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Risk factors for mortality of adult inpatients with Coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis of retrospective studies

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is an emerging disease that was first reported in Wuhan city, the capital of Hubei province in China, and has subsequently spread worldwide. Risk factors for mortality have not been well summarized. Current meta-analysis of retrospective cohort studies was done to summarize available findings on the association between age, gender, comorbidities and risk of death from COVID-19 infection.

Methods: Online databases including Web of Science, PubMed, Scopus and Google scholar were searched to detect relevant publications up to 22 March 2020, using relevant keywords. To pool data, random-effects model was used. Furthermore, sensitivity analysis and publication bias test were also done.

Results: In total, six retrospective studies with 22,350 COVID-19 infected patients and 741 cases of death were included in the current meta-analysis. A significant positive association was found between older age (≥65 years old) and COVID-19 mortality (combined effect size=2.39 (over twofold), 95% CIs=1.75-3.28, p<0.001). Such finding was also seen for hypertension (combined effect size=3.29 (over threefold), 95% CIs=1.54-7.05, p=0.002), diabetes (combined effect size=3.11 (over threefold), 95% CIs=1.10-8.80, p=0.032), chronic obstructive pulmonary disease (COPD) (combined effect size=7.69 (over sevenfold), 95% CIs=5.65-10.47, p<0.001) and cardiovascular diseases (CVDs) (combined effect size=7.39 (over sevenfold), 95% CIs=2.88-18.96, p<0.001).

Conclusions: Older age, hypertension, diabetes, COPD and CVDs were associated with greater risk of death from COVID-19 infection. These findings could help clinicians to identify patients with poor prognosis at an early stage.

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Keywords: COVID-19; novel coronavirus; SARS-CoV-2; Mortality; Meta-analysis.

Introduction

In December, 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously known as 2019-nCoV) was first reported in Wuhan city, the capital of Hubei province in China, and has subsequently spread to other regions of China and 199 countries and territories (1-3). SARS-CoV-2, which belongs to a unique clade of the sarbecovirus subgenus of the Orthocoronavirinae subfamily (4), was later designated coronavirus disease 2019 (COVID-19) in February, 2020, by World Health Organization.

Patients with COVID-19 present primarily with fever, dry cough and fatigue or myalgia (5). Although most patients with COVID-19 are thought to have a favorable prognosis, older patients and those with chronic diseases may have worse outcomes (6). Patients with chronic underlying conditions may develop viral pneumonia, dyspnea and hypoxemia within 1week after onset of the disease, which may progress to respiratory or end-organ failure and even death (7).

Several studies have reported the clinical characteristics and risk factors associated with death in patients with COVID-19 pneumonia (2, 6, 8-11). We are aware of no systematic review and meta-analysis that summarized available findings in this regard. Thus, we aimed to systematically review the present evidences on the association between age, gender, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular diseases (CVDs) and risk of death from COVID-19 infection, and to summarize the available findings in a meta-analysis.

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Materials and methods

Study protocol

The present systematic review and meta-analysis were planned, conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (12).

Search strategy

We performed a literature search using the online databases of ISI Web of Science, PubMed, Scopus and Google scholar for relevant publications up to 22 March 2020. The following medical subject headings (MeSH) and non-MeSH keywords were used in our search strategy: ("novel coronavirus" OR "SARS-CoV-2" OR "COVID-19") AND ("death" OR "mortality" OR "survival" OR "fatal outcome"). Literature search was done by two independent researchers (MP and SY). We also searched the reference lists of the relevant articles to identify missed studies. No restriction was applied on language and time of publication. To facilitate the screening process of articles from databases, all literature searches were downloaded into an EndNote library (version X8, Thomson Reuters, Philadelphia, USA).

Eligibility Criteria

In our meta-analysis, eligible articles were included if they met the following inclusion criteria: (1) all studies assessing the association between age, gender, comorbidities and mortality risk from COVID-19 infection as the major outcomes of interest; (2) observational studies with retrospective

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design; (3) those that reported hazard ratios (HRs), odds ratios (ORs) or relative risks (RRs) along with 95% confidence intervals (CIs) for the relationship between risk factors and COVID-19 mortality. Review articles, expert opinion articles, theses and books were excluded.

