

# Impact of cardiovascular diseases on severity of COVID-19 patients: A systematic review

Pinki Mishra,<sup>1</sup>*MSc*, Rizwana Parveen,<sup>1</sup>*PhD*, Ram Bajpai,<sup>2</sup>*PhD*, Mohammed Samim,<sup>3</sup>*PhD*, Nidhi Bharal Agarwal,<sup>1</sup>*MPharm, PhD*.

## ABSTRACT

**Introduction:** Coronavirus disease 2019 (COVID-19) cases are increasing rapidly worldwide. Similar to Middle East respiratory syndrome where cardiovascular diseases were present in nearly 30% of cases, the increased presence of cardiovascular comorbidities remains true for COVID-19 as well. The mechanism of this association remains unclear at this time. Therefore, we reviewed the available literature and tried to find the probable association between cardiovascular disease with disease severity and mortality in COVID-19 patients.

**Methods:** We searched Medline (via PubMed) and Cochrane Central Register of Controlled Trials for articles published until Sept 5, 2020. Nineteen articles were included involving 6,872 COVID-19 patients.

**Results:** The random-effect meta-analysis showed that cardiovascular disease was significantly associated with severity and mortality for COVID-19: odds ratio (OR) 2.89, 95% confidence interval (CI) 1.98–4.21 for severity and OR 3.00, 95% CI 1.67–5.39 for mortality, respectively. Risk of COVID-19 severity was higher in patients having diabetes, hypertension, chronic obstructive pulmonary disease, malignancy, cerebrovascular disease and chronic kidney disease. Similarly, patients with diabetes, hypertension, chronic liver disease, cerebrovascular disease and chronic kidney disease were at higher risk of mortality.

**Conclusion:** Our findings showed that cardiovascular disease has a negative effect on health status of COVID-19 patients. However, large prevalence studies demonstrating the consequences of comorbid cardiovascular disease are urgently needed to understand the extent of these concerning comorbidities.

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**Keywords:** Cardiovascular disease, COVID-19, SARS-CoV-2

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) has spread rapidly from China to other countries around the world, with the World Health Organization characterising it as a global pandemic on 12 March 2020.<sup>1,2</sup> The number of fatalities owing to COVID-19 is escalating rapidly.<sup>3</sup> COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the 7th known human coronavirus. SARS-CoV-2 is assumed to have originated in bats, similar to many other coronaviruses, as it shares 89–96% nucleotide identity with bat coronaviruses. Similar to SARS and Middle East respiratory syndrome (MERS), it is believed SARS-CoV-2 moved from bats to an intermediate host and then to humans. SARS-CoV-2 infection is triggered by viral surface spike protein binding

to the human angiotensin-converting enzyme 2 (ACE2) receptor following activation of the spike protein by transmembrane protease serine 2. ACE2 is expressed in the lung (primarily Type II alveolar cells) and tends to be the predominant portal of entry. ACE2 is highly expressed in the heart as well, counteracting the effects of angiotensin II in states with excessive activation of the renin-angiotensin system such as hypertension, congestive heart failure and atherosclerosis. There is growing evidence linking COVID-19 to increased morbidity and mortality from cardiovascular disease (CVD).<sup>4</sup>

Different studies have identified the clinical characteristics and epidemiological findings of patients with COVID-19, and some of the clinical observations have shown a rapid deterioration in the condition of

<sup>1</sup> Centre for Translational and Clinical Research, School of Chemical & Life Sciences, Jamia Hamdard, New Delhi, India

<sup>2</sup> School of Primary, Community and Social Care, Keele University, UK

<sup>3</sup> Department of Chemistry, School of Chemical & Life Sciences, Jamia Hamdard, New Delhi, India.

Correspondence: Dr Nidhi Bharal Agarwal, Centre for Translational and Clinical Research, School of Chemical & Life Sciences, Jamia Hamdard, New Delhi-110062, India.

Email: [nidhi.bharal@gmail.com](mailto:nidhi.bharal@gmail.com), [nidhiagarwal@jamiyahamdard.ac.in](mailto:nidhiagarwal@jamiyahamdard.ac.in)

some COVID-19 patients.<sup>3,5-7</sup> With the rise in the number of confirmed cases and the accumulating clinical data, the cardiovascular manifestations induced by this viral infection has generated considerable concern.<sup>3</sup> COVID-19 relates with cardiovascular system on various levels, increasing morbidity in patients with underlying cardiovascular conditions and provoking myocardial injury and dysfunction.<sup>4</sup>

