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Systematic Review and Meta-Analysis of Sex-Specific COVID-19 Clinical Outcomes

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Systematic Review and Meta-Analysis of Sex-Specific COVID-19

Clinical Outcomes

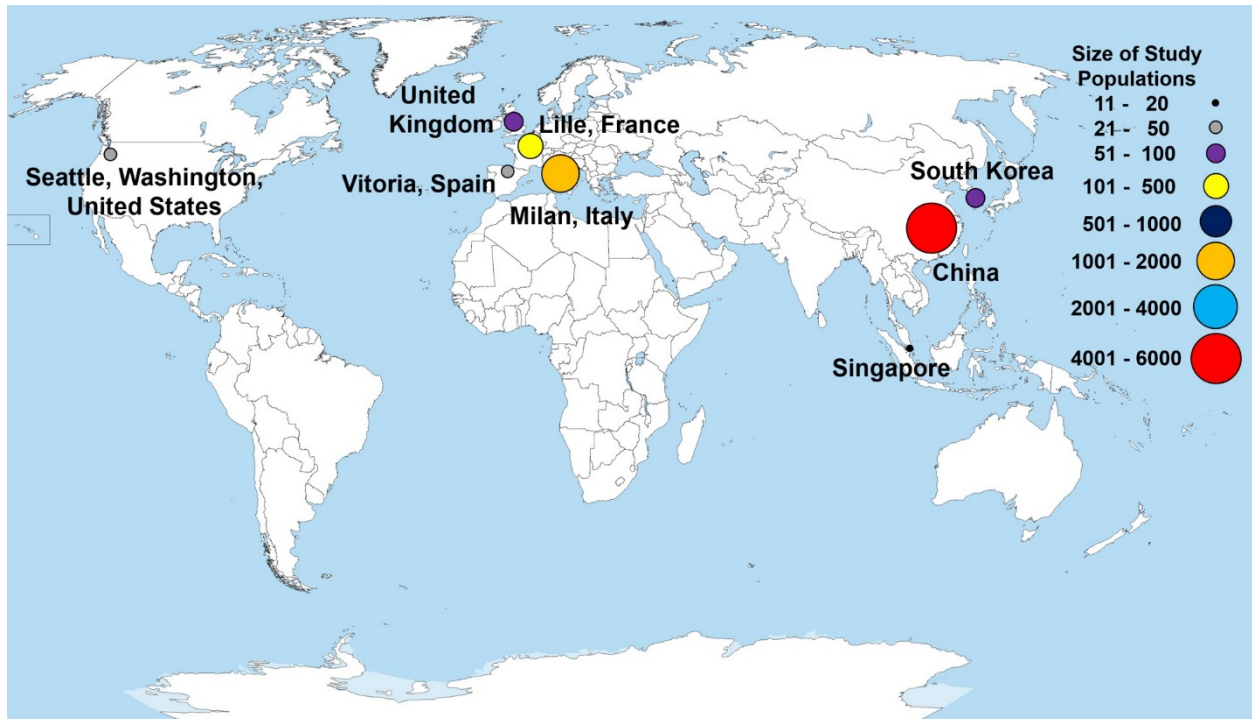
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Keywords: COVID-19, SARS-CoV-2, coronavirus, male, disparity, clinical outcomes, mortality, pandemic



Countries and population samples for the selected studies used in the meta-analysis.

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Abstract

To successfully mitigate the extraordinary devastation caused by the Coronavirus disease 2019 (COVID-19) pandemic, it is crucial to identify important risk factors for this disease. One such neglected health determinant is the sex of the patient. This is an essential clinical characteristic, as it can factor into a patient's clinical management and preventative measures. Some clinical studies have shown disparities in the proportion between males and females that have more severe clinical outcomes or, subsequently, die from this disease. However, this association has not been unequivocally established. Thus, the purpose of this investigation was to examine the association between male sex and COVID-19 severity. We systematically reviewed the literature, identified non-randomized studies that matched predetermined selection criteria, and performed a meta-analysis to evaluate the proportion of males among four disease severity categories. Appropriate assessment strategies were implemented to assess and minimize potential biases. The results of this meta-analysis indicated that males constituted a significantly higher proportion of those who had adverse clinical outcomes and died from COVID-19. As the coronavirus spread from the East to the West, male sex remained a consistent risk factor. Our results support the establishment of the male sex as an important risk factor for this disease. Early identification and appropriate medical care for males with lab-confirmed COVID-19 may substantially change the course of clinical prognosis, resulting in greater numbers of lives saved.

1 Introduction

Males and females have distinct biological, immunological, and endocrine differences that result in different disease processes and outcomes. Sex-specific differential gene expression and molecular-level variation have been reported to influence blood pressure, cardiovascular health, and kidney function (Convertino, 1998; Reckelhoff, 2001; Fischer et al., 2002; Kang and Miller, 2002; Sandberg and Ji, 2003; Hilliard et al., 2013). Females, in general, have a heightened capability to activate a greater and more robust immune response, offering protection against many infectious disease processes, but may predispose them to an array of autoimmune diseases (Fairweather and Rose, 2004; Pennell et al., 2012; Rubtsova et al., 2015; Klein and Flanagan, 2016; vom Steeg and Klein, 2016; Jaillon et al., 2019). Males and females also express immunological dimorphisms. Females have two X chromosomes in comparison to the XY in males. The random transcriptional inactivation of X chromosomes in females may also help offset certain mutation-related dysregulation of the immune system (Taneja, 2018). Differences in endocrine system regulation in females compared to males significantly affect disease processes including respiratory, cardiovascular, and renal disease (Hilliard et al., 2013; Blenck et al., 2016; Channappanavar et al., 2017; Palmisano et al., 2018; Vermillion et al., 2018; Wensveen et al., 2019). As nations across the world navigate their way through the Coronavirus disease 2019 (COVID-19) pandemic, clinical, research, and public health experts have observed that this disease does not affect all individuals alike.

Since the beginning of 2020, the world's healthcare professionals have tirelessly attempted to mitigate the impact of the COVID-19 pandemic. With over 3.5 million confirmed cases and 243,000 deaths worldwide as of May 5th, 2020, a post-COVID-19 pandemic era is not within the near foreseeable future (WHO, 2020). The United States, one of the epicenters for the disease, has

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documented over 1.1 million confirmed cases and 68,000 deaths related to COVID-19 (CDC, 2020; WHO, 2020). Many recent studies have highlighted certain risk factors that cause specific populations to be disproportionately susceptible to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Currently known risk factors for severe clinical outcomes of COVID-19 include: advanced age (65 years and older), chronic lung diseases, immunocompromised status, and other comorbidities such as hypertension, diabetes, and/or cardiovascular disease (Emami et al., 2020; Grasselli et al., 2020; Remuzzi and Remuzzi, 2020; Shahid et al., 2020; Zheng et al., 2020).

Observations in COVID-19 patient data involving clinical characteristics highlight specific disparities in males and females. A recent case-series study looking at COVID-19 and SARS patients showed that while males and females had the similar disease prevalence, males with COVID-19 were at higher risk for worse clinical outcomes and death (Jin et al., 2020). In this study, as the patient age and the documented comorbidities (i.e., cardiovascular diseases, diabetes, chronic lung diseases, or hypertension) increased, the risk of severity and mortality in both COVID-19 and SARS patients increased. However, the mortality rate in males was 2.4 times that of their age-matched female counterparts (70.3% and 29.7%, respectively).

Furthermore, a nationwide COVID-19 surveillance study conducted in Italy indicated that male mortality rates related to COVID-19 were disproportionately higher than that of female patients with a ratio as much as 4 to 1 (Remuzzi and Remuzzi, 2020). Other systematic reviews performed to characterize clinical features or risk factors for COVID-19, have also identified the sex-specific disparities in disease severity and mortality (Li et al., 2020a; Zheng et al., 2020). However, the clinical importance of male sex as a risk factor for COVID-19 has mainly been overlooked or explained as a potential confounder to other environmental factors such as smoking

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or tobacco product usage (Cai, 2020). While various studies have made observations of the sex-specific disparities of COVID-19, this specific relationship has not been adequately established. The sex-specific disease severity is an important clinical consideration as it affects all patient populations. Recognition of male sex as a risk factor for COVID-19 will impact both preventative measures and clinical patient management protocols.

The goal of this systematic review and meta-analysis is to identify whether males are more susceptible to COVID-19, severe forms of the disease, or mortality related to COVID-19. To address this question, we systematically reviewed the literature using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We performed a meta-analysis of the selected study populations comparing male and female COVID-19 patients. This review incorporated three online databases and research studies published between December 15th, 2019, and April 16th, 2020. We characterized the influence of sex as a risk factor for COVID-19 measuring the following clinical outcomes: all lab-confirmed cases, severe cases, critically ill cases, and mortality.

2. Methods

2.1 Literature Search and Research Study Selection

We performed a comprehensive systematic research literature search of three online databases, PubMed (LitCOVID), Embase (OVID), and Web of Science (WoS), from December 15th, 2019, to April 16th, 2020. We identified all research articles related to COVID-19 that contained any sex-specific patient or clinical characterizations. The search terms and keywords used to identify research studies for the meta-analysis were: COVID-19, male, female, men, women, sex, and gender. We reviewed references of review, perspectives, systematic reviews, and

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meta-analysis articles of the include articles to ensure comprehensiveness of our search. All our search results were evaluated using the PRISMA statement. We reviewed the abstracts and tables of each of the articles to identify the presence of sex-specific (male and female) COVID-19 case numbers.

