Gender-based disparities in COVID-19 patient outcomes

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Accepted 5 February 2021
Published Online First 12 March 2021

ABSTRACT

Studies reported to date suggest that men with COVID-19 have more severe disease and worse outcomes when compared with women. The explanation for this finding is not entirely clear. The goal of this study was to compare clinical characteristics, inflammatory biomarkers and clinical outcome between men and women. This retrospective study included patients with COVID-19 admitted to 10 Virginia hospitals from January 1, 2020, to June 15, 2020. Demographic data, comorbidities, and inflammatory markers, including C reactive protein (CRP), D-dimer, ferritin, and the neutrophil:lymphocyte ratio, as well as patient outcomes, were compared between men and women. During the study period, 701 patients with PCR-confirmed COVID-19 infection were admitted. The patient's mean age was 61±17 years. There were 370 men (52.8%). There was no difference in age, racial distribution, and comorbidities in the male patients compared with the female patients. However, both the baseline and peak levels of CRP and ferritin were significantly higher in men as compared with women. While the baseline D-dimer was similar between the sexes, men had a significantly higher maximal D-dimer. Men had evidence of greater disease severity, with a significantly greater admission to the intensive care unit and borderline higher hospital mortality. Our study supports the observation that COVID-19 causes more severe disease in men. The greater disease severity in men was not due to the effect of age or comorbidities; however, in keeping with experimental studies, men had evidence of a heightened inflammatory response, likely contributing to disease severity.

Significance of this study

What is already known about this subject?

- COVID-19 is a highly heterogenous disease with multiple factors influencing the severity of disease.
- Male gender has been reported to increase the severity of COVID-19 disease as well as the mortality rate.
- The mechanism underlying the gender differential in disease severity is unclear.

What are the new findings?

- In this multi-institutional observational study, we reconfirmed that COVID-19 was associated with a worse outcome in men.
- There were no significant differences in age, racial distribution, or comorbidities when comparing the male to female patients.
- However, the levels of the inflammatory biomarkers, C reactive protein and ferritin, were significantly higher in men as compared with women. Furthermore, the peak D-dimer was significantly higher in men.

How might these results change the focus of research or clinical practice?

- A more exuberant inflammatory response appears to underlie the gender differences of COVID-19 infection. This finding should lead future research to further explore the immunological reasons underlying this observation.
- Further, the approach to anti-inflammatory therapy in the pulmonary phase of COVID-19 may be gender specific.

INTRODUCTION

SARS-CoV-2 has caused a worldwide pandemic with over 30 million reported infections and 1 million deaths. Numerous factors have been reported to increase the risk of death, including inoculum size, patients' age, the presence of comorbidities and obesity.[1–5] Policies and public health efforts have not addressed the gendered impacts of disease outbreaks. The response to the disease (COVID-19) appears no different. We are not aware of any gender analysis of the outbreak by global health institutions or governments in affected countries or in preparedness phases. Some studies have reported men to have a higher mortality than women; however, the differing characteristics of male and female patients with COVID-19 and the potential explanation for this observation have not been clearly identified.[1–3] Recognizing the extent to which disease outbreaks affect women and men differently is a fundamental step to understanding the primary and secondary effects of a health emergency on different individuals and communities, and for creating effective, equitable policies and interventions. The goal of this study was to contrast the clinical features of men and women hospitalized with COVID-19

To cite: Marik PE, DePerrior SE, Ahmad Q, *et al*. *J Investig Med* 2021;**69**:814–818.

Table 1 Demographic and clinical characteristics of male and female patients with COVID-19

	Male (n=370)	Female (n=331)	P value	Values missing (%)
Age (years)	62 (16)	61 (19)	0.914	0 (0)
Race, n (%)			0.31	0 (0)
Non-Hispanic black	137 (37.0)	141 (42.6)		
Non-Hispanic white	108 (29.2)	94 (28.4)		
Hispanic/Latino	85 (23.0)	71 (21.5)		
Other/unknown	40 (10.8)	25 (7.6)		
Hypertension	114 (30.8)	122 (36.9)	0.091	0 (0)
Diabetes	162 (43.8)	130 (39.2)	0.227	0 (0)
Heart failure	84 (22.7)	65 (19.6)	0.322	0 (0)

Categorical variables are presented as count (per cent). Age is presented as mean (SD).

infection using the data from a multisystem hospital database.