CVD was a common comorbidity in patients with SARS and MERS. In SARS, the prevalence of diabetes mellitus (DM) and CVD was 11% and 8%, respectively.<sup>4</sup> DM and hypertension were prevalent in about 50% of cases of MERS, while CVD was present in nearly 30% of patients. The increased presence of cardiovascular comorbidities remains true for COVID-19 as well, most particularly among those with more severe disease.<sup>4</sup> Data from China's National Health Commission showed that 35% of COVID-19 patients had hypertension, and 17% had coronary heart disease. The mechanism of this association remains unclear at this time. Possible causes include a greater prevalence of CVD in those with increasing age, a functionally compromised immune system, elevated levels of ACE2, or COVID-19 predisposition among those with CVD.<sup>4</sup>

Evidence suggest increased risk of mortality in COVID-19 patients with comorbidities.<sup>8</sup> A case series reported hypertension, CVD, diabetes, and chronic kidney disease to be the most common comorbidities with severe clinical outcomes. However, chronic obstructive pulmonary disease (COPD) was uncommon.<sup>9</sup> A retrospective study demonstrated hypertension, CVD, diabetes and COPD to be the most common chronic medical illnesses in COVID-19 patients.<sup>10</sup> Another retrospective study revealed high prevalence of hypertension, CVD and cerebrovascular disease among deceased patients than among recovered patients.<sup>11</sup>

Several studies have demonstrated higher prevalence of CVD in COVID-19 patients;<sup>12-14</sup> however, the effect of CVD on disease prognosis in COVID-19 patients needs further exploration. Although several meta-analyses have assessed the association of various comorbidities and disease severity in COVID-19 patients,<sup>15-18</sup> only few have emphasised the effect of CVD in COVID-19 patients.<sup>16-18</sup> Additionally, several meta-analyses lack assessment of the effect of CVD in patients specifically receiving or not receiving intensive care unit (ICU) care and mortality.<sup>16,18</sup> The understanding of the relationship could be beneficial in early vigilant monitoring and improved management of COVID-19 patients at high risk of mortality. Thus, in the present systematic review, we aim to assess the association of CVD with the severity and mortality of COVID-19.

## METHODS

Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines for systematic reviews<sup>19</sup> and meta-analysis of observational studies in epidemiology (MOOSE) guidelines<sup>20</sup> were followed for designing, conducting and reporting this systematic literature review.

### Data sources and searches

We searched Medline (via PubMed) and Cochrane Central Register of Controlled Trials until 5 September 2020 using the keywords “COVID-19 and cardiovascular disease”, “SARS-CoV-2 and cardiovascular disease”, “COVID-19 and comorbidities”. We also searched grey literature using Google Scholar and reference list of eligible articles.

### Inclusion and exclusion

The studies assessing comorbid CVD according to disease severity were included. We included observational studies that includes case-control, cross-sectional, and both retrospective and prospective cohort designs. We also included case series with sample size  $\geq 30$  patients as the disease we are trying to study is new. We excluded reviews, editorials, case reports, letters, meta-analysis, consensus reports, studies in language other than English, and studies not reporting the required data. The first author searched data and screened article for eligibility. The senior author double checked all the included articles and any disagreement was resolved by the third author.

### Quality assessment

Two reviewers/authors assessed the quality of data in the included studies using the US National Institutes of Health (NIH) quality assessment tools developed by the National Heart, Lung, and Blood Institute (NHLBI).<sup>21</sup> The NIH tool was preferred because it is comprehensive and widely accepted for an exhaustive assessment of data quality. The tools were designed to assist reviewers in focusing on concepts that are key for critical appraisal of the internal validity of a study. The tools were not designed to provide a list of factors comprising a numeric score. The tools were specific to individual types of included study designs and are described in more detail below. The tools included items for evaluating potential flaws in study methods or implementation, including sources of bias (e.g. patient selection, performance, attrition and detection), confounding, study power, the strength of causality in the association between interventions and outcomes, and other factors. Quality reviewers could select “yes”, “no”, or “cannot

determine/not reported/not applicable” in response to each item on the tool. For each item where “no” was selected, reviewers were instructed to consider the potential risk of bias that could be introduced by that flaw in the study design or implementation. Cannot determine and not reported were also noted as representing potential flaws. Each of the quality assessment tools had a detailed guidance document, which was also developed by the methodology team and NHLBI.

### Outcomes

The expected outcomes are (1) severity of COVID-19 including ICU admission, and (2) mortality due to confirmed COVID-19. Only intra-hospital mortality was considered.

