



Article

Blood Profiling of Athletes after COVID-19: Differences in Blood Profiles of Post-COVID-19 Athletes Compared to Uninfected Athletic Individuals—An Exploratory Analysis

Shirin Vollrath ^{1,*} , Lynn Matits ^{1,2} , Achim Jerg ¹, Jule Zorn ¹, Lucas John ¹ , Jürgen Michael Steinacker ¹ and Daniel Alexander Bizjak ¹

¹ Division of Sports and Rehabilitation Medicine, Department of Medicine, Ulm University Hospital, 89075 Ulm, Germany; lynn.matits@uni-ulm.de (L.M.); achim.jerg@uniklinik-ulm.de (A.J.); jule.zorn@tum.de (J.Z.); lucas.john@tum.de (L.J.); juergen.steinacker@uniklinik-ulm.de (J.M.S.); daniel.bizjak@uniklinik-ulm.de (D.A.B.)

² Division of Clinical & Biological Psychology, Institute of Psychology and Education, Ulm University, 89075 Ulm, Germany

* Correspondence: shirin.vollrath@uniklinik-ulm.de; Tel.: +49-731-500-45374

Abstract: Blood profiling data in athletic populations and their respective responses to SARS-CoV-2 infection are lacking. Thus, this exploratory pilot study aimed to analyze and compare clinical blood markers in previously infected trained athletes (ATH; 30 m/29 f) and a not previously infected healthy athletic control group (HC; 12 m/19 f). The ATH group undertook a sports medical examination which included extended blood analyses. Blood profiles with a total of 74 variables were assessed (blood counts, pro-/inflammatory and immunological markers, and micronutrients), and the ATH group was compared to the age-matched HC group with comparable athletic back grounds, though without previous SARS-CoV-2-infections. The ATH group showed increased IgG, Troponin-T, and complement/acute-phase protein activation and decreased electrolyte/micronutrient concentrations compared to the HC group. Several markers regarding erythrocytic function and coagulation were different in the ATH group, whereas in the HC group, higher TSH, ALT, and triglyceride concentrations were observed. Subgroup analyses according to sex revealed more differences between the women of the ATH and HC groups (for 18 different variables) than between the men (for 6 different variables), especially for immunological and metabolic variables. In particular, the erythrocytic system and electrolyte/micronutrient status should be observed frequently and sex-specifically in this underrepresented subpopulation of athletic individuals after COVID-19 because infection, as well as high training volumes, may put an additional strain on these parameters.

Keywords: blood analysis; COVID-19; inflammation; physical activity; athletes; reference values; long-term changes; sex differences



Citation: Vollrath, S.; Matits, L.; Jerg, A.; Zorn, J.; John, L.; Steinacker, J.M.; Bizjak, D.A. Blood Profiling of Athletes after COVID-19: Differences in Blood Profiles of Post-COVID-19 Athletes Compared to Uninfected Athletic Individuals—An Exploratory Analysis. *Biomedicines* **2023**, *11*, 1911. <https://doi.org/10.3390/biomedicines11071911>

Academic Editor: Javier Gonzalo Ocejo-Vinyals

Received: 1 June 2023

Revised: 29 June 2023

Accepted: 2 July 2023

Published: 6 July 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

SARS-CoV-2 infection can lead to several long-lasting complications which have been summarized by post-COVID studies and can have different physiological and psychological outcomes [1]. Symptoms include fatigue, general pain or discomfort, attention disorders, sleep disturbances, hair loss, shortness of breath, and anxiety or depression, with up to 32 additional different complications having been observed [2,3]. The sheer quantity of these volatile symptoms underlines that there is not one “common denominator” causing the long-term adverse health effects. The proposed mechanisms include a hyperinflammatory immune response, a so-called cytokine storm, mitochondrial damage, and decreased red blood cell rheological function [4–8]. Furthermore, it has been shown that altered blood parameters correlate with depressive symptoms and that an individual’s perception of recovery may be impaired over a longer period of time after COVID-19 infection [9,10].

The different virus variants, as well as individual health and vaccine statuses, make the prognosis of disease severity even more difficult. Therefore, robust and valid clinical blood or saliva markers would be very useful for healthcare advisers/physicians for monitoring the health statuses of their patients or for intervening to reduce the detrimental results of SARS-CoV-2 infections.

Although the positive health effect of regular physical exercise on immune function is well known [11], the “athletic population” comprises only a minor percentage of the world-wide population [12]. As consequence, the pandemic has led to medical studies mostly focusing on the general population, which has tendencies toward highly sedentary lifestyles, obesity, and cardiovascular disease burdens, and this generalizes study results for COVID-19 without discriminating between regular exercising individuals and sedentary ones. However, the responses observed in athletes may reveal phylogenetic—currently defined “normal”—human responses after a SARS-CoV-2 infection, while routinely used thresholds of clinical blood markers and cardiovascular features such as heart frequency differ in athletes. This may result in medical advice that is not suitable or relevant for this specific population [13–15].

Blood profiles in acutely infected COVID-19-patients without comorbidities have shown that the blood markers interleukin-6 (IL-6) and tumor-necrosis-factor-alpha (TNF- α) are strong predictors for disease severity and death [16], while there are also non-cytokine biomarkers such D-dimers, C-reactive protein (CRP), and ferritin that are also elevated in COVID-19-infected patients compared to non-COVID-19-infected people [17,18].

Furthermore, increased T-cell activation has been observed and is indicated by the level of soluble interleukin IL-2 receptor (sIL-2R), regardless of age, in children and adults with severe COVID-19 infection [19]. Regarding the virus variants before Omicron, Conti et al. observed that in addition to the cytokine IL-6, IL-1 β contributes to disease severity by driving inflammation [20].

As all these results have been determined in different study populations without connections to physical activity level and regular exercise, and the possible transfer of these data to individuals with high degrees of physical fitness is still largely unknown.

Thus, the aim of this pilot study was to examine the blood profiles of physically active individuals post-COVID-19 infection and compare them with the blood levels of non-infected control athletes to identify abnormalities in blood markers due to COVID-19.

2. Materials and Methods

2.1. Recruitment

Participants were recruited from consecutive athletic patients after previous SARS-CoV-2 infection at the Department of Sports and Rehabilitation Medicine, University Ulm, during March 2020 and July 2021, and they provided informed consent to participate in extended blood profiling. Some individuals were also part of the national study CoSmo-S (COVID-19 in German Competitive Sports [21]) while attending physical examinations after COVID-19 infection for the evaluation of their exercise capacity and physical resilience. Subjects in the age-matched healthy control group were recruited during presentations for their annual routine check-ups at the same facility, but they were not participating in another study and their clinical data were analyzed retrospectively. To avoid inclusion of individuals with a previous, non-detected subclinical SARS-CoV-2 infection in the control group, the analysis included mainly individuals with at least two to three negative SARS-CoV-2 PCR tests over the preceding three months before inclusion.