2.2 Eligibility criteria

The inclusion criteria for research article selection was as stated below. Study population: patients with lab-confirmed COVID-19 diagnosis. Study design: case series or cross-sectional study that did not exclude any lab-confirmed COVID-19 patients. Outcomes measure: at least one outcome reported with male to female ratio among lab-confirmed clinical cases, severe cases, critical cases, and mortality. Research study: only peer-reviewed research publications were included. Commentary articles, perspectives, review articles, and surveillance reports were excluded. The following case definitions were used in this study. All cases were lab-confirmed COVID-19 patients. Severe cases were defined as having at least one of the following clinical findings: (a) breathing rate $\geq 30/\text{min}$, (b) oxygen saturation (SpO_2) $\leq 93\%$ at rest, or (c) ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) ≤ 300 mmHg. The severe case definition followed the American Thoracic Society guidelines for community-acquired pneumonia (Metlay et al., 2019). Critical cases were defined as: (a) received mechanical ventilation; (b) clinically diagnosed with shock symptoms, (c) received care in the intensive care unit (ICU) or (d) transfer to a higher level of medical care.

2.3 Data Extraction and Quality Assessment

All articles identified through the keyword search from the online databases were organized into an Excel[®] spreadsheet. Following the removal of duplicates, articles were subjected to evaluation, and five investigators did data extraction. Research studies were screened using the

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abstract and any tabulated clinical characteristics of COVID-19 patients. Directly after that, research articles were again screened to identify any discrepancies by an independent investigator. The screened articles were assessed against the study selection criteria by two independent investigators, and any differences in selected articles were revisited, and a definitive determination was made.

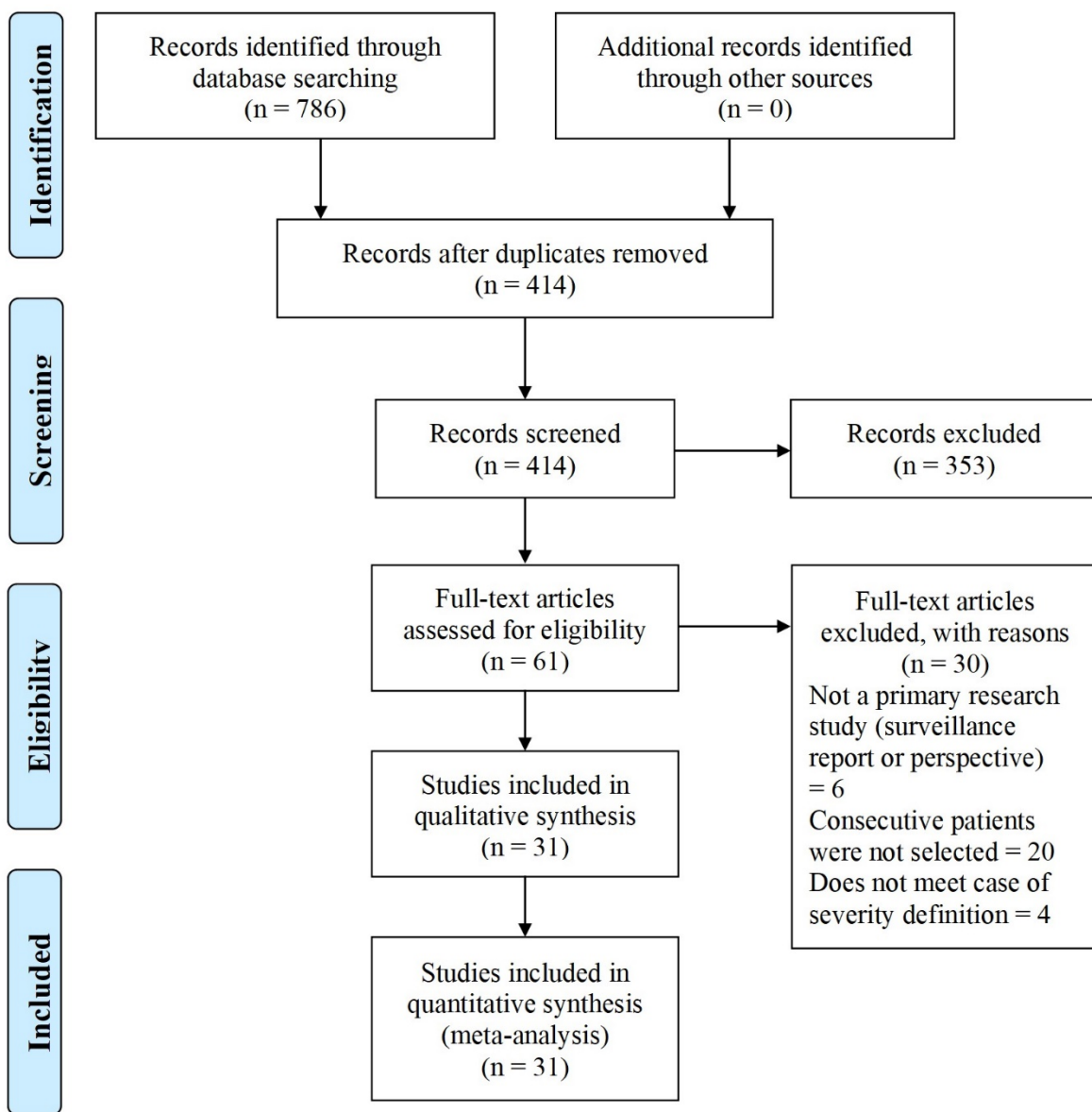


Figure 1. COVID-19 sex-specific disease severity flow diagram of the inclusion criteria of studies eligible for meta-analysis. Flow diagram template adopted from the PRISMA approach to meta-analysis (Moher et al., 2009).

2.4 Selected Study Bias Risk Assessment

A bias risk assessment was conducted on studies included in the meta-analysis utilizing the methodological index for non-randomized studies (Minors) criteria at the study level (Slim et al., 2003). Each of the selected articles was scored with 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The highest score possible was 16 for non-comparative studies according to Minors guidelines.

2.5 Statistical Analysis of Selected Data Sets

Statistical analysis was conducted using *R* (R Core Team, 2019) with the meta-analysis packages *meta* (Balduzzi et al., 2019) and *dmetar* (Harrer et al., 2019). The principal summary measures of the meta-analysis were proportions of males in four different COVID-19 categories. The four groups were: (a) all confirmed COVID-19 cases, (b) severe cases of COVID-19 as defined in Section 2.3, (c) critically ill cases of COVID-19 as defined in Section 2.3, and (d) deaths associated with COVID-19. Agresti-Coull confidence intervals were used for individual studies. Studies were combined using the inverse variance method on the raw proportions with the DerSimonian-Laird estimator for the between-groups variance estimator (τ^2) and the Jackson method for combined confidence intervals. Transformations of raw proportions were calculated for the combined estimates (*log*, *logit*, *arcsin*, and *Freeman-Tukey double arcsin*), but the results were so similar they are not shown. The proportion of variation in treatment effects was estimated with I^2 . To assess bias across studies, funnel plots were constructed for each of the four different

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categories, and Egger's bias test conducted. In order to determine if there were region-specific differences among populations in Asian and Western countries, we sub-divided the COVID-19 critically ill patient populations into these two regions and analyzed them.

2.6 Clinical Outcomes Median Age Calculation

To combine the ages, in 20 of the articles, the median age of patients was given, along with sometimes interquartile range, sometimes min and max. In 10 of the articles, mean and standard deviation (SD) were presented. In one article (Easom et al., 2020), the mean age was given without SD. We used linear regression on the other 10 (mean, SD) pairs to estimate the SD to be 14.5 years. To combine the ages, we chose to convert means to medians because there would be fewer unknown statistics to estimate, and typical disease distributions are skewed. To convert, we fit a negative binomial distribution to the mean and SD using the method of moments. With the complete list of medians, we used *R*'s *metamedian* (McGrath et al., 2020) package to obtain summarized confidence intervals for each of the four categories.

3. Results

3.1 Research Study Selection and Quality Assessment

We identified 786 research articles that matched our search terms. After the duplicated were removed, 414 unique research articles were screened. Following the screening process, 353 articles with incomplete data were excluded. We then identified 61 research articles with sex-specific case numbers and reviewed full-length articles to assess their eligibility for our study according to the selection criteria. Thirty articles did not fit the selection criteria and were excluded from the meta-analysis. Reasons for exclusion were: not a primary research study (a surveillance report or perspective), did not include consecutive patients or did not meet with the case or severity

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definitions. The 31 research articles eligible for this meta-analysis were used for qualitative synthesis and quantitative analysis (Figure 1). The 31 eligible articles were subjected to a bias assessment using the Minors criteria at the study level (Slim et al., 2003). All 31 selected articles scored between 12 and 14 points, with 16 being the highest for non-randomized controlled studies (Table 1). The relatively high scores indicated that we were likely not introducing any significant systemic biases.