### Data extraction

Data were inputted into a standardised data extraction table (Microsoft Excel) and independently checked by a second reviewer/author for accuracy. The following variables were extracted: name of the first author, year of publication, study design, location, age, gender, currently smoking, comorbidities, and number of patients in severe and non-severe/ survivor and non-survivor groups with comorbid CVD.

### Data synthesis

We performed an exploratory meta-analysis to understand the magnitude and direction of effect estimate. For dichotomous outcomes, odds ratios (OR) were calculated and presented with respective 95% confidence intervals (CI). Mantel-Haenszel random-effects meta-analysis using DerSimonian and Laird method was used to pool ORs. Heterogeneity between studies was assessed using the chi-square-based Cochran's Q statistic ( $P < 0.1$  considered as the presence of heterogeneity) and I-squared ( $I^2$ ) statistics ( $> 50\%$  representing moderate heterogeneity).<sup>22</sup> Forest plot was produced, and subgroup analysis was conducted according to study design. The 95% prediction interval (PI) was calculated, which estimates the uncertainty bounds for a new study evaluating that same association by considering between-study heterogeneity. Publication bias was assessed only for severity outcome by visual inspection of funnel plot as it qualified the requirement of minimum number of studies ( $\geq 10$  studies).<sup>22</sup> Egger's regression test was applied to assess small study effect ( $P < 0.1$  considered as the presence of small study effect).<sup>23</sup> All statistical analyses were conducted on Stata software version 16.1 (StataCorp LLC, College Station, US), and a  $P$  value less than 0.05 was considered statistically significant.

## RESULTS

### Search results

The systematic search yielded a total of 3,040 publications. Five studies were found from other sources. After removing duplicates, 2,148 articles were found to be potential publications for screening. After the application of predefined inclusion and exclusion criteria, a total of 19 studies were included for the meta-analysis (Fig. 1).

### Study characteristics

Six studies reported comorbid CVD in survivors and non-survivors, and 13 studies were reported in ICU care/severe and non-ICU care/non-severe patients in two studies. The included 19 studies enrolled a total of 6,872 patients, including 3,849 men and 3,023 women. The demographic characteristics of the subjects included in these studies are provided in Table 1.

### Quality assessment

We assessed the quality of data in the included studies using the NIH quality assessment tools (Table 1). The quality assessment indicated that most included studies were of acceptable quality. All the papers clearly stated the research question or objective, the study population was clearly specified and defined, and all the subjects were selected from the same or similar populations.

### Association between cardiovascular disease and disease severity

The association of CVD with COVID-19 severity was analysed in 13 studies, which enrolled a total of 2,762 patients, with 400 of them having previous history of CVD. The random-effects analysis led to an OR of 2.89 (95% CI 1.98–4.21,  $I^2$  40.2%) (Fig. 2). We also estimated the severity by study design in subgroup analysis. Both case-series (OR 3.63, 95% CI 1.44–9.13,  $I^2$  15.7%) and observational (OR 2.77, 95% CI 1.80–4.27,  $I^2$  48.3%) studies showed higher odds of COVID-19 severity among CVD patients. The overall estimated 95% PI (1.07–7.80) indicated a clear impact of COVID-19 severity among CVD patients when designing a new study. Visually, it seems that most studies fall under the 95% pseudo limits, indicating less/no evidence of publication bias (Fig. 4). However, we cannot ignore the impact of small study effects (Eggers regression test  $P = 0.050$ ).

### Association between cardiovascular disease and mortality

The analysis considering mortality due to COVID-19 retrieved 6 studies evaluating 4,110 individuals, with

