biologics

MDPI

Review

A Review on the Impact of the SARS-CoV-2 Omicron Subvariant on Elderly Patients with Diverse Co-Morbidities

Avinash Khadela [1], Shruti Soni [1], Kaivalya Megha [1], Shivam Bhagat [1] and Vivek P. Chavda [2,*]

[1] Department of Pharmacology, L. M. College of Pharmacy, Navrangpura, Ahmedabad 380009, Gujarat, India
[2] Department of Pharmaceutics and Pharmaceutical Technology, L. M. College of Pharmacy, Navrangpura, Ahmedabad 380009, Gujarat, India
* Correspondence: vivek.chavda@lmcp.ac.in

Abstract: The SARS-CoV-2 virus has caused a catastrophic impact on the world for the past 3 years. The virus has now returned with the emergence of the Omicron (B.1.1.529) variant. Within two months of its first emergence in South Africa, Omicron became the most dominating SARS-CoV-2 variant around the world, being the cause of the majority of new infections at present. Omicron has presented with the greatest transmission rate of all the previous variants despite the presence of mass vaccinations and acquired immunity. Several monoclonal antibodies and mRNA vaccines have failed to produce desired effects owing to a large number of mutations present in the Omicron variant. The introduction of the booster dose of the present mRNA vaccines has proven to be a great addition to the therapeutic armamentarium against the Omicron variant. Immunocompromised patients including the elderly, cancer patients, organ transplant recipients, and those with multiple comorbidities have been at a greater risk of developing severe diseases since the pre-Omicron era. The emergence of Omicron again raised a threat against this population. The protection from severe disease and mortality rates through the utilization of multiple immunizations and monoclonal antibodies has been controversial in this subgroup of patients. Thus, designing large-scale studies to evaluate the effectiveness of monoclonal antibodies and vaccines in these patients can provide evidence-based recommendations to improve survival in this population. This article attempts to discuss the different subvariants of Omicron, differences in the mutational aspects along with the particular focus on the consequences of the Omicron infection in the elderly population with diverse comorbidities.

Keywords: Omicron; SARS-CoV-2; variant; mutations; immunocompromised; organ transplant; elderly; vaccines

Citation: Khadela, A.; Soni, S.; Megha, K.; Bhagat, S.; Chavda, V.P. A Review on the Impact of the SARS-CoV-2 Omicron Subvariant on Elderly Patients with Diverse Co-Morbidities. *Biologics* **2023**, *3*, 138–157. https://doi.org/10.3390/biologics3020008

Academic Editor: Seth Pincus

Received: 20 March 2023
Revised: 31 May 2023
Accepted: 1 June 2023
Published: 9 June 2023

1. Introduction

In the past three years, the COVID-19 pandemic has affected nearly every part of the world and remains a major public health concern to date. As reported by the World Health Organization (WHO) statistics, the COVID-19 pandemic has been the cause of 662 million cases and 6.7 million deaths (as of 15 January 2023). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the culprit behind this deadly global pandemic. This pandemic has left an impact on people that will last for many generations. The SARS-CoV-2 virus infects humans in three clinical phases, which are mostly overlapped. The first phase is termed the nasal phase, in which the virus binds to the angiotensin-converting enzyme 2 (ACE2) receptors present on the cell surface. Following this binding, the virus enters the host cells and starts replicating by taking over the intracellular organelles [1]. In the second phase, also called the pulmonary phase, the virus invades the lung tissues, and the levels of inflammatory markers increase. Individuals who have progressed to this stage encounter increased myalgia, lethargy, and dyspnea [2]. Of all the patients infected with the virus, only a few patients progress to the third phase. In this phase, a rapid deterioration is seen in

the patient's condition including multiple organ dysfunction and acute respiratory distress syndrome (ARDS). This necessitates intensive care unit admission and invasive ventilation. However, mortality remains high in the patients who have progressed to this stage, despite maximal intensive care efforts [3,4]. Since its emergence, the SARS-CoV-2 virus has evolved, resulting in the development of numerous variants. WHO classifies the variants further into three classes: variants of concern (VOCs), variants of interest (VOIs), and variants under monitoring (VUMs). For any novel variant to be characterized as VOC, it has to exhibit higher transmissibility, a difference in clinical presentation, a worse prognosis, and reduced effectiveness of previous immunization and treatment modalities. The former VOCs include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) [5]. On 24 November 2021, another novel variant namely Omicron (B.1.1.529) was reported by South Africa. Soon, on 26 November 2021, the WHO declared it as VOC, replacing the Delta (B.1.617.2) variant [6]. The exceptionally higher transmissibility of this variant led to its rapid spread all around the world, to at least 185+ countries [7]. At present, it is thought to be the cause of more than 99% of new infections. Compared with the Delta variant, the Omicron variant is 10 times more contagious and twice as infectious [8]. The multiplication of Omicron in the human bronchus is 70 times quicker compared with the classic SARS-CoV-2 variant and the Delta variant [9].

Since the early phase of the pandemic, the case–fatality rates were observed to be increasing in an age-dependent manner. Additionally, the severity of the disease and mortality rates were observed to be higher in those having multiple comorbid conditions, specifically hypertension, cardiovascular diseases, metabolic disorders, and kidney diseases [10]. The Omicron variant is associated with less severe overall disease than the earlier variants [11]. The mechanisms leading to severe diseases and overall dismal outcomes in these patients are not entirely clear yet.

In this review, we attempt to shed light on the emergence and mutations of the Omicron variant and the impact of the same on the immunodeficient population. Moreover, a brief discussion has been added regarding the efficacy of current vaccination strategies, as well as future directions.

2. Mutations in the Omicron Variant

The prime reason behind increased concerns of a deadlier wave of pandemic following the emergence of the Omicron variant was the presence of a substantial number of mutations in the spike protein [12]. The Omicron variant exhibited increased transmissibility and higher odds of reinfection even in the fully vaccinated population and in those who were previously infected by other variants [13]. However, identical to the previous VOCs, the Omicron variant relies on angiotensin-converting enzyme 2 (ACE2) receptors for entry into the host cells [14]. Omicron exhibited a combination of all the concerning mutations from the previous VOCs with several exclusive mutations in the spike, as well as non-spike proteins [15]. The non-spike proteins harboring mutations in the Omicron variant include viral envelope proteins, membrane proteins, nucleocapsid proteins, nonstructural proteins, and the furin cleavage site [16]. The Omicron variant has almost 60 mutations in total, from which 50 are amino-acid-altering mutations and the other 10 are non-amino-acid mutations. The spike protein of the Omicron variant includes 32 mutations, and 15 of them are localized in the receptor-binding domain (RBD) [17]. The previous VOC Delta (B.1.617.2) had barely two mutations in the RBD. RBD is present on the spike protein and plays a critical role in the binding of SARS-CoV-2 with the host cells, initiating the entry of the virus and subsequent replication processes. Moreover, it is a primary target for neutralizing antibodies (Nabs), as well as vaccines against SARS-CoV-2 [18]. Hence, these mutations have rendered the Omicron variant resistant to the virus targeting monoclonal antibodies, as well as the vaccines. The mutations in the spike protein improve the affinity of the virus to the ACE-2 receptor, increasing transmissibility [19]. P681H, N679K, and H655Y mutations are present in the furin cleavage site, which impacts the entry of the virus into cells and increases the transmissibility of the virus [20]. Additionally, viral

transmissibility and infectivity of Omicron are also improved by the N501Y, D6146, N440K, and T478K mutations [21]. The nucleocapsid protein of the Omicron includes R203K and G204R mutations [22]. The amino terminal domain (NTD) has T95I and G142D mutations, which prolong the infection and aid in the escape from NTD-targeted antibodies [23]. To strengthen these claims, Planas et al. conducted an in vitro study on the serum of patients infected with the Omicron variant and reported that Omicron was not neutralized by sera collected from COVID-19 patients after more than 6 months of recovery [24]. These characteristics of the Omicron led to the rapid transmission of the virus into many countries despite successful mass vaccinations and immunization from infections with previous variants [25]. Hence, this led to concerns over the reliability of the acquired immunity of the population from previous infections against the Omicron. The evolution of the SARS-CoV-2 did not cease after the appearance of the Omicron variant. Numerous sublineages of Omicron have emerged, namely BA.1/B.1.1.529.1 (the initial Omicron variant), BA.1.1, and BA.2/B.1.1.529.2, BA.3/BA.1.1.529.3, BA.4, BA.5, BA.2.12.1, and BA.2.11 [26]. All of these sublineages vary in their viral mutations, clinical presentation, and pathological characteristics. Out of the listed subvariants, BA.1, BA.1.1, and BA.2 are found to be the most encountered in circulation [27]. The BA.1/B.1.1.529.1 is the original form of the Omicron variant and is usually determined by the presence of S-gene target failure (SGTF) [28]. BA.1.1 is a subvariant of BA.1 exhibiting R346K mutation in the spike protein [14]. The BA.2 lineage has 8 unique alterations, which are not present in other subvariants, and lacks 13 mutations found in the BA.1. BA.2 has shown a higher binding affinity for ACE-2, providing it with a selection advantage over other variants [29]. Following its emergence, BA.2 rapidly became prevalent in countries including India, Denmark, Singapore, and Norway [30]. The BA.4 and BA.5 variants were first detected in South Africa in January and February of 2022 and resulted in a fifth wave of SARS-CoV-2, accounting for nearly 50% of reported cases in South Africa [31]. BA.4/5 has additional R493Q, Del69-70, F486V, and L452R mutations on the spike protein compared with BA.1. The BA.4/5 variants are found to have higher transmissibility than the other Omicron sublineages and higher odds of reinfection [32]. The capability of BA.4/5 to evade the neutralizing antibodies produced by the BA.1 infection is a potential reason behind these observations. Furthermore, compared with BA.2, BA.4/5 is 4.2-fold resistant to the sera obtained from vaccinated and boosted individuals [33]. Various variants and subvariants of SARS-CoV-2 with their time of first occurrence are graphically represented in Figure 1.

The WHO used the Greek alphabet to label key SARS-CoV-2 variants, e.g., Alpha, Beta, Gamma, and Delta. The Pango dynamic nomenclature is now a globally used method for the classification of SARS-CoV-2. Pango lineages are fine-scaled phylogenetic labels created to be appropriate for outbreak investigations at a regional or national scale. As a result, Pango nomenclature comprises a significant number of lineages that cover the complete genetic diversity of SARS-CoV-2, with many of them being genetically quite similar to each other.

