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Original Article

Associations of pre-existing cardiovascular morbidity with severity and the fatality rate in COVID-19 patients: a systematic review and meta-analysis

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ABSTRACT

Objectives: The aim of this study was to evaluate the association of pre-existing cardiovascular comorbidities, including hypertension and coronary heart disease, with coronavirus disease 2019 (COVID-19) severity and mortality.

Methods: PubMed, ScienceDirect, and Scopus were searched between January 1, 2020, and July 18, 2020, to identify eligible studies. Random-effect models were used to estimate the pooled event rates of pre-existing cardiovascular disease comorbidities and odds ratio (OR) with 95% confidence intervals (95% CIs) of disease severity and mortality associated with the exposures of interest.

Results: A total of 34 studies involving 19,156 patients with COVID-19 infection met the inclusion criteria. The prevalence of pre-existing cardiovascular disease in the included studies was 14.0%. Pre-existing cardiovascular disease in COVID-19 patients was associated with severe outcomes (OR, 4.1; 95% CI, 2.9 to 5.7) and mortality (OR, 6.1; 95% CI, 2.9 to 12.7). Hypertension and coronary heart disease increased the risk of severe outcomes by 2.6 times (OR, 2.6; 95% CI, 1.9 to 3.6) and 2.5 times (OR, 2.5; 95% CI, 1.7 to 3.8), respectively. No significant publication bias was indicated.

Conclusion: COVID-19 patients with pre-existing cardiovascular comorbidities have a higher risk of severe outcomes and mortality. Awareness of pre-existing cardiovascular comorbidity is important for the early management of COVID-19.

Keywords: Coronary disease; COVID-19; Hypertension

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Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic poses a significant public health threat to all nations worldwide [1,2]. As of August 23, 2021, COVID-19 has infected approximately 212,763,099 people, including roughly 4,447,912 patients who have died. Regrettably, these numbers have kept increasing worldwide, indicating that the peak is far from over and the global community remains on edge as the number of infected patients continues to escalate.

Several studies from different countries have reported that pre-existing cardiovascular comorbidities are prevalent among COVID-19 patients [3–6]. Understanding the association of cardiovascular comorbidities with the severity and outcomes of COVID-19 may highlight a cohort of patients who require more intensive monitoring during the early phase of infection [7,8]. Epidemiological studies have reported different mortality rates for COVID-19 patients with cardiac manifestations and pre-existing cardiovascular diseases, particularly hypertension and coronary artery disease [8].

Several studies have investigated the association between pre-existing cardiac disease and COVID-19 severity and fatality, and the pooled effects have been estimated in a number of meta-analyses. However, previous reviews varied in how COVID-19 severity was defined; did not report the country of the studies, and reported substantial heterogeneity. Therefore, the present meta-analysis was performed with the following aims: (1) to estimate the overall prevalence rate of pre-existing cardiovascular disease and cardiac manifestations in COVID-19 patients, and (2) to evaluate the association of pre-existing hypertension and coronary heart disease with the severity of COVID-19 and the mortality rate in COVID-19 patients using a random-effect model that incorporates heterogeneity.

Materials and Methods

Data Search

Three databases (PubMed, Science Direct, and Scopus) were searched between January 1, 2020, and July 18, 2020. The following combined keywords were used for searching the databases: cardiovascular and COVID-19; cardiovascular and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); cardiovascular, and SARS-CoV-2; cardiovascular, hypertension, and COVID-19. Furthermore, the lists of references of all relevant studies were also manually checked to identify further studies. The protocol for this meta-analysis is registered at PROSPERO CRD42020191768. The meta-analysis was reported following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [9].

Study Selection

The study selection was limited to articles in English and studies on adult humans. Case reports, review articles, and editorials were excluded from this analysis. Studies were selected if they provided adequate details on pre-existing cardiovascular disease comorbidities, particularly in patients with positive diagnoses for COVID-19 and hypertension. Studies that did not provide enough details on the number of cases with severe or fatal outcomes were excluded.

Data Abstraction

For studies that met the inclusion criteria, the following data were extracted from each study using a standardized form: the surname of the first author; the design of the study; ratios of clinical characteristics of interest; sample size, country, data relevant to cardiovascular disease comorbidities factor; and pertinent data for arrhythmia and acute cardiac injury as outcomes, and the number of cases with severe and non-severe outcomes, and the number of survivors and non-survivors. As reported in the included studies, severe disease was identified if patients needed to be admitted to the intensive care unit, needed vital life support, or required mechanical ventilation. Non-survivors were defined as cases of death. Two investigators (FA and MA) extracted the relevant data.

Quality Assessment

We used the Joanna Briggs Institute (JBI) critical appraisal checklist for case series to assess the risk of bias [10]. The JBI includes 10 items dealing with confounding, selection, and information bias to assess the internal validity of the case series. The answers for each of the 10 items in the JBI checklist could be "yes," "no," "unclear," or "not applicable." A detailed description of how to use the JBI tool is provided by Munn et al. in 2020 [10]. It is advised that the results of the quality assessment of the included studies should not be shortened and reported as a score [10]. The quality assessment of the included studies in this meta-analysis was carried out by SA.

Quantitative Data Synthesis and Analysis

Data analysis was carried out using Comprehensive Meta-Analysis V2 (Biostat, Englewood, NJ, USA). A p-value of <0.05 was considered statistically significant. Random-effect models were used to estimate the pooled event rates of pre-existing cardiovascular disease comorbidities as

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well as the odds ratio (OR) with 95% confidence intervals (95% CIs) of disease severity and mortality associated with the exposures of interest. A random-effect model was used to incorporate heterogeneity among studies [11]. Heterogeneity in any analysis was tested by using the I^2 statistic ($p < 0.1$), which estimates the percentage of variation in study results that is explained by between-study heterogeneity rather than sampling error. Usually, an I^2 value >50% indicates considerable heterogeneity [11]. Funnel plots and Egger test were used to assess the presence of publication bias.