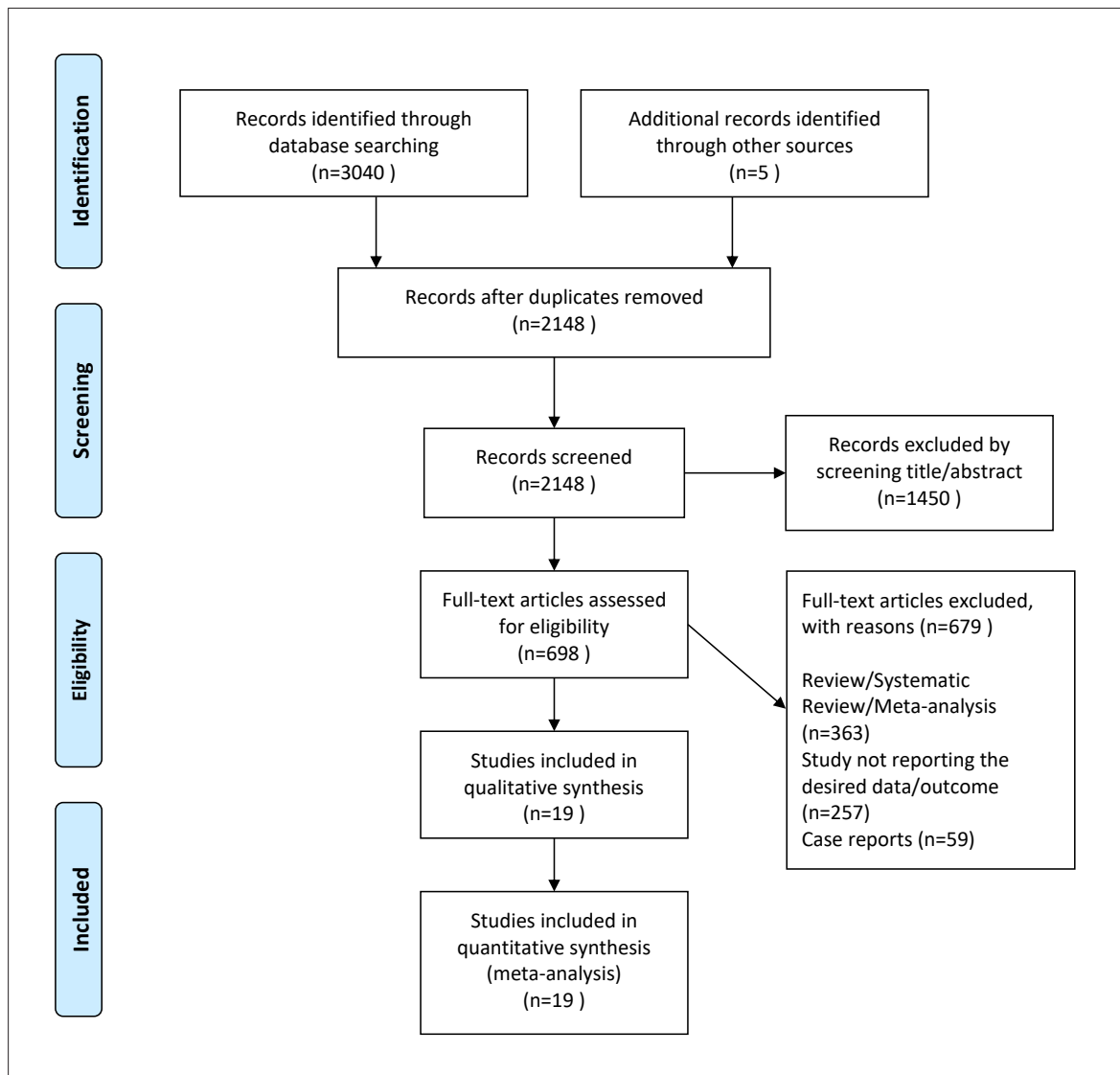


Fig. 1. Flow diagram of the number of studies screened and included in the meta-analysis.  
n=number of patients

441 having CVD. The random-effects analysis resulted in a pooled OR of 3.00 (95% CI 1.67–5.39,  $P$  68.5%) (Fig. 3). We also estimated the mortality by a study design in subgroup analysis. Both case-series (OR 3.63, 95% CI 1.44–9.14) and observational (OR 2.94, 95% CI 1.47–5.88,  $P$  73.4%) studies showed higher odds of COVID-19 mortality among CVD patients. The overall estimated 95% PI includes null value (0.50–17.89), indicating that it depends on several other factors while designing a new study.

#### Risk of severity and mortality due to comorbidities

Risk of COVID-19 severity was higher in patients having diabetes (OR 2.07 [1.44, 2.97]), hypertension

(OR 2.04 [1.26, 3.31]), COPD (OR 2.29 [1.28, 4.10]), malignancy (OR 2.66 [1.68, 4.20]), cerebrovascular disease (OR 2.78 [1.14, 6.79]) and chronic kidney disease (OR 2.16 [1.24, 3.77]) as co-morbidities. The risk of mortality due to COVID-19 was higher in patients with diabetes (OR 1.90 [1.50, 2.42]), hypertension (OR 2.33 [1.68, 3.22]), chronic liver disease (OR 4.34 [1.61, 11.67]), cerebrovascular disease (OR 4.79 [2.02, 11.37]) and chronic kidney disease (OR 2.99 [1.10, 8.13]). Comorbidities such as chronic liver disease, human immunodeficiency virus infection, hyperlipidaemia and hepatitis B were not found statistically significant with the severity outcome (Table 2). COPD, malignancy and hepatitis B were not significant with the mortality outcome.

