2019 (COVID-19) have already been published, most include only individual or small autopsy case studies with limited post-mortem examinations [4–6]. Complete autopsies of very old patients are rare [7–9]. These studies suggest that inflammation, hypercoagulation and endothelitis are the main pathophysiological processes leading to death in COVID-19. However, the mechanisms and causes of death in older patients with SARS-CoV-2 infection are still poorly understood [10–12]. Such information may help

clinicians to improve clinical management and to reduce mortality [13–16]. In order to explore this issue, we correlated clinical findings with pathological findings and analyzed the causes of death in a case series of 12 older patients who had been hospitalized in acute geriatric care.

2. Materials and Methods

2.1. Design, Setting and Population Study

The study was set up in the geriatrics hospital in Geneva, Switzerland, with 176 beds in acute care units dedicated to infected SARS-CoV-2 patients. These patients were ineligible for intensive care according to goals of care determinations. The hospital serves a population of about 500,000 inhabitants. We included all patients hospitalized in the geriatrics hospital with a positive PCR SARS-CoV-2 test from 13 March to 2 May 2020, who died and for whom we obtained a written autopsy authorization from their representative. All patients were part of the COVIDAge study, a retrospective monocentric study approved by the ethical committee of Geneva and registered in clinicaltrials.gov [17].

2.2. Data Collection

Clinical, biological, and radiological data were collected from electronic medical records, including causes of death determined by clinicians. All patients were evaluated within the first 24 h using the following clinical and geriatric assessment scales that are validated for use in older populations: Cumulative Illness Rating Scale-Geriatric (CIRS-G, range: 0–56), Functional Independence Measure (FIM, range: 18–126), Clinical Frailty Scale (CFS, range: 1–9), Body Mass Index (BMI), Pneumonia Severity Index (PSI, range: 51–395), CURB-65 Severity Score (CURB-65, range: 0–5) [18–23] (Appendix A).

2.3. Autopsy Techniques

All autopsies were performed with a post-mortem delay between 25 and 96 h (mean 45 h) and conducted by two resident pathologists at the Division of Pathology, (FS and GA). In all cases a complete full body autopsy was performed, including brain in all but one case. All organs where eviscerated and analyzed either immediately or after 48 h of 4% formalin fixation. For each patient, 4 kidney samples were taken for electron microscopy analysis and in most cases multiples frozen sections for further analysis. After fixation, organs were dissected and multiple tissue samples taken and paraffin-embedded. 3–4 µm thick sections were prepared and stained with hematoxylin and eosin. Special stains and/or immunostainings were performed on selected samples. All slides were analyzed by the senior pathologist (JAL) and the same two residents (FS, GA), aware of the clinical history and evolution of the patient.

2.4. Clinical and Pathological Confrontation

Causes of death reported by clinicians in the record and the autopsy request were compared with autopsy findings.

3. Results

3.1. Clinical Characteristics

During the study period, 264 older people were hospitalized with COVID-19. The youngest patient was 75 years old and the oldest 95 years old (median of 86 years old). Post-mortem examinations were conducted on 12 (14.8%) of the 81 patients with SARS-CoV-2 who died in our hospital. Patients' characteristics are illustrated in Table 1.

Table 1. Clinical characteristics of the 12 patients.

Patient No.	Sex	Age (years)	Clinical Medical History	Time from Symptoms to Death (Days)	CIRS-G (Range 0–56)	Clinical Frailty Scale (Range 1–9)	FIM (Range 18–126)	Radiologic Pulmonary Infiltrates
1	F	87	Arterial hypertension, primary biliary cirrhosis, chronic lymphocytic leukemia	10	27	9	107	multifocal
2	F	86	Asthma, Factor V Leiden, lower limb neuropathy	7	19	8	MD	multifocal
3	F	83	Arterial hypertension, ischemic and valvular heart disease, arteriosclerosis, stroke, dementia, diabetes, lower limb neuropathy	3	23	6	MD	multifocal
4	M	86	Dilated cardiomyopathy, pacemaker	6	15	5	101	multifocal
5	F	95	Arterial hypertension, dementia, diabetes	8	24	9	MD	multifocal
6	M	91	Arterial hypertension, ischemic heart disease, lower limb arterial insufficiency, dyslipidemia, asthma, deep vein thrombosis	21	11	5	86	local
7	F	81	Arterial hypertension, dementia, chronic hepatitis C, chronic kidney failure, breast cancer, depression	15	22	8	25	multifocal
8	F	88	Arterial hypertension, pulmonary embolism, epilepsy, chronic kidney failure	8	24	8	MD	local
9	M	88	Arterial hypertension, ischemic, valvular and rhythmic heart disease, COPD, pulmonary arterial hypertension, chronic kidney failure	5	21	5	MD	multifocal
10	M	81	Arterial hypertension, ischemic heart disease, diabetes, dyslipidemia, chronic kidney failure, metastatic bladder cancer	22	21	8	103	multifocal
11	M	75	Arterial hypertension, ischemic heart disease, arteriosclerosis, IgA nephropathy, chronic kidney failure, stroke, dementia, cirrhosis, arteriosclerosis	25	32	6	73	multifocal
12	M	81	Arterial hypertension, diabetes, dyslipidemia, stroke, dementia, chronic kidney failure, lower limb neuropathy	11	13	MD	35	multifocal

Abbreviations: CIRS-G: Cumulative Illness Rating Scale-Geriatric; COPD: chronic obstructive pulmonary disease; FIM: Functional Independence Measure; MD: Missing Data.

The median age was 85 years old (interquartile range (IQR), 75–95 years); half were female. Eight patients (75%) were living at home, three patients had a prior hospitalization in the preceding 6 months. The most frequent comorbidities were hypertension (83%), heart disease (50%), chronic kidney disease (50%), dementia (42%), and diabetes (33%). Only one patient had known chronic obstructive pulmonary disease. The median and IQR of FIM, CFS and CIRS-G was 86 (25–107), 8 (5–9), and 22 (11–32) respectively, consistent with moderately high levels of functional impairment, frailty, and comorbidity burden. The mean number of medications at admission was 9 (3–18) and the mean BMI was 25.6 (21.4–47.7; 3 missing data). The average duration from first symptoms to death was 9 days (3–25). The characteristics of autopsied patients with non survivors in the COVIDAge

study were quite similar [17]. The median age of the non-survivors was 87 years (IQR: 80.5–93.3), the median CIRS-G was 21.2 (IQR: 15.9–26.5), and 69.3% received antibiotics. There were slightly more male deaths (63.2%) in the COVIDAge cohort and the CFS was lower 6.5 (IQR: 5.1–8.9) but not statistically significant.

The most common symptoms at admission were fever (100%), cough (83%), asthenia (77%) and dyspnea (72%). Three patients had delirium and one had digestive symptoms. CURB-65 and PSI scores were 2 (1–3) and 137 (106–185) respectively. Pulmonary infiltrates on chest X-ray were multifocal in ten cases and local in two. Thoracic CT scan was performed in two patients and revealed multifocal infiltrates and pleural effusion.

During hospitalization, all patients required a fraction of inspired oxygen (FiO_2) greater than 50% and had fever. All patients developed hypoxemic respiratory failure, 5 (42%) acute heart failure treated with diuretics, 4 (33%) acute renal failure, and one delirium. An associated bacterial pneumonia was suspected by the clinician in 8 (66%) patients and antibiotic therapy was prescribed despite the absence of bacterial respiratory pathogens in sputum and blood cultures. One patient who had *Escherichia coli* bacteremia developed pancytopenia. All patients were treated with prophylactic anticoagulation therapy except one who initially received higher doses for the treatment of deep vein thrombosis. Patient 3 received hydroxychloroquine and lopinavir-ritonavir according to local guidelines.

Patients 2, 3, 4, and 9 died in the first week of disease. Patient 3 died suddenly a few hours after admission, a rhythm disorder was suspected. Patients 4 and 9 died with signs of cardiac failure and suspicion of associated bacterial pneumonia. These three last patients had severe cardiac comorbidities. Five patients (42%) died in the second week of disease. They developed acute respiratory distress syndrome (ARDS) and in three cases acute renal failure. Patients 6, 10, and 11 died after 15 days. Patient 6 had been hospitalized one month before for a fall, leading to a deep vein thrombosis diagnosis. He developed a severe delirium due to hypernatremia, nosocomial bacterial pneumonia with left heart failure and a severe macroscopic hematuria leading to discontinuation of the anticoagulation. Patient 10 presented with multiorgan failure at day 20. Patient 11 had persistent fever and hypoxemia, developed acute renal failure with liver cholestasis, and increasing oxygen needs at day 15; he was treated with 3 antibiotics successively.

3.2. Autopsy Findings

3.2.1. Lungs

At gross examination, lungs of all patients were heavy and congested, with a mean weight of 1584 g (range 1050–1984). At section, they showed condensation in patchy areas, sometimes even fibrous thick areas, or complete consolidation of the entire parenchyma. An interesting characteristic was the clear limit between involved and normal appearing areas of lung tissue. This pattern is not typically seen in ARDS cases and fits well with the radiologic aspect. In cases of bacterial superinfection, patchy round white dense areas were observed. Upon histological examination, alveolar damage (AD) at the exudative or proliferative phase and/or organizing pneumonia (OP) were observed and could be present alone or together. Lung damage was severe in 8 cases (67%). Of these, the pattern of exudative phase of AD was found prevalent in 6 cases (associated with a short time duration of illness) and proliferative phase of AD and OP in 2 cases (associated with a more prolonged illness). In four cases, signs of bacterial superinfection pneumonia were present (3 out of 4 with bronchoaspiration signs such as the presence of food particles). Microthrombi were present in three cases, of which one had central pulmonary embolism in the left pulmonary artery (patient 6). One case showed eosinophilic pneumonia (patient 11). Detailed lung pathology is shown in Table 2. An illustration of a typical SARS-CoV-2 lung injury is show in Figure 1.

Table 2. Autopsy finding.

Patient No.	Time from Symptoms to Death (Days)	Lung Autopsy Findings								Other Non Pulmonary Death-Related Autopsy Findings
		AD: Patchy Exudative	AD: Diffuse Exudative	AD: Patchy Proliferative	AD: Diffuse Prolferative	OP: Patchy	OP: Diffuse	Bacterial Pneumonia	Other Lung Findings	
1	10		XXX							
2	7		XXX					Foci		Signs of heart failure
3	3	XX								Signs of heart failure
4	6		XXX	XX						Signs of heart failure
5	8		XXX			X		Foci		
6	21					X		Large	Central left pulmonary embolism	
7	15		XX							
8	8	X					XX		Interstitial pneumonia Rare peripheric thrombi	
9	5	X		X					Signs of pulmonary hypertension	Ischemic heart disease
10	22	X			XXX				Peripheric thrombi and microthrombi	Small acute septal myocardial infarct and signs of heart failure
11	25	XX					XXX		Eosinophilic pneumonia	
12	11		XXX			X		Foci		

Abbreviations: AD: Alveolar Damage, OP: Organizing Pneumonia, X: Slight, XX: Moderate, XXX: Severe.

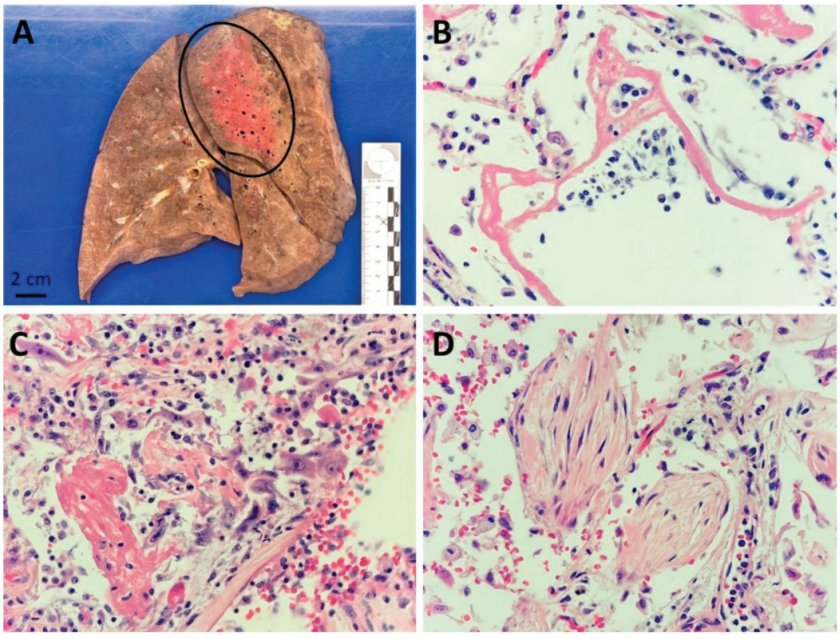


Figure 1. Lung pathology associated with SARS-CoV-2 infection: (**A**) Sagittal macroscopic section of a formalin fixed right lung, showing a condensed area in the posterior part of the upper lobe (encircled area), patient n 7; (**B**) Alveolar damage at exudative stage with prominent eosinophilic hyaline membranes (HE 400×), patient n 2; (**C**) Alveolar damage at proliferative stage with proliferation of alveolar pneumocytes (HE 400×), patient n 10; (**D**) Organizing pneumonia with intra-alveolar fibroblast plugs (HE 400×), patient n° 11.

3.2.2. Heart and Vessels

All twelve patients presented an ischemic and/or hypertensive cardiopathy, with signs of heart failure in four cases. Coronary stenosis or stenting were seen in eleven patients, and old or recent myocardial damage in nine patients. Moderate to severe generalized atherosclerosis was found in all patients (50% moderate and 50% severe). No myocarditis or vasculitis was discovered.

3.2.3. Kidney

Chronic vascular nephropathy was observed in all cases, signs of diabetic nephropathy were found in two and acute or subacute tubular necrosis in five patients. In one case, predominantly distributed in the superficial renal medullary, nonspecific foci of acute tubulointerstitial nephritis were present. Patient 10 had a thrombus in one interlobular artery. No structures typical of coronavirus particles were seen in electron microscopy.

3.2.4. Brain

A brain autopsy was performed in eleven patients. Neurodegenerative signs were present in four patients (Alzheimer and/or Lewy body disease). Ten patients presented a variable degree of atherosclerosis of the circle of Willis. Patient 10 was the only one with microthrombi of a few small meningeal vessels and acute cortical microinfarcts of the frontal lobes. Patient 12 had one subacute infarct of the left pons. Patient 8 had an old bilateral parasagittal infarct centered on the precentral and postcentral gyri. No encephalitis or vasculitis was observed.

3.2.5. Main Other Findings

Patients 1, 7, and 11 had a cirrhosis and/or liver steatosis, patient 10 had metastatic urothelial carcinoma, patient 6 had a necrotizing myopathy and patient 5 cachexia. Bone marrow was normal or reactive, without hematologic disease.

3.3. Clinicians' Cause of Death and Pathologists' Findings

The clinicopathological comparison of causes of death was concordant in six cases (50%) (Table 3). Undetected diagnoses (new primary or contributory cause of death) were found in six cases: Pulmonary embolism (one case), acute myocardial infarct (one case), eosinophilic pneumonia (one case) and heart failure (three cases). The cause of death presumed by the clinician was in each case a hypoxemic respiratory failure due to COVID-19. At autopsy, severe hypoxemic pneumonia (ARDS) due to COVID-19 was confirmed as the unique cause of death in only five cases. Five patients had additional diseases: autopsies of patients 2, 3, and 4 revealed signs of acute heart failure (pulmonary edema, shock liver and multiple organ congestion), patient 10 had a small acute cardiac infarct and patient 11 had signs of eosinophilic pneumonia. Autopsy revealed that two patients died from another cause than COVID-19: Patient 6 from a pulmonary embolism (anticoagulation had been discontinued due to severe hemorrhage) and bacterial pneumonia (21 days after symptom onset) and patient 9 from a probable arrhythmia due to pulmonary hypertension and ischemic cardiac disease.

Table 3. Clinical and pathological confrontation.

Patient No.	Sex	Age (Years)	Time from Symptoms to Death (Days)	Complications during Hospitalization	Clinical Suspicion Cause of Death	Cause of Death at Autopsy *
1	F	87	10	Anemia due to bleeding; Acute renal failure	HRFdue to COVID-19	HRFdue to COVID-19
2	F	86	7		HRFdue to COVID-19	HRFdue to COVID-19 and heart failure
3	F	83	3	Urinary retention	HRFdue to COVID-19	HRFdue to COVID-19 and heart failure
4	M	86	6	Global cardiac failure; Sacral ulcer; Suspicion of bacterial pneumonia;	HRFdue to COVID-19 and heart failure	HRFdue to COVID-19 and heart failure
5	F	95	8	Escherichia coli bacteremia; Pancytopenia; Suspicion of bacterial pneumonia; Acute renal failure	HRFdue to COVID-19 and sepsis with Escherichia coli bacteremia	HRFdue to COVID-19
6	M	91	21	Left heart failure; Delirium; Hypernatremia; Macroscopic hematuria; Suspicion bacterial pneumonia	HRFdue to COVID-19 and delirium	Pulmonary embolism and bacterial pneumonia
7	F	81	15		HRFdue to COVID-19	HRFdue to COVID-19
8	F	88	8	Arterial hypertention	HRFdue to COVID-19	HRFdue to COVID-19
9	M	88	5	Left heart failure; Suspicion of bacterial pneumonia	HRFdue to COVID-19	Probable arythmia due to pulmonary hypertension and ischemic heart disease
10	M	81	22	Atrial fibrillation; Suspicion of bacterial pneumonia; Multiorganic failure	HRFdue to COVID-19	HRFdue to COVID-19 and small acute myocardial infarct
11	M	75	25	Acute renal failure; Liver cholestase; Anemia; Suspicion of bacterial pneumonia; Unexplicated persisting inflammation	HRFdue to COVID-19	HRFdue to COVID-19 and eosinophilic pneumonia
12	M	81	11	**Hypoglycemia; Acute renal failure; Left heart failure; Suspicion of bacterial pneumonia**	HRFdue to COVID-19	HRFdue to COVID-19

Abbreviations: AD: Alveolar Damage; OP: Organizing Pneumonia; HRF: Hypoxemic Respiratory Failure. * Cause of death presumed by the pathologist. All the patients presented signs of acute respiratory distress syndrome due to COVID-19.

Interestingly, deaths that occurred in the second week of active disease were related only to SARS-CoV-2 pneumonia whereas deaths that occurred earlier were related, at least in part, to cardiac comorbidities, mainly heart failure; deaths that occurred later were related to complications of the disease and/or its therapy (Figure 2).

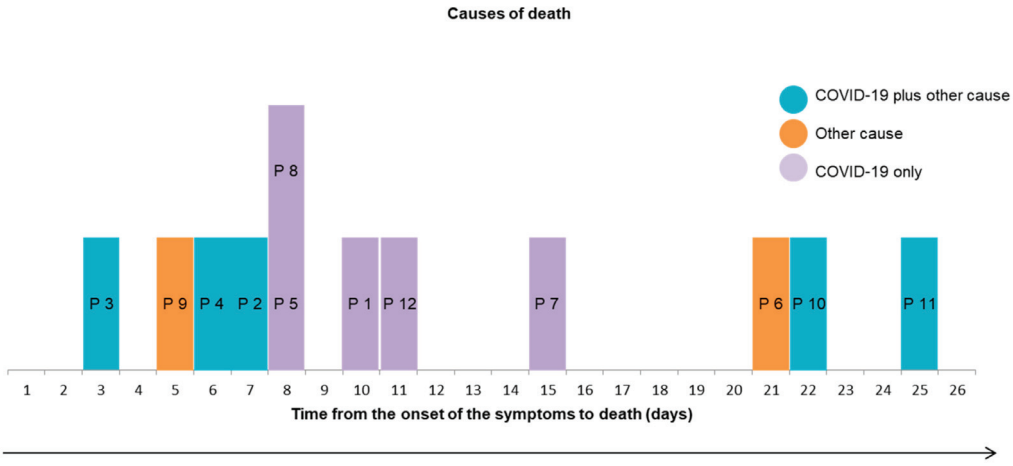


Figure 2. Causes of death according to time to death. Abbrevations: P: Patient.

Eight patients had been treated with antibiotics for bacterial pneumonia which was not confirmed at autopsy in five cases (patients 4, 8, 9, 10, 11). One patient died rapidly with a bacterial pneumonia without antibiotics (patient 2). Five patients developed acute tubular necrosis but this was not notified by the clinician on the autopsy questionnaire for three of them.

4. Discussion

To our knowledge, this is the first autopsy series of very old patients hospitalized in a geriatrics hospital and who died with a SARS-CoV-2 confirmed infection. The overall comorbidity burden was high and associated with severe frailty. The autopsies identified different or additional contributory causes of death and potentially treatable undetected diagnoses in approximately half the cases. This is higher than a similar report in a slightly younger German cohort (mean age 79 years) where SARS-CoV-2 pneumonia was not the only cause of death in 11% of the cases and was not the cause at all in 5% [24].

An interesting finding of our study is the timing of the different causes of death (Figure 2) suggesting that early detection and therapy of decompensated comorbidities, especially heart failure, may help decrease mortality during the first week of the disease in older patients and that prevention of late complications including ischemic and thromboembolic events and side effects of possibly unnecessary antibiotic therapy may improve survival after the second week.

Bacterial superinfection was shown in half of the cases on antibiotics. The current literature has highlighted that bacterial pneumonia was rarely associated with COVID-19 infection whereas patients were often treated with antibiotics, as suggested in several therapeutic guidelines generated at the beginning of the pandemic. In fact, co-infections are rare and have been mainly described in intensive care units due to prolonged intubation [25]. Our findings support the principle of limiting routine prescription of antibiotics in SARS-CoV-2 pneumonia and extend it to the older population above 75 years of age [26]. However, the diagnostic of pneumonia in elderly patients is challenging because symptoms are less specific and decompensated comorbidities are frequently associated [27]. The differentiation between viral versus bacterial pneumonia may also be difficult as the

microorganism causing bacterial pneumonia is identified in only a minority of patients [28]. Patient 2 did not receive antibiotic but signs of bacterial pneumonia were finally found on the autopsy.

We report one case of eosinophilic pneumonia, a rare and heterogeneous syndrome. Its clinical presentation may include fever, dry cough, dyspnea, chest pain, and bilateral reticular ground glass opacities on imaging [29]. In our case, we believe the use of piperacillin-tazobactam was the most probable cause even though, to our knowledge, only 4 cases of eosinophilic pneumonia due to piperacillin-tazobactam have been described in the literature [30]. Importantly, prior cases of SARS-CoV-2 related eosinophilic pneumonia have been reported, suggesting a potential link between SARS-CoV-2 and eosinophilic pneumonia; further autopsy studies will be needed to clarify this issue [31–33].

Other pulmonary findings of our cohort were similar to those described in other studies [34–36]. We observed the two main pulmonary patterns found in common cases of viral pneumonia: Alveolar damage and organizing pneumonia. As expected, the exudative phase of alveolar damage was the prevalent pattern in patients who died early (but not only) and the proliferative phase of diffuse alveolar damage or the organizing pneumonia, were prevalent in patients who died at least 6 days after the onset of the symptoms. The presence of pulmonary microthrombi has been extensively discussed in the medical literature, mainly in relation to potential preventive therapy [37]. Wichmann et al. showed that 58% of deaths during COVID-19 were caused by venous thromboembolism [9]. Rapkiewicz et al. and Lax et al. showed microthrombi in all autopsies [8,38]. On the other hand, Bradley et al. observed rare microthrombi and no endothelitis in a cohort of 14 patients [39]. In our series, only three patients had fibrinous microthrombi including one with a history of venous thrombosis in whom longstanding anticoagulation therapy had been discontinued because of severe hematuria.

Many of our patients had acute heart failure and one had an acute myocardial ischemia but unlike other studies, no myocarditis was found [40].

Acute renal failure was also common and related to decompensated chronic vascular and diabetic nephropathies. The incidence of acute kidney injury (AKI) during SARS-CoV-2 infection varies from 0.5% to 80.3% [41]. It is more frequent in critically ill patients. Different mechanisms have been described: Direct effect of the virus and secondary mechanisms linked to the hemodynamic (hypo-perfusion), thrombotic micro-angiopathy, humoral response to the virus, and activation of the complement system [41]. Histologically, nonspecific acute or subacute tubular necrosis was observed in five of our patients and none of them had lymphocyte infiltration. This is in line with the results of Pei et al. who described varying degrees of acute tubular necrosis without lymphocyte infiltration [42]. We also observed a thrombus in one interlobular renal artery and nonspecific foci of acute tubulointerstitial nephritis in another one, but no evidence of endarteritis, nor tubulitis or fibrinous microthrombi as mentioned in other studies. [43]. Contrary to several other reports, electron microscopy did not reveal any coronavirus particle in our series [44].

The post-mortem brain analysis showed common lesions for geriatric patients without any pathology directly related to SARS-CoV-2 infection; this is consistent with other findings in older patients [45].

We found a necrotizing myopathy in one case probably related to treatment with statins for many years. Among older patients, necrotizing myopathies are most frequently triggered by statins and we did not find any description of SARS-CoV-2 induced necrotizing myopathy in the literature [46].

Our study has several limitations. PCR was not performed in the tissue to detect the virus, since the infection was already confirmed. As well, given its monocentric retrospective design and its relatively small sample size it may not be representative of all older populations. However, it includes all autopsied COVID-19 cases during the first wave in a well described cohort of older people from the COVIDAge study representing a population with a broad range of comorbidities and frailty status often encountered

in acute geriatric care [17]. Importantly, there were no major demographic or clinical differences between autopsied and non-autopsied deceased patients.

5. Conclusions

The post-mortem pathological examination revealed one or several undetected diagnoses in half the cases. Although COVID-19 hypoxemic respiratory failure was the main cause of death, autopsies showed that acute decompensation from chronic comorbidities during the first week of COVID-19 disease and complications in the third week were either a direct cause of death or contributed significantly to mortality in older hospitalized COVID-19 patients. Early detection and treatment of heart failure, prevention of thromboembolic complications, and avoidance of unnecessary antibiotic therapy may help decrease mortality in older patients hospitalized with COVID-19. More studies based on autopsies are needed in very elderly patients.

Author Contributions: Conceptualization, A.M.-P., C.F.S., V.P., G.A., F.S. and J.A.L.; methodology, V.P. and J.A.L.; validation, V.P., J.A.L. and G.G.; formal analysis, F.S.; investigation, A.M.-P., C.F.S., D.D.M.F.; resources, C.S., A.M.; data curation, C.S., A.M.; writing—original draft preparation, A.M.-P., C.F.S., V.P., F.S. and J.A.L.; writing—review and editing, all authors; visualization, D.Z., G.G.; supervision, V.P. and J.A.L. All authors have read and agreed to the published version of the manuscript.

Funding: We did not benefit from any specific funding source.

Institutional Review Board Statement: The study was conducted according to the guidelines of the declaration of Helsinki, and approved by the ethical committee of Geneva (protocol code: 2020-00819; date of approval: 16 April 2020).

Informed Consent Statement: All autopsy authorization were obtained from their representative.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethics and general data production regulation.

Acknowledgments: We acknowledge all patients and their family, and all health care workers involved in the diagnosis and treatment of patients in the Trois-Chêne Hospital site of University Hospital of Geneva. We thank Gergekci and El Biali for their assistance in gerontopharmacology and Pache, Moll and the autopsy preparators of the Division of Pathology.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

- Cumulative Illness Rating Scale-Geriatric (CIRS-G, range: 0–56) measures the cumulative comorbidity burden in 14 organ systems each rated from 0 (no impairment) to 5 (extremely severe life threatening impairment) [18]. This scale, designed for the elderly, evaluates the severity of illnesses as a function of the effect of disability.
- Functional Independence Measure (FIM, range: 18–126): it is an 18 items tool that explores an individual's physical, psychological and social function. It is used to assess the level of disability of a patient as well as the changes in his or her condition following rehabilitation or medical intervention [19]. The higher the score, the greater the patient's functional abilities.
- Clinical Frailty Scale (CFS, range: 1–9): it evaluates specific areas such as comorbidity, function and cognition to generate a fragility score ranging from 1 (very fit) to 9 (terminally ill). It thus summarizes the overall level of ability or frailty of an older adult after being assessed by an experienced clinician [20].
- Body Mass Index (BMI), is a formula for measuring body-weight adjusted for height. For people 70 years of age and older, the cut-off value for screening for undernutrition is BMI < 21 kg/m^2 [21].
- Pneumonia Severity Index (PSI, range: 51–395) is a clinical prediction scale that physicians can use to calculate the likelihood of morbidity and mortality in patients

with community-acquired pneumonia. This score is also frequently used to predict the need for hospitalization in people with pneumonia [22].
- CURB-65 Severity Score (CURB-65, range: 0–5) determines the severity of a pneumopathy, and thus to decide whether the patient should be referred to an outpatient or an inpatient clinic [23].

References

1. Chen, N.; Zhou, M.; Dong, X.; Qu, J.; Gong, F.; Han, Y.; Qiu, Y.; Wang, J.; Liu, Y.; Wei, Y.; et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet* **2020**, *395*, 507–513. [CrossRef]
2. Weekly Epidemiological Update—20 October 2020. Available online: https://www.who.int/publications/m/item/weekly-epidemiological-update---20-october-2020 (accessed on 24 October 2020).
3. Wang, L.; He, W.; Yu, X.; Hu, D.; Bao, M.; Liu, H.; Zhou, J.; Jiang, H. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. *J. Infect.* **2020**, *80*, 639–645. [CrossRef]
4. Aguiar, D.; Lobrinus, J.A.; Schibler, M.; Fracasso, T.; Lardi, C. Inside the lungs of COVID-19 disease. *Int. J. Leg. Med.* **2020**, *134*, 1271–1274. [CrossRef]
5. Youd, E.; Moore, L. COVID-19 autopsy in people who died in community settings: The first series. *J. Clin. Pathol.* **2020**, *73*, 840–844. [CrossRef]
6. Wang, C.; Xie, J.; Zhao, L.; Fei, X.; Zhang, H.; Tan, Y.; Nie, X.; Zhou, L.; Liu, Z.; Ren, Y.; et al. Alveolar macrophage dysfunction and cytokine storm in the pathogenesis of two severe COVID-19 patients. *EBioMedicine* **2020**, *57*, 102833. [CrossRef]
7. Falasca, L.; Nardacci, R.; Colombo, D.; Lalle, E.; Di Caro, A.; Nicastri, E.; Antinori, A.; Petrosillo, N.; Marchioni, L.; Biava, G.; et al. Postmortem Findings in Italian Patients with COVID-19: A Descriptive Full Autopsy Study of Cases with and Without Comorbidities. *J. Infect. Dis.* **2020**, *222*, 1807–1815. [CrossRef]
8. Lax, S.F.; Skok, K.; Zechner, P.; Kessler, H.H.; Kaufmann, N.; Koelblinger, C.; Vander, K.; Bargfrieder, U.; Trauner, M. Pulmonary Arterial Thrombosis in COVID-19 With Fatal Outcome: Results from a Prospective, Single-Center, Clinicopathologic Case Series. *Ann. Intern. Med.* **2020**, *173*, 350–361. [CrossRef]
9. Wichmann, D. Autopsy Findings and Venous Thromboembolism in Patients with COVID-19. *Ann. Intern. Med.* **2020**, *173*, 1030. [CrossRef]
10. Maggi, E.; Canonica, G.W.; Moretta, L. COVID-19: Unanswered questions on immune response and pathogenesis. *J. Allergy Clin. Immunol.* **2020**, *146*, 18–22. [CrossRef]
11. Merad, M.; Martin, J.C. Pathological inflammation in patients with COVID-19: A key role for monocytes and macrophages. *Nat. Rev. Immunol.* **2020**, *20*, 355–362. [CrossRef]
12. Azkur, A.K.; Akdis, M.; Azkur, D.; Sokolowska, M.; van de Veen, W.; Brüggen, M.-C.; O'Mahony, L.; Gao, Y.; Nadeau, K.; Akdis, C.A. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy* **2020**, *75*, 1564–1581. [CrossRef] [PubMed]
13. Pomara, C.; Li Volti, G.; Cappello, F. COVID-19 Deaths: Are We Sure It Is Pneumonia? Please, Autopsy, Autopsy, Autopsy! *J. Clin. Med.* **2020**, *9*, 1259. [CrossRef]
14. Sperhake, J.-P. Autopsies of COVID-19 deceased? Absolutely! *Leg. Med.* **2020**, *47*, 101769. [CrossRef] [PubMed]
15. Cordasco, F.; Scalise, C.; Sacco, M.A.; Bonetta, C.F.; Zibetti, A.; Cacciatore, G.; Caputo, F.; Ricci, P.; Aquila, I. The silent deaths of the elderly in long-term care facilities during the Covid-19 pandemic: The role of forensic pathology. *Med. Leg. J.* **2020**, *88*, 66–68. [CrossRef]
16. Sessa, F.; Bertozzi, G.; Cipolloni, L.; Baldari, B.; Cantatore, S.; D'Errico, S.; Di Mizio, G.; Asmundo, A.; Castorina, S.; Salerno, M.; et al. Clinical-Forensic Autopsy Findings to Defeat COVID-19 Disease: A Literature Review. *J. Clin. Med.* **2020**, *9*, 2026. [CrossRef]
17. Mendes, A.; Serratrice, C.; Herrmann, F.R.; Genton, L.; Périvier, S.; Scheffler, M.; Fassier, T.; Huber, P.; Jacques, M.-C.; Prendki, V.; et al. Predictors of In-Hospital Mortality in Older Patients with COVID-19: The COVIDAge Study. *J. Am. Med. Dir. Assoc.* **2020**, *21*, 1546–1554.e3. [CrossRef]
18. Salvi, F.; Miller, M.D.; Grilli, A.; Giorgi, R.; Towers, A.L.; Morichi, V.; Spazzafumo, L.; Mancinelli, L.; Espinosa, E.; Rappelli, A.; et al. A Manual of Guidelines to Score the Modified Cumulative Illness Rating Scale and Its Validation in Acute Hospitalized Elderly Patients. *J. Am. Geriatr. Soc.* **2008**, *56*, 1926–1931. [CrossRef]
19. Linacre, J.M.; Heinemann, A.W.; Wright, B.D.; Granger, C.V.; Hamilton, B.B. The structure and stability of the Functional Independence Measure. *Arch. Phys. Med. Rehabil.* **1994**, *75*, 127–132. [CrossRef]
20. Rockwood, K.; Song, X.; MacKnight, C.; Bergman, H.; Hogan, D.B.; McDowell, I.; Mitnitski, A. A global clinical measure of fitness and frailty in elderly people. *CMAJ* **2005**, *173*, 489–495. [CrossRef]
21. Winter, J.E.; MacInnis, R.J.; Wattanapenpaiboon, N.; Nowson, C.A. BMI and all-cause mortality in older adults: A meta-analysis. *Am. J. Clin. Nutr.* **2014**, *99*, 875–890. [CrossRef]
22. Fine, M.J.; Auble, T.E.; Yealy, D.M.; Hanusa, B.H.; Weissfeld, L.A.; Singer, D.E.; Coley, C.M.; Marrie, T.J.; Kappor, W.N. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N. Engl. J. Med.* **1997**, *336*, 243–250. [CrossRef]

23. Lim, W.; van der Eerden, M.M.; Laing, R.; Boersma, W.G.; Karalus, N.; Town, G.I.; Lewis, S.A.; Macfarlane, J.T. Defining community acquired pneumonia severity on presentation to hospital: An international derivation and validation study. *Thorax* **2003**, *58*, 377–382. [CrossRef]
24. Edler, C.; Schröder, A.S.; Aepfelbacher, M.; Fitzek, A.; Heinemann, A.; Heinrich, F.; Klein, A.; Langenwalder, F.; Lütgehetmann, M.; Meissner, K.; et al. Dying with SARS-CoV-2 infection-an autopsy study of the first consecutive 80 cases in Hamburg, Germany. *Int. J. Leg. Med.* **2020**, *134*, 1275–1284. [CrossRef]
25. Langford, B.J.; So, M.; Raybardhan, S.; Leung, V.; Westwood, D.; MacFadden, D.R.; Soucy, J.-P.R.; Daneman, N. Bacterial co-infection and secondary infection in patients with COVID-19: A living rapid review and meta-analysis. *Clin. Microbiol. Infect.* **2020**, *26*, 1622–1629. [CrossRef]
26. Sieswerda, E.; de Boer, M.G.J.; Bonten, M.M.J.; Boersma, W.G.; Jonkers, R.E.; Aleva, R.M.; Kullberg, B.-J.; Schouten, J.A.; Van de Garde, E.M.W.; Verheij, T.J.; et al. Recommendations for antibacterial therapy in adults with COVID-19—an evidence based guideline. *Clin. Microbiol. Infect.* **2021**, *27*, 61–66. [CrossRef]
27. Prendki, V.; Scheffler, M.; Huttner, B.; Garin, N.; Herrmann, F.; Janssens, J.-P.; Marti, C.; Carballo, S.; Roux, X.; Serratrice, C.; et al. Low-dose computed tomography for the diagnosis of pneumonia in elderly patients: A prospective, interventional cohort study. *Eur. Respir. J.* **2018**, *51*, 1702375. [CrossRef]
28. Prendki, V.; Huttner, B.; Marti, C.; Mamin, A.; Fubini, P.E.; Meynet, M.P.; Scheffler, M.; Montet, X.; Janssens, J.-P.; Reny, J.L.; et al. Accuracy of comprehensive PCR analysis of nasopharyngeal and oropharyngeal swabs for CT-scan-confirmed pneumonia in elderly patients: A prospective cohort study. *Clin. Microbiol. Infect.* **2019**, *25*, 1114–1119. [CrossRef]
29. Bartal, C.; Sagy, I.; Barski, L. Drug-induced eosinophilic pneumonia: A review of 196 case reports. *Medicine* **2018**, *97*, e9688. [CrossRef]
30. Tseng, O.L.-I.; Kelsall, J.T.; Wilcox, P.G. Piperacillin-associated pulmonary infiltrates with eosinophilia: A case report. *Can. Respir. J.* **2010**, *17*, e24–e26. [CrossRef]
31. Murao, K.; Saito, A.; Kuronuma, K.; Fujiya, Y.; Takahashi, S.; Chiba, H. Acute eosinophilic pneumonia accompanied with COVID-19: A case report. *Respirol. Case Rep.* **2020**, *8*, e00683. [CrossRef]
32. Lindsley, A.W.; Schwartz, J.T.; Rothenberg, M.E. Eosinophil responses during COVID-19 infections and coronavirus vaccination. *J. Allergy Clin. Immunol.* **2020**, *146*, 1–7. [CrossRef]
33. Tseng, C.-T.; Sbrana, E.; Iwata-Yoshikawa, N.; Newman, P.C.; Garron, T.; Atmar, R.L.; Peters, C.J.; Couch, R.B. Immunization with SARS Coronavirus Vaccines Leads to Pulmonary Immunopathology on Challenge with the SARS Virus. *PLoS ONE* **2012**, *7*, e35421. [CrossRef]
34. Tian, S.; Hu, W.; Niu, L.; Liu, H.; Xu, H.; Xiao, S.-Y. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients with Lung Cancer. *J. Thorac. Oncol.* **2020**, *15*, 700–704. [CrossRef]
35. Schaller, T.; Hirschbühl, K.; Burkhardt, K.; Braun, G.; Trepel, M.; Märkl, B.; Claus, R. Postmortem Examination of Patients With COVID-19. *JAMA* **2020**, *323*, 2518–2520. [CrossRef]
36. Bösmüller, H.; Traxler, S.; Bitzer, M.; Häberle, H.; Raiser, W.; Nann, D.; Frauenfeld, L.; Vogelsberg, A.; Klingel, K.; Fend, F. The evolution of pulmonary pathology in fatal COVID-19 disease: An autopsy study with clinical correlation. *Virchows Arch.* **2020**, *477*, 349–357. [CrossRef]
37. Carsana, L.; Sonzogni, A.; Nasr, A.; Rossi, R.S.; Pellegrinelli, A.; Zerbi, P.; Rech, R.; Colombo, R.; Antinori, S.; Corbellino, M.; et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: A two-centre descriptive study. *Lancet Infect. Dis.* **2020**, *20*, 1135–1140. [CrossRef]
38. Rapkiewicz, A.V.; Mai, X.; Carsons, S.E.; Pittaluga, S.; Kleiner, D.E.; Berger, J.S.; Thomas, S.; Adler, N.M.; Charytan, D.M.; Gasmi, B.; et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: A case series. *EClinicalMedicine* **2020**, *24*, 100434. [CrossRef] [PubMed]
39. Bradley, B.T.; Maioli, H.; Johnston, R.; Chaudhry, I.; Fink, S.L.; Xu, H.; Najafian, B.; Deutsch, G.; Lacy, J.M.; Williams, T.; et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: A case series. *Lancet* **2020**, *396*, 320–332. [CrossRef]
40. Eketunde, A.O.; Mellacheruvu, S.P.; Oreoluwa, P. A Review of Postmortem Findings in Patients with COVID-19. *Cureus* **2020**, *12*, e9438.
41. Migliaccio, M.G.; Di Mauro, M.; Ricciolino, R.; Spiniello, G.; Carfora, V.; Verde, N.; Mottola, F.F.; Coppola, N. Renal Involvement in COVID-19: A Review of the Literature. *Infect. Drug Resist.* **2021**, *14*, 895–903. [CrossRef]
42. Pei, G.; Zhang, Z.; Peng, J.; Liu, L.; Zhang, C.; Yu, C.; Ma, Z.; Huang, Y.; Liu, W.; Yao, Y.; et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. *J. Am. Soc. Nephrol.* **2020**, *31*, 1157–1165. [CrossRef] [PubMed]
43. Jhaveri, K.D.; Meir, L.R.; Flores Chang, B.S.; Parikh, R.; Wanshoo, R.; Barilla-LaBarca, M.L.; Bijol, V.; Hajizadeh, N. Thrombotic microangiopathy in a patient with COVID-19. *Kidney Int.* **2020**, *98*, 509–512. [CrossRef]
44. Ronco, C.; Reis, T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. *Nat. Rev. Nephrol.* **2020**, *16*, 308–310. [CrossRef]

45. Matschke, J.; Lütgehetmann, M.; Hagel, C.; Sperhake, J.P.; Schröder, A.S.; Edler, C.; Mushumba, H.; Fitzek, A.; Allweiss, L.; Dandri, M.; et al. Neuropathology of patients with COVID-19 in Germany: A post-mortem case series. *Lancet Neurol.* **2020**, *19*, 919–929. [CrossRef]
46. Pinal-Fernandez, I.; Casal-Dominguez, M.; Mammen, A.L. Immune-Mediated Necrotizing Myopathy. *Curr. Rheumatol. Rep.* **2018**, *20*, 21. [CrossRef] [PubMed]

Journal of
Clinical Medicine

MDPI

Article

How SARS-CoV-2 Pandemic Changed Traumatology and Hospital Setting: An Analysis of 498 Fractured Patients

Marco Brayda-Bruno [1], Riccardo Giorgino [2,*], Enrico Gallazzi [3], Ilaria Morelli [4], Francesca Manfroni [1], Matteo Briguglio [1], Riccardo Accetta [1], Laura Mangiavini [1,5] and Giuseppe Maria Peretti [1,5]

[1] IRCCS Orthopedic Institute Galeazzi, 20144 Milan, Italy; marco.brayda@spinecaregroup.it (M.B.-B.); francesca.manfroni89@gmail.com (F.M.); matteo.briguglio@grupposandonato.it (M.B.); riccacc@gmail.com (R.A.); laura.mangiavini@unimi.it (L.M.); giuseppe.peretti@unimi.it (G.M.P.)
[2] Residency Program in Orthopedics and Traumatology, University of Milan, 20122 Milan, Italy
[3] Ortopedia e Traumatologia 3, ASST Centro Specialistico Ortopedico Traumatologico G. Pini–CTO, 20122 Milan, Italy; enrico.gallazzi@gmail.com
[4] U.O.C. Ortopedia e Traumatologia Nuovo Ospedale di Legnano ASST Ovest Milanese, 20025 Legnano, Italy; ilaria.morelli90@gmail.com
[5] Department of Biomedical Sciences for Health, University of Milan, 20122 Milan, Italy
* Correspondence: riccardo.giorgino@unimi.it

Abstract: Background: SARS-CoV-2 pandemic is one of the biggest challenges for many health systems in the world, making lots of them overwhelmed by the enormous pressure to manage patients. We reported our Institutional Experience, with specific aims to describe the distribution and type of treated injuries, and the organizational setup of our hospital. Methods: Data of fractured patients admitted for surgical treatment in the time frames 9 March 2020–4 May 2020 and 1 March 2019–31 May 2019 were collected and compared. Furthermore, surgery duration and some parameters of effectiveness in health management were compared. Results: A total of 498 patients were included. Mean age significantly lower age in 2019 and femoral fractures were significantly more frequent 2020. Mean surgery time was significantly longer in 2020. Mortality rate difference between the two years was found to be statistically significant. Time interval between diagnosis and surgery and between diagnosis and discharge/decease was significantly lower in 2020. In 2020, no patient admitted with a negative swab turned positive in any of the following tests for SARS-CoV-2. Conclusions: The COVID-19 pandemic has modified the epidemiology of hospitalized patients for traumatic reasons, leading to an increased admission of older patients with femoral fractures. Nevertheless, our institutional experience showed that an efficient change in the hospital organization, with an improvement of several parameters of effectiveness in health management, led to a null infection rate between patients.

Keywords: SARS-CoV-2; fractures; traumatology; hospital setting; health care management

Citation: Brayda-Bruno, M.; Giorgino, R.; Gallazzi, E.; Morelli, I.; Manfroni, F.; Briguglio, M.; Accetta, R.; Mangiavini, L.; Peretti, G.M. How SARS-CoV-2 Pandemic Changed Traumatology and Hospital Setting: An Analysis of 498 Fractured Patients. *J. Clin. Med.* **2021**, *10*, 2585. https://doi.org/10.3390/jcm10122585

Academic Editor: Alessandra Falchi

Received: 9 May 2021
Accepted: 10 June 2021
Published: 11 June 2021

1. Introduction

The Novel Coronavirus 2019 (SARS-CoV-2) pandemic is one of the biggest challenges for the National Health Systems (NHS) in modern times. Since the first reported case in December 2019 in Wuhan, Hubei province, China [1], the infection has spread worldwide, with cases reported in all countries [2]. Due to the severity of the clinical picture, during the first pandemic wave more than 20% of patients eventually require admission to Intensive Care Units (ICU) with a long stay [3]. Thus, many of the health systems in the world were overwhelmed by the enormous pressure to manage those patients. Italy was one of the first countries hit by the pandemic first wave, with more than 233,000 total cases, 157,000 healed, 33,000 deaths and 86,000 hospital admissions up to 31 May 2020 (data from the Italian Ministry of Health website: https://www.salute.gov.it/imgs/C_17_notizie_4839_0_file.pdf (accessed on 31 May 2020)) [4].

This unprecedented situation called for unprecedented measures. Starting from 8 March and until 4 May 2020, a 'Phase 1' response was implemented: our Region, Lombardy, Italy, was quarantined, with only essential works allowed; gatherings were forbidden, and leaving the house for groceries was allowed once a week only for one member per family [5,6]. Furthermore, this occurrence called for a prompt response also by the Health Ministry and NHS Authorities, pressured to reorganize and rationalize the NHS in order to provide as many ICU beds as possible to treat positive severe ill patients [7]. At the same time, great attention was paid to maintaining the capability to treat other medical and surgical emergencies and limiting as much as possible the risk of intrahospital spreading of the infection. Thus, our Regional Health System was reorganized following the Hub-Spoke model [8,9]. In this context, our Institution was identified as Hub for 'Minor' trauma, defined as low-energy, single-district trauma requiring an orthopedic surgical treatment. Hub hospitals were obliged to organize separate pathways, with 'clean' areas for non-SARS-CoV-2 patients, and 'dirty' areas for SARS-CoV-2 positive patients after hospital triage, in order to treat both type of patients with minimal contagion risk [10]. Furthermore, safety of Healthcare Professionals was a priority, with implementation of a training program to learn how to properly dress and undress with personal protective equipment (PPE: gloves, surgical face masks, goggles, face shield and gowns, as well as items for specific procedures) and to make correct use of them.

In this context, we reported our Institutional Experience during the first wave response to the COVID-19 pandemic, with specific aims to describe the distribution and type of treated injuries, and the organizational setup of our hospital. In particular, we tested these specific hypotheses: (1) the lockdown modified the population behavior, thus modifying the epidemiology and injury distribution of minor trauma patients; (2) our activity produced a high level of quality and effectiveness through the evaluation of technical times in the treatment of trauma patients; (3) the internal organizational system was effective in limiting in-hospital spread of the disease among patients and healthcare workers.

2. Materials and Methods

2.1. Study Population and Methods

The electronic registry of our institution was searched for patients with fractures admitted for surgical treatment in the time frames 9 March 2020–4 May 2020 (pandemic group) and 1 March 2019–31 May 2019 (non-pandemic group). Patients with nasopharyngeal swab positive for SARS-CoV2 were included as well. The anonymized demographic and clinical data of all included patients were extracted. Age, fracture distribution, differences in death rate and discharge type were compared between the two groups. Furthermore, surgery duration and the time intervals between diagnosis and surgery and between diagnosis and discharge/death during hospital stay were analyzed as parameters of clinical efficiency and compared.

2.2. Hospital Organization

Our facility is located in a 9-story building, with a cave-square shape. The two basement floors host: Emergency and Radiology departments, Clinical Chemistry and Microbiology Laboratories, offices, Nuclear Magnetic Resonance Unit, locker rooms, storages and research laboratories. Both basement floors are connected to the internal yard. Management offices, a cafeteria, several offices for outpatient visits and a wide hall with front desks are present on the ground floor. First floor hosts outpatient rooms, the dentistry unit, the rehabilitation gym and some operatory rooms for day-hospital surgery. The other floors are entirely dedicated to surgical and rehabilitation inpatients wards, usually hospitalized in double rooms. Some areas on the 5th and 6th floors include operatory rooms. The Intensive Care Unit (ICU) is also on the 5th floor, while the remaining part of the 6th hosts some offices and research labs.

With the beginning of COVID-19 pandemic in March 2020, the following changes have been implemented to limit in-hospital disease spread:

- Only non-deferrable outpatient visits and radiological exams were allowed, and the access of patients' relatives was possible only in case of real need, to reduce hospital overcrowding. Social distancing rules have been applied in all the waiting rooms, spacing and reducing seats with dedicated elevators.
- The second floor was entirely converted into a COVID-19 unit, hosting both hospitalized patients with SARS-CoV-2-related respiratory disease and positive patients with surgical fractures (during the acute surgical care). The 3rd floor was transformed into a pre-COVID unit, hosting surgical patients admitted trough emergency unit and before the results of nasopharyngeal swab. Based on the results, they were sorted into the COVID unit of the 2nd floor or into the clean area. The passage of healthcare workers (HCWs) was allowed only from the pre-COVID to the COVID unit, never inversely, according to a gradient from suspect to ascertained cases. As the number of positive cases decreased, the pre-COVID unit was transferred into a small, separated area on the 2nd floor.
- The 4th floor was the 'COVID-free' area, entirely dedicated to surgical inpatients with negative swabs.
- The operatory rooms on the 5th story were converted into COVID-ICU.
- The 6th floor hosted the COVID-free ICU, while the surgical unit was split into non-communicant COVID and COVID-free surgical units, with separate accesses.
- All the COVID areas were provided with changing rooms with showers for HCWs.
- All the ward rooms, generally hosting two patients, were transformed to host only one patient.
- Patients transfers between the COVID areas (COVID unit, operatory room and ICU) and between the COVID-free areas occurred through different pathways, corridors and elevators. Corpses were transported through the COVID pathway.
- No courtesy visits on assistance to hospitalized patients were allowed anymore, except for pediatric patients with one parent swabbed and not allowed to leave the room.
- HCWs access was guaranteed only through the main entrance. Outpatients entered the hospital through the main entrance; when needing hospitalization, patients entered through the emergency department (ED). Due to the high prevalence of SARS-CoV-2 in Lombardy, all patients arriving at hospital filled in a short anamnestic questionnaire regarding respiratory symptoms or possible personal contacts with cases of COVID-19. Fever screening with thermal cameras was mandatory for all people entering the hospital: if allowed (with temperature <37.5 °C), they were provided with a new surgical mask, that both workers and patients had to wear inside the hospital (even during oxygen therapy or in the operatory rooms, if tolerated).

2.3. SARS-CoV-2 Testing

In our facility, each patient underwent a SARS-CoV-2 nasopharyngeal swab at admission (even when transferred from other hospitals), after 3 days from admission and then every 5 days until discharge. The rate of COVID-19-negative patients at admission, whose SARS-CoV-2 nasopharyngeal swabs turned positive during hospitalization, was analyzed. This was attributed to possible in-hospital disease spreading only if the swabs turned positive 3 days from the negative test at admission.

2.4. Statistical Analysis

Statistical analyses were performed using GraphPad Prism (version 8, GraphPad Prism Software Inc.). Contingency tables with Chi-square test calculation were used to compare categorical variable distribution between the two groups. For 2 by 2 contingency tables, odds ratios (OR) were calculated, and reliability expressed through 95% confidence intervals (CI). Unpaired Student's *t*-test was used to compare continuous variables, and results reported as t(degrees of freedom), *p*-value. Statistical significance was set at $p \leq 0.05$. The raw data used to support the findings of this study are included within the Supplementary Information File as a Microsoft Excel worksheet.

3. Results

A total of 498 patients were included, 146 patients in 2019 and 352 in 2020, overall reporting 512 fractures (153 in 2019 and 359 in 2020). Indeed, 14 patients reported more than one fracture. The overall mean age was 67 ± 23 years, with a significantly lower age in 2019 (61 ± 24.5 years versus 69 ± 21.5, t(496) = 3.6251, p-value = 0.0003). Fracture distribution is reported in Figure 1.

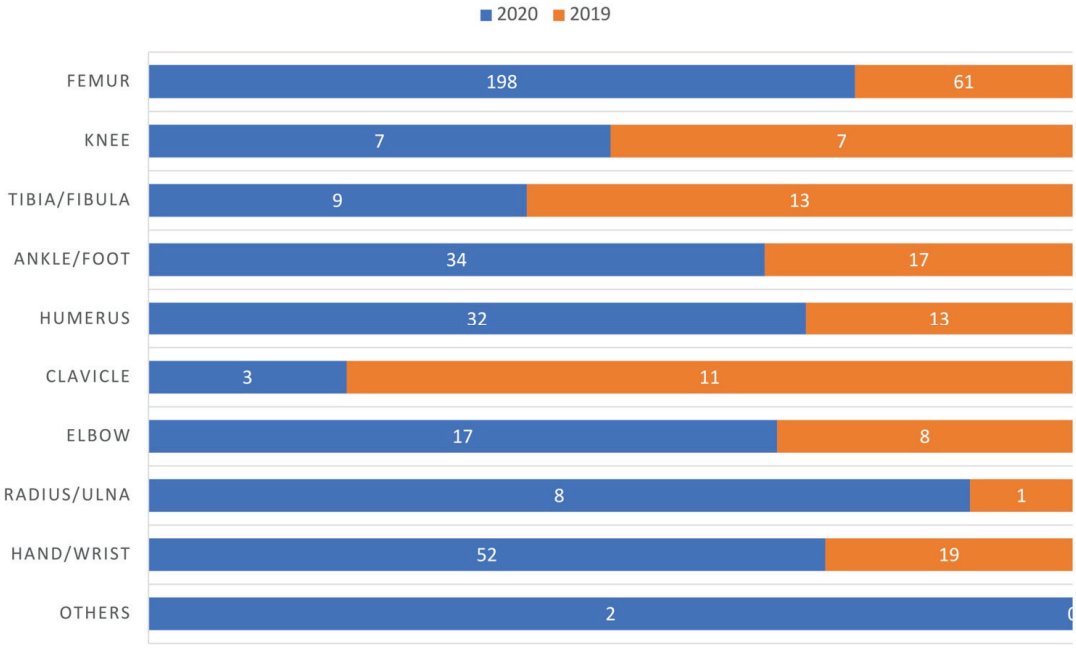


Figure 1. Typification of fractures. Femoral fractures were significantly more frequent in 2020 (p-value = 0.0137).

Femoral fractures were significantly more frequent in the pandemic group (181 out of 352 in 2020 versus 57 out of 146 fractures in 2019, p-value = 0.0137). Interestingly, mean surgery time was significantly longer in 2020 rather than in 2019 (89 ± 36.7 min and 78 ± 31.3 min, respectively; t(496) = 3.1739, p-value = 0.0016). After surgery, 89 patients (61%) from the non-pandemic group were discharged home, 56 (38,4%) were transferred into rehabilitation facilities and one (0,7%) into nursing home. Similarly, 212 (60,2%) patients from the pandemic group were discharged home, 124 (35,2%) transferred into rehabilitation facilities and 6 into nursing homes (1,7%), while 10 patients died during their hospital stay (2,8%). The mortality rate difference between the two years was found to be statistically significant (p-value = 0.0389) (Table 1). Among the 10 deaths, 3 patients died from serious comorbidities and 7 from COVID-related thromboembolic events. More precisely, 4 patients died between day 0 and day 2 and 6 patients between day 8 and day 10.

Table 1. Differences in patients admitted between 2019 and 2020.

	2019	2020	p-Value
Mean age (years)	61 ± 24.5	69 ± 21.5	0.0003
Femoral fractures/total fractures	57/146	181/352	0.0137
Mean surgical time (minutes)	78 ± 31.3	89 ± 36.7	0.0016
Diagnosis-to-surgery time (days)	5.2 ± 6.7	3.5 ± 4.2	0.0007
Diagnosis-to-discharge/decease time (days)	9.3 ± 6.3	8.1 ± 5.2	0.0284
Deceased patients	0/146	10/352	0.0389

Furthermore, the time interval between diagnosis and surgery in 2020 was 3.5 ± 4.2 days, in contrast to 2019 when it was 5.2 ± 6.7 days (t(496) = 3.4128, *p*-value = 0.0007). Additionally, the time interval between diagnosis and discharge/decease was significantly lower in 2020 compared to 2019 (8.1 ± 5.2 days and 9.3 ± 6.3 days, respectively; t(496) = 2.1988, *p*-value = 0.0284) (Figure 2). In the pandemic group, no patient admitted with a negative swab turned positive in any of the following tests for SARS-CoV-2.

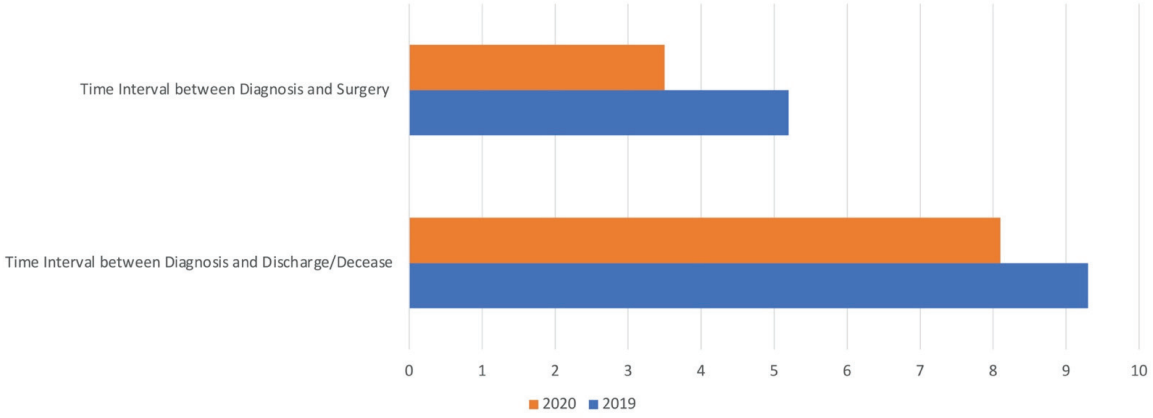


Figure 2. Parameters of effectiveness in health management. Time interval between diagnosis and surgery and between diagnosis and discharge/decease were significantly lower in 2020 (respectively, *p*-value = 0.0007 and *p*-value = 0.0284).

4. Discussion

Our findings revealed that, with the structural and organizational changes adopted in our hospital, our facility faced, with success, the first pandemic wave increase in hospital admissions due to trauma Hub designation. During the first pandemic wave, an epidemiological change, compared to 2019, was found with regards to the admitted patients, presenting a higher mean age and mainly femoral fractures. Despite the patients admitted during 2020 were mainly frail older adults, no in-hospital COVID-19 spreading was found. This could be explained with the rigid separation between COVID and COVID-free areas at our facility, close monitoring with repeated nasopharyngeal swabs during hospitalization and reduced time intervals from diagnosis to surgical treatment and to discharge. Furthermore, the increase in surgical time could reflect first of all the strict application of PPE wearing protocols, in order to reduce SARS-CoV-2 diffusion.

The first aim of our study was to analyze the variation of orthopedic treatment request during quarantine: epidemiological data are valuable, both for surgeons and for stakeholders, in order to optimize the personnel and instrumentation required to manage specific types of fractures. We previously reported [10] that during the March 2020 lockdown the percentage of ER admissions as white and green code (walking wounded) markedly decreased when compared to the same time span during 2019. Similar reduction was reported in several countries in the world during the SARS epidemic [11,12]. On the contrary, admission triages as yellow and red code (urgent patients, including femoral fractures) markedly increased in same time frame. This higher volume of fracture-related admission could be a consequence of the centralization of minor trauma to Hub hospitals during the emergency. Furthermore, it could be due to a decreased home-assistance to older adults by the caregivers, in order to avoid disease spreading, during the lockdown. Other studies evaluated the impact of lockdown in trauma admission. Giorgi et al. reported an increase in high energy traumas that caused vertebral fracture at the early stage of the March lockdown compared to the same time span of the previous year in a major trauma hub [13]. Ogliari et al. [14] reported a decrease in overall fractures admitted to a Fracture Clinic, while

observing the same amount of hip fractures admitted during lockdown when compared to prior period before the lockdown; the authors evidenced a change in epidemiology of injury due to the reduced traffic and work activities (lockdown), thus suggesting hospitals to prepare accordingly. Conversely, Poggetti et al. [15] reported the same amount of hand and wrist fractures prior and during the lockdown; they, however, noted a change in etiology, with less sport and traffic related injuries and more domestic accidents, with a shift towards patients with older age. Interestingly, Bram et al. [16] reported a 2.5 SD fold decrease in pediatric fractures during the lockdown, mainly due to cessation of organized sport and the prohibition of playground use. In this context, our paper offers a different perspective, due to the Hub organization of the Italian NHS: since most of the fractures were shifted to the Hub hospitals, with only two minor trauma Hub serving a metropolitan area of roughly 1.5 million inhabitants, our data are less biased by the pathology 'dispersion' and could better reflect the real-life scenario. The second aim of this study was to evaluate some parameters of hospital clinical efficiency in a different scenario, as the surgical times and the time frames passed from diagnosis to surgery and from diagnosis to discharge. Surgical times were longer in the pandemic group, and this could be explained by the time needed to wear the adequate PPEs, as well as by the fact that PPEs and apprehension due to possible intraoperative HCWs contagion may have slowed down the global surgical times (admission to OR, patient preparation and positioning and post-surgical management). On the other hand, both diagnosis-surgery and diagnosis-discharge times were reduced, and this could be considered as an overall improvement in clinical efficiency during the pandemic. This may be due to the rigid internal organization, as the protocols applied may have automatized and quickened the everyday procedures. Unluckily, since the deceased patients were considered as discharges, the death of 10 patients surely contributed to reduce the diagnosis-discharge time. On the other hand, the higher mortality rate is aligned with other studies reporting an increased mortality rate for COVID-19 fractured patients [17–19]. The third aim of this paper was to evaluate the effectiveness of the applied hospital measures to reduce the risk of contagion between patients. Overall, we had no cases of swabs turned positive among patients hospitalized in the 'clean' area. This was an excellent result, underlining the effectiveness of the measures adopted. In fact, COVID-19 diffusion among hospitalized patients was one of the most severe issues to manage during the first Italian outbreak [20,21]. During epidemics, hospitals and nursing homes could become real pitfalls for the disaster response phase [20]. Especially at the beginning of a pandemic, hospitals, that are already hosting frail people, such as older adults or patients with several comorbidities, are overcrowded with an increasing number of contagious people. If the viral pathogen is not rapidly recognized, and preventive measures are not immediately implemented, nosocomial transmission is a dangerous consequence both for inpatients and medical personnel [22].

The currently ongoing SARS-CoV-2 pandemic is the biggest challenge that the National health Systems handled in the last century. Most of the European countries faced the early 2020 outbreak of March and April, and Italy was the first and most affected country [23]. Afterwards, an overall case reduction during summer was perceived [24]. Therefore, during the fall, the direst predictions were confirmed, and a new outbreak affected the European Union. In Italy, the total number of cases registered in October was almost 300,000, surpassing by far the total number of cases registered in March and April [4]. Furthermore, with an increasing number of patients currently requiring ICU, the NHS was again on the verge of collapse [25]. Orthopedic practice was also markedly affected by the pandemic. Elective surgical activity is currently limited only to cases with severe pain and functional limitation, or risk of disease progression. As described in a previous paper [13], the NHS is again being reorganized to face the ongoing second emergency, with the goal of rationalizing care and reducing the risk of in-hospital contagion. Indeed, most of trauma occurring in our metropolitan area are shifted to three 'Hub' hospitals, one for major traumas and two for minor traumas. Similar organizational models are currently being implemented in other parts of the country and across Europe [26]. In this context,

it is of utmost importance to report the experience acquired during the first outbreak. In addition to the encouraging results regarding the management of a health emergency, our results appear valuable in the possible future comparison with what happens during the further COVID-19 waves.

5. Conclusions

This work reports our institutional experience during the first wave of SARS-CoV-2 pandemic when we were able to set an optimal organization of the hospital, an example to consider and eventually adapt in the light of specific needs. The new hospital assessment included an increase of dedicated beds, ORs and health-care personnel, thus leading to an improvement of numerous parameters of effectiveness in health management. Furthermore, we showed an ideal inpatient protection, with a rigid separation between COVID and COVID-free area, a strict personnel flow from clean to COVID areas and close inpatients monitoring with serial swabs, which led to a null infection rate between patients. These organizational changes are also easily reproducible in other little single-building multistory facilities, and should be considered in order to limit in-hospital disease spreading.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm10122585/s1.

Author Contributions: Conceptualization, R.G., M.B.-B. and G.M.P.; methodology, G.M.P. and L.M.; software, I.M. and M.B.; validation, R.G., I.M., L.M.; investigation, M.B.; resources, F.M., R.G. and R.A.; data curation, R.G., F.M., E.G., I.M.; writing—original draft preparation, R.G., E.G., I.M. and L.M.; writing—review and editing, G.M.P. and M.B.; visualization, L.M.; supervision, G.M.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval were waived for this study, due to sensitive and personal data were anonymously treated.

Informed Consent Statement: Patient consent was waived due to sensitive and personal data were anonymously treated.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy.

Acknowledgments: The authors wish to thank all the personnel which has served and sacrificed in this emergency.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; et al. A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.* **2020**. [CrossRef] [PubMed]
2. Mallapaty, S. Why does the coronavirus spread so easily between people? *Nature* **2020**. [CrossRef] [PubMed]
3. Immovilli, P.; Morelli, N.; Antonucci, E.; Radaelli, G.; Barbera, M.; Guidetti, D. COVID-19 mortality and ICU admission: The Italian experience. *Crit. Care* **2020**. [CrossRef]
4. PCM-DPC Dati Forniti dal Ministero Della Salut. Available online: https://www.salute.gov.it/imgs/C_17_notizie_4839_0_file.pdf (accessed on 31 May 2020).
5. Briguglio, M.; Giorgino, R.; Dell'Osso, B.; Cesari, M.; Porta, M.; Lattanzio, F.; Banfi, G.; Peretti, G.M. Consequences for the elderly after COVID-19 isolation: FEaR (frail elderly amid restrictions). *Front. Psychol.* **2020**, *11*. [CrossRef]
6. Sebastiani, G.; Massa, M.; Riboli, E. Covid-19 epidemic in Italy: Evolution, projections and impact of government measures. *Eur. J. Epidemiol.* **2020**, *35*, 341–345. [CrossRef]
7. Craxì, L.; Vergano, M.; Savulescu, J.; Wilkinson, D. Rationing in a pandemic: Lessons from Italy. *Asian Bioeth. Rev.* **2020**, *12*, 325–330. [CrossRef] [PubMed]
8. Borghesi, M.; Zilio, F.; Braito, G.; Dallago, M.; Muraglia, S.; Todaro, D.; Bonmassari, R. How to keep the cath-lab of a hub center "covid free" during the pandemic in a hub & spoke cardiology network: A single center experience and literature review. *Minerva Cardiol. Angiol.* **2021**. [CrossRef]

9. Morelli, I.; Luceri, F.; Giorgino, R.; Accetta, R.; Perazzo, P.; Mangiavini, L.; Maffulli, N.; Peretti, G.M. COVID-19: Not a contraindication for surgery in patients with proximal femur fragility fractures. *J. Orthop. Surg.* **2020**, *15*, 285. [CrossRef]
10. Luceri, F.; Morelli, I.; Accetta, R.; Mangiavini, L.; Maffulli, N.; Peretti, G.M. Italy and COVID-19: The changing patient flow in an orthopedic trauma center emergency department. *J. Orthop. Surg.* **2020**. [CrossRef]
11. Man, C.Y.; Yeung, R.S.D.; Chung, J.Y.M.; Cameron, P.A. Impact of SARS on an emergency department in Hong Kong. *Emerg. Med.* **2003**. [CrossRef]
12. Heiber, M.; Lou, W.Y.W. Effect of the SARS outbreak on visits to a community hospital emergency department. *Can. J. Emerg. Med.* **2006**. [CrossRef]
13. Giorgi, P.D.; Villa, F.; Gallazzi, E.; Debernardi, A.; Schirò, G.R.; Crisà, F.M.; Talamonti, G. The Management of Emergency Spinal Surgery during the COVID-19 Pandemic in Italy. *Bone Jt. J.* **2020**. [CrossRef]
14. Ogliari, G.; Lunt, E.; Ong, T.; Marshall, L.; Sahota, O. The impact of lockdown during the COVID-19 pandemic on osteoporotic fragility fractures: An observational study. *Arch. Osteoporos.* **2020**. [CrossRef]
15. Andrea, P.; Andrea, D.C.; Maria, N.A.; Chiara, S.; Sandra, P. How hand and wrist trauma has changed during Covid-19 emergency in Italy: Incidence and distribution of acute injuries. What to learn? *J. Clin. Orthop. Trauma* **2020**. [CrossRef]
16. Bram, J.T.; Johnson, M.A.; Magee, L.C.; Mehta, N.N.; Fazal, F.Z.; Baldwin, K.D.; Riley, J.; Shah, A.S. Where have all the fractures gone? The epidemiology of pediatric fractures during the COVID-19 pandemic. *J. Pediatr. Orthop.* **2020**. [CrossRef] [PubMed]
17. Kumar Jain, V.; Lal, H.; Kumar Patralekh, M.; Vaishya, R. Fracture management during COVID-19 pandemic: A systematic review. *J. Clin. Orthop. Trauma* **2020**, *11*, S431–S441. [CrossRef]
18. Hall, A.J.; Clement, N.D.; Farrow, L.; MacLullich, A.M.J.; Dall, G.F.; Scott, C.E.H.; Jenkins, P.J.; White, T.O.; Duckworth, A.D. IMPACT-Scot report on COVID-19 and hip fractures. *Bone Jt. J.* **2020**, *102*, 1219–1228. [CrossRef] [PubMed]
19. Kayani, B.; Onochie, E.; Patil, V.; Begum, F.; Cuthbert, R.; Ferguson, D.; Bhamra, J.S.; Sharma, A.; Bates, P.; Haddad, F.S. The effects of COVID-19 on perioperative morbidity and mortality in patients with hip fractures. *Bone Jt. J.* **2020**, *102*, 1136–1145. [CrossRef] [PubMed]
20. Trabucchi, M.; De Leo, D. Nursing homes or besieged castles: COVID-19 in Northern Italy. *Lancet Psychiatry* **2020**, *7*, 387–388. [CrossRef]
21. Fumagalli, S.; Salani, B.; Gabbani, L.; Mossello, E.; Ungar, A. Covid-19 cases in a no-Covid-19 geriatric acute care setting. A sporadic occurrence? *Eur. J. Intern. Med.* **2020**, *77*, 141–142. [CrossRef] [PubMed]
22. Fagiuoli, S.; Lorini, F.L.; Remuzzi, G. Adaptations and lessons in the province of Bergamo. *N. Engl. J. Med.* **2020**, *8*, 323–328. [CrossRef] [PubMed]
23. Perazzo, P.; Giorgino, R.; Briguglio, M.; Zuffada, M.; Accetta, R.; Mangiavini, L.; Peretti, G.M. From standard to escalated anticoagulant prophylaxis in fractured older adults with SARS-CoV-2 undergoing accelerated orthopedic surgery. *Front. Med.* **2020**, *7*, 566770. [CrossRef] [PubMed]
24. Meyer, A.; Sadler, R.; Faverjon, C.; Cameron, A.R.; Bannister-Tyrrell, M. Evidence that higher temperatures are associated with a marginally lower incidence of COVID-19 cases. *Front. Public Health* **2020**, *8*, 367. [CrossRef] [PubMed]
25. Coronavirus (COVID-19) Patients in ICU in Italy as of June 2021, by Region. Available online: https://www.Statista.Com/Statistics/1105054/Coronavirus-Recoveries-by-Region.-in-Italy/ (accessed on 6 June 2021).
26. Looi, M.K. Covid-19: Is a second wave hitting Europe? *BMJ* **2020**, *371*, m4113. [CrossRef] [PubMed]

Journal of
Clinical Medicine

MDPI

Article

Chest X-ray Score and Frailty as Predictors of In-Hospital Mortality in Older Adults with COVID-19

Sara Cecchini [1], Mirko Di Rosa [2,*], Luca Soraci [3], Alessia Fumagalli [4], Clementina Misuraca [4], Daniele Colombo [4], Iacopo Piomboni [5], Francesca Carnevali [1], Enrico Paci [1], Roberta Galeazzi [6], Piero Giordano [7], Massimiliano Fedecostante [8], Antonio Cherubini [8] and Fabrizia Lattanzio [9]

[1] Department of Radiology, IRCCS INRCA, 60127 Ancona, Italy; s.cecchini@inrca.it (S.C.); f.carnevali@inrca.it (F.C.); e.paci@inrca.it (E.P.)
[2] Unit of Geriatric Pharmacoepidemiology and Biostatistics, IRCCS INRCA, 60124 Ancona, Italy
[3] Unit of Geriatric Medicine, IRCSS INRCA, 87100 Cosenza, Italy; l.soraci@inrca.it
[4] Respiratory Unit, IRCCS INRCA, 23880 Casatenovo, Italy; a.fumagalli@inrca.it (A.F.); c.misuraca@inrca.it (C.M.); d.colombo@inrca.it (D.C.)
[5] Department of Medicine and Health Sciences, University of Molise, 86100 Campobasso, Italy; i.piomboni@studenti.unimol.it
[6] Laboratory of Chemical-Clinical and Molecular Analysis, IRCCS INRCA, 60127 Ancona, Italy; r.galeazzi@inrca.it
[7] Internal Medicine and Geriatrics, Hypertension Excellence Centre of the European Society of Hypertension, IRCCS INRCA, 60127 Ancona, Italy; p.giordano@inrca.it
[8] Geriatria, Accettazione Geriatrica e Centro di Ricerca per L'invecchiamento, IRCCS INRCA, 60127 Ancona, Italy; m.fedecostante@inrca.it (M.F.); a.cherubini@inrca.it (A.C.)
[9] Scientific Direction, IRCCS INRCA, 60124 Ancona, Italy; f.lattanzio@inrca.it
* Correspondence: m.dirosa@inrca.it; Tel.: +39-071-800-4604

Citation: Cecchini, S.; Di Rosa, M.; Soraci, L.; Fumagalli, A.; Misuraca, C.; Colombo, D.; Piomboni, I.; Carnevali, F.; Paci, E.; Galeazzi, R.; et al. Chest X-ray Score and Frailty as Predictors of In-Hospital Mortality in Older Adults with COVID-19. *J. Clin. Med.* **2021**, *10*, 2965. https://doi.org/10.3390/jcm10132965

Academic Editors: Riccardo Giorgino and Filippo Migliorini

Received: 10 June 2021
Accepted: 29 June 2021
Published: 1 July 2021

Abstract: Background. The purpose of this study was to evaluate the prognostic impact of chest X-ray (CXR) score, frailty, and clinical and laboratory data on in-hospital mortality of hospitalized older patients with COVID-19. Methods. This retrospective study included 122 patients 65 years or older with positive reverse transcription polymerase chain reaction for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and with availability to CXRs on admission. The primary outcome of the study was in-hospital mortality. Statistical analysis was conducted using Cox regression. The predictive ability of the CXR score was compared with the Clinical Frailty Scale (CFS) and fever data using Area Under the Curve (AUC) and net reclassification improvement (NRI) statistics. Results. Of 122 patients, 67 died during hospital stay (54.9%). The CXR score (HR: 1.16, 95% CI, 1.04–1.28), CFS (HR: 1.27; 95% CI, 1.09–1.47), and presence of fever (HR: 1.75; 95% CI, 1.03–2.97) were significant predictors of in-hospital mortality. The addition of both the CFS and presence of fever to the CXR score significantly improved the prediction of in-hospital mortality (NRI, 0.460; 95% CI, 0.102 to 0.888; AUC difference: 0.117; 95% CI, 0.041 to 0.192, $p = 0.003$). Conclusions. CXR score, CFS, and presence of fever were the main predictors of in-hospital mortality in our cohort of hospitalized older patients with COVID-19. Adding frailty and presence of fever to the CXR score statistically improved predictive accuracy compared to single risk factors.

Keywords: chest radiographic score; COVID-19 pneumonia; frailty; in-hospital mortality

1. Introduction

The recent outbreak of the novel coronavirus disease in 2019 (COVID-19) has endangered the well-being of healthcare systems worldwide. As of 31 May 2021, the number of cases in Italy has reached more than 4.2 million, with more than 124,000 deaths attributed to COVID-19 [1]. Since the start of the pandemic, older patients exhibited susceptibility to developing more aggressive disease courses and were at a higher risk of mortality related to the disease [2,3]. Several multidimensional scoring systems have been proposed for

risk stratification in hospitalized older COVID-19 patients [4–6] and were further associated with decreased in-hospital survival and accelerated clinical deterioration [7]; age, respiratory function, laboratory data, and the presence of comorbidities and neurological functions were the main predictors used [4–6,8] as they were related to a worse prognosis in this setting [4–6,8–10].

Another valuable prognostic factor determined to be associated with in-hospital mortality was the radiological severity of lung involvement during COVID-19 pneumonia [11–13]. Whereas chest CT scans carry a higher sensitivity in detecting lung involvement from the early phase of the disease [14,15], portable CXRs offer the undisputed advantage of minimizing the risk of cross-infection and reducing the movement of patients [13]; simultaneously, CXR scans demonstrate an overall balanced accuracy in diagnosing COVID-19 pneumonia in the acute care setting [16,17]. COVID-19 features on chest radiographs have been extensively described [18,19] and previous studies examined the predictive power of several CXR scores in COVID-19 pneumonia [12,20–23]. Most CXR scores included only qualitative information regarding the distribution and extension of pulmonary infiltrates [12,20–22]; in comparison, the recently validated ISARIC 4C Deterioration score [24] had the advantage of integrating both clinical and radiological data and was able to predict in-hospital clinical deterioration and death among hospitalized adults with COVID-19. However, radiological information was in this case limited to the presence of pulmonary infiltrates, with no other qualitative detail of their distribution and severity; moreover, currently none of the abovementioned scoring systems were specifically validated in the geriatric setting. In addition, assessment of frailty status was often not considered despite its recognized prognostic importance in hospitalized older adults with COVID-19 [8,9].

Although the frailty and severity of radiological involvement seems to be the expression of two different health status dimensions, described as a condition of increased vulnerability to poor resolution of homeostasis following stress and as a measure of the severity of lung involvement, their combined evaluation may help in capturing the overall risk of death in older patients with COVID-19.

For this reason, the aims of our study were to (a) evaluate the association between CXR score, frailty, clinical symptoms, and in-hospital mortality in a selected population of older hospitalized patients with COVID-19; (b) to compare predictive accuracy of in-hospital CXRs, frailty, and clinical symptoms in the same population; and to assess which of them might be better implemented in standard clinical practice to improve prognostic risk stratification.

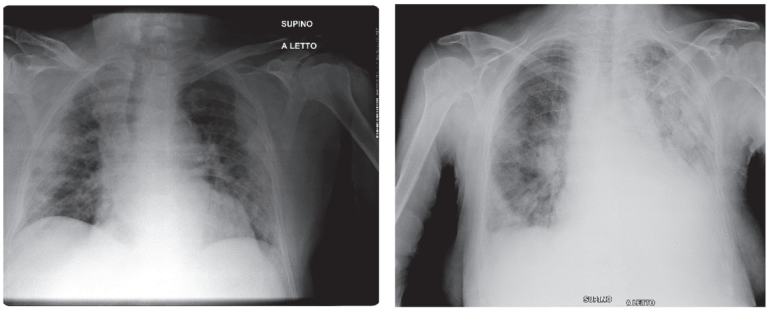
2. Materials and Methods

2.1. Study Design and Inclusion Criteria

This was a retrospective observational study including 122 patients with a confirmed diagnosis of COVID-19 admitted to the acute geriatric ward of an Italian hospital from 1 March to 30 April 2020. Inclusion criteria were the following: patients aged over 65 years, SARS-CoV-2 infection (COVID-19) confirmed by reverse transcription polymerase chain reaction, and CXR performed immediately at the hospital admission. The study was approved by the Ethics Committee of INRCA IRCCS. Demographic, clinical, and laboratory data were extracted from electronic health records. Clinical data included symptoms and signs of infection such as fever, cough, dyspnea, diarrhea, nausea, and vomit. Frailty was graded according to the Rockwood Clinical Frailty Scale (CFS) that evaluates patient functional abilities 2 weeks before hospital admission and was specifically validated in the population of individuals of 65 years of age or more [25]. The CFS is an ordinal scale that ranks frailty from 1 to 9 (from being very fit to terminally ill), with higher scores indicating progressively higher degrees of frailty; patients with a CFS score > 4 were considered to be frail.

All patients underwent anteroposterior (AP) CXRs at hospital admission, performed directly in the isolation wards through portable X-ray units (GE VMX Mobile X-Ray). Two radiologists independently reviewed each admission of CXRs for the presence of

consolidation, ground-glass opacities, reticular opacities, and pleural effusion according to the Fleischner Society glossary of terms [26]. Radiological involvement of lung parenchyma related to COVID-19 was described according to (a) the distribution of the disease (mostly peripheral or perihilar predominance); (b) the laterality of findings (unilateral or bilateral involvement); and (c) the predominance (upper, lower, or diffuse). In order to quantify the extension of pulmonary findings, a simplified version of the Radiographic Assessment of Lung Edema (RALE) severity score was used [18,27]. We chose this score as it has been proven to identify changes in the course of COVID-19, even though the radiologist assesses the lungs as a whole without dividing them into sectors. This allowed us to accelerate patients' evaluation in conditions of high workflow burden. According to this adapted score, which was previously validated for COVID-19 infection [18], each lung was classified for the extension of involvement by consolidation, ground-glass opacities, and reticular opacities from 0 to 4 (0 = no involvement; 1 = <25%; 2 = 25–50%; 3 = 50–75%; and 4 = ≥75% of involvement), and the scores of both lungs were summed with a maximum value of 8 (an example can be seen in Figure 1).



(**A**) (**B**)

Figure 1. Examples of CXR scores in two patients with COVID-19 pneumonia. (**A**) presents consolidation with basal, peripheral, and bilateral predominance (right lung score + left lung score = total score; 3 + 3 = 6). (**B**) presents areas of consolidation and ground-glass opacity with subpleural and basal predominance in right lung, and diffuse areas of consolidation and ground-glass opacity in left lung (the calculation right lung score + left lung score = total score; 3 + 4 = 7).

2.2. Outcome

The outcome of the present study was in-hospital mortality. Patients who died were censored at the day of death, while survivors were censored at the day of discharge.

2.3. Statistical Analysis

Demographic, clinical, radiological, and laboratory characteristics of patients, both survivors and non-survivors, were compared by Student's *t*-test or Mann–Whitney U test when appropriate for continuous variables and chi-square test for categorical ones. The association between each variable and mortality was explored by unadjusted Cox proportional hazard models. The CXR score, frailty, and variables significantly associated with the outcome in preliminary models were included in multivariable analysis. Five multivariable Cox proportional hazard models were built to obtain adjusted estimates of the association between exposure variables and the study outcome. The accuracy of exposure variables in predicting mortality was estimated by the Area Under the Receiver Operating Characteristic Curve (ROC). Finally, we investigated the additive effect of the CFS and other significant predictors on the predictive ability of the CXR score. Changes in Area Under the Curve (AUC) and categorical net reclassification index (NRI) with 1000 bootstrap samples to estimate 95% CIs were calculated. Statistical analysis was conducted using the Stata 15.1 Software Package for Windows (StataCorp, College Station, TX, USA).

3. Results

General characteristics of patients divided according to in-hospital mortality are reported in Table 1.

The study population consisted of 122 patients aged 87.1 ± 6.0 years with a slight female gender predominance (n = 67, 54.9%). Overall, 67 out of 122 patients (54.9%) died during hospital stay, with higher rates among women (53.7%). Patients who died were characterized by higher CXR and CFS scores, and there was a greater prevalence of dementia and congestive heart failure compared to the survivors ($p < 0.05$). Among the symptoms, fever and dyspnea at presentation were significantly more prevalent among patients who died.

Baseline chest radiography was positive in 84 patients with a CXR-sensitivity of 68.8%. Ground-glass opacities were the most common finding (65.5%), followed by reticular opacities (20.2%) and consolidation (14.3%). Peripheral distribution (57.1%) and lower zone distribution (69.0%) were the more common locations and most patients had bilateral involvement (56.0%). The CXR score significantly differed between survivors and non-survivors: while among survivors the maximum CXR score was four, patients who died had CXR scores ranging from zero to eight; moreover, all patients with a total CXR score greater than four at baseline chest radiography (n = 17) had fatal outcomes.

Unadjusted Cox regression analysis demonstrated that age, CXR score, CFS, congestive heart failure, dementia, fever, and dyspnea, and abnormal procalcitonin values were significantly associated with in-hospital mortality while stroke and comorbidity scores were nearly significantly associated with in-hospital mortality (Table 1). The above variables were included in the multivariable fully adjusted Cox proportional hazard models and four main predictors of in-hospital mortality were finally identified. In Model 1, including age, male gender, CXR score, CFS, and comorbidity score, the variables associated with mortality were found to be the CXR score (HR: 1.16; 95% CI 1.04–1.28), male gender (HR: 1.71; 95% CI 1.01–2.89), and CFS (HR: 1.27; 95% CI 1.09–1.47). Data were similar for Model 2, including single diagnoses instead of the comorbidity score. Conversely, in the models adjusted with the inclusion of either clinical or laboratory data, CFS and fever were the only significant predictors of the outcome (Table 2).

The Receiver Operating Characteristic curves for in-hospital mortality (Table 3) illustrated that the CXR score was a predictor of a fatal outcome in our study cohort of inpatients aged 70 to 101 years old with good accuracy (AUC = 0.70), slightly higher than that of the CFS (AUC = 0.67) and presence of fever (AUC = 0.61). Net reclassification analysis demonstrated that adding the CFS to the CXR score significantly improved the prediction of in-hospital mortality (continuous NRI = 0.355, 95% CI = 0.065–0.788; ΔAUC = 0.080, 95% CI = 0.006–0.153; p = 0.033). The addition of both CFS and presence of fever to the CXR score further improved the prediction of in-hospital mortality (continuous NRI=0.460, 95% CI = 0.102–0.888; ΔAUC = 0.117, 95% CI= 0.041–0.192; p = 0.003) in comparison to the model using only the CXR score.

