The Role of Sex in the Risk of Mortality From COVID-19 Amongst Adult Patients: A Systematic Review

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Abstract

A worldwide outbreak of coronavirus disease 2019 (COVID-19), identified as being caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), was classified as a Public Health Emergency of International Concern by the World Health Organisation (WHO) on January 30, 2020. Initial sex-disaggregated mortality data emerging from the Wuhan province of China identified male sex as a risk factor for increased COVID-19 mortality.

In this systematic review, we aimed to assess the role of sex in the risk of mortality from COVID-19 in adult patients through comparison of clinical markers and inflammatory indexes.

A systematic search was conducted on the following databases: PubMed, WHO COVID-19 database, Ovid MEDLINE, and Web of Science between the dates of June 15, 2020, and June 30, 2020. Key search terms used included: "sex", "gender", "SARS-COV-2", "COVID" and "mortality". We accepted the following types of studies concerning adult COVID-19 patients: retrospective cohort, observational cohort, case series, and applied research. Further studies were extracted from reference searching. The risk of bias was determined using the National Institutes of Health Quality Assessment Tool for Observational Cohort, Cross-Sectional Studies, and Case Series.

We identified a total of 16 studies published between January 2020 and June 2020 for analysis in this systematic review. Our study population consisted of 11 cohort studies, four case series, and one genetic study, including a total of 76,555 participants. Ten of the studies included in this review observed a higher risk of mortality among males compared to females, and eight of these studies found this risk to be statistically significant.

Sex-disaggregated COVID-19 mortality data identifies male patients with comorbidities as being at an increased risk of mortality worldwide. Further investigation revealed differences in immune response regulated by sex hormones, angiotensin-converting enzyme 2 (ACE2) expression, and health behaviours as contributing factors to increased risk of mortality from COVID-19 among males.

Nine out of the 16 studies included were conducted in China. In order to comprehensively assess sex-differences in the risk of mortality from COVID-19, more studies will need to be conducted worldwide. Sex-disaggregated COVID-19 data published in the medical literature is limited; however, it has become evident that male sex is an important risk factor for mortality. Further exploration into the impact of sex on this pandemic is required to develop targeted therapies, as well as public health policies, and to prevent sex bias in treatment.

Introduction And Background

In December 2019, a rise in pneumonia cases of unknown aetiology was seen in the Wuhan province of China. Approximately one month later, the coronavirus disease 19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the pathogenic source of the disease [1]. The virus is transmitted by talking, coughing, sneezing, aerosols and is now thought to be airborne [2]. The rapidly spreading and contagious nature of the virus led to a Public Health Emergency of International Concern being declared by the World Health Organisation (WHO) as of January 30, 2020 [3].

Mild illness may present with symptoms such as fever, malaise, headache, muscle pain, dry cough, and sore throat. However, more severe disease may progress to Acute Respiratory Distress Syndrome (ARDS) and death [3].

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As of June 30, 2020, England had 39,177 COVID-19 fatalities of which 56.9% were males and 43.1% were females [4]. Further exploration into the impact of sex on this pandemic is required to develop targeted therapies and public health policies. Sex-disaggregated analysis of the COVID-19 outbreak is important, as mortality data from 49 countries indicates that males have a higher overall mortality rate than females [4]. Although male and female susceptibility is the same, it has become evident that the male sex is an important risk factor for mortality [5].

In this systematic review we aimed to assess the role of sex in the risk of mortality from COVID-19 in adult patients through comparison of clinical markers and inflammatory indexes.

**Review Methodology**

**Search Strategy**

A systematic search was conducted on the following electronic databases: PubMed, WHO COVID-19 database, Ovid MEDLINE, and Web of Science between the dates of June 15, 2020, and June 30, 2020. This systematic review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and has been registered on PROSPERO (identifier number: CRD42020196076) [6].

A search strategy containing keywords was implemented across all search domains. Our search strategy consists of the following keywords: “male”, “female”, “men”, “women”, “sex”, “gender”, “corona”, “COVID-19”, “Cov2”, “SARS”, “SARS-COV-2”, “SARS-2”, “SARS-corona”, “severe acute respiratory syndrome”, “hormone”, “androgen”, “testosterone”, “oestrogen”, “estrogen”, “oestradiol”, “estradiol”, “ACE2”, “ACE-2”, “TMPRSS2”, “mortality”, “morbidity”, “death”. One example of a search string used is: “((COVID-19) OR (Coronavirus)) AND ((Gender) OR (sex) OR (male) OR (female)) AND ((mortality) OR (death rate))”.

**Selection Criteria**

The preliminary search yielded 1092 papers. After removal of duplicates, 655 abstracts and titles were screened for relevancy, through which 598 papers were excluded. The remaining 57 papers underwent full text screening. An additional 25 papers were retrieved through screening of relevant references. A total of 82 papers underwent full text screening. After applying inclusion and exclusion criteria, 16 papers were selected for analysis in this systematic review.

We accepted the following types of studies: retrospective cohort, observational cohort, case series, and applied research. Papers from any country concerning confirmed COVID-19 adult patients were accepted if they were written in English. Papers concerning paediatric (being under 18 years of age) and pregnant patients were excluded. Papers addressing other viral respiratory diseases, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), were also excluded.

