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# Does gender influence clinical expression and disease outcomes in COVID-19? A systematic review and meta-analysis

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ABSTRACT

*Background:* Severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) was characterized at the end of 2019, and soon spread around the world, generating a pandemic. It has been suggested that men are more severely affected by the viral disease (COVID-19) than women.
*Objective:* The aim of this systematic literature review (SRL) and meta-analysis was to analyse the influence of gender on COVID-19 mortality, severity, and disease outcomes. A SRL was performed in PubMed and Embase, searching terms corresponding to the 'PEO' format: population = adult patients affected with COVID-19; exposure = gender; outcome = any available clinical outcomes by gender, including mortality and disease severity. The search covered the period from January 1 to April 30, 2020. Exclusion criteria were: case reports/series, reviews, commentaries, languages other than English. Full-text, original articles were included. Data on study type, country, and patients' characteristics were extracted. Study quality was evaluated using the Newcastle–Ottawa scale (NOS). From a total of 950 hits generated by the database search, 85 articles fulfilling the inclusion criteria were selected.
*Results:* A random-effects meta-analysis was performed to compare mortality, recovery rates, and disease severity in men compared with women. The male to female ratio for cases was 1:0.9. A significant association was found between male sex and mortality (OR = 1.81; 95% CI 1.25–2.62), as well as a lower chance of recovery in men (OR = 0.72; 95% CI 0.55–0.95). Male patients were more likely to present with a severe form of COVID-19 (OR = 1.46; 95% CI 1.10–1.94).
*Conclusions:* Males are slightly more susceptible to SARS-CoV2 infection, present with a more severe disease, and have a worse prognosis. Further studies are warranted to unravel the biological mechanisms underlying these observations.


## Introduction

In December 2019 a cluster of pneumonia cases of unknown origin was recognized in Wuhan, China (Huang et al., 2020). Full-length genome sequencing from five patients at the early stage of the outbreak unravelled the discovery of a novel coronavirus with a high homology with the 2003 severe acute respiratory syndrome coronavirus (SARS-CoV). The novel coronavirus was thus named SARS-CoV-2 (initially designated as 2019-nCoV), and shortly after its characterization it started to spread rapidly outside China. The disease caused by SARS-Cov-2 (coronavirus disease 2019, COVID-19) immediately raised concerns over its ability to cause severe illness through acute hypoxemic respiratory failure, possibly resulting in death (Chen et al., 2020a). Furthermore, the speed of human-to-human transmission required prompt adoption of containment measures (Li et al., 2020a). Nevertheless, the constantly increasing numbers of cases outside China prompted the World Health Organization (WHO) to declare COVID-19 as a pandemic on March 11, 2020.

Among the actions taken by health institutions or governments to study and mitigate the COVID-19 pandemic, gender-specific analysis and measures are lacking. However the pandemic might impact very differently on men and women, both for social and biological reasons (Wenham et al., 2020). From a social standpoint, most healthcare workers are women in several world regions, including the Americas, Europe, South-East Asia, the Western Pacific, and Eastern Mediterranean areas. Furthermore, they have a predominant role in family caring in many countries (Gupta, 2019). Thus, they could represent highly exposed individuals. On the other hand, from a biological standpoint, men might be less favored. For example, high levels of expression of the cell entry

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receptor angiotensin-converting enzyme 2 (ACE2), used by SARS-CoV-2 to invade human cells, have been demonstrated in male Leydig and Sertoli cells (Wang and Xu, 2020). This could be one of the explanations for the higher mortality in men highlighted by some reports (Li et al., 2020b; Zhang et al., 2020a).

Nevertheless, until now, a synthesis of the available literature regarding gender differences, including definition of a precise effect size for these differences, has not been performed. Based on the existing knowledge gaps, the aim of our systematic literature review (SLR) was to collect evidence on differential disease prevalence as well as clinical outcomes of COVID-19 in males and females, including mortality, severity of clinical expression, and any other described disease characteristics.

## Methods

### *Data sources and search*

A systematic review, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA), was undertaken (Moher et al., 2009). PubMed and Embase were searched for the publication period from January 1 to April 30, 2020. The scope of the literature search was based on the population, exposure, outcome (PEO) format. The population (P) of interest was adult (≥18 years) patients affected with COVID-19; the exposure (E) was gender (male/female); the outcomes were any available clinical outcomes by gender, including percentages of affected patients, mortality, and disease severity.

The literature search was performed using the following keys: ["Sex" OR "gender" OR "male" OR "female"] AND ["SARS-Cov2" OR "novel coronavirus" OR "COVID-19" OR "2019-nCoV"] AND ["clinical course" OR "clinical presentation" OR "therapy" OR "illness" OR "outcome" OR "mortality" OR "morbidity" OR "epidemiology" OR "intensive care unit" OR "hospital stay"]

### *Study selection*

Exclusion criteria were reviews, editorials, case reports and case series, papers in any language other than English, and studies on children or pregnant women. We included, instead, full-text studies presenting gender-specific outcomes in adult patients affected with coronavirus. The types of study considered for inclusion were observational cross-sectional studies, case-control studies, and observational longitudinal studies. Two reviewers (AO, ML) assessed each title and abstract for suitability for inclusion, according to the inclusion/exclusion criteria, followed by a full-text review if necessary. Discrepancies were resolved by consensus.