Table 1. Sample description.

	All $n = 122$	Survivors $n = 55$	Non-Survivors $n = 67$	p	Unadjusted HR (95% CI)
Male gender, n(%)	55 (45.1%)	24 (43.6%)	31 (46.3%)	0.771	1.03 (0.63–1.66)
Age, mean ± SD	87.1 ± 6.0	86.1 ± 6.7	87.9 ± 5.3	0.089	1.06 (1.01–1.10)
CXR score, median (IQR), range	2 (3), 0–8	1 (2), 0–4	2 (4), 0–8	<0.001	1.17 (1.06–1.30)
CFS, median (IQR), range	7 (4), 2–9	6 (4), 2–8	7 (3), 2–9	0.001	1.29 (1.13–1.46)
Diagnoses					
Hypertension, n(%)	95 (78.5%)	43 (78.2%)	52 (78.8%)	0.936	1.10 (0.61–1.99)
Diabetes, n(%)	32 (26.2%)	11 (20.0%)	21 (31.3%)	0.156	1.42 (0.85–2.39)
Stroke, n(%)	17 (13.9%)	5 (9.1%)	12 (17.9%)	0.162	1.86 (0.99–3.50)
Cancer, n(%)	13 (10.7%)	4 (7.3%)	9 (13.4%)	0.273	1.36 (0.67–2.75)
COPD, n(%)	26 (21.3%)	13 (23.6%)	13 (19.4%)	0.570	0.83 (0.45–1.52)
Asthma, n(%)	4 (3.3%)	3 (5.5%)	1 (1.5%)	0.227	0.42 (0.06–3.06)
Angina, n(%)	7 (5.8%)	3 (5.6%)	4 (6.0%)	0.923	0.86 (0.31–2.38)
Myocardial Infarction, n(%)	21 (17.6%)	9 (17.0%)	12 (18.2%)	0.864	1.00 (0.53–1.88)
Atrial Fibrillation, n(%)	30 (24.8%)	10 (18.2%)	20 (30.3%)	0.124	1.31 (0.77–2.23)
CHF, n(%)	25 (20.8%)	6 (11.1%)	19 (28.8%)	0.018	1.76 (1.02–3.05)
Dementia, n(%)	69 (56.6%)	24 (43.6%)	45 (67.2%)	0.009	2.31 (1.38–3.86)
CKD, n(%)	42 (35.0%)	17 (31.5%)	25 (37.9%)	0.465	1.22 (0.74–2.01)
Previous ADRs, n(%)	9 (7.4%)	4 (7.3%)	5 (7.5%)	0.968	0.85 (0.34–2.14)
Concomitant Bacterial Infections, n(%)	10 (8.4%)	5 (9.3%)	5 (7.7%)	0.759	0.87 (0.35–2.17)
Comorbidity score, median(IQR), range	5 (1), 3–12	5 (2), 4–11	5 (1), 3–12	0.085	1.14 (0.99–1.32)
Symptoms					
Fever, n(%)	64 (52.5%)	22 (40.0%)	42 (62.7%)	0.013	1.70 (1.03–2.81)
Cough, n(%)	39 (33.1%)	19 (34.5%)	20 (31.7%)	0.747	0.81 (0.48–1.39)
Dyspnea, n(%)	88 (72.1%)	29 (52.7%)	59 (88.1%)	<0.001	3.38 (1.61–7.09)
Diarrhea, n(%)	11 (9.0%)	6 (10.9%)	5 (7.5%)	0.508	0.61 (0.24 1.54)
Nausea, n(%)	5 (4.1%)	4 (7.3%)	1 (1.5%)	0.109	0.34 (0.05–2.48)
Vomit, n(%)	4 (3.3%)	2 (3.6%)	2 (3.0%)	0.841	0.48 (0.11–2.04)
Abnormal lab parameters					
WBC ($\times 10^3/\mu$L), n(%)	51 (41.8%)	21 (38.2%)	30 (44.8%)	0.462	1.24 (0.76–2.02)
Lymphocytes ($\times 10^3/\mu$L), n(%)	67 (54.9%)	32 (58.2%)	35 (52.2%)	0.512	0.70 (0.42–1.18)
CPK (U/L), n(%)	44 (36.4%)	25 (46.3%)	19 (28.4%)	0.041	1.89 (0.74–4.82)
LDH (U/L), n(%)	76 (62.8%)	27 (50.0%)	49 (73.1%)	0.009	2.55 (0.98–6.65)

Table 1. *Cont.*

	All $n = 122$	Survivors $n = 55$	Non-Survivors $n = 67$	p	Unadjusted HR (95% CI)
eGFR (mL/min/1.73 m^2), n(%)	105 (86.1%)	44 (80.0%)	61 (91.0%)	0.080	2.26 (0.97–5.26)
NLR, n(%)	77 (63.1%)	31 (56.4%)	46 (68.7%)	0.161	1.33 (0.79–2.23)
CRP (mg/dL), n(%)	115 (94.2%)	49 (89.1%)	66 (98.5%)	0.080	0.52 (0.07–3.80)
D-dimer (ng/mL), n(%)	116 (95.9%)	53 (98.2%)	63 (94.0%)	0.258	1.09 (0.39–3.05)
Procalcitonin (ng/mL), n(%)	73 (59.8%)	28 (50.9%)	45 (67.2%)	0.125	2.61 (1.17 5.83)
IL-6 (pg/mL), n(%)	98 (80.3%)	38 (69.1%)	60 (89.5%)	0.005	1.48 (0.58–3.75)

Abbreviations: COPD = Chronic Obstructive Pulmonary Disease; CHF = Congestive Heart Failure; CKD = Chronic Kidney Disease; ADR = Adverse Drug Reaction; CFS = Clinical Frailty Scale; WBC = White Blood Cell; CPK = Creatine Phosphokinase; LDH = Lactate Dehydrogenase; eGFR = estimated Glomerular Filtration Rate; NLR = Neutrophils Lymphocytes Ratio; CPR = C Reactive Protein; IL-6 = Interleukin 6; HR (95% CI) = Hazard Ratio (95% Confidence Interval); SD = standard deviation; and IQR = InterQuartile Range. *Notes*: p-value from χ^2 test, t-test, or Mann–Whitney U test as appropriate. *Normal values for lab parameters*: $1 \times 10^3/\mu L \leq WBC \leq 4 \times 10^3/\mu L$; $1 \times 10^3/\mu L \leq Lymphocytes \leq 4 \times 10^3/\mu L$; 26 U/L $\leq$ CPK $\leq$ 192 U/L (female), 39 U/L $\leq$ CPK $\leq$ 308 U/L (male); LDH $\leq$ 280 U/L; eGFR < 60mL/min/1.73 m^2; 1 $\leq$ NRL $\leq$ 3.53; CRP $\leq$ 1mg/dL; D-dimer $\leq$ 250 ng/mL; Procalcitonin $\leq$ 0.15 ng/mL; and IL-6 $\leq$ 15 pg/mL.

Table 2. Cox proportional hazards models for CXR, CFS, clinical, and laboratory data for death during hospitalization.

$n = 122$	Model 1	Model 2	Model 3	Model 4	Model 5
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
CXR score	1.16 (1.04–1.28)	1.14 (1.01–1.27)	1.12 (0.99–1.26)	1.11 (0.99–1.26)	1.10 (0.97–1.25)
Age	1.04 (0.99–1.10)	1.04 (0.99–1.10)	1.04 (0.98–1.10)	1.04 (0.98–1.10)	1.04 (0.98–1.11)
Male gender	1.71 (1.01–2.89)	1.70 (1.01–2.87)	1.71 (0.99–2.94)	1.73 (1.01–2.95)	1.87 (1.05–3.32)
CFS	1.27 (1.09–1.47)	1.21 (1.01–1.45)	1.28 (1.09–1.49)	1.24 (1.03–1.49)	1.23 (1.04–1.46)
Comorbidity score	1.12 (0.96–1.31)	-	1.12 (0.95–1.32)	-	1.11 (0.94–1.32)
Stroke	-	1.38 (0.69–2.75)	-	1.15 (0.57–2.31)	-
CHF	-	1.19 (0.67–2.11)	-	1.17 (0.66–2.08)	-
Dementia	-	1.29 (0.64–2.58)	-	1.11 (0.55–2.21)	-
Fever	-	-	1.75 (1.03–2.97)	1.71 (1.00–2.93)	-
Dyspnea	-	-	1.59 (0.70–3.64)	1.60 (0.69–3.66)	-
Abnormal CPK (U/L)	-	-	-	-	0.99 (0.39–2.54)
Abnormal LDH (U/L)	-	-	-	-	2.29 (0.82–6.38)
Abnormal D-dimer (ng/mL)	-	-	-	-	0.69 (0.21–2.23)
Abnormal Procalcitonin (ng/mL)	-	-	-	-	1.72 (0.77–3.84)
Abnormal IL-6 (pg/mL)	-	-	-	-	1.27 (0.42–3.86)

Abbreviations: CFS = Clinical Frailty Scale; CHF = Congestive Heart Failure; CI = Confidence Interval; CPK = Creatine phosphokinase; CXR = Chest X-ray; HR = Hazard Ratio; IL-6 = Interleukin 6; and LDH = Lactated Dehydrogenase. *Note*: Model 1: including CXR score, age, male gender, CFS, and comorbidity score. Model 2: alike to Model 1 but using stroke, CHF, and dementia instead of comorbidity score. Model 3: Model 1 + fever and dyspnea. Model 4: Model 2 + fever and dyspnea. Model 5: Model 1 + abnormal CPK, abnormal LDH, abnormal D-dimer, and abnormal IL-6.

Table 3. Accuracy of the CXR score and net reclassification analysis for death during hospitalization.

Outcome	Addition	AUC (95% CI)	Overall NRI (95% CI)	ΔAUC (95% CI)	*p*
Death (*n* = 122)		0.701 (0.611–0.790)			
	CFS		0.355 (0.065–0.788)	0.080 (0.006–0.153)	0.033
	Fever		0.454 (−0.336–0.794)	0.026 (−0.350–0.086)	0.410
	CFS and Fever		0.460 (0.102–0.888)	0.117 (0.041–0.192)	0.003

Abbreviations: AUC = Area Under the Curve; CFS = Clinical Frailty Scale; CI = Confidence Interval; CXR = Chest X-ray; and NRI = Net Reclassification Improvement.

The distribution of the CXR score in each CFS category by death and survival is displayed in Figure 2.

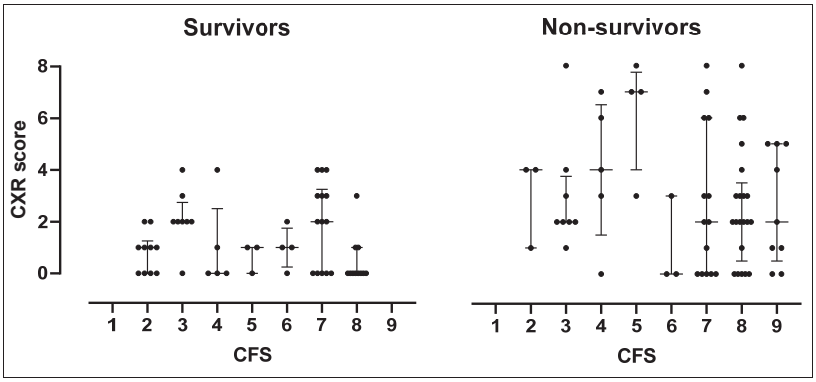


Figure 2. Column plot of the RX score in each CFS group and by death.

In patients who survived, the CXR score ranged from zero to four and was distributed in all CFS categories. Among patients who died, severely frail ones (CFS score 7–9) had a median CXR score of two, which was lower than that (4) of mildly or moderately frail patients (CFS score 1–6).

4. Discussion

Our study demonstrated that the CXR score, frailty status, and presence of fever were significant predictors of in-hospital mortality among older hospitalized patients with COVID-19. The strength of the association between either the CXR score or presence of fever and mortality was slightly reduced after introducing the CFS into the analysis. However, net reclassification analysis demonstrated that the model combining the CFS, CXR score, and presence of fever predicted the outcome with better accuracy compared to single risk factors. This may underline the importance of a multidimensional assessment including frailty, clinical, and radiological features when assessing hospitalized older patients with COVID-19.

This is the first study specifically comparing the predictive ability of frailty, radiological findings, and clinical data in hospitalized COVID-19 individuals aged 65 years or older. Older individuals represent a cluster of patients at higher risk for developing life-threatening respiratory failure related to COVID-19 due to the severity of lung involvement, immunosenescence and multimorbidity [28], and frailty. Frailty itself may contribute to increased vulnerability to more severe disease presentations.

As expected, frailty was a significant predictor of death in our study as well. In fact, patients with an increased CFS score were at a higher risk of death independent of the CXR

findings. Compared to other frailty tools, the Rockwood CFS has the advantage of being specifically validated in older hospitalized people. Furthermore, it was suggested by the National Institute for Health and Care Excellence (NICE) guidelines for the assessment of older patients with COVID-19 [29] and proven to accurately predict in-hospital outcomes in this population [8,30]. Among clinical symptoms, fever was the only symptom to be significantly associated with the outcome in the study, maintaining its predictive weight in four out of five fully adjusted models, second only to the CFS. This result confirms previous evidence regarding the prognostic weight of fever and respiratory symptoms in hospitalized older patients with COVID-19 [10].

Radiological involvement of lung parenchyma due to COVID-19 pneumonia was demonstrated to be a marker of disease severity [21,31] and a predictor of poor outcomes in several hospitalized cohorts [21–23,31] but its prognostic weight in the geriatric population was not evaluated before. The features of radiological COVID-19 lung involvement in our cohort were similar to those reported in recent literature, including ground-glass opacities, peripheral distribution, lower zone distribution, and bilateral involvement [18,19]. Sensitivity of CXRs performed at hospital admission was about 68.8% in accordance with previous studies [12,18,22]. The CXR scores predicted in-hospital death with good accuracy (AUC: 0.70) and all patients with an overall score greater than four died during hospital stay. However, the association with mortality was decreased in models including the CFS, apart from those including the CXR score. This could be explained by the fact that CFS and CXR scores appeared to be independent from each other, capturing two different health status dimensions. In fact, the radiological severity of the disease did not increase with increasing frailty and severely frail patients died independently from the CXR score. NRI analysis finally illustrated that an integrated prognostic model combining the CFS, CXR score, and presence of fever in geriatric inpatients with COVID-19 yielded the highest prognostic accuracy in relation to in-hospital mortality (AUC: 0.80).

Our findings confirm the importance of both the radiological severity of COVID-19 pneumonia and frailty status in predicting poor outcomes in hospitalized older patients with COVID-19. It is arguable that, although these two factors were independent from each other, their combined evaluation may aid in improving prognostic risk stratification. From a clinical perspective, this relevant finding suggests the need of implementing multidimensional assessment integrating both clinical and radiological data in the acute geriatric setting; indeed, having easy-to-use diagnostic scores such as the CXR score and CFS may help accelerate the identification of more vulnerable older patients requiring targeted treatment approaches.

The limitations of this study are worth mentioning. Firstly, the retrospective study design and lack of a non-COVID-19 group may have limited the evaluation of sensitivity and specificity of the CXR score. Secondly, the small sample size may have decreased the precision of the estimates and did not allow for the estimation of a fully adjusted model in order to avoid overfitting issues; thus, other larger studies are necessary to validate these findings. Thirdly, in our study, we applied a visual evaluation of radiographic findings that may have influenced final results; in this regard, it would be desirable to implement artificial intelligence to increase the accuracy of CXR image analysis.

5. Conclusions

In conclusion, the CFS, CXR score, and presence of fever were the main predictors of in-hospital mortality in our cohort of hospitalized older patients with a confirmed diagnosis of COVID-19. The model integrating the three risk factors yielded the highest prognostic accuracy, which may be helpful for clinicians in identifying high-risk patients needing more intensive and tailored interventions.

Author Contributions: Conceptualization, S.C., F.C., E.P., M.D.R., L.S., and F.L.; data curation, M.D.R.; formal analysis, M.D.R.; funding acquisition, F.L.; investigation, S.C., F.C., D.C., E.P., A.C., and F.L.; writing—original draft preparation, S.C., M.D.R., L.S., I.P., A.F., C.M., R.G., P.G., and M.F.;

writing—review and editing, D.C., F.C., E.P., A.C., and F.L. All authors have read and agreed to the published version of the manuscript.

Funding: The study was funded by intramural research funds (Ricerca Corrente) received from the Italian National Research Center on Aging (IRCCS INRCA).

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of INRCA IRCCS.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author. The data are not publicly available as they contain information that could compromise the privacy of the research participants.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Available online: covid19.who.int/region/euro/country/it (accessed on 31 May 2021).
2. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* **2020**, *395*, 1054–1062. [CrossRef]
3. Wei, C.; Liu, Y.; Liu, Y.; Zhang, K.; Su, D.; Zhong, M.; Meng, X. Clinical characteristics and manifestations in older patients with COVID-19. *BMC Geriatr.* **2020**, *20*, 395. [CrossRef] [PubMed]
4. Liang, W.; Liang, H.; Ou, L.; Chen, B.; Chen, A.; Li, C.; Li, Y.; Guan, W.; Sang, L.; Lu, J.; et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients with COVID-19. *JAMA Intern. Med.* **2020**, *180*, 1081–1089. [CrossRef]
5. Haimovich, A.D.; Ravindra, N.G.; Stoytchev, S.; Young, H.P.; Wilson, F.P.; Van Dijk, D.; Schulz, W.L.; Taylor, R.A. Development and Validation of the Quick COVID-19 Severity Index: A Prognostic Tool for Early Clinical Decompensation. *Ann. Emerg. Med.* **2020**, *76*, 442–453. [CrossRef] [PubMed]
6. Knight, S.R.; Ho, A.; Pius, R.; Buchan, I.; Carson, G.; Drake, T.M.; Dunning, J.; Fairfield, C.J.; Gamble, C.; Green, C.A.; et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: Development and validation of the 4C Mortality Score. *BMJ* **2020**, *370*, m3339. [CrossRef] [PubMed]
7. Covino, M.; De Matteis, G.; Burzo, M.L.; Russo, A.; Forte, E.; Carnicelli, A.; Piccioni, A.; Simeoni, B.; Gasbarrini, A.; Franceschi, F.; et al. Predicting In-Hospital Mortality in COVID -19 Older Patients with Specifically Developed Scores. *J. Am. Geriatr. Soc.* **2021**, *69*, 37–43. [CrossRef] [PubMed]
8. Hewitt, J.; Carter, B.; Vilches-Moraga, A.; Quinn, T.J.; Braude, P.; Verduri, A.; Pearce, L.; Stechman, M.; Short, R.; Price, A.; et al. The effect of frailty on survival in patients with COVID-19 (COPE): A multicentre, European, observational cohort study. *Lancet Public Health* **2020**, *5*, e444–e451. [CrossRef]
9. Chinnadurai, R.; Ogedengbe, O.; Agarwal, P.; Money-Coomes, S.; Abdurrahman, A.Z.; Mohammed, S.; Kalra, P.A.; Rothwell, N.; Pradhan, S. Older age and frailty are the chief predictors of mortality in COVID-19 patients admitted to an acute medical unit in a secondary care setting- a cohort study. *BMC Geriatr.* **2020**, *20*, 409. [CrossRef]
10. Keeley, P.; Buchanan, D.; Carolan, C.; Pivodic, L.; Tavabie, S.; Noble, S. Symptom burden and clinical profile of COVID-19 deaths: A rapid systematic review and evidence summary. *BMJ Support. Palliat. Care* **2020**, *10*, 381. [CrossRef]
11. Yang, W.; Sirajuddin, A.; Zhang, X.; Liu, G.; Teng, Z.; Zhao, S.; Lu, M. The role of imaging in 2019 novel coronavirus pneumonia (COVID-19). *Eur. Radiol.* **2020**, *30*, 4874–4882. [CrossRef]
12. Moroni, C.; Cozzi, D.; Albanesi, M.; Cavigli, E.; Bindi, A.; Luvarà, S.; Busoni, S.; Mazzoni, L.N.; Grifoni, S.; Nazerian, P.; et al. Chest X-ray in the emergency department during COVID-19 pandemic descending phase in Italy: Correlation with patients' outcome. *Radiol. Med.* **2021**, *126*, 661–668. [CrossRef]
13. Brogna, B.; Bignardi, E.; Brogna, C.; Volpe, M.; Lombardi, G.; Rosa, A.; Gagliardi, G.; Capasso, P.; Gravino, E.; Maio, F.; et al. A Pictorial Review of the Role of Imaging in the Detection, Management, Histopathological Correlations, and Complications of COVID-19 Pneumonia. *Diagnostics* **2021**, *11*, 437. [CrossRef]
14. Borakati, A.; Perera, A.; Johnson, J.; Sood, T. Diagnostic accuracy of X-ray versus CT in COVID-19: A propensity-matched database study. *BMJ Open* **2020**, *10*, e042946. [CrossRef]
15. Brogna, B.; Bignardi, E.; Brogna, C.; Alberigo, M.; Grappone, M.; Megliola, A.; Salvatore, P.; Fontanella, G.; Mazza, E.; Musto, L. Typical CT findings of COVID-19 pneumonia in patients presenting with repetitive negative RT-PCR. *Radiography* **2021**, *27*, 743–747. [CrossRef]
16. Cozzi, A.; Schiaffino, S.; Arpaia, F.; Della Pepa, G.; Tritella, S.; Bertolotti, P.; Menicagli, L.; Monaco, C.G.; Carbonaro, L.A.; Spairani, R.; et al. Chest x-ray in the COVID-19 pandemic: Radiologists' real-world reader performance. *Eur. J. Radiol.* **2020**, *132*, 109272. [CrossRef] [PubMed]

17. Schiaffino, S.; Tritella, S.; Cozzi, A.; Carriero, S.; Blandi, L.; Ferraris, L.; Sardanelli, F. Diagnostic Performance of Chest X-Ray for COVID-19 Pneumonia During the SARS-CoV-2 Pandemic in Lombardy, Italy. *J. Thorac. Imaging* **2020**, *35*, W105–W106. [CrossRef] [PubMed]
18. Wong, H.Y.F.; Lam, H.Y.S.; Fong, A.H.-T.; Leung, S.T.; Chin, T.W.-Y.; Lo, C.S.Y.; Lui, M.M.-S.; Lee, J.C.Y.; Chiu, K.W.-H.; Chung, T.W.-H.; et al. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. *Radiology* **2020**, *296*, E72–E78. [CrossRef] [PubMed]
19. Vancheri, S.G.; Savietto, G.; Ballati, F.; Maggi, A.; Canino, C.; Bortolotto, C.; Valentini, A.; Dore, R.; Stella, G.M.; Corsico, A.G.; et al. Radiographic findings in 240 patients with COVID-19 pneumonia: Time-dependence after the onset of symptoms. *Eur. Radiol.* **2020**, *30*, 6161–6169. [CrossRef]
20. Balbi, M.; Caroli, A.; Corsi, A.; Milanese, G.; Surace, A.; Di Marco, F.; Novelli, L.; Silva, M.; Lorini, F.L.; Duca, A.; et al. Chest X-ray for predicting mortality and the need for ventilatory support in COVID-19 patients presenting to the emergency department. *Eur. Radiol.* **2021**, *31*, 1999–2012. [CrossRef]
21. Borghesi, A.; Maroldi, R. COVID-19 outbreak in Italy: Experimental chest X-ray scoring system for quantifying and monitoring disease progression. *Radiol. Med.* **2020**, *125*, 509–513. [CrossRef] [PubMed]
22. Cozzi, D.; Albanesi, M.; Cavigli, E.; Moroni, C.; Bindi, A.; Luvarà, S.; Lucarini, S.; Busoni, S.; Mazzoni, L.N.; Miele, V. Chest X-ray in new Coronavirus Disease 2019 (COVID-19) infection: Findings and correlation with clinical outcome. *Radiol. Med.* **2020**, *125*, 730–737. [CrossRef] [PubMed]
23. Toussie, D.; Voutsinas, N.; Finkelstein, M.; A Cedillo, M.; Manna, S.; Maron, S.Z.; Jacobi, A.; Chung, M.; Bernheim, A.; Eber, C.; et al. Clinical and Chest Radiography Features Determine Patient Outcomes in Young and Middle Age Adults with COVID-19. *Radiology* **2020**, *297*, E197–E206. [CrossRef] [PubMed]
24. Gupta, R.K.; Harrison, E.M.; Ho, A.; Docherty, A.B.; Knight, S.R.; van Smeden, M.; Abubakar, I.; Lipman, M.; Quartagno, M.; Pius, R.; et al. Development and validation of the ISARIC 4C Deterioration model for adults hospitalised with COVID-19: A prospective cohort study. *Lancet Respir. Med.* **2021**, *9*, 349–359. [CrossRef]
25. Rockwood, K.; Theou, O. Using the Clinical Frailty Scale in Allocating Scarce Health Care Resources. *Can. Geriatr. J.* **2020**, *23*, 210–215. [CrossRef]
26. Hansell, D.M.; Bankier, A.A.; MacMahon, H.; McLoud, T.C.; Müller, N.L.; Remy, J. Fleischner Society: Glossary of Terms for Thoracic Imaging. *Radiology* **2008**, *246*, 697–722. [CrossRef]
27. Warren, M.A.; Zhao, Z.; Koyama, T.; A Bastarache, J.; Shaver, C.M.; Semler, M.W.; Rice, T.W.; A Matthay, M.; Calfee, C.S.; Ware, L.B. Severity scoring of lung oedema on the chest radiograph is associated with clinical outcomes in ARDS. *Thorax* **2018**, *73*, 840–846. [CrossRef]
28. Maltese, G.; Corsonello, A.; Di Rosa, M.; Soraci, L.; Vitale, C.; Corica, F.; Lattanzio, F. Frailty and COVID-19: A Systematic Scoping Review. *J. Clin. Med.* **2020**, *9*, 2106. [CrossRef] [PubMed]
29. NICE. *COVID-19 Rapid Guideline: Critical Care in Adults*; NICE: London, UK, 2020.
30. Sablerolles, R.S.G.; Lafeber, M.; Kempen, J.A.L.V.; A van de Loo, B.P.; Boersma, E.; Rietdijk, W.J.R.; A Polinder-Bos, H.; Mooijaart, S.P.; van der Kuy, H.; Versmissen, J.; et al. Association between Clinical Frailty Scale score and hospital mortality in adult patients with COVID-19 (COMET): An international, multicentre, retrospective, observational cohort study. *Lancet Health Longev.* **2021**, *2*, e163–e170. [CrossRef]
31. Maroldi, R.; Rondi, P.; Agazzi, G.M.; Ravanelli, M.; Borghesi, A.; Farina, D. Which role for chest x-ray score in predicting the outcome in COVID-19 pneumonia? *Eur. Radiol.* **2021**, *31*, 4016–4022. [CrossRef]

Journal of
Clinical Medicine

MDPI

Article

Prognostic Role of Subcutaneous and Visceral Adiposity in Hospitalized Octogenarians with COVID-19

Max Scheffler [1], Laurence Genton [2], Christophe E. Graf [3], Jorge Remuinan [1], Gabriel Gold [4], Dina Zekry [5], Christine Serratrice [5], François R. Herrmann [4] and Aline Mendes [4,*]

[1] Division of Radiology, Diagnostic Department, University Hospitals of Geneva, 1205 Geneva, Switzerland; max.scheffler@hcuge.ch (M.S.); jorge.remuinan@hcuge.ch (J.R.)
[2] Unit of Clinical Nutrition, Faculty of Medicine, University Hospitals of Geneva, 1205 Geneva, Switzerland; laurence.genton@hcuge.ch
[3] Division of Internal Medicine and Rehabilitation, Department of Rehabilitation and Geriatrics, Faculty of Medicine, University Hospitals of Geneva, 1205 Geneva, Switzerland; christophe.graf@hcuge.ch
[4] Division of Geriatrics, Department of Rehabilitation and Geriatrics, Faculty of Medicine, University Hospitals of Geneva, 1205 Geneva, Switzerland; gabriel.gold@unige.ch (G.G.); francois.herrmann@hcuge.ch (F.R.H.)
[5] Division of Internal Medicine for the Aged, Department of Rehabilitation and Geriatrics, Faculty of Medicine, University Hospitals of Geneva, 1205 Geneva, Switzerland; dina.zekry@hcuge.ch (D.Z.); christine.serratrice@hcuge.ch (C.S.)
* Correspondence: aline.mendes@hcuge.ch; Tel.: +41-079-553-83-65

Abstract: Background: We investigated the prognostic significance of visceral and subcutaneous adiposity in octogenarians with COVID-19. Methods: This paper presents a monocentric retrospective study that was conducted in acute geriatric wards with 64 hospitalized patients aged 80+ who had a diagnosis of COVID-19 and who underwent a chest CT scan. A quantification of the subcutaneous, visceral, and total fat areas was performed after segmentations on the first abdominal slice caudal to the deepest pleural recess on a soft-tissue window setting. Logistic regression models were applied to investigate the association with in-hospital mortality and the extent of COVID-19 pneumonia. Results: The patients had a mean age of 86.4 $\pm$ 6.0 years, and 46.9% were male, with a mean BMI of 24.1 $\pm$ 4.4Kg/m^2 and mortality rate of 32.8%. A higher subcutaneous fat area had a protective effect against mortality (OR 0.416; 0.183–0.944 95% CI; $p = 0.036$), which remained significant after adjustments for age, sex, and BMI (OR 0.231; 0.071–0.751 95% CI; $p = 0.015$). Inversely, higher abdominal circumference, total fat area, subcutaneous fat area, and visceral fat were associated with worse COVID-19 pneumonia, with the latter presenting the strongest association after adjustments for age, sex, and BMI (OR 2.862; 1.523–5.379 95% CI; $p = 0.001$). Conclusion: Subcutaneous and visceral fat areas measured on chest CT scans were associated with prognosis in octogenarians with COVID-19.

Keywords: subcutaneous fat; visceral fat; chest CT; COVID-19; mortality

Citation: Scheffler, M.; Genton, L.; Graf, C.E.; Remuinan, J.; Gold, G.; Zekry, D.; Serratrice, C.; Herrmann, F.R.; Mendes, A. Prognostic Role of Subcutaneous and Visceral Adiposity in Hospitalized Octogenarians with COVID-19. *J. Clin. Med.* **2021**, *10*, 5500. https://doi.org/10.3390/jcm10235500

Academic Editors: Riccardo Giorgino and Filippo Migliorini

Received: 27 October 2021
Accepted: 23 November 2021
Published: 24 November 2021

1. Introduction

Before the launch of the current vaccination campaigns around the world, older people were the most severely affected by the COVID-19 pandemic [1]. Older patients show reduced muscle strength and an increased proportion of fat tissue [2,3] that is independent of body mass index (BMI) [4]. These body composition characteristics have been described as independent determinants of bad prognosis in the course of COVID-19 by different studies [5–7].

Obesity is associated with a higher prevalence of other risk factors that are related to the COVID-19 severity, such as hypertension and diabetes, but is also recognized as a source of chronic inflammation and as a modulator of the immune response [8,9]. Consequently, obesity and the balance between subcutaneous and visceral adiposity may not only increase the susceptibility of acquiring the infection but also the disease severity, including

the risk of a cytokine storm. After becoming directly infected by SARS-CoV-2 via ACE receptors [10,11], the adipocytes of the visceral fat in obese patients secrete IL-6 and increase the production and release of leptin, which enhances the proinflammatory state [12–14]. Conversely, adiponectin, a protein hormone that is mostly produced by subcutaneous fat but that is abnormally reduced in obese patients counteracts this inflammatory state by reducing the secretion of IL-6 and TNF-α and by increasing the production of anti-inflammatory cytokines by the adipocytes [15,16]. Therefore, central obesity, i.e., high visceral fat, would be one of the main triggers for the underlying exacerbated inflammatory state that is associated with severe COVID-19 [17,18].

Moreover, a high proportion of visceral fat is also observed in patients with normal BMI, raising the question of whether a "global" measure of body composition such as BMI alone or the quantification of subcutaneous and visceral fat would have the strongest relationship with prognosis in older patients.

Thus, we conducted a study to investigate the association of visceral and subcutaneous adiposity as measured by a chest CT scan with the radiological extent of COVID-19 pneumonia and in-hospital mortality in a population of hospitalized older patients. We make the hypothesis that the visceral and subcutaneous adiposity as measured by chest CT scan is associated with poor outcomes in COVID-19.

2. Materials and Methods

2.1. Design, Setting and Participants

This was a monocentric retrospective study that included patients who were hospitalized in acute wards in the Geriatric Hospital. The Geriatric Hospital was in charge of all of the hospital admissions of older patients with COVID-19 in a geographic region covering an area of approximately five hundred thousand inhabitants. Hospitalized patients with COVID-19 had one or more of these clinical features: (a) pneumonia with a severity assessed by a CURB-65 score ≥ 2; (b) new dependence on oxygen or increase of oxygen needs; (c) a respiratory rate ≥ 20 breaths/minute; (d) decompensated chronic diseases; (e) severely altered general state of health; and (f) deteriorating clinical course.

We admitted 235 patients with SARS-CoV-2 infection from 13 March 2020 to 15 May 2020, all of whom were screened for the presence of COVID-19-related pneumonia by means of chest CT scan. Among them, 64 patients had a chest CT scan performed according to routine clinical practice and recommendations and were included in the present analysis. This subgroup was representative of all of the patients who had been admitted to the hospital according to a feasibility analysis performed before the launch of this study by comparing the patients who underwent a chest CT scan and those who did not.

Of the population presented here, no patient was admitted to the intensive care wards after a shared decision process with the patients and their family members and/or representatives. The only exclusion criterion was refusal to participate in a research study, which was not documented in any medical records; hence, all of the patients who were hospitalized during the study period were included in the analysis.

As outcomes, we defined the extent of COVID-19-associated pneumonia visually as quantified by the chest CT scans and by in-hospital mortality. This study was approved by the local committee for ethics in research (Project-Id: 2020-00819; NCT04385212).

2.2. Data Collection

Data regarding the demographics, clinical, and laboratory values were collected based on the information available from the patients' medical records. Among preexisting comorbidities, we listed the presence of hypertension, diabetes, dyslipidemia, heart failure, chronic obstructive pulmonary disease (COPD), kidney disease, liver disease, active neoplasia, cognitive impairment, Parkinson's disease, history of stroke, smoking status, and immunosuppression. Several scales and scores based on the clinical data retrieved at hospital admission and clinical data detailed thereafter were also included in the dataset. The cumulative illness rating scale for geriatrics (CIRS-G) measured the chronic medical

illness ("morbidity") burden in 14 individual body systems and assigned grades for each body system that ranged from 0 (no disease) to 4 (very severe) [19]. The total score for this assessment ranges from 0 to 56 points. The confusion assessment method (CAM) was the standard screening tool to detect delirium [20]. The clinical frailty scale (CFS) is a 9-point scale based on clinical judgment that varies from 1 "Very fit" to 9 "Terminally ill" [21]. It has been validated to predict death or the need for institutional care. The functional independence measure (FIM) takes into account physical, psychological, and social functions and was performed within the first 24 h of hospital admission. The scoring system ranges from 18 points (extreme disability) to 126 points (complete independence) [22]. The CURB-65 score is a four-item score that is used to estimate mortality related to community-acquired pneumonia and can help to determine inpatient vs. outpatient treatment [23]. The nutritional risk screening (NRS-2002) score assesses the severity of malnutrition (0–3 points) and the severity of the acute disease (0–3 points), with total scores ranging from 0 to 7, with 3–7 points indicating nutritional risk. An additional point is added for patients who are aged 70 or older [24].

2.3. CT Scans Acquisitions, Interpretation and Quantification

All of the chest CT scans were performed using a Somatom AS+ machine (Siemens Healthineers, Erlangen, Germany). An unenhanced chest CT scan was obtained to quantify COVID-19-associated pneumonia and to estimate the degree of consolidation or pleural effusion, and contrast-enhanced studies were performed when there were clinical or biological signs of associated pulmonary embolism. Acquisition parameters were kilovoltage setting, 100–120 kV; pitch, 0.9–1.2; slice thickness, 2 mm with 1 mm increment; automatic tube current modulation (unenhanced scans); and kilovoltage setting, 100–120 kV; pitch, 1.2; slice thickness, 1.5 mm with 1 mm increment; and automatic tube current modulation (CT angiography for research of pulmonary embolism). Patients were in the supine position for all scans, and acquisition took place during end-inspiration breathhold whenever possible. If applicable, the injected contrast medium was Accupaque 350 (GE Healthcare, Oslo, Norway, or GE Healthcare, Cork, Ireland).

For this study, visceral and parietal fat surface measurements were performed by a trained radiologic technologist (J.R.) using the Osirix MD application for Mac (Version 12.0.1, Pixmeo, Bernex, Switzerland) and using the 2D segmentation region of interest (ROI) growth tool while adjusting the density intervals around the chosen starting points. The segmentations were performed on the first abdominal slice caudal to the deepest pleural recess on a soft-tissue window setting. Illustrative examples are shown in Figure 1A,B. Upper abdominal circumference was determined by the same person on the same slice using the Osirix MD closed polygon ROI tool, as shown in Figure 1C. The degree COVID-19-induced lung affection was assessed for all patients by a staff radiologist (M.S.) on a PACS workstation in a lung window setting and using multiplanar reconstruction. Stage 1 was assigned if 0–25% of the lung parenchyma was affected, stage 2 was assigned for 26–50% affection, stage 3 was assigned for 51–75% affection, and stage 4 was assigned for >75% affection. An example for stage 3 affection is provided in Figure 1D.

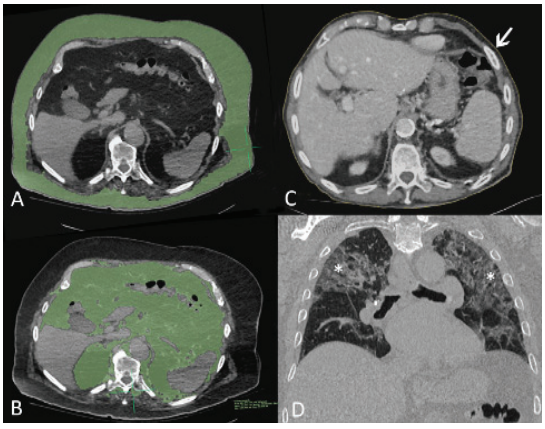


Figure 1. Computed tomography (CT) images of three patients with COVID-19 pneumonia. (**A**,**B**), axial images of 89-year-old man, soft tissue window setting. The first slice caudal to the pleural recesses shows overlay segmented parietal (**A**) and visceral (**B**) fat in green. (**C**) axial image of 93-year-old man, soft tissue window setting. Fine yellow line (arrow) delineates body circumference on the first slice caudal to pleural recesses. (**D**) Coronal-oblique reconstructed image of 86-year-old man in lung window setting shows stage 3 lung infiltrates with ground glass opacities, intralobular septal thickening, and parenchymal bands (asterisks).

2.4. Statistical Analysis

Categorical variables were described as absolute numbers and proportions, while continuous variables were described as means and standard deviations. We performed a two-group comparison (survivors vs. non-survivors) using the Chi-square test or the *t*-test, depending on the variable type. The Mann–Whitney u test was used to compare the ordinal variables. Results were considered statistically significant when p values were <0.05.

Regarding outcomes, we used ordered logistic regression models and logistic regression models to investigate the relationship between the fat measures and the radiological extent of COVID-19 pneumonia as mentioned above and in-hospital mortality, respectively. Univariate (Model 1) and multivariate analysis were performed, with adjustments being made for age and sex (Model 2) and age, sex, and BMI (Model 3) for each measure of adiposity. Results were expressed as the Odds Ratio (OR) followed by the 95% confidence interval and its respective p-value and pseudo-R^2, which is the proportion of variance that is explained by the model. Then, we studied the association of our best-adjusted model with in-hospital mortality by calculating the area under the receiver operating characteristic (AUC) curve. Statistical analysis was performed using the Stata® software (version 16.1, StataCorp 2019, College Station, TX, USA).

3. Results

3.1. Characteristics of the Study Population

In the group of 64 patients who underwent chest CT scans, the mean age was of 86.4 ± 6.0 years, and 46.9% were male. The time from the beginning of symptom onset to hospital admission was 3.5 ± 3.1 days, and the mean LOS in acute care was 12.5 ± 5.6 days. The patients were frequently frail (CFS: 5.7 ± 1.8), with a high disease burden and functional impairment according to their CIRS-G (19.3 ± 6.1) and FIM scores (75.5 ± 31.1). The most prevalent comorbidities were hypertension (68.8%) followed by cognitive disorders (51.6%), dyslipidemia (40.6%), and heart failure (40%). It is worth noting that the majority of patients were categorized as being of a normal weight (46%), followed by the categories of overweight (28.6%) and underweight (15.9%). A minority of patients in this cohort was classified as obese (9.5%) according to BMI. Moreover, 78.2% of the patients had

a nutritional risk according to the NRS (≥3) performed at admission. Pulmonary embolism was detected in one patient in the non-survivor group ($p = 0.328$).

The deceased patients ($n = 21$) were mainly male (76.2% vs. 32.6%; $p = 0.001$) and had a shorter LOS than the survivors (10.0 ± 6.1 vs. 13.7 ± 5.0; $p = 0.025$). A detailed description of the characteristics of the population is shown in Table 1.

Table 1. Characteristics of the study population.

Characteristics	Intra-Hospital Death			
	Total	No	Yes	*p* Value
N	64	43	21	
Age, year	86.4 ± 6.0	86.3 ± 5.8	86.7 ± 6.6	0.797
Male sex	30 (46.9%)	14 (32.6%)	16 (76.2%)	0.001
Time from symptoms to hospital admission, day	3.6 ± 3.1	4.1 ± 3.5	2.6 ± 1.7	0.026
Length of stay, day	12.5 ± 5.6	13.7 ± 5.0	10.0 ± 6.1	0.025
FIM	75.5 ± 31.1	82.5 ± 28.4	52.9 ± 29.8	0.005
CFS	5.7 ± 1.8	5.2 ± 1.7	6.8 ± 1.4	<0.001
CIRS-G	19.3 ± 6.1	18.3 ± 6.4	21.1 ± 5.0	0.060
CAM	13 (20.6%)	6 (14.0%)	7 (35.0%)	0.092
CURB-65				0.648
1	10 (15.6%)	8 (18.6%)	2 (9.5%)	
2	29 (45.3%)	20 (46.5%)	9 (42.9%)	
3	23 (35.9%)	14 (32.6%)	9 (42.9%)	
4	2 (3.1%)	1 (2.3%)	1 (4.8%)	
ARDS	16 (25.0%)	3 (7.0%)	13 (61.9%)	<0.001
BMI kg/m^2	24.1 ± 4.4	23.6 ± 4.3	25.1 ± 4.6	0.217
BMI kg/m^2				0.247
<20	10 (15.9%)	8 (18.6%)	2 (10.0%)	
20–24.9	29 (46.0%)	21 (48.8%)	8 (40.0%)	
25–29.9	18 (28.6%)	10 (23.3%)	8 (40.0%)	
30+	6 (9.5%)	4 (9.3%)	2 (10.0%)	
NRS				0.315
0–2	14 (21.9%)	13 (30.2%)	1 (4.8%)	
3–4	20 (31.3%)	10 (23.3%)	10 (47.6%)	
5–7	30 (46.9%)	20 (46.5%)	10 (47.6%)	
Hypertension	44 (68.8%)	31 (72.1%)	13 (61.9%)	0.566
Dyslipidemia	26 (40.6%)	16 (37.2%)	10 (47.6%)	0.588
Heart Failure	24 (40.0%)	13 (32.5%)	11 (55.0%)	0.105
Diabetes	14 (21.9%)	9 (20.9%)	5 (23.8%)	>0.99
Kidney disease	14 (21.9%)	10 (23.3%)	4 (19.0%)	>0.99
Liver disease	4 (6.3%)	2 (4.7%)	2 (9.5%)	0.592
COPD	4 (6.3%)	3 (7.0%)	1 (4.8%)	>0.99
Smoking				0.789
No smoking	46 (71.9%)	32 (74.4%)	14 (66.7%)	
Past	15 (23.4%)	9 (20.9%)	6 (28.6%)	
Present	3 (4.7%)	2 (4.7%)	1 (4.8%)	
Parkinson disease	3 (4.8%)	2 (4.7%)	1 (5.0%)	>0.99
Cognitive disorders	33 (51.6%)	23 (53.5%)	10 (47.6%)	0.791

Table 1. *Cont.*

Characteristics	Intra-Hospital Death			
	Total	No	Yes	*p* Value
Stroke	16 (25.8%)	11 (26.2%)	5 (25.0%)	>0.99
Known swallowing disorders	4 (6.3%)	2 (4.7%)	2 (9.5%)	0.592
Active neoplasia	5 (7.8%)	3 (7.0%)	2 (9.5%)	>0.99
Immunosuppression	3 (4.7%)	2 (4.7%)	1 (4.8%)	>0.99
Albumin	35.5 ± 8.0	35.7 ± 8.8	34.8 ± 5.2	0.641
C-Reactive Protein	56.2 ± 66.1	48.0 ± 41.2	73.9 ± 100.2	0.279
Lymphocytes nb-abs	1.3 ± 1.2	1.3 ± 1.3	1.1 ± 0.7	0.395
Radiological Measures				
Extent of COVID-19 pneumonia				0.813
0–25%	33 (54.1%)	22 (53.7%)	11 (55.0%)	
26–50%	13 (21.3%)	10 (24.4%)	3 (15.0%)	
51–75%	11 (18.0%)	7 (17.1%)	4 (20.0%)	
76–100%	4 (6.6%)	2 (4.9%)	2 (10.0%)	
AC (mm)	714.0 ± 196.3	743.9 ± 183.6	652.9 ± 211.6	0.101
TF (mm^2)	267.5 ± 143.0	285.4 ± 142.6	231.1 ± 140.1	0.156
SF (mm^2)	126.2 ± 86.4	142.7 ± 85.0	92.6 ± 81.1	0.028
VF (mm^2)	141.3 ± 84.0	142.7 ± 81.9	138.5 ± 90.2	0.858

Abbreviations: FIM = functional independence measure; CFS = clinical frailty scale; CIRS-G = cumulative illness rating scale for geriatrics; CAM = confusion assessment method; ARDS = acute respiratory distress syndrome; BMI = body mass index; NRS = nutritional risk screening; TF = total fat area (mm^2); AC = upper abdominal circumference (mm); SF = subcutaneous fat area (mm^2); VT = visceral fat area (mm^2).

3.2. Adiposity Measures and the Radiological Extent of COVID-19 Pneumonia

More than half of the patients in this cohort presented stage 1 (0–25%) lung involvement at chest CT, with no differences being determined between the survivors and non-survivors. In the univariate analysis, age, sex, and BMI were not significantly associated with the extent of pneumonia in the chest CT scans. On the other hand, we observed a significant association among all four measures of adiposity (upper abdominal circumference, total fat area, subcutaneous fat area, and visceral fat area) with the extent of COVID-19 pneumonia in the univariate and multiple models. Specifically, each increase of 1 dm^2 in the visceral fat area increased the risk of being in a category of more severe pulmonary involvement by more than 2.6 times after adjustments for age, sex, and BMI. Visceral fat presented the strongest association with this outcome, as presented in Table 2.

Table 2. Univariate and multiple ordered logistic regression models for the association with the extent of COVID-19 pneumonia.

Extent of COVID-19 Pneumonia	Model 1—Univariate				Model 2—Adjusted For Age and Sex				Model 3—Adjusted for Age, Sex and BMI			
	OR	95% CI	*p* Value	R^2	OR	95% CI	*p* Value	R^2	OR	95% CI	*p* Value	R^2
Age	1.011	0.932–1.095	0.794	0.5%								
Male sex	1.678	0.637–4.416	0.294	0.8%								
BMI	1.004	0.905–1.114	0.934	0.1%	0.001	0.001–0.055	0.985	0.5%				
Upper abdominal circumference	1.041	1.014–1.068	0.003	7.3%	1.041	1.014–1.069	0.002	8.0%	1.042	1.015–1.071	0.002	8.2%
Total fat area	1.766	1.230–2.537	0.002	7.9%	1.806	1.249–2.609	0.002	9.1%	1.851	1.27–2.695	0.001	9.5%
Subcutaneous fat area	1.817	1.078–3.060	0.025	3.7%	1.856	1.094–3.149	0.022	4.7%	1.917	1.124–3.271	0.017	4.8%
Visceral fat area	2.692	1.461–4.961	0.001	7.9%	2.784	1.489–5.206	0.001	9%	2.862	1.523–5.379	0.001	9.3%

Abbreviations: BMI = body mass index (kg/m^2); TF = total fat area (dm^2); AC = upper abdominal circumference (dm); SF = subcutaneous fat area (dm^2); VT = visceral fat area (dm^2).

3.3. Adiposity Measures and In-Hospital Mortality

Of the total 64 patients, 21 (32.8%) died during hospitalization. Survivors had a higher subcutaneous fat area than the non-survivors did (142.7 ± 85.0 vs. 92.6 ± 81.1; $p = 0.028$) no significant difference was detected for the visceral and total fat areas, nor were any significant differences found for the upper abdominal circumference (Table 1).

A higher subcutaneous fat area had a protective effect against mortality, as each increase by 1 dm^2 reduced the risk of dying by approximately 59% in the univariate analysis model. This association remained significant in the multivariate models, with an even higher strength association being observed after adjustments for age, sex, and BMI (OR 0.231; 0.071–0.751 95% CI; $p = 0.015$). A ROC curve was computed for this model (subcutaneous fat adjusted for age, sex, and BMI) and was compared to age, sex, and BMI alone using the likelihood ratio test. We detected an 11% gain in explaining the variance of the outcome (mortality) to the effect of the subcutaneous fat area only (Figure 2).

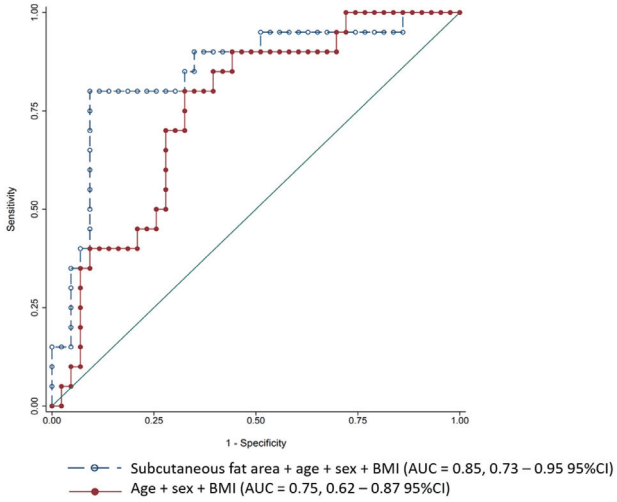


Figure 2. Receiver operating characteristic (ROC) curves for mortality prediction. Abbreviations: BMI = body mass index; AUC = area under the receiver operating characteristic curve; CI = confidence interval.

Although weaker than the effect of the subcutaneous fat area, higher upper abdominal circumference and the total fat area also presented an association with survival in the multivariate models. There was no association with the visceral fat area or BMI with in-hospital mortality (Table 3).

Table 3. Univariate and multiple logistic regression models for the association of in-hospital mortality.

	Model 1—Univariate				Model 2—Adjusted for Age and Sex				Model 3—Adjusted for Age, Sex and BMI			
In-Hospital Mortality	**OR**	**95% CI**	***p* Value**	**R^2**	**OR**	**95% CI**	***p* Value**	**R^2**	**OR**	**95% CI**	***p* Value**	**R^2**
Age	1.012	0.927–1.105	0.784	0.9%								
Male sex	6.628	2.017–21.781	0.002	13.8%								
BMI	1.083	0.958–1.223	0.201	2.1%	1.102	0.956–1.271	0.182	15.3%				
Upper abdominal circumference	0.975	0.946–1.003	0.086	3.9%	0.953	0.914–0.994	0.025	23.1%	0.95	0.913–0.989	0.013	25.2%
Total fat area	0.746	0.496–1.119	0.158	2.7%	0.579	0.342–0.982	0.043	19.8%	0.578	0.336–0.993	0.047	21.2%
Subcutaneous fat area	0.416	0.183–0.944	0.036	6.8%	0.219	0.067–0.717	0.012	25.5%	0.231	0.071–0.751	0.015	26.4%
Visceral fat area	0.941	0.500–1.769	0.85	0.4%	0.783	0.385–1.591	0.499	14.4%	0.78	0.376–1.617	0.505	15.8%

Abbreviations: BMI = body mass index (kg/m^2); TF = total fat area (dm^2); AC = upper abdominal circumference (dm); SF = subcutaneous fat area (dm^2); VT = visceral fat area (dm^2).

4. Discussion

This study, which was conducted in a population of hospitalized octogenarians with COVID-19, demonstrated that the subcutaneous and visceral fat areas had a significant effect on prognosis, albeit different effects. While a higher subcutaneous fat area was protective against mortality, with visceral fat showing no significant affect against morality, a higher proportion of visceral fat was strongly associated with greater radiological COVID-19-related pneumonia severity. Additionally, we demonstrated the feasibility and clinical relevance of body composition measures assessed by chest CT scans in this specific population.

COVID-19 leads to significant changes in body composition. A post hoc analysis performed in a population consisting mainly of patients in the overweight/obesity categories (70%) showed that among survivors, nearly 30% lost 5% or more of their body weight, with those presenting acute respiratory distress syndrome (ARDS) losing up to 18% of their body weight [25]. The systemic inflammatory response that occurs with severe infection triggers catabolic states, followed by increased lipolysis and skeletal muscle wasting [26]. Drawing a parallel with the results of our study, we hypothesize that in these largely non-obese frail patients, subcutaneous fat is a strategic source of energy supply, thus explaining the protective effect observed against in-hospital mortality. Furthermore, subcutaneous adipocytes have anti-inflammatory properties that are mediated by the secretion of adiponectin. This hormonal balance between subcutaneous and proinflammatory visceral adipocytes may be another important mechanism explaining our results [27].

We did not find any relationship between the visceral fat area and mortality in this population. We believe the special characteristics of our very old study population may explain the differences between our results and previous reports with a similar methodology [6,7,18,28–30]. We built up new information on the role of adiposity in very old patients that does not preclude the notion that a high proportion of visceral fat, especially in younger obese patients, triggers inflammation and more severe disease, as established by the previous evidence.

In our study, a higher visceral fat area was strongly associated with g SARS-CoV-2 having greater lung involvement at hospital admission. It is worth noting that our CT scans were performed relatively early, close to hospital admission, and they do not reflect the overall severity of the disease during follow-up, which is corroborated by the fact that more than half of the patients presented with stage 1 pneumonia. Interestingly, our results raise the question of whether a higher visceral fat area could play a role as a marker of early pulmonary involvement in COVID-19.

One of the main strengths of this study was its participants, with this study being the first in this domain to specifically investigate a group of 80+ patients to date. The use of chest CT scans allowed us to adapt a routinely performed diagnostic test to add new measures of body composition, specifically visceral and subcutaneous fat mass.

However, this study has several limitations. Only one measure of body composition was performed at the beginning of hospitalization in the subgroup of patients, which does not allow us to conclude the impact of the changes that took place during the hospital stay. Furthermore, the obese category was only represented by a few patients in this study, meaning that this should be the object of further study in this research field. Additionally, the small number of participants and deaths may have contributed to the lack of power in some models as well as to the lack of power in the comparison between groups, as the survivors and non-survivors had similar morbidity profiles. Finally, the radiological features of COVID-19-related pneumonia do not necessarily correlate with the severity of respiratory status, which should be integrated into multivariate models in future analysis.

5. Conclusions

In conclusion, the subcutaneous and visceral fat areas measured on routinely performed chest CT scans presented a significant prognostic role in a population of octogenar-

ians with COVID-19. Importantly, these specific body composition measures were more relevant prognostic markers than BMI.

Author Contributions: Conceptualization, A.M., M.S., C.S. and L.G.; methodology, F.R.H., M.S., J.R. and A.M.; validation, C.S., G.G., C.E.G. and D.Z.; formal analysis, A.M., F.R.H., M.S. and J.R.; data curation, A.M. and F.R.H.; writing—original draft preparation, A.M.; writing—review and editing, all authors.; supervision, G.G., D.Z. and C.E.G.; project administration, C.E.G. and D.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Geneva (Project-Id: 2020-00819; NCT04385212).

Informed Consent Statement: Patient consent was waived due to the retrospective design of the study, which used clinical data available from medical records.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author (A.M.) upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Mendes, A.; Serratrice, C.; Herrmann, F.R.; Genton, L.; Périvier, S.; Scheffler, M.; Fassier, T.; Huber, P.; Jacques, M.-C.; Prendki, V.; et al. Predictors of In-hospital mortality in older patients with COVID-19: The COVIDAge Study. *J. Am. Med. Dir. Assoc.* **2020**, *21*, 1546–1554.e3. [CrossRef]
2. Hirani, V.; Blyth, F.; Naganathan, V.; Le Couteur, D.G.; Seibel, M.J.; Waite, L.M.; Handelsman, D.J.; Cumming, R.G. Sarcopenia Is associated with incident disability, Institutionalization, and mortality in community-dwelling older men: The concord health and ageing in men project. *J. Am. Med. Dir. Assoc.* **2015**, *16*, 607–613. [CrossRef]
3. Cerri, A.P.; Bellelli, G.; Mazzone, A.; Pittella, F.; Landi, F.; Zambon, A.; Annoni, G. Sarcopenia and malnutrition in acutely ill hospitalized elderly: Prevalence and outcomes. *Clin. Nutr.* **2015**, *34*, 745–751. [CrossRef]
4. Flegal, K.M.; Kruszon-Moran, D.; Carroll, M.D.; Fryar, C.D.; Ogden, C.L. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA* **2016**, *315*, 2284–2291. [CrossRef]
5. Petrilli, C.M.; Jones, S.A.; Yang, J.; Rajagopalan, H.; O'Donnell, L.; Chernyak, Y.; Tobin, K.A.; Cerfolio, R.J.; Francois, F.; Horwitz, L.I. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective Cohort Study. *BMJ* **2020**, *369*, 1966. [CrossRef]
6. Watanabe, M.; Caruso, D.; Tuccinardi, D.; Risi, R.; Zerunian, M.; Polici, M.; Pucciarelli, F.; Tarallo, M.; Strigari, L.; Manfrini, S. Visceral Fat Shows the Strongest Association with the Need of Intensive Care in Patients with COVID-19. *Metabolism* **2020**, *111*, 154319. [CrossRef]
7. Petersen, A.; Bressem, K.; Albrecht, J.; Thieß, H.-M.; Vahldiek, J.; Hamm, B.; Makowski, M.R.; Niehues, A.; Niehues, S.M.; Adams, L.C. The Role of Visceral Adiposity in the Severity of COVID-19: Highlights from A unicenter Cross-sectional Pilot Study in Germany. *Metabolism* **2020**, *110*, 154317. [CrossRef]
8. Calabrò, P.; Golia, E.; Maddaloni, V.; Malvezzi, M.; Casillo, B.; Marotta, C.; Calabro, R.; Golino, P. Adipose Tissue-Mediated Inflammation: The Missing Link between Obesity and Cardiovascular Disease? *Intern. Emerg. Med.* **2009**, *4*, 25–34. [CrossRef] [PubMed]
9. Barazzoni, R.; Bischoff, S.C.; Busetto, L.; Cederholm, T.; Chourdakis, M.; Cuerda, C.; Delzenne, N.; Genton, L.; Schneider, S.; Singer, P.; et al. Nutritional Management of Individuals with Obesity and COVID-19: ESPEN Expert statements and Practical Guidance. *Clin. Nutr.* **2021**. [CrossRef] [PubMed]
10. Gupte, M.; Boustany-Kari, C.M.; Bharadwaj, K.; Police, S.; Thatcher, S.; Gong, M.C.; English, V.L.; Cassis, L.A. ACE2 is expressed in mouse adipocytes and regulated by a high-fat diet. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2008**, *295*, R781–R788. [CrossRef] [PubMed]
11. Bourgonje, A.R.; Abdulle, A.E.; Timens, W.; Hillebrands, J.-L.; Navis, G.J.; Gordijn, S.J.; Bolling, M.C.; Dijkstra, G.; Voors, A.A.; Osterhaus, A.D.; et al. Angiotensin-Converting Enzyme 2 (ACE2), SARS-CoV-2 and the Pathophysiology of Coronavirus Disease 2019 (COVID-19). *J. Pathol.* **2020**, *251*, 228–248. [CrossRef]
12. Zarkesh-Esfahani, H.; Pockley, A.G.; Wu, Z.; Hellewell, P.G.; Weetman, A.P.; Ross, R.J.M. Leptin Indirectly Activates Human Neutrophils via Induction of TNF-Alpha. *J. Immunol.* **2004**, *172*, 1809–1814. [CrossRef]
13. Guglielmi, V.; Colangeli, L.; D'Adamo, M.; Sbraccia, P. Susceptibility and Severity of Viral Infections in Obesity: Lessons from Influenza to COVID-19. Does Leptin Play a Role? *Int. J. Mol. Sci.* **2021**, *22*, 3183. [CrossRef] [PubMed]
14. Kiernan, K.; MacIver, N.J. The Role of the Adipokine Leptin in Immune Cell Function in Health and Disease. *Front. Immunol.* **2020**, *11*, 3656. [CrossRef] [PubMed]

15. Ouchi, N.; Parker, J.L.; Lugus, J.J.; Walsh, K. Adipokines in Inflammation and Metabolic Disease. *Nat. Rev. Immunol.* **2011**, *11*, 85–97. [CrossRef]
16. Ohashi, K.; Shibata, R.; Murohara, T.; Ouchi, N. Role of Anti-inflammatory Adipokines in Obesity-Related Diseases. *Trends. Endocrinol. Metab.* **2014**, *25*, 348–355. [CrossRef] [PubMed]
17. Tchernof, A.; Després, J.-P. Pathophysiology of Human Visceral Obesity: An update. *Physiol. Rev.* **2013**, *93*, 359–404. [CrossRef] [PubMed]
18. Favre, G.; Legueult, K.; Pradier, C.; Raffaelli, C.; Ichai, C.; Iannelli, A.; Redheuil, A.; Lucidarme, O.; Esnault, V. Visceral Fat is Associated to the Severity of COVID-19. *Metabolism* **2021**, *115*, 154440. [CrossRef]
19. Salvi, F.; Miller, M.D.; Grilli, A.; Giorgi, R.; Towers, A.L.; Morichi, V.; Spazzafumo, L.; Mancinelli, L.; Espinosa, E.; Rappelli, A.; et al. A Manual of Guidelines to Score the Modified Cumulative Illness Rating Scale and its Validation in Acute Hospitalized Elderly Patients. *J. Am. Geriatr. Soc.* **2008**, *56*, 1926–1931. [CrossRef]
20. Inouye, S.K.; van Dyck, C.H.; Alessi, C.A.; Balkin, S.; Siegal, A.P.; Horwitz, R.I. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. *Ann. Intern. Med.* **1990**, *113*, 941–948. [CrossRef]
21. Rockwood, K.; Song, X.; MacKnight, C.; Bergman, H.; Hogan, D.B.; McDowell, I.; Mitnitski, A. A global clinical measure of fitness and frailty in elderly people. *CMAJ* **2005**, *173*, 489–495. [CrossRef] [PubMed]
22. Linacre, J.M.; Heinemann, A.W.; Wright, B.D.; Granger, C.V.; Hamilton, B.B. The structure and stability of the Functional Independence Measure. *Arch. Phys. Med. Rehabil.* **1994**, *75*, 127–132. [CrossRef]
23. Lim, W.; van der Eerden, M.M.; Laing, R.; Boersma, W.; Karalus, N.; Town, G.I.; Lewis, S.A.; Macfarlane, J. Defining community acquired pneumonia severity on presentation to hospital: An international derivation and validation study. *Thorax* **2003**, *58*, 377–382. [CrossRef] [PubMed]
24. Kondrup, J.; Rasmussen, H.H.; Hamberg, O.; Stanga, Z. Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): A new method based on an analysis of controlled clinical trials. *Clin. Nutr.* **2003**, *22*, 321–336. [CrossRef]
25. Di Filippo, L.; De Lorenzo, R.; D'Amico, M.; Sofia, V.; Roveri, L.; Mele, R.; Saibene, A.; Rovere-Querini, P.; Conte, C. COVID-19 is associated with clinically significant weight loss and risk of malnutrition, independent of hospitalisation: A post-hoc anaysis of a prospective cohort study. *Clin. Nutr.* **2021**, *40*, 2420–2426. [CrossRef]
26. Englert, J.A.; Rogers, A.J. Metabolism, Metabolomics, and Nutritional Support of Patients with Sepsis. *Clin. Chest. Med.* **2016**, *37*, 321–331. [CrossRef]
27. Liu, D.; Zhang, T.; Wang, Y.; Xia, L. The Centrality of Obesity in the Course of Severe COVID-19. *Front. Endocrinol.* **2021**, *12*, 620566. [CrossRef]
28. Battisti, S.; Pedone, C.; Napoli, N.; Russo, E.; Agnoletti, V.; Nigra, S.G.; Dengo, C.; Mughetti, M.; Conte, C.; Pozzilli, P.; et al. Computed Tomography Highlights Increased Visceral Adiposity Associated with Critical Illness in COVID-19. *Diabetes. Care* **2020**, *43*, 129–130. [CrossRef]
29. Deng, M.; Qi, Y.; Deng, L.; Wang, H.; Xu, Y.; Li, Z.; Meng, Z.; Tang, J.; Dai, Z. Obesity as a Potential Predictor of Disease Severity in Young COVID-19 Patients: A Retrospective Study. *Obesity* **2020**, *28*, 1815–1825. [CrossRef]
30. Yang, Y.; Ding, L.; Zou, X.; Shen, Y.; Hu, D.; Hu, X.; Li, Z.; Kamel, I.R. Visceral Adiposity and High Intramuscular Fat Deposition Independently Predict Critical Illness in Patients with SARS-CoV-2. *Obesity* **2020**, *28*, 2040–2048. [CrossRef]

Journal of
Clinical Medicine

MDPI

Article

COVID-19 in Elderly Patients Surgically Treated for Lower Limbs Fracture

Alessandra Colombini [1,*,†], Michele Davide Maria Lombardo [2,†], Laura de Girolamo [1], Elena De Vecchi [3], Riccardo Giorgino [2], Giuseppe Maria Peretti [1,4], Giuseppe Banfi [1,5] and Laura Mangiavini [1,4]

[1] Laboratorio di Biotecnologie Applicate all'Ortopedia, IRCCS Istituto Ortopedico Galeazzi, 20161 Milan, Italy; laura.degirolamo@grupposandonato.it (L.d.G.); giuseppe.peretti@unimi.it (G.M.P.); banfi.giuseppe@hsr.it (G.B.); laura.mangiavini@unimi.it (L.M.)
[2] Residency Program in Orthopedics and Traumatology, University of Milan, 20122 Milan, Italy; mdm.lombardo@gmail.com (M.D.M.L.); riccardo.giorgino93@gmail.com (R.G.)
[3] Laboratory of Clinical Chemistry and Microbiology, IRCCS Istituto Ortopedico Galeazzi, 20161 Milan, Italy; elena.devecchi@grupposandonato.it
[4] Department of Biomedical Sciences for Health, University of Milan, 20133 Milan, Italy
[5] Vita-Salute San Raffaele University, 20132 Milan, Italy
* Correspondence: alessandra.colombini@grupposandonato.it; Tel.: +39-02-6621-4067
† These authors contributed equally to this work.

Abstract: Background: The coronavirus disease 2019 (COVID-19) pandemic outbreak has posed new problems in the context of patients suffering from other diseases. In particular, musculoskeletal sequelae related to the state of debilitation associated with COVID-19 are important to consider in elderly patients undergoing surgery after lower limbs fracture, especially in the post-operative period. The objective of this study was to evaluate whether COVID-19 influenced biochemical parameter, recovery and mortality of surgically treated patients suffering from lower extremity fractures. Methods: Laboratory and clinical data of 30 patients were extrapolated and analyzed in the pre-operative and post-operative periods. Among these patients, 13 had COVID-19 infection (COVID-19 +), whereas 17 had no signs of COVID-19 infections (COVID-19 −). Long-term clinical and functional outcomes were also analyzed. Results: Lower calcium, slightly higher values of CRP and much higher values of CPK and AST were observed pre-operatively in COVID-19 + patients, who also showed higher prevalence of long-term sequelae than COVID-19 − patients. Conclusions: COVID-19 affects long-term outcome of elderly patients with lower limb fractures in a multifactorial way. First, the virus directly damages the muscle tissue. Secondly, the lung function impairment worsens the overall performance, making rehabilitation more challenging.

Keywords: fractures; lower limbs; surgery; COVID-19; elderly; clinical biochemistry; mortality; long-term consequences

Citation: Colombini, A.; Lombardo, M.D.M.; de Girolamo, L.; De Vecchi, E.; Giorgino, R.; Peretti, G.M.; Banfi, G.; Mangiavini, L. COVID-19 in Elderly Patients Surgically Treated for Lower Limbs Fracture. *J. Clin. Med.* **2022**, *11*, 168. https://doi.org/10.3390/jcm11010168

Academic Editor: Francisco Guillen-Grima

Received: 13 December 2021
Accepted: 26 December 2021
Published: 29 December 2021

1. Introduction

Fractures of the lower limbs, especially proximal femoral fractures, are quite common in the elderly. This segment of the population is considered particularly fragile due to the numerous comorbidities that can occur with increasing years; hence, it represents a critical group of patients. For these patients, coronavirus disease 2019 (COVID-19) is a further danger. In fact, it was reported that case fatality ratio (CFR) of COVID-19 increases with age. Considering an overall Italian CFR of 7.2%, its values ranged from less than 0.4% in 40 s or younger patients, 1% in 50 s, 3.5% in 60 s, 12.8% in 70 s to 20.2% in 80 s and above [1]. Moreover, COVID-19 has been reported to be independently associated with an increased early mortality rate in hip fracture patients [2,3]. In particular, a meta-analysis conducted on data of the first wave of the pandemic reported a 13% of prevalence of COVID-19 in hip fracture patients with a higher crude mortality rate (35%) compared to that of patients without COVID-19 (8%) [4].

In addition, musculoskeletal sequelae were evidenced in the short term, and they probably persist in the long term after COVID-19 infection [5]. In particular, more than one-third of patients with COVID-19 reported myalgias and generalized weakness [6–10]; elevated creatine kinase (CK) levels are prevalent in hospitalized, particularly severe, patients [11,12]. For example, 19% of 214 Chinese patients had CK levels of >200 U/L (cutoff for clinically elevated CK), with an upper range of 12,216 U/L [13]. Muscle injury is likely related to the inflammatory status, malnutrition, prolonged physical inactivity, mechanical ventilation and treatment with myotoxic drugs such as dexamethasone [14].

In the musculoskeletal context, falls, which represent the most common mechanism for hip fracture during the pandemic outbreak, can be considered low-energy injuries associated with COVID-19 infection in elderly [15].

The aim of the present study was to evaluate whether COVID-19 influenced post-surgical biochemical parameters, recovery and mortality in patients undergoing surgery after fracture of the femur, tibia or fibula, compared to patients without COVID-19 in the first and second wave of the pandemic in Italy.

2. Materials and Methods

2.1. Study Population

From April 2020 to November 2020, 30 patients having femur, tibia or fibula fractures were enrolled at IRCCS Istituto Ortopedico Galeazzi. Written informed consent for the participation in this study was obtained from all participants (protocol "Costituzione di una banca di materiale biologico da paziente (biobanca) per lo studio di patologie che interessano l'apparato muscolo-scheletrico e il sistema nervoso centrale"; NCT03208062). The study protocol was approved by the San Raffaele Hospital Ethical Review Board. Demographic and clinical data and serum samples of the enrolled patients were collected.

Before surgery, all patients underwent nasopharyngeal swab to determine whether they were infected with SARS-CoV-2 and were hospitalized in a dedicated area, awaiting the result of the molecular test. In case of infection, the patients were transferred to a dedicated ward.

All patients were treated surgically, under spinal anesthesia, within 48 h from clinical presentation. They received peri-operative antibiotic and anti-thromboembolic prophylaxis and analgesic therapy.

Rehabilitation began, where possible, the day after surgery in order to allow for an early verticalization.

As soon as they stabilized from a clinical point of view, the patients were transferred to a facility dedicated to rehabilitation, and they were discharged once they reached ambulatory autonomy. In case of persisting lack of independence, the patients were sent to long-term care facilities or to their home with assistance.

2.2. Clinical Data Collection and Patient Follow-Up

Data concerning age, sex, diagnosis, relevant comorbidities, pharmacological treatments, complications and post-surgical transfusion of the patients were collected. The time elapsed between the surgery and the standing positioning of the patient and the mean overall stay in rehabilitation were evaluated.

Patients were also evaluated after 8–14 months to assess the long-term outcomes and complications after orthopedic healing. During the follow-up, the most frequently reported complications of COVID-19 infection in the literature were searched in addition to the outcomes closely related to fractures and their management [16], such as level of independence, return to sociability, mental fog and fatigue.

The clinical analysis was carried out by telephone interview by medical staff experienced in remote assessment. This was executed in order to minimize patient transfers as much as possible, given the pandemic period.

2.3. Diagnosis of COVID-19 Infection

Quantitative reverse transcription–polymerase chain reaction (qRT-PCR) of nasopharyngeal swabs were performed to assess the presence of COVID-19. Briefly, viral RNA was extracted using total RNA Purification Kit (Norgen, ON, Canada) and the molecular detection of the SARS-CoV-2 genome was analyzed by RT-PCR using COVID-19 HT Screen kit (Clonit, Italy), targeting N1 and N2 genes.

Among the 30 enrolled patients, SARS-CoV-2 genes were detected in 13 patients (COVID-19 +), whereas 17 were negative for COVID-19 infection (COVID-19 −).

2.4. Evaluation of Biochemical Parameters

Routine blood tests were performed on patients' admission and post-surgical intervention.

Hematological analyses (hemoglobin, white blood cells, platelets, neutrophils, lymphocytes and monocytes) were performed on a Sysmex XN-2000 (Sysmex, Kobe, Japan).

Coagulation tests (prothrombin time, activated partial thromboplastin time and fibrinogen) were analyzed on a Sysmex CS 2500 (Sysmex, Japan).

Biochemical parameters (urea, creatinine, creatine phosphokinase, aspartate aminotransferase, C-reactive protein and calcium) were measured on an Atellica® CH Analyzer (Siemens Healthineers, Erlangen, Germany).

A complete list of the analyzed parameters with their acronym and unit of measure is reported in Table 1.

Table 1. List of the analyzed parameters.

Category	Sample	Parameter (Acronym)	Unit of Measure
Hematological	Whole blood	White blood cells (WBC)	$10^3/\mu L$
		Neutrophil count (Neu)	$10^3/\mu L$
		Lymphocyte count (Lympho)	$10^3/\mu L$
		Monocyte count (Mono)	$10^3/\mu L$
		Hemoglobin (Hb)	g/dL
		Platelets	$10^3/\mu L$
Coagulation	Plasma	Prothrombin time (PT)	s
		Activated partial thromboplastin time (APTT)	s
		Fibrinogen	mg/dL
Biochemical	Serum	Urea (Urea)	mg/dL
		Creatinine (Crea)	mg/dL
		Creatine phosphokinase (CPK)	U/L
		Aspartate aminotransferase (AST)	U/L
		C-reactive protein (CRP)	mg/dL
		Calcium (Ca)	mg/dL

2.5. Statistical Analysis

For the analysis of biochemical data, Kolmogorov–Smirnov normality test was used to assess the data distribution. Unpaired *t* test or Mann–Whitney test to compare two groups one-way ANOVA or Kruskal–Wallis tests were used to compare three groups in case of Gaussian or non-Gaussian distribution of the data, respectively.

GraphPad Prism 6.0 (GraphPad Software, San Diego, CA, USA) was used for the statistical analysis of data. A p value of ≤ 0.05 was considered significative, $0.09 \geq p > 0.05$ was considered as a tendency.

The evaluation of the presence of long-term sequelae in COVID-19 + and COVID-19 − patients was performed using Chi-square test for dichotomous variables and through the Wilcoxon signed rank test for continuous variables (IMB SPSS Statistics, v. 26).

3. Results

3.1. Clinical Features of the Patients

Thirty patients, all affected by a fracture of the lower limb, were included in the study; in particular, 28 suffered a proximal femoral fracture, 1 a tibial fracture and 1 a hip peri-prosthetic fracture. Among the 30 patients, 13 were COVID-19 + and 17 were COVID-19 −.

There were 24 women (80% of the total) and 6 men (20% of the total).

The average age of all analyzed patients was 80.6 ± 9.3 years, the average age of COVID-19 + patients was 79.5 ± 8.6 years and that of COVID-19 − patients was 81.4 ± 9.9.

Post-operative pharmacological treatments included Low Molecular Weight Heparin (LMWH), antibiotic prophylaxis, nonsteroidal anti-inflammatory drugs (NSAIDS) and steroids administration.

At least one post-operative blood transfusion was performed in 66.7% of patients; of those, 61.6% were COVID-19 + and 70.6% were COVID-19 −.

In our cohort, 3 patients (10% of the total) were hospitalized in the Intensive Care Unit (ICU) after surgery. All 3 patients were COVID-19 +. One of these patients died from post-operative cardiological complications. None of the COVID-19 − patients required ICU hospitalization after surgery.

Supplementary Table S1 shows clinical data of each patient included in the study.

For overall patients, the mean time elapsed between the surgery and the standing positioning was 3.3 ± 1.3 days; in particular, it was 3.2 ± 1.8 and 3.4 ± 1.3 days for COVID-19 + and COVID-19 − patients, respectively.

The mean overall stay in rehabilitation wards was 76.2 days ± 46.4; in particular, it was 75.4 days ± 46.5 and 76, 7 ± 47.7 days for COVID-19 + and COVID-19 − patients, respectively.

3.2. Follow-Up of the Patients

The time elapsed between hospital admission and the mean follow-up of all patients analyzed was 11.7 ± 2.4 months: 9.9 ± 2.8 months and 13.0 ± 0.4 months for COVID-19 + and COVID-19 − patients, respectively. At follow-up, 36.7% of patients regained a level of independence comparable to that prior to the fracture. This percentage drops to 10% in patients with COVID-19 infection. Return to sociability as before the pathological event was reported in 61.5% of COVID-19 + patients compared to 64.7% of COVID-19 − patients. A higher percentage of COVID-19 + patients (69.2%) complained of sleep disorders compared to 41.2% of COVID-19 − patients.

Among COVID-19 + patients, 76.9% complained about a certain degree of mental fog, described as focus trouble or difficulty to remember commonly used names and words. This percentage drops to 17.6% for COVID-19 − patients. Similarly, 76.9% of COVID-19 + and 23.5% of COVID-19 − patients complained of fatigue. Gastrointestinal problems such as loss of appetite, nausea and diarrhea were reported by 61.5% of COVID-19 + patients and 23.5% of COVID-19 − patients. As expected, 46.2% of COVID-19 + patients developed lung problems versus 5.9% of COVID-19 − subjects, following hospitalization for fracture. Moreover, 6.9% of COVID-19 + patients developed dyspnea on moderate exertion, whereas none of the COVID-19 − subjects developed this kind of symptom. After surgery and rehabilitation, 61.5% of COVID-19 + and 35.3% of COVID-19 − patients complained of arthomyalgia.

The association between COVID-19 positivity during hospitalization and the presence of long-term sequelae were further investigated.

In order to analyze the impact that COVID-19 has on people's health status and quality of life, the odds ratios of the most frequent clinical manifestations such as mental fog, dyspnea and fatigue in relation to the pathology were calculated and are showed in Table 2.

Table 2. Significative odds ratio for most frequent clinical manifestation.

	N	%	OR	95% CI	*p*
Mental Fog					
COVID	10	76.9	15.6	2.6–93.6	<0.005
Non COVID	3	17.6			
Dyspnea					
COVID	10	76.9	10.8	2.0–59.8	<0.05
Non COVID	4	23.5			
Fatigue					
COVID	10	76.9	53.3	4.8–586.2	<0.005
Non COVID	1	5.9			

A total of 38.5% of COVID-19 + patients required the use of a new chronic drug therapy following surgery, compared to 17.6% of COVID-19 − patients.

Two COVID-19 − subjects (11.7%) died after surgery and hospitalization.

3.3. Hematological and Coagulation Parameters of the Patients

No modifications were observed in the number of white blood cells, in particular neutrophils and lymphocytes, neither from pre-surgery to day 2 post-surgery nor between COVID-19 − and COVID-19 + patients. An increased number of monocytes was noted on day 1 after surgery in COVID-19 − patients ($0.9 \pm 0.3 \times 10^3/\mu L$ versus $0.6 \pm 0.2 \times 10^3/\mu L$ pre-surgery, $p = 0.05$). COVID-19 + patients showed a higher number of monocytes pre-surgery in comparison with COVID-19 − patients ($0.8 \pm 0.3 \times 10^3/\mu L$ versus $0.6 \pm 0.2 \times 10^3/\mu L$ pre-surgery, tendency $p = 0.06$), without changes during the two first days after surgery.

Platelet levels were stable in all patients during the first two days after surgery, without differences between groups. Moreover, no differences were observed between the two sets in pre-surgery prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen.

Hemoglobin levels significantly decreased from pre-surgery to day 1 and day 2 after surgery in all patients (11.7 ± 1.3 g/dL pre-surgery, 10.0 ± 1.0 g/dL day 1 post-surgery, 9.4 ± 1.5 g/dL day 2 post-surgery, $p < 0.0001$) and in both COVID-19 − (11.7 ± 1.3 g/dL pre-surgery, 9.8 ± 1.1 g/dL day 1 post-surgery, 9.1 ± 1.5 g/dL day 2 post-surgery, $p < 0.0001$) and COVID-19 + (11.8 ± 1.3 g/dL pre-surgery, 10.2 ± 1.0 g/dL day 1 post-surgery, 9.8 ± 1.5 g/dL day 2 post-surgery, $p < 0.001$) categories, without differences between groups.

Figure 1 shows the levels of hematological and coagulation parameters in all patients.

3.4. Biochemical Parameters

No changes in urea and creatinine levels were observed neither during the first two days after surgery nor between groups. Calcium levels decreased from pre-surgery to day 1 and day 2 post-surgery in all groups (8.8 ± 0.5 mg/dL pre-surgery, 8.2 ± 0.5 mg/dL day 1 post-surgery, 7.8 ± 0.6 mg/dL day 2 post-surgery for all patients, $p < 0.0001$; 9.0 ± 0.4 mg/dL pre-surgery, 8.4 ± 0.5 mg/dL day 1 post-surgery, 7.8 ± 0.5 mg/dL day 2 post-surgery for COVID-19 −, $p < 0.0001$; 8.6 ± 0.6 mg/dL pre-surgery, 8.0 ± 0.4 mg/dL day 1 post-surgery, 7.8 ± 0.6 mg/dL day 2 post-surgery for COVID-19 +, $p < 0.001$). Lower levels of calcium were observed in COVID-19 + patients pre-surgery ($p = 0.02$) and day 1

post-surgery (tendency, $p = 0.06$) in comparison with COVID-19 – subjects; these values became similar on the second day after surgery.

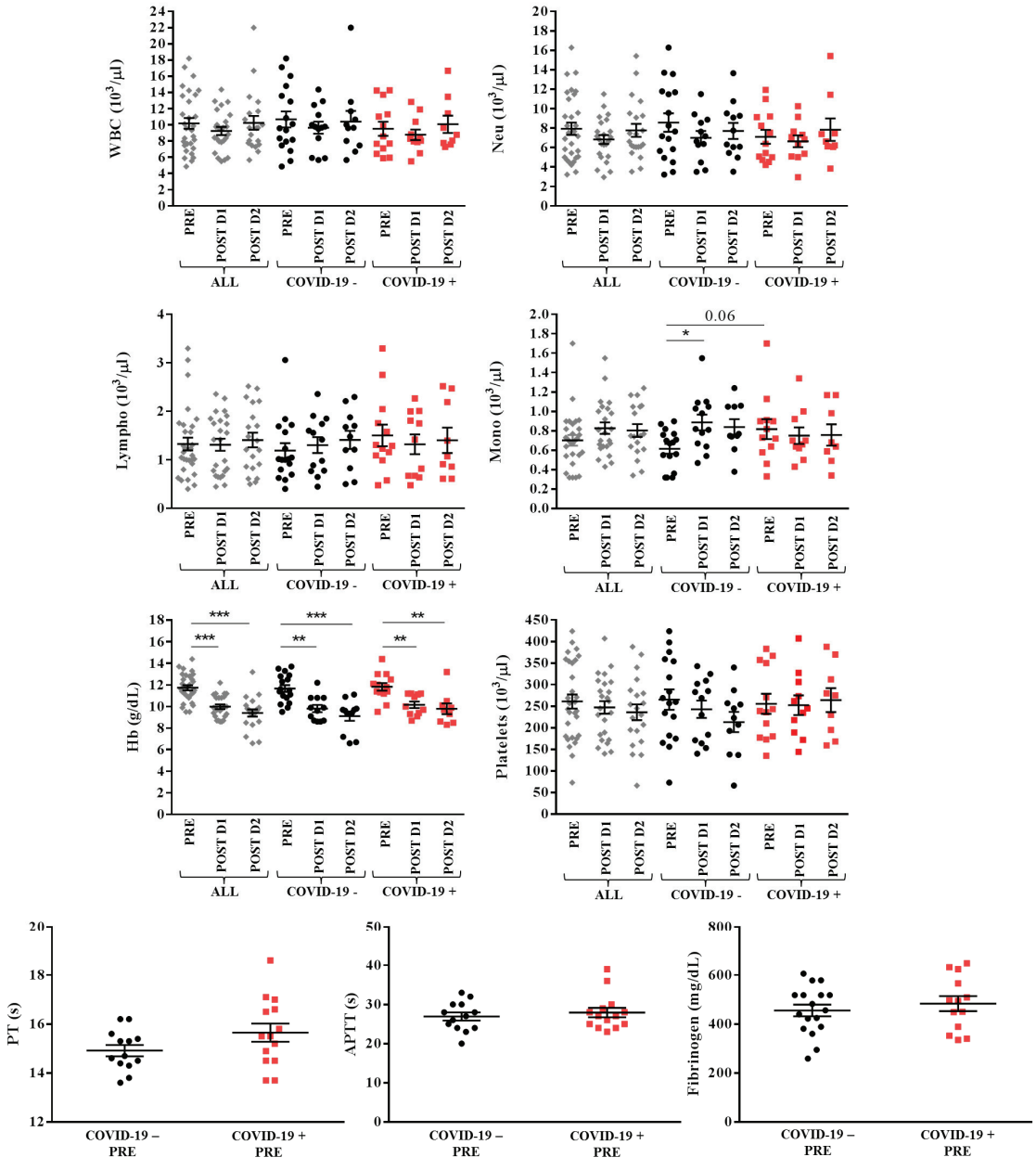


Figure 1. Hematological and coagulation parameters in overall (ALL, grey), COVID-19 − (black) and COVID-19 + (red) patients with lower limbs fractures registered pre- (PRE), day 1 (POST D1) and day 2 (POST D2) post-surgery. Mean with SEM are showed. * $p \leq 0.05$, ** $p < 0.02$, *** $p < 0.001$.

The inflammatory marker C-reactive protein (CRP) increased from pre-surgery to day 1 and day 2 post surgery in all (5.7 ± 5.0 mg/dL pre-surgery, 12.2 ± 6.8 mg/dL day 1 post-surgery, 17.0 ± 9.1 mg/dL day 2 post-surgery, $p < 0.0001$) and COVID-19 − (4.5 ± 3.9 mg/dL pre-surgery, 13.1 ± 7.3 mg/dL day 1 post-surgery, 18.5 ± 10.4 mg/dL day 2 post-surgery, $p < 0.0001$) patients, whereas in COVID-19 + patients values increased only from pre-surgery (7.4 ± 6.0 mg/dL) to day 2 post-surgery (15.3 ± 7.4 mg/dL, $p = 0.03$) since these patients started from higher pre-surgical levels of this protein. No differences in CRP levels were observed between groups.