Results

Search Results and Study Characteristics

A total of 1,601 articles were identified from the 3 databases examined and other sources. After excluding duplicated or overlapping articles and removing reviews and editorials, 169 articles met the primary search criteria. For the quantitative part of our study, 34 studies that reported the event rate of pre-existing cardiovascular disease, arrhythmia, or acute cardiac injury as disease complications were included in the meta-analysis (Figure 1). Most studies

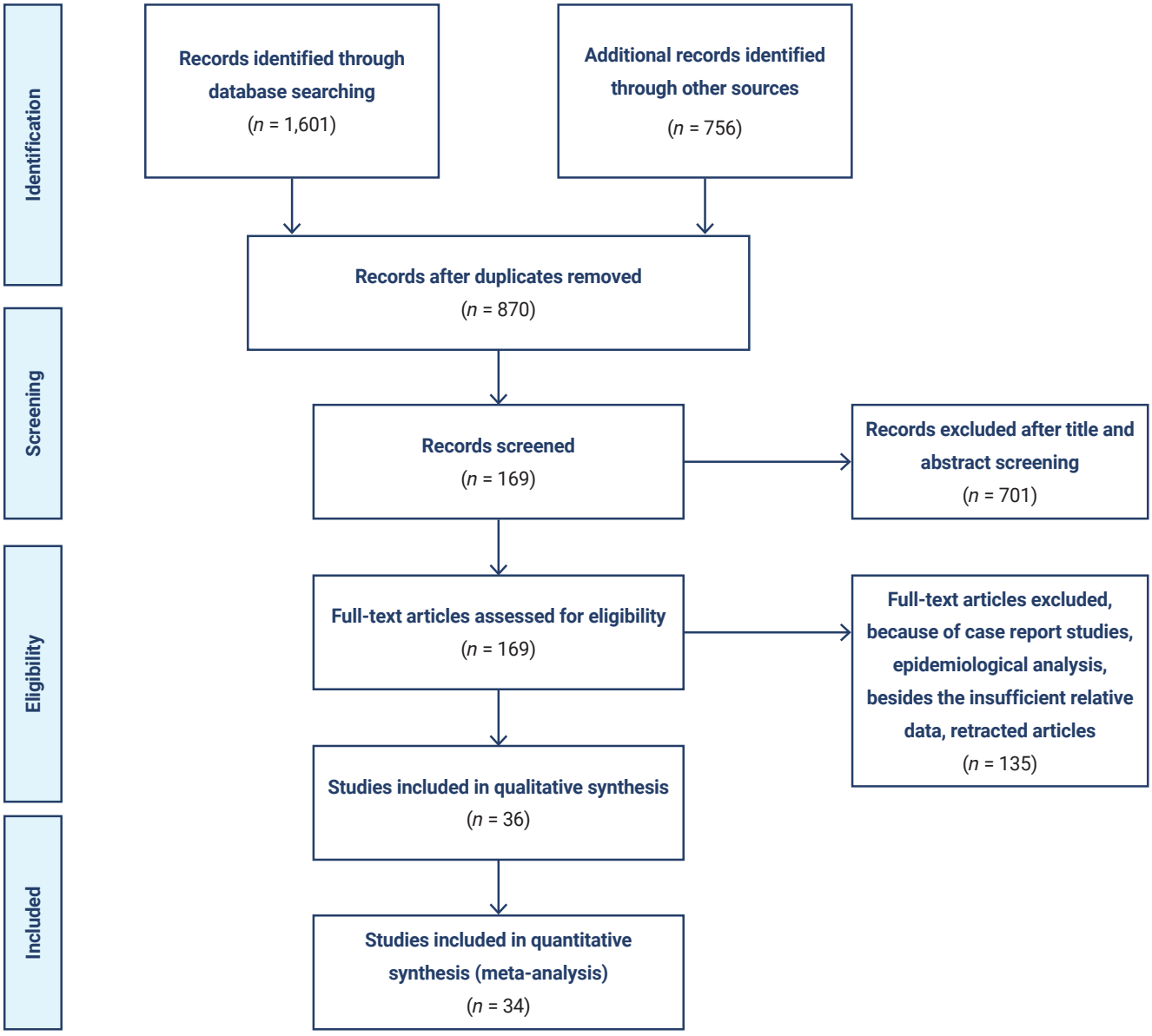

Figure 1. Flow chart of the literature search and study selection.

were conducted in China (n=21) and the United States of America (n=8), while 4 studies were conducted in Italy and 1 study reported results from different parts of the world. The setting for most of the included studies was the hospital (Table 1) [3–5,12–42].

Quantitative Analysis

The proportions of cardiovascular disease comorbidities and cardiac manifestations in COVID-19 patients

Relevant data regarding the event rate of pre-existing cardiovascular diseases, including hypertension and coronary heart disease, in 19,156 patients with COVID-19 were collected from 34 studies (Table 1) [3–5,12–42]. The pooled prevalence of pre-existing cardiovascular diseases or coronary heart disease among the included studies was 14% (95% CI, 11% to 18%), as is shown in Figure 2.

Pre-existing cardiovascular disease, hypertension, and coronary heart disease and the risk of severity outcomes and mortality in COVID-19

Table 2 summarizes the results of the current analysis. COVID-19 patients with pre-existing cardiovascular comorbidities were 4 times more likely to have severe outcomes (OR, 4.1; 95% CI, 2.9 to 5.7) (Figure 3) or not survive the disease (OR, 6.1; 95% CI; 2.9 to 12.7) (Figure 4), compared to patients with no pre-existing cardiovascular or coronary heart diseases. Severe disease was defined as patients needing to be admitted to the intensive care unit, needing vital life support, or requiring mechanical ventilation. Hypertension as a comorbid factor was associated with 2.6 times higher risk for severe outcomes (OR, 2.6; 95% CI, 1.9 to 3.6) and a 3 times higher fatality rate (OR, 3.2; 95% CI, 2.0 to 5.0) (Figures 5 and 6). However, coronary heart disease was associated with a 2.5 times higher risk for severe outcomes (OR, 2.5; 95% CI, 1.7 to 3.8) (Figure 7).