2.2. Study Population

The inclusion criteria for the enrolled participants were: athletes aged ≥ 18 years with a previous SARS-CoV-2 infection and a proof of such previous infection by (1) positive SARS-CoV-2 PCR or (2) antibody detection against SARS-CoV-2 with typical symptoms and (3) extensive blood profiling during the study visits. Athletes were defined as such if they exercised at least three times per week, with a metabolic equivalent of

>20 h/week (e.g., cycling at 20 km/h = 7.1 metabolic equivalents [22]). Athletes with a positive SARS-CoV-2 PCR test within the preceding two weeks, insufficient German language skills, refusal of venous blood collection, and current diseases (acute and chronic) that did not allow for admission as estimated by the study physician were excluded [21].

The blood profiles of the included athletes (ATH) were compared to the blood profiles of age-matched, vaccinated, healthy controls (HC; N = 31, 12 m/19 f, aged 31.1 ± 10.4 years, body mass of 72.8 ± 13.9 kg, body height of 176.1 ± 8.93 cm, and BMI of 23.4 ± 3.5 kg/m²) without prior SARS-CoV-2 infection and fitness statuses as well as anthropometric variables (sex, age, body mass, height, and BMI) that were comparable to those of the ATH group. Table 1 shows detailed information about the study population.

Table 1. Anthropometric data, training volume before disease, symptoms during acute phase, and persistent symptoms of the study population.

		ATH		HC
Sex (f/m)		29/30		19/12
		Mean ($\pm$ SD)		Mean ($\pm$ SD)
Age (years)	N (59)	34.5 $\pm$ 12.2	N (31)	31.9 $\pm$ 10.4
Body mass (kg)	N (59)	73.9 $\pm$ 15.2	N (18)	72.8 $\pm$ 13.9
Height (cm)	N (59)	175.6 $\pm$ 9.3	N (21)	176.1 $\pm$ 8.93
BMI (height/(body mass) ²)	N (59)	23.9 $\pm$ 3.9	N (18)	23.4 $\pm$ 3.5
Time since infection (months)	N (59)	3.8 $\pm$ 2.68		
Sport type *		Frequency		Frequency
Endurance		42 (60.0%)		12 (29.3%)
Resistance		11 (15.7%)		11 (26.8%)
Team or combat sports		16 (22.9%)		3 (7.3%)
Technical sports		1 (1.4%)		0
Missing		0		15 (36.6%)
Training volume (before infection)		Number		Number
0–3 h/week		0		2 (6.5%)
3–5 h/week		28 (47.5%)		6 (19.4%)
6–10 h/week		16 (27.1%)		7 (22.6%)
10–15 h/week		8 (13.6%)		0
>15 h/week		5 (8.5%)		1 (3.2%)
Missing		2 (3.4%)		15 (48.4%)
Symptoms during acute phase *		Frequency		Frequency
Fever (missing)		25 (7)		
Cough (missing)		30 (7)		
Ageusia/anosmia (missing)		16 (22)		
Rhinitis (missing)		28 (7)		
Throat pain (missing)		25 (7)		
Dyspnea under load (missing)		24 (7)		
Dyspnea during rest (missing)		18 (7)		
Diarrhea (missing)		7 (22)		
Headache (missing)		19 (22)		
Persistent symptoms *		Frequency		Frequency
Fatigue and performance decreases		33		
Sleeping disorders		15		
Neurocognitive disorders		15		
Respiratory disorders		20		
Autonomic disorders		12		
Muscle pain		11		
Psychological-related items		2		
Immunological disorders		3		
No symptoms		21		
Missing		2		

* multiple choice possible.

2.3. Blood Sampling and Analysis

For the blood profiling, 9 mL of EDTA-anticoagulated and 9 mL of serum blood samples (Sarstedt, Nümbrecht, Germany) were taken from veins in the participants' forearms. Blood sampling was conducted before the patients were physically active. Fasting state and sampling in the morning were preferred, but there were no prerequisites for sampling. In total, 74 individual blood variables were determined and analyzed by clinical standards with a DXH Coulter or a Sysmex system (based on resistance measurement principles (impedance measurements and the Coulter measurement principle), photometric measurements, and differentiation in flow cells by means of laser via VCSn technology (volume, conductivity, and scatter)), as well as ECLIA (Roche Immunoassay Analyzer Cobas 8000, Cobas t 711, and Cobas t 511, Rotkreuz, Suisse) and ELISA measurements.

For providing a reasonable overview, we grouped the respective 74 variables in the following subcategories: (1) blood cell system, (2) inflammation/immunology, (3) coagulation, (4) damage markers, (5) electrolytes/micronutrients, and (6) metabolism.

2.4. Statistical Analysis

Data analysis was performed with R, version 4.1.1 (2021-08-10; Non Profit/Open Access), and IBM SPSS Statistics, version 28.0.0.0 (IBM Deutschland GmbH, Ehningen, Germany). The graphics and figures were created with GraphPad PRISM (Version 9.3, La Jolla, CA, USA). To investigate whether there were differences in the blood parameters of athletes who suffered from COVID-19 compared to the fit healthy controls, two-tailed unpaired Wilcoxon tests were conducted. To detect possible differences between the anthropometric data and the training volumes before COVID-19 infection, Mann–Whitney U-tests and a Pearson chi-square test were conducted. Robust linear regression models were performed to analyze the influence of the time that had passed between infection and blood-taking on the concentrations of the blood parameters (R-package: “Robust” [23]). For IL-1 β , IL-6, IL-8, IL-10, TNF- α , CRP, Troponin-T, Folic acid, D-dimers, and CH50, values below the limit of detection were replaced by half of the corresponding detection limit. Separately conducted subgroup-analyses for the control variables (age, sex, and time passed between infection and blood-taking) were performed additionally. For all analyses, an α -level of 0.050 was considered as significant. The adjusted significance level was $p < 0.0007$ when considering multiple testing (Bonferroni correction). All data are presented as means $\pm$ standard deviations if not otherwise stated.

2.5. Ethics, Consent, and Permissions

All participating athletes took part voluntarily and provided informed consent prior to inclusion. The study was performed in accordance with the Declaration of Helsinki. The study was approved by the ethics committee of Ulm University (EK 408/20). The study has been registered in the German Clinical Trials Register (DRKS00023717). The study reporting adheres to the CONSORT guidelines for reporting clinical trials.

3. Results

3.1. Blood Variables: Comparison between the Athletes and the Healthy Athletic Control Group

3.1.1. Blood Cell System

Regarding the sub-group of white blood cells, the leukocyte concentration was increased in the ATH group compared to the HC group ($p = 0.034$), whereas the absolute lymphocyte concentration ($p = 0.023$) was decreased in the ATH group. Regarding differences in the red blood cell system, the soluble transferrin receptor ($p < 0.001$) showed increased values in the ATH group compared to the HC group (Figure 1).