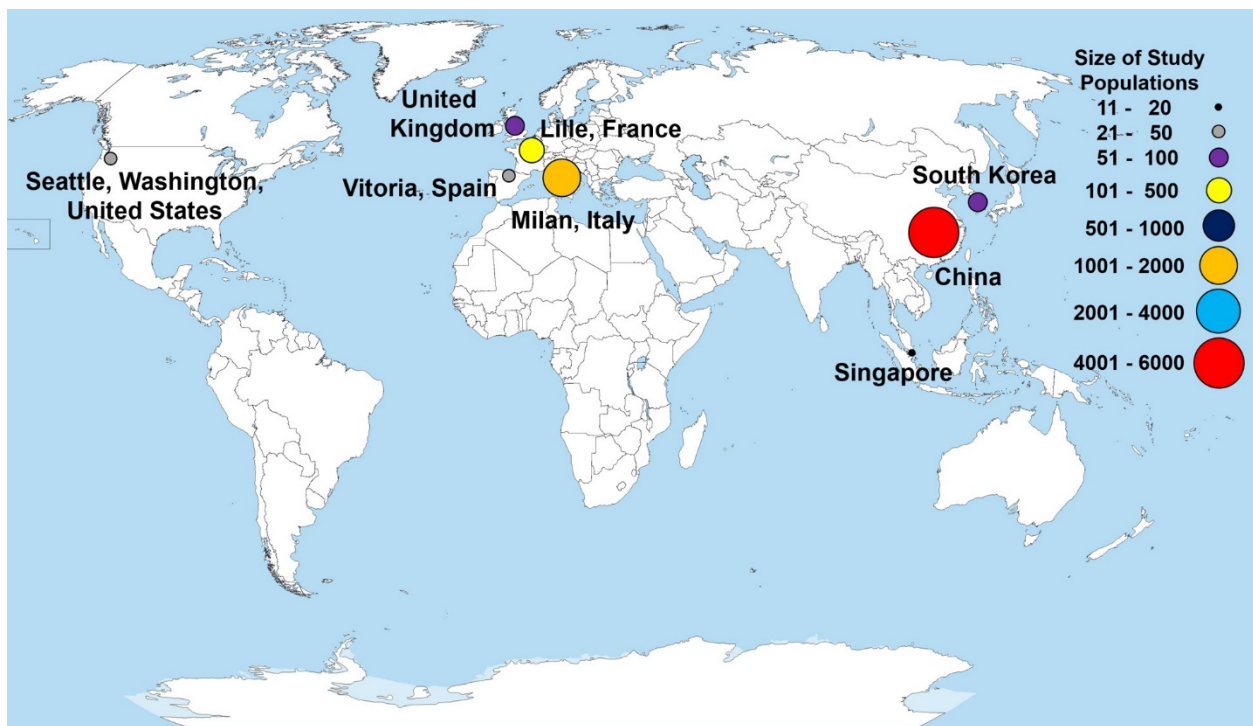


Figure 2. Countries and locations for the selected studies used in the meta-analysis. Total patient populations in each of the study locations are illustrated with a colored circle and correspond to the size of study populations. Each point represents a research study, except for China, which represents the total patient population from 24 different studies. The world map was obtained from Wikimedia Commons, the free media repository licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license.

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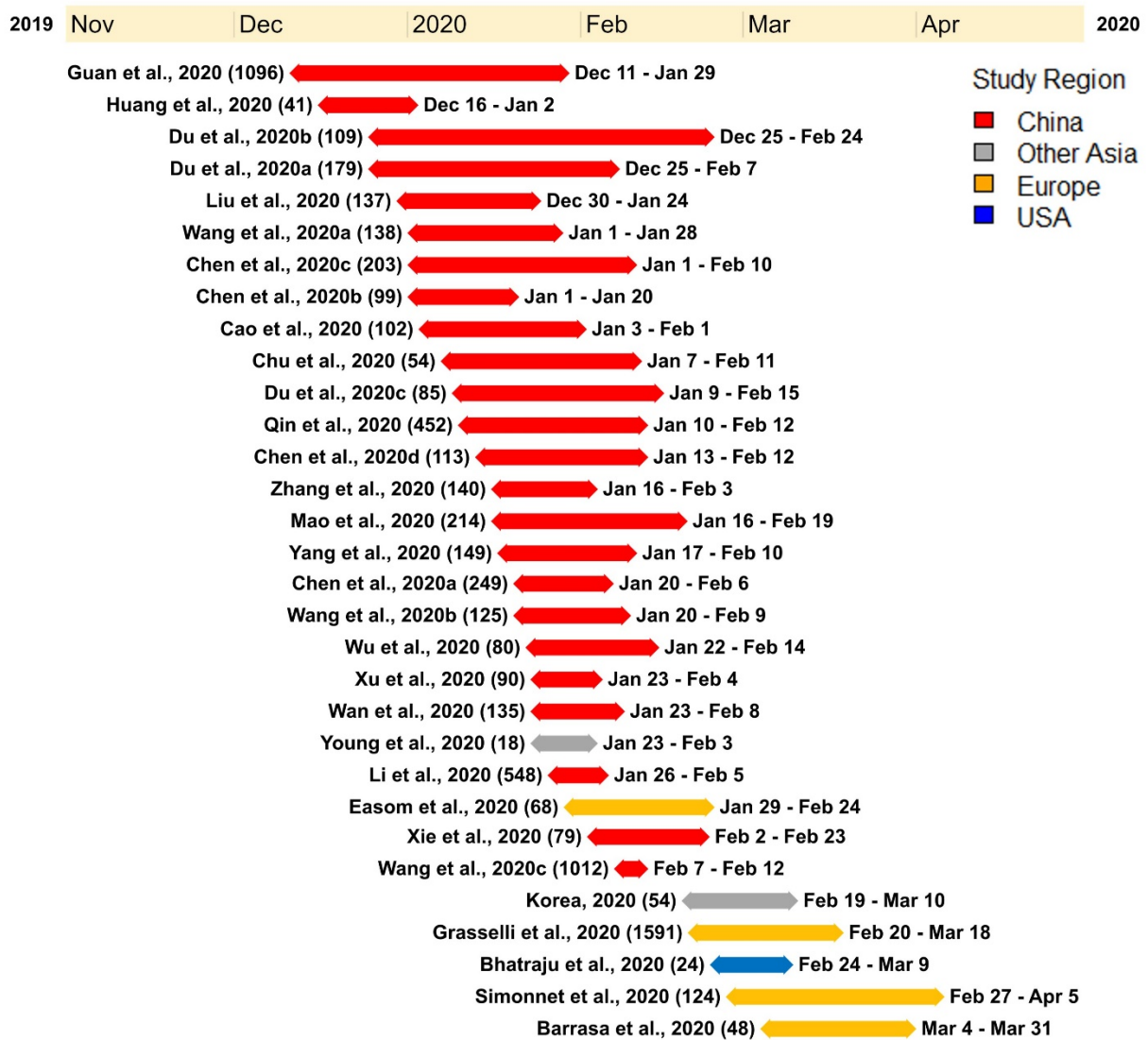


Figure 3. A timeline illustrating the study period of each of the research studies used for the meta-analysis. Each research study used for the meta-analysis is represented by the study name, (study sample), duration of the study with a line corresponding to the length of the study, and the start and end date of the study. The studies were ordered according to the start date of each study.

3.2 Study Population Demographics

Within our selected studies, 7556 lab-confirmed COVID-19 cases were identified. Of these 31 studies, 24 were from various cities in China and included a sample of 5629 lab-confirmed cases. Two studies were from South Korea and Singapore, which included a sample of 72 lab-confirmed cases. The other five studies were from Europe and North America, having a sample of 1855 lab-confirmed cases (Figure 2 and Table 2). Most of the early studies came from China with study periods from December 11th, 2019, to February 24th, 2020. Most of the later studies came from other countries with study periods from January 23rd to April 5th, 2020 (Figure 3). These patterns reflect the movement of epicenters for COVID-19 from the East to the West.

3.3 Meta-Analysis and Bias Assessment

The principal quantitative results are contained in the forest plots shown on the left side of Figures 4 and 5. The individual confidence intervals are shown, by study, with the combined proportion for each group and confidence interval at the bottom. A random-effects model was used for the combined proportion to check for heterogeneity (τ^2 = between-group variation and I^2 = proportion of total variation in the estimates of treatment effects due to heterogeneity). The heterogeneity statistics (τ^2 and I^2) are shown at the bottom left of the forest plots.

3.4 Sex-Specific COVID-19 Case Distribution

A total of 23 studies with 5408 lab-confirmed COVID-19 cases were analyzed (Table 3). Our results from the randomized effects model meta-analysis showed that in the sex-distribution of all COVID-19 cases, males accounted for 53% (95% CI [0.51, 0.55]) (Figure 4a). Female patients made up 47% of all COVID-19 cases. There is moderate heterogeneity between the set of overall population proportions ($I^2 = 64\%$, $\tau = 0.05$). A funnel plot was drawn to assess the

publication bias (Figure 4b). The publication bias test results: Egger’s test ($p = 0.88$) indicated that there was no publication bias.