Quality of the Included Studies

Table S1 shows the quality assessment of the studies on cardiovascular disease as a comorbidity in COVID-19 patients using JBI's tool [3–5,12–42]. Most of the studies did not define participants' eligibility criteria. Moreover, most studies were unclear regarding whether they included consecutive participants and whether the inclusion was complete. The majority of the studies diagnosed COVID-19 and the outcomes of interest using valid and reliable methods. All included studies in this analysis reported the demographic and the clinical characteristics, as well as the outcomes of the participants. However, most of the multi-center studies did not present the demographic and the

Table 1. Number of patients with CVD comorbidities among coronavirus disease 2019 patients

Study	Country	Condition	Setting	Comorbidities	Sample size (n)	Events (n)	Non-events (n)	Severe cases ratio	Non-severe cases ratio	Non-survivors	Survivors
Wang et al. [3]	China	CVD	Zhongnan Hospital of Wuhan, University in Wuhan, China	HP, CVD, DM, CLD, CRVD, COPD, CKD, Ca, HIV	138	20	115	9/36	11/102		
Goyal et al. [14]	USA	CAD	An 862-bed quaternary referral center and an affiliated 180-bed nonteaching community hospital in Manhattan	DM, obesity, HP, COPD, asthma, CAD	393	54	339	25/130	29/263		
Zhang et al. [15]	China	CVD	Zhongnan Hospital of Wuhan University, Wuhan, China	HP, CVD, DM, CLD, CRVD, COPD, CKD, Ca, immunosuppression	221	22	199	13/55	9/166		
Hu et al. [16]	USA	CVD	Tianyou Hospital, Wuhan University of Science and Technology, China	HP, CVD, DM, CLD, CRVD, COPD, CKD, Ca, cirrhosis	323	34	289	30/172	4/151		
Guo et al. [17]	China	CHD	The Seventh Hospital of Wuhan City, China	HP, CHD, DM, COPD, CKD, Ca, cardiomyopathy	187	29	158				
Zhang et al. [18]	China	CVD	The Seventh Hospital of Wuhan City, China	HP, DM, CHD, HL, CG, CVD, CKD, CRVD, COPD, arrhythmia cholelithiasis, fatty liver, thyroid diseases	140	15	125	10/58	5/82		

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Table 1. Continued

Study	Country	Condition	Setting	Comorbidities	Sample size (*n*)	Events (*n*)	Non-events (*n*)	Severe cases ratio	Non-severe cases ratio	Non-survivors	Survivors
Du et al. [19]	China	CHD	Hannan Hospital and Wuhan Union Hospital of Wuhan City, China	HP, DM, CHD, CRVD, CLD, COPD, CKD, Ca	85	10	75				
Rosenberg et al. [20]	USA	CVDs	25 hospitals in the New York City, metropolitan region	Obesity, cancer, CKD, COPD, DM, HP, CAD, CHD, dementia	1,438	468	1,000				
Lei et al. [21]	China	CVDs	Renmin Hospital, Zhongnan Hospital, Tongji Hospital, and Central Hospital in Wuhan	HP, Ca, DM, CVD, CRVD, COPD, CKD	34	7	27	6/15	1/19		
Mercuro et al. [22]	USA	CVDs	An academic tertiary care center in Boston, Massachusetts	HP, CHF, DM, CAD, AF, COPD, asthma	90	19	71				
Saleh et al. [23]	USA	CVDs	14 hospitals of the New York State Northwell Health system	HP, HL, DM, AF, CAD, COPD, CKD, CHF	201	52	149				
Inciardi et al. [24]	Italy	Cardiac disease	Civil Hospitals of Brescia, Lombardy, Italy	HP, HL, DM, HF, AF, CAD, COPD, CKD, Ca	99	53	46				
Bhatla et al. [25]	USA	CVDs	The Hospital of the University of Pennsylvania	CHD, HF, HP, AF, DM, COPD, CLD, CKD	700	203	497			48/79	155/621
Sala et al. [26]	Italy	CAD	Seven COVID units at a third-level hub center, San Raffaele Hospital, Italy	CAD, COPD, HP, DM, Obesity, AF	132	9	123				
Enzmann et al. [27]	USA	CVD	Three hospitals in the Dakotas	Asthma, CHF, CVD, DM, RD, CKD, cirrhosis, Ca, immunosuppression	150	93	57				
Guan et al. [4]	China	CHD	552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China	COPD, DM, HP, CHD, CRVD, HBV, CKD, immunosuppression	1,099	27	1,072	10/173	17/926		
Qin et al. [28]	China	CVD	Tongji Hospital	COPD, HP, CVD, CLD, DM, tuberculosis, Ca, CKD	452	27	425	24/286	3/166		
Huang et al. [29]	China	CVD	2 hospitals in the Hubei provinces, China	HP, DM, CHD, Ca	223	13	210	9/98	4/125		
Huang et al. [30]	China	CVD	Designated hospital in Wuhan	DM, HP, CVD, COPD, Ca, CLD	41	6	35	3/13	3/28		
Wan et al. [31]	China	CVD	Chongqing University Three Gorges Hospital,	DM, CVD, HP, COPD, Ca, CLD	135	7	128	6/40	1/95		
Shi et al. [32]	China	CVD	Renmin Hospital of Wuhan University	HP, DM, CAD, CRVD, CHF, CKD, COPD, Ca, HBV	416	61	355	36/82	25/334		
Zhou et al. [33]	China	CVD	Jinyintan Hospital and Wuhan Pulmonary Hospital	HP, DM, CHD, COPD, Ca, CKD	191	59	132			41/54	18/137
Lagi et al. [34]	Italy	CHD	University Hospital, Florence, Italy	DM, COPD, CHD, HP, HBV, CRVD, CKD	84	12	72	5/16	7/68		
Wang et al. [35]	China	CVD	Zhongnan Hospital of Wuhan University in Wuhan and Xishui Hospital, Hubei Province, China	HP, CVD, DM, CLD, CVD, COPD, CKD	107	13	94			7/19	6/88