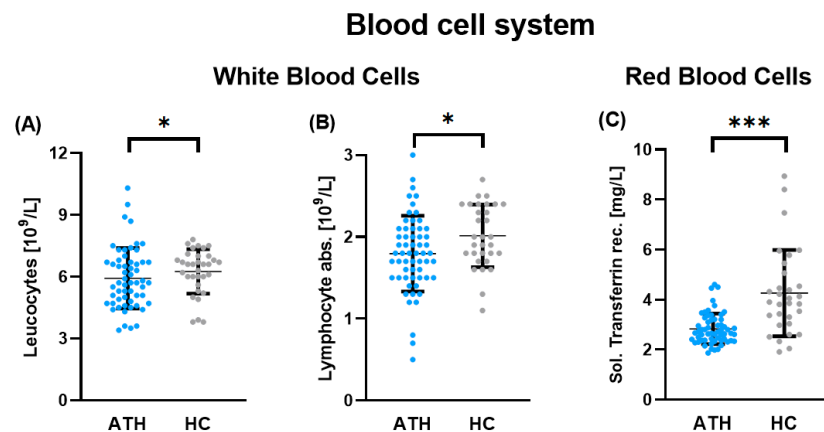


Figure 1. Blood cell system-specific differences between the previously COVID-19-infected athletes (ATH) and the healthy controls (HC) with comparable fitness statuses. Of the 27 variables grouped in the blood cell system, in the sub-group of white blood cells, significant differences for (A) leucocyte (ATH 6.3 ± 1.0 vs. HC 5.9 ± 1.5 $10^9/L$) and (B) absolute lymphocyte (ATH 1.8 ± 0.5 vs. HC 2.0 ± 0.4 $10^9/L$) concentrations were observed. In the sub-group of red blood cells, the specific variable (C) soluble transferrin receptor (ATH 4.3 ± 1.7 vs. HC 2.8 ± 0.6 mg/L) concentration was significantly different between the ATH and HC groups. * $p \leq 0.05$ and *** $p \leq 0.001$ for the ATH group compared to the HC group.

3.1.2. Inflammation/Immunology

Increased values for the SARS-CoV-2 spike antibody ($p < 0.001$), CRP ($p = 0.012$), IgG ($p = 0.013$), and LBP ($p = 0.004$) were determined for the ATH group compared to the HC group (Figure 2, Table S1). The complement-specific analyte CH50 ($p = 0.045$) and complement C3c ($p = 0.030$) showed increased values in the ATH group (Figure 3a,b).

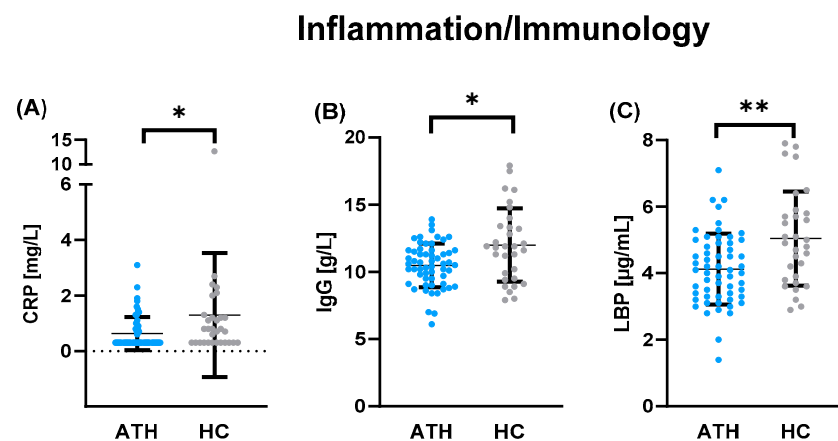


Figure 2. Differences in the variables regarding immunology/inflammation between the previously infected athletes (ATH) and the healthy controls (HC) with comparable fitness statuses. Of the 17 variables grouped for inflammation/immunology, the (A) CRP (ATH 1.3 ± 2.2 vs. HC 0.6 ± 0.6 mg/L), (B) IgG (ATH 12.0 ± 2.7 vs. HC 10.5 ± 1.6 g/L), and (C) LBP (ATH 5.0 ± 1.4 vs. HC 4.1 ± 1.1 $\mu g/mL$) concentrations were significantly different between the ATH and HC groups. * $p \leq 0.05$ and ** $p \leq 0.01$ for the ATH group compared to the HC group.

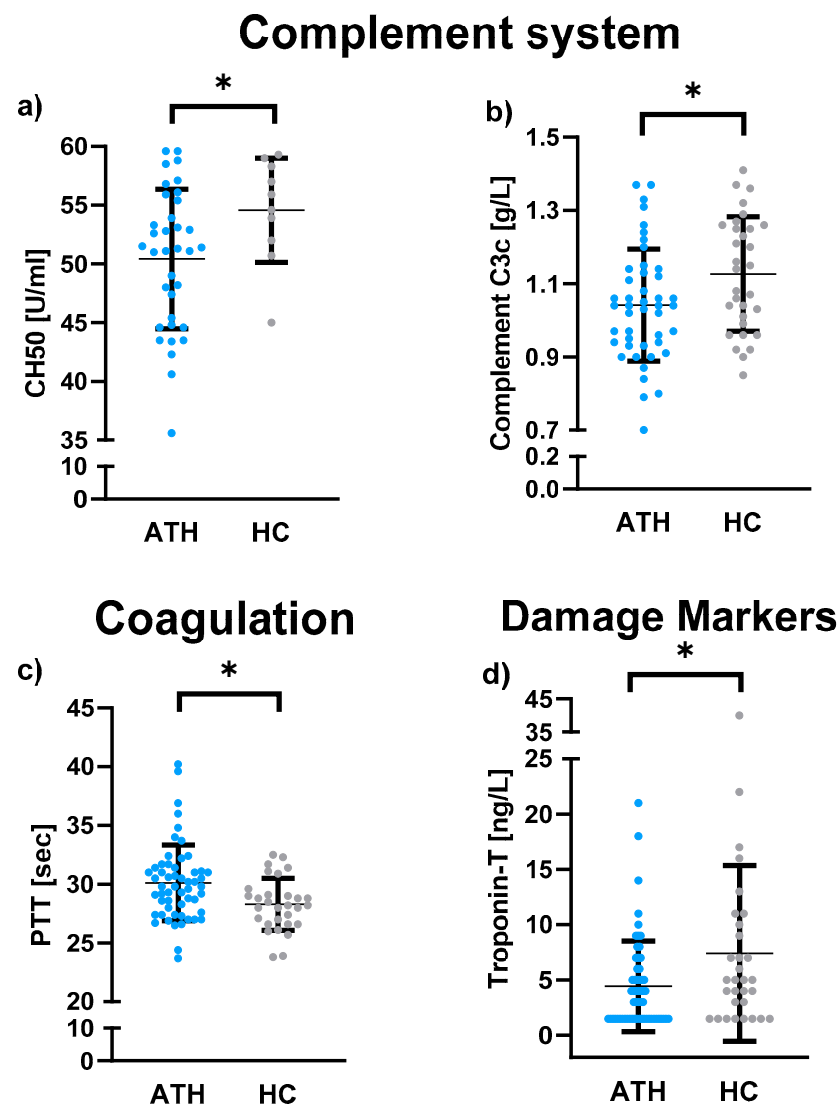


Figure 3. Differences in the variables grouped for the (a,b) immunology/complement systems, (c) coagulation, and (d) damage markers between the previously COVID-19-infected athletes (ATH) and the healthy controls (HC) with comparable fitness statuses. The levels of CH50 (ATH 54.6 ± 4.4 vs. HC 50.4 ± 5.9) and complement C3c (ATH 1.1 ± 0.2 vs. HC 1.0 ± 0.2 g/L), sub-grouped from immunology, differed between the ATH and HC groups. Troponin-T concentrations in the ATH group (7.4 ± 8.0 ng/L) were significantly increased compared to the HC group (4.4 ± 4.1 ng/L), whereas there were no differences for the other seven variables grouped as damage markers (e.g., creatine kinase, urea, and NT-Pro BNP). Of the six variables grouped under coagulation, PTT (ATH 28.3 ± 2.2 vs. HC 30.1 ± 3.2 s) was significantly different between the ATH and HC groups, * $p \leq 0.05$.