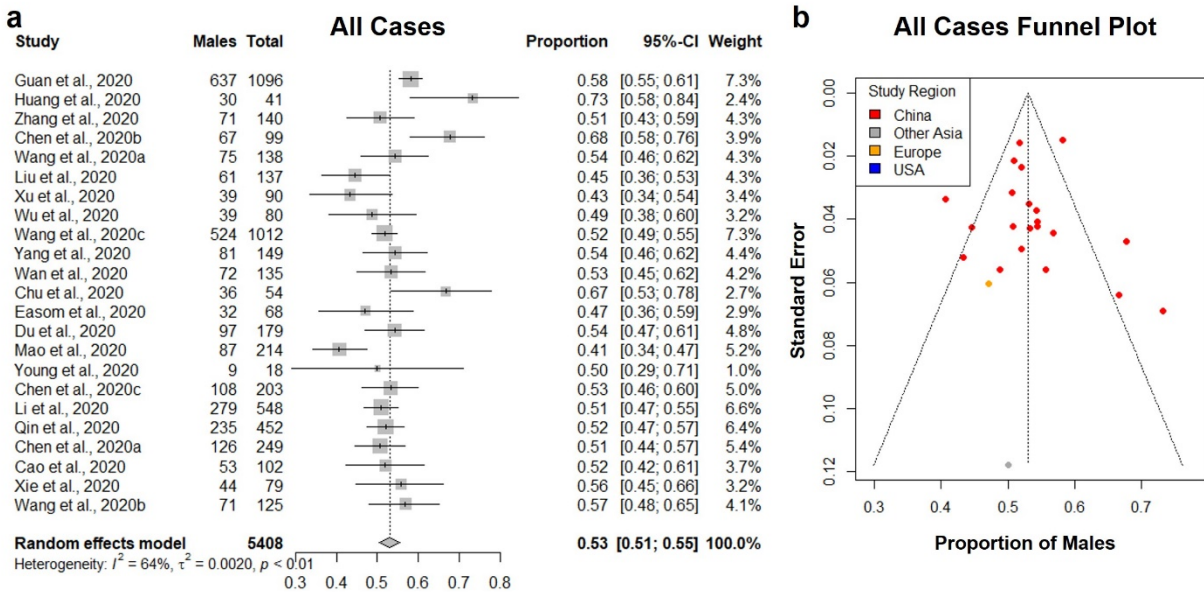


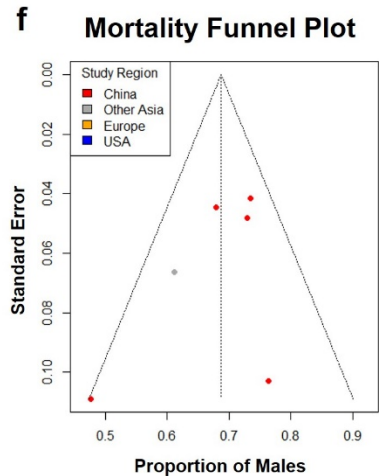
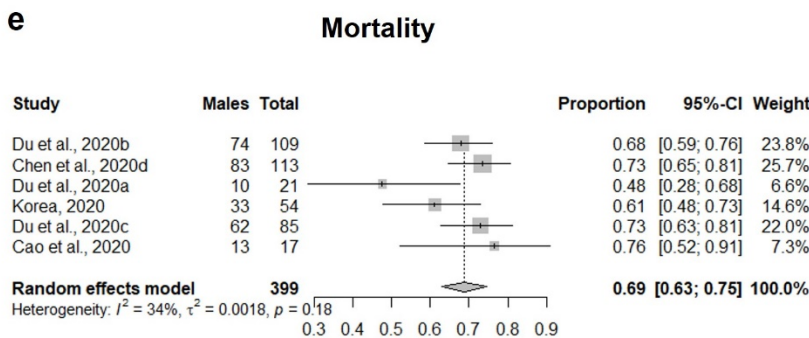
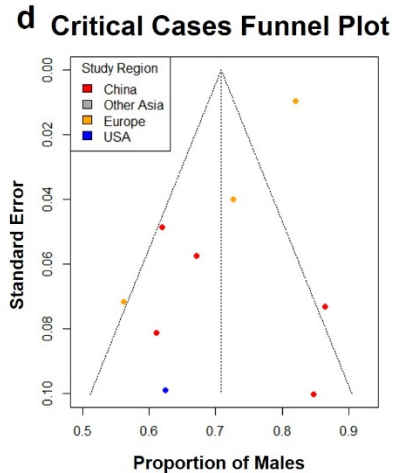
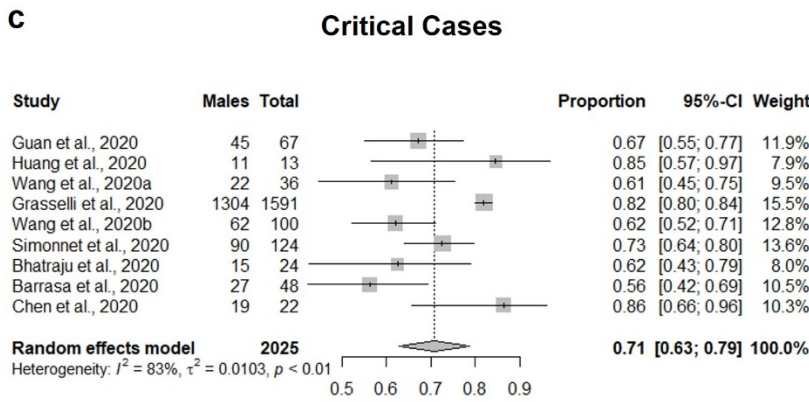
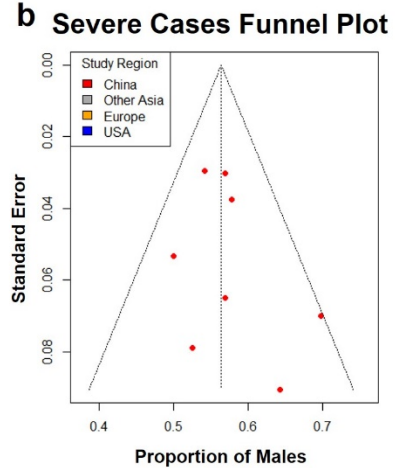
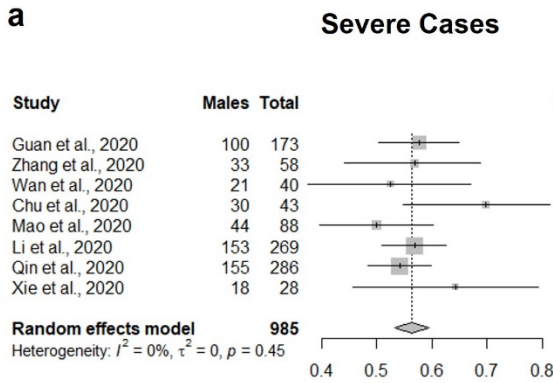
Figure 4. Proportion of males in all lab-confirmed COVID-19 cases. (a) Forest plot of sex-distribution in all lab-confirmed COVID-19 cases in each of the studies. Proportions of males and the 95% confidence intervals are indicated. (b) Funnel plot with 95% confidence region of sex-distribution in all lab-confirmed COVID-19 cases in each of the studies.

3.5 Sex-Specific COVID-19 Severe Case Distribution

A total of 8 studies with 985 severe COVID-19 cases were analyzed (Table 4). Our results from the randomized effects model meta-analysis showed that in the sex-distribution of all COVID-19 severe cases, males accounted for 56% (95% CI [0.53, 0.59]) (Figure 5a). Female patients made up 44% of all COVID-19 severe cases. There is no heterogeneity for the severe population proportions ($I^2 = 0\%$, $\tau = 0.0$). A funnel plot was drawn to assess the publication bias

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(Figure 5b). The publication bias test results: Egger's test (p -value = 0.40) indicated that there was no publication bias.



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Figure 5. Proportion of males in COVID-19 severe cases, critical cases, and mortalities. (a, c, e) Forest plot of sex-distribution in COVID-19 cases in each of the studies. Proportions of males and the 95% confidence intervals are indicated. (a) Severe cases defined as having at least one of the following clinical findings: breathing rate $\geq 30/\text{min}$, pulse oximeter oxygen saturation (SpO_2) $\leq 93\%$ at rest, or ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) ≤ 300 mmHg. (c) Critical case defined as: received mechanical ventilation, clinically diagnosed with shock, received care in the intensive care unit (ICU), or transferred to a higher level of medical care. (e) Mortality defined as all deaths in COVID-19 patients that occurred during the study period. (b, d, f) Funnel plot with 95% confidence region of sex-distribution in COVID-19 severe cases, critical cases, and mortality in each of the studies.

3.6 Sex-Specific COVID-19 Critically Ill Case Distribution

A total of 9 studies with a total of 2025 critical COVID-19 cases were analyzed (Table 5). Our results from the randomized effects model meta-analysis showed that in the sex-distribution of all COVID-19 critically ill cases, males accounted for 71% (95% CI [0.63, 0.79]) (Figure 5c). Female patients made up 29% of all COVID-19 critical cases. There was strong heterogeneity between the critical population proportions ($I^2 = 83\%$, $\tau = 0.10$). A funnel plot was drawn to assess the publication bias (Figure 5d). The publication bias test results: Egger's test (p-value = 0.02) indicated that there could be some publication bias introduced by the Grasselli et al. (2020) study.

3.7 Sex-Specific COVID-19 Mortality Distribution

A total of 6 studies with a total of 399 mortalities related to COVID-19 cases were analyzed (Table 6). Our results from the randomized effects model meta-analysis showed that in the sex-

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distribution of all COVID-19 mortalities, males accounted for 69% (95% CI [0.63, 0.75]) (Figure 5e). Female patients made up 31% of all COVID-19 mortalities. The heterogeneity for the mortality population proportions is low ($I^2 = 34\%$, $\tau = 0.04$). A funnel plot was drawn to assess the publication bias (Figure 5f). The publication bias test results: Egger's test ($p = 0.26$) indicated that there was no observable publication bias.

3.8 Sex-Specific COVID-19 Distribution in Asia and the West

Sex-specific differences in clinical outcomes of COVID-19 cases in China were thought to be related to cultural and social differences in males and females (Cai, 2020). We investigated if our study results hold in different regions of the world. COVID-19 critically ill patient data sets were divided into two groups: Asia and West, and subgroup analyses were performed.

A total of 5 studies from Asia, with a total of 238 critical COVID-19 cases were analyzed. Our results from the randomized effects model meta-analysis showed that in the sex-distribution of COVID-19 critically ill cases from Asia, males accounted for 71% (95% CI [0.61, 0.81]) (Figure 6a). Female patients made up 29% of all COVID-19 critical cases in Asia. There was moderate heterogeneity between the critical population proportions ($I^2 = 64\%$, $\tau = 0.0082$). A funnel plot was drawn to assess the publication bias in studies from Asia (Figure 6b). The publication bias test results: Egger's test ($p\text{-value} = 0.26$) indicated that there was no observable publication bias.

A total of 4 studies from Western regions with a total of 1787 critical COVID-19 cases were analyzed. Our results from the randomized effects model meta-analysis showed that in the sex-distribution of COVID-19 critically ill cases from the West, males accounted for 70% (95% CI [0.59, 0.82]) (Figure 6c). Female patients made up 30% of all COVID-19 critical cases in the West. There was strong heterogeneity between the critical population proportions ($I^2 = 86\%$, $\tau = 0.0103$). A funnel plot was drawn to assess the publication bias in studies from the West (Figure

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6b). The publication bias test results: Egger's test (p-value = 0.04) indicated that there could be some publication bias introduced by the Grasselli et al. (2020) study, as indicated previously. This comparative subgroup analysis of Asia and the West indicated that there was no geography-specific difference in the proportion of critically ill COVID-19 male patients. However, indicated by the moderate to strong heterogeneity observed, there are likely variations in male proportion between different studies and regions.

