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In-depth analysis of laboratory parameters reveals the interplay between sex, age, and systemic inflammation in individuals with COVID-19☆

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ABSTRACT

Background: The progression and severity of COVID-19 vary significantly in the population. While the hallmarks of SARS-CoV-2 and severe COVID-19 within routine laboratory parameters are emerging, the impact of sex and age on these profiles is still unknown.
Methods: A multidimensional analysis was performed involving millions of records of laboratory parameters and diagnostic tests for 178 887 individuals from Brazil, of whom 33 266 tested positive for SARS-CoV-2. Analyzed data included those relating to complete blood cell count, electrolytes, metabolites, arterial blood gases, enzymes, hormones, cancer biomarkers, and others.
Findings: COVID-19 induced similar alterations in laboratory parameters in males and females. CRP and ferritin were increased, especially in older men with COVID-19, whereas abnormal liver function tests were common across several age groups, except for young women. Low peripheral blood basophils and eosinophils were more common in the elderly with COVID-19. Both male and female COVID-19 patients admitted to intensive care units displayed alterations in the coagulation system, and higher values for neutrophils, CRP, and lactate dehydrogenase.
Conclusions: Our study uncovered the laboratory profiles of a large cohort of COVID-19 patients, which formed the basis of discrepancies influenced by aging and biological sex. These profiles directly linked COVID-19 disease presentation to an intricate interplay between sex, age, and immune activation.

☆ Big Data analysis of laboratory results from a large number of COVID-19 patients and controls revealed distinct disease profiles influenced by age and sex, which may underly the occurrence of severe disease.

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Introduction

The new coronavirus SARS-CoV-2 has spread rapidly throughout the world, causing an unprecedented pandemic. As of February 2021, Brazil was the third-highest country in terms of number of infections and the second in terms of cumulative deaths, with a total of more than 10 million COVID-19 (coronavirus disease 2019) cases and over 250 000 deaths (WHO, 2021). The virus is easily transmitted between humans and triggers a wide spectrum of clinical manifestations (Guan et al., 2020a, b), ranging from asymptomatic or mild illness to severe disease. SARS-CoV-2 infection has been associated with respiratory, gastrointestinal, hepatic, and neurological dysfunction, which can lead to acute respiratory distress syndrome, multiple organ failure, and death in severe cases (Tay et al., 2020).

Since SARS-CoV-2 is a systemic infection, inflammatory responses can induce changes in the cellular and biochemical composition of the peripheral blood (Tay et al., 2020). For instance, a significant proportion of patients exhibit a variety of alterations in distinct organs, such as the gastrointestinal tract (Ng and Tilg, 2020), liver (Feng et al., 2020), kidneys (Ronco et al., 2020), and heart (Zheng et al., 2020). Such extrapulmonary manifestations are associated with potential alterations in circulating levels of several biochemical parameters, such as bilirubin, urea, creatinine, myoglobin, and coagulation factors.

COVID-19 also shows sexual disparity with regard to morbidity and mortality. A sex-stratified analysis revealed that, even after adjusting for age, the effects of comorbidities on COVID-19 mortality were higher in men compared with women (Dudley and Lee, 2020). This disparity can be explained by a combination of factors, such as biological differences (chromosomal, hormonal, etc.) and gender-specific behavioral factors, as well as pre-existing rates of comorbidities (Gebhard et al., 2020; Haitao et al., 2020). Therefore, it is expected that the results of laboratory assays may vary according to sex and age.

To date, no systematic analysis of blood parameters has been performed on a large number of COVID-19 patients, and particularly in the context of age- and sex-related changes observed in the absence of SARS-CoV-2 infection. By analyzing millions of records of laboratory parameters from over 30 000 subjects infected with SARS-CoV-2 from two hospitals and one diagnostics company in Brazil (collected between February 26, 2020—when the pandemic reached Brazil—and June 30, 2020), our study revealed unique profiles for males and females with COVID-19, across different ages. Such large-scale analysis may provide critical information on COVID-19 pathogenesis related to sex and age. Our study also showed that the combination of several biochemical parameters and surrogates of inflammatory responses may be used to assess disease severity.

Materials and methods

Dataset

Three publicly available datasets from the 'COVID-19 Data Sharing/BR' repository, which contains information about laboratory parameters and demographics, as well as diagnostic tests, were downloaded at: https://repositoriodatasharingfapesp.uspdigital.usp.br/ (2020-06-30). The repository is an initiative of the São Paulo Research Foundation (FAPESP), in collaboration with the University of São Paulo and with the participation of the Fleury Institute, Sírio-Libanês Hospital and the Israelita Albert Einstein Hospital. The data for individuals with COVID-19 were collected from February 26, 2020 to June 30, 2020, whereas the control data (individuals without COVID-19) were collected from November 1, 2019 to June 30, 2020. The names of the laboratory tests were translated into English and the common tests performed by the three sites were identified. If a given test was carried out more than once for the same subject, the result for the one performed at the earliest date after positive diagnosis of SARS-CoV-2 (by PCR or IgM) was collected. Only 271 individuals were diagnosed with COVID-19, based solely on a positive IgM assay. For the COVID-19 cases, records collected before the day of positive diagnosis of SARS-CoV-2 or that were collected over 15 days after the day of positive diagnosis of SARS-CoV-2 were removed. Laboratory parameters measured in fewer than 100 subjects or that contained discrete (i.e. categorical) values were also removed from the analysis.

Univariate analysis

The Anderson–Darling normality test was used to identify normally distributed laboratory parameters. The Student *t*-test was used to identify the changes between groups of samples, with p-values adjusted for multiple testing using the Benjamini and Hochberg method. The cutoffs used to identify a significant change were an adjusted p-value < 0.05 and a $\log_2$ fold change >0.4. Comparisons with fewer than 20 samples in both groups (i.e. COVID-19 cases and controls) were not considered. Plots were created using the ggplot2 R package (https://ggplot2.tidyverse.org) and edited in CorelDraw software.