Figure 2 shows the levels of biochemical parameters in patients.

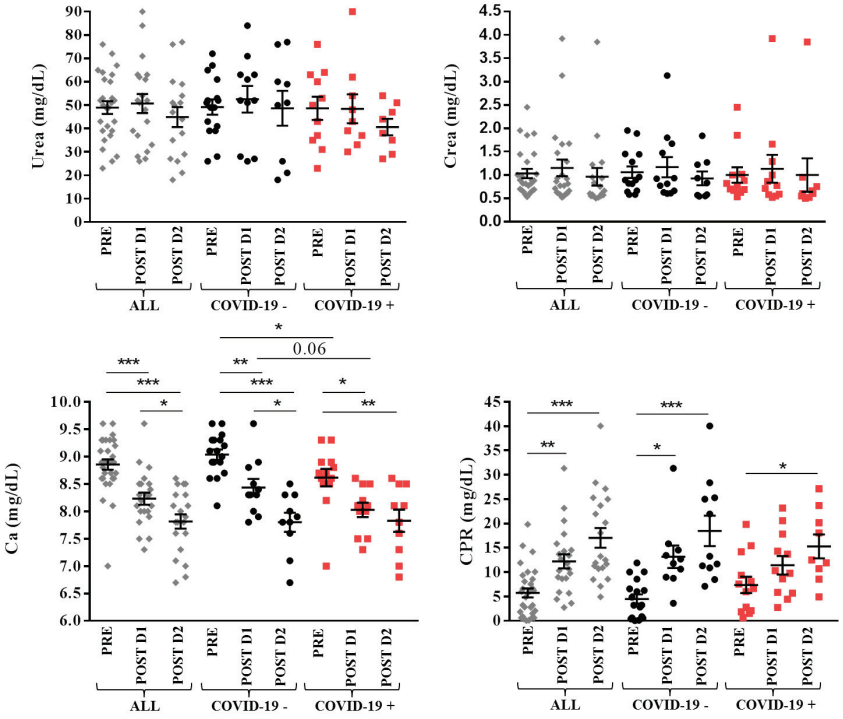


Figure 2. Biochemical parameters in overall (ALL, grey), COVID-19 − (black) and COVID-19 + (red) patients with lower limbs fractures registered pre- (PRE), day 1 (POST D1) and day 2 (POST D2) post-surgery. Mean with SEM are showed. * $p \leq 0.05$, ** $p < 0.02$, *** $p < 0.001$.

Muscular markers creatine phosphokinase (CPK) and aspartate aminotransferase (AST) showed post-surgical increase in COVID-19 − group (112.5 ± 124.4 U/L pre-surgery, 272.6 ± 173.7 U/L day 1 post-surgery, $p = 0.002$ and 20.1 ± 8.6 U/L pre-surgery, 30.2 ± 24.3 U/L post-surgery, tendency $p = 0.09$, respectively). For these markers, COVID-19 + patients showed higher pre-surgical levels which remained high post-surgery (Figure 3).

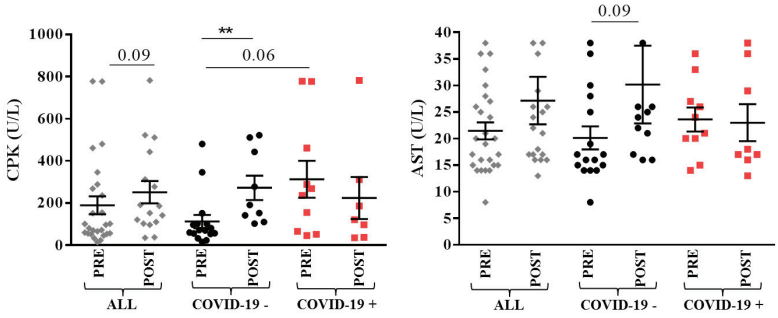


Figure 3. Muscular markers in overall (ALL, grey), COVID-19 − (black) and COVID-19 + (red) patients with lower limbs fractures registered pre- (PRE) and day 1–5 (POST) post-surgery. Mean with SEM are showed. ** $p < 0.01$.

4. Discussion

The data of the present study revealed that the long-term orthopedic complications in patients suffering simultaneously from a fragility fracture of the lower limb and COVID-19 infection are, in general, comparable to fractured subjects that did not experience this viral infection during hospitalization.

From a laboratory point of view, our data show that the level of CRP is increased in the pre-operative period in COVID-19 + patients. This is compatible with a viral infection pre-existing at the fracture of the lower limb.

The lower levels of calcium observed in COVID-19 + are in agreement with literature reports showing that calcium balance is a primal hit of COVID-19, closely related with the virus-associated multiple organ injuries, the increase in inflammatory cytokines [17] and the poor prognosis [18,19]. The hypocalcemia correlates with the disease severity [20,21]; thus, the calcium levels may be useful as a laboratory marker of COVID-19 aggressiveness [22].

Of note, muscle damage markers, especially CPK and AST, display higher values in COVID-19 + patients. The important systemic inflammation in COVID-19 patients can impact nearly every organ system, including the musculoskeletal system [11]. One-quarter to one-half of COVID-19 symptomatic patients suffer from myalgia and generalized weakness [9,10]: this evidence may suggest direct muscle damage caused by SARS-CoV-2 [23]. Indeed, specific receptors used by the virus to enter the cell have been detected both in the nervous system and in the muscular tissue; this finding may thus explain the particular tropism of the virus for the muscle. In this case, the receptors that have been identified to be responsible are the angiotensin-converting enzyme 2 ACE2 and the serine protease TMPRSS2 [5].

From a clinical point of view, the hospitalization length and the rehabilitation program were not significantly modified between the two groups of patients. However, COVID-19 + patients presented significantly more long-term sequelae, such as mental fog, dyspnea and fatigue. Thus, our data confirm previous studies reporting long-term disabling problems after SARS-CoV-2 infection [16].

These concomitant pathlogies can negatively impact the recovery after a fracture in elderly patients, who usually suffer from other comorbidities.

Indeed, elderlies are more subjected to complications after a fracture. For example, the traumatic event may cause thrombotic and consequent cardiovascular problems. In addition, the prolonged immobilization and hospitalization frequently lead to the development of pressure sores, pneumonia and urinary tract infections in these fragile patients. In this context, the concomitant SARS-CoV-2 infection may further worsen the clinical outcomes, especially in the long-term. Our data did not show a significant worse outcome in these patients compared to subjects without SARS-CoV-2 infection; however, a larger sample size and a longer follow-up may highlight clinical differences between the two groups. In

fact, the main limitation of this study is the insufficient sample size, which could prevent detecting significant difference or bias.

In conclusion, lower limb fractures in the elderly population represent life-threatening injuries, and surgery is required to provide effective pain relief, enable early mobilization and reduce morbidity and mortality. Despite the presence of SARS-CoV-2 infection, the multifactorial worsening of the long-term outcome of these patients should be carefully managed. In addition, the myalgias and fatigue consequent to the muscular damage caused by the virus may negatively impact the rehabilitation. Moreover, the COVID-19 related lung damage worsens the respiratory function, affecting the patient's general performance. In this complex contest, particular attention should be paid to treatment of the long-term COVID-19 sequelae in order to improve the clinical outcomes of these fragile patients.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm11010168/s1, Table S1. Clinical data of the patients.

Author Contributions: Conceptualization, A.C., M.D.M.L. and L.M.; methodology, L.d.G. and E.D.V.; software, A.C. and M.D.M.L.; validation, G.B., G.M.P. and L.M.; formal analysis, A.C., M.D.M.L. and R.G.; investigation, A.C. and M.D.M.L.; resources, L.d.G. and E.D.V.; data curation, A.C. and M.D.M.L.; writing—original draft preparation, A.C. and M.D.M.L.; writing—review and editing, G.B., G.M.P. and L.M.; visualization, L.d.G., G.B. and G.M.P.; supervision, L.M.; project administration, A.C. and L.d.G.; funding acquisition, A.C. and L.d.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Italian Ministry of Health, "Ricerca Corrente".

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the San Raffaele Hospital Ethical Review Board protocol "Costituzione di una banca di materiale biologico da paziente (biobanca) per lo studio di patologie che interessano l'apparato muscolo-scheletrico e il sistema nervoso centrale" of 19 February 2020, amended on 13 October 2020.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement: https://osf.io/jmt7z/?view_only=9318c6fa68d64f4a9931acf713213aff Last accessed date: 13 September 2021.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Chen, Y.; Klein, S.L.; Garibaldi, B.T.; Li, H.; Wu, C.; Osevala, N.M.; Li, T.; Margolick, J.B.; Pawelec, G.; Leng, S.X. Aging in COVID-19: Vulnerability, immunity and intervention. *Ageing Res. Rev.* **2021**, *65*, 101205. [CrossRef]
2. Hall, A.J.; Clement, N.D.; Farrow, L.; MacLullich, A.M.J.; Dall, G.F.; Scott, C.E.H.; Jenkins, P.J.; White, T.O.; Duckworth, A.D.; IMPACT-Scot Study Group. IMPACT-Scot report on COVID-19 and hip fractures. *Bone Jt. J.* **2020**, *102-B*, 1219–1228. [CrossRef]
3. Clement, N.D.; Hall, A.J.; Makaram, N.S.; Robinson, P.G.; Patton, R.F.L.; Moran, M.; Macpherson, G.J.; Duckworth, A.D.; Jenkins, P.J. IMPACT-Restart: The influence of COVID-19 on postoperative mortality and risk factors associated with SARS-CoV-2 infection after orthopaedic and trauma surgery. *Bone Jt. J.* **2020**, *102-B*, 1774–1781. [CrossRef]
4. Clement, N.D.; Ng, N.; Simpson, C.J.; Patton, R.F.L.; Hall, A.J.; Simpson, A.; Duckworth, A.D. The prevalence, mortality, and associated risk factors for developing COVID-19 in hip fracture patients: A systematic review and meta-analysis. *Bone Jt. Res.* **2020**, *9*, 873–883. [CrossRef]
5. Disser, N.P.; De Micheli, A.J.; Schonk, M.M.; Konnaris, M.A.; Piacentini, A.N.; Edon, D.L.; Toresdahl, B.G.; Rodeo, S.A.; Casey, E.K.; Mendias, C.L. Musculoskeletal Consequences of COVID-19. *J. Bone Jt. Surg. Am. Vol.* **2020**, *102*, 1197–1204. [CrossRef]
6. Wu, J.; Li, J.; Zhu, G.; Zhang, Y.; Bi, Z.; Yu, Y.; Huang, B.; Fu, S.; Tan, Y.; Sun, J.; et al. Clinical Features of Maintenance Hemodialysis Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Clin. J. Am. Soc. Nephrol. CJASN* **2020**, *15*, 1139–1145. [CrossRef]
7. Sun, P.; Qie, S.; Liu, Z.; Ren, J.; Li, K.; Xi, J. Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: A single arm meta-analysis. *J. Med. Virol.* **2020**, *92*, 612–617. [CrossRef] [PubMed]
8. Zhu, J.; Ji, P.; Pang, J.; Zhong, Z.; Li, H.; He, C.; Zhang, J.; Zhao, C. Clinical characteristics of 3062 COVID-19 patients: A meta-analysis. *J. Med. Virol.* **2020**, *92*, 1902–1914. [CrossRef] [PubMed]

9. Nasiri, M.J.; Haddadi, S.; Tahvildari, A.; Farsi, Y.; Arbabi, M.; Hasanzadeh, S.; Jamshidi, P.; Murthi, M.; Mirsaeidi, M. COVID-19 Clinical Characteristics, and Sex-Specific Risk of Mortality: Systematic Review and Meta-Analysis. *Front. Med.* **2020**, *7*, 459. [CrossRef] [PubMed]
10. Xu, P.; Sun, G.D.; Li, Z.Z. Clinical characteristics of two human-to-human transmitted coronaviruses: Corona Virus Disease 2019 vs. Middle East Respiratory Syndrome Coronavirus. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 5797–5809. [CrossRef]
11. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020**, *395*, 497–506. [CrossRef]
12. Guan, W.J.; Ni, Z.Y.; Hu, Y.; Liang, W.H.; Ou, C.Q.; He, J.X.; Liu, L.; Shan, H.; Lei, C.L.; Hui, D.S.C.; et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N. Engl. J. Med.* **2020**, *382*, 1708–1720. [CrossRef]
13. Mao, L.; Jin, H.; Wang, M.; Hu, Y.; Chen, S.; He, Q.; Chang, J.; Hong, C.; Zhou, Y.; Wang, D.; et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* **2020**, *77*, 683–690. [CrossRef] [PubMed]
14. Ali, A.M.; Kunugi, H. Skeletal Muscle Damage in COVID-19: A Call for Action. *Medicina* **2021**, *57*, 372. [CrossRef]
15. Gawronska, K.; Lorkowski, J. Falls as One of the Atypical Presentations of COVID-19 in Older Population. *Geriatr. Orthop. Surg. Rehabil.* **2021**, *12*, 2151459321996619. [CrossRef]
16. Michele Davide Maria Lombardo, A.F.; Peretti, G.M.; Mangiavini, L.; Battezzati, A.; Bertoli, S.; Boneschi, F.M.; Zuccotti, G.V. Long-Term Coronavirus Disease 2019 Complications in Inpatients and Outpatients: A One-Year Follow-up Cohort Study. *Open Forum Infect. Dis.* **2021**, *8*, ofab384. [CrossRef]
17. Zhou, X.; Chen, D.; Wang, L.; Zhao, Y.; Wei, L.; Chen, Z.; Yang, B. Low serum calcium: A new, important indicator of COVID-19 patients from mild/moderate to severe/critical. *Biosci. Rep.* **2020**, *40*, BSR20202690. [CrossRef] [PubMed]
18. Lippi, G.; South, A.M.; Henry, B.M. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). *Ann. Clin. Biochem.* **2020**, *57*, 262–265. [CrossRef] [PubMed]
19. Cappellini, F.; Brivio, R.; Casati, M.; Cavallero, A.; Contro, E.; Brambilla, P. Low levels of total and ionized calcium in blood of COVID-19 patients. *Clin. Chem. Lab. Med.* **2020**, *58*, e171–e173. [CrossRef]
20. di Filippo, L.; Formenti, A.M.; Doga, M.; Pedone, E.; Rovere-Querini, P.; Giustina, A. Radiological Thoracic Vertebral Fractures are Highly Prevalent in COVID-19 and Predict Disease Outcomes. *J. Clin. Endocrinol. Metab.* **2021**, *106*, e602–e614. [CrossRef]
21. di Filippo, L.; Formenti, A.M.; Rovere-Querini, P.; Carlucci, M.; Conte, C.; Ciceri, F.; Zangrillo, A.; Giustina, A. Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19. *Endocrine* **2020**, *68*, 475–478. [CrossRef] [PubMed]
22. di Filippo, L.; Doga, M.; Frara, S.; Giustina, A. Hypocalcemia in COVID-19: Prevalence, clinical significance and therapeutic implications. *Rev. Endocr. Metab. Disord.* **2021**, 1–10. [CrossRef] [PubMed]
23. Li, L.Q.; Huang, T.; Wang, Y.Q.; Wang, Z.P.; Liang, Y.; Huang, T.B.; Zhang, H.Y.; Sun, W.M.; Wang, Y.P. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J. Med. Virol.* **2020**, *92*, 577–583. [CrossRef] [PubMed]

Journal of
Clinical Medicine

MDPI

Article

The Effects of Wearing a Medical Mask on the Masticatory and Neck Muscle Activity in Healthy Young Women

Michał Ginszt [1,*], Grzegorz Zieliński [2], Jacek Szkutnik [3], Marcin Wójcicki [3], Michał Baszczowski [2], Monika Litko-Rola [3], Ingrid Rózyło-Kalinowska [4] and Piotr Majcher [1]

[1] Department of Rehabilitation and Physiotherapy, Medical University of Lublin, 20-093 Lublin, Poland; zaklad.rehabilitacji@umlub.pl
[2] Department of Sports Medicine, Medical University of Lublin, 20-093 Lublin, Poland; grzegorz.zielinski@umlub.pl (G.Z.); michal.baszczowski@umlub.pl (M.B.)
[3] Independent Unit of Functional Masticatory Disorder, Medical University of Lublin, 20-093 Lublin, Poland; zakladzaburzen@umlub.pl (J.S.); marcin.wojcicki@umlub.pl (M.W.); monika.litko@umlub.pl (M.L.-R.)
[4] Department of Dental and Maxillofacial Radiodiagnostics, Medical University of Lublin, 20-093 Lublin, Poland; rozylo.kalinowska@umlub.pl
* Correspondence: michal.ginszt@umlub.pl

Abstract: The objective of this study was to analyze the influence of wearing a medical mask on masticatory and neck muscle activity in healthy young women. We recruited 66 healthy women aged from 18 to 30 years (mean 23.6 ± 2.3 years). The temporalis anterior (TA), the superficial part of the masseter muscle (MM), the anterior bellies of the digastric muscle (DA), and the middle part of the sternocleidomastoid muscle (SCM) potentials were recorded at rest and during functional activity using an eight-channel device for surface electromyography—BioEMG III^{TM}. There was a statistically significant decrease in mean TA activity during medical mask measurement compared to no mask examination at rest (2.16 μV vs. 2.58 μV; $p = 0.05$; ES = 0.2). Significant decreases in resting RMS values were also observed during the medical mask phase in comparison to no mask examination concerning the left MM (1.75 μV vs. 2.17 μV; $p = 0.01$; ES = 0.3), and mean bioelectrical activity of the MM (1.81 μV vs. 2.15 μV; $p = 0.02$; ES = 0.2). The differences between the two conditions did not reach the assumed significance level ($p > 0.05$) in terms of other indices. Wearing a medical mask has a small effect on decreasing the resting potentials of the temporalis anterior and masseter muscles without changing the parameters of activity and asymmetry within the stomatognathic system.

Keywords: COVID-19; SARS-CoV-2; surface electromyography; masticatory muscles; medical mask

Citation: Ginszt, M.; Zieliński, G.; Szkutnik, J.; Wójcicki, M.; Baszczowski, M.; Litko-Rola, M.; Rózyło-Kalinowska, I.; Majcher, P. The Effects of Wearing a Medical Mask on the Masticatory and Neck Muscle Activity in Healthy Young Women. *J. Clin. Med.* **2022**, *11*, 303 . https://doi.org/10.3390/jcm11020303

Academic Editors: Riccardo Giorgino, Filippo Migliorini and Bruno Chrcanovic

Received: 29 November 2021
Accepted: 6 January 2022
Published: 7 January 2022

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded RNA virus that can be transmitted from human to human through respiratory secretions, causing various clinical symptoms leading to coronavirus disease 2019 (COVID-19) [1]. It is known that COVID-19 can be transmissible from presymptomatic, paucisymptomatic, and asymptomatic people. Thus, reducing disease spread requires preventive management of COVID-19, which includes vaccination, quarantine, personal protective equipment (e.g., face masks, gloves), hand hygiene, and physical distancing [2,3]. The preponderance of scientific evidence suggests that face mask wearing lowers transmissibility per contact by reducing transmission of infected respiratory particles [4]. Moreover, the face mask may reduce the inoculum of the virus to which a mask-wearer is exposed, which will result in milder disease [5,6]. Therefore, face masks are recommended to reduce the chances that the wearer spreads SARS-CoV-2, especially in healthcare settings [7,8]. On the other hand, many countries introduced the requirement to wear face masks in public spaces, making it commonplace in 2021 [9].

According to many health and epidemiological benefits of wearing face masks during the COVID-19 pandemic, several studies have examined the possible negative consequences of applying face masks [10]. Scientific reports presented evidenced changes in respiratory physiology of mask wearers with a significant correlation of O_2 drop [11,12], CO_2 rise [13–15], heart rate increase [16], headache [17–21], and temperature and moisture rise under the face masks [16]. The above-mentioned physiological changes may contribute to headaches during the prolonged mask wearing with a shift towards hypoxia and hypercapnia [10]. On the other hand, several mechanical factors such as the irritation of cervical nerves and associated structures in the neck and head area caused by the face mask straps pressuring the nerve strands also contribute to headaches [18]. As the face mask covers the face and the masticatory muscles, especially the masseter muscle, it is also possible that the activity of these muscle groups will be affected. Moreover, a face mask with a loop around each ear can put pressure on the temporalis muscle. However, the direct influence of the face mask on the activity of the above-mentioned muscles has not yet been scientifically investigated.

Extended wearing of face masks by the general population may lead to relevant effects and consequences in various medical areas. Thus, a comprehensive risk-benefit analysis is critical regarding the potential long-term impacts of face masks. So far, there is a lack of studies analyzing the effect of using the face mask on the muscles within the stomatognathic system. Therefore, in our study of a homogeneous cohort, we tested the effects of wearing medical masks on resting and functional masticatory and neck muscle activity. To the best of our knowledge, this is the first study analyzing changes in electromyographic activity and asymmetry of masticatory and cervical spine muscles during medical mask wearing. We hypothesize that wearing a medical mask significantly influence the activity of the masticatory and neck muscles.

2. Materials and Methods

2.1. Study Population

The presented study was carried out between May 2021 and September 2021 at the Department of Functional Masticatory Disorders, Medical University of Lublin, Poland. The measurements were carried out according to the Helsinki Declaration's recommendations and with the Bioethics Committee's consent of the Medical University of Lublin (KE-0254/81/2021). All participants were informed about the aim of the study and have given written permission for the research.

We recruited 66 healthy women aged from 18 to 30 years (mean 23.6 $\pm$ 2.3 years) basing on following exclusion criteria: the occurrence of headache and cervical spine pain within the month preceding the examination; the occurrence of orofacial pain within the month prior to the test; head and neck injuries within the last six months before the study; previous head and neck surgical treatment within the last six months before the examination; pregnancy; craniofacial trauma; class II and III of the bite according to Angle's classification; open bite; lack of four support zones in dental arches; lack of more than four teeth within both dental arches; carious or damaged dental tissues; any periodontal pathology; any pathology or asymmetry in craniofacial structures; any form of temporomandibular disorders (TMDs) according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD); condition during orthodontic treatment; possession of dental prostheses (regardless of type); Botox therapy; neurological disorders. Moreover, participants unable to wear a medical mask due to an underlying medical condition were not eligible. The clinical RDC/TMD examination was performed by the same experienced dentist specializing in dental prosthetics (author M.L-R.). Next, the ultrasound scanning was performed using M-Turbo ultrasound machine equipped with the 15–16 MHz linear transducer, with scan depth up to 6 cm (SonoSite Inc, Bothell, WA, USA) by experienced dentists specializing in medical radiology (author M.W.). The ultrasound examination was preformed to assess the temporomandibular joint structures and confirm the RDC/TMD examination results.

2.2. Study Protocol

The study consisted of two phases, with sEMG measurements of all four masticatory activities of each phase. Participants completed each of the four masticatory activities when they wore no mask and a certified disposable three-layer medical mask (Type II 50PSC, 000-994, Abeba GmbH, St. Ingbert, Germany) with 5 min of rest between measurements. There was a random selection of the initial phase. The medical mask always covered the subject's nose and mouth, as presented in Figure 1. The position of the mask was the same for all subjects, and it did not cause any discomfort for the participants.

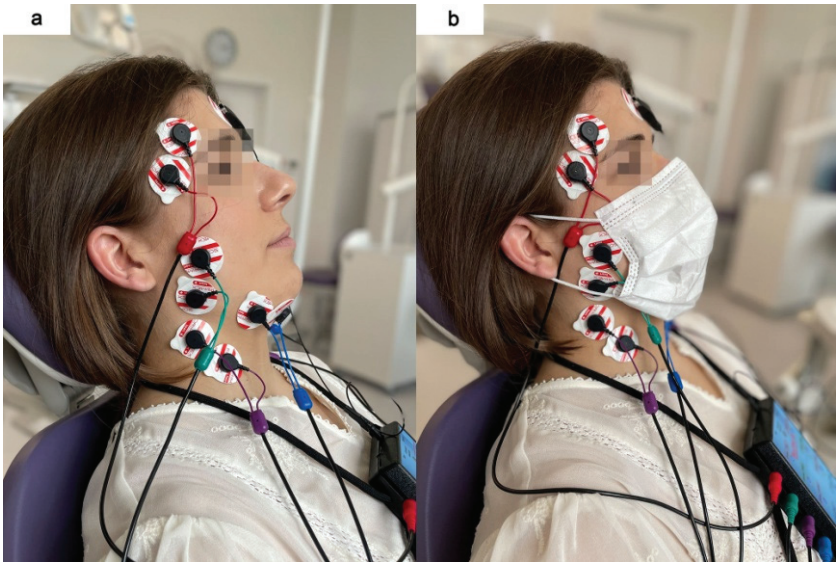


Figure 1. Electromyographic examination during two conditions: without (**a**) and with medical mask (**b**).

The muscle activity was recorded using an eight-channel device for surface electromyography—BioEMG III^{TM} (BioResearch Associates, Inc., Milwaukee, WI, USA). Electromyographic signals were obtained from eight channels. Masticatory and neck muscle activity was measured during four activities: during resting mandibular position (ten seconds), during clenching in intercuspal position (three times for three seconds each, with two seconds of rest between), during clenching on dental cotton rolls between teeth (three times for three seconds each, with two seconds of rest between) and during active maximum mouth opening (three times for three seconds each, with two seconds of rest between). The average of the three measurements of each variable was used for analysis.

2.3. Electromyographic Examination

The sEMG examinations were conducted between 8 and 12 a.m. to minimize the influence of daily fluctuations of muscle activity. The electromyographic measurements were carried out in the same dental chair in a sitting position (the body perpendicular to the ground, the head resting on the chair's headrest, and the lower limbs upright and arranged parallel). The height of the headrest was adjusted individually to set the head, neck, and torso of the subjects in a straight line.

Before placing the surface electrodes, the skin was cleaned with 90% ethanol solution to reduce skin impedance. Next, surface electrodes (Ag/AgCl with a diameter of 30 mm and a conductive surface of 16 mm (SORIMEX, Toruń, Poland) were placed bilaterally following the course of the muscle fibers of the temporalis anterior (TA), the superficial

part of the masseter muscle (MM), the anterior bellies of the digastric muscle (DA), and the middle part of the sternocleidomastoid muscle (SCM) according to the SENIAM (Surface EMG for Non-Invasive Assessment of Muscles) guidelines [22]. Placing surface electrodes was performed by the same physiotherapist (author G.Z.). The reference electrode was placed on the forehead, in the center of the frontal bone. The arrangement of the electrodes symmetrically on the skin covering the examined muscles on both sides was preceded by palpation of the muscles during mandibular and head/neck movements. The electrodes on the superficial masseter muscle were located along the line from the mandible angle to the inferior border of the zygomatic bone. The electrodes on the anterior part of the temporal muscle were arranged along a perpendicular line from the superior border of the zygomatic bone to a cranial bone (in the projection of the sphenoid bone). The electrodes on the anterior bellies of the digastric muscle were placed approximately 1 cm medial to the base of the mandible. The electrodes on the sternocleidomastoid muscle were placed in the middle part of the muscle belly. The edges of the surface electrodes were in contact to maintain a constant spacing between the electrodes, as presented in Figure 1 [22].

2.4. sEMG Signal Processing and Normalization

Microvolt signals were amplified with minimal noise to 5000 times their original levels. The noise was reduced by 40 dB using the Noise Buster digital filtering in the BioPAK Measurement System, which automatically removes 99% of any remaining 50/60 Hz noise. The automatic processing of the electromyographic signal based on root mean square (RMS) calculations in the BioPAK program allowed us to obtain the average bioelectric values, which were then used for the sEMG analysis (Figure 2). Moreover, all the electromyographic signals were confirmed visually before each RMS processing.

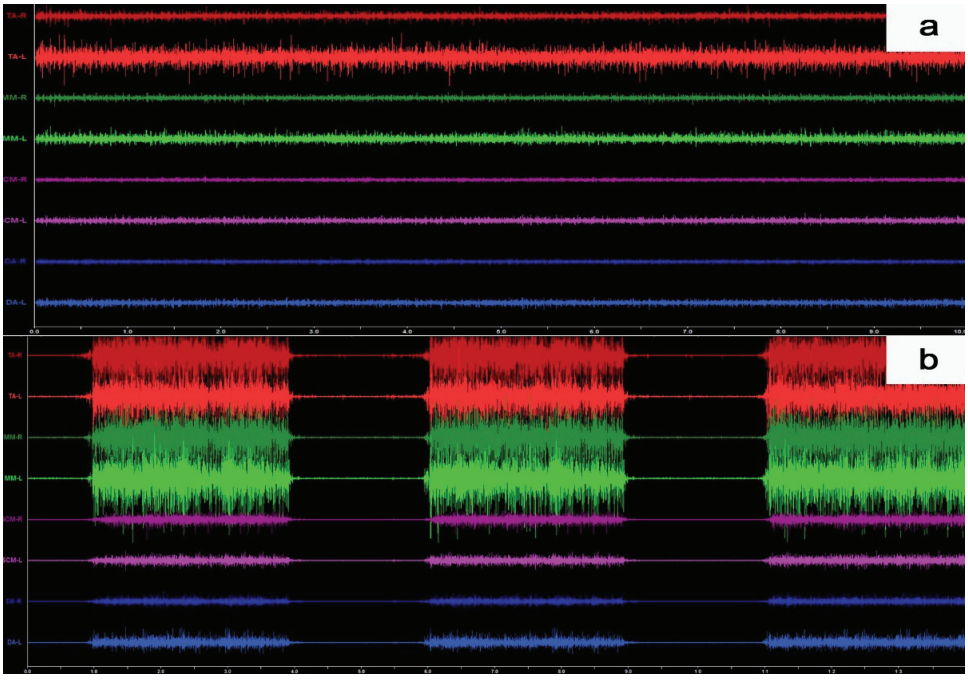


Figure 2. Example of the surface electromyography traces during resting activity (**a**) and maximum voluntary clenching in the intercuspal position (**b**).

The following asymmetry (AsI) and activity (AcI) calculations were used for the normalization of the mean bioelectric activity from the average temporalis anterior, masseter, digastric, and sternocleidomastoid muscles RMS potentials, according to Naeije et al. [23] and Ferrairo et al. [24]. The AsI varies between +100 and −100, with an AsI of +100 describing only right muscle activity, −100 meaning only left muscle activity, and 0 meaning equal left and right muscle activity. The AcI varies between +100 and −100. The negative (−) values indicate the predominance of the temporalis anterior and positive (+) values suggest a masseter muscle advantage [25].

$$\text{Temporalis anterior asymmetry index } (AsI_{TA}) = (TA_{right} - TA_{left}) / (TA_{right} + TA_{left}) \times 100 \quad (1)$$

$$\text{Masseter muscle asymmetry index } (AsI_{MM}) = (MM_{right} - MM_{left}) / (MM_{right} + MM_{left}) \times 100 \quad (2)$$

$$\text{Digastric muscle asymmetry index } (AsI_{DA}) = (DA_{right} - DA_{left}) / (DA_{right} + DA_{left}) \times 100 \quad (3)$$

$$\text{Sternocleidomastoid muscle asymmetry index } (AsI_{SCM}) = (SCM_{right} - SCM_{left}) / (SCM_{right} + SCM_{left}) \times 100 \quad (4)$$

$$\text{Activity index right-sided } (AcI_{R}) = (MM_{right} - TA_{right}) / (MM_{right} + TA_{right}) \times 100 \quad (5)$$

$$\text{Activity index left-sided } (AcI_{L}) = (MM_{left} - TA_{left}) / (MM_{left} + TA_{left}) \times 100 \quad (6)$$

$$\text{Activity index both-sided } (AcI_{Total}) = (MM_{right} + MM_{left} - TA_{right} - TA_{left}) / (MM_{right} + MM_{left} + TA_{right} + TA_{left}) \times 100 \quad (7)$$

2.5. Statistical Analysis

The checklist developed by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative was used to assess the methodological quality of the presented study [26]. The repeatability of the sEMG protocol was proved by duplicate sEMG measurements on 10 participants. The two independent sEMG measurements were separated by 5 min rest between all masticatory activities. There were no significant differences ($p > 0.05$) between repeated sEMG records in all analyzed variables (resting mandibular position, maximum voluntary clenching, maximum voluntary clenching on cotton rolls between teeth, maximum mouth opening).

Statistical analysis was carried out using Statistica 13.3 analytics software (TIBCO Software Inc., Palo Alto, CA, USA). First, the normality of the distribution of variables was verified using the Shapiro–Wilk test and the Kolmogorov–Smirnov test (with Lillierfors correction). The Student *t*-test (T) or Mann–Whitney U test (Z) was used depending on the distribution. The significance level was set at 0.05. Effect sizes were determined for Z-test using the Cohen d method and interpreted as small (0.2), medium (0.5), and large (0.8) effect sizes [27,28].

3. Results

3.1. RMS sEMG Activity

There was a statistically significant decrease in mean temporalis anterior activity during medical mask measurement compared to no mask examination at rest (2.16 μV vs. 2.58 μV; $p = 0.05$; ES = 0.2). Significant decreases in resting RMS values were also observed during the medical mask phase in comparison to no mask examination concerning the left masseter muscle (1.75 μV vs. 2.17 μV; $p = 0.01$; ES = 0.3), and mean bioelectrical activity of the masseter muscles (1.81 μV vs. 2.15 μV; $p = 0.02$; ES = 0.2). In terms of other indices, the differences between the two conditions did not reach the assumed significance level ($p > 0.05$) (Table 1).

Table 1. The comparison of the root mean square (RMS) sEMG activity between no mask and medical mask measurements.

Masticatory Activity	RMS sEMG Activity	No Mask Measurement $n = 66$		Medical Mask Measurement $n = 66$		Test	Test Result	p
		M (μV)	SD (μV)	M (μV)	SD (μV)			
Resting activity	TA_R	2.45	1.71	2.04	1.28	Z	1.84	0.07
	TA_L	2.71	1.65	2.29	1.48	Z	1.73	0.08
	TA_{Mean}	2.58	1.48	2.16	1.20	Z	2.00	0.05 * ES = 0.2
	MM_R	2.14	1.16	1.87	1.12	Z	1.77	0.08
	MM_L	2.17	1.06	1.75	0.96	Z	2.75	0.01 * ES = 0.3
	MM_{Mean}	2.15	1,.03	1.81	0.96	Z	2.35	0.02 * ES = 0.2
	DA_R	1.87	0.83	1.89	1.07	Z	0.67	0.50
	DA_L	1.75	0.76	1.78	0.98	Z	0.30	0.77
	DA_{Mean}	1.81	0.77	1.83	0.99	Z	0.53	0.59
	SCM_R	1.23	0.42	1.13	0.31	Z	1.36	0.17
	SCM_L	1.34	0.46	1.24	0.41	Z	1.20	0.23
	SCM_{Mean}	1.28	0.39	1.18	0.30	Z	1.27	0.20
Maximum voluntary clenching in intercuspal position	TA_R	136.46	80.88	121.40	72.88	Z	1.12	0.26
	TA_L	134.46	67.33	121.91	68.21	T	1.06	0.29
	TA_{Mean}	135.46	70.05	121.66	68.37	Z	1.12	0.26
	MM_R	143.25	86.80	120.77	83.17	Z	1.65	0.10
	MM_L	139.44	85.97	120.28	79.74	Z	1.29	0.20
	MM_{Mean}	141.35	83.30	120.53	78.99	Z	1.47	0.14
	DA_R	22.13	14.76	19.38	13.49	Z	1.12	0.26
	DA_L	23.50	19.94	18.99	15.29	Z	1.47	0.14
	DA_{Mean}	22.82	15.61	19.18	13.47	Z	1.52	0.13
	SCM_R	10.58	7.57	8.60	6.04	Z	1.60	0.11
	SCM_L	10.18	8.14	8.52	6.39	Z	1.19	0.23
	SCM_{Mean}	10.38	7.51	8.56	5.77	Z	1.40	0.16
Maximum voluntary clenching with dental cotton rolls between teeth	TA_R	124.13	68.93	125.27	68.69	Z	−0.28	0.78
	TA_L	122.34	60.90	123.45	64.05	Z	−0.02	0.98
	TA_{Mean}	123.24	62.23	124.36	64.27	Z	−0.08	0.93
	MM_R	160.33	79.99	154.80	75.60	Z	0.35	0.73
	MM_L	159.39	82.41	151.83	76.70	Z	0.38	0.70
	MM_{Mean}	159.86	77.94	153.31	71.58	Z	0.44	0.66
	DA_R	23.07	11.62	22.00	10.59	Z	0.52	0.61
	DA_L	23.77	14.10	21.54	13.80	Z	1.37	0.17
	DA_{Mean}	23.42	11.80	21.77	11.23	Z	0.98	0.33
	SCM_R	12.62	7.27	13.30	14.42	Z	0.92	0.36
	SCM_L	11.73	6.98	11.45	8.27	Z	0.73	0.46
	SCM_{Mean}	12.17	6.77	12.38	9.50	Z	0.71	0.48
Maximum active mouth opening	TA_R	7.00	3.70	9.49	19.02	Z	−0.27	0.79
	TA_L	6.77	3.96	13.00	48.71	Z	0.03	0.98
	TA_{Mean}	6.89	3.42	11.25	25.97	Z	−0.39	0.70
	MM_R	9.07	8.57	10.71	11.52	Z	−0.46	0.64
	MM_L	8.29	5.82	9.45	7.19	Z	−0.29	0.77
	MM_{Mean}	8.68	6.93	10.08	8.93	Z	−0.45	0.65
	DA_R	74.54	36.91	80.72	39.30	Z	−0.93	0.35
	DA_L	75.98	38.99	83.95	40.66	Z	−1.21	0.23
	DA_{Mean}	75.26	36.10	82.33	37.67	Z	−1.04	0.30
	SCM_R	8.90	6.53	10.67	10.92	Z	−0.47	0.64
	SCM_L	8.72	7.29	10.36	10.80	Z	−0.73	0.47
	SCM_{Mean}	8.81	6.63	10.52	10.44	Z	−0.57	0.57

TA—temporalis anterior; MM—masseter muscle; DA—digastric muscle; SCM—sternocleidomastoid muscle; R—right side; L—left side; M—mean; SD—standard deviation; ES—effect size; * Significant difference.

3.2. Asymmetry and Activity Indices

Statistical analysis showed that there were no significant differences ($p > 0.05$) between no mask and medical mask measurements in terms of all asymmetry and activity indices during resting and functional masticatory activities (Tables 2 and 3).

Table 2. The comparison of the mean asymmetry index (AsI) between no mask and medical mask measurements.

Masticatory Activity	Asymmetry Index	No Mask Measurement $n = 66$		Medical Mask Measurement $n = 66$		Z	p
		M	SD	M	SD		
Resting activity	AsI_{TA}	−4.59	25.32	−3.96	24.09	0.06	0.95
	AsI_{MM}	−1.12	16.96	2.33	18.66	−0.91	0.36
	AsI_{DA}	2.50	10.06	2.00	11.42	0.42	0.68
	AsI_{SCM}	−4.19	14.05	−3.96	13.67	−0.08	0.93
Maximum voluntary clenching in intercuspal position	AsI_{TA}	−0.43	19.97	0.19	19.47	−0.25	0.80
	AsI_{MM}	2.92	17.51	1.51	19.13	0.47	0.64
	AsI_{DA}	0.07	22.82	2.17	20.24	−0.48	0.63
	AsI_{SCM}	3.08	18.49	0.93	20.33	0.50	0.62
Maximum voluntary clenching with dental cotton rolls between teeth	AsI_{TA}	−0.57	14.67	0.55	14.43	−0.50	0.62
	AsI_{MM}	0.68	14.36	1.60	15.60	−0.28	0.78
	AsI_{DA}	−0.69	18.04	2.85	17.45	−1.31	0.19
	AsI_{SCM}	4.15	17.72	3.80	20.90	0.36	0.72
Maximum active mouth opening	AsI_{TA}	2.06	18.39	2.73	25.14	0.17	0.86
	AsI_{MM}	0.64	19.31	2.23	16.54	−0.33	0.74
	AsI_{DA}	−0.62	11.96	−1.51	13.59	0.36	0.72
	AsI_{SCM}	1.93	16.59	0.98	17.79	0.52	0.61

AsI_{TA}—Asymmetry index for temporalis anterior; AsI_{MM}—Asymmetry index for masseter muscle; AsI_{DA}—Asymmetry index for digastric muscle; AsI_{SCM}—Asymmetry index for sternocleidomastoid muscle.

Table 3. The comparison of the mean activity index (AcI) between no mask and medical mask measurements.

Masticatory Activity	Activity Index	No Mask Measurement $n = 66$		Medical Mask Measurement $n = 66$		Test	Test Result	p
		M	SD	M	SD			
Resting activity	AcI_R	−4.05	30.86	2.79	28.50	T	−0.24	0.81
	AcI_L	−7.71	31.63	8.42	32.30	T	0.13	0.90
	AcI_{Total}	−6.94	29.36	−6.34	29.31	T	−0.12	0.91
Maximum voluntary clenching in intercuspal position	AcI_R	0.08	25.20	−4.78	25.86	Z	1.19	0.23
	AcI_L	−3.05	26.29	−6.21	24.45	Z	0.91	0.36
	AcI_{Total}	−1.66	22.21	−5.47	21.97	Z	1.04	0.30
Maximum voluntary clenching with dental cotton rolls between teeth	AcI_R	13.11	21.64	11.87	20.77	T	0.34	0.74
	AcI_L	12.05	18.18	10.88	18.30	Z	0.37	0.71
	AcI_{Total}	12.72	16.99	11.57	16.63	Z	0.35	0.72

AcI_R—Activity index right-sided; AcI_L—Activity index left-sided; AcI_{Total}—Activity index both-sided.

4. Discussion

By the end of June 2020, nearly 90% of the global population lived in countries that had laws requiring mask use in public locations, and community mask use was recommended by almost all major public health organizations [4]. Many medical data support the legitimacy of using face masks in public places. The epidemiological model suggests that face masks wearing is most effective at reducing the spread of the virus when compliance is high [29]. Moreover, medical mask wearing lowers transmissibility

per contact by reducing transmission of infected respiratory particles [4]. On the other hand, prolonged face mask use may lead to relevant effects and consequences in respiratory physiology [10]. Thus, a comprehensive risk-benefit analysis is critical regarding the potential long-term impacts of face masks.

As the face mask covers the face and the masticatory muscles, especially the masseter muscle, it is also possible that the masseter muscle activity will be changed while wearing the mask. In addition, a mask with a loop around each ear can put pressure on the temporalis muscle. So far, there is a lack of studies analyzing the impact of using the face mask on the muscles within the stomatognathic system. Therefore, we tested the effects of wearing medical masks on resting and functional masticatory and neck muscle activity. Our hypothesis that wearing a medical mask significantly influences the activity of the masticatory and neck muscles seems to be confirmed in the presented research. The obtained results indicate that wearing medical masks is related to changes in masticatory muscle activity during resting mandibular position. Surprisingly, wearing a medical mask while electromyographic measurement yielded a significant decrease in resting temporalis anterior and masseter muscle activity compared to the no mask procedure. However, we cannot clearly explain the significant differences observed between the two conditions within the resting masticatory activity. Changes in the electromyographic patterns of masticatory muscles may be associated with the irritation of cervical nerves and associated structures in the neck and head area caused by the face mask straps and mask loops around the ears [18]. Pietropaoli et al. showed a moderate correlation between electric values and palpation-induced pain of both temporalis anterior and masseter muscles [30]. Previous studies indicated the associations between myofascial pain and increased masticatory muscle activity during rest [31,32], which is clearly in opposition to our findings. Moreover, the position of the mask did not cause any discomfort for the participants in our study. Hence the hypothesis that mask-induced discomfort affects muscle activity does not fit the model of pain-induced muscle activity. On the other hand, there were no significant differences in the asymmetry and activity indices between no mask and medical mask measurements. More specifically, changes within temporalis anterior and masseter muscle bioelectric activity did not affect the electromyographic balance among masticatory muscle activity at rest. Reorganization of muscle activity within masticatory muscles may occur in the case of a pain response or abnormal electromyographic activity in chronic TMDs [30,33]. In our study, the temporalis anterior and masseter muscles have similar properties of activity and symmetry regardless of the mask. However, in our opinion, the changes in RMS electromyographic parameters while wearing the medical mask deserve attention and further research to define and validate this mechanism.

As a final comment, we emphasize that there were only significant differences within RMS muscle activity between no mask and medical mask measurements, without changes within the activity and asymmetry parameters. Therefore, we suggest further studies investigating the long-term effect of wearing a medical mask on the activity of the masticatory muscles.

Our study has several limitations that could be addressed in future work. Firstly, a generalization of our findings is limited by the short-term follow-up used in the presented research. Therefore, a more extended observation period is recommended to determine the long-term effects of wearing medical masks. Secondly, the study sample consists of a homogeneous group. We decided to include only healthy young women in the presented research to minimize the influence of gender, age, and health factors on the study results. Thus, future studies should include the male population with an expanded age range. Moreover, it would be worth assessing whether the medical mask influences the symptoms of TMDs and episodes of bruxism in patients with masticatory dysfunctions. Thirdly, the diagnostics criteria for TMDs were replaced by DC/TMDs in 2014. However, in our study, the previous version was used. There is no validated Polish version of the DC/TMDs so far. Therefore, the RDC/TMDs protocol was used.

5. Conclusions

Wearing a face mask has a small effect on decreasing the resting potentials of the temporalis anterior and masseter muscles without changing the parameters of activity and asymmetry within the stomatognathic system.

Author Contributions: Conceptualization, M.G.; methodology, M.G., G.Z., J.S., I.R.-K. and P.M.; formal analysis, M.G. and G.Z.; investigation, M.G., G.Z., J.S., M.W., M.B. and M.L.-R.; resources, M.G., G.Z., I.R.-K. and P.M.; data curation, M.G. and G.Z.; writing—original draft preparation, M.G. and G.Z.; supervision, M.G., I.R.-K. and P.M.; project administration, M.G. and P.M.; funding acquisition, P.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the Declaration of Helsinki guidelines and approved by the Bioethics Committee of the Medical University of Lublin (KE-0254/81/2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: We acknowledge support from the Medical University of Lublin for Open Access Publishing.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Chan, J.F.-W.; Yuan, S.; Kok, K.-H.; To, K.K.-W.; Chu, H.; Yang, J.; Xing, F.; Liu, J.; Yip, C.C.-Y.; Poon, R.W.-S.; et al. A Familial Cluster of Pneumonia Associated with the 2019 Novel Coronavirus Indicating Person-to-Person Transmission: A Study of a Family Cluster. *Lancet* **2020**, *395*, 514–523. [CrossRef]
2. Rahmani, A.M.; Mirmahaleh, S.Y.H. Coronavirus Disease (COVID-19) Prevention and Treatment Methods and Effective Parameters: A Systematic Literature Review. *Sustain. Cities Soc.* **2021**, *64*, 102568. [CrossRef]
3. Fowlkes, A.; Gaglani, M.; Groover, K.; Thiese, M.S.; Tyner, H.; Ellingson, K.; Cohorts, H.-R. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers before and during B.1.617.2 (Delta) Variant Predominance—Eight U.S. Locations, December 2020–August 2021. *MMWR Morb. Mortal. Wkly. Rep.* **2021**, *70*, 1167–1169. [CrossRef] [PubMed]
4. Howard, J.; Huang, A.; Li, Z.; Tufekci, Z.; Zdimal, V.; van der Westhuizen, H.-M.; von Delft, A.; Price, A.; Fridman, L.; Tang, L.-H.; et al. An Evidence Review of Face Masks against COVID-19. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2014564118. [CrossRef]
5. Chan, J.F.-W.; Yuan, S.; Zhang, A.J.; Poon, V.K.-M.; Chan, C.C.-S.; Lee, A.C.-Y.; Fan, Z.; Li, C.; Liang, R.; Cao, J.; et al. Surgical Mask Partition Reduces the Risk of Noncontact Transmission in a Golden Syrian Hamster Model for Coronavirus Disease 2019 (COVID-19). *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2020**, *71*, 2139–2149. [CrossRef]
6. Gandhi, M.; Beyrer, C.; Goosby, E. Masks Do More Than Protect Others During COVID-19: Reducing the Inoculum of SARS-CoV-2 to Protect the Wearer. *J. Gen. Intern. Med.* **2020**, *35*, 3063–3066. [CrossRef] [PubMed]
7. Coclite, D.; Napoletano, A.; Gianola, S.; Del Monaco, A.; D'Angelo, D.; Fauci, A.; Iacorossi, L.; Latina, R.; Torre, G.L.; Mastroianni, C.M.; et al. Face Mask Use in the Community for Reducing the Spread of COVID-19: A Systematic Review. *Front. Med.* **2020**, *7*, 594269. [CrossRef] [PubMed]
8. Bartoszko, J.J.; Farooqi, M.A.M.; Alhazzani, W.; Loeb, M. Medical Masks vs N95 Respirators for Preventing COVID-19 in Healthcare Workers: A Systematic Review and Meta-Analysis of Randomized Trials. *Influenza Other Respir. Viruses* **2020**, *14*, 365–373. [CrossRef] [PubMed]
9. Royo-Bordonada, M.A.; García-López, F.J.; Cortés, F.; Zaragoza, G.A. Face Masks in the General Healthy Population. Scientific and Ethical Issues. *Gac. Sanit.* **2021**, *35*, 580–584. [CrossRef]
10. Kisielinski, K.; Giboni, P.; Prescher, A.; Klosterhalfen, B.; Graessel, D.; Funken, S.; Kempski, O.; Hirsch, O. Is a Mask That Covers the Mouth and Nose Free from Undesirable Side Effects in Everyday Use and Free of Potential Hazards? *Int. J. Environ. Res. Public Health* **2021**, *18*, 4344. [CrossRef] [PubMed]
11. Pifarré, F.; Zabala, D.D.; Grazioli, G.; i Maura, I.D.Y. COVID-19 and Mask in Sports. *Apunt. Sports Med.* **2020**, *55*, 143–145. [CrossRef]
12. Beder, A.; Büyükkoçak, U.; Sabuncuoğlu, H.; Keskil, Z.A.; Keskil, S. Preliminary Report on Surgical Mask Induced Deoxygenation during Major Surgery. *Neurocir. Astur. Spain* **2008**, *19*, 121–126. [CrossRef]
13. Rebmann, T.; Carrico, R.; Wang, J. Physiologic and Other Effects and Compliance with Long-Term Respirator Use among Medical Intensive Care Unit Nurses. *Am. J. Infect. Control* **2013**, *41*, 1218–1223. [CrossRef]

14. Roberge, R.J.; Coca, A.; Williams, W.J.; Powell, J.B.; Palmiero, A.J. Physiological Impact of the N95 Filtering Facepiece Respirator on Healthcare Workers. *Respir. Care* **2010**, *55*, 569–577.
15. Georgi, C.; Haase-Fielitz, A.; Meretz, D.; Gäsert, L.; Butter, C. The Impact of Commonly-Worn Face Masks on Physiological Parameters and on Discomfort During Standard Work-Related Physical Effort. *Dtsch. Arzteblatt Int.* **2020**, *117*, 674–675. [CrossRef]
16. Li, Y.; Tokura, H.; Guo, Y.P.; Wong, A.S.W.; Wong, T.; Chung, J.; Newton, E. Effects of Wearing N95 and Surgical Facemasks on Heart Rate, Thermal Stress and Subjective Sensations. *Int. Arch. Occup. Environ. Health* **2005**, *78*, 501–509. [CrossRef]
17. Rosner, E. Adverse Effects of Prolonged Mask Use among Healthcare Professionals during COVID-19. *J. Infect. Epidemiol.* **2020**. [CrossRef]
18. Ong, J.J.Y.; Bharatendu, C.; Goh, Y.; Tang, J.Z.Y.; Sooi, K.W.X.; Tan, Y.L.; Tan, B.Y.Q.; Teoh, H.-L.; Ong, S.T.; Allen, D.M.; et al. Headaches Associated With Personal Protective Equipment—A Cross-Sectional Study Among Frontline Healthcare Workers During COVID-19. *Headache* **2020**, *60*, 864–877. [CrossRef]
19. Jacobs, J.L.; Ohde, S.; Takahashi, O.; Tokuda, Y.; Omata, F.; Fukui, T. Use of Surgical Face Masks to Reduce the Incidence of the Common Cold among Health Care Workers in Japan: A Randomized Controlled Trial. *Am. J. Infect. Control.* **2009**, *37*, 417–419. [CrossRef]
20. Ramirez-Moreno, J.M.; Ceberino, D.; Gonzalez Plata, A.; Rebollo, B.; Macias Sedas, P.; Hariramani, R.; Roa, A.M.; Constantino, A.B. Mask-Associated "de Novo" Headache in Healthcare Workers during the COVID-19 Pandemic. *Occup. Environ. Med.* **2021**, *78*, 548–554. [CrossRef]
21. Bharatendu, C.; Ong, J.J.Y.; Goh, Y.; Tan, B.Y.Q.; Chan, A.C.Y.; Tang, J.Z.Y.; Leow, A.S.; Chin, A.; Sooi, K.W.X.; Tan, Y.L.; et al. Powered Air Purifying Respirator (PAPR) Restores the N95 Face Mask Induced Cerebral Hemodynamic Alterations among Healthcare Workers during COVID-19 Outbreak. *J. Neurol. Sci.* **2020**, *417*, 117078. [CrossRef]
22. Hermens, H.J.; Freriks, B.; Disselhorst-Klug, C.; Rau, G. Development of Recommendations for SEMG Sensors and Sensor Placement Procedures. *J. Electromyogr. Kinesiol.* **2000**, *10*, 361–374. [CrossRef]
23. Naeije, M.; McCarroll, R.S.; Weijs, W.A. Electromyographic Activity of the Human Masticatory Muscles during Submaximal Clenching in the Inter-Cuspal Position. *J. Oral Rehabil.* **1989**, *16*, 63–70. [CrossRef] [PubMed]
24. Ferrario, V.F.; Sforza, C.; Miani, A.; D'Addona, A.; Barbini, E. Electromyographic Activity of Human Masticatory Muscles in Normal Young People. Statistical Evaluation of Reference Values for Clinical Applications. *J. Oral Rehabil.* **1993**, *20*, 271–280. [CrossRef]
25. Ginszt, M.; Zieliński, G. Novel Functional Indices of Masticatory Muscle Activity. *J. Clin. Med.* **2021**, *10*, 1440. [CrossRef]
26. von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gøtzsche, P.C.; Vandenbroucke, J.P.; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. *J. Clin. Epidemiol.* **2008**, *61*, 344–349. [CrossRef]
27. Fritz, C.O.; Morris, P.E.; Richler, J.J. Effect Size Estimates: Current Use, Calculations, and Interpretation. *J. Exp. Psychol. Gen.* **2012**, *141*, 2–18. [CrossRef] [PubMed]
28. Lakens, D. Calculating and Reporting Effect Sizes to Facilitate Cumulative Science: A Practical Primer for *t*-Tests and ANOVAs. *Front. Psychol.* **2013**, *4*, 863. [CrossRef]
29. Tian, L.; Li, X.; Qi, F.; Tang, Q.-Y.; Tang, V.; Liu, J.; Li, Z.; Cheng, X.; Li, X.; Shi, Y.; et al. Calibrated Intervention and Containment of the COVID-19 Pandemic. *arXiv* **2020**, arXiv:2003.07353.
30. Pietropaoli, D.; Ortu, E.; Giannoni, M.; Cattaneo, R.; Mummolo, A.; Monaco, A. Alterations in Surface Electromyography Are Associated with Subjective Masticatory Muscle Pain. *Pain Res. Manag.* **2019**, *2019*, 6256179. [CrossRef] [PubMed]
31. Manfredini, D.; Cocilovo, F.; Favero, L.; Ferronato, G.; Tonello, S.; Guarda-Nardini, L. Surface Electromyography of Jaw Muscles and Kinesiographic Recordings: Diagnostic Accuracy for Myofascial Pain. *J. Oral Rehabil.* **2011**, *38*, 791–799. [CrossRef] [PubMed]
32. Zieliński, G.; Byś, A.; Szkutnik, J.; Majcher, P.; Ginszt, M. Electromyographic Patterns of Masticatory Muscles in Relation to Active Myofascial Trigger Points of the Upper Trapezius and Temporomandibular Disorders. *Diagnostics* **2021**, *11*, 580. [CrossRef] [PubMed]
33. Mapelli, A.; Zanandréa Machado, B.C.; Giglio, L.D.; Sforza, C.; De Felício, C.M. Reorganization of Muscle Activity in Patients with Chronic Temporomandibular Disorders. *Arch. Oral Biol.* **2016**, *72*, 164–171. [CrossRef] [PubMed]

Journal of
Clinical Medicine

MDPI

Article

Mortality Predictive Value of the C_2HEST Score in Elderly Subjects with COVID-19—A Subanalysis of the COLOS Study

Piotr Rola [1,*,†], Adrian Doroszko [2,†], Małgorzata Trocha [3], Katarzyna Giniewicz [4], Krzysztof Kujawa [4], Marek Skarupski [5], Jakub Gawryś [2], Tomasz Matys [2], Ewa Szahidewicz-Krupska [2], Damian Gajecki [2], Barbara Adamik [6], Krzysztof Kaliszewski [7], Katarzyna Kilis-Pstrusinska [8], Krzysztof Letachowicz [9], Agnieszka Matera-Witkiewicz [10], Michał Pomorski [11], Marcin Protasiewicz [12], Konrad Majchrzak [9], Janusz Sokołowski [13], Ewa Anita Jankowska [14,15,‡] and Katarzyna Madziarska [9,‡]

[1] Department of Cardiology, Provincial Specialized Hospital, Iwaszkiewicza 5 Str., 59-220 Legnica, Poland
[2] Clinical Department of Internal Medicine, Hypertension and Clinical Oncology, Wroclaw Medical University, Borowska 213, 50-556 Wroclaw, Poland; adrian.doroszko@umw.edu.pl (A.D.); jakub.gawrys@umw.edu.pl (J.G.); tomasz.matys@umw.edu.pl (T.M.); ewa.szahidewicz-krupska@umw.edu.pl (E.S.-K.); damian.gajecki@umw.edu.pl (D.G.)
[3] Department of Pharmacology, Wroclaw Medical University, Mikulicz-Radecki Street 2, 50-345 Wroclaw, Poland; malgorzata.trocha@umw.edu.pl
[4] Statistical Analysis Centre, Wroclaw Medical University, K. Marcinkowski Street 2-6, 50-368 Wroclaw, Poland; katarzyna.giniewicz@umw.edu.pl (K.G.); krzysztof.kujawa@umw.edu.pl (K.K.)
[5] Faculty of Pure and Applied Mathematics, Wroclaw University of Science and Technology, Wybrzeże Wyspiańskiego Street 27, 50-370 Wroclaw, Poland; marek.skarupski@pwr.edu.pl
[6] Clinical Department of Anaesthesiology and Intensive Therapy, Wroclaw Medical University, Borowska Street 213, 50-556 Wroclaw, Poland; barbara.adamik@umw.edu.pl
[7] Department of General, Minimally Invasive and Endocrine Surgery, Wroclaw Medical University, Borowska Street 213, 50-556 Wroclaw, Poland; krzysztof.kaliszewski@umw.edu.pl
[8] Clinical Department of Paediatric Nephrology, Wroclaw Medical University, Borowska Street 213, 50-556 Wroclaw, Poland; katarzyna.kilis-pstrusinska@umw.edu.pl
[9] Clinical Department of Nephrology and Transplantation Medicine, Wroclaw Medical University, Borowska Street 213, 50-556 Wroclaw, Poland; krzysztof.lechtanowicz@umw.edu.pl (K.L.); konrad.majchrzak@gmail.com (K.M.); katarzyna.madziarska@umw.edu.pl (K.M.)
[10] Screening of Biological Activity Assays and Collection of Biological Material Laboratory, Wroclaw Medical University Biobank, Wroclaw Medical University, Borowska Street 211A, 50-556 Wroclaw, Poland; agnieszka.matera-witkiewicz@umw.edu
[11] Clinical Department of Gynecology and Obstetrics, Wroclaw Medical University, Borowska Street 213, 50-556 Wroclaw, Poland; michal.pomorski@umw.edu.pl
[12] Clinical Department and Clinic of Cardiology, Wroclaw Medical University, Borowska Street 213, 50-556 Wroclaw, Poland; marcin.protasiewicz@umw.edu.pl
[13] Department of Emergency Medicine, Wroclaw Medical University, Borowska Street 213, 50-556 Wroclaw, Poland; janusz.sokolowski@umw.edu.pl
[14] Institute of Heart Diseases, Wroclaw Medical University, Borowska Street 213, 50-556 Wroclaw, Poland; ewa.jankowska@umw.edu.pl
[15] Institute of Heart Diseases, University Hospital in Wroclaw, Borowska Street 213, 50-556 Wroclaw, Poland
* Correspondence: piotr.rola@gmail.com; Tel.: +48-76-7211-443
† These authors contributed equally to this work.
‡ These authors contributed equally to this work.

Citation: Rola, P.; Doroszko, A.; Trocha, M.; Giniewicz, K.; Kujawa, K.; Skarupski, M.; Gawryś, J.; Matys, T.; Szahidewicz-Krupska, E.; Gajecki, D.; et al. Mortality Predictive Value of the C_2HEST Score in Elderly Subjects with COVID-19—A Subanalysis of the COLOS Study. *J. Clin. Med.* **2022**, *11*, 992. https://doi.org/10.3390/jcm11040992

Academic Editor: Roland Bingisser

Received: 17 December 2021
Accepted: 10 February 2022
Published: 14 February 2022

Abstract: Senility has been identified among the strongest risk predictors for unfavorable COVID-19-outcome. However, even in the elderly population, the clinical course of infection in individual patients remains unpredictable. Hence, there is an urgent need for developing a simple tool predicting adverse COVID-19-outcomes. We assumed that the C2HEST-score could predict unfavorable clinical outcomes in the elderly subjects with COVID-19-subjects. Methods: We retrospectively analyzed 1047 medical records of patients at age > 65 years, hospitalized at the medical university center due to COVID-19. Subsequently, patients were divided into three categories depending on their C2HEST-score result. Results: We noticed significant differences in the *in-hospital* and 3-*month* and 6-*month* mortality-which was the highest in *high-risk*-C2HEST-stratum reaching 35.7%, 54.4%, and 65.9%, respectively. The *medium-risk*-stratum mortalities reached 24.1% 43.4%, and 57.6% and for

low-risk-stratum 14.4%, 25.8%, and 39.2% respectively. In the C2HEST-score model, a change from the *low* to the *medium* category increased the probability of death intensity approximately two-times. Subsequently, transfer from the *low-risk* to the *high-risk*-stratum raised all-cause-death-intensity 2.7-times. Analysis of the secondary outcomes revealed that the C2HEST-score has predictive value for acute kidney injury, acute heart failure, and cardiogenic shock. Conclusions: C2HEST-score analysis on admission to the hospital may predict the mortality, acute kidney injury, and acute heart failure in elderly subjects with COVID-19.

Keywords: COVID-19; elderly; C_2HEST-score; SARS-CoV2; mortality; risk-score; outcomes; senility; predictive value

1. Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) causing Coronavirus disease 2019 (COVID-19), firstly described as a local cluster of pneumonia in Wuhan, Hubei, China [1], despite initial widespread use of preventive measures for personal protection [2], has spread worldwide and evolved into a global pandemic, affecting healthcare systems all over the world.

Although many risk factors for the disease progression have been identified, clinical course of infection in individual patients remains still uncertain. Senility, male gender, obesity, previously diagnosed cardiovascular disorders, diabetes, and chronic pulmonary diseases, are known as mortality risk factors [3]. Furthermore, various laboratory abnormalities, including immunological, hematological, and biochemical changes along with specific computed tomography findings are postulated [4] to predict the severity of the disease and its outcome. Among the mentioned risk factors, particularly advanced age (over 65 years) is the most prominent risk factor for an unfavorable outcome [5]. Despite the high risk attributed to this subpopulation, clinical experience indicates that the course of COVID-19 is heterogeneous, ranging from asymptomatic to fatal cases. Facing limited resources during COVID-19 pandemic, adequate selection of patients with the highest probability of unfavorable outcome is crucial for designing individualized diagnostic and therapeutic strategy.

The C2HEST-score is a simple, well-established [6] scoring system, allowing stratification of the risk of developing atrial fibrillation (AF). Recently Liang et al. [7] demonstrated that the C_2HEST score could also predict adverse outcomes including death and hospitalization among patients with heart failure. Considering that the individual components of the C2HEST score are identical to those risk factors attributed to worse clinical course of COVID-19, we assumed that the C2HEST could predict an unfavorable clinical outcome in COVID-19. In this study, based on the data from the COLOS registry, we performed a subanalysis of the elderly population with COVID-19 assessing the diagnostic performance of the C2HEST score for fatal and non-fatal clinical outcomes.

2. Materials and Methods

2.1. Study Design and Population

In the present study, we described the clinical characteristics of 1047 elderly (over 65 years) Patients with COVID-19 hospitalized at the University Hospital in Wroclaw between February 2020 and June 2021. All medical records were collected as part of the COronavirus in Lower Silesia—the COLOS registry. Subjects chosen to this study were retrospectively selected out of all (2184) COLOS study participants. The sole inclusion criterion to this subanalysis was age of >65 years in the Patients with COVID-19. There were no other additional exclusion criteria regarding, patient's clinical characteristic, comorbidities nor severity of COVID-19. Figure 1 presents study protocol.

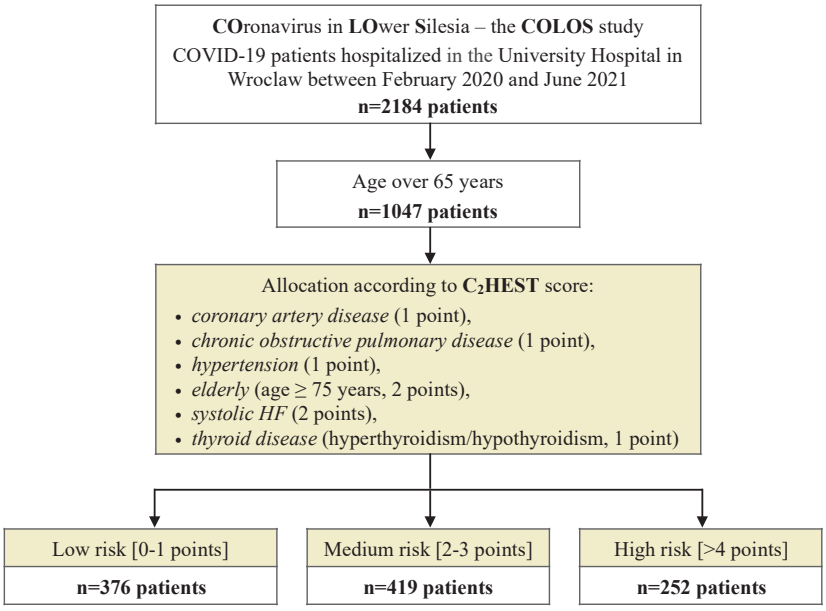


Figure 1. A flow chart presenting the study protocol.

The initial diagnosis of SARS-CoV2 was confirmed with reverse transcription–polymerase chain reaction (RT-PCR) for viral RNA of nasopharyngeal swab specimens.

The COLOS study protocol has been approved by the Institutional Review Board and Ethics Committee at the Wroclaw Medical University, Wroclaw, Poland (No: KB-444/2021). The written informed consent to participate was waived due to the retrospective, observational nature of the study. The Bioethics Committee approved the publication of fully anonymized data.

2.2. Clinical Follow-Up and Outcomes

All the study participants underwent clinical assessment during the hospital admission. Past medical history, home medication, and vital parameters were assessed in every subject. Similarly, initial blood samples were drawn in every patient at the time of hospital admission, during the course of hospitalization and at discharge time. Clinical follow-up included the whole in-hospital period and ended on the day of discharge or death. In the post-discharge period, data regarding death were collected up to 6 months.

The primary outcomes included: in-hospital mortality, 3-month and 6-month all-cause mortality, the end of hospitalization other than due to death (discharge home/emergency transfer to another center–deterioration/transfer for rehabilitation). Secondary outcomes included: the need for mechanical ventilation support, myocardial injury, shock, acute heart failure, pulmonary embolism, stroke, acute kidney injury, acute liver dysfunction, pneumonia, sepsis, systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), and bleedings.

2.3. Study Groups

Patients were assigned to one out of the three arms depending on their C2HEST score result calculated on the hospital admission. Six variables, including coronary artery disease (1 point), chronic obstructive pulmonary disease (1 point), hypertension (1 point), elderly (age $\geq$ 75 years, 2 points), systolic HF (2 points), and thyroid disease (1 point) were taken into account and defined basing on the patient past medical history and interview at the

time of admission. Moreover, in subsequent sensitivity analyses, the "thyroid disease" was replaced more precisely with "hyperthyroidism" and "hypothyroidism".

After calculating the C2HEST score, patients were allocated to the separate groups depending on the result:

- the *low-risk* of 0 to 1 point,
- the *medium-risk* of 2 to 3 points,
- the *high-risk* of $\geq$ 4 points.

2.4. Statistical Analysis

Descriptive data are presented as numbers and percentages for categorical variables, and as mean with standard deviation range (minimum–maximum) and number of non-missing values for numerical variables. As omnibus test chi-square test was used for categorical variables with more than 5 expected cases in each group, whereas Fisher exact test was used for cases with fewer cell counts. Welch's ANOVA was performed for continuous variables due to unequal variances between risk-strata and sample size large enough for appropriateness of asymptotic results. Post-hoc analysis for continuous variables was performed using the Games–Howell test with Tukey correction. For categorical variables, post-hoc test was the same as the omnibus test, but performed in subgroups with Bonferroni correction.

In-hospital mortality and all-cause mortality data were available as right-censored data, thus time-dependent ROC analysis with Inverse Probability of Censoring Weighting (IPCW) estimation was performed for those variables. The C_2HEST score was assessed through the time dependent area under the curve (AUC). Log-rank test was used to confirm differences in survival curves between risk strata. Proportional hazard assumption was verified using Grambsch–Therneau test. A Cox proportional hazard model was used to analyze the hazard ratio (HR) for the C_2HEST score, its components, and risk strata.

For secondary outcomes, due to their dichotomic nature, a logistic regression model was fitted. Classical ROC analysis was performed, and AUC measure was used for assessing predictive capabilities. Odds ratio (OR) was reported as effect size for influence of the C_2HEST score, its components, and risk strata.

All statistical analyses were performed with R version 4.0.4 using packages time–ROC, pROC [8], survival [9], coin [10], and odds ratio [11]. A significance level of 0.05 was selected for all statistical analyses.

3. Results

3.1. Patients Baseline Characteristics

Baseline Patient Characteristics are summarized in the Table 1. The *medium-risk* group was the most numerous (419 subjects) and most of the patients in this group were female. Patients in the *high-risk* stratum were older, when compared to other groups. These patients had also the highest prevalence of comorbidities including hypertension, diabetes (DM), dyslipidemia, atrial fibrillation (AF), previous myocardial infract (MI) and percutaneous coronary intervention (PCI), valvular heart diseases, stroke, chronic obstructive pulmonary disease (COPD), heart failure (HF), chronic kidney diseases (CKD), and peripheral artery disease (PAD) history.

Due to the higher prevalence of cardiovascular disease in the *high-risk* stratum, we observed differences in the treatment applied before hospitalization. Subjects in this group more frequently received angiotensin-converting-enzyme inhibitors (ACEI), mineralocorticoid receptor antagonists (MRA), b-blockers, diuretics, statins, vitamin K antagonists (VKA), new oral anticoagulants (NOAC), acetylsalicylic acid, the P_2Y_{12} inhibitors, and insulin. On the other hand, patients in the *low-risk* group more often were given immunosuppressants other than oral corticosteroid. All the data regarding treatment applied before hospitalization is shown in Table 2.

Table 1. Baseline characteristics of the study cohort after C_2HEST risk stratification.

Variables, Units (N)	Low Risk (0–1) Mean ± SD Min–Max (N) or n/N(% of Risk Category)	Medium Risk (2–3) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	High Risk (>4) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	OMNIBUS *p* Value	*p*-Value (for Post-Hoc Analysis)
		demographics			
Age, years (1047)	69.0 ± 2.79 65–74 (376)	79.0 ± 8.11 65–100 (419)	80.3 ± 7.26 65–100 (252)	**<0.0001**	**<0.0001** [a,b] 0.082 [c]
Male gender (1047)	211/376 (56.11%)	172/419 (41.1%)	123/252 (48.8%)	**0.00012**	**<0.0001** [a] 0.2578 [b] 0.18001 [c]
BMI, kg/m^2 (207)	28.5 ± 4.59 20.05–40.4 (81)	28.57 ± 5.17 18.6–47.75 (66)	27.29 ± 5.39 16.41–45.82 (60)	0.30822	N/A
Cigarette smoking never/previous/current (1043)	348/376 (92.55%) 16/376 (4.26%) 12 376 (3.19%)	377/416 (90.63%) 25/416 (6.01%) 14/416 (3.37%)	203/251 (80.88%) 32/251 (12.75%) 16/251 (6.37%)	**<0.0001**	**1.0** [a] **0.00014** [b] **0.00412** [c]
		Co-morbidities			
Hypertension (1047)	194/376 (51.6%)	296/419 (70.64%)	228/252 (90.48%)	**<0.0001**	**<0.0001** [a,b,c]
DM (1045)	106/376 (28.2%)	130/418 (29.7%)	103/251 (41.0%)	**0.00091**	1.0 [a] **0.0018** [b] **0.00578** [c]
Dyslipidemia (506)	104/152 (68.42%)	149/196 (76.02%)	133/158 (84.18%)	**0.0049**	0.4353 [a] **0.0052** [b] **0.02339** [c]
AF/AFL (1047)	32/376 (8.51%)	97/419 (23.15%)	124/252 (49.2%)	**<0.0001**	**<0.0001** [a,b,c]
Previous coronary revascularization (1047)	5/376 (1.33%)	26/419 (6.21%)	97/252 (38.5%)	**<0.0001**	**0.0023** [a] **<0.0001** [b,c]
Previous MI (1047)	8/376 (2.13%)	39/419 (9.31%)	103/252 (40.9%)	**<0.0001**	**<0.00011** [a] **<0.0001** [b,c]
HF (1047)	0/376 (0%)	32/419 (7.64%)	180/252 (71.43%)	**<0.0001**	**<0.0001**[a,b,c]
Moderate or severe valvular heart disease or previous valve heart surgery (1047)	6/376 (1.6%)	23/419 (5.49%)	48/252 (19.05%)	**<0.0001**	**0.0188** [a] **<0.0001** [b,c]
PAD (1047)	16/376 (4.26%)	25/419 (5.97%)	38/252 (15.05%)	**<0.0001**	1.0 [a] **<0.0001** [b] **0.00047** [c]
Previous stroke/TIA (1047)	25/376 (6.65%)	53/419 (12.65%)	52/252 (20.63%)	**<0.0001**	**0.0196** [a] **<0.0001** [b] **0.0243** [c]
CKD (1047)	25/376 (6.65%)	56/(13.37%)	82/252 (32.54%)	**<0.0001**	**0.00789** [a] **<0.0001** [b,c]
Haemodialysis (1047)	4/376 (1.06%)	13/492 (3.1%)	11/252 (4.37%)	**0.0332**	0.2464 [a] 0.0507 [b] 1.0 [c]

Table 1. *Cont.*

Variables, Units (N)	Low Risk (0–1) Mean ± SD Min–Max (N) or n/N(% of Risk Category)	Medium Risk (2–3) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	High Risk (>4) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	OMNIBUS *p* Value	*p*-Value (for Post-Hoc Analysis)
Asthma (1047)	12/376 (3.19%)	16/419 (3.82%)	10/252 (3.97%)	0.847	N/A
COPD (1047)	4/376 (1.06%)	20/419 (4.77%)	38/252 (15.08%)	**<0.0001**	**0.0134** [a] **<0.0001** [b,c]
Thyroid disease, none/hypothyroidism/ hyperthyroidism, (1047)	363/376 (96.5%) 12/376 (3.19%) 1/376 (0.27%)	368/419 (87.8%) 44/419 (10.5%) 7/419 (1.67%)	189/252 (75.0%) 58/252 (23.02%) 5/252 (1.98%)	**<0.0001**	**<0.0001** [a,b] **0.000018** [c]

Continuous variables are presented as: mean ± SD, range (minimum–maximum) and number of non-missing values. Categorized variables are presented as: a number with a percentage. Information about the numbers with valid values is provided in the left column. Abbreviations: N—valid measurements, n—number of patients with parameter above cut-off point, SD—standard deviation, BMI—body mass index, DM—Diabetes mellitus, AF/AFL—Atrial fibrillation/flutter, MI—myocardial infarction, HF—Heart failure, PAD—Peripheral artery disease, TIA—transient ischemic attack, CKD—Chronic kidney disease, COPD—Chronic obstructive pulmonary disease, N/A—non-applicable, [a]—*low-risk* vs. *medium-risk*, [b]—*low-risk* vs. *high-risk*, [c]—*medium-risk* vs. *high-risk*; Bold text—statistically significant values.

Table 2. Baseline characteristics of the study cohort-treatment applied before hospitalization.

Variables, Units (N)	Low Risk (0–1) n/N (% of Risk Category)	Medium Risk (2–3) n/N (% of Risk Category)	High Risk (>4) n/N (% of Risk Category)	OMNIBUS *p*-Value	*p*-Value (for Post-Hoc Analysis)
Treatment applied before hospitalization					
ACEI (1047)	66/376 (17.55%)	96/419 (22.91%)	106/252 (42.06%)	**<0.0001**	0.2230 [a] **<0.0001** [b,c]
ARBs (1047)	31/376 (8.24%)	34/419 (8.11%)	29/252 (11.51%)	0.2721	N/A
MRAs (1047)	9/376 (2.39%)	26/419 (6.21%)	43/252 (17.06%)	**<0.0001**	**0.04377** [a] **<0.0001** [b,c]
Sacubitril/valsartan (1047)	1/376 (0.27%)	3/419 (0.72%)	1/252 (0.4%)	0.8502	N/A
β-blocker (1047)	93/376 (24.73%)	141/419 (33.65%)	143/252 (56.75%)	**<0.0001**	**0.02232** [a] **<0.0001** [b,c]
Digitalis glycoside (1047)	3/376 (0.8%)	5/419 (1.2%)	10/252 (3.97%)	**0.0129**	1.0 [a] **0.0259** [b] **0.0844** [c]
Calcium channel blocker (non-dihydropiridines) (1047)	6/376 (1.6%)	10/419 (2.39%)	13/252 (5.16%)	**0.0236**	1.0 [a] 0.0614 [b] 0.2718 [c]
Calcium channel blocker (dihydropiridines) (1047)	44/376 (11.7%)	69/419 (16.47%)	69/252 (27.38%)	**<0.0001**	**<0.0001** [a.b] **0.00467** [c]
α-adrenergic blocker (1047)	45/376 (11.9%)	34/419 (8.11%)	39/252 (14.2%)	**<0.0001**	0.2065 [a] **<0.0001**[b] **0.0030** [c]

Table 2. *Cont.*

Variables, Units (N)	Low Risk (0–1) n/N (% of Risk Category)	Medium Risk (2–3) n/N (% of Risk Category)	High Risk (>4) n/N (% of Risk Category)	OMNIBUS *p*-Value	*p*-Value (for Post-Hoc Analysis)
Thiazide or thiazide-like diuretic (1047)	30/376 (7.97%)	43/419 (10.26%)	32/252 (12.7%)	0.152	N/A
Loop diuretic (1047)	22/376 (5.85%)	50/419 (11.93%)	73/252 (28.97%)	**<0.0001**	**0.0127** [a] **<0.0001** [b,c]
Statin (1047)	59/376 (15.69%)	106/419 (25.3%)	113/252 (44.84%)	**<0.0001**	**0.0035** [a] **<0.0001** [b,c]
Acetylsalicylic acid (1047)	40/376 (10.64%)	79/419 (18.85%)	72/252 (28.57%)	**<0.0001**	**0.005** [a] **<0.0001** [b] **0.0143** [c]
The second antiplatelet drug-P_2Y_{12} inhibitor (1047)	3/376 (0.8%)	6/419 (1.43%)	20/252 (7.94%)	**<0.0001**	1.0 [a] **<0.0001** [b] **0.00017** [c]
LMWH (1047)	30/376 (8.0%)	35/419 (8.35%)	24/252 (9.52%)	0.7856	N/A
VKA (1047)	4/376 (1.06%)	13/419 (3.1%)	21/252 (8.33%)	**<0.0001**	0.2464 [a] **<0.0001**[b] **0.00149** [c]
NOAC (1047)	9/376 (2.39%)	33/419 (7.88%)	49/252 (19.44%)	**<0.0001**	**0.003** [a] **<0.0001**[b, c]
Insulin (1047)	30/376 (7.98%)	23/419 (5.49%)	32/252 (12.7%)	**0.0041**	0.6203 [a] 0.2123 [b] **0.0049** [c]
Metformin (1047)	56/376 (14.89%)	58/419 (13.84%)	44/252 (17.46%)	0.4437	N/A
SGLT2 inhibitor (1047)	3/376 (0.8%)	5/419 (1.19%)	9/252 (3.57%)	**0.0274**	1.0 [a] 0.0504 [b] 0.1487 [c]
Oral antidiabetics other than SGLT2 inhibitor and metformin (1047)	19/376 (5.05%)	33/419 (7.88)	24/252 (9.52%)	0.0874	N/A
Proton pump inhibitor (1047)	30/376 (8.0%)	61/419 (14.56%)	80/252 (31.75%)	**<0.0001**	**0.0154** [a] **<0.0001** [b,c]
Oral corticosteroid (1047)	18/376 (4.79%)	21/419 (5.01%)	4/252 (1.59)	0.068	N/A
Immunosuppression other than oral corticosteroid (1047)	11/376 (2.93%)	17/419 (4.06%)	1/252 (0.37%)	**0.0194**	1.0 [a] 0.146 [b] **0.0284** [c]

Categorized variables are presented as: a number with a percentage. Information about the numbers with valid values is provided in the left column. Abbreviations: N—valid measurements. n—number of patients with parameter above the cut-off point. ACEI—angiotensin-converting-enzyme inhibitors. ARBs—angiotensin receptor blockers. MRAs—mineralocorticoid receptor antagonists. LMWH—low molecular weight heparin. VKA—vitamin K antagonists. NOAC—novel oral anticoagulants. SGLT2 inhibitors—sodium glucose co-transporter-2 inhibitors. N/A—non-applicable. [a]—*low risk* vs. *medium risk*. [b]—*low risk* vs. *high risk*. [c]—*medium risk* vs. *high risk*. Bold text—statistically significant values.

The high-risk group had a significantly higher prevalence of dyspnea with rales, wheezing, pulmonary congestion, and peripheral edema on admission. No other significant differences in prevalence of other symptoms among the three C_2HEST risk strata were observed. Noteworthy, there were no differences regarding the Vulnerable Elderly Survey (VES-13) nor the Glasgow Coma Scale (GCS) on admission. All patient-reported symptoms, vital signs, and abnormalities measured during a physical examination at hospital admission are summarized in the Table 3.

Table 3. Patient-reported symptoms, vital signs, and abnormalities measured during physical examination at hospital admission in the studied cohort after C_2HEST risk stratification.

Variables, Units (N)	Low Risk (0–1) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	Medium Risk (2–3) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	High Risk (>4) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	OMNIBUS *p*-Value	*p*-Value (for Post-Hoc Analysis)
Patient-reported symptoms					
Cough (1047)	94/376 (25%)	105/419 (25.06%)	64/252 (25.4%)	0.9931	N/A
Dyspnoea (1047)	153/376 (40.69%)	172/419 (41.05)	135/252 (53.57%)	**0.0019**	1.0 [a] **0.0059** [b] **0.0064** [c]
Chest pain (1047)	18/376 (4.79%)	29/419 (6.92%)	24/252 (9.52%)	0.068	N/A
Hemoptysis (1047)	1/376 (0.27%)	2/419 (0.48%)	4/252 (1.59%)	0.15	N/A
Smell dysfunction (1047)	11/376 (2.93%)	10/419 (2.29%)	4/252 (1.59%)	0.56	N/A
Taste dysfunction (1047)	9/376 (2.39%)	9/419 (2.15%)	6/252 (2.38%)	0.968	N/A
Abdominal pain (1047)	25/376 (6.65%)	23/419 (5.49%)	16/252 (6.35%)	0.78	N/A
Diarrhoea (1047)	29/376 (7.71%)	29/419 (6.92%)	17/252 (6.75%)	0.872	N/A
Nausea and/or vomiting (1047)	18/376 (4.79%)	23/419 (5.49%)	13/252 (5.16%)	0.905	N/A
Measured vital signs					
Body temperature °C (522)	36.98 ± 0.87 35.0–40.0 (189)	36.89 ± 0.9 35.0–40.0 (203)	36.94 ± 0.89 35.2–40.0 (130)	0.572	N/A
Heart rate beats/minute (823)	86.64 ± 16.72 60–150 (280)	84.06 ± 16.52 50–160 (325)	84.75 ± 18.92 36–170 (218)	0.156	N/A
Respiratory rate breaths/minute (152)	18.25 ± 6.1 12–50 (52)	18.79 ± 5.71 12–45 (58)	19.52 ± 6.33 12–50 (42)	0.619	N/A
SBP mmHg (832)	134.92 ± 23.13 60–237 (283)	134.55 ± 25.87 50–270 (327)	134.0 ± 24.39 70–210 (222)	0.912	N/A
DBP mmHg (826)	78.23 ± 13.8 40–150 (282)	77.54 ± 13.68 40–157 (322)	75.54 ± 15.43 40–143 (222)	0.1197	N/A
SpO2 on room air, % (FiO_2 = 21%) (587)	90.5 ± 7.85 50–100 (194)	89.2 ± 9.74 50–100 (238)	90.02 ± 8.48 50–99 (155)	0.3383	N/A
Abnormalities detected during physical examination					
Cracles (1047)	56/376 (14.89%)	84/419 (20.05%)	58/252 (23.02%)	**0.029**	0.21 [a] **0.0391** [b] 1.0 [c]
Wheezing (1047)	35/376 (9.31%)	51/419 (12.17%)	61/252 (24.21%)	**<0.0001**	**0.071** [a] **<0.0001** [b] **0.00024** [c]

Table 3. *Cont.*

Variables, Units (N)	Low Risk (0–1) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	Medium Risk (2–3) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	High Risk (>4) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	OMNIBUS *p*-Value	*p*-Value (for Post-Hoc Analysis)
Pulmonary congestion (1047)	66/376 (17.55%)	90/419 (21.48%)	71/252 (28.17%)	**0.0066**	**0.5784** [a] 0.066 [b] 0.1831 [c]
Peripheral oedema (1047)	27/376 (7.18%)	48/419 (11.46%)	47/274 (18.65%)	**<0.0001**	**0.1581** [a] **<0.0001** [b] **0.04** [c]
VES-13, points mean ± SD min–max N = 75	4.24 ± 2.99 1–9 17	5.58 ± 3.3 1–12 36	6.54 ± 2.89 3–13 22	0.067	N/A
GCS, points mean ± SD min–max N = 402	14.57 ± 1.75 3–15 133	14.38 ± 1.81 3–15 160	14.18 ± 2.27 3–15 109	0.305	N/A

Continuous variables are presented as: mean ± SD, range (minimum–maximum) and number of non-missing values. Categorized variables are presented as: a number with a percentage. Information about the numbers with valid values is provided in the left column. Abbreviations: SD—standard deviation, OMNIBUS—analysis of variance, N—valid measurements, n—number of patients with parameter above cut-off point, SBP—Systolic blood pressure, DBP—Diastolic blood pressure; VES—Vulnerable Elders Survey, GCS—Glasgow Coma Scale, [a]—*low risk vs. medium risk*, [b]—*low risk vs. high risk*, [c]—*medium risk vs. high risk*.