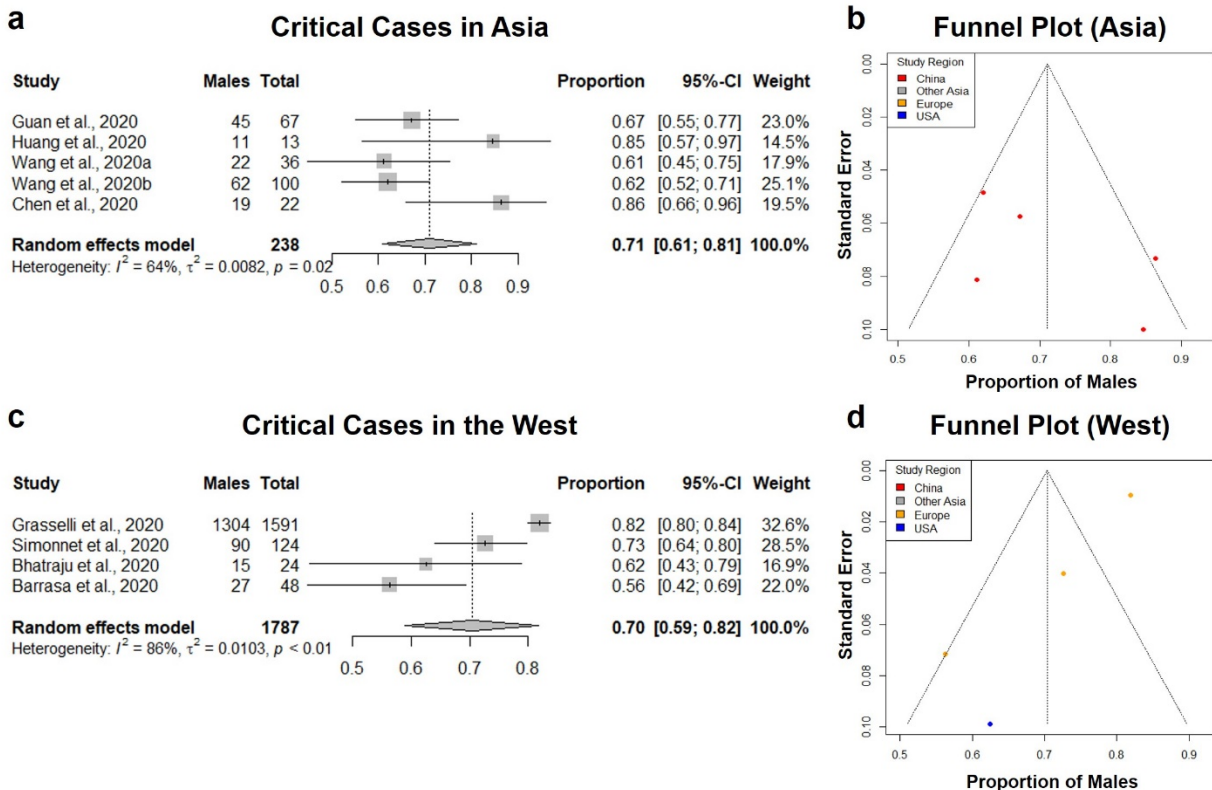


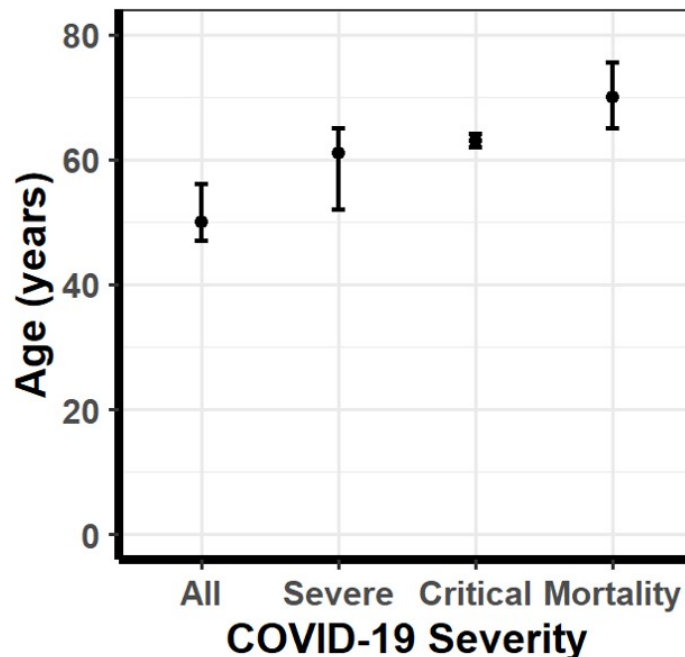
Figure 6. Comparison in the proportion of males in COVID-19 critical cases in Asia and in the West. (a, c) Forest plot of sex-distribution in COVID-19 critical cases in each of the studies. Proportions of males and the 95% confidence intervals are indicated. Critical case defined as: received mechanical ventilation, clinically diagnosed with shock, received care in the intensive care unit (ICU) or transferred to a higher level of medical care. (a) Critical cases in Asian countries.

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(c) Critical Cases in western countries. (b, d) Funnel plot with 95% confidence region of sex-distribution in COVID-19 critical cases in each of the studies.

3.9 Disease severity stratification and age distribution

When extracting male and female proportions for each of the four COVID-19 disease severity categories, we obtained the age distributions of the cases stated as a mean \pm SD or median and interquartile range (IQR). Using a skewed distribution assumption, the ages were aggregated as medians with 95% confidence intervals. The median age for all COVID-19 cases was 50, severe cases was 61, critically ill cases was 63, and mortality was 70 (Figure 7). A Kruskal-Wallis ranked-sum test conducted on the medians showed that age was significantly different between the COVID-19 disease severity groups (chi-squared = 24.07, df = 3, p-value = < 0.0001). Our data confirm that advanced age is a risk factor for more severe clinical outcomes and mortality related to COVID-19.



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Figure 7. Median age of COVID-19 patients stratified according to disease severity. Median age of COVID-19 patients in all cases, severe cases, critically ill cases, and mortalities. Error bars represent 95% confidence intervals of the median. The median age for all COVID-19 cases was 50, severe cases was 61, critically ill cases was 63, and mortality was 70. A Kruskal-Wallis ranked-sum test conducted on the medians showed that age was significantly different amount the COVID-19 disease severity groups (chi-squared = 24.07, df = 3, p-value = <0.0001).

4. Discussion

In our systematic review and meta-analysis, we set forth to address the question of whether male sex is a risk factor for COVID-19 susceptibility, severe forms of the disease, or mortality related to COVID-19. Systematically reviewing all literature from December 15th, 2019, to April 16th, 2020, we selected 31 research studies that met our selection criteria and performed a meta-analysis on COVID-19 clinical outcomes. Our quality assessment measures indicated low heterogeneity in terms of a single-arm meta-analysis, and the sensitivity analysis showed that there was minimal publication bias. As of the time of completing this manuscript, there were no randomized controlled trials with COVID-19 patients that could address this particular question. The use of non-randomized studies for the meta-analysis is a limitation of this study. However, Abraham et al. (2010) suggested that, in the absence of randomized, controlled trials, that a well-designed meta-analysis is used non-randomized controlled trials can also present a high level of evidence (Abraham et al., 2010).

The four clinical outcome categories (overall, severe, critical, mortality) exhibited different levels of heterogeneity in our random-effects models. The explanation for these differences is most likely the region of the studies done within each category. The 23 overall studies exhibited 64%

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heterogeneity with one from Singapore and one from Great Britain. The eight severe studies exhibited 0% heterogeneity, all being from China. The nine critical studies exhibited 83% heterogeneity, with five from China, three from Europe, and one from the United States. The six mortality studies exhibited 35% heterogeneity, with five from China and one from Korea. The use of a randomized effects model for our meta-analysis takes into account these heterogeneities observed between different studies and regions. Based on the random-effects models shown, there appears to be a difference in the proportions of males with COVID-19 between at least some of the studies or regions. Due to the study designs, their sampling methods, and limited regions included in this study, it is neither possible nor wise to be more specific. This is a potential avenue for further research.

Our meta-analysis showed that while males accounted for 53% of all COVID-19 cases, males accounted for an increasing proportion of severe cases (56%), critically ill cases (71%), and mortalities (69%) compared to their counterpart. While similar male to female disproportions was observed among a few other studies looking at clinical characteristics of COVID-19, our study provides a comprehensive synthesis of data available across different world regions. This study helps establish male sex as a risk factor for COVID-19 clinical outcomes and shows that it is consistent in Asia and Western regions.

This study results do not come as a surprise. Several studies conducted on the two previous coronavirus epidemics, SARS CoV-1 in 2002-2003 and MERS in 2012-2013, showed similar patterns with a male predominance toward greater severity and mortality risks. Studies on mortality rates during the MERS-CoV epidemic showed the male sex to be a risk factor (Matsuyama et al., 2016; Nam et al., 2017; Park et al., 2018). Epidemiological studies with SARS-CoV-1 showed similar patterns (Karlberg et al., 2004). To further support previous

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epidemiological observations, in controlled mouse model experiments, SARS-CoV-1 has displayed infectious dose-dependent higher mortality rates in male mice compared to female mice (Channappanavar et al., 2017). The mounting amount of evidence showing differences among males and female clinical outcomes to coronavirus infections highlights the importance of patient sex in determining the COVID-19 prognosis.

From a clinical standpoint, this information is very pertinent to the practice of patient care. As COVID-19 clinical outcomes are strongly associated with male sex, this can help guide preventative and treatment strategies. Male patients will likely warrant more aggressive inpatient care measures, and especially those that have other COVID-19 risk factors such as advanced age or underlying comorbidities. Susceptible males with other known risk factors may need to take extra precautions to help prevent SARS-CoV-2 infection. Infected males can be encouraged to obtain medical care at an earlier stage of the disease. In cases that require hospitalization, physicians can be more aggressive in their medical management of male patients.