Table 1. Demographic characteristics

Author, year	Study design	Location	Sample size	Mean age (Range)	Gender n (%)		Current smoker (%)	Comorbidities	Outcome (%)	Quality index
					Male	Female				
Huang et al., 2020 <sup>30</sup>	Prospective case-series	China	41	49 (41–58)	30 (73)	11 (27)	7	DIA, HTN, COPD, CLD, Malignancy	Severity (31.7)	Good
Wang D et al., 2020 <sup>27</sup>	Retrospective case-series	China	138	56 (42–68)	75 (54.3)	63 (45.7)	NA	DIA, HTN, COPD, Malignancy, CeVD, CKD, HIV	Severity (26.08)	Good
Zhang et al., 2020 <sup>28</sup>	Retrospective cohort	China	140	57 (25–87)	71 (50.7)	69 (49.3)	1.4	DIA, HTN, COPD, Hyperlipidemia	Severity (41.42)	Fair
Wan et al., 2020 <sup>31</sup>	Retrospective case-series	China	135	47 (36–55)	72 (53.3)	63 (46.7)	6.7	DIA, HTN, COPD, Malignancy, CLD	Severity (29.62)	Good
Guan et al., 2020 <sup>32</sup>	Retrospective cohort	China	1099	47 (35–58)	637 (58.1) <sup>a</sup>	459 (41.9) <sup>a</sup>	12.6 <sup>b</sup>	DIA, HTN, COPD, Malignancy, CeVD, CKD, Hep-B	Severity (15.74)	Fair
Li et al., 2020 <sup>2</sup>	Retrospective cohort	China	312	69.2±7.3	187	125	10.3	DIA, HTN, COPD, Malignancy, CLD, CKD, CeVD	Severity (33.65)	Fair
Buckner et al., 2020 <sup>9</sup>	Retrospective cohort	US	105	69 (23–97)	53 (50)	52 (50)	NA	DIA, HTN, COPD, malignancy, CKD, HIV	Severity (48.57)	Fair
Cao et al., 2020 <sup>10</sup>	Retrospective cohort	China	80	53±20	38 (47.5)	42 (52.5)	NA	DIA, HTN, COPD	Severity (33.75)	Fair
Jiang et al., 2020 <sup>33</sup>	Retrospective cohort	China	59	64 (56–72)	29 (49)	30 (51)	NA	DIA, HTN, COPD, malignancy, CLD	Severity (74.57)	Fair
Zhao et al., 2020 <sup>34</sup>	Retrospective cohort	China	29	56 (31.5–66)	14 (48.3)	15 (51.7)	NA	DIA, HTN	Severity (72.41)	Fair
Colombi et al., 2020 <sup>35</sup>	Retrospective cohort	Italy	236	68 (66–70)	177 (75)	59 (25)	3	DIA, COPD, malignancy, CLD, CKD	Severity (45.76)	Fair
Deng et al., 2020 <sup>36</sup>	Retrospective cohort	China	112	65 (49–70.8)	57 (50.9)	55 (49.1)	NA	DIA, HTN, malignancy	Severity (59.82)	Fair
Wei et al., 2020 <sup>37</sup>	Retrospective cohort	China	276	51 (41–58)	155 (56.2)	121 (43.8)	NA	DIA, HTN, COPD, malignancy, CeVD	Severity (5.07)	Fair
Chen et al., 2020 <sup>11</sup>	Retrospective case-series	China	274	62 (44–70)	171 (62)	103 (38)	4	DIA, HTN, Hep-B malignancy, CLD, CeVD, CKD, HIV	Mortality (58.75)	Good

DIA: diabetes; HTN: hypertension; COPD: chronic obstructive pulmonary disorder; CLD: chronic liver disease; CeVD: cerebrovascular disease; CKD: chronic kidney disease; HIV: human immunodeficiency virus; Hep-B: hepatitis B; NA: not available

<sup>a</sup> Out of 1,096

<sup>b</sup> Out of 1,085

Note: Data are presented as Median (interquartile range [IQR]) or number and percentage (%).