Temporal age profiling

For each year of age (stratified by sex and COVID-19 diagnostic), the median and 95% confidence interval for each laboratory parameter were calculated. Using ggplot2 R, a smooth line (loess method) was fitted on the points and the lines for recent infection vs no infection were compared for each sex, using the Kolmogorov–Smirnov test (FDR cutoff <0.01). Ages with two or fewer values were not included in the median calculation.

Intensive care unit (ICU) analysis

The Sírio-Libanês Hospital had identified data from patients admitted to the ICU (n = 285). For each subject, the first date recorded as when laboratory data were collected in the ICU was considered as day 0. The median and 95% confidence interval for each laboratory parameter on each day were calculated for male and female patients. Reference normal values of the parameters were obtained from physicians and displayed on the graphs. Finally, specific laboratory parameters were grouped into biomarkers of disease activity.

Results

Laboratory parameter data from two hospitals and one diagnostics company in Brazil were made publicly available by the São Paulo Research Foundation (FAPESP). The repository holds open-access anonymized data for 175 887 individuals tested for SARS-CoV-2, of which 39 391 had tested positive using a combination of IgM/IgA/IgG serology and RT-PCR tests (Supplemental Figure 1A). RT-PCR or IgM tests were positive in 33 266

subjects, suggesting recent infection with SARS-CoV-2, and were herein defined as COVID-19 cases. All remaining individuals were classified as controls, including the 6125 subjects who showed IgA (N = 900) or IgG (N = 5225) seroreactivity towards SARS-CoV-2 antigens. The age distributions of male and female COVID-19 cases were similar (Supplemental Figure 1B). In total, over 4.5 million records of 434 laboratory parameters and diagnostic tests were analyzed (see methods).

The subjects were divided into three age groups: 0–12 years old (N = 5218), 13–60 years old (N = 146 404), and ≥61 years old (N = 22 657). Age information was not available for 1608 individuals. Univariate analyses were then performed to compare values of laboratory parameters between COVID-19 cases and controls within each age group. No significant differences were found between females and males in the 0–12 years group (Supplemental Table 1). COVID-19 induced more alterations in the laboratory parameters in males compared with females in those between 13 and 60 years old, in contrast with older individuals, where several parameters were altered by COVID-19 in both men and women (Figure 1). Male and female COVID-19 patients had a lower levels of basophils and eosinophils, as well as significantly higher levels of gamma-glutamyl transferase (GGT), C-reactive protein (CRP), and ferritin when compared with control individuals in the same age group (Figure 1, Supplemental Table 1).

A profile of key clinical chemistry parameters for male and female COVID-19 cases compared with control cases was generated across age groups (Figure 2). The analysis revealed important differences relating to age and sex, even in the absence of COVID-19. While alterations in several parameters were seen in COVID-19 cases, the absolute levels were critically dependent on whether patients were male or female, with the most perturbed laboratory markers found in male COVID-19 cases (Figure 2).

The absolute counts of cell populations for the complete blood count profile in COVID-19 cases and controls were compared by sex and age (Figure 3). Lower counts of platelets, basophils, lymphocytes, and eosinophils were observed in COVID-19 cases compared with controls in both males and females (Figure 3).

Two hundred and eighty-five COVID-19 patients were admitted to the intensive care unit (ICU). The median number of days in ICU was 15 (Figure 4A), and 74% of patients were male (Figure 4B), with 165 individuals aged ≥60 years of age (range 20–88) (Figure 4C). Daily changes in laboratory parameters during ICU stay were