In addition to preventative and COVID-19 treatment measures, this presents a unique clinical opportunity to address male and female differences at the molecular level, immunological response, and endocrine function (Sandberg and Ji, 2003; vom Steeg and Klein, 2016; Taneja, 2018). For example, SARS-CoV-2 binds to the Angiotensin-converting enzyme 2 (ACE2) receptors and use it as a mechanism for host cell entry (Hoffmann et al., 2020). Males have been shown to express more ACE2 receptors within the renin-angiotensin-aldosterone system (RAAS) (Komukai et al., 2010). This is likely to play an essential role in the severity of this disease observed in males (Komukai et al., 2010). Differences in male and female immunological responses will also be a clinically significant factor that can be appropriately modulated to better serve COVID-19 patients (Pennell et al., 2012; Jaillon et al., 2019). Besides sex-specific

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differences in immunological responses, hormonal regulation and the role of estrogen and testosterone in priming the ACE2 receptor sensitivity could hold the key to better explain the higher COVID-19 severity and mortality rates observed in males (Mishra et al., 2016; Bukowska et al., 2017). In an age of personalized medicine, if molecular level of differences in the disease processes of SARS-CoV-2 infection can be characterized, clinicians can use targeted therapy using to promote health equality and help save more patient lives.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

TG led the systematic review, helped prepare the tables and figure, and aided in writing and editing. BMP aided in the analytical evaluation of curated articles, writing, and editing. JA, AB, and DR research students analyzed data and joined in discussions. JW performed statistical analyses; drafted statistical sections. RSG conceptualized the problem and aided in writing and editing.

Supplementary Material

Supplementary Materials are provided as a separate file.

References

- Abraham, N.S., Byrne, C.J., Young, J.M., and Solomon, M.J. (2010). Meta-analysis of well-designed nonrandomized comparative studies of surgical procedures is as good as randomized controlled trials. *J Clin Epidemiol* 63(3), 238-245. doi: 10.1016/j.jclinepi.2009.04.005.
- Balduzzi, S., Rucker, G., and Schwarzer, G. (2019). How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* 22(4), 153-160. doi: 10.1136/ebmental-2019-300117.
- Barrasa, H., Rello, J., Tejada, S., Martín, A., Balziskueta, G., Vinuesa, C., et al. (2020). SARS-Cov-2 in Spanish Intensive Care: Early Experience with 15-day Survival In Vitoria. *Anaesth Crit Care Pain Med*. doi: 10.1016/j.accpm.2020.04.001.
- Bhatraju, P.K., Ghassemieh, B.J., Nichols, M., Kim, R., Jerome, K.R., Nalla, A.K., et al. (2020). Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. *N Engl J Med*. doi: 10.1056/NEJMoa2004500.
- Blenck, C.L., Harvey, P.A., Reckelhoff, J.F., and Leinwand, L.A. (2016). The Importance of Biological Sex and Estrogen in Rodent Models of Cardiovascular Health and Disease. *Circ Res* 118(8), 1294-1312. doi: 10.1161/circresaha.116.307509.
- Bukowska, A., Spiller, L., Wolke, C., Lendeckel, U., Weinert, S., Hoffmann, J., et al. (2017). Protective regulation of the ACE2/ACE gene expression by estrogen in human atrial tissue from elderly men. *Exp Biol Med (Maywood)* 242(14), 1412-1423. doi: 10.1177/1535370217718808.
- Cai, H. (2020). Sex difference and smoking predisposition in patients with COVID-19. *Lancet Respir Med* 8(4), e20. doi: 10.1016/s2213-2600(20)30117-x.
- Cao, J., Tu, W.J., Cheng, W., Yu, L., Liu, Y.K., Hu, X., et al. (2020). Clinical Features and Short-term Outcomes of 102 Patients with Corona Virus Disease 2019 in Wuhan, China. *Clin Infect Dis*. doi: 10.1093/cid/ciaa243.
- CDC (2020). *Coronavirus Disease 2019 (COVID-19) Cases in the U.S.* [Online]. Available: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html> [Accessed May 6th, 2020].
- Channappanavar, R., Fett, C., Mack, M., Ten Eyck, P.P., Meyerholz, D.K., and Perlman, S. (2017). Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. *J Immunol* 198(10), 4046-4053. doi: 10.4049/jimmunol.1601896.
- Chen, J., Qi, T., Liu, L., Ling, Y., Qian, Z., Li, T., et al. (2020a). Clinical progression of patients with COVID-19 in Shanghai, China. *J Infect* 80(5), e1-e6. doi: 10.1016/j.jinf.2020.03.004.
- Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., et al. (2020b). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395(10223), 507-513. doi: 10.1016/s0140-6736(20)30211-7.
- Chen, T., Dai, Z., Mo, P., Li, X., Ma, Z., Song, S., et al. (2020c). Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China

COVID-19 Sex-Specific Clinical Outcomes

- (2019): a single-centered, retrospective study. *J Gerontol A Biol Sci Med Sci*. doi: 10.1093/gerona/glaa089.
- Chen, T., Wu, D., Chen, H., Yan, W., Yang, D., Chen, G., et al. (2020d). Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *Bmj* 368, m1091. doi: 10.1136/bmj.m1091.
- Chu, J., Yang, N., Wei, Y., Yue, H., Zhang, F., Zhao, J., et al. (2020). Clinical characteristics of 54 medical staff with COVID-19: A retrospective study in a single center in Wuhan, China. *J Med Virol*. doi: 10.1002/jmv.25793.
- Convertino, V.A. (1998). Gender differences in autonomic functions associated with blood pressure regulation. *Am J Physiol* 275(6), R1909-1920. doi: 10.1152/ajpregu.1998.275.6.R1909.
- Du, R.H., Liang, L.R., Yang, C.Q., Wang, W., Cao, T.Z., Li, M., et al. (2020a). Predictors of Mortality for Patients with COVID-19 Pneumonia Caused by SARS-CoV-2: A Prospective Cohort Study. *Eur Respir J*. doi: 10.1183/13993003.00524-2020.
- Du, R.H., Liu, L.M., Yin, W., Wang, W., Guan, L.L., Yuan, M.L., et al. (2020b). Hospitalization and Critical Care of 109 Decedents with COVID-19 Pneumonia in Wuhan, China. *Ann Am Thorac Soc*. doi: 10.1513/AnnalsATS.202003-225OC.
- Du, Y., Tu, L., Zhu, P., Mu, M., Wang, R., Yang, P., et al. (2020c). Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study. *Am J Respir Crit Care Med*. doi: 10.1164/rccm.202003-0543OC.
- Easom, N., Moss, P., Barlow, G., Samson, A., Taynton, T., Adams, K., et al. (2020). Sixty-eight consecutive patients assessed for COVID-19 infection: Experience from a UK Regional infectious diseases Unit. *Influenza Other Respir Viruses*. doi: 10.1111/irv.12739.
- Emami, A., Javanmardi, F., Pirbonyeh, N., and Akbari, A. (2020). Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis. *Arch Acad Emerg Med* 8(1), e35.
- Fairweather, D., and Rose, N.R. (2004). Women and autoimmune diseases. *Emerg Infect Dis* 10(11), 2005-2011. doi: 10.3201/eid1011.040367.
- Fischer, M., Baessler, A., and Schunkert, H. (2002). Renin angiotensin system and gender differences in the cardiovascular system. *Cardiovasc Res* 53(3), 672-677. doi: 10.1016/s0008-6363(01)00479-5.
- Grasselli, G., Zangrillo, A., Zanella, A., Antonelli, M., Cabrini, L., Castelli, A., et al. (2020). Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *Jama*. doi: 10.1001/jama.2020.5394.
- Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., He, J.X., et al. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. doi: 10.1056/NEJMoa2002032.
- Harrer, M., Cuijpers, P., Furukawa, T., and Ebert, D.D. (2019). *dmatar: Companion R Package For The Guide 'Doing Meta-Analysis in R'. R package version 0.0.9000*. [Online]. Available: <http://dmatar.protectlab.org> [Accessed May 8th, 2020].

COVID-19 Sex-Specific Clinical Outcomes

- Hilliard, L.M., Sampson, A.K., Brown, R.D., and Denton, K.M. (2013). The "his and hers" of the renin-angiotensin system. *Curr Hypertens Rep* 15(1), 71-79. doi: 10.1007/s11906-012-0319-y.
- Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., et al. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 181(2), 271-280.e278. doi: 10.1016/j.cell.2020.02.052.
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., et al. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395(10223), 497-506. doi: 10.1016/s0140-6736(20)30183-5.
- Jaillon, S., Berthenet, K., and Garlanda, C. (2019). Sexual Dimorphism in Innate Immunity. *Clin Rev Allergy Immunol* 56(3), 308-321. doi: 10.1007/s12016-017-8648-x.
- Jin, J.-M., Bai, P., He, W., Wu, F., Liu, X.-F., Han, D.-M., et al. (2020). Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Frontiers in Public Health* 8(152). doi: 10.3389/fpubh.2020.00152.
- Kang, A.K., and Miller, J.A. (2002). Effects of gender on the renin-angiotensin system, blood pressure, and renal function. *Curr Hypertens Rep* 4(2), 143-151. doi: 10.1007/s11906-002-0039-9.
- Karlberg, J., Chong, D.S., and Lai, W.Y. (2004). Do men have a higher case fatality rate of severe acute respiratory syndrome than women do? *Am J Epidemiol* 159(3), 229-231. doi: 10.1093/aje/kwh056.
- Klein, S.L., and Flanagan, K.L. (2016). Sex differences in immune responses. *Nat Rev Immunol* 16(10), 626-638. doi: 10.1038/nri.2016.90.
- Komukai, K., Mochizuki, S., and Yoshimura, M. (2010). Gender and the renin-angiotensin-aldosterone system. *Fundam Clin Pharmacol* 24(6), 687-698. doi: 10.1111/j.1472-8206.2010.00854.x.
- Korea, C. (2020). Analysis on 54 Mortality Cases of Coronavirus Disease 2019 in the Republic of Korea from January 19 to March 10, 2020. *J Korean Med Sci* 35(12), e132. doi: 10.3346/jkms.2020.35.e132.
- Li, L.Q., Huang, T., Wang, Y.Q., Wang, Z.P., Liang, Y., Huang, T.B., et al. (2020a). COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol*. doi: 10.1002/jmv.25757.
- Li, X., Xu, S., Yu, M., Wang, K., Tao, Y., Zhou, Y., et al. (2020b). Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol*. doi: 10.1016/j.jaci.2020.04.006.
- Liu, K., Fang, Y.Y., Deng, Y., Liu, W., Wang, M.F., Ma, J.P., et al. (2020). Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)*. doi: 10.1097/cm9.0000000000000744.
- Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., et al. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. doi: 10.1001/jamaneurol.2020.1127.

