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Distinct type I interferon responses between younger women and older men contribute to the variability of COVID-19 outcomes: Hypothesis generating insights from COVID-19 convalescent individuals

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ABSTRACT

Background/Objective: Older age and male sex have been consistently found to be associated with dismal outcomes among COVID-19 infected patients. In contrast, premenopausal females present the lowest mortality among adults infected by SARS-CoV-2. The goal of the present study was to investigate whether peripheral blood type I interferon (IFN) signature and interleukin (IL)-6 serum levels -previously shown to contribute to COVID-19-related outcomes in hospitalized patients- is shaped by demographic contributors among COVID-19 convalescent individuals.

Patients and Methods: Type I IFN-inducible genes in peripheral blood, as well as serum IL-6 levels were quantified in 61 COVID-19 convalescent healthy individuals (34 females, 27 males; age range 18–70 years, mean 35.7 ± 15.9 years) who recovered from COVID-19 without requiring hospitalization within a median of 3 months prior to inclusion in the present study. Among those, 17 were older than 50 years (11 males, 6 females) and 44 equal to or less than 50 years (16 males, 28 females). Expression analysis of type I IFN-inducible genes (MX-1, IFIT-1, IFI44) was performed by real time PCR and a type I IFN score, reflecting type I IFN peripheral activity, was calculated. IL-6 and C-reactive protein levels were determined by a commercially available ELISA.

Results: COVID-19 convalescent individuals older than 50 years exhibited significantly decreased peripheral blood type I IFN scores along with significantly increased IL-6 serum levels compared to their younger counterparts less than 50 years old (5.4 ± 4.3 vs 16.8 ± 24.7, $p = 0.02$ and 10.6 ± 16.9 vs 2.9 ± 8.0 ng/L, $p = 0.03$, respectively). Following sex stratification, peripheral blood type I IFN score was found to be significantly higher in younger females compared to both younger and older males (22.9 ± 29.2 vs 6.3 ± 4.6 vs 4.5 ± 3.7, $p = 0.01$ and $p = 0.002$, respectively). Regarding IL-6, an opposite pattern was observed, with the highest levels being detected among older males and the lowest levels among younger females (11.6 ± 18.9 vs 2.5 ± 7.8 ng/L, $p = 0.03$).

Conclusion: Constitutive higher type I IFN responses and dampened IL-6 production observed in younger women of premenopausal age, along with lower type I IFN responses and increased IL-6 levels in older males, could account for the discrete clinical outcomes seen in the two population groups, as consistently revealed in COVID-19 epidemiological studies.

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1. Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global pandemic that has infected, as per October 2021, 250 million people worldwide leading to 5 million deaths [1]. Advanced age and male sex have been previously designated as predictors of adverse outcomes among COVID-19 individuals [2–5], whereas comorbidities per se, expected in advanced age, being unable to abundantly account for the increased risk [6]. On the other hand, human immune systems are extremely variable, either as a result of environmental exposures or due to the influence of genetic contributors [7]. Age and sex have indeed shown to modulate host immune responses, which in turn have been postulated to be the major drivers of heterogeneous clinical presentations and outcomes among COVID-19 patients [8–10], ranging from asymptomatic or mild respiratory complaints to severe pneumonia, acute respiratory distress syndrome (ARDS) and death [11].

A growing body of evidence support that impaired type I interferon (IFN) responses fail to regulate viral replication leading to uncontrolled inflammatory responses and ultimately to cytokine release syndrome [12,13]; accordingly, therapeutic blockade of the proinflammatory cytokines interleukin (IL)-1 and IL-6 improved disease outcomes among COVID-19 patients with hypoxia and evidence of systemic inflammatory responses [14,15]. Of interest, a cross regulation of type I IFNs and proinflammatory cytokines has been previously demonstrated [16–18] and type I IFN activation has been associated with lower IL-6-induced C-Reactive Protein (CRP) serum levels in lupus patients [19]. Moreover, neutralizing antibodies against type I IFNs have been detected in about 4 % of elderly patients with COVID-19 in association with low type I IFN activity and severe outcomes, including death [20]. In line with these observations, recent data revealed that autoantibodies against type I IFN were associated with lower nasal type I IFN immunity in severely affected COVID-19 patients [21]. Additionally, genetic variations presented as inborn errors in innate sensors or their downstream IFN signaling leading to impaired type I IFN responses, have been also associated with life-threatening COVID-19 infection [22–24].

Though it is well established that age and sex modulate immune responses [25], data on how they influence type I IFN activity and IL-6 production is limited. In a longitudinal 24-year study, IFNα levels were shown to decline by the age of 55 to 60 years [26]. An earlier study revealed blunted in vitro IFNα and IFNγ production by human peripheral blood mononuclear cells derived from individuals older than 50 years [27]. Moreover, plasmacytoid dendritic cells -the major producers of IFNα- have been shown to be more activated in females, mediated by TLR7 gene expression being higher in females after puberty [28].

In the current report, we investigated whether peripheral blood type I IFN activity and IL-6 serum levels among healthy COVID-19 convalescent individuals is shaped by demographic contributors. Moreover, potential associations with antibody responses against spike (S)-protein were explored.

2. Patients and methods

2.1. Study participants

Blood samples implemented in the current study were collected in the setting of a previous work exploring the presence of serum antibodies against SARS-CoV-2 S-protein in members of the National and Kapodistrian University of Athens (NKUA), Athens, Greece, during June-November 2020 [29]. To be included in the present study, individuals had to show evidence of detectable antibody titers to SARS-CoV-2 S-protein. All 61 COVID-19 convalescent individuals included (34 females, 27 males; age range 18–70 years, mean 35.7 ± 15.9 years), had recovered from asymptomatic or oligosymptomatic COVID-19 not requiring hospitalization within a median of 3 months prior to blood sampling. Among those, 17 aged over 50 years (11 males, 6 females) and 44 aged equal to or less than 50 years (16 males, 28 females). Five out of 61 individuals (8.2 %) had hypertension, and only one (1.6 %) suffered from cardiovascular disease. None of the study participants suffered by an autoimmune or genetic disease which could affect type I IFN blood activity. Levels of antibodies to S-protein receptor-binding domain (RBD) were available for all patients and have been previously determined by the implementation of a quantitative assay described in detail elsewhere [29].

The protocol was approved by the Ethics and Bioethics Committee of the School of Medicine, NKUA (protocol #312/02–06-2020) and study participants provided a written informed consent.

2.2. RNA extraction - quantitation of type I IFN score

Upon blood sampling we proceeded with the treatment of the whole blood using the erythrocyte lysis buffer to eliminate the erythrocytes. Following centrifugation, a pellet of cells was obtained composed mainly by white blood cells and thrombocytes and RNA was extracted using the TRI-Tidy Reagent (AppliChem, Germany) reagent according to the manufacturer's instructions and immediately stored at −80 °C. The quantity and quality of RNA samples were spectrophotometrically tested (Biospec Nano, Japan).