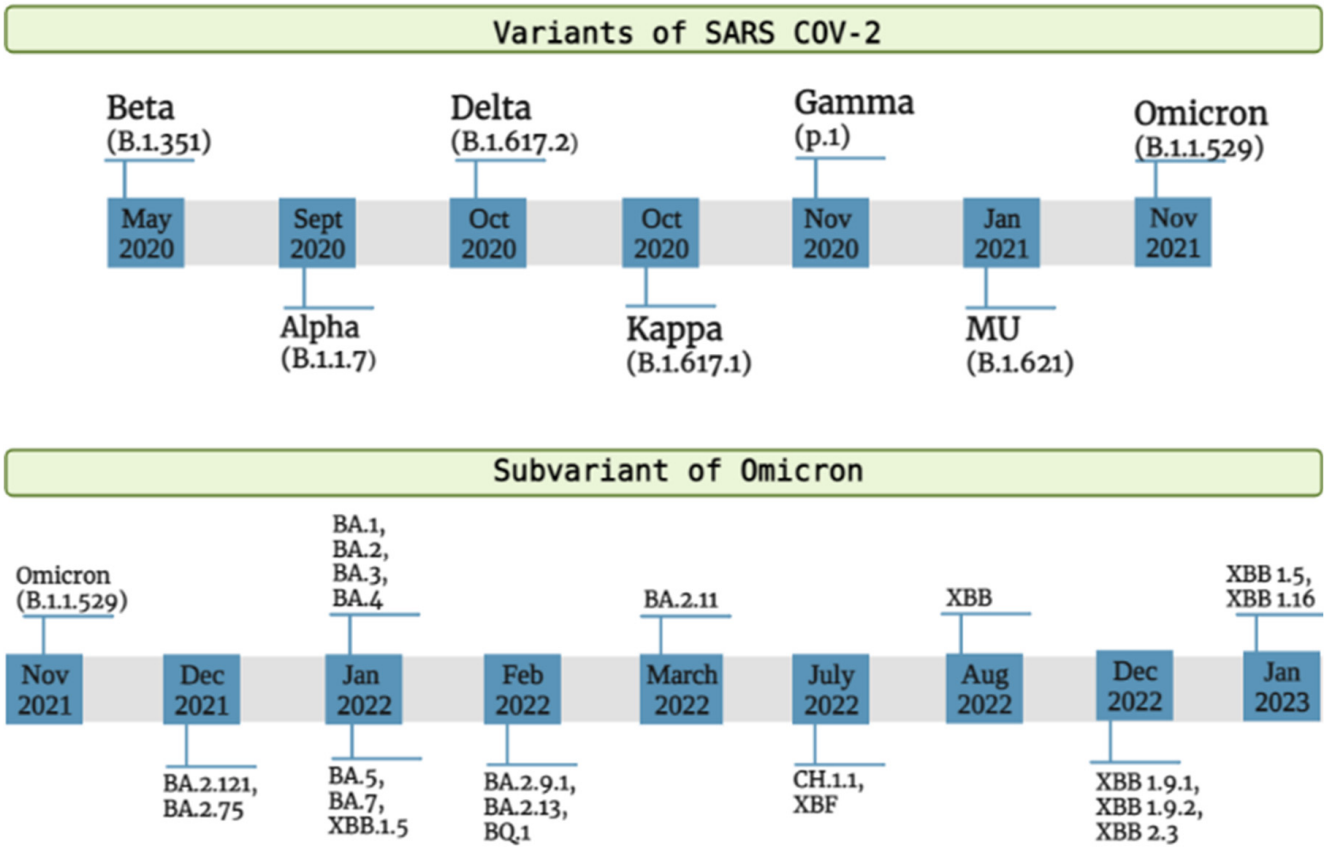

Figure 1. Periodically identified variants of SARS COV-2 and subvariants of Omicron.

3. The Severity and Clinical Presentation

However, on the bright side, the Omicron variant has shown a reduced risk of hospitalization, intensive care, and mortality compared with preceding variants. Research by Wolter et al. reported that in South Africa, individuals with Omicron infections had 80% lower odds of being hospitalized compared with those with non-Omicron infections [34]. Even among those hospitalized, the need for intensive care and mortality were 18.5% vs. 29.9% and 2.7% vs. 28.1% for the Omicron and Delta variants, respectively [35]. Another analysis by the U.K. Health security agencies reported that the need for emergency care with the Omicron variant was 50–57% less compared with the Delta variant [14]. Moreover, a lesser involvement of the lower respiratory tract is seen along with quick recovery from the illness. The common symptoms of the Omicron variant include cough, fever, sore throat, and tiredness, accompanied by myalgia [36]. These symptoms are very common health issues that are mostly ignored by the patients, providing the virus an abundant amount of incubation time to invade other parts of the body. Unlike the earlier SARS-CoV-2 variants, the Omicron variant does not impair the olfactory function owing to its lower alkalinity and hydrophobicity. This results in the lower solubility of the virus in mucus and a reduction in olfactory epithelial infections [37]. A study by Menni et al. reported that anosmia was found to be unusual in the patients infected with the Omicron variant when compared with the Delta variant (16·7% vs. 52·7%) [38]. Additionally, in the case of a computed tomography (CT) scan, the patients infected with the Omicron variant exhibited increased thickening of bronchial walls but less severe disease compared with earlier variants [39]. Gastrointestinal symptoms such as diarrhea and vomiting are found to be extremely common in patients infected with the Omicron variant [4].

Despite the lower rates of hospital admissions and mortality, elderly patients were more prone to be infected with the Omicron variant owing to high comorbidity burdens [40]. Moreover, the severity of the disease in Omicron-infected elderly individuals and those with

comorbidities such as cardiovascular diseases, diabetes, and chronic respiratory diseases was increased as well [41]. Several studies have reported that old age and chronic illnesses have a significant influence on Ct values/viral loads. As elderly patients are more likely to have comorbidities, lower Ct values and higher viral loads are commonly observed in these patients. The higher odds of severe illness in patients with comorbidities can be attributed to hyperinflammation and delayed viral clearance. Additionally, it was observed that the patients with comorbidities had higher levels of C-reactive protein (CRP), neutrophils, white blood cells (WBCs), and procalcitonin, indicating the potential correlation between inflammation and a higher number of comorbidities, impacting the immune response to the COVID-19 virus. It was observed that in patients with a high burden of comorbidities, the severity of the disease was significantly associated with lower Ct values compared with those with a lower burden of comorbidities [42].

A study from Sweden by Kahn et al. reported that among vaccinated populations, the risk of severe disease caused by the Omicron variant was significantly low. The results from this study were adjusted for age, sex, vaccinations, and comorbidities. It was highlighted that despite having a low risk of severe disease in the general population, elderly individuals and middle-aged men with two or more comorbidities were at higher risk for progressing toward severe disease from the Omicron variant. Additionally, when comparing the vaccinated population with comorbidities above and below 65 years of age, it was found that the risk of severe disease was higher in the population greater than 65 years of age [43]. These revelations point toward the impact of old age on the severity of the disease.

A comparison of critically ill patients between the Delta and Omicron variants reported that the mortality rates were higher in the Omicron variant subgroup (52.94% compared with 41.9% in the Delta group). However, the patients in the Omicron subgroup were associated with a higher number of comorbidities including pre-existing pulmonary diseases and acute kidney injury (AKI) [44]. Thus, the higher rates of mortality in critically ill patients from the Omicron variant in this study can be linked to the presence of comorbidities in this population. Nevertheless, the reason behind the presence of a higher number of comorbidities in the Omicron-infected individuals is not clear.

In the case of unvaccinated individuals and in those who were naïve from the infections with previous SARS-CoV-2 variants, the odds of being hospitalized from the Omicron variant was 75% similar to the Delta variant [45]. This implies that the reduced mortality and morbidity observed during the Omicron wave might be largely due to the presence of acquired immunity from previous infections and mass vaccination instead of the structural properties of the virus. The 69-70 deletion mutation in the Omicron, which results in the modification of the structure of the spike protein, allows it to escape detection by the polymerase chain reaction (PCR) test [28]. Thus, the PCR test results for the Omicron variant are highly uncertain. However, due to the lack of alternative efficient diagnostic techniques, PCR tests remain the current standard for the detection of COVID-19 [46]. Researchers must work towards identifying sections in the viral genome that are not rapidly modified over time and have recognizable features. The characteristics of different Omicron subvariants along with their mutations and transmission rates are presented in Figure 2.

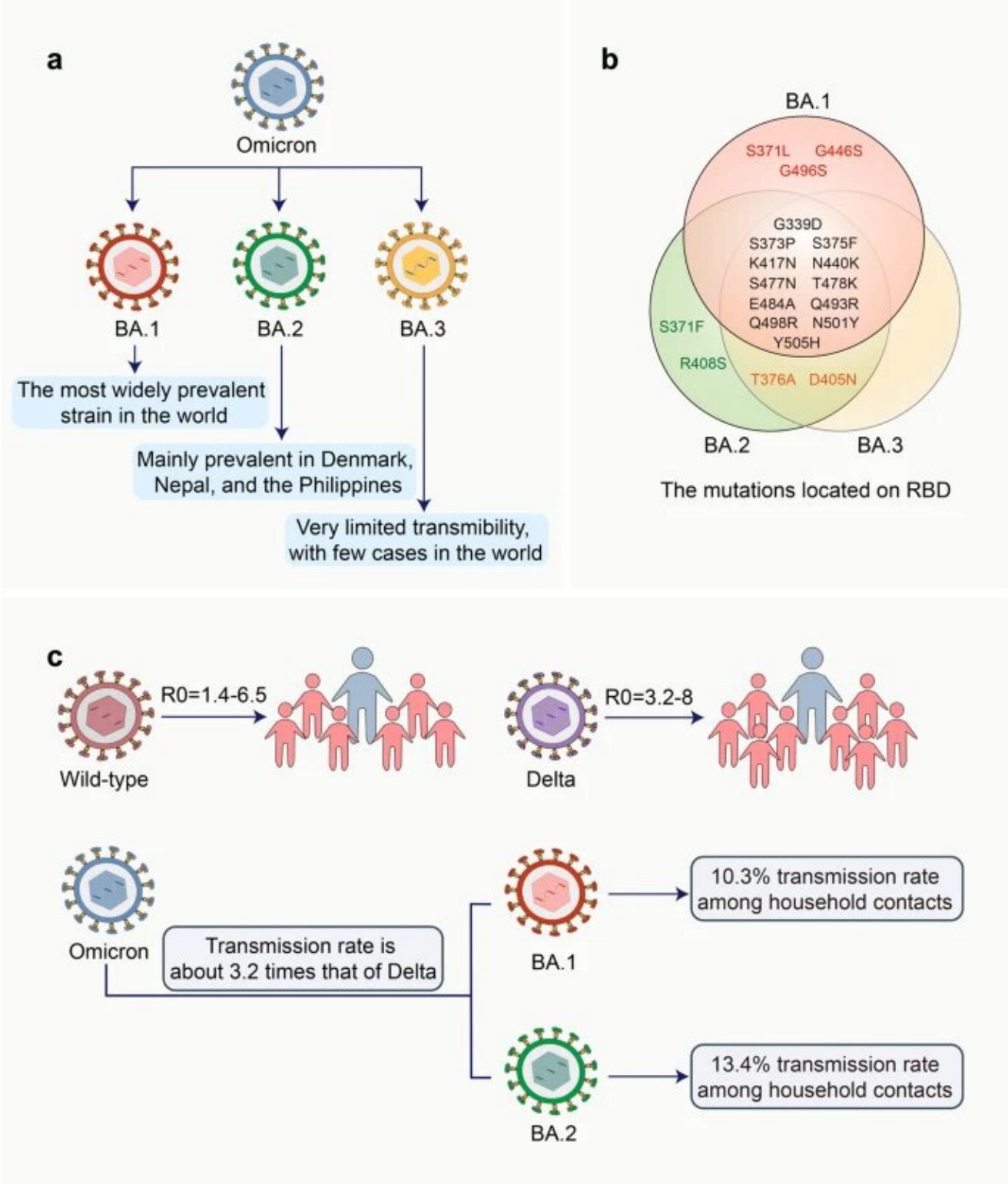

Figure 2. Various subvariants of Omicron and their mutations (adapted from [47] under a Creative Commons Attribution 4.0 International License). (**a**) Prevalence of Omicron subvariants BA.1, BA.2 and BA.3 worldwide. (**b**) Venn diagram of various mutations present in the RBD of Omicron subvariants BA.1, BA.2 and BA.3. (**c**) Transmission rates of SARS-CoV-2- wild-type, Delta, and Omicron variants.

