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Gender Difference Is Associated With Severity of Coronavirus Disease 2019 Infection: An Insight From a Meta-Analysis

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Objectives: Coronavirus disease 2019 is a novel infection now causing pandemic around the world. The gender difference in regards to the severity of coronavirus disease 2019 infection has not been well described thus far. Our aim was to investigate how gender difference can affect the disease severity of coronavirus disease 2019 infection.

Data Sources: A comprehensive literature search of PubMed and Embase databases was conducted from December 1, 2019, to March 26, 2020. An additional manual search of secondary sources was conducted to minimize missing relevant studies. There were no language restrictions.

Study Selection: Studies were included in our meta-analysis if it was published in peer-reviewed journals and recorded patient characteristics of severe versus nonsevere or survivor versus nonsurvivor in coronavirus disease 2019 infection.

Data Extraction: Two investigators independently screened the search, extracted the data, and assessed the quality of the study.

Data Synthesis: Our search identified 15 observational studies with a total of 3,494 patients (1,935 males and 1,559 females) to be included in our meta-analysis. Males were more likely to develop severe coronavirus disease 2019 infection compared with females (odds ratio, 1.31; 95% CI, 1.07–1.60). There was no significant heterogeneity ($I^2 = 12\%$) among the studies.

Conclusions: This meta-analysis suggests that the male gender may be a predictor of more severe coronavirus disease 2019 infection. Further accumulation of evidence from around the world is warranted to confirm our findings.

Key Words: coronavirus disease 2019; gender; severity

Coronavirus disease 2019 (COVID-19) is a novel infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Since the first cluster of its disease in Wuhan, China, was reported in December 2019, the infection has rapidly expanded worldwide, making World Health Organization (WHO) to declare this as a pandemic on March 11, 2020 (2). The clinical manifestation of the disease varies from fever, myalgia, nonproductive cough to acute respiratory distress syndrome, fulminant myocarditis, and death (3, 4). Recognition of the clinical risk factors of severe COVID-19 infection is a high priority to effectively manage this emerging threat of the new virus. Reports have consistently shown that the older age and comorbidities such as hypertension, respiratory system disease and, cardiovascular disease are associated with worse outcomes of COVID-19 (5, 6). Gender difference in its association with susceptibility and severity of infectious disease is reported in the past for several other infectious organisms (7). However, the gender difference in regards to the severity of COVID-19 infection has not well been delineated thus far. Therefore, the aim of this study was to investigate how gender difference can affect the disease severity of COVID-19 infection.

MATERIALS AND METHODS

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (8).

Data Sources and Search

We performed a comprehensive literature search of PubMed and Embase databases from December 1, 2019, to March 26, 2020. The

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following search terms were applied to include all relevant studies documenting gender information on COVID-19 infection and its association with outcomes: "coronavirus 2019 or 2019-nCoV or sars cov 2 or COVID-19 or COVID; sex or gender or male or female or clinical characteristic or clinical features of clinical course or risk factor." We conducted an additional manual search of secondary sources, including commentaries and citations of initially identified articles to minimize the risk of missing relevant studies.

Study Selection

Studies were included in our meta-analysis when it was: 1) published in peer-reviewed journals and 2) study that recorded patient characteristics of severe versus nonsevere or survivor versus nonsurvivor in COVID-19 infection. There was no restriction on publication language. Duplicate reports from the same study population were excluded. No contact was made to the authors since there were no missing outcomes for the analysis.

Data Extraction and Quality Assessment

The search was screened by two investigators (H.U., T.K.) independently to assess the eligibility of each study. After the initial screen through titles and abstracts, the full-texts of articles were retrieved and assessed if there were any potential correlations. Any disagreement in the process of study selection and data extraction were resolved by input from the third author (H.T.) (9).

For each eligible study, we extracted the study characteristics (author name, study design, location of the study), patient characteristics (number of patients, age, gender, and comorbidities), and outcome measures.

The Newcastle-Ottawa Assessment Scale was used for each study to assess the quality of the studies (10).