One microgram of total RNA was reverse transcribed into cDNA with Superscript III reverse transcriptase (Thermo Fisher Scientific, USA). Complementary DNA samples were diluted 1:10 with nuclease-free water (Qiagen, Germany) immediately after synthesis and stored at −20 °C.

Quantitative real-time polymerase chain reaction (qRT-PCR) was implemented to quantify the expression of selected genes using the Bio-Rad IQ5 thermocycler and the KAPA SYBR FAST Mastermix (KAPA Biosystems, South Africa), as previously described [30]. Briefly, genes preferentially induced by type I IFNs were selected, including IFN-induced protein with tetratricopeptide repeats 1 (IFIT1), interferon induced protein 44 (IFI44) and myxovirus (influenza virus) resistance 1 (MX1). Glyceraldehyde phosphate dehydrogenase (GAPDH) was used as an internal control and normalization gene (housekeeping gene). A reference sample was included in each PCR plate, to ensure normalization across experiments. Type I IFN score was calculated as previously described [30,31]. In detail, mean and SD levels of each IFN inducible gene (IFIG) in 5 healthy individuals consistently used as standards in our lab (IFIT 1: 1.26 ± 0.45; MX1: 1.05 ± 0.41; IFI44: 1.21 ± 0.45) was used to standardize expression levels of each gene for each study subject using the following formula: (RE IFIG subject - Mean HC)/SD HC. The standardized expression levels were subsequently summed for each patient to provide an IFN type I expression score as the sum of each study subject's relative expression for each of 3 genes preferentially induced by type I IFNs.

2.3. Determination of IL-6 and CRP

The levels of IL-6 and high-sensitive (HS) CRP were measured using the Elecsys IL-6 and CRP HS assays (both from Roche Diagnostics GmbH, Mannheim, Germany), performed according to the manufacturer's instructions in a Cobas e 801 analyzer (Roche Diagnostics). The detection limit for IL-6 was 1.5 pg/mL and for CRP HS 0.15 mg/L.

2.4. Statistics

All statistical analyses were performed using SPSS v.25.0 (IBM, Armonk, NY, U.S.) and GraphPad Prism 9 (GraphPad Software, San Diego, CA, U.S.), with the level of statistical significance being set at 0.05. Chi square or Fisher's exact test were performed to compare the frequencies of categorical variables and Mann-Whitney/Kruskal Wallis or *t*-test were employed for detecting significant differences in numerical variables. Spearman's correlation coefficients were calculated to detect correlations between numerical variables.

3. Results

3.1. Demographics and clinical characteristics of study participants.

In Suppl. Table 1, demographics and clinical characteristics of all study participants are displayed.

3.2. Effect of age and sex on type I IFN score, IL-6, CRP, and anti-S protein RBD levels

Of note, correlation analysis revealed a negative correlation between age and type I IFN inducible gene expression (Figs 1A, D-F and a positive correlation with IL-6 levels Fig. 1B). Consequently, a negative correlation between type I IFN peripheral blood score and serum IL-6 levels in study participants was detected ($r = -0.30$, $p = 0.04$; Fig. 1C). Following stratification by age as shown in Fig. 2A, type I IFN scores were found significantly decreased among individuals aged over 50 years ($n = 17$) compared to their younger counterparts ($n = 44$) (5.4 ± 4.3 vs 16.8 ± 24.7, $p = 0.02$). Inversely, IL-6 levels were significantly higher in the older compared to the younger age group (10.6 ± 16.9 vs 2.9 ± 8.0 ng/L, $p = 0.03$; Fig. 2B). No statistically significant differences were detected in CRP and anti-RBD serum levels between the 2 age groups (Fig. 2C and 2D). No significant correlations between S-protein RDB response and type I IFN score were detected (Suppl. Fig. 1).

We next sought to explore whether the differences detected in both peripheral blood type I IFN scores and serum IL-6 levels between the two age groups could be influenced by sex-specific effects. Indeed, as shown in Fig. 3A, type I IFN score was significantly increased in younger females compared to both young and older males (22.9 ± 29.2 vs 6.3 ± 4.6 vs 4.5 ± 3.7, $p = 0.01$ and $p = 0.002$, respectively by Mann Whitney test). When Kruskal Wallis statistical test was applied the corresponding p-value across groups was 0.005. This pattern was consistent for each of the type I IFN inducible genes implicated in the calculation of type I IFN score (Suppl. Fig. 2). An opposite pattern was observed in serum IL-6 levels, with the highest levels being detected among male individuals over 50 years old and the lowest levels among younger females (11.6 ± 18.9 vs 2.5 ± 7.8 ng/L, $p = 0.03$ by Mann Whitney test; Fig. 3B). No other comparisons between groups revealed statistically significant differences. When Kruskal Wallis statistical test was applied, the corresponding p-value across groups for IL-6 levels was 0.19. CRP serum levels -although higher in the older groups- did not differ between males and females (Fig. 3C, p-value by Kruskal Wallis test 0.30). Regarding serum anti-S protein RBD antibody levels, female participants older than 50 years had a 6-times lower titer compared to younger male individuals (30.2 ± 41.6 vs 182.3 ± 215.5, $p = 0.02$), and no other differences were observed among the different groups (Fig. 3D, p-value by Kruskal Wallis 0.25).

No statistically significant difference between time interval between active infection and actual sampling was detected between distinct age and sex groups ($p = 0.59$, by Kruskal Wallis test). The median values (range) for the younger male group (less/equal than 50 years old) were 10.5 (7–19) weeks, for the older male group (>50 years old) were 10.5 (4–16) weeks, for the younger female group the corresponding value was 12 (6–18) weeks and for the older female group 10 weeks (10,10).

4. Discussion

In the present study, we found that healthy individuals aged equal to or less than 50 years with previous exposure to SARS-CoV-2 and a robust anti-SARS-CoV-2 antibody response had significantly increased peripheral blood type I IFN scores, along with significantly decreased IL-6 serum levels compared to their older (>50 years) counterparts. Further stratification by sex, revealed that the differences detected in the two age groups are mainly related to the increased type I IFN scores among younger females and the dampened type I IFN responses among older individuals and an exactly opposite pattern for IL-6, with significantly higher serum IL-6 levels in older males. Diminished type I IFN responses have been previously shown to unleash a chronic