COVID-19 Sex-Specific Clinical Outcomes

- Matsuyama, R., Nishiura, H., Kutsuna, S., Hayakawa, K., and Ohmagari, N. (2016). Clinical determinants of the severity of Middle East respiratory syndrome (MERS): a systematic review and meta-analysis. *BMC Public Health* 16(1), 1203. doi: 10.1186/s12889-016-3881-4.
- McGrath, S., Zhao, X., Steele, R., Thombs, B.D., and Benedetti, A. (2020). Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. *Stat Methods Med Res*, 962280219889080. doi: 10.1177/0962280219889080.
- Metlay, J.P., Waterer, G.W., Long, A.C., Anzueto, A., Brozek, J., Crothers, K., et al. (2019). Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 200(7), e45-e67. doi: 10.1164/rccm.201908-1581ST.
- Mishra, J.S., Hankins, G.D., and Kumar, S. (2016). Testosterone downregulates angiotensin II type-2 receptor via androgen receptor-mediated ERK1/2 MAP kinase pathway in rat aorta. *J Renin Angiotensin Aldosterone Syst* 17(4). doi: 10.1177/1470320316674875.
- Moher, D., Liberati, A., Tetzlaff, J., and Altman, D.G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6(7), e1000097. doi: 10.1371/journal.pmed.1000097.
- Nam, H.S., Park, J.W., Ki, M., Yeon, M.Y., Kim, J., and Kim, S.W. (2017). High fatality rates and associated factors in two hospital outbreaks of MERS in Daejeon, the Republic of Korea. *Int J Infect Dis* 58, 37-42. doi: 10.1016/j.ijid.2017.02.008.
- Palmisano, B.T., Zhu, L., Eckel, R.H., and Stafford, J.M. (2018). Sex differences in lipid and lipoprotein metabolism. *Mol Metab* 15, 45-55. doi: 10.1016/j.molmet.2018.05.008.
- Park, J.E., Jung, S., Kim, A., and Park, J.E. (2018). MERS transmission and risk factors: a systematic review. *BMC Public Health* 18(1), 574. doi: 10.1186/s12889-018-5484-8.
- Pennell, L.M., Galligan, C.L., and Fish, E.N. (2012). Sex affects immunity. *J Autoimmun* 38(2-3), J282-291. doi: 10.1016/j.jaut.2011.11.013.
- Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., et al. (2020). Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. doi: 10.1093/cid/ciaa248.
- R_Core_Team (2019). *A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. [Online]. Available: <https://www.R-project.org/> [Accessed May 8th, 2020].
- Reckelhoff, J.F. (2001). Gender differences in the regulation of blood pressure. *Hypertension* 37(5), 1199-1208. doi: 10.1161/01.hyp.37.5.1199.
- Remuzzi, A., and Remuzzi, G. (2020). COVID-19 and Italy: what next? *Lancet* 395(10231), 1225-1228. doi: 10.1016/s0140-6736(20)30627-9.
- Rubtsova, K., Marrack, P., and Rubtsov, A.V. (2015). Sexual dimorphism in autoimmunity. *J Clin Invest* 125(6), 2187-2193. doi: 10.1172/jci78082.

COVID-19 Sex-Specific Clinical Outcomes

- Sandberg, K., and Ji, H. (2003). Sex and the renin angiotensin system: implications for gender differences in the progression of kidney disease. *Adv Ren Replace Ther* 10(1), 15-23. doi: 10.1053/jarr.2003.50006.
- Shahid, Z., Kalayanamitra, R., McClafferty, B., Kepko, D., Ramgobin, D., Patel, R., et al. (2020). COVID-19 and Older Adults: What We Know. *J Am Geriatr Soc*. doi: 10.1111/jgs.16472.
- Simonnet, A., Chetboun, M., Poissy, J., Raverdy, V., Noulette, J., Duhamel, A., et al. (2020). High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity (Silver Spring)*. doi: 10.1002/oby.22831.
- Slim, K., Nini, E., Forestier, D., Kwiatkowski, F., Panis, Y., and Chipponi, J. (2003). Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 73(9), 712-716. doi: 10.1046/j.1445-2197.2003.02748.x.
- Taneja, V. (2018). Sex Hormones Determine Immune Response. *Front Immunol* 9, 1931. doi: 10.3389/fimmu.2018.01931.
- Vermillion, M.S., Ursin, R.L., Attreed, S.E., and Klein, S.L. (2018). Estriol Reduces Pulmonary Immune Cell Recruitment and Inflammation to Protect Female Mice From Severe Influenza. *Endocrinology* 159(9), 3306-3320. doi: 10.1210/en.2018-00486.
- vom Steeg, L.G., and Klein, S.L. (2016). Sex Matters in Infectious Disease Pathogenesis. *PLoS Pathog* 12(2), e1005374. doi: 10.1371/journal.ppat.1005374.
- Wan, S., Xiang, Y., Fang, W., Zheng, Y., Li, B., Hu, Y., et al. (2020). Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol*. doi: 10.1002/jmv.25783.
- Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., et al. (2020a). Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama*. doi: 10.1001/jama.2020.1585.
- Wang, R., Pan, M., Zhang, X., Fan, X., Han, M., Zhao, F., et al. (2020b). Epidemiological and clinical features of 125 Hospitalized Patients with COVID-19 in Fuyang, Anhui, China. *Int J Infect Dis*. doi: 10.1016/j.ijid.2020.03.070.
- Wang, X., Fang, J., Zhu, Y., Chen, L., Ding, F., Zhou, R., et al. (2020c). Clinical characteristics of non-critically ill patients with novel coronavirus infection (COVID-19) in a Fangcang Hospital. *Clin Microbiol Infect*. doi: 10.1016/j.cmi.2020.03.032.
- Wensveen, F.M., Šestan, M., Turk Wensveen, T., and Polić, B. (2019). 'Beauty and the beast' in infection: How immune-endocrine interactions regulate systemic metabolism in the context of infection. *Eur J Immunol* 49(7), 982-995. doi: 10.1002/eji.201847895.
- WHO (2020). *Coronavirus disease (COVID-19) Situation Report 106* [Online]. Available: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports> [Accessed May 6th, 2020].
- Wu, J., Liu, J., Zhao, X., Liu, C., Wang, W., Wang, D., et al. (2020). Clinical Characteristics of Imported Cases of COVID-19 in Jiangsu Province: A Multicenter Descriptive Study. *Clin Infect Dis*. doi: 10.1093/cid/ciaa199.

COVID-19 Sex-Specific Clinical Outcomes

- Xie, H., Zhao, J., Lian, N., Lin, S., Xie, Q., and Zhuo, H. (2020). Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: A retrospective study. *Liver Int.* doi: 10.1111/liv.14449.
- Xu, X., Yu, C., Qu, J., Zhang, L., Jiang, S., Huang, D., et al. (2020). Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. *Eur J Nucl Med Mol Imaging* 47(5), 1275-1280. doi: 10.1007/s00259-020-04735-9.
- Yang, W., Cao, Q., Qin, L., Wang, X., Cheng, Z., Pan, A., et al. (2020). Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. *J Infect* 80(4), 388-393. doi: 10.1016/j.jinf.2020.02.016.
- Young, B.E., Ong, S.W.X., Kalimuddin, S., Low, J.G., Tan, S.Y., Loh, J., et al. (2020). Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *Jama* 323(15), 1488-1494. doi: 10.1001/jama.2020.3204.
- Zhang, J.J., Dong, X., Cao, Y.Y., Yuan, Y.D., Yang, Y.B., Yan, Y.Q., et al. (2020). Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. doi: 10.1111/all.14238.
- Zheng, Z., Peng, F., Xu, B., Zhao, J., Liu, H., Peng, J., et al. (2020). Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *J Infect*. doi: 10.1016/j.jinf.2020.04.021.

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Tables

Table 1. Bias risk assessment on the studies included in the meta-analysis using the methodological index for non-randomized studies (Minors) criteria (Slim et al., 2003).

Study Reference	Study Population	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	Score
Barrasa et al., 2020	48	2	2	2	2	2	2	2	0	14
Bhatraju et al., 2020	24	2	2	2	2	2	1	1	0	12
Cao et al., 2020	102	2	2	2	2	2	1	1	0	12
Chen et al., 2020a	249	2	2	2	2	2	1	1	0	12
Chen et al., 2020b	99	2	2	2	2	2	2	2	0	14
Chen et al., 2020c	203	2	2	2	2	2	2	2	0	14
Chen et al., 2020d	113	2	2	2	2	2	1	2	0	13
Chu et al., 2020	54	2	2	2	2	2	1	1	0	12
Du et al., 2020a	179	2	2	2	2	2	2	1	0	13
Du et al., 2020b	109	2	2	2	2	2	2	2	0	14
Du et al., 2020c	85	2	2	2	2	2	2	2	0	14
Easom et al., 2020	68	2	2	2	2	2	2	2	0	14
Grasselli et al., 2020	1591	2	2	2	2	2	2	2	0	14
Guan et al., 2020	1096	2	2	2	2	2	1	1	0	12
Huang et al., 2020	41	2	2	2	2	2	1	1	0	12
Korea, 2020	54	2	2	2	2	2	2	2	0	14
Li et al., 2020b	548	2	2	2	2	2	1	2	0	13
Liu et al., 2020	137	2	2	2	2	2	2	2	0	14
Mao et al., 2020	214	2	2	2	2	2	1	1	0	12
Qin et al., 2020	452	2	2	2	2	2	1	1	0	12
Simonnet et al., 2020	85	2	2	2	2	2	1	1	0	12
Wan et al., 2020	135	2	2	2	2	2	1	1	0	12
Wang et al., 2020a	138	2	2	2	2	2	1	1	0	12
Wang et al., 2020b	125	2	2	2	2	2	2	2	0	12
Wang et al., 2020c	1012	2	2	2	2	2	1	2	0	13
Wu et al., 2020	80	2	2	2	2	2	2	2	0	14
Xie et al., 2020	79	2	2	2	2	2	1	1	0	12
Xu et al., 2020	90	2	2	2	2	2	2	2	0	14
Yang et al., 2020	149	2	2	2	2	2	2	2	0	14
Young et al., 2020	18	2	2	2	2	2	2	2	0	14
Zhang et al., 2020	140	2	2	2	2	2	1	1	0	12

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(1) A clearly stated aim; (2) Inclusion of consecutive patients; (3) Prospective collection of data; (4) Endpoints appropriate to the aim of the study; (5) Unbiased assessment of the study endpoint; (6) Follow-up period appropriate to the aim of the study; (7) Loss to follow-up less than 5%; (8) Prospective calculation of the study size. The items are scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies.

