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Clinical Determinants of the Severity of Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis

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Abstract

Background: SARS-CoV-2 is an emerging pathogen, and coronavirus disease 2019 (COVID-19) has been declared a global pandemic. We aim to summarize current evidence regarding the risk of death and the severity of COVID-19 as well as risk factors for severe COVID-19.

Methods: The PubMed, Embase, and Web of Science databases as well as some Chinese databases were searched for clinical and epidemiological studies on COVID-19. We conducted a meta-analysis to examine COVID-19-related death and risk factors for the severity of COVID-19.

Results: A total of 55 studies fulfilled the criteria for this review. The case fatality risk ranged from 0 to 61.5%, with a pooled estimate of 3.3%. The risks of ICU admission, acute respiratory distress syndrome (ARDS)and severe COVID-19 were 24.9%, 20.9% and 26.6%, respectively. Factors related to the risk of severe COVID-19 were older age (MD=10.09, 95% CI:7.03, 13.16), male sex (OR=1.62, 95% CI:1.32, 1.99), hypertension (OR=2.34, 95% CI:1.47, 3.73), diabetes (OR=2.25, 95% CI:1.68, 3.03), chronic renal disease (OR=3.60, 95% CI:1.53, 8.46), heart disease (OR=2.76, 95% CI:1.78, 4.30), respiratory disease (OR=3.74, 95% CI:2.15, 6.49), cerebrovascular disease (OR=2.21, 95% CI:1.23, 3.98), higher D-dimer levels (SMD=0.62, 95% CI:0.28, 0.96), and higher IL-6 levels (SMD=2.21, 95% CI:0.11, 4.31). However, liver disease (OR=0.63, 95% CI: 0.36, 1.10) was found to be a nonsignificant predictor of the severity of COVID-19.

Conclusions: The case fatality risk of COVID-19 and the risk of severe manifestations were not very high, and variances in the study designs and regions led to high heterogeneity among the studies. Male sex, older age, comorbidities such as hypertension, diabetes, cardiovascular disease, respiratory disease and cerebrovascular disease could increase the risk of developing a severe case of COVID-19. Laboratory parameters, such as D-dimer and IL-6 levels, could affect the prognosis of COVID-19.

Background

Cases of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have continuously been reported since December 2019. As of 28 April 2020, the total number of laboratory-confirmed cases around the world reached over 2.9 million cases according to the World Health Organization (WHO), including 202,733 deaths [1]. The first large outbreaks of COVID-19 were reported in China, and with the spread of SARS-CoV-2, the disease has attracted increasing international interest regarding its epidemiology, clinical features, and treatment.

The most common symptoms of COVID-19 are fever and cough, and some people have myalgia, fatigue, diarrhea, headache and hemoptysis. The majority of these patients have abnormal chest CT imaging, and several patients develop acute respiratory distress syndrome (ARDS) or even death[2]. To estimate the clinical burden of COVID-19, particular attention to the risk of developing severe clinical manifestations is warranted. The case fatality risk (CFR) is a measure of the risk of death among cases diagnosed with a disease[3], while the risks of ARDS and admission to an intensive care unit (ICU) are also useful for

quantifying COVID-19 severity. However, it is also critical to identify risk factors for severe disease among patients infected with SARS-CoV-2. Although some previous studies have assessed risk factors associated with severe cases[4–6], the conclusions have differed. Because of this variability, it is necessary to conduct a systematic review and meta-analysis to evaluate the risks of COVID-19, focusing on indices related to severity, and to determine the risk factors for severe disease among patients with SARS-CoV-2.

Methods

Search strategy and selection criteria

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[7]. Our systematic review protocol is described briefly in Additional file 1.

Eligibility criteria

Our target condition of interest is confirmed cases of COVID-19 regardless of treatment status. Therefore, only retrospective observational studies focused on patients infected with SARS-CoV-2 were eligible for inclusion if clinical outcomes (the primary outcome was death; secondary outcomes included incidence of SARS-CoV-2-related ARDS and the proportion of ICU admission) were explicitly documented or if data on disease severity were reported. The studies investigating risk factors related to severity by epidemiologic or medical condition were preferred, but this was not necessary. Studies were excluded if they were not published in English or Chinese. Case reports with only one or two cases were also excluded.

