

The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: A systematic review and meta-analysis

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Abstract

Background: Whether cardiovascular disease (CVD) and its traditional risk factors predict severe coronavirus disease 2019 (COVID-19) is uncertain, in part, because of potential confounding by age and sex.

Methods: We performed a systematic review of studies that explored pre-existing CVD and its traditional risk factors as risk factors of severe COVID-19 (defined as death, acute respiratory distress syndrome, mechanical ventilation, or intensive care unit admission). We searched PubMed and Embase for papers in English with original data (≥ 10 cases of severe COVID-19). Using random-effects models, we pooled relative risk (RR) estimates and conducted meta-regression analyses.

Results: Of the 373 publications identified in our search, 15 papers met our inclusion criteria, with 51,845 COVID-19 patients including 9,066 severe cases. Older age was consistently associated with severe COVID-19 in all eight eligible studies, with RR ~ 5 in >60 - 65 vs. <50 years. Two studies showed no change in the RR of age after adjusting for covariate(s). In univariate analyses, factors significantly associated with severe COVID-19 were male sex (14 studies; pooled RR=1.70, [95%CI 1.52-1.89]), hypertension (10 studies; 2.74 [2.12-3.54]), diabetes (11 studies; 2.81 [2.01-3.93]), and CVD (9 studies; 3.58 [2.06-6.21]). RR for male sex was likely to be independent of age. Meta-regression analyses were suggestive of confounding by age for the other three factors. Only two studies reported multivariable analysis, with one showing non-significant association for CVD and the other demonstrating adjusted RR ~ 2 for hypertension and diabetes. No study explored renin-angiotensin system inhibitors as a risk factor for severe COVID-19.

Conclusions: In addition to older age and male sex, hypertension, diabetes, and CVD were associated in univariate analyses with severe COVID-19. Although there is still uncertainty

regarding the magnitude of potential confounding, these risk factors can be used to inform objective decisions on COVID-19 testing, clinical management, and workforce planning.

Introduction

Cases of coronavirus disease 2019 (COVID-19) are rapidly increasing globally. As of April 5, 2020, more than 1.2 million cases have been confirmed and ~70,000 deaths have been reported in ~180 countries.¹ Several studies have rapidly provided crucial data (e.g., incubation period) related to various aspects of the novel coronavirus (SARS-CoV-2 : severe acute respiratory syndrome coronavirus 2) infection.² However, risk factors for the severity and prognosis of COVID-19 are poorly understood. Such information is critical to identify high risk patients and to facilitate planning (e.g., forecasting the need for hospital beds and mechanical ventilators). These risk factors will also have implications for workforce allocation (e.g., assignment of healthcare providers with specific risk factors to positions with reduced risk of exposure to COVID-19).

To date, several studies have reported that a history of cardiovascular disease (CVD) and traditional CVD risk factors, e.g., age, male sex, current smoking, hypertension, and diabetes, are associated with severe COVID-19. However, other than age, results have been inconsistent. Furthermore, few studies accounted for potential confounding by age and sex when they evaluated other potential risk factors. For example, some studies reported that hypertension is a risk factor of severe COVID-19, but their observations may simply reflect the fact that hypertension is more common in older adults.³ Nonetheless, despite the lack of robust evidence, this observation, together with the fact SARS-CoV-2 uses angiotensin-converting enzyme 2 as an entry to human body,⁴ has raised a concern about continued use of renin-angiotensin system increase among some clinicians and researchers.^{5,6}

In this context, we conducted a systematic review of studies reporting cardiovascular risk factors and their relation to severe manifestation of COVID-19 (i.e., death, acute respiratory distress syndrome [ARDS], the need of mechanical ventilator support, and admission to an intensive care unit [ICU]), with a particular interest on studies that adjusted for key confounders such as age and sex.

Methods

Search strategy

We conducted this systematic review following the PRISMA Statement. According to the pre-determined protocol, we systematically searched PubMed and Embase for eligible reports (search terms are listed in Web Appendix 1). We included full reports or letters with original data written in English. Eligible study designs were cohort study, cross-sectional, case series, and clinical trials. We conducted the literature search on March 20, 2020 and restricted to publications after December 1, 2019.

Our review included studies that reported adult patients, aged 18 years or older. There was no restriction with respect to gender, race/ethnicity, and comorbidities. The primary outcome of interest was severe COVID-19 defined by any of the following: all-cause mortality, ICU admission, ARDS, or the need for mechanical ventilation. We included studies reporting at least 10 cases of severe COVID-19. To obtain reliable estimates with enough number of outcomes and considering clinical cascade (e.g., death as the final outcome), when one study reported results for multiple outcomes, we prioritized any composite outcome followed by ICU admission, ARDS, the need of mechanical ventilation, and mortality.