Data extraction and assessment for study quality

Two investigators (MP and AS) extracted the following data from the included studies: study design, the first author's name, the publication year, age and gender of patients, sample size, exposure (risk factors), outcome (the risk of mortality), exposure and outcome assessment methods, most adjusted risk estimate (HRs, ORs, RRs) with 95% confidence intervals and adjusted confounding variables.

The Newcastle–Ottawa Scale (NOS) was used for assessing the quality of included retrospective cohort studies based on the following three major components: selection of the study patients, adjustment for potential confounding variables and assessment of outcome (13). Based on this scale, a maximum of nine points can be awarded to each study. In the present study, articles with the NOS score of ≥ 5 were considered as high quality publications.

Statistical analysis

We used HRs, ORs, and RRs (and their 95% confidence intervals) reported for the association between risk factors and mortality from COVID-19 infection, to calculate log RRs and their standard errors (SEs). Then, the overall effect size for mortality in relation to risk factors was calculated using random-effects model. For examining the between-study heterogeneity, we

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109 performed the Cochran's Q test ($I^2 \geq 50\%$ were considered between-study heterogeneity) (14). To
110 identify potential sources of heterogeneity, we did subgroup analysis according to the predefined
111 criteria as follows: age (≥65 vs. <65), gender (male vs. female), hypertension (yes vs. no), diabetes
112 (yes vs. no), COPD (yes vs. no) and CVDs (yes vs. no). In addition to the main analysis, we carried
113 out sensitivity analysis to find if the overall estimate depended on the effect size from a single
114 study. Assessing the publication bias was done by the formal test of Egger (15). All statistical
115 analyses were conducted using Stata, version 14.0 (Stata Corp, College Station, TX, USA). P-
116 values were considered significant at level of < 0.05.

117

118 *Results*

119 *Search results*

120 In our initial search, we found 135 papers. Of these, 15 duplicates, 17 non-English, 26 non-human,
121 46 reviews and 17 studies that did not fulfill our eligibility criteria were excluded, leaving 14
122 papers for further evaluation. Out of remaining 14 papers, 8 were excluded because of the
123 following reason: did not report HRs, ORs or RRs with 95% CIs. Finally, we included 6
124 retrospective studies in the current systematic review and meta-analysis (Figure 1).

125

126 *Study characteristics*

127 All studies were conducted in Wuhan, China and used retrospective cohort design (2, 6, 8-11). The
128 sample size of studies varied from 172 to 20812 patients (mean age, 58.7 years). Five studies used

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real-time reverse transcriptase–polymerase chain reaction (RT-PCR) (2, 6, 8, 10, 11) and one study used clinical features (9) to identify COVID-19 infection. The NOS scores ranged between 5 to 8.

Demographic characteristics and risk of death from COVID-19

In the meta-analysis of six effect sizes, obtained from six studies (2, 6, 8-11) (22,350 patients and 741 cases of death), we found that older age (≥65 years old) was associated with a 239% (over twofold) increased risk of COVID-19 mortality (combined effect size=2.39, 95% CIs=1.75-3.28, $p<0.001$, $I^2=95.4\%$, $p_{heterogeneity}<0.001$) (Figure 2). Combining five effect sizes from five studies (2, 6, 8-10) revealed no significant association between gender (male vs. female) and COVID-19 mortality (combined effect size=1.25, 95% CIs=0.75-2.09, p=0.399, $I^2=83.8\%$, $p_{heterogeneity}<0.001$) (Figure 2).

Comorbidities and risk of death from COVID-19

Totally, fifteen effect sizes from five studies (2, 6, 8, 10, 11) with a total of 21,640 patients and 652 cases of death were extracted for the association between comorbidities and COVID-19 mortality. Combining the reported estimates, we found a significant positive association between hypertension (combined effect size=3.29, 95% CIs=1.54-7.05, p=0.002, $I^2=86.3\%$, $p_{heterogeneity}<0.001$), diabetes (combined effect size=3.11, 95% CIs=1.10-8.80, p=0.032, $I^2=91.3\%$, $p_{heterogeneity}<0.001$), COPD (combined effect size=7.69, 95% CIs=5.65-10.47, $p<0.001$, $I^2=0.0\%$, $p_{heterogeneity}=0.919$), CVDs (combined effect size=7.39, 95% CIs=2.88-18.96, $p<0.001$, $I^2=61.5\%$, $p_{heterogeneity}=0.075$) and risk of death from COVID-19 (Figure 3). We found that hypertension, diabetes, COPD and CVDs were associated with 329% (over threefold), 311% (over threefold),

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769% (over sevenfold) and 739% (over sevenfold) higher risk of COVID-19 mortality, respectively.