Our outcome of interest was mortality rate of males and females diagnosed with COVID-19. Indicators that we regarded as potential reasons for the difference in mortality included: immunoglobulin G (IgG) antibody levels, immune cell levels, inflammatory indexes, receptor expression, hormone levels, behavioural factors, and disease severity.

Two reviewers screened the abstracts and titles retrieved from the searches. The third reviewer conducted a final check on the relevance of the papers against the inclusion and exclusion criteria. Data retrieved from the studies were collated into tabular form outlining the study design and main findings. Figure 1 shows the PRISMA flow diagram detailing the study identification, screening, and selection process.
FIGURE 1: PRISMA flow diagram

PRISMA flow diagram to show study identification, screening, inclusion and exclusion against specific predefined criteria.

COVID-19: coronavirus disease 2019, WHO: World Health Organization, SARS: severe acute respiratory syndrome, MERS: Middle East respiratory syndrome

Risk of Bias Assessment

Risk of bias was assessed using the National Institutes of Health (NIH) Quality Assessment Tool for Cohort, Cross-Sectional Studies and Case series [7]. Two review authors assessed the risk of bias and this was reviewed by the third author.

Results

We identified a total of 16 studies published between January 2020 and June 2020 for analysis in this systematic review. Our study population consisted of 11 cohort studies, four case series and one genetic study, including a total of 76,555 participants. The characteristics and main outcomes of each study are summarised in Table 1.

| Reference     | Country | Study Design       | Sample Population | % Males | % Females | Study Purpose                                                                 | Outcome/Conclusions                                                                 |
|---------------|---------|--------------------|-------------------|---------|-----------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Qin L. et al (2020) [8] | China   | Retrospective Cohort Study | 548 COVID-19 inpatients | 56.9    | 43.1      | To investigate how the effect of sex on inflammation affects COVID-19 outcomes | Mortality was higher in males (22.2% vs 10.4%). Relative Risk for mortality was 2.2 for males compared to females. Males had higher rates of lymphopenia, thrombocytopenia. Multiple linear regression method revealed greater levels of inflammation indexes in males. |
| Asfahan S. et al (2020) | China   | Retrospective      | 44,672 COVID-19 patients | 51.4    | 48.6      | To describe mortality characteristics for COVID-19 from publicly               | 81% of deaths were in the ages above 60 years. 63.8% of deaths were males. Logistic regression risk factors showed that only age and comorbidities significantly affected mortality. Sex |
| Reference | Study Design | Country | Study Type | Sample Size | Duration | Objective | Findings |
|-----------|--------------|---------|------------|-------------|----------|-----------|----------|
| Borobia AM. et al (2020) [10] | Cohort study | Spain | Retrospective | 2226 COVID-19 in-patients | 48.2 | 51.8 | To describe the clinical characteristics of hospitalized patients with COVID-19 | Mortality was higher in males than females (26.6% vs. 15.1%). Compared with the entire cohort, the patients admitted to the ICU had a higher male/female ratio (3.2 vs. 0.93). In multivariate logistic regression model, male sex was associated with higher probability of death from COVID-19. |
| Yang X. et al (2020) [11] | Retrospective Cohort Study | China | Retrospective | 52 critically ill COVID-19 adults | 67 | 33 | To describe the clinical course and outcome of critically ill patients with COVID-19 | 67% of critically ill patients were males. (Critically ill patients were defined as those admitted to the Intensive Care Unit (ICU) who required mechanical ventilation or had a fraction of inspired oxygen of at least 60% or more) |
| Li X. et al (2020) [12] | Cohort study | China | Retrospective | 269 COVID-19 inpatients | 56.9 | 43.1 | To evaluate the severity on admission, complications and outcomes of COVID-19 patients | Multivariable Cox proportional hazards regression analysis showed that male sex is a risk factor (adjusted HR, 1.7; 95% CI, 1.0-2.8). Other risk factors identified: Older age, leukocytosis, hyperglycaemia, high lactate dehydrogenase, high corticosteroid dose, cardiac injury. |
| Shi Y. et al (2020) [13] | Cohort study | China | Retrospective | 49 severe COVID-19 inpatients | 73.5 | 26.5 | To explore host risk factors. To establish a score system to identify high risk patients | Out of the 49 severe patients, 36 were male and 13 were female. There were significantly more males among the severe cases (P=0.003). On multivariate analysis, male sex is associated with severe disease at admission (OR 3.68 [95% CI 1.75–7.75], P = 0.001). |
| Liu Y. (2020) [14] | Cohort study | China | Retrospective | 245 COVID-19 patients | 46.5 | 53.5 | To investigate whether neutrophil-to-lymphocyte ratio (NLR) can serve as a predictor of hospital mortality | The odd ratio for mortality was 1.10 in males (CI 1.02-1.10; P=0.016). Sensitivity analysis was used to convert NLR into a categorical tertile variable. Males made up 61% of tertile 3 (most severe tertile). NLR is an independent risk factor for mortality especially in males. |
| Jin J. et al (2020) [5] | Cohort study | China | Retrospective | 37 cases from public data set of the first patients who died of COVID-19 and 1019 who survived | 50.8 | 49.2 | To compare the severity and mortality between male and female patients with COVID-19 | The number of males who died from COVID-19 is 2.4 times that of females (70.3 vs. 28.7%, P = 0.018). |
| Zeng F. et al (2020) [15] | Cohort study | China | Retrospective | 331 COVID-19 inpatients | 38.4 | 61.6 | To investigate if there is a difference in serum IgG antibody between males and females | IgG antibody tended to be stronger in female patients in the early phase of infection. In female patients, the concentration of COVID-19 IgG antibody continuously increased from mild to severe status and then decreased in recovering patients. In male patients, the IgG antibody rose from mild to general status and then decreased from general status patients to recovering patients. Females patients generated a high level of COVID-19 IgG antibody relative to male patients in severe status. Female level was higher in week 2-4 but after week 4 there was no longer a difference between the sexes. |
| Li M. et al (2020) [14] | Cohort study | China | Retrospective | 31 GTex normal tissues | N/A | N/A | To investigate the difference in ACE2 expression in different human tissue to understand COVID-19 mechanism of infection | No significant difference found in ACE2 expression between males and females. Negative correlation found between ACE2 and CD8\(^+\) cells, interferon response and B cells in female lungs. Positive correlation found between ACE2 and CD8\(^+\), interferon response and B cells in male lungs. |