4. Impact of Omicron on the Immunocompromised Population

Old age represents one of the prime risk factors for the clinical vulnerability of human beings, with the highest impact seen in the cardiovascular and immune systems. Moreover, the elderly population is more prone to developing viral infections, resulting in a dismal prognosis [48]. Since the early phase of the pandemic, the case–fatality rates were observed to be increasing in an age-dependent manner, with considerably higher mortality rates observed in patients aged more than 80 years [49]. Additionally, individuals with comorbidities such as diabetes mellitus, hypertension, obesity, coronary artery disease, and pulmonary and renal diseases suffered dismal outcomes after being infected with the SARS-CoV-2 [50]. The ACE2 receptor, responsible for the entry of SARS-CoV-2, is not only present in the lungs but also in the endothelium and heart, which leads to microvascular dysfunction in patients with severe disease [51]. The incidence of myocardial damage was found to be two times greater in patients of more than 60 years of age, compared with younger individuals [52]. A study by Ward et al. evaluated the risk of death due to COVID-19 in patients infected with the Delta versus the Omicron variants in England. In this study, it was highlighted that the risk of COVID-19-related death with Omicron was reduced in people aged 18–59 years (number of deaths: Delta—46, Omicron—11; Hazard ratio = 0.14) than in people aged >70 years (number of deaths: Delta—113, Omicron—135; Hazard ratio = 0.44) [53]. Another study in Hong Kong by Mefsin et al. analyzed the epidemiology of infections with the BA.2 variant. In this study, it was observed that in the study population, out of all deaths due to BA.2 subvariant, 92.7% (8482/9146) were reported in individuals of age >65 years and 71.1% (6500/9146) in those with more than 80 years of age. These results can be attributed to the absence of complete vaccination in older adults, as only 20% of people >80 years of age were primarily vaccinated in Hong Kong during the study duration [54].

The physiological deterioration due to the aging process can significantly dysregulate the immune system, leading to a decline in the activation of adaptive and innate immune responses in elderly individuals. The term used to describe this age-associated remodeling of the immune system is immunosenescence. These processes can give rise to an exacerbated inflammatory response and can increase the susceptibility to various infections [55]. These physiological changes lead to a reduction in innate as well as adaptive immune responses, making the elderly population more susceptible to catching various infections [56]. Another term, called inflamm-aging, refers to a latent proinflammatory state, as a result of alterations in the intracellular communication mechanism. This condition leads to higher levels of inflammatory mediators such as interleukin-1, interleukin-6, CRP, and TNF-α in serum. This immune system dysregulation aids in the pathogenesis of SARS-CoV-2, leading to severe infections and higher mortality in elderly individuals [57]. The age-induced atrophy of the thymus gland in older individuals renders them unable to fight newer pathogens, due to a reduction in the naïve T-cell population [58].

In elderly individuals, the main pathological feature that leads to mortality from SARS-CoV-2 is the presence of a cytokine storm in the lungs [59]. The uncontrolled immune responses in the elderly following the pathogen insult result in higher rates of tissue damage that compromise lung function [60]. This is generally seen in individuals with severe COVID-19 infection [59]. More than half of the patients who have progressed to the fatal stages of COVID-19 experience a cytokine storm, of which, almost 82% of the cases are more than 60 years old [61]. Thus, elderly patients require early clinical attention and interventions to prevent deterioration and to reduce the mortality rates from the Omicron variants.

4.1. Renal Diseases

When discussing the potential correlation between severe COVID-19 disease and the presence of comorbidities, the prime focus is commonly set on cardiac and metabolic conditions such as hypertension, diabetes, and ischemic heart diseases. However, several studies have highlighted renal disease as an independent risk factor for COVID-19-associated

mortality [62]. A ten-fold increase in mortality rates was observed in patients with chronic kidney disease (CKD) and COVID-19 compared with CKD patients without COVID-19. The higher exposure rates to healthcare facilities in patients undergoing maintenance dialysis treatment is a potential factor contributing to the higher incidence of COVID-19 infections in these patients [63]. A study by Chen et al. focused on identifying the higher-risk comorbidities and fragile populations among Omicron patients, who were hospitalized. The results from this study concluded that viral shedding time was prolonged in patients aged >70 years old and in those with stage 4–5 CKD, cancer, and cardiac diseases. Even between these risk factors, cancer, CKD stage 4–5, and long-term bedridden status led to more severe diseases compared with those with metabolic and heart conditions and the elderly [64]. On the other hand, full immunization/booster vaccination resulted in significant protection and reduced viral shedding time. Patients with severe CKD are at the highest risk of mortality even when compared with lung disease, hypertension, and chronic heart diseases. The impairment of innate immunity along with a dysfunctional immune system leading to a higher inflammatory state is found to be the potential reason for such outcomes [65].

4.2. Cancer

Cancer is a highly prevalent comorbid condition commonly observed in patients with old age. Dysregulation of the immune system in these patients renders them susceptible to developing severe disease when infected with SARS-CoV-2. Since the early phase of the pandemic, several studies have reported the dismal impact of COVID-19 infection on cancer patients and survivors, resulting in higher mortality rates. Patients with cancer or cancer survivors were found to have 2–3-fold higher odds of developing severe disease and death compared with the general population [66]. Even in these patients, mortality rates were notably high in patients aged >65 years old and those with metastatic disease [67]. The development of cancer itself is integrally associated with the downregulation of immune responses. Moreover, patients with solid or hematological malignancies are inherently prone to developing frequent infections as they have lymphopenia, neutropenia, and concurrent administration of cytotoxic or immunosuppressive treatments [68,69]. A specific type of immune system targeting treatment called immune checkpoint inhibitors (ICIs) is utilized to direct the body's inherent immune responses toward growing cancer cells. These agents tend to upregulate the general immune responses that may harm the body's healthy tissues, resulting in numerous adverse events. One of the frequently encountered adverse events includes pneumonitis, which can overlap with COVID-19-related pneumonia in these patients and can lead to higher mortality rates [70]. Additionally, the overactivation of the immune system due to these therapies can potentiate the cytokine storm, resulting in significant tissue damage [71]. Hence, compared with the general population, higher prophylactic measures should be utilized in patients with solid and hematological malignancies to avoid severe consequences and to reduce mortality rates. The neutralizing response against the Omicron variant was found to be significantly weak in patients with hematological cancers, compared with the earlier VOCs [72]. Several reports suggest that administering the fourth dose of the COVID-19 vaccine can be beneficial for immunocompromised patients with cancer [73].

4.3. Solid Organ Transplant Recipients (SOTRs)

Solid organ transplant recipients (SOTRs) are susceptible to severe COVID-19 infections owing to the ongoing exogenous immunosuppression in these patients [74]. Additionally, preventive strategies against COVID-19 including booster vaccinations have failed to produce sufficient immunogenic response in this population [75]. Despite the development and implementation of mass vaccination programs worldwide, the rate of breakthrough infections in the SOTRs is 82-fold higher [76]. The administration of booster doses can provide some degree of protection, but the data are insufficient to strengthen these claims.

The potential risk factors for severe disease in SOTRs include the use of corticosteroids, African American race, and a history of coronary artery diseases [77].

Compared with the general population, higher morbidity and mortality rates were found to be present in the liver transplant recipients (LTRs) owing to the immunosuppression and higher number of comorbidities in these patients [78]. Even after the basic immunization and booster vaccination, sufficient protection against the Omicron variant was absent in these patients. The lack of protection from immunization in LTRs is mainly due to weaker cellular and humoral responses resulting in lower T-cell reactions, lower median antibody titers, and low seroconversion rates [79]. A study by Herting et al. reported that during the Omicron wave, the majority of LTRs with breakthrough infections suffered from mild disease, which demonstrates the high real-world efficacy of vaccines in this population. In this study, nearly 90% of the LTR population who required hospitalization were of either more than 60 years of age or had multiple co-morbid conditions [80].

The BA.4 and BA.5 subvariants of Omicron are the highly transmissible variants, showcasing a greater ability to evade the Nab responses, including those induced by previous natural infections [81]. However, the mechanism of this immune evasion in immunocompromised individuals is not entirely known. Compared with the BA.1 variant, the neutralizing antibody response was 17-fold lower against the BA.4/5. The risk of Ba.4/5 remains high in SOTRs regardless of previous infections or immunization status [75]. A study by Wong et al. evaluated the impact of the Omicron variant in pancreas and kidney transplant recipients and reported that the hospitalization rates remained high even in the presence of triple-dose vaccinations in this population [82]. The research studies evaluating the outcomes of the Omicron in elderly individuals with diverse comorbidities are summarized in Table 1.

Despite numerous studies reporting the dismal outcomes from COVID-19 infection in the elderly multimorbid population, the standard evidence-based therapeutic strategies for treating these individuals are lacking, as the majority of treatment guidelines focus on the severity of the disease instead of the host immunity status [83]. This lack of knowledge can be attributed to the exclusion of immunocompromised patients from randomized trials due to safety concerns [84]. To fill these knowledge gaps and to develop evidence-based treatment recommendations for these patients, ongoing trials should focus on recruiting these patients. Innovative trial designs combined with well-studied primary and secondary endpoints should be implemented to justify the heterogenicity of immunodeficient populations.

Table 1. Clinical outcomes following the Omicron infection in immunocompromised patients.

Reference	Study Name	No. of Participants	Patient Condition	Study Outcome
Chen et al. [65]	Identification of CKD, bedridden history and cancer as higher-risk comorbidities and their impact on the prognosis of hospitalized Omicron patients: a multi-center cohort study	847	Omicron infected patients with com-morbidities (heart condition, metabolic disease, CKD stage 4–5, isolated hypertension, cancer)	The results from this study reported a prolonged viral shedding time in patients aged >70 years old, those with stage 4–5 chronic kidney disease (CKD), cancer and cardiac diseases. Even between these risk factors, cancer, CKD stage 4–5, and long-term bedridden status led to more severe diseases compared with those with metabolic and heart conditions and the elderly.