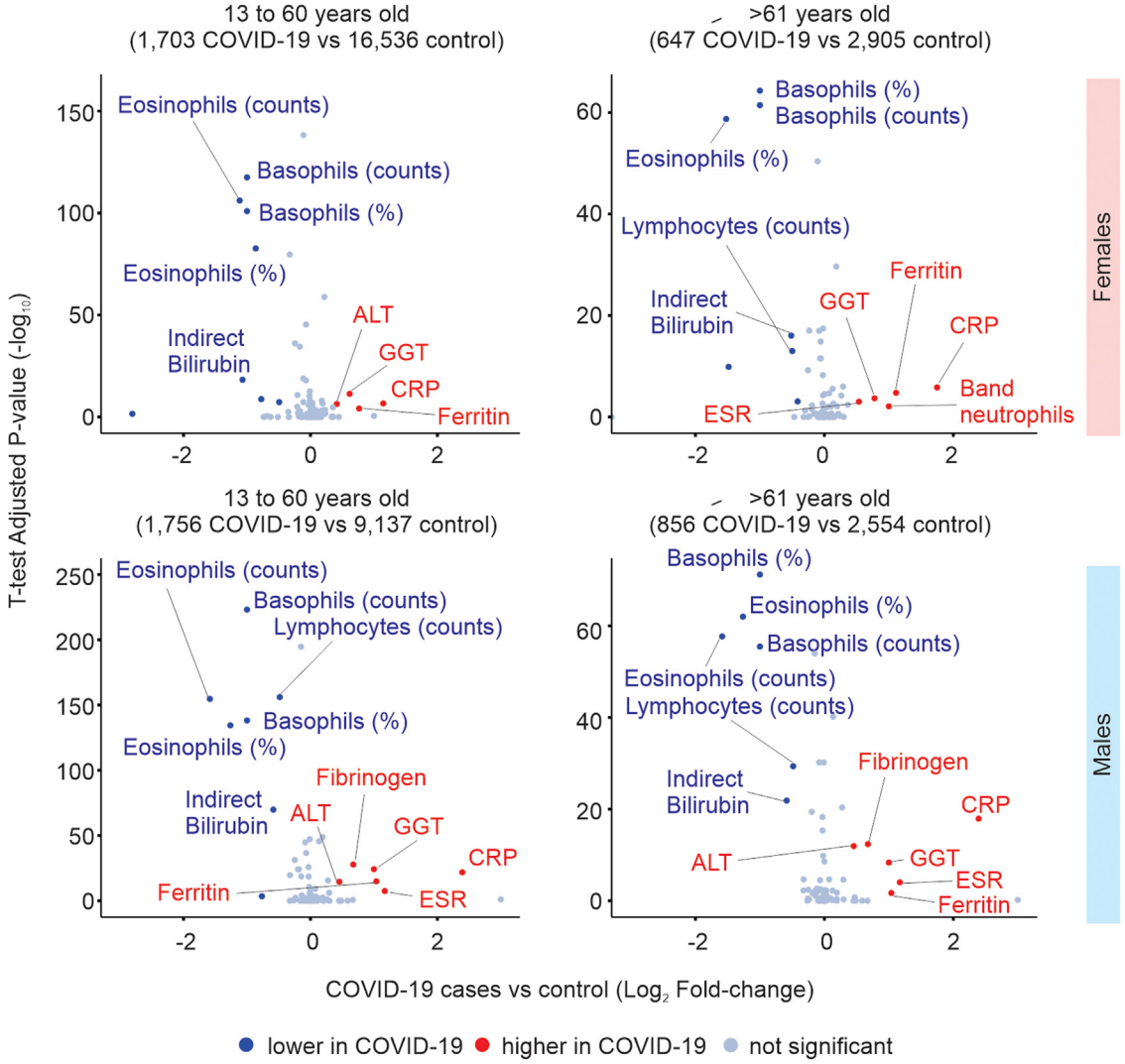

Figure 1. Alterations induced by COVID-19. Volcano plots showing the differences in the levels of laboratory parameters between COVID-19 cases and controls. Female subjects are shown on the top and male subjects on the bottom. The age group is indicated above each volcano plot and the number of individuals is shown in parenthesis. The x-axis shows the $\log_2$ fold changes between COVID-19 cases and controls, and the y-axis shows the$\log_{10}$ adjusted p-values for the analyzed laboratory parameters (dots). Red and blue dots show, respectively, the laboratory parameters that were significantly higher or lower in COVID-19 cases compared with controls (adjusted p-value <0.05 and log2 fold change >0.4).