### *Data extraction and quality assessment*

A predefined data extraction sheet was used to gather the following data from all included studies: study design, country, infection definition, population (e.g. hospitalized patients versus general population), setting, and number of included patients. The quality of the extracted studies was then evaluated using the Newcastle–Ottawa scale (NOS) for cross-sectional, cohort, and case-control studies (Wells et al., 2013). NOS study quality was then graded according to the total score. Cross-sectional studies were graded as follows: very good = 6–7; good = 5; satisfactory = 4; unsatisfactory = 0–3. Cohort and case-control studies were graded as follows: very good = 9–10; good = 7–8; satisfactory = 5–6; unsatisfactory = 0–4, as previously described (Lodge et al., 2015).

A PRISMA flowchart was subsequently generated for the final selection of studies to be included (see Results).

### *Data synthesis and analysis*

Categorical data were reported as number (percentage). The numbers of male and female individuals were pooled to obtain a general male:female ratio.

A meta-analysis was performed on studies that were deemed to be of at least satisfactory quality to evaluate mortality and disease severity in males compared with females. In order to do this, a random-effects meta-analysis, using the Dersimonian–Laird method, was performed using Stata SE version 16 (Copyright 1985–2019, StataCorp LLC, College Station, Texas 77845, USA). The random-effects model was chosen because it was unknown whether there was a 'true' effect size underlying all studies, which would indicate the use of a fixed-effects meta-analysis; thus, we selected a more conservative approach. Data were expressed as Odds Ratio (OR) with 95% confidence interval (95% CI). The statistical heterogeneity of our meta-analysis was assessed using the $I^2$ statistic. Forest plots were produced to represent effect sizes. Funnel plots were produced to assess outliers or reporting bias.

## Results

### *Study selection*

A total of 950 hits were generated by the database search. After removing duplicates, the remaining 814 references were assessed for eligibility first through reading of titles and abstracts; 608 articles were excluded during this process, mainly due to wrong type of publication (reviews, case reports, case series) or because they were conducted in other populations of interest (children, pregnant women). Full texts were examined in 134 cases; of these, 49 were excluded. Thirteen articles had different outcomes (e.g. performances of diagnostic methods), 14 articles presented data from other populations (e.g. screening of the general population) without sex-specific data, and 22 articles were excluded because of study type (case series, reviews). The remaining 85 articles were considered for qualitative evaluation.

The PRISMA flowchart is displayed in Figure 1.

### *Study characteristics*

The 85 studies included in the qualitative assessment were thoroughly examined to identify the following: author, country, study design, number of participants, study period, type of patients (general population, hospitalized patients, patients admitted to intensive care unit, dead), infection definition (laboratory-confirmed diagnosis through SARS-CoV-2 detection in pharyngeal swab specimens by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) or clinical suspicion). The results of the data extraction are displayed in Appendix Table 1. The designs of the included studies were as follows: longitudinal cohort ($n$ = 55), cross-sectional ($n$ = 28), and case-control ($n$ = 2).

### *Quality assessment*

Among the 55 longitudinal cohort designs, nine were of unsatisfactory quality, 17 were evaluated as satisfactory, 17 as good, and 12 as very good. The cross-sectional design studies included one study of unsatisfactory quality, eight satisfactory studies, 12 studies that were graded as good, and seven as very good. One case-control study was judged as unsatisfactory and the other as satisfactory. In general, comparability (i.e outcome adjustment for relevant confounders) was one of the domains in which many studies, both longitudinal and cross-sectional, were graded lower. In fact, many papers presented crude outcomes and