Search strategy and study selection

International (PubMed, Embase, Web of Science) and Chinese (CNKI, WanFang, CBM, Chinese Medical Journal database) databases were searched using the following keywords: “2019 novel coronavirus disease”, “2019-nCoV”, “coronavirus disease-19”, “coronavirus disease 2019”, “COVID-19”, “2019 novel coronavirus infection”, “clinical characteristics”, and “clinical features”. The search strategy for PubMed is described in Additional file 2. The search was performed on 15 March 2020. Additional relevant articles were identified by manually searching the reference lists of the included articles. Two authors independently screened the titles and abstracts, and according to eligibility criteria, duplicates and ineligible studies were excluded. Then, the authors reviewed the full texts of the remaining studies to determine their eligibility. Disagreements during the review process were resolved by discussion with other authors.

Data extraction

We classified the included literature into four types: (i) retrospective studies, i.e., studies that retrospectively analyzed the data of COVID-19 patients from medical records; (ii) case reports, i.e., studies

that specifically reported the clinical course of individual patients; (iii) ICU studies, i.e., studies whose data were all from ICU patients; and (iv) surveillance studies, i.e., studies that described outcomes of patients from data gathered by the government.

The following data were extracted from each study: first author, geographic region, study design, sample size, the proportions of deceased patients infected with SARS-CoV-2, the incidence of ARDS, patients admitted to the ICU, and characteristics of both severe and nonsevere patients, including gender, age, underlying comorbidities and laboratory examination.

Statistical and meta analyses

First, proportions were transformed using the Freeman-Tukey double arcsine or arcsine method[8]. Then, we performed a meta-analysis of the proportions related to severity in the R software. RevMan5.3 software was used to perform a meta-analysis on relevant risk factors, such as age, gender, and underlying comorbidities. For binary variables, we calculated odds ratios (ORs) and associated 95% confidence intervals (CIs). The heterogeneity was evaluated by the chi-square test and I^2 statistics. If heterogeneity was obvious ($I^2 > 50\%$, $P < 0.05$), we selected the random effects model for meta-analysis; if heterogeneity was absent ($I^2 < 50\%$, $P > 0.05$), we selected the fixed effects model. To explore the possible sources of heterogeneity, we conducted subgroup analyses based on the study design and geographic region.

Results

In total, 625 articles were identified through the abovementioned databases, and 3 articles were identified by manual searching. After removing 81 duplicate studies and reviewing the titles and abstracts, 131 articles remained for full-text screening. Finally, 55[6, 9–62] papers were included in this systematic review and meta-analysis (Fig. 1). Among these studies, there were 3 case reports[12, 36, 44], 3 ICU studies[22, 25, 55], 8 surveillance studies[15, 17, 31, 37–39, 42, 53] and 41 retrospective studies. Most of the included studies were from China, including the Wuhan area and outside of the Wuhan area.

Forty-eight studies including 8134 patients reported the estimated CFR, and the sample sizes ranged from 3 in a case report[12] to 1265 in a surveillance study[31]. The estimated CFR ranged from 0 to 61.5%, while the pooled CFR was 3.3% (95% CI: 1.5, 5.4). The proportions of ARDS and ICU admission were reported in 16 and 19 studies, respectively. The pooled proportion of ICU admission was 24.9% (95% CI: 13.0, 39.1), and the pooled proportion of ARDS was 20.9% (95% CI: 10.8, 33.3). The pooled incidence rate of severe cases was 26.6% (95% CI: 20.1, 33.6) for 35 studies. The between-studies estimate of heterogeneity for CFR, calculated with I^2 statistics, was 93%, and it was 97% for the rest of the abovementioned proportion. The forest plots are shown in Fig. 2.

The risk of death, ARDS, ICU admission and severe cases were stratified by study design and geographic region. The results of subgroup analyses are presented in Table 1. The CFR in ICU studies and case reports was obviously larger than that in retrospective studies and surveillance studies. ICU studies

yielded the highest pooled risks of ARDS, ICU admission and severe cases. When comparing data between the Wuhan area and outside of the Wuhan area, the risk of death, ARDS, ICU admission and severe cases were all larger in studies that were conducted in Wuhan than in those conducted outside of Wuhan.