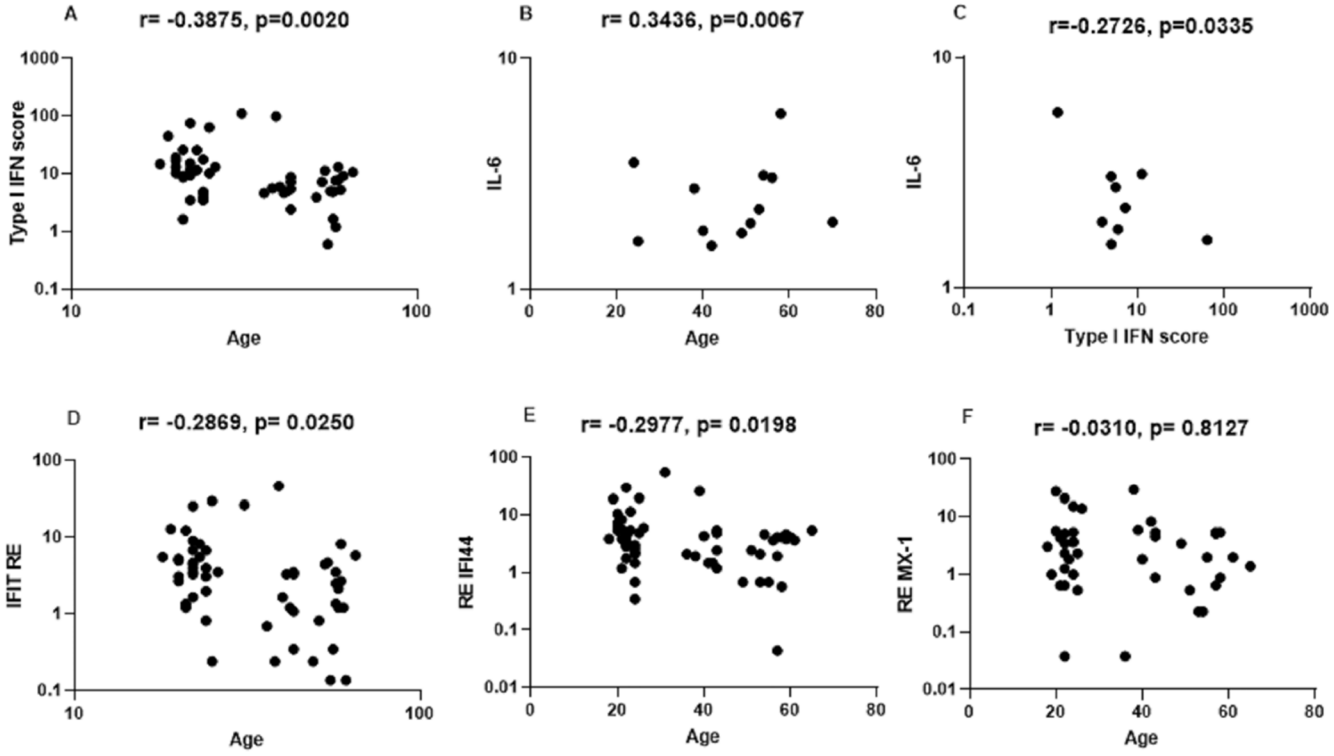

Fig. 1. Correlation plots between age, type I interferon (IFN) score (A), type I IFN inducible genes (D-F) and interleukin (IL)-6 levels (B). In panel C, a negative correlation between type I peripheral blood score and serum IL-6 levels is displayed. Data distribution was not normal and therefore Spearman's rho coefficients were calculated.

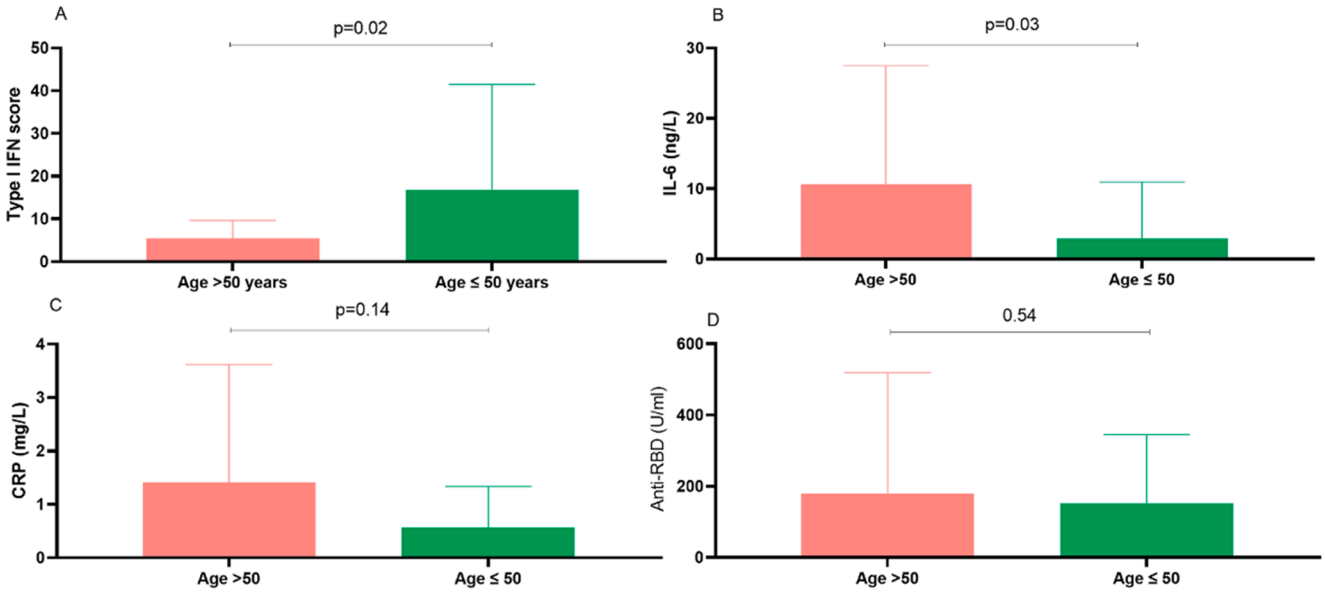

Fig. 2. Comparative analysis of type I interferon (IFN) score (A), interleukin (IL)-6 (B) and C-reactive protein (CRP) serum levels (C), and anti-S-protein receptor-binding domain (RBD) antibody titers (D) between healthy COVID-19 convalescent individuals aged over 50 years (n = 17) compared to those less/equal to 50 years (n = 44). Mean values and SDs are shown. Statistical analysis was performed by Mann Whitney nonparametric test.