Data Synthesis and Analysis

The endpoints were the rate of severe COVID-19 infection and death. Severe COVID-19 infection was defined by each study. For each included study, the total number and event number for each gender were extracted in regard to each outcome. The pooled results were presented as odds ratios (ORs) and 95% CI. Review Manager Version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) was used to conduct statistical analysis. A random-effect model was used for the analysis. Mantel-Haenszel effect

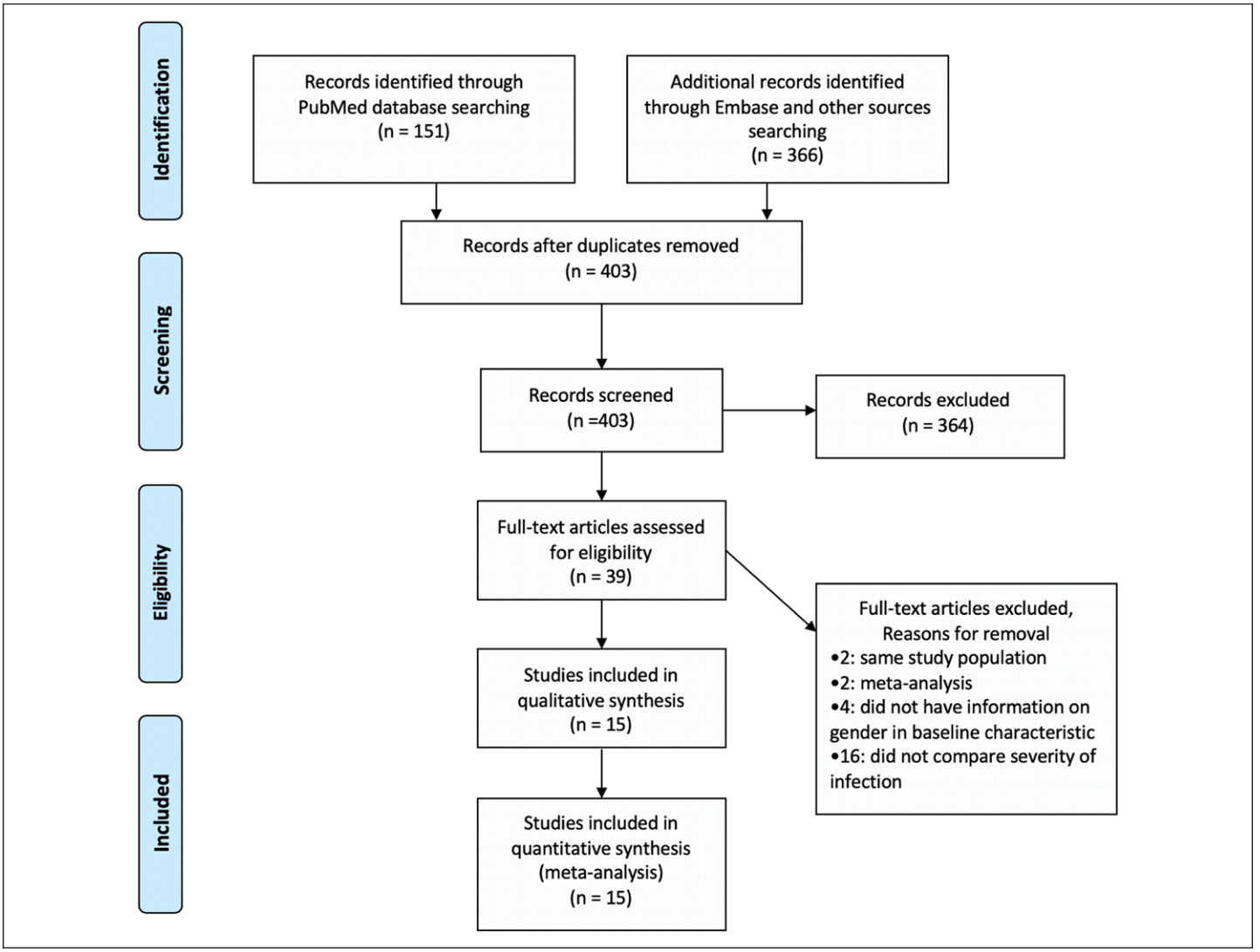


Figure 1. Flow diagram of study selection.

model was used to calculate the pooled OR and 95% CI of categorical variables.