Sensitivity analysis and publication bias

Findings from sensitivity analysis showed that overall estimates on the association of demographic characteristics and comorbidities with COVID-19 mortality did not depend on a single study. Furthermore, based on the results of Egger's test (hypertension; P=0.077, diabetes; P= 0.65, COPD; P=0.456 and CVDs; P=0.401), we found no evidence of publication bias.

Discussion

Findings from the current systematic review and meta-analysis supported the hypothesis that older age (≥65 years old), hypertension, diabetes, COPD and CVDs were associated with higher risk of mortality from COVID-19 infection. To the best of our knowledge, current study is the first meta-analysis to summarize earlier retrospective studies on the association between demographic characteristics, comorbidities and risk of death from COVID-19.

Our findings are partially in agreement with previous narrative review (16). Previously, older age has been reported as an important risk factor for mortality in SARS and Middle East respiratory syndrome (MERS) (17, 18). The current meta-analysis confirmed that increased age (≥65 years old) was associated with death in COVID-19 patients. The age-dependent defects in B-cell and T-cell function and the excess production of type 2 cytokines could lead to prolonged proinflammatory responses and deficiency in control of viral replication, potentially leading to

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poor outcome (19). In addition, elderly patients may have other risk factors, such as sarcopenia and comorbidities (11).

Previous studies suggested that COVID-19 infection is more likely to affect older males with comorbidities, and can result in fatal respiratory diseases such as acute respiratory disease syndrome (10, 20). Interestingly, SARS and MERS also infected more males compared to females (21, 22). Differences in the levels and type of circulating sex hormones in males and females might influence the susceptibility of COVID-19 infection. Previous study showed that sex hormones modulate the responses of adaptive and innate immunity (23). However, our findings showed that gender was not a risk factor for mortality in COVID-19 patients.

The other risk factors related to death include hypertension, diabetes, respiratory system disease and CVDs. A previous study showed that hypertension and diabetes are more prevalent in patients with severe MERS infection (22). Similarly, the mortality rate of influenza was significantly higher in patients with hypertension, metabolic disease, CVDs and respiratory system disease (24). Previous studies reported that high protein expression of angiotensin converting enzyme 2 (ACE2) receptor, the receptor for COVID-19, in specific organs correlated with organ failures in SARS patients (25-28). It has been shown that circulating ACE2 levels are higher in patients with hypertension, diabetes and CVDs (29, 30). Therefore, patients with these comorbidities may be more prone to die from COVID-19 infection because of the high expression of ACE2 receptor, though further research on the mechanism is needed.

The pathogenesis of COVID-19 is still not completely understood. Cytokine storm is thought to play an important role in disease severity (31). Neutrophilia was found in both the lung and peripheral blood of patients with SARS (32, 33). The severity of lung damage correlated with higher numbers of neutrophils and macrophages in the peripheral blood and extensive pulmonary

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infiltration of these cells in patients with MERS (34-36). Neutrophils are the main source of cytokines and chemokines. The generation of cytokine storm can lead to acute respiratory distress syndrome, which is a leading cause of death in patients with SARS and MERS (36, 37). This may explain the positive association between high fever and acute respiratory distress syndrome found at the early stages of COVID-19 infection (6).

The present study has some limitations. First, interpretation of our meta-analysis findings might be limited by the small sample size. However, by including studies conducted in different designated hospitals for COVID-19, we believe our findings are representative of cases in Wuhan, China. Second, our meta-analysis did not include data such as smoking history and body mass index, which are potential risk factors for disease severity and mortality.

Conclusion

Older age, hypertension, diabetes, COPD and CVDs were associated with greater risk of death from COVID-19 infection. The results of the present meta-analysis could help clinicians to identify high risk groups that should receive off-label medications or invasive supportive care, as soon as possible.

Contributors: MP, SY, AS and MHJ conceived the study conception and design. MP, SY and PS contributed to the literature search. MP, SY, AS and MD performed the acquisition of data. MP, SY, MHJ and MD conducted the analysis and interpretation of data. MP, AS, PS and MD drafted the manuscript. MP, MHJ and MD contributed to critical revision of the manuscript.