Table 1
subgroup analyses

subgroup	CFR(95% CI) (%)	Risk of ARDS(95% CI) (%)	Risk of ICU admission(95% CI) (%)	Risk of severe cases(95% CI) (%)
design				
retrospective study	3.3(1.5,5.8)	14.1(6.2,24.7)	11.4(4.6,20.6)	28.3(20.6,36.7)
ICU study	20.0(0.0,78.7)	87.4(50.5,100.0)	100(98.6,100))	100(92.2,100)
surveillance study	0.5(0.1,1.3)	3.4(2.4,4.5)	5.0(3.8,6.4)	10.1(5.9,15.3)
case report	16.5(2.7,38.6)	0.0(0.0,0.6)	33.3(0.2,85.6)	40.0(6.0,81.3)
region				
Wuhan	10.0(5.9,14.8)	28.3(17.9,40.0)	38.5(20.7,58.0)	40.0(27.4,53.2)
outside of Wuhan	0.0(0.0,0.1)	12.6(0.7,35,8)	13.2(0.8,37.4)	18.3(12.2,25.3)

Age and gender distributions related to the severity of COVID-19 are shown in Fig. 3. Eight studies assessed older age as a risk factor for severe patients. The pooled OR for the association between male sex and severe COVID-19 was 1.62 (95% CI: 1.32, 1.99).

A meta-analysis of the association between seven selected comorbidities is shown in Fig. 4. The pooled ORs were larger than 1 for six underlying comorbidities, including hypertension, diabetes, renal disease, heart disease, respiratory disease and cerebrovascular disease. However, for liver disease, the pooled OR was 0.63 (95% CI: 0.36, 1.10). Among these underlying medical conditions, the association between respiratory disease and the severity of COVID-19 had the highest OR value of 3.74 (95% CI: 2.15, 6.49), followed by renal disease with an OR of 3.60 (95% CI: 1.53, 8.46). Heterogeneity was only present in the comorbidities of hypertension (I^2 = 64%, P = 0.001).

D-dimer and interleukin-6 (IL-6) levels were regarded as risk factors and were also assessed by a small number of studies. For D-dimer levels, the combined results of eight studies were statistically significant (SMD = 0.62, 95% CI: 0.28, 0.96), and the I^2 value was 76%. In terms of IL-6 levels, there was an apparent difference between the severe group and the nonsevere group (SMD = 2.21, 95% CI: 0.11, 4.31), but the

included studies showed substantial heterogeneity (I^2 = 99%, P < 0.00001). Figure 5 shows the forest plots.

Discussion

The rapid spread of SARS-CoV-2, which occurs via human-to-human transmission, has caused a large global outbreak and is a serious public health issue. SARS-CoV-2, a zoonotic betacoronavirus, attacks alveolar epithelial cells, and its symptoms can vary from asymptomatic infection to death[63–64].

We performed a systematic review of the articles that examined the risk of severe manifestations and death due to SARS-CoV-2 and the risk factors for the severity of COVID-19. In our studies, the CFR and the risks of ARDS, ICU admission and severe COVID-19 were estimated. A majority of the included articles were from China, and the pooled CFR was 3.3%, which was similar to the crude fatality ratio in China reported by the WHO[65]. However, the overall CFR in Italy (7.2%) is much higher[66]. Basu used a statistical model to estimate the CFR for COVID-19 among symptomatic cases, and the outcome was 1.3% (95% CI: 0.6, 2.1)[67]. This suggests that our findings may apply to China rather than the entire world. The pooled risks of ARDS, ICU admission and severe patients were 20.9%, 24.9% and 26.6%, respectively. Compared with SARS and MERS, COVID-19 has a smaller CFR, and fewer patients develop severe disease[68–70]. Nevertheless, because of its wide spread, COVID-19 has become a threat to human beings. Subgroup analyses suggested that study design and geographic region may be sources of high heterogeneity.

The results of the meta-analysis indicate that male and elderly patients are more likely to progress to severe COVID-19. Patients with underlying medical conditions are at risk of severe COVID-19, such as hypertension, diabetes, renal disease, heart disease, respiratory disease and cerebrovascular disease. Another meta-analysis showed that smoking is a risk factor for COVID-19 severity[71]. The generation of IgG antibodies in female patients was stronger than that in male patients in the early phase of disease and in severe status[72]. Therefore, the poor habit and discrepancy in SARS-CoV-2 IgG antibody levels may partly explain why men tend to develop severe cases more often than women. Older age means a greater likelihood of having comorbid chronic diseases and a decline in the body’s immunity, which are consistent with our findings.