Potential risk factors of interest were pre-existing CVD (including cardiac disease and cerebrovascular disease) and its traditional risk factors recognized in major CVD clinical guidelines: age, sex, smoking, hypertension, and diabetes. We found only one study reporting severity of COVID-19 by lipids (low-density lipoprotein). We categorized risk factors into sociodemographic factors (age, sex, and smoking) and clinical factors (hypertension, diabetes, and pre-existing CVD).

Study selection

One author (N.D.) conducted the literature search, exported eligible publications to EndNote X8 reference manager (Thomson Reuters, Philadelphia, Pennsylvania), and uploaded them to Covidence (Melbourne, Australia), a platform for literature screening. Eight reviewers (N.D., M.K., Y.G., Y.H., Y.M., X.H., M.C., and J.I.) worked in pairs to independently screen titles and abstracts. For research letters without abstracts, reviewers used text content for the initial screening. All conflicts were resolved by one of two lead reviewers (N.D., M.K.). For all publications accepted at this step, the same pairs performed the full detailed text review to evaluate final eligibility. The two lead reviewers resolved any conflicts.

Data collection and quality assessment

The same eight reviewers collected relevant data elements from each identified publication and recorded in Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA). Overall quality was based on the Newcastle Ottawa Quality Assessment Scale (NOS),⁷ which includes eight items about selection, comparability, and outcome (Web Appendix 2). The NOS score for cohorts studies ranges from 0 to 9; a score greater than 6 was considered high-quality. For cross-sectional studies, we applied an adapted form of the NOS.⁸ The maximum score was 10, and 7 points were used to identify studies with high quality. The paired reviewers resolved conflicts related to their own data collection and quality assessment.

Data synthesis and analysis

We summarized relative risk estimates (odds ratios or hazard ratios) of the association between each risk factor and the primary outcome from the relevant studies. We pooled these estimates using random-effects meta-analysis. When studies did not report these measures of association but the prevalence of risk factors of interest by the outcome status (e.g., survivors vs. non-survivors), we calculated crude odds ratios and their 95% CIs. In this process, when there was any cell with zero count, we added 0.5 to each cell, as appropriate.⁹

Potential confounding by age and sex is relevant to prior CVD, hypertension, and diabetes, since these comorbidities become more prevalent with increased age.³ Because most studies did not report adjusted risk estimates for these comorbidities, we ran meta-regression with random-effects for log odds ratio or log hazard ratio for these comorbidities by the difference in mean or median age between those with vs. without primary outcome across eligible studies. To obtain reliable estimates, we conducted meta-regression for any analyses with at least five studies. We also depicted funnel plots and visually checked the possibility of publication bias. Heterogeneity of study estimates was assessed by I^2 statistic, and $I^2 > 75\%$ was considered high heterogeneity.¹⁰ A p-value < 0.05 was considered statistically significant. All analyses were conducted with STATA 14 or 15 (StataCorp, LLC, College Station, Texas, USA).

Results

Search results

Our systematic review identified 373 potentially eligible publications after removing duplicate publications (Figure 1). Of these, 322 publications were excluded after screening titles and abstracts. Of the remaining 51 publications reviewed with full-text screening, we excluded 36 publications that did not meet our inclusion criteria, leaving 15 publications¹¹⁻²⁵ for our qualitative and quantitative analyses. Most of these publications were considered high quality (Web Table 1). Of the included studies, death was reported in 13 studies, ICU admission in 9 studies, ARDS in 7 studies, and mechanical ventilation in 6 studies. Two studies reported a composite outcome.

Study characteristics

Most studies reported COVID-19 patients from China (14 studies) and were small with sample size < 300 (10 studies) (Table 1). All studies included confirmed COVID-19 patients with laboratory tests. A total of 51,845 COVID-19 patients were included in these studies, with 9,066

patients manifesting severe disease. Most studies exclusively investigated hospitalized COVID-19 cases. Average or median age ranged from 38 to 63 years, and 45% to 73% of participants were male. Most studies reported the prevalence of CVD risk factors; the prevalence of hypertension ranged from 12.8% to 35%, diabetes from 5.3% to 22%, and pre-existing CVD from 2.5% to 21.7%.

Sociodemographic factors: age, sex, and smoking

Older age was associated with higher risk of severe COVID-19 in all eight studies with relevant estimates (Table 2). This pattern was confirmed in national surveys database in the US, China, and Italy²⁶ (published after our literature search), without any clear thresholds (Web Table 2). The case fatality rate in those three databases exceeded 1% around age of 50-55 years and 10% above 80-85 years (above 70 years in Italy). Only two studies reported the relative risk by age in both unadjusted and multivariable models; both studies observed that the effect size of age was not materially changed after adjustment for comorbidities.^{12,25}

Most studies showed a higher risk of severe COVID-19 in men than in women, with a pooled crude relative risk estimate of severe COVID-19 between men and women of 1.70 (95% CI 1.52-1.89) (Figure 2A). Meta-regression demonstrated consistent results regardless of differences in mean or median age between those with vs. without severe COVID-19 (Web Figure 1). A funnel plot did not indicate major publication bias (Web Figure 2A).