3.1.3. Coagulation

The PTT levels ($p = 0.008$) were decreased in the ATH group compared to the HC group (Figure 3c). A trend was observable where there were higher D-dimer levels in the ATH group ($p = 0.054$).

3.1.4. Damage Markers

Of the eight variables grouped in the cardiac/muscular damage markers, only troponin-T was increased in the ATH group compared to the HC group ($p = 0.034$) (Figure 3d).

3.1.5. Electrolytes/Micronutrients

Regarding electrolytes and micronutrients, potassium ($p < 0.001$) and sodium ($p = 0.039$), as well as zinc ($p = 0.015$), were decreased in the ATH group compared to the HC group (Figure 4).

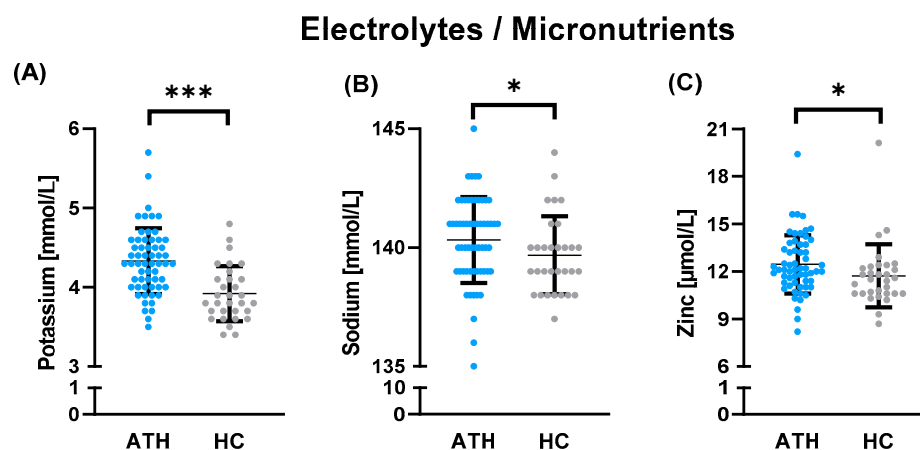


Figure 4. Differences in the variables grouped under electrolytes/micronutrients between the previously COVID-19-infected athletes (ATH) and the healthy controls (HC) with comparable fitness statuses. Of the five variables grouped under electrolytes/micronutrients, (A) potassium (ATH 3.9 ± 0.4 vs. HC 4.3 ± 0.4 mmol/L), (B) sodium (ATH 139.7 ± 1.6 vs. HC 140.3 ± 1.8 mmol/L), and (C) zinc (ATH 11.7 ± 2.0 vs. HC 12.4 ± 1.8 μ mol/L) concentrations were significantly different between the ATH and HC groups. $*$ $p \leq 0.05$ and $***$ $p \leq 0.001$ for the ATH group compared to the HC group.

3.1.6. Metabolism

In the ATH group, ALT ($p = 0.031$) was increased while its coenzyme vitamin B6 ($p = 0.005$) was decreased compared to the HC group. Triglyceride ($p = 0.022$) concentrations were decreased in the ATH group compared to the HC group, while the thyroid-stimulating metabolic hormone TSH (which stimulates the thyroid gland) ($p = 0.026$) and vitamin D 25OH (an antioxidant with immunostabilizing, calcium homeostasis, bone metabolism, and muscle functions; $p = 0.001$), as well as the total protein content ($p = 0.009$), were higher in the ATH group.

A detailed grouping and the results of the analyses of all variables can be found in Table S1.

3.2. Blood Variables: Changes in the Variables Depending on Sex

A subgroup analysis of the women between the ATH and HC groups revealed differences in the leukocyte ($p = 0.038$), soluble transferrin receptor ($p < 0.001$), absolute lymphocyte ($p = 0.039$), MCHC ($p = 0.021$), MTV ($p = 0.041$), FT4 ($p = 0.028$), thyroid-stimulating hormone (TSH) ($p = 0.006$), complement C3c ($p = 0.014$), TNF- α ($p = 0.022$), LBP ($p = 0.005$), D-dimer ($p = 0.027$), PTT ($p = 0.022$), calculated GFR CKD EPI ($p = 0.032$), potassium ($p < 0.001$), sodium ($p = 0.046$), vitamin B6 ($p = 0.019$), vitamin D25OH ($p = 0.017$), and total protein content ($p = 0.039$) concentrations.

A subgroup analysis of the men between the ATH and HC groups showed significant differences in the soluble transferrin receptor ($p < 0.001$), uric acid ($p = 0.012$), troponin-T ($p = 0.001$), zinc ($p = 0.038$), potassium ($p = 0.018$), and vitamin D25OH ($p = 0.026$) concentrations.

A detailed analysis of the results of all the variables is provided in Tables 1 and S2.

3.3. Blood Variables: Changes in the Variables Depending on the Time since Infection

Testing on the contribution of the variable time since infection was performed, and significant differences were observed for the ALT ($p = 0.05$), AST ($p = 0.02$), erythropoietin ($p = 0.01$), folic acid ($p = 0.05$), and TNF-alpha ($p = 0.02$) concentrations in the ATH group.

A detailed analysis of the results of all the variables is provided in Table S3.

4. Discussion

Although there are manifold variations in symptoms and their respective severity during and after a SARS-CoV-2 infection [2], recent reviews have estimated that negative long-term health effects affect up to 80% of all COVID-19-infected people, with symptoms persisting for 4 weeks and longer [3,24].

However, it is not only individuals with comorbidities or previous disease burdens that have been hospitalized as even elite athletes with high levels of physical fitness can suffer from the effects of infection. Martinez et al. [25] screened 789 professional athletes that had tested positive for SARS-CoV-2 before returning to their sports. In total, 30 athletes had abnormal screenings (elevated troponin, abnormal ECG, and abnormal echocardiography) [25]. As athletes normally exhibit cardiovascular health with normal BMIs and less life-style associated disease burdens than the so-called general population [13,14,26], the transferability of “abnormal values” in this underrepresented group remains questionable.

Thus, in our exploratory pilot analysis, we focused on the blood profiles of COVID-19-infected professional and recreational athletes of both sexes to compare different blood variables with the values of a healthy study population with comparable fitness statuses, and we examined the applicability / transferability of the observed long-term blood changes to the general population.