3.2. Laboratory Assays

The initial laboratory parameters as well as those measured at the end of hospitalization are pooled in the Table 4. At admission, the *high-risk* group was characterized by the lowest level of haemoglobin and blood platelet count. At the same time, this cohort had a significantly higher potassium ion concertation with coexisting elevated INR. Similar observation was made for the renal function parameters. In the *high-risk* group, we observed higher serum level of urea and creatine coexisting with lower eGFR and albumin values. Subjects from the *high-risk* stratum had initially highest mean level of cardiac injury biomarkers (BNP, NT-proBNP and troponin). Compared with patients in the *low-risk* stratum, those in the high-risk had higher serum TSH level, but without significant differences regarding the peripheral thyroid hormones.

Table 4. Laboratory parameters measured during the hospitalization in the studied cohort.

Parameter	Time of Assessment	Units	Low Risk (0–1)	Medium Risk (2–3)	High Risk (>4)	OMNIBUS *p*-Value	*p*-Value for Post-Hoc Analysis
			Mean ± SD Min–Max (N) or n/N (% of Risk Category) (N)	Mean ± SD Min–Max (N) or n/N (% of Risk Category) (N)	Mean ± SD Min–Max (N) or n/N (% of Risk Category) (N)		
Complete Blood Count (CBC)							
Leucocytes (1020)	On admission	$10^3/\mu L$	8.8 ± 8.75 0.51–150.93 (364)	9.55 ± 12.26 0.51–215.97 (410)	9.37 ± 8.13 1.19–99.73 (246)	0.5472	N/A
(1020)	On discharge		9.17 ± 5.97 0.67–53.2 (364)	10.83 ± 17.42 0.44–314.44 (410)	10.2 ± 7.38 1.19–58.49 (246)	0.063	N/A
Lymphocytes (697)	On admission	$10^3/\mu L$	1.17 ± 1.65 0.06–24.82 (237)	1.16 ± 1.13 0.11–12.1 (278)	1.44 ± 5.78 0.09–78.58 (182)	0.8223	N/A
(677)	On discharge		1.57 ± 1.02 0.06–9.03 (237)	1.48 ± 1.97 0.05–26.71 (278)	1.55 ± 5.04 0.14–66.97 (182)	0.787	N/A
Haemoglobin (1020)	On admission	g/dL	13.11 ± 2.12 3.9–18.3 (364)	12.55 ± 2.33 4.5–18.9 (410)	11.93 ± 2.49 5.3–18.8 (246)	**<0.0001**	**0.001** [a] **<0.0001** [b] **0.005** [c]
(1020)	On discharge		12.5 ± 2.18 7.1–18.3 (364)	11.91 ± 2.33 4.5–18.9 (410)	11.56 ± 2.35 5.5–17.6 (246)	**<0.0001**	**0.0008** [a] **<0.0001** [b] 0.154 [c]
Platelets (1020)	On admission	$10^3/\mu L$	245.79 ± 110.26 0–671 (364)	228.85 ± 114.82 3–740 (410)	216.78 ± 94.0 8–578 (246)	**0.0023**	0.092 [a] **0.002** [b] 0.31 [c]
(1020)	On discharge		272.04 ± 119.9 6–720 (364)	241.95 ± 118.27 3–694 (410)	211.63 ± 97.47 4–592 (246)	**<0.0001**	**<0.001** [a] **<0.0001** [b] **0.001** [c]
Acid-base balance in the arterial blood gas							
PH (175)	On admission		7.43 ± 0.08 7.2–7.54 (43)	7.43 ± 0.07 7.1–7.54 (74)	7.41 ± 0.08 7.09–7.54 (58)	0.3236	N/A
PaO2 (175)	On admission	<60 mmHg respiratory insufficiency	27/43 (62.79%)	44/74 (59.46%)	34/58 (58.62%)	0.9073	N/A
		≥60 mmHg	16/43 (37.21%)	30/74 (40.54%)	24/58 (41.38%)		
PaCO2 (175)	On admission		76.3 ± 34.37 26.8–100 (43)	75.46 ± 48.27 28.6–100 (74)	72.91 ± 36.32 23.7–100 (58)	0.8821	N/A
		≥45 mmHg hypercapnia	7/43 (16.28%)	8/74 (10.81%)	10/58 (17.24%)	0.5265	N/A
		<45 mmHg	36/43 (83.72%)	66/74 (89.19%)	48/58 (82.76%)		
			36.57 ± 8.0 25.2–61.4 (43)	36.58 ± 8.02 23–67 (74)	38.9 ± 11.43 19.7–88.4 (58)	0.3899	N/A

Table 4. *Cont.*

Parameter	Time of Assessment	Units	Low Risk (0–1)	Medium Risk (2–3)	High Risk (>4)	OMNIBUS *p*-Value	*p*-Value for Post-Hoc Analysis
			Mean ± SD Min–Max (N) or n/N (% of Risk Category) (N)	Mean ± SD Min–Max (N) or n/N (% of Risk Category) (N)	Mean ± SD Min–Max (N) or n/N (% of Risk Category) (N)		
HCO3 standard (171)	On admission	mmol/L	25.05 ± 3.7 12.1–30.7 (42)	24.47 ± 4.17 14.3–39.5 (71)	24.43 ± 4.72 13.5–38.6 (58)	0.6908	N/A
BE (74)	On admission		1.64 ± 3.08 (–)3.3–7.1 (17)	2.15 ± 4.88 (–)12.5–15.7 (37)	2.41 ± 5.55 (–)7.4–14.6 (20)	0.8345	N/A
Lactates (157)	On admission		2.7 ± 2.28 0.7–12.8 (38)	2.03 ± 0.85 0.5–5.7 (66)	2.55 ± 1.91 0.6–12.0 (53)	0.0602	N/A
			Electrolytes. inflammatory and iron biomarkers				
Na (1015)	On admission	mmol/L	137.89 ± 5.16 106–159 (362)	137.81 ± 7.37 101–175 (407)	138.1 ± 6.98 108–174 (246)	0.8784	N/A
K (1018)	On admission	mmol/L	4.07 ± 0.66 2.0–7.5 (363)	4.12 ± 0.7 2.4–6.08 (409)	4.27 ± 0.8 2.53–8.7 (246)	**0.0066**	0.602 [a] **0.005** [b] 0.044 [c]
CRP (1015)	On admission	mg/L	93.03 ± 91.05 0.32–496.98 (361)	84.51 ± 88.21 0.29–538.55 (408)	76.19 ± 80.82 0.4–390.94 (246)	0.0574	N/A
Procalcitonin (748)	On admission	ng/mL	1.36 ± 6.32 0.01–61.28 (266)	2.02 ± 13.06 0.01–196.04 (289)	1.486.25 0.01–60.77 (193)	0.7464	N/A
IL-6 (330)	On admission	pg/mL	66.81 ± 155.27 2–1000 (141)	41.58 ± 53.49 2–398 (120)	62.78 ± 98.77 2–421 (69)	0.0751	N/A
D-dimer (804)	On admission	µg/L	4.56 ± 13.34 0.18–118.32 (298)	6.37 ± 16.17 0.2–127.24 (319)	5.77 ± 17.97 0.22–128.0 (187)	0.301	N/A
Prothrombin rate (958)	On admission	%	82.6 ± 15.73 37–128 (343)	79.43 ± 21.33 7–131 (382)	70.49 ± 26.47 2–124 (252)	**<0.0001**	**0.058** [a] **<0.0001** [b,c]
INR (958)	On admission	>1.5	12/344 (3.49%)	40/381 (10.5%)	55/233 (23.61%)	**<0.0001**	**0.0014** [a] **<0.0001** [b,c]
aPTT (927)	On admission	>60 s	3/331 (2.11%)	6/369 (1.63%)	10/227 (4.41%)	0.092	N/A
Urea (970)	On admission	mg/dL	57.13 ± 46.17 8–307 (345)	67.31 ± 49.77 12–353 (389)	77.66 ± 52.55 12–369 (236)	**<0.0001**	**0.012** [a] **<0.0001**[b] **0.04** [c]
Creatinine (1017)	On admission	mg/dL	1.3 ± 1.31 0.49–14.77 (361)	1.42 ± 1.15 0.48–9.56 (410)	1.75 ± 1.54 0.44–11.3 (246)	**0.0009**	**0.349** [a] **0.0006** [b] **0.012** [c]
(1017)	On discharge		1.16 ± 1.04 0.44–14.82 (361)	1.39 ± 1.2 0.43–9.09 (410)	1.59 ± 1.34 0.43–9.27 (246)	**<0.0001**	**0.01** [a] **<0.0001**[b] 0.134 [c]

Table 4. *Cont.*

Parameter	Time of Assessment	Units	Low Risk (0–1)	Medium Risk (2–3)	High Risk (>4)	OMNIBUS *p*-Value	*p*-Value for Post-Hoc Analysis
			Mean ± SD Min–Max (N) or n/N (% of Risk Category) (N)	Mean ± SD Min–Max (N) or n/N (% of Risk Category) (N)	Mean ± SD Min–Max (N) or n/N (% of Risk Category) (N)		
eGFR (1017)	On admission	ml/min/1.73 m^2	71.33 ± 27.92 3–170 (361)	6.29 ± 27.45 4–137 (410)	52.99 ± 28.95 5–180 (246)	**<0.0001**	**<0.0001** [a,b] **0.004** [c]
Total protein (334)	On admission	g/L	5.99 ± 0.8 3.8–7.7 (100)	5.87 ± 0.89 3.6–8.2 (123)	5.73 ± 0.9 3.3–8.2 (111)	0.0909	N/A
Albumin (363)	On admission	g/L	3.16 ± 0.54 1.7–4.4 (116)	3.09 ± 0.55 1.1–4.4 (130)	2.95 ± 0.62 0.7–4.9 (117)	**0.0191**	0.528 [a] **0.014** [b] 0.151 [c]
AST (740)	On admission	IU/L	70.12 ± 177.91 5–2405 (257)	69.44 ± 281.44 7–4776 (290)	90.01 ± 339.29 8–3866 (193)	0.7435	N/A
ALT (821)	On admission	IU/L	55.67 ± 113.23 4–1411 (285)	49.33 ± 206.01 4–3700 (329)	54.0 ± 149.9 5–1361 (207)	0.8911	N/A
Bilirubin (736)	On admission	U/L	0.91 ± 1.34 0.3–15.1 (257)	0.83 ± 0.74 0.2–9.2 (296)	0.88 ± 0.72 0.1–6.6 (183)	0.6838	N/A
LDH (623)	On admission	U/L	466.34 ± 561.39 129–7100 (232)	389.48 ± 191.8 44–1172 (237)	453.63 ± 768.4 71–9505 (154)	0.0978	N/A
			Cardiac biomarkers				
BNP (244)	On admission	pg/mL	198.97 ± 295.09 1.7–1674 (71)	411.54 ± 765.61 3–4890.6 (85)	950.94 ± 2052.17 12.4–13,368.4 (88)	**0.00051**	0.052 [a] **0.003** [b] 0.059 [c]
(244)	On discharge		187.85 ± 236.76 1.7–1130.8 (71)	456.81 ± 1251.89 3–10,662.8 (85)	894.93 ± 1965.08 11.9–13,368.4 (88)	**0.00104**	0.133 [a] **0.003** [b] 0.188 [c]
NT-proBNP (239)	On admission	ng/mL	2647.61 ± 91,184.03 12–70,000 (63)	8356.29 ± 14,376.9 49.6–70,000 (87)	13,371.9 ± 18,707.7 119.6–70,000 (89)	**<0.0001**	**0.01** [a] **<0.0001** [b] **0.116** [c]
(239)	On discharge		2591.46 ± 6818.7 12–35,000 (63)	9044.29 ± 15,277.1 49.6–70,000 (87)	12,370.9 ± 16,896.4 119.6–70,000 (89)	**<0.0001**	**0.002** [a] **<0.0001** [b] 0.359 [c]

Table 4. *Cont.*

Parameter	Time of Assessment	Units	Low Risk (0–1)	Medium Risk (2–3)	High Risk (>4)	OMNIBUS *p*-Value	*p*-Value for Post-Hoc Analysis
			Mean ± SD Min–Max (N) or n/N (% of Risk Category) (N)	Mean ± SD Min–Max (N) or n/N (% of Risk Category) (N)	Mean ± SD Min–Max (N) or n/N (% of Risk Category) (N)		
Troponin T *normal value*: *F* ≤ *15.6* pg/mL *M* ≤ *34.2* pg/mL (665)	On admission	pg/mL	171.38 ± 899.58 0.2–11,398.7 (228)	1968.15 ± 12,515.9 2.0–125,593 (263)	658.56 ± 2437.77 3.3–21,022.9 (174)	**0.0037**	0.055 [a] **0.034** [b] 0.226 [c]
Troponin T (665)	On discharge		152.13 ± 890.6 0.2–12,391.6 (228)	1490.76 ± 9509.94 1.5–109,360 (263)	664.38 ± 2887.8 1.8–29,828.3 (174)	**0.0074**	0.062 [a] 0.064 [b] 0.385 [c]
LDL-cholesterol. (268)	On admission	mg/dL	87.7 ± 40.22 6–205 (80)	89.79 ± 41.8 23–230 (106)	75.59 ± 42.83 14–210 (82)	0.0554	N/A
			Hormones				
TSH (474)	On admission	mIU/L	1.35 ± 1.52 0.07–14.08 (149)	1.35 ± 1.69 0.01–12.1 (188)	2.24 ± 4.09 0–38.24 (137)	**0.049**	1.0 [a] **0.045** [b] 0.046 [c]
fT4 n (194)	On admission	pmol/L	12.78 ± 2.27 6.68–19.05 (58)	13.03 ± 3.4 7.56–36.6 (79)	13.48 ± 4.17 7.87–35.46 (57)	0.5257	N/A
fT3 (176)	On admission	pmol/L	2.08 ± 0.63 1.2–4.01 (57)	1.88 ± 0.77 0.95–4.45 (71)	1.93 ± 0.97 0.95–6.85 (48)	0.2684	N/A

Continuous variables are presented as: mean ± SD. range (minimum–maximum) and number of non-missing values. Categorized variables are presented as: a number with a percentage. Information about the numbers with valid values is provided in the left column. Abbreviations: N—valid measurements. n—number of patients with parameter above cut-off point. SD—standard deviation. N/A—non-applicable. [a]*—low risk vs. medium risk.* [b]*—low risk vs. high risk.* [c]*—medium risk vs. high risk.*

3.3. Drug Therapy and Applied Treatment during Hospitalization

3.3.1. Drug Therapy

Overall, there were no differences among applied treatment during hospitalization between the three C2HEST risk-strata. The only exception was the prevalence of convalescent plasma application. Subjects from the low-risk stratum more often received this therapy. Data regarding the general management of study subjects are presented in the Table 5.

3.3.2. Treatment Procedures

Greater C2HEST score was associated with the more frequent use of catecholamines. On the other hand, patients in the *low-risk* stratum statically more often did not require any respiratory support. Interestingly, we observed a higher prevalence of patients treated with invasive ventilation in this group (Table 6).

Table 5. Therapies applied during the hospitalization in the studied cohort.

Variables. Units (N)	Low Risk (0–1)	Medium Risk (2–3)	High Risk (>4)	OMNIBUS *p* Value	*p* Value (for Post-Hoc Analysis)
	n/N (% of Risk Category)	n/N (% of Risk Category)	n/N (% of Risk Category)		
Applied treatment and procedures					
Systemic corticosteroid (1047)	212/376 (56.38%)	211/419 (50.36%)	129/252 (51.19%)	0.2021	N/A
Convalescent plasma (1047)	56/376 (14.89%)	32/419 (7.64%)	27/252 (10.71%)	**0.0048**	**0.005** [a] 0.48885 [b] 0.6648 [c]
Tocilizumab (1047)	6/376 (1.6%)	2/419 (0.48%)	1/252 (0.4%)	0.2223	N/A
Remdesivir (1047)	68/376 (18.09%)	59/419 (14.08%)	32/252 (12.7%)	0.1312	N/A
Antibiotic (1047)	230/376 (61.17%)	264/419 (63.01%)	175/252 (69.44%)	0.09451	N/A

Categorized variables are presented as: a number with a percentage. Information about the numbers with valid values is provided in the left column. Abbreviations: N—valid measurements. n—number of patients with parameter above cut-off point. SD—standard deviation. N/A—non-applicable. [a]*—low risk vs. medium risk.* [b]*—low risk vs. high risk.* [c]*—medium risk vs. high risk;* Bold text—statistically significant values Bold text-statistically significant values.

Table 6. Applied treatment and procedures.

Variables, Units (N)	Low Risk (0–1)	Medium Risk (2–3)	High Risk (>4)	OMNIBUS *p*-Value	*p*-Value (for Post-Hoc Analysis)
	Mean ± SD Min–Max (N) or n/N (% of Risk Category)	Mean ± SD Min–Max (N) or n/N (% of Risk Category)	Mean ± SD Min–Max (N) or n/N (% of Risk Category)		
Applied treatment and procedures					
The most advanced respiratory support applied during the hospitalization (1047)					
no oxygen	159/376 (42.29%)	168/418 (40.19%)	86/252(34.13%)		0.9925 [a]
high flow nasal cannula	21/376 (5.59%)	36/418 (8.61%)	22/252 (8.73%)	**0.0415**	**0.0188** [b]
(non-invasive ventilation)	47/376 (12.5%)	41/418 (9.81%)	19/252 (7.54%)		0.6137 [c]
invasive ventilation					
Oxygenation parameters from the period of qualification for advanced respiratory support:					
SpO2 (284)	87.35 ± 9.89 50–99 (86)	86.19 ± 9.79 55–99 (116)	85.53 ± 9.86 59–99 (82)	0.4815	N/A
Respiratory rate, breaths/minute (62)	25.64 ± 6.96 14–40 (14)	30.11 ± 14.0 13–66 (27)	29.52 ± 13.19 14–72 (21)	0.3147	
Duration of mechanical ventilation, days (616)	1.89 ± 5.52 0–39 (222)	1.4 ± 5.18 0–51 (240)	1.14 ± 4.07 0–29 (154)	0.3134	N/A

Table 6. *Cont.*

Variables, Units (N)	Low Risk (0–1) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	Medium Risk (2–3) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	High Risk (>4) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	OMNIBUS *p*-Value	*p*-Value (for Post-Hoc Analysis)
Therapy with catecholamines (1047)	44/376 (11.7%)	36/419 (8.6%)	37/252 (14.7%)	**0.0486**	0.5433 [a] 0.9949 [b] 0.0601 [c]
Coronary angiography (1047)	5/376 (1.3%)	10/419 (2.4%)	7/252 (2.8%)	0.4036	N/A
Coronary revascularization (1047)	4/376 (1.1%)	9/419 (2.1%)	6/252 (2.4%)	0.3893	N/A
Hemodialysis (1047)	16/376 (4.3%)	11/419 (2.6%)	11/252 (4.7%)	0.3644	N/A

Continuous variables are presented as: mean ± SD, range (minimum–maximum) and number of non-missing values. Categorized variables are presented as: a number with a percentage. Information about the numbers with valid values is provided in the left column. Abbreviations: N—valid measurements, n—number of patients with parameter above cut-off point, SD—standard deviation, ANOVA—analysis of variance, N/A—non-applicable, [a]—*low risk vs. medium risk*, [b]—*low risk vs. high risk*, [c]—*medium risk vs. high risk*.

3.4. Clinical Outcome

3.4.1. Correlation of C2HEST Score Results and Mortality

The data regarding associations between the C2HEST risk stratum and mortality are presented in Table 7. We noticed significant differences regarding in-hospital, then the 3-month and 6-month mortality, which was the highest in high-risk C2HEST stratum reaching 35.7%, 54.4%, and 65.9%, respectively. Noteworthy, in the medium-risk stratum, the mortality rate reached 24.1%, 43.4%, and 57.6%, whereas in the low-risk stratum, it reached 14.4%, 25.8%, and 39.2%, respectively.

Table 7. Total and in-hospital all-cause mortality in the C_2HEST risk strata.

Variables, Units (N)	Low Risk (0–1) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	Medium Risk (2–3) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	High Risk (>4) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	OMNIBUS *p*-Value	*p*-Value (for Post-Hoc Analysis)
			All-cause mortality rate		
In-hospital mortality (1047)	54/376 (14.4%)	101/419 (24.1%)	90/252 (35.7%)	**<0.0001**	**0.00223 [a]** **<0.0001 [b]** **0.005 [c]**
3-month mortality (1047)	97/376 (25.8%)	182/419 (43.4%)	137/252 (54.4%)	**<0.0001**	**<0.0001 [a, b]** **0.023 [c]**
6-month mortality (810)	102/260 (39.2%)	190/330 (57.6%)	145/220 (65.9%)	**<0.0001**	**<0.0001 [a, b]** 0.1832 [c]

Categorized variables are presented as: a number with a percentage. Abbreviations: N—valid measurements, n—number of patients with parameter above cut-off point, SD—standard deviation, ANOVA—analysis of variance, N/A—non-applicable, [a]—*low risk vs. medium risk*, [b]—*low risk vs. high risk*, [c]—*medium risk vs. high risk*. Bold text—statistically significant values.

The time-depended discriminatory performance of the C2HEST score on all-cause mortality is presented in Figure 2. The time-dependent AUC for the C2HEST score in predicting all-cause mortality in period reaching from the day of hospital admission up to 240 days after the initial diagnosis was above 60.

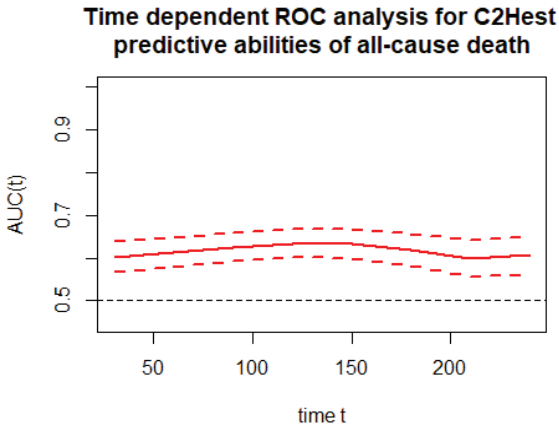


Figure 2. Time-dependent ROC analysis for the C_2HEST predictive abilities of all-cause death.

Figure 3 shows the monthly time-dependent receiver operating characteristics (time–ROC) related to the C2HEST score. During a whole period, C2HEST maintained at similar level, allowing to predict the mortality with AUC ranging from 60.2 to 63.4.

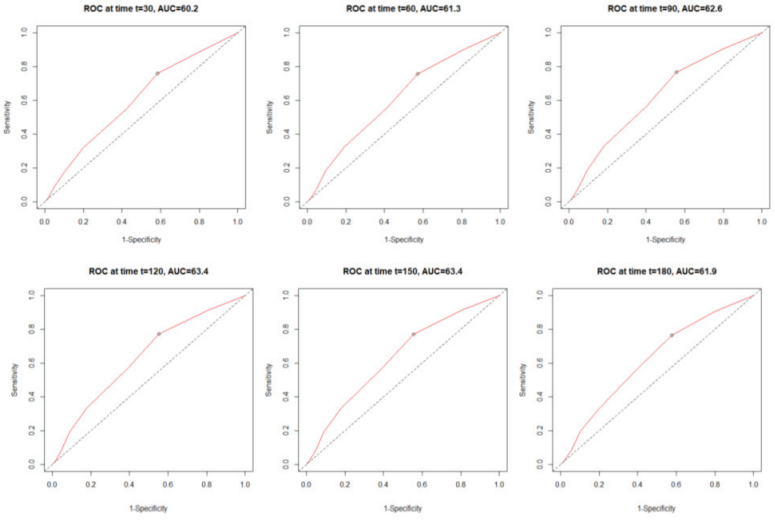


Figure 3. Time-dependent receiver operating characteristic (time–ROC) curves for the C_2HEST score in predicting total mortality.

As a next part of the assessment of the C2HEST score performance in predicting all-cause mortality among elderly subjects with COVID-19, survival curves for all C2HEST strata using Kaplan–Meier functions were estimated. The p value for Log-rank test was <0.0001. Figure 4 shows time-depending survival probability for the three risk strata.

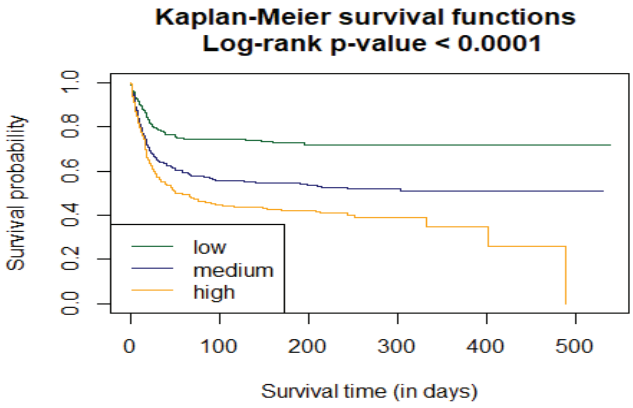


Figure 4. Analysis of the in-hospital probability of survival for the *low*, *medium*, and *high* C_2HEST risk strata.

Additionally, two Cox models were analyzed to assess the effect of the C2HEST score stratification on COVID-19 mortality. In the overall model for the uncategorized C2HEST score value, the Grambsch–Therneau test rejected the null hypothesis. The confidence intervals and p values were omitted as they might have been unreliable. On the other hand, considering the categorized-model change from the *low* to the *medium* category increased death intensity approximately 2-times. Subsequently, transfer between the *low-risk* stratum to *high-risk* stratum raised all-cause death intensity 2.7 times. (Table 8.)

Table 8. The total all-cause-death Hazard Ratios for C_2HEST risk stratification.

	Total Death		
Overall	**HR**	**95%CI**	***p*-Value**
	1.21	**NA**	**NA**
	Risk strata		
Low risk vs. Medium risk	1.94	1.531–2.467	**<0.0001**
Low risk vs. High risk	2.70	2.104–3.473	**<0.0001**

The associations of individual C_2HEST score components with mortality are presented in Table 9. The highest prognostic value for all-cause-death beyond age had coronary artery disease and heart failure components.

Table 9. Associations of individual C_2HEST score components with mortality.

	Component	HR	CI min.	CI max.	*p*-Value
All-cause mortality	Coronary artery disease	1.457	1.143	1.856	0.0023
	COPD	1.128	0.787	1.615	0.5118
	Age > 75	1.852	1.528	2.243	< 0.0001
	Thyroid disease	0.781	0.579	1.052	0.1041
	Hypertension	0.867	0.706	1.065	0.1738
	HFrEF	1.412	1.117	1.783	0.0038

COPD—Chronic obstructive pulmonary disease, HFrEF—heart failure with reduce ejection fraction.

Finally, to verify that the adequacy of the original risk stratification (the low/medium/high-risk categories for 0–1/2–3/≥4 points) provides the best possible stratification regarding the difference in Kaplan–Meier survival curves, all the possible C2HEST intervals were

analyzed, and for each, the log-rank statistics were calculated (Table 10). The highest value of log-rank test statistics was obtained for the original C2HEST-score risk strata.

Table 10. The Log-rank statistics for matching the C2HEST risk strata for in-hospital mortality.

	h2	h3	h4	h5	h6	h7	h8
m1		54.9289	45.309	36.9829	22.3874	19.5331	4.391
m2		55.5515	**64.8647**	62.9116	55.5126	54.8399	7.4052
m3			43.3222	40.8103	33.8943	33.4495	5.7835
m4				36.9734	36.2196	36.2402	5.9926
m5					25.3749	24.3364	4.862
m6						5.0713	2.2214
m7							0.7235

m—medium. h—high. Bold text—highest statistical significant

3.4.2. Correlation of the C_2HEST Score with Secondary Outcome

All clinical non-fatal events and hospitalization are shown in Table 11. Patients in the *high-risk* stratum were more likely to develop acute kidney injury, acute heart failure, and cardiogenic shock. Noteworthy, no-significant differences were reported in the occurrence of pneumonia, SEPSIS, systemic inflammatory response syndrome (SIRS), and multi-organ dysfunction syndrome (MODS). Additionally, there were no differences in the ratio of thromboembolic events (deep vein thrombosis, pulmonary embolism). Similarly, an increase in the C2HEST score did not raise the prevalence of total or gastrointestinal bleedings.

Table 11. Clinical non-fatal events and hospitalization outcomes in the C_2HEST risk strata.

	Low Risk (0–1)	**Medium Risk (2–3)**	**High Risk (>4)**		
Variables, Units (N)	**Mean ± SD Min–Max (N) or n/N (% of Risk Category)**	**Mean ± SD Min–Max (N) or n/N (% of Risk Category)**	**Mean ± SD Min–Max (N) or n/N (% of Risk Category)**	**OasMNIBUS *p*-Value**	***p*-Value (for Post-Hoc Analysis)**
		Hospitalization			
Duration of hospitalization, days (1047)	13.45 ± 115.35 1–131 (376)	13.13 ± 13.98 1–124 (419)	15.79 ± 15.77 1–121 (252)	0.07693	N/A
Admission at ICU (1047)	46/376 (12.2%)	32/419 (7.6%)	24/252 (9.5%)	0.0916	N/A
End of hospitalization (1047)					
death	54/376 (14.4%)	101/419 (24.1%)	90/252 (36.6%)	**<0.0001**	**0.000283** [a] **<0.0001** [b] **0.04329** [c]
discharge home–full recovery	210/376 (55.9%)	176/419 (42.0%)	92/252 (36.6%)		
transfer to another hospital–worsening	57/376 (15.2%)	87/419 (20.8%)	44/252 (17.5%)		
transfer to another hospital–in recovery	55/376 (14.6%)	55/419 (13.1%)	26/252 (10.3%)		
		Clinical events			
Aborted cardiac arrest (1047)	9/376 (2.4%)	1/419 (0.2%)	5/252 (2.0%)	**0.0127**	**0.0242** [a] 1.0 [b] 0.0906 [c]

Table 11. *Cont.*

Variables, Units (N)	Low Risk (0–1) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	Medium Risk (2–3) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	High Risk (>4) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	OasMNIBUS *p*-Value	*p*-Value (for Post-Hoc Analysis)
Shock (1047)	39/376 (10.4%)	37/419 (8.8%)	29/252 (11.6%)	0.515	N/A
hypovolemic shock	9/376 (2.4%)	6/419 (1.4%)	5/252 (2.0%)	0.6274	N/A
cardiogenic shock	0/376 (0%)	9/419 (2.2%)	13/252 (5.2%)	**<0.0001**	**0.0349** [a] **<0.0001** [b] 0.1734 [c]
septic shock	31/376 (8.2%)	25/419 (6.0%)	19/252 (7.5%)	0.4454	N/A
Venous thromboembolic disease (1047)	28/376 (7.5%)	28/419 (6.7%)	15/252 (0.8%)	0.7619	N/A
Pulmonary embolism (1047)	24/376 (6.4%)	25/419 (6.0%)	13/252 (6.0%)	0.972	N/A
Deep vein thrombosis (1047)	1/376 (0.3%)	1/419 (0.2%)	0/252 (0.0%)		
MI (1047)	4/376 (1.1%)	9/419 (2.2%)	7/252 (2.8%)	0.2629	N/A
Acute HF (1047)	3/376 (0.8%)	14/419 (3.3%)	44/252 (17.5)	**<0.0001**	0.0773 [a] **<0.0001** [b,c]
Stroke/TIA (1047)	6/376 (1.6%)	16/419 (3.8%)	7/252 (2.8%)	0.1623	N/A
Pneumonia (1047)	224/376 (59.6%)	264/419 (63.0%)	168/252 (66.7%)	0.1939	N/A
SIRS (1040)	37/373 (9.9%)	38/416 (9.1%)	33/251 (13.1%)	0.2412	N/A
Sepsis (405)	2/137 (1.5%)	7/153 (4.6%)	6/115 (5.2%)	0.1866	N/A
Acute kidney injury (1047)	37/376 (9.8%)	59/419 (14.1%)	53/252 (21.0%)	**0.000432**	0.2546 [a] **0.000422** [b] 0.0769 [c]
Acute liver dysfunction (981)	7/352 (2.0%)	17/398 (4.3%)	13/231 (5.6%)	0.0623	N/A
MODS (1047)	6/376 (1.6%)	5/419 (1.2%)	6/252 (2.4%)	0.4735	N/A
LA (157)	5/38 (13.2%)	5/66 (7.6%)	6/53 (11.3%)	0.6287	N/A
Hyperlactaemia (157)	28/38 (73.7%)	43/66 (65.2%)	32/53 (60.4%)	0.4174	N/A
Bleedings (1047)	19/376 (5.2%)	21/419 (5.2%)	22/252 (8.7%)	0.09539	N/A
Intracranial bleeding (1047)	2/376 (0.5%)	8/419 (1.9%)	1/252 (0.4%)	0.1166	N/A
Respiratory tract bleeding (1047)	6/376 (1.6%)	2/419 (0.5%)	6/252 (2.4%)	0.0833	N/A
Gastrointestinal tract bleeding (1047)	9/376 (2.4%)	8/419 (1.9%)	10/252 (4.0%)	0.2667	

Table 11. *Cont.*

Variables, Units (N)	Low Risk (0–1) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	Medium Risk (2–3) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	High Risk (>4) Mean ± SD Min–Max (N) or n/N (% of Risk Category)	OasMNIBUS *p*-Value	*p*-Value (for Post-Hoc Analysis)
Urinary tract bleeding (1047)	3/1418 (0.8%)	4/492 (1.0%)	5/252 (2.0%)	0.4017	N/A

Continuous variables are presented as: mean ± SD range (minimum–maximum) and number of non-missing values. Categorized variables are presented as: a number with a percentage. Abbreviations: N—valid measurements, n—number of patients with parameter above cut-off point, SD—standard deviation, ANOVA—analysis of variance, ICU—intensive care unit, MI—myocardial infarction, HF—heart failure, TIA-transient ischemic attack, SIRS—systemic inflammatory response syndrome, MODS—multiple organ dysfunction syndrome, LA—lactic acidosis, N/A—non-applicable, [a]—*low risk vs. medium risk*, [b]—*low risk vs. high risk*, [c]—*medium risk vs. high risk*.

Summarized discriminatory performance of the C_2HEST score on the clinical events is presented in Table 12 and in the Supplementary Materials.

Table 12. Discriminatory performance of the C_2HEST score on the clinical events.

CLINICAL EVENT	AUC	SENSITIVITY	SPECIFICITY
End of hospitalization–full recovery	**0.584**	**0.439**	**0.708**
End of hospitalization–deterioration	**0.511**	**0.697**	**0.371**
End of hospitalization–rehabilitation	**0.459**	**0.015**	**0.986**
End of hospitalization–death	**0.633**	**0.616**	**0.580**
All-cause shock	0.521	0.914	0.156
Hypovolemic shock	0.477	0.900	0.149
Cardiogenic shock	**0.774**	**1.000**	**0.367**
Septic shock	0.498	0.920	0.154
Pulmonary embolism	0.491	0.087	0.941
Deep vein thrombosis	0.463	0.222	0.940
Venous thromboembolic disease	0.487	0.085	0.941
Myocardial infarction	0.609	0.650	0.537
Myocardial injury	0.612	0.769	0.396
Acute heart failure	**0.824**	**0.721**	**0.789**
Stroke/TIA	0.582	0.655	0.539
SIRS	0.531	0.537	0.539
Sepsis	0.655	0.800	0.495
Acute kidney injury	**0.605**	**0.624**	**0.560**
Acute liver dysfunction	0.626	0.811	0.365
MODS	0.577	0.647	0.537
All bleedings	0.579	0.354	0.766
Intracranial bleeding	0.581	0.727	0.537
Respiratory tract bleeding	0.556	0.428	0.762
Upper-GI-tract bleeding	0.583	0.300	0.873
Lower-GI-tract-bleeding	0.529	0.571	0.642
Urinary tract bleeding	0.619	0.416	0.873
Pneumonia	0.543	0.489	0.5729

TIA—transient ischemic attack, SIRS—systemic inflammatory response syndrome MODS—multiple organ dysfunction syndrome, GI—gastrointestinal. Bold text—statistically significant values.

The associations of individual C2HEST score components with endpoints are presented in the Supplementary Materials. Since Obesity and Diabetes mellitus constitute important comorbidities affecting the COVID-19 outcome, we decided to perform a sub-analysis including these two parameters to the modified C2HEST score (C2HEST-OD), which has further increased the predictive performance of the score. The data on the C2HEST-OD score is presented in the Supplementary Materials.

4. Discussion

Advanced age is considered as an independent predictor of in-hospital mortality in the course of COVID-19 [12]. Combined with comorbidities and frailty, it leads to the increased risk of an unfavorable outcome in this specific population. The high prevalence of atypical symptoms [13] and more rapid progression of disease indicated that the development of a simple risk-scoring system faced with limited resources could optimize the treatment process.

Some elderly subjects can recover spontaneously without any medical intervention when the disease course is mild. However, in severe cases, despite the use of intensive pharmacological therapy, non-invasive and invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), the prognosis remains poor. Therefore, it is crucial to identify potentially severe cases and implement immediately effective treatment to prevent the progression of the disease from its beginning. Interestingly, there were no significant differences on admission in terms of the Vulnerable Elderly Score (VES-13), which is a simple scoring system capable of identifying vulnerable elderly people in the community and includes factors such as age, self-assessed health, functional limitations, and impairments [14]. Health vulnerability is associated with a higher risk of mortality and functional decline in older people in the community. However, few studies have evaluated the role of the Vulnerable Elders Survey (VES-13) in predicting clinical outcomes of hospitalized patients [15,16]. One of the recent studies, based on the small cohort (n=91) suggests that elderly patients (>60 years) classified as extremely vulnerable had more unfavorable outcomes after hospitalization for COVID-19—super vulnerability was an independent predictor of death and the need for invasive mechanical ventilation during hospitalization—a final VES-13 score between 8 and 10 was associated with poor outcomes [17]. Our results show a lack of significant differences in the VES-13 between the three C2HEST strata. Similarly, we did not observe differences in the GCS score between the risk strata, which could point thus at an independent predicting value of the C2HEST score in the fatal and non-fatal outcomes of elderly subjects with COVID-19. In the Supplementary Materials, we have presented the usefulness of the C2HEST score in elderly subjects who were admitted directly to the intensive care unit (due to COVID severity) vs. those admitted to the non-intensive ward of the medical university center due to COVID-19. The C2HEST score revealed to determine the outcome (mortality and non-fatal adverse clinical events) irrespective of the initial symptom severity. Noteworthy, C2HEST score also predicted the mortality irrespective of the transfer to the ICU, which might point at its additional value in better predicting the need for advanced supportive care and performing better triage of subjects being at greater risk for death who could take an advantage of earlier escalation of the monitoring and supportive care.

Since SARS-CoV-2 affects mainly the respiratory system, classic parameters of ventilation (respiratory rate, oxygen saturation, and PaO2/FiO2) are often used in clinical practice to assess the disease severity. Similar, due to the postulated critical role of inflammatory response in severe COVID-19 systematic inflammation factors, CRP, interleukin-6, [18] and interleukin-8 [19], neutrophil-to-lymphocyte ratio [20] are assumed to correlate with clinical outcome.

However, satisfactory methods for predicting the outcome of hospitalized COVID-19 especially in elderly subjects are still missing. Therefore, we conducted this study to assess the predictive value of C2HEST score in elderly (over 65 years) patients with COVID-19. In the past, the C2HEST score was validated as a simple tool for predicting AF in the general [6] and post-stroke [21] population.

Considering that all the variables (coronary artery disease [22]; chronic obstructive pulmonary disease [23]; hypertension [24]; elderly [25]; systolic heart failure [26]; thyroid disease [27]) of the scale are also factors of an unfavorable prognosis among patients with COVID-19, we assumed C2HEST could predict other clinical outcomes in elderly patients with COVID-19.

Initial laboratory parameters seem to support this theory. In our cohort, the high-risk C2HEST stratum had a higher prevalence of renal insufficiency, initial anemia, and elevated

markers of heart injury. A notable trend in the initially higher level of inflammatory parameters was observed, albeit without statistical significance. Lack of statistical significance between C2HEST-dependent risk-groups in terms of initial inflammatory markers and primary respiratory parameters allows presuming that this scale not only selects initially extremely severe cases with poor prognosis, but was able to predict the outcome of the COVID-19 infection from all-comers elderly cohort.

The C2HEST score analyzed as categorical variable well correlated with mortality, acute renal and cardiac complications. When calculated, C2HEST scores were grouped into *low*, *intermediate*, and *high-risk* strata; all three categories were associated with significant differences in terms of the in-hospital mortality for each of the study groups. Moreover, this relationship referred also to the three-month and six-month mortality. Furthermore, the log-rank statistics performed in this study confirmed that the original stratum allocation system used in the C2HEST scale provides the best possible model of mortality stratification.

Our data suggest that among all individual CHEST score components, the highest prognostic value for mortality had an age, coronary artery disease, and heart failure. Surprisingly, previously well-established in general population risk-factors COPD and hypertension [24,28] had no effect on the survival curve in the elderly population.

Among other interesting findings of our study were significant differences in the prevalence of respiratory support applied during the hospitalization. Not surprisingly, patients in the *low-risk* stratum statically less frequently required respiratory support. However, at the same time, they were more prone to deteriorate and required invasive ventilation in intensive care unit (ICU). Probably in the face of limited resources, subjects in this stratum, due to lower prevalence of comorbidities, were predisposed to receive this advanced treatment while patients in *high-risk* stratum had not been qualified for that kind of escalated therapy.

Recently, we observed an instantly growing number of risk scores and predictive models designed for a similar purpose. Especially the elder population with co-occurring immunological changes named collectively as "immunosenescence" [29]—connected with a decrease of innate and adaptive immune responses and exacerbation in the production of inflammatory cytokines—during the aging process is susceptible to various infections and requires careful initial assessment. Some of them use advanced mathematical models based on machine learning. The vast majority of these models use the initial laboratory features, along with respiratory parameters as differentiating variables [30–33] which may reduce their usefulness in common clinical practice. Moreover, introducing novel scales or scoring systems requires detailed validation and is much more difficult to implement to the common clinical use by medical practitioners. As a result, analysis of the usefulness of the pre-existing scales in the other entity may have much further going practical implication, especially while meeting the urgent need during the COVID-19 pandemic. The C2HEST score seems to be one of the few, well-validated, based only on a simple medical history, and can be applied at early stages of hospital admission or even during the pre-hospital triage.

An interesting concept might be also a multidimensional assessment of a potential risk factor of an unfavorable outcome of COVID-19 in the elderly population, a merger of the C2HEST risk score with some basic clinical factor. Since obesity and diabetes constitute important comorbidities which could affect the COVID-19 outcome, including these parameters to this analysis could further improve the prognostic value of such modified C2HEST-OD which is presented in the Supplementary Materials. Nevertheless, as specified above, the validation of the new scale and introducing it to the clinical practice would take much time which is critical in the pandemic setting. Noteworthy, the CHA2DS2Vasc score, commonly used in clinical practice for estimating the risk of stroke in people with atrial fibrillation (AF), includes comorbidities such as diabetes, but also congestive heart failure, hypertension, prior stroke/TIA or thromboembolism, vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque), and sex category. Similar to the C2HEST score, it is well validated and based on the simple analysis of comorbidities. We postulate that the CHA2DS2Vasc score might also have prognostic value in predicting

the COVID-19 outcome in elderly subjects, which requires further detailed and extensive analyses. Additional data including laboratory parameters, frailty assessment value, or radiological features could increase the predictive power of the C2HEST score. Such a combined model could allow for the accurate selection of subjects hospitalized with COVID-19 with the urgent need of introducing life-saving intervention. However, this approach may significantly increase complications of the scale, reducing its practical usefulness.

Limitations

This study has several limitations. First, the retrospective character and a single-center registry could affect clinical outcomes. Secondly, the study covered a relatively long period and was carried out in the face of limited resources, which could affect therapeutic methods. Finally, some clinical data and baseline laboratory assays are incomplete, hindering proper interpretation of the results.

5. Conclusions

This is the first presentation that the C_2HEST score could predict adverse outcomes including the in hospital and six-month-mortality as well as the non-fatal clinical events reflecting deterioration, such as acute kidney injury, acute heart failure, and cardiogenic shock among elderly patients admitted to the hospital with COVID-19. The simplicity of this scale combined with variables based only on the past medical history with omission of laboratory assays allows assuming that the C2HEST score can be a helpful tool for pre-hospital risk stratification in elderly subjects with SARS-CoV-2 infection.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11040992/s1. Figure S1: 95% Asymptotic OR Confidence Interval (low vs. high); Figure S2: 95% Asymptotic OR Confidence Interval (low vs. high & Overall); Figure S3: Kaplan-Meier survival function; Table S1: The strength of the association between CH2EST-score and study endpoints; Table S2: All-cause mortality; Table S3: In-hospital mortality; Table S4: The strength of the association between CH2EST-score and study endpoints; Table S5: The C2HEST predictive value in transfer of COVID-19 elderly subjects to the ICU following clinical deterioration; Table S6: The logistic regression model.

Author Contributions: Conceptualization, P.R., A.D., M.T., E.A.J. and K.M. (Katarzyna Madziarska); methodology, P.R., A.D., M.T. and K.M. (Katarzyna Madziarska); software, K.G., K.K. (Krzysztof Kujawa) and M.S.; validation, K.K. (Krzysztof Kujawa), K.G. and M.S.; formal analysis, K.G., K.K. (Krzysztof Kujawa), M.S. and A.D.; investigation, P.R., A.D., M.T., J.G., T.M., E.S.-K., D.G., B.A., K.K. (Krzysztof Kujawa), K.K.-P., K.L., A.M.-W., M.P. (Michał Pomorski), M.P. (Marcin Protasiewicz), K.M. (Konrad Majchrzak), J.S., E.A.J. and K.M. (Katarzyna Madziarska); resources, P.R., A.D., M.T., J.G., T.M., E.S.-K., D.G., B.A., K.K. (Krzysztof Kaliszewski), K.K.-P., K.L., A.M.-W., M.P. (Michał Pomorski), M.P. (Marcin Protasiewicz), K.M. (Konrad Majchrzak), J.S., E.A.J. and K.M. (Katarzyna Madziarska); data curation, P.R., A.D., M.T., J.G., T.M., E.S.-K., D.G., B.A., K.K. (Krzysztof Kaliszewski), K.K.-P., K.L., A.M.-W., M.P. (Michał Pomorski), M.P. (Marcin Protasiewicz), K.M. (Konrad Majchrzak), J.S., E.A.J. and K.M. (Katarzyna Madziarska); writing—original draft preparation, P.R., A.D., M.T., E.A.J. and K.M. (Katarzyna Madziarska); writing—review and editing, A.D., E.A.J., and K.M. (Katarzyna Madziarska); visualization, K.G., K.K. (Krzysztof Kujawa), M.S., P.R., A.D., M.T., E.A.J. and K.M. (Katarzyna Madziarska); supervision, A.D., M.T., E.A.J. and K.M. (Katarzyna Madziarska); project administration, A.D., M.T., E.A.J. and K.M. (Katarzyna Madziarska). All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Bioethics Committee of Wroclaw Medical University, Wroclaw, Poland (Signature number: KB-444/2021).

Informed Consent Statement: The routine data were collected retrospectively; therefore, written informed consent to participate in the study was not required. The Bioethics Committee approved the publication of anonymized data.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Acknowledgments: The authors are grateful to all the staff and the patients at the study center who contributed to this work.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; et al. A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.* **2020**, *382*, 727–733. [CrossRef] [PubMed]
2. Maniaci, A.; Ferlito, S.; Bubbico, L.; Ledda, C.; Rapisarda, V.; Iannella, G.; La Mantia, I.; Grillo, C.; Vicini, C.; Privitera, E.; et al. Comfort rules for face masks among healthcare workers during COVID-19 spread. *Ann. Ig.* **2021**, *33*, 615–627. [PubMed]
3. Gao, Y.D.; Ding, M.; Dong, X.; Zhang, J.J.; KursatAzkur, A.; Azkur, D.; Gan, H.; Sun, Y.L.; Fu, W.; Li, W.; et al. Risk factors for severe and critically ill COVID-19 patients: A review. *Allergy* **2021**, *76*, 428–455. [CrossRef] [PubMed]
4. Marin, B.G.; Aghagoli, G.; Lavine, K.; Yang, L.; Siff, E.J.; Chiang, S.S.; Salazar-Mather, T.P.; Dumenco, L.; Savaria, M.C.; Aung, S.N.; et al. Predictors of COVID-19 severity: A literature review. *Rev. Med. Virol.* **2021**, *31*, 1–10. [CrossRef] [PubMed]
5. Maestre-Muñiz, M.M.; Arias, Á.; Arias-González, L.; Angulo-Lara, B.; Lucendo, A.J. Prognostic Factors at Admission for In-Hospital Mortality from COVID-19 Infection in an Older Rural Population in Central Spain. *J. Clin.* **2021**, *10*, 318. [CrossRef]
6. Li, Y.G.; Pastori, D.; Farcomeni, A.; Yang, P.S.; Jang, E.; Joung, B.; Wang, Y.T.; Guo, Y.T.; Lip, G. A simple clinical risk score (C2HEST) for predicting incident atrial fibrillation in Asian subjects: Derivation in 471,446 Chinese subjects, with internal validation and external application in 451,199 Korean subjects. *Chest* **2019**, *155*, 510–518. [CrossRef]
7. Liang, W.; Wu, Y.; Xue, R.; Wu, Z.; Wu, D.; He, J.; Dong, Y.; Lip, G.Y.; Zhu, W.; Liu, C. C 2 HEST score predicts clinical outcomes in heart failure with preserved ejection fraction: A secondary analysis of the TOPCAT trial. *BMC Med.* **2021**, *19*, 44. [CrossRef]
8. Robin, X.; Turck, N.; Hainard, A.; Tiberti, N.; Lisacek, F.; Sanchez, J.C.; Müller, M. pROC: An open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinform.* **2011**, *12*, 77. [CrossRef]
9. Therneau, T. A Package for Survival Analysis in R. R Package Version 3.2-7. Available online: https://CRAN.R-project.org/package=survival (accessed on 16 December 2021).
10. Hothorn, T.; Hornik, K.; Van De Wiel, M.A.; Zeileis, A. A lego system for conditional inference. *Am. Stat.* **2006**, *60*, 257–263. [CrossRef]
11. Schratz, P. *R Package 'Oddsratio': Odds Ratio Calculation for GAM(M)s & GLM(M)s*, Version 1.0.2. 2017. Available online: https://doi.org/10.5281/zenodo.1095473 (accessed on 1 December 2021).
12. Gupta, S.; Hayek, S.S.; Wang, W.; Chan, L.; Mathews, K.S.; Melamed, M.L.; Brenner, S.K.; Leonberg-Yoo, A.; Schenck, E.J.; Radbel, J.; et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. *JAMA Intern. Med.* **2020**, *180*, 1436–1447. [CrossRef]
13. García-Cabrera, L.; Pérez-Abascal, N.; Montero-Errasquín, B.; Rexach Cano, L.; Mateos-Nozal, J.; Cruz-Jentoft, A. Characteristics, hospital referrals and 60-day mortality of older patients living in nursing homes with COVID-19 assessed by a liaison geriatric team during the first wave: A research article. *BMC Geriatr.* **2021**, *21*, 610. [CrossRef]
14. Min, L.; Yoon, W.; Mariano, J.; Wenger, N.S.; Elliott, M.N.; Kamberg, C.; Saliba, D. The vulnerable elders-13 survey predicts 5-year functional decline and mortality outcomes in older ambulatory care patients. *J. Am. Geriatr. Soc.* **2009**, *57*, 2070–2076. [CrossRef]
15. Bell, S.P.; Schnelle, J.; Nwosu, S.K.; Schildcrout, J.; Goggins, K.; Cawthon, C.; Mixon, A.S.; Vasilevskis, E.E.; Kripalani, S. Development of a multivariable model to predict vulnerability in older American patients hospitalised with cardiovascular disease. *BMJ Open* **2015**, *5*, e008122. [CrossRef] [PubMed]
16. Ho, F.K.; Petermann-Rocha, F.; Gray, S.R.; Jani, B.D.; Katikireddi, S.V.; Niedzwiedz, C.L.; Foster, H.; Hastie, C.E.; Mackay, D.F.; Gill, J.M.R.; et al. Is older age associated with COVID-19 mortality in the absence of other risk factors? General population cohort study of 470,034 participants. *PLoS ONE* **2020**, *15*, e0241824. [CrossRef] [PubMed]
17. Assis, F.C.; Silva, M.; Geber-Júnior, J.C.; Roschel, H.; Peçanha, T.; Drager, L.F.; Santana, A. Association of health vulnerability with adverse outcomes in older people with COVID-19: A prospective cohort study. *Clinics* **2021**, *76*, e3369. [CrossRef] [PubMed]
18. Liu, F.; Li, L.; Xu, M.; Wu, J.; Luo, D.; Zhu, Y.; Li, B.; Song, X.; Zhou, X. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J. Clin. Virol.* **2020**, *127*, 104370. [CrossRef]
19. Li, L.; Li, J.; Gao, M.; Fan, H.; Wang, Y.; Xu, X.; Chen, C.; Liu, J.; Kim, J.; Aliyari, R.; et al. Interleukin-8 as a biomarker for disease prognosis of coronavirus disease-2019 patients. *Front. Immunol.* **2021**, *11*, 3432. [CrossRef] [PubMed]
20. Li, X.; Liu, C.; Mao, Z.; Xiao, M.; Wang, L.; Qi, S.; Zhou, F. Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: A systematic review and meta-analysis. *Crit. Care* **2020**, *24*, 647. [CrossRef] [PubMed]
21. Li, Y.G.; Bisson, A.; Bodin, A.; Herbert, J.; Grammatico-Guillon, L.; Joung, B.; Wang, Y.T.; Lip, G.Y.; Fauchier, L. C2 HEST Score and prediction of incident atrial fibrillation in poststroke patients: A French Nationwide Study. *J. Am. Heart Assoc.* **2019**, *8*, e012546. [CrossRef]
22. Loffi, M.; Piccolo, R.; Regazzoni, V.; Di Tano, G.; Moschini, L.; Robba, D.; Quinzani, F.; Esposito, G.; Franzone, A.; Danzi, G.B. Coronary artery disease in patients hospitalised with Coronavirus disease 2019 (COVID-19) infection. *Open Heart* **2020**, *7*, e001428. [CrossRef] [PubMed]

23. Jung, Y.; Wee, J.H.; Kim, J.H.; Choi, H.G. The Effects of Previous Asthma and COPD on the Susceptibility to and Severity of COVID-19: A Nationwide Cohort Study in South Korea. *J. Clin. Med.* **2021**, *10*, 4626. [CrossRef] [PubMed]
24. Du, Y.; Zhou, N.; Zha, W.; Lv, Y. Hypertension is a clinically important risk factor for critical illness and mortality in COVID-19: A meta-analysis. *Nutr. Metab. Cardiovasc. Dis.* **2021**, *31*, 745–755. [CrossRef] [PubMed]
25. Grasselli, G.; Greco, M.; Zanella, A.; Albano, G.; Antonelli, M.; Bellani, G.; Bonanomi, E.; Cabrini, L.; Carlesso, E.; Castelli, G.; et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern. Med.* **2020**, *180*, 1345–1355. [CrossRef] [PubMed]
26. Lvarez-Garcia, J.; Lee, S.; Gupta, A.; Cagliostro, M.; Joshi, A.A.; Rivas-Lasarte, M.; Contreras, J.; Mitter, S.S.; LaRocca, G.; Tlachi, P.; et al. Prognostic impact of prior heart failure in patients hospitalized with COVID-19. *J. Am. Coll. Cardiol.* **2020**, *76*, 2334–2348. [CrossRef]
27. Damara, F.A.; Muchamad, G.R.; Ikhsani, R.; Syafiyah, A.H.; Bashari, M.H. Thyroid disease and hypothyroidism are associated with poor COVID-19 outcomes: A systematic review, meta-analysis, and meta-regression. *Diabetes Metab. Syndr. Clin. Res. Rev.* **2021**, *15*, 102312. [CrossRef]
28. Gerayeli, F.V.; Milne, S.; Cheung, C.; Li, X.; Yang, C.W.; Tam, A.; Choi, L.H.; Bae, A.; Sin, D.D. COPD and the risk of poor outcomes in COVID-19: A systematic review and meta-analysis. *EClin. Med.* **2021**, *33*, 100789. [CrossRef]
29. Pietrobon, A.J.; Teixeira, F.M.E.; Sato, M.N. Immunosenescence and Inflammaging: Risk Factors of Severe COVID-19 in Older People. *Front. Immunol.* **2020**, *11*, 579220. [CrossRef]
30. Gao, Y.; Cai, G.Y.; Fang, W.; Li, H.Y.; Wang, S.Y.; Chen, L.; Yu, Y.; Liu, D.; Xu, S.; Cui, P.F.; et al. Machine learning based early warning system enables accurate mortality risk prediction for COVID-19. *Nat. Commun.* **2020**, *11*, 5033. [CrossRef]
31. Bertsimas, D.; Lukin, G.; Mingardi, L.; Nohadani, O.; Orfanoudaki, A.; Stellato, B.; Wiberg, H.; Gonzalez-Garcia, S.; Parra-Calderon, C.L.; Robinson, K.; et al. COVID-19 mortality risk assessment: An international multi-center study. *PLoS ONE* **2020**, *15*, e0243262. [CrossRef]
32. Yadaw, A.S.; Li, Y.C.; Bose, S.; Iyengar, R.; Bunyavanich, S.; Pandey, G. Clinical features of COVID-19 mortality: Development and validation of a clinical prediction model. *Lancet Digit. Health* **2020**, *2*, e516–e525. [CrossRef]
33. Du, R.-H.; Liang, L.-R.; Yang, C.-Q. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: A Prospective Cohort Study. *Eur. Respir. J.* **2020**, *55*, 2000524. [CrossRef] [PubMed]

Journal of
Clinical Medicine

MDPI

Article

Development of New Mental and Physical Health Sequelae among US Veterans after COVID-19

Nilang Patel [1,2,*], Bassam Dahman [3,4,5] and Jasmohan S. Bajaj [1,6]

[1] Department of Medicine, Virginia Commonwealth University, Richmond, VA 23298, USA; jasmohan.bajaj@vcuhealth.org
[2] Division of Nephrology, Central Virginia VA Health Care System, 1201 Broad Rock Boulevard, Richmond, VA 23249, USA
[3] Department of Health Behavior and Policy, Virginia Commonwealth University, Richmond, VA 23298, USA; bassam.dahman@vcuhealth.org
[4] Department of Biostatistics, Virginia Commonwealth University, Richmond, VA 23298, USA
[5] Senior Health and Policy Analyst (WOC), Central Virginia VA Health Care System, Richmond, VA 23249, USA
[6] Division of Gastroenterology and Hepatology, Central Virginia VA Health Care System, Richmond, VA 23249, USA
* Correspondence: nilang.patel3@va.gov; Tel.: +1-804-675-5596; Fax: +1-804-675-5159

Abstract: Background:COVID-19 sequelae among veterans need evaluation. **Design:** Propensity-score-matched retrospective cohort study. **Participants:** A total 778,738 veterans, who were tested for COVID-19 at VA facilities between 20 February 2020–27 March 2021. **Main Outcomes:** Development of new physical and mental health conditions (incidence) during the follow-up period of 7 days to 3 months after the diagnosis of COVID-19. **Results:** Out of 778,738 veterans, 149,205 (19.2%) were inpatients and 629,533 (80.8%) were outpatients. 123,757 (15.9%) diagnosed with COVID-19. Mean age was 61 ± 15.4, mostly men (89%) who were White (68%) and non-Hispanic (88%). In hospitalized patients, COVID-19 is associated with significantly higher incidences of physical conditions (venous thromboembolism (5.8% vs. 2.9%, $p < 0.001$), pulmonary circulation disorder (5.1% vs. 2.9%, $p < 0.001$), chronic lung disease (8.4% vs. 4.3%, $p < 0.001$), acute kidney injury (16.4% vs. 9.3%, $p < 0.001$), chronic kidney disease (6.5% vs. 4.8%, $p < 0.001$), cardiac arrhythmia (15.2% vs. 10.9%, $p < 0.001$), complicated hypertension (12% vs. 8.5%, $p < 0.001$), coagulopathy (6.1% vs. 2.6%, $p < 0.001$), fluid/electrolyte disorders (24.4% vs. 12.6%, $p < 0.001$) and neurological disorders (7.1% vs. 3.8%, $p < 0.001$)) and mental health conditions (depressive episode (6.6% vs. 4.3%, $p < 0.001$), adjustment disorder (2.5% vs. 1.7%, $p < 0.001$), insomnia (4.9% vs. 3.2%, $p < 0.001$) and dementia (3.0% vs. 1.9%, $p < 0.001$)) compared to propensity-matched hospitalized COVID-19 negative patients. In outpatient settings, COVID-19 diagnosis is associated with smaller increase in the incidences of the physical sequelae. **Conclusions:** In this propensity-score-matched analysis of US veterans, COVID-19 survivors, especially those who were hospitalized, developed new physical and mental health sequelae at a significantly higher rate than those without COVID-19.

Keywords: COVID-19; mental sequelae; physical sequelae; veterans

Citation: Patel, N.; Dahman, B.; Bajaj, J.S. Development of New Mental and Physical Health Sequelae among US Veterans after COVID-19. *J. Clin. Med.* **2022**, *11*, 3390. https://doi.org/10.3390/jcm11123390

Academic Editors: Riccardo Giorgino and Filippo Migliorini

Received: 19 April 2022
Accepted: 9 June 2022
Published: 13 June 2022

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection presents with a wide clinical spectrum ranging from asymptomatic cases to life-threatening illness. During the early part of the Coronavirus disease 2019 (COVID-19) pandemic, the emphasis was on life-threatening health consequences like severe respiratory failure, cytokine storm, thromboembolism, and death. However, as the experience with the COVID-19 has grown, a greater recognition of post-acute sequelae emerged [1,2] This could be due to the persistence of the virus in several organs and the vascular endothelium [3–6] The predictors and clinical

burden of this syndrome that spans mental and physical health are being recognized across many populations but need to be described among the US Veterans.

Veterans have been vaccinated from the early part of 2021, and from mid-2021 less virulent COVID-19 variants (Alpha, Beta, Gamma, Delta, Omicron, etc.) have emerged. Vaccination, less virulent strains, and better therapeutic options have positively affected the severity and mortality of COVID-19. In general, as the years passed, milder forms of COVID-19 emerged. However, the question remains as to how the infection by the initial strain of SARS-CoV-2 affected the veterans. This vulnerable group of patients tends to be older, have higher comorbidities and disabilities, and be from lower socioeconomically disadvantaged groups than the general US population [7–9]. Given the larger disease burden in veterans at baseline, it is important to investigate the potential consequences of COVID-19 beyond the acute illness phase. In this study, we have investigated the development of new physical and mental conditions among veterans after the initial phase of COVID-19 infection.

2. Method

2.1. Data Source

Veteran Affairs (VA) has the largest integrated health care system in the US. All healthcare data were extracted to the VA's Corporate Data Warehouse (CDW), which is a national electronic health data repository. To facilitate COVID-19 research, VA Informatics and Computing Infrastructure (VINCI) analysts created COVID-19 Shared Data Resource, which includes analytic tables extracted from the VA's CDW for all patients tested for SARS-CoV-2.

2.2. Definition of Positive or Negative COVID-19 and Index Date

Patients were defined as COVID-19-positive if they had at least one positive polymerase chain reaction test during the study period. Patients were defined as COVID-19-negative if all polymerase chain reaction tests were negative. Final adjudication of COVID-19 status was performed by the VA National Surveillance Tool: the single, authoritative data source for the determination of positive and negative cases within the Veterans Health Administration.

The index date for all analyses was defined as the date of the earliest positive test (for COVID-19-positive patients) or the date of the earliest negative test (for COVID-19-negative patients), unless the patient had been admitted to a VA hospital during the preceding 15 days, in which case the date of admission served as the index date.

2.3. Study Population

We identified patients who were tested for COVID-19 at VA facilities between 20 February 2020 and 27 March 2021, for any indication, and who had at least one primary care follow-up in the previous 18 months. We excluded patients who are defined as employees and others, keeping only veterans with proven established care at the VA healthcare system. We excluded patients who died within 3 months of the index date or who did not have a minimum of 3 months of follow-up after the index date.

COVID-19-positive patients who were initially admitted and then discharged were categorized as the COVID-19-positive hospitalized cohort, whereas COVID-19 positive patients who were managed as outpatients at the time of diagnosis were categorized as the COVID-19-positive outpatient cohort.

Patients who were admitted and then discharged for other health conditions during the study period with consistent COVID-19 negative tests were categorized as COVID-19-negative hospitalized cohort, whereas patients who had COVID-19 negative tests and were managed as outpatients were categorized as the COVID-19-negative outpatient cohort.

2.4. Data Extraction

Available data included demographics variables like age, sex, ethnicity, race, body-mass index, and comorbid conditions. We extracted baseline comorbid conditions from CDW based on ICD-10 diagnosis codes occurring in the 2 years prior to the index date from outpatient or inpatient setting. We used the Charlson Comorbidity Index (CCI) to estimate the overall burden of baseline comorbidity.

Prevalent conditions are collected for all patients. To be considered, a prevalent health condition should have been previously recorded as ICD-10 codes in either inpatient or outpatient settings any time before the index date. For an example, to define that a patient has ischemic heart disease as a prevalent health condition, he/she should have one of the listed ICD-10 codes (ischemic heart disease—I20, I21, I22, I23 or I25) on any previous inpatient or outpatient visit. Detailed list of all ICD-10 codes for all physical and mental health conditions are listed in the supplement.

Incident conditions are defined as the development of new physical and mental health conditions (ICD-10 codes) during the follow-up, in the patients who did not have those physical and mental health conditions (ICD-10 codes) as prevalent conditions before the index date. The follow-up period is defined as 7 days to 3 months after the index date. For example, if the patient did not have a depressive episode diagnosis (ICD-10 code F32) before the index date and was subsequently, during the follow-up period, diagnosed with a depressive episode based on the ICD-10 code, then it will be considered an incident condition.

2.5. Outcomes

The primary outcome was the development of new physical and mental health conditions (incidence) during follow-up period in the COVID-19 positive versus the COVID-19 negative patients.

We have analyzed the following four groups: (A) COVID-19-positive hospitalized patient. (B) COVID-19-negative hospitalized patients. (C) COVID-19-positive patients managed as an outpatient. (D) COVID-19-negative patients managed as an outpatient.

2.6. Statistical Analysis

Patient characteristics were summarized using means and standard deviations (std) for continuous variables and percentages for categorical variables, and differences were tested with *t*-tests and χ^2 tests, respectively.

Propensity score matching: To minimize the effects of potential confounders, and to adjust for the potential bias due to the nonrandom balance of the baseline characteristics between the COVID-19-positive and -negative patients, a propensity-matched analysis was applied [10]. Propensity scores were calculated for each subject as the predicted probability of testing positive for COVID-19 using a logistic regression model, adjusting for: age, sex, race, ethnicity, BMI, smoking status, CCI at 2 years, and state of residence. Since the patient is required to have a minimum of 3 months of the follow-up period, patients with an index date later than 27 December 2020 are not included in the analysis. Predominantly all patients were unvaccinated and infected with the initial strain of SARS-CoV-2. So, we did not match for vaccination status and SARS-CoV-2 variants. Patients were matched 1:1 without replacement using a nearest-neighbor approach with caliper restrictions. The covariate balance between the full and matched samples were evaluated using the standardized mean difference (see Supplement Section SX). Outcomes were analyzed in the propensity-matched samples using χ^2 tests and unadjusted logistic regressions.

Stratified analysis of the incidence of the different physical and mental conditions in the full sample and in the propensity-matched samples was performed to evaluate the differences between the COVID-19 positive and negative cohorts; stratified by being in the hospitalized or the outpatient cohorts. Then a comparison between the hospitalized patients and the outpatients was performed among the COVID-19-positive patients only. All analyses were limited to patients who did not have the outcome condition prior to the index date.

Incidence rates were compared in the propensity-matched samples using χ^2 tests. The odds ratios and 95% confidence intervals of acquiring the physical or mental condition between the comparison groups were estimated using unadjusted logistic regressions, regressing the mental or physical condition on the COVID-19 diagnosis status to compare between positive and negative cases, or on the hospitalization status to compare between the outpatient and hospitalized cohorts.

As a sensitivity analysis, the follow-up period was redefined as 15 days post index date to 3 months, and the outcomes were extracted from that period. All analyses were repeated using this definition. Another sensitivity analysis was performed by matching the hospitalized to outpatient patients among the COVID-19-positive sample. The comparison in the outcomes between hospitalized and outpatient cohorts was repeated using this matched sample.

All statistical analyses were performed using SAS Enterprise Guide version 8.2 (SAS Inc., Cary, NC, USA). Two-sided $p< 0.001$ was considered statistically significant.

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. This study was approved by the institutional review board of the Central Virginia VA healthcare system. Being a retrospective cohort analysis, a waiver of the informed consent was granted.

3. Results

Patients: We analyzed 1,309,075 patients from the VA healthcare system who were tested for COVID-19 during the study period of 20 February 2020 to 27 March 2021. After excluding various conditions as showed in Figure 1, we included 778,738 veterans for the final cohort analysis. Out of these, 149,205 (19.2%) were in the hospitalized cohort and 629,533 (80.8%) in the outpatient cohort, and 16,702 (11.2%) veterans were diagnosed with COVID-19 in the hospitalized cohort, while 107,055 (17.0%) veterans were diagnosed with COVID-19 in the outpatient cohort (Figure 1).

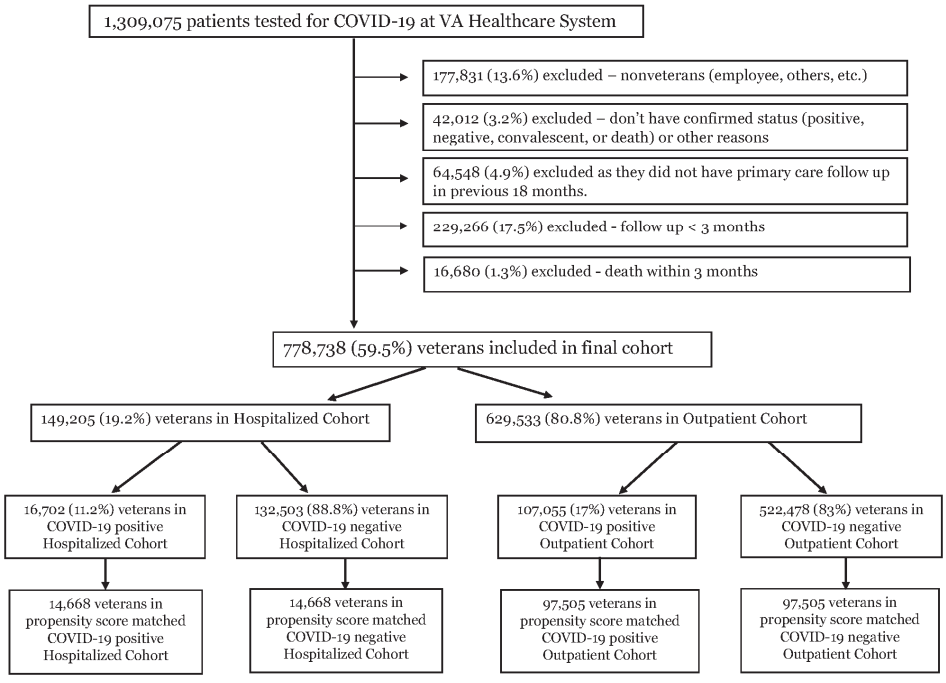


Figure 1. Flowchart.

Mean age was 61 (±15.4). Most of the patients were male (89%), non-Hispanic ethnicity (88%), and White (68%). (Table S1). In bivariate analysis of demographic variables at baseline, Hispanic ethnicity, Black race, and higher BMI are associated with COVID-19 positivity. However, slightly higher comorbidity burden (CCI) and older age were found in COVID-19 negative patients (Table 1).

Incidence of physical and mental health conditions between COVID-19-negative and COVID-19-positive patients' unmatched samples, stratified by the hospitalized and outpatient cohort, is reported in Table S2.

After propensity-score-matched analysis, the hospitalized COVID-19-positive and -negative groups had 14,668 patients each, and each of the outpatient COVID-19-positive and -negative groups had 97,505 patients (Figure 1).

Incidence of the physical and mental health conditions is reported in Table 2. Likelihoods of developing the physical and mental health conditions among COVID-19-positive patients compared to COVID-19-negative patients are reported in Figure 2.

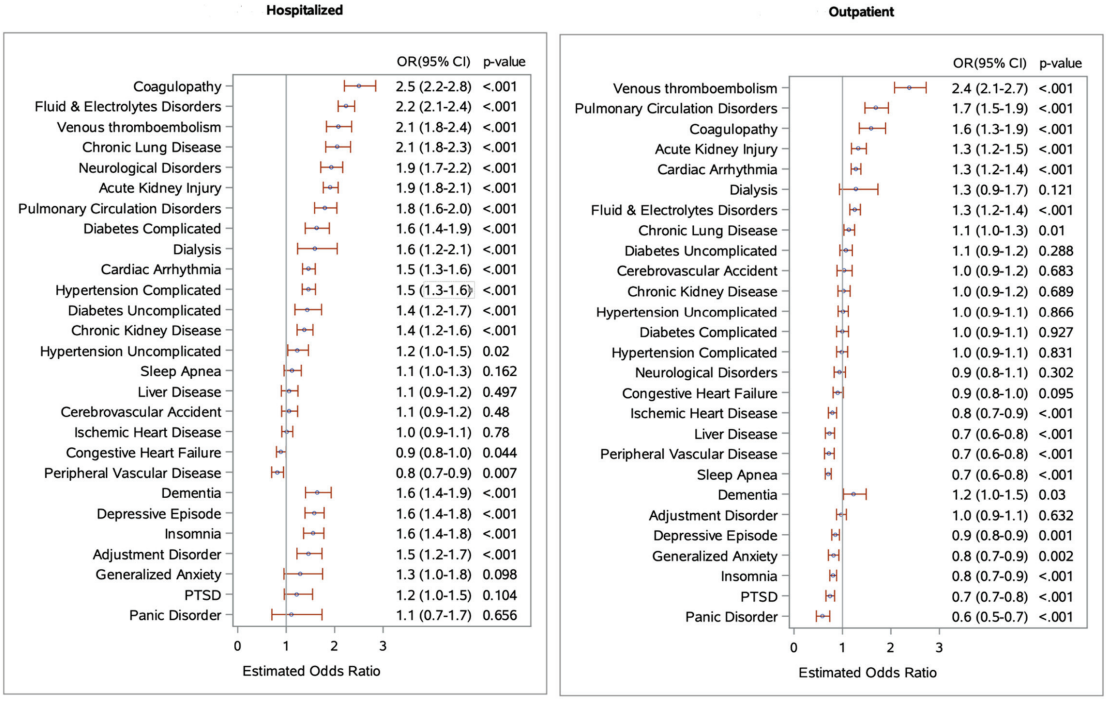


Figure 2. Likelihood of development of new physical and mental health conditions in COVID-19-positive patients compared to COVID-19-negative patients. The figure (**a**) represents the odds ratio for the development of new physical and mental health conditions among propensity-score-matched hospitalized COVID-19 positive patients versus hospitalized COVID-19-negative patients during the follow-up period of 7 days to 3 months of diagnosis. For example—COVID-19-positive patients are 1.4 times (OR: 1.4, 95% CI 1.2–1.6) more likely to develop chronic kidney disease than COVID-19-negative patients during the follow-up period of 7 days to 3 months of diagnosis. The figure (**b**) represents the odds ratio for the development of new physical and mental health conditions among matched outpatient COVID-19-positive patients versus outpatient COVID-19-negative patients.

Table 1. Baseline Characteristics of patients in different cohorts.

	Hospitalized Cohort				Outpatient Cohort			
	Total, *n* (%)	**COVID-19-Negative, *n* (%)**	**COVID-19-Positive, *n* (%)**	***p* Value**	**Total, *n* (%)**	**COVID-19-Negative, *n* (%)**	**COVID-19-Positive, *n* (%)**	***p* Value**
Age, mean (±SD)	68.0 ± 12.8	68.1 ± 12.8	67.8 ± 13.3	0.02	59.4 ± 15.5	59.5 ± 15.4	58.4 ± 16.2	<0.001
Gender								
Male	140,125 (93.9%)	124,371 (93.9%)	15,754 (94.3%)	0.02	550,403 (87.4%)	455,736 (87.2%)	94,667 (88.4%)	<0.001
Female	9080 (6.1%)	8132 (6.2%)	948 (5.7%)		79,130 (12.6%)	66,742 (12.8%)	12,388 (11.6%)	
Ethnicity								
Non-Hispanic	135,545 (90.8%)	120,639 (91.0%)	14,906 (89.2%)	<0.001	552,005 (87.7%)	460,315 (88.1%)	91,690 (85.6%)	<0.001
Hispanic	9314 (6.2%)	7963 (6.0%)	1351 (8.09%)		56,244 (9.0%)	44,698 (8.6%)	11,546 (10.8%)	
Unknown	4346 (2.9%)	3901 (2.9%)	445 (2.7%)		21,284 (3.3%)	17,465 (3.3%)	3819 (3.6%)	
Race								
White	103,974 (69.7%)	93,517 (70.6%)	10,457 (62.6%)	<0.001	426,534 (67.8%)	354,595 (67.9%)	71,939 (67.2%)	<0.001
Black or African American	34,237 (22.9%)	29,344 (22.1%)	4893 (29.3%)		140,655 (22.3%)	116,821 (22.4%)	23,834 (22.3%)	
American Indian or Alaska Native	1121 (0.8%)	973 (0.7%)	148 (0.9%)		5178 (0.8%)	4159 (0.8%)	1019 (1.0%)	
Asian	807 (0.5%)	687 (0.5%)	120 (0.7%)		8045 (1.3%)	6990 (1.3%)	1055 (1.0%)	
Native Hawaiian or Other Pacific Islander	1009 (0.7%)	862 (0.7%)	147 (0.9%)		5921 (0.9%)	4906 (0.9%)	1015 (1.0%)	
BMI, mean (±SD)	29.2 ± 6.96	29.1 ± 6.94	30.1 ± 7.04	<0.001	30.3 ± 6.23	30.1 ± 6.21	31.2 ± 6.23	<0.001
CCI, mean (±SD)	3.18 ± 2.73	3.18 ± 2.73	3.14 ± 2.73	0.09	1.66 ± 2.08	1.70 ± 2.11	1.48 ± 1.94	<0.001

Table 2. Incidence of physical and mental conditions between COVID-19-negative vs. -positive patients (Matched sample).

	Hospitalized Cohort			Outpatient Cohort		
	COVID-19 Negative, *n* (%)	**COVID-19 Positive, *n* (%)**	***p* Value**	**COVID-19 Negative, *n* (%)**	**COVID-19 Positive, *n* (%)**	***p* Value**
Pulmonary						
Venous Thromboembolism	384 (2.9%)	769 (5.8%)	<0.001	293 (0.3%)	696 (0.7%)	<0.001
Pulmonary Circulation Disorders	386 (2.9%)	673 (5.1%)	<0.001	299 (0.3%)	507 (0.5%)	<0.001
Sleep Apnea	306 (3.4%)	330 (3.8%)	0.16	1238 (2.1%)	906 (1.5%)	<0.001
Chronic Lung Disease	404 (4.3%)	768 (8.4%)	<0.001	777 (1.1%)	907 (1.2%)	0.01
Renal						
Acute Kidney Injury	1070 (9.3%)	1834 (16.4%)	<0.001	506 (0.6%)	677 (0.7%)	<0.001
Chronic Kidney Disease	510 (4.8%)	665 (6.5%)	<0.001	514 (0.6%)	523 (0.6%)	0.69
Dialysis	98 (0.7%)	154 (1.1%)	<0.001	73 (0.1%)	93 (0.1%)	0.12

Table 2. *Cont.*

	Hospitalized Cohort			Outpatient Cohort		
	COVID-19 Negative, *n* (%)	**COVID-19 Positive, *n* (%)**	***p* Value**	**COVID-19 Negative, *n* (%)**	**COVID-19 Positive, *n* (%)**	***p* Value**
Cardiovascular						
Ischemic Heart Disease	664 (7.5%)	679 (7.6%)	0.78	751 (1.0%)	601 (0.8%)	<0.001
Cerebrovascular Accident	321 (2.5%)	332 (2.7%)	0.48	333 (0.4%)	342 (0.4%)	0.68
Congestive Heart Failure	717 (6.6%)	644 (6.0%)	0.04	610 (0.7%)	557 (0.6%)	0.10
Peripheral Vascular Disease	386 (3.5%)	319 (2.8%)	0.007	486 (0.6%)	355 (0.4%)	<0.001
Cardiac Arrhythmia	929 (10.9%)	1317 (15.2%)	<0.001	1106 (1.5%)	1442 (1.9%)	<0.001
Hypertension Uncomplicated	270 (10.6%)	312 (12.7%)	0.02	717 (2.0%)	720 (2.0%)	0.87
Hypertension Complicated	845 (8.5%)	1168 (12.0%)	<0.0001	590 (0.7%)	585 (0.7%)	0.83
Endocrine						
Diabetes Uncomplicated	192 (2.4%)	249 (3.4%)	<0.001	529 (0.8%)	539 (0.8%)	0.29
Diabetes Complicated	289 (3.3%)	428 (5.2%)	<0.001	525 (0.7%)	506 (0.7%)	0.93
Others						
Liver Disease	294 (2.4%)	311 (2.5%)	0.50	546 (0.6%)	407 (0.5%)	<0.001
Coagulopathy	341 (2.6%)	817 (6.1%)	<0.001	219 (0.2%)	351 (0.4%)	<0.001
Fluid and Electrolytes Disorders	1229 (12.6%)	2316 (24.4%)	<0.001	912 (1.1%)	1167 (1.4%)	<0.001
Neurological Disorders	458 (3.8%)	817 (7.1%)	<0.001	512 (0.6%)	484 (0.6%)	0.30
Mental Disorders						
Depressive Episode	428 (4.3%)	655 (6.6%)	<0.001	979 (1.5%)	875 (1.3%)	<0.001
Panic Disorder	36 (0.3%)	40 (0.3%)	0.66	189 (0.2%)	111 (0.1%)	<0.001
Generalized Anxiety	74 (0.5%)	96 (0.7%)	0.10	481 (0.6%)	394 (0.4%)	0.002
PTSD	126 (1.1%)	151 (1.4%)	0.10	625 (1.0%)	486 (0.7%)	<0.001
Adjustment Disorders	214 (1.7%)	308 (2.5%)	<0.001	730 (0.9%)	720 (0.9%)	0.63
Insomnia	367 (3.2%)	553 (4.9%)	<0.001	1118 (1.5%)	932 (1.2%)	<0.001
Dementia	251 (1.9%)	393 (3.0%)	<0.001	197 (0.2%)	240 (0.3%)	0.03

3.1. COVID-19 Positive versus Negative Comparisons

Pulmonary: In the hospitalized cohort, COVID-19 diagnosis is associated with a 5.8% incidence of venous thromboembolism (VTE) compared to 2.9% in the COVID-19-negative group ($p < 0.001$). Similarly, the incidence of pulmonary circulation disorder and chronic lung disease are 5.1% and 8.4% in the COVID-19-positive group, compared to 2.9% and 4.3% in the COVID-19-negative group, respectively ($p < 0.001$). When we compared the outpatient cohort, we found that COVID-19 diagnosis is associated with a rise in the incidence of the above conditions, but the incidence rate is much smaller. (Table 2).

Renal: In the hospitalized cohort, we noted a 16.4% incidence of acute kidney injury (AKI) in the COVID-19-positive group compared to 9.3% in the COVID-19-negative group ($p < 0.001$). Interestingly, AKI incidence was also high in the COVID-19-positive outpatient cohort. Incidence of dialysis (1.1% vs. 0.69%, $p < 0.001$) and chronic kidney disease (CKD) (6.5% vs. 4.8%, $p < 0.001$) were high in the hospitalized COVID-19-positive group compared to the hospitalized COVID-19-negative group. However, they were not much different in the outpatient cohort. (Table 2).

Cardiovascular: We found a higher incidence of cardiac arrhythmias (15.2% vs. 10.9%, $p < 0.001$) and complicated hypertension (12% vs. 8.5%, $p < 0.001$) in hospitalized COVID-19-positive patients versus hospitalized COVID-19-negative patients. A higher incidence of cardiac arrhythmias (1.9% vs. 1.5%, $p < 0.001$) was also noted in the outpatient setting in the COVID-19-positive patients. Interestingly, the incidence of CHF and PVD were higher in hospitalized COVID-19-negative cohort, while the incidence of ischemic heart disease and cerebrovascular accidents (CVA) were not much different between groups. (Table 2).

Other physical conditions: COVID-19 diagnosis was also associated with higher incidence of fluid and electrolyte disorders (24.4% vs. 12.6%, $p < 0.001$), coagulopathy (6.1% vs 2.6%, $p < 0.001$), and neurological disorders (7.1% vs. 3.8%, $p < 0.001$) in the hospitalized cohort. Even with the outpatient cohort, a higher incidence of coagulopathy and fluid–electrolyte disorder were noted, but absolute values were low. (Table 2).

Mental health disorders: In the hospitalized cohort, COVID-19 was associated with a significantly higher incidence of depressive disorder (6.6% vs. 4.3%, $p < 0.001$), adjustment disorder (2.5% vs. 1.7%, $p < 0.001$), insomnia (4.9% vs. 3.2%, $p < 0.001$), and dementia (3.0% vs. 1.9%, $p < 0.001$) compared to the matched COVID-19-negative patients. There was not much difference in the outpatient cohort. (Table 2).

3.2. COVID-19 Positive Patients Hospitalized versus Outpatient Comparison

This comparison showed that hospitalized patients with COVID-19 had a significantly higher incidence and odds of development of physical and mental health conditions compared to those who were managed as an outpatient. (Table 3, Figure S1).

Table 3. Incidence of physical and mental conditions between COVID-19-positive hospitalized vs. COVID-19-positive outpatient cohort (matched sample).

All COVID-19-Positive Patients	TOTAL, *n* (%)	Hospitalized, *n* (%)	Outpatients, *n* (%)	*p* Value
Pulmonary				
Venous Thromboembolism	912 (3.37%)	763 (5.74%)	149 (1.08%)	<0.001
Pulmonary Circulation Disorders	790 (2.92%)	667 (5.03%)	123 (0.892%)	<0.001
Sleep Apnea	457 (2.59%)	333 (3.83%)	124 (1.39%)	<0.001
Chronic Lung Disease	950 (5.09%)	769 (8.44%)	181 (1.89%)	<0.001
Renal				

Table 3. *Cont.*

All COVID-19-Positive Patients	TOTAL, *n* (%)	Hospitalized, *n* (%)	Outpatients, *n* (%)	*p* Value
Acute Kidney Injury	2013 (8.45%)	1826 (16.3%)	187 (1.48%)	<0.001
Chronic Kidney Disease	777 (3.75%)	664 (6.48%)	113 (1.08%)	<0.001
Dialysis	186 (0.661%)	154 (1.10%)	32 (0.226%)	<0.001
Cardiovascular				
Ischemic Heart Disease	799 (4.32%)	675 (7.56%)	124 (1.30%)	<0.001
Cerebrovascular Accident	409 (1.63%)	334 (2.69%)	75 (0.588%)	<0.001
Congestive Heart Failure	799 (3.55%)	642 (5.94%)	157 (1.34%)	<0.001
Peripheral Vascular Disease	407 (1.77%)	318 (2.82%)	89 (0.758%)	<0.001
Cardiac Arrhythmia	1560 (8.46%)	1312 (15.1%)	248 (2.53%)	<0.001
Hypertension Uncomplicated	396 (7.28%)	312 (12.6%)	84 (2.82%)	<0.001
Hypertension Complicated	1326 (6.46%)	1165 (11.9%)	161 (1.50%)	<0.001
Endocrine				
Diabetes Uncomplicated	333 (2.27%)	250 (3.42%)	83 (1.12%)	<0.001
Diabetes Complicated	514 (3.07%)	431 (5.21%)	83 (0.979%)	<0.001
Others				
Liver Disease	371 (1.50%)	310 (2.53%)	61 (0.486%)	<0.001
Coagulopathy	911 (3.37%)	811 (6.11%)	100 (.728%)	<0.001
Fluid and Electrolytes Disorders	2603 (12.5%)	2318 (24.4%)	285 (2.51%)	<0.001
Neurological Disorders	949 (3.98%)	815 (7.10%)	134 (1.09%)	<0.001
Mental Disorders				
Depressive Episode	783 (3.83%)	654 (6.56%)	129 (1.23%)	<0.001
Panic Disorder	56 (0.196%)	40 (0.280%)	16 (0.112%)	<0.001
Generalized Anxiety	133 (0.489%)	95 (0.698%)	38 (0.280%)	<0.001
PTSD	209 (0.953%)	151 (1.37%)	58 (0.532%)	<0.001
Adjustment Disorder	412 (1.64%)	304 (2.44%)	108 (0.855%)	<0.001
Insomnia	682 (2.97%)	550 (4.86%)	132 (1.13%)	<0.001
Dementia	465 (1.78%)	392 (3.04%)	73 (0.553%)	<0.001

The sensitivity analysis by redefining the follow-up period as 15 days post index date to 3 months showed consistent results for all outcomes. (Tables S3 and S4).