Only three studies reported associations of current smoking with severe COVID-19, with only one study reaching statistical significance (Figure 2B). The pooled estimate of relative risk for severe COVID-19 was 2.01 (95% CI 0.83-4.86). Only one study reported the association across three categories of current smoking (odds ratio 2.84 [1.57-5.14]), former smoking (6.27 [2.20-17.90]) vs. never smoking.¹⁵ The corresponding funnel plot is shown in Web Figure 2B.

Clinical factors: hypertension, diabetes, and prior CVD

All of the 10 eligible studies with data on hypertension reported a positive association of hypertension with severe COVID-19 (Figure 3A), with the pooled relative risk estimate of 2.74 (95% CI 2.12-3.54). Most eligible studies also demonstrated a positive association between diabetes and severe COVID-19 (Figure 3B), with a pooled relative risk estimate of 2.81 (2.01-3.93). Similarly, a majority of eligible studies showed a positive association between prior CVD and severe COVID-19, with the pooled relative risk of 3.58 (2.06-6.21) (Figure 3C). None of these meta-analyses demonstrated high heterogeneity with $I^2 > 75\%$. There was no indication of publication bias for these comorbidities (Web Figure 2C-E). In the one available study that assessed low-density lipoprotein as a risk factor of COVID-19, Wu et al reported that higher levels were associated with lower risk of severe COVID-19 (0.63 [0.44-0.88] per 1 mmol/L increment)²²; no other lipid fractions were reported.

Potential confounding by age and sex

Among the identified studies, only two studies reported age-adjusted relative risk estimates of these clinical factors. Specifically, Zhou et al showed that adjusting for age attenuated the association between severe COVID-19 and coronary heart disease from 21.40 (4.64-98.76) to 2.14 (0.26-17.79).²⁵ In contrast, Liang et al only reported estimates from a multivariable model including age, with an adjusted odds ratio 1.88 (1.22-2.90) for hypertension and 2.21 (1.33-3.66) for diabetes.¹⁷ In that study, cancer and chronic obstructive pulmonary disease had similar independent associations with severe COVID-19.

Meta-regression analyses demonstrated that studies with greater age difference between those with vs. without severe COVID-19 tended to have greater relative risk according to the presence of hypertension, diabetes, and pre-existing CVD, indicating some levels of potential confounding by age (Figure 4), although none of the analyses reached statistical significance. A similar pattern was seen for CVD and the difference in the proportion of male sex between those with vs. without severe COVID-19 (Web Figure 3). On the other hand, meta-

regression did not indicate that a higher proportion of male sex confounded the association of hypertension and diabetes with severe COVID-19.

Discussion

To our knowledge, this is the first systematic review and meta-analysis focusing on the relationship of severe COVID-19 with CVD and its risk factors. We confirmed a robust association of age and male sex with severe COVID-19. Their contributions are likely to be independent of each other. A few studies demonstrated positive associations of current smoking with severe COVID-19. Several studies reported that pre-existing CVD, hypertension, and diabetes were also associated with severe COVID-19. However, only two studies that reported estimates for these comorbidities adjusted for age and/or sex. One study found that the association between coronary heart disease and severe COVID-19 was no longer statistically significant after age adjustment,²⁵ whereas the other showed independent associations of hypertension and diabetes with severe COVID-19 in analyses that adjusted for age and a few other comorbidities.¹⁷ Although the primary estimate was not statistically significant, our meta-regression analyses indicated some degree of confounding by age, but not necessarily by sex, for the associations of hypertension, diabetes, and prior CVD with severe COVID-19.

The positive association of sociodemographic factors (age, male sex, and smoking) with severe COVID-19 is consistent with reports of other infectious diseases (e.g., influenza virus and SARS in 2003).²⁷⁻²⁹ There are several plausible mechanisms. Older age is linked to reduced immune reaction, more comorbidities, and limited organ reserve.^{3,27,30} Male sex is related to higher prevalence of comorbidities, less frequency of washing hands, and immunological disadvantage given X-chromosome coding proteins in the immune system,^{2,31,32} whereas smoking can damage respiratory system.³³

In our meta-analysis, we confirmed overall positive crude associations of CVD, hypertension, and diabetes with severe COVID-19, with pooled relative risk estimates around 3-

3.5. An important question is whether these associations are independent of major confounders, particularly age. Although we could not obtain a definite answer as very few studies ran multivariable models, our meta-regression analysis indicated some degree of confounding by age. One study by Zhou et al showed substantial attenuation of the association between coronary heart disease and severe COVID-19. On the other hand, Liang et al showed independent associations of hypertension and diabetes with severe COVID-19 in a relatively large sample size of 1,590 patients. There is also biologic plausibility. Hypertension and diabetes are leading risk factors for CVD and kidney diseases, and there is evidence that COVID-19 damages these organs.^{34,35}