After the blood profile analysis, we observed a presumably still-increased immune response in the ATH group, which was underlined by the increased total leucocyte and higher neutrophil concentrations, as well as the increased CRP concentrations, compared to the HC group. An altered and persistent immune response following COVID-19 infection has been observed in different studies, with a high prevalence of increased circulating immune cells in individuals suffering from long COVID [27–29]. We did not test for immune cell subpopulations in our exploratory study, and so no conclusions could be drawn for, e.g., altered T-cell or B-cell activities in the ATH group, but the thresholds for leucocyte and lymphocyte concentrations in athletes may not be generally applicable due to acute long-term training changes and transient increases after intense training sessions [30]. Interestingly, CRP as an acute-phase protein was still elevated in the ATH group compared to the HC group, even though the infections had been overcome. CRP may be helpful during the acute phase of the disease [31,32], and it appears that this marker may indicate ongoing inflammation after recovery from the disease. However, abnormal CRP values can be caused by high training intensity or competition [33,34]. Therefore, using reference values from a normal population can lead to the overestimation of this marker.

A published work by Phetsouphanh et al. [35] examined 28 especially pro- and anti-inflammatory and immunologic serum biomarkers in 31 long COVID patients and compared them with age-matched, previously SARS-CoV-2-infected but asymptomatic individuals as well as 16 healthy controls at three different time points up to 8 months after infection. They identified six biomarkers associated with long COVID and proposed a panel of these pro-inflammatory cytokines (interferon β (IFN- β), IFN- $\lambda 1$, IFN- γ , CXCL9, CXCL10, IL-8, and soluble T cell immunoglobulin mucin domain) [35]. In contrast, in our study, the ATH group’s pro- or anti-inflammatory cytokine concentrations did not differ from those of the HC group. Instead, the immune systems of the ATH groups showed increased complement activations, which was determined by the increased CH50 and complement C3c levels, as well as the increased IgG levels, even in the weeks after COVID-19 infection.

The activation of the complement system represents a fast and efficient response of the innate immune system to pathogenic invasion and is a reasonable immune adaptation to the SARS-CoV2 infection in healthy individuals [36], which was supported by the higher

concentrations of IgG-antibodies [37] in the ATH group compared to the SARS-CoV-2-uninfected HC group. It is known that consistent moderate exercise can improve innate immune function and has beneficial effects on the body's defense against pathogens [38], and so perhaps long-term adaptations of the innate immune system are reasonable effects after COVID-19 infection. We previously showed that athletes' immune responses differ in response to training and competition compared to those of a normal population, and an immunological matrix appears to be advisable for monitoring immune status [39].

However, there are also non-cytokine biomarkers such D-dimers and ferritin that are also elevated in acutely infected COVID-19 patients compared to non-COVID-19-infected people [17], and these persist even after the acute period. Mandal et al. [18] observed increased D-dimers in individuals suffering from long COVID [18]. In our study, a trend for increased D-dimers could be observed in the ATH group, but this attenuated effect compared to the study by Mandal et al. could again be due to the differences in physical fitness status and age distribution as our respective colleagues examined a study population with a mean age of 59.9 years in comparison to the ATH group's mean age of 34.5 years.

In addition to D-dimer levels, coagulation assessed by PTT and internal laboratory standard quick-values differed in the ATH group compared to the HC group. In conjunction with increased reticulocyte hemoglobin contents, soluble transferrin receptors, and MCH levels, as well as time changes for the variables erythropoietin and relative reticulocytes concentrations since infection, the hematopoietic system appeared to be affected, in the long-term, in the ATH group. Altered reticulocyte and erythrocyte development and morphology are now frequently observed in acute cases and long COVID patients, with possible consequences for physical fitness and symptoms such as fatigue [40–43]. Kubánková et al. reported that COVID-19 patients had significantly more heterogeneously sized and deformed red blood cells than the healthy control subjects, and Gérard et al. reported mushroom-shaped phenotypes [41,42], both affecting hemorheological properties and increasing the risk for thrombotic and impaired coagulation events. Even after recovery, individuals showed altered phenotypes and significant pathological abnormalities in microcirculation, though not to the extent that that which appeared during the acute phase of infection [42,44]. Kronstein-Wiedemann et al. [43] identified red blood cell precursors as a direct target of SARS-CoV-2 and suggested that SARS-CoV-2 induced dysregulation in hemoglobin- and iron-metabolism, which contributed to the severe systemic course of COVID-19 due to, among others, impaired hemoglobin biosynthesis and the enhanced formation of zinc-protoporphyrin IX [43].

Given the already increased turnover of red blood cells due to training with the concomitantly increased need for micronutrients such as iron and zinc [45–47], the observed decreases in vitamin B6, zinc, potassium, sodium, and creatinine in the ATH group may be especially important in the prevention of disease severity in athletes. While micronutrient deficiency is often observed in the general populations of developing and even industrialized countries with potential health and socioeconomic consequences [48,49], athletic fitness also depends on sufficient macro- and micro-nutrient concentrations. It is known that physical exercise alone produces decreases in the erythrocyte concentrations of iron, magnesium, and phosphor, with subsequently possible detrimental effects on performance [26], and based on our data, an additional micronutrient supplementation during and after COVID-19 infection with zinc, potassium, and sodium may be advisable. Moreover, the differences between the ATH group and the comparably fit HC group in the above-mentioned vitamin B and creatinine levels contributed to the assumption of an increased nutritional demand after infection.

In addition, hypoproteinemia was observed during infection, and an association between COVID-19 infection and a hypercatabolic state was shown [6]. We observed higher protein contents and vitamin D concentrations in the ATH group compared to the HC group, which was relatively unexpected given the comparable fitness levels and physical activity statuses, in addition to the increased amounts of outdoor activity, dietary supplementation (vitamin D), and nutritional awareness, as well as the greater muscu-

lar/metabolic statuses (total protein) of the athletes. Unfortunately, we did not have data on the athletes' nutrition/supplementation behaviors during and after infection, which may have provided further insights into the different eating habits and training distributions. However, the observed data underline that regular exercise as prevention and/or adjuvant therapy may—outside of COVID-19 infection—exert positive effects on immune system function, and thus, it can presumably lower virus-induced complications [50,51].

Given the beneficial effects of regular exercise and high levels of cardiovascular fitness, together with increasing evidence for lowered COVID-19 severity and mortality in athletes [52,53], more focus on COVID-19 treatments should pertain to preventive measures such as physical exercise and maintaining a normal body weight and be prescribed and advised by all health care practitioners. As we observed in the sex-divided analyses, more differences were observed between the ATH and HC groups for the women (18 different variables) than for the men (six different variables), and sex-specific differences should always be kept in mind. Now, increasing numbers of studies have shown greater long-term symptom susceptibility in women after COVID-19 infection [54], and explanatory approaches have included differences in immune responses and cardiovascular comorbidities, as well as androgenic responses [55,56]. Moreover, female athletes have additional micro-nutritional needs and hormonal differences compared to men and their peers in the general population, and these can affect their health and performance [57]. Thus, the focus of further research and treatment decisions should always include sex-specific differences.

Strengths and Limitations

Based on the 74 different blood variables analyzed in the athletes, a first database containing information about the long-term effects of COVID-19 in physically active individuals was obtained. Due to the comparable control group, which may also have had abnormal variable values due to physical activity, small changes in the immune and blood systems of the previously infected athletes could be detected. However, the training volumes differed slightly but not significantly between the study and control groups. These small differences may have influenced the blood variables to a small extent. Moreover, the recruited study population included athletes of different sport types with a relatively heterogeneous distribution and exercise experience. In addition, this exploratory pilot was performed using the blood profiles of only 90 participants, which may have contributed to non-significant statistical results when we considered multiple testing. Attention should also be paid to the implementation period. The data were collected from March 2020 to July 2021, when the SARS-CoV-2 Alpha to Delta variants were the most prevalent. Therefore, the results are not directly applicable to populations infected with other virus variants. In addition, the effect of vaccination prior to infection may have had an impact on the changes in the blood variables. Nevertheless, further evaluation is ongoing, and this exploratory design has provided first insights into post-COVID-infection status in an up-to-now underrepresented athletic population.