RESULTS

Literature Search and Study Characteristics

A total of 403 articles were identified after initial database searching and additional records review. After title and abstract screening, 39 articles were extracted for full-text article assessment. Two studies were excluded due to reporting duplicate of the same population (1, 11), two were excluded due to the meta-analysis nature of the original article, four were excluded due to lack of information on gender, and 16 were excluded due to the lack of comparison between severity of the infection. Finally, our search identified 15 observational studies (12–26) to be included in our meta-analysis (**Fig. 1**). Eleven studies compared characteristics of severe versus nonsevere and four compared survivors versus nonsurvivors of COVID-19 infection. The analysis included a total of 3,494 patients with 1,935 (55.4%) males and 1,559 (44.6%) females. The details of the study and patient characteristics are summarized in **Table 1**. All except one report were from China. The median age ranged from 42.0 to 60.0. The definition of severe COVID-19 infection for each included study is summarized in **Table S1** (Supplemental Digital Content 1, http://links.lww.com/CCX/A208). The result of quality assessment by the Newcastle-Ottawa Assessment Scale is summarized in **Table S2** (Supplemental Digital Content 1, http://links.lww.com/CCX/A208).

Clinical Outcomes

Males were more likely to develop severe COVID-19 infection compared with females (OR, 1.31; 95% CI, 1.07–1.60). There was no significant heterogeneity (I^2 = 12%) among the studies (**Fig. 2**). There was no significant difference in mortality between males and females (OR, 1.53; 95% CI, 0.87–2.69) without significant heterogeneity (I^2 = 17%) among studies (**Fig. 3**).

DISCUSSION

The salient findings of this meta-analysis are that males were more likely to develop severe COVID-19 infections compared with females, while there was no significant difference in mortality between gender.

Studies have reported significant differences between men and women in regards to prevalence, severity, and even response to vaccination to several other viral illnesses, partially explained by the biological difference in antiviral, inflammatory, and cellular immune response to viruses (27, 28). These differences are not only limited to virus but also seen in certain bacteria and parasites (29). Understanding the epidemiology of gender difference in susceptibility and vulnerability to a certain outbreak of infection may be important to effectively respond to or prepare for the public health crisis by minimizing the health, economic and social impact of the emerging outbreak (7, 30).

Reports from WHO Europe and Chinese Centers for Disease Control and Prevention widely agree that the COVID-19 infections are seen more frequently in males compared with females (53.6%

TABLE 1. Study and Patient Characteristics

Study	Study Location	Total (*n*)	Age (yr)	Female (%)	Male (%)	Hypertension (%)	Diabetes Mellitus (%)	Cardiovascular Disease (%)	Current Smoker (%)
Severe vs nonsevere									
Gao et al (12)	Anhui, China	43	43.7 ± 12.1	39.5	60.5	16.3	30.2	70	–
Guan et al (13)	Multicenter, China	1,099	47.0 (35.0–58.0)	41.9	58.1	15	7.4	2.5	12.6
Qin et al (14)	Wuhan, China	452	58 (47–67)	48	52	29.5	16.4	5.9	1.5
Shi et al (15)	Zhejiang, China	487	46 ± 19	46.8	53.2	20.3	6	2.3	8.2[a]
Tian et al (16)	Beijing, China	262	47.5	51.5	48.5	–	–	–	–
Wan et al (17)	Chongqing, China	135	47 (36–55)	46.7	53.3	9.6	8.9	5.2	6.7
Wang et al (18)	Wuhan, China	138	56 (42–68)	45.7	54.3	31.2	14	14.5	–
Wang et al (19)	Wuhan China	69	42.0 (35.0–62.0)	54	46	13	10	12	–
Wu et al (20)	Wuhan China	201	51 (43–60)	36.3	63.7	19.4	10.9	4	–
Young et al (21)	Singapore	18	47 (31–72)	50	50	–	–	–	–
Zhang et al (22)	Wuhan China	140	57 (25–87)	49.3	50.7	30	12.1	5	1.4
Survivor vs nonsurvivor									
Tang et al (23)	Wuhan, China	183	54.1 ± 16.2	46.4	53.6	–	–	–	–
Yang et al (24)	Wuhan, China	52	59.7 ± 13.3	33	67	–	17	10	4
Yuan et al (25)	Wuhan, China	27	60 (47–69)	55	45	19	22	11	–
Zhou et al (26)	Wuhan, China	191	56 (46–67)	38	62	30	19	8	6