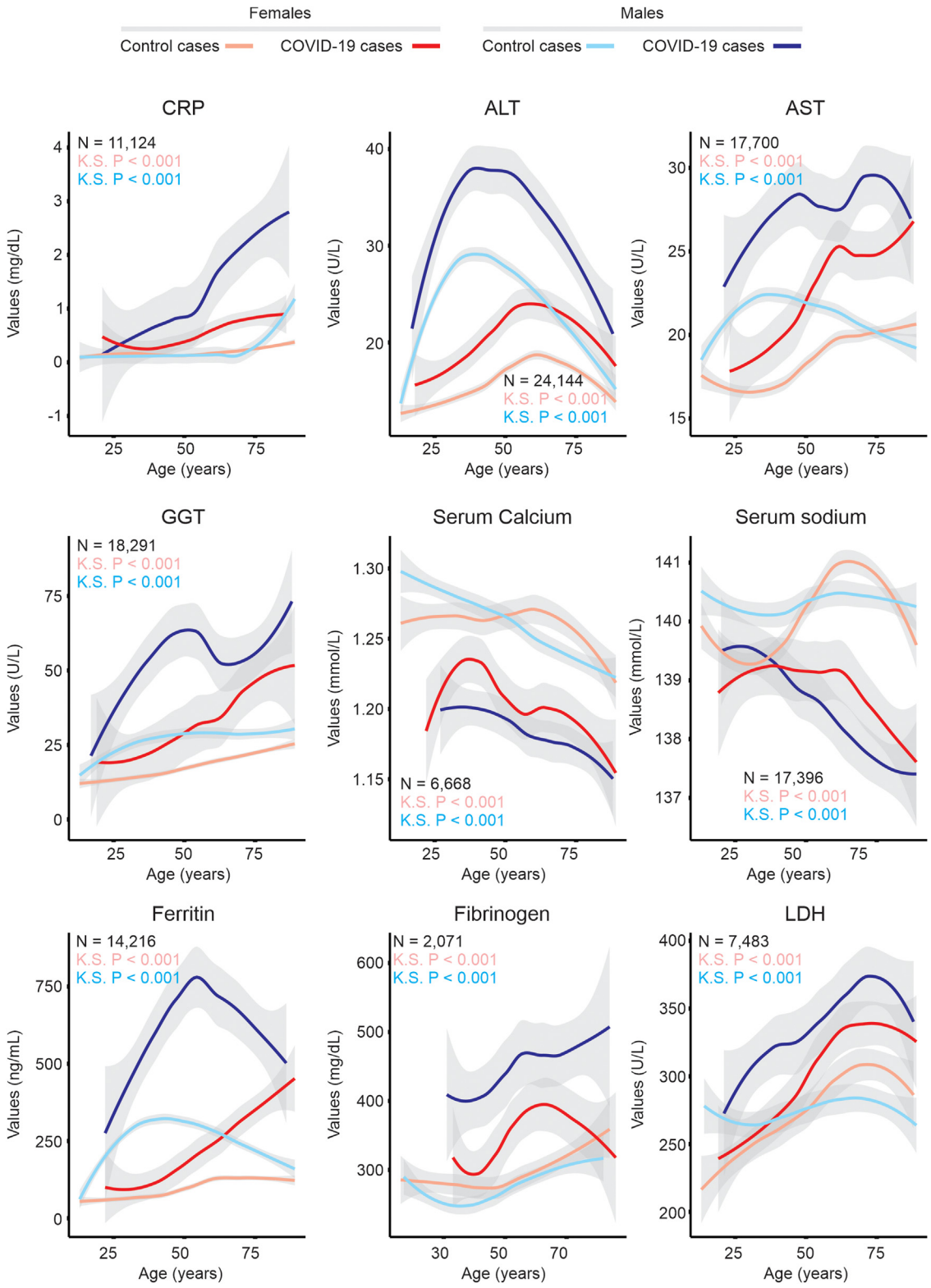

Figure 2. Selected laboratory parameter temporal profiles for male and female COVID-19 patients. The *x*-axis shows the age of individuals and the *y*-axis shows the fitted median values (thick line) for the laboratory parameter displayed above each graph. The shaded area represents the 95% confidence interval. Female COVID-19 cases and controls are shown as red and brown lines, respectively. Male COVID-19 cases and control cases are shown as dark blue and light blue lines, respectively. The number of individuals (*N*) utilized in the analysis, and the Kolmogorov–Smirnov test *p*-value (K.S.) between the COVID-19 curve and the control curve for each sex are indicated.

examined, with several remaining significantly altered throughout this period compared with reference values for age (Figure 4D and S2). Significant elevation of the coagulation markers activated partial thromboplastin time (aPTT) and prothrombin time (PT/INR) was seen. While aPTT values detected in critically ill male COVID-19 patients returned back to normal after 30 days in ICU, they remained altered in female COVID-19 patients in ICU (Figure 4D). The curve for aPTT followed a similar trend as the curve for lactate

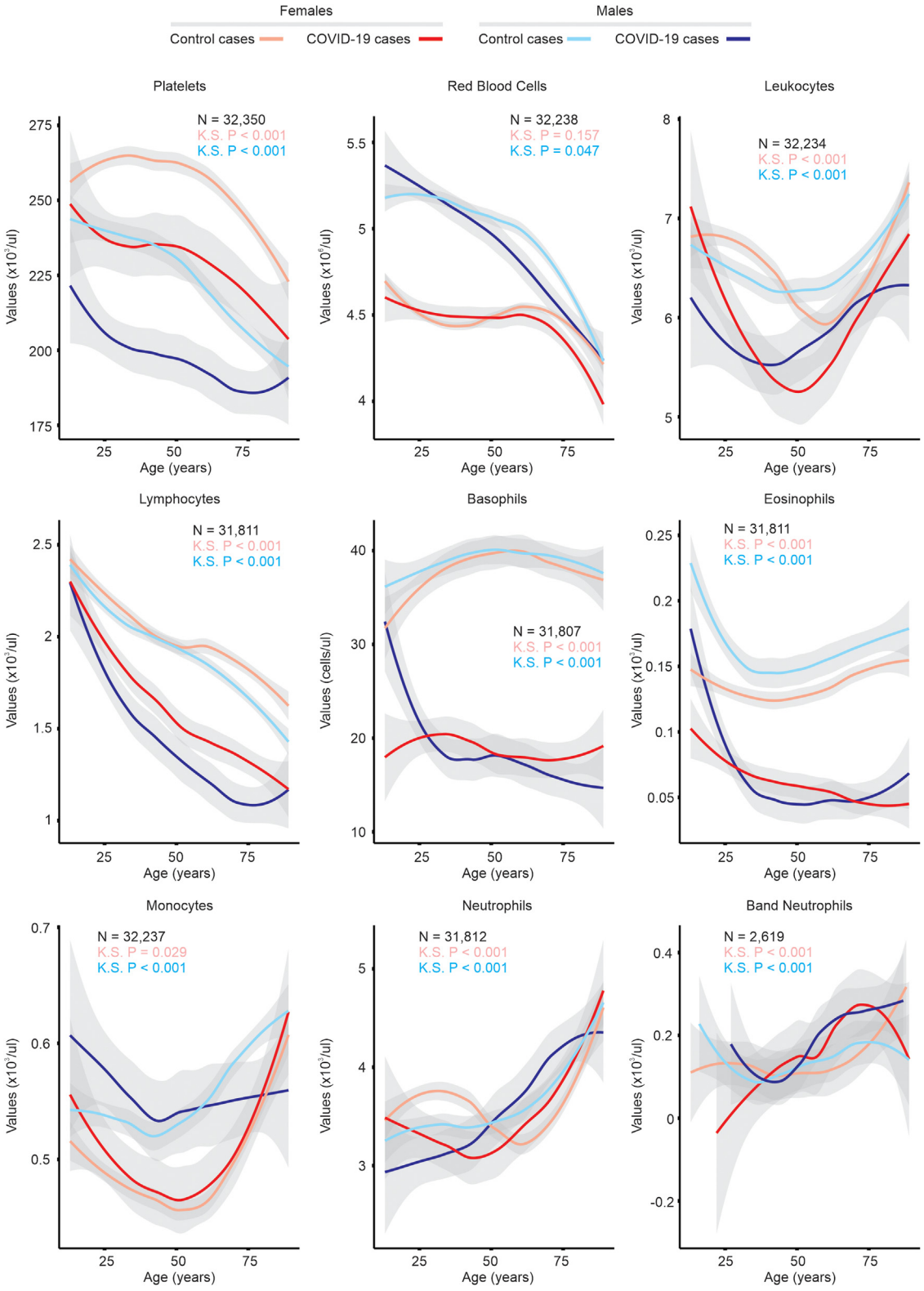

Figure 3. Analysis of complete blood count tests in COVID-19 cases. The *x*-axis shows the age of individuals and the *y*-axis shows the fitted median values (thick line) for the cell type displayed above each graph. The shaded area represents the 95% confidence interval. Female COVID-19 cases and controls are shown as red and brown lines, respectively. Male COVID-19 cases and control cases are shown as dark blue and light blue lines, respectively. The number of individuals (*N*) utilized in the analysis, and the Kolmogorov–Smirnov test *p*-value (K.S.) between the COVID-19 curve and the control curve for each sex are indicated.

dehydrogenase (LDH) (Figure 4D), reinforcing the link between activation of coagulation and inflammatory pathways.