5. Conclusions

Although the general immune response of previously SARS-CoV-2-infected athletes regarding the complement and IgG systems appears comparable to the that of their uninfected fit peers, the observed values may be interpreted as an enhanced long-term immune response in athletes that differs from the now-normally unfit general population. Furthermore, the healthy lifestyles and/or the high fitness levels of both groups may have led to a faster convalescence after acute illness and fewer long-term impacts on the study population. Due to their greater athletic activities, a special emphasis should be given to monitoring the micronutrient statuses of athletes after COVID-19 infection in conjunction with their apparently increased blood turnover rates. Several clinical thresholds should be used with caution in the treatment of athletes as their blood variables may differ due to their greater levels of physical fitness, sex-specific differences, and adaptations in their haemopoietic systems. As this study did not aim to identify so-called post-COVID con-

ditions or long COVID disease states, the determined values may be helpful in further examinations of such patients and in hypothesis-building for further research.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/biomedicines11071911/s1>, Table S1: Differences between the ATH and HC groups regarding blood values; Table S2: Differences between the women in the ATH and HC groups; Table S3: Differences between the ATH and HC groups controlled for age.

Author Contributions: Conceptualization, D.A.B., S.V., L.M. and J.M.S.; methodology, S.V., D.A.B., L.M., J.Z. and L.J.; validation, D.A.B., S.V., L.M. and A.J.; formal analysis, D.A.B., A.J., S.V., L.M., J.M.S. and J.Z.; investigation, S.V., D.A.B., J.Z. and A.J.; resources, D.A.B. and J.M.S.; data curation, L.M., S.V. and D.A.B.; writing—original draft preparation, D.A.B. and S.V.; writing—review and editing, D.A.B., S.V., L.M., J.M.S., J.Z. and L.J.; visualization, L.M., D.A.B. and S.V.; supervision, J.M.S. and D.A.B.; project administration, J.M.S. and A.J.; funding acquisition, J.M.S. 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 Ethics Committee of Ulm University (EK 408/20) (07/2020) (trial registration: DRKS00023717; date of registration: 15 June 2021 (retrospectively registered)).

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

Data Availability Statement: All data are available on reasonable request from the authors. The results will be publicly available at the German Clinical Trials Register (https://www.drks.de/drks_web/navigate.do?navigationId=start, accessed on 15 July 2022) at the end of the Cosmo-S study.

Acknowledgments: The authors thank Jasmine Leonike Buhl for her invaluable technical assistance and contributions to the development and achievement of this research, and they thank all the volunteers who participated in this study.

Conflicts of Interest: The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

References

1. National Institute for Health and Care Excellence (Great Britain). *COVID-19 Rapid Guideline: Managing the Long-Term Effects of COVID-19*; National Institute for Health and Care Excellence (NICE): London, UK, 2020; ISBN 9781473139435.
2. Cirulli, E.T.; Schiabor Barrett, K.M.; Riffle, S.; Bolze, A.; Neveux, I.; Dabe, S.; Grzymalski, J.J.; Lu, J.T.; Washington, N.L. Long-term COVID-19 symptoms in a large unselected population, 2020. *medRxiv* **2020**. [[CrossRef](#)]
3. Lopez-Leon, S.; Wegman-Ostrosky, T.; Perelman, C.; Sepulveda, R.; Rebolledo, P.A.; Cuapio, A.; Villapol, S. More than 50 Long-term effects of COVID-19: A systematic review and meta-analysis. *Sci. Rep.* **2021**, *11*, 16144. [[CrossRef](#)]
4. Bizjak, D.A.; John, L.; Matits, L.; Uhl, A.; Schulz, S.V.W.; Schellenberg, J.; Peifer, J.; Bloch, W.; Weiß, M.; Grüner, B.; et al. SARS-CoV-2 Altered Hemorheological and Hematological Parameters during One-Month Observation Period in Critically Ill COVID-19 Patients. *Int. J. Mol. Sci.* **2022**, *23*, 15332. [[CrossRef](#)] [[PubMed](#)]
5. Barkas, F.; Filippas-Ntekouan, S.; Kosmidou, M.; Liberopoulos, E.; Liontos, A.; Milonidis, H. Anakinra in Hospitalized non-Intubated Patients with Coronavirus Disease 2019: A Systematic review and meta-analysis. *Rheumatology* **2021**, *60*, 5527–5537. [[CrossRef](#)] [[PubMed](#)]
6. Al Maqbali, M.; Al Badi, K.; Al Sinani, M.; Madkhali, N.; Dickens, G.L. Clinical Features of COVID-19 Patients in the First Year of Pandemic: A Systematic Review and Meta-Analysis. *Biol. Res. Nurs.* **2022**, *24*, 172–185. [[CrossRef](#)]
7. García, L.F. Immune Response, Inflammation, and the Clinical Spectrum of COVID-19. *Front. Immunol.* **2020**, *11*, 1441. [[CrossRef](#)] [[PubMed](#)]
8. Sudre, C.H.; Murray, B.; Varsavsky, T.; Graham, M.S.; Penfold, R.S.; Bowyer, R.C.; Pujol, J.C.; Klaser, K.; Antonelli, M.; Canas, L.S.; et al. Attributes and predictors of long COVID. *Nat. Med.* **2021**, *27*, 626–631. [[CrossRef](#)]
9. Zorn, J.; Vollrath, S.; Matits, L.; Schönfelder, M.; Schulz, S.V.W.; Jerg, A.; Steinacker, J.M.; Bizjak, D.A. Relationship between physical performance and perception of stress and recovery in daily life post COVID-19—An explorative study. *PLoS ONE* **2023**, *18*, e0285845. [[CrossRef](#)]
10. Matits, L.; Munk, M.; Bizjak, D.A.; Kolassa, I.-T.; Karrasch, S.; Vollrath, S.; Jerg, A.; Steinacker, J.M. Inflammation and severity of depressive symptoms in physically active individuals after COVID-19—An exploratory immunopsychological study investigating the effect of inflammation on depressive symptom severity. *Brain Behav. Immun. Health* **2023**, *30*, 100614. [[CrossRef](#)]
11. Kallen, V.; Scherder, R.; Cramer, M.J.; Stam, J.; Johnson, B.; Scherder, E. Neutralizing a Springboard for Inflammation: Physical Activity to Control the Immune Network. *Healthcare* **2021**, *9*, 196. [[CrossRef](#)] [[PubMed](#)]