Table 1. *Cont.*

Reference	Study Name	No. of Participants	Patient Condition	Study Outcome
Kahn et al. [43]	Risk of severe COVID-19 from the Delta and Omicron variants about vaccination status, sex, age, and comorbidities–surveillance results from southern Sweden, July 2021 to January 2022	29,539	Patients with Omicron infection and with co-morbidity and without co-morbidity.	The data from the study concluded that patients more than >65 years, unvaccinated, and having more than 2 risk factors are at higher risk as compared with the vaccinated population.
Hao et al. [42]	Clinical characteristics and analysis of risk factors for disease progression of patients with SARS-CoV-2 Omicron variant infection: A retrospective study of 25,207 cases in a Fangcang hospital	1952	Patients age higher than 65, COVID-19-positive and co-morbidities	This study illustrates that a higher no. of elderly patients with severe infection indicates that Omicron causes severe infection due to patient age and co-morbidities
Corriero et al. [44]	COVID-19 Variants in Critically Ill Patients: A Comparison of the Delta and Omicron Variant Profiles	65	Omicron and Delta variant infection patients with existing co-morbidities	This study suggests that if a patient is infected with Omicron but vaccinated and has any co-morbidities, then vaccination provides better protection to the patient against Omicron infection.
Monoclonal antibodies				
Gliga et al. [85]	Rapid Selection of Sotrovimab Escape Variants in Severe Acute Respiratory Syndrome Coronavirus 2 Omicron-Infected Immunocompromised Patients	57	Omicron-infected patients with immunodeficiency	Combination therapy of at least >2 mAbs is mandatory to treat immunocompromised patients with Omicron infection.
Young-xu et al. [86]	Tixagevimab/Cilgavimab for Prevention of COVID-19 during the Omicron Surge: Retrospective Analysis of National VA Electronic Data	1848	Immunocompromised patient with SARS CoV-2 infection	The result of the study illustrates that T/C reduces the rate of Omicron infection and hospitalization rate in a patient more than 50 age.
Huygens et al. [87]	Sotrovimab Resistance and Viral Persistence After Treatment of Immunocompromised Patients Infected With the Severe Acute Respiratory Syndrome Coronavirus 2 Omicron Variant	47	Immunocompromised patients with SARS CoV-2 Positivity	This work demonstrates how immuno-compromised individuals who are unable to clear SARS-CoV-2 infection despite antiviral medication might act as a source of novel variations in the viral genome. These patients need to be closely monitored until complete viral clearance is confirmed.
Antiviral therapy				

Table 1. *Cont.*

Reference	Study Name	No. of Participants	Patient Condition	Study Outcome
Al-obaidi et al. [88]	The Impact of Nirmatrelvir-Ritonavir in Reducing Hospitalizations Among High-Risk Patients With SARS-CoV-2 During the Omicron Predominant Era	3621	Vaccinated and unvaccinated patients with infection of Omicron and co-morbidities, and some of them were immunocompromised	The statistic of the study demonstrates that the NR regimen helps to prevent hospitalization and reduces the risk of any further complication.
Zhong et al. [89]	The efficacy of paxlovid in elderly patients infected with SARS-CoV-2 omicron variants: Results of a non-randomized clinical trial	142	An elderly patient infected with SARS-CoV-2 Omicron	This study concluded that in patients who had received paxlovid during Omicron infection, a reduction in the nucleic acid shedding time was observed compared with the control group.
Impacts of vaccination				
Tan et al. [90]	Clinical severity of COVID-19 with omicron variant predominance about vaccination status, age, comorbidities–a single center in Selangor, Malaysia	2279	The presence of various comorbidities was assessed in the COVID-19-positive patients.	The severity of COVID-19 was found to be potentially increased with age, in the presence of comorbid conditions, as well as among unvaccinated people, according to this study's findings.
Nevejan et al. [91]	The Severity of COVID-19 among Hospitalized Patients: Omicron Remains a Severe Threat for Immunocompromised Hosts	1036	SARS CoV-2 Delta-variant- and Omicron-variant-positive patients were included with and without any immunocompromised condition	Elderly, immunocompromised, and non-vaccinated patients were at higher risk of mortality and hospitalization rate because of Omicron infection, but if immunocompromised patients were vaccinated, then reduce the hospitalization and mortality rate.
Jassat et al. [92]	A cohort study of post-COVID-19 condition across the Beta, Delta, and Omicron waves in South Africa: 6-month follow-up of hospitalized and nonhospitalized participants	842	Patients infected with Beta, Delta, and Omicron having existing immunocompromised condition	The study found that South African individuals had a significant prevalence of persistent symptoms at 6 months but that those who were infected during the Omicron BA.1 wave had a lower risk of developing PCC.
Cancer patients				
Nuemann et al. [93]	Patients with CLL have a lower risk of death from COVID-19 in the Omicron era	477	An elderly patient with Omicron variant positivity and CLL	In the study, during the Omicron wave patients were administered MAbs which will decrease the severity and illness of the patient along with reduced hospitalization
Lee et al. [67]	Impact of COVID-19 on case fatality rate of Patients with Cancer during the Omicron Wave	285	Patients with cancer and co-morbidities and Omicron positivity	This study demonstrates that elderly patients with cancer and other co-morbidities were at higher risk of severe diseases and showed higher mortality rates.

Table 1. *Cont.*

Reference	Study Name	No. of Participants	Patient Condition	Study Outcome
Organ transplant recipients				
Malahe et al. [40]	Clinical Characteristics and Outcomes of Immunocompromised Patients with Coronavirus Disease 2019 Caused by the Omicron Variant: A Prospective, Observational Study	114	Organ transplant patient with Omicron infection	This study concluded that decreased mortality rate and hospitalization rates were observed in immunocompromised patients who were infected with the Omicron variant.
Ferreira et al. [75]	Impact of Omicron BA.1 infection on BA.4/5 immunity in transplant recipients	75	Organ transplant patient with Omicron BA.1 and BA4/5 infection	This study indicates that SOTRs who recovered from BA.1 infection acquire BA.4/5 cross-neutralizing responses, although at a noticeably lower frequency and lower titer, with levels fading over time in the majority of patients.
Wong et al. [82]	COVID-19 Infection with the Omicron SARS-CoV-2 Variant in a Cohort of Kidney and Kidney Pancreas Transplant Recipients: Clinical Features, Risk Factors, and Outcomes	41	Kidney- or pancreas-transplanted patients diagnosed with Omicron	Transplanted patients are at a high risk of developing severe infection with the Omicron variant; early sortovimab therapy was found to decrease the hospitalization rate
Solera et al. [94]	Impact of Vaccination and Early Monoclonal Antibody Therapy on Coronavirus Disease 2019 (COVID-19) Outcomes in Organ Transplant Recipients During the Omicron Wave	300	Consecutive SOT recipient with Omicron infection	Early monoclonal antibody therapy and earlier receipt of 3 mRNA vaccine doses were independently linked with considerably lowered disease severity in a group of SOT patients with Omicron variant infection.

5. Effect of Monoclonal Antibodies and Vaccines against the Omicron Variant

Monoclonal antibodies (mAbs) are a class of biological therapies that are utilized to treat a wide range of diseases, including infectious diseases such as COVID-19. [95]. mAbs exert their mechanism by targeting the spike protein of the COVID-19 virus, which is essential for virus entry into human cells. Therefore, they have the potential to reduce the severity of the COVID-19 infection in humans [96]. mAbs have been integral in the treatment of COVID-19, especially in high-risk patients. Combinations of antibodies, such as bamlanivimab/etesevimab or casirivimab/imdevimab, have been available since late 2020 and have succeeded in halting the disease progression [97]. Additionally, these therapies may have a prophylactic effect on individuals at risk who have recently been exposed to the SARS-CoV-2 virus [95]. Three authorized mAb regimens, including casirivimab/imdevimab, bamlanivimab, and bamlanivimab/etesevimab, have shown remarkable efficacy in treating the SARS-CoV-2 infection [98].

However, the emergence of the Omicron variant in November 2021 led to a significant increase in infection rates, and the effectiveness of casirivimab/imdevimab against Omicron was compromised due to mutations in the spike protein [99]. Specifically, the neutralizing activity of casirivimab was found to be diminished against Omicron variants BA.2.12.1, BA.4, and BA.5, while imdevimab retained its neutralizing activity. The com-

bination of casirivimab and imdevimab showed reduced neutralizing activity against the Omicron variants compared with the original strain. Different mAbs, such as tixagevimab, cilgavimab, and bebtelovimab, demonstrated varying levels of neutralizing activity against the Omicron variants. Bebtelovimab showed effectiveness in combating the BA.2.12.1, BA.4, and BA.5 variants of the Omicron variant. However, it is important to consider that these variants may exhibit reduced susceptibility to combination therapies involving tixagevimab and cilgavimab [100].

Nine monoclonal antibodies in development or approved for clinical use have failed to neutralize Omicron, including COV2–2196, S309, COV2–2130, REGN10987, REGN10933, LY-CoV016, LY-CoV555, and Celltrion (CT-P59) [101]. Two mAbs have been identified as efficient neutralizing agents against Omicron, including sotrovimab and DXP-604 [101].

To address the challenges posed by the Omicron variant, a new monoclonal antibody called sotrovimab was introduced in January 2022. Sotrovimab demonstrated efficacy against Omicron in vitro, making it a promising treatment option for early SARS-CoV-2 infection [102]. However, concerns were raised about the use of single mAbs in immunocompromised patients, as it was suggested that this approach could promote the emergence of escape mutations in the spike protein.

Recent reports have indicated the occurrence of mutations after sotrovimab therapy in Omicron-infected patients, particularly in immunocompromised individuals [103]. However, the risk factors and longitudinal development of resistance in these patients are still not well understood. Notably, immunocompromised patients show a substantial rate of prolonged viral shedding even after receiving sotrovimab, which was considered the standard therapy for high-risk patients at the time. A majority of the high-risk patients who exhibited sotrovimab-specific escape mutations were infected with the BA.1 variant, while a smaller proportion were infected with the BA.2 variant [103].

Studies have shown that a significant proportion of immunodeficient patients (32.6%) who experienced prolonged viral replication also exhibited sotrovimab escape mutations. This highlights the potential for viral mutations to occur in immunocompromised individuals and underscores the need for caution when using single mAbs or antiviral agents such as remdesivir in this patient population [85]. New SARS-CoV-2 variants tend to emerge more frequently in immunocompromised patients with persistent infections.

Based on available studies, the administration of a single mAb or antiviral drug should be avoided in immunocompromised patients due to the risk of emergent mutations. Instead, combination therapies involving at least two mAbs or other antivirals such as remdesivir, molnupiravir, and nirmatrelvir/ritonavir should be considered when treating immunodeficient patients with SARS-CoV-2 infection.