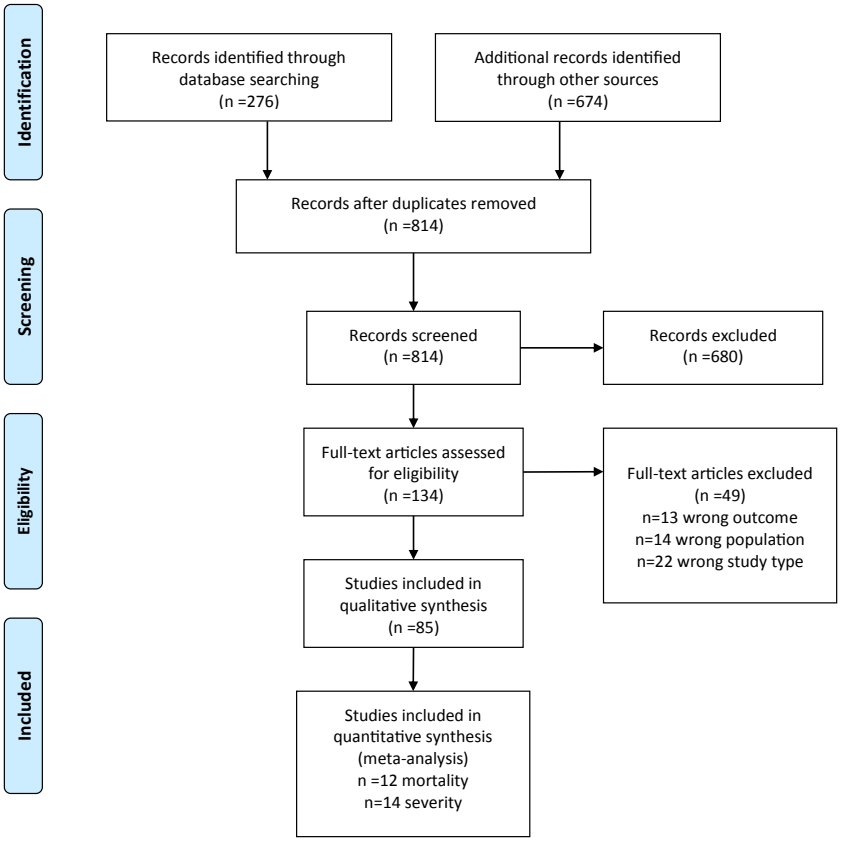


**Figure 1.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for study inclusion.

did not correct for major confounders such as age and sex, except—in some cases—minimal stratification by sex and/or age for very relevant outcomes, such as death.

*Studies included in the meta-analyses*

The first gender-related aspect to be examined was disease prevalence. Across all studies, there were a total of 33934 males and 32969 females, corresponding to a male-to-female ratio of about 1:0.9 (this ratio excluded a study conducted specifically in health workers, as the M:F ratio here might be influenced by the female prevalence in health workers) (CDC COVID-19 Response Team, 2020; Gupta, 2019).

Secondly, a random-effects meta-analysis was conducted on studies that presented sex-specific mortality data and were deemed to be of at least satisfactory quality (Table 1) (Zhang et al., 2020a; Al-Rousan and Al-Najjar, 2020; Cao et al., 2020; Du et al., 2020; Korea Centers for Disease Control et al., 2020; Meng et al., 2020; Richardson et al., 2020; Tang et al., 2020; Zhang et al., 2020b; Zhou et al., 2020). Two studies were not included in the meta-analysis because they only presented a group of deceased patients, and thus it was not possible to derive data for survivors (Du RH and Yin, 2020; Chen et al., 2020b). Data pooling resulted in a significant association between male sex and mortality (OR = 1.81; 95% CI 1.25–2.62) (Forest plot shown in Figure 2A). Among the included studies, two were conducted in the general population, while 11 included only hospitalized patients, with one specifically focusing on intensive care unit (ICU) patients. Sensitivity analyses were therefore conducted for these different populations to assess the robustness of our results. In the hospitalized patients not admitted to ICU, as well as in the general population, a significantly higher chance of death in males was confirmed (OR = 1.81; 95% CI 1.25–2.62 and OR = 2.62; 95% CI 1.62–4.24, respectively) (Figure 2B and C). Only one study on patients admitted to the ICU was available, thus a meta-analysis was not possible (Zhang et al., 2020b). Overall heterogeneity was significant ($I^2$ = 60.1%, $p$ = 0.004), but this decreased when examining only hospitalized patients not in ICU, and tended to zero in the sensitivity analyses for the general populations (Figure 2B and C).

As a countercheck to our observations on mortality, we performed a meta-analysis on those papers describing recovery rates by gender (Figure 3A). Six studies were included, with quality ranging from satisfactory to very good: the pooled effect size displayed a negative association between male sex and recovery (OR = 0.72; 95% CI 0.55–0.95). Heterogeneity of the included studies was modest ($I^2$ = 16.2) but statistically significant ($p$ = 0.006).

Finally, a further meta-analysis to compare disease severity between genders was carried out. Fourteen studies providing data on COVID-19 severity, which were judged to be of at least satisfactory quality, were included: one study had been conducted on the general population, whereas all the others related to hospitalized patients (not in ICU) (Table 1) (Li et al., 2020b; Zhang et al., 2020b; Chu et al., 2020; Guan et al., 2020; Liu et al., 2020a; Pan et al., 2020; Shi et al., 2020; Tian et al., 2020; Wang et al., 2020; Zhang et al., 2020c; Zhang et al., 2020d; Zhao et al., 2020; Zheng et al., 2020a; Zheng et al., 2020b). Only one study was not included due to poor evaluation according to the NOS (Wan et al., 2020). Pooled data showed a higher chance of male patients presenting with a severe form of COVID-19 (OR = 1.46; 95% CI 1.10–1.94) (Figure 3B). The heterogeneity across studies was relevant and statistically significant, with $I^2$ = 81.2 ($p < 0.0001$).