12. Marques, A.; Henriques-Neto, D.; Peralta, M.; Martins, J.; Demetriou, Y.; Schönbach, D.M.I.; de Matos, M.G. Prevalence of Physical Activity among Adolescents from 105 Low, Middle, and High-income Countries. *Int. J. Environ. Res. Public Health* **2020**, *17*, 3145. [CrossRef] [PubMed]
13. Banfi, G.; Mauri, C.; Morelli, B.; Di Gaetano, N.; Malgeri, U.; Melegati, G. Reticulocyte count, mean reticulocyte volume, immature reticulocyte fraction, and mean spheroid cell volume in elite athletes: Reference values and comparison with the general population. *Clin. Chem. Lab. Med.* **2006**, *44*, 616–622. [CrossRef]
14. Díaz Martínez, A.E.; Alcaide Martín, M.J.; González-Gross, M. Basal Values of Biochemical and Hematological Parameters in Elite Athletes. *Int. J. Environ. Res. Public Health* **2022**, *19*, 3059. [CrossRef]
15. Pedlar, C.R.; Newell, J.; Lewis, N.A. Blood Biomarker Profiling and Monitoring for High-Performance Physiology and Nutrition: Current Perspectives, Limitations and Recommendations. *Sports Med.* **2019**, *49*, 185–198. [CrossRef]
16. Del Valle, D.M.; Kim-Schulze, S.; Huang, H.-H.; Beckmann, N.D.; Nirenberg, S.; Wang, B.; Lavin, Y.; Swartz, T.H.; Madduri, D.; Stock, A.; et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat. Med.* **2020**, *26*, 1636–1643. [CrossRef]
17. Leisman, D.E.; Ronner, L.; Pinotti, R.; Taylor, M.D.; Sinha, P.; Calfee, C.S.; Hirayama, A.V.; Mastroianni, F.; Turtle, C.J.; Harhay, M.O.; et al. Cytokine elevation in severe and critical COVID-19: A rapid systematic review, meta-analysis, and comparison with inflammatory syndromes. *Lancet* **2020**, *8*, 1233–1244. [CrossRef] [PubMed]
18. Mandal, S.; Barnett, J.; Brill, S.E.; Brown, J.S.; Denny, E.K.; Hare, S.S.; Heightman, M.; Hillman, T.E.; Jacob, J.; Jarvis, H.C.; et al. 'Long-COVID': A cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* **2021**, *76*, 396–398. [CrossRef] [PubMed]
19. Grazioli, S.; Tavaglione, F.; Torriani, G.; Wagner, N.; Rohr, M.; L'Huillier, A.G.; Leclercq, C.; Perrin, A.; Bordessoule, A.; Beghetti, M.; et al. Immunological Assessment of Pediatric Multisystem Inflammatory Syndrome Related to Coronavirus Disease 2019. *J. Pediatr. Infect. Dis. Soc.* **2021**, *10*, 706–713. [CrossRef]
20. Conti, P.; Ronconi, G.; Caraffa, A.; Gallenga, C.E.; Ross, R.; Frydas, I.; Kritas, S.K. Induction of pro-inflammatory cytokines (IL-1 and IL-6 and lung inflammation by coronavirus-19 (Covi-19 or SARS-CoV-2): Anti-inflammatory strategies. *J. Biol. Regul. Homeost. Agents* **2020**, *34*, 11–15.
21. Niess, A.M.; Widmann, M.; Gaidai, R.; Götz, C.; Schubert, I.; Castillo, K.; Sachs, J.P.; Bizjak, D.; Vollrath, S.; Wimbauer, F.; et al. COVID-19 in German Competitive Sports: Protocol for a Prospective Multicenter Cohort Study (CoSmo-S). *Int. J. Public Health* **2022**, *67*, 1604414. [CrossRef]
22. Jetté, M.; Sidney, K.; Blümchen, G. Metabolic equivalents (METs) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin. Cardiol.* **1990**, *13*, 555–565. [CrossRef]
23. Wang, Z. Unified Robust Estimation, 2020. Available online: <https://arxiv.org/pdf/2010.02848> (accessed on 25 July 2022).
24. Domingo, F.R.; Waddell, L.A.; Cheung, A.M.; Cooper, C.L.; Belcourt, V.J.; Zuckermann, A.M.E.; Corrin, T.; Ahmad, R.; Boland, L.; Laprise, C.; et al. Prevalence of long-term effects in individuals diagnosed with COVID-19: An updated living systematic review. *MedRxiv* **2021**. [CrossRef]
25. Martinez, M.W.; Tucker, A.M.; Bloom, O.J.; Green, G.; DiFiori, J.P.; Solomon, G.; Phelan, D.; Kim, J.H.; Meeuwisse, W.; Sills, A.K.; et al. Prevalence of Inflammatory Heart Disease Among Professional Athletes with Prior COVID-19 Infection Who Received Systematic Return-to-Play Cardiac Screening. *JAMA Cardiol.* **2021**, *6*, 745–752. [CrossRef]
26. Mariño, M.M.; Grieta, F.J.; Bartolomé, I.; Siquier-Coll, J.; Román, V.T.; Muñoz, D. Influence of physical training on erythrocyte concentrations of iron, phosphorus and magnesium. *J. Int. Soc. Sports Nutr.* **2020**, *17*, 8. [CrossRef] [PubMed]
27. Galán, M.; Vigón, L.; Fuertes, D.; Murciano-Antón, M.A.; Casado-Fernández, G.; Domínguez-Mateos, S.; Mateos, E.; Ramos-Martín, F.; Planelles, V.; Torres, M.; et al. Persistent Overactive Cytotoxic Immune Response in a Spanish Cohort of Individuals With Long-COVID: Identification of Diagnostic Biomarkers. *Front. Immunol.* **2022**, *13*, 848886. [CrossRef] [PubMed]
28. Glynn, P.; Tahmasebi, N.; Gant, V.; Gupta, R. Long COVID following mild SARS-CoV-2 infection: Characteristic T cell alterations and response to antihistamines. *J. Investig. Med.* **2022**, *70*, 61–67. [CrossRef] [PubMed]
29. Siemińska, I.; Węglarczyk, K.; Surmiak, M.; Kurowska-Baran, D.; Sanak, M.; Siedlar, M.; Baran, J. Mild and Asymptomatic COVID-19 Convalescents Present Long-Term Endotype of Immunosuppression Associated With Neutrophil Subsets Possessing Regulatory Functions. *Front. Immunol.* **2021**, *12*, 748097. [CrossRef]
30. Gomes, J.H.; Mendes, R.R.; Franca, C.S.; Da Silva-Grigoletto, M.E.; Da Pereira Silva, D.R.; Antonioli, A.R.; de Oliveira e Silva, A.M.; Quintans-Júnior, L.J. Acute leucocyte, muscle damage, and stress marker responses to high-intensity functional training. *PLoS ONE* **2020**, *15*, e0243276. [CrossRef]
31. Zhang, Z.-L.; Hou, Y.-L.; Li, D.-T.; Li, F.-Z. Laboratory findings of COVID-19: A systematic review and meta-analysis. *Scand. J. Clin. Lab. Investig.* **2020**, *80*, 441–447. [CrossRef]
32. 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]
33. Kleiven, Ø.; Bjørkavoll-Bergseth, M.; Melberg, T.; Skadberg, Ø.; Bergseth, R.; Selvåg, J.; Auestad, B.; Aukrust, P.; Aarsland, T.; Ørn, S. High physical fitness is associated with reduction in basal- and exercise-induced inflammation. *Scand. J. Med. Sci. Sports* **2018**, *28*, 172–179. [CrossRef]