Patients with COVID-19 may present with very different complications, such as liver or kidney impairment (Gholizadeh et al., 2020; Hong et al., 2020), systemic inflammation (Gao et al., 2020), and coagulopathy (Franchini et al., 2020). The laboratory parameters were manually classified into biomarkers of disease activity, including organ damage, problems in lipid or glucose

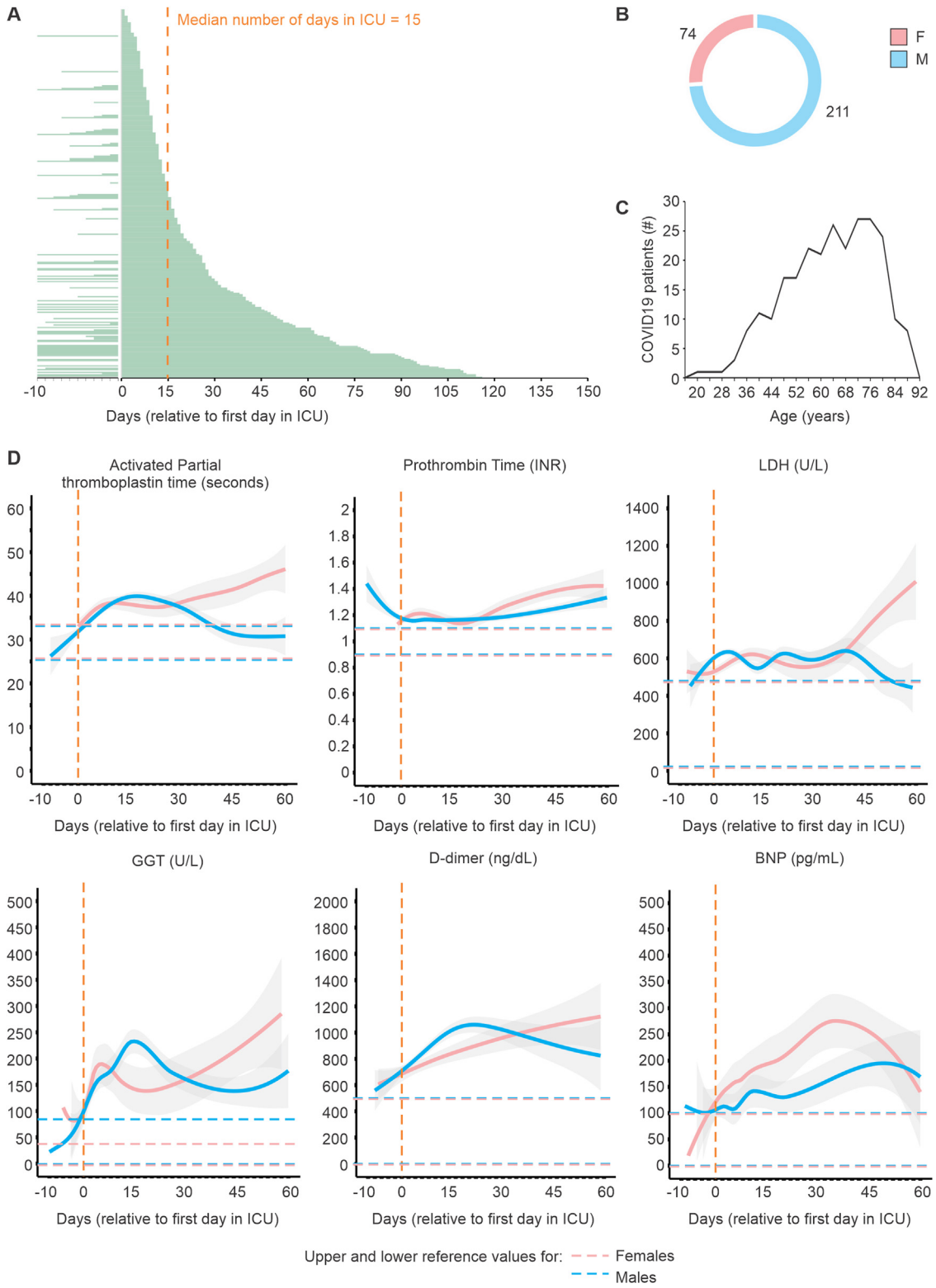

Figure 4. Time course analysis of COVID-19 patients in ICU. (A) Number of days in ICU. Each patient is represented by a green line. The dashed vertical line shows the median number of days in ICU. (B) Number of female and male patients in ICU. Males are represented in blue and females in pink. (C) Age distribution of patients in ICU. (D) Daily records of laboratory parameters in patients admitted to to ICU. The dashed vertical line represents the day of the first record in ICU. Values are shown on the *y*-axis and the units are displayed in parenthesis on top of each graph. The blue and pink lines represent the median values for male and female COVID-19 patients in ICU, respectively. The shaded area represents the 95% confidence interval. Horizontal dashed lines mark the upper and lower reference normal values for males (blue) and females (pink).