4. Discussion

In a large propensity-score-matched analysis of the Veteran population we found that COVID-19 survivors have a significantly higher rate of the development of new physical and mental health sequelae. The risk of developing these sequelae increase in those who required hospitalization for COVID-19.

Veterans are predisposed to several mental health disorders stemming from war-related and other exposures. This burden is higher among US veterans compared to the general population. After critical illnesses, a subgroup of patients develops adjustment disorders or even PTSD. We found that veterans who required hospitalization for COVID-19 have higher incidence of development of new mental health disorders, mainly depressive episodes, adjustment disorder, PTSD, insomnia, and dementia, compared to matched

COVID-19-negative hospitalized patients and the matched COVID-19-positive outpatient group. This increase was not trivial since it was 1.3 to 10 folds compared to the matched groups. The increase was highest in dementia, insomnia, and depressive disorder, and relatively lower for PTSD and panic episodes. These data extend other studies into the US veteran realm [1,11,12]. In a recently published French study, at 4-month follow-up telephone interviews 17.5% reported memory problems, and 20.7% reported cognitive symptoms [13] The neuroinvasive properties of SARS-CoV-2 and neuroinflammation are some of the speculative mechanisms that could explain higher neuropsychiatric manifestation in COVID-19 patients [3,4,14]. These are important consequences that need a priori goal-setting for the patient and the VHA system as a whole. Even under the usual circumstances, mental health disorders among veterans are independently associated with greater health care utilization, rates of disability, and mortality [15–17]. Social isolation, anxiety, fear of contagion, uncertainty, chronic stress, and the economic difficulties of the pandemic may lead to the development or exacerbation of depression, anxiety, substance use, and other psychiatric disorders among vulnerable populations [18]. Therefore, any additional increase in the incidence of mental health illnesses among veterans is a concerning finding and needs more attention to prevent long-term health consequences.

These mental health changes were accompanied by major alterations in renal, lung, cardiovascular, and thrombotic complications. As expected, lung-related complications were greater in those recovering from COVID-19 with almost double the incidence of chronic lung disease and pulmonary circulatory disorder in COVID-19 survivors. Our result is consistent with previously reported data, where 63–71% COVID-19 survivors had radiological abnormalities consistent with pulmonary dysfunction, 19% had fibrotic lesions in the lung, and 25–53% had decreased diffusion capacity for carbon monoxide [13,19,20]. These results focused on the lung complications, and validated the dataset and potentially the methodology used to determine the incidence of complications after COVID-19 in this dataset. Prior analyses of renal complications in patients post-COVID have shown a worsening eGFR trajectory, proteinuria, hematuria, and new-onset kidney failure as an outpatient [13,21]. Our analyses point towards a greater rate of AKI in hospitalized veterans with COVID-19 compared to those hospitalized without it. Since we excluded patients who died within 3 months, our AKI incidence is lower than previously reported in the literature [22]. Also, in keeping with prior literature, we found almost a doubling of VTE incidence in hospitalized COVID-19 survivors. This is likely exacerbated by endothelial dysfunction, cytokine release, and various pro-inflammatory milieux in this condition [23]. Previously reported data showed the incidence of VTEs almost up to 50%; however, it also carries a very high mortality rate [24,25]. Since we have excluded veterans who died within 3 months of having COVID-19, our reported incidence is lower. We also found a higher incidence of cardiac arrhythmia in COVID-19 survivors. Some prior uncontrolled studies that did not distinguish prevalence from incidence describe a rate of cardiac arrhythmia in COVID-19 in the range of 6–21% [26–28]. Medications, direct COVID-19 cardiac injury, or electrolyte disorders could be contributory [29].

We also found that the incidences of several other conditions were higher in COVID-19-negative survivors compared to those with COVID-19. Specifically, these were related to CHF and PVD. Similar behavior seen in other conditions such as cirrhosis [30], it is likely that patients seeking admission for COVID-19-unrelated issues during the pandemic are more advanced in their disease process. At baseline, US veterans have a larger comorbid condition burden than the general US population. In our cohort, this was demonstrated by the higher baseline Charleston comorbidity index in the COVID-19-negative group. Therefore, these results as a whole demonstrate that, despite propensity-matching, there is a selective increase in incidence of mental health, thromboembolic, pulmonary, and renal complications in hospitalized survivors of COVID-19 but not in the usual conditions responsible for pre-COVID-19 care in VHA, such as PVD and CHF. This adds confidence that the data is specific for COVID-19 and not simply a function of hospitalization during the pandemic in the VA system.

Our study has several strengths. We have a large study population with propensity-score-matched analysis to focus on COVID-19-related impacts, have also analyzed hospitalized to non-hospitalized COVID-19 patients, and done sensitivity analysis. Because we have relied on administrative data, our study is not subject to biases inherent in self-report studies or questionnaire-based studies of long COVID-19 outcomes.

Our study has several limitations. First, our study population is predominantly male veterans, so the result cannot be generalized to other US populations. Second, although, we have only included veterans with established primary care in the VA healthcare system, some veterans might have obtained the care outside the VA system. Third, we have only captured illness based on ICD-10 codes. Fourth, despite the propensity score-matching, there could be residual confounding factors. Fifth, since there is no consistent definition of post-acute sequelae, we were not able to determine pre-discharge variables that could determine who develops this diagnosis. Instead, we treated all new diseases as potentially related to COVID-19 and analyzed the severity of COVID-19 (hospitalized or not) as a comparator. Lastly, clinicians might have paid more attention to the patient during the follow-up visit after the COVID-19 diagnosis and that could have led to improved detection of the health conditions (e.g., dementia), which had been present but remained undiagnosed before COVID-19 diagnosis.

We conclude that in a large propensity-score-matched analysis, veterans who survived COVID-19 developed new physical and mental health comorbidities at a much higher rate compared to those who were hospitalized without COVID-19 and those with COVID-19 without hospitalization. Since, veterans have a higher comorbidity burden to begin with, any additional increase in the incidence of physical and mental health sequelae resulting from COVID-19 is a concerning finding that needs to inform policy and healthcare system changes within the VHA and beyond.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11123390/s1.

Author Contributions: Conceptualization, N.P. and J.S.B.; methodology, N.P. and B.D.; software, B.D.; validation, N.P., J.S.B. and B.D.; formal analysis, B.D.; data curation, B.D.; writing—original draft preparation, N.P.; writing—review and editing, N.P., B.D., J.S.B.; visualization, B.D.; supervision, N.P.; project administration, N.P.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of McGuire VA Medical Center (protocol ID 02599 and date of approval 07/07/2020).

Informed Consent Statement: Patient consent was waived due to retrospective cohort analysis.

Acknowledgments: This study was supported using data from the VA COVID-19 Shared Data Resource. This work was supported using resources and facilities of the Department of Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI), VA HSR RES 13-457.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Huang, C.; Huang, L.; Wang, Y.; Li, X.; Ren, L.; Gu, X.; Kang, L.; Guo, L.; Liu, M.; Zhou, X.; et al. 6-month consequences of COVID-19 in patients discharged from hospital: A cohort study. *Lancet* **2021**, *397*, 220–232. [CrossRef]
2. Venkatesan, P. NICE guideline on long COVID. *Lancet Respir. Med.* **2021**, *9*, 129. [CrossRef]
3. Fisicaro, F.; Di Napoli, M.; Liberto, A.; Fanella, M.; Di Stasio, F.; Pennisi, M.; Bella, R.; Lanza, G.; Mansueto, G. Neurological Sequelae in Patients with COVID-19: A Histopathological Perspective. *Int. J. Environ. Res. Public Health* **2021**, *18*, 1415. [CrossRef] [PubMed]
4. Tan, B.-H.; Liu, J.-M.; Gui, Y.; Wu, S.; Suo, J.-L.; Li, Y.-C. Neurological involvement in the respiratory manifestations of COVID-19 patients. *Aging* **2021**, *13*, 4713–4730. [CrossRef] [PubMed]

5. Roshdy, A.; Zaher, S.; Fayed, H.; Coghlan, J.G. COVID-19 and the Heart: A Systematic Review of Cardiac Autopsies. *Front. Cardiovasc. Med.* **2020**, *7*, 626975. [CrossRef] [PubMed]
6. Bhatnagar, J.; Gary, J.; Reagan-Steiner, S.; Estetter, L.B.; Tong, S.; Tao, Y.; Denison, A.M.; Lee, E.; DeLeon-Carnes, M.; Li, Y.; et al. Evidence of SARS-CoV-2 Replication and Tropism in the Lungs, Airways and Vascular Endothelium of Patients with Fatal COVID-19: An Autopsy Case-Series. *J. Infect. Dis.* **2021**, *223*, 752–764. [CrossRef] [PubMed]
7. Nelson, K.M.; Starkebaum, G.A.; Reiber, G.E. Veterans using and uninsured veterans not using Veterans Affairs (VA) health care. *Public Health Rep.* **2007**, *122*, 93–100. [CrossRef]
8. Randall, M.; Kilpatrick, K.E.; Pendergast, J.F.; Jones, K.R.; Vogel, W.B. Differences in patient characteristics between Veterans Administration and community hospitals. Implications for VA planning. *Med. Care* **1987**, *25*, 1099–1104. [CrossRef]
9. Kazis, L.E.; Miller, D.R.; Clark, J.; Skinner, K.; Lee, A.; Rogers, W.; Spiro, A., 3rd; Payne, S.; Fincke, G.; Selim, A.; et al. Health-related quality of life in patients served by the Department of Veterans Affairs: Results from the Veterans Health Study. *Arch. Intern. Med.* **1998**, *158*, 626–632. [CrossRef]
10. Austin, P.C. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivar. Behav. Res.* **2011**, *46*, 399–424. [CrossRef]
11. Taquet, M.; Luciano, S.; Geddes, J.R.; Harrison, P.J. Bidirectional associations between COVID-19 and psychiatric disorder: Retrospective cohort studies of 62,354 COVID-19 cases in the USA. *Lancet Psychiatry* **2021**, *8*, 130–140. [CrossRef]
12. Wang, Y.; Zhu, L.Y.; Ma, Y.F.; Bo, H.X.; Deng, H.B.; Cao, J.; Wang, Y.; Wang, X.J.; Xu, Y.; Lu, Q.D.; et al. Association of insomnia disorder with sociodemographic factors and poor mental health in COVID-19 inpatients in China. *Sleep Med.* **2020**, *75*, 282–286. [CrossRef] [PubMed]
13. The Writing Committee for the COMEBAC Study Group; Morin, L.; Savale, L.; Pham, T.; Colle, R.; Figueiredo, S.; Harrois, A.; Gasnier, M.; Lecoq, A.-L.; Meyrignac, O.; et al. Four-Month Clinical Status of a Cohort of Patients After Hospitalization for COVID-19. *JAMA* **2021**, *325*, 1525. [CrossRef] [PubMed]
14. Borah, P.; Deb, P.K.; Chandrasekaran, B.; Goyal, M.; Bansal, M.; Hussain, S.; Shinu, P.; Venugopala, K.N.; Al-Shar'i, N.A.; Deka, S.; et al. Neurological Consequences of SARS-CoV-2 Infection and Concurrence of Treatment-Induced Neuropsychiatric Adverse Events in COVID-19 Patients: Navigating the Uncharted. *Front. Mol. Biosci.* **2021**, *8*, 627723. [CrossRef] [PubMed]
15. Trivedi, R.B.; Post, E.P.; Sun, H.; Pomerantz, A.; Saxon, A.J.; Piette, J.D.; Maynard, C.; Arnow, B.; Curtis, I.; Fihn, S.D.; et al. Prevalence, Comorbidity, and Prognosis of Mental Health Among US Veterans. *Am. J. Public Health* **2015**, *105*, 2564–2569. [CrossRef] [PubMed]
16. Nichter, B.; Norman, S.; Haller, M.; Pietrzak, R.H. Physical health burden of PTSD, depression, and their comorbidity in the U.S. veteran population: Morbidity, functioning, and disability. *J. Psychosom. Res.* **2019**, *124*, 109744. [CrossRef]
17. Hall, K.S.; Beckham, J.C.; Bosworth, H.B.; Sloane, R.; Pieper, C.F.; Morey, M.C. PTSD is negatively associated with physical performance and physical function in older overweight military veterans. *J. Rehabil. Res. Dev.* **2014**, *51*, 285–296. [CrossRef]
18. Sher, L. The impact of the COVID-19 pandemic on suicide rates. *QJM* **2020**, *113*, 707–712. [CrossRef]
19. Zhao, Y.-M.; Shang, Y.-M.; Song, W.-B.; Li, Q.-Q.; Xie, H.; Xu, Q.-F.; Jia, J.-L.; Li, L.-M.; Mao, H.-L.; Zhou, X.-M.; et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* **2020**, *25*, 100463. [CrossRef]
20. Huang, Y.; Tan, C.; Wu, J.; Chen, M.; Wang, Z.; Luo, L.; Zhou, X.; Liu, X.; Huang, X.; Yuan, S.; et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir. Res.* **2020**, *21*, 163. [CrossRef]
21. Nugent, J.; Aklilu, A.; Yamamoto, Y.; Simonov, M.; Li, F.; Biswas, A.; Ghazi, L.; Greenberg, J.H.; Mansour, S.G.; Moledina, D.G.; et al. Assessment of Acute Kidney Injury and Longitudinal Kidney Function After Hospital Discharge Among Patients With and Without COVID-19. *JAMA Netw. Open* **2021**, *4*, e211095. [CrossRef]
22. Chan, L.; Chaudhary, K.; Saha, A.; Chauhan, K.; Vaid, A.; Zhao, S.; Paranjpe, I.; Somani, S.; Richter, F.; Miotto, R.; et al. AKI in Hospitalized Patients with COVID-19. *J. Am. Soc. Nephrol.* **2021**, *32*, 151–160. [CrossRef] [PubMed]
23. Loo, J.; Spittle, D.A.; Newnham, M. COVID-19, immunothrombosis and venous thromboembolism: Biological mechanisms. *Thorax* **2021**, *76*, 412–420. [CrossRef] [PubMed]
24. Wichmann, D.; Sperhake, J.P.; Lütgehetmann, M.; Steurer, S.; Edler, C.; Heinemann, A.; Heinrich, F.; Mushumba, H.; Kniep, I.; Schröder, A.S.; et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19. *Ann. Intern. Med.* **2020**, *173*, 268–277. [CrossRef] [PubMed]
25. Middeldorp, S.; Coppens, M.; Van Haaps, T.F.; Foppen, M.; Vlaar, A.P.; Müller, M.C.A.; Bouman, C.C.S.; Beenen, L.F.M.; Kootte, R.S.; Heijmans, J.; et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J. Thromb. Haemost.* **2020**, *18*, 1995–2002. [CrossRef]
26. Wang, D.; Hu, B.; Hu, C.; Zhu, F.; Liu, X.; Zhang, J.; Wang, B.; Xiang, H.; Cheng, Z.; Xiong, Y.; et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* **2020**, *323*, 1061–1069. [CrossRef]
27. Gopinathannair, R.; Merchant, F.M.; Lakkireddy, D.R.; Etheridge, S.P.; Feigofsky, S.; Han, J.K.; Kabra, R.; Natale, A.; Poe, S.; Saha, S.A.; et al. COVID-19 and cardiac arrhythmias: A global perspective on arrhythmia characteristics and management strategies. *J. Interv. Card. Electrophysiol.* **2020**, *59*, 329–336. [CrossRef]
28. Sala, S.; Peretto, G.; De Luca, G.; Farina, N.; Campochiaro, C.; Tresoldi, M.; Dagna, L.; Zangrillo, A.; Gulletta, S.; Della Bella, P. Low prevalence of arrhythmias in clinically stable COVID-19 patients. *Pacing Clin. Electrophysiol.* **2020**, *43*, 891–893. [CrossRef]

29. Manolis, A.S.; Manolis, T.A.; Apostolopoulos, E.J.; Papatheou, D.; Melita, H. COVID-19 infection and cardiac arrhythmias. *Trends Cardiovasc. Med.* **2020**, *30*, 451–460. [CrossRef]
30. Bajaj, J.S.; Garcia-Tsao, G.; Biggins, S.W.; Kamath, P.S.; Wong, F.; McGeorge, S.; Shaw, J.; Pearson, M.; Chew, M.; Fagan, A.; et al. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: Multicentre matched cohort. *Gut* **2021**, *70*, 531–536. [CrossRef]

Journal of
Clinical Medicine

MDPI

Article

Multimorbidity and Frailty Are the Key Characteristics of Patients Hospitalized with COVID-19 Breakthrough Infection during Delta Variant Predominance in Italy: A Retrospective Study

Andrea Ticinesi [1,2,*], Alberto Parise [2], Nicoletta Cerundolo [2], Antonio Nouvenne [2], Beatrice Prati [2], Giulia Chiussi [2], Angela Guerra [1,2] and Tiziana Meschi [1,2]

[1] Department of Medicine and Surgery, University of Parma, Via Antonio Gramsci 14, 43126 Parma, Italy
[2] Geriatric-Rehabilitation Department, Azienda Ospedaliero-Universitaria di Parma, Via Antonio Gramsci 14, 43126 Parma, Italy
* Correspondence: andrea.ticinesi@unipr.it

Abstract: The aims of this study were to describe the characteristics of patients hospitalized with delta SARS-CoV-2 breakthrough infection, and to identify factors associated with pneumonia on chest Computed Tomography (CT) and mortality. The clinical records of 229 patients (105 F), with a median age of 81 (interquartile range, IQR, 73–88) years old, hospitalized between June and December 2021 after completion of the primary vaccination cycle, were retrospectively analyzed, retrieving data on comorbidities, Clinical Frailty Scale (CFS), clinical presentation and outcomes. Multimorbidity (91.7% with ≥2 chronic illnesses) and frailty (61.6% with CFS ≥ 5) were highly prevalent. CFS (OR 0.678, 95% CI 0.573–0.803, $p < 0.001$) and hypertension were independently associated with interstitial pneumonia. Mortality was 25.1% and unrelated with age. PaO_2/FiO_2 on blood gas analysis performed upon admission (OR 0.986, 95% CI 0.977–0.996, $p = 0.005$), and CFS (OR 1.723, 95% CI 1.152–2.576, $p = 0.008$) were independently associated with mortality only in subjects < 85 years old. Conversely, serum PCT levels were associated with mortality in subjects ≥ 85 years old (OR 3.088, 95% CI 1.389–6.8628, $p = 0.006$). In conclusion, hospitalization for COVID-19 breakthrough infection mainly involved geriatric patients, with those aged ≥ 85 more characterized by decompensation of baseline comorbidities rather than typical COVID-19 respiratory symptoms.

Keywords: SARS-CoV-2; vaccine failure; viral pneumonia; geriatric patient; comorbidity

Citation: Ticinesi, A.; Parise, A.; Cerundolo, N.; Nouvenne, A.; Prati, B.; Chiussi, G.; Guerra, A.; Meschi, T. Multimorbidity and Frailty Are the Key Characteristics of Patients Hospitalized with COVID-19 Breakthrough Infection during Delta Variant Predominance in Italy: A Retrospective Study. *J. Clin. Med.* **2022**, *11*, 5442. https://doi.org/10.3390/jcm11185442

Academic Editors: Filippo Migliorini and Riccardo Giorgino

Received: 31 August 2022
Accepted: 15 September 2022
Published: 16 September 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Mass vaccination campaigns against Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) have substantially modified the clinical and epidemiologic characteristics of Coronavirus Disease-19 (COVID-19) [1]. Vaccines have shown a good, though incomplete, capacity of hindering SARS-CoV-2 transmission by reducing viral loads and duration of viral shedding [2,3] and have substantially mitigated the burden of COVID-19 symptoms, namely fever and dyspnea, in subjects with breakthrough infection [4].

Several studies have confirmed that the clinical course and outcomes of COVID-19 are substantially different in vaccinated subjects, with lower risk of hospital admission, progression to severe disease, need of oxygen or ventilatory support, and death [5–13]. In the earliest phases of the vaccination campaign, these results were also reported for older patients [6], whose high burden of chronic illnesses and frailty was associated with increased risk of severe COVID-19 course in the pre-vaccination era [14,15].

However, a population study based in England has recently shown that SARS-CoV-2 vaccine breakthrough infections may still retain substantial clinical severity and risk of adverse outcomes in selected high-risk groups, including older, immunocompromised or

dialyzed subjects [16]. A nation-wide study from Scotland pointed out that severe course of COVID-19 breakthrough infection, requiring hospitalization, was significantly associated with age ≥ 80 years old, ≥5 chronic diseases and previous hospital admission for other reasons [17]. Several conditions frequently present in older age, including diabetes [18], cancer [19] and dementia [20], have also been associated with increased risk of breakthrough SARS-CoV-2 infection and clinical severity.

Interestingly, in a recent systematic review and meta-analysis of studies comparing the clinical manifestations of COVID-19 between vaccinated and unvaccinated subjects, breakthrough infection was not associated with reduced risk of hospitalization, invasive ventilation or mortality [21]. This apparently puzzling result could however be influenced by changes of the characteristics of patients requiring hospitalization for COVID-19, with more subjects with pre-existing frailty and multimorbidity and more admissions for reasons unrelated to SARS-CoV-2 infection [22].

In the second half of 2021, concomitantly with the surge of the SARS-CoV-2 delta variant, breakthrough infections have accounted for a substantial and increasing portion of COVID-19 hospitalizations in developed countries and particularly in Italy, due to the high rates of vaccination reached among the general population [23]. In spite of this, few reports have systematically described the clinical characteristics of these patients in terms of comorbidities, frailty, clinical presentation and care needs during hospital stay.

The objective of this retrospective single-center study was thus to describe the clinical features, outcomes and care needs of patients admitted with COVID-19 breakthrough infection in a large regional hospital in Northern Italy in the period of maximum circulation of the delta variant (June–December 2021), and to identify factors associated with the presence of interstitial pneumonia and adverse outcome.

2. Materials and Methods

2.1. Study Design, Setting, and Population

The study was conducted at the Internal Medicine unit of the Geriatric-Rehabilitation Department of Parma University-Hospital, in Northern Italy. Since the earliest phases of the first pandemic wave, this unit was converted into a COVID-19 unit, serving a catchment area of around 450,000 inhabitants (province of Parma, Emilia-Romagna region) [24]. In 2021, the main criterion for admission to this unit was a positive reverse transcriptase-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 on nasopharyngeal swabs. Thus, admitted patients had COVID-19, but did not necessarily have respiratory involvement and the main reason of hospitalization could be, in some cases, unrelated to COVID-19.

Included in this retrospective study were all patients ≥ 18 years old who were admitted between 1 June and 31 December 2021 (period of maximum diffusion of the delta variant in Italy) with positive RT-PCR test and had completed the primary anti-SARS-CoV-2 vaccination cycle more than 14 days before admission (i.e., two doses of mRNA BNT162b2, mRNA-1273 or ChAdOx1-S vaccines, one dose of Ad26.COV2.S vaccine). In subjects with previous COVID-19 infection, the primary vaccination cycle was considered completed 14 days after receiving the first dose of any vaccine. Subjects who had already received a third "booster" dose of vaccine, recommended in Italy to over 65 and frail subjects from September 2021 and to all the general population from November 2021, were included as well.

All subjects who were vaccinated with other vaccines not approved for human use in the European Union, refused to complete the primary cycle after receiving a first dose, were exempted from vaccination for medical reasons, or completed the primary vaccination cycle in the fourteen days preceding admission were excluded from the study. Informed consent denial for data treatment was also another exclusion criterion.

2.2. Data Collection and Study Endpoints

Members of the study team reviewed all discharge forms and records of eligible patients, to retrieve information of interest. Data on chronic comorbidities, including

the Cumulative Illness Rating Scale (CIRS) [25], frailty measured with the Rockwood Clinical Frailty Scale (CFS) [26], drugs taken before admission, type and dates of anti-SARS-CoV-2 vaccine administration, duration and type of COVID-19-related symptoms before admission, if any, were collected. The CIRS Comorbidity Score (CIRS-CS) was calculated as the sum of ranks of disease severity, from 0 to 4, assigned to each of 14 items representing the main organs and systems involved by chronic diseases [25]. The CIRS Severity Index (CIRS-SI) was calculated as the number of items ranking 3 or 4 in the CIRS scale [25]. CFS ranked from 1 (very fit subject) to 9 (terminal illness) basing on clinical evaluation of each patient's physical and cognitive performance [26].

Vital signs, lab tests including arterial blood gas analysis and chest CT findings on admission were also considered, if available. The extension of chest CT involvement due to interstitial pneumonia was measured through calculation of the CT visual score, whose procedures are detailed elsewhere [27].

Administration of therapies against COVID-19 (corticosteroids, remdesivir, anti-interleukin-6 drugs), timing to the first RT-PCR test negative for SARS-CoV-2, maximal level of oxygen or ventilatory support needed, duration of hospital stay and need of escalation of care intensity (i.e., transferal to subintensive or intensive care units) were also considered as key elements for defining the clinical course.

The primary endpoint was the presence of severe forms of COVID-19 needing oxygen or ventilatory support and exhibiting a chest CT visual score of at least 5%. Hospital mortality and need of transferal to subintensive or intensive care units were considered as secondary endpoints.

To better describe the clinical characteristics and care needs of patients with COVID-19 breakthrough infection, after careful revision of the clinical presentation, course and resources used during hospital stay, study participants were also classified according to the following scale [22]:

- Asymptomatic for COVID-19 (admission for reasons unrelated to COVID-19, unexpected finding of a positive RT-PCR test);
- Paucisymptomatic for COVID-19 (complex clinical presentation with some symptoms compatible with COVID-19 in presence of another index disease requiring most diagnostic and therapeutical resources);
- Symptomatic for COVID-19 (typical presentation with frequent respiratory failure and positive chest CT findings).

2.3. Statistical Analyses

Continuous variables were expressed as median and interquartile range (IQR) and discrete variables as percentage. The clinical and laboratory characteristics of participants were compared after stratification according to chest CT findings (positive versus indeterminate or negative for COVID-19) using Mann–Whitney and chi square tests and, where appropriate, Quade non-parametric Ancova or logistic regression for adjustment for age and sex. A comparison of the clinical and laboratory characteristics was also made according to the categorization as asymptomatic, paucisymptomatic and symptomatic for COVID-19, using Kruskal–Wallis test with significance values adapted to Bonferroni correction for multiple testing, chi-square test, non-parametric Ancova and logistic regression tests for age and sex adjustments. Stepwise logistic regression tests were applied for identifying anamnestic clinical factors independently associated with the presence of interstitial pneumonia on chest CT.

The clinical and laboratory characteristics of participants were also compared after stratification by outcome (hospital mortality) with Mann–Whitney and chi square tests and, where appropriate, Quade non-parametric Ancova or logistic regression for adjustment for age and sex. The same tests were used to compare the characteristics of deceased subjects with and without radiological evidence of pneumonia. Logistic regression models, accounting for all variables with significant differences on descriptive analysis, were then

applied to identify factors independently associated with mortality on the whole population of participants and after stratification by age < 85 and ≥85 years old.

The SPSS package (v.28, IBM, Armonk, NY, USA) was used for analyses. *p* values were considered significant when <0.05.

3. Results

3.1. General Characteristics of Participants and Factors Associated with Positive Chest CT

A total number of 670 patients were admitted to the COVID-19 unit during the study period. Among these, 234 (34.9%) fulfilled inclusion criteria and were classified as having COVID-19 breakthrough infection. Since 5 patients denied informed consent for participation and data treatment, the study population was composed of 229 subjects (124 M, 105 F), with a median age of 81 (IQR 73–88) years old.

Participants had a very high burden of multimorbidity: 210 subjects out of 229 (91.7%) had ≥2 chronic conditions (median 5, IQR 3–7), with a CIRS Comorbidity Score median of 12 (IQR 7–16) and a CIRS Severity Index median of 2 (IQR 1–3). According to the CFS, 58 participants (25.3%) were classified as fit (CFS score 1–3), 30 (13.1%) as pre-frail (CFS score 4), 78 (34.1%) as moderately frail (CFS score 5–6), and 63 (27.5%) as severely frail (CFS score 7–9).

The characteristics of participants, stratified according to positive or negative/indeterminate chest CT findings for COVID-19, are depicted in Table 1. One hundred and thirty-eight patients (60.2%) had chest CT signs compatible with COVID-19 pneumonia. They were younger (age median 79, IQR 71–84, vs. 85, IQR 77–90 years old, $p < 0.001$), less frail (CFS scale median 5, IQR 3–6, vs. 6, IQR 5–7, $p = 0.005$ adjusted for age and sex), but had similar burden of multimorbidity (number of chronic illnesses median 4, IQR 3–6, vs. 5, IQR 3–7, $p = 0.692$ adjusted for age and sex) compared to patients with negative or indeterminate chest CT. The two groups also exhibited substantial differences in lab tests upon admission, but were similar for time elapsed between completion of the vaccine cycle and hospital admission.

Table 1. Comparison of the clinical and laboratory characteristics and outcomes of patients with breakthrough infection categorized according chest CT findings.

	CT Indeterminate or Negative (*n* = 91)	CT Positive (*n* = 138)	*p*	*p* *	*p* * < 0.05 OR
Demography and personal history					
Age, years	85 (77–90)	79 (71–84)	**<0.001**	-	
Females, %	53	41	0.090	-	
Chronic illnesses, number	5 (3–7)	4 (3–6)	0.316	0.692	
CFS score	6 (5–7)	5 (3–6)	**<0.001**	**0.005**	
Hypertension, %	56	65	0.164	**0.048**	1.80 (1.00–3.22)
Cardiac disease, %	54	45	0.188	0.369	
Diabetes, %	19	18	0.914	0.968	
Obesity, %	8	14	0.119	0.162	
Dyslipidemia, %	21	19	0.706	0.791	
CKD, %	15	12	0.408	0.672	
Cancer, %	7	5	0.628	0.658	
Dementia, %	32	24	0.186	0.845	
CIRS-CS	13 (8–17)	11 (7–16)	0.164	0.930	
CIRS-SI	2 (2–3)	2 (1–3)	0.095	0.845	
Vaccination anti-SARS-CoV-2					
Doses of vaccine received, n	2 (2–2)	2 (2–2)	0.258	0.731	
3 vaccine doses received, %	11	11	0.977	0.807	
Time from second vaccine dose, days	172 (98–219)	181 (104–232)	0.479	0.209	
Time from third vaccine dose, days	22 (14–45)	11 (5–22)	**0.048**	0.103	
BNT162b2 vaccine, %	63	69	0.331	0.278	
mRNA-1273 vaccine, %	27	7	**<0.001**	**0.001**	0.26 (0.11–0.58)
ChAdOx1-S vaccine, %	9	17	0.067	0.129	
Ad26.COV2.S vaccine, %	1	7	**0.049**	**0.044**	12.48 (1.07–146.27)

Table 1. *Cont.*

	CT Indeterminate or Negative (*n* = 91)	CT Positive (*n* = 138)	*p*	*p* *	*p* * < 0.05 OR
Clinical presentation upon admission					
PaO_2/FiO_2, mmHg	329 (293–376)	300 (265–354)	**0.010**	**0.002**	
Duration of symptoms, days	2 (1–4)	5 (3–7)	**<0.001**	**<0.001**	
Fever, %	29	70	**<0.001**	**<0.001**	5.40 (3.00–9.71)
Cough, %	18	43	**<0.001**	**<0.001**	3.49 (1.83–6.64)
Dyspnea, %	31	52	**0.001**	**<0.001**	3.18 (1.74–5.82)
Blood tests on admission					
Haemoglobin, g/dL	11.6 (10.7–13.2)	13.2 (11.9–14.3)	**<0.001**	**<0.001**	
Platelet count, 1000/mm^3	198 (147–264)	184 (155–253)	0.275	0.216	
Neutrophil count, n/mm^3	4187 (3050–6883)	4804 (3431–7942)	0.085	**0.028**	
Lymphocyte count, n/mm^3	1003 (771–1556)	928 (620–1403)	0.060	**0.008**	
Creatinine, mg/dL	0.9 (0.7–1.3)	0.9 (0.8–1.3)	0.317	0.113	
C-Reactive Protein, mg/L	39 (15–77)	75 (37–128)	**<0.001**	**<0.001**	
Procalcitonin, ng/mL	0.10 (0.06–0.22)	0.13 (0.07–0.38)	0.098	**0.019**	
D-dimer, ng/mL	1290 (544–2479)	704 (429–1273)	**0.004**	0.098	
CPK, IU/L	86 (45–187)	115 (64–242)	0.056	0.115	
LDH, IU/L	207 (173–236)	273 (220–341)	**<0.001**	**<0.001**	
AST, IU/L	26 (19–35)	32 (24–52)	**<0.001**	**0.001**	
Clinical course and outcome					
NIV, %	6	25	**<0.001**	**0.001**	5.41 (2.02–14.52)
IV, %	0	4	0.069	-	
Hospital death, %	24	26	0.746	0.080	
Time before RT-PCR negative, days	13 (7–22)	20 (11–25)	**0.023**	**0.007**	
Hospital stay, days	14 (8–23)	16 (9–28)	0.165	**0.027**	

CT = Computed Tomography; CFS = Clinical Frailty Scale; CKD = Chronic Kidney Disease; CIRS-CS = Cumulative Illness Rating Scale-Comorbidity Score; CIRS-SI = Cumulative Illness Rating Scale—Severity Index; CPK = Creatine Phosphokinase; LDH = Lactate Dehydrogenase; AST = Aspartate Aminotranspherase; NIV = Non-Invasive Ventilation; IV = Invasive mechanical Ventilation; RT-PCR = Reverse-Transcriptase Polymerase-Chain Reaction. Data are shown as median and IQR or percentages. Crude comparisons were made with Mann–Whitney test or chi-square test, as appropriate. * *p* adjusted for age and sex with Quade non-parametric Ancova or logistic regression. *p* values < 0.05 are indicated in bold.

Furthermore, 38 patients (16.5%, median age 83, IQR 73–89 years old) were classified as asymptomatic, 69 patients (30.1%, median age 86, IQR 81–90 years old) as paucisymptomatic, and 122 patients (53.4%, median age 78, IQR 70–83) as symptomatic. A comparison of the clinical and laboratory characteristics of patients included in these three categories is shown in Supplementary Material (Table S1).

At a stepwise multivariate logistic regression analysis, accounting for age, sex, CFS, CIRS-CS, chronic illnesses and timing from the last vaccine dose, the only variables with significant association with a positive chest CT were the CFS (OR 0.678, 95% CI 0.573–0.803, $p < 0.001$) and presence of hypertension (OR 1.883, 95% CI 1.049–3.380, $p = 0.034$).

3.2. Factors Associated with Mortality

Fifty-eight participants out of 229 (25.3%) died during hospital stay. The clinical characteristics of patients who died, in comparison with survivors, are shown in Table 2.

Patients who died were older, with higher CFS scores and more compromised respiratory exchanges upon admission. However, only 36 of them had positive chest CT for COVID-19. The remaining 22 (38%) deceased without any typical sign of COVID-19 on chest CT. Table 3 shows a comparison of the clinical characteristics between these two groups of subjects.

Table 2. Comparison of the clinical and laboratory characteristics of patients with breakthrough infection categorized by hospital outcome (survival vs. death).

	Survivors (n = 171)	Dead (n = 58)	p	p *	p * < 0.05 OR
Demography and personal history					
Age, years	78 (68–86)	86 (82–91)	**<0.001**		
Females, %	46	45	0.856		
Chronic illnesses, number	4 (2–6)	6 (4–7)	**<0.001**	0.205	
CFS score	5 (3–6)	6 (6–7)	**<0.001**	**0.004**	
Hypertension, %	59	69	0.180	0.784	
Cardiac disease, %	46	57	0.137	0.960	
Diabetes, %	19	17	0.802	0.720	
Obesity, %	13	7	0.181	0.738	
Dyslipidemia, %	19	22	0.540	0.504	
CKD, %	11	21	**0.047**	0.337	
Cancer, %	3	14	**0.002**	**0.003**	7.37 (1.95–27.80)
Dementia, %	20	48	**<0.001**	0.069	
CIRS-CS	10 (6–15)	15 (10–18)	**<0.001**	0.070	
CIRS-SI	2 (1–3)	3 (2–4)	**<0.001**	0.062	
Vaccination anti-SARS-CoV-2					
Doses of vaccine received, n	2 (2–2)	2 (2–2)	0.195	0.998	
3 vaccine doses received, %	11	12	0.745	0.887	
Time from second vaccine dose, days	174 (100–219)	203 (107–246)	**0.040**	0.300	
Time from third vaccine dose, days	14 (10–35)	16 (10–26)	0.883	0.896	
BNT162b2 vaccine, %	64	72	0.260	0.319	
mRNA-1273 vaccine, %	11	28	**0.003**	0.082	
ChAdOx1-S vaccine, %	19	0	**<0.001**	-	
Ad26.COV2.S vaccine, %	6	0	0.060	-	
Clinical presentation upon admission					
PaO_2/FiO_2, mmHg	324 (282–375)	276 (227–315)	**<0.001**	**0.001**	
Duration of symptoms, days	4 (1–7)	3 (2–5)	0.381	0.857	
Fever, %	53	55	0.738	0.193	
Cough, %	34	31	0.687	0.537	
Dyspnea, %	38	60	**0.003**	0.064	
Blood tests on admission					
Haemoglobin, g/dL	12.6 (11.3–14.0)	12.4 (10.8–13.9)	0.298	0.918	
Platelet count, 1000/mm^3	194 (150–263)	184 (152–258)	0.390	0.912	
Neutrophil count, n/mm^3	4438 (3092–6840)	6264 (4009–8588)	**0.004**	**0.024**	
Lymphocyte count, n/mm^3	1069 (776–1516)	719 (471–1033)	**<0.001**	**0.001**	
Creatinine, mg/dL	0.9 (0.7–1.2)	1.1 (0.7–1.5)	0.055	0.743	
C-Reactive Protein, mg/L	55 (21–90)	90 (38–163)	**<0.001**	**0.004**	
Procalcitonin, ng/mL	0.09 (0.05–0.20)	0.32 (0.11–1.18)	**<0.001**	**<0.001**	
D-dimer, ng/mL	679 (422–1375)	1341 (758–2297)	**<0.001**	**0.045**	
CPK, IU/L	98 (57–200)	125 (46–276)	0.469	0.565	
LDH, IU/L	234 (186–293)	290 (218–352)	**0.002**	**0.001**	
AST, IU/L	29 (22–38)	33 (23–56)	0.064	**0.031**	
Clinical course and outcome					
Chest CT positive for COVID-19, %	60	62	0.745	0.080	
NIV, %	14	27	**0.033**	**0.003**	3.66 (1.54–8.69)
IV, %	1	5	0.068	**0.004**	20.96 (2.62–167.37)
Hospital death age < 75, % (N)		2 (1)			
Hospital death age < 85, % (N)		41 (24)			
Hospital death age ≥ 85, % (N)		59 (34)			
Time before RT-PCR negative, days	15 (8–23)	22 (7–31)	0.463	0.724	
Hospital stay, days	15 (8–24)	18 (8–30)	0.459	0.657	

CT = Computed Tomography; CFS = Clinical Frailty Scale; CKD = Chronic Kidney Disease; CIRS-CS = Cumulative Illness Rating Scale-Comorbidity Score; CIRS-SI = Cumulative Illness Rating Scale-Severity Index; CPK = Creatine Phosphokinase; LDH = Lactate Dehydrogenase; AST = Aspartate Aminotranspherase; NIV = Non-Invasive Ventilation; IV = Invasive mechanical Ventilation; RT-PCR = Reverse-Transcriptase Polymerase-Chain Reaction. Data are shown as median and IQR or percentages. Crude comparisons were made with Mann–Whitney test or chi-square test, as appropriate. * p adjusted for age and sex with Quade non-parametric Ancova or logistic regression. p values < 0.05 are indicated in bold.

Table 3. Comparison of the clinical and laboratory characteristics of patients who died with COVID-19 breakthrough infection categorized according to chest CT findings.

	Dead with Negative Chest CT (n = 22)	Dead with Positive Chest CT (n = 36)	p	p *
Demography and personal history				
Age, years	89 (85–93)	84 (80–90)	**0.019**	-
Females, %	55	39	0.245	-
Chronic illnesses, number	6 (4–7)	6 (4–8)	0.517	0.613
CFS score	7 (6–7)	6 (5–7)	**0.016**	0.214
Hypertension, %	55	78	0.063	0.121
Cardiac disease, %	55	58	0.777	0.937
Diabetes, %	23	14	0.387	0.272
Obesity, %	0	11	0.105	-
Dyslipidemia, %	14	28	0.210	0.353
CKD, %	14	11	0.300	0.308
Cancer, %	14	14	0.978	0.234
Dementia, %	45	50	0.737	0.239
CIRS-CS	13 (10–16)	16 (11–20)	0.251	0.393
CIRS-SI	3 (2–4)	3 (2–4)	0.430	0.424
Vaccination anti-SARS-CoV-2				
Doses of vaccine received, n	2 (2–2)	2 (2–2)	0.590	0.975
3 vaccine doses received, %	9	14	0.586	0.838
Time from second vaccine dose, days	177 (112–206)	225 (106–256)	0.059	**0.048**
Clinical presentation upon admission				
PaO_2/FiO_2, mmHg	300 (260–324)	257 (185–307)	0.060	0.085
Duration of symptoms, days	3 (1–5)	4 (2–6)	**0.024**	0.051
Fever, %	41	64	0.088	0.249
Cough, %	23	36	0.285	0.523
Dyspnea, %	41	72	**0.018**	**0.017**
Blood tests on admission				
Haemoglobin, g/dL	11.4 (10.0–12.8)	12.8 (11.4–14.4)	**0.013**	**0.037**
Platelet count, 1000/mm^3	196 (131–260)	184 (156–253)	0.728	0.820
Neutrophil count, n/mm^3	6720 (3901–8241)	6194 (4225–9198)	0.917	0.674
Lymphocyte count, n/mm^3	802 (555–1193)	665 (458–1014)	0.253	0.619
Creatinine, mg/dL	0.9 (0.6–1.5)	1.1 (0.8–1.6)	0.131	0.169
C-Reactive Protein, mg/L	67 (29–125)	109 (41–230)	**0.033**	**0.015**
Procalcitonin, ng/mL	0.33 (0.11–1.66)	0.32 (0.10–1.18)	0.868	0.876
D-dimer, ng/mL	1550 (586–3453)	1297 (764–1982)	0.508	0.851
CPK, IU/L	118 (39–215)	131 (52–367)	0.310	0.473
LDH, IU/L	220 (189–284)	315 (231–374)	**0.005**	**0.006**
AST, IU/L	28 (20–39)	42 (27–77)	**0.024**	**0.040**
Clinical course and outcome				
NIV, %	15	33	0.138	0.275
IV, %	0	8	0.164	-
Hospital stay, days	16 (7–32)	20 (8–30)	**0.024**	0.844

CT = Computed Tomography; CFS = Clinical Frailty Scale; CKD = Chronic Kidney Disease; CIRS-CS = Cumulative Illness Rating Scale-Comorbidity Score; CIRS-SI = Cumulative Illness Rating Scale-Severity Index; CPK = Creatine Phosphokinase; LDH = Lactate Dehydrogenase; AST = Aspartate Aminotranspherase; NIV = Non-Invasive Ventilation; IV = Invasive mechanical Ventilation; RT-PCR = Reverse-Transcriptase Polymerase-Chain Reaction. Data are shown as median and IQR or percentages. Crude comparisons were made with Mann–Whitney test or chi-square test, as appropriate. * p adjusted for age and sex with Quade non-parametric Ancova or logistic regression. p values < 0.05 are indicated in bold.

Logistic regression models, exploring factors associated with mortality in the studied population, are shown in Table 4. Specifically, increasing CFS scores (OR 1.746, 95% CI 1.220–2.500, p = 0.002), altered serum levels of procalcitonin on admission (OR 2.569, 95% CI 1.237–5.335, p = 0.011) and decreasing values of PaO_2/FiO_2 on arterial blood gas analysis on admission (OR 0.989, 95% CI 0.982–0.997, p = 0.008) were the only factors independently associated with hospital mortality on a stepwise logistic regression model (Table 4, model 2).

Table 4. Logistic regression models exploring factors independently associated with mortality in the studied population.

	Odds Ratio	95% Confidence Interval	*p*
	Model 1		
Age, years	1.080	1.025–1.138	**0.004**
Sex, F vs. M	0.542	0.268–1.096	0.088
Chest CT, positive vs. negative or indeterminate	2.779	1.298–5.953	**0.009**
CFS score	1.740	1.288–2.351	**<0.001**
	Model 2		
PaO_2/FiO_2, mmHg	0.989	0.982–0.997	**0.008**
CFS score	1.746	1.220–2.500	**0.002**
Procalcitonin classes	2.569	1.237–5.335	**0.011**
	Model 3		
PaO_2/FiO_2, mmHg	0.987	0.977–0.996	**0.005**
CFS score	1.723	1.152–2.576	**0.008**
	Model 4		
Procalcitonin classes	3.088	1.389–6.862	**0.006**

Model 1 accounting for age, sex, chest CT and CFS. Model 2: stepwise method accounting for age, sex, CFS, chest CT findings, cancer, CIRS-CS, CIRS-SI, timing from last vaccine dose, lymphocyte count, neutrophil count, PaO_2/FiO_2, LDH, D-dimer, CRP, procalcitonin stratified by classes (class 1 < 0.05 ng/mL, class 2 $\geq$ 0.05 and <0.5 ng/mL, class 3 $\geq$ 0.5 and <2 ng/mL, class 4 $\geq$ 2 ng/mL). Model 3: only patients < 85 years old; stepwise method accounting for age, sex, CFS, chest CT findings, cancer, CIRS-CS, CIRS-SI, timing from last vaccine dose, lymphocyte count, neutrophil count, PaO_2/FiO_2, CRP, procalcitonin classes. Model 4: only patients $\geq$ 85 years old; stepwise method accounting for all variables listed in model 3. CT = Computed Tomography; CFS = Clinical Frailty Scale; CIRS-CS = Cumulative Illness Rating Scale-Comorbidity Score; CIRS-SI = Cumulative Illness Rating Scale-Severity Score; LDH = Lactate Dehydrogenase; CRP = C-Reactive protein. *p* values < 0.05 are indicated in bold.

To better explore the role of age on mortality in patients hospitalized with COVID-19 breakthrough infection, the studied population was categorized according to the 85 years old cut-off. Interestingly, the CFS (OR 1.723, 95% CI 1.152–2.576, $p = 0.008$) and admission PaO_2/FiO_2 (OR 0.986, 95% CI 0.977–0.996, $p = 0.005$) were independently associated with mortality only in subjects aged <85 years old, but not in subjects aged $\geq$ 85 years old, where altered serum procalcitonin level was the only parameter independently associated with mortality (OR 3.088, 95% CI 1.389–6.862, $p = 0.006$) (Table 4, models 3 and 4).

4. Discussion

Patients admitted with COVID-19 breakthrough infection in an internal medicine ward in Italy in the second half of 2021, during predominance of the SARS-CoV-2 delta variant, were characterized by older age and elevated burden of frailty and multimorbidity. Interestingly, those subjects who were admitted with symptomatic forms of COVID-19 and interstitial pneumonia were on average younger and with lower CFS scores than those with negative or indeterminate chest CT findings. Mortality was not different in these two groups, and was mainly associated with frailty and severity of respiratory impairment in patients < 85 years old, and with serum procalcitonin in patients $\geq$ 85 years old.

Older frail subjects are more vulnerable to COVID-19 breakthrough infections, because the senescent immune system and chronic activation of inflammatory response typical of frailty syndrome lead to reduced anti-spike antibody titers after vaccination [28,29]. Measures of frailty in nursing home residents, in fact, show an inverse association with antibody titers and duration of the serological response after SARS-CoV-2 vaccination [28,29]. Anti-spike antibody levels are strong predictors of the risk of COVID-19 breakthrough infection and its clinical course in adult subjects with normal immune function [30] and in nursing home residents [31]. Longitudinal studies have also shown a measurable decline

of vaccine effectiveness against SARS-CoV-2 infection after six months of completion of the primary vaccination cycle, especially in people aged ≥ 60 years old [32]. All these findings were the bases for the recommendation of receiving a booster dose six months after the completion of the primary vaccination cycle, especially for frail subjects.

In subjects with severe multimorbidity and high CFS scores, COVID-19 may overlap with other cardio-respiratory and neurological diseases, contributing to decompensate them. For example, SARS-CoV-2 infection, even in the absence of clinical and radiological signs of pneumonia, is associated with increased risk of congestive heart failure decompensation [33], chronic obstructive pulmonary disease exacerbation [34], and delirium superimposed on dementia [35,36]. These circumstances generate complex clinical pictures in which it may be particularly difficult to disentangle the contribution of COVID-19 and pre-existing diseases to acute symptoms and radiological findings [22]. Furthermore, the immune response to breakthrough infection after anti-SARS-CoV-2 vaccine, although not optimal, remains measurable and able to modify the natural history of the disease even in the oldest and frailest subjects [6,37–40]. Indeed, centenarians have shown a better capacity of coping with COVID-19 infection and its consequences, with lower mortality than other groups of geriatric patients [41]. Finally, the apparently reduced frequency of pneumonia in oldest old frail patients hospitalized for COVID-19 may be the result of the increased frequency of RT-PCR testing these patients receive because of precarious clinical conditions and repeated emergency department visits, increasing the probability of detection of asymptomatic and paucisymptomatic infections [42].

In our group of patients with breakthrough infection, mortality was similar in those with and without COVID-19 pneumonia. These findings match those of previous studies reporting a paradoxical increase in mortality for the vaccinated, in comparison with unvaccinated, patients admitted to hospital, due to the average older age and higher burden of frailty and multimorbidity of the vaccinated [43–46]. In fact, frailty and multimorbidity can influence mortality even when the respiratory involvement in COVID-19 is mild, independently from the intrinsic pathogenicity of SARS-CoV-2 [46,47].

As such, in patients younger than 85 years old with COVID-19 breakthrough infection, mortality was influenced by the severity of respiratory involvement and pre-existing level of frailty (Table 4, Model 3), while, in patients aged 85 or older, by the level of systemic inflammation and the risk of bacterial superinfection, mirrored by serum procalcitonin levels (Table 4, Model 4). In this age range, frailty does not influence mortality in an independent way, probably as a result of a "ceiling" effect due to the diffusion of high CFS scores. Interestingly, these findings are similar to those obtained by our research group in the pre-vaccine era, where serum procalcitonin levels on hospital admission constituted an independent predictor of adverse outcomes only in the oldest old age group [48]. It can be assumed that, in oldest old subjects, the high mortality associated with SARS-CoV-2 breakthrough infection is more influenced by decompensation of pre-existing diseases and concomitant bacterial infections, rather than by COVID-19 itself. SARS-CoV-2 may also involve more severely other organs, and not the lungs, in vaccinated oldest old patients [49].

Conversely, the COVID-19-related factors, including the severity of hypoxemia, presence of ground-glass abnormalities and lung parenchymal infiltrates on chest CT, may still play a relevant prognostic role only in subjects younger than 85. However, the extension of lung parenchymal abnormalities on chest CT, that in previous studies was strongly associated with the severity of respiratory failure and mortality [50–52], did not constitute a significant predictor of adverse outcomes in our population with breakthrough infection, suggesting that further research is needed on this issue.

Our study has some limitations. First, we could not perform a reliable comparison among recipients of different vaccines, due to the policy of administration in Italy in 2021, where the mRNA-1273 vaccine was almost exclusively reserved to older subjects with frailty, while ChAdOx1-S and Ad26.COV2.S vaccines were initially reserved to older fit subjects, and then withdrawn from use. Second, we focused only on a period of dominance of SARS-CoV-2 delta variant, preceding the mass administration of vaccine booster doses.

Thus, the findings may not be automatically transferred to patients infected by omicron SARS-CoV-2 variant, especially after having received three or more vaccine doses. The single-center design of the study may imply that the findings reflect local policies of hospital admission and management of COVID-19 patients, that are not necessarily the same elsewhere. Finally, the absence of data on unvaccinated patients who were admitted in the same period prevents any comparison between the clinical severity of vaccinated and unvaccinated subjects needing hospital admission.

In spite of this, we provide evidence that patients with COVID-19 breakthrough infection needing hospital admission are mainly geriatric patients with complex clinical needs due to multimorbidity and elevated burden of frailty, and that their mortality remains high even when no signs of pneumonia are present on chest radiology. Thus, in the mass vaccination era, the hospital organization of care should take into account these circumstances to meet the complex needs of these patients [22].

5. Conclusions

Patients hospitalized with COVID-19 breakthrough infection in Italy during the dominance of the SARS-CoV-2 delta variant were characterized by older age, multiple comorbidities and elevated burden of frailty. Extreme degrees of frailty, however, were inversely associated with the presence of chest CT signs of interstitial pneumonia. Mortality was associated with frailty and severity of respiratory failure only in subjects younger than 85. Instead, in the oldest old subjects, the only independent prognostic factor was represented by serum procalcitonin levels, suggesting that the high level of mortality in this age range was more associated with decompensation of previous chronic diseases than with the COVID-19 course.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11185442/s1, Table S1: Comparison of the clinical characteristics and outcomes of patients with COVID-19 breakthrough infection, categorized according to the clinical priority of COVID-19 symptoms.

Author Contributions: Conceptualization and methodology: A.T., A.P. and T.M.; Investigation: A.T., A.P., N.C., A.N., B.P. and G.C.; Formal analysis: A.T. and A.G.; Manuscript draft: A.T.; Supervision: T.M.; Manuscript revision for substantial intellectual content: all authors. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study protocol was approved by the local Ethics Committee (Comitato Etico dell'Area Vasta Emilia Nord, Emilia-Romagna Region) under the ID 959/2021/OSS/AOUPR (date of approval 11 January 2022). The study was conducted in compliance with the Declaration of Helsinki and its later amendments.

Informed Consent Statement: Informed consent was obtained in written form from all patients who were contactable by the research team during the study period. For all other patients (either deceased or uncontactable upon reasonable effort), informed consent collection was waived.

Data Availability Statement: Access to data, in anonymous form, can be obtained upon reasonable and motivated request to the corresponding author. The subject entitled for data control and management is the Parma University-Hospital (Azienda Ospedaliero-Universitaria di Parma).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Talenti, A.; Arvin, A.; Corey, L.; Corti, D.; Diamond, M.S.; García-Sastre, A.; Garry, R.F.; Holmes, E.C.; Pang, P.S.; Virgin, H.W. After the pandemic: Perspectives on the future trajectory of COVID-19. *Nature* **2021**, *596*, 495–504. [CrossRef]
2. Ke, R.; Martinez, P.P.; Smith, R.L.; Gibson, L.L.; Achenbach, C.J.; McFall, S.; Qi, C.; Jacob, J.; Dembele, E.; Bundy, C.; et al. Longitudinal analysis of SARS-CoV-2 vaccine breakthrough infections reveals limited infectious virus shedding and restricted tissue distribution. *Open Forum Infect. Dis.* **2022**, *9*, ofac192. [CrossRef] [PubMed]

3. Puhach, O.; Adea, K.; Hulo, N.; Sattonnet, P.; Genecand, C.; Iten, A.; Jacquérioz, F.; Kaiser, L.; Vetter, P.; Eckerle, I.; et al. Infectious viral load in unvaccinated and vaccinated individuals infected with ancestral, Delta or Omicron SARS-CoV-2. *Nat. Med.* **2022**, *28*, 1491–1500. [CrossRef]
4. Richard, S.A.; Epsi, N.J.; Lindholm, D.A.; Malloy, A.M.W.; Maves, R.C.; Berjohn, C.M.; Lalani, T.; Smith, A.G.; Mody, R.M.; Ganesan, A.; et al. COVID-19 patient-reported symptoms using FLU-PRO Plus in a cohort study: Associations with infecting genotype, vaccine history, and return to health. *Open Forum Infect. Dis.* **2022**, *9*, ofac255. [CrossRef]
5. Tenforde, M.W.; Self, W.H.; Adams, K.; Gaglani, M.; Ginde, A.A.; McNeal, T.; Ghamande, S.; Douin, D.J.; Talbot, H.K.; Casey, J.D.; et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. *JAMA* **2021**, *326*, 2043–2054. [PubMed]
6. Lopez Bernal, J.; Andrews, N.; Gower, C.; Robertson, C.; Stowe, J.; Tessier, E.; Simmons, R.; Cottrell, S.; Roberts, R.; O'Doherty, M.; et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: Test negative case-control study. *BMJ* **2021**, *373*, n1088. [PubMed]
7. Epaulard, O.; Abgrall, S.; Lefebvre, M.; Faucher, J.F.; Michon, J.; Frentiu, E.; Blanchi, S.; Janssen, C.; Charbonnier, G.; Fresse, A.; et al. Impact of vaccination on the symptoms of hospitalised patients with SARS-CoV-2 delta variant (B.1.617.1) infection. *Clin. Microbiol. Infect.* **2022**, *in press*. [CrossRef]
8. Stupica, D.; Collinet-Adler, S.; Kejžar, N.; Jagodic, Z.; Poljak, M.; Nahtigal Klevišar, M. The impact of SARS-CoV-2 primary vaccination in a cohort of patients hospitalized for acute COVID-19 during delta variant predominance. *J. Clin. Med.* **2022**, *11*, 1191. [CrossRef]
9. Wolff, M.; Gilabert, M.; Hernández, R. Clinical outcomes in hospitalized vaccine-breakthrough coronavirus disease 2019 cases compared with contemporary unvaccinated hospitalized adults. *Open Forum Infect. Dis.* **2022**, *9*, ofac122.
10. Naik, B.R.; Kumar, S.A.; Rachegowda, N.; Ullas, L.Y.; Revanth, R.B.; Venkata Sai Aluru, N.R. Severity of COVID-19 infection using chest computed tomography severity score index among vaccinated and unvaccinated COVID-19-positive healthcare workers: An analytical cross-sectional study. *Cureus* **2022**, *14*, e22087.
11. Myers, L.C.; Kipnis, P.; Greene, J.; Lawson, B.; Escobar, G.J.; Fireman, B.H.; Klein, N.P.; Liu, V.X. Adults hospitalized with breakthrough COVID-19 have lower mortality than matched unvaccinated adults. *J. Intern. Med.* **2022**, *292*, 377–384. [CrossRef] [PubMed]
12. Suleyman, G.; Fadel, R.; Alsaadi, A.; Sueng, L.N.; Ghandour, A.; Alkhatib, A.; Singh, T.; Parsons, A.; Miller, J.; Ramesh, M.; et al. Progression to critical illness and death in patients with breakthrough hospitalizations. *Open Forum Infect. Dis.* **2022**, *9*, ofac2013. [CrossRef] [PubMed]
13. Niessen, F.A.; Knol, M.J.; Hahné, S.J.M.; VECTOR Study Group; Bonten, M.J.M.; Bruijning-Verhagen, P.C.J.L. Vaccine effectiveness against COVID-19 related hospital admission in the Netherlands: A test-negative case-control study. *Vaccine* **2022**, *40*, 5044–5049. [CrossRef] [PubMed]
14. Marengoni, A.; Zucchelli, A.; Vetrano, D.L.; Armellini, A.; Botteri, E.; Nicosia, F.; Romanelli, G.; Beindorf, E.A.; Giansiracusa, P.; Garrafa, E.; et al. Beyond chronological age: Frailty and multimorbidity predict in-hospital mortality in patients with coronavirus disease 2019. *J. Gerontol. A Biol. Sci. Med. Sci.* **2021**, *76*, e38–e45. [CrossRef]
15. Ticinesi, A.; Nouvenne, A.; Cerundolo, N.; Parise, A.; Prati, B.; Guerra, A.; Meschi, T. Trends of COVID-19 Admissions in an Italian Hub during the Pandemic Peak: Large Retrospective Study Focused on Older Subjects. *J. Clin. Med.* **2021**, *10*, 1115. [CrossRef]
16. The OpenSAFELY Collaborative; Green, A.; Curtis, H.; Hulme, W.; Williamson, E.; McDonald, H.; Bhaskaran, K.; Rentsch, C.; Schultze, A.; MacKenna, B.; et al. Describing the population experiencing COVID-19 vaccine breakthrough following second vaccination in England: A cohort study from OpenSAFELY. *BMC Med.* **2022**, *20*, 243.
17. Agrawal, U.; Katikireddi, S.V.; McCowan, C.; Mulholland, R.H.; Azcoaga-Lorenzo, A.; Amele, S.; Fagbamigbe, A.F.; Vasileiou, E.; Grange, Z.; Shi, T.; et al. COVID-19 hospital admissions and deaths after BNT162b2 and ChAdOx1 nCoV-19 vaccinations in 2.57 million people in Scotland (EAVE II): A prospective cohort study. *Lancet Respir. Med.* **2021**, *9*, 1439–1449. [CrossRef]
18. Marfella, R.; Sardu, C.; D'Onofrio, N.; Prattichizzo, F.; Scisciola, L.; Messina, V.; La Grotta, R.; Balestrieri, M.L.; Maggi, P.; Napoli, C.; et al. Glycaemic control is associated with SARS-CoV-2 breakthrough infections in vaccinated patients with type 2 diabetes. *Nat. Comm.* **2022**, *13*, 2318. [CrossRef]
19. Lee, L.Y.W.; Starkey, T.; Ionescu, M.C.; Little, M.; Tilby, M.; Tripathy, A.R.; McKenzie, H.S.; Al-Hajji, Y.; Barnard, M.; Benny, L.; et al. Vaccine effectiveness against COVID-19 breakthrough infections in patients with cancer (UKCCEP): A population-based test-negative case-control study. *Lancet Oncol.* **2022**, *23*, 748–757. [CrossRef]
20. Wang, L.; Davis, P.B.; Kaelber, D.C.; Xu, R. COVID-19 breakthrough infections and hospitalizations among vaccinated patients with dementia in the United States between December 2020 and August 2021. *Alzheimers Dement.* **2022**. *online first*. [CrossRef]
21. Lee, C.J.; Woo, W.; Kim, A.Y.; Yon, D.K.; Lee, S.W.; Koyanagi, A.; Kim, M.S.; Tizaoui, K.; Dragioti, E.; Radua, J.; et al. Clinical manifestations of COVID-19 breakthrough infections: A systematic review and meta-analysis. *J. Med. Virol.* **2022**, *94*, 4234–4245. [CrossRef] [PubMed]
22. Ticinesi, A.; Nouvenne, A.; Parise, A.; Prati, B.; Meschi, T. Defining SARS-CoV-2 breakthrough infection needing hospitalization in mass vaccination era: From disease-centered to patient-centered care. *Acta Biomed.* **2022**, *93*, e2022182. [PubMed]

23. Loconsole, D.; Centrone, F.; Morcavallo, C.; Campanella, S.; Accogli, M.; Sallustio, A.; Peccarisi, D.; Stufano, A.; Lovreglio, P.; Chironna, M. Changing features of COVID-19: Characteristics of infections with the SARS-CoV-2 delta (B.1.617.2) and alpha (B.1.1.7) variants in Southern Italy. *Vaccines* **2021**, *9*, 1354. [CrossRef] [PubMed]
24. Meschi, T.; Rossi, S.; Volpi, A.; Ferrari, C.; Sverzellati, N.; Brianti, E.; Fabi, M.; Nouvenne, A.; Ticinesi, A. Reorganization of a large academic hospital to face COVID-19 outbreak: The model of Parma, Emilia-Romagna region, Italy. *Eur. J. Clin. Investig.* **2020**, *50*, e13250. [CrossRef] [PubMed]
25. Salvi, F.; Miller, M.D.; Grilli, A.; Giorgi, R.; Towers, A.L.; Morichi, V.; Spazzafumo, L.; Mancinelli, L.; Espinosa, E.; Rappelli, A.; et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *J. Am. Geriatr. Soc.* **2008**, *56*, 1926–1931. [CrossRef] [PubMed]
26. Rockwood, K.; Song, X.; MacKnight, C.; Bergman, H.; Hogan, D.B.; McDowell, I.; Mitnitski, A. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* **2005**, *173*, 489–495. [CrossRef]
27. Nouvenne, A.; Zani, M.D.; Milanese, G.; Parise, A.; Baciarello, M.; Bignami, E.G.; Odone, A.; Sverzellati, N.; Meschi, T.; Ticinesi, A. Lung Ultrasound in COVID-19 Pneumonia: Correlations with Chest CT on Hospital admission. *Respiration* **2020**, *99*, 617–624. [CrossRef] [PubMed]
28. Dyer, A.H.; Noonan, C.; McElheron, M.; Batten, I.; Reddy, C.; Connolly, E.; Pierpoint, R.; Murray, C.; Leonard, A.; Higgins, C.; et al. Previous SARS-CoV-2 infection, age, and frailty are associated with 6-month vaccine-induced anti-spike antibody titer in nursing home residents. *J. Am. Med. Dir. Assoc.* **2022**, *23*, 434–439. [CrossRef]
29. Shapiro, J.R.; Sitaras, I.; Park, H.S.; Aytenfisu, T.Y.; Caputo, C.; Li, M.; Lee, J.; Johnston, T.S.; Li, H.; Wouters, C.; et al. Association of frailty, age, and biological sex with SARS-CoV-2 mRNA vaccine-induced immunity in older adults. *Clin. Infect. Dis.* **2022**, *75*, S61–S71. [CrossRef]
30. Kim, M.H.; Nam, Y.; Son, N.H.; Heo, N.; Kim, B.; Kang, E.; Shin, A.; Yang, A.J.; Park, Y.S.; Kim, H.; et al. Antibody level predicts the clinical course of breakthrough infection of COVID-19 caused by delta and omicron variants: A prospective cross-sectional study. *Open Forum Infect. Dis.* **2022**, *9*, ofac262. [CrossRef]
31. Torres, I.; Bellido-Blasco, J.B.; Gimeno, C.; Burgos, J.S.; Albert, E.; Moya-Malo, R.; Gascó-Laborda, J.C.; Tornero, A.; Soriano, J.; Meseguer-Ferrer, N.; et al. SARS-CoV-2 delta-variant breakthrough infections in nursing home residents at midterm after Comirnaty®COVID-19 vaccination. *J. Med. Virol.* **2022**, *94*, 3776–3782. [CrossRef] [PubMed]
32. Fabiani, M.; Puopolo, M.; Morciano, C.; Spuri, M.; Alegiani, S.S.; Filia, A.; D'Ancona, F.; Del Manso, M.; Riccardo, F.; Tallon, M.; et al. Effectiveness of mRNA vaccines and waning of protection against SARS-CoV-2 infection and severe COVID-19 during predominant circulation of the delta variant in Italy: Retrospective cohort study. *BMJ* **2022**, *376*, e069052. [CrossRef] [PubMed]
33. Sokolski, M.; Trenson, S.; Sokolska, J.M.; D'Amario, D.; Meyer, P.; Poku, N.K.; Biering-Sørensen, T.; Højbjerg Lassen, M.C.; Skaarup, K.G.; Barge-Caballero, E.; et al. Heart failure in COVID-19: The multicentre, multinational PCHF-COVICAV registry. *ESC Heart Fail.* **2021**, *8*, 4955–4967. [CrossRef] [PubMed]
34. Halpin, D.M.G.; Criner, G.J.; Papi, A.; Singh, D.; Anzueto, A.; Martinez, F.J.; Agusti, A.A.; Vogelmeier, C.F. Global initiative for diagnosis, management, and prevention of chronic obstructive lung disease. The 2020 GOLD Science Committee Report on COVID-19 and chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2021**, *203*, 24–36. [CrossRef] [PubMed]
35. Mendes, A.; Herrmann, F.R.; Périvier, S.; Gold, G.; Graf, C.E.; Zekry, D. Delirium in older patients with COVID-19: Prevalence, risk factors, and clinical relevance. *J. Gerontol. A Biol. Sci. Med. Sci.* **2021**, *76*, e142–e146. [CrossRef]
36. Ticinesi, A.; Cerundolo, N.; Parise, A.; Nouvenne, A.; Prati, B.; Guerra, A.; Lauretani, F.; Maggio, M.; Meschi, T. Delirium in COVID-19: Epidemiology and clinical correlations in a large group of patients admitted to an academic hospital. *Aging Clin. Exp. Res.* **2020**, *32*, 2159–2166. [CrossRef]
37. Delbrück, M.; Hoehl, S.; Toptan, T.; Schenk, B.; Grikscheit, K.; Metzler, M.; Herrmann, E.; Ciesek, S. Low but recoverable markers of humoral immune response to BNT162b2 in elderly LTCF residents five to seven months after two-dose vaccination. *Front. Aging* **2022**, *3*, 883724. [CrossRef]
38. Salmerón Rios, S.; Mas Romero, M.; Cortés Zamora, E.B.; Tabernero Sahuquillo, M.T.; Romero Rizos, L.; Sánchez-Jurado, P.M.; Sánchez-Nievas, G.; Blas Señalada, J.J.; García Nogueras, I.; Estrella Cazalla, J.D.; et al. Immunogenicity of the BNT162b2 vaccine in frail or disabled nursing home residents: COVID-A Study. *J. Am. Geriatr. Soc.* **2021**, *69*, 1441–1447. [CrossRef]
39. Cabezas, C.; Coma, E.; Mora-Fernandez, N.; Li, X.; Martinez-Marcos, M.; Fina, F.; Fabregas, M.; Hermosilla, E.; Jover, A.; Contel, J.C.; et al. Associations of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with Covid-19 in nursing homes and healthcare workers in Catalonia: Prospective cohort study. *BMJ* **2021**, *374*, n1868. [CrossRef]
40. Rivasi, G.; Bulgaresi, M.; Bandinelli, C.; Balzi, D.; Tarantini, F.; Tognelli, S.; Lorini, C.; Buscemi, P.; Baggiani, L.; Landini, G.; et al. Long-term effects of SARS-CoV-2 vaccination in the nursing home setting. *J. Am. Geriatr. Soc.* **2022**, *70*, 1336–1341. [CrossRef]
41. Marcon, G.; Tettamanti, M.; Capacci, G.; Fontanel, G.; Spanò, M.; Nobili, A.; Forloni, G.; Franceschi, C. COVID-19 mortality in Lombardy: The vulnerability of the oldest old and the resilience of male centenarians. *Aging* **2020**, *12*, 15186–15195. [CrossRef] [PubMed]
42. Di Lego, V.; Sánchez- Romero, M.; Prskawetz, A. The impact of COVID-19 vaccines on case-fatailty rate: The importance of monitoring breakthrough infections. *Int. J. Infect. Dis.* **2022**, *119*, 178–183. [CrossRef] [PubMed]

43. Otto, M.; Burrell, A.J.C.; Neto, A.S.; Alliegro, P.V.; Trapani, T.; Cheng, A.; Udy, A.A. SPRINT-SARI Australia Investigators. Clinical characteristics and outcomes of critically ill patients with 1, 2 and 3 doses of vaccination against COVID-19 in Australia. *Intern. Med. J.* **2022**. *ahead of print*. [CrossRef] [PubMed]
44. Brosh-Nissimov, T.; Maor, Y.; Elbaz, M.; Lipman-Arens, S.; Wiener-Well, Y.; Hussein, K.; Orenbuch-Harroch, E.; Cohen, R.; Zimhony, O.; Chazan, B.; et al. Hospitalised patients with breakthrough COVID-19 following vaccination during two distinct waves in Israel, January to August 2021: A multicentre comparative cohort study. *Euro Surveill.* **2022**, *27*, 2101026. [CrossRef]
45. Díaz-Menéndez, M.; de la Calle-Prieto, F.; Montejano, R.; Arsuaga, M.; Jiménez-González, M.; Pérez-Blanco, V.; Marcelo, C.; Vásquez-Manau, J.; Lázaro, F.; Arribas, J.R. Clinical characteristics and outcome of hospitalized elderly patients with COVID-19 after vaccine failure. *Vaccine* **2022**, *40*, 4307–4311. [CrossRef]
46. Stepanova, M.; Lam, B.; Younossi, E.; Felix, S.; Ziayee, M.; Price, J.; Pham, H.; de Avila, L.; Terra, K.; Austin, P.; et al. The impact of variants and vaccination on the mortality and resource utilization of hospitalized patients with COVID-19. *BMC Infect. Dis.* **2022**, *22*, 702. [CrossRef]
47. Malézieux-Picard, A.; Ferrer Soler, C.; De Macedo Ferreira, D.; Gaud-Luethi, E.; Serratrice, C.; Mendes, A.; Zekry, D.; Gold, G.; Lobrinus, J.A.; Arnoux, G.; et al. Undetected causes of death in hospitalized elderly with COVID-19: Lessons from autopsy. *J. Clin. Med.* **2021**, *10*, 1337. [CrossRef]
48. Ticinesi, A.; Nouvenne, A.; Prati, B.; Guida, L.; Parise, A.; Cerundolo, N.; Bonaguri, C.; Aloe, R.; Guerra, A.; Meschi, T. The Clinical Significance of Procalcitonin Elevation in Patients over 75 Years Old Admitted for COVID-19 Pneumonia. *Mediat. Inflamm.* **2021**, *2021*, 5593806. [CrossRef]
49. Tuttolomondo, D.; Frizzelli, A.; Aiello, M.; Bertorelli, G.; Majori, M.; Chetta, A. Beyond the lung involvement in COVID-19 patients. *Minerva Med.* **2022**, *113*, 558–568. [CrossRef]
50. Liu, H.; Wang, J.; Geng, Y.; Li, K.; Wu, H.; Chen, J.; Chai, X.; Li, S.; Zheng, D. Fine-grained assessment of COVID-19 severity based on clinic-radiological date using machine learning. *Int. J. Environ. Res. Public Health* **2022**, *19*, 10665. [CrossRef]
51. Mohammad-Rahimi, H.; Nadimi, M.; Ghalyanchi-Langeroudi, A.; Taheri, M.; Ghafouri-Fard, S. Application of machine learning in diagnosis of COVID-19 through X-ray and CT images: A scoping review. *Front. Cardiovasc. Med.* **2021**, *8*, 638011. [CrossRef] [PubMed]
52. Francone, M.; Iafrate, F.; Masci, G.M.; Coco, S.; Cilia, F.; Manganaro, L.; Panebianco, V.; Andreoli, C.; Colaiacomo, M.C.; Zingaropoli, M.A.; et al. Chest CT score in COVID-19 patients: Correlation with disease severity and short-term prognosis. *Eur. Radiol.* **2020**, *30*, 6808–6817. [CrossRef] [PubMed]

Journal of
Clinical Medicine

MDPI

Article

Management of Femur Fractures during COVID-19 Pandemic Period: The Influence of Vaccination and Nosocomial COVID-19 Infection

Marianna Faggiani [1,*], Salvatore Risitano [2], Alessandro Aprato [2], Luigi Conforti [1] and Alessandro Massè [2]

[1] ASL TORINO 5, Department of Orthopaedic Surgery and Traumatology, 10024 Turin, Italy
[2] Città della Salute e della Scienza di Torino, Department of Orthopaedic Surgery and Traumatology, 10126 Turin, Italy
* Correspondence: mari.faggiani@hotmail.it

Abstract: The COVID-19 pandemic management has led to a significant change in orthopedic surgical activity. During the pandemic, femur fractures in patients over 65 years of age have maintained a constant incidence. Our study will focus on this fragile population, analyzing the incidence of SARS-CoV-2 infection during hospital stays and the clinical and radiographic orthopedic outcomes. We also evaluated the va\riation of COVID-19 infection after health professionals' vaccinations, and the influence of inter-hospital transfers caused by logistical and organizational aspects of the pandemic. **Material and Methods:** This is a descriptive and prospective study from 13 October 2020 to 15 March 2021. Participants were patients over 65 years of age with diagnoses of proximal femoral fractures with r surgical treatments indicated. We compared the SARS-CoV-2 infected patients during the stay with non-infected cases. A second evaluation was carried out dividing the patients into those who underwent inter-hospital transfers and a group without transfers. We subdivided the study period into two, according to the percentage of healthcare workers vaccinated against SARS-CoV-2. The reported clinical variables included the Parker and Palmer Score, the Nottingham Hip Fracture Score, the Harris Hip Score, mortality, the Rush Score, and evaluation of reduction in radio-lucent lines in prosthetic implants. **Results**: Ninety-three patients were studied. The whole positive COVID cohort (11.83%) was hospitalized during the period when less than 80% of health workers were vaccinated ($p = 0.02$). The COVID cohort and the patients transferred before surgery had longer stays in the Emergency Room ($p = 0.019$; $p = 0.00007$) and longer lengths of stay compared to the other patients ($p = 0.00001$; $p = 0.001$). Mortality was higher both in the infected group and in the patients who underwent a transfer before the surgical procedure (18.18% vs. 1.22 %; $p = 0.003$. 25% vs. 6.85%; $p = 0.02$). In terms of orthopedic outcomes measured through the third month of follow-up, we found worse score results in functional and radiographic outcomes in the COVID positive cohort and in the transferred patients' cohort. **Conclusions**: The impact of the COVID-19 pandemic on patients treated for proximal femur fracture was statistically significant. Patients with Coronavirus during hospitalization obtained poor short-term radiographic and functional results and increased peri-operative mortality. The incidence of intra-hospital infection was high during the period in which health professionals were not yet covered by the anti-COVID vaccination cycle. Patients who were transferred between two hospitals due to pandemic-related management issues also achieved reduced outcomes compared to non-transferred cases, with increased mortality.

Keywords: COVID-19; femur fractures; COVID-19 vaccination

Citation: Faggiani, M.; Risitano, S.; Aprato, A.; Conforti, L.; Massè, A. Management of Femur Fractures during COVID-19 Pandemic Period: The Influence of Vaccination and Nosocomial COVID-19 Infection. *J. Clin. Med.* **2022**, *11*, 6605. https://doi.org/10.3390/jcm11226605

Academic Editors: Filippo Migliorini and Riccardo Giorgino

Received: 9 October 2022
Accepted: 2 November 2022
Published: 8 November 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Coronaviridae is a family of viruses with a single-stranded RNA genome. SARS (Severe Acute Respiratory Syndrome) is an atypical form of pneumonia caused by the Coronovirus-1 [1,2]. This disease produced an epidemic in China that developed from November 2002 to July 2003. During autumn of 2019, the health authorities of the city of

Wuhan (China) found the first case of a patient showing a different respiratory disease, referred to as "pneumonia of unknown cause" [3,4]. The cause was subsequently identified as a new type of virus classified as Coronavirus-2 (SARS-CoV-2) [2,5]. This virus spreads through respiratory droplets and aerosols produced by the infected subjects. It exhibits an initial nonspecific symptomatology like flu with cough, fever, and dyspnea. The condition can evolve into severe hypoxic respiratory failure [6,7].

The World Health Organization (WHO) declared a SARS-CoV-2 pandemic on 11 March 2020 [6]. Italy was the first European nation to face this health emergency. Northern Italy was more involved than the rest of the country [8]. Measures imposed for contagion containment upset every aspect of society and subverted hospital organization, altering the incidence of traumatic pathology [9–11]. During the first pandemic period, road accidents were reduced by 77% and sports accidents by almost 100% [9,12]. Accidents at home experienced a minor increase [5]. A systematic review carried out by the Orthopedic Surgeons of Wuhan (China) showed that the incidence of SARS-CoV-2 infection in orthopedic wards was almost 20% more than the incidence among total inpatients [4,13].

Guidelines (16 March 2020) issued by the Italian Society of Orthopedic and Traumatology (SIOT) indicated that orthopedic and traumatological surgery cannot be suspended and must be reorganized instead [3,4]. During the pandemic period, femur fractures in patients over 65 years old maintained a constant incidence [14,15]. These elderly fractures remain a surgical priority [16,17]. These fragile patients need to walk as early as possible, and be allowed rapid rehabilitations and reduced hospitalization time [18,19]. The literature has shown that early surgery leads to a significant reduction in mortality and peri-operative complications such as urinary tract infections (2.5%), respiratory complications (4.5%) and cardiac (3.2%) or decubitus injuries (2.4%) [20–23]. Moreover, according to more up-to-date studies, a concomitant infection by SARS-CoV-2 leads to an increase in complications and perioperative mortality in these surgical orthopedic patients [17,18]. In a multicentric study, 89% of positive patients who presented post-operative complications greater than the negative and 20% who experienced respiratory distress syndrome and multiorgan insufficiency [18,19]. On 13 October 2020, the Italian Infective Disease Department prolonged the emergency period. On 21 December 2020, the European Medicine Agency (EMA) authorized the first vaccine against SARS-CoV-2, called COMIRNATY (developed and produced by Pfizer/Biomtech). The Italian Drug Agency (AIFA) approved COMIRNATY the next day; therefore, the vaccination campaign against SARS-CoV-2 was launched on 27 December. The national strategic plan provided for vaccination first of health staff and fragile guests of the Health Care Residences. The World Health Organization recommended that individual governments identify vaccine hesitancy areas [9,10]. In Italy, health workers who opposed vaccination were suspended.

Our study will focus on patients over 65 years old with proximal femur fractures, analyzing the incidence of the inpatients' onset of SARS-CoV-2 infection and its negative influence on clinical and radiographic orthopedic outcomes. We also will analyze variations in the incidence of SARS-CoV-2 infections among patients after the health professionals were vaccinated and the influence of inter-hospital transfers (caused by pandemic related logistical and organizational issues) in this fragile population.

2. Material and Methods

2.1. Study Design and Participants

This is a descriptive and prospective study from 13 October 2020 (on the day that the Italian government prolonged the state of national alarm due to COVID-19) until 15 March 2021 [6,8,9]. Included participants were patients over 65 years of age presenting to our Emergency Department with clinical and radiographic diagnoses of proximal femoral fractures (31-A-B and C according to the OTA/AO classification) with indications for surgical treatment. Exclusion criteria were patients with femoral shaft fractures, open fractures, pathological fractures, periprosthetic or peri-implant fractures, polytrauma, or nonoperative fractures and patients diagnosed with COVID-19 (determined by a polymerase chain

reaction, PCR, test from nose swab samples at the entrance to the Emergency Department) [24]. Our department of orthopedics and traumatology covers an area distributing the work between two different hospitals with patients present in both emergency rooms, operating rooms, and orthopedic wards. During the emergency period, according to national health restrictions (D.L. n. 125 of 7 October 2020, converted into law n. 159 of 27 November 2020), our health department planned the transfer of all surgical patients to a single reference hospital, leaving open only the services of the E.R. in the other one. The health professionals were equipped with every protective device and were subjected to anti-SARS-CoV-2 vaccination beginning 1 January 2021. All patients infected by the COVID virus during the stay were transferred to a COVID-19 ward. The elderly population is more immune compromised. They developed an inflammatory storm syndrome that further complicates the host defense mechanism [25]. For symptomatic patients a corporate protocol based on steroids, antivirals, and oxygen therapy was used.

All surgical procedures were performed with the same implant (Gamma 3 Nail Stryker for internal osteosynthesis and Gladiator Bipolar System for the arthroplasty) and by the same surgical team composed of four orthopedic specialists. The choice of cementation during the arthroplasty procedure was made at the time of surgery according to the bone stock. To compare the data, we divided the sample into two groups: patients who were SARS-CoV-2 infected during the stay, diagnosed by a PCR test from nose swab sample (Group A), and cases not infected (Group B). A second evaluation was carried out dividing the patients into a sample that underwent an inter-hospital transfer (Group C) and a group without any transfers (Group D). We subdivided the study period into two, according to the percentage of healthcare workers vaccinated against SARS-CoV-2 (with double doses of Pfizer/Biomtech): Time 0 (from 15 October 2020 to 10 February 2021), when the percentage of vaccination was less than 80% and Time 1 (from 11 February 2021 to 15 March 2021), when that percentage was more than 80%.

The main objective was to analyze the impact of surgical logistic management during the COVID-19 pandemic on fragile patients with proximal femur fractures. We focused the analysis on the clinical and radiographic orthopedic outcomes (at time of 3 months of follow-up) and the mortality incidence of patients who were infected by SARS-CoV-2 during the stay compared to patients not infected. Secondly, we wanted to evaluate the variation of SARS-CoV-2 incidence in this elderly population before and after the health professionals' vaccinations (Time 0 vs. Time 1) [12]. Our third goal was to analyze the influence of the inter-hospital transfers on the orthopedic outcomes and mortality incidence in proximal femur fracture patients. The Institutional Review Board of our institution defined this study as exempt from IRB approval (descriptive study) and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and informed consent to the processing of data was obtained from all patients at the entrance to the hospital.

2.2. Data Collection

All data were collected prospectively from the electronic medical records by only one investigator (an orthopedic resident). Demographic variables were sex, age, and residence (nursing home or family home). The reported clinical variables included the type of fracture (according to AO/OTA classification 31 A, B and C) [24], the American Society of Anesthesiologists (ASA) classification, comorbidity, pre-trauma mobility (calculated by the Parker and Palmer Score, PPM Score) [15], and risk of mortality in the 30 days post-surgery (according to Nottingham Hip Fracture Score, NHFS) [15]. The laboratory variables included hemoglobin (Hb); the number of post-treatment transfusions (our anesthesiologic protocol recommends transfusion of two bags of hematite below 10 g/dl of hemoglobin for cardiopathic patients); the type of surgical procedure performed (fracture fixation or hip replacement); the surgical procedure and physiotherapy (post-operative treatment was performed according to the same rehabilitation protocol); delay in days since presentation to the Emergency Department; oxygen therapy during the stay; number

of transfers; lengthening of stay; SARS-CoV-2 related variables (PCR SARS-CoV-2 test results); abnormality of the pulmonary clinical picture radiographically evaluated; state of vaccination against SARS-CoV-2 of health workers and inpatients; type and number of post-surgical complications; range of motion and functional outcomes (expressed by the Harris Hip Score at 30 days and 3 months after surgery) [26,27]; evaluation of the antero-posterior and lateral radiographic views at 30 days and 3 months post-surgery (according to the Rush Score for the internal osteosynthesis procedures; and evaluation of the reduction of the radio-lucent line in prosthetic implants) [28].

2.3. Statistical Analysis

The statistical analysis of the data obtained was carried out using the software Statistical Package for Social Science version 22.0 for Macintosh (SPSS)® (IBM Corp, Chicago, IL, USA). Continuous variables were presented as the mean and the standard deviation, and categorical variables were presented as the number and percentage. We used the Student's Test T, the Mann-Whitney U test, and the chi-square test to compare differences between ordinal and categorical variables where appropriate. Statistically significant results for values of $p < 0.05$ were considered relevant. The force of the correlation identified among the continuous variables was subsequently analyzed using Spearman's Rho and the force of the correlation among the ordinal variables was analyzed with Kendall's Tau-b.

3. Results

Over the study period, 117 patients with neck femur fracture were admitted. 20.51% ($n = 20$) of cases were excluded because they did not satisfy the required criteria. At last, the total sample included 93 patients. Tables 1–3 show a summary of the main variables collected. The average age of the sample was 83.75 years (65–98, DS 19.3), 21.50% ($n = 20$) male and 78.5% ($n = 73$) female. Before the trauma, a percentage of 83.87% ($n = 78$) lived in their private home. According to the Parker and Palmer score, 6.51% ($n = 7$) of patients had a pre-trauma mobility score of less than three points, 40.92% ($n = 44$) between four and five points, and 31.62% ($n = 34$) over 5. On average, our sample reported a NHFS score of 5.24% (2.8–11.8) and mode 4.6 (DS 2.67). A percentage of 13.95% ($n = 15$) showed no significant comorbidity at the trauma time, 59.52% ($n = 64$) between one and three comorbidity and only 7.44% ($n = 8$) more than three concomitant diseases. A percentage of 23.25% ($n = 25$) had an ASA score of two40.92 ($n = 44$) of three and only 16% ($n = 17$) of four. In 3.23% ($n = 3$) was diagnosed with a femoral fracture OTA/AO 31A1, in 45.16% ($n = 42$) 31A2 and in 12.91% ($n = 12$) 31A3. Fractures type 31B/C corresponded to 31.26% ($n = 30$). A percentage of 55.91% ($n = 52$) were treated with internal synthesis, 20.43% ($n = 19$) with partial hip replacement and only two subjects (2.15%) were managed with total hip replacement.