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Table 1. Continued

Study	Country	Condition	Setting	Comorbidities	Sample size (*n*)	Events (*n*)	Non-events (*n*)	Severe cases ratio	Non-severe cases ratio	Non-survivors	Survivors
Chen et al. [36]	China	CVD	Wuhan Tongji Hospital	HP, DM, CVD, CHF, COPD, Ca, HBV, HIV, CRVD, CKD, CG, metabolic arthritis, autoimmune disease	274	23	251			16/19	7/36
Yang et al. [37]	China	Chronic cardiac disease	Wuhan Jin Yin-Tan Hospital	CVD, COPD, CRVD, DM, Ca, Dementia	52	5	47			3/32	2/20
Chen et al. [12]	China	CVD	Wuhan Jinyintan Hospital	CVD, CRVD, Ca	99	40	59				
Jin et al. [38]	China	CVD	The Health Commission of Zhejiang province in designated hospitals	HP, DM, CLD, Ca, CKD, CHD COPD, immunosuppression	651	5	646				
Richardson et al. [13]	USA	CVD	12 hospitals in New York City, Long Island, and Westchester County, New York	Ca, CVD, HP, CAD, CHF, COPD asthma	5,700	966	4,734				
Yan et al. [39]	China	CVD	Tongji Hospital, Wuhan, China	HP, CVD, CRVD, CKD, COPD, CLD	193	31	162			27/108	4/85
Guan et al. [40]	China	Cardiovascular disease	575 hospitals in 31 provinces/ autonomous regions/provincial municipalities across mainland China	HP, DM, COPD, Ca, CVD	1,590	59	1,531	20/59	234/1,531		
Gold et al. [41]	USA	CVD	Seven hospitals in metropolitan Atlanta	DM, CVD, CHF, Arrhythmia, COPD, asthma, Obesity, HP, CKD, Ca	305	78	227				
Grasselli et al. [5]	Italy	CVD	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan	HP, CVD, HL, DM, Ca, COPD, CKD, CLD	1,591	223	1,368				
Wang et al. [42]	China	CVD	Tongji Hospital	HP, DM, CVD, COPD	344	40	304			22/133	18/211
Wang et al. [3]	China	HP	Zhongnan Hospital of Wuhan University in Wuhan, China	HP, CVD, DM, CLD, CRVD, COPD, CKD, Ca, HIV	138	43	95	21/36	21/102		
Goyal et al. [14]	USA	HP	An 862-bed quaternary referral center and an affiliated 180-bed nonteaching community hospital in Manhattan	DM, Obesity, HP, COPD, Asthma, CAD	393	197	196	70/130	127/263		
Zhang et al. [15]	China	HP	Zhongnan Hospital of Wuhan University, Wuhan, China	HP, CVD, DM, CLD, CRVD, COPD, CKD, Ca, immunosuppression	221	55	166	26/55	28/166		
Hu et al. [16]	USA	HP	Tianyou Hospital, Wuhan University of Science and Technology, China	HP, CVD, DM, CLD, CRVD, COPD, CKD, Ca, cirrhosis	323	105	218	66/172	39/151		
Guo et al. [17]	China	HP	The Seventh Hospital of Wuhan City, China	HP, CHD, DM, COPD, CKD, Ca, cardiomyopathy	187	61	126				
Zhang et al. [18]	China	HP	The Seventh Hospital of Wuhan City, China	HP, DM, CHD, HL, CG, CVD, CKD, CRVD, COPD, arrhythmia cholelithiasis, fatty liver, thyroid diseases	140	42	98	22/58	20/82		

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Du et al. [19]	China	HP	Hannan Hospital and Wuhan Union Hospital of Wuhan City, China	HP, DM, CHD, CRVD, CLD, COPD, CKD, Ca	85	32	53				
Rosenberg et al. [20]	USA	HP	25 hospitals in the New York City, metropolitan region	Obesity, cancer, CKD, COPD, DM, HP, CAD, CHD, dementia	1,438	816	622				
Lei et al. [21]	China	HP	Renmin Hospital, Zhongnan Hospital, Tongji Hospital, and Central Hospital in Wuhan	HP, Ca, DM, CVD,CRVD,COPD, CKD	34	13	21	9/15	4/19		
Mercuro et al. [22]	USA	HP	An academic tertiary care center in Boston, Massachusetts	HP, CHF, DM, CAD, AF, COPD, asthma	90	48	42				
Saleh et al. [23]	USA	HP	14 hospitals of the New York State Northwell Health system	HP, HL, DM, AF, CAD, COPD, CKD, CHF	201	121	80				
Inciardi et al. [24]	Italy	HP	Civil Hospitals of Brescia, Lombardy, Italy	HP, HL, DM, HF, AF, CAD, COPD, CKD, Ca	99	63	36				
Bhatla et al. [25]	USA	HP	The Hospital of the University of Pennsylvania	CHD, HF, HP, AF, DM, COPD, CLD, CKD	700	347	353	62/79	285/621		
Sala et al. [26]	Italy	HP	Seven COVID units at a third-level hub center, San Raffaele Hospital, Italy	CAD, COPD, HP, DM, obesity, AF	132	60	72				
Guan et al. [4]	China	HP	552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China	COPD, DM, HP, CHD, CRVD, HBV, CKD, immunosuppression	1,099	165	934	41/173	124/926		
Qin et al. [28]	China	HP	Tongji Hospital	COPD, HP, CVD, CLD, DM, tuberculosis, Ca, CKD	452	135	317	105/286	30/166		
Huang et al. [29]	China	HP	2 hospitals in the Hubei provinces, China	HP, DM, CHD, Ca	223	40	180	38/98	12/125		
Huang et al. [30]	China	HP	Designated hospital in Wuhan	DM, HP, CVD, COPD, Ca, CLD	41	6	35	2/13	4/28		
Wan et al. [31]	China	HP	Chongqing University Three Gorges Hospital	DM, CVD, HP, COPD, Ca, CLD	135	13	122	4/40	9/95		
Shi et al. [32]	China	HP	Renmin Hospital of Wuhan University	HP, DM, CAD, CRVD, CHF, CKD, COPD, Ca, HBV	416	127	289	49/82	78/334		
Zhou et al. [33]	China	HP	Jinyintan Hospital and Wuhan Pulmonary Hospital	HP, DM, CHD, COPD, Ca, CKD	191	58	133			26/54	32/137
Lagi et al. [34]	Italy	HP	University Hospital, Florence, Italy	DM, COPD, CHD, HP, HBV, CRVD, CKD	84	31	53	5/16	26/68		
Wang et al. [35]	China	HP	Zhongnan Hospital of Wuhan University in Wuhan and Xishui Hospital, Hubei Province, China	HP, CVD, DM, CLD, CVD, COPD, CKD	107	26	81			10/19	16/88
Richardson et al. [13]	USA	HP	12 hospitals in New York City, Long Island, and Westchester County, New York	Ca, CVD, HP, CAD, CHF, COPD, asthma	5,700	3026	2674				

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Table 1. Continued

Study	Country	Condition	Setting	Comorbidities	Sample size (*n*)	Events (*n*)	Non-events (*n*)	Severe cases ratio	Non-severe cases ratio	Non-survivors	Survivors
Yan et al. [39]	China	HP	Tongji Hospital, Wuhan, China	HP, CVD, CRVD, CKD, COPD, CLD	193	73	120			57/108	16/85
Guan et al. [40]	China	HP	575 hospitals in 31 provinces/ autonomous regions/provincial municipalities across mainland China	HP, DM, COPD, Ca, CVD	1,590	269	1,321				
Gold et al. [41]	USA	HP	Seven hospitals in metropolitan Atlanta	DM, CVD, CHF, Arrhythmia, COPD, asthma, Obesity, HP, CKD, Ca	305	206	99				
Grasselli et al. [5]	ITALY	Hypertension	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan	HP, CVD, HL, DM, Ca, COPD, CKD, CLD	1,591	509	1,082				
Wang et al. [42]	China	Hypertension	Tongji hospital	HP, DM, CVD, COPD	344	141	203			69/133	72/211

CVD, cardiovascular disease; HP, hypertension; DM, diabetes mellitus; CLD, chronic liver disease; CRVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; Ca, cancer; HIV, human immunodeficiency virus; CAD, coronary artery disease; CHD, coronary heart disease; HL, hyperlipidemia; CG, chronic gastritis; CHF, congestive heart failure; AF, atrial fibrillation; HF, heart failure; RD, rheumatologic disease; HBV, hepatitis B virus infection.

clinical characteristics by site or clinic.