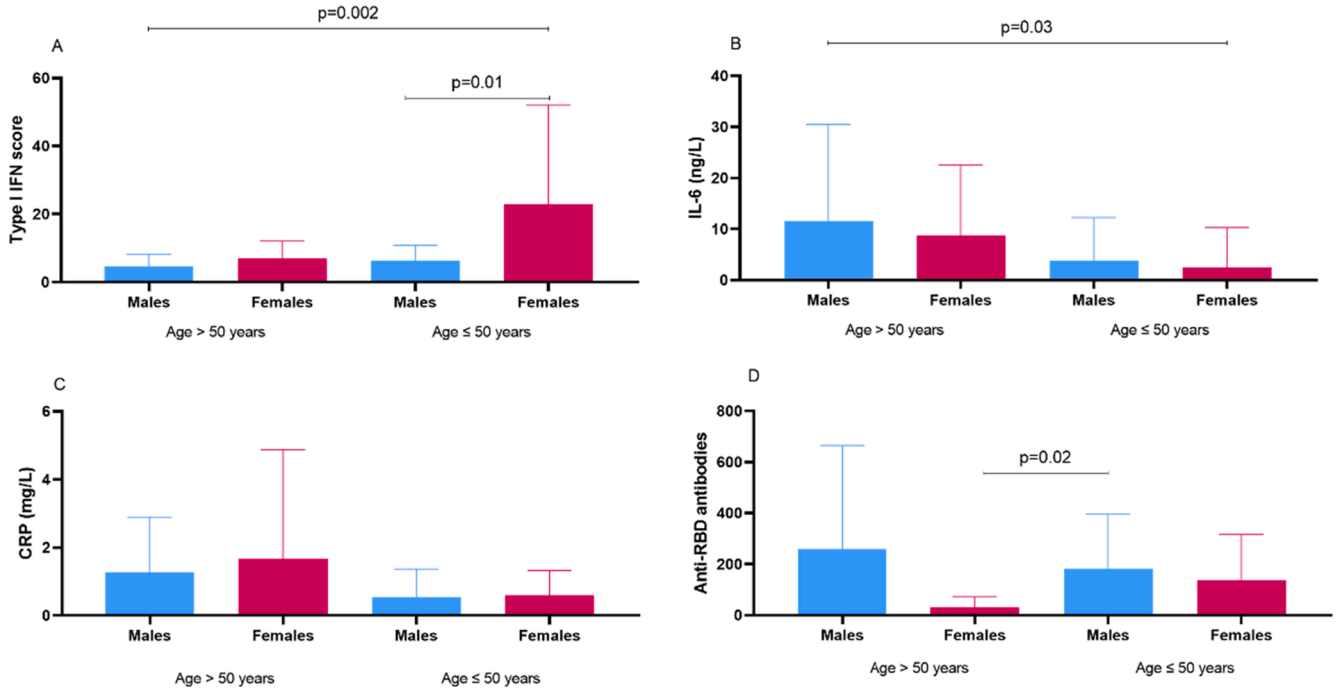

Fig. 3. Comparative analysis of type I interferon (IFN) score (A), interleukin (IL)-6 (B), C-reactive protein (CRP) serum levels (C), and anti-S-protein receptor-binding domain (RBD) antibody titers (D) among male and female participants older than 50 years compared to younger (≤50 years) male and females. Mean values and SDs are shown and significant associations (performed using by Mann Whitney nonparametric test) are marked. When Kruskal Wallis statistical test was applied the corresponding p-value for type I IFN score across groups was 0.005 and 0.19 for IL-6 levels.

inflammatory response with profound IL-6 production and increased mortality, possibly because of impaired viral clearance [12]. The significance of type I IFNs in host defense antiviral responses has been well documented in the setting of various viral infections of the respiratory system [32]. In this context, dampened type I IFN production has been associated with increased susceptibility to human rhinovirus (HRV) infection and higher viral load [33], while influenza virus prohibits IFN binding and signaling through IFNA1R degradation in order to escape from the immune surveillance [34]. Given the negative correlation between type I IFN score and IL-6 serum levels detected in this cohort, the possibility of a negative regulation of type I IFN responses on IL-6 production as previously shown for other proinflammatory cytokines could be possible [16,18].

Since all participants were asymptomatic at the time of sampling, we postulate that heterogeneous constitutive host immune responses, shaped by both age and sex, could provide an explanation for the increased mortality rates following COVID-19 infection, among older male patients, along with the favorable outcomes among younger female

patients [5,35]. The latter have been also shown to display higher type I IFN signatures in their peripheral blood compared to younger males and older females, in line with epidemiological data, supporting an advantageous response against COVID-19 infection among younger females [23]. Additionally, older age has been associated with more frequent incidence of co-morbidities and the co-occurrence of COVID-19 infection and comorbidity has been correlated with an increased risk for hospitalization, admission to intensive care unit, intubation and mortality [36].

The highest levels of type I IFNs among women of premenopausal age detected in the present report, is compatible with previous reports, suggesting that type I IFN production by plasmacytoid dendritic cells -the main type I IFN producers- is enhanced in response to TLR7 stimulation in the presence of appropriate ligands (eg. ssRNA) in females compared to males, as a result of both estrogens and X-chromosome dosage effects [37]. Conversely, IL-6 levels have been found to be lower in premenopausal women with COVID-19 and linked to a reduced mortality [38].

A growing body of data reveals sex-based differences as main determinants for the diverse susceptibility/severity of infectious and autoimmune diseases, as well as response to vaccination [39]. Of note, sexual dimorphism is associated with viral susceptibility; it has been previously reported that HBV and HCV infections are more frequent in men, while the spontaneous clearance of HCV is more efficient in women than men [40].

The same holds true for COVID-19 infection-related outcomes, with a consistent excess of mortality in males, in all age groups [3,35]. Though it is not entirely clear, differences in host genetic and hormonal background between males and females have been shown to account for this diversity [41]. For instance, lung expression and circulating ACE2 levels -the receptor of SARS-CoV-2 entry- were found to be higher in males compared to females [42,43], potentially as a result of hormonal influences [44]; additionally, sex steroid hormones were shown to be associated with increased mortality post COVID-19 infection [45]. Moreover, it has been previously suggested that estrogen signaling in female mice may directly suppress SARS-CoV-2 replication through disruption of cellular metabolism [46].

To our interest, a most recent study revealed that autoantibody responses following COVID-19 infection are dependent on the sex of affected individuals, with an overall antibody response being more prominent in women after asymptomatic infection; in contrast, autoantibody reactivity was more profound in men following at least a mild symptomatic infection [47]. Given that type I IFNs and IL-6 are both involved in antibody production via distinct operating mechanisms [48,49], our findings could provide further insights in distinct autoantibody responses between different age and sex groups. While humoral immune responses have been previously shown to be enhanced upon IFNα and IFNβ signaling in B or T cells and type I IFNs have been consistently found to upregulate B-cell activating factor, a key mediator of B-cell survival and proliferation [17,50,51], we did not detect any significant association between antibody titer and type I IFN peripheral blood activity. Quite surprisingly, in a recently published study by Mueller et al in the setting of hospitalized COVID-19 infected individuals, IFNα has been shown to negatively correlate with antibody production, indicating that either antibodies dampen viral loads and subsequently IFNα or on the contrary, heightened IFNα levels interrupt antibody production [52].

In view of the previously shown favorable effects of IL-6 blockade [53] and administration of IFNβ in hospitalized patients with COVID-19 [54], together with the ying-yang observed between type I IFNs and IL-6 across sex and age groups, it would be tempting to hypothesize that concomitant administration of these agents could maximize therapeutic efficacy among high risk populations. However, such data are currently lacking.

A limitation of our study is the relatively small number of patients over 50 years of age included in the analysis, as they constitute a subgroup of our previous study which had a different study design [10]. Moreover, in the absence of comparative data on actively infected inpatient and outpatient individuals, it is difficult to suggest that type I IFN score along with IL-6 levels could predict COVID-19 related outcomes. However, in a recently published study from our group including 123 consecutive SARS-CoV2 infected individuals seeking evaluation in a hospital setting [55], 55 were females and 68 were males. Of note, among females, only 7 out of 55 (12.7 %) were less than 50 years old compared to 23 out of 68 males (33.8 %). These data indirectly imply that women of premenopausal age were less likely to seek medical attention in a hospital setting, presumably due to less severe disease. Along the same lines, in a parallel study from our group in consecutive unvaccinated patients without underlying medical conditions, it was shown that the number of female patients was half than men across all age groups [56]. Unfortunately we were not able to directly prove that basal type I IFN responses could predict a more robust immune response during viral infection due to the study design; however it is counterintuitive that higher constitutive type I IFN responses are associated with more robust type I IFN and IL-6 responses during active infection.