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and explore risk factors associated with mortality. Independent risk factors for mortality were increasing age, male sex, and chronic comorbidity, including obesity.

Multivariable Cox proportional hazards ratio model: Female sex was associated with lower mortality (0.81 hazard ratio, CI (95%) 0.75 to 0.86, P<0.001).

Gene term enrichment analysis for the 94 upregulated genes identified three significantly altered pathways upon SARS-CoV-2 infection: “cytokine-mediated signalling pathway”, “IL-17 signalling pathway”, and “defence response to other organism”. Comparison of transcriptomic profile of lung tissue from healthy women and men revealed female lung tissues has a more similar phenotype to that induced upon SARS-CoV-2 infection than identical tissues from men.

Total Testosterone (TT) and calculated Free Testosterone (cFT) showed a significant decline according to worsening outcomes. Linear regressions showed that for each nmol/L decrease in TT and 10 pmol/L decrease in cFT, the probability of worse clinical outcomes increased [TT (p=0.017), cFT (p=0.007)]. Lower baseline levels of TT and cFT levels predict poor mortality in COVID-19 infected males admitted to Respiratory Intensive Care Unit (RICU).

Male sex was independently associated with ICU admission (OR= 2.0, P=0.006) and significantly associated with mortality (OR=1.8, P= 0.03). Multivariable analysis of patient characteristics and need for mechanical ventilation in ICU showed high association with male sex (OR=2.9, P=0.001).

The majority of critically ill patients admitted to ICU were older men. 82% of COVID-19 inpatients admitted to ICU from February 20th to March 8th 2020 were male. The median age of patients admitted to ICU was 63 years old.

### TABLE 1: Sixteen inclusion studies detailing study country, type, population, purpose and main outcomes.

| Study | Country | Type | Population | Purpose | Main Outcomes |
|-------|---------|------|------------|---------|---------------|
| Docherty A. et al (2020) [17] | UK | Observational Cohort Study | 20,133 COVID in-patients | 60 | 40 |
| Fagone P. et al (2020) [18] | Italy | Genetic Study | 134 healthy lung tissue samples | 70 | 30 |
| Rastrelli G. et al (2020) [19] | Italy | Case Series | 31 male COVID-19 inpatients recovered in Respiratory Intensive care (RICU) | 100 | 0 |
| Richardson S. et al (2020) [20] | USA | Case Series | 5700 COVID-19 in-patients | 60.3 | 39.7 |
| Suleyman G. et al (2020) [21] | USA | Case Series | 462 COVID-19 in-patients | 44.1 | 55.9 |
| Grasselli G. et al (2020) [22] | Italy | Case Series | 1591 COVID-19 in-patients admitted to ICU | 82 | 18 |

### Sex and Mortality From COVID-19

Ten studies from the database search observed higher risk of mortality amongst males compared to females. Eight studies found male sex to be significantly associated with increased risk of mortality from COVID-19. One study found no significant association between male sex and mortality after adjusting for confounders. Figure 2 indicates which studies have observed an increased risk of mortality in males and those in which this association is significant.
FIGURE 2: Male sex and mortality from COVID-19

This figure shows which of the included studies observed an increased risk of mortality due to male sex, and which studies observed a significant association (p<0.05).