The introduction of messenger RNA (mRNA) vaccines to combat SARS-CoV-2 and the implementation of mass vaccination programs globally provided significant protection against the ongoing pandemic. Despite that, many fully vaccinated individuals suffered from reinfections during the Delta wave. However, the severity of the infection was found to be remarkably low in these patients. The emergence of a highly mutated Omicron variant raised concerns regarding the efficacy of present immunization strategies. The highest number of mutations in the Omicron variant is present in the spike protein, which is the core target of vaccine design. One research study indicated that the present neutralizing antibodies (Nab) might still attach to the mutated spike protein of the Omicron, but with low affinity compared with previous variants. This indicates that up to some extent, the antibodies generated due to past infection and vaccinations may protect against Omicron. Even low Nab concentrations were capable of protection against severe illness and death. The efficacy of vaccines is typically measured immediately after vaccination and six months after the first dose. Numerous studies indicated that a decline in the Nab levels was seen following 3–8 months of vaccination. David Khoury et al. reported that after six months of immunization, the efficacy of vaccines against Omicron had dropped to 7.5%, 28.1%, and 40.4% for the Covishield, BNT16262, and Moderna vaccines, respectively. This implied the addition of a booster dose of existing vaccines to strengthen the protection against

Omicron. It was found that booster doses increased the efficacy of mRNA vaccines to 86.2% and 98.2% against symptomatic infections and severe disease, respectively [104,105]. One more study reported that there was an 81% lesser risk of hospitalization in Omicron patients who received three doses of vaccines compared with unvaccinated cases [106]. Thus, to diminish the impact of Omicron and to prevent the worsening of the pandemic, the Technical Advisory Group on COVID-19 vaccines composition (TAG-Co--VAC) widely encouraged the implementation of booster dose vaccination programs, globally [16]. The quest for improved protection against SARS-Cov-2 did not end after the introduction of one booster dose. To further enhance the protection and to restore the fading protection from initial vaccinations, a second booster/fourth dose of mRNA vaccines was introduced. It was primarily studied in the elderly population, as young and healthy individuals had already acquired sufficient protection from previous vaccinations and infections. Hence, the potential benefits of a second booster in young people did not outweigh the socioeconomic costs. Moreover, it was studied that in individuals with high pre-booster immunity, minimal to no benefits were observed following the administration of the second booster, owing to the immune ceiling effects [107]. In older adults, the benefits of a second booster dose were encouraging. According to the US Center for Disease Control and Prevention data, the administration of a second booster in individuals of age >50 years reduced the risk of mortality by three times compared with people with only one booster dose [108]. A study in Israel demonstrated that although the second booster provided higher protection against Omicron, a decrease in protection was observed following the fourth week of vaccination [109,110]. A study by Nissimov et al. evaluated the benefits of the fourth dose in patients having a mean age of 80 years who were hospitalized for SARS-CoV-2 infection. It was reported that the administration of the fourth dose was related to higher protection against mechanical ventilation and death (OR 0.51; 95% CI 0.3–0.87) [111]. Another study evaluating the impact of the fourth dose of vaccine on residents of long-term care facilities reported that even though it protected the elderly against hospitalization and mortality, the protection against infection was found to be moderate [112]. Even though the protection provided by the second booster dose is highly beneficial to the elderly against the Omicron variant, the sustainability of this protection is not certain. The researchers must work towards identifying the frequency of repetition of these vaccines, which is of higher importance in the older population, as they have a dysfunctional immune system [113]. Additionally, the reduction in the efficacy of current vaccines against Omicron has obligated the development of more potent vaccination strategies while keeping the viral evolution in mind [95].

6. Conclusions

Owing to the constant evolution of SARS-CoV-2, many variants have emerged since the initial outbreak. Most recently, the Omicron variant has dominated the pandemic on a global scale due to its rapid transmission worldwide. It has become the most prevalent SARS-CoV-2 variant replacing the Delta variant as the VOC. The emergence of the Omicron variant was followed by many challenges as well as some silver linings. The Omicron variant was found to be highly mutated, resulting in higher transmission rates. Moreover, these mutations enabled the Omicron to escape the Nabs from previous vaccinations and infections with other variants. The disease severity from the Omicron variant was found to be significantly less severe compared with other variants, providing some solace in the fear of a deadlier pandemic. Immunocompromised individuals, including the elderly, cancer patients, multimorbid patients, and organ transplant recipients are at higher risk of progressing to severe disease and COVID-19-related mortality. Several studies have concluded that even in elderly patients, the presence of comorbidities including CKD and cardiovascular diseases were prime risk factors for the development of severe disease. The impairment of innate, as well as adaptive, immune responses in this population leads to prolonged viral shedding time and exaggerated response, resulting in cytokine storm in the lungs. Thus, these patients should be prioritized in the clinical settings

and should be given early attention to prevent deterioration. The present immunization strategies including booster vaccinations have failed to produce a sufficient response in these patients. Additionally, single therapy with monoclonal antibodies has found to be ineffective in reducing the severity of the disease. The use of Sotrovimab, a mAb introduced specifically for the immunodeficient population, was associated with escape variants and viral persistence as well. The lack of concrete evidence regarding the management of immunodeficient patients infected with the Omicron variant is largely due to the exclusion of these patients from routine clinical trials. Designing large-scale studies to evaluate and understand the clinical outcomes and long-term effects of various treatment strategies and vaccination can provide more critical insights for the future. The emergence of the Omicron variant is a reminder that the threat of the emergence of novel, more fatal, and highly mutated variants can never be disregarded. Thus, remaining vigilant and ensuring that every eligible individual is vaccinated with booster doses is essential.

Author Contributions: Conceptualization, V.P.C. and A.K.; data curation, K.M. and S.B.; writing—original draft preparation, S.S., K.M. and S.B.; writing—review and editing, S.S. and A.K.; visualization, K.M. and S.B.; supervision, V.P.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

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

References

1. Chouaki Benmansour, N.; Carvelli, J.; Vivier, E. Complement cascade in severe forms of COVID-19: Recent advances in therapy. *Eur. J. Immunol.* **2021**, *51*, 1652–1659. [CrossRef] [PubMed]
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] [PubMed]
3. 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]
4. Ameratunga, R.; Leung, E.; Woon, S.T.; Chan, L.; Steele, R.; Lehnert, K.; Longhurst, H. SARS-CoV-2 Omicron: Light at the End of the Long Pandemic Tunnel or Another False Dawn for Immunodeficient Patients? *J. Allergy Clin. Immunol. Pract.* **2022**, *10*, 2267–2273. [CrossRef]
5. Tracking SARS-CoV-2 Variants, WHO. Available online: https://www.who.int/activities/tracking-SARS-CoV-2-variants (accessed on 31 May 2023).
6. Viana, R.; Moyo, S.; Amoako, D.G.; Tegally, H.; Scheepers, C.; Althaus, C.L.; Anyaneji, U.J.; Bester, P.A.; Boni, M.F.; Chand, M.; et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. *Nature* **2022**, *603*, 679–686. [CrossRef]
7. He, X.; Hong, W.; Pan, X.; Lu, G.; Wei, X. SARS-CoV-2 Omicron variant: Characteristics and prevention. *MedComm* **2021**, *2*, 838–845. [CrossRef]
8. Chen, J.; Wang, R.; Wang, M.; Wei, G.W. Mutations Strengthened SARS-CoV-2 Infectivity. *J. Mol. Biol.* **2020**, *432*, 5212–5226. [CrossRef]
9. Pulliam, J.R.C.; van Schalkwyk, C.; Govender, N.; von Gottberg, A.; Cohen, C.; Groome, M.J.; Dushoff, J.; Mlisana, K.; Moultrie, H. Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa. *Science* **2022**, *376*, eabn4947. [CrossRef]
10. Bigdelou, B.; Sepand, M.R.; Najafikhoshnoo, S.; Negrete, J.A.T.; Sharaf, M.; Ho, J.Q.; Sullivan, I.; Chauhan, P.; Etter, M.; Shekarian, T.; et al. COVID-19 and Preexisting Comorbidities: Risks, Synergies, and Clinical Outcomes. *Front. Immunol.* **2022**, *13*, 890517. [CrossRef]
11. Burki, T.K. Omicron variant and booster COVID-19 vaccines. *Lancet Respir. Med.* **2022**, *10*, e17. [CrossRef]
12. Chavda, V.P.; Bezbaruah, R.; Deka, K.; Nongrang, L.; Kalita, T. The Delta and Omicron Variants of SARS-CoV-2: What We Know So Far. *Vaccines* **2022**, *10*, 1926. [CrossRef] [PubMed]
13. Karim, S.S.A.; Karim, Q.A. Omicron SARS-CoV-2 variant: A new chapter in the COVID-19 pandemic. *Lancet* **2021**, *398*, 2126–2128. [CrossRef]