Table 1. Demographic data of the sample.

	Total Sample
Patients	93
Sex	
Male	20 (21.50%)
Female	73 (78.5%)
Age	83.75 years (65–98)
Home status	
Own Home	78 (83.87%)
Nursing Home	15 (16.13%)

Table 1. *Cont.*

	Total Sample
Relevant comorbitidy	
no comorbidity	15 (13.95%)
beetween 1 and 3	64 (59.52%)
>3	8 (7.44%)
PPM classification	
≤3 points	7 (6.51%)
beetween 4 and 5 points	44 (40.92%)
>5 points	34 (31.62%)
NHFS score	2.8-11.8 (5.24%)
ASA	
≤2 grade	25 (23.25%)
3 grade	44 (40.92%)
4 grade	12 (16%)
OTA/AO	
31A1	3 (3.23%)
31A2	42 (45.16%)
31A3	12 (12.91%)
31B/C	30 (31.26%)
Surgical procedure	
ORIF	52 (55.91%)
Partial hip replacement	19 (20.43%)
Total hip replacement	2 (2.15%)

Table 2. Positive cohort with the negative Cohort.

	COVID-19 Positive Cohort (Group A)	Covid-19 Negative Cohort (Group B)	*p* Value
	11 (11.83%)	82 (88.17%)	
Hospitalization at Time 0	11 (100%)	43 (52.43%)	$p = 0.02$
Hospitalization at Time 1	0	39 (47.56%)	$p = 0.02$
Intensive Care Unit	8 (72.73%)	4 (4.88%)	$p = 0.000019$
E.R. > 24 h	7 (63.64%)	18 (22%)	$p = 0.019$
Length of stay, average	21 days (10–32)	14 days (7–22)	$p = 0.00001$
Mortality in ward	2 (18.18%)	1 (1.22%)	$p = 0.003$
Mortality from surgery to 3 months of follow-up	4 (36%)	5 (6%)	$p = 0.007$
HHS 80–89 points (3 months)	2 (18.18%)	27 (33.33%)	$p = 0.00001$
RUSH score 18–24 points (3 months)	1 (10.20%)	33 (40.42%)	$p = 0.00002$

Table 3. Main results obtained comparing transferred patients' cohort with the not transferred group.

	Transferred Patients' Cohort (Group C)	Not Transferred Patients' Cohort (Group D)	*p* Value
	20 (21.50%)	73 (78.50%)	
Surgery < 24 h	2 (10%)	18 (24.66%)	$p = 0.00007$
Length of stay < 15 days	15 (75%)	65 (89%)	$p = 0.001$
Mortality from surgery to 3 months of follow- up	5 (25%)	5 (6.85%)	$p = 0.02$
HHS 80–89 points (3 months)	2 (10%)	27 (37%)	$p = 0.00001$
RUSH score 18–24 points (3 months)	1 (5.20%)	22 (30.5%)	$p = 0.003$

3.1. COVID-19 Positive Cohort Vs. COVID-19 Negative Cohort

Among the sample, 11 (11.83%) were confirmed COVID positive by testing after the surgical procedure (Group A). Comparing demographic characteristics of Group A to Group B (COVID-19 negative cohort), the average age ($p = 0.31$), the gender ($p = 0.41$), the ASA score ($p = 0.40$), the PPM Score ($p = 0.38$), the NHFS ($p = 1.22$) and the type of fractures were comparable ($p = 0.10$) (Table 2). In terms of hospital quality measures, the whole positive COVID group was hospitalized during the period when less than 80% of health workers had been vaccinated (Time 0) ($p = 0.02$) and 72.73% ($n = 8$) needed high-flow oxygen and admission to the Intensive Care Unit ($p = 0.000019$). Group A had a longer stay in the Emergency Room (E.R.) compared to Group B ($p = 0.019$): a percentage of 63.64% ($n = 7$) of the first group remained in the E.R. more than 24 h, compared to only 22% ($n = 18$) of Group B. The positive cohort had a longer length of stay compared to the other patients (average of 21 days vs. 14 days, $p = 0.00001$). A percentage of 18.18% ($n = 2$) of infected patients, had died in the ward after the surgical procedure compared to only 1.22% ($n = 1$) of the not infected patients ($p = 0.003$). In terms of orthopedic outcomes measured to the third month of follow-up, we identified a worse score in functional (HHS 80–89 points: 18.18% vs. 33.33%) and radiographic (Rush Score 18–24 Rush Score: 10.20% vs. 40.42%) outcomes in the COVID positive cohort ($p = 0.00001$; $p = 0.00002$). SARS-CoV-2 infection during the stay and mortality relationship after discharge was also significant: 36% ($n = 4$) of subjects of Group A died in around three months after discharge compared to only 6% ($n = 5$) of the second group ($p = 0.007$).

3.2. Transferred Patients' Cohort Vs. Not Transferred Patients' Cohort

Twenty (21.51%) patients were transferred before the surgery (Group C) because of pandemic related logistics. Comparing Group C vs. D (not transferred patients), the average age ($p = 0.61$), the gender ($p = 0.71$), the ASA score ($p = 1.40$), the PPM Score ($p = 0.22$), the NHFS ($p = 0.45$) and the types of fractures were comparable ($p = 2.10$) (Table 3). Ten percent% ($n = 2$) of Group C and 24.66% ($n = 18$) of Group D underwent surgery within 24 h from the time of E.R. access ($p = 0.00007$). The surgery was delayed beyond 24 h (within 48 h) in 55% ($n = 11$) of transferred patients' cohort than the 45.20% ($n = 33$) of Group D ($p = 0.008$). The first group showed a duration of stay less than 15 days in 75% ($n = 15$) of cases vs. 89% ($n = 65$) of the second ($p = 0.001$). Furthermore, the indirect impact of COVID-19 management could be seen, as there was higher mortality among patients who underwent a transfer before the surgical procedure, compared to other patients (25% vs. 6.85%; $p = 0.02$). Up to the third month of follow-up, the subjects of Group C attained worse clinical and radiographic outcomes than Group D (HHS 80–89 points: 10% vs. 37%; Rush Score 18–24 Rush Score: 5.20% vs. 30.5%) ($p = 0.00001$; $p = 0.003$). For purely cognitive purposes, it was found that 54.22% of patients in our study sample completed the vaccination cycle (double dose) anti- SARS-CoV-2 by June 2021, but none completed the cycle during the period of hospitalization.

4. Discussion

Cases of an unidentified form of viral pneumonia were first reported in Wuhan city, China in December 2019. The virus is believed to be acquired from a zoonotic source. This unknown virus gradually spread across the whole world. The common symptoms observed in patients with COVID-19 are fever, cough, severe headache, and fatigue. Italy was one of the worst-affected countries in the first months of the pandemic [5]. A series of containment policies have been implemented since the start of the outbreak. The Italian government declared the quarantine of 11 municipalities in Northern Italy on 21 February, which was then extended to the whole country the next day [6,10]. The restrictions adopted on 13 October 2020 implemented the containment of SARS-CoV-2 contagion [20].

The pandemic management led to a significant change in orthopedic clinical and surgical activity. During this historic period, the incidence of proximal femur fractures in patients over 65 years of age did not show a reduction in cases [6,27]. The Local Health Department, therefore, had to undertake some managerial choices to allow a reorganization of the hospitalized patients. The femur fracture in the fragile patient requires multidisciplinary treatment, an approach that is difficult to manage even in a non-pandemic time [11,14]. These fragile subjects, victims of trauma, must receive surgery urgently [11,27]. Numerous studies support the close correlation between increased mortality and delayed orthopedic treatment [27]. The metanalysis conducted by Moja et al. shows how a delay in surgery beyond 48 h increases not only the risk of mortality, but also the risk of prolonged hospitalization [23]. Simunovic's study shows that the delay in treatment also leads to an increase in non-orthopedic perioperative complications [24]. As pointed out in some studies in recent years, the pandemic has greatly influenced the timing of femur fractures management, increasing time before diagnosis and treatment, thus increasing post-surgical mortalities [15,16,29]. The Coronavirus disease (COVID-19) has created severe humanitarian and socio-economic issues in the world [15,30].

The innovation of our study, compared to previous studies, was the analysis of the incidence of intra-hospital infection with SARS-CoV-2 in a sample consisting of patients with proximal femur fractures negative to molecular swab at the time of hospitalization. It also investigated how the pandemic management influenced the clinical and functional results of the patients under examination. On 21 December 2020 the European Medicine Agency (EMA) authorized the first vaccine against SARS-CoV-2, and on 27 December the first vaccination campaign against SARS-CoV-2 in Italy was launched, aimed at health staff and fragile populations. In view of these new events, it was decided to include in our analysis an even more up-to-date variable: the influence of the vaccination of health professionals compared to the incidence of infection in our inpatient population.

The proximal femur fractures included in our study (from 15 October 2020 to 31 March 2021) were 93, average age 83.75 years (65–98). The subjects included had to be necessarily negative to the PCR swab carried out in the E.R. The incidence of SARS-CoV-2 infection during the stay was 11.83% (11 patients), less than some data from the literature indicates [4,31]. It has been shown that 100% of the subjects infected were hospitalized at Time 0 (from 15 October 2020 to 10 February 2021), a period during which less than 80% of health care personnel were vaccinated against SARS-CoV-2 ($p = 0.02$). A long period spent in the E.R. before hospitalization led to an increased risk of onset of disease due to Coronavirus (time spent in E.R. > 24 h: 36% Group A vs. 22% Group B; $p = 0.019$). SARS-CoV-2 disease increased discharge times (stay > 15 days: Group A 27.27% vs. Group B 11.11%; $p = 0.00001$), intra-hospital mortality (Group A 18% vs. Group B 1.23%; $p = 0.003$) and mortality within 30 days after discharge (Group A 36% vs. Group B 6%; $p = 0.007$). Functional and radiographic outcomes were also lower in those who found the virus during the hospital stay (HHS Good: Group A 18.18% vs. Group B 33.33%; $p = 0.00001$). During the period examined, due to management problems related to the pandemic, it was necessary to transfer 20 victims of proximal femur fractures (21.51% of the sample analyzed) to reference hospitals. Ten percent of the transferred subjects underwent surgery within 24 h of E.R. access, compared to 22% of patients belonging to the other group ($p = 0.00007$). A stay of

less than 15 days distinguished 89% of the subjects not transferred compared to 75% of the other patients ($p = 0.001$). The transfer of patients and therefore the delay of treatment negatively affected their prognosis: Mortality was higher in this group compared to those not transferred (25% Group C vs. 6.85% Group D; $p = 0.02$). Functional results were also better in patients admitted without transfer (HHS Good: 10% Group C vs. 37% Group D; $p = 0.00001$).

The limits of the study are many: first, the low sample size. The short-term follow-up does not allow us to have a complete picture of the outcomes. Moreover, the peculiarity of the health conditions examined does not allow to reproduce and compare the same analyses in other samples.

5. Conclusions

The impact of the pandemic from SARS-CoV-2 compared to the clinical course of patients treated for a proximal femur fracture was statistically significant. Patients with Coronavirus during hospitalization compared to negative patients, obtained poor short-term radiographic and functional results and increased peri-operative mortality. The incidence of intra-hospital infection was high over the period in which health professionals were not yet covered by the anti-COVID vaccination cycle. Patients who were transferred between two hospitals, due to pandemic-related management issues, also achieved reduced outcomes compared to non-transferred cases, with increased mortality. From our study, therefore, it appears that delayed treatment in fragile patients entails an increased risk of complications, reduced functional recovery, and increased mortality.

Author Contributions: Validation, S.R., A.A., L.C. and A.M.; Writing—review & editing, M.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study did not require ethical approval and it was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Rahbari, M.; Rahlfs, S.; Jortzik, E.; Bogeski, I.; Becker, K. H_2O_2 dynamics in the malaria parasite Plasmodium falciparum. *PLoS ONE* **2017**, *12*, e0174837. [CrossRef]
2. Yesudhas, D.; Srivastava, A.; Gromiha, M.M. COVID-19 outbreak: History, mechanism, transmission, structural studies and therapeutics. *Infection* **2021**, *49*, 199–213. [CrossRef] [PubMed]
3. Adams, J.G.; Walls, R.M. Supporting the Health Care Workforce during the COVID-19 Global Epidemic. *JAMA—J. Am. Med. Assoc.* **2020**, *323*, 1439–1440. [CrossRef] [PubMed]
4. Guo, X.; Wang, J.; Hu, D.; Wu, L.; Gu, L.; Wang, Y.; Zhao, J.; Zeng, L.; Zhang, J.; Wu, Y. Survey of COVID-19 Disease among Orthopaedic Surgeons in Wuhan, People's Republic of China. *J. Bone Jt. Surg. Am. Vol.* **2020**, *102*, 847–854. [CrossRef]
5. Turatto, F.; Mazzalai, E.; Pagano, F.; Migliara, G.; Villari, P.; de Vito, C. A Systematic Review and Bibliometric Analysis of the Scientific Literature on the Early Phase of COVID-19 in Italy. *Front. Public Health* **2021**, 9. [CrossRef] [PubMed]
6. Giuntoli, M.; Bonicoli, E.; Bugelli, G.; Valesini, M.; Manca, M.; Scaglione, M. Lessons learnt from COVID 19: An Italian multicentric epidemiological study of orthopaedic and trauma services. *J. Clin. Orthop. Trauma* **2020**, *11*, 721–727. [CrossRef]
7. D'Amico, F.; Baumgart, D.C.; Danese, S.; Peyrin-Biroulet, L. Diarrhea During COVID-19 Infection: Pathogenesis, Epidemiology, Prevention, and Management. *Clin. Gastroenterol. Hepatol.* **2020**, *18*, 1663–1672. [CrossRef]
8. Venkatesan, A.; Iyengar, K.; Loh, W.Y.C. Strategies in reconfiguration of hand injuries management during COVID-19 pandemic. *J. Clin. Orthop. Trauma* **2020**, *11*, 697–699. [CrossRef] [PubMed]
9. Umakanthan, S.; Lawrence, S. Predictors of COVID-19 vaccine hesitancy in Germany: A cross-sectional, population-based study. *Postgrad. Med. J.* **2022**, *98*, 756–764. [CrossRef]
10. Umakanthan, S.; Patil, S.; Subramaniam, N.; Sharma, R. COVID-19 Vaccine Hesitancy and Resistance in India Explored through a Population-Based Longitudinal Survey. *Vaccines* **2021**, *24*, 1064. [CrossRef]
11. Morelli, I.; Luceri, F.; Giorgino, R.; Accetta, R.; Perazzo, P.; Mangiavini, L.; Maffulli, N.; Peretti, G.M. COVID-19: Not a contraindication for surgery in patients with proximal femur fragility fractures. *J. Orthop. Surg. Res.* **2020**, *15*, 285. [CrossRef]

12. Wong, J.S.H.; Cheung, K.M.C. Impact of COVID-19 on Orthopaedic and Trauma Service: An Epidemiological Study. *J. Bone Jt. Surg. —Am. Vol.* **2020**, *102*, E80. [CrossRef]
13. Mi, B.; Chen, L.; Xiong, Y.; Xue, H.; Zhou, W.; Liu, G. Characteristics and early prognosis of covid-19 infection in fracture patients. *J. Bone Jt. Surg. —Am. Vol.* **2020**, *102*, 750–758. [CrossRef]
14. Lim, M.A.; Pranata, R. Coronavirus disease 2019 (COVID-19) markedly increased mortality in patients with hip fracture—A systematic review and meta-analysis. *J. Clin. Orthop. Trauma* **2021**, *12*, 187–193. [CrossRef] [PubMed]
15. Rasidovic, D.; Ahmed, I.; Thomas, C.; Kimani, P.K.-U.; Wall, P.; Mangat, K.; NOF-COV19 Study Collaborative Group. Impact of COVID-19 on clinical outcomes for patients with fractured hip: A multicentre observational cohort study. *Bone Jt. Open* **2020**, *1*, 697–705. [CrossRef] [PubMed]
16. Dupley, L.; Oputa, T.J.; Bourne, J.T.; Lum, J.; Hodhody, G.; Rogers, S.; Mcloughlin, K.; Murphy, L.; Konarski, A.; Almari, F.; et al. 30-day mortality for fractured neck of femur patients with concurrent COVID-19 infection. *Eur. J. Orthop. Surg. Traumatol.* **2020**, *31*, 341–347. [CrossRef]
17. Khan, S.K.; Kalra, S.; Khanna, A.; Thiruvengada, M.M.; Parker, M.J. Timing of surgery for hip fractures: A systematic review of 52 published studies involving 291,413 patients. *Injury* **2009**, *40*, 692–697. [CrossRef] [PubMed]
18. Maniscalco, P.; Poggiali, E.; Quattrini, F.; Ciatti, C.; Magnacavallo, A.; Vercelli, A.; Domenichini, M.; Vaienti, E.; Pogliacomi, F.; Ceccarelli, F. Proximal femur fractures in covid-19 emergency: The experience of two orthopedics and traumatology departments in the first eight weeks of the Italian epidemic. *Acta Biomed.* **2020**, *91*, 89–96. [CrossRef] [PubMed]
19. Wright, E.V.; Musbahi, O.; Singh, A.; Somashekar, N.; Huber, C.P.; Wiik, A.V. Increased perioperative mortality for femoral neck fractures in patients with coronavirus disease 2019 (COVID-19): Experience from the United Kingdom during the first wave of the pandemic. *Patient Saf. Surg.* **2021**, *15*, 8. [CrossRef]
20. van de Laarschot, D.M.; McKenna, M.J.; Abrahamsen, B.; Langdahl, B.; Cohen-Solal, M.; Guañabens, N.; Eastell, R.; Ralston, S.H.; Zillikens, M.C. Medical management of patients after atypical femur fractures: A systematic review and recommendations from the European Calcified Tissue society. *J. Clin. Endocrinol. Metab.* **2020**, *105*, 1682–1699. [CrossRef]
21. DePhillipo, N.N.; Larson, C.M.; O'Neill, O.R.; LaPrade, R.F. Guidelines for Ambulatory Surgery Centers for the Care of Surgically Necessary/Time-Sensitive Orthopaedic Cases During the COVID-19 Pandemic. *J. Bone Jt. Surg. Am. Vol.* **2020**, *102*, 933–936. [CrossRef]
22. Moja, L.; Piatti, A.; Pecoraro, V.; Ricci, C.; Virgili, G.; Salanti, G.; Germagnoli, L.; Liberati, A.; Banfi, G. Timing Matters in Hip Fracture Surgery: Patients Operated within 48 Hours Have Better Outcomes. A Meta-Analysis and Meta- Regression of over 190,000 Patients. *PLoS ONE* **2012**, *7*, e46175. [CrossRef]
23. Simunovic, N.; Devereaux, P.J.; Sprague, S.; Guyatt, G.H.; Schemitsch, E.; DeBeer, J.; Bhandari, M. Effect of early surgery after hip fracture on mortality and complications: Systematic review and meta-analysis. *CMAJ* **2010**, *182*, 1609–1616. [CrossRef] [PubMed]
24. Buckley, R.E.; Moran, G.C.; Apivatthakakul, T. *AO Principles of Fracture Management*, 3rd ed.; Thieme: Leipzig, Germany, 2018.
25. Fader, A.N.; Huh, W.K.; Kesterson, J.; Pothuri, B.; Wethington, S.; Wright, J.D.; Bakkum-Gamez, J.N.; Soliman, P.T.; Sinno, A.; Leitao, M.; et al. When to Operate, Hesitate and Reintegrate: Society of Gynecologic Oncology Surgical Considerations during the COVID-19 Pandemic. *Gynecol. Oncol.* **2020**, *158*, 236–243. [CrossRef] [PubMed]
26. Nilsdotter, A.; Bremander, A. Measures of hip function and symptoms: Harris Hip Score (HHS), Hip Disability and Osteoarthritis Outcome Score (HOOS), Oxford Hip Score (OHS), Lequesne Index of Severity for Osteoarthritis of the Hip (LISOH), and American Academy of Orthopedic Surgeons (AAOS) Hip and Knee Questionnaire. *Arthritis Care Res.* **2011**, *63* (Suppl. 11), S200–S207. [CrossRef]
27. Aprato, A.; Bechis, M.; Buzzone, M.; Bistolfi, A.; Daghino, W.; Massè, A. No rest for elderly femur fracture patients: Early surgery and early ambulation decrease mortality. *J. Orthop. Traumatol.* **2020**, *21*, 12. [CrossRef]
28. Frank, T.; Osterhoff, G.; Sprague, S.; Garibaldi, A.; Bhandari, M.; Slobogean, G.P. The Radiographic Union Score for Hip (RUSH) Identifies Radiographic Nonunion of Femoral Neck Fractures. *Clin. Orthop. Relat. Res.* **2016**, *474*, 1396–1404. [CrossRef] [PubMed]
29. Coleman, J.R.; Burlew, C.C.; Platnick, K.B.; Campion, E.; Pieracci, F.; Lawless, R.; Werner, N.; Coleman, J.; Hoehn, M.; Moore, E.E.; et al. Maintaining Trauma Care Access During the COVID-19 Pandemic: An Urban, Level-1 Trauma Center's Experience. *Ann. Surg.* **2020**, *272*, e58–e60. [CrossRef] [PubMed]
30. Umakanthan, S.; Bukelo, M.; Gajula, S.S. The Commonwealth Caribbean COVID-19: Regions Resilient Pathway During Pandemic. *Front. Public Health* **2022**, *10*, 844333. [CrossRef] [PubMed]
31. Umakanthan, S.; Sahu, P.; Ranade, A.V.; Bukelo, M.M.; Rao, J.S.; Abrahao-Machado, L.F.; Dahal, S.; Kumar, H.; Dhananjaya, K.V. Origin, transmission, diagnosis and management of coronavirus disease 2019 (COVID-19). *Ostgrad. Med. J.* **2020**, *96*, 753–758. [CrossRef]

Journal of
Clinical Medicine

MDPI

Article

COVID-19 Clinical Features and Outcomes in Elderly Patients during Six Pandemic Waves

Roxana Manuela Fericean [1,2], Ovidiu Rosca [1], Cosmin Citu [3], Diana Manolescu [4], Vlad Bloanca [5], Ana-Olivia Toma [6,*], Estera Boeriu [7], Catalin Dumitru [3], Madhavi Ravulapalli [8], Vlad Barbos [2,9] and Cristian Oancea [10]

[1] Department XIII, Discipline of Infectious Diseases, "Victor Babes" University of Medicine and Pharmacy Timisoara, Eftimie Murgu Square 2, 300041 Timisoara, Romania
[2] Doctoral School, "Victor Babes" University of Medicine and Pharmacy Timisoara, Eftimie Murgu Square 2, 300041 Timisoara, Romania
[3] Department of Obstetrics and Gynecology, "Victor Babes" University of Medicine and Pharmacy Timisoara, Eftimie Murgu Square 2, 300041 Timisoara, Romania
[4] Department of Radiology, "Victor Babes" University of Medicine and Pharmacy Timisoara, Eftimie Murgu Square 2, 300041 Timisoara, Romania
[5] Department of Plastic Surgery, "Victor Babes" University of Medicine and Pharmacy Timisoara, Eftimie Murgu Square 2, 300041 Timisoara, Romania
[6] Department of Microbiology, "Victor Babes" University of Medicine and Pharmacy Timisoara, Eftimie Murgu Square 2, 300041 Timisoara, Romania
[7] Department of Pediatrics, Discipline of Pediatric Oncology and Hematology, "Victor Babes" University of Medicine and Pharmacy Timisoara, Eftimie Murgu Square 2, 300041 Timisoara, Romania
[8] School of General Medicine, Bhaskar Medical College, Amdapur Road 156-162, Hyderabad 500075, India
[9] Department of Urology, "Victor Babes" University of Medicine and Pharmacy Timisoara, Eftimie Murgu Square 2, 300041 Timisoara, Romania
[10] Center for Research and Innovation in Precision Medicine of Respiratory Diseases, "Victor Babes" University of Medicine and Pharmacy Timisoara, Eftimie Murgu Square 2, 300041 Timisoara, Romania
* Correspondence: toma.olivia@umft.ro

Citation: Fericean, R.M.; Rosca, O.; Citu, C.; Manolescu, D.; Bloanca, V.; Toma, A.-O.; Boeriu, E.; Dumitru, C.; Ravulapalli, M.; Barbos, V.; et al. COVID-19 Clinical Features and Outcomes in Elderly Patients during Six Pandemic Waves. *J. Clin. Med.* **2022**, *11*, 6803. https://doi.org/10.3390/jcm11226803

Academic Editors: Filippo Migliorini and Riccardo Giorgino

Received: 27 October 2022
Accepted: 15 November 2022
Published: 17 November 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Many elderly patients with severe SARS-CoV-2 infections and COVID-19 infections are admitted to intensive care units. Age was previously identified as an independent risk factor for death and contributed to the greater severity of COVID-19. The elderly may have diminished lung functions, poor reactions to artificial ventilation, and compromised immune systems. However, it is yet uncertain how each pandemic wave and the predominant SARS-CoV-2 strains contribute to varying results and how patient groups such as the elderly are impacted. Comparing six COVID-19 pandemic waves, the objective of this study was to examine the variation in case severity, symptomatology, ICU hospitalizations, and mortality among SARS-CoV-2-infected elderly individuals. The study followed a retrospective design, including 60 eligible patients older than 70 years in each of the six pandemic wave groups, after matching them by the number of comorbidities and gender. SARS-CoV-2 infection during the first, third, and fourth pandemic waves had a significantly higher risk of mortality for hospitalized patients. Confusion and dyspnea at admission were significant risk factors for ICU admission in elderly patients ($\beta = 1.92$, respectively $\beta = 3.65$). The laboratory parameters identified decreased lymphocytes ($\beta = 2.11$), elevated IL-6 ($\beta = 1.96$), and procalcitonin ($\beta = 2.46$) as the most significant risk factors. The third and fourth COVID-19 waves had considerably more severe infections (31.7% and 26.7%) than the sixth wave (13.3%). Median ICU stay and percentage of patients receiving oxygen support also differed across pandemic waves. However, mortality rates between the six pandemic waves were similar. The average length of hospitalization varied dramatically among the six pandemic waves. Although senior patients are more likely to have worse COVID-19 outcomes after hospitalization, this risk is mitigated by the greater prevalence of comorbidities and frailty among the elderly. The six pandemic waves that were specifically evaluated did not reveal considerably disproportionate variations in terms of patient mortality; however, during the fourth pandemic wave, there were likely more hospitalized patients with severe COVID-19 in Romania. It is probable that certain circulating SARS-CoV-2 strains were more infectious, resulting

in an increase in infections and a strain on healthcare systems, which might explain the variations found in our research.

Keywords: COVID-19; SARS-CoV-2 infection; elderly patients; viral epidemiology; infectious diseases

1. Introduction

In most individuals, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) produces no symptoms or moderate symptoms; it is less lethal than other viral infections, even though 20% of cases, such as those involving elderly persons and those with numerous comorbidities, may develop severe forms and immune system overactivation [1–3]. The symptoms of coronavirus disease 2019 (COVID-19) include fever, fatigue, and a dry cough. Interstitial pneumonia, thrombo-embolic events, and acute respiratory distress syndrome (ARDS) are all potential severe symptoms of SARS-CoV-2 infection in at-risk groups such as the elderly [4–7]. Overactivation of the immune system, triggering a cytokine storm, may produce these effects, although a wide variability of clinical outcomes was hypothesized to exist between circulating SARS-CoV-2 variants [8,9].

All age groups are vulnerable to SARS-CoV-2 infection, and the median hospitalized cohort age is 50–60, with a higher rate of intensive care unit (ICU) admissions and mortality after the age of 65 [10–12]. Men are more likely to have SARS-CoV-2 than women of comparable age, and they have a higher prevalence among hospitalized patients needing critical care, which may indicate a difference in severity; although, recent investigations had divergent outcomes [13–15]. These symptoms and manifestations have remained all throughout the COVID-19 pandemic development, with almost three years since its onset. However, several investigations show that different SARS-CoV-2 genotypes display different symptomatology and infection severity [16,17].

Many elderly COVID-19 patients with severe infections are admitted to critical care units with elevated inflammatory markers and D-dimer concentrations. The inflammatory cell infiltration in the lungs triggers the cytokine storm syndrome in COVID-19 patients [18–20]. Some experts feel that rapid treatment of this cytokine storm in its early stage with immunomodulators, corticosteroids, and cytokine antagonists is an essential component in decreasing mortality rates and reducing ICU hospitalizations [21–23]. Aging contributes to the increased severity of COVID-19, and it was previously observed as an independent risk factor for mortality. Elderly individuals may have reduced lung function and a poor response to mechanical ventilation, as well as a weakened immune system [24–26].

Although the COVID-19 vaccination campaign was spread worldwide by early 2021, reaching an impressive number of vaccinated patients until 2022, the efficacy of two or even three doses started to become lower as time passed, and the SARS-CoV-2 virus continued suffering different mutations [27–31]. Therefore, it was observed that during different spikes of the pandemic, the spread of infection and its severity changed, encountering more or less hospitalized and severely ill COVID-19 patients. To the best of our knowledge, there are little data on the dynamics of SARS-CoV-2 viral symptoms in elderly patients hospitalized in Romania throughout the last six pandemic waves. Therefore, the purpose of this research was to describe the variance in case severity, symptomatology, ICU hospitalizations, and death among SARS-CoV-2-infected elderly patients in a parallel comparison between six COVID-19 pandemic waves.

2. Materials and Methods

2.1. Study Design and Ethics

The current research was designed as a retrospective cohort study of hospitalized elderly patients with COVID-19. Patients included in the study were admitted at the Infectious Diseases and Pulmonology Hospital, "Victor Babes", in the period starting in March 2020 until August 2022. The research protocol was approved on 28 February 2022 by

the Ethics Committee of the "Victor Babes" University of Medicine and Pharmacy from Timisoara, Romania, and by the Ethics Committee of the hospital, with approval number 05. This time span covers both the pre- and post-COVID-19 immunization phases. The study took place at the University of Medicine and Pharmacy "Victor Babes" in Timisoara, under the Infectious Disease Department. The goal of this study was to perform retrospective research by gathering information from the paper and electronic hospital records of elderly patients diagnosed with COVID-19 who were hospitalized during the study period.

2.2. Inclusion Criteria

A database and patient paper record search were conducted to determine the number of elderly patients admitted to the hospital with a SARS-CoV-2 infection. Patients were included if they matched the following criteria: (1) being older than 70 years; (2) their paper records mentioned the ICD-10 diagnosis code of COVID-19 [32]; (3) the hospitalization occurred due to SARS-CoV-2 infection as the main diagnosis, without other acute conditions at admission; (4) being vaccinated or unvaccinated against SARS-CoV-2; and (5) having a SARS-CoV-2 infection confirmed by a PCR test. According to existing guidelines, the SARS-CoV-2 infection was considered mild, moderate, or severe as follows: (a) presenting to the hospital with a respiratory distress syndrome or respiratory rates higher than 30/min; (b) the finger oxygen saturation measured after 5 min of rest was lower than 93%; (c) PaO2 (the arterial oxygen partial pressure)/FiO2 (the inspired oxygen fraction) $\leq$ 300 mmHg; and (d) affected lung area on computed tomography (CT) of more than 50% [33,34]. The COVID-19 status was defined by a positive polymerase chain reaction test (PCR) from oropharyngeal and nasal swabs using multiplex RT-PCR [35]. A predefined patient personal form was used to gather demographic, clinical, and outcome data from electronic medical records and identify the patients' age distribution.

The elderly age of being older than 70 years was considered based on several studies that demonstrated a significantly higher proportion of hospital admissions and changes in mortality rates from SARS-CoV-2 infection after passing this age [36,37]. The acquired patient information was categorized by the pandemic wave at the time of hospital admission as follows: (1) The first wave in Romania was assumed to have occurred between March and October 2020, when Wuhan-Hu-1 (NCBI Reference Sequence: NC 045512.2) was the predominant variation in circulation [38]; (2) the second COVID-19 wave occurred between October 2020 and February 2021, with Clade variants (S: D614G) being the predominant viral strains [39]; (3) the third pandemic wave occurred between February and July 2021, with the Alpha (B.1.1.7) variation being the predominant circulating virus [40]; (4) the fourth COVID-19 wave occurred between July and December of 2021, the Delta (B1617.2) SARS-CoV-2 variant being the most prevalent strain [41,42]; (5) the Omicron viral strain produced the fifth pandemic wave in Romania between December 2021 and March 2022 [43]; (6) lastly, the sixth wave in Romania lasted from March 2022 to July 2022 [44]. For each wave, 60 individuals were included in the study, for a total of 360 elderly adults whose gender and comorbidities were matched with a control group of adults younger than 70 years. It was determined using a convenience sampling method that a total minimum of 139 adult patients younger than 70 years that were hospitalized for SARS-CoV-2 infection is sufficient to provide the statistical power needed for the control group.

2.3. Study Variables

The variables considered for analysis were the following: (1) the baseline characteristics of study participants (age, body mass index, gender, area of residence, smoking status, alcohol consumption status, number of comorbidities, COVID-19 vaccination status, and COVID-19 vaccine types); (2) paraclinical findings of the study participants (red blood cell count, white blood cell count, lymphocytes, hemoglobin, hematocrit, alanine aminotransferase, ferritin, erythrocyte sedimentation rate, c-reactive protein, fibrinogen, procalcitonin, d-dimers, interleukin-6, and creatinine; (3) clinical findings and disease outcomes (number of signs and symptoms at admission, clinical signs and symptoms, COVID-19 outcomes,

disease severity, duration of hospitalization, ICU admission, viral clearance, SOFA score, duration of ICU stay, intubated patients, oxygen supplementation, and mortality).

2.4. Statistical Analysis

The statistical analysis was performed with IBM SPSS v.27 (SPSS. Inc., Chicago, IL, USA), while the significance threshold was set for an alpha value of 0.05. The absolute and relative frequencies of categorical variables were computed and compared using the Chi-square and Fisher's tests. For the comparison of mean rank differences among nonparametric variables, the Kruskal–Wallis test was used. Parametric continuous variables that followed a normal distribution were compared by mean and standard deviation with the ANOVA test (analysis of variance). A Kaplan-Meier curve was plotted for probabilities of mortality based on the sputum culture results, while the Cox regression identified the hazard ratio for mortality in each of the four groups.

3. Results

3.1. Normal Weight vs. Overweight Patients

A total of 360 elderly patients (≥70 years) were included for data analysis, in comparison with a control group of 234 adults younger than 70 years, as presented in Table 1. The two study groups were matched by gender proportions and number of comorbidities. The average age of patients in the control group was 60.9 years, compared to 73.6 years in the group of interest. There were no significant differences in their baseline characteristics, except for the body mass index and vaccination status, which were significantly higher in the older patients, compared with the younger adults (25.6 vs. 24.2, p-value = 0.002), respectively (15.6% vaccinated patients older than 70 vs. 9.8% in younger adults, p-value = 0.044). The most commonly used vaccine was the BNT162b2 in 83.9% of older patients, compared to 60.9% in the control group.

Table 1. Comparison of baseline characteristics.

Baseline Characteristics	<70 Years (n = 234)	≥70 Years (n = 360)	p-Value
Background data			
Age (years), mean ± SD	60.9 ± 7.8	73.6 ± 8.1	<0.001
BMI, mean ± SD	24.2 ± 5.0	25.6 ± 5.4	0.002
Gender (men)	129 (55.1%)	198 (55.0%)	0.975
Area of residence (urban)	137 (58.5%)	192 (53.3%)	0.211
Smoking	66 (28.2%)	84 (23.3%)	0.181
Alcohol consumer	29 (12.4%)	46 (12.8%)	0.890
Number of comorbidities			0.999
0	15 (6.4%)	36 (6.4%)	
1	34 (14.5%)	31 (14.4%)	
2	106 (45.3%)	72 (45.3%)	
≥3	79 (33.8%)	74 (33.9%)	
COVID-19 vaccination status			0.044
Yes	23 (9.8%)	56 (15.6%)	
No	211 (90.2%)	304 (84.4%)	
COVID-19 vaccine	**(n = 23)**	**(n = 56)**	0.073
BNT162b2	14 (60.9%)	47 (83.9%)	
mRNA-1273	6 (26.1%)	5 (8.9%)	
Ad26.COV2.S	3 (13.0%)	4 (7.1%)	

Data reported as n (%) and calculated using Chi-square test and Fisher's exact test unless specified differently; BMI—Body Mass Index; BNT162b2—Pfizer BioNTech; mRNA-1273—Moderna; Ad26.COV2.S—Astra Zeneca.

Table 2 presents the paraclinical findings among the two study groups. It was observed that the white blood cell count was significantly higher in the control group compared to the elderly (40.6% of samples outside the normal range vs. 31.9%, p-value = 0.031). Similarly, the lymphocyte count was decreased in the elderly (44.4% vs. 54.3%, p-value = 0.019). Among the inflammatory markers, CRP, procalcitonin, and IL-6 were statistically significantly more elevated among patients older than 70 years.

Table 2. Paraclinical findings.

Paraclinical Findings	Normal Range	<70 Years (*n* = 234)	≥70 Years (*n* = 360)	*p*-Value
RBC (millions/mm^3)	4.35–5.65	72 (30.8%)	107 (29.7%)	0.785
WBC (thousands/mm^3)	4.5–11.0	95 (40.6%)	115 (31.9%)	0.031
Lymphocytes (thousands/mm^3)	1.0–4.8	127 (54.3%)	160 (44.4%)	0.019
Hemoglobin (g/dL)	13.0–17.0	55 (23.5%)	92 (25.5%)	0.571
Hematocrit (%)	36–48	59 (25.2%)	94 (26.1%)	0.806
ALT (U/L)	7–35	67 (28.6%)	113 (31.4%)	0.475
Ferritin (ng/mL)	20–250	70 (29.9%)	96 (26.7%)	0.388
ESR (mm/h)	0–22	105 (44.9%)	189 (51.1%)	0.069
CRP (mg/L)	0–10	83 (35.5%)	187 (51.9%)	0.001
Fibrinogen (g/L)	2–4	63 (26.9%)	111 (30.8%)	0.306
Procalcitonin (ug/L)	0–0.25	26 (11.1%)	69 (19.2%)	0.008
D-dimers (ng/mL)	<250	23 (9.8%)	54 (15.0%)	0.066
IL-6 (pg/mL)	0–16	53 (22.6%)	127 (35.2%)	0.001
Creatinine (µmol/L)	0.74–1.35	14 (6.0%)	38 (10.6%)	0.054

Data reported as % outside the normal range and calculated using the Chi-square test and Fisher's exact test unless specified differently; RBC—Red Blood Cells; WBC—White Blood Cells; ESR—Erythrocyte Sedimentation Rate; CRP—C-reactive Protein; IL-6—Interleukin 6; ALT—Alanine Aminotransferase.

The clinical presentation and outcomes in elderly patients hospitalized with COVID-19 and adult patients are presented in Table 3, and it was observed that older patients had significantly fewer symptoms at admission compared to the younger group. Among clinical signs and symptoms, it was observed that patients older than 70 presented with significantly more digestive symptoms (16.4% vs. 8.5%, *p*-value = 0.005), as well as a higher proportion of them having dyspnea and confusion as presenting symptoms (16.9% vs. 10.3%, *p*-value = 0.022), respectively 10.6% vs. 4.7% (*p*-value = 0.011). Contrarily, fever was significantly more often observed among younger patients (75.6% vs. 66.1%, *p*-value = 0.013).

Table 3. Clinical presentation and outcomes in elderly patients hospitalized with COVID-19 and adult patients.

Variables *	<70 Years (*n* = 234)	≥70 Years (*n* = 360)	*p*-Value
Number of signs and symptoms at admission			0.010
0	9 (3.8%)	36 (10.0%)	
1	34 (14.5%)	50 (13.9%)	
2	97 (41.5%)	163 (45.3%)	
≥3	94 (40.2%)	111 (30.8%)	
Clinical signs and symptoms			
Digestive symptoms	20 (8.5%)	59 (16.4%)	0.005
Anosmia	42 (17.9%)	55 (15.3%)	0.389
Ageusia	58 (24.8%)	74 (20.6%)	0.225
Fatigue	16 (69.7%)	267 (74.2%)	0.229
Dyspnea	24 (10.3%)	61 (16.9%)	0.022
Confusion	11 (4.7%)	38 (10.6%)	0.011
Headache	23 (9.8%)	44 (12.2%)	0.367
Fever	177 (75.6%)	238 (66.1%)	0.013
Cough	153 (65.4%)	255 (70.8%)	0.161
COVID-19 Outcomes			
Severe COVID-19	29 (12.4%)	71 (19.7%)	0.019
Severe imaging features	37 (15.8%)	83 (23.1%)	0.031
Mean duration of hospital stay	12.7 ± 3.3	14.1 ± 4.0	<0.001
Median duration from symptom onset until hospital admission	4.5 (6.5)	3.5 (3.0)	<0.001
Viral clearance	12 (9)	14 (12)	<0.001
ICU admissions	18 (7.7%)	53 (14.7%)	0.009
Median duration from hospital admission to ICU admission	5.0 (7.0)	3.5 (3.0)	<0.001
SOFA score	4.4 (3.1)	6.5 (4.8)	<0.001
Median duration of ICU stay	7.3 (6.6)	5.6 (4.9)	<0.001
Severe in-hospital complications	24 (10.3%)	59 (16.4%)	0.035
Intubation	11 (4.7%)	34 (9.4%)	0.032
Oxygen supplementation	86 (36.8%)	159 (44.2%)	0.072
Mortality	8 (3.4%)	27 (7.5%)	0.039

* Data reported as *n* (%) and calculated using the Chi-square test and Fisher's exact test unless specified differently; BMI—Body Mass Index; ICU—Intensive Care Unit; SOFA—Sequential Organ Failure Assessment.

As expected, COVID-19 outcomes were significantly more often affecting the elderly (19.7% vs. 12.4%, p-value = 0.019). As a consequence, the mean duration of hospitalization was significantly higher than in younger patients (14.1 days vs. 12.7 days, p-value < 0.001). Additionally, the SOFA score and proportion of patients admitted to the ICU were higher in patients older than 70 years (median SOFA score = 6.5 vs. 4.4, p-value < 0.001), respectively, 14.7% ICU admission among the elderly patients, compared to 7.7% in the control group (p-value = 0.009). The duration of hospitalization and ICU stay were higher in the group of older patients, in correlation with a higher mortality rate of 7.5%, compared to 3.5% among the hospitalized younger patients (p-value = 0.039).

3.2. Dynamic Comparison of COVID-19 Pandemic Waves

Table 4 describes the clinical findings of elderly patients hospitalized with SARS-CoV-2 infection over six pandemic waves. It was observed that the COVID-19 severity of hospitalized patients was significantly higher during the third and fourth waves (31.7% and 26.7%, compared with the sixth wave of 13.3% severe infections). The mean duration of hospitalization was observed to vary significantly between the six pandemic waves that were analyzed (p-value < 0.001), with the longest hospital stay being observed during the fourth wave (16.4 days), followed by the first wave with an average of 15.3 days. The shortest hospitalization was during the 5th and 6th waves, with 10.3 and 10.5 days, respectively. Other statistically significant differences between the pandemic waves were the median duration of ICU stay and the proportion of patients requiring oxygen supplementation. The longest median duration of hospitalization was during the first wave (7.1 days), followed by the second wave with 6.6 days, while the shortest ICU stay was during the fourth wave (5.2 days, p-value = 0.001), as seen in Figure 1a. Despite these differences, the mortality did not significantly change during the six pandemic waves (Figure 1b). Regarding the biological findings measured during the pandemic waves, there was no statistically significant change, as seen in Table 5.

Table 4. Clinical findings of elderly patients (≥70 years old) hospitalized with SARS-CoV-2 infection stratified by COVID-19 pandemic wave.

Clinical Findings	1st Wave (n = 60)	2nd Wave (n = 60)	3rd Wave (n = 60)	4th Wave (n = 60)	5th Wave (n = 60)	6th Wave (n = 60)	p-Value
Severe COVID-19	11 (18.3%)	9 (15.0%)	16 (26.7%)	19 (31.7%)	8 (13.3%)	8 (13.3%)	0.046
Severe imaging features	12 (20.0%)	8 (13.3%)	17 (28.3%)	21 (35.0%)	12 (20.0%)	13 (21.7%)	0.085
Mean duration of hospital stay	15.3 ± 4.0	15.0 ± 4.3	14.1 ± 4.0	16.4 ± 5.2	10.3 ± 3.7	10.5 ± 3.9	<0.001
Median duration from symptom onset until hospital admission	2.0 (2.0)	3.0 (2.5)	3.5 (3.0)	3.0 (2.5)	3.5 (3.0)	4.0 (2.5)	0.122
Viral clearance	15 (11)	14 (13)	16 (14)	15 (12)	14 (11)	14 (12)	0.683
ICU admissions	8 (13.3%)	8 (13.3%)	12 (20.0%)	14 (23.3%)	6 (10.0%)	5 (8.3%)	0.152
Median duration from hospital admission to ICU admission	5.0 (3.0)	4.5 (3.5)	4.0 (3.0)	3.5 (3.0)	3.5 (3.0)	4.0 (3.5)	0.360
SOFA score	5.6 (4.6)	5.8 (4.8)	6.7 (4.9)	6.5 (4.3)	6.8 (5.0)	6.5 (4.8)	0.062
Median duration of ICU stay	7.1 (3.4)	6.6 (3.9)	5.7 (4.0)	5.2 (3.5)	5.4 (3.4)	5.9 (4.2)	0.001
Severe in-hospital complications	7 (11.7%)	8 (13.3%)	13 (21.9%)	15 (25.0%)	7 (11.7%)	9 (15.0%)	0.227
Intubation	4 (6.7%)	5 (8.3%)	7 (11.7%)	10 (16.7%)	4 (6.7%)	4 (6.7%)	0.334
Oxygen supplementation	21 (35.0%)	24 (40.0%)	35 (58.3%)	36 (60.0%)	20 (33.3%)	23 (38.3%)	0.004
Mortality	3 (5.0%)	3 (5.0%)	5 (8.3%)	9 (15.0%)	4 (6.7%)	3 (5.0%)	0.215

Data reported as n (%) and calculated using the Chi-square test and Fisher's exact test unless specified differently; ICU—Intensive Care Unit; SOFA—Sequential Organ Failure Assessment.

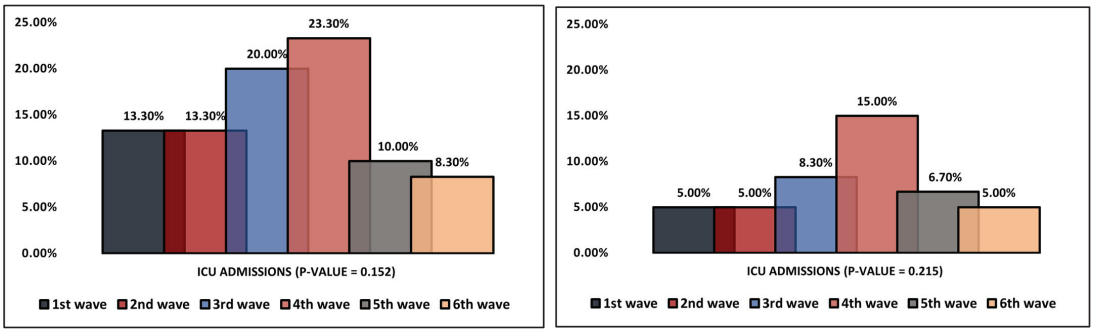
Table 5. Paraclinical findings of elderly patients (≥70 years old) hospitalized with SARS-CoV-2 infection stratified by COVID-19 pandemic wave.

Paraclinical Findings	Normal Range	1st Wave (n = 60)	2nd Wave (n = 60)	3rd Wave (n = 60)	4th Wave (n = 60)	5th Wave (n = 60)	6th Wave (n = 60)	p-Value
RBC (millions/mm^3)	4.35–5.65	20 (32.8%)	23 (37.7%)	13 (21.3%)	17 (27.9%)	16 (26.2%)	18 (29.5%)	0.454
WBC (thousands/mm^3)	4.5–11.0	18 (29.5%)	23 (37.7%)	16 (26.2%)	21 (34.4%)	20 (32.8%)	17 (27.9%)	0.750

Table 5. *Cont.*

Paraclinical Findings	Normal Range	1st Wave (*n* = 60)	2nd Wave (*n* = 60)	3rd Wave (*n* = 60)	4th Wave (*n* = 60)	5th Wave (*n* = 60)	6th Wave (*n* = 60)	*p*-Value
Lymphocytes (thousands/mm^3)	1.0–4.8	24 (40.0%)	23 (38.3%)	28 (46.7%)	29 (48.3%)	26 (43.3%)	30 (50.0%)	0.752
Hemoglobin (g/dL)	13.0–17.0	13 (21.3%)	18 (29.5%)	14 (23.0%)	14 (23.0%)	17 (27.9%)	16 (26.2%)	0.889
Hematocrit (%)	36–48	14 (23.0%)	18 (29.5%)	15 (25.0%)	16 (26.7%)	14 (23.0%)	17 (27.9%)	0.949
ALT (U/L)	7–35	17 (27.9%)	19 (31.7%)	20 (33.3%)	27 (45.0%)	17 (27.9%)	13 (21.3%)	0.134
Ferritin (ng/mL)	20-250	15 (25.0%)	12 (20.0%)	16 (26.7%)	17 (27.9%)	12 (20.0%)	14 (23.3%)	0.855
ESR (mm/h)	0–22	32 (53.3%)	30 (50.0%)	28 (46.7%)	36 (60.0%)	35 (58.3%)	28 (46.7%)	0.552
CRP (mg/L)	0–10	29 (48.3%)	31 (51.7%)	27 (45.0%)	38 (63.3%)	32 (53.3%)	30 (50.0%)	0.449
Fibrinogen (g/L)	2–4	19 (31.7%)	18 (29.5%)	15 (25.0%)	17 (27.9%)	20 (33.3%)	21 (34.4%)	0.871
Procalcitonin (ug/L)	0–0.25	11 (18.3%)	9 (15.0%)	13 (21.7%)	15 (25.0%)	15 (25.0%)	9 (15.0%)	0.555
D-dimers (ng/mL)	<250	10 (16.7%)	11 (54.0%)	9 (15.0%)	13 (21.7%)	14 (23.0%)	10 (16.7%)	0.839
IL-6 (pg/mL)	0–16	21 (34.4%)	20 (32.8%)	23 (37.7%)	22 (36.7%)	24 (40.0%)	17 (27.9%)	0.813
Creatinine (μmol/L)	0.74–1.35	8 (13.3%)	8 (13.3%)	6 (10.0%)	9 (15.0%)	4 (6.7%)	5 (8.3%)	0.659

Data reported as % outside the normal range and calculated using the Chi-square test and Fisher's exact test unless specified differently; RBC—Red Blood Cells; WBC—White Blood Cells; ESR—Erythrocyte Sedimentation Rate; CRP—C-reactive Protein; IL-6—Interleukin 6; ALT—Alanine Aminotransferase.



(**a**) (**b**)

Figure 1. (**a**,**b**) Dynamic comparison of ICU admissions and mortality in elderly patients (≥70 years old) hospitalized with SARS-CoV-2 infection during six COVID-19 pandemic waves.

3.3. Risk Analysis

The risk analysis for ICU admission in SARS-CoV-2 infected elderly patients was evaluated in Table 6, in comparison with the control group of adults younger than 70. It was observed that the SARS-CoV-2 infection during the first, third, and fourth pandemic waves had a significantly higher risk for mortality, as seen in Figure 2. Among the clinical and paraclinical predictors for ICU admission in the elderly, it was observed that confusion and dyspnea at admission were significant risk factors (β = 1.92 and β = 3.65, respectively). The laboratory parameters identified decreased lymphocytes (β = 2.11), elevated IL-6 (β = 1.96), and procalcitonin (β = 2.46) as the most significant risk factors for ICU admission in the admitted elderly patients.

Table 6. Regression analysis for risk of ICU admission in SARS-CoV-2-infected elderly patients.

	β for ICU Admission *	(95% CI of β)	Significance
≥70 years (constant) ^	1.93	1.15–3.66	0.020
Covariates (predictors)—pandemic waves			
1st pandemic wave	2.12	1.48–4.20	0.004
2nd pandemic wave	1.59	0.92–2.84	0.261
3rd pandemic wave	2.36	1.28–3.78	0.033
4th pandemic wave	2.04	1.13–4.09	0.028
5th pandemic wave	1.33	0.90–1.83	0.402
6th pandemic wave	1.58	0.87–1.96	0.317

Table 6. *Cont.*

	β for ICU Admission *	(95% CI of β)	Significance
Covariates (predictors)—clinical and paraclinical			
Confusion	1.92	1.20–2.47	0.001
Dyspnea	3.65	1.46–5.39	<0.001
Decreased WBC	1.09	0.91–1.43	0.063
Decreased lymphocytes	2.11	1.34–3.06	<0.001
Elevated procalcitonin	2.46	1.52–3.88	<0.001
Elevated IL-6	1.96	1.31–2.95	0.001
Elevated CRP	1.13	0.98–1.42	0.051

* Dependent (response) variable; ^ Estimated risk in univariate analysis; CI—Confidence Interval.

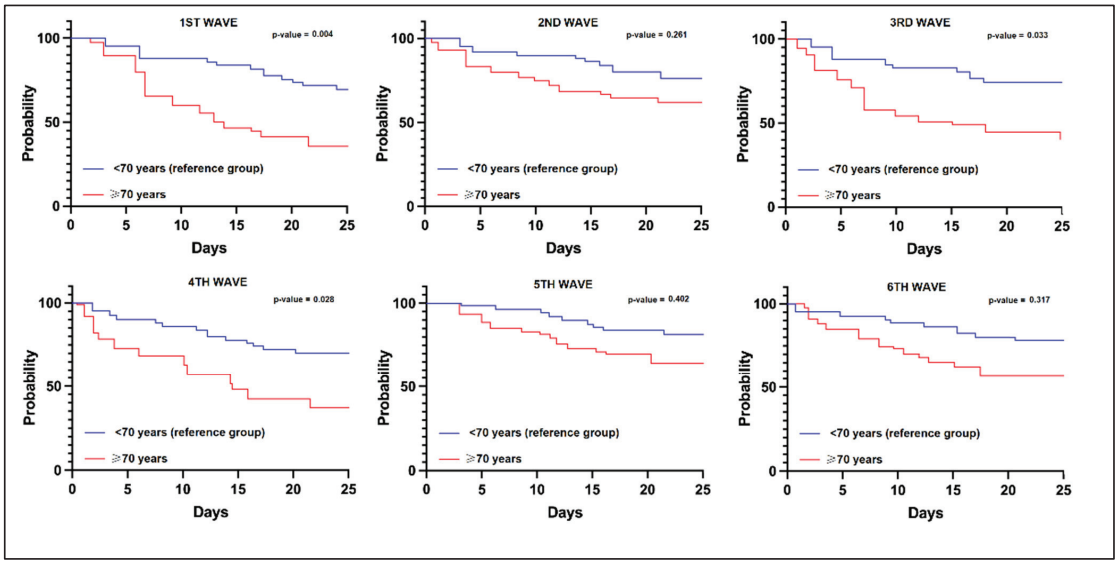


Figure 2. Kaplan-Meier probability analysis for mortality in elderly patients based on the pandemic wave.

4. Discussion

4.1. Literature Findings

In all six waves, fever, cough, and tiredness were the symptoms that occurred most often. Concomitant symptoms that occurred less frequently included a runny nose, headache, and digestive symptoms. Although the first, third, and fourth pandemic waves were observed to bring a significantly higher risk for mortality in the elderly patients hospitalized for COVID-19, the bias risk has to be weighed, considering that the patients admitted to a tertiary clinic and treated were the most difficult cases. Therefore, during peak pandemic waves, it was possible that only the more severe cases were hospitalized. These findings are consistent with previous research [1]; although, we did not evaluate the Pneumonia Severity Index (PSI) score, which was reported to be greater when compared to young and middle-aged adults. It is important to note that among senior patients, the proportion of patients complaining of more severe dyspnea and tachypnea was greater in patients admitted to the ICU, as well as delirium and abdominal discomfort that may accompany cases with a severe evolution [45]. On the other side, constitutional symptoms such as fever and headache were more prevalent in survivors.

Increasing numbers of investigations have shown that older people may have unusual clinical presentations, with fever appearing less commonly in older patients than in younger patients, which was consistent with our findings [46]. Moreover, it appears that delirium and neuropsychiatric symptoms in this patient population are increasing significantly

in COVID-19 patients older than 70 years. In a recent meta-analysis of patients with SARS-CoV-2 infection, the prevalence of delirium was almost 30% in those older than 65, compared to less than 15% in the general hospitalized adult population [47], which was associated with an approximately 45% mortality when delirium was present at admission.

Regarding the laboratory findings, it was shown that older patients did not vary significantly from other adults in terms of their WBC, NLR, and procalcitonin levels, although lymphocytes found in the elderly were much lower than in the adult population. On the other hand, the level of CRP found in older individuals was shown to be significantly greater [48]. A comparison of the laboratory findings between the group of elderly patients who survived SARS-CoV-2 infection and those who did not, based on a follow-up period of four weeks, revealed that the number of neutrophils had significantly increased, whereas the number of lymphocytes, monocytes, and platelets had decreased among the deceased patients during the later phases of the infection. However, they did not follow the evolution of laboratory parameters during hospitalization, only at admission. Other findings were that the prothrombin time was considerably extended, coupled with an increase in kidney markers, cardiac markers, and D-dimers [49].

Other studies reported similar results when analyzing hospitalized patients who survived the SARS-CoV-2 infection, identifying that the older population exhibited lower levels of ferritin, procalcitonin, and lymphocytes. It has also been shown that elevated levels of D-dimers, CRP, and a high NLR score are related to a worse prognosis [50], where elevated D-dimers had the best sensitivity and specificity for negative outcomes, followed by CRP levels and NLR score. Other studies that researched the conventionally tested biological markers found an association between LDH and AST with lower pulmonary function, ICU admission, and death [51]. In other investigations, including older individuals with COVID-19, other variables related to mortality, such as frailty, have also been reported. For instance, a recent systematic study that included data from almost one million individuals indicates that frailty and being underweight increased the chance of SARS-CoV-2 infection-associated death by more than five-fold [52].

Prompt identification of COVID-19-related complications is of extreme importance in vulnerable patients such as the elderly. In this case, chest imaging is the most important diagnostic technique for determining pulmonary complications during acute SARS-CoV-2 infection. A bilateral multilobar ground-glass opacification with a peripheral or posterior distribution, primarily in the lower lobes, is one of the typical hallmarks of COVID-19 [53]. In a limited number of instances, particularly those affecting old patients, an atypical first imaging appearance of consolidative opacities superimposed over ground-glass opacity may be seen. It was observed that the elderly had a significantly higher incidence of multiple lobe involvement compared to the younger and middle-aged groups [54].

Although there were more older patients who were vaccinated than younger adults in our cohort, the severity of SARS-CoV-2 infection was much greater among the elderly. It is well advised that the elderly are a high-risk population that should be provided immunization with priority, but it was observed that the antibody response after vaccination was typically lower due to the steady reduction of the immune system with age and the immunological response of neutralizing antibodies after vaccination dropped more abruptly in older individuals than the adult patients with the same vaccines and number of doses [55]. On the contrary, it was also observed that in patients older than 60 years, the rates of severe SARS-CoV-2 infections were significantly lower by almost 20% among those who received a third booster dose of the Pfizer-BioNTech vaccine compared to those who did not receive the third dose [56]. However, current findings show that mRNA-based COVID-19 vaccination boosters are effective against the Omicron variant, but with a lower effect; although, data on the elderly are few [57].

This research identified substantial differences between the six COVID-19 pandemic waves in Romania. Similar studies are few on reporting a complete comparison of each wave with the purpose of determining the variability of SARS-CoV-2 mutations and severity of infections. Another study that took place in Thailand showed that the severity of the

third wave represented by the Delta strain was greater than that of prior waves, which is similar to our findings [58]. It is, however, unknown if the difference is attributable to the absence of effective social distancing measures and public health initiatives or a more dangerous mutation of the SARS-CoV-2 virus. On the other hand, the greatest detrimental effects on public health were caused by the first wave. Another study comparing Delta solely and Omicron found a case fatality ratio of 3.4% for Delta and 1.9% for Omicron, indicating a difference of around twice. Consequently, Omicron is less severe than Delta based on these metrics, with the exact severity reduction compared to Delta depending on how the number of infections is assessed [59].

4.2. Study Limitations and Strengths

As a first limitation, there is the possibility of human error in the creation of digital data from paper medical records, and the quality of the data that was studied in a retrospective cohort design may have been lower than expected. The second constraint is that there was a very low number of participants in each individual group's sample, despite the fact that the total number of participants was sufficient to satisfy the statistical power requirements. The third limitation of the current study would be the monocentric design, which can limit the generalization of our findings. A higher rate of COVID-19 complications at admission can occur in patients with multiple comorbidities. To prevent the bias risk of multiple comorbidities in elderly patients, it was opted to include in the study only patients admitted for SARS-CoV-2 infection, excluding those who got infected during their hospital stay for a different diagnosis. Comorbidities such as arterial hypertension and diabetes mellitus were identified more often in some of the study groups, predisposing them to worse outcomes and higher mortality rates, as they seem to be related to a more severe infection [60,61]. Lastly, patients with a previous infection are presumed to develop a stronger immunity against the virus, which could distort the result in this study [62,63]. However, the only way to verify if a patient had a previous SARS-CoV-2 infection or hospitalization for COVID-19 was to check in the hospital's database if the patient was admitted before, and it was not possible to check if the patient was admitted elsewhere.

5. Conclusions

Although elderly patients are likely to have worse COVID-19 outcomes during hospitalization, the risk is weighted by the higher proportion of comorbidities and frailty of the elderly. The six pandemic waves that were particularly analyzed did not show significantly disproportionate differences regarding patient mortality; although, during the fourth wave, there were probably more patients with severe COVID-19 admitted to the hospital. It is likely that some circulating SARS-CoV-2 viral strains were more contagious, causing more infections and creating an overload on the healthcare systems, which might explain the changes observed in our study. Biological parameters also did not vary significantly among the elderly patients during the six waves that were analyzed, although patients older than 70 were more likely to present with dyspnea, confusion, and digestive symptoms, associated with lower lymphocyte levels and higher IL-6 levels. It is, therefore, difficult to diagnose and treat elderly people who have SARS-CoV-2 infection because they are more prone to developing severe clinical consequences from the virus. According to the information that is now available, a customized strategy that targets both the positive and negative consequences of therapy choices need to be made available to older persons. It is imperative that hospitals and residential care facilities that provide long-term care immediately develop appropriate healthcare plans for their older patients. To ensure that COVID-19 patients have access to the most productive therapy choices, fragility must be addressed. Until further advancements can be made in therapy, it is advised that the elderly population be kept isolated from the rest of the community when COVID-19 epidemics occur.

Author Contributions: Conceptualization: R.M.F. and O.R.; methodology: R.M.F. and O.R.; software: V.B. (Vlad Bloanca) and V.B. (Vlad Barbos); validation: C.C.; formal analysis: C.C.; investigation: D.M.; resources: D.M.; data curation: V.B. (Vlad Bloanca) and V.B. (Vlad Barbos); writing—original draft preparation: R.M.F. and V.B. (Vlad Bloanca); writing—review and editing: A.-O.T., M.R. and E.B.; visualization: A.-O.T. and E.B.; supervision: C.D. and C.O.; project administration: C.O. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Victor Babes" Clinical Hospital for Infectious Diseases and Pulmonology in Timisoara on 28 February 2022 with approval number 05.

Informed Consent Statement: Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement: Data available on request.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Perrotta, F.; Corbi, G.; Mazzeo, G.; Boccia, M.; Aronne, L.; D'Agnano, V.; Komici, K.; Mazzarella, G.; Parrella, R.; Bianco, A. COVID-19 and the elderly: Insights into pathogenesis and clinical decision-making. *Aging Clin. Exp. Res.* **2020**, *32*, 1599–1608. [CrossRef]
2. Lebrasseur, A.; Fortin-Bédard, N.; Lettre, J.; Raymond, E.; Bussières, E.-L.; Lapierre, N.; Faieta, J.; Vincent, C.; Duchesne, L.; Ouellet, M.-C.; et al. Impact of the COVID-19 Pandemic on Older Adults: Rapid Review. *JMIR Aging* **2021**, *4*, e26474. [CrossRef]
3. Grigoras, M.L.; Citu, I.M.; Citu, C.; Chiriac, V.D.; Gorun, F.; Levai, M.C.; Manolescu, D.; Rosca, O.; Bratosin, F.; Gurumurthy, S.; et al. Evaluation of FIB-4, NFS, APRI and Liver Function Tests as Predictors for SARS-CoV-2 Infection in the Elderly Population: A Matched Case-Control Analysis. *J. Clin. Med.* **2022**, *11*, 5149. [CrossRef]
4. Myall, K.J.; Martinovic, J.L.; West, A. How COVID-19 interacts with interstitial lung disease. *Breathe* **2022**, *18*, 210158. [CrossRef]
5. Farshbafnadi, M.; Zonouzi, S.K.; Sabahi, M.; Dolatshahi, M.; Aarabi, M.H. Aging & COVID-19 susceptibility, disease severity, and clinical outcomes: The role of entangled risk factors. *Exp. Gerontol.* **2021**, *154*, 111507. [CrossRef] [PubMed]
6. Chiumello, D.; Modafferi, L.; Fratti, I. Risk Factors and Mortality in Elderly ARDS COVID-19 Compared to Patients without COVID-19. *J. Clin. Med.* **2022**, *11*, 5180. [CrossRef] [PubMed]
7. Citu, C.; Burlea, B.; Gorun, F.; Motoc, A.; Gorun, O.M.; Malita, D.; Ratiu, A.; Margan, R.; Grigoras, M.L.; Bratosin, F.; et al. Predictive Value of Blood Coagulation Parameters in Poor Outcomes in COVID-19 Patients: A Retrospective Observational Study in Romania. *J. Clin. Med.* **2022**, *11*, 2831. [CrossRef] [PubMed]
8. Mendiola-Pastrana, I.R.; López-Ortiz, E.; de la Loza-Zamora, J.G.R.; González, J.; Gómez-García, A.; López-Ortiz, G. SARS-CoV-2 Variants and Clinical Outcomes: A Systematic Review. *Life* **2022**, *12*, 170. [CrossRef]
9. Maurya, R.; Mishra, P.; Swaminathan, A.; Ravi, V.; Saifi, S.; Kanakan, A.; Mehta, P.; Devi, P.; Praveen, S.; Budhiraja, S.; et al. SARS-CoV-2 Mutations and COVID-19 Clinical Outcome: Mutation Global Frequency Dynamics and Structural Modulation Hold the Key. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 868414. [CrossRef]
10. ISARIC Clinical Characterisation Group. COVID-19 symptoms at hospital admission vary with age and sex: ISARIC multinational study. *Infection* **2021**, *49*, 889–905. [CrossRef]
11. Pouw, N.; van de Maat, J.; Veerman, K.; Oever, J.T.; Janssen, N.; Abbink, E.; Reijers, M.; de Mast, Q.; Hoefsloot, W.; van Crevel, R.; et al. Clinical characteristics and outcomes of 952 hospitalized COVID-19 patients in The Netherlands: A retrospective cohort study. *PLoS ONE* **2021**, *16*, e0248713. [CrossRef] [PubMed]
12. Pilut, C.N.; Citu, C.; Gorun, F.; Bratosin, F.; Gorun, O.M.; Burlea, B.; Citu, I.M.; Grigoras, M.L.; Manolescu, D.; Gluhovschi, A. The Utility of Laboratory Parameters for Cardiac Inflammation in Heart Failure Patients Hospitalized with SARS-CoV-2 Infection. *Diagnostics* **2022**, *12*, 824. [CrossRef] [PubMed]
13. Fabião, J.; Sassi, B.; Pedrollo, E.; Gerchman, F.; Kramer, C.; Leitão, C.; Pinto, L. Why do men have worse COVID-19-related outcomes? A systematic review and meta-analysis with sex adjusted for age. *Braz. J. Med Biol. Res.* **2022**, *55*, e11711. [CrossRef] [PubMed]
14. Fortunato, F.; Martinelli, D.; Caputo, S.L.; Santantonio, T.; Dattoli, V.; Lopalco, P.L.; Prato, R. Sex and gender differences in COVID-19: An Italian local register-based study. *BMJ Open* **2021**, *11*, e051506. [CrossRef] [PubMed]
15. Jin, J.M.; Bai, P.; He, W.; Wu, F.; Liu, X.F.; Han, D.M.; Liu, S.; Yang, J.K. Gender Differences in Patients with COVID-19: Focus on Severity and Mortality. *Front. Public Health* **2020**, *8*, 152. [CrossRef]
16. de Souza, G.A.P.; Le Bideau, M.; Boschi, C.; Ferreira, L.; Wurtz, N.; Devaux, C.; Colson, P.; La Scola, B. Emerging SARS-CoV-2 Genotypes Show Different Replication Patterns in Human Pulmonary and Intestinal Epithelial Cells. *Viruses* **2021**, *14*, 23. [CrossRef]

17. Fericean, R.M.; Citu, C.; Manolescu, D.; Rosca, O.; Bratosin, F.; Tudorache, E.; Oancea, C. Characterization and Outcomes of SARS-CoV-2 Infection in Overweight and Obese Patients: A Dynamic Comparison of COVID-19 Pandemic Waves. *J. Clin. Med.* **2022**, *11*, 2916. [CrossRef]
18. Jung, C.; Fjølner, J.; Bruno, R.R.; Wernly, B.; Artigas, A.; Pinto, B.B.; Schefold, J.C.; Wolff, G.; Kelm, M.; Beil, M.; et al. Differences in mortality in critically ill elderly patients during the second COVID-19 surge in Europe. *Crit. Care* **2021**, *25*, 344. [CrossRef]
19. Gkoufa, A.; Maneta, E.; Ntoumas, G.N.; E Georgakopoulou, V.; Mantelou, A.; Kokkoris, S.; Routsi, C. Elderly adults with COVID-19 admitted to intensive care unit: A narrative review. *World J. Crit. Care Med.* **2021**, *10*, 278–289. [CrossRef]
20. Papava, I.; Dehelean, L.; Romosan, R.S.; Bondrescu, M.; Dimeny, C.Z.; Domuta, E.M.; Bratosin, F.; Bogdan, I.; Grigoras, M.L.; Tigmeanu, C.V.; et al. The Impact of Hyper-Acute Inflammatory Response on Stress Adaptation and Psychological Symptoms of COVID-19 Patients. *Int. J. Environ. Res. Public Health* **2022**, *19*, 6501. [CrossRef]
21. Rangappa, P. Cytokine Storm and Immunomodulation in COVID-19. *Indian J. Crit. Care Med.* **2021**, *25*, 1288–1291. [CrossRef] [PubMed]
22. Pinheiro, M.M.; Fabbri, A.; Infante, M. Cytokine storm modulation in COVID-19: A proposed role for vitamin D and DPP-4 inhibitor combination therapy (VIDPP-4i). *Immunotherapy* **2021**, *13*, 753–765. [CrossRef] [PubMed]
23. Manolescu, D.; Timar, B.; Bratosin, F.; Rosca, O.; Citu, C.; Oancea, C. Predictors for COVID-19 Complete Remission with HRCT Pattern Evolution: A Monocentric, Prospective Study. *Diagnostics* **2022**, *12*, 1397. [CrossRef] [PubMed]
24. Starke, K.R.; Reissig, D.; Petereit-Haack, G.; Schmauder, S.; Nienhaus, A.; Seidler, A. The isolated effect of age on the risk of COVID-19 severe outcomes: A systematic review with meta-analysis. *BMJ Glob. Health* **2021**, *6*, e006434. [CrossRef]
25. Bogdan, I.; Citu, C.; Bratosin, F.; Malita, D.; Romosan, I.; Gurban, C.V.; Bota, A.V.; Turaiche, M.; Bratu, M.L.; Pilut, C.N.; et al. The Impact of Multiplex PCR in Diagnosing and Managing Bacterial Infections in COVID-19 Patients Self-Medicated with Antibiotics. *Antibiotics* **2022**, *11*, 437. [CrossRef]
26. Rouatbi, S. The aging lung face to COVID-19. *Tunis Med.* **2022**, *100*, 91–94.
27. Marincu, I.; Citu, C.; Bratosin, F.; Bogdan, I.; Timircan, M.; Gurban, C.V.; Bota, A.V.; Braescu, L.; Grigoras, M.L. Clinical Characteristics and Outcomes of COVID-19 Hospitalized Patients: A Comparison between Complete mRNA Vaccination Profile and Natural Immunity. *J. Pers. Med.* **2022**, *12*, 259. [CrossRef]
28. Chemaitelly, H.; Abu-Raddad, L.J. Waning effectiveness of COVID-19 vaccines. *Lancet* **2022**, *399*, 771–773. [CrossRef]
29. Citu, I.M.; Citu, C.; Gorun, F.; Sas, I.; Bratosin, F.; Motoc, A.; Burlea, B.; Rosca, O.; Malita, D.; Gorun, O.M. The Risk of Spontaneous Abortion Does Not Increase Following First Trimester mRNA COVID-19 Vaccination. *J. Clin. Med.* **2022**, *11*, 1698. [CrossRef]
30. Moghadas, S.M.; Vilches, T.N.; Zhang, K.; Wells, C.R.; Shoukat, A.; Singer, B.H.; Meyers, L.A.; Neuzil, K.M.; Langley, J.M.; Fitzpatrick, M.C.; et al. The impact of vaccination on COVID-19 outbreaks in the United States. *Clin. Infect. Dis.* **2021**, *73*, 2257–2264. [CrossRef]
31. Citu, I.M.; Citu, C.; Gorun, F.; Sas, I.; Tomescu, L.; Neamtu, R.; Motoc, A.; Gorun, O.M.; Burlea, B.; Bratosin, F.; et al. Immunogenicity Following Administration of BNT162b2 and Ad26.COV2.S COVID-19 Vaccines in the Pregnant Population during the Third Trimester. *Viruses* **2022**, *14*, 307. [CrossRef] [PubMed]
32. World Health Organization. *ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision*, 2nd ed.; World Health Organization: Geneva, Switzerland, 2004; Available online: https://apps.who.int/iris/handle/10665/42980 (accessed on 14 November 2022).
33. Hu, J.; Wang, Y. The Clinical Characteristics and Risk Factors of Severe COVID-19. *Gerontology* **2021**, *67*, 255–266. [CrossRef] [PubMed]
34. Cerbu, B.; Pantea, S.; Bratosin, F.; Vidican, I.; Turaiche, M.; Frent, S.; Borsi, E.; Marincu, I. Liver Impairment and Hematological Changes in Patients with Chronic Hepatitis C and COVID-19: A Retrospective Study after One Year of Pandemic. *Medicina* **2021**, *57*, 597. [CrossRef]
35. Tombuloglu, H.; Sabit, H.; Al-Khallaf, H.; Kabanja, J.H.; Alsaeed, M.; Al-Saleh, N.; Al-Suhaimi, E. Multiplex real-time RT-PCR method for the diagnosis of SARS-CoV-2 by targeting viral N, RdRP and human RP genes. *Sci. Rep.* **2022**, *12*, 2853. [CrossRef]
36. Gómez-Belda, A.B.; Fernández-Garcés, M.; Mateo-Sanchis, E.; Madrazo, M.; Carmona, M.; Piles-Roger, L.; Artero, A. COVID-19 in older adults: What are the differences with younger patients? *Geriatr Gerontol Int.* **2021**, *21*, 60–65. [CrossRef]
37. Prendki, V.; Tiseo, G.; Falcone, M. Caring for older adults during the COVID-19 pandemic. *Clin. Microbiol. Infect.* **2022**, *28*, 785–791. [CrossRef] [PubMed]
38. Steenblock, C.; Schwarz, P.E.H.; Ludwig, B.; Linkermann, A.; Zimmet, P.; Kulebyakin, K.; Tkachuk, V.A.; Markov, A.G.; Lehnert, H.; de Angelis, M.H.; et al. COVID-19 and metabolic disease: Mechanisms and clinical management. *Lancet Diabetes Endocrinol.* **2021**, *9*, 786–798. [CrossRef]
39. Ganji, R.; Reddy, P.H. Impact of COVID-19 on Mitochondrial-Based Immunity in Aging and Age-Related Diseases. *Front. Aging Neurosci.* **2021**, *12*, 614650. [CrossRef]
40. Lazar, M. Sequencing of the SARS-CoV-2 Virus Genome in Romania. National Institute of Medical-Military Research and Development "Cantacuzino". Available online: https://cantacuzino.mapn.ro/pages/view/249 (accessed on 5 August 2022).
41. Hodcroft, E.B.; Zuber, M.; Nadeau, S.; Vaughan, T.G.; Crawford, K.H.D.; Althaus, C.L.; Reichmuth, M.L.; Bowen, J.E.; Walls, A.C.; Corti, D.; et al. Spread of a SARS-CoV-2 variant through Europe in the summer of 2020. *Nature* **2021**, *595*, 707–712. [CrossRef]
42. Dascalu, S.; Geambasu, O.; Raiu, C.V.; Azoicai, D.; Popovici, E.D.; Apetrei, C. COVID-19 in Romania: What Went Wrong? *Front. Public Health* **2021**, *9*, 813941. [CrossRef]

43. Streinu-Cercel, A.; Săndulescu, O.; Miron, V.D.; Paraschiv, S.; Casangiu, C.; Hohan, R.; Bănică, L.; Surleac, M.; Streinu-Cercel, A. Undetected Omicron Transmission in Romania—Report of the First Detected Case of Locally Acquired Omicron Infection and Complete Epidemiological Investigation. *Diagnostics* **2022**, *12*, 348. [CrossRef] [PubMed]
44. Popa, A.D.; Antoniu, S.A.; Enache, A.I.; Popa, I.V.; Dragomir, R.A.; Burlacu, A. Development and Validation of a Questionnaire to Assess Knowledge and Attitudes toward COVID-19 Preventive Measures in Romania. *Healthcare* **2022**, *10*, 1827. [CrossRef]
45. Goetzl, E.J.; Huang, M.; Kon, J.; Patel, K.; Schwartz, J.B.; Fast, K.; Ferrucci, L.; Madara, K.; Taub, D.D.; Longo, D.L. Gender specificity of altered human immune cytokine profiles in aging. *FASEB J.* **2010**, *24*, 3580–3589. [CrossRef] [PubMed]
46. Vigezzi, G.P.; Bertuccio, P.; Amerio, A.; Bosetti, C.; Gori, D.; Cavalieri d'Oro, L.; Iacoviello, L.; Stuckler, D.; Zucchi, A.; Gallus, S.; et al. Lost In Lombardia Project Investigators. Older Adults' Access to Care during the COVID-19 Pandemic: Results from the LOckdown and LifeSTyles (LOST) in Lombardia Project. *Int. J. Environ. Res. Public Health* **2022**, *19*, 11271. [CrossRef]
47. Shao, S.C.; Lai, C.C.; Chen, Y.H.; Chen, Y.C.; Hung, M.J.; Liao, S.C. Prevalence, incidence and mortality of delirium in patients with COVID-19: A sys-tematic review and meta-analysis. *Age Ageing* **2021**, *50*, 1445–1453. [CrossRef]
48. Liu, K.; Chen, Y.; Lin, R.; Han, K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. *J. Infect.* **2020**, *80*, e14–e18. [CrossRef] [PubMed]
49. Wang, L.; He, W.; Yu, X.; Hu, D.; Bao, M.; Liu, H.; Zhou, J.; Jiang, H. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. *J. Infect.* **2020**, *80*, 639–645. [CrossRef]
50. Bastug, A.; Bodur, H.; Erdogan, S.; Gokcinar, D.; Kazancioglu, S.; Kosovali, B.D.; Ozbay, B.O.; Gok, G.; Turan, I.O.; Yilmaz, G.; et al. Clinical and laboratory features of COVID-19: Predictors of severe prognosis. *Int. Immunopharmacol.* **2020**, *88*, 106950. [CrossRef] [PubMed]
51. Battaglini, D.; Lopes-Pacheco, M.; Castro-Faria-Neto, H.C.; Pelosi, P.; Rocco, P.R.M. Laboratory Biomarkers for Diagnosis and Prognosis in COVID-19. *Front. Immunol.* **2022**, *13*, 857573. [CrossRef]
52. Saragih, I.D.; Advani, S.; Saragih, I.S.; Suarilah, I.; Susanto, I.; Lin, C.-J. Frailty as a Mortality Predictor in Older Adults with COVID-19: A Systematic Review and Me-ta-Analysis of Cohort Studies. *Geriatr. Nurs.* **2021**, *42*, 983–992. [CrossRef]
53. Rinaldi, L.; Milione, S.; Fascione, M.C.; Pafundi, P.C.; Altruda, C.; Di Caterino, M.; Monaco, L.; Reginelli, A.; Perrotta, F.; Porta, G.; et al. Relevance of lung ultrasound in the diagnostic algorithm of respiratory diseases in a real-life setting: A multicentre prospective study. *Respirology* **2019**, *25*, 535–542. [CrossRef] [PubMed]
54. Singhal, S.; Kumar, P.; Singh, S.; Saha, S.; Dey, A.B. Clinical features and outcomes of COVID-19 in older adults: A systematic review and meta-analysis. *BMC Geriatr.* **2021**, *21*, 321. [CrossRef]
55. Newman, J.; Thakur, N.; Peacock, T.P.; Bialy, D.; Elrefaey, A.M.E.; Bogaardt, C.; Horton, D.L.; Ho, S.; Kankeyan, T.; Carr, C.; et al. Neutralizing antibody activity against 21 SARS-CoV-2 variants in older adults vaccinated with BNT162b2. *Nat. Microbiol.* **2022**, *7*, 1180–1188. [CrossRef] [PubMed]
56. Bar-On, Y.M.; Goldberg, Y.; Mandel, M.; Bodenheimer, O.; Freedman, L.; Kalkstein, N.; Mizrahi, B.; Alroy-Preis, S.; Ash, N.; Milo, R.; et al. Faculty Opinions recommendation of Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. *N. Engl. J. Med.* **2021**, *385*, 1393–1400. [CrossRef] [PubMed]
57. Garcia-Beltran, W.F.; St Denis, K.J.; Hoelzemer, A.; Lam, E.C.; Nitido, A.D.; Sheehan, M.L.; Berrios, C.; Ofoman, O.; Chang, C.C.; Hauser, B.M.; et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron vari-ant. *Cell* **2022**, *185*, 457–466. [CrossRef]
58. Kunno, J.; Supawattanabodee, B.; Sumanasrethakul, C.; Wiriyasivaj, B.; Kuratong, S.; Kaewchandee, C. Comparison of Different Waves during the COVID-19 Pandemic: Retrospective Descriptive Study in Thailand. *Adv. Prev. Med.* **2021**, *2021*, 5807056. [CrossRef]
59. Sigal, A.; Milo, R.; Jassat, W. Estimating disease severity of Omicron and Delta SARS-CoV-2 infections. *Nat. Rev. Immunol.* **2022**, *22*, 267–269. [CrossRef]
60. Behera, J.; Ison, J.; Voor, M.J.; Tyagi, S.C.; Tyagi, N. Diabetic Covid-19 severity: Impaired glucose tolerance and pathologic bone loss. *Biochem. Biophys. Res. Commun.* **2022**, *620*, 180–187. [CrossRef]
61. Peng, M.; He, J.; Xue, Y.; Yang, X.; Liu, S.; Gong, Z. Role of Hypertension on the Severity of COVID-19: A Review. *J. Cardiovasc. Pharmacol.* **2021**, *78*, e648–e655. [CrossRef]
62. Dhillon, R.A.; Qamar, M.A.; Gilani, J.A.; Irfan, O.; Waqar, U.; Sajid, M.I.; Mahmood, S.F. The mystery of COVID-19 reinfections: A global systematic review and meta-analysis. *Ann. Med. Surg.* **2021**, *72*, 103130. [CrossRef]
63. Ren, X.; Zhou, J.; Guo, J.; Hao, C.; Zheng, M.; Zhang, R.; Huang, Q.; Yao, X.; Li, R.; Jin, Y. Reinfection in patients with COVID-19: A systematic review. *Glob. Health Res. Policy* **2022**, *7*, 12. [CrossRef] [PubMed]

Journal of
Clinical Medicine

MDPI

Article

The Clinical Course and Outcomes of Patients Hospitalized Due to COVID-19 during Three Pandemic Waves in Poland: A Single Center Observational Study

Carlo Bieńkowski [1,2,*], Justyna D. Kowalska [1,2], Marcin Paciorek [1,2], Piotr Wasilewski [1,3], Paweł Uliczny [1], Ewelina Garbacz-Łagożna [1], Andrzej Pihowicz [1], Monika Mrozińska [1], Tomasz Dyda [1], Michał Makowiecki [1,2], Joanna Puła [1,2] and Andrzej Horban [1,2]

[1] Hospital for Infectious Diseases in Warsaw, 01-201 Warsaw, Poland
[2] Department of Adults' Infectious Diseases, Medical University of Warsaw, 01-201 Warsaw, Poland
[3] Faculty of Medicine, Collegium Medicum, Cardinal Stefan Wyszynski University in Warsaw, 01-201 Warsaw, Poland
* Correspondence: carlo.bienkowski@gmail.com; Tel.: +48-22-33-55-301

Abstract: Background: The first case of coronavirus disease 2019 (COVID-19) in Poland was reported on 4 March 2020. We aim to compare the clinical course and outcomes of patients hospitalized in the Hospital for Infectious Diseases in Warsaw due to COVID-19 during three pandemic waves. Materials and methods: The medical data were collected for all patients diagnosed with COVID-19 hospitalized in our hospital from 6 March 2020 till 30 November 2021. COVID-19 diagnosis was confirmed by nasopharyngeal swabs using real-time polymerase chain reaction assay (RT-PCR) or SARS-CoV-2 antigen test. COVID-19 waves were defined based on the number and dynamics of cases. Results: Altogether, 2138 patient medical records were analyzed. The majority of the cohort was male (1235/2138, 57.8%), and the median age was 65 years [IQR: 50–74 years]. Patients hospitalized during the third wave had lower oxygen saturation on admission ($p < 0.001$) and were more likely to receive oxygen supplementation ($p < 0.001$). Serious complications, including pneumothorax ($p < 0.001$) and thromboembolic complications ($p < 0.001$), intensive care unit admission ($p = 0.034$), and death ($p = 0.003$), occurred more often in patients of the third wave. Conclusions: During the third wave, patients in our cohort experienced a more severe course of the disease and poorer outcomes.

Keywords: COVID-19; SARS-CoV-2; pandemic; epidemic waves

Citation: Bieńkowski, C.; Kowalska, J.D.; Paciorek, M.; Wasilewski, P.; Uliczny, P.; Garbacz-Łagożna, E.; Pihowicz, A.; Mrozińska, M.; Dyda, T.; Makowiecki, M.; et al. The Clinical Course and Outcomes of Patients Hospitalized Due to COVID-19 during Three Pandemic Waves in Poland: A Single Center Observational Study. *J. Clin. Med.* **2022**, *11*, 7386. https://doi.org/10.3390/jcm11247386

Academic Editors: Filippo Migliorini and Riccardo Giorgino

Received: 12 November 2022
Accepted: 9 December 2022
Published: 13 December 2022

1. Introduction and Background

At the end of 2019, a rapid increase in cases of severe acute respiratory syndrome, caused by the new coronavirus 2 (SARS-CoV-2) virus, was observed, and on 11 March, a new pandemic was declared [1]. In Poland, the first coronavirus disease 2019 (COVID-19) case was reported on 4 March 2020. Up until December 2022, in Poland, the incidence has been estimated at 0.94 per 100,000 population, with a total of 6,351,408 confirmed cases and 118,306 reported deaths [2].