| Study              | Risk of Mortality due to Male Sex | Significant Association (p<0.05) |
|--------------------|----------------------------------|---------------------------------|
| Qin L. et al       | ↑                                | ✓                               |
| Asfahan S. et al   | ↑                                | x                               |
| Borobia AM. et al  | ↑                                | ✓                               |
| Yang X. et al      | .                                | .                               |
| Li X. et al        | ↑                                | ✓                               |
| Shi Y. et al       | ↑                                | ✓                               |
| Liu Y. et al       | ↑                                | ✓                               |
| Jin J. et al       | ↑                                | ✓                               |
| Zeng F. et al      | .                                | .                               |
| Li M. et al        | .                                | .                               |
| Docherty A. et al  | ↑                                | ✓                               |
| Fagone P. et al    | .                                | .                               |
| Rastrelli G. et al | .                                | .                               |
| Richardson S. et al| ↑                                | .                               |
| Suleyman G. et al  | ↑                                | ✓                               |
| Grasselli G. et al | .                                | .                               |

Key

↑ - Increased risk of mortality
· - No data available
✓ - Statistically significant association
x - No significant association

FIGURE 2: Male sex and mortality from COVID-19

This figure shows which of the included studies observed an increased risk of mortality due to male sex, and which studies observed a significant association (p<0.05).

Risk of Bias Assessment Results

Table 2 summarises the risk of bias results assessed using the NIH quality assessment tool [7].
NiH Risk of Bias Assessment

| Reference  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|
| Qin L. et al | Y | Y | NA | Y | N | Y | N | Y | Y | Y | NA | Y | Y | NA | NR | Y |
| Asfahan S. et al | Y | N | NA | Y | NA | Y | NR | N | Y | NA | Y | NA | NA | Y |
| Borobia AM. et al | Y | Y | NA | Y | N | Y | Y | Y | Y | N | Y | NA | NR | Y |
| Yang X. et al | Y | Y | NA | Y | Y | Y | Y | Y | Y | Y | N | Y | NA | NR | Y |
| Li X. et al | Y | Y | NA | Y | Y | Y | Y | Y | Y | NA | Y | NA | NR | Y |
| Shi Y. et al | Y | Y | NA | Y | N | Y | NR | N | N | NA | N | NA | NA | N |
| Liu Y. et al | Y | Y | Y | Y | Y | Y | Y | N | N | NA | N | Y | N | Y |
| Jin J. et al | Y | N | NA | N | N | Y | NA | Y | N | N | Y | NA | NA | Y |
| Zeng F. et al | Y | Y | NA | Y | N | N | NR | Y | N | NA | Y | NA | NA | NR |
| Li M. et al | Y | Y | NA | NR | N | N | NR | NA | Y | N | Y | NA | NA | Y |
| Docherty A. et al | Y | Y | NA | N | Y | Y | Y | Y | N | Y | NA | NR | Y |
| Fagone P. et al | Y | Y | NA | NA | N | Y | NA | NA | Y | NA | Y | NA | NA | NR |

**Case Series**

| Reference  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|------------|---|---|---|---|---|---|---|---|---|
| Rastrelli G. et al | Y | Y | Y | Y | NA | Y | Y | Y |
| Richardson S. et al | Y | Y | Y | Y | NA | Y | Y | Y |
| Suleyman G. et al | Y | Y | Y | Y | NA | Y | Y | Y |
| Grasselli G. et al | Y | Y | Y | Y | Y | N | Y | Y |

Key: Y = Yes, N = No, NA = Not applicable, NR = Not reported

**TABLE 2: Results of the National Institutes of Health Quality Assessment Tool for Cohort, Cross-Sectional Studies, and Case series [7] for the 16 inclusion studies.**

Cohort and Cross-Sectional Studies: 1. Was the research question or objective in this paper clearly stated? 2. Was the study population clearly specified and defined? 3. Was the participation rate of eligible persons at least 50%? 4. Were all the subjects selected or recruited from the same or similar populations? 5. Were the cases consecutive? 6. Were the cases comparable? 7. Was the intervention clearly described? 8. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 9. Was the length of follow-up adequate? 10. Were the outcome assessors blinded to the exposure status of participants? 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 12. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Case Series: 1. Was the study question or objective clearly stated? 2. Was the study population clearly and fully described, including a case definition? 3. Were the cases consecutive? 4. Were the subjects comparable? 5. Was the intervention clearly described? 6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? 7. Was the length of follow-up adequate? 8. Were the statistical methods well-described? 9. Were the results well-described?

**Discussion**

We undertook a comprehensive search of the literature concerning sex-disaggregated mortality from COVID-19 in order to summarize the potential underlying reasons for the disparity in mortality rate. We found that published evidence suggests the female sex has a protective role against COVID-19 mortality. Main reasons for this finding include the higher levels of the circulating form of ACE2 in females, the immune system's response, and female hormones, which tend to display disease-preventing behaviors.
Sex Differences in ACE2 Expression

Differences in angiotensin-Converting Enzyme 2 (ACE2) expression between sexes is thought to contribute to the higher male mortality rate. ACE2 degrades Angiotensin II into Angiotensin 1-7, counteracting the Renin-Angiotensin System (RAS) axis. This reduces the effects of the RAS axis which usually increases blood pressure, sympathetic tone, vasoconstriction, inflammation, and fibrosis. ACE2 also serves as the primary receptor for SARS-CoV-2 cellular invasion[23]. The viral spike protein contains the S1 domain, which serves as a receptor-binding portion, and the S2 domain which facilitates cellular-viral fusion[24, 25]. The high affinity of SARS-CoV-2 for the ACE2 receptor facilitates viral spread between person to person[26]. It is also thought that SARS-CoV-2 infection downregulates ACE2 expression, reducing its protective role and explaining the progression of patients into ARDS[23].