Assessment of Publication Bias

Publication bias was evaluated visually using a funnel plot. As shown in Figure 8 on the event rate of pre-existing cardiovascular comorbidity, a visual symmetry indicates the absence of publication bias. The Egger test also revealed no significant publication bias (Egger test, $p = 0.09$).

Discussion

In the present meta-analysis, we examined 36 independent studies reporting clinical data on 19,156 patients with COVID-19 worldwide. The studies included in this meta-analysis include the latest research available on COVID-19 from January to July 2020. Our pooled analyses indicated that pre-existing cardiovascular diseases, in particular hypertension and coronary heart disease, are prevalent among patients with COVID-19. Our pooled analyses also clearly showed that the presence of pre-existing cardiovascular disease, including hypertension and coronary heart disease, is associated with COVID-19 severity and/or fatality. This association can be confounded by older age, patients with poor outcomes may be older and have more cardiovascular events [43]. In this analysis meta-regression (data are not shown) using the method of moments of the effect of age, reported as mean or median, on association of pre-existing cardiovascular disease with COVID-19 outcomes revealed that age was significantly associated only with estimated OR for severity in patients with pre-existing cardiovascular disease.

In comparison, another meta-analysis of 6 published studies from China including 1,527 patients with COVID-19 that reported a 16.4% prevalence of cardio-cerebrovascular disease [44]. Another analysis of 7 Chinese studies showed that the prevalence of cardiovascular disease and that of hypertension were 21% and 8%, respectively [45]. Our meta-analysis on data from different countries reported a 14% prevalence of cardiovascular disease.

Pre-existing cardiovascular disease was associated with a 4-fold and 6-fold greater risk of disease severity and fatality, respectively. A previous study that analysed data of COVID-19 patients until March 20, 2020 found that cardiovascular disease increased the odds of combined critical/fatal cases of COVID-19 by 5 times [46] and in particular, hypertension was found to increase the odds of combined critical and fatal cases by 2.7 times. The main difference between our analysis and that by Zheng et al. [46] is that we analysed data separately for COVID-19 severity and mortality, while Zheng et al. [46] combined

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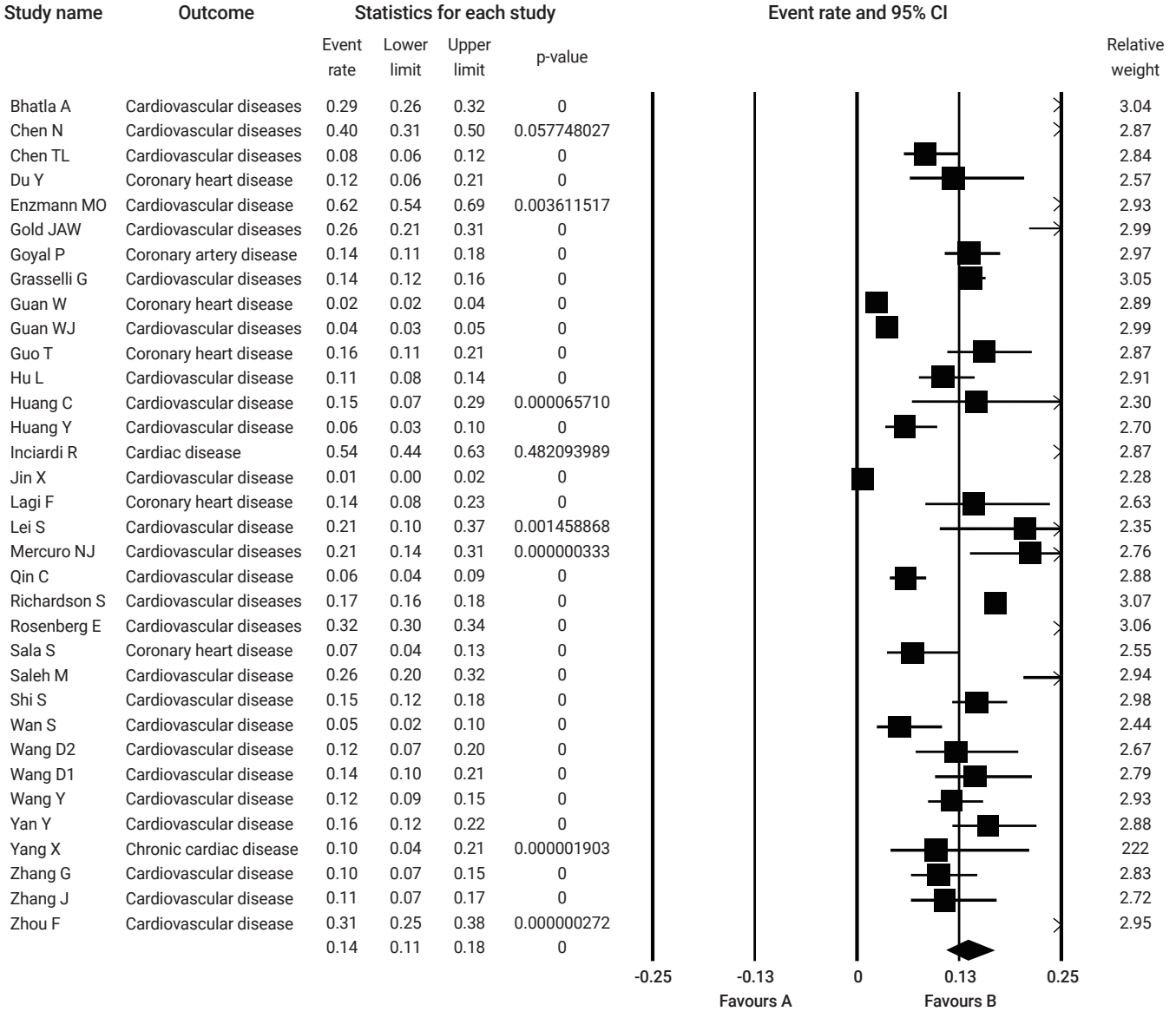

Figure 2. Pooled event rate of pre-existing cardiovascular disease in patients with coronavirus disease 2019. CI, confidence interval.