Ideally, a non-convalescent group would be desirable, but due to COVID-19 spread and widespread vaccination programs, it is difficult to detect non convalescent individuals. However, these results could be the basis for generating new hypotheses deserving further consideration, given the diverse outcomes between distinct age/sex groups consistently reported in COVID-19 epidemiological studies.

In conclusion, higher constitutive type I IFNs and impaired IL-6 responses among women of premenopausal age could account for the favorable outcomes compared to the older male populations, in whom lower type I IFNs and higher IL-6 levels were detected. Therefore, based on these results we hypothesize that robust innate immune responses among younger females might protect them against hospitalization and severe disease outcomes. Larger studies are required to confirm these findings.

5. Institutional review board statement

Ethics and Bioethics Committee of the School of Medicine, NKUA (protocol #312/02–06-2020).

6. Informed consent statement

Ethics and Bioethics Committee of the School of Medicine, NKUA (protocol #312/02–06-2020).

Author contributions

Conceived, designed, and supervised the study, C.P.M., P.P.S..; experiments, C.S., I.V.K., E.M.; analyzed data, C.P.M., P.M., E.T., O.E.T., P.P.S.; statistical analyses, C.P.M., C.S.; drafted the manuscript: C.P.M., P.P.S.; edited the manuscript: C.P.M., E.T., M.A.D., O.E.T., P.P.S.; all authors critically reviewed the manuscript and agreed to its published version.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2022.155964.