Available studies provide scant evidence related to the hypothesized adverse effect of renin-angiotensin system inhibitors on severity of COVID-19 infection. As noted above, there is biological plausibility for potential associations of COVID-19 with hypertension and diabetes, two comorbidities associated with use of renin-angiotensin system inhibitors. Only one study reported the prevalence of renin-angiotensin system inhibitors use.¹³ In this study, ~30% of patients reported prevalent hypertension, but only ~5% of patients were taking renin-angiotensin system inhibitors.¹³ Thus, it is reasonable that many expert organizations recommend continuing this category of medications until better evidence becomes available.⁴

Our results can potentially be used to guide decision-making. While the lack of discrete age thresholds for severe COVID-19 complicates this process, data on case fatality rates from three countries (Web Table 2) suggest that age older than 60 or 65 years confers high risk of severe COVID-19 (relative risk > ~5 compared to <50 years). Our results also indicate male sex is an independent risk factor with a pooled relative risk of ~1.7. Although it is very likely that the pooled crude relative risk of ~3-3.5 for hypertension, diabetes, and CVD overestimate their impact beyond age and sex, all or some of them may each confer 1.5-2 times greater risk. Thus, using these factors, it is possible to estimate, at least crudely, the risk of severe COVID-19. For example, a man aged 60-65 years old, with either hypertension, diabetes, or prior CVD would

have a risk of ~15 fold higher risk (approximation of $5 \times 1.7 \times 2$) compared to a woman younger than 50 years without any of these clinical factors. Such information could be used to inform decisions on testing for COVID-19, clinical management of COVID-19, and workforce planning.

Our study has some limitations. First, reflecting the fact that the outbreak started from China, most studies were from China. However, given similar case-fatality rates and clinical manifestations across different countries, it seems likely that these results are largely generalizable. Nonetheless, we need to acknowledge regional variations of some risk factors (e.g., ~25-fold difference in the prevalence of smoking in men vs. women in China³⁶) and thus future investigations in different regions would be valuable. Second, we did not include non-English publications. Third, most studies reported odds ratios, which are known to overestimate risk ratio when the prevalence of exposures is relatively high. Fourth, we cannot deny the possibility that some patients were included in multiple studies especially in the China CDC report¹⁴ and other Chinese studies. Nonetheless, the pooled estimates were largely similar in analyses that excluded the China CDC data (data not shown). Finally, the literature of COVID-19 is growing rapidly, and thus there is a lag time from our literature search and publication. On the other hand, our systematic review has several strengths: in-depth review of CVD and its risk factors, a clinically relevant definitions of severe COVID-19 that minimize subjective reporting, meta-regression to explore potential confounding, and relatively short elapsed time of ~2 weeks between the literature search and manuscript submission.

In conclusion, our systematic review and meta-analysis found robust associations of older age and male sex as risk factors of severe COVID-19. Few studies reported the association between current smoking and severe COVID-19. In unadjusted analyses, hypertension, diabetes, and prior CVD were significantly associated with severe COVID-19. However, only two-studies conducted age-adjusted analyses, with one relatively large study showing independent contributions of hypertension and diabetes to severe COVID-19. No study explicitly assessed the relationship of renin-angiotensin system inhibitors with COVID-19. Our

results suggest that the combination of age, male sex, and CVD risk factors identify a substantial gradient in the risk of developing severe COVID-19 compared to those without any of these factors.

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Disclosures

None.

Figure legends

Figure 1. Flow chart of study selection

Figure 2. Forest plots of relative risk estimates of severe COVID-19 according to male vs. female sex (A) and current vs. non-current smoking (B)

Figure 3. Forest plots of relative risk estimates of severe COVID-19 according to hypertension (A), diabetes (B), and prior CVD (C)

Figure 4. Meta-regression of relative risk estimates of severe COVID-19 for hypertension (A), diabetes (B), and prior CVD (C) by age difference between severe vs. non-severe COVID-19

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Table 1. Summary of studies included in systematic review