**Table 1**
Studies included in the meta-analysis on: (a) mortality and recovery rates (the latter are highlighted with an asterisk); (b) disease severity.

| Study characteristics and participants | | | | | | | | Newcastle–Ottawa scale evaluation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Author | Country | Study type | Age, mean ± SD or median (IQR) | M | F | Deceased M | Deceased F | Selection | Comparability | Outcome | Total |
| (a) | | | | | | | | | | | |
| Al-Rousan and Al-Najjar (2020)* | South Korea | Cross-sectional | ns | 1 218 | 1 547 | 36 | 17 | 3 | 1 | 2 | 6 |
| Cao et al. (2020)* | China | Cohort | 54 (37–67) | 53 | 49 | 13 | 4 | 4 | 0 | 3 | 7 |
| Du et al. (2020)* | China | Cohort | 58 ± 14 | 97 | 82 | 10 | 11 | 4 | 1 | 3 | 8 |
| Korea CDC et al. (2020) | Korea | Cohort | ns | 1 591 | 2 621 | 13 | 9 | 4 | 1 | 3 | 8 |
| Meng et al. (2020)* | China | Cohort | 57 ± 15 | 86 | 82 | 16 | 24 | 3 | 2 | 3 | 8 |
| Richardson et al. (2020)* | US | Cohort | 63 (52–75) | 3 437 | 2 263 | 337 | 216 | 4 | 0 | 3 | 7 |
| Tang et al. (2020)* | China | Cohort | 54.1 ± 16.2 | 98 | 85 | 16 | 5 | 4 | 0 | 3 | 7 |
| Yuan et al. (2020) | China | Cohort | 60 (47–69) | 12 | 15 | 4 | 6 | 4 | 0 | 3 | 7 |
| Zhang et al. (2020c) | China | Cohort | 55 (39–66) | 108 | 113 | 7 | 2 | 4 | 0 | 3 | 7 |
| Zhang et al. (2020a) | China | Cohort | 73 (38–91) | 11 | 8 | 5 | 3 | 4 | 0 | 2 | 6 |
| Zhang et al. (2020b) | South Korea | Cohort | 56 (44–69) | 321 | 542 | 15 | 10 | 4 | 2 | 3 | 9 |
| Zhou et al. (2020) | China | Cohort | 56 (46–67) | 119 | 72 | 38 | 16 | 4 | 0 | 2 | 6 |
| (b) | | | | | | | | | | | |
| Chu et al. (2020) | China | Cross-sectional | 39 (26–73) | 36 | 18 | 30 | 13 | 3 | 0 | 2 | 5 |
| Guan et al. (2020) | China | Cross-sectional | 47 (35–58) | 637 | 459 | 100 | 73 | 3 | 0 | 3 | 6 |
| Li et al. (2020b) | China | Cohort | 60 (48–69) | 279 | 269 | 153 | 116 | 4 | 2 | 3 | 9 |
| Liu et al. (2020a) | China | Cross-sectional | 41.6 ± 14.5 | 41 | 32 | 10 | 13 | 3 | 0 | 2 | 5 |
| Pan et al. (2020) | China | Cohort | 57 (43–67) | 15 766 | 16 817 | 3 702 | 3 437 | 4 | 2 | 3 | 9 |
| Shi et al. (2020) | China | Cohort | 46 ± 19 | 259 | 228 | 36 | 16 | 4 | 0 | 2 | 6 |
| Tian et al. (2020) | China | Cross-sectional | 47 (ns) | 127 | 56 | 26 | 20 | 3 | 0 | 2 | 5 |
| Wang et al. (2020) | China | Cohort | 41 ± 15 | 71 | 54 | 16 | 9 | 4 | 0 | 2 | 6 |
| Zhang et al. (2020c) | China | Cohort | 55 (39–66) | 108 | 113 | 35 | 20 | 4 | 0 | 3 | 7 |
| Zhang et al. (2020d) | China | Cohort | 49 (39–58) | 53 | 42 | 31 | 11 | 2 | 0 | 3 | 5 |
| Zhang et al. (2020a) | China | Cohort | 56 (44–69) | 321 | 542 | 205 | 204 | 4 | 2 | 3 | 9 |
| Zhao et al. (2020) | China | Cross-sectional | 43 (ns) | 48 | 39 | 8 | 6 | 3 | 0 | 2 | 5 |
| Zheng et al. (2020a) | China | Cross-sectional | 45 (33–57) | 80 | 81 | 14 | 16 | 4 | 0 | 2 | 6 |
| Zheng et al. (2020b) | China | Cohort | 55 (44–65) | 58 | 38 | 49 | 25 | 4 | 0 | 3 | 7 |

The Newcastle–Ottawa scale for cross-sectional, cohort, and case-control studies evaluates, for each study, three domains: selection, comparability, and outcome. These are graded up to a maximum of 4 for selection (5 in the case of cross-sectional studies), 2 for comparability, and 3 for outcome. Studies were then graded overall according to the total score. Cross-sectional studies were graded as follows: very good = 6–7; good = 5; satisfactory = 4; unsatisfactory = 0–3. Cohort studies were graded as follows: very good = 9–10; good = 7–8; satisfactory = 5–6; unsatisfactory = 0–4.