There are several biological mechanisms that appear to influence the immune system and by which patients with underlying health conditions are at an increased risk of severe COVID-19. Current evidence indicates that neutrophils in diabetes patients lack chemotaxis and oxidative killing potential and that leukocyte bactericidal activity is reduced[73–74]. Abnormal activation of the renin-angiotensin-aldosterone system (RAAS) plays an important role in the occurrence of hypertension, and angiotensin II is known to foster inflammation, oxygenation and fibrosis, which may aggravate lung injury[75]. However, although several published studies have confirmed that SARS-CoV-2 can enter the body through angiotensin-converting enzyme 2 (ACE2), whether RAAS inhibitors have a higher risk of COVID-19 is still unclear[76–78]. Both respiratory diseases, such as asthma and chronic obstructive pulmonary disease,

and chronic kidney disease can impair innate immune cell function, leading to severe outcomes when patients are infected with pathogens[79–80]. However, we are surprised that there was no significant association between preexisting chronic liver disease and COVID-19 severity according to our meta-analysis. Relevant mechanisms require further study.

Our analysis showed that the levels of IL-6 and D-dimer in severe COVID-19 are obviously higher than those in nonsevere patients. Wang et al. reported that IL-6 and IL-10 levels in plasma were significantly higher in the SpO2 < 90% group than in the SpO2 < 90% group[61]. Chang et al. indicated that hs-CRP and PCT can also be used to predict the risk of severity in patients with COVID-19[58]. Chen et al. stated that the levels of interleukin-2 receptor (IL-2R) and IL-6 in the serum in the severe group were significantly higher, but the levels of tumor necrosis factor-α (TNF-α), IL-1, IL-8, IL-10 and hs-CRP were not significantly different between the severe group and the common group[32]. Huang et al. examined a large set of laboratory data and found that ICU patients had higher plasma levels of IL-2, IL-7, IL-10, GSCF and TNF-α[9]. In conclusion, inflammatory storms may play an important role in the severity of COVID-19. However, given the lack of data, we failed to estimate other inflammatory mediators in this meta-analysis.

There are some limitations to the present study: 1) all of the included studies are retrospective observational studies with insufficient ability to deduce causality; 2) most patients in our meta-analysis were Chinese, so the outcomes may be limited to predicting patients in general, including other countries and races; 3) predictors of severity in the present study are limited, and exploring more predictors requires more relevant and carefully designed studies and individual data.

Conclusion

This study provided a quantitative pooled risk of fatality and severity and identified risk factors for COVID-19 severity. To some degree, this study demonstrated the current state of our knowledge about COVID-19 and its impact on human health outcomes. Paying attention to these risk factors can reduce the risk of death.

Abbreviations

COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ARDS: acute respiratory distress syndrome; CFR: case fatality risk; ICU: intensive care unit; OR: odds ratios; CI: confidence intervals; IL-6: interleukin-6; RAAS: renin-angiotensin-aldosterone system; ACE2: angiotensin-converting enzyme 2.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The collected datasheet is available from the authors (Wu Y.L.) upon request.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' contributions

Wu Y.L. conceived the systematic review. Wu Y. L and Li H implemented the systematic review of the literature. Wu Y. L and Li H performed statistical analyses. Wu Y. L and Li H drafted the early version of the manuscript. Wu Y. L substantially rewrote the text. Li S. J further revised the manuscript.