metabolism, systemic inflammation, coagulation, and acid–base imbalance in blood gases (Supplemental Table 2). Then, for each COVID-19 patient, the earliest recorded levels of laboratory parameters after positive diagnosis were compared with the respective reference values by sex. Alterations were similar between male and female COVID-19 patients who were admitted to ICU (Figure 5A). For instance, alterations in the frequency of immune cells were detected in 98% of both male and female

COVID-19 patients (Figure 5A). While 50.4% of male COVID-19 patients showed evidence of coagulopathy, only 39.7% of female patients had similar abnormalities (Figure 5A). When only ICU patients were considered, these numbers increased to 91.3% (males) and 82.8% (females) (Figure 5A). Furthermore, a large fraction of ICU patients showed evidence of elevated liver function tests and renal impairment, as well as disturbances of the acid–base balance and systemic immune response (Figure 5B). Ten laboratory parameters were altered in a larger fraction of ICU patients compared with all COVID-19 patients not admitted to the ICU. These included CRP, IL-6, neutrophils, ESR, fibrinogen, glucose, LDH, transferrin saturation (TS), albumin, and total iron binding capacity (TIBC) (Figure 5C). These parameters further indicate that COVID-19 severity is directly linked to disturbances in coagulation and in the systemic immune response.

Discussion

Our in-depth analysis of routinely collected laboratory parameters in individuals with COVID-19 revealed that the changes seen were critically dependent on age and sex. This has significant implications for understanding the pathogenesis of COVID-19, as well as for developing predictive models of SARS-CoV-2 infection and severe disease. For instance, our results showed that elderly male patients have significantly more abnormal laboratory values, including higher levels of inflammatory markers, compared with elderly females. The disproportionate male-to-female ratios of SARS-CoV-2 infection prevalence, morbidity, and mortality have not been reported around the world (Scully et al., 2020). Severity and case fatality rates are significantly higher among men than women (Michelozzi et al., 2020; Qian et al., 2020).

Recent studies have considered the role of biological sex differences in explaining differences in outcome (Ding et al., 2020). Sex hormones mediate differences in innate immune cells and functional responses to SARS, MERS, influenza, and other viruses in the respiratory tract (Karlberg et al., 2004; Channappanavar et al., 2017; Kadel and Kovats, 2018). Our findings provide further support for exploring these hormonal influences in SARS-CoV-2 outcome, in order to explain why premenopausal women may be relatively protected from severe COVID-19 compared with men.

Increased levels of markers such as CRP, ferritin, fibrinogen, LDH, and GGT could be detected in many COVID-19 patients. Ferritin and CRP have been widely described as consequences of the production of pro-inflammatory cytokines, such as IL-6, and the complement activation that may contribute to the systemic inflammatory response in patients with COVID-19 (Risitano et al., 2020). These changes were most marked in older men, although once patients were admitted to ICU, very similar profiles were observed between men and women.