References

[1] W.C.C.-D.W.C.C.-D.W.V. Data, (5:45pm CEST, 22 October 2021).
[2] M. O'Driscoll, G. Ribeiro Dos Santos, L. Wang, D.A.T. Cummings, A.S. Azman, J. Paireau, A. Fontanet, S. Cauchemez, H. Salje, Age-specific mortality and immunity patterns of SARS-CoV-2, Nature 590 (2021) 140–145.
[3] M. Alkhouli, A. Nanjundappa, F. Annie, M.C. Bates, D.L. Bhatt, Sex Differences in Case Fatality Rate of COVID-19: Insights From a Multinational Registry, Mayo Clin Proc 95 (2020) 1613–1620.
[4] J.S. Mathad, M.H. Lee, A. Chalem, M.K. Frey, E. Chapman-Davis, R.V. Kopparam, A.K. Dayal, G. Wald, L.C. Pinheiro, M.J. Satlin, P. Goyal, M.M. Safford, M. Salvatore, K. Holcomb, Sex-Related Differences in Clinical Presentation and Risk Factors for Mortality in Patients Hospitalized With Coronavirus Disease 2019 in New York City, Open Forum Infect Dis 8 (2021) ofab370.
[5] L.J. Ahrenfeldt, M. Otavova, K. Christensen, R. Lindahl-Jacobsen, Sex and age differences in COVID-19 mortality in Europe, Wien Klin Wochenschr 133 (2021) 393–398.
[6] E.J. Williamson, A.J. Walker, K. Bhaskaran, S. Bacon, C. Bates, C.E. Morton, H. J. Curtis, A. Mehrkar, D. Evans, P. Inglesby, J. Cockburn, H.I. McDonald, B. MacKenna, L. Tomlinson, I.J. Douglas, C.T. Rentsch, R. Mathur, A.Y.S. Wong, R. Grieve, D. Harrison, H. Forbes, A. Schultze, R. Croker, J. Parry, F. Hester, S. Harper, R. Perera, S.J.W. Evans, L. Smeeth, B. Goldacre, Factors associated with COVID-19-related death using OpenSAFELY, Nature 584 (2020) 430–436.
[7] P. Brodin, M.M. Davis, Human immune system variation, Nat Rev Immunol 17 (2017) 21–29.
[8] A.F. Rendeiro, J. Casano, C.K. Vorkas, H. Singh, A. Morales, R.A. DeSimone, G. B. Ellsworth, R. Soave, S.N. Kapadia, K. Saito, C.D. Brown, J. Hsu, C. Kyriakides, S. Chiu, L.V. Cappelli, M.T. Cacciapuoti, W. Tam, L. Galluzzi, P.D. Simonson, O. Elemento, M. Salvatore, G. Inghirami, Profiling of immune dysfunction in COVID-19 patients allows early prediction of disease progression, Life Sci Alliance 4 (2021).
[9] D. Birra, M. Benucci, L. Landolfi, A. Merchionda, G. Loi, P. Amato, G. Licata, L. Quartuccio, M. Triggiani, P. Moscato, COVID 19: a clue from innate immunity, Immunol Res 68 (2020) 161–168.
[10] P.P. Sfikakis, K.M. Verrou, G. Ampatziadis-Michailidis, O. Tsitsilonis, D. Paraskevis, E. Kastritis, E. Lianidou, P. Moutsatsou, E. Terpos, I. Trougakos, V. Chini, M. Manoloukos, P. Moulos, G.A. Pavlopoulos, G. Kollias, P. Hatzis, M. A. Dimopoulos, Blood Transcriptomes of Anti-SARS-CoV-2 Antibody-Positive Healthy Individuals Who Experienced Asymptomatic Versus Clinical Infection, Front Immunol 12 (2021), 746203.
[11] Z. Wu, and J.M. McGoogan, Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 323 (2020) 1239-1242.
[12] J. Hadjadj, N. Yatim, L. Barnabei, A. Corneau, J. Boussier, N. Smith, H. Pere, B. Charbit, V. Bondet, C. Chenevier-Gobeaux, P. Breillat, N. Carlier, R. Gauzit, C. Morbieu, F. Pene, N. Marin, N. Roche, T.A. Szwebel, S.H. Merkling, J. M. Treluyer, D. Veyer, L. Mouthon, C. Blanc, P.L. Tharaux, F. Rozenberg, A. Fischer, D. Duffy, F. Rieux-Laucat, S. Kerneis, B. Terrier, Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients, Science 369 (2020) 718–724.
[13] A. Ronit, S.E. Jorgensen, C. Roed, R. Eriksson, U.W. Iepsen, R.R. Plovsing, M. Storgaard, F. Gustafsson, A.E. Hansen, T.H. Mogensen, Host Genetics and Antiviral Immune Responses in Adult Patients With Multisystem Inflammatory Syndrome, Front Immunol 12 (2021), 718744.
[14] I. Navarro-Millan, S.E. Sattui, A. Lakhanpal, D. Zisa, C.H. Siegel, M.K. Crow, Use of Anakinra to Prevent Mechanical Ventilation in Severe COVID-19: A Case Series, Arthritis Rheumatol 72 (2020) 1990–1997.
[15] R.C. Group, Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial, Lancet 397 (2021) 1637–1645.
[16] A.K. Palucka, J.P. Blanck, L. Bennett, V. Pascual, J. Banchereau, Cross-regulation of TNF and IFN-alpha in autoimmune diseases, Proc Natl Acad Sci U S A 102 (2005) 3372–3377.
[17] C.P. Mavragani, T.B. Niewold, N.M. Moutsopoulos, S.R. Pillemer, S.M. Wahl, M. K. Crow, Augmented interferon-alpha pathway activation in patients with Sjogren's syndrome treated with etanercept, Arthritis Rheum 56 (2007) 3995–4004.
[18] G. Guarda, M. Braun, F. Staehli, A. Tardivel, C. Mattmann, I. Forster, M. Farlik, T. Decker, R.A. Du Pasquier, P. Romero, J. Tschopp, Type I interferon inhibits interleukin-1 production and inflammasome activation, Immunity 34 (2011) 213–223.
[19] H. Enocsson, B. Gullstrand, M.L. Eloranta, J. Wettero, D. Leonard, L. Ronnblom, A. A. Bengtsson, C. Sjowall, C-Reactive Protein Levels in Systemic Lupus Erythematosus Are Modulated by the Interferon Gene Signature and CRP Gene Polymorphism rs1205, Front Immunol 11 (2020), 622326.
[20] P. Bastard, A. Gervais, T. Le Voyer, J. Rosain, Q. Philippot, J. Manry, E. Michailidis, H.H. Hoffmann, S. Eto, M. Garcia-Prat, L. Bizien, A. Parra-Martinez, R. Yang, L. Haljasmagi, M. Migaud, K. Sarekannu, J. Maslovskaja, N. de Prost, Y. Tandjaoui-Lambiotte, C.E. Luyt, B. Amador-Borrero, A. Gaudet, J. Poissy, P. Morel, P. Richard, F. Cognasse, J. Troya, S. Trouillet-Assant, A. Belot, K. Saker, P. Garcon, J. G. Riviere, J.C. Lagier, S. Gentile, L.B. Rosen, E. Shaw, T. Morio, J. Tanaka, D. Dalmau, P.L. Tharaux, D. Sene, A. Stepanian, B. Megarbane, V. Triantafyllia, A. Fekkar, J.R. Heath, J.L. Franco, J.M. Anaya, J. Sole-Violan, L. Imberti, A. Biondi, P. Bonfanti, R. Castagnoli, O.M. Delmonte, Y. Zhang, A.L. Snow, S.M. Holland, C. Biggs, M. Moncada-Velez, A.A. Arias, L. Lorenzo, S. Boucherit, B. Coulibaly, D. Anglicheau, A.M. Planas, F. Haerynck, S. Duvlis, R.L. Nussbaum, T. Ozcelik, S. Keles, A.A. Bousfiha, J. El Bakkouri, C. Ramirez-Santana, S. Paul, Q. Pan-Hammarstrom, L. Hammarstrom, A. Dupont, A. Kurolap, C.N. Metz, A. Aiuti, G. Casari, V. Lampasona, F. Ciceri, L.A. Barreiros, E. Dominguez-Garrido, M. Vidigal, M. Zatz, D. van de Beek, S. Sahanic, I. Tancevski, Y. Stepanovskyy, O. Boyarchuk, Y. Nukui, M. Tsumura, L. Vidaur, S.G. Tangye, S. Burrel, D. Duffy, L. Quintana-Murci, A. Klocperk, et al., Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths, Sci Immunol 6 (2021).
[21] J. Lopez, M. Mommert, W. Mouton, A. Pizzorno, K. Brengel-Pesce, M. Mezidi, M. Villard, B. Lina, J.C. Richard, J.B. Fassier, V. Cheynet, B. Padey, V. Duliere, T. Julien, S. Paul, P. Bastard, A. Belot, A. Bal, J.L. Casanova, M. Rosa-Calatrava, F. Morfin, T. Walzer, S. Trouillet-Assant, Early nasal type I IFN immunity against SARS-CoV-2 is compromised in patients with autoantibodies against type I IFNs, J Exp Med 218 (2021).
[22] T. Asano, B. Boisson, F. Onodi, D. Matuozzo, et al., X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19, Sci Immunol 6 (2021).
[23] Q. Zhang, P. Bastard, Z. Liu, J. Le Pen, M. Moncada-Velez, J. Chen, M. Ogishi, I.K. D. Sabli, S. Hodeib, C. Korol, J. Rosain, K. Bilguvar, J. Ye, A. Bolze, B. Bigio, R. Yang, A.A. Arias, Q. Zhou, Y. Zhang, F. Onodi, S. Korniotis, L. Karpf, Q. Philippot, M. Chbihi, L. Bonnet-Madin, K. Dorgham, N. Smith, W.M. Schneider, B.S. Razooky, H.H. Hoffmann, E. Michailidis, L. Moens, J.E. Han, L. Lorenzo, L. Bizien, P. Meade, A.L. Neehus, A.C. Ugurbil, A. Corneau, G. Kerner, P. Zhang, F. Rapaport, Y. Seeleuthner, J. Manry, C. Masson, Y. Schmitt, A. Schluter, T. Le Voyer, T. Khan, J. Li, J. Fellay, L. Roussel, M. Shahrooei, M.F. Alosaimi, D. Mansouri, H. Al-Saud, F. Al-Mulla, F. Almourfi, S.Z. Al-Muhsen, F. Alsohime, S. Al Turki, R. Hasanato, D. van de Beek, A. Biondi, L.R. Bettini, M. D'Angio, P. Bonfanti, L. Imberti, A. Sottini, S. Paghera, E. Quiros-Roldan, C. Rossi, A.J. Oler, M.F. Tompkins, C. Alba, I. Vandernoot, J.C. Goffard, G. Smits, I. Migeotte, F. Haerynck, P. Soler-Palacin, A. Martin-Nalda, R. Colobran, P.E. Morange, S. Keles, F. Colkesen, T. Ozcelik, K.K. Yasar, S. Senoglu, S.N. Karabela, C. Rodriguez-Gallego, G. Novelli, S. Hraiech, Y. Tandjaoui-Lambiotte, X. Duval, C. Laouenan, C.-S. Clinicians, C. Clinicians, C.G. Imagine, C.C.S.G. French, et al., Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science 370, 2020.
[24] C.I. van der Made, A. Simons, J. Schuurs-Hoeijmakers, G. van den Heuvel, T. Mantere, S. Kersten, R.C. van Deuren, M. Steehouwer, S.V. van Reijmersdal, M. Jaeger, T. Hofste, G. Astuti, J. Corominas Galbany, V. van der Schoot, H. van der Hoeven, W. Hagmolen Of Ten Have, E. Klijn, C. van den Meer, J. Fiddelaers, Q. de Mast, C.P. Bleeker-Rovers, L.A.B. Joosten, H.G. Yntema, C. Gilissen, M. Nelen, J.W. M. van der Meer, H.G. Brunner, M.G. Netea, F.L. van de Veerdonk, and A. Hoischen, Presence of Genetic Variants Among Young Men With Severe COVID-19. JAMA 324 (2020) 663-673.
[25] S.L. Klein, K.L. Flanagan, Sex differences in immune responses, Nat Rev Immunol 16 (2016) 626–638.
[26] K. Uno, K. Yagi, M. Yoshimori, M. Tanigawa, T. Yoshikawa, S. Fujita, IFN production ability and healthy ageing: mixed model analysis of a 24 year longitudinal study in Japan, BMJ Open 3 (2013).
[27] J. Abb, H. Abb, F. Deinhardt, Age-related decline of human interferon alpha and interferon gamma production, Blut 48 (1984) 285–289.
[28] K. Webb, H. Peckham, A. Radziszewska, M. Menon, P. Oliveri, F. Simpson, C. T. Deakin, S. Lee, C. Ciurtin, G. Butler, L.R. Wedderburn, Y. Ioannou, Sex and Pubertal Differences in the Type 1 Interferon Pathway Associate With Both X Chromosome Number and Serum Sex Hormone Concentration, Front Immunol 9 (2018) 3167.
[29] O.E. Tsitsilonis, D. Paraskevis, E. Lianidou, E. Terpos, A. Akalestos, V. Pierros, E. G. Kostaki, E. Kastritis, P. Moutsatsou, M. Politou, A. Scorilas, T. Sphicopoulos, N. Thomaidis, I.P. Trougakos, A. Tsakris, N. Voulgaris, C.C. Daskalaki, Z. Evangelakou, C. Fouki, D.D. Gianniou, S. Gumeni, I.V. Kostopoulos, M. S. Manola, N. Orologas-Stavrou, C. Panteli, E.D. Papanagnou, P. Rousakis, A. D. Sklirou, S. Smilkou, D. Stergiopoulou, S. Tsiodras, M.A. Dimopoulos, P. P. Sfikakis, SARS-CoV-2 Infection Is Asymptomatic in Nearly Half of Adults with Robust Anti-Spike Protein Receptor-Binding Domain Antibody Response, Vaccines (Basel) 9 (2021).
[30] A. Nezos, F. Gravani, A. Tassidou, E.K. Kapsogeorgou, M. Voulgarelis, M. Koutsilieris, M.K. Crow, C.P. Mavragani, Type I and II interferon signatures in Sjogren's syndrome pathogenesis: Contributions in distinct clinical phenotypes and Sjogren's related lymphomagenesis, J Autoimmun 63 (2015) 47–58.
[31] K.A. Kirou, C. Lee, S. George, K. Louca, I.G. Papagiannis, M.G. Peterson, N. Ly, R. N. Woodward, K.E. Fry, A.Y. Lau, J.G. Prentice, J.G. Wohlgemuth, M.K. Crow, Coordinate overexpression of interferon-alpha-induced genes in systemic lupus erythematosus, Arthritis Rheum 50 (2004) 3958–3967.
[32] F. McNab, K. Mayer-Barber, A. Sher, A. Wack, A. O'Garra, Type I interferons in infectious disease, Nat Rev Immunol 15 (2015) 87–103.
[33] Y. Xi, A. Finlayson, O.J. White, M.L. Carroll, J.W. Upham, Rhinovirus stimulated IFN-alpha production: how important are plasmacytoid DCs, monocytes and endosomal pH? Clin Transl Immunology 4 (2015), e46.
[34] C. Xia, M. Vijayan, C.J. Pritzl, S.Y. Fuchs, A.B. McDermott, B. Hahm, Hemagglutinin of Influenza A Virus Antagonizes Type I Interferon (IFN) Responses by Inducing Degradation of Type I IFN Receptor 1, J Virol 90 (2015) 2403–2417.
[35] M.S. Green, D. Nitzan, N. Schwartz, Y. Niv, V. Peer, Sex differences in the case-fatality rates for COVID-19-A comparison of the age-related differences and consistency over seven countries, PLoS One 16 (2021), e0250523.
[36] H.C. Maltezou, K. Papadima, K. Gkolfinopoulou, G. Ferentinos, E. Mouratidou, A. Andreopoulou, A. Pavli, I. Magaziotou, T. Georgakopoulou, K. Mellou, R. Vorou,