[a]History of smoking.

Values are mean ± SD or % or median (interquartile range). Dashes indicate data not available.

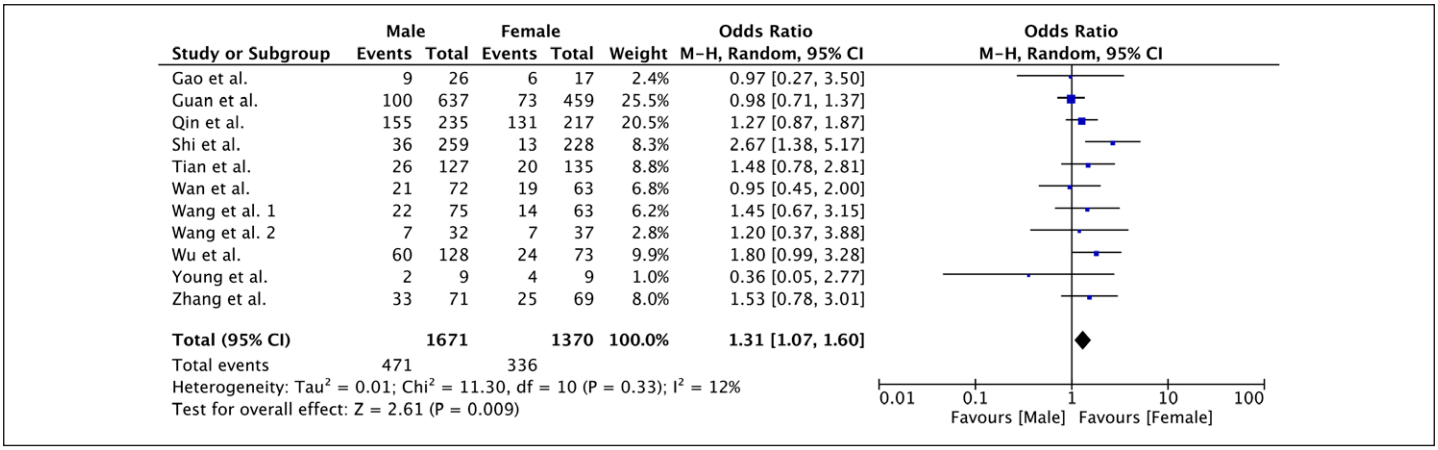
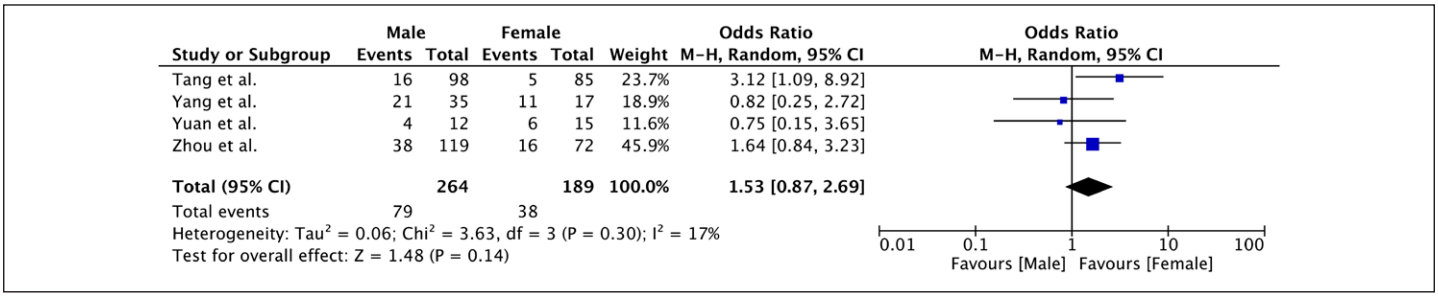