Reference	Journal	Region	Sample size	Inpatient, %	Severe, %	Age, median (IQI) or mean (SD) in y	Male, %	Smoking, %	HTN, %	Diabetes, %	CVD, %
Cao	Intensive Care Med	China	102	100	17.6	54 (37-67)	52	-	27.5	10.8	4.9
Chen	J Infect	China	249	100	8.8	51 (36-64)	50.6	-	-	-	21.7
Cheng	Kidney International	China	701	100	16.1	63 (50-71)	52.4	-	33.4	14.3	
China CDC	CCDC Weekly	China	44,672	NR	18.5	-	51.4	-	12.8	5.3	4.2
Guan	N Engl J Med	China	1099	100	6.1	47 (35-58)	58.1	12.6	15	7.4	2.5
Huang	Lancet	China	41	100	32	49 (41-58)	73	7	-	-	15
Liang	Lancet Oncology	China	1590	100	8.2	48.8 (16.2)	57.2	7	-	-	-
Ruan	Intensive Care Med	China	150	100	45	-	68	-	35	-	8.7
Tang	J Thromb Haemost	China	183	100	11.5	54.1 (16.2)	53.6	-	-	-	-
US CDC	MMWR	US	2449	31.4	4.9	-	-	-	-	-	-
Wang	JAMA	China	138	100	26.1	56 (42-68)	54.3	-	31.2	10.1	14.5
Wu	JAMA Intern Med	China	201	100	41.8	51 (43-60)	63.7	-	19.4	10.9	4
Yang	Lancet Respir	China	52	100	67	59.7 (13.3)	67	4	-	17	10
Yuan	PLoS One	China	27	100	41	60 (47-69)	45	-	19	22	11
Zhou	Lancet	China	191	100	31	56 (46-67)	62	6	30	19	8

All studies were published in 2020.

Abbreviations: COVID-19: coronavirus disease 2019; CVD: cardiovascular disease; HTN: hypertension; NR, not reported.

Table 2. Relative risk estimate of severe COVID-19 by age in eight eligible studies

Study	No. of events	Age, per-year increment	Across categories	
			Reference	Comparison
Chen	22 ICU admission	1.08 (1.04-1.13)		
Cheng	113 death		≤65	>65: 2.43 (1.66-3.56)
China CDC	1,023 death		20-29	30-39: 1.23 (0.51-2.94) 40-49: 2.29 (1.03-5.15) 50-59: 6.79 (3.17-14.54) 60-69: 19.3 (9.1-40.8) 70-79: 44.6 (21.1-94.6) ≥80: 89.4 (42.0-190.5)
Liang	131 composite endpoints	*1.048 (1.033-1.064)		
US CDC	121 ICU admission		20-44	45-54: 2.80(1.43-5.49) 55-64: 2.41(1.21-4.83) 65-74: 4.33(2.29-8.20) 75-84: 5.78(2.90-11.51) ≥85: 3.29(1.40-7.76)
Wu	84 ARDS		<65	≥65: 3.26 (2.08-5.11)
Yang	32 death		30-49	50-59: 6.75 (1.16-39.20) 60-69: 5.50 (1.06-28.42) ≥70: 27.00 (2.34-311.17)
Zhou	54 death	1.14 (1.09–1.18)		

Abbreviations: ARDS: acute respiratory distress syndrome; COVID-19: coronavirus disease 2019; ICU: intensive care unit

*This study only reported an estimate adjusted for sex, cancer, hypertension, obstructive pulmonary disease, and diabetes.