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Figures

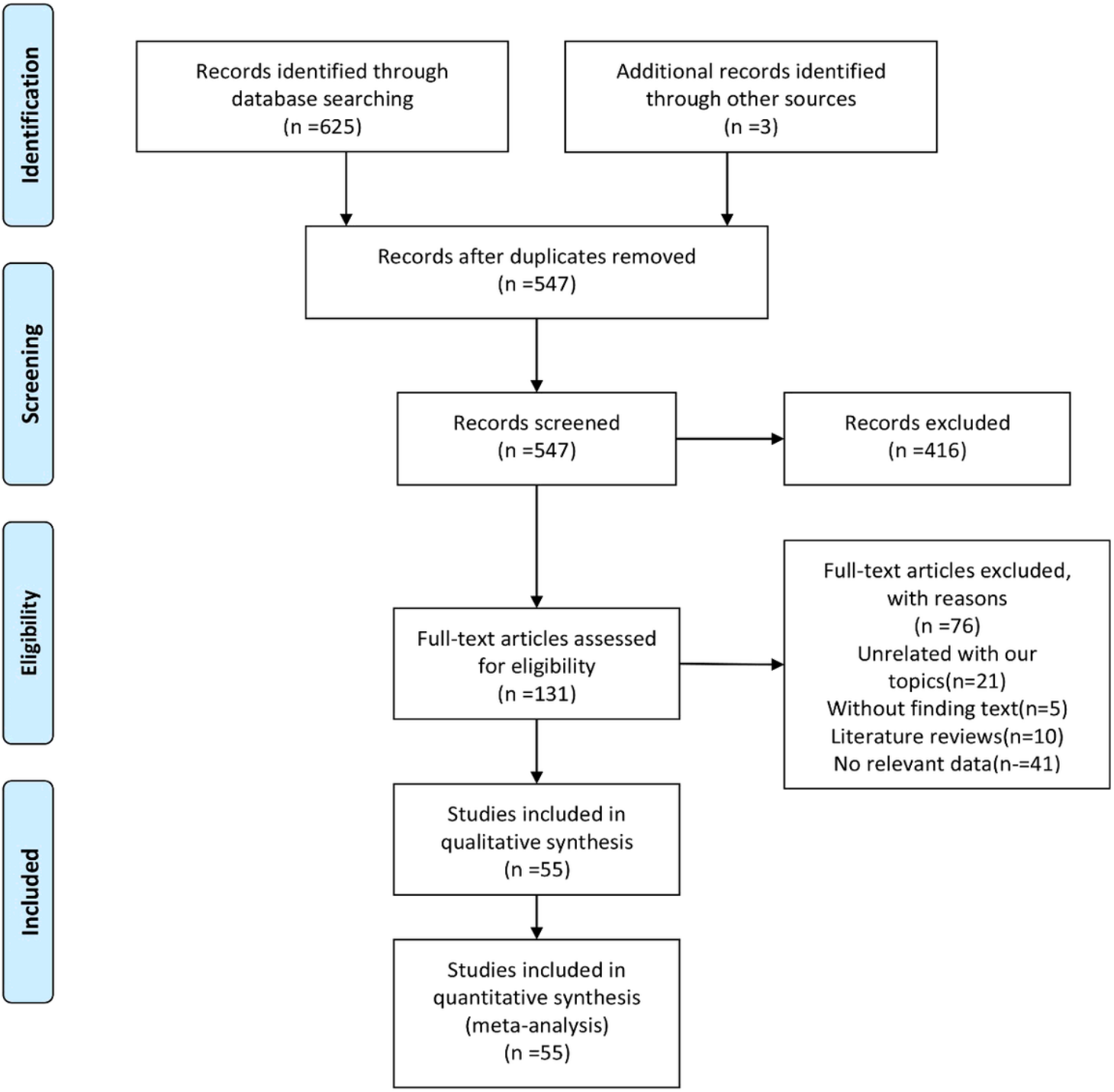

Figure 1

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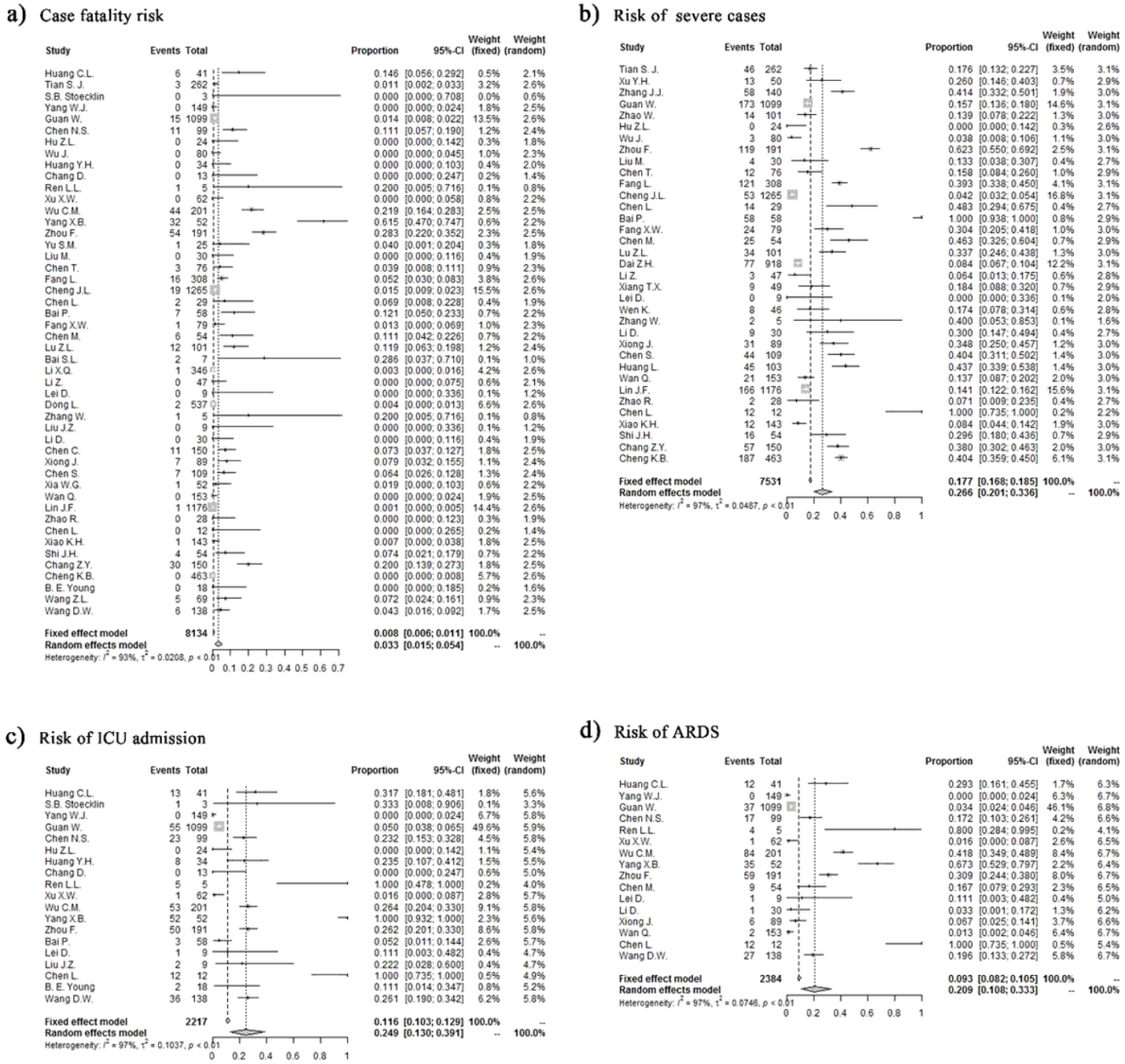