Table 2. Effect of cardiovascular comorbidities on severity and mortality outcomes associated with coronavirus disease 2019

Comorbidity	Severity		Mortality	
	No. of studies	OR (95% CI)	No. of studies	OR (95% CI)
Pre-existing cardiovascular diseases	14	4.1 (2.9 to 5.7)	7	6.1 (2.9 to 12.7)
Hypertension	14	2.6 (1.9 to 3.6)	4	3.2 (2.0 to 5.0)
Coronary heart disease	4	2.5 (1.7 to 3.8)	-	-

OR, odds ratio; CI, confidence interval; -, no data available to run analysis.

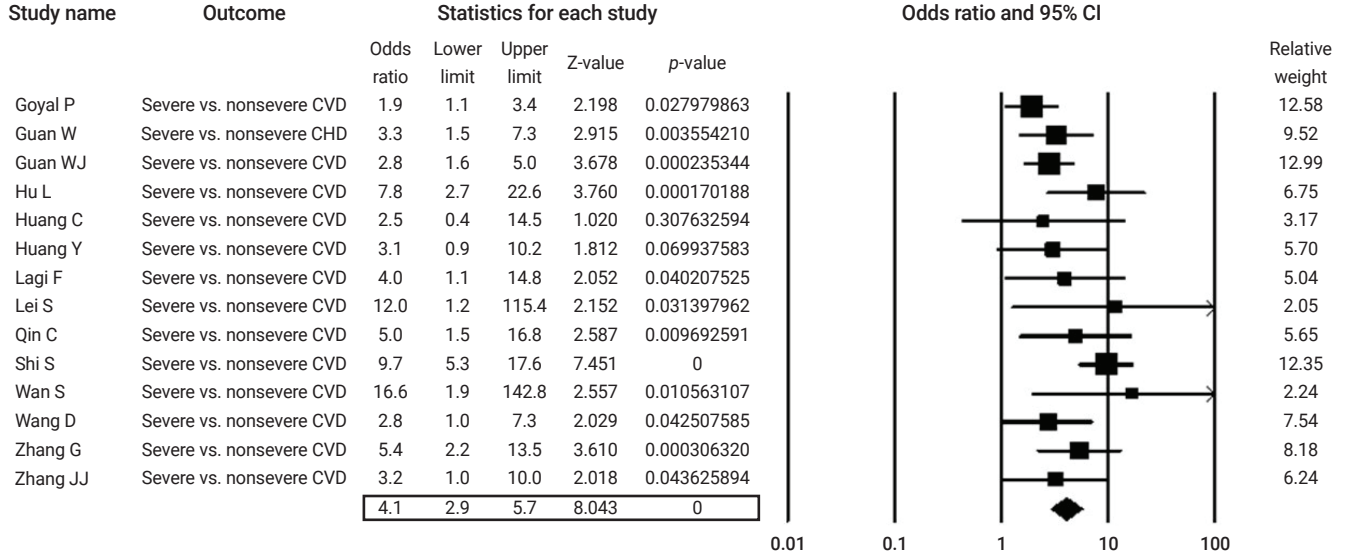

Figure 3. Forest plot of the odds ratios of pre-existing cardiovascular disease (CVD) in severe cases compared to non-severe cases of coronavirus disease 2019.
CI, confidence interval; CHD, coronary heart disease.

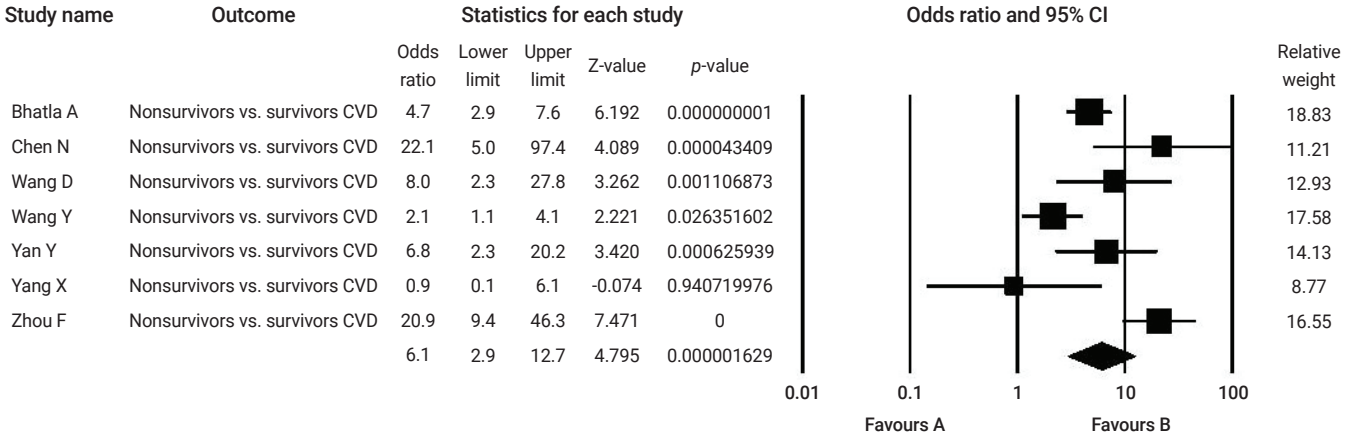

Figure 4. Forest plot of the odds ratios of pre-existing cardiovascular disease (CVD) in non-survivor compared to survivor coronavirus disease 2019 patients. CI, confidence interval.