Poland's health policy has developed alongside the pandemic. However, at the beginning, every person with suspected SARS-CoV-2 infection had to be hospitalized, and every person with confirmed COVID-19 had to be isolated until the disease was no longer contagious. In addition, the testing policy was not unified, and not everyone was tested; therefore, some infections were not diagnosed. Testing for the variant types of SARS-CoV-2 was also not common practice [3]. However, we have data showing that different SARS-CoV-2 variants were causing more severe or less severe courses of the disease, with the delta variant (B.1.617.2) being the most dangerous and having the poorest outcomes [4–6].

Despite the introduction of immunomodulator drugs and antivirals, two and a half years after the pandemic started, an optimal treatment is still lacking. Data from real-world experience could be applicable to practice guidelines [7].

Vaccination against COVID-19 was introduced at the end of December 2020, but not everyone was eligible to receive the vaccine at that time. Healthcare workers were prioritized, and then elderly patients and those with underlying medical conditions [3,8].

The pandemic's development changed during the different epidemic waves. An increase in the death rate of Polish citizens was observed throughout the whole pandemic and during each wave, which had a great influence on Polish society [9].

With multiple factors changing over time, we therefore aimed to investigate the clinical course and outcomes of patients hospitalized in a major infectious diseases hospital in Warsaw due to COVID-19 over three different pandemic waves. Despite the availability of national epidemiological data, it was important to characterize the data from a single center in which a standardized approach to the care of COVID-19 patients had been implemented.

2. Material and Methods

2.1. Local Standard of Care

Since March 2020, when the pandemic started in Poland, local standard operating procedures (SOPs) have been established in the Hospital for Infectious Diseases in Warsaw. These local SOPs unified questionnaires on medical history and standardized laboratory test panels on admission and during hospitalization, radiological diagnostics, and medical treatment, including etiotropic therapy, based on national guidelines [7,10,11], and were implemented into our standard of care. Our hospital's bed capacity for COVID-19 patients was 96 beds across all wards and six beds for the intensive care units (ICUs).

Medical history comprised data on COVID-19 symptoms, including the onset of symptoms, concomitant diseases, and chronic treatment. In addition, every patient was assessed using the World Health Organization's ordinal scale for clinical improvement on the day of admission [12].

The medical data for every patient diagnosed with COVID-19 who was hospitalized in the Hospital for Infectious Diseases in Warsaw from 6 March 2020 till 30 November 2021 were collected through a prospectively designed electronic case report form (eCRF). The data concerning laboratory tests performed during hospitalization were exported from the electronic database. Information on any treatment received during hospitalization, COVID-19 complications or other events, and outcomes were input into the eCRF by hospital physicians.

2.2. Study Design

Only patients diagnosed with SARS-CoV-2, which was based on positive results from nasopharyngeal swabs using real-time reverse transcriptase polymerase chain reaction assay (RT-PCR), or SARS-CoV-2 antigen test, were included in the analysis. Patients who were not infected, based on the tests, were not included in the analysis.

Nasopharyngeal swab samples collected from patients suspected of having a SARS-CoV-2 infection were stored for up to 48 h at 4–8 °C until they were analyzed in a dedicated viral transport inactivation and stabilization buffer. SARS-CoV-2 RNA from respiratory specimens was isolated using a ready set of IVD reagents based on the reverse magnetic bead capturing method: a TANBead Nucleic Acid Extraction Kit in combination with a Maelstrom 4800 automated nucleic acid purification platform (Taiwan Advanced Nanotech Inc., Taoyuan City, Taiwan). Qualitative testing for new coronavirus RNA was performed using a Viasure SARS-CoV-2 Real-Time PCR Detection IVD Kit (CerTest, San Mateo de Gallego, Zaragoza, Spain). The amplification and detection of fluorescence signals from specific molecular probes targeted at the ORF1ab (FAM channel) and N (ROX channel) genes of the SARS-CoV-2 gene sequences were completed using a Bio-Rad CFX96 thermocycler (Bio-Rad Laboratories, Inc., Hercules, CA, USA). The amplification parameters of the internal control were verified in terms of inhibition. The results were evaluated by laboratory personnel for the correct functioning of the process. An assessment of the results of the clinical sample tests was done after the examination and acceptance of valid positive and negative control results following each run. In accordance with the assay manufacturer's recommendations,

a Ct value of 40 was adopted as the cut-off value. In cases where SARS-CoV-2 target genes gave a negative result and there was an absence of signal, or that the Ct value was >40 of the internal control, the result was considered invalid, and retesting was requested.

COVID-19 waves were defined based on the number and the dynamics of the cases. A wave was distinguished, in Poland, after observing an increase, then a peak, followed by a decrease in new cases. In addition, these waves were identified by comparing the COVID-19 incidence increases and decreases with the SARS-CoV-2 variant that was dominant at that time [9–13]. We therefore defined the following three COVID-19 waves: the first wave from 6 March 2020 to 31 January 2021, the second wave from 1 February 2021 to 31 July 2021, and the third wave from 1 August 2021 to 30 November 2021.

Only variables that were available for 85% or more of the patients were included in the analysis.

2.3. Statistical Analysis

Non-parametric tests were used for group comparisons, the Kruskal–Wallis test for continuous variables, and the Chi-squared test for nominal variables. A value of $p < 0.05$ was considered significant, and all statistical tests were two-sided.

Logistic regression models were used to identify factors associated with death for each wave separately. Candidate predictors were entered into the model irrespective of the results of the univariate analysis. After entering all variables into the model, the variables that showed the least significant associations were subsequently excluded until all variables remained significant ($p < 0.05$).

Factors that were significant in the univariate models ($p < 0.0.5$) were included in the multivariate model and are presented as odds ratios (OR) at 95% CI (confidence intervals).

The study was conducted according to the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) guidelines [13].

Statistical analyses were performed using the R program, version 4.1.1 (2021, Vienna, Austria).

3. Results

In total, the medical records of 2138 patients were analyzed. The median age of our patients was 65 years [IQR: 50–74 years]. The most common age group was for patients aged >70 years (743/2138; 34.8%). The majority of the cohort consisted of male patients (1235/2138; 57.8%). Healthcare workers constituted 6.5% of all our patients (132/2138). On admission 1377/2138 (64.4%) of patients required oxygen supplementation, and presented with a median oxygen saturation of 93% [IQR: 88%–97%]. The three most common COVID-19 symptoms were cough (1655/2138; 79.4%), malaise (1557/2138; 74.8%), and fever (1560/2138; 74.6%). After one week of hospitalization, 864/2138 (40.4%) people required oxygen therapy. The two most common complications were superinfections, including nosocomial infections (261/2138; 12.3%), and bacterial pneumonia (248/2138; 11.7%). Unfavorable COVID-19 outcomes were defined as ICU admission or death, and these occurred in 180/2138 (8.4%) and 274/2138 (12.8%) cases, respectively (See Table 1).

Table 1. Baseline characteristics and clinical data for patients hospitalized in the Hospital for Infectious Diseases in Warsaw due to COVID-19 during three pandemic waves from 2020 to 2021 in Poland.

Characteristic	Total n = 2138	1st Wave n = 1225	2nd Wave n = 687	3rd Wave n = 226	p-Value
Age in years, median [IQR *]	64 [50–74]	63 [48–73]	65 [53–74]	64 [50–74]	0.051
Aged 18–50 years, n (%)	527 (24.6)	323 (26.4)	145 (21.1)	59 (26.1)	
Aged 50–60 years, n (%)	326 (15.2)	190 (15.5)	97 (14.1)	39 (17.3)	0.008
Aged 60–70 years, n (%)	542 (25.4)	282 (23.0)	210 (30.6)	50 (22.1)	
Aged >70 years, n (%)	743 (34.8)	430 (35.1)	235 (34.2)	78 (34.5)	
Male sex, n (%)	1235 (57.8)	726 (59.3)	380 (55.3)	129 (57.1)	0.238
BMI in kg/m^2, median [IQR]	28.4 [25.2–32.4]	28.3 [24.9–32.0]	28.5 [26.0–32.8]	29.0 [24.6–33.8]	0.08
Healthcare worker, n (%)	132 (6.5)	112 (9.7)	14 (2.1)	6 (2.7)	<0.001

Table 1. *Cont.*

Characteristic	Total *n* = 2138	1st Wave *n* = 1225	2nd Wave *n* = 687	3rd Wave *n* = 226	*p*-Value
Comorbidities					
Past myocardial infarction, *n* (%)	152 (7.2)	65 (5.4)	70 (10.3)	17 (7.6)	<0.001
Heart failure, *n* (%)	229 (10.8)	131 (10.8)	71 (10.4)	27 (12.1)	0.781
Atrial fibrillation/flutter, *n* (%)	191 (9.1)	113 (9.3)	61 (9.0)	17 (7.6)	0.701
Hypertension, *n* (%)	1042 (49.1)	588 (48.4)	341 (50.0)	113 (50.4)	0.732
Peripheral vascular disease, *n* (%)	73 (3.5)	39 (3.2)	31 (4.6)	3 (1.4)	0.062
Stroke or TIA **, *n* (%)	94 (4.4)	49 (4.0)	36 (5.3)	9 (4.0)	0.439
Hemiplegia, *n* (%)	65 (3.1)	33 (2.7)	27 (4.0)	5 (2.3)	0.244
Dementia, *n* (%)	111 (5.2)	59 (4.9)	33 (4.8)	19 (8.4)	0.072
COPD ***, *n* (%)	111 (5.2)	59 (4.9)	37 (5.4)	15 (6.8)	0.486
Asthma, *n* (%)	134 (6.4)	79 (6.6)	47 (6.9)	8 (3.6)	0.197
Interstitial lung disease, *n* (%)	20 (0.9)	9 (0.7)	8 (1.2)	3 (1.4)	0.524
Connective tissue disease, *n* (%)	45 (2.1)	24 (2.0)	15 (2.2)	6 (2.7)	0.784
Gastric ulcer, *n* (%)	60 (2.8)	39 (3.2)	18 (2.6)	3 (1.3)	0.28
Liver disease					
None, *n* (%)	2068 (97.6)	1177 (97.1)	674 (98.7)	217 (97.2)	
Chronic hepatitis or cirrhosis without portal hypertension, *n* (%)	39 (1.8)	24 (2.0)	9 (1.3)	6 (2.7)	
Cirrhosis and portal hypertension with no history of esophageal varices bleeding, *n* (%)	10 (0.5)	10 (0.8)	0 (0.0)	0 (0.0)	0.111
Cirrhosis and portal hypertension with a history of bleeding from esophageal varices, *n* (%)	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	
Diabetes mellitus					
None or diet-controlled, *n* (%)	1725 (81.1)	1008 (82.8)	530 (77.5)	187 (83.5)	
Requiring pharmacotherapy, without diabetes-associated organ damage, *n* (%)	339 (15.9)	176 (14.4)	135 (19.7)	28 (12.5)	0.016
Requiring pharmacotherapy, with diabetes-associated organ damage, *n* (%)	62 (2.9)	34 (2.8)	19 (2.8)	9 (4.0)	
Kidney failure ****, *n* (%)	375 (17.7)	186 (15.3)	139 (20.6)	50 (22.1)	0.003
Tumor					
None, *n* (%)	1988 (93.9)	1150 (94.6)	631 (92.9)	207 (92.8)	
Without metastases, *n* (%)	108 (5.1)	54 (4.4)	40 (5.9)	14 (6.3)	0.586
With metastases, *n* (%)	22 (1.0)	12 (1.0)	8 (1.2)	2 (0.9)	
Lymphoma, *n* (%)	26 (1.2)	15 (1.2)	7 (1.0)	4 (1.8)	0.666
AIDS *****, *n* (%)	24 (1.1)	15 (1.2)	8 (1.2)	1 (0.5)	0.596
HIV ****** infection					
None, *n* (%)	2090 (98.7)	1199 (98.6)	668 (98.5)	223 (99.6)	
Not treated	6 (0.3)	4 (0.3)	2 (0.3)	0 (0.0)	0.801
On treatment	22 (1.0)	13 (1.1)	8 (1.2)	1 (0.4)	
Immunosuppressive treatment, *n* (%)	61 (2.9)	35 (2.9)	16 (2.4)	10 (4.5)	0.262
Past alcohol abuse (>1 month), *n* (%)	63 (3.2)	27 (2.3)	26 (4.2)	10 (5.0)	0.032
Alcohol abuse during last month, *n* (%)	37 (2.0)	19 (1.8)	11 (1.8)	7 (3.4)	0.272
Smoker, *n* (%)	116 (5.9)	63 (5.4)	40 (6.5)	13 (6.4)	0.625
Non-smoker for at least for 6 months, *n* (%)	336 (17.4)	181 (16.0)	121 (20.0)	34 (17.2)	0.113
Clinical evaluation on admission					
Oxygen saturation on admission as %, median [IQR]	93.0 [88.0–97.0]	94.0 [90.0–97.0]	90.0 [85.0–94.0]	91.0 [86.5–96.0]	<0.001
Time interval between first symptoms and admission in days, median [IQR]	8.0 [6.0–11.0]	8.0 [6.0–11.0]	8.0 [6.0–11.0]	7.0 [5.0–10.0]	0.022

Table 1. *Cont.*

Characteristic	Total n = 2138	1st Wave n = 1225	2nd Wave n = 687	3rd Wave n = 226	p-Value
The three most common symptoms (malaise, fever, cough), *n* (%)	2012 (95.3)	1136 (93.3)	658 (98.2)	218 (96.9)	<0.001
Fever >38 degrees Celsius, *n* (%)	1560 (74.6)	880 (73.0)	513 (77.6)	167 (74.9)	0.088
Musculoskeletal pain, *n* (%)	836 (40.7)	497 (42.1)	272 (41.3)	67 (31.2)	0.01
Sore throat, *n* (%)	306 (14.9)	170 (14.4)	106 (16.1)	30 (14.2)	0.579
Rhinitis, *n* (%)	256 (12.5)	135 (11.5)	86 (13.1)	35 (16.7)	0.094
Cough, *n* (%)	1655 (79.4)	934 (77.7)	544 (81.9)	177 (81.2)	0.077
Dyspnea, *n* (%)	1301 (62.2)	690 (57.3)	465 (69.7)	146 (65.8)	<0.001
Chest pain, *n* (%)	351 (17.1)	229 (19.4)	98 (14.9)	24 (11.2)	0.003
Hemoptysis, *n* (%)	51 (2.5)	25 (2.1)	19 (2.9)	7 (3.3)	0.435
Dysgeusia, *n* (%)	464 (22.6)	300 (25.4)	131 (19.9)	33 (15.6)	<0.001
Dysosmia, *n* (%)	452 (22.0)	299 (25.3)	118 (17.9)	35 (16.5)	<0.001
Headache, *n* (%)	590 (28.8)	363 (30.7)	181 (27.5)	46 (21.9)	0.024
Nausea/emesis, *n* (%)	369 (18.0)	209 (17.7)	132 (20.1)	28 (13.1)	0.062
Diarrhea, *n* (%)	488 (23.7)	263 (22.2)	177 (26.9)	48 (22.2)	0.07
Abdominal pain, *n* (%)	191 (9.3)	116 (9.8)	65 (9.9)	10 (4.7)	0.052
Malaise, *n* (%)	1557 (74.8)	852 (71.1)	543 (81.7)	162 (74.3)	<0.001
Conjunctivitis, *n* (%)	66 (3.2)	34 (2.9)	29 (4.4)	3 (1.4)	0.059
Laboratory findings on admission					
C-reactive protein concentration in mg/L (norm: <10 mg/L), median [IQR]	63.0 [34.0–160.0]	60.0 [30.0–159.2]	69 [43.8–166.0]	63.5 [32.5–148.0]	<0.001
Procalcitonin concentration in ng/ml (norm: <0.5 ng/ml), median [IQR]	0.1 [0.0–0.2]	0.0 [0.0–0.1]	0.1 [0.0–0.2]	0.1 [0.1–0.4]	<0.001
Interleukin 6 concentration in pg/ml (norm: <6.65 pg/ml), median [IQR]	43.2 [18.2–87.3]	37.9 [16.1–77.4]	51.8 [22.4–95.1]	40.2 [16.1–100.0]	<0.001
D-dimers concentration in ng/L (norm: <500 ng/L), median [IQR]	1059.8 [680.2–1799.0]	1011.8 [638.0–1793.3]	1127.6 [775.1–1818.3]	1076.4 [625.0–1781.5]	0.002
Fibrinogen concentration in g/L (norm: 2.2–5.0), median [IQR]	6.7 [5.3–8.2]	6.5 [5.2–8.1]	7.0 [5.6–8.7]	6.1 [4.7–7.9]	<0.001
Platelet count in 1000 cells/mm^3 (norm: 125.3–396.2 cells/mm^3), median [IQR]	214.0 [163.0–282.0]	219.0 [168.0–291.0]	207.0 [157.2–271.0]	204.0 [156.2–271.5]	0.001
Creatinine concentration between 46 and 92 μmol/L, *n* (%)	1477 (69.9)	868 (71.6)	467 (69.2)	142 (62.8)	0.101
Creatinine concentration <46 μmol/L, *n* (%)	81 (3.8)	46 (3.8)	26 (3.9)	9 (4.0)	
Creatinine concentration >92 μmol/L, *n* (%)	555 (26.3)	298 (24.6)	182 (27.0)	75 (33.2)	
Urea concentration between 2.5 and 7.1 mmol/L, *n* (%),	1350 (64.0)	794 (65.6)	427 (63.5)	129 (57.1)	0.105
Urea concentration >7.1 mmol/L, *n* (%)	702 (33.3)	388 (32.1)	225 (33.5)	89 (39.4)	
Sodium concentration between 137 and 145 mmol/L, *n* (%)	1229 (58.4)	739 (61.2)	344 (51.0)	146 (65.2)	<0.001
Sodium concentration <137 mmol/L, *n* (%)	830 (39.4)	447 (37.0)	317 (47.0)	66 (29.5)	
Sodium concentration >145 mmol/L, *n* (%)	47 (2.2)	22 (1.8)	13 (1.9)	12 (5.4)	
Potassium concentration between 3.6 and 5.0 mmol/L, *n* (%)	1704 (80.9)	984 (81.4)	538 (79.8)	182 (81.2)	0.421
Potassium concentration <3.6 mmol/L, *n* (%)	299 (14.2)	166 (13.7)	106 (15.7)	27 (12.1)	
Potassium concentration >5.0 mmol/L, *n* (%)	59 (4.9)	30 (4.5)	15 (6.7)	104 (4.9)	
Alanine aminotransferase activity between 4 and 35 U/L in women and 4 and 50 U/L in men, *n* (%)	1327 (63.0)	804 (66.3)	394 (58.7)	129 (57.3)	<0.001
Alanine aminotransferase concentration >35 U/L in women and >50 U/L in men, *n* (%)	781 (37.0)	408 (33.7)	277 (41.3)	96 (42.7)	
Aspartate aminotransferase activity between 10 and 36 U/L in women and 10–59 U/L in men, *n* (%)	1034 (49.2)	659 (54.6)	278 (41.7)	97 (42.9)	<0.001

Table 1. *Cont.*

Characteristic	Total n = 2138	1st Wave n = 1225	2nd Wave n = 687	3rd Wave n = 226	p-Value
Aspartate aminotransferase >36 U/L in women and >59 U/L in men, *n* (%)	1066 (50.8)	548 (45.4)	389 (58.3)	129 (57.1)	
Lipase activity in U/L between 23 and 300 U/L, *n* (%)	1602 (82.7)	883 (82.6)	533 (81.7)	186 (86.1)	0.34
Lipase activity >300 U/L, *n* (%)	304 (15.7)	172 (16.1)	107 (16.4)	25 (11.6)	
Phosphocreatine kinase between 30 and 135 U/L in women and 30 and 170 U/L in men, *n* (%)	855 (42.3)	511 (44.3)	266 (40.7)	78 (36.1)	
Phosphocreatine kinase >135 U/L in women and >170 U/L in men, *n* (%)	712 (35.2)	356 (30.9)	257 (39.3)	99 (45.8)	<0.001
Treatment					
Chloroquine, *n* (%)	28 (1.3)	26 (2.1)	1 (0.1)	1 (0.4)	0.001
Hydroxychloroquine, *n* (%)	32 (1.5)	32 (2.7)	0 (0.0)	0 (0.0)	<0.001
Tocilizumab, *n* (%)	36 (1.7)	16 (1.3)	11 (1.6)	9 (4.0)	0.015
Remdesivir, *n* (%)	1035 (49.0)	434 (35.8)	466 (68.6)	135 (60.5)	<0.001
Steroids, *n* (%)	1351 (63.9)	639 (52.8)	547 (80.7)	165 (73.0)	<0.001
Heparin, *n* (%)	1737 (83.8)	914 (77.1)	627 (94.4)	196 (87.5)	<0.001
Azithromycin, *n* (%)	374 (18.3)	259 (22.1)	98 (15.0)	17 (7.7)	<0.001
Other antibiotics, *n* (%)	1646 (79.0)	888 (74.4)	589 (88.3)	169 (76.1)	<0.001
Complications during hospitalization					
Supraventricular arrhythmias, *n* (%)	52 (2.5)	23 (1.9)	22 (3.3)	7 (3.2)	0.144
Ventricular arrhythmias, *n* (%)	25 (1.2)	7 (0.6)	16 (2.4)	2 (0.9)	0.002
Myocardial infarction, *n* (%)	37 (1.7)	15 (1.2)	17 (2.5)	5 (2.2)	0.114
Stroke, *n* (%)	16 (0.8)	6 (0.5)	9 (1.3)	1 (0.4)	0.118
Pneumothorax, *n* (%)	26 (1.2)	5 (0.4)	11 (1.6)	10 (4.5)	<0.001
Nosocomial infection, *n* (%)	261 (12.3)	133 (11.0)	100 (14.7)	28 (12.5)	0.062
Bacterial pneumonia, *n* (%)	248 (11.7)	129 (10.7)	90 (13.2)	29 (12.9)	0.209
Thromboembolic complications, *n* (%)	129 (6.1)	46 (3.8)	57 (8.4)	26 (11.6)	<0.001
Gastrointestinal hemorrhage, *n* (%)	20 (0.9)	16 (1.3)	3 (0.4)	1 (0.4)	0.119
ICU ****** admission, *n* (%)	180 (8.4)	90 (7.3)	62 (9.0)	28 (12.4)	0.034
Death, *n* (%)	274 (12.8)	131 (10.7)	105 (15.3)	36 (16.8)	0.003

* IQR, interquartile range. ** TIA, transient ischemic attack. *** COPD, chronic obstructive pulmonary disease. **** Kidney injury, defined as a glomerular filtration rate of <60 mL/min/1.73 m^2. ***** AIDS, acquired immunodeficiency syndrome. ****** HIV, human immunodeficiency virus. ****** ICU, intensive care unit.

3.1. Comparison between Three Pandemic Waves

3.1.1. Clinical Evaluation on Admission and Comorbidities

We compared patients' characteristics and clinical outcomes across three time periods. The majority of hospitalized patients were aged >70 years for all three waves (1st, 430/1225, 35.1%; 2nd, 235/687, 34.2%; 3rd, 78/226, 34.5%; $p = 0.008$). Healthcare workers were more likely to be hospitalized during the first pandemic wave than the second and third waves (112/1225, 9.7% vs. 14/687, 2.1% vs. 6/226, 2.7%, respectively. $p > 0.001$). In terms of comorbidities, having a history of myocardial infarction was more frequent in patients during the second wave than the first and third waves (70/687, 10.3% vs. 65/1225, 5.4% vs. 17/226, 7.6%, respectively. $p < 0.001$). Diabetes mellitus requiring pharmacotherapy, but without diabetes-associated organ damage, was also more often found in patients of the second wave than in those patients hospitalized during the first and third waves (135/687, 19.7% vs. 176/1225, 14.4% vs. 28/226, 12.5%, respectively. $p = 0.016$). Any kidney failure defined as having a glomerular filtration rate <60 mL/min/1.73 m^2 at admission was more common in third-wave patients compared to those hospitalized during the first and second waves (50/226, 22.1% vs. 186/1225, 15.3% vs. 139/687, 20.6%, respectively. $p = 0.003$). Patients who had abused alcohol up to 30 days before hospital admission were more likely to be hospitalized during the third compared to the first and second waves

(10/226, 5.0% vs. 27/1225, 2.3% vs. 26/687, 4.2%, respectively. $p = 0.032$) (Table 1). Patients hospitalized during the first wave had higher oxygen saturation on admission than those hospitalized during the second and third waves (median 94% [IQR: 90–97%] vs. median 90% [IQR: 85–94%] vs. median 91% [IQR: 86.5–96%], respectively. $p < 0.001$). During the second wave, more patients required oxygen supplementation (537/687, 78.2% vs. 679/1225, 55.3% vs. 162/226, 71.7%. $p < 0.001$) than first- and third-wave hospitalized patients, respectively (Table 1). The shortest time interval between the first symptoms and hospital admission was observed in patients hospitalized during the third wave compared to those admitted during the first and second waves (median 7 days [IQR 5–10] vs. median 8 days [IQR: 6–11] vs. median 8 days [IQR: 6–11], respectively. $p = 0.022$). The three most common COVID-19 symptoms were more likely to be present in patients hospitalized during the second wave compared to those admitted during the first and third waves (658/687, 98.2% vs. 1136/1225, 93.3% vs. 218/226, 96.9%, respectively. $p < 0.001$). However, symptoms such as musculoskeletal pain (497/1225, 42.1% vs. 272/687, 41.3% vs. 67/226, 31.2%. $p = 0.010$), chest pain (229/1225, 19.4% vs. 98/687, 14.9% vs. 24/226, 11.2%. $p = 0.003$), dysgeusia (300/1225, 25.4% vs. 131/687, 19.9% vs. 33/226, 15.6%. $p < 0.001$), dysosmia (299/1225, 25.3% vs. 118/687, 17.9% vs. 35/226, 16.5%. $p < 0.001$), and headache (363/1225, 30.7% vs. 181/687, 27.5% vs. 46/226, 21.9%. $p = 0.024$) were more frequently present in patients during the first COVID-19 wave than the second and third waves, respectively. On the other hand, malaise (543/687, 81.7% vs. 852/1225, 71.1% vs. 162/226, 74.2%. $p < 0.001$) and dyspnea (465/687, 69.7% vs. 690/1225, 57.3% vs. 146/226, 65.8%. $p < 0.001$) were more frequent in patients during the second wave compared to those hospitalized during the first and third pandemic waves, respectively (Table 1).

3.1.2. Laboratory Findings

In terms of baseline laboratory measurement results, the patients hospitalized during the second pandemic wave had higher inflammatory markers (C-reactive protein concentration in mg/L: 69.0 [IQR: 43.8–166.0] vs. 60.0 [IQR: 30.0–159.2] vs. 63.5 [IQR: 32.5–148.0]. $p < 0.001$; procalcitonin concentration in ng/mL: 0.1 [IQR: 0.0–0.2] vs. 0.0 [0.0–0.1] vs. 0.1 [IQR: 0.1–0.4]. $p < 0.001$; and interleukin 6 concentration in pg/mL: 51.8 [IQR: 22.4–95.1] vs. 37.9 [IQR: 16.1–77.4] vs. 40.2 [IQR: 16.1–100.0]. $p < 0.001$); higher D-dimers concentration in ng/L (1127.6 [IQR: 775.1–1818.3] vs. 1011.8 [IQR: 638.0–1793.3] vs. 1076.4 [625.0–1781.5]. $p = 0.002$); and higher fibrinogen concentration in g/L (7.0 [IQR: 5.6–8.7] vs. 6.5 [5.2–8.1] vs. 6.1 [4.7–7.9]. $p < 0.001$) compared to patients admitted during the first and third waves, respectively.

3.1.3. Treatment

We also compared the use of specific treatments across the three waves. Patients during the first wave were more likely to be treated with chloroquine (1st, 26/1225, 2.1% vs. 2nd, 1/687, 0.1% vs. 3rd, 1/226, 0.4%. $p = 0.001$), hydroxychloroquine (32/1225, 2.7% vs. 0/687, 0.0% vs. 0/226, 0.0%, respectively. $p < 0.001$), and azithromycin (259/1225, 22.1% vs. 98/687, 15.0% vs. 17/226, 7.7%, respectively. $p < 0.001$) compared to the remaining waves. However, patients hospitalized during the second wave were more frequently treated with remdesivir (2nd, 466/786, 68.6% vs. 1st, 434/1225, 35.8% vs. 3rd, 135/226, 60.5%. $p < 0.001$), steroids (547/687, 80.7% vs. 639/1225, 52.8% vs. 165/226, 73.0%, respectively. $p < 0.001$), heparin (627/687, 94.4% vs. 914/1225, 77.1% vs. 196/226, 87.5%, respectively. $p < 0.001$), and other antibiotics than azithromycin (589/687, 88.3% vs. 888/1225, 74.4%, vs. 169/226, 76.1%, respectively. $p < 0.001$). At the same time, tocilizumab was more frequently administered to patients hospitalized during the third wave (9/226, 4.0% vs. 16/1225, 1.3% vs. 11/687, 1.6%. $p = 0.015$) (Table 1) than the first and third, respectively.

3.1.4. Complications

Serious complications including pneumothorax (10/226, 4.5% vs. 5/1225, 0.4% vs. 11/687, 1.6%. $p < 0.001$) and thromboembolic complications (26/226, 11.6% vs. 46/1225, 3.8% vs. 57/687, 8.4%. $p < 0.001$), intensive care unit admission (28/226, 12.4% vs. 90/1225,

7.3% vs. 62/687, 9.0%. $p = 0.034$), and death (36/226, 16.8% vs. 131/1225, 10.7% vs. 105/687, 15.3%. $p = 0.003$) were more often in patients hospitalized during the third pandemic wave compared to those admitted during the first and second wave, respectively. However, ventricular arrhythmias were more frequent in patients during the second wave compared to those admitted during the first and third waves (16/687, 2.4% vs. 7/1225 vs. 2/226, 0.9%, respectively. $p = 0.002$) (Table 1).

3.1.5. Multivariate Analysis

Logistic regression model analysis showed the factors that were independently associated with death in COVID-19 patients hospitalized during the three pandemic waves in the hospital (Figures 1 and 2).

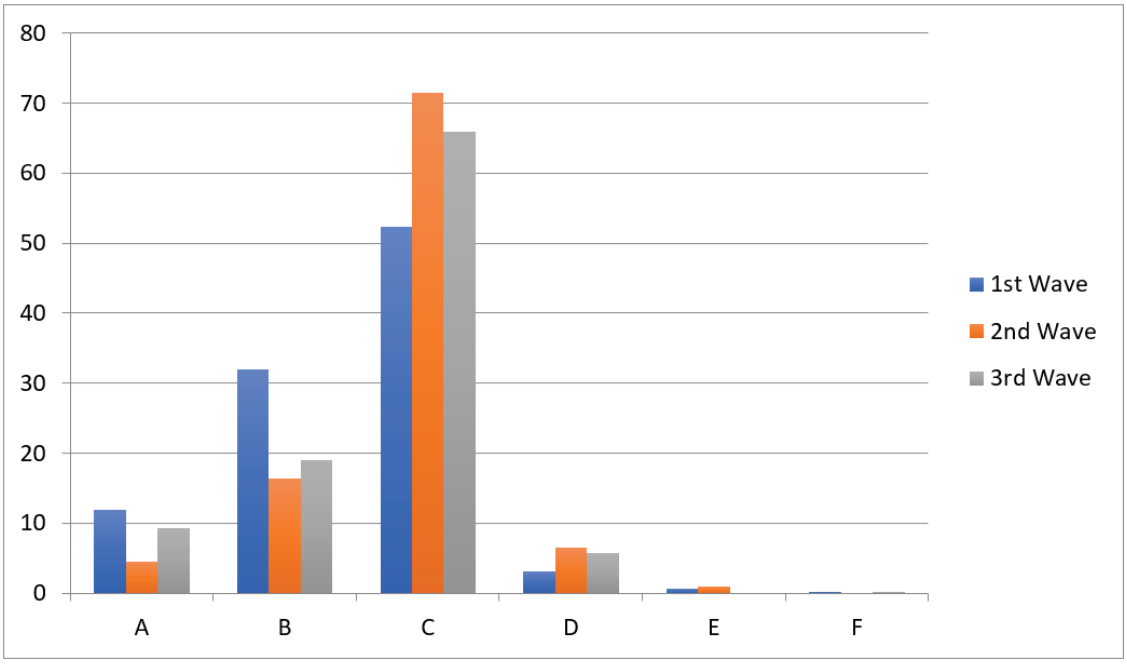


Figure 1. Ordinal scale for clinical improvement on the day of admission for patients hospitalized in the Hospital for Infectious Diseases in Warsaw due to COVID-19 between March 2020 and November 2021 ($p < 0.001$). Results are presented in percentage (%) of patients (y-axis). Legend: (A) Hospitalized, not requiring oxygen supplementation and not requiring medical care. (B) Hospitalized, not requiring oxygen supplementation but requiring medical care. (C) Hospitalized, requiring normal oxygen supplementation. (D) Hospitalized, requiring non-invasive ventilation with high-flow oxygen equipment (helmet, high-flow oxygen nasal cannula, HFNC). (E) Hospitalized, requiring invasive mechanical ventilation or ECMO. (F) Death.

1. During the first wave (Figure 2):
    a. 50–60 years age range, OR 407.37; 95% CI 2.17–223,060.46, $p = 0.035$;
    b. Oxygen saturation on admission, OR 0.82; 95% CI 0.71–0.92, $p = 0.003$;
    c. Myocardial infarction in the past, OR 30.44; 95% CI 2.53–597.84, $p = 0.011$;
    d. Heart failure, OR 0.04; 95% CI 0.00–0.65, $p = 0.042$;
    e. Stroke or TIA, OR 29.86; 95% CI 1.33–1278.97, $p = 0.047$;
    f. Dementia, OR 43.93; 95% CI 3.54–1158.45, $p = 0.008$;
    g. Sore throat, OR 0.01; 95% CI 0.00–0.20, $p = 0.012$;
    h. Dysgeusia, OR 0.02; 95% CI 0.00–0.68, $p = 0.041$;

i. Ventricular arrhythmias as COVID-19 complication, OR 168.58; 95% CI 1.43–56,448.69, $p = 0.045$;
j. ICU admission, OR 15,973.93; 95% CI 634.60–2,260,123.88, $p < 0.001$;
k. Azithromycin administration before admission, OR 0.01; 95% CI 0.00–0.21, $p = 0.010$.

2. During the second wave (Figure 3):
   a. Oxygen saturation on admission, OR 0.92; 95% CI 0.86–0.98, $p = 0.008$;
   b. Diabetes mellitus requiring pharmacotherapy, and with diabetes-associated organ damage, OR 0.01; 95% CI 0.00–0.24, $p = 0.006$;
   c. Atrial fibrillation/flutter, OR 5.28; 95% CI 1.29–22.09, $p = 0.020$;
   d. Supraventricular arrhythmias as COVID-19 complication, OR 29.09; 95% CI 2.46–426.20, $p = 0.010$;
   e. Pneumothorax as complication, OR <0.001; 95% CI 0.00–0.07, $p = 0.014$;
   f. Bacterial pneumonia as complication OR, 7.98; 95% CI 1.90–35.79, $p = 0.005$;
   g. ICU admission, OR 151.44; 95% CI 30.98–943.98, $p < 0.001$.
3. During the third wave:
   a. None of the factors that were significant in the univariate model were significant in the multivariate analysis.

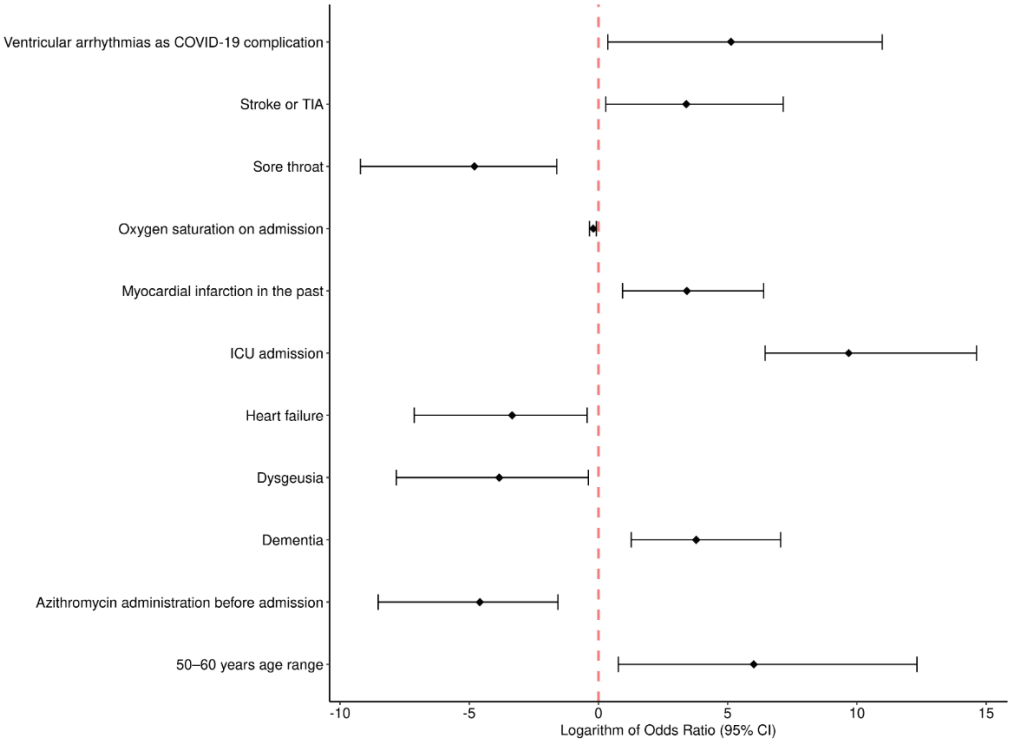


Figure 2. Multivariate logistic regression model analysis of the factors independently associated with death during the first COVID-19 wave in the Hospital for Infectious Diseases in Warsaw (Poland).

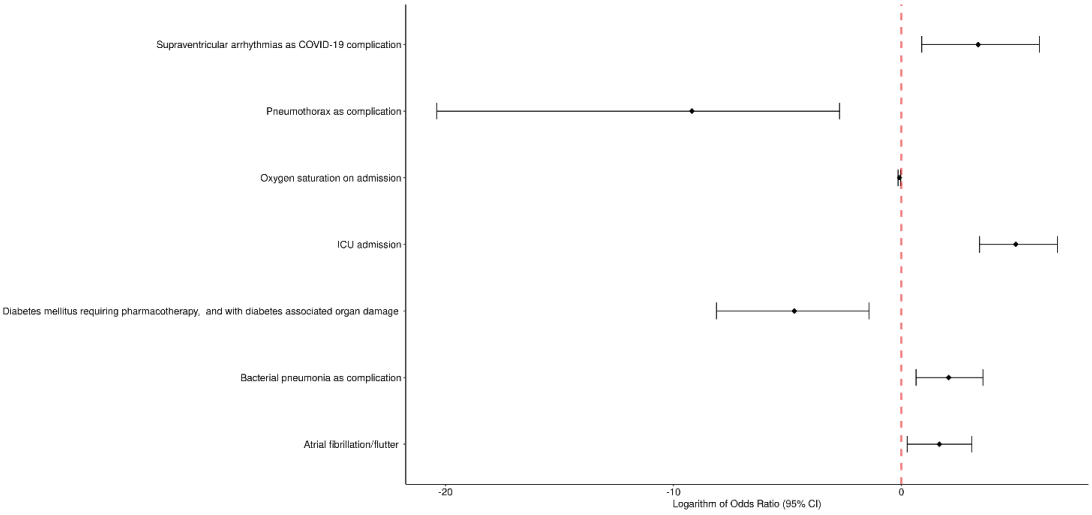


Figure 3. Multivariate logistic regression model analysis of the factors independently associated with death during the second COVID-19 wave in the Hospital for Infectious Diseases in Warsaw (Poland).

4. Discussion

To our knowledge, this is the first study in Poland conducted in a single center that compares the clinical features and outcomes of patients hospitalized due to COVID-19 during three pandemic waves. Other studies from around the world comparing COVID-19 waves are difficult to compare with our study due to the different wave definitions and the different SARS-CoV-2 variants dominating each wave [14–17].

However, in Poland, there have been studies where death-associated factors were analyzed, but only in comparison to two pandemic waves or to one [18,19]. In addition, it was important to characterize the data from a single center in which a standardized approach to COVID-19 patient care had been implemented. Every piece of real-life data might be useful for the management of future COVID-19 patients.

COVID-19 has mainly been asymptomatic or taken a mild course; however, the clinical spectrum of the disease is vast and includes severe progressive pneumonia and acute respiratory distress syndrome, both of which may be accompanied by a cytokine storm, thromboembolic complications, and/or multiple organ dysfunction [1,20,21]. Regarding the fact that patients with more severe courses require hospitalization, our cohort consisted of individuals who were most vulnerable to infection; therefore, the most numerous group were elderly patients. In addition, these patients more often had underlying medical conditions that may have predisposed them to COVID-19 and required medical care. However, during the first pandemic wave, every patient with a suspected SARS-CoV-2 infection had to undergo hospital observation; and so, during the first wave, a milder course may have been observed (Table 1).

The clinical evaluation on admission revealed that patients hospitalized during the first wave were less severely hypoxic. However, they had a more diverse range of different symptoms. During this period, the alfa variant was the most commonly observed variant in our region [2,22–24]. On the other hand, the shortest period from disease onset to hospital admission was observed in the third wave. Moreover, inflammatory markers were also more elevated in patients during this period, which may correspond to the fact that, during this wave, the delta variant was the most dominant form in our region [2,22–24].

During the pandemic, a search began for a safe and effective COVID-19 treatment [25,26]. At the beginning, there were some data suggesting that chloroquine and hydroxychloroquine (anti-inflammatory drugs) may have reduced the mortality rate in SARS-CoV-2

infected individuals, especially when the therapy was combined with azithromycin. However, the meta-analyses show otherwise; what is more, this combination of drugs may have increased mortality [27–29]. Macrolides themselves also did not show any beneficial effect for patients with COVID-19 [30]. It was the case that these drugs were used significantly more frequently in our hospital during the first pandemic wave, when there was still not much data on the treatment's efficacy and safety, although we did not observe a higher mortality in our cohort during this period (Table 1).

During the second wave, more valuable data were obtained, and treatment recommendations were more certain [31]. Therefore, in our cohort during this period, we observed significantly increased administration of remdesivir and corticosteroids (Table 1). Moreover, due to new and improved data on bacterial superinfections and thromboembolic complications, a significant increase in antibiotics other than both azithromycin and heparin administration was observed (Table 1).

As for tocilizumab, there were some conflicting reports, some suggesting that it does not improve clinical presentation when combined with standards of care [32]. However, Flisiak et al. showed that tocilizumab administration in patients with SARS-CoV-2 infection reduces mortality and speeds up clinical improvement if the patient has a high IL-6 concentration and requires oxygen supplementation [33]. These data were published in the middle of the second pandemic wave in Poland; therefore, its implementation in everyday treatment was observed to be significantly higher during the third wave (Table 1).

In Poland, vaccines for COVID-19 were introduced at the end of December 2020 [8]. The fact that healthcare workers (HCWs) are at risk of acquiring the infection during their work duties may explain why the biggest number of HCWs were hospitalized due to COVID-19 during the first wave, when the vaccines had not yet been introduced [8,34].

Severe complications, including ICU admission and death, were most common during the third wave, which also corresponded to disease severity on admission and the delta variant being dominant [2,22–24,35].

We have shown many factors that influenced deaths during the first and second pandemic waves; however, none of these seemed to be death predictors in the third pandemic wave, when our patients had the worst outcomes. Our study has more of a descriptive nature, and we have aimed to show medical history data, comorbidities, treatment, and COVID-19 complications.

Some important limitations are evident due to the fact that our study is of a retrospective, observational nature. First, most of our patients were symptomatic, as asymptomatic cases were less likely to seek medical care. However, during the beginning of the first wave, every patient suspected of being SARS-CoV-2 infected was hospitalized, which may provide some clinical presentation bias when being compared to the second and third waves. Moreover, the clinical course of the disease may have been influenced by the currently applied standard of care, which varied over time as new recommendations were introduced. Moreover, due to the large number of patients in each population, it is easier to obtain significant results in the univariate analysis.

There are also some strengths worth mentioning however: we had a large, representative cohort of 2138 COVID-19 patients with known outcomes. Moreover, we had local SOPs for collecting medical history, laboratory testing, and patient management, which altogether provided a more unified system for the management of patients with COVID-19.

To conclude; we have described patients' characteristics at baseline for three pandemic waves. We also found that there were some differences between the waves in comorbidities, treatment, and complications. The data indicates that for all three waves, COVID-19 was a severe disease in hospitalized patients with a high risk of poor outcomes. The patients of the third wave were the most severely ill on admission and had poorer outcomes; however, none of the factors influencing death during the first and second wave predicted death in the third wave.

Author Contributions: Conceptualization: C.B., J.D.K., M.P., P.W., P.U., E.G.-Ł., A.P., M.M. (Monika Mrozińska), T.D., M.M. (Michał Makowiecki), J.P. and A.H.; investigation: C.B., J.D.K., M.P., P.W., P.U., E.G.-Ł., A.P., M.M. (Monika Mrozińska), T.D., M.M. (Michał Makowiecki), J.P. and A.H.; resources: C.B., J.D.K., M.P., P.W., P.U., E.G.-Ł., A.P., M.M. (Monika Mrozińska), T.D., M.M. (Michał Makowiecki), J.P. and A.H.; writing—original draft preparation: C.B.; supervision: J.D.K., M.P. and A.H.; writing—review and editing: C.B., J.D.K., M.P. and A.H. All authors have read and agreed to the published version of the manuscript.

Funding: The study was funded from a research grant issued by the Medical Research Agency. Grant Number: 2020/ABM/COVID19/0077.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Medical University of Warsaw with approval number: AKBE/154/2022.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data sets used and/or analyzed during the current study can be made available by the corresponding author on reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Flisiak, R.; Rzymski, P.; Zarębska-Michaluk, D.; Rogalska, M.; Rorat, M.; Czupryna, P.; Lorenc, B.; Ciechanowski, P.; Kozielewicz, D.; Piekarska, A.; et al. Demographic and Clinical Overview of Hospitalized COVID-19 Patients during the First 17 Months of the Pandemic in Poland. *J. Clin. Med.* **2022**, *11*, 117. [CrossRef] [PubMed]
2. Current Data Polish COVID-19 Epidemiological Sutiation. Available online: https://koronawirusunas.pl/ (accessed on 3 March 2022).
3. Włodarczyk, W.C. Remarks on COVID-19 Pandemic in Poland: A Health Policy Perspective. *Zesz. Nauk. Ochr. Zdrowia* **2020**, *18*, 126–148. [CrossRef]
4. Ong, S.W.X.; Chiew, C.J.; Ang, L.W.; Mak, T.M.; Cui, L.; Toh, M.P.H.S.; Lim, Y.D.; Lee, P.H.; Lee, T.H.; Chia, P.Y.; et al. Clinical and Virological Features of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variants of Concern: A Retrospective Cohort Study Comparing B.1.1.7 (Alpha), B.1.351 (Beta), and B.1.617.2 (Delta). *Clin. Infect. Dis.* **2021**, *75*, e1128–e1136. [CrossRef] [PubMed]
5. Toyoshima, Y.; Nemoto, K.; Matsumoto, S.; Nakamura, Y.; Kiyotani, K. SARS-CoV-2 genomic variations associated with mortality rate of COVID-19. *J. Hum. Genet.* **2020**, *65*, 1075–1082. [CrossRef]
6. Wrenn, J.O.; Pakala, S.B.; Vestal, G.; Shilts, M.H.; Brown, H.M.; Bowen, S.M.; Strickland, B.A.; Williams, T.; Mallal, S.A.; Jones, I.D.; et al. COVID-19 severity from Omicron and Delta SARS-CoV-2 variants. *Influenza Other Respir. Viruses* **2022**, *16*, 832–836. [CrossRef]
7. Flisiak, R.; Zarębska-Michaluk, D.; Flisiak-Jackiewicz, M.; Rzymski, P. Updates in Management of SARS-CoV-2 Infection. *J. Clin. Med.* **2022**, *11*, 4472. [CrossRef]
8. Skrzat-Klapaczyńska, A.; Bieńkowski, C.; Kowalska, J.; Paciorek, M.; Puła, J.; Krogulec, D.; Stengiel, J.; Pawełczyk, A.; Perlejewski, K.; Osuch, S.; et al. The Beneficial Effect of the COVID-19 Vaccine Booster Dose among Healthcare Workers in an Infectious Diseases Center. *Vaccines* **2022**, *10*, 552. [CrossRef]
9. Orlewska, K.; Kozieł, D.; Klusek, J.; Orlewska, E. Burden of COVID-19 Mortality and Morbidity in Poland in 2020. *Int. J. Environ. Res. Public Health* **2022**, *19*, 5432. [CrossRef]
10. Flisiak, R.; Horban, A.; Jaroszewicz, J.; Kozielewicz, D.; Mastalerz-Migas, A.; Owczuk, R.; Parczewski, M.; Pawłowska, M.; Piekarska, A.; Simon, K.; et al. Management of SARS-CoV-2 infection: Recommendations of the Polish Association of Epidemiologists and Infectiologists as of April 26, 2021. *Pol. Arch. Intern. Med.* **2021**, *131*, 487–496. [CrossRef]
11. Flisiak, R.; Parczewski, M.; Horban, A.; Jaroszewicz, J.; Kozielewicz, D.; Pawłowska, M.; Piekarska, A.; Simon, K.; Tomasiewicz, K.; Zarębska-Michaluk, D. Management of SARS-CoV-2 infection: Recommendations of the Polish Association of Epidemiologists and Infectiologists. Annex no. 2 as of October 13, 2020. *Pol. Arch. Intern. Med.* **2020**, *130*, 915–918. [CrossRef]
12. Khodaverdi, M.; Price, B.S.; Santangelo, S.L.; Anzalone, A.; Kimble, W.; Porterfield, J.Z.; Vest, M.T.; Hodder, S.L.; Hendricks, B.; Rosen, C.j.; et al. 447. An Ordinal Scale Assessing SARS-CoV-2 Infected Patient Outcomes Using Electronic Health Records. *Open Forum Infect. Dis.* **2021**, *8*, S324–S325. [CrossRef]
13. von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gøtzsche, P.C.; Vandenbroucke, J.P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *J. Clin. Epidemiol.* **2008**, *61*, 344–349. [CrossRef] [PubMed]
14. Stidsen, J.V.; Green, A.; Rosengaard, L.; Højlund, K. Risk of severe COVID-19 infection in persons with diabetes during the first and second waves in Denmark: A nationwide cohort study. *Front. Endocrinol.* **2022**, *13*, 1025699. [CrossRef] [PubMed]
15. Hadadi, A.; Pirzadeh, M.; Kazemian, S.; Ashraf, H.; Ebrahimi, M.; Karbalai Saleh, S.; Talebpour, M. COVID-19 in Iran: Clinical presentations and outcomes in three different surges of COVID-19 infection. *Virol. J.* **2022**, *19*, 123. [CrossRef] [PubMed]

16. Cusinato, M.; Gates, J.; Jajbhay, D.; Planche, T.; Ong, Y.E. Increased risk of death in COVID-19 hospital admissions during the second wave as compared to the first epidemic wave: A prospective, single-centre cohort study in London, UK. *Infection* **2022**, *50*, 457–465. [CrossRef]
17. Bowen, A.; Zucker, J.; Shen, Y.; Huang, S.; Yan, Q.; Annavajhala, M.K.; Uhlemann, A.-C.; Kuhn, L.; Sobieszczyk, M.; Castor, D. Reduction in Risk of Death Among Patients Admitted With COVID-19 Between the First and Second Epidemic Waves in New York City. *Open Forum Infect. Dis.* **2022**, *9*, ofac436. [CrossRef] [PubMed]
18. Ziuzia-Januszewska, L.; Januszewski, M.; Sosnowska-Nowak, J.; Janiszewski, M.; Dobrzyński, P.; Jakimiuk, A.A.; Jakimiuk, A.J. COVID-19 Severity and Mortality in Two Pandemic Waves in Poland and Predictors of Poor Outcomes of SARS-CoV-2 Infection in Hospitalized Young Adults. *Viruses* **2022**, *14*, 1700. [CrossRef]
19. Oda, Y.; Shimada, M.; Shiraishi, S.; Kurai, O. Treatment and outcome of COVID-19 patients in a specialized hospital during the third wave: Advance of age and increased mortality compared with the first/second waves. *JA Clin. Rep.* **2021**, *7*, 85. [CrossRef]
20. Fang, X.; Li, S.; Yu, H.; Wang, P.; Zhang, Y.; Chen, Z.; Li, Y.; Cheng, L.; Li, W.; Jia, H.; et al. Epidemiological, comorbidity factors with severity and prognosis of COVID-19: A systematic review and meta-analysis. *Aging* **2020**, *12*, 12493–12503. [CrossRef]
21. Deshmukh, V.; Motwani, R.; Kumar, A.; Kumari, C.; Raza, K. Histopathological observations in COVID-19: A systematic review. *J. Clin. Pathol.* **2021**, *74*, 76–83. [CrossRef]
22. National Institutes of Health. RT-COVAR Map of SARS-CoV-2 Variants and Mutations from National Institute of Public Health. 2022. Available online: https://covar.mi2.ai/poland/regions (accessed on 3 April 2022).
23. Yakovleva, A.; Kovalenko, G.; Redlinger, M.; Liulchuk, M.G.; Bortz, E.; Zadorozhna, V.I.; Scherbinska, A.M.; Wertheim, J.O.; Goodfellow, I.; Meredith, L.; et al. Tracking SARS-COV-2 Variants Using Nanopore Sequencing in Ukraine in Summer 2021. *Res. Sq.* **2021**. [CrossRef]
24. GISAID Data on SARS-CoV-2 Variants in Each Country. Available online: https://covariants.org/per-country?region=World (accessed on 3 March 2022).
25. Zhang, C.; Jin, H.; Wen, Y.F.; Yin, G. Efficacy of COVID-19 Treatments: A Bayesian Network Meta-Analysis of Randomized Controlled Trials. *Front. Public Health* **2021**, *9*, 729559. [CrossRef] [PubMed]
26. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): A randomised controlled trial. *Lancet Infect. Dis.* **2021**. [CrossRef]
27. Singh, B.; Ryan, H.; Kredo, T.; Chaplin, M.; Fletcher, T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. *Cochrane Database Syst. Rev.* **2021**, *2*, Cd013587. [CrossRef] [PubMed]
28. Million, M.; Roussel, Y.; Gautret, P.; Raoult, D. Effect of hydroxychloroquine and azithromycin on SARS-CoV-2 clearance in COVID-19 patients, a meta-analysis. *Int. J. Antimicrob. Agents* **2021**, *57*, 106240. [CrossRef] [PubMed]
29. Fiolet, T.; Guihur, A.; Rebeaud, M.E.; Mulot, M.; Peiffer-Smadja, N.; Mahamat-Saleh, Y. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: A systematic review and meta-analysis. *Clin. Microbiol. Infect.* **2021**, *27*, 19–27. [CrossRef]
30. Verdejo, C.; Vergara-Merino, L.; Meza, N.; Pérez-Bracchiglione, J.; Carvajal-Juliá, N.; Madrid, E.; Rada, G.; Rojas Reyes, M.X. Macrolides for the treatment of COVID-19: A living, systematic review. *Medwave* **2020**, *20*, e8074. [CrossRef]
31. National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available online: https://www.covid19treatmentguidelines.nih.gov (accessed on 7 April 2022).
32. Zarębska-Michaluk, D.; Jaroszewicz, J.; Rogalska, M.; Martonik, D.; Pabjan, P.; Berkan-Kawińska, A.; Bolewska, B.; Oczko-Grzesik, B.; Kozielewicz, D.; Tudrujek-Zdunek, M.; et al. Effectiveness of Tocilizumab with and without Dexamethasone in Patients with Severe COVID-19: A Retrospective Study. *J. Inflamm. Res.* **2021**, *14*, 3359–3366. [CrossRef]
33. Flisiak, R.; Jaroszewicz, J.; Rogalska, M.; Łapiński, T.; Berkan-Kawińska, A.; Bolewska, B.; Tudrujek-Zdunek, M.; Kozielewicz, D.; Rorat, M.; Leszczyński, P.; et al. Tocilizumab Improves the Prognosis of COVID-19 in Patients with High IL-6. *J. Clin. Med.* **2021**, *10*, 1583. [CrossRef]
34. Kowalska, J.D.; Skrzat-Klapaczyńska, A.; Bursa, D.; Balayan, T.; Begovac, J.; Chkhartishvili, N.; Gokengin, D.; Harxhi, A.; Jilich, D.; Jevtovic, D.; et al. HIV care in times of the COVID-19 crisis—Where are we now in Central and Eastern Europe? *Int. J. Infect. Dis.* **2020**, *96*, 311–314. [CrossRef]
35. Gujski, M.; Jankowski, M.; Rabczenko, D.; Goryński, P.; Juszczyk, G. Characteristics and Clinical Outcomes of 116,539 Patients Hospitalized with COVID-19—Poland, March–December 2020. *Viruses* **2021**, *13*, 1458. [CrossRef] [PubMed]

Journal of
Clinical Medicine

MDPI

Article

Epidemiology and Outcomes of Hypernatraemia in Patients with COVID-19—A Territory-Wide Study in Hong Kong

Benjamin Y. F. So [1,†], Chun Ka Wong [2,†], Gordon Chun Kau Chan [3,†], Jack Kit Chung Ng [3], Grace Chung Yan Lui [4], Cheuk Chun Szeto [3], Ivan Fan Ngai Hung [5], Hung Fat Tse [2], Sydney C. W. Tang [1], Tak Mao Chan [1], Kai Ming Chow [3,*] and Desmond Y. H. Yap [1,*]

[1] Division of Nephrology, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China
[2] Division of Cardiology, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China
[3] Division of Nephrology, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China
[4] Division of Infectious Diseases, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China
[5] Division of Infectious Diseases, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China
* Correspondence: chow_kai_ming@alumni.cuhk.net (K.M.C.); desmondy@hku.hk (D.Y.H.Y.); Tel.: +852-35054809 (K.M.C.); +852-22554385 (D.Y.H.Y.)
† These authors contributed equally to this work.

Abstract: Background: Dysnatraemias are commonly reported in COVID-19. However, the clinical epidemiology of hypernatraemia and its impact on clinical outcomes in relation to different variants of SARS-CoV-2, especially the prevailing Omicron variant, remain unclear. Methods: This was a territory-wide retrospective study to investigate the clinical epidemiology and outcomes of COVID-19 patients with hypernatraemia at presentation during the period from 1 January 2020 to 31 March 2022. The primary outcome was 30-day mortality. Key secondary outcomes included rates of hospitalization and ICU admission, and costs of hospitalization. Results: In this study, 53,415 adult COVID-19 patients were included for analysis. Hypernatraemia was observed in 2688 (5.0%) patients at presentation, of which most cases (99.2%) occurred during the local "5th wave" dominated by the Omicron BA.2 variant. Risk factors for hypernatraemia at presentation included age, institutionalization, congestive heart failure, dementia, higher SARS-CoV-2 Ct value, white cell count, C-reactive protein and lower eGFR and albumin levels ($p < 0.001$ for all). Patients with hypernatraemia showed significantly higher 30-day mortality (32.0% vs. 5.7%, $p < 0.001$) and longer lengths of stay (12.9 ± 10.9 vs. 11.5 ± 12.1 days, $p < 0.001$) compared with those with normonatraemia. Multivariate analysis revealed hypernatraemia at presentation as an independent predictor for 30-day mortality (aHR 1.32, 95% CI 1.14–1.53, $p < 0.001$) and prolonged hospital stays (OR 1.55, 95% CI 1.17–2.05, $p = 0.002$). Conclusions: Hypernatraemia is common among COVID-19 patients, especially among institutionalized older adults with cognitive impairment and other comorbidities during large-scale outbreaks during the Omicron era. Hypernatraemia is associated with unfavourable outcomes and increased healthcare utilization.

Keywords: hypernatraemia; sodium; COVID-19; epidemiology; outcomes

Citation: So, B.Y.F.; Wong, C.K.; Chan, G.C.K.; Ng, J.K.C.; Lui, G.C.Y.; Szeto, C.C.; Hung, I.F.N.; Tse, H.F.; Tang, S.C.W.; Chan, T.M.; et al. Epidemiology and Outcomes of Hypernatraemia in Patients with COVID-19—A Territory-Wide Study in Hong Kong. *J. Clin. Med.* **2023**, *12*, 1042. https://doi.org/10.3390/jcm12031042

Academic Editors: Riccardo Giorgino and Filippo Migliorini

Received: 21 December 2022
Revised: 18 January 2023
Accepted: 24 January 2023
Published: 29 January 2023

1. Introduction

Disorders of sodium and water balance are common in hospitalized patients, particularly the elderly [1,2]. Although hypernatraemia occurs less frequently than hyponatraemia [3,4], it is associated with dramatically increased morbidity and mortality across a wide range of medical and surgical conditions [5]. Hypernatraemia most commonly

arises as a result of hypotonic fluid loss, insufficient intake of free water, or, less commonly, excess sodium intake or intoxication [6]. Under physiological conditions, the human body possesses robust regulatory mechanisms that defend against fluctuations in sodium balance via control of renal sodium and water excretion, stimulation of thirst by crosstalk with the hypothalamic–pituitary system and expression of homeostatic receptors in the skin. These mechanisms are sometimes overwhelmed in acutely ill patients, resulting in varying degrees of hypernatraemia [6]. Such derangements are particularly exaggerated in frail older adults, especially those with cognitive impairment, who are unable to compensate for ongoing fluid losses [7].

Dysnatraemias are commonly reported in COVID-19 [8]. Most reports thus far have focused on hyponatraemia, which occurs commonly among patients with COVID-19 and may be a marker of disease severity [9–11]. However, hypernatraemia (commonly defined as a plasma or serum sodium level of greater than 145 mmol/L0) has also been observed in COVID-19, and may be more specific than hyponatraemia for predicting poor disease outcomes in COVID-19, as shown by a recent meta-analysis including seven studies [12]. The pathophysiology of hyponatraemia and hypernatraemia in COVID-19 appears to be disparate and therefore ought to be studied independently.

Most previous reports on dysnatraemias in COVID-19, including those on hypernatraemia, were published in the pre-Omicron era [8,13,14]. However, each variant of SARS-CoV-2 may be associated with a distinct constellation of clinical symptoms and end-organ complications [15]. Furthermore, the rapidly evolving Omicron outbreak has crippled healthcare systems around the world, including in Hong Kong, leading to a sea change in the clinical phenotype of patients presenting to healthcare services with COVID-19. In Hong Kong, the "5th wave" of COVID-19 driven by the Omicron BA.2 subvariant overwhelmed the public healthcare system rapidly, with a significant proportion of the population infected, including a large number of frail nursing home residents, many of whom presented with severe, life-threatening hypernatraemia [16,17]. Here, we report on the territory-wide prevalence and clinical correlates of patients diagnosed with COVID-19 and hypernatraemia at presentation, with particular emphasis on ongoing outbreaks due to Omicron subvariants.

2. Materials and Methods

2.1. Study Design and Patient Selection

This study was a territory-wide retrospective observational cohort study. Adult patients who tested positive for SARS-CoV-2 by RT-PCR (reverse transcription polymerase chain reaction) in respiratory samples, and with serum sodium (Na) levels available on the same day from 1 January 2020 to 31 March 2022, were identified from the Clinical Data Analysis and Reporting System (CDARS) database of the Hong Kong Hospital Authority. CDARS is an electronic database that captures comprehensive clinical data of all patients registered in public hospitals and clinics in Hong Kong. Previous data validation for use in cohort studies showed high coding accuracy [18,19]. Retrieved data included patients' demographics, institutionalization (defined by patients who utilized the service of the Community Geriatric Assessment Team, which delivers outreach service to elderly homes and institutions), diagnoses, hospitalization, prescriptions, laboratory results and deaths. All data retrieved were deidentified to ensure patient privacy and confidentiality. The disease diagnosis was cross-checked with the diagnosis coding in CDARS using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (Supplementary Table S1). The estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration (CKD-EPI) 2009 creatinine equation. Hypernatraemia and normonatraemia were defined as serum Na being above 145 mmol/L, and from 135 to 145 mmol/L, respectively. In Hong Kong, all patients with COVID-19 who required hospital admission were admitted to public hospitals. Treatment, including the use of antiviral and/or immunomodulatory therapies (Table 1), of patients with COVID-19 was at clinicians' discretion and according to prevailing protocols at the time. Concur-

rent comorbidity load was further weighed using Charlson Comorbidity Index (CCI) [20] (Supplementary Table S1).

Table 1. Antiviral and immunomodulatory therapies used in Hong Kong for COVID-19.

Antiviral Therapy	Immunomodulatory Therapy
Interferon beta-1b Lopinavir/Ritonavir Molnupiravir Nirmatrelvir/Ritonavir Ribavirin Remdesivir	Baricitinib Dexamethasone Tocilizumab

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA IRB UW 13-625), and the study was conducted in compliance with the Declaration of Helsinki.

2.2. Outcomes

All subjects were followed for at least 90 days or until death. The primary outcome was 30-day mortality following diagnosis of COVID-19. The secondary outcomes included rate of hospitalization and intensive care unit (ICU) hospitalization. In addition, we evaluated the impact of hypernatraemia on hospitalization and length of stay (LOS) among the surviving cohort. We also compared the rates of hypernatraemia among local waves driven by different SARS-CoV-2 variants (Table 2). The costs of hospitalization were estimated from the nominal daily costs of general medical and ICU beds (653.8 USD/day and 3128.2 USD/day, respectively) multiplied by the LOS in the respective beds.

Table 2. Time period and dominant SARS-CoV-2 variant during each local breakthrough wave during COVID-19.

Wave	Time Period	Dominant SARS-CoV-2 Variant
2nd	1–30 April 2020	D614G [21]
3rd	15 June–30 September 2020	B.1.1.63 [22]
4th	1 November 2022–28 February 2021	B.1.36.27 [22]
5th	1 January–31 March 2022	Omicron BA.2

2.3. Statistical Analysis

Statistical analysis was performed using SPSS for Mac software version 27.0 (IBM corporation, Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation, while categorical data were presented as number (percentage). Patients were grouped according to the presence/absence of hypernatraemia at presentation for analysis. Data were compared between groups using chi-square test, Student's *t*-test or Mann–Whitney U test as appropriate. Time-to-event analysis was performed for the primary outcome using the Kaplan–Meier method and compared using the log-rank test. Furthermore, multivariate logistic and Cox proportional hazard regression analysis were performed to adjust for confounders. Factors known to affect COVID-19 outcomes and clinical parameters significantly different between patients with hyper- and normonatraemia were adjusted for in the multivariate analysis model. A *p*-value below 0.05 was considered statistically significant. All probabilities were two-tailed.

3. Results

3.1. Patient Characteristics

The data from a total of 53,415 adult patients were retrieved and included for final analysis (Figure 1). A total of 2688 (5.0%) adult patients with COVID-19 had hypernatraemia

on presentation, while 36,182 (67.7%) had normonatraemia. A total of 14,545 (27.2%) patients who had hyponatraemia at presentation were excluded from the comparative analysis to avoid skewing the results. The clinical characteristics of COVID-19 patients with hypernatraemia or normonatraemia at presentation, and their hospitalization, ICU admission and treatment data are summarized in Tables 3 and 4.

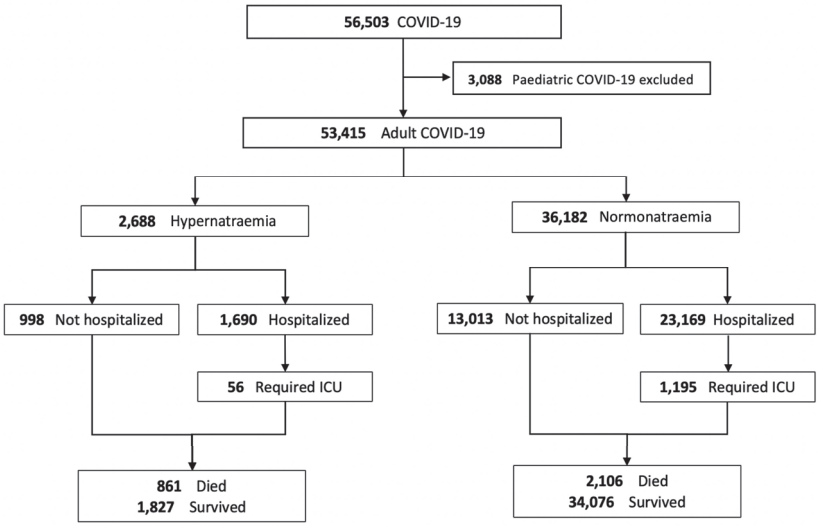


Figure 1. Disposition of patients with COVID-19 and the relationship with blood sodium levels.

Table 3. Clinical characteristics of COVID-19 patients with hypernatraemia or normonatraemia at presentation.

	Hypernatraemia (n = 2688)	Normonatraemia (n = 36,182)	p-Value
Age	86.3 ± 10.5	62.4 ± 22.0	<0.001 [a]
Age older than 65, No. (%)	2550 (94.9%)	17,679 (48.9%)	<0.001 [b]
Male, No. (%)	1300 (48.4%)	18,103 (50.0%)	0.095 [b]
Institutionalized, No. (%)	1823 (67.8%)	6533 (18.1%)	<0.001 [b]
Charlson Comorbidity Index	2.71 ± 2.20	1.41 ± 1.92	<0.001 [a]
Major comorbidities			
Diabetes mellitus	793 (29.5%)	7184 (19.9%)	<0.001 [b]
Hypertension	1691 (62.9%)	13,618 (37.6%)	<0.001 [b]
Ischaemic heart disease	452 (16.8%)	3724 (10.3%)	<0.001 [b]
Cerebrovascular accident	544 (20.2%)	2847 (7.9%)	<0.001 [b]
Cardiac arrhythmia	497 (18.5%)	3858 (10.7%)	<0.001 [b]
Congestive heart failure	367 (13.7%)	2676 (7.4%)	<0.001 [b]
Chronic obstructive airway disease	159 (5.9%)	1604 (4.4%)	<0.001 [b]
Asthma	50 (1.9%)	593 (1.6%)	0.4 [b]
Pneumoconiosis	38 (1.4%)	242 (0.7%)	<0.001 [b]
Dementia	1072 (39.9%)	3380 (9.3%)	<0.001 [b]
Chronic liver disease	208 (7.7%)	2026 (5.6%)	<0.001 [b]
Active malignancy	576 (17.7%)	5517 (15.2%)	0.001 [b]
Chronic kidney disease			<0.001 [b]
Stage 1	67 (2.5%)	12,037 (33.3%)	
Stage 2	842 (31.3%)	16,915 (46.7%)	
Stage 3	715 (26.6%)	4860 (13.4%)	

Table 3. *Cont.*

	Hypernatraemia (*n* = 2688)	Normonatraemia (*n* = 36,182)	*p*-Value
Stage 4	616 (22.9%)	1435 (4.0%)	
Stage 5	448 (16.7%)	934 (2.6%)	
Laboratory parameters			
SARS-CoV-2 RT-PCR Ct value on admission	23.0 ± 6.4	23.5 ± 6.8	0.006 [a]
Haemoglobin (g/dL)	11.8 ± 2.6	12.8 ± 2.2	<0.001 [a]
White cell count (10^9/L)	11.3 ± 7.4	7.0 ± 4.0	<0.001 [a]
Neutrophil (10^9/L)	7.3 ± 4.5	4.9 ± 3.4	<0.001 [a]
Lymphocyte (10^9/L)	1.0 ± 1.4	1.3 ± 1.0	<0.001 [a]
Neutrophil to lymphocyte ratio	13.5 ± 13.1	5.6 ± 7.2	<0.001 [a]
Platelet (10^9/L)	231 ± 104	223 ± 88	0.05 [a]
Sodium (mmol/L)	153.2 ± 7.0	138.6 ± 2.3	<0.001 [a]
Potassium (mmol/L)	4.1 ± 0.9	3.9 ± 0.5	<0.001 [a]
Urea (mmol/L)	21.8 ± 13.6	6.7 ± 6.1	<0.001 [a]
Creatinine (µmol/L)	188 ± 167	103 ± 124	<0.001 [a]
eGFR (by CKD-EPI equation) (mL/min/1.73 m^2)	43.6 ± 26.5	79.7 ± 31.1	<0.001 [a]
Albumin (g/L)	29.3 ± 6.2	36.8 ± 6.4	<0.001 [a]
C-reactive protein (mg/L)	11.0 ± 8.7	3.7 ± 5.9	<0.001 [a]
Calcium (mmol/L)	2.25 ± 0.23	2.23 ± 0.15	<0.001 [a]
Phosphate (mmol/L)	1.26 ± 0.57	1.09 ± 0.37	<0.001 [a]
Plasma osmolality (mOsm/kg)	354 ± 29	302 ± 33	<0.001 [a]
Thyroid-stimulating hormone (mIU/L)	1.3 ± 2.9	1.7 ± 3.8	0.049 [a]
Creatine kinase (U/L)	405 ± 1527	250 ± 1599	<0.001 [a]
D-dimer (ng/mL)	1886 ± 2594	862 ± 1567	<0.001 [a]
Urine sodium (mmol/L)	47.7 ± 32.2	50.3 ± 40.7	0.7 [a]
Urine osmolality (mOsm/kg)	559 ± 148	438 ± 196	<0.001 [a]

Data are presented as mean ± standard deviation unless specified and compared using Student's *t*-test [a] and chi-square test [b]. COVID-19, novel coronavirus disease-2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription polymerase chain reaction; Ct value, cycle threshold value; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration.

Table 4. Predictors for hypernatraemia at presentation in patients with COVID-19.

	Univariate Model		Multivariate Model	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Demographics				
Age	1.09 (1.08–1.09)	<0.001	1.03 (1.03–1.04)	<0.001
Institutionalization	9.57 (8.78–10.42)	<0.001	2.37 (2.00–2.82)	<0.001
SARS-CoV-2 RT-PCR Ct value	0.99 (0.99–0.99)	0.006	1.04 (1.02–1.05)	<0.001
Comorbidities				
CHF	1.98 (1.76–2.23)	<0.001	0.76 (0.59–0.97)	0.03
Dementia	6.44 (5.91–7.01)	<0.001	1.80 (1.50–2.14)	<0.001
Laboratory parameters				
Haemoglobin	0.84 (0.83–0.86)	<0.001	1.15 (1.11–1.20)	<0.001
White cell count	1.17 (1.16–1.18)	<0.001	1.06 (1.04–1.07)	<0.001
eGFR (by CKD-EPI equation)	0.96 (0.96–0.96)	<0.001	0.97 (0.97–0.97)	<0.001
C-reactive protein	1.11 (1.11–1.12)	<0.001	1.02 (1.01–1.03)	<0.001
Albumin	0.86 (0.85–0.86)	<0.001	0.92 (0.91–0.94)	<0.001

CHF, congestive heart failure; CI, confidence interval; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; COVID-19, novel coronavirus disease-2019; Ct value, cycle threshold value; eGFR, estimated glomerular filtration rate; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Among the hypernatraemic patients, a baseline sodium level within 6 months of the index hospitalization was available for 2118 (78.8%). The mean prehospitalization sodium level was 139.6 ± 3.4 mmol/L. Only 76 (3.6%) patients had pre-existing hypernatraemia. Patients with hypernatraemia were older (86.3 ± 10.5 years vs. 62.4 ± 22.0, $p < 0.001$) and

more likely to be institutionalized (67.8% vs. 18.1%, $p < 0.001$). Before adjustment for baseline variables, these patients had higher SARS-CoV-2 viral load (Ct values 23.0 ± 6.4 vs. 23.5 ± 6.8, $p = 0.006$), C-reactive protein (11.0 ± 8.7 mg/L vs. 3.7 ± 5.9 mg/L, $p < 0.001$), creatine kinase (405 ± 1527 U/L vs. 250 ± 1599 U/L, $p < 0.001$) and D-dimer levels (1886 ± 2594 ng/mL vs. 862 ± 1567 ng/mL, $p < 0.001$) on univariate analysis (Table 3). They were more likely to receive immunomodulatory therapy (58.7% vs. 23.0%, $p < 0.001$) during the disease course, though the antiviral agent utilization was lower (21.7% vs. 25.3%, $p < 0.001$) (Table 4). COVID-19 patients with hypernatraemia at presentation had higher CCI than those with normonatraemia (2.71 ± 2.20 vs. 1.41 ± 1.92, $p < 0.001$). Among components of CCI, dementia (39.9% vs. 9.3%, $p < 0.001$), diabetes mellitus (29.5% vs. 19.9%, $p < 0.001$) and cerebrovascular accident (20.2% vs. 7.9%, $p < 0.001$) were more frequent in patients with hypernatraemia (Table 5). They also presented with higher white cell and neutrophil counts, but lower lymphocyte counts and haemoglobin levels ($p < 0.001$ for all). eGFR (43.6 ± 26.5 mL/min vs. 79.7 ± 31.1 mL/min/1.73 m^2, $p < 0.001$) and serum albumin levels (29.3 ± 6.2 g/L vs. 36.8 ± 6.4 g/L, $p < 0.001$) were lower in COVID-19 patients with hypernatraemia compared with those with normonatraemia.

Table 5. Charlson Comorbidity Index and its components in COVID-19 patients with hypernatraemia or normonatraemia at presentation.

	Hypernatraemia (n = 2688)	Normonatraemia (n = 36,182)	p-Value
Charlson Comorbidity Index Score	2.71 ± 2.20	1.41 ± 1.92	<0.001 [a]
Components of Charlson Comorbidity Index			
Acute myocardial infarction	452 (16.8%)	3724 (10.3%)	<0.001 [b]
Congestive heart failure	367 (13.7%)	2676 (7.4%)	<0.001 [b]
Peripheral vascular disease	16 (0.6%)	102 (0.3%)	0.004 [b]
Cerebrovascular disease	544 (20.2%)	2847 (7.9%)	<0.001 [b]
Dementia	1072 (39.9%)	3380 (9.3%)	<0.001 [b]
Chronic lung disease	159 (5.9%)	1604 (4.4%)	<0.001 [b]
Rheumatic disease	362 (13.5%)	3743 (10.3%)	<0.001 [b]
Peptic ulcer	253 (9.4%)	1662 (4.6%)	<0.001 [b]
Mild liver disease	191 (7.1%)	1833 (5.1%)	<0.001 [b]
Moderate to serious liver disease	19 (0.7%)	217 (0.6%)	0.5 [b]
Mild to moderate diabetes	793 (29.5%)	7184 (19.9%)	<0.001 [b]
Diabetes with chronic complications	341 (12.7%)	2338 (6.5%)	<0.001 [b]
Hemiplegia or paraplegia	156 (5.8%)	803 (2.2%)	<0.001 [b]
Kidney disease	460 (17.1%)	1041 (2.9%)	<0.001 [b]
Malignancy	451 (16.8%)	5090 (14.1%)	<0.001 [b]
Solid, metastatic tumour	24 (0.9%)	433 (1.2%)	0.2 [b]
Leukaemia	5 (0.2%)	54 (0.1%)	0.6 [b]
Lymphoma	7 (0.3%)	104 (0.3%)	0.8 [b]
AIDS	4 (0.1%)	23 (0.1%)	0.1 [b]

Data are presented as mean ± standard deviation unless specified and compared using Student's t-test [a] and chi-square test [b].

Most COVID-19 cases with hypernatraemia (99.2%) occurred during the "5th wave", driven by the Omicron BA.2 variant (Table 6). The incidence rate of hypernatraemia was significantly higher during the "5th wave" compared with previous local waves (6.2% vs. 0.2%, $p < 0.001$) (Tables 6 and 7).

Table 6. Clinical outcomes in COVID-19 patients with hypernatraemia or normonatraemia at presentation and relationship with different local waves.

	Hypernatraemia (n = 2688)	Normonatraemia (n = 36,182)	p-Value
Death within 30 days	860 (32.0%)	2051 (5.7%)	<0.001 [b]
Local wave (Time periods; dominant SARS-CoV-2 variant)			<0.001 [b]
2nd wave (1 to 30 April 2020; D614G [21])	1 (0.1%)	746 (92.7%)	
3rd wave (15 June–30 September 2020; B.1.1.63 [22])	12 (0.4%)	2808 (90.1%)	
4th wave (1st November 2020–28 February 2021; B.1.36.27 [22])	7 (0.1%)	4514 (88.9%)	
5th wave (1 January–31 March 2022; Omicron BA.2)	2667 (6.2%)	26,484 (66.2%)	
COVID-19 Treatments			
Antiviral therapy	584 (21.7%)	9168 (25.3%)	<0.001 [b]
Immunomodulatory therapy	1577 (58.7%)	8333 (23.0%)	<0.001 [b]
Healthcare utilization in surviving patients	Hypernatraemia (n = 1827)	Normonatraemia (n = 34,076)	p-Value
Duration of hospitalization	12.9 ± 10.9	11.5 ± 12.1	<0.001 [a]
Hospitalization for > 14 days	334 (35.2%)	5540 (26.2%)	<0.001 [b]
ICU admission	40 (4.2%)	1043 (4.9%)	0.3 [b]
Duration of ICU admission	7.9 ± 19.5	7.8 ± 13.0	0.9 [a]
ICU hospitalization for > 7 days (%, among hospitalized in ICU)	9 (22.5%)	294 (28.2%)	0.4 [b]

Data are presented as mean ± standard deviation unless specified and compared using Student's t-test [a] and chi-square test [b]. COVID-19, coronavirus disease-2019; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 7. Clinical characteristics of COVID-19 patients with hypernatraemia at presentation during the different local waves of COVID-19.

	2nd Wave (n = 1)	3rd Wave (n = 12)	4th Wave (n = 7)	5th Wave (n = 2667)	p-Value
Age	75	68.3 ± 15.8	82.4 ± 15.2	86.4 ± 10.3	<0.001 [a]
Age older than 65, No. (%)	1 (100%)	7 (58.3%)	6 (85.7%)	2536 (95.1%)	<0.001 [b]
Male, No. (%)	0 (0%)	5 (41.7%)	3 (42.9%)	1292 (48.4%)	0.7 [b]
Institutionalized, No. (%)	0 (0%)	4 (33.3%)	3 (42.9%)	1816 (68.1%)	0.01 [b]
SARS-CoV-2 RT-PCR Ct value	34.7	25.1 ± 7.9	25.6 ± 6.2	23.1 ± 6.4	0.1 [a]
Charlson Comorbidity Index	0	2.33 ± 2.77	3.14 ± 2.41	2.71 ± 2.19	0.5 [a]
Comorbidities, No. (%)					
Diabetes mellitus	0 (0%)	3 (25.0%)	2 (28.6%)	788 (29.6%)	0.9 [b]
Hypertension	0 (0%)	6 (50.0%)	4 (57.1%)	1681 (63.0%)	0.4 [b]
Ischaemic heart disease	0 (0%)	1 (8.3%)	4 (57.1%)	447 (16.8%)	0.06 [b]
Cerebrovascular accident	0 (0%)	2 (16.7%)	0 (0%)	542 (20.3%)	0.7 [b]
Cardiac arrhythmia	0 (0%)	1 (8.3%)	2 (28.6%)	494 (18.5%)	0.8 [b]
Congestive heart failure	0 (0%)	0 (0%)	2 (28.6%)	365 (13.7%)	0.5 [b]
COAD	0 (0%)	0 (0%)	0 (0%)	159 (6.0%)	0.9 [b]
Asthma	0 (0%)	0 (0%)	0 (0%)	50 (1.9%)	1.0 [b]
Pneumoconiosis	0 (0%)	0 (0%)	0 (0%)	38 (1.4%)	1.0 [b]
Dementia	0 (0%)	2 (16.7%)	1 (14.3%)	1069 (40.1%)	0.2 [b]
Chronic liver disease	0 (0%)	1 (8.3%)	2 (28.6%)	129 (4.8%)	0.07 [b]
Active malignancy	0 (0%)	3 (25.0%)	2 (28.6%)	470 (17.6%)	0.8 [b]
Chronic kidney disease, No. (%)					<0.001 [b]
Stage 1	0 (0%)	6 (50.0%)	0 (0%)	60 (2.2%)	
Stage 2	0 (0%)	3 (25.0%)	2 (28.6%)	837 (31.4%)	
Stage 3	1 (100%)	1 (8.3%)	2 (28.6%)	711 (26.7%)	

Table 7. *Cont.*

	2nd Wave (*n* = 1)	3rd Wave (*n* = 12)	4th Wave (*n* = 7)	5th Wave (*n* = 2667)	*p*-Value
Stage 4	0 (0%)	1 (8.3%)	3 (42.9%)	612 (22.9%)	
Stage 5	0 (0%)	1 (8.3%)	0 (0%)	447 (16.8%)	
Laboratory parameters					
Haemoglobin (g/dL)	10.4	12.9 ± 2.4	11.5 ± 2.2	11.8 ± 2.6	0.6 [a]
White cell count (10^9/L)	18.7	6.8 ± 1.8	9.6 ± 5.1	11.3 ± 7.5	0.2 [a]
Neutrophil (10^9/L)	15.7	4.3 ± 1.5	6.5 ± 3.2	9.5 ± 5.7	0.006 [a]
Lymphocyte (10^9/L)	0.7	1.8 ± 0.9	1.3 ± 1.4	1.0 ± 1.4	0.4 [a]
Neutrophil to lymphocyte ratio	23.1	3.4 ± 3.1	18.3 ± 18.9	13.6 ± 13.1	0.05 [a]
Platelet (10^9/L)	183	246 ± 78	186 ± 66	231 ± 104	0.8 [a]
Potassium (mmol/L)	4.0	3.8 ± 0.6	4.2 ± 1.0	4.1 ± 0.9	0.7 [a]
Urea (mmol/L)	22.2	8.3 ± 5.8	19.0 ± 12.2	21.9 ± 13.6	0.007 [a]
Creatinine (umol/L)	118.0	92.7 ± 64.7	142.1 ± 54.7	188.5 ± 167.9	0.3 [a]
eGFR (by CKD-EPI) (mL/min/1.73 m^2)	39.0	76.9 ± 31.5	41.7 ± 24.7	43.5 ± 26.4	<0.001 [a]
Albumin (g/L)	21.0	37.8 ± 5.8	30.5 ± 6.0	29.3 ± 6.1	<0.001 [a]
C-reactive protein (mg/L)	8.4	2.5 ± 4.0	6.6 ± 7.8	11.1 ± 8.7	0.008 [a]
Calcium (mmol/L)	2.26	2.28 ± 0.14	2.07 ± 0.14	2.25 ± 0.23	0.3 [a]
Phosphate (mmol/L)	1.30	0.99 ± 0.15	1.51 ± 1.04	1.27 ± 0.57	0.5 [a]
Plasma osmolality (mOsm/kg)	355	357 ± 26	361 ± 28	354 ± 29	0.8 [a]
Thyroid stimulating hormone (mIU/L)	2.8	3.8 ± 7.4	1.3 ± 1.7	1.3 ± 2.8	0.09 [a]
D-dimer (ng/mL)	253	247 ± 116	315 ± 625	1892 ± 2597	0.3 [a]

Data are presented as mean ± standard deviation unless specified and compared using Student's *t*-test [a] and chi-square test [b]. CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; COAD, chronic obstructive airway disease; Ct value, cycle threshold value; eGFR, estimated glomerular filtration rate; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

3.2. Predictors of Hypernatraemia in COVID-19 Patients

Multivariate analysis showed that age, institutionalization, congestive heart failure, dementia, higher SARS-CoV-2 Ct value (thus, lower viral loads), lower haemoglobin, higher white cell count, higher C-reactive protein and lower eGFR and lower albumin levels were associated with a higher risk of hypernatraemia in COVID-19 infection, after adjusting for confounding factors (Table 4).