Figure 2. Forrest plot comparing male versus female risk of developing severe coronavirus disease 2019 infection. *df* = degrees of freedom, M-H = Mantel-Haenszel.



Figures 3. Forrest plot comparing male versus female risk of mortality with coronavirus disease 2019 infection. *df* = degrees of freedom, M-H = Mantel-Haenszel.

vs 46.4% and 51.4% vs 48.6%, respectively) (31, 32). However, the gender difference on the impact of disease severity of COVID-19 infection is not as well understood due to relatively small study size of each study. Although Guan et al (13) have shown no significant gender difference in requirements of ICU care, Shi et al (15) have found males to be associated with refractoriness of COVID-19 infection. By performing a meta-analysis of studies comparing severe versus nonsevere COVID-19 infection, we were able to provide the largest scale of evidence on gender disparity of severity of COVID-19 infection, concluding that males were more likely to develop severe COVID-19 infection compared with females. In our analysis, mortality was not significantly different between the gender; however, it is likely that the study population was small to exhibit significant differences.

Interestingly, similar findings of males being more susceptible and mounting more severe reaction to virus have been reported in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), an infection caused by a similar yet different stream of coronavirus. A report from Hong Kong investigating characteristic of SARS have documented males to have significantly higher case fatality rate compared with females (33). Furthermore, MERS has been reported to have a significantly higher incidence in males compared with females (7, 34).

The observed findings of gender difference in susceptibility and vulnerability to COVID-19 infection may be multifactorial. Gender differences in behavior may contribute to our findings of males being more susceptible to severe COVID-19 infection. For instance, in the Chinese population, men are reported to have a higher prevalence of smoking compared with women (35). Since all except one of the studies included in the present analysis are reported from China, this could have affected our result. However, to date, there is no firm evidence that smoking is the risk factor of severe COVID-19 infection. Furthermore, underlying differences in gene expression may be associated with different rates of severe COVID-19 infection between gender. For instance, an expression of angiotensin-converting enzyme 2 (ACE2) may also have a significant role in the observed gender difference in COVID-19 infection outcomes. Emerging evidence has suggested that ACE2 is a co-receptor for SARS-CoV-2 viral entry into the human cell that plays a significant role of the pathogenesis of this virus (36). The recent study has suggested that ACE2 expression was higher in Asian males (37), which may have potentially contributed to the findings of this analysis. Other explanations to why men were associated with severe outcomes compared with women in response to COVID-19 infection may involve differences in immunologic reaction and the lack of protective effect of estrogen signaling seen in females; an insight derived from a study of MERS and SARS (38).

The present analysis has several limitations. First, the included studies were retrospective observational studies, and the pooled OR are unadjusted. Furthermore, the lack of individual patient-level data limits our ability to adjust for potential confounders. However, our meta-analysis is valuable since previous studies have shown conflicting results of gender difference in the severity of COVID-19. Second, the definition of severe illness was variable

among the studies. Therefore, the results must be cautiously interpreted in regard to potential heterogeneity. Finally, all but one of the included studies were reported from China, potentially limiting its applicability to other countries and races. Nonetheless, this report is thus far the largest study comparing gender difference of vulnerability to this emerging COVID-19 infection.

CONCLUSIONS

This meta-analysis suggests that the male gender may be a predictor of more severe COVID-19 infection but does not predict mortality. Further accumulation of evidence from around the world is warranted to confirm our findings.

Supplemental digital content is available for this article. Direct URL citations appear in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

The authors have disclosed that they do not have any potential conflicts of interest.

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