ACE2 is expressed on the PAR region of the X chromosome, which has a greater chance of escaping X chromosomal inactivation[27]. ACE2 is also upregulated by androgens leading to disparity in ACE2 expression in some organs between the sexes[27, 28]. The paradox of ACE2 upregulation may lead to lower male mortality due to a few theories. There are two types of ACE2: the membrane-bound, which provides the viral entry point, and the circulating form which has a cardiovascular protective function. It is thought that females express more of the circulating ACE2 providing protection against disease progression into ARDS[29].

Viks et al. suggest that the testes may serve as a reservoir for SARS-CoV-2, delaying viral clearance and increasing the likelihood of systemic tissue damage. The high levels of ACE2 expression and the immune-privileged nature of this organ concur with this theory[30]. It is also thought that amino acid substitutions can influence viral S1-ACE2 interaction and viral infectivity. Due to hemizygosity in males, carrying a viral-boosting allelic variant of ACE2 may lead to increased susceptibility to severe disease[31, 32]. Li et al. propose that increased male mortality can be attributed to the increased likelihood of a cytokine storm in the lungs, accelerating progression into ARDS. They found a positive correlation between ACE2 expression and immune cell levels (Natural Killer (NK) cells, CD8+ cells) in male lung tissue whereas the opposite was found in females[33].

Role of Sex Hormones

Previous literature shows that differences in sex hormones impact the immune system and therefore may play a role in SARS-CoV-2 clearance. It is thought that testosterone (T) has both protective and adverse effects on mortality risk.

Low levels of T appear to be linked with increased susceptibility of respiratory diseases[34]. Rastrelliet al. demonstrate that low levels of Tand circulating free testosterone (cFT) are predictors for adverse outcomes and mortality from COVID-19[19]. This concurs with existing literature in which an association between hypogonadism and proinflammatory cytokine levels is observed[35, 36]. Severe infections are also associated with a reduction in numbers of CD4+ T cells, CD8+ T cells, B cells, and NK cells. The presence of androgen receptors (AR) on these cells suggests that T is important in their function[34].

In addition to this, T plays a complex role in coagulation which could affect male mortality rate. Intravascular thrombosis and endothelial dysfunction complicate COVID-19 prognosis. Published evidence indicates this occurs more frequently in males than females[33]. T augments activation and aggregation of platelets by increasing platelet expression of thromboxane A2 receptors[36]. In contrast, a negative correlation between serum T levels and platelet reactivity has been discovered by an ex vivo study[37]. T enhances the production of endothelial nitric oxide, a potent vasodilator and inhibitor of platelet recruitment. Mean platelet volume, a biological indicator of platelet activation, is seen to be increased in hypogonadal males[38]. Therefore, it could be hypothesised that T protects males against new thrombotic events in COVID-19, an effect that is lost through hypogonadism[33].

T has a cardioprotective role and promotes myocardial health. Thus, males with hypogonadism are predisposed to increased cardiovascular risk from COVID-19. T is vital in regulating glucose and maintaining favourable lipid metabolism[35]. Furthermore, being a rapid onset vasodilator, T reduces blood pressure by blocking calcium channel opening. Males with cardiovascular diseases (CVD) tend to have lower serum T levels[39]. This further illustrates the importance of T in protecting against chronic CVD, as well as acute cardiac injury, which is typically associated with severe COVID-19 disease[17, 33, 40].

Although hypogonadism appears to be a risk factor for mortality, a contradictory “Testosterone driven COVID-19” theory exists[28]. Transmembrane Protease Serine 2 (TMPRSS2) cleaves the viral S protein at two sites allowing penetration changes on which viral entry into cells depends. It is thought that increased male mortality could be attributed to the androgen regulation of TMPRSS2. There is discourse in the literature as some papers find that there is no significant difference in TMPRSS2 expression in the lungs between the sexes[41]. However, other papers find that males have significantly higher (P=0.029) expression of TMPRSS2 at the pulmonary level which may lead to viral progression and poorer outcomes[32].
Oestrogen (E) is thought to have a protective role against COVID-19 mortality in females. Lower female mortality could be attributed to stimulating immune cell development, namely B cells, leading to humoral anti-viral responses. Receptors present on various leukocytes induce pro-inflammatory cytokine production such as interleukin (IL)-12, tumor necrosis factor-alpha (TNF-alpha) and chemokine (C-C motif) ligand 2 (CCL2) [42]. The activated lymphocytes and alveolar macrophages increase type 1 and 2 interferon (IFN) production, reducing viral load.

Scotland et al. suggest that E may also affect leukocyte function. They found that female mice have an increased number of resident T lymphocytes and that their tissue macrophages have a higher density of toll-like receptor (TLR), specifically TLR2 and TLR4; this allows rapid detection and elimination of pathogens [43]. Channappanavar et al. also demonstrate E’s protective role as they found oophorectomy or treating female mice with an ER antagonist resulted in increased mortality from SARS-CoV-1, whereas gonadectomy did not affect mortality [44]. This finding may also be applicable to SARS-CoV-2, providing a potential explanation for higher male COVID-19 mortality.