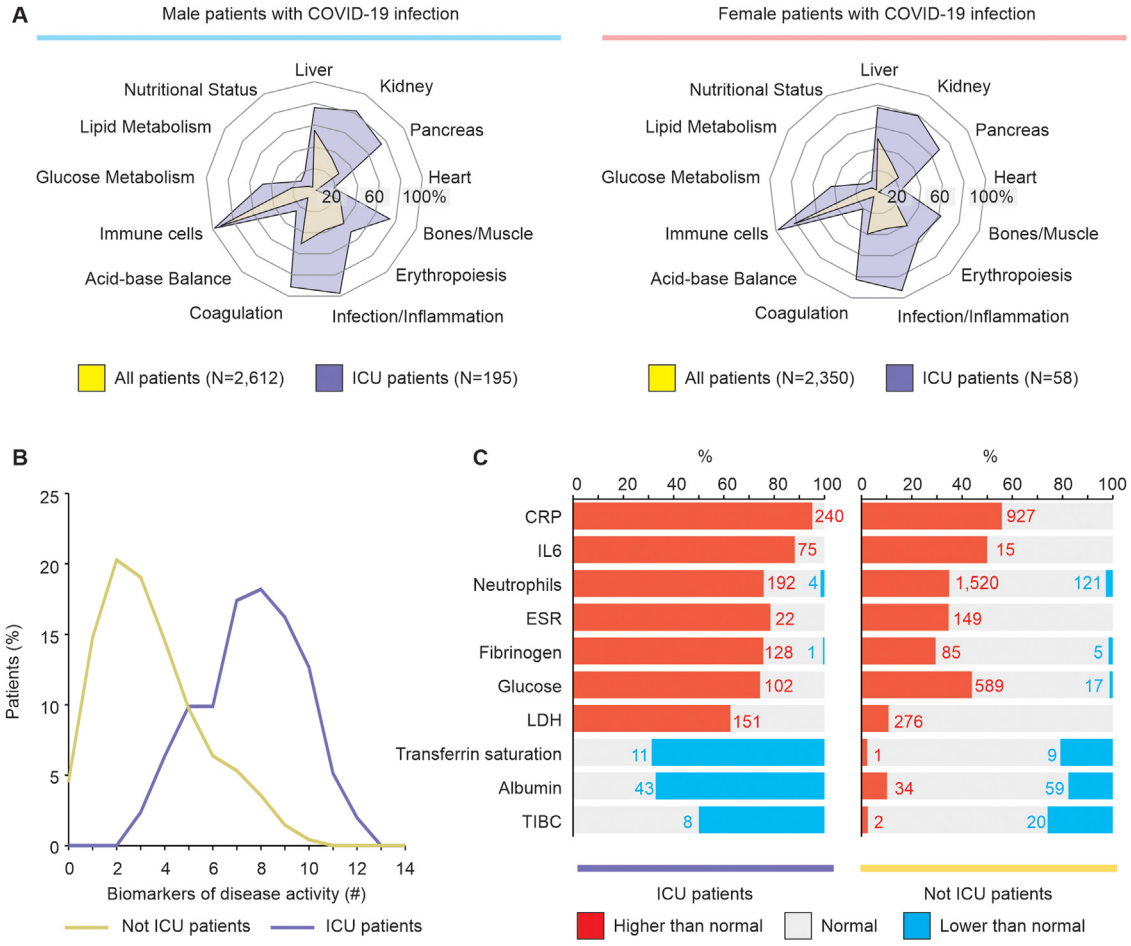

Figure 5. Biomarkers of disease activity in COVID-19 patients. (A) Fraction of patients with altered biomarkers of disease activity. Alterations in at least one laboratory parameter for each biomarker of disease activity were detected for male (left) and female (right) COVID-19 patients who were admitted (purple) or not admitted (yellow) to ICU. The graph shows the subjects with alterations as a fraction of the total number of subjects. (B) Number of biomarkers of disease activity detected in COVID-19 patients. The purple and yellow lines indicate, respectively, the fractions of COVID-19 patients who were admitted or not admitted to ICU. (C) Laboratory parameters altered in ICU COVID-19 patients. Each bar represents the fraction of individuals who were admitted (left) or not admitted (right) to ICU, showing values above (red) or below (blue) the normal levels for a specific parameter. Numbers of individuals with alterations are indicated.

Our findings from complete blood count analysis revealed that both male and female COVID-19 patients had low levels of platelets, basophils, and eosinophils. Platelet numbers reduced with age in both men and women, with a similar reduction in COVID-19 patients compared with controls across age and sex. Thrombocytopenia is thought to be an early predictor of disease severity (Arachchillage and Laffan, 2020; Bomhof et al., 2020; Zhou et al., 2020). While lymphopenia is considered a feature of COVID-19, our analysis shows that the reduction in cell count is modest compared with patients without SARS-CoV-2 of a similar age and same sex. Little is known about the roles of basophils and eosinophils in COVID-19. Eosinophils may enhance antiviral immunity during infection, and can activate viral antigen-specific CD8+ T cells (Samarasinghe et al., 2017). Moreover, previous studies suggest that female sex hormones regulate eosinophil numbers both *in vitro* and *in vivo* (Kadel and Kovats, 2018). Using 989 patients, Li et al. reported that eosinopenia and elevated CRP effectively distinguish SARS-CoV-2-positive patients from SARS-CoV-2-negative patients with COVID-19-like symptoms (Li et al., 2020). Using hematological data from over 30 000 people across all ages, our study demonstrated that eosinopenia and low levels of basophils were more accentuated in COVID-19 patients compared with other hematological parameters, especially in men older than 25 years of age.

The major limitation of our study was the lack of information regarding patient comorbidities and clinical outcomes, other than admission to ICU. Patients admitted to ICU or those who died from COVID-19, as well as those with comorbidities increasing the risk of severe disease (Guan et al., 2020a, b), may display substantial variation in laboratory markers (Velavan and Meyer, 2020). Overall, several of the observed abnormalities were accentuated in patients admitted to ICU, although our study identified 10 markers that appeared to be more perturbed than others when compared with patients with COVID-19 not admitted to ICU. Interestingly, this included an elevated neutrophil count, which was not significantly different between COVID-19 and control patients overall. This may be related to increased bacterial coinfection in COVID-19 ICU patients, but also highlights potential differences between biomarkers associated with SARS-CoV-2 infection and those related to more severe disease. We also acknowledge that the differences seen in the temporal profiles may fall on a spectrum. Even though some laboratory values in COVID-19 patients fell in the normal range, they differed significantly from those in patients without COVID-19.

Another important limitation of our work is that we considered individuals positive for IgM as cases of recent infection. IgM assays may produce a high number of false positive cases, as IgM antibodies frequently appear later in the acute process (when PCR results is already negative). However, only a very small fraction of the COVID-19 cases here (N = 271) was based solely on an IgM positive assay.

We also did not have information regarding the causes of any illness in the control group—the individuals without SARS-CoV-2 infection. It is important to remember that the differences we describe for COVID-19 may have been relative to individuals with other infections and not necessarily healthy controls. This is, however, also a key strength of our study when considering the utility of our findings for predictive models of SARS-CoV-2 infection and COVID-19-specific severity markers.

By analyzing both soluble and cellular markers in a large number of individuals, our study demonstrated that age and sex influenced the results for the laboratory parameters measured and monitored in COVID-19 patients. Our findings should help guide further studies into COVID-19 pathogenesis, as well as the development of predictive models of SARS-CoV-2 infection and severe disease.

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Disclaimer

The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Conflicts of interest

None declare.

Data and materials availability

All the original data is available at https://repositoriodatasharingfapesp.uspdigital.usp.br/ (2020-06-30).

Ethical approval

All data sourced by the research team were de-identified. The Ethics Committee deemed the study exempt from patients' informed consent because the data were all from secondary sources and publicly available.