* Studies included in both meta-analyses for mortality and recovery rate; SD = standard deviation; IQR = interquartile range; M = males; F = females.

*Risk of bias across studies*

In order to assess the risk of bias across studies, a visual inspection using a funnel plot was performed for the studies included in the meta-analyses on mortality, on recovery rate, and on disease severity (Figure 4A-C). In the first case, the funnel plot displayed a symmetrical appearance. For the analysis on recovery, despite the small number of included studies, no major outlier was noted. The funnel plot for studies included in the disease severity meta-analysis showed a few outliers, but in both directions, suggesting true heterogeneity rather than publication bias.

*Studies not included in the quantitative synthesis (meta-analysis)*

Further to the extraction of gender-specific outcomes related to COVID-19 infection, some results of the SLR could not be included in a quantitative analysis, but are still of interest. These are outlined below.

Firstly, a large Chinese study, considering as a composite endpoint (a) admission to ICU, (b) the use of mechanical ventilation, or (c) death, found that females constituted only 32.8% of the subpopulation reaching the composite endpoint (22 females versus 45 males) (Guan et al., 2020). However, a formal statistical analysis to assess whether female sex was negatively associated with this endpoint was not performed. Another work, by Li et al., highlighted that males had a higher hazard rate (HR) for mortality even after adjustment for age, blood leukocyte count, lactate dehydrogenase (LDH), cardiac injury, hyperglycemia, and administration of corticosteroids, lopinavir/ritonavir, and umifenovir (HR 1.72; 95% CI 1.05–2.82; $p$ = 0.032). Accordingly, female sex was found to be protective for in-hospital death (Zhou et al., 2020). In contrast, male sex seemed not to be independently associated with ICU admission in a retrospective study (Chen et al., 2020c).

Only one paper among those selected systematically evaluated gender differences in COVID-19 characteristics and prognosis. This study confirmed that males with comorbidities presented a higher risk of critical illness than males without comorbidities (OR = 3.82, 95% CI 1.28–11.43), while this association tended towards the null for female sex (Meng et al., 2020). Differences in disease expression were limited to a higher prevalence of headache and more favourable laboratory examinations in females. In particular, females had a lower neutrophil-to-lymphocyte ratio (NLR), as well as lower levels of ferritin, transaminase, bilirubin, LDH, kidney function indices, C-reactive protein, and procalcitonin (Meng et al., 2020). On the subject of laboratory examinations, one work investigated the prognostic value of N-terminal pro-B-type natriuretic peptide (nt-proBNP) on COVID-19 mortality: significant differences between male and females were not highlighted with this marker, although nt-proBNP per se was a significant predictor