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Table 1. Characteristics of studies included in the meta-analysis.

Authors (year)	Design of study	Country	Mean age (y)	Sample size	Sex	Death cases	COVID-19[a] detection	Demographic and clinical characteristics	HR, OR or RR (95%CI)[b]	Adjustment
Wu et al. (2020)	Retrospective cohort	China	51	201	F/M	44	real-time RT-PCR	Age (≥65 vs <65 years) Gender (male vs female) Hypertension (yes vs no) Diabetes (yes vs no)	HR: 6.17 (3.26-11.67) HR: 0.56 (0.30-1.05) HR: 1.70 (0.92-3.14) HR: 1.58 (0.80-3.13)	-
Zhou et al. (2020)	Retrospective cohort	China	56	191	F/M	54	real-time RT-PCR	Age (≥65 vs <65 years) Gender (male vs female) Hypertension (yes vs no) Diabetes (yes vs no) COPD (yes vs no) CVDs (yes vs no)	OR: 1.10 (1.03-1.17) OR: 0.61 (0.31-1.20) OR: 3.05 (1.57-5.92) OR: 2.85 (1.35-6.05) OR: 5.40 (0.96-30.40) OR: 2.14 (0.26-17.79)	study center
Caramelo et al. (2020)	Retrospective cohort	China	-	20812	F/M	504	real-time RT-PCR	Age (≥65 vs <65 years) Gender (male vs female) Hypertension (yes vs no) Diabetes (yes vs no) COPD (yes vs no) CVDs (yes vs no)	OR: 18.82 (7.20-41.55) OR: 1.85 (1.60-2.13) OR: 7.42 (6.33-8.79) OR: 9.03 (7.39-11.35) OR: 7.79 (5.54-10.43) OR: 12.83 (10.27-15.86)	age, gender and comorbidities
Cheng et al. (2020)	Consecutive cohort	China	63	710	F/M	89	respiratory rate > 30/min, or oxygen saturation ≤ 93%, or PaO2/FiO2 ratio ≤ 300mmHg	Age (≥65 vs <65 years) Gender (male vs female)	HR: 2.51 (1.64-3.86) HR: 2.44 (1.53-3.87)	age, gender, disease severity, leukocyte count and lymphocyte count
Su et al. (2020)	Retrospective cohort	China	71.6	172	F/M	32	real-time RT-PCR	Age (≥65 vs <65 years) Gender (male vs female) Hypertension (yes vs no) Diabetes (yes vs no) COPD (yes vs no) CVDs (yes vs no)	OR: 26.00 (7.50-89.8) OR: 1.53 (0.75–3.13) OR: 3.50 (1.10-10.80) OR: 1.90 (0.60-5.50) OR: 7.40 (0.80-67.00) OR: 5.10 (1.70-15.60)	-
Wang et al. (2020)	Retrospective cohort	China	47.8	264	F/M	18	real-time RT-PCR	Age (≥65 vs <65 years) Hypertension (yes vs no)	OR: 1.07 (1.01-1.13) OR: 2.24 (0.57-8.72)	-

Abbreviations: [a]COVID-19: Coronavirus diseases 2019, [b]HR: Hazard ratio, OR: Odds ratio, RR: Relative risk.