Superscript numbers: refer to References

Table 1. Demographic characteristics (Cont'd)

Author, year	Study design	Location	Sample size	Mean age (Range)	Gender n (%)		Current smoker (%)	Comorbidities	Outcome (%)	Quality index
					Male	Female				
Zhou et al., 2020 <sup>38</sup>	Retrospective cohort	China	191	56 (46–67)	119 (62)	72 (38)	6	DIA, HTN, COPD, malignancy, CKD	Mortality (71.72)	Fair
Wang L et al., 2020 <sup>39</sup>	Retrospective cohort	China	339	69 (65–76)	166 (49)	173 (51.0)	NA	DIA, HTN, COPD, malignancy, CLD, CeVD, CKD	Mortality (80.82)	Fair
Pan et al., 2020 <sup>40</sup>	Case-control	China	124	68 (61–75)	85 (68.5)	39 (31.5)	NA	DIA, HTN, COPD	Mortality (28.22)	Good
Rastad et al., 2020 <sup>41</sup>	Retrospective cohort	Iran	2957	54.8 (16.9)	53.7 (1589)	46.3 (1368)	NA	DIA	Mortality (89.82)	Fair
Deng et al., 2020 <sup>42</sup>	Retrospective cohort	China	225	NA	124 (55.1)	101 (44.9)	NA	NA	Mortality (51.55)	Fair

DIA: diabetes; HTN: hypertension; COPD: chronic obstructive pulmonary disorder; CLD: chronic liver disease; CeVD: cerebrovascular disease; CKD: chronic kidney disease; HIV: human immunodeficiency virus; Hep-B: hepatitis B; NA: not available

<sup>a</sup> Out of 1,096

<sup>b</sup> Out of 1,085

Note: Data are presented as Median (interquartile range [IQR]) or number and percentage (%).

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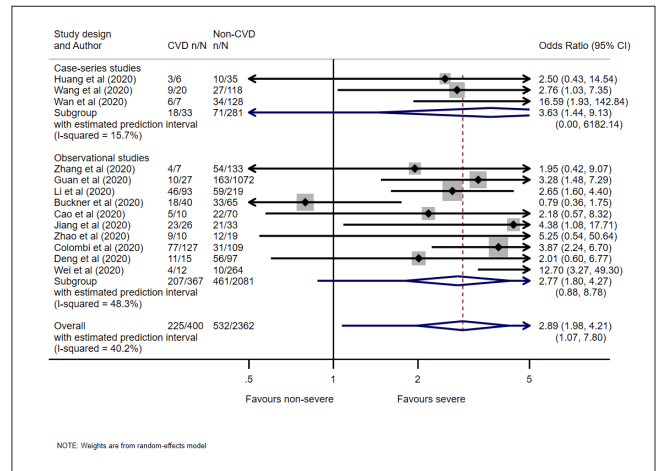


Fig. 2. Association of cardiovascular disease and COVID-19 severity.

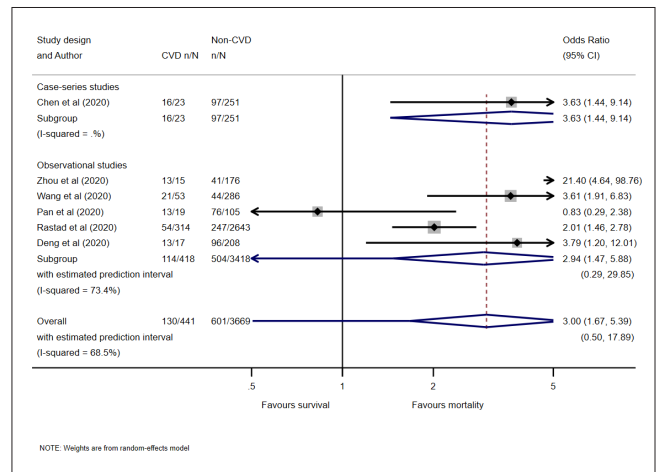


Fig. 3. Association of cardiovascular disease and COVID-19 mortality.

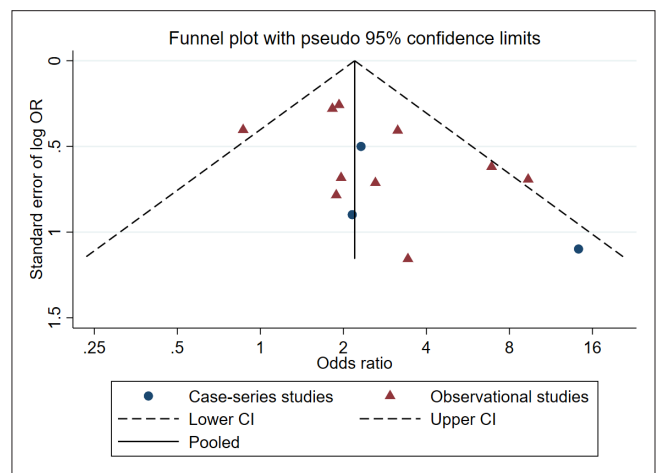


Fig. 4. Funnel plot assessing publication bias.