14. Guo, Y.; Han, J.; Zhang, Y.; He, J.; Yu, W.; Zhang, X.; Wu, J.; Zhang, S.; Kong, Y.; Guo, Y.; et al. SARS-CoV-2 Omicron Variant: Epidemiological Features, Biological Characteristics, and Clinical Significance. *Front. Immunol.* **2022**, *13*, 877101. [CrossRef] [PubMed]
15. Jung, C.; Kmiec, D.; Koepke, L.; Zech, F.; Jacob, T.; Sparrer, K.M.J.; Kirchhoff, F. Omicron: What Makes the Latest SARS-CoV-2 Variant of Concern So Concerning? *J. Virol.* **2022**, *96*, e0207721. [CrossRef] [PubMed]
16. Rana, R.; Kant, R.; Huirem, R.S.; Bohra, D.; Ganguly, N.K. Omicron variant: Current insights and future directions. *Microbiol. Res.* **2022**, *265*, 127204. [CrossRef] [PubMed]
17. Torjesen, I. COVID-19: Omicron may be more transmissible than other variants and partly resistant to existing vaccines, scientists fear. *BMJ* **2021**, *375*, n2943. [CrossRef] [PubMed]
18. Gu, H.; Krishnan, P.; Ng, D.Y.M.; Chang, L.D.J.; Liu, G.Y.Z.; Cheng, S.S.M.; Hui, M.M.Y.; Fan, M.C.Y.; Wan, J.H.L.; Lau, L.H.K.; et al. Probable Transmission of SARS-CoV-2 Omicron Variant in Quarantine Hotel, Hong Kong, China, November 2021. *Emerg. Infect. Dis.* **2022**, *28*, 460–462. [CrossRef] [PubMed]
19. Naresh, G.; Guruprasad, L. Mutations in the receptor-binding domain of human SARS CoV-2 spike protein increases its affinity to bind human ACE-2 receptor. *J. Biomol. Struct. Dyn.* **2022**, *41*, 2368–2381. [CrossRef]
20. Peacock, T.P.; Goldhill, D.H.; Zhou, J.; Baillon, L.; Frise, R.; Swann, O.C.; Kugathasan, R.; Penn, R.; Brown, J.C.; Sanchez-David, R.Y.; et al. The furin cleavage site in the SARS-CoV-2 spike protein is required for transmission in ferrets. *Nat. Microbiol.* **2021**, *6*, 899–909. [CrossRef]
21. Chen, J.; Gao, K.; Wang, R.; Wei, G.W. Prediction and mitigation of mutation threats to COVID-19 vaccines and antibody therapies. *Chem. Sci.* **2021**, *12*, 6929–6948. [CrossRef]
22. Choi, B.; Choudhary, M.C.; Regan, J.; Sparks, J.A.; Padera, R.F.; Qiu, X.; Solomon, I.H.; Kuo, H.H.; Boucau, J.; Bowman, K.; et al. Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host. *N. Engl. J. Med.* **2020**, *383*, 2291–2293. [CrossRef] [PubMed]
23. Cerutti, G.; Guo, Y.; Zhou, T.; Gorman, J.; Lee, M.; Rapp, M.; Reddem, E.R.; Yu, J.; Bahna, F.; Bimela, J.; et al. Potent SARS-CoV-2 neutralizing antibodies directed against spike N-terminal domain target a single supersite. *Cell Host Microbe* **2021**, *29*, 819–833.e7. [CrossRef] [PubMed]
24. Planas, D.; Saunders, N.; Maes, P.; Guivel-Benhassine, F.; Planchais, C.; Buchrieser, J.; Bolland, W.H.; Porrot, F.; Staropoli, I.; Lemoine, F.; et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature* **2022**, *602*, 671–675. [CrossRef] [PubMed]
25. Chavda, V.P.; Apostolopoulos, V. Omicron variant (B.1.1.529) of SARS-CoV-2: Threat for the elderly? *Maturitas* **2022**, *158*, 78–81. [CrossRef] [PubMed]
26. Yu, J.; Collier, A.Y.; Rowe, M.; Mardas, F.; Ventura, J.D.; Wan, H.; Miller, J.; Powers, O.; Chung, B.; Siamatu, M.; et al. Neutralization of the SARS-CoV-2 Omicron BA.1 and BA.2 Variants. *N. Engl. J. Med.* **2022**, *386*, 1579–1580. [CrossRef]
27. Alba, J.M.G.; Pérez-Martínez, Z.; Boga, J.A.; Rojo-Alba, S.; de Oña, J.G.; Alvarez-Argüelles, M.E.; Rodríguez, G.M.; Gonzalez, I.C.; González, I.H.; Coto, E.; et al. Emergence of New SARS-CoV2 Omicron Variants after the Change of Surveillance and Control Strategy. *Microorganisms* **2022**, *10*, 1954. [CrossRef]
28. Kumar, S.; Karuppanan, K.; Subramaniam, G. Omicron (BA.1) and sub-variants (BA.1.1, BA.2, and BA.3) of SARS-CoV-2 spike infectivity and pathogenicity: A comparative sequence and structural-based computational assessment. *J. Med. Virol.* **2022**, *94*, 4780–4791. [CrossRef]
29. Yamasoba, D.; Kimura, I.; Nasser, H.; Morioka, Y.; Nao, N.; Ito, J.; Uriu, K.; Tsuda, M.; Zahradnik, J.; Shirakawa, K.; et al. Virological characteristics of the SARS-CoV-2 Omicron BA.2 spike. *Cell* **2022**, *185*, 2103–2115.e19. [CrossRef]
30. CoVariants. Available online: https://covariants.org/variants/21L.Omicron (accessed on 13 February 2023).
31. Mohapatra, R.K.; Kandi, V.; Sarangi, A.K.; Verma, S.; Tuli, H.S.; Chakraborty, S.; Chakraborty, C.; Dhama, K. The recently emerged BA.4 and BA.5 lineages of Omicron and their global health concerns amid the ongoing wave of COVID-19 pandemic-Correspondence. *Int. J. Surg.* **2022**, *103*, 106698. [CrossRef]
32. Tegally, H.; Moir, M.; Everatt, J.; Giovanetti, M.; Scheepers, C.; Wilkinson, E.; Subramoney, K.; Makatini, Z.; Moyo, S.; Amoako, D.G.; et al. Emergence of SARS-CoV-2 Omicron lineages BA.4 and BA.5 in South Africa. *Nat. Med.* **2022**, *28*, 1785–1790. [CrossRef]
33. Wang, Q.; Guo, Y.; Iketani, S.; Nair, M.S.; Li, Z.; Mohri, H.; Wang, M.; Yu, J.; Bowen, A.D.; Chang, J.Y.; et al. Antibody evasion by SARS-CoV-2 Omicron subvariants BA.2.12.1, BA.4 and BA.5. *Nature* **2022**, *608*, 603–608. [CrossRef] [PubMed]
34. Wolter, N.; Jassat, W.; Walaza, S.; Welch, R.; Moultrie, H.; Groome, M.; Amoako, D.G.; Everatt, J.; Bhiman, J.N.; Scheepers, C.; et al. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: A data linkage study. *Lancet* **2022**, *399*, 437–446. [CrossRef]
35. Maslo, C.; Friedland, R.; Toubkin, M.; Laubscher, A.; Akaloo, T.; Kama, B. Characteristics and Outcomes of Hospitalized Patients in South Africa During the COVID-19 Omicron Wave Compared With Previous Waves. *JAMA* **2022**, *327*, 583–584. [CrossRef]
36. Meo, S.A.; Meo, A.S.; Al-Jassir, F.F.; Klonoff, D.C. Omicron SARS-CoV-2 new variant: Global prevalence and biological and clinical characteristics. *Eur. Rev. Med. Pharmacol. Sci.* **2021**, *25*, 8012–8018. [CrossRef] [PubMed]
37. Butowt, R.; Bilińska, K.; von Bartheld, C. Why Does the Omicron Variant Largely Spare Olfactory Function? Implications for the Pathogenesis of Anosmia in Coronavirus Disease 2019. *J. Infect. Dis.* **2022**, *226*, 1304–1308. [CrossRef]

38. Menni, C.; Valdes, A.M.; Polidori, L.; Antonelli, M.; Penamakuri, S.; Nogal, A.; Louca, P.; May, A.; Figueiredo, J.C.; Hu, C.; et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: A prospective observational study from the ZOE COVID Study. *Lancet* **2022**, *399*, 1618–1624. [CrossRef] [PubMed]
39. Tsakok, M.T.; Watson, R.A.; Saujani, S.J.; Kong, M.; Xie, C.; Peschl, H.; Wing, L.; MacLeod, F.K.; Shine, B.; Talbot, N.P.; et al. Reduction in Chest CT Severity and Improved Hospital Outcomes in SARS-CoV-2 Omicron Compared with Delta Variant Infection. *Radiology* **2023**, *306*, 261–269. [CrossRef]
40. Malahe, S.R.K.; Hoek, R.A.S.; Dalm, V.; Broers, A.E.C.; den Hoed, C.M.; Manintveld, O.C.; Baan, C.C.; van Deuzen, C.M.; Papageorgiou, G.; Bax, H.I.; et al. Clinical Characteristics and Outcomes of Immunocompromised Patients With Coronavirus Disease 2019 Caused by the Omicron Variant: A Prospective, Observational Study. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2023**, *76*, e172–e178. [CrossRef]
41. Yan, F.; Huang, F.; Xu, J.; Yang, P.; Qin, Y.; Lv, J.; Zhang, S.; Ye, L.; Gong, M.; Liu, Z.; et al. Antihypertensive drugs are associated with reduced fatal outcomes and improved clinical characteristics in elderly COVID-19 patients. *Cell Discov.* **2020**, *6*, 77. [CrossRef]
42. Ying-Hao, P.; Yuan-Yuan, G.; Hai-Dong, Z.; Qiu-Hua, C.; Xue-Ran, G.; Hai-Qi, Z.; Hua, J. Clinical characteristics and analysis of risk factors for disease progression of patients with SARS-CoV-2 Omicron variant infection: A retrospective study of 25207 cases in a Fangcang hospital. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 1009894. [CrossRef]
43. Kahn, F.; Bonander, C.; Moghaddassi, M.; Rasmussen, M.; Malmqvist, U.; Inghammar, M.; Björk, J. Risk of severe COVID-19 from the Delta and Omicron variants in relation to vaccination status, sex, age and comorbidities-surveillance results from southern Sweden, July 2021 to January 2022. *Euro Surveill. Bull. Eur. Sur Les Mal. Transm. Eur. Commun. Dis. Bull.* **2022**, *27*, 2200121. [CrossRef] [PubMed]
44. Corriero, A.; Ribezzi, M.; Mele, F.; Angrisani, C.; Romaniello, F.; Daleno, A.; Loconsole, D.; Centrone, F.; Chironna, M.; Brienza, N. COVID-19 Variants in Critically Ill Patients: A Comparison of the Delta and Omicron Variant Profiles. *Infect. Dis. Rep.* **2022**, *14*, 492–500. [CrossRef] [PubMed]
45. Shrestha, L.B.; Foster, C.; Rawlinson, W.; Tedla, N.; Bull, R.A. Evolution of the SARS-CoV-2 omicron variants BA.1 to BA.5: Implications for immune escape and transmission. *Rev. Med. Virol.* **2022**, *32*, e2381. [CrossRef]
46. Osterman, A.; Badell, I.; Basara, E.; Stern, M.; Kriesel, F.; Eletreby, M.; Öztan, G.N.; Huber, M.; Autenrieth, H.; Knabe, R.; et al. Impaired detection of omicron by SARS-CoV-2 rapid antigen tests. *Med. Microbiol. Immunol.* **2022**, *211*, 105–117. [CrossRef] [PubMed]
47. Fan, Y.; Li, X.; Zhang, L.; Wan, S.; Zhang, L.; Zhou, F. SARS-CoV-2 Omicron variant: Recent progress and future perspectives. *Signal Transduct. Target. Ther.* **2022**, *7*, 141. [CrossRef] [PubMed]
48. Rivera-Torres, J.; Girón, N.; San José, E. COVID-19: A Comprehensive Review on Cardiovascular Alterations, Immunity, and Therapeutics in Older Adults. *J. Clin. Med.* **2023**, *12*, 488. [CrossRef]
49. Gabrielli, M. COVID-19 in Older Adults at the Time of the Omicron Variant. *J. Clin. Med.* **2022**, *11*, 5273. [CrossRef]
50. Gao, Y.; Chen, Y.; Liu, M.; Shi, S.; Tian, J. Impacts of immunosuppression and immunodeficiency on COVID-19: A systematic review and meta-analysis. *J. Infect.* **2020**, *81*, e93–e95. [CrossRef]
51. Verdecchia, P.; Cavallini, C.; Spanevello, A.; Angeli, F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur. J. Intern. Med.* **2020**, *76*, 14–20. [CrossRef]
52. Fu, L.; Liu, X.; Su, Y.; Ma, J.; Hong, K. Prevalence and impact of cardiac injury on COVID-19: A systematic review and meta-analysis. *Clin. Cardiol.* **2021**, *44*, 276–283. [CrossRef]
53. Ward, I.L.; Bermingham, C.; Ayoubkhani, D.; Gethings, O.J.; Pouwels, K.B.; Yates, T.; Khunti, K.; Hippisley-Cox, J.; Banerjee, A.; Walker, A.S.; et al. Risk of COVID-19 related deaths for SARS-CoV-2 omicron (B.1.1.529) compared with delta (B.1.617.2): Retrospective cohort study. *BMJ* **2022**, *378*, e070695. [CrossRef]
54. Mefsin, Y.M.; Chen, D.; Bond, H.S.; Lin, Y.; Cheung, J.K.; Wong, J.Y.; Ali, S.T.; Lau, E.H.Y.; Wu, P.; Leung, G.M.; et al. Epidemiology of Infections with SARS-CoV-2 Omicron BA.2 Variant, Hong Kong, January–March 2022. *Emerg. Infect. Dis.* **2022**, *28*, 1856–1858. [CrossRef]
55. Canan, C.H.; Gokhale, N.S.; Carruthers, B.; Lafuse, W.P.; Schlesinger, L.S.; Torrelles, J.B.; Turner, J. Characterization of lung inflammation and its impact on macrophage function in aging. *J. Leukoc. Biol.* **2014**, *96*, 473–480. [CrossRef] [PubMed]
56. 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] [PubMed]
57. Fuentes, E.; Fuentes, M.; Alarcón, M.; Palomo, I. Immune System Dysfunction in the Elderly. *An. Acad. Bras. Cienc.* **2017**, *89*, 285–299. [CrossRef] [PubMed]
58. Franceschi, C.; Bonafè, M.; Valensin, S.; Olivieri, F.; De Luca, M.; Ottaviani, E.; De Benedictis, G. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann. N. Y. Acad. Sci.* **2000**, *908*, 244–254. [CrossRef] [PubMed]
59. Kovacs, E.J.; Boe, D.M.; Boule, L.A.; Curtis, B.J. Inflammaging and the Lung. *Clin. Geriatr. Med.* **2017**, *33*, 459–471. [CrossRef]
60. Fericean, R.M.; Oancea, C.; Reddyreddy, A.R.; Rosca, O.; Bratosin, F.; Bloanca, V.; Citu, C.; Alambaram, S.; Vasamsetti, N.G.; Dumitru, C. Outcomes of Elderly Patients Hospitalized with the SARS-CoV-2 Omicron B.1.1.529 Variant: A Systematic Review. *Int. J. Environ. Res. Public Health* **2023**, *20*, 2150. [CrossRef]