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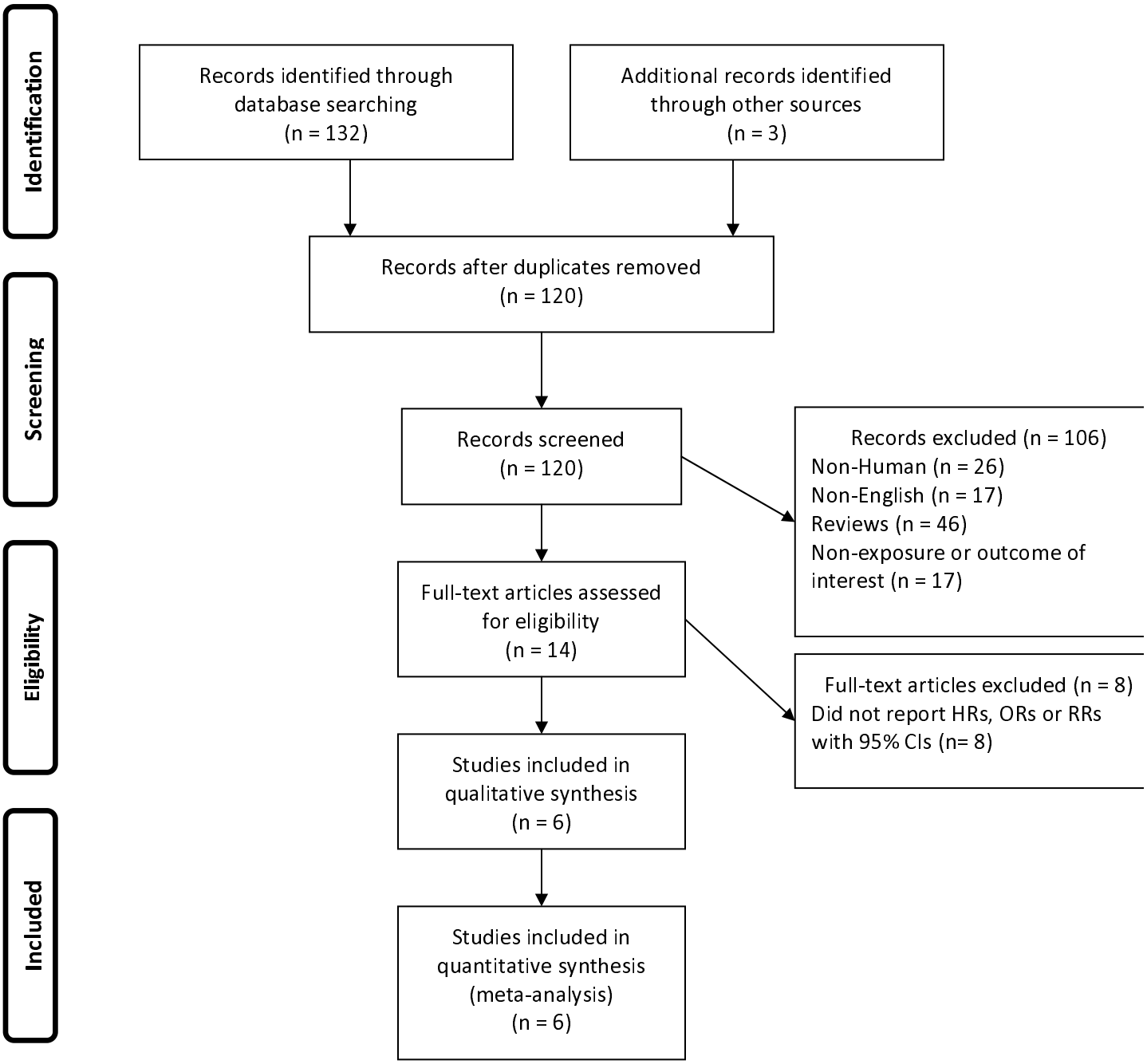

Figure 1. Flow chart of study selection.