Figure 1. Flow chart of study selection

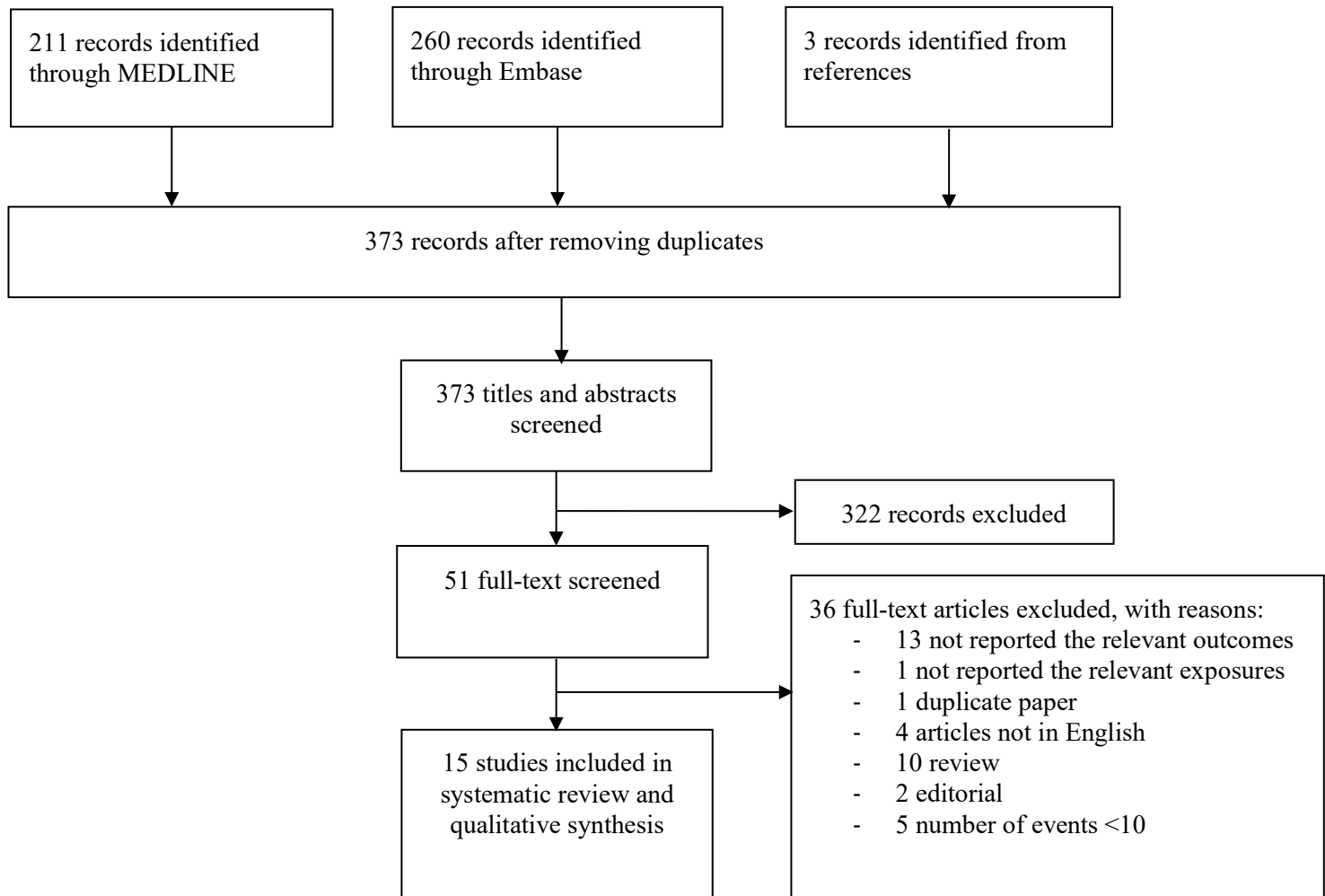
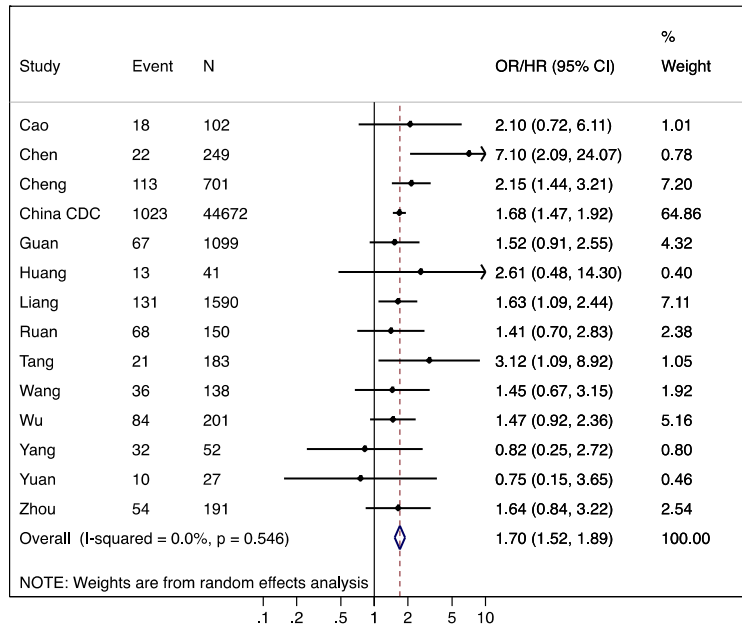
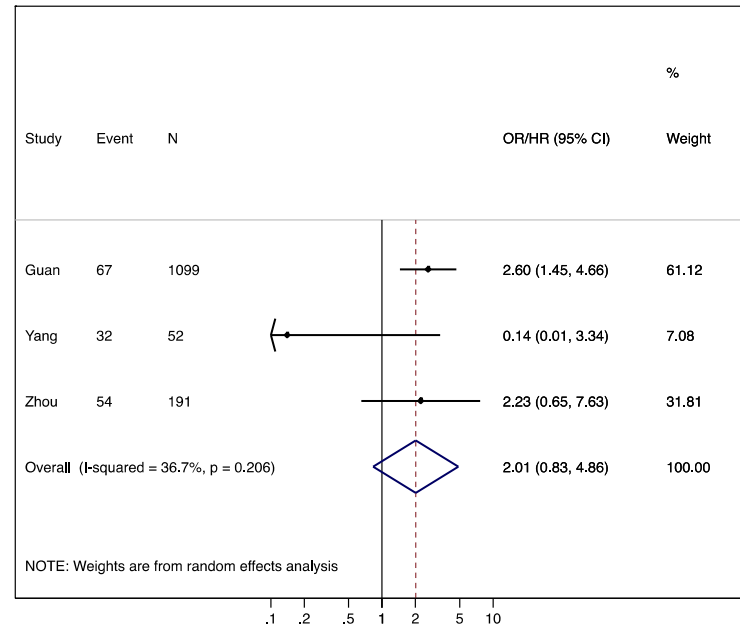