data on COVID-19 critical conditions and mortality. Another previous meta-analysis [44] that included only studies from China reported that comorbid hypertension increased COVID-19 severity by 2-fold, suggesting the prognostic impact of this comorbidity. Our results clearly confirm previous findings and add to them. Li et al. [44] were not able to provide data on cardiovascular comorbidities and death from COVID-19 as data collection was incomplete, and most of the included studies in their analysis did not analyse comorbidities in death cases. Another analysis by Luo et al. [47] included a larger number of studies and found that hypertension was associated with 2.5 times higher odds of mortality; however, considerable heterogeneity was also reported. In this analysis, the relationship between hypertension comorbidity and COVID-19-induced death was pooled using data from China and other countries using a random-effect model to account for heterogeneity. Hypertension was associated with a 3-fold increased fatality rate. The American Heart Association and the American College of Cardiology define hypertension as systolic blood pressure (BP) ≥130 or diastolic BP ≥80 mmHg, and hypertension is a primary risk factor associated with atherosclerotic cardiovascular disease [48]. In line with our analysis, several studies identified high rates of hypertension among severely symptomatic COVID-19 patients [5,12,13]. Roughly half of United States patients

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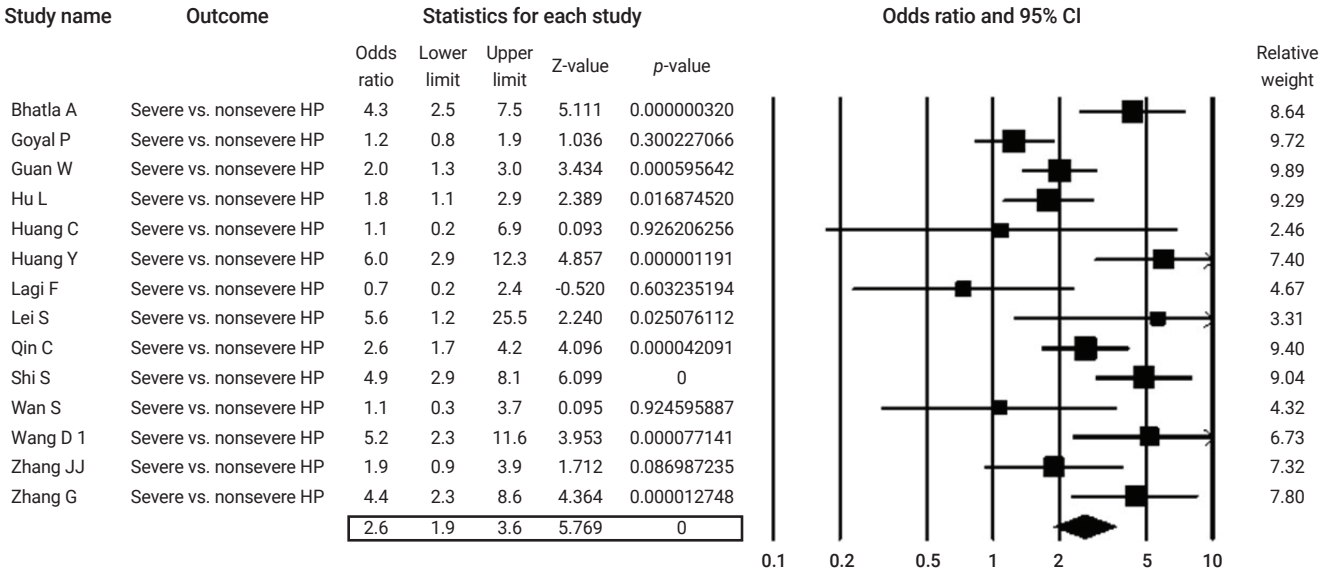

Figure 5. Forest plot of the odds ratios of pre-existing hypertension (HP) in severe compared to non-severe coronavirus disease 2019 cases. CI, confidence interval.

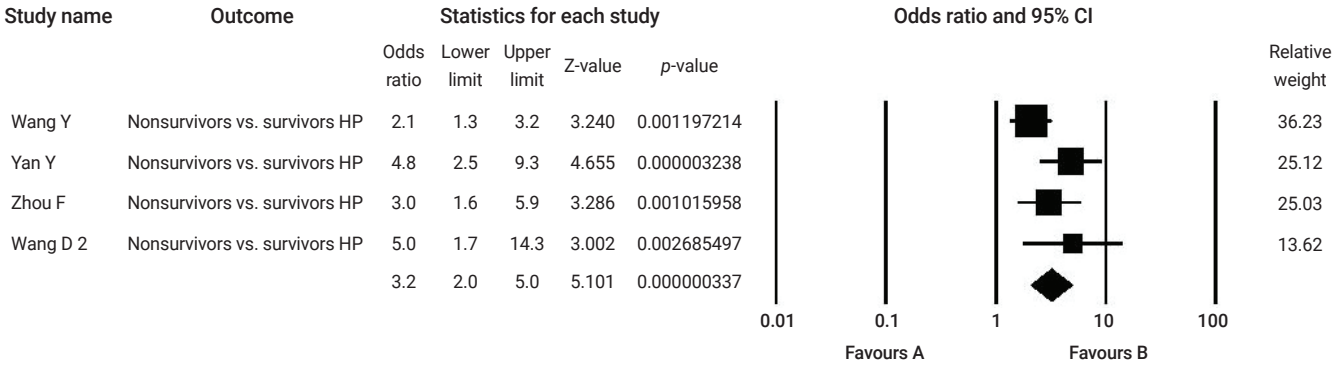

Figure 6. Forest plot of the odds ratios of pre-existing hypertension (HP) non-survivor compared to survivor coronavirus disease 2019 patients. CI, confidence interval.

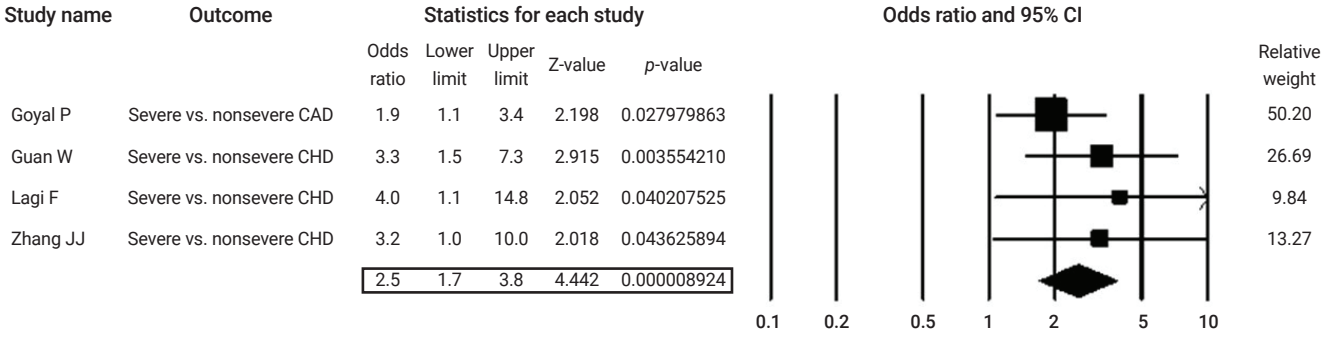

Figure 7. Forest plot of the odds ratios of pre-existing coronary heart disease (CHD) in severe cases compared to non-severe coronavirus disease 2019 cases.
CAD, coronary artery disease; CI, confidence interval.