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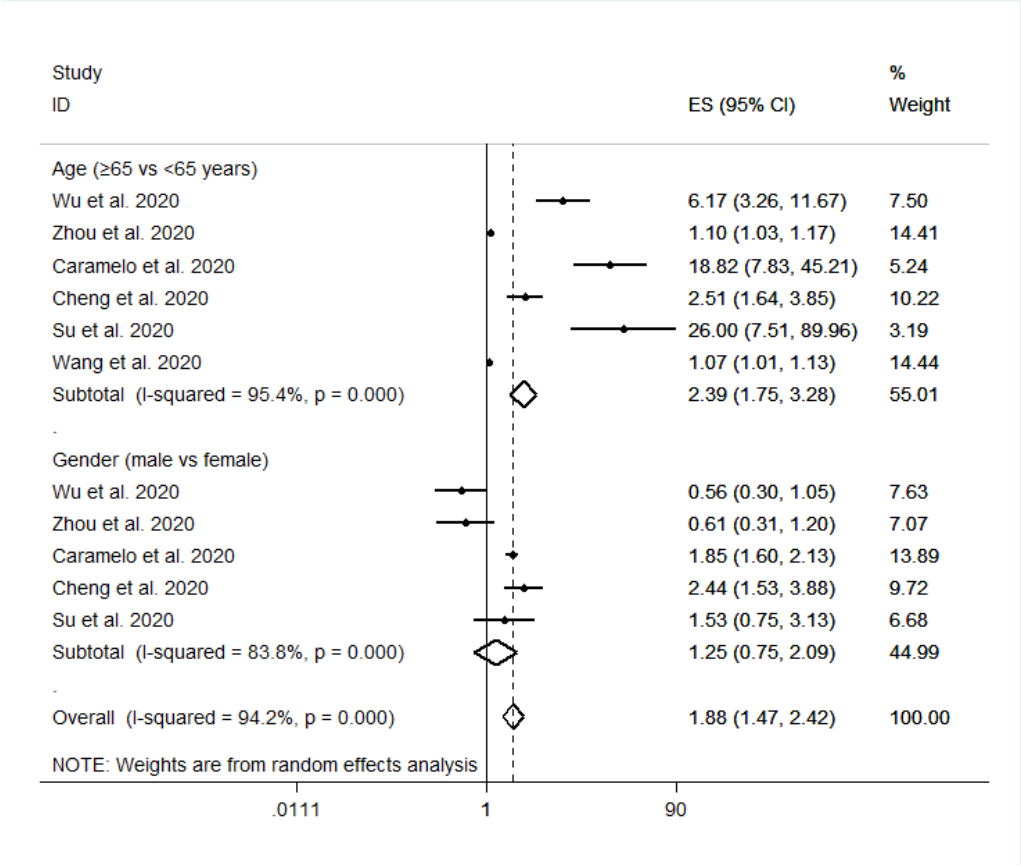

Figure 2. Forest plot for the association between age, gender and risk of mortality from COVID-19 using random-effects model.

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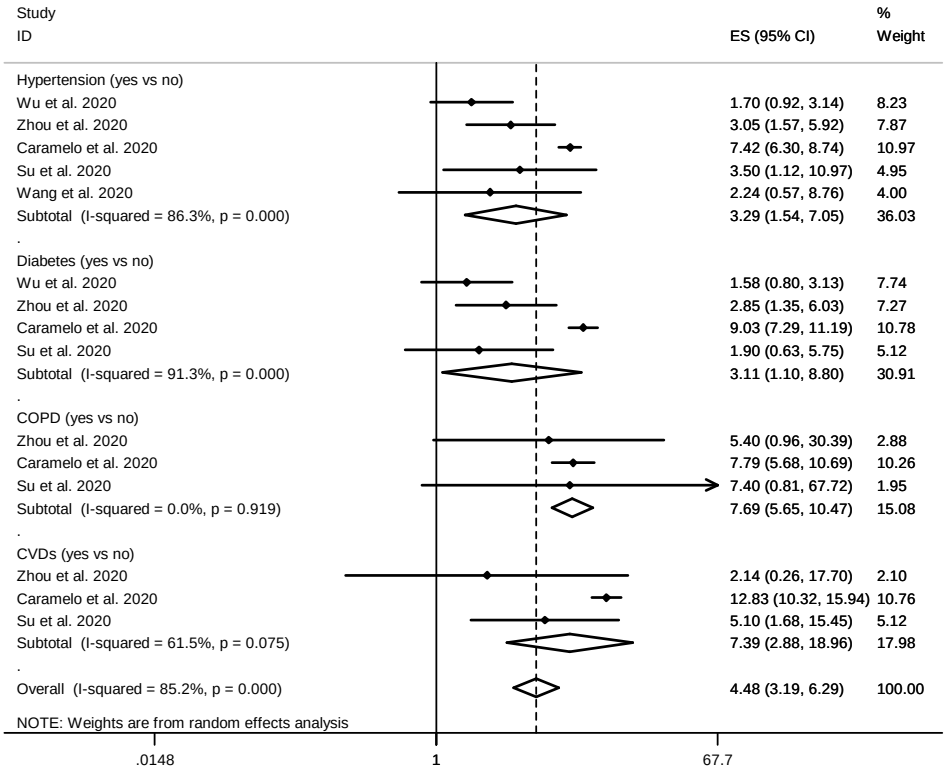

Figure 3. Forest plot for the association between comorbidities and risk of mortality from COVID-19 using random-effects model. Chronic obstructive pulmonary disease (COPD), Cardiovascular diseases (CVDs).