Sex Differences in Immune Regulation

A study conducted by Zeng et al. highlights that females produce more serum (SARS-CoV-2) IgG in comparison to males in severe disease status [45]. TLR7, a pattern recognition receptor, is expressed on the X chromosome and can bypass X chromosomal inactivation [42]. Female X chromosomal homozygosity results in a greater gene dosage and expression of TLR7, allowing for stronger antigen detection [45]. TLR7 presenting plasmacytoid dendritic cells in females produce more type 1 IFN following ligand stimulation when compared to males [45]. In the presence of TLR7, type 1 IFN enhances B cell-mediated immunoglobulin secretion as well as asproiferation [46]. These biological processes provide an explanation for higher serum IgG in females.

Gene term enrichment analysis of the genes upregulated in SARS-CoV-2 infection in human lung epithelium identify the ‘cytokine-mediated signalling pathway’ as the most significantly altered pathway [18]. Qin et al. observe that COVID-19 disease severity is positively correlated with inflammation [7]. Following viral invasion of the lungs, aberrant release of inflammatory cytokines (soluble IL-2, IL-6, IL-8, IL-10) and proteins (LDH, ferritin, high-sensitivity CRP [hs-CRP]) damage the alveolar epithelial cell barrier causing increased hypoxia leading to ARDS [8, 17]. Inflammatory indexes within this cohort are significantly higher in females. This is worth noting as mortality within this cohort was twice as likely in males and this could be as a result of the immunopathogenic damage caused by excess cytokine storms promoting acute lung injury [8].

Gene term enrichment analysis may provide further explanation for these sex-based differences in cytokine expression. Several Differentially Expressed Genes (DEGs) identified upon SARS-CoV-2 infection of human lung epithelium are found to be modulated by sex hormones. Neutrophil chemotactic factor CXCL1 and dendritic cell chemotactic factor CCL20 are significant DEGs upregulated in SARS-CoV-2 infection. Both factors are regulated by AR, providing further evidence for the role of excess cytokine storms observed in males increasing mortality [18].

SARS-CoV-2 infection is known to result in significant lymphocytopenia, the extent of which differs between sexes [8, 10, 11, 14]. Yang et al. observe lymphocytopenia in 80% of their most critically ill patients [11]. Qin et al. similarly note that male COVID-19 patients have a lower overall lymphocyte count compared to females when adjusting for age and comorbidity [8]. Additionally, previous research finds that females have higher CD4+ T cell counts than age-matched males, and after in vitro stimulation females produce higher numbers of activated CD4+ T cells [44]. The greater reserve of CD4+ lymphocytes, combined with lower risk of lymphocytopenia in SARS-CoV-2 infection, may potentially decrease the risk of mortality from COVID-19 in females.

Sex Differences in Behaviour

Behavioural differences are also thought to contribute to the difference in COVID-19 mortality between sexes. Males tend to partake in higher-risk behaviours such as smoking and drinking alcohol; the WHO reports that 40% of males worldwide smoke compared to 9% of females [47]. Additionally, it is thought that females are more likely to follow hygiene and preventative routines [48].

A study by Guan et al. finds an association between disease severity and smoking. Smokers make up a greater proportion of severe COVID-19 patients compared to non-severe patients (16.9% and 11.8%, respectively) [49]. However, it is worth noting that in this study sex is not taken into consideration. Bergemont et al. observe an association between cigarette smoke and increased heme oxygenase-1 induction (HO-1) of lung fibroblasts in mice. HO-1 is thought to have anti-viral and cytoprotective properties [50]. This confounds the previous understanding of the relationship between smoking and SARS-CoV-2 infection. Therefore, further research and clarification are needed to determine the precise mechanisms of this relationship.
Strengths and limitations

Our review has several strengths. The search strategy we implemented contained a comprehensive list of search words resulting in an in-depth analysis of available evidence. We adopted a pragmatic search strategy approach, appropriate for an ongoing pandemic setting, which aligned with PRISMA guidelines and WHO recommendations for rapidly reviewing evidence in the context of emergencies. Papers also underwent an extensive appraisal before being included in our review. Astwo reviewers assessed potential studies while a third reviewer verified this. Although the risk of bias assessment showed most of the studies used had little or no bias, we found that disease severity was measured differently between studies. As a result, comparison of patients between studies must be done carefully.

There are several limitations to our review. We limited our electronic database search due to the dynamic and rapidly evolving nature of the COVID-19 pandemic, therefore we included publications only in English between January 2020 and June 2020. Our search strategy was also focused solely on sex and COVID-19 mortality; no comparisons were made regarding the role of sex in the SARS and MERS outbreaks. Additionally, nine out of the six studies used were conducted in China. In order to comprehensively assess sex differences in the risk of mortality from COVID-19, more studies will need to be conducted worldwide.

Sex-disaggregated COVID-19 data published in medical literature is limited; however, it has become evident that the male sex is an important risk factor for mortality. Further exploration into the impact of sex on this pandemic is required in order to develop targeted therapies, as well as public health policies, and to prevent sex bias in treatment.