61. Paranjpe, I.; Russak, A.J.; De Freitas, J.K.; Lala, A.; Miotto, R.; Vaid, A.; Johnson, K.W.; Danieletto, M.; Golden, E.; Meyer, D.; et al. Retrospective cohort study of clinical characteristics of 2199 hospitalised patients with COVID-19 in New York City. *BMJ Open* **2020**, *10*, e040736. [CrossRef]
62. ERA-EDTA Council; ERACODA Working Group. Chronic kidney disease is a key risk factor for severe COVID-19: A call to action by the ERA-EDTA. *Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc. Eur. Ren. Assoc.* **2021**, *36*, 87–94. [CrossRef]
63. Dwyer, K.M.; Sum, C.; Johnson, D.W. Impact of COVID-19 on the worsening crisis of chronic kidney disease: The imperative to fund early detection is now. *Intern. Med. J.* **2022**, *52*, 680–682. [CrossRef]
64. Chung, E.Y.M.; Palmer, S.C.; Natale, P.; Krishnan, A.; Cooper, T.E.; Saglimbene, V.M.; Ruospo, M.; Au, E.; Jayanti, S.; Liang, A.; et al. Incidence and Outcomes of COVID-19 in People With CKD: A Systematic Review and Meta-analysis. *Am. J. Kidney Dis. Off. J. Natl. Kidney Found.* **2021**, *78*, 804–815. [CrossRef] [PubMed]
65. Chen, X.; Wang, H.; Ai, J.; Shen, L.; Lin, K.; Yuan, G.; Sheng, X.; Jin, X.; Deng, Z.; Xu, J.; et al. Identification of CKD, bedridden history and cancer as higher-risk comorbidities and their impact on prognosis of hospitalized Omicron patients: A multi-centre cohort study. *Emerg. Microbes Infect.* **2022**, *11*, 2501–2509. [CrossRef] [PubMed]
66. Bakouny, Z.; Hawley, J.E.; Choueiri, T.K.; Peters, S.; Rini, B.I.; Warner, J.L.; Painter, C.A. COVID-19 and Cancer: Current Challenges and Perspectives. *Cancer Cell* **2020**, *38*, 629–646. [CrossRef]
67. Lee, M.; Quinn, R.; Pradhan, K.; Fedorov, K.; Levitz, D.; Fromowitz, A.; Thakkar, A.; Shapiro, L.C.; Kabarriti, R.; Ruiz, R.E.; et al. Impact of COVID-19 on case fatality rate of patients with cancer during the Omicron wave. *Cancer Cell* **2022**, *40*, 343–345. [CrossRef] [PubMed]
68. Tian, Y.; Qiu, X.; Wang, C.; Zhao, J.; Jiang, X.; Niu, W.; Huang, J.; Zhang, F. Cancer associates with risk and severe events of COVID-19: A systematic review and meta-analysis. *Int. J. Cancer* **2021**, *148*, 363–374. [CrossRef] [PubMed]
69. Rolston, K.V. Infections in Cancer Patients with Solid Tumors: A Review. *Infect. Dis. Ther.* **2017**, *6*, 69–83. [CrossRef] [PubMed]
70. Postow, M.A.; Sidlow, R.; Hellmann, M.D. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. *N. Engl. J. Med.* **2018**, *378*, 158–168. [CrossRef]
71. Mangalmurti, N.; Hunter, C.A. Cytokine Storms: Understanding COVID-19. *Immunity* **2020**, *53*, 19–25. [CrossRef]
72. Barrière, J.; Carles, M.; Audigier-Valette, C.; Re, D.; Adjtoutah, Z.; Seitz-Polski, B.; Gounant, V.; Descamps, D.; Zalcman, G. Third dose of anti-SARS-CoV-2 vaccine for patients with cancer: Should humoral responses be monitored? A position article. *Eur. J. Cancer* **2022**, *162*, 182–193. [CrossRef]
73. Barrière, J.; Zalcman, G.; Fignon, L.; Peiffer-Smadja, N.; Audigier-Valette, C.; Carles, M. Omicron variant: A clear and present danger for patients with cancer. *Eur. J. Cancer* **2022**, *165*, 25–26. [CrossRef]
74. Kates, O.S.; Haydel, B.M.; Florman, S.S.; Rana, M.M.; Chaudhry, Z.S.; Ramesh, M.S.; Safa, K.; Kotton, C.N.; Blumberg, E.A.; Besharatian, B.D.; et al. Coronavirus Disease 2019 in Solid Organ Transplant: A Multicenter Cohort Study. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2021**, *73*, e4090–e4099. [CrossRef]
75. Ferreira, V.H.; Hu, Q.; Kurtesi, A.; Solera, J.T.; Ierullo, M.; Gingras, A.C.; Kumar, D.; Humar, A. Impact of Omicron BA.1 infection on BA.4/5 immunity in transplant recipients. *Am. J. Transplant. Off. J. Am. Soc. Transplant. Am. Soc. Transpl. Surg.* **2023**, *23*, 278–283. [CrossRef]
76. Qin, C.X.; Moore, L.W.; Anjan, S.; Rahamimov, R.; Sifri, C.D.; Ali, N.M.; Morales, M.K.; Tsapepas, D.S.; Basic-Jukic, N.; Miller, R.A.; et al. Risk of Breakthrough SARS-CoV-2 Infections in Adult Transplant Recipients. *Transplantation* **2021**, *105*, e265–e266. [CrossRef] [PubMed]
77. Ko, J.Y.; Danielson, M.L.; Town, M.; Derado, G.; Greenlund, K.J.; Kirley, P.D.; Alden, N.B.; Yousey-Hindes, K.; Anderson, E.J.; Ryan, P.A.; et al. Risk Factors for Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization: COVID-19-Associated Hospitalization Surveillance Network and Behavioral Risk Factor Surveillance System. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2021**, *72*, e695–e703. [CrossRef] [PubMed]
78. Azzi, Y.; Bartash, R.; Scalea, J.; Loarte-Campos, P.; Akalin, E. COVID-19 and Solid Organ Transplantation: A Review Article. *Transplantation* **2021**, *105*, 37–55. [CrossRef] [PubMed]
79. Rabinowich, L.; Grupper, A.; Baruch, R.; Ben-Yehoyada, M.; Halperin, T.; Turner, D.; Katchman, E.; Levi, S.; Houri, I.; Lubezky, N.; et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. *J. Hepatol.* **2021**, *75*, 435–438. [CrossRef] [PubMed]
80. Herting, A.; Jahnke-Triankowski, J.; Harberts, A.; Schaub, G.M.; Lütgehetmann, M.; Ruether, D.F.; Fischer, L.; Addo, M.M.; Lohse, A.W.; Schulze Zur Wiesch, J.; et al. Clinical Outcomes of SARS-CoV-2 Breakthrough Infections in Liver Transplant Recipients during the Omicron Wave. *Viruses* **2023**, *15*, 297. [CrossRef] [PubMed]
81. Hachmann, N.P.; Miller, J.; Collier, A.Y.; Ventura, J.D.; Yu, J.; Rowe, M.; Bondzie, E.A.; Powers, O.; Surve, N.; Hall, K.; et al. Neutralization Escape by SARS-CoV-2 Omicron Subvariants BA.2.12.1, BA.4, and BA.5. *N. Engl. J. Med.* **2022**, *387*, 86–88. [CrossRef]
82. Wong, G.; Rowlandson, M.; Sabanayagam, D.; Ginn, A.N.; Kable, K.; Sciberras, F.; Au, E.; Draper, J.; Arnott, A.; Sintchenko, V.; et al. COVID-19 Infection With the Omicron SARS-CoV-2 Variant in a Cohort of Kidney and Kidney Pancreas Transplant Recipients: Clinical Features, Risk Factors, and Outcomes. *Transplantation* **2022**, *106*, 1860–1866. [CrossRef]
83. Takashita, E.; Kinoshita, N.; Yamayoshi, S.; Sakai-Tagawa, Y.; Fujisaki, S.; Ito, M.; Iwatsuki-Horimoto, K.; Halfmann, P.; Watanabe, S.; Maeda, K.; et al. Efficacy of Antiviral Agents against the SARS-CoV-2 Omicron Subvariant BA.2. *N. Engl. J. Med.* **2022**, *386*, 1475–1477. [CrossRef]