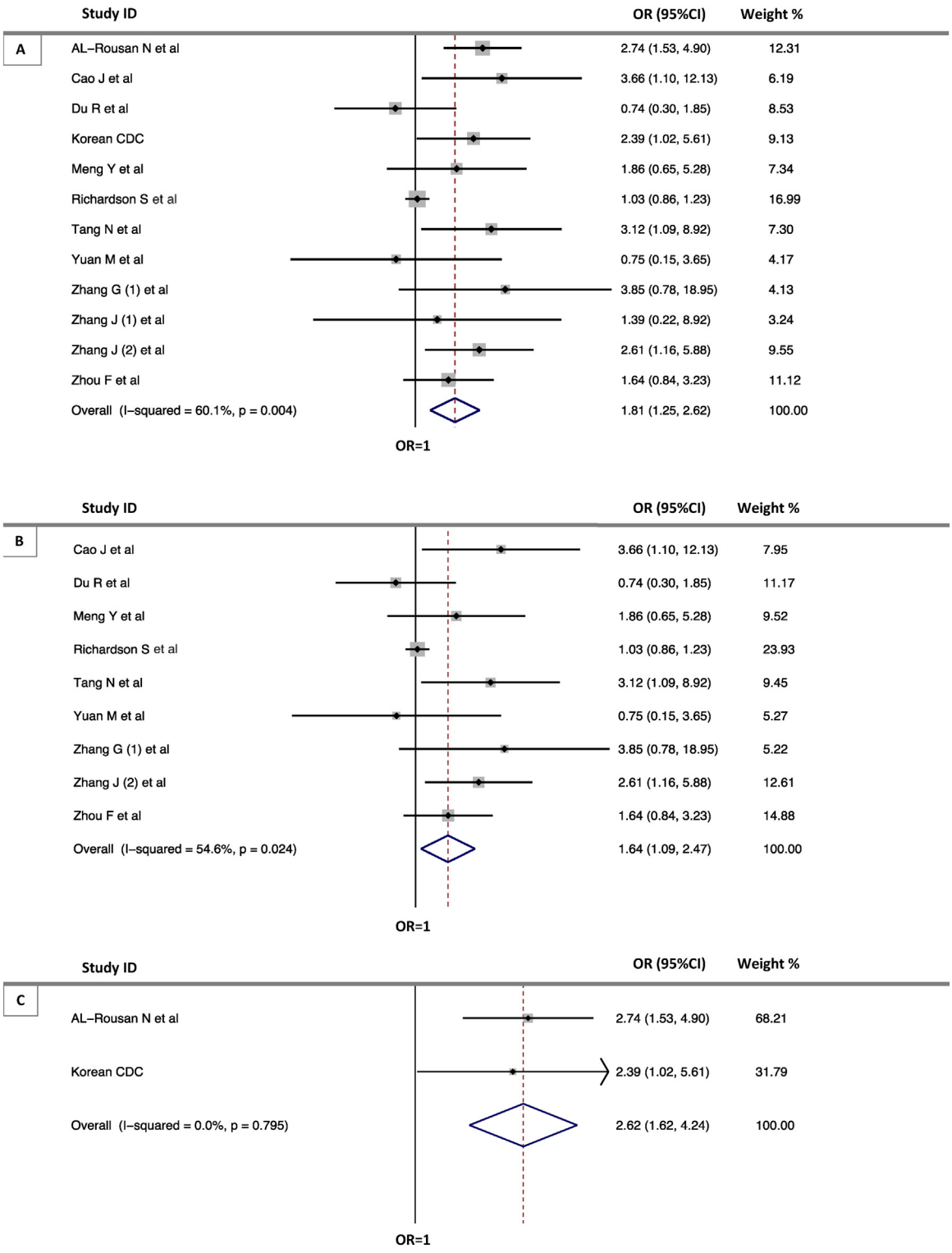


**Figure 2.** Meta-analysis of mortality in males versus females: (A) across studies overall; (B) in hospitalized, non-critical patients only; (C) in the general population.

of in-hospital death (Ma et al., 2020). Fan et al. showed that elevated transaminase and cholestasic enzymes were associated with a longer hospital stay, and that patients presenting these abnormalities were more frequently male than female (Fan et al., 2020). When evaluating NLR, it was found that in the male sex NLR was significantly associated with mortality, whereas the same was not observed in the female sex (Liu et al., 2020b).

With regard to the infection kinetics, a retrospective study found that male sex was independently associated with the duration of SARS-CoV-2 RNA shedding (OR = 3.24; 95% CI 1.31–8.02, $p$ = 0.011) (Xu et al., 2020). This finding was confirmed by another independent study, which assessed the virus RNA not only in respiratory samples, but also in stool and serum samples, and drew similar conclusions (Zheng et al., 2020b).