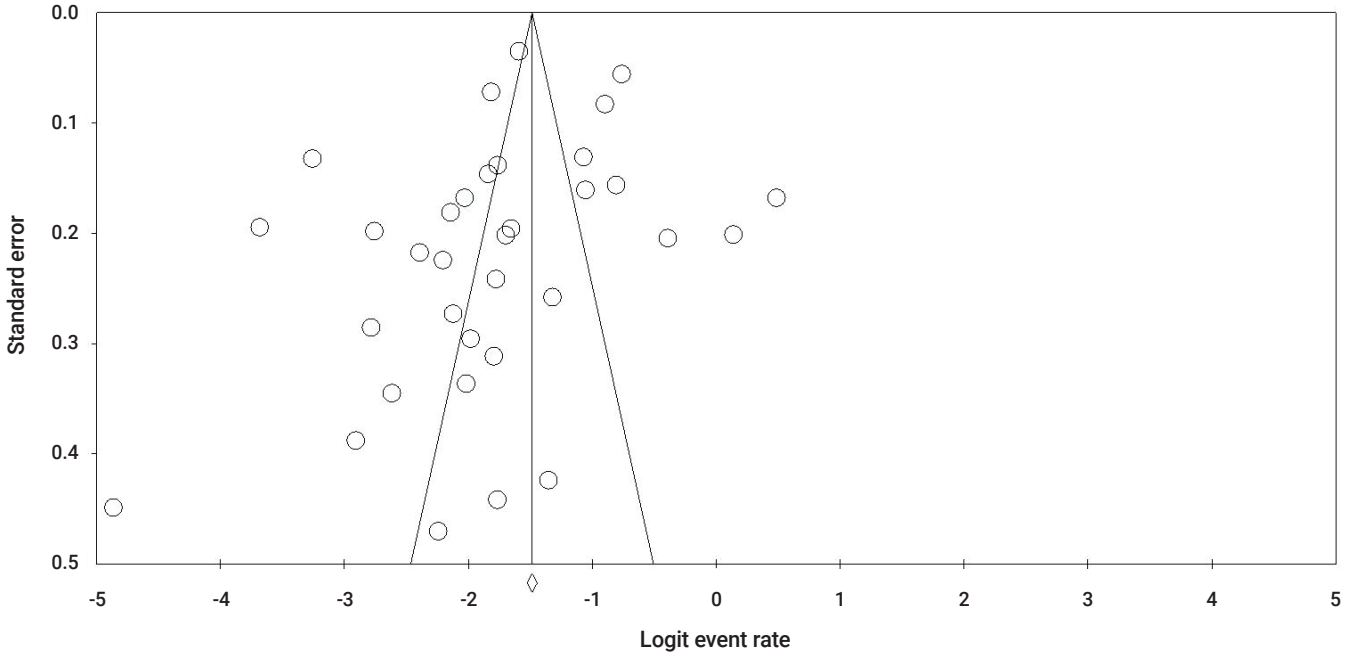

Figure 8. Funnel plot for publication bias based on cardiovascular comorbidity.

with hypertension are prescribed angiotensin-converting enzyme (ACE) inhibitors, aldosterone receptor blockers, and aldosterone antagonists, collectively called renin-angiotensin-aldosterone system (RAAS) inhibitors [49]. The modulator of the RAAS is the ACE2 receptor, which is used by SARS-CoV-2 to bind via its spike (S) protein to allow entry into attached cells. The activation of the RAAS is suggested as a mechanism for severe lung injury, especially in COVID-19 patients [50]. Inhibition of the protective signaling pathways in cardiac myocytes may result in secondary the downregulation of ACE2 expression within the myocardium. Finally, COVID-19 infection induces profound changes in coagulation pathways that create a hypercoagulable state and risk of microvascular thrombosis [51].

A strength of our pooled analysis is that it included more studies than some of the previous ones, and thus a larger sample size from different countries compared to the previous meta-analyses. Hence, our pooled analysis is the most inclusive and up-to-date analysis. The mechanism by which pre-existing cardiovascular disease increases the risk of COVID-19 adverse outcomes is also thought to be through the way that drugs for this disease work [52]. However, studies did not report data on the type of medications prescribed for each comorbidity, and hence we were not able to perform subgroup analyses by medication type. Such analyses are needed in further research. Another strength of this analysis is that visual symmetry in the funnel plot indicates the absence of publication bias. A limitation of this analysis is that most studies did not report the eligibility criteria and whether participants were recruited consecutively. Therefore, selection bias is a likely concern in the included studies. Other biases in the included studies are less likely since all studies sufficiently addressed other points in the JBI tool. Another limitation of this analysis is the possible effect of confounding factors including age, sex, and presence of other comorbidities that contribute to heterogeneity of the included studies. However, we used a random-effect model that addresses heterogeneity.

Conclusion

In summary, the present evidence showed that pre-existing cardiovascular disease in general, as well as hypertension and coronary heart disease, are highly associated with the severity and the mortality rate of COVID-19. Awareness of pre-existing cardiovascular comorbidities is important for the early management of COVID-19.

Supplementary Material

Table S1. Quality assessment of the studies on cardiovascular disease as a comorbidity in coronavirus disease 2019 patients using the Joanna Briggs Institute's tool. Supplementary data are available at https://doi.org/10.24171/j.phrp.2021.0186.

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Notes

Ethics Approval
Not applicable.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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Availability of Data
The datasets are not publicly available but are available from the corresponding author upon reasonable request.

Authors' Contributions
Conceptualization: FA; Data curation: FA, SA, MA; Formal analysis: SA; Investigation: FA; Methodology: FA, SA; Project administration: FA; Software: SA; Supervision: FA; Validation: all authors; Visualization: FA, SA; Writing–original draft: FA, SA; Writing–review & editing: all authors.

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