## DISCUSSION

Recent evidence on SARS-CoV-2 suggests that the presence of comorbidities increases mortality risk in COVID-19 patients.<sup>8</sup> Cardiac disease and diabetes are the most important components in predicting adverse outcomes.<sup>12</sup> Thus, the present systematic review was conducted to assess the association of CVD with disease severity in COVID-19 patients. The meta-analysis was based on data from 19 studies on COVID-19 patients. The present meta-analysis demonstrated that the presence of CVD is lower in survivors than in non-survivors of COVID-19 patients. However, there was no difference in CVD prevalence in patients requiring and not requiring ICU care. Additionally, a positive association between CVD and disease severity was found. Several studies have demonstrated higher prevalence of CVD in COVID-19 patients, however, the effect of the prevalence of CVD on severity of the disease needs further exploration. A recent meta-analysis on the comorbidities suggested CVD as one of the most prevalent comorbidities (5±4, 95% CI 4–7%) in COVID-19 patients. Significant difference was found in CVD between severe and non-severe groups.<sup>13</sup> Another similar meta-analysis demonstrated the pooled prevalence of CVD to be 12.11% (95% CI 4.40–22.75%).<sup>14</sup> A meta-analysis reported the proportions of CVD in patients with COVID-19 to be 17.1%. The incidences of cardio-cerebrovascular disease were about 3-fold higher in ICU/severe cases than in their non-ICU/severe counterparts.<sup>12</sup> A retrospective study showed that 85.54% of severe patients had diabetes or CVD, which was significantly higher than that of the mild group.<sup>24</sup> A cohort study demonstrated that COVID-19 patients with comorbid chronic hypertension were higher in the deceased group when compared to the recovered group.<sup>3–11</sup>

Although the pathophysiology involved in this comorbidity remains unexplained, several hypotheses have been proposed. It is suggested that viral infection causes direct damage to cardiomyocyte. Moreover, SARS-CoV viral RNA has been detected in 35% autopsied human heart samples from patients infected with SARS-CoV.<sup>4</sup> Human pathogenic coronaviruses, SARS-CoV and SARS-CoV-2 bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels.<sup>12</sup> A preclinical study demonstrated that pulmonary infection with the human SARS-CoV in mice led to an ACE2-dependent myocardial infection with a marked decrease in ACE2 expression.<sup>25</sup> The expression of ACE2 is significantly increased in patients being treated with ACE inhibitors and angiotensin II type-I receptor blockers. Use of

Table 2. Risk of severity and mortality due to different comorbidities in COVID-19 patients

Comorbidity	Severity outcome					Mortality outcome						
	No. of reports	n/N	OR (95% CI)	P value	PI	I <sup>2</sup> (%)	No. of reports	n/N	OR (95% CI)	P value	PI	I <sup>2</sup> (%)
Diabetes	13	757/2762	2.07 (1.44, 2.97)	P<0.001	(0.81, 5.28)	39.5	6	731/4110	1.90 (1.50, 2.42)	P<0.001	(1.35, 2.68)	0.0
Hypertension	11	628/2497	2.04 (1.26, 3.31)	0.004	(0.42, 9.97)	72.1	5	430/1153	2.33 (1.68, 3.22)	P<0.001	(1.02, 5.30)	28.5
COPD	12	736/2733	2.29 (1.28, 4.10)	0.005	(0.56, 9.44)	36.1	3	208/654	2.67 (0.65, 10.92)	0.171	(0.00, 28.30)	72.5
Malignancy	9	584/2401	2.66 (1.68, 4.20)	P<0.001	(1.53, 4.62)	0.0	4	341/1029	1.85 (0.80, 4.24)	0.148	(0.30, 11.45)	0.0
CLD	5	310/783	1.10 (0.45, 2.69)	0.827	(0.26, 4.69)	0.0	3	287/838	4.34 (1.61, 11.67)	0.004	(0.00, 38.86)	32.8
CeVD	4	328/1825	2.78 (1.14, 6.79)	0.024	(0.13, 58.04)	35.6	2	178/613	4.79 (2.02, 11.37)	P<0.001	–	0.0
CKD	5	473/1890	2.16 (1.24, 3.77)	0.007	(0.87, 5.33)	0.0	3	232/804	2.99 (1.10, 8.13)	0.032	(0.00, 19.79)	0.0
HIV	2	87/243	1.28 (0.14, 11.73)	0.830	–	0.0	–	–	–	–	–	–
Hyperlipidaemia	1	58/140	0.55 (0.10, 2.94)	0.484	–	–	–	–	–	–	–	–
Hepatitis B	1	286/1373	0.24 (0.03, 1.78)	0.163	–	–	1	113/274	1.20 (0.36, 4.02)	0.772	–	–