MATERIALS AND METHODS

We conducted an electronic chart review of patients with a confirmed diagnosis of COVID-19 who were admitted to the Sentara Healthcare System, the largest healthcare system in the Eastern region of Virginia. Data of patients with COVID-19 who were discharged from hospital between January 2020 and June 2020 were collected. Patients were adult (18 and above) and had confirmed SARS-CoV-2 infection diagnosed by nasal PCR. International Classification of Diseases, 10th Revision, codes were used to extract clinical data from the electronic medical record (EMR) system (EPIC, Verona, Wisconsin, USA). The raw EMR data received from Sentara Health System was organized, managed, and analyzed by the Eastern Virginia Medical School-Sentara Healthcare Analytics and Delivery Science Institute staff. Epidemiological, clinical, laboratory, treatment, and outcomes data were obtained from the EMR.

Descriptive statistics were calculated and distributions assessed for all variables. Missing data were assessed. Continuous variables were summarized as mean and SD, which were normally distributed, and median and IQR, which where not normally distributed. Categorical variables were summarized as count and per cent. Student's t-test and Mann-Whitney U test for non-normal distributions were used to assess differences in continuous variables by sex. χ^2 tests were used to assess the associations between sex and categorical variables. All analyses were conducted in SAS V.9.4, with p values of less than 0.05 considered statistically significant.

RESULTS

During the study period, 701 patients were admitted with PCR-confirmed COVID-19 infection. The patients' mean age was 61±17 years. There were 370 men (52.8%) and 331 women. The patients were 39.6% non-Hispanic black and 28.8% non-Hispanic white. During the study period, 188 patients (26.8%) were admitted to the intensive care unit (ICU) with a hospital mortality of 10.9%. The demographic and clinical characteristics of the patients stratifed by gender are provided in table 1. The laboratory data, including baseline and maximal biomarker levels and the clinical outcomes of the patients, are provided in table 2. There were no significant differences in age, racial distribution, or comorbidities when comparing the male patients to the female patients. The baseline and maximal levels of the inflammatory biomarkers, namely, C reactive protein (CRP) and ferritin, were significantly higher in men as compared with women. While the baseline D-dimer did not differ significantly between men and women, the maximal D-dimer was significantly higher in men. The increase in

Table 2 Laboratory data and outcomes of the male and female patients with COVID-19

	Male (n=370)	Female (n=331)	P value	Values missing (%)
Initial BUN (mg/dL)	18 (20)	15 (17)	0.0002	27 (3.9)
Initial creatinine (mg/dL)	1.1 (1.0)	0.9 (0.7)	<0.0001	27 (3.9)
Initial WBC (10^9/mL)	6.7 (3.8)	6.7 (3.7)	0.459	194 (27.7)
Initial lymphocyte count (10^9/mL)	1.0 (0.6)	1.1 (0.7)	0.0004	37 (5.3)
Initial neutrophil count (10^9/mL)	5.5 (3.9)	4.8 (3.8)	0.203	37 (5.3)
Initial N:L ratio	5.5 (5.7)	4.5 (4.9)	0.002	37 (5.3)
Initial CRP (µg/mL)	9.7 (12.7)	6.9 (9.2)	0.0003	181 (25.8)
Max CRP (µg/mL)	12.1 (14.7)	8.8 (13.8)	0.0008	181 (25.8)
Percentage increase in CRP	24	27	0.64	
Initial ferritin (ng/mL)	878 (1096)	576 (947)	<0.0001	222 (31.7)
Max ferritin (ng/mL)	1,137 (1,341)	655 (1145)	<0.0001	222 (31.7)
Percentage increase in ferritin	29	13	0.02	
Initial D-dimer (ng/mL)	1.1 (2.0)	0.9 (1.4)	0.157	180 (25.7)
Max D-Dimer (ng/mL)	1.7 (6.3)	1.4 (2.9)	0.02	180 (25.7)
Percentage increase in D-dimer	54	55	0.85	
ICU admission	117 (31.6)	71 (21.4)	0.002	0 (0)
Hospital mortality	49 (13.2%)	28 (8.8%)	0.06	0 (0)

Categorical variables are presented as count (per cent). All biomarkers are presented as median (IQR) due to non-normal distributions.
Bolded p values indicate significance at 0.05 level.
BUN, blood urea nitrogen; CRP, C reactive protein; ICU, intensive care unit; N:L, neutrophil:lymphocyte ratio; WBC, white blood cell.