CRediT authorship contribution statement

Felipe ten-Caten: Conceptualization, Data curation, Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Patrícia Gonzalez-Dias:** Conceptualization, Data curation, Investigation, Formal analysis, Writing - original draft, Writing - review & editing. **Ícaro Castro:** Data curation, Formal analysis, Writing - review & editing. **Rodrigo L.T. Ogava:** Data curation, Formal analysis, Writing - review & editing. **Jeevan Giddaluru:** Data curation, Formal analysis, Writing - review & editing. **Juan Carlo S. Silva:** Data curation, Formal analysis, Writing - review & editing. **Felipe Martins:** Data curation, Formal analysis, Writing - review & editing. **André N.A. Gonçalves:** Data curation, Formal analysis, Writing - review & editing. **André G. Costa-Martins:** Data curation, Formal analysis, Writing - review & editing. **José D. Araujo:** Data curation, Formal analysis, Writing - review & editing. **Ana Carolina Viegas:** . **Fernando Q. Cunha:** Writing - review & editing. **Sandra Farsky:** Writing - review & editing. **Fernando A. Bozza:** Writing - original draft, Writing - review & editing. **Anna S. Levin:** Writing - original draft, Writing - review & editing. **Pia S. Pannaraj:** Writing - original draft, Writing - review & editing. **Thushan I. de Silva:** Writing - original draft, Writing - review & editing. **Paola Minoprio:** Writing - original draft, Writing - review & editing. **Fabiano Pinheiro da Silva:** Writing - original draft, Writing - review & editing. **Bruno B. Andrade:** Writing - original draft, Writing - review & editing. **Helder I. Nakaya:** Conceptualization, Investigation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Writing - original draft, Writing - review & editing.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.03.016.

References

Arachchillage DRJ, Laffan M. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18(5):1233–4.

Bomhof G, Mutsaers PGNJ, Leebeek FWG, Te Boekhorst PAW, Hofland J, Croles FN, et al. COVID-19-associated immune thrombocytopenia. Br J Haematol 2020;190(2):e61–4.

Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S. Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection. J Immunol 2017;198(10):4046–53.

Ding T, Zhang J, Wang T, Cui P, Chen Z, Jiang J, et al. Potential influence of menstrual status and sex hormones on female SARS-CoV-2 infection: a cross-sectional study from multicentre in Wuhan, China. Clin Infect Dis 2020;ciaa1022, doi: http://dx.doi.org/10.1093/cid/ciaa1022 Published: 22 July 2020.

Dudley JP, Lee NT. Disparities in age-specific morbidity and mortality from SARS-CoV-2 in China and the Republic of Korea. Clin Infect Dis 2020;71(15):863–5.

Feng G, Zheng KI, Yan QQ, Rios RS, Targher G, Byrne CD, et al. COVID-19 and liver dysfunction: current insights and emergent therapeutic strategies. J Clin Transl Hepatol 2020;8(1):18–24.

Franchini M, Marano G, Cruciani M, Mengoli C, Pati I, Masiello F, et al. COVID-19-associated coagulopathy. Diagnosis (Berl) 2020;7(4):357–63.

Gao YM, Xu G, Wang B, Liu BC. Cytokine storm syndrome in coronavirus disease 2019: a narrative review. J Intern Med 2020;289(2):147–61.

Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. Biol Sex Differ 2020;11(1):29.

Gholizadeh P, Safari R, Marofi P, Zeinalzadeh E, Pagliano P, Ganbarov K, et al. Alteration of liver biomarkers in patients with SARS-CoV-2 (COVID-19). J Inflamm Res 2020;13:285–92.

Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020a;55(5).

Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020b;382(18):1708–20.

Haitao T, Vermunt JV, Abeykoon J, Ghamrawi R, Gunaratne M, Jayachandran M, Narang K, Parashuram S, Suvakov S, Garovic VD. COVID-19 and sex differences: mechanisms and biomarkers. Mayo Clin Proc 2020;95(10):2189–203.

Hong D, Long L, Wang AY, Lei Y, Tang Y, Zhao JW, et al. Kidney manifestations of mild, moderate and severe coronavirus disease 2019: a retrospective cohort study. Clin Kidney J 2020;13(3):340–6.

Kadel S, Kovats S. Sex hormones regulate innate immune cells and promote sex differences in respiratory virus infection. Front Immunol 2018;9:1653.

Karlberg J, Chong DS, Lai WY. Do men have a higher case fatality rate of severe acute respiratory syndrome than women do?. Am J Epidemiol 2004;159(3):229–31.

Li Q, Ding X, Xia G, Chen HG, Chen F, Geng Z, et al. Eosinopenia and elevated C-reactive protein facilitate triage of COVID-19 patients in fever clinic: a retrospective case-control study. EClinicalMedicine 2020;100375.

Michelozzi P, de'Donato F, Scortichini M, De Sario M, Noccioli F, Rossi P, et al. Mortality impacts of the coronavirus disease (COVID-19) outbreak by sex and age: rapid mortality surveillance system, Italy, 1 February to 18 April 2020. Euro Surveill 2020;25(19).

Ng SC, Tilg H. COVID-19 and the gastrointestinal tract: more than meets the eye. Gut 2020;69(6):973–4.

Qian J, Zhao L, Ye RZ, Li XJ, Liu YL. Age-dependent gender differences of COVID-19 in mainland China: comparative study. Clin Infect Dis 2020;71(9):2488–94.

Risitano AM, Mastellos DC, Huber-Lang M, Yancopoulou D, Garlanda C, Ciceri F, et al. Complement as a target in COVID-19?. Nat Rev Immunol 2020;20(6):343–4.

Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med 2020;8(7):738–42.

Samarasinghe AE, Melo RC, Duan S, LeMessurier KS, Liedmann S, Surman SL, et al. Eosinophils promote antiviral immunity in mice infected with influenza A virus. J Immunol 2017;198(8):3214–26.

Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol 2020;20(7):442–7.

Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020;20(6):363–74.

Velavan TP, Meyer CG. Mild versus severe COVID-19: laboratory markers. Int J Infect Dis 2020;95:304–7.

WHO. WHO Coronavirus Disease (COVID-19) Dashboard. Geneva: World Health Organization; 2021 2020. W. H. Organization. Available online: https://covid19.who.int/.

Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17(5):259–60.

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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(10229):1054–62.