Figure 2. Forest plots of relative risk estimates of severe COVID-19 according to male vs. female sex (A) and current vs. non-current smoking (B)

(A) Male vs. female sex



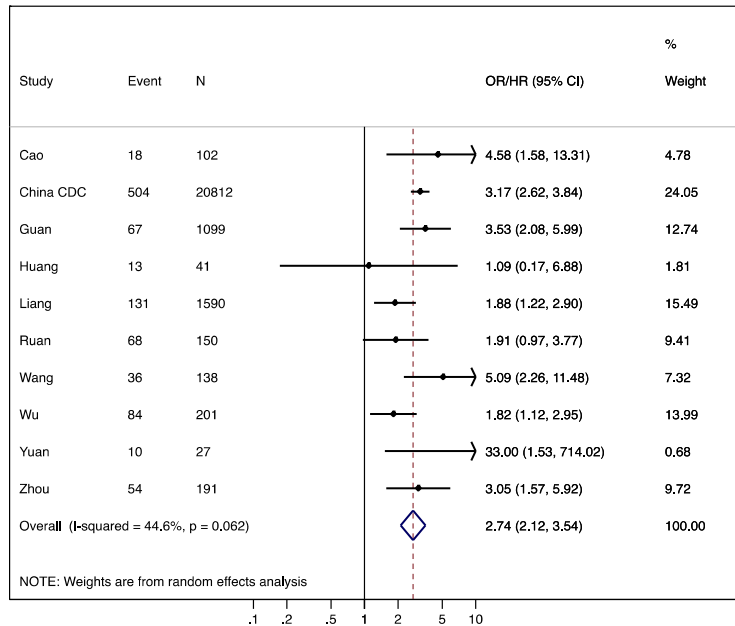
(B) Current vs. non-current smoking



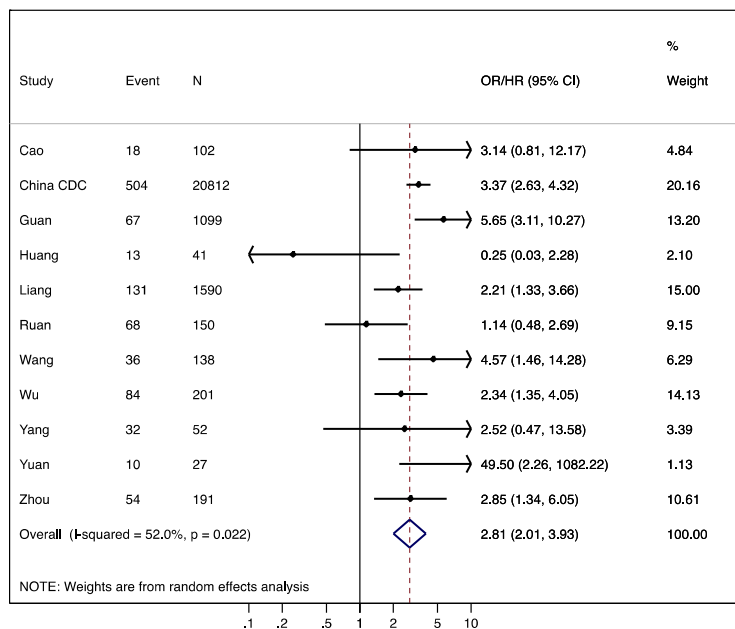
Liang et al adjusted for age, cancer, hypertension, obstructive pulmonary disease, and diabetes.

Figure 3. Forest plots of relative risk estimates of severe COVID-19 according to hypertension (A), diabetes (B), and prior CVD (C)