A. Antoniadou, A. Stathakarou, A. Chrysochoou, C. Gogos, A. Karaiskou, A. Kotanidou, A. Koutsoukou, M. Marangos, A. Mentis, S. Metallidis, A. Papa, A. Pefanis, A. Tsakris, N.V. Sipsas, Coronavirus disease 2019 pandemic in Greece, February 26 - May 3, 2020: The first wave, Travel Med Infect Dis 41 (2021), 102051.

[37] S. Laffont, N. Rouquie, P. Azar, C. Seillet, J. Plumas, C. Aspord, J.C. Guery, X-Chromosome complement and estrogen receptor signaling independently contribute to the enhanced TLR7-mediated IFN-alpha production of plasmacytoid dendritic cells from women, J Immunol 193 (2014) 5444–5452.

[38] E.P. Scully, G. Schumock, M. Fu, G. Massaccesi, J. Muschelli, J. Betz, E.Y. Klein, N. E. West, M. Robinson, B.T. Garibaldi, K. Bandeen-Roche, S. Zeger, S.L. Klein, A. Gupta, Sex and Gender Differences in Testing, Hospital Admission, Clinical Presentation, and Drivers of Severe Outcomes From COVID-19, Open Forum Infect Dis 8 (2021) ofab448.

[39] J.G. Markle, E.N. Fish, SeXX matters in immunity, Trends Immunol 35 (2014) 97–104.

[40] L. Gay, C. Melenotte, I. Lakbar, S. Mezouar, C. Devaux, D. Raoult, M.K. Bendiane, M. Leone, J.L. Mege, Sexual Dimorphism and Gender in Infectious Diseases, Front Immunol 12 (2021), 698121.

[41] M. Lipsitch, Estimating case fatality rates of COVID-19, Lancet Infect Dis 20 (2020) 775.

[42] T. Tukiainen, A.C. Villani, A. Yen, M.A. Rivas, J.L. Marshall, R. Satija, M. Aguirre, L. Gauthier, M. Fleharty, A. Kirby, B.B. Cummings, S.E. Castel, K.J. Karczewski, F. Aguet, A. Byrnes, G.T. Consortium, D.A. Laboratory, G. Coordinating Center -Analysis Working, G. Statistical Methods groups-Analysis Working, G.g. Enhancing, N.I.H.C. Fund, Nih/Nci, Nih/Nhgri, Nih/Nimh, Nih/Nida, N. Biospecimen Collection Source Site, R. Biospecimen Collection Source Site, V. Biospecimen Core Resource, B. Brain Bank Repository-University of Miami Brain Endowment, M. Leidos Biomedical-Project, E. Study, I. Genome Browser Data, E.B. I. Visualization, I. Genome Browser Data, U.o.C.S.C. Visualization-Ucsc Genomics Institute, T. Lappalainen, A. Regev, K.G. Ardlie, N. Hacohen, and D.G. MacArthur, Landscape of X chromosome inactivation across human tissues. Nature 550 (2017) 244-248.