3.3. Mortality

A total of 4390 of the 53,415 patients had died at 30 days of follow-up (pooled mortality rate of 8.2%). The 30-day mortality rate was significantly higher in the hypernatraemic group compared with normonatraemic controls (32.0% vs. 5.7%, $p < 0.001$) (Table 6 and Figure 2). Patients who died had a higher incidence rate of hypernatraemia at presentation (19.6% vs. 3.7%, $p < 0.001$), accompanied by higher mean plasma Na levels at presentation (138.7 ± 10.1 vs. 136.8 ± 6.1 mmol/L, $p < 0.001$) (Table 8). Patients who died were older, had more comorbidities (CCI, 2.82 ± 2.32 vs. 1.58 ± 1.99, $p < 0.001$) and showed a higher prevalence of institutionalization (45.1% vs. 20.6%, $p < 0.001$) (Table 8). The rates of antiviral (26.9% vs. 27.8%, $p = 0.02$) and immunomodulatory (26.2% vs. 67.2%, $p < 0.001$) therapy use were lower in patients who eventually died. Multivariate analysis demonstrated hypernatraemia at presentation as an independent predictor for 30-day mortality (adjusted hazard ratio (aHR) 1.32, 95% CI 1.14–1.53, $p < 0.001$) (Table 9).

Table 8. Clinical characteristics of COVID-19 patients who died within 30 days.

	Died (*n* = 4318)	Survived (*n* = 49,025)	*p*-Value
Age	83.2 ± 11.5	65.4 ± 21.3	<0.001 [a]
Age older than 65, No. (%)	3979 (92.1%)	27,137 (55.3%)	<0.001 [b]

Table 8. *Cont.*

	Died (*n* = 4318)	Survived (*n* = 49,025)	*p*-Value
Male, No. (%)	2596 (60.1%)	25,044 (51.0%)	<0.001 [b]
Institutionalized, No. (%)	1972 (45.7%)	10,099 (20.6%)	<0.001 [b]
Serum sodium (mmol/L)	138.7 ± 10.2	136.8 ± 6.1	<0.001 [a]
Hypernatraemia, No. (%)	860 (29.5%)	1828 (5.1%)	<0.001 [b]
Charlson Comorbidity Index	2.8 ± 2.3	1.6 ± 2.0	<0.001 [a]
Comorbidities			
Diabetes mellitus	1470 (34.0%)	11,475 (23.4%)	<0.001 [b]
Hypertension	2707 (62.7%)	20,512 (41.8%)	<0.001 [b]
Ischaemic heart disease	859 (19.9%)	5562 (11.3%)	<0.001 [b]
Cerebrovascular accident	822 (19.0%)	4395 (9.0%)	<0.001 [b]
Cardiac arrhythmia	986 (22.8%)	5610 (11.4%)	<0.001 [b]
Congestive heart failure	760 (17.6%)	3755 (7.6%)	<0.001 [b]
Chronic obstructive airway disease	414 (9.6%)	2303 (4.7%)	<0.001 [b]
Asthma	72 (1.7%)	850 (1.7%)	0.8 [b]
Pneumoconiosis	111 (2.6%)	370 (0.8%)	0.001 [b]
Dementia	1093 (25.3%)	5091 (10.4%)	<0.001 [b]
Chronic liver disease	376 (8.7%)	2891 (5.9%)	<0.001 [b]
Active malignancy	905 (21.0%)	8090 (16.5%)	<0.001 [b]
Chronic kidney disease			<0.001[b]
Stage 1	244 (5.7%)	14,401 (29.3%)	
Stage 2	1513 (35.0%)	23,548 (48.0%)	
Stage 3	1192 (27.6%)	7252 (14.8%)	
Stage 4	762 (17.6%)	2205 (4.5%)	
Stage 5	607 (14.1%)	1691 (3.4%)	
COVID-19 treatments			
Antiviral therapy	1200 (27.8%)	13,220 (26.9%)	0.02 [b]
Immunomodulatory therapy	2919 (67.6%)	12,375 (26.2%)	<0.001 [b]

Data are presented as mean ± standard deviation unless specified and compared using Student's *t*-test [a] and chi-square test [b]. COVID-19, coronavirus disease-2019.

Table 9. Risk factors for 30-day mortality in patients with COVID-19.

	Univariate Model		Multivariate Model	
	HR (95% CI)	*p*-Value	Adjusted HR (95% CI)	*p*-Value
Hypernatraemia	6.97 (6.44–7.55)	<0.001	1.32 (1.14–1.53)	<0.001
Demographics				
Age	1.06 (1.06–1.06)	<0.001	1.03 (1.02–1.04)	<0.001
Male sex	1.35 (1.27–1.43)	<0.001	1.18 (1.04–1.34)	0.01
Comorbidities				
Charlson Comorbidity Index	1.26 (1.24–1.27)	<0.001		
Diabetes mellitus	1.71 (1.61–1.83)	<0.001		
Hypertension	2.37 (2.22–2.52)	<0.001		
Ischaemic heart disease	1.97 (1.83–2.12)	<0.001		
Cerebrovascular accident	2.31 (2.15–2.50)	<0.001		
COAD	2.07 (1.87–2.29)	<0.001	1.50 (1.22–1.83)	<0.001
Active malignancy	1.56 (1.45–1.68)	<0.001		
Dementia	2.62 (2.45–2.81)	<0.001		
Congestive heart failure	2.48 (2.29–2.68)	<0.001		
Arrhythmia	2.28 (2.13–2.45)	<0.001	1.22 (1.05–1.42)	0.01
Chronic liver disease	1.50 (1.35–1.67)	<0.001		

Table 9. *Cont.*

	Univariate Model		Multivariate Model	
	HR (95% CI)	***p*-Value**	**Adjusted HR (95% CI)**	***p*-Value**
Laboratory parameters				
SARS-CoV-2 RT-PCR Ct value	0.97 (0.96–0.97)	<0.001	0.98 (0.97–0.99)	<0.001
Haemoglobin	0.79 (0.78–0.80)	<0.001	0.96 (0.93–0.99)	0.004
White cell count	1.02 (1.02–1.02)	<0.001	1.01 (1.00–1.02)	0.006
eGFR (by CKD-EPI)	0.97 (0.97–0.97)	<0.001	0.99 (0.99–0.99)	<0.001
Albumin	0.88 (0.87–0.88)	<0.001	0.96 (0.95–0.97)	<0.001
C-reactive protein	1.10 (1.10–1.11)	<0.001	1.05 (1.05–1.06)	<0.001
D-dimer (every 1000 units rise)	1.22 (1.20–1.23)	<0.001	1.03 (1.00–1.06)	0.04
COVID-19 Treatment				
Antiviral therapy	0.75 (0.70–0.80)	<0.001		
Immunomodulatory therapy	4.43 (4.15–4.72)	<0.001	2.20 (1.88–2.58)	<0.001

CI, confidence interval; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; COAD, chronic obstructive airway disease; COVID-19, coronavirus disease-2019; Ct value, cycle threshold value; eGFR, estimated glomerular filtration rate; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

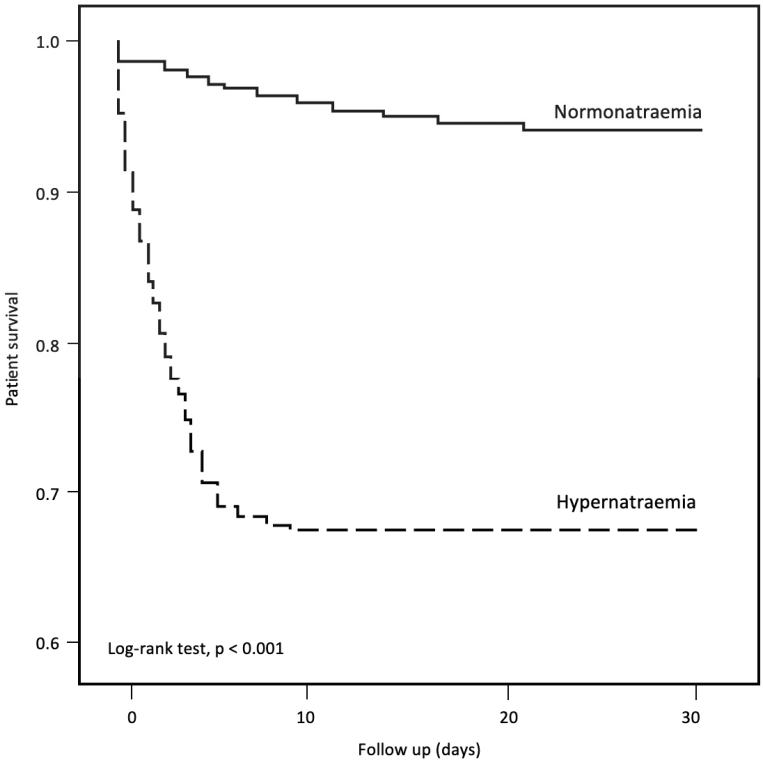


Figure 2. Thirty-day mortality in COVID-19 patients with hypernatraemia and normonatraemia.

3.4. Impact on Healthcare Utilization

We analysed healthcare utilization in surviving patients with hypernatraemia or normonatraemia at presentation. There was no difference in the hospitalization rates between patients with hypernatraemia and normonatraemia (62.9% vs. 64.0%, $p = 0.2$). However, the overall LOS was longer (12.9 ± 10.9 vs. 11.5 ± 12.1 days, $p < 0.001$) among surviving patients

with hypernatraemia, with a greater proportion of patients with prolonged hospitalization (i.e., >14 days) (35.2% vs. 26.2%, $p < 0.001$) (Tables 6 and 10). Multivariate analysis revealed hypernatraemia at presentation as an independent predictor for prolonged hospitalization (i.e., LOS > 7 days) in COVID-19 (odds ratio (OR) 1.55, 95% CI 1.17–2.05, $p = 0.002$). Other predictors identified from the same model include institutionalization (OR 1.27, 95% CI 1.06–1.52, $p = 0.009$), SARS-CoV-2 PCR Ct value (OR 0.94, 95% CI 0.93–0.94, $p < 0.001$), the presence of chronic liver disease (OR 1.45, 95% CI 1.13–1.86, $p = 0.004$), biochemical parameters such as white cell count (OR 0.97, 95% CI 0.95–0.98, $p < 0.001$), eGFR (OR 0.99, 95% CI 0.99–0.99, $p = 0.001$), albumin (OR 1.02, 95% CI 1.01–1.03, $p = 0.002$), C-reactive protein (OR 1.04, 95% CI 1.03–1.06, $p < 0.001$) and the need for COVID-19 treatment including antiviral (OR 1.44, 95% CI 1.27–1.64, $p < 0.001$) and immunomodulatory therapies (OR 1.57, 95% CI 1.35–1.82, $p < 0.001$) (Table 10). Among patients with hypernatraemia who survived to hospital discharge, those who required intensive care unit care had a 5.5-fold higher overall cost of hospitalization than those managed solely in general wards (USD 18,141 (IQR 4730-31,552) vs. USD 5558 (IQR 2289-8827), $p < 0.001$). Nonetheless, the cost of hospitalization did not differ between patients with mild, moderate and severe hypernatraemia at presentation.

Table 10. Risk factors for prolonged hospitalization (i.e., >7 days) among surviving patients with COVID-19.

	Univariate Model		Multivariate Model	
	OR (95% CI)	***p*-Value**	**Adjusted OR (95% CI)**	***p*-Value**
Hypernatraemia	1.44 (1.24–1.66)	<0.001	1.55 (1.17–2.05)	0.002
Demographics				
Age	0.99 (0.99–1.00)	0.007		
Male sex	1.17 (1.11–1.23)	<0.001		
Institutionalization	1.16 (1.09–1.24)	<0.001	1.27 (1.06–1.52)	0.009
SARS-CoV-2 RT-PCR Ct value	0.93 (0.93–0.93)	<0.001	0.94 (0.93–0.94)	<0.001
Comorbidities				
Dementia	1.15 (1.06–1.26)	0.001		
Chronic liver disease	1.02 (1.92–1.14)	0.7	1.45 (1.13–1.86)	0.004
Laboratory parameters				
Haemoglobin	1.06 (1.05–1.07)	<0.001		
White cell count	0.97 (0.97–0.98)	<0.001	0.97 (0.95–0.98)	<0.001
eGFR (by CKD-EPI)	0.99 (0.99–1.00)	0.02	0.99 (0.99–0.99)	0.001
Albumin	1.01 (1.00–1.01)	0.002	1.02 (1.01–1.03)	0.002
C-reactive protein	1.02 (1.02–1.03)	<0.001	1.04 (1.03–1.06)	<0.001
Treatment for COVID-19				
Antiviral therapy	1.98 (1.88–2.09)	<0.001	1.44 (1.27–1.64)	<0.001
Immunomodulatory therapy	1.93 (1.82–2.05)	<0.001	1.57 (1.35–1.82)	<0.001

CI, confidence interval; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; COVID-19, coronavirus disease-2019; Ct value, cycle threshold value; eGFR, estimated glomerular filtration rate; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

4. Discussion

In this territory-wide retrospective cohort study involving 53,415 patients with COVID-19, we observed a substantial rate of hypernatraemia at presentation to hospital, especially during the "5th wave" caused by the Omicron BA.2 subvariant in Hong Kong. COVID-19 patients with hypernatraemia at presentation generally showed worse clinical outcomes, with significantly increased 30-day mortality. Patients with hypernatraemia at presentation who survived their acute hospital stay tended to have longer LOS, and accrued higher healthcare costs. Importantly, COVID-19 patients with hypernatraemia at presentation were

overwhelmingly elderly, and a significant proportion of them were institutionalized, in stark contrast to those with normonatraemia.

The rate of hypernatraemia in COVID-19 appears to be context-specific, and can be significantly affected by patient characteristics, healthcare settings and infection control policies. During the earliest waves of COVID-19 in the spring of 2020, the prevalence of hypernatraemia in Hong Kong was merely 0.1% (Table 7). During the same period, in which the outbreak was all driven by the same ancestral strain of COVID, hypernatraemia was reported in 3.7% and 9.1% of COVID-19 patients in Europe and the United States, respectively [8,13]. The meticulous case tracking and mass quarantine practiced in Hong Kong at the time enabled early detection of cases with mild to moderate symptoms and hospitalization of virtually all positive cases. The prevalence of hypernatraemia surged to 6.2% when the healthcare system was overwhelmed by the "5th wave" (caused by the Omicron BA.2 subvariant) in Hong Kong [16,17,23]. COVID-19 patients, especially the elderly, often presented late to medical care after a protracted waiting time at home or in nursing homes, during which they developed dehydration and hypernatraemia. The finding that advanced age, institutionalization and dementia were predictors for hypernatraemia in COVID-19 patients lends further support to our postulation. After adjustment for demographic variables and other risk factors, an inverse relationship between viral load and hypernatraemia was observed, suggesting that these patients might be late presenters, when viral shedding was already waning. Physical and neurocognitive inability to compensate for ongoing insensible fluid losses in these elderly institutionalized patients likely contributed to the development of hypernatraemia.

Our results highlight that hypernatraemia during large COVID-19 outbreaks is a symptom of an overburdened, dysfunctional healthcare system. Hypernatraemia and its associated adverse outcomes can potentially be prevented or mitigated if at-risk individuals are closely monitored and given adequate fluid replacement. This is particularly important as we identified hypernatraemia as a strong predictor of mortality in our cohort, even after adjusting for other comorbidities. In a large European registry, hypernatraemia predicted mortality and development of sepsis [8]. A registry analysis from New York showed that inpatient mortality was particularly increased in patients with severe hypernatraemia complicating COVID-19 [13]. Hypernatraemia per se does not appear to be pathogenic in COVID-19; in fact, some experimental studies suggest that therapeutic induction of hypernatraemia may protect against lung injury [24–28]. Instead, we speculate that hypernatraemia during acute illnesses may be a surrogate marker of frailty, especially in the geriatric population. The close correlation between hypernatraemia in COVID-19 and excess mortality was likely exaggerated in this group of patients with a background of frailty, compounded with poor oral fluid and food intake during acute illness. The role of medications such as diuretics remains to be further elucidated.

There are several limitations in this territory-wide observational cohort study. First, owing to the retrospective observational nature of this study, a definitive causal relationship between hypernatraemia and mortality could not be determined. Whether mortality related to hypernatraemia could be mitigated by appropriate fluid management remains speculative, as only the sodium level on initial presentation was captured in the analysis, and serial values were not fully analysed. Second, due to the constraints of this registry analysis, certain clinical variables, including vital signs, disease severity scores or frailty indices were not available for most patients. Although hypernatraemia is classically associated with dehydration, a significant proportion of hypernatraemic patients could in fact be hypervolaemic, especially in the critically ill population [29]; however, fluid status could not be determined with confidence in our cohort. Third, reporting bias may occur as the registry analysis mostly captures patients who were hospitalized or who reported their diagnosis to the official reporting system. Fourth, hypernatraemia may be masked by other biochemical abnormalities, especially hyperglycaemia [30]. As paired plasma glucose and sodium levels were not available for all patients, there is a possibility that the rate of hypernatraemia may have been underestimated.

These limitations notwithstanding, this study's key strength lies in its large sample size, with over 50,000 patients with COVID-19 analysed with a specific focus on hypernatraemia. All patients were followed for at least 90 days or until death, allowing for evaluation of various key short- to medium-term outcomes. Second, since all patients in our study were diagnosed by RT-PCR performed on upper respiratory tract specimens, we were able to examine the correlations between the viral loads and clinical outcomes to determine if there was a genuine causal link between infection per se and development of hypernatraemia. Finally, with data available from different waves of COVID-19 in Hong Kong, we were able to delineate longitudinal trends in the prevalence of hypernatraemia among presenting patients. Based on these trends, we surmise that the rate of hypernatraemia can be highly variable during different outbreaks of COVID-19, depending both on the demographics of the populations affected and the robustness of the healthcare system.

5. Conclusions

Hypernatraemia at presentation is associated with excess mortality and prolonged hospitalization among COVID-19 patients. Advanced age, dementia and institutionalization are important risk factors for hypernatraemia in COVID-19 patients. An inverse relationship between viral load of SARS-CoV-2 and hypernatraemia suggests that these patients often present late to healthcare services, highlighting a key area for improvement.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jcm12031042/s1: Supplementary Table S1: ICD9 diagnostic code used for data retrieval in the Clinical Data Analysis and Reporting System (CDARS) database of the Hong Kong Hospital Authority.

Author Contributions: Conceptualization, B.Y.F.S., C.K.W., G.C.K.C. and D.Y.H.Y.; methodology, C.K.W., G.C.K.C. and D.Y.H.Y.; validation, B.Y.F.S., C.K.W., G.C.K.C. and D.Y.H.Y.; formal analysis, B.Y.F.S., C.K.W. and G.C.K.C.; investigation, B.Y.F.S., C.K.W. and G.C.K.C.; data curation, C.K.W. and G.C.K.C.; writing—original draft preparation, B.Y.F.S., C.K.W. and G.C.K.C.; writing—review and editing, B.Y.F.S., G.C.Y.L., K.M.C. and D.Y.H.Y.; supervision, J.K.C.N., G.C.Y.L., C.C.S., I.F.N.H., H.F.T., S.C.W.T., T.M.C., K.M.C. and D.Y.H.Y. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA IRB UW 13-625).

Informed Consent Statement: Patient consent was waived due to use of anonymized information.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to institution-level internal policies.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Turgutalp, K.; Ozhan, O.; Gok Oguz, E.; Yilmaz, A.; Horoz, M.; Helvaci, I.; Kiykim, A. Community-acquired hypernatremia in elderly and very elderly patients admitted to the hospital: Clinical characteristics and outcomes. *Med. Sci. Monit.* **2012**, *18*, CR729–CR734. [CrossRef]
2. Bozkurt Babus, S.; Kose, A.; Erdogan, S.; Kiraz, M.; Iyikesici, F. Risk factors and mortality in elderly patients with severe hyponatremia admitted to the emergency department. *Ir. J. Med. Sci.* **2022**, 1–10. [CrossRef] [PubMed]
3. Castello, L.M.; Gavelli, F.; Baldrighi, M.; Salmi, L.; Mearelli, F.; Fiotti, N.; Patrucco, F.; Bellan, M.; Sainaghi, P.P.; Ronzoni, G.; et al. Hypernatremia and moderate-to-severe hyponatremia are independent predictors of mortality in septic patients at emergency department presentation: A sub-group analysis of the need-speed trial. *Eur. J. Intern. Med.* **2021**, *83*, 21–27. [CrossRef]
4. Lindner, G.; Herschmann, S.; Funk, G.C.; Exadaktylos, A.K.; Gygli, R.; Ravioli, S. Sodium and potassium disorders in patients with COPD exacerbation presenting to the emergency department. *BMC Emerg. Med.* **2022**, *22*, 49. [CrossRef] [PubMed]

5. Wester, C.; Zhang, T.S.; Harrington, M.A.; Halawi, M.J. Sodium Abnormalities Are an Independent Predictor of Complications in Total Joint Arthroplasty: A Cautionary Tale! *J. Arthroplast.* **2021**, *36*, 3859–3863. [CrossRef]
6. Chand, R.; Chand, R.; Goldfarb, D.S. Hypernatremia in the intensive care unit. *Curr. Opin. Nephrol. Hypertens.* **2022**, *31*, 199–204. [CrossRef] [PubMed]
7. Chassagne, P.; Druesne, L.; Capet, C.; Menard, J.F.; Bercoff, E. Clinical presentation of hypernatremia in elderly patients: A case control study. *J. Am. Geriatr. Soc.* **2006**, *54*, 1225–1230. [CrossRef]
8. Ruiz-Sanchez, J.G.; Nunez-Gil, I.J.; Cuesta, M.; Rubio, M.A.; Maroun-Eid, C.; Arroyo-Espliguero, R.; Romero, R.; Becerra-Munoz, V.M.; Uribarri, A.; Feltes, G.; et al. Prognostic Impact of Hyponatremia and Hypernatremia in COVID-19 Pneumonia. A HOPE-COVID-19 (Health Outcome Predictive Evaluation for COVID-19) Registry Analysis. *Front. Endocrinol.* **2020**, *11*, 599255. [CrossRef]
9. Akbar, M.R.; Pranata, R.; Wibowo, A.; Irvan; Sihite, T.A.; Martha, J.W. The Prognostic Value of Hyponatremia for Predicting Poor Outcome in Patients with COVID-19: A Systematic Review and Meta-Analysis. *Front. Med.* **2021**, *8*, 666949. [CrossRef]
10. De Carvalho, H.; Letellier, T.; Karakachoff, M.; Desvaux, G.; Caillon, H.; Papuchon, E.; Bentoumi-Loaec, M.; Benaouicha, N.; Canet, E.; Chapelet, G.; et al. Hyponatremia is associated with poor outcome in COVID-19. *J. Nephrol.* **2021**, *34*, 991–998. [CrossRef]
11. Islam, M.K.; Hasan, P.; Sharif, M.M.; Khan, T.D.; Ratul, R.H.; Hossain, F.S.; Molla, M.M.A. Hyponatremia in COVID-19 patients: Experience from Bangladesh. *Health Sci. Rep.* **2022**, *5*, e565. [CrossRef]
12. Song, H.; Chia, A.Z.Q.; Tan, B.K.J.; Teo, C.B.; Lim, V.; Chua, H.R.; Samuel, M.; Kee, A. Electrolyte imbalances as poor prognostic markers in COVID-19: A systemic review and meta-analysis. *J. Endocrinol. Investig.* **2022**, *46*, 235–259. [CrossRef] [PubMed]
13. Hirsch, J.S.; Uppal, N.N.; Sharma, P.; Khanin, Y.; Shah, H.H.; Malieckal, D.A.; Bellucci, A.; Sachdeva, M.; Rondon-Berrios, H.; Jhaveri, K.D.; et al. Prevalence and outcomes of hyponatremia and hypernatremia in patients hospitalized with COVID-19. *Nephrol. Dial. Transpl.* **2021**, *36*, 1135–1138. [CrossRef] [PubMed]
14. Liu, D.; Mowrey, W.; Fisher, M.; Basalely, A.; McCarthy, J.; Kumar, N.; Thakkar, J.; Azzi, Y.; Brogan, M.; Golestaneh, L.; et al. Associations of Dysnatremia with COVID-19 Status and Mortality. *Kidney360* **2022**, *3*, 1323–1331. [CrossRef] [PubMed]
15. Skarbinski, J.; Wood, M.S.; Chervo, T.C.; Schapiro, J.M.; Elkin, E.P.; Valice, E.; Amsden, L.B.; Hsiao, C.; Quesenberry, C.; Corley, D.A.; et al. Risk of severe clinical outcomes among persons with SARS-CoV-2 infection with differing levels of vaccination during widespread Omicron (B.1.1.529) and Delta (B.1.617.2) variant circulation in Northern California: A retrospective cohort study. *Lancet Reg. Health Am.* **2022**, *12*, 100297. [CrossRef] [PubMed]
16. Ma, A.; Parry, J. When Hong Kong's "dynamic zero" covid-19 strategy met omicron, low vaccination rates sent deaths soaring. *BMJ* **2022**, *377*, o980. [CrossRef]
17. Chen, L.L.; Abdullah, S.M.U.; Chan, W.M.; Chan, B.P.; Ip, J.D.; Chu, A.W.; Lu, L.; Zhang, X.; Zhao, Y.; Chuang, V.W.; et al. Contribution of low population immunity to the severe Omicron BA.2 outbreak in Hong Kong. *Nat. Commun.* **2022**, *13*, 3618. [CrossRef]
18. Cheung, K.S.; Chan, E.W.; Wong, A.Y.S.; Chen, L.; Wong, I.C.K.; Leung, W.K. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: A population-based study. *Gut* **2018**, *67*, 28–35. [CrossRef] [PubMed]
19. Cheung, K.S.; Chen, L.; Chan, E.W.; Seto, W.K.; Wong, I.C.K.; Leung, W.K. Statins reduce the progression of non-advanced adenomas to colorectal cancer: A postcolonoscopy study in 187 897 patients. *Gut* **2019**, *68*, 1979–1985. [CrossRef] [PubMed]
20. Tuty Kuswardhani, R.A.; Henrina, J.; Pranata, R.; Anthonius Lim, M.; Lawrensia, S.; Suastika, K. Charlson comorbidity index and a composite of poor outcomes in COVID-19 patients: A systematic review and meta-analysis. *Diabetes Metab. Syndr.* **2020**, *14*, 2103–2109. [CrossRef]
21. To, K.K.; Chan, W.M.; Ip, J.D.; Chu, A.W.; Tam, A.R.; Liu, R.; Wu, A.K.; Lung, K.C.; Tsang, O.T.; Lau, D.P.; et al. Unique Clusters of Severe Acute Respiratory Syndrome Coronavirus 2 Causing a Large Coronavirus Disease 2019 Outbreak in Hong Kong. *Clin. Infect. Dis.* **2021**, *73*, 137–142. [CrossRef]
22. Chan, W.M.; Ip, J.D.; Chu, A.W.; Tse, H.; Tam, A.R.; Li, X.; Kwan, M.Y.; Yau, Y.S.; Leung, W.S.; Chik, T.S.; et al. Phylogenomic analysis of COVID-19 summer and winter outbreaks in Hong Kong: An observational study. *Lancet Reg. Health West Pac.* **2021**, *10*, 100130. [CrossRef] [PubMed]
23. Kwok, W.C.; Wong, C.K.; Ma, T.F.; Ho, K.W.; Fan, L.W.; Chan, K.F.; Chan, S.S.; Tam, T.C.; Ho, P.L. Modelling the impact of travel restrictions on COVID-19 cases in Hong Kong in early 2020. *BMC Public Health* **2021**, *21*, 1878. [CrossRef]
24. Bihari, S.; Prakash, S.; Dixon, D.L.; Cavallaro, E.; Bersten, A.D. Induced hypernatremia in patients with moderate-to-severe ARDS: A randomized controlled study. *Intensive Care Med. Exp.* **2021**, *9*, 33. [CrossRef]
25. Bihari, S.; Dixon, D.L.; Lawrence, M.D.; Bersten, A.D. Induced hypernatraemia is protective in acute lung injury. *Respir. Physiol. Neurobiol.* **2016**, *227*, 56–67. [CrossRef] [PubMed]
26. Safdar, Z.; Wang, P.; Ichimura, H.; Issekutz, A.C.; Quadri, S.; Bhattacharya, J. Hyperosmolarity enhances the lung capillary barrier. *J. Clin. Investig.* **2003**, *112*, 1541–1549. [CrossRef] [PubMed]
27. Quadri, S.K.; Bhattacharjee, M.; Parthasarathi, K.; Tanita, T.; Bhattacharya, J. Endothelial barrier strengthening by activation of focal adhesion kinase. *J. Biol. Chem.* **2003**, *278*, 13342–13349. [CrossRef]
28. Safdar, Z.; Yiming, M.; Grunig, G.; Bhattacharya, J. Inhibition of acid-induced lung injury by hyperosmolar sucrose in rats. *Am. J. Respir Crit. Care Med.* **2005**, *172*, 1002–1007. [CrossRef]

29. Sarahian, S.; Pouria, M.M.; Ing, T.S.; Sam, R. Hypervolemic hypernatremia is the most common type of hypernatremia in the intensive care unit. *Int. Urol. Nephrol.* **2015**, *47*, 1817–1821. [CrossRef]
30. Yanagawa, Y.; Omori, K.; Obinata, M.; Ohsaka, H.; Ishikawa, K.; Kitamura, S.; Kitagawa, Y.; Ihara, Y. Significance of hypernatremia following the correction of severe hyperglycemia. *Am. J. Emerg. Med.* **2014**, *32*, 800–801. [CrossRef]

Journal of
Clinical Medicine

MDPI

Article

Age and Comorbidity Burden of Patients Critically Ill with COVID-19 Affect Both Access to and Outcome of Ventilation Therapy in Intensive Care Units

Marie Louise de Hesselle [1], Stefan Borgmann [2], Siegbert Rieg [3], Jörg Janne Vehreschild [4,5,6], Sebastian Rasch [7], Carolin E. M. Koll [5,6], Martin Hower [8], Melanie Stecher [5,6], Daniel Ebert [1], Frank Hanses [9,†], Julia Schumann [1,*,†] and on behalf of the LEOSS Study Group [‡]

[1] University Clinic and Outpatient Clinic for Anesthesiology and Operative Intensive Care, University Medicine Halle (Saale), 06112 Halle (Saale), Germany
[2] Department of Infectious Diseases and Infection Control, Ingolstadt Hospital, 85049 Ingolstadt, Germany
[3] Department of Medicine II, University of Freiburg, 79106 Freiburg, Germany
[4] Department II of Internal Medicine, Hematology/Oncology, Goethe University Frankfurt, 60323 Frankfurt, Germany
[5] Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, 50931 Cologne, Germany
[6] German Center for Infection Research (DZIF), Partner Site Bonn-Cologne, 50937 Cologne, Germany
[7] Department of Internal Medicine II, University Hospital Rechts der Isar, School of Medicine, Technical University of Munich, 81675 Munich, Germany
[8] Department of Pneumology, Infectious Diseases, Internal Medicine and Intensive Care, Klinikum Dortmund GmbH, 44137 Dortmund, Germany
[9] Emergency Department and Department for Infection Control and Infectious Diseases, University Hospital Regensburg, 93053 Regensburg, Germany
* Correspondence: julia.schumann@uk-halle.de; Tel.: +49-345-557-1776
† These authors contributed equally to this work.
‡ Membership of the LEOSS Study Group is provided in the Acknowledgments.

Citation: de Hesselle, M.L.; Borgmann, S.; Rieg, S.; Vehreschild, J.J.; Rasch, S.; Koll, C.E.M.; Hower, M.; Stecher, M.; Ebert, D.; Hanses, F.; et al. Age and Comorbidity Burden of Patients Critically Ill with COVID-19 Affect Both Access to and Outcome of Ventilation Therapy in Intensive Care Units. *J. Clin. Med.* **2023**, *12*, 2469. https://doi.org/10.3390/jcm12072469

Academic Editors: Filippo Migliorini and Riccardo Giorgino

Received: 28 February 2023
Accepted: 20 March 2023
Published: 24 March 2023

Abstract: During the COVID-19 pandemic, large numbers of elderly, multimorbid people required treatment in intensive care units. This study investigated how the inherent patient factors age and comorbidity burden affected the treatment strategy and the outcome achieved. Retrospective analysis of data from intensive care patients enrolled in the Lean European Open Survey on SARS-CoV2-Infected Patients (LEOSS) cohort found that a patient's age and comorbidity burden in fact influenced their mortality rate and the use of ventilation therapy. Evidence showed that advanced age and multimorbidity were associated with the restrictive use of invasive ventilation therapies, particularly ECMO. Geriatric patients with a high comorbidity burden were clustered in the subcohort of non-ventilated ICU patients characterized by a high mortality rate. The risk of death generally increased with older age and accumulating comorbidity burden. Here, the more aggressive an applied procedure, the younger the age in which a majority of patients died. Clearly, geriatric, multimorbid COVID-19 patients benefit less from invasive ventilation therapies. This implies the need for a holistic approach to therapy decisions, taking into account the patient's wishes.

Keywords: COVID-19; SARS-CoV-2; age; comorbidities; intensive care medicine; ventilation; ECMO; mortality

1. Introduction

Coronavirus disease 2019 (COVID-19), an infectious disease triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a pandemic. The disorder is characterized by a wide spectrum of clinical manifestations. This heterogeneity in clinical presentation points to host factors as a key to disease severity and progression [1].

Indeed, the elderly adult population and those with comorbidities are disproportionately affected by the COVID-19 pandemic in terms of hospitalizations and mortality [1–6]. There is an ongoing debate that the poor outcomes among senior adults may be the consequence of a high prevalence of comorbidities, a weak immune system, and a greater degree of frailty in this population [4,5,7,8]. An in-depth review of published data indicates that biological age, rather than chronological age, may play a role in COVID-19 prognosis [7,9–11]. The constriction of physiological reserves combined with an impaired ability to properly respond to acute challenges may translate into an increased susceptibility to stressors, such as a viral infection [5,6,12]. Frailty is not a mandatory component of the aging process. Rather, numerous adults attain a high age without being frail. The frail elderly population represents a specific patient group, which, compared to the general population, is characterized by a compromised immune system, a diminished diversity of the gut microbiota, and a persistent state of inflammation [4,5,11]. Accumulating evidence in the literature suggests that those factors collectively contribute to the severity of the COVID-19 disease and the high mortality rate [4,5,11].

The management of critically ill COVID-19 patients is another influencing factor that is still understudied. The COVID-19 pandemic led to a massive influx of patients into hospitals and especially intensive care units (ICUs). Due to limited ICU capacity, criteria for ICU admission and use of mechanical ventilation or extracorporeal membrane oxygenation (ECMO) were frequently tightened [2,5]. This may have had a particular impact on elderly and comorbid patients. Reports indicate that medical staff awareness of a patient's advanced age and frailty may result in a curtailment of intensive care measures [2,6,10]. By implication, such special handling of a certain group of patients will affect the treatment outcome.

The disproportionate need for intensive care in frail older adults following SARS-CoV-2 infection contrasts with the limited number of studies that have examined the intensive care management of these patients in detail. The present study aimed to retrospectively highlight the potential influence of patient-specific determinants, i.e., age and comorbidity burden. The primary objective was to determine whether the decision for a ventilation regimen in the ICU was indeed co-determined by these intrinsic patient factors. The secondary objective was to assess whether and to what extent age and comorbidity burden were related to treatment outcome, with a separate assessment for ventilation regimes. Such knowledge is crucial for developing targeted interventions and deriving appropriate recommendations for action.

2. Materials and Methods

2.1. Patient Cohort

The study was based on a cohort from the Lean European Open Survey on SARS-CoV-2-Infected Patients (LEOSS) [13]. The LEOSS project was established in March 2020 as a non-interventional, multicenter network focusing on data from hospitalized COVID-19 patients. A prerequisite for enrollment in the LEOSS registry was a confirmed diagnosis of COVID-19 disease (PCR or rapid antigen test as an acceptable alternative). More detailed information about LEOSS may be obtained from the project's website (https://leoss.net, accessed on 8 March 2023) or the German Clinical Trials Register (DRKS, No. S00021145).

Anonymized patient data were retrospectively entered into the LEOSS registry upon termination of acute care, i.e., either when the treatment was finished or when the patient was deceased. The clinical data were reported by an electronic case report form (eCRF) utilizing an online platform, ClinicalSurveys.net, developed by the University Hospital Cologne (UHC), Germany, and hosted by QuestBack, Oslo, Norway, on servers at the UHC [14]. To guarantee anonymity throughout the entire analysis, a customized LEOSS scientific use file (SUF) was created based on the principles of the LEOSS public use file (PUF) described in Jakob et al. [14]. Both vertical (categorical scoring of numeric variables) and horizontal data aggregation (data aggregation within disease phases) were used to prevent re-identification. Four phases were used for categorization, which can be broadly

characterized as asymptomatic/mild symptoms (uncomplicated phase), a need for oxygen supplementation (complicated phase), a need for critical care (critical phase), and the recovery phase. An in-depth description of the clinical phase definition as well as of the recorded data items are available on https://leoss.net (accessed on 8 March 2023) and in [15]. Patients of all ages were included. Age was recorded categorically. Age ranges were defined so that cases of adult patients could be examined in 10-year increments. For pediatric patients, smaller age increments were considered to reflect differences in developmental stages between age groups.

2.2. Study Design

The LEOSS case registry collects patient data from study sites in Austria, Belgium, Bosnia and Herzegovina, Germany, Italy, Latvia, Spain, Switzerland, Turkey, and the United Kingdom, with the vast majority of data coming from Germany. The present study focused on intensive care at the beginning of the COVID-19 pandemic, which was characterized by a health system overload (first wave of the pandemic until the transition to the second wave, i.e., March to October 2020 in Germany). To this end, all patients treated at either of the LEOSS partner centers between 23 March 2020 and 12 October 2020, who entered the critical phase as defined by the LEOSS database [15] at some point within onset of their COVID-19 disease, were fully enrolled, allowing a total number of 840 patients to be included. Critical phase was declared when at least one of the indicated criteria was met: the need for catecholamines, life-threatening cardiac arrhythmias, the need for unplanned mechanical ventilation (invasive or non-invasive), prolongation (>24 h) of planned mechanical ventilation, liver failure with Quick < 50% or INR > 3.5, a qSOFA score of $\geq$2, or acute renal failure with a need for dialysis. Interest was focused on a potential influence of age and comorbidity burden on the applied ventilation strategy and patient outcome. To this end, of the specific critical care data elements available from the LEOSS registry, the following data elements were analyzed: (i) patient characteristics (age, comorbidities, Charlson comorbidity index), (ii) the ventilation treatments performed (no ventilation, non-invasive ventilation, invasive ventilation, ECMO), and (iii) the outcome (recovery, in-hospital mortality).

2.3. Data Quality

To ensure the quality of the data, several plausibility checks were built into the eCRF during its construction, which generate warning messages in case of incorrect entries. In addition, medical staff from the LEOSS centers and the project group checked the accuracy and plausibility of the data both during entry and prior to data analysis.

There was no missing data regarding the following parameters analyzed: type of ventilation therapy, Charlson comorbidity index, and number of comorbidities. For the parameters age and outcome, the proportion of missing data was low (0.7% and 1.1%, respectively) and of the MCAR type (missing completely at random). In the statistical analysis, the missing was accepted and the corresponding cells were left blank.

2.4. Statistical Analysis

All data handling, the statistical analysis, and numerical calculations were performed with R (R Development Core Team, Vienna, Austria, version 4.1.1, 2021). Data were all reported as categorical variables (numbers and percentages). Survival was analyzed using Kaplan–Meier curves and log rank test. In addition, Cox regression was used to study the association between ventilation regime and survival, taking as reference the variable invasive ventilation with the largest size. Both univariate analysis and multivariable Cox regression were performed, adjusting for the potential confounders of age, number of comorbidities, and Charlson comorbidity index. Results were presented as hazard ratio (HR) with 95% confidence interval (CI). A log rank value $p < 0.05$ was considered for statistical significance.

3. Results

3.1. Characteristics of the Study Population

The study was based on aggregate SARS-CoV-2-positive patients admitted to an intensive care unit of a LEOSS study center during the study period (n = 840; Figure 1). The absolute majority of patients were Caucasian. There was also a clustering of patients of male gender and of patients older than 45 years of age. Median age was 66 to 75 years. The number of comorbidities documented for an individual patient ranged from 0 to 14, with only 13.9% of patients having no reported comorbidities and 22.0% of patients having only one reported comorbidity. More details of comorbidities are provided in Table 1. Normal weight was present in 25.2% of patients. In 73.4% of cases, BMI was elevated (>24.9), whereas underweight (BMI < 18.5) was seen in as few as 1.4% of cases. Median BMI was 25 to 29.9. Ventilation therapies performed included non-invasive ventilation (10.4%; 87/840; type of non-invasive ventilation not specified), invasive ventilation (58.5%; 492/840), and ECMO (13.6%; 114/840). A total of 147 patients (17.5%) did not receive any ventilation therapy. The documented duration of ventilation therapy ranged from 0 to 9 weeks. Treatment was performed in prone position in 8.0% of non-invasively ventilated patients, 62.0% of invasively ventilated patients, and 81.6% of ECMO-treated patients. In general, intensive care treatment was required for a period of 0 to 3 weeks in the majority of patients (66.2% of cases), but lengths of treatment of up to 10 weeks have also been recorded. The overall in-hospital mortality rate was 46.0%, with increased mortality specifically in the non-ventilated group (53.7%; 79/147) and the ECMO group (62.3%; 71/114).

Table 1. Comorbidities of the study cohort (n = 840).

Comorbidity	No. (%)
Hypertension	512 (61.0)
Diabetes without end-organ damage	155 (18.5)
Chronic kidney disease	145 (17.3)
Coronary artery disease	140 (16.7)
Atrial fibrillation	134 (16.0)
Chronic heart failure	94 (11.2)
Chronic obstructive pulmonary disease (COPD)	83 (9.9)
Diabetes with end-organ damage	81 (9.6)
Acute kidney injury	80 (9.5)
Cerebrovascular disease	78 (9.3)
Solid tumor	73 (8.7)
Myocardial infarction	64 (7.6)
Dementia	63 (7.5)
Chronic pulmonary disease	51 (6.1)
Peripheral vascular disease	42 (5.0)
On dialysis	34 (4.0)
Asthma	31 (3.7)
Carotid artery disease	31 (3.7)
Rheumatic disease	30 (3.6)
Hemiplegia	27 (3.2)
Lymphoma	27 (3.2)
Atrioventricular block	25 (3.0)
Chronic liver disease	25 (3.0)
Organ transplantation	20 (2.4)
Peptic ulcer	20 (2.4)
Aortic stenosis	18 (2.1)
Leukemia	15 (1.8)
Solid tumor, metastasized	12 (1.4)
Liver cirrhosis	7 (0.8)

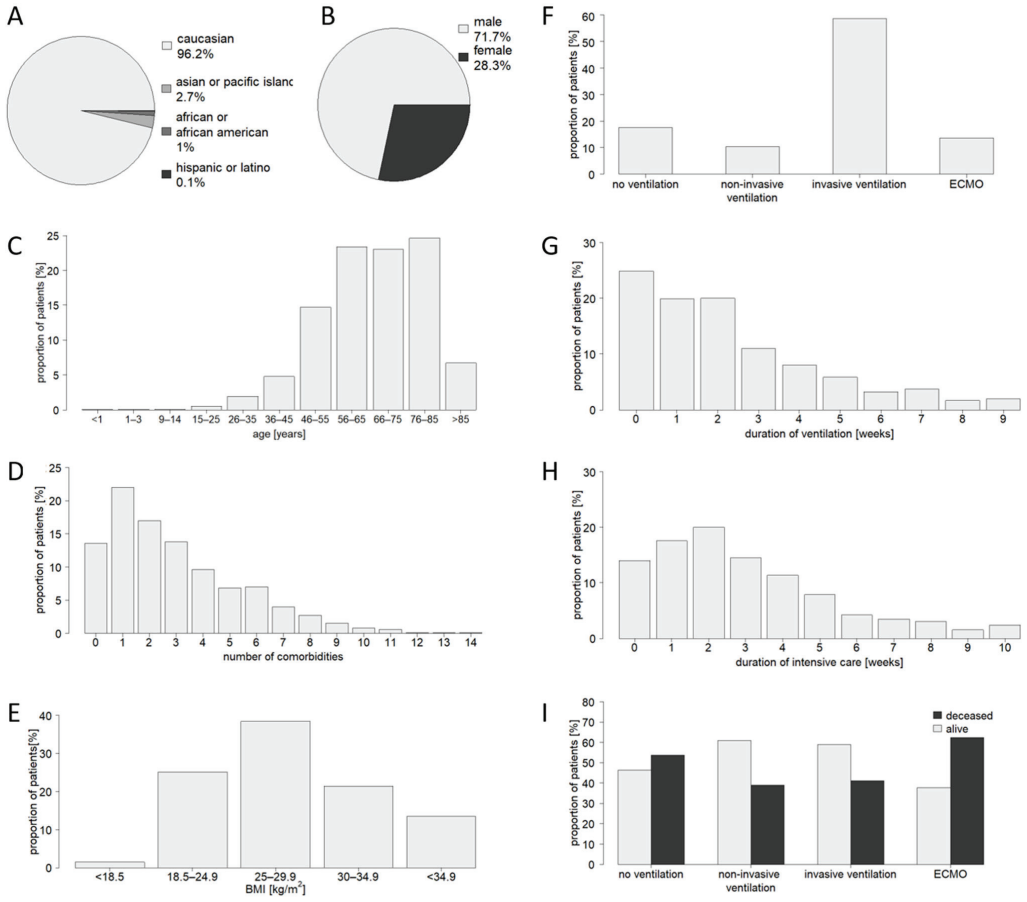


Figure 1. Characteristics of the study cohort (n = 840). (**A**): Ethnic distribution, (**B**): gender distribution, (**C**): age distribution, (**D**): distribution of comorbidity burden, (**E**): BMI distribution, (**F**): frequency of use of certain ventilation therapies, (**G**): duration of ventilation, (**H**): duration of intensive care, (**I**): hospital outcome by treatment group.

3.2. Patient Age and Comorbidity Influence the Ventilation Strategy in Critical Care

Ventilation strategy is based on acute respiratory distress syndrome (ARDS) severity while considering clinical factors, such as organ dysfunction and frailty. The majority of intubated patients (73%) had moderate to severe ARDS (PaO2/FiO2 < 200 mmHg), while non-invasively ventilated patients had predominantly mild ARDS (PaO2/FiO2 200–300 mmHg). No non-invasively ventilated patients with severe ARDS were documented. Patients who were intubated also had more severe organ failure. Median sequential organ failure assessment (SOFA) scores were 12 for ECMO patients and 9.5 for invasively ventilated patients. A median SOFA score of three was documented in the non-ventilated and non-invasively ventilated groups. Data on frailty, as rated by the clinical frailty scale (CFS), were not available. Thus, patient age and comorbidity burden were used to assess the potential influence of patient factors on treatment decisions.

In the group of non-ventilated patients, there was a distinct rightward shift to higher age (Figure 2). In contrast, in the group of ECMO patients, a leftward shift to lower age was found and no patients of advanced age (>85 years) underwent ECMO procedure. Moreover, the majority of this patient group (58.9% of cases) was also not ventilated despite

critical illnesses. It is also noted that in the few documented pediatric patients receiving intensive care, no ventilation was performed up to the age of 3 years. Substantial disparities were also observed with respect to Charlson comorbidity index (Figure 3). A widespread range of Charlson comorbidity index was found in the group of non-ventilated patients. However, in ventilated patients, there was a leftward shift to lower Charlson comorbidity index values with increasing invasiveness of therapy. Specifically, this was evident in the group of ECMO patients, indicating a cautious use of high-invasive ventilation techniques in a setting of severe morbidity burden. Actually, the group of ECMO patients was characterized by a below-average comorbidity burden (Figure 4). No comorbidities were found in 24.6% of cases and only one comorbidity in 29.8% of cases. The maximum number of comorbidities reported for individual ECMO patients was seven (compared with fourteen in the non-ventilated group, eleven in the non-invasively ventilated group, and twelve in the invasively ventilated group). Although this seems contradictory at first, this observation might relate to the age structure of this patient cohort. Patients of advanced age (>85 years), typically characterized by a high comorbidity burden, were primarily treated non-invasively and did not receive ECMO therapy in any case. Overall, the data suggested a preselection in treatment decisions. Unfortunately, the LEOSS dataset does not include information on advance directives. Thus, it is not possible to assess the extent to which the observed differences are due to a possible higher proportion of patient-desired limitation of life-sustaining measures (LLST) in elderly, multimorbid patients.

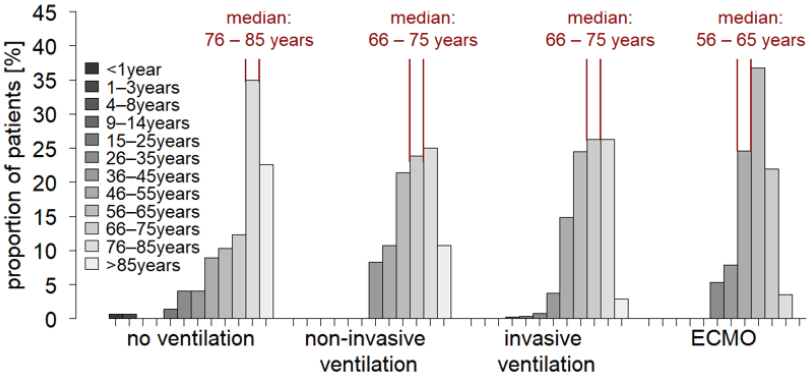


Figure 2. Distribution of age in COVID-19 patients in intensive care grouped by ventilation therapy received (total cohort, n = 840).

3.3. Patient Age and Comorbidity Have an Impact on the Outcome of Critical Care Treatment

In total, 386 of 840 patients (46.0%) died during their hospitalization with differences between ventilation groups: death was significantly more common in non-ventilated patients and ECMO-treated patients compared to patients receiving non-invasive or invasive ventilation (Figure 5A). Indeed, univariate analysis showed an effect of ventilation regimen on mortality (Figure 5B). This is also reflected in the documented 30-day mortality and median survival time for the treatment groups (Table 2). While the majority of both non-invasively and invasively ventilated patients reached the recovery phase, the median survival time of ECMO-treated patients was 35 days and that of non-ventilated patients was only 13 days.

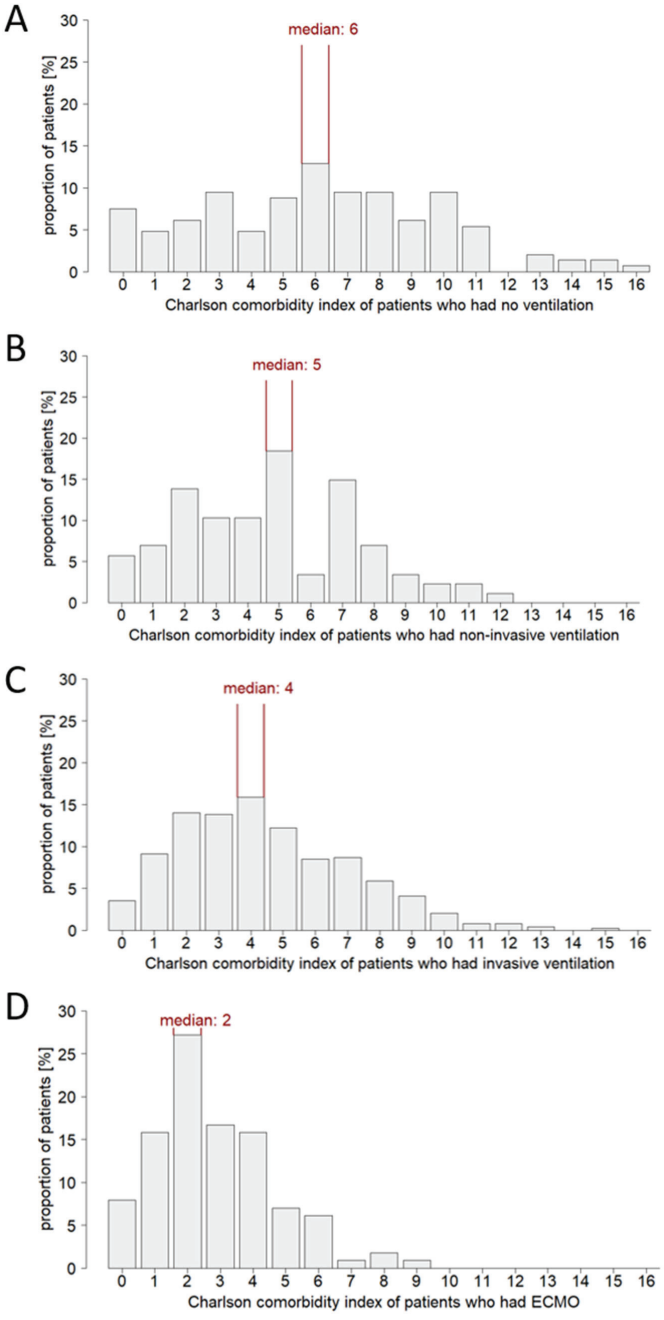


Figure 3. Distribution of the Charlson comorbidity index in COVID-19 patients receiving intensive care. (**A**): Sub-cohort of non-ventilated patients (n = 147), (**B**): sub-cohort of non-invasively ventilated patients (n = 87), (**C**): sub-cohort of invasively ventilated patients (n = 492), (**D**): sub-cohort of ECMO patients (n = 114).

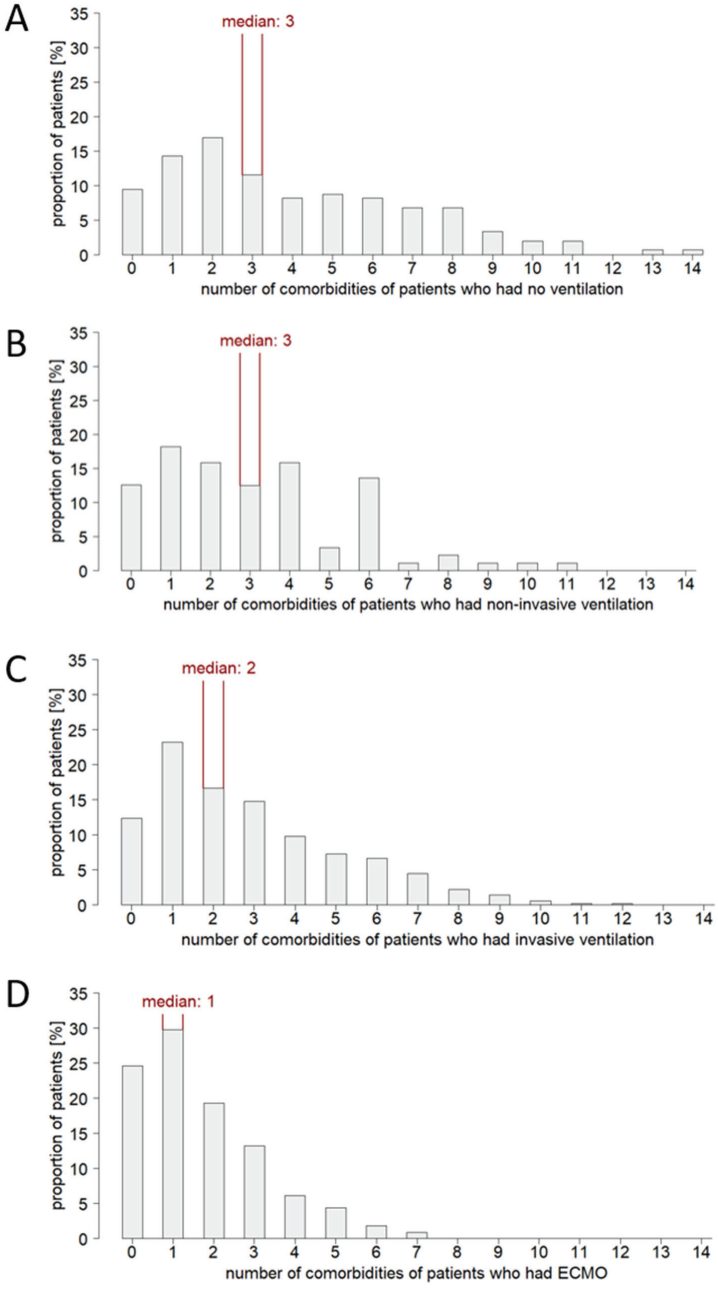


Figure 4. Distribution of the number of comorbidities in COVID-19 patients receiving intensive care. (**A**): Sub-cohort of non-ventilated patients (n = 147), (**B**): sub-cohort of non-invasively ventilated patients (n = 87), (**C**): sub-cohort of invasively ventilated patients (n = 492), (**D**): sub-cohort of ECMO patients (n = 114).

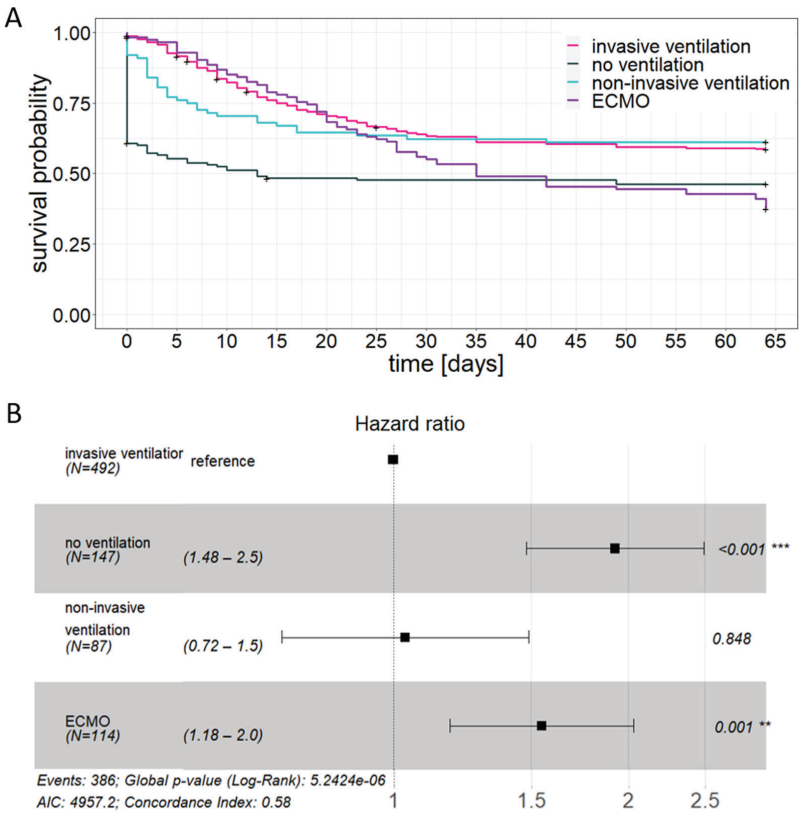


Figure 5. Association between ventilation regime and survival. (**A**): Unadjusted Kaplan–Meier analysis, (**B**): Forest plot depicting univariate Cox regression. ** $p < 0.01$, *** $p < 0.001$.

Table 2. Median survival time and 30-day mortality by ventilation therapy received before and after adjustment for the confounding factors age, Charlson comorbidity index, and number of comorbidities.

	Median Survival Time [Days]		**30-Day Mortality [%]**	
	unadjusted	adjusted	unadjusted	adjusted
no ventilation	13	-	52.4	38.6
non-invasive ventilation	-	-	37.7	28.4
invasive ventilation	-	-	36.6	34.5
ECMO	35	26	44.9	57.5

Multivariable adjustment for clinical variables demonstrated that, in addition to the well-known confounders "ARDS severity" (HR horovitz index: 1.279; 95% CI 1.034–1.582) and "organ dysfunction" (HR SOFA score: 1.072; 95% CI 1.006–1.142), age and comorbidity burden also have an influence (Figure 6A). Accordingly, Kaplan–Meier survival analysis adjusted by the confounding factors age, Charlson comorbidity index, and number of comorbidities, revealed distinct alterations regarding 30-day mortality and median survival time, which specifically concerned the non-ventilated and the ECMO-treated patients (Figure 6B, Table 2). A median survival time could only be determined for the ECMO-treated group and was reduced to 26 days. In contrast, the adjusted 30-day mortality of the non-ventilated group approached that of the invasively ventilated group.

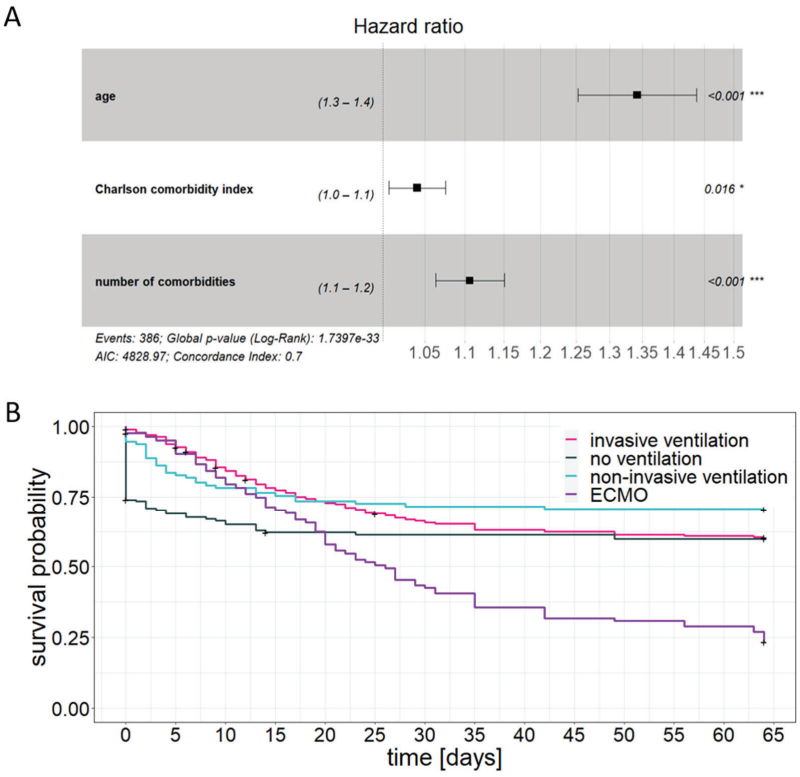


Figure 6. Confounding factors age, Charlson comorbidity index, and number of comorbidities. (**A**): Forest plot depicting multivariable Cox regression, (**B**): adjusted Kaplan–Meier analysis. * $p < 0.05$, *** $p < 0.001$.

The impact of age on outcome is clearly seen when comparing the age distribution of deceased and recovered patients. The risk of death in hospital increases with age regardless whether patients were ventilated non-invasively, invasively, or additionally treated by ECMO. However, depending on the invasiveness of the therapy, there was a shift in the age at which the turning point in the ratio between recovered and deceased patients was reached (Figure A1). While in the group of non-invasively ventilated patients, a majority of deaths were documented only from the age >85 years, whereas in the group of invasively ventilated patients, this was already the case from the age group 76–85 years, and in ECMO patients from the age group 46–55 years.

The comparison of deceased and recovered patients also reveals the influence of comorbidity burden on outcome. For COVID-19 patients with no or only one documented comorbidities, the proportion who reached the recovery phase was higher than the proportion who died. However, starting with a documented number of two comorbidities, this ratio reversed (Figure A2A). Likewise, a rightward shift of the Charlson comorbidity index to higher values was observed in deceased patients compared to recovered patients (Figure A2B). In the recovered group, values ranging from 0 to 12 were documented, with the majority of patients (21.1%) having a Charlson comorbidity index of two. This contrasts with the group of deceased patients, where a Charlson comorbidity index of two was documented in only 6.7%, and values as high as sixteen were reported. The association between a high number of comorbidities or a high Charlson comorbidity index and an increased mortality risk was evident for all sub-cohorts by ventilation type. Certain comorbidities clustered in patients who died of COVID-19. These were primarily cardiovascular comor-

bidities (chronic heart failure, atrial fibrillation, coronary artery disease, aortic stenosis, and hypertension). However, pulmonary comorbidities (chronic lung disease) and metastatic solid tumors were also significantly more common in deceased patients.

4. Discussion

The present study addressed the impact of the inherent factors of critically ill patients with COVID-19, namely age and comorbidity burden, on the ventilation therapy applied on ICU as well as treatment outcome. The resulting data underscore the relevance of both confounding factors. Remarkably, the influence was twofold. First, highly advanced age and multimorbidity were associated with the restrictive use of invasive ventilation therapies, specifically ECMO. This may have contributed to the relatively high mortality observed in the sub-cohort of non-ventilated ICU patients. On the other hand, as invasiveness of ventilation therapy increased, the age at which treatment was successfully completed by the majority of patients declined.

The S3 guideline "Recommendations for inpatient therapy of patients with COVID-19" (AWMF registry number 113/001; [16]), which applies in Germany and therefore to the majority of patients in the LEOSS registry, recommends an apparatus-based therapy escalation in acute respiratory failure due to COVID-19. In case of progressive deterioration of gas exchange and increased oxygen demand (PaO2/FiO2 < 150 mmHg and respiratory rate >30/min) accompanied by organ dysfunction, intubation and invasive ventilation should be considered. The implementation of these recommendations is reflected in the study cohort. The majority of patients with severe ARDS and a high degree of organ dysfunction were intubated. However, the data also suggest that not only disease severity, but also age and comorbidity burden may have contributed to the treatment choice. ECMO was limited for patients older than 3 years and younger than 85 years. In contrast, a clustering of individuals older than 76 years was observed in the sub-cohort of non-ventilated patients. A shift was also seen in terms of patient comorbidity burden: the more invasive a ventilation option, the lower the comorbidity burden of the patients receiving it. Thus, in the sub-cohort of non-ventilated patients, individuals with a Charlson comorbidity index up to 16 and a total number of documented comorbidities up to 14 were found. In the sub-cohort of ECMO patients, however, the maximum Charlson comorbidity index was nine and the maximum comorbidity count was seven. Apparently, geriatric, multimorbid patients were treated less aggressively without exhausting all treatment options. One can assume that the limited ICU capacities in the first acute COVID-19 pandemic wave added to the reserved usage of invasive ventilation. On the other hand, it is known that about 50% of the elderly population (>60 years) in Germany has composed an advance directive [17]. Therefore, it can be speculated that the limited use of mechanical ventilation in this patient group was primarily in response to patient wishes rather than based on a physician triage system. In fact, a recent study of elderly ($\geq$80 years) ICU patients reported more frequent withholding or withdrawal of life-sustaining measures in COVID-19 patients compared to non-COVID-19 patients [18]. The same study also found an increased 30-day mortality in COVID-19 patients compared to non-COVID-19 patients. However, it remains unclear whether this finding reflects a more active policy of withholding treatment or an inherent increased mortality risk due to COVID-19 [18]. Overall, these findings highlight the need for comprehensive research on LLST. Critical care databases should include advance directives as a mandatory data point. Healthcare professionals' assessment of a patient's risk-benefit profile may be another factor which is worthy of discussion. In the S3 guideline referred to above, it is stated that clinical factors, including age and comorbidities, should be considered when deciding whether to intubate a patient [16]. In addition to the assessment of severity, frailty is often used as a decision-making aid [2,19,20]. This approach raises the question of whether age and multimorbidity are not only risk factors for needing intensive care [1–6,8,21–24], but also influence the success of certain intensive care interventions.

The present study clearly demonstrates that age and comorbidity burden affect the outcome of intensive care treatment of COVID-19 patients. Remarkably, the age at which treatment could be completed with survival in the majority of patients was observed to shift in relation to the invasiveness of the ventilation therapy performed: the more invasive a ventilation option, the earlier the turning point was reached. Apparently, age, therapeutic intervention, and treatment success were interlinked. A critical factor for treatment success is a patient's disease severity. Mechanical ventilation and, even more so, ECMO are used in patients with a serious course of disease, which per se implies an elevated mortality risk. Multiple mechanisms discussed to contribute to more severe disease progression are age-associated. These include pre-existing malfunctions, immune senescence, age-related limitations of lung function, the coagulation system, and the endothelial barrier, as well as imbalances in nutritional status and intestinal dysbiosis, which are more common in the elderly [4,5,7,8]. Another influencing factor is the violence of the therapy performed. With the increasing invasiveness of a treatment, the probability of undesirable side effects rises, which may negatively affect the outcome. It is known that advanced age elevates the risk of such side effects [10]. Therefore, the harm–benefit balance of invasive ventilation strategies becomes rather critical with age.

The group of non-ventilated patients was characterized by a high proportion of very old, multimorbid individuals and also by a substantial mortality rate. The available data do not allow us to conclusively determine whether a more aggressive treatment of these patients would have been associated with better outcomes. Nonetheless, the findings of this study underscore the importance of a holistic approach in decision-making to ensure that treatment is proportionate and meets the patient's wishes. Advanced age is a relative (not an absolute) contraindication to the use of ECMO, although no threshold has been established [25]. In general, the decision to use invasive ventilation therapies, such as mechanical ventilation or ECMO, should be made after careful consideration of potential benefits and harms, especially in patients of advanced age [25,26]. Chronological age is not a good indicator of outcome here. Rather, the patient's health status should also be considered. Accordingly, the frailty of a patient is discussed as a suitable prognostic marker [2,4–7,9,11,27]. Specifically, the use of the clinical frailty scale (CFS) is recommended for priority setting, decision-making, and pandemic triage [2,4,6,9,11]. As a caveat, focusing on CFS (in analogy to the traditional focus on patient age) has the potential to perpetuate established patterns of inequity. This is especially true for older, frail individuals who desire comprehensive intensive care. The extent to which CFS played a role in decision-making in the study population cannot be estimated because CFS data were not available from the patients.

Our analyses based on LEOSS have the advantage of a standardized protocol and data from different regions and sectors. However, the majority of patients included were from Germany, limiting the generalizability of our results. A clear limitation of our study is its retrospective observational nature. The LEOSS registry did not collect data on patients' frailty as assessed by CFS. The lack of knowledge about whether patients were frail and to what extent severely limits the interpretation of the data. Information on the type of non-invasive ventilation used was also not available. It was not possible to determine the prevalence of advance directives among ICU patients because this element was included in LEOSS at a later stage. Our data represent patients recruited during the first pandemic wave. The extent to which the data are different from patients who were in intensive care for SARS-CoV-2 infection later in the pandemic is unknown but may be of interest for investigation.

5. Conclusions

Our study highlights the impact of age and comorbidity burden on the outcome of COVID-19 patients receiving intensive care. Our data further point toward a relationship between the type and invasiveness of a therapeutic measure, the patient age, and the outcome. The more aggressive an applied procedure, the younger the age in which a

majority of patients died in hospital. In addition, our study spotlights that specifically geriatric and multimorbid patients are predominately excluded from invasive ventilation regimens, such as ECMO, thus precluding an assessment of the potential benefit of these therapeutic approaches for that patient population.

Author Contributions: Conceptualization, S.B., D.E. and J.S.; methodology, S.B. and J.S.; validation, M.L.d.H., D.E. and J.S.; formal analysis, M.L.d.H. and J.S.; investigation, M.L.d.H., D.E. and J.S.; data curation, S.B., S.R. (Siegbert Rieg), J.J.V., S.R. (Sebastian Rasch), C.E.M.K., M.H., M.S., F.H. and LEOSS Study Group; writing—original draft preparation, J.S.; writing—review and editing, M.L.d.H., S.B. and D.E.; visualization, M.L.d.H.; supervision, J.S.; project administration, J.S. All authors have read and agreed to the published version of the manuscript.

Funding: The LEOSS registry was supported by the German Centre for Infection Research (DZIF) and the Willy Robert Pitzer Foundation.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. Approval for LEOSS was obtained by the applicable local ethics committees of all participating centers and registered at the German Clinical Trails Register (DRKS, No. S00021145).

Informed Consent Statement: Patient consent was waived as the study was based on a scientific use file (SUF) generated from the Lean European Open Survey on SARS-CoV-2-Infected Patients (LEOSS) registry. For the LEOSS database, data collection was performed fully anonymized, only once per case, and retrospectively after treatment had finished or the patient had died.

Data Availability Statement: Patient data from the LEOSS registry are subject to the LEOSS governance, data use, and access policy (policy text available on https://leoss.net, accessed on 8 March 2023).

Acknowledgments: We express our deep gratitude to all study teams supporting the LEOSS study. The LEOSS study group contributed at least 5 per mille to the analyses of this study: University Hospital Regensburg (Frank Hanses), University Hospital Freiburg (Siegbert Rieg), Technical University of Munich (Christoph Spinner), Hospital Ingolstadt (Stefan Borgmann), Klinikum Dortmund gGmbH, Hospital of University Witten/Herdecke (Martin Hower), University Hospital Frankfurt (Maria Vehreschild), University Hospital Wuerzburg (Nora Isberner), University Hospital Tuebingen (Siri Göpel), Hospital Maria Hilf GmbH Moenchengladbach (Juergen vom Dahl), University Hospital Augsburg (Christoph Roemmele), University Hospital Jena (Maria Madeleine Ruethrich), University Hospital Cologne (Norma Jung), University Hospital Erlangen (Richard Strauss), University Hospital Ulm (Beate Gruener), Hospital Bremen-Center (Christian Hohmann), Hospital Ernst von Bergmann (Lukas Tometten), Hospital Passau (Julia Lanznaster), University Hospital Saarland (Robert Bals), Municipal Hospital Karlsruhe (Christian Degenhardt), University Hospital Duesseldorf (Bjoern-Erik Jensen), University Hospital Heidelberg (Uta Merle), Johannes Wesling Hospital Minden Ruhr University Bochum (Kai Wille), University Hospital Dresden (Katja de With), Bundeswehr Hospital Koblenz (Dominic Rauschning), University Hospital of Giessen and Marburg (Janina Trauth), University Hospital Essen (Sebastian Dolff), University Hospital Schleswig-Holstein Kiel (Anette Friedrichs), Elbland Hospital Riesa (Joerg Schubert), Malteser Hospital St. Franziskus Flensburg (Milena Milovanovic), Marien Hospital Herne Ruhr University Bochum (Timm Westhoff), Clinic Munich (Wolfgang Guggemos), Catholic Hospital Bochum (St. Josef Hospital) Ruhr University Bochum (Kerstin Hellwig), Practice for general medicine Elisabeth Schroedter & Gabriele Mueller-Joerger Kuenzelsau (Gabriele Mueller-Joerger), Hospital Universitari Arnau de Vilanova (Juan Antonio Schoenenberger-Arnaiz), Hospital Braunschweig (Jan Kielstein), Hospital Leverkusen (Lukas Eberwein), University Hospital Munich/LMU (Michael von Bergwelt-Baildon), Agaplesion Diakonie Hospital Rotenburg (David Heigener), Thorax University Hospital Heidelberg (Felix Herth), Evangelisches Hospital Saarbruecken (Mark Neufang). The LEOSS study infrastructure group: Jörg Janne Vehreschild (Goethe University Frankfurt), Susana M. Nunes de Miranda (University Hospital of Cologne), Carolin E. M. Koll (University Hospital of Cologne), Melanie Stecher (University Hospital of Cologne), Lisa Pilgram (Goethe University Frankfurt), Nick Schulze (University Hospital of Cologne), Sandra Fuhrmann (University Hospital of Cologne), Annika Claßen (University Hospital of Cologne), and Bernd Franke (University Hospital of Cologne) und Fabian Praßer (Charité, Universitätsmedizin Berlin).

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

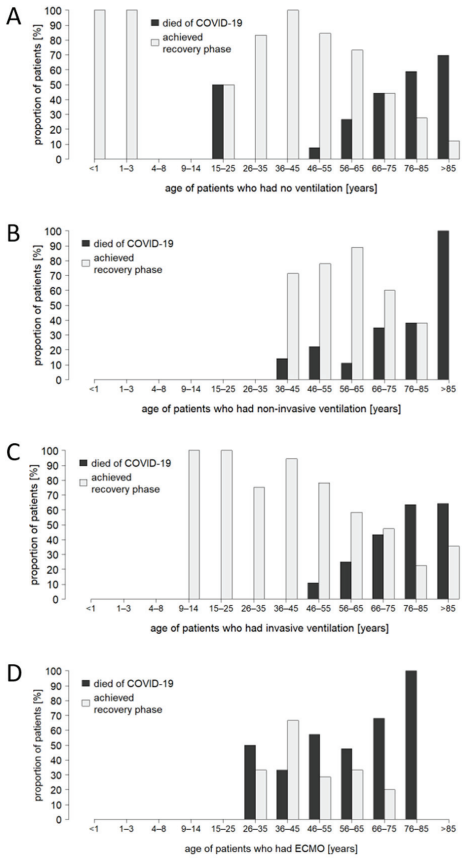


Figure A1. Distribution of age in recovered and deceased COVID-19 patients receiving intensive care. (**A**): Sub-cohort of non-ventilated patients (n = 147), (**B**): sub-cohort of non-invasively ventilated patients (n = 87), (**C**): sub-cohort of invasively ventilated patients (n = 492), (**D**): sub-cohort of ECMO patients (n = 114).

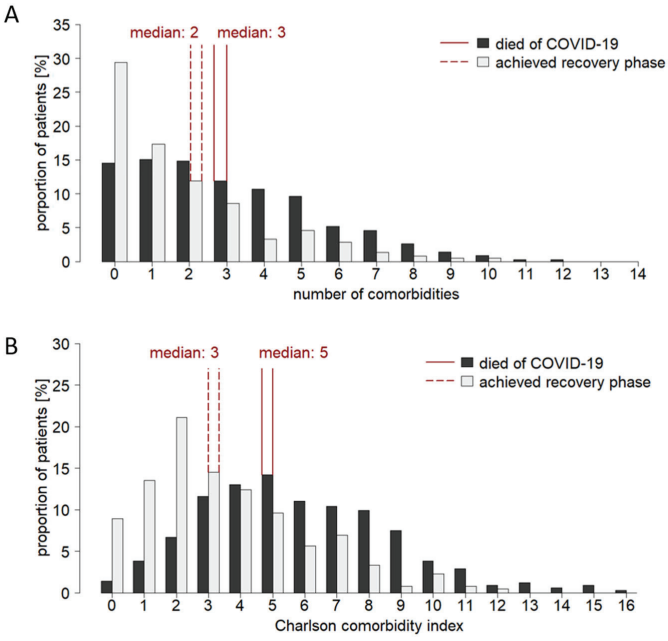


Figure A2. Distribution of (**A**) the number of comorbidities and (**B**) the Charlson comorbidity index in recovered and deceased COVID-19 patients receiving intensive care (total cohort, n = 840).

References

1. Chen, Y.; Klein, S.L.; Garibaldi, B.T.; Li, H.; Wu, C.; Osevala, N.M.; Li, T.; Margolick, J.B.; Pawelec, G.; Leng, S.X. Aging in COVID-19: Vulnerability, immunity and intervention. *Ageing Res. Rev.* **2021**, *65*, 101205. [CrossRef]
2. Jung, C.; Flaatten, H.; Fjolner, J.; Bruno, R.R.; Wernly, B.; Artigas, A.; Pinto, B.B.; Schefold, J.C.; Wolff, G.; Kelm, M.; et al. The impact of frailty on survival in elderly intensive care patients with COVID-19: The COVIP study. *Crit. Care* **2021**, *25*, 149. [CrossRef] [PubMed]
3. Oba, S.; Altinay, M.; Salkaya, A.; Turk, H.S. Evaluation of the effect of clinical characteristics and intensive care treatment methods on the mortality of covid-19 patients aged 80 years and older. *BMC Anesthesiol.* **2021**, *21*, 291. [CrossRef] [PubMed]
4. Welch, C. Age and frailty are independently associated with increased COVID-19 mortality and increased care needs in survivors: Results of an international multi-centre study. *Age Ageing* **2021**, *50*, 617–630. [CrossRef]
5. Hussien, H.; Nastasa, A.; Apetrii, M.; Nistor, I.; Petrovic, M.; Covic, A. Different aspects of frailty and COVID-19: Points to consider in the current pandemic and future ones. *BMC Geriatr.* **2021**, *21*, 389. [CrossRef] [PubMed]
6. Lewis, E.G.; Breckons, M.; Lee, R.P.; Dotchin, C.; Walker, R. Rationing care by frailty during the COVID-19 pandemic. *Age Ageing* **2021**, *50*, 7–10. [CrossRef]
7. Polidori, M.C.; Sies, H.; Ferrucci, L.; Benzing, T. COVID-19 mortality as a fingerprint of biological age. *Ageing Res. Rev.* **2021**, *67*, 101308. [CrossRef]
8. Pijls, B.G.; Jolani, S.; Atherley, A.; Derckx, R.T.; Dijkstra, J.I.R.; Franssen, G.H.L.; Hendriks, S.; Richters, A.; Venemans-Jellema, A.; Zalpuri, S.; et al. Demographic risk factors for COVID-19 infection, severity, ICU admission and death: A meta-analysis of 59 studies. *BMJ Open* **2021**, *11*, e044640. [CrossRef]
9. Hewitt, J.; Carter, B.; Vilches-Moraga, A.; Quinn, T.J.; Braude, P.; Verduri, A.; Pearce, L.; Stechman, M.; Short, R.; Price, A.; et al. The effect of frailty on survival in patients with COVID-19 (COPE): A multicentre, European, observational cohort study. *Lancet Public Health* **2020**, *5*, E444–E451. [CrossRef]
10. Smithard, D.G.; Abdelhameed, N.; Han, T.; Pieris, A. Age, Frailty, Resuscitation and Intensive Care: With Reference to COVID-19. *Geriatrics* **2021**, *6*, 36. [CrossRef]
11. Pott Junior, H.; Cominetti, M.R. Comorbidities predict 30-day hospital mortality of older adults with COVID-19. *Geriatr. Nurs.* **2021**, *42*, 1024–1028. [CrossRef]
12. Eiras Poco, P.C.; Romero Aliberti, M.J.; Dias, M.B.; Takahashi, S.d.F.; Leonel, F.C.; Altona, M.; Venys, A.L.; Shin-Ike, I.A.; Garcia, B.A.; Sumita, L.H.; et al. Divergent: Age, Frailty, and Atypical Presentations of COVID-19 in Hospitalized Patients. *J. Gerontol. Ser. A-Biol. Sci. Med. Sci.* **2021**, *76*, E46–E51. [CrossRef]

13. Meintrup, D.; Borgmann, S.; Seidl, K.; Stecher, M.; Jakob, C.E.M.; Pilgram, L.; Spinner, C.D.; Rieg, S.; Isberner, N.; Hower, M.; et al. Specific Risk Factors for Fatal Outcome in Critically Ill COVID-19 Patients: Results from a European Multicenter Study. *J. Clin. Med.* **2021**, *10*, 3855. [CrossRef] [PubMed]
14. Jakob, C.E.M.; Kohlmayer, F.; Meurers, T.; Vehreschild, J.J.; Prasser, F. Design and evaluation of a data anonymization pipeline to promote Open Science on COVID-19. *Sci. Data* **2020**, *7*, 435. [CrossRef]
15. Jakob, C.E.M.; Borgmann, S.; Duygu, F.; Behrends, U.; Hower, M.; Merle, U.; Friedrichs, A.; Tometten, L.; Hanses, F.; Jung, N.; et al. First results of the "Lean European Open Survey on SARS-CoV-2-Infected Patients (LEOSS)". *Infection* **2020**, *49*, 63–73. [CrossRef]
16. Kluge, S.; Malin, J.J.; Fichtner, F.J.; Müller, O.; Skoetz, N.; Karagiannidis, C. Recommendations on the In-Hospital Treatment of Patients with COVID-19. *Dtsch. Arztebl. Int.* **2021**, *118*, 865–871. [CrossRef] [PubMed]
17. IfD Allensbach. Patientenverfügungen–Umfrage zur Verbreitung in Deutschland nach Altersgruppe 2014. Available online: https://de.statista.com/statistik/daten/studie/375267/umfrage/patientenverfuegungen-verbreitung-in-deutschland-nach-altersgruppen/ (accessed on 8 March 2023).
18. Guidet, B.; Jung, C.; Flaatten, H.; Fjolner, J.; Artigas, A.; Pinto, B.B.; Schefold, J.C.; Beil, M.; Sigal, S.; van Heerden, P.V.; et al. Increased 30-day mortality in very old ICU patients with COVID-19 compared to patients with respiratory failure without COVID-19. *Intensive Care Med.* **2022**, *48*, 797–799. [CrossRef] [PubMed]
19. Guidet, B.; Flaatten, H.; Boumendil, A.; Morandi, A.; Andersen, F.H.; Artigas, A.; Bertolini, G.; Cecconi, M.; Christensen, S.; Faraldi, L.; et al. Withholding or withdrawing of life-sustaining therapy in older adults (=80 years) admitted to the intensive care unit. *Intensive Care Med.* **2018**, *44*, 1598–1601. [CrossRef]
20. Jung, C.; Flaatten, H.; Lange, D.; de Beil, M.; Guidet, B. The relationship between treatment limitations and pressure on intensive care units in elderly patients. *Intensive Care Med.* **2022**, *48*, 124–125. [CrossRef]
21. Sjogren, L.; Stenberg, E.; Thuccani, M.; Martikainen, J.; Rylander, C.; Wallenius, V.; Olbers, T.; Kindblom, J.M. Impact of obesity on intensive care outcomes in patients with COVID-19 in Sweden-A cohort study. *PLoS ONE* **2021**, *16*, e0257891. [CrossRef]
22. Kwok, S.; Adam, S.; Ho, J.H.; Iqbal, Z.; Turkington, P.; Razvi, S.; Le Roux, C.W.; Soran, H.; Syed, A.A. Obesity: A critical risk factor in the COVID-19 pandemic. *Clin. Obes.* **2020**, *10*, 12403. [CrossRef]
23. Mason, K.E.; Maudsley, G.; McHale, P.; Pennington, A.; Day, J.; Barr, B. Age-Adjusted Associations between Comorbidity and Outcomes of COVID-19: A Review of the Evidence from the Early Stages of the Pandemic. *Front. Public Health* **2021**, *9*, 584182. [CrossRef]
24. Treskova-Schwarzbach, M.; Haas, L.; Reda, S.; Pilic, A.; Borodova, A.; Karimi, K.; Koch, J.; Nygren, T.; Scholz, S.; Schoenfeld, V.; et al. Pre-existing health conditions and severe COVID-19 outcomes: An umbrella review approach and meta-analysis of global evidence. *BMC Med.* **2021**, *19*, 212. [CrossRef] [PubMed]
25. Tonna, J.E.; Abrams, D.; Brodie, D.; Greenwood, J.C.; Mateo-Sidron, J.A.R.; Usman, A.; Fan, E. Management of Adult Patients Supported with Venovenous Extracorporeal Membrane Oxygenation (VV ECMO): Guideline from the Extracorporeal Life Support Organization (ELSO). *Asaio J.* **2021**, *67*, 601–610. [CrossRef] [PubMed]
26. Badulak, J.; Antonini, M.V.; Stead, C.M.; Shekerdemian, L.; Raman, L.; Paden, M.L.; Agerstrand, C.; Bartlett, R.H.; Barrett, N.; Combes, A.; et al. Extracorporeal Membrane Oxygenation for COVID-19: Updated 2021 Guidelines from the Extracorporeal Life Support Organization. *Asaio J.* **2021**, *67*, 485–495. [CrossRef]
27. Chinnadurai, R.; Ogedengbe, O.; Agarwal, P.; Money-Coomes, S.; Abdurrahman, A.Z.; Mohammed, S.; Kalra, P.A.; Rothwell, N.; Pradhan, S. Older age and frailty are the chief predictors of mortality in COVID-19 patients admitted to an acute medical unit in a secondary care setting—A cohort study. *BMC Geriatr.* **2020**, *20*, 409. [CrossRef] [PubMed]

MDPI
St. Alban-Anlage 66
4052 Basel
Switzerland
www.mdpi.com

Journal of Clinical Medicine Editorial Office
E-mail: jcm@mdpi.com
www.mdpi.com/journal/jcm

MDPI

Academic Open
Access Publishing

mdpi.com

ISBN 978-3-0365-9305-0