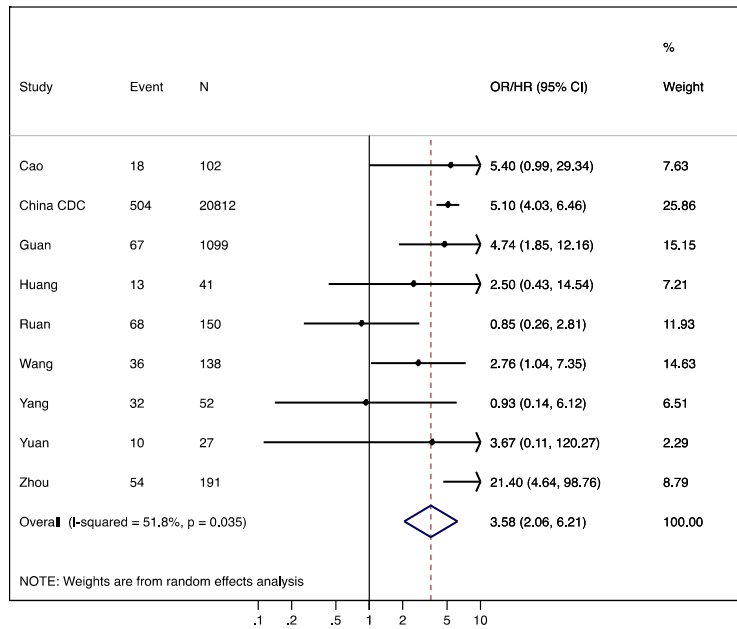
(A) Hypertension



(B) Diabetes

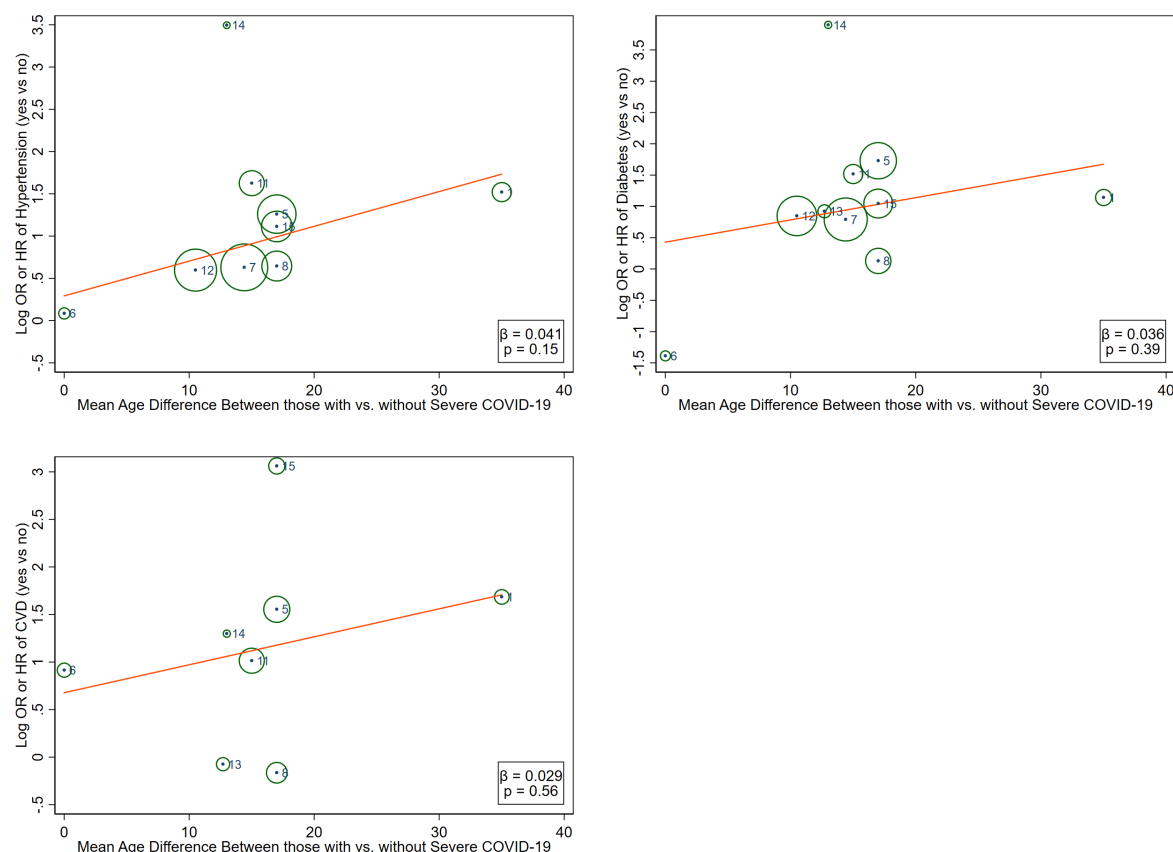


(C) Prior CVD



Liang et al only reported estimates adjusted for age, cancer, hypertension, obstructive pulmonary disease, and diabetes. The event number and total number of China CDC paper are different from Tables 1 and 2 because of missing value in comorbidity.

Figure 4. Meta-regression of odds ratio or hazard ratios of severe COVID-19 for hypertension, diabetes, and CVD by age difference between severe vs. non-severe COVID-19



List of studies: 1 Cao, et al, Intensive Care Med; 2 Chen, et al, J Infect; 3 Cheng, et al, Kidney International; 4 China CDC, CCDC Weekly; 5 Guan et al, N Eng J Med; 6 Huang et al, Lancet; 7 Liang et al, Lancet Oncology; 8 Ruan et al, Intensive Care Med; 9 Tang et al, J Thromb Haemost; 10 US CDC, MMWR; 11 Wang et al, JAMA; 12 Wu et al, JAMA Intern Med; 13 Yang et al, Lancet Respir; 14 Yuan et al, PLoS One; 15 Zhou et al, Lancet