[43] S.K. Patel, E. Velkoska, L.M. Burrell, Emerging markers in cardiovascular disease: where does angiotensin-converting enzyme 2 fit in? Clin Exp Pharmacol Physiol 40 (2013) 551–559.

[44] J. Liu, H. Ji, W. Zheng, X. Wu, J.J. Zhu, A.P. Arnold, K. Sandberg, Sex differences in renal angiotensin converting enzyme 2 (ACE2) activity are 17beta-oestradiol-dependent and sex chromosome-independent, Biol Sex Differ 1 (2010) 6.

[45] I.E. van Zeggeren, A. Boelen, D. van de Beek, A.C. Heijboer, A.P.J. Vlaar, M.C. Brouwer, and U.M.C.C.-B. Amsterdam, Sex steroid hormones are associated with mortality in COVID-19 patients: Level of sex hormones in severe COVID-19. Medicine (Baltimore) 100 (2021) e27072.

[46] R. Channappanavar, C. Fett, M. Mack, P.P. Ten Eyck, D.K. Meyerholz, S. Perlman, Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection, J Immunol 198 (2017) 4046–4053.

[47] Y. Liu, J.E. Ebinger, R. Mostafa, P. Budde, J. Gajewski, B. Walker, S. Joung, M. Wu, M. Brautigam, F. Hesping, E. Rupieper, A.S. Schubert, H.D. Zucht, J. Braun, G. Y. Melmed, K. Sobhani, M. Arditi, J.E. Van Eyk, S. Cheng, J. Fert-Bober, Paradoxical sex-specific patterns of autoantibody response to SARS-CoV-2 infection, J Transl Med 19 (2021) 524.

[48] A. Le Bon, G. Schiavoni, G. D'Agostino, I. Gresser, F. Belardelli, D.F. Tough, Type i interferons potently enhance humoral immunity and can promote isotype switching by stimulating dendritic cells in vivo, Immunity 14 (2001) 461–470.

[49] O. Dienz, S.M. Eaton, J.P. Bond, W. Neveu, D. Moquin, R. Noubade, E.M. Briso, C. Charland, W.J. Leonard, G. Ciliberto, C. Teuscher, L. Haynes, M. Rincon, The induction of antibody production by IL-6 is indirectly mediated by IL-21 produced by CD4+ T cells, J Exp Med 206 (2009) 69–78.

[50] K. Fink, K.S. Lang, N. Manjarrez-Orduno, T. Junt, B.M. Senn, M. Holdener, S. Akira, R.M. Zinkernagel, H. Hengartner, Early type I interferon-mediated signals on B cells specifically enhance antiviral humoral responses, Eur J Immunol 36 (2006) 2094–2105.

[51] Z. Brkic, L. van Bon, M. Cossu, C.G. van Helden-Meeuwsen, M.C. Vonk, H. Knaapen, W. van den Berg, V.A. Dalm, P.L. Van Daele, A. Severino, N.I. Maria, S. Guillen, W.A. Dik, L. Beretta, M.A. Versnel, T. Radstake, The interferon type I signature is present in systemic sclerosis before overt fibrosis and might contribute to its pathogenesis through high BAFF gene expression and high collagen synthesis, Ann Rheum Dis 75 (2016) 1567–1573.

[52] Y.M. Mueller, T.J. Schrama, R. Ruijten, M.W.J. Schreurs, D.G.B. Grashof, H.J. G. van de Werken, G.J. Lasinio, D. Alvarez-Sierra, C.H. Kiernan, M.D. Castro Eiro, M. van Meurs, I. Brouwers-Haspels, M. Zhao, L. Li, H. de Wit, C.A. Ouzounis, M.E. P. Wilmsen, T.M. Alofs, D.A. Laport, T. van Wees, G. Kraker, M.C. Jaimes, S. Van Bockstael, M. Hernandez-Gonzalez, C. Rokx, B.J.A. Rijnders, R. Pujol-Borrell, P. D. Katsikis, Stratification of hospitalized COVID-19 patients into clinical severity progression groups by immuno-phenotyping and machine learning, Nat Commun 13 (2022) 915.

[53] W.H.O.R.E.A.f.C.-T.W. Group, M. Shankar-Hari, C.L. Vale, P.J. Godolphin, D. Fisher, J.P.T. Higgins, F. Spiga, J. Savovic, J. Tierney, G. Baron, J.S. Benbenishty, L.R. Berry, N. Broman, A.B. Cavalcanti, R. Colman, S.L. De Buyser, L.P.G. Derde, P. Domingo, S.F. Omar, A. Fernandez-Cruz, T. Feuth, F. Garcia, R. Garcia-Vicuna, I. Gonzalez-Alvaro, A.C. Gordon, R. Haynes, O. Hermine, P.W. Horby, N.K. Horick, K. Kumar, B.N. Lambrecht, M.J. Landray, L. Leal, D.J. Lederer, E. Lorenzi, X. Mariette, N. Merchante, N.A. Misnan, S.V. Mohan, M.C. Nivens, J. Oksi, J.A. Perez-Molina, R. Pizov, R. Porcher, S. Postma, R. Rajasuriar, A.V. Ramanan, P. Ravaud, P.D. Reid, A. Rutgers, A. Sancho-Lopez, T.B. Seto, S. Sivapalasingam, A.S. Soin, N. Staplin, J.H. Stone, G.W. Strohbehn, J. Sunden-Cullberg, J. Torre-Cisneros, L.W. Tsai, H. van Hoogstraten, T. van Meerten, V.C. Veiga, P.E. Westerweel, S. Murthy, J.V. Diaz, J. C. Marshall, and J.A.C. Sterne, Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. JAMA 326 (2021) 499-518.

[54] J.P. Sosa, M.M. Ferreira Caceres, J. Ross Comptis, J. Quiros, F.S. Principe-Meneses, A. Riva-Moscoso, M.P. Belizaire, F.Q. Malanyaon, K. Agadi, S.S. Jaffery, J. Sahajwani, A. Arshia, A. Senatus, G. Verdecia, L. Akano, A.A. Razzack, S. Salam, V.K. Gadamidi, S. Marian, Effects of Interferon Beta in COVID-19 adult patients, Systematic Review. Infect Chemother 53 (2021) 247–260.

[55] V.E. Georgakopoulou, P. Lembessis, C. Skarlis, A. Gkoufa, N.V. Sipsas, C. P. Mavragani, Hematological Abnormalities in COVID-19 Disease: Association With Type I Interferon Pathway Activation and Disease Outcomes, Front. Med. 9 (2022), 850472, https://doi.org/10.3389/fmed.2022.850472.

[56] V.E. Georgakopoulou, N.I. Vlachogiannis, D. Basoulis, I. Eliadi, G. Georgiopoulos, G. Karamanakos, S. Makrodimitri, S. Samara, M. Triantafyllou, P.M. Voutsinas, F. Ntziora, M. Psichogiou, M. Samarkos, P.P. Sfikakis, N.V. Sipsas, A Simple Prognostic Score for Critical COVID-19 Derived from Patients without Comorbidities Performs Well in Unselected Patients, J Clin Med. 11 (7) (2022 Mar 25) 1810.