34. Nyborg, C.; Melau, J.; Bonnevie-Svendsen, M.; Mathiasen, M.; Melsom, H.S.; Storsve, A.B.; Hisdal, J. Biochemical markers after the Norseman Extreme Triathlon. *PLoS ONE* **2020**, *15*, e0239158. [\[CrossRef\]](#)
35. Phetsouphanh, C.; Darley, D.R.; Wilson, D.B.; Howe, A.; Munier, C.M.L.; Patel, S.K.; Juno, J.A.; Burrell, L.M.; Kent, S.J.; Dore, G.J.; et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat. Immunol.* **2022**, *23*, 210–216. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Hollenberg, M.D.; Epstein, M. The innate immune response, microenvironment proteinases, and the COVID-19 pandemic: Pathophysiologic mechanisms and emerging therapeutic targets. *Kidney Int. Suppl.* **2022**, *12*, 48–62. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Schiffner, J.; Backhaus, I.; Rimmel, J.; Schulz, S.; Möhlenkamp, T.; Klemens, J.M.; Zapf, D.; Solbach, W.; Mischnik, A. Long-Term Course of Humoral and Cellular Immune Responses in Outpatients After SARS-CoV-2 Infection. *Front. Public Health* **2021**, *9*, 732787. [\[CrossRef\]](#) [\[PubMed\]](#)
38. Shephard, R.J.; Shek, P.N. Potential impact of physical activity and sport on the immune system—a brief review. *Br. J. Sports Med.* **1994**, *28*, 247–255. [\[CrossRef\]](#)
39. Bizjak, D.A.; Treff, G.; Zügel, M.; Schumann, U.; Winkert, K.; Schneider, M.; Abendroth, D.; Steinacker, J.M. Differences in Immune Response During Competition and Preparation Phase in Elite Rowers. *Front. Physiol.* **2021**, *12*, 803863. [\[CrossRef\]](#)
40. Grau, M.; Ibershoff, L.; Zacher, J.; Bros, J.; Tomschi, F.; Diebold, K.F.; Predel, H.-G.; Bloch, W. Even patients with mild COVID-19 symptoms after SARS-CoV-2 infection show prolonged altered red blood cell morphology and rheological parameters. *J. Cell. Mol. Med.* **2022**, *26*, 3022–3030. [\[CrossRef\]](#)
41. Gérard, D.; Ben Brahim, S.; Lesesve, J.F.; Perrin, J. Are mushroom-shaped erythrocytes an indicator of COVID-19? *Br. J. Haematol.* **2021**, *192*, 230. [\[CrossRef\]](#)
42. Kubánková, M.; Hohberger, B.; Hoffmanns, J.; Fürst, J.; Herrmann, M.; Guck, J.; Kräter, M. Physical phenotype of blood cells is altered in COVID-19. *Biophys. J.* **2021**, *120*, 2838–2847. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Kronstein-Wiedemann, R.; Stadtmüller, M.; Traikov, S.; Georgi, M.; Teichert, M.; Yosef, H.; Wallenborn, J.; Karl, A.; Schütze, K.; Wagner, M.; et al. SARS-CoV-2 Infects Red Blood Cell Progenitors and Dysregulates Hemoglobin and Iron Metabolism. *Stem. Cell Rev. Rep.* **2022**, *18*, 1809–1821. [\[CrossRef\]](#)
44. Pretorius, E.; Vlok, M.; Venter, C.; Bezuidenhout, J.A.; Laubscher, G.J.; Steenkamp, J.; Kell, D.B. Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. *Cardiovasc. Diabetol.* **2021**, *20*, 172. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Smith, J.A. Exercise, training and red blood cell turnover. *Sports Med.* **1995**, *19*, 9–31. [\[CrossRef\]](#)
46. Schmidt, W.; Maassen, N.; Trost, F.; Böning, D. Training induced effects on blood volume, erythrocyte turnover and haemoglobin oxygen binding properties. *Eur. J. Appl. Physiol. Occup. Physiol.* **1988**, *57*, 490–498. [\[CrossRef\]](#)
47. Weight, L.M.; Byrne, M.J.; Jacobs, P. Haemolytic effects of exercise. *Clin. Sci.* **1991**, *81*, 147–152. [\[CrossRef\]](#)
48. Rautiainen, S.; Manson, J.E.; Lichtenstein, A.H.; Sesso, H.D. Dietary supplements and disease prevention—A global overview. *Nat. Rev. Endocrinol.* **2016**, *12*, 407–420. [\[CrossRef\]](#) [\[PubMed\]](#)
49. Bailey, R.L.; West, K.P.; Black, R.E. The epidemiology of global micronutrient deficiencies. *Ann. Nutr. Metab.* **2015**, *66* (Suppl. S2), 22–33. [\[CrossRef\]](#) [\[PubMed\]](#)
50. Baeke, F.; Takiishi, T.; Korf, H.; Gysemans, C.; Mathieu, C. Vitamin D: Modulator of the immune system. *Curr. Opin. Pharmacol.* **2010**, *10*, 482–496. [\[CrossRef\]](#)
51. Yisak, H.; Ewunetebi, A.; Kefale, B.; Mamuye, M.; Teshome, F.; Ambaw, B.; Yideg Yitbarek, G. Effects of Vitamin D on COVID-19 Infection and Prognosis: A Systematic Review. *Risk Manag. Healthc. Policy* **2021**, *14*, 31–38. [\[CrossRef\]](#)
52. Jakobsson, J.; Cotgreave, I.; Furberg, M.; Arnberg, N.; Svensson, M. Potential Physiological and Cellular Mechanisms of Exercise That Decrease the Risk of Severe Complications and Mortality Following SARS-CoV-2 Infection. *Sports* **2021**, *9*, 121. [\[CrossRef\]](#)
53. Nieman, D.C. Exercise Is Medicine for Immune Function: Implication for COVID-19. *Curr. Sports Med. Rep.* **2021**, *20*, 395–401. [\[CrossRef\]](#)
54. Bai, F.; Tomasoni, D.; Falcinella, C.; Barbanotti, D.; Castoldi, R.; Mulè, G.; Augello, M.; Mondatore, D.; Allegrini, M.; Cona, A.; et al. Female gender is associated with long COVID syndrome: A prospective cohort study. *Clin. Microbiol. Infect.* **2022**, *28*, e9–e611. [\[CrossRef\]](#)
55. Bienvenu, L.A.; Noonan, J.; Wang, X.; Peter, K. Higher mortality of COVID-19 in males: Sex differences in immune response and cardiovascular comorbidities. *Cardiovasc. Res.* **2020**, *116*, 2197–2206. [\[CrossRef\]](#) [\[PubMed\]](#)
56. Mohamed, M.S.; Moulin, T.C.; Schiöth, H.B. Sex differences in COVID-19: The role of androgens in disease severity and progression. *Endocrine* **2021**, *71*, 3–8. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Holtzman, B.; Ackerman, K.E. Recommendations and Nutritional Considerations for Female Athletes: Health and Performance. *Sports Med.* **2021**, *51*, 43–57. [\[CrossRef\]](#) [\[PubMed\]](#)

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.