Conclusions

In conclusion, data emerging worldwide suggests that the male sex has a significant role in increasing risk of COVID-19 mortality amongst adult patients. This association may be explained by the findings that males tend to have lower serum IgG antibody generation, decreased CD4+ T cell reserves, and lower circulating ACE2 expression when compared to females. Male sex is also found to be associated with increased disease severity upon hospital admission, higher rates of ICU admission, and increased clinical markers such as lymphopenia and inflammatory indexes. Conversely, female sex is found to play a significant role in lowering risk of mortality from COVID-19.

Additional Information

Disclosures

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References

1. Shereen M, Khan S, Kazmi A, Bashir N, Siddique R: COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020, 24:91-98. 10.1016/j.jare.2020.03.005
2. Morawska L, Milton D: It is time to address airborne transmission of COVID-19. Clin Infect Dis. 2020, 10.1093/cid/ciaa939
3. Cascella M, Rajnik M, Cuomo A, Dulebohn S, Napoli R: Features, Evaluation and Treatment Coronavirus (COVID-19). StatPearls Publishing, 2020.
4. Global Health 50/50. COVID-19 Sex-disaggregated Data Tracker. (2020). Accessed: June 27 2020: https://globalhealth5050.org/covid19/sex-disaggregated-data-tracker/.
5. Jin J, Bai P, He W, et al.: Gender differences in patients with COVID-19: focus on severity and mortality. Front Public Health. 2020, 8:152. 10.3389/fpubh.2020.00152
6. Moher D, Liberati A, Tetzlaff J, Altman D: Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009, 6(7):e1000097. 10.1371/journal.pmed.1000097
7. Quality assessment tool for observational cohort and cross-sectional studies. (2020). Accessed: June 16 2020: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.
8. Qin L, Li X, Shi J, et al.: Gendered effects on inflammation reaction and outcome of COVID-19 patients in Wuhan. J Med Virol. 2020, 1-9. 10.1002/jmv.26137
9. Asfahan S, Deokar K, Dutt N, Niasr R, Jain P, Agarwal M: Extrapolation of mortality in COVID-19.
Exploring the role of age, sex, co-morbidities and health-care related occupation. Monaldi Arch Chest Dis. 2020, 90: 10.4081/monaldi.2020.1325
10. Borobia A, Carcas A, Arnaulch F, et al.: A cohort of patients with COVID-19 in a major teaching hospital in Europe. J Clin Med. 2020, 9:1735. 10.3390/jcm9061735
11. Yang X, Yu Y, Xu J, et al.: Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020, 8:475-481. 10.1016/s2213-2600(20)30079-5
12. Li X, Xu S, Yu M, et al.: Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020, 146:110-118. 10.1016/j.jaci.2020.04.006
13. Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng J: Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. Crit Care. 2020, 24:10.1186/s13054-020-2835-7
14. Liu Y, Du X, Chen J, et al.: Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infection. 2020, 81:6-12. 10.1016/j.jinf.2020.04.002
15. Zeng F, Dai C, Cai P, et al.: A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: a possible underlying different outcome between sex. J Med Virol. 2020, 1-5. 10.1002/jmv.25989
16. Li M, Li L, Zhang Y, Wang X: Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty. 2020, 45: 10.18634/jmv-2020-004662-x
17. Docherty A, Harrison E, Green C, et al.: Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020, 369:m185
18. Fagone P, Ciurleo R, Lombardo S, et al.: Transcriptional landscape of SARS-CoV-2 infection dismantles pathogenic pathways activated by the virus, proposes unique sex-specific differences and predicts tailored therapeutic strategies. Autoimmun Rev. 2020, 19:102571. 10.1016/j.autrev.2020.102571
19. Rastrelli G, Di Stasi V, Inglese F, et al.: Low testosterone levels predict clinical adverse outcomes in SARS-CoV-2 pneumonia patients. Andrology. 2020, 1-11. 10.1111/andr.12821
20. Richardson S, Hirsch J, Narasimhan M, et al.: Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020, 325:2052. 10.1001/jama.2020.6775
21. Suleyman G, Fadil R, Malette K, et al.: Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in metropolitan Detroit. JAMA Network Open. 2020, 3:2012270. 10.1001/jamanetworkopen.2020.12270
22. Grasselli G, Zangrillo A, Ranella A, et al.: Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020, 325:1574. 10.1001/jama.2020.5394
23. Cheng H, Wang Y, Wang G: Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. J Med Virol. 2020, 92:92-10. 10.1002/jmv.25785
24. Li W, Moore MJ, Vasilieva N, et al.: Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2005, 426:450-454. 10.1038/nature02145
25. Coutard B, Vallee C, de Lamballerie X, Canard B, Seidah NG, Decroly E: The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Arterial Press. 2020, 176:104742. 10.1016/j.artr.2020.104742
26. Wrapp D, Wang N, Corbett K, et al.: Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020, 367:1260-1263. 10.1126/science.abc2507
27. Wambier C, Gorren A: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen mediated. J Am Acad Dermatol. 2021, 84:308-309. 10.1016/j.jaad.2020.04.032
28. Bronshman K, Hodgin J, Smithies O, Maeda N, Gallagher P: Tissue specific regulation of ACE/ACE2 and AT1/AT2 receptor gene expression by estrogen in ApoE/Eta knock-out mice. Exp Physiol. 2009, 94:658-664. 10.1113/expphysiol.2007.041806
29. Lambert D, Yarski M, Warner F, et al.: Tumor necrosis factor-α convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2). J Biologic Chem. 2005, 280:30113-30119. 10.1016/j.jbc.2005.05.054
30. Vilke J, Lippi G, Henry B: Do sex-specific immunobiological factors and differences in angiotensin converting enzyme 2 (ACE2) expression explain increased severity and mortality of COVID-19 in males?. Diagnosis. 2020, 10.1515/dx-2020-0054
31. Procko E: The sequence of human ACE2 is suboptimal for binding the S spike protein of SARS coronavirus 2. bioRxiv. 2020, 5:949256. 10.1101/2020.05.16.949256
32. Asselta R, Paraboschi EM, Mantovani A, Duga S: ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. Aging (Albany NY). 2020, 12:10087-10098. 10.18632/aging.105415
33. Giagulli VA, Guastamacchia E, Magrone T, Jirillo E, Lisco G, De Pergola G, Triggiani V: Worsen progression of COVID-19 in men: is testosterone a key factor?. Andrology. 2020, 1-12. 10.1111/andr.12836
34. Liva SM, Voskuhl RR: Testosterone acts directly on CD4+ T lymphocytes to increase IL-10 production. J Immunol. 2001, 167:2060-2067. 10.4049/jimmunol.167.4.2060
35. Haifner S, Mykkänen L, Valder R, Katz M: Relationship of sex hormones to lipids and lipoproteins in nonobese men. J Clin Endocrinol Metab. 1997, 77:1610-1615. 10.1210/clin.77.6.8263149
36. Clay A, Mathur R, Halushka PV: Testosterone increases human platelet thromboxane A2 receptor density and aggregation responses. Circulation. 1991, 95:2742-2747. 10.1161/01.CIR.91.11.2742
37. Karolczak K, Konieczna L, Kostka T, Witas P, Solsyński, Baczek T, Watala C: Testosterone and dihydrotestosterone reduce platelet activation and reactivity in older men and women. Aging (Albany NY). 2018, 10:902-909. 10.18632/aging.101438
38. Carlioglu A, Durmaz SA, Kibar YI, Ozturk Y, Tay A: Mean platelet volume in a patient with male hypogonadotropic hypogonadism: the relationship between low testosterone, metabolic syndrome, impaired
fasting glucose and cardiovascular risk. Blood Coagul Fibrinolysis. 2015, 26:811-815. 10.1097/MBC.0000000000000353