CRP (baseline to maximal value) was 24% for men and 27% for women (not significant); similarly, the increase in D-dimer was 54% for men and 55% for women (not significant). However, the increase in ferritin was 29% for men compared with 13% for women (p=0.02). The baseline neutrophil:lymphocyte ratio, a marker of disease severity, was significantly higher in men. Men had evidence of greater disease severity, with a significantly greater admission to the ICU and borderline higher hospital mortality.

In table 2, the per cent of values missing was presented for each variable. Missing data were limited to laboratory values since not all laboratory tests were collected for all patients. Here missing indicates that a certain laboratory test was not available in the dataset for the patient across the course of treatment. Per cent missing ranged from 3% for blood urea nitrogen and creatinine to 32% for ferritin. Patterns of missingness were assessed, and complete case analysis was appropriate for each test given sufficient power to detect meaningful effects with available sample size. Thus, the degree of missingness would not limit our ability to detect significant results at the 0.05 significance level.

DISCUSSION

A dysregulated host immune response appears to be the main driver behind severe COVID-19 disease.[6 7] In this study, we have demonstrated that the inflammatory response to SARS-CoV-2 differs between men and women, and this finding likely contributes to the increased disease severity (high ICU admission rate) and mortality noted in men. It is noteworthy that the baseline levels of D-dimer were similar in men and women; however, the maximal D-dimer levels were significantly higher in men. This finding is likely explained by the fact that the inflammatory response results in a small vessel endothelialitis in the lung,[8 9] which in turn activates the clotting cascade, resulting in microvascular and macrovascular thrombosis. The higher peak D-dimer in men may reflect a more severe endotheliaitis and clot burden; however, as we did not record clotting complications, this association will require further validation. The baseline and maximal levels of CRP and ferritin were signinfcatly higher in men. However, the percentage increase in CRP was proportionally similar in men and in women, while the percentage increase in ferritin was significantly greater in men. The differential increase in CRP versus ferritin between men and women is an interesting observation that remains unexplained. The sex difference in inflammatory response between men and women may be specific to COVID-19. Although the incidence of sepsis is higher in men than in women, there does not appear to be a significant difference in sepsis-associated mortality between the sexes.[10–13] Furthermore, in patients with septic shock, cytokine profiles have been reported to be similar between men and women.[14]

Age and comorbidities have been demonstrated to be important predictors of disease severity and mortality in patients with COVID-19.[1–5] However, in our study, these variables did not differ between men and women. Our study, therefore, suggests that men and women respond differently to the SARs-CoV-2 virus, with men having a heightened inflammatory response. A number of mechanisms may explain this observation.

ACE-2 is expressed on cells of the nasal and oral mucosa and on type II pneumocytes and is the essential binding protein for entrance of SARS-CoV-2 into the cell.[15 16] Binding of the SARS-CoV-2 spike protein to ACE2 results in fusion of the virus with the cell membrane and internalization of the virus–ACE2 complex with decreased surface ACE2 expression.[17] ACE2 functions as a major regulator of the renin–angiotensin axis by converting angiotensin I and angiotensin II into angiotensin 1–9 and angiotensin 1–7 (Ang 1–7), respectively.[18 19] Ang 1–7 is a pulmonary vasodilator and has anti-inflammatory effects. Lung tissue has high RAS activity, as is the leading site of angiotensin II synthesis. Loss of ACE2 disturbs the ACE1/ACE2 balance favoring the production of angiotensin II, which is a potent pulmonary vasoconstrictor and promotes inflammation and oxidative stress.[19] In patients with H7N9 influenzae, high angiotensin II levels were associated with disease severity and mortality.[20] Experimental studies in models of acute respiratory distress syndrome as well as SARS-CoV-2-induced lung injury have demonstrated that reduced ACE2 levels are associated with worse lung injury.[17 21] Furthermore, contrary to expectations, a negative correlation exists between ACE2 expression and COVID-19 fatality.[22] The gene for ACE2 is located on the X chromosome,[19] and women express significantly higher levels of ACE2 than men.[22] This male–female differential expression of ACE2 with decreased Ang 1–7 may partly explain the greater risk of respiratory failure and lung injury in men.