Table 2. Demographics of all studies included in the meta-analysis with sex-specific disease severity.

Study Reference	Country (City or Province)	Study Population	Age ¹ (<i>mean</i> or median)	All cases ² (male %)	Severe cases ³ (male %)	Critical cases ⁴ (male %)	Mortality (male %)
Barrasa et al., 2020	Spain (Vitoria)	48	63.2	-	-	56.3	-
Bhatraju et al., 2020	United States (Seattle)	24	64.0	-	-	62.5	-
Cao et al., 2020	China (Wuhan)	102	54.0	52.0	-	-	76.5
Chen et al., 2020a	China (Shanghai)	249	51.0	50.6	-	86.4	-
Chen et al., 2020b	China (Wuhan)	99	55.5	67.7	-	-	-
Chen et al., 2020c	China (Wuhan)	203	54.0	53.2	-	-	-
Chen et al., 2020d	China (Wuhan)	113	68.0	-	-	-	73.5
Chu et al., 2020	China (Wuhan)	54	39.0	66.7	69.8	-	-
Du et al., 2020a	China (Wuhan)	179	57.6	54.2	-	-	47.6
Du et al., 2020b	China (Wuhan)	109	70.7	-	-	-	67.9
Du et al., 2020c	China (Wuhan)	85	65.8	-	-	-	72.9
Easom et al., 2020	United Kingdom	68	42.5	47.1	-	-	-
Grasselli et al., 2020	Italy (Milan)	1591	63.0	-	-	82.0	-
Guan et al., 2020	China	1096	47.0	58.1	57.8	67.2	-
Huang et al., 2020	China (Wuhan)	41	49.0	73.2	-	84.6	-
Korea, 2020	South Korea	54	75.5	-	-	-	61.1
Li et al., 2020b	China (Wuhan)	548	60.0	50.9	56.9	-	-
Liu et al., 2020	China (Wuhan)	137	57.0	44.5	-	-	-
Mao et al., 2020	China (Wuhan)	214	52.7	40.7	50.0	-	-
Qin et al., 2020	China (Wuhan)	452	58.0	52.0	54.2	-	-
Simonnet et al., 2020	France (Lille)	124	60	-	-	72.6	-
Wan et al., 2020	China (Chongqing)	135	47.0	53.3	52.5	-	-
Wang et al., 2020a	China (Wuhan)	138	56.0	54.3	-	61.1	-
Wang et al., 2020b	China (Fuyang)	125	38.8	56.8	-	-	-

COVID-19 Sex-Specific Clinical Outcomes

Study Reference	Country (City or Province)	Study Population	Age ¹ (<i>mean</i> or median)	All cases ² (male %)	Severe cases ³ (male %)	Critical cases ⁴ (male %)	Mortality (male %)
Wang et al., 2020c	China (Wuhan)	1012	50.0	51.8	-	62.0	-
Wu et al., 2020	China (Jiangsu)	80	<i>46.1</i>	48.8	-	-	-
Xie et al., 2020	China (Wuhan)	79	60.0	55.7	64.3	-	-
Xu et al., 2020	China (Wuhan)	90	50.0	43.3	-	-	-
Yang et al., 2020	China (Wenzhou)	149	<i>45.1</i>	54.4	-	-	-
Young et al., 2020	Singapore	18	47.0	50.0	-	-	-
Zhang et al., 2020	China (Wuhan)	140	57.0	50.7	56.9	-	-

¹ Mean or median age of the study population for each research study. In the event a study had a severity or mortality sub-population, age is listed for only the total study population. Mean ages are indicated in *italics*.

² All consecutive patients with lab confirmed case of COVID-19 within the study period.

³ Severe case defined as having at least one of the following clinical findings: (a) breathing rate ≥ 30 /min, (b) pulse oximeter oxygen saturation (SpO₂) $\leq 93\%$ at rest, or (c) ratio of partial pressure of arterial oxygen (PaO₂) to fraction of inspired oxygen (FiO₂) ≤ 300 mmHg

⁴ Critical case defined as: (a) received mechanical ventilation; (b) clinically diagnosed with shock, (c) received care in the intensive care unit (ICU) or (d) transferred to a higher level of medical care

COVID-19 Sex-Specific Clinical Outcomes

Table 3. All confirmed cases of COVID-19 included in the meta-analysis.

Study Reference	Age ¹ (<i>mean</i> or median)	Total number of cases ²	Number of male cases	Number of female cases	All cases (male %)
Cao et al., 2020	54.0	102	53	49	52.0
Chen et al., 2020a	51.0	249	126	123	50.6
Chen et al., 2020b	55.5	99	67	32	67.7
Chen et al., 2020c	54.0	203	108	95	53.2
Chu et al., 2020	39.0	54	36	18	66.7
Du et al., 2020a	57.6	179	97	82	54.2
Easom et al., 2020	42.4	68	32	36	47.1
Guan et al., 2020	47.0	1096	637	459	58.1
Huang et al., 2020	49.0	41	30	11	73.2
Li et al., 2020b	60.0	548	279	269	50.9
Liu et al., 2020	57.0	137	61	76	44.5
Mao et al., 2020	52.7	214	87	127	40.7
Qin et al., 2020	58.0	452	235	217	52.0
Wan et al., 2020	47.0	135	72	63	53.3
Wang et al., 2020a	56.0	138	75	63	54.3
Wang et al., 2020b	38.8	125	71	54	56.8
Wang et al., 2020c	50.0	1012	524	488	51.8
Wu et al., 2020	46.1	80	39	41	48.8
Xie et al., 2020	60.0	79	44	35	55.7
Xu et al., 2020	50.0	90	39	51	43.3
Yang et al., 2020	45.1	149	81	68	54.4
Young et al., 2020	47.0	18	9	9	50.0
Zhang et al., 2020	57.0	140	71	69	50.7

¹ Mean or median age of the study population reported by each research study. Mean ages are indicated in *italics*.

² All consecutive patients with lab-confirmed case of COVID-19 within the study period.

COVID-19 Sex-Specific Clinical Outcomes

Table 4. All severe cases of COVID-19 included in the meta-analysis.

Study Reference	Age ¹ (<i>mean</i> or median)	Total no. of severe cases ²	No. of male severe cases	No. of female severe cases	Severe cases (male %)
Chu et al., 2020	38.0	43	30	13	69.8
Guan et al., 2020	52.0	173	100	73	57.8
Li et al., 2020b	65.0	269	153	116	56.9
Mao et al., 2020	58.2	88	44	44	50.0
Qin et al., 2020	61.0	286	155	131	54.2
Wan et al., 2020	56.0	40	21	19	52.5
Xie et al., 2020	62.5	28	18	10	64.3
Zhang et al., 2020	64.0	58	33	25	56.9

¹ Mean or median age of the study population reported by each research study. Mean ages are indicated in *italics*.

² Severe case defined as having at least one of the following clinical findings: (a) breathing rate $\geq 30/\text{min}$, (b) pulse oximeter oxygen saturation (SpO_2) $\leq 93\%$ at rest, or (c) ration of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ≤ 300 mmHg

Table 5. All critical cases of COVID-19 included in the meta-analysis.

Study Reference	Age ¹ (<i>mean</i> or median)	Total no. of critical cases ²	No. of male critical cases	No. of female critical cases	Critical cases (male %)
Barrasa et al., 2020	63.2	48	27	21	56.3
Bhatraju et al., 2020	64.0	24	15	9	62.5
Chen et al., 2020a	51.0	22	19	3	86.4
Grasselli et al., 2020	63.0	1591	1304	287	82.0
Guan et al., 2020	63.0	67	45	22	67.2
Huang et al., 2020	49.0	13	11	2	84.6
Simonnet et al., 2020	60	124	90	34	75.3
Wang et al., 2020a	66.0	36	22	14	61.1
Wang et al., 2020c	55.5	100	62	38	62.0

¹ Mean or median age of the study population reported by each research study. Mean ages are indicated in *italics*.

COVID-19 Sex-Specific Clinical Outcomes

² Critical case defined as: (a) received mechanical ventilation; (b) clinically diagnosed with shock, (c) received care in the intensive care unit (ICU) or (d) transferred to a higher level of medical care

Table 6. All deaths in COVID-19 patients included in the meta-analysis.

Study Reference	Age ¹ (<i>mean</i> or median)	Total number of deaths ²	Number of male deaths	Number of female deaths	Mortality (male %)
Cao et al., 2020	<i>72.0</i>	17	13	4	76.5
Chen et al., 2020d	<i>68.0</i>	113	83	30	73.5
Du et al., 2020a	<i>70.2</i>	21	10	11	47.6
Du et al., 2020b	<i>70.7</i>	109	74	35	67.9
Du et al., 2020c	<i>65.8</i>	85	62	23	72.9
Korea, 2020	<i>75.5</i>	54	33	21	61.1

¹ Mean or median age of the study population reported by each research study. Mean ages are indicated in *italics*.

² All consecutive number of deaths in COVID-19 patients that occurred during the study period.