84. Trøseid, M.; Hentzien, M.; Ader, F.; Cardoso, S.W.; Arribas, J.R.; Molina, J.M.; Mueller, N.; Hites, M.; Bonnet, F.; Manuel, O.; et al. Immunocompromised patients have been neglected in COVID-19 trials: A call for action. *Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis.* **2022**, *28*, 1182–1183. [CrossRef] [PubMed]
85. Gliga, S.; Lübke, N.; Killer, A.; Gruell, H.; Walker, A.; Dilthey, A.T.; Thielen, A.; Lohr, C.; Flaßhove, C.; Krieg, S.; et al. Rapid Selection of Sotrovimab Escape Variants in Severe Acute Respiratory Syndrome Coronavirus 2 Omicron-Infected Immunocompromised Patients. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2023**, *76*, 408–415. [CrossRef] [PubMed]
86. Akinosoglou, K.; Rigopoulos, E.A.; Kaiafa, G.; Daios, S.; Karlafti, E.; Ztriva, E.; Polychronopoulos, G.; Gogos, C.; Savopoulos, C. Tixagevimab/Cilgavimab in SARS-CoV-2 Prophylaxis and Therapy: A Comprehensive Review of Clinical Experience. *Viruses* **2022**, *15*, 118. [CrossRef] [PubMed]
87. Huygens, S.; Oude Munnink, B.; Gharbharan, A.; Koopmans, M.; Rijnders, B. Sotrovimab Resistance and Viral Persistence after Treatment of Immunocompromised Patients Infected with the Severe Acute Respiratory Syndrome Coronavirus 2 Omicron Variant. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2023**, *76*, e507–e509. [CrossRef]
88. Al-Obaidi, M.M.; Gungor, A.B.; Murugapandian, S.; Thajudeen, B.; Mansour, I.; Wong, R.C.; Tanriover, B.; Zangeneh, T.T. The Impact of Nirmatrelvir-Ritonavir in Reducing Hospitalizations Among High-Risk Patients With SARS-CoV-2 During the Omicron Predominant Era. *Am. J. Med.* **2023**, *136*, 577–584. [CrossRef]
89. Zhong, W.; Jiang, X.; Yang, X.; Feng, T.; Duan, Z.; Wang, W.; Sun, Z.; Chen, L.; Nie, X.; Zhu, C.; et al. The efficacy of paxlovid in elderly patients infected with SARS-CoV-2 omicron variants: Results of a non-randomized clinical trial. *Front. Med.* **2022**, *9*, 980002. [CrossRef]
90. Tan, K.T.; Benedict, S.L.H.; Chang, C.Y.; Chidambaram, S.K.; Abd Jamil, I.; Bahrudin, M.S.; Kandasamy, S.S.; Khor, C.S. Clinical severity of COVID-19 with omicron variant predominance in relation to vaccination status, age, comorbidities- a single center in Selangor, Malaysia. *Med. J. Malays.* **2022**, *77*, 558–563.
91. Nevejan, L.; Ombelet, S.; Laenen, L.; Keyaerts, E.; Demuyser, T.; Seyler, L.; Soetens, O.; Van Nedervelde, E.; Naesens, R.; Geysels, D.; et al. Severity of COVID-19 among Hospitalized Patients: Omicron Remains a Severe Threat for Immunocompromised Hosts. *Viruses* **2022**, *14*, 2736. [CrossRef]
92. Jassat, W.; Mudara, C.; Vika, C.; Welch, R.; Arendse, T.; Dryden, M.; Blumberg, L.; Mayet, N.; Tempia, S.; Parker, A.; et al. A cohort study of post-COVID-19 condition across the Beta, Delta, and Omicron waves in South Africa: 6-month follow-up of hospitalized and nonhospitalized participants. *Int. J. Infect. Dis. IJID Off. Publ. Int. Soc. Infect. Dis.* **2023**, *128*, 102–111. [CrossRef]
93. Niemann, C.U.; da Cunha-Bang, C.; Helleberg, M.; Ostrowski, S.R.; Brieghel, C. Patients with CLL have a lower risk of death from COVID-19 in the Omicron era. *Blood* **2022**, *140*, 445–450. [CrossRef] [PubMed]
94. Solera, J.T.; Árbol, B.G.; Alshahrani, A.; Bahinskaya, I.; Marks, N.; Humar, A.; Kumar, D. Impact of Vaccination and Early Monoclonal Antibody Therapy on Coronavirus Disease 2019 Outcomes in Organ Transplant Recipients During the Omicron Wave. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2022**, *75*, 2193–2200. [CrossRef] [PubMed]
95. Taylor, P.C.; Adams, A.C.; Hufford, M.M.; de la Torre, I.; Winthrop, K.; Gottlieb, R.L. Neutralizing monoclonal antibodies for treatment of COVID-19. *Nat. Rev. Immunol.* **2021**, *21*, 382–393. [CrossRef] [PubMed]
96. Focosi, D.; McConnell, S.; Casadevall, A.; Cappello, E.; Valdiserra, G.; Tuccori, M. Monoclonal antibody therapies against SARS-CoV-2. *Lancet Infect. Dis.* **2022**, *22*, e311–e326. [CrossRef]
97. Falcone, M.; Tiseo, G.; Valoriani, B.; Barbieri, C.; Occhineri, S.; Mazzetti, P.; Vatteroni, M.L.; Suardi, L.R.; Riccardi, N.; Pistello, M.; et al. Efficacy of Bamlanivimab/Etesevimab and Casirivimab/Imdevimab in Preventing Progression to Severe COVID-19 and Role of Variants of Concern. *Infect. Dis. Ther.* **2021**, *10*, 2479–2488. [CrossRef]
98. Savoldi, A.; Morra, M.; De Nardo, P.; Cattelan, A.M.; Mirandola, M.; Manfrin, V.; Scotton, P.; Giordani, M.T.; Brollo, L.; Panese, S.; et al. Clinical efficacy of different monoclonal antibody regimens among non-hospitalised patients with mild to moderate COVID-19 at high risk for disease progression: A prospective cohort study. *Eur. J. Clin. Microbiol. Infect. Dis. Off. Publ. Eur. Soc. Clin. Microbiol.* **2022**, *41*, 1065–1076. [CrossRef] [PubMed]
99. Konyak, B.M.; Sharma, M.; Kharia, S.; Pandey, R.P.; Chang, C.M. A Systematic Review on the Emergence of Omicron Variant and Recent Advancement in Therapies. *Vaccines* **2022**, *10*, 1468. [CrossRef]
100. Takashita, E.; Yamayoshi, S.; Simon, V.; van Bakel, H.; Sordillo, E.M.; Pekosz, A.; Fukushi, S.; Suzuki, T.; Maeda, K.; Halfmann, P.; et al. Efficacy of Antibodies and Antiviral Drugs against Omicron BA.2.12.1, BA.4, and BA.5 Subvariants. *N. Engl. J. Med.* **2022**, *387*, 468–470. [CrossRef]
101. Planas, D.; Veyer, D.; Baidaliuk, A.; Staropoli, I.; Guivel-Benhassine, F.; Rajah, M.M.; Planchais, C.; Porrot, F.; Robillard, N.; Puech, J.; et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature* **2021**, *596*, 276–280. [CrossRef]
102. Destras, G.; Bal, A.; Simon, B.; Lina, B.; Josset, L. Sotrovimab drives SARS-CoV-2 omicron variant evolution in immunocompromised patients. *Lancet Microbe* **2022**, *3*, e559. [CrossRef]
103. Martin-Blondel, G.; Marcelin, A.G.; Soulié, C.; Kaisaridi, S.; Lusivika-Nzinga, C.; Dorival, C.; Nailler, L.; Boston, A.; Melenotte, C.; Cabié, A.; et al. Sotrovimab to prevent severe COVID-19 in high-risk patients infected with Omicron BA.2. *J. Infect.* **2022**, *85*, e104–e108. [CrossRef] [PubMed]
104. Khoury, D.; Steain, M.; Triccas, J.; Sigal, A.; Davenport, M.; Cromer, D.J.G.S. Analysis: A meta-analysis of Early Results to predict Vaccine efficacy against Omicron. *medRxiv* **2021**. [CrossRef]

105. Khoury, D.S.; Cromer, D.; Reynaldi, A.; Schlub, T.E.; Wheatley, A.K.; Juno, J.A.; Subbarao, K.; Kent, S.J.; Triccas, J.A.; Davenport, M.P. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat. Med.* **2021**, *27*, 1205–1211. [CrossRef] [PubMed]
106. Andrews, N.; Stowe, J.; Kirsebom, F.; Toffa, S.; Rickeard, T.; Gallagher, E.; Gower, C.; Kall, M.; Groves, N.; O'Connell, A.M.; et al. COVID-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. *N. Engl. J. Med.* **2022**, *386*, 1532–1546. [CrossRef]
107. Munro, A.P.S.; Feng, S.; Janani, L.; Cornelius, V.; Aley, P.K.; Babbage, G.; Baxter, D.; Bula, M.; Cathie, K.; Chatterjee, K.; et al. Safety, immunogenicity, and reactogenicity of BNT162b2 and mRNA-1273 COVID-19 vaccines given as fourth-dose boosters following two doses of ChAdOx1 nCoV-19 or BNT162b2 and a third dose of BNT162b2 (COV-BOOST): A multicentre, blinded, phase 2, randomised trial. *Lancet Infect. Dis.* **2022**, *22*, 1131–1141. [CrossRef]
108. Chia, T.R.T.; Young, B.E.; Chia, P.Y. The Omicron-transformer: Rise of the subvariants in the age of vaccines. *Ann. Acad. Med. Singap.* **2022**, *51*, 712–729. [CrossRef]
109. Bar-On, Y.M.; Goldberg, Y.; Mandel, M.; Bodenheimer, O.; Amir, O.; Freedman, L.; Alroy-Preis, S.; Ash, N.; Huppert, A.; Milo, R. Protection by a Fourth Dose of BNT162b2 against Omicron in Israel. *N. Engl. J. Med.* **2022**, *386*, 1712–1720. [CrossRef]
110. Magen, O.; Waxman, J.G.; Makov-Assif, M.; Vered, R.; Dicker, D.; Hernán, M.A.; Lipsitch, M.; Reis, B.Y.; Balicer, R.D.; Dagan, N. Fourth Dose of BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. *N. Engl. J. Med.* **2022**, *386*, 1603–1614. [CrossRef]
111. Brosh-Nissimov, T.; Hussein, K.; Wiener-Well, Y.; Orenbuch-Harroch, E.; Elbaz, M.; Lipman-Arens, S.; Maor, Y.; Yagel, Y.; Chazan, B.; Hershman-Sarafov, M.; et al. Hospitalized Patients With Severe Coronavirus Disease 2019 During the Omicron Wave in Israel: Benefits of a Fourth Vaccine Dose. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2023**, *76*, e234–e239. [CrossRef]
112. Muhsen, K.; Maimon, N.; Mizrahi, A.Y.; Boltyansky, B.; Bodenheimer, O.; Diamant, Z.H.; Gaon, L.; Cohen, D.; Dagan, R. Association of Receipt of the Fourth BNT162b2 Dose with Omicron Infection and COVID-19 Hospitalizations among Residents of Long-term Care Facilities. *JAMA Intern. Med.* **2022**, *182*, 859–867. [CrossRef]
113. Cao, Y.; Wang, J.; Jian, F.; Xiao, T.; Song, W.; Yisimayi, A.; Huang, W.; Li, Q.; Wang, P.; An, R.; et al. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. *Nature* **2022**, *602*, 657–663. [CrossRef] [PubMed]