39. Jones TH, Kelly DM: Randomized controlled trials-mechanistic studies of testosterone and the cardiovascular system. Asian J Androl. 2018, 20:120-150. 10.4103/aja.aja_6_18

40. Wang D, Hu B, Hu C, et al.: Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020, 323:1061-1069. 10.1001/jama.2020.1585

41. Stopczak KH, Mucci LA, Antonarakis ES, Nelson PS, Kantoff PW: TMPRSS2 and COVID-19: serendipity or opportunity for intervention?. Cancer Discov. 2020, 10:779-782. 10.1158/2159-8290.CD-20-0451

42. Pisitkun P, Deane J, Dhillippantoni M, Tarasenko T, Satterthwaite A, Bolland S: Autoreactive B cell responses to RNA-related antigens due to TLR7 gene duplication. Science. 2006, 312:1669-1672. 10.1126/science.1124978

43. Scotland RS, Stables MJ, Madali S, Watson P, Gilroy DW: Sex differences in resident immune cell phenotype underlie more efficient acute inflammatory responses in female mice. Blood. 2011, 118:5918-5927. 10.1182/blood-2011-05-340281

44. 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, 198:4046-4053. 10.4049/jimmunol.1601896

45. Berghöfer B, Frommer T, Haley G, Fink L, Bein G, Hackstein H: TLR7 ligands induce higher IFN-α production in females. J Immunol. 2006, 177:2088-2096. 10.4049/jimmunol.177.4.2088

46. Pasare C, Medzhitov R: Control of B-cell responses by Toll-like receptors. Nature. 2005, 438:364-368. 10.1038/nature04267

47. 10 facts on Gender and Tobacco. (2020). Accessed: June 29 2020: https://www.who.int/gender/documents/10facts_gender_tobacco_en.pdf.

48. Johnson H, Sholcosky D, Gabello K, Ragni R, Ogosnoky N: Sex differences in public restroom handwashing behavior associated with visual behavior prompts. Percept Mot Skills. 2003, 97:805-810. 10.2466/pms.2003.97.3.805

49. Guan W, Ni Z, Hu Y, et al.: Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020, 382:1708-1720. 10.1056/nejmoa2002052

50. Hooper P: COVID-19 and heme oxygenase: novel insight into the disease and potential therapies. Cell Stress Chaperones. 2020, 4:1-4. 10.1007/s12192-020-00112-9