n: total cases; N: total study participants; OR: odds ratio; CI: confidence intervals; PI: prediction interval; COPD: chronic obstructive pulmonary disorder; CLD: chronic liver disease; CeVD: cerebrovascular disease; CKD: chronic kidney disease; HIV: human immunodeficiency syndrome

thiazolidinediones and ibuprofen can also increase ACE2. Consequently, the increased expression of ACE2 would facilitate infection with COVID-19.<sup>26</sup> Hypoxaemia can be also an important cause of cardiac injury. Severe SARS-CoV-2 infection leading to pneumonia may cause significant gas exchange obstruction, leading to hypoxaemia. Hypoxia-induced influx of calcium ions also leads to injury and apoptosis of cardiomyocytes. High concentration of IL-1 $\beta$ , IFN- $\gamma$ , IP-10 and MCP-1 has been detected in COVID-19 patients, which may cause activated T helper-1 (Th1) cell responses. Studies suggest association of cytokine storm with disease severity. Anxiety leading to repeated downpours of catecholamines and the side effects of medication received may also lead to myocardial damage.<sup>12</sup>

The present study revealed significant association of diabetes, hypertension, COPD, malignancy and chronic kidney disease (CKD) with severity of COVID-19. The results also demonstrate significant association of diabetes, hypertension, chronic liver disease, cerebrovascular disease and CKD with mortality in COVID-19 patients. A similar meta-analysis demonstrated diabetes mellitus and hypertension to be moderately associated with severity and mortality, respectively, for COVID-19.<sup>15</sup> A retrospective study showed hypertension, diabetes, CVD, and malignancy to be the most common coexisting conditions in COVID-19 patients. Compared with patients who did not require ICU care, patients requiring ICU care had comorbidities, including hypertension, diabetes, CVD and cerebrovascular disease.<sup>27</sup> Another meta-analysis revealed the presence of comorbid cerebrovascular and CVD to be associated with increased risk for poor outcome in COVID-19.<sup>17</sup> A meta-analysis revealed that patients with comorbid CVD, hypertension, diabetes, congestive heart failure, CKD and cancer have a greater risk of mortality compared to those without these comorbidities.<sup>18</sup>

Diseases such as hypertension, diabetes and CVD, and their susceptibility conditions, may be related to the pathogenesis of COVID-19. Several standard features are shared between chronic diseases and infectious disorders, such as the pro-inflammatory state, and the attenuation of the innate immune response. Patients with any comorbidity had poorer clinical outcomes. A higher number of comorbidities correlate with poorer clinical outcomes. An exhaustive assessment of comorbidities may help establish risk stratification of patients with COVID-19 upon hospital admission.<sup>13</sup> Major gaps in the knowledge of the origin, duration of human transmission, epidemiology, and clinical spectrum of disease need to be fulfilled by future studies.<sup>28</sup>

COVID-19 has had a crippling effect on the healthcare systems around the world with cancellation of elective medical services and disturbance in daily life. COVID-19 has significantly affected the normal working of health care organisations. It has made patients stay away from accident and emergency departments, and prevent them from reaching out for urgent medical conditions such as heart diseases and cancer.<sup>29</sup>

### Limitations

This systematic review and updated meta-analysis have several limitations that need to be mentioned. We included retrospective studies (cross-sectional, retrospective cohort and case series) in the lack of prospective studies. The number of studies by design in the meta-analysis were limited. Most of the included studies were conducted exclusively in China, which limits its wider applicability of results. Several comorbidities could have been coexisting with CVD in the same individual that might influence the impact severity and mortality, and we were unable to assess their combined effect. Severity outcome showed moderate heterogeneity (40.2%) even after adding additional studies. However, mortality outcome showed slightly higher heterogeneity (68.5%). The potential reasons for such higher heterogeneity have been explained in the discussion section. We were also not able to assess the influence of other CVD risk factors such as age, obesity and type of diabetes, etc. for COVID-19 severity and/or mortality. Although we did an extensive search, we may have inadvertently missed relevant studies. Exclusion of studies in languages other than English may have resulted in missing out relevant studies. People with CVD may not have been able to seek help due to the overwhelmed health system, which could have led to more mortality due to CVD. Therefore, we were not 100% sure that all mortalities were related to COVID-19.

### CONCLUSION

Our findings showed that comorbid CVD has a negative effect on health status of COVID-19 patients. However, large prevalence studies demonstrating the consequences of comorbid CVD are urgently needed to understand the magnitude of these concerning comorbidities. Extensive studies are required to fill the major gaps in understanding the disease to establish risk stratification of the patients.

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