Figure 2

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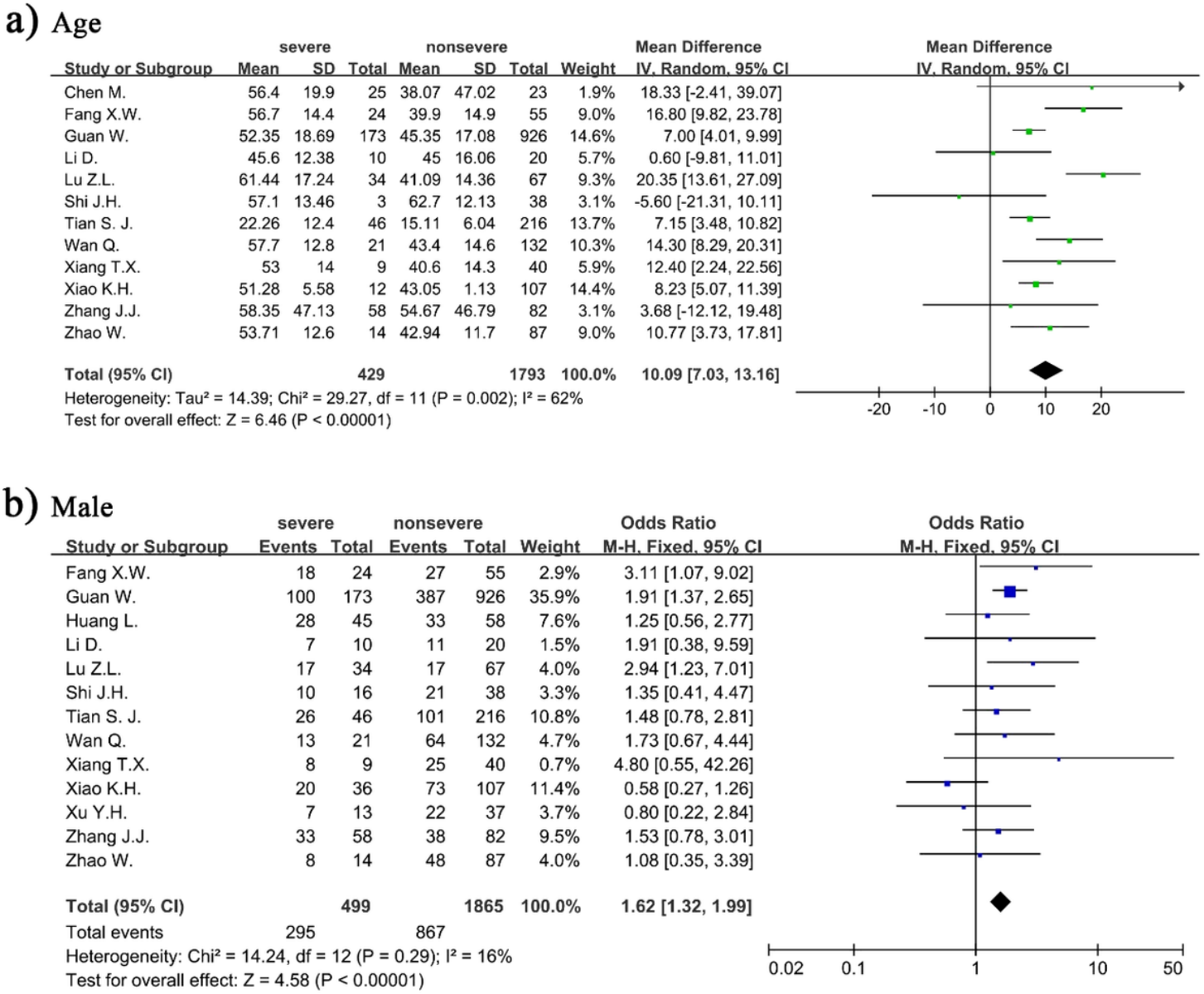