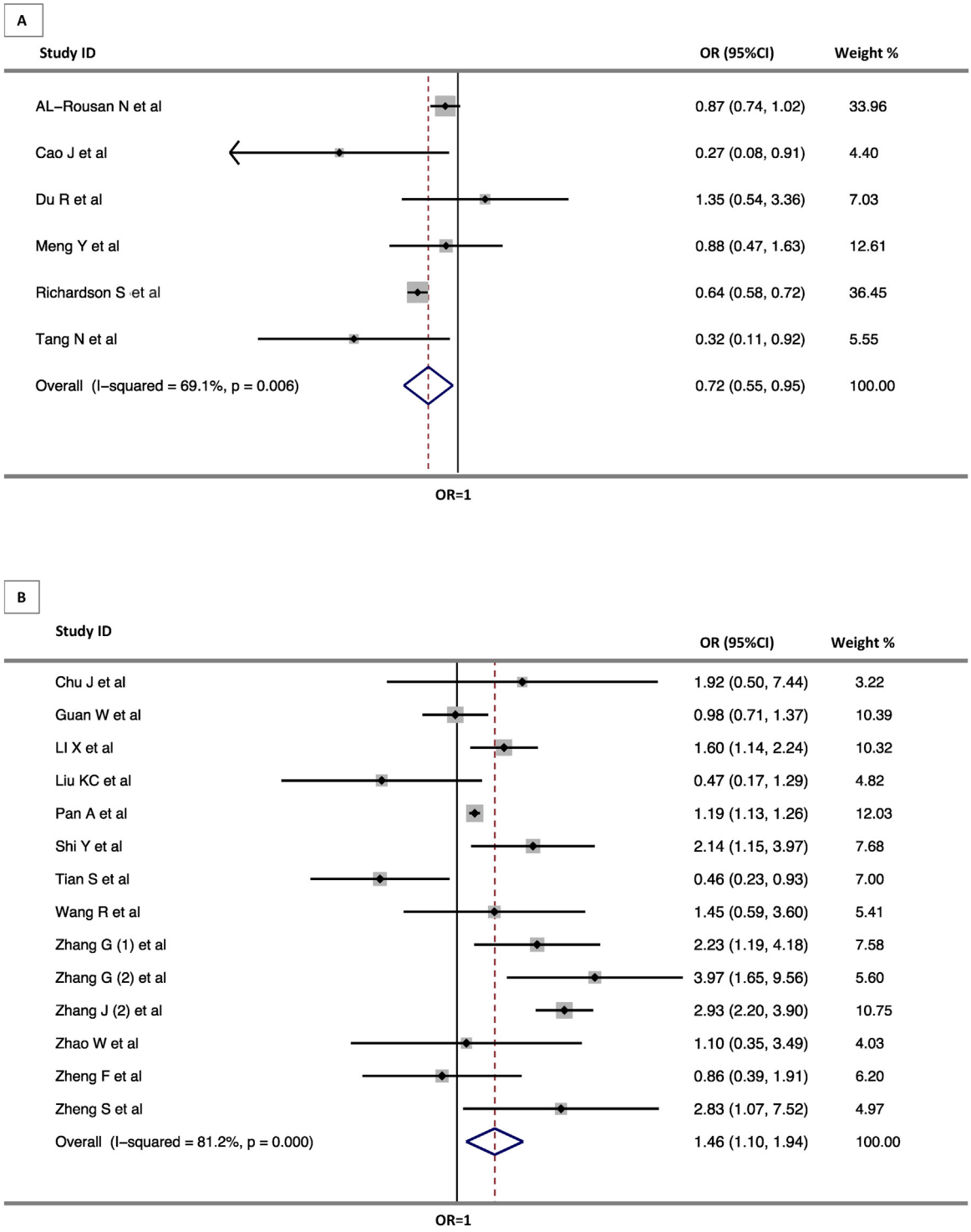


**Figure 3.** Meta-analysis of (A) recovery rates and (B) disease severity in males versus females.

## Discussion

The results of our SLR and meta-analysis indicated that male sex seems to be a risk factor for mortality (both in the general population and in hospitalized patients), for a lower recovery rate, and for disease severity in COVID-19.

Our SLR did not a highlight a striking difference between male and female gender regarding disease susceptibility, with a male-to-female ratio of 1:0.9 calculated for our pooled studies. However, this slight difference might not be accidental: the higher proneness of men to COVID-19 could be related to differences in innate immunity, steroid hormones, and factors related to sex chromosomes (Conti and Younes, 2020). Since some important immune regulatory genes are located on the X chromosome, female individuals—equipped with two copies—might be advantaged due to a higher expression of toll-like receptor-7 (TLR7), which is

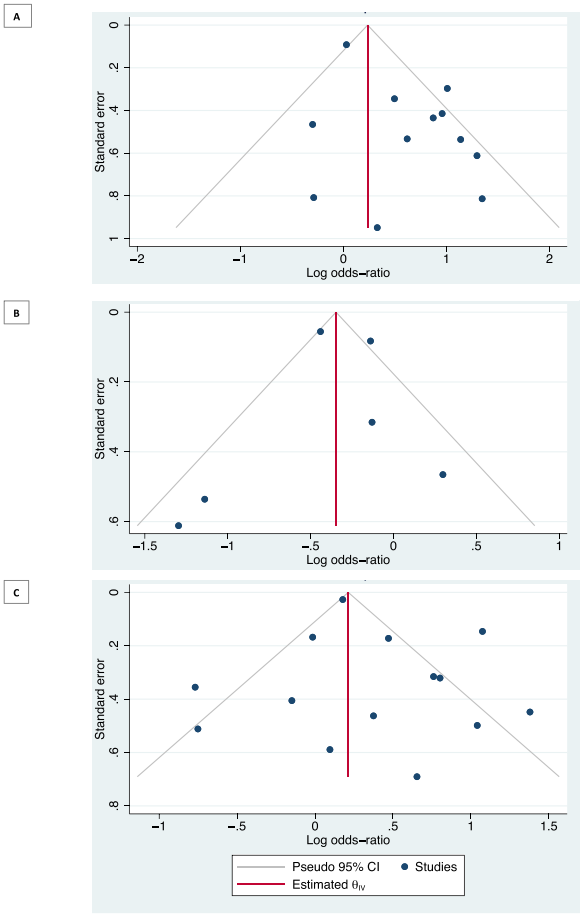


**Figure 4.** Funnel plots for the meta-analyses on (A) mortality, (B) recovery rate, and (C) disease severity.

crucial in the defence against viral infections. Moreover, females seem to show a higher expression of CD4+ lymphocytes, guaranteeing a better virus clearance (Conti and Younes, 2020).

Regarding mortality, a higher case fatality rate in males has already been suggested in a previous scoping review on the clinical characteristics of SARS-CoV-2 infection (Borges do Nascimento et al., 2020), but until now a specific search on gender-related outcomes has not been performed, and a pooled effect size for mortality risk in males has not been calculated. The results of our work suggest that male patients affected with COVID-19 have an overall 61% higher chance to die from the infection than their female peers. Importantly, this difference seems to hold despite the setting—general population or hospitalized patients. This, again, points toward biological explanations for the differences in infection outcomes between male and females. It has been observed that, in the most severe cases, SARS-CoV-2 can induce an exaggerated production of pro-inflammatory cytokines (referred to as a 'cytokine storm or, better, 'secondary hemophagocytic lymphohistiocytosis'—sHLH), possibly leading to multi-organ failure and death (Tufan et al., 2020). This mechanism might be less frequently triggered in women, because a lower production of pro-inflammatory cytokines, including interleukin (IL)-6, has been observed in women, in spite of a more prompt and effective antiviral response (Conti and Younes, 2020).