Apart from the differential expression of ACE2, the X-chromosome carries about 1200 genes, including genes for cytokines/cytokine receptors, toll-like receptor (TLR)-mediated signaling pathway genes, nuclear factor-κβ (NF-κβ) and mitogen-activated protein kinase signaling genes, genes involved in apoptosis, and immune-modulators such as CD40 ligand and forkhead box protein P3.[23] The differential expression of these genes may be partly responsible for differences in innate and adaptive immunity between men and women. High copy numbers of TLR7 (located on the X-chromosome) and elevated interferon regulatory factor-7 expression in women induce increased interferon-β, which may protect against viral infections.[24]

Sex hormones likely play a role in modulating the immune response to a pathogen. It has been suggested that testosterone may lead to increased disease severity in patients with COVID-19 infection by increasing the expression of the transmembrane protease, serine 2 (TMPRSS2), which is required for priming of the spike protein for cell fusion. The human TMPRSS2 gene has an androgen response element, and in humans, androgens are the only known transcription promoters for the TMPRSS2 gene.[25] Unlike expression of ACE2, increased expression of TMPRSS2 results in greater entry of SARS-CoV-2 into the cell. Androgenetic alopecia (baldness) is androgen mediated and is dependent on genetic variants found in the androgen receptor located on the X chromosome.[26] Goren *et al* reported that 71% of men admitted to a hospital in Spain with severe COVID-19 infection had clinically significant androgenic alopecia compared with a prevalence of 31%–53% in age-matched controls.[26]

While testosterone may be 'harmful', evidence suggest that estrogens may be protective in women with COVID-19 disease. Estrogens are known to suppress

monocyte–macrophage recruitment by downregulating chemokine expression during inflammation and inhibiting TLR4-mediated NF-κβ activation in macrophages.[27 28] In a murine experimental model, male mice were more susceptible to SARS-CoV infection compared with age-matched female mice.[29] In this study, the degree of sex bias to SARS-CoV infection increased with the advancing age of the mice. Furthermore, enhanced susceptibility of male mice to SARS-CoV was associated with elevated virus titers with increased accumulation of inflammatory monocyte macrophages and neutrophils in the lungs of male mice. Levels of proinflammatory cytokines tumor necrosis factor- α, interleukin (IL)-1 and IL-6 were significantly higher in male mice compared with female mice. Finally, gonadectomy did not affect disease outcome in male mice, while ovariectomy or estrogen receptor antagonists caused increased mortality in the female mice. This animal model appears to mirror the findings of our study with an exuberant, and ineffective, cytokine response underlying the increased disease severity in males (men and male mice). In addition, ex-vivo studies in humans demonstrated that X-linked mosaicism of genes of the innate immune response (in women) was associated with reduced cytokine production following TLR4 activation by lipopolysaccharide, and this finding was independent of sex hormones.[30]

While it appears that men with COVID-19 have a more robust inflammatory response than women and that this may account for the greater disease severity in men, additional factors may play a contributory role. Sex-specific differences in antibody responses against SARS-CoV-2 have been reported.[31] SARS-CoV-2 causes a major shift in cellular metabolism[32]; these changes may differ between the sexes. Women are more likely than men to take dietary supplements, including vitamin D.[33] Vitamin D insufficiency increases the cytokine storm and is associated with a greater risk of death from COVID-19 than vitamin D-sufficient individuals.[34–36]

Our study has several limitations. Most importantly, the duration of symptoms prior to presentation to hospital was not extractable from the EMR. It is possible that men presented later to hospital than women and therefore were farther into their inflammatory disease with higher initial inflammatory biomarkers, ICU admissions and deaths. Future studies should evaluate this potential confounder. The treatment of patients was standardized, using a system-wide protocol; it possible, though unlikely, that treatment varied according to the patients' sex. We did not perform ex vivo testing to assess T-cell function nor the humoral immune response. Furthermore, we did not measure type I interferons nor a panel of proinflammatory mediators. These factors and those listed previously should be evaluated in future studies.

In conclusion, our study supports the observation that COVID-19 causes more severe disease in men. The greater disease severity in men was not due to the effect of age or comorbidities; however, in keeping with experimental studies, men had evidence of a heightened inflammatory response. Estrogens suppress the production of proinflammatory cytokines, and this may be the major mechanism explaining the sex differential in patients with COVID-19.

Acknowledgements We thank the Sentara Quality Research Institute and the Sentara Healthcare system for their support in providing electronic medical record data for this project.

Contributors QA, SEDP, and PEM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis. Study concept and design: PEM, QA, and SEDP. Acquisition, analysis, or interpretation of data: SEDP, PEM, QA, and SD. Drafting of the manuscript: QA, SEDP, SD, PEM. Critical revision of the manuscript: all authors. Administrative and technical support: SD. PEM takes responsibility for the content of the manuscript, including the data and analysis.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the Eastern Virginia Medical School Institutional Review Board (#20–07 XX-0148), and informed consent was waived since it was a retrospective study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article. Deidentified subject data from which the study is composed is available upon reasonable peer request.

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