Figure 3

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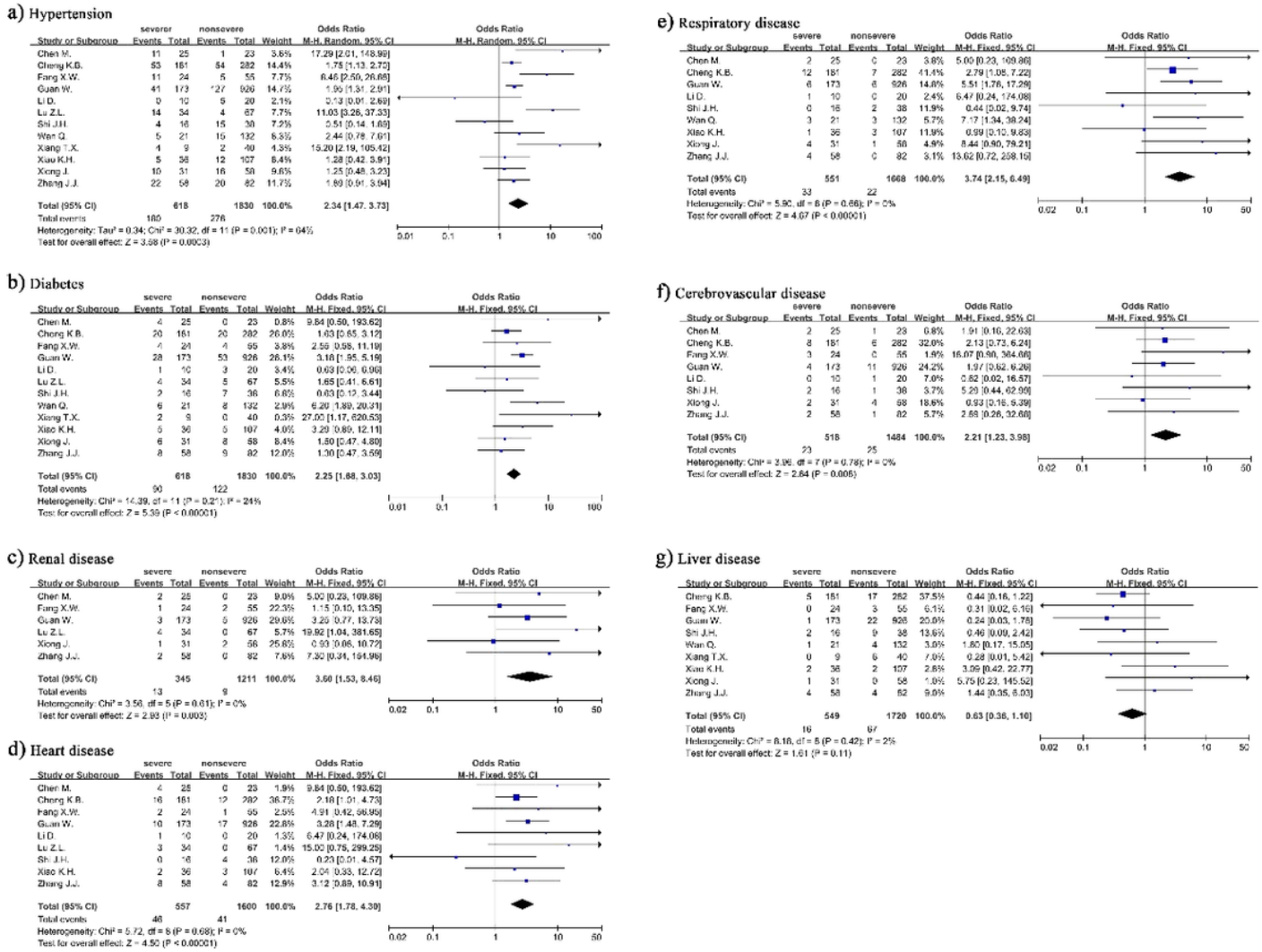