In order to examine the issue of mortality from a different perspective, we also evaluated whether there was a difference in recovery rates between genders. This analysis was slightly different from previous analyses because all examined cohort studies extended their observation period up to a certain point in time; however, for practical reasons, they did not follow all patients up to death or recovery. Thus, at the end of the study, a proportion of patients might still have been hospitalized. In this context, the recovery rate could also give an indication of patients who were discharged more rapidly versus those still hospitalized. This analysis confirmed, again, that male sex was negatively associated with recovery in the observation period. Accordingly, our SLR results retrieved data about prolonged viral RNA shedding in men for SARS-Cov-2, suggesting slower recovery (Zheng et al., 2020b; Xu et al., 2020).

Regarding disease severity, our meta-analysis showed that men have a significantly higher risk of severe disease. The degree of observed heterogeneity was rather high across studies, which might reflect the different definitions of disease severity. Indeed, two studies used the American Thoracic Society definition for severe community-acquired pneumonia (Guan et al., 2020; Zhang et al., 2020c; Metlay et al., 2019), while others used the definition from the Chinese National Health commission (Zhang et al., 2020a; Liu et al., 2020a; Pan et al., 2020; Zhang et al., 2020d; Zheng et al., 2020a; Zheng et al., 2020b). Two studies applied their own definitions, such as 'patients with dyspnea or respiratory failure' (Tian et al., 2020), or based them on defined specific levels of oxygen dependence (Wang et al., 2020). Finally, in a few cases the definition was not clearly specified (though we might hypothesize that Chinese authors based theirs on the national guidelines) (Li et al., 2020b; Chu et al., 2020; Shi et al., 2020; Zhao et al., 2020). Nonetheless, it is undeniable that all these definitions included patients with severe respiratory failure and reflected a high-risk clinical situation, so this is unlikely to affect the true clinical relevance of the meta-analysis.

In line with our results, even reports focusing on single negative prognostic factors highlighted how these were often increased in men—examples include elevated transaminase and cholestasic enzymes or NLR (Fan et al., 2020; Liu et al., 2020b). It is conceivable that disease phenotype, and thus severity, might be influenced by hormonal factors. One study conducted on nine pregnant women infected with COVID-19 highlighted that high estrogen levels and increased estrogen receptor signaling were not associated with severe disease (Chen et al., 2020d). Consistent with this observation, previous animal studies on SARS-CoV found that the estrogen depletion in infected female mice, by ovariectomy or treatment with an estrogen receptor antagonist, dramatically increased morbidity and mortality (Channappanavar et al., 2017). It might be reasonable to hypothesize that this could also apply to SARS-CoV-2. The importance of estrogen in the immune response to viruses is linked to the presence of estrogen receptors on the surface of innate immune cells such as monocytes, macrophages, and neutrophils. Through this receptor, the production of type I and III interferon by innate immune cells, which is crucial for decreasing virus titres, is enhanced (Suba, 2020). This even led to the proposal of hormone replacement therapy as a potential treatment aimed at limiting COVID-19 severity (Suba, 2020). An additional risk factor in males could be represented by the testis, as an analysis of transcription patterns for ACE2 found this receptor to be primarily expressed in spermatogonia, as well as in Leydig and Sertoli cells. ACE2-positive spermatogonia express a higher number of genes associated with viral reproduction and transmission, and a lower number of genes related to spermatogenesis (Wang and Xu, 2020). Thus, there may be multiple biological explanations for the higher disease severity in males.

The limitations of this work relate to the fact that the literature on COVID-19 continues to accumulate, with new information and new papers published each day; therefore, this work cannot be considered as exhaustive. Moreover, the fact that we restricted our choice to full-text studies in English could have limited our results. The strengths of this work lie in the gender medicine perspective

and the validated methodology, which allowed for the collection of good-quality evidence for the estimation of effect sizes. Moreover, meta-analyses have been considered to be the highest level of evidence (Evidence-Based Medicine Working Group, 1992). Although it is true that the quality of evidence also depends on the quality of the included studies, our results can be considered reliable because we limited the meta-analyses to studies of at least satisfactory quality.

In conclusion, we showed that male patients with COVID-19 have a higher risk of mortality and experience greater disease severity compared with females. While male sex should be considered a negative prognostic factor, more studies are warranted to completely elucidate (and possibly target with therapy) all the biological mechanisms underlying this susceptibility.

## Ethical statement

No ethical approval was deemed necessary for this study according to our national regulations.

## Funding source

No funding was received for this study.

## Conflicts of interest

The authors have no conflicts of interest to disclose.

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