Figure 4

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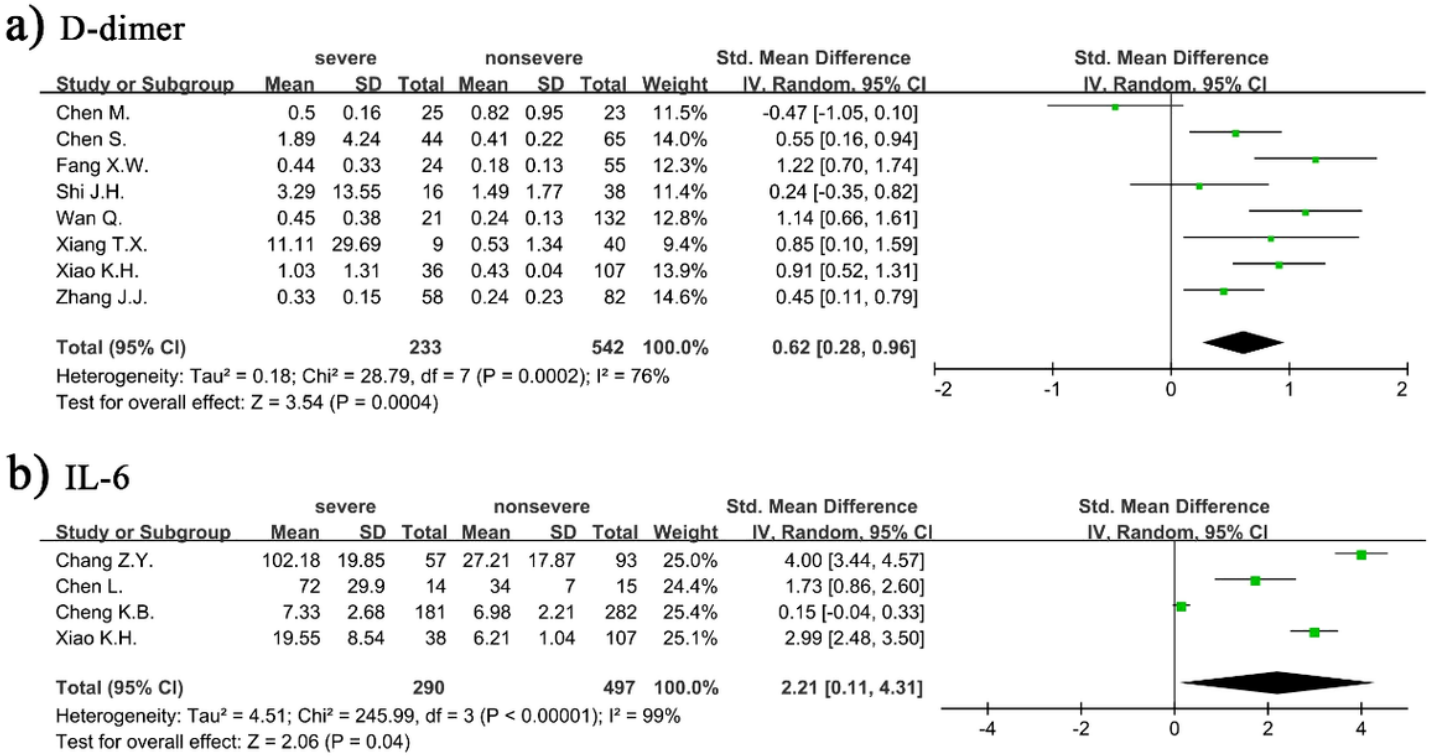

Figure 5

Figure 5

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