**Impact of cardiovascular diseases on disease severity and mortality in COVID-19 patients: a systematic review and an updated meta-analysis**

Running Title: COVID-19 severity and cardiovascular disease

Pinki Mishraa, Rizwana Parveena, Ram Bajpaib, Mohammed Samimc, Nidhi Bharal Agarwala

aCentre for Translational and Clinical Research, School of Chemical & Life Sciences, Jamia Hamdard, New Delhi-110062, India.

bSchool of Primary, Community and Social Care, Keele University, Staffordshire ST5 5BG, UK

cDepartment of Chemistry, School of Chemical & Life Sciences, Jamia Hamdard, New Delhi-110062, India.

Corresponding author

Nidhi Bharal Agarwal, M.Pharm., Ph.D.

Centre for Translational and Clinical Research

School of Chemical & Life Sciences

Jamia Hamdard

New Delhi-110062, India

Phone: +91-9818334770

E-mail address: nidhi.bharal@gmail.com

Orcid ID: <https://orcid.org/0000-0002-2509-3026>

**ABSTRACT**

**Introduction:** Coronavirus disease 2019 (COVID-19) cases are increasing rapidly worldwide. Similar to Middle East respiratory syndrome (MERS) 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 6872 COVID-19 patients.

**Results:** The random-effect meta-analysis showed that cardiovascular disease was significantly associated with severity and mortality for COVID-19 [OR 2.89 95% 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, COPD, 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.

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

**INTRODUCTION**

Coronavirus disease 2019 (COVID-19), a highly infectious disease has spread rapidly from China to other countries around the world. World Health Organization characterized COVID-19 as global pandemic on March 12, 20201,2. The number of fatalities owing to COVID-19 is escalating rapidly3. COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). This novel virus is the seventh 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 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 (TMPRSS2). 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 (HTN), congestive heart failure (CHF), and atherosclerosis. There is growing evidence linking COVID-19 to increased morbidity and mortality from cardiovascular disease (CVD)4.

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 some COVID-19 patients3,5–7. 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 concern3. COVID-19 relates with cardiovascular system on various levels, increasing morbidity in patients with underlying cardiovascular conditions and provoking myocardial injury and dysfunction4.

Cardiovascular disease was a common comorbidity in patients with COVID-19 precursors SARS and MERS. In SARS, the prevalence of diabetes mellitus (DM) and CVD was 11% and 8% respectively. DM and hypertension (HTN) 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. Data from China's National Health Commission (NHC) showed that 35% of COVID-19 patients had HTN, 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 CVDs4.

Evidence suggest increased risk of mortality in COVID-19 patients with comorbidities8. A case series reported hypertension, CVD, diabetes, and chronic kidney disease to be the most common comorbidities with severe clinical outcomes. However, COPD was uncommon9. A retrospective study demonstrated hypertension, cardiovascular disease, diabetes and COPD to be the most common chronic medical illnesses in COVID-19 patients10. Another retrospective study revealed high prevalence of hypertension, CVD, and cerebrovascular disease among deceased patients than among recovered patients11.

Several studies have demonstrated higher prevalence of CVD in COVID-19 patients12–14, however, the effect of CVD on disease prognosis in COVID-19 patients need further exploration. Although, several meta-analysis have assessed the association of various comorbidities and disease severity in COVID-19 patients15–18, only few have emphasized on the effect of CVD in COVID-19 patients16–18. Additionally, several meta-analysis lack assessment of the effect of CVD in patients specifically receiving or not receiving ICU care and mortality16,18. 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-Analysis (PRISMA) guidelines for systematic reviews19 and meta-analysis of observational studies in epidemiology (MOOSE) guidelines20 were followed for designing, conduct and reporting this systematic literature review.

*Data sources and searches*

We searched Medline (via PubMed) and Cochrane Central Register of Controlled Trials until Sept 5, 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 cardiovascular disease 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 ≥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. First author (PM) searched data and screened article for eligibility. Senior author (RP) double checked all the included articles and any disagreement was resolved by third author (RB).

*Quality assessment*

Two reviewers (PM and RP) assessed the quality of data in the included studies using the National Institute of Health (NIH) quality assessment tools developed by National Heart, Lung, and Blood Institute (NHLBI)21. 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 include (1) Severity of COVID-19 including: Intensive Care Unit (ICU) admission and (2) mortality due to confirmed COVID-19. Only intra-hospital mortality was considered.

*Data extraction*

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

*Data synthesis*

We performed an exploratory meta-analysis to understand the magnitude and direction of effect estimate. For dichotomous outcomes, Odds ratios (ORs) were calculated and presented with respective 95% confidence intervals (CIs). Mantel-Haenszel random-effects meta-analysis using DerSimonian and Laird method was used to pool ORs. Heterogeneity between studies was assessed using the χ2-based Cochran's Q statistic (p<0.1 considered as the presence of heterogeneity) and I-squared (*I2*) statistics (>50% representing moderate heterogeneity)22. 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 (≥10 studies)22. Egger’s regression test was applied to assess small study effect (p<0.1 considered as the presence of small study effect)23. All statistical analyses were conducted on Stata software version 16.1 (StataCorp LLC, College Station, Texas, USA), and a *p*-value less than 0.05 was considered statistically significant result.

**RESULTS**

*Search results*

The systematic search yielded a total of 3040 publications. Five studies were found from other sources. After removing duplicates, 2148 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 (Figure 1).

*Study characteristics*

Six studies reported comorbid cardiovascular disease 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 6872 patients, including 3849 males and 3023 females. 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 National Institute of Health (NIH) quality assessment tools and presented in the 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 with COVID-19 severity was analyzed in 13 studies, enrolling a total of 2762 patients being 400 with previous history of cardiovascular disease. The random-effects analysis lead to an OR of 2.89 (95% CI: 1.98-4.21 *I2*: 40.2%) (Figure 2). We also estimated the severity by study design in subgroup analysis. Both case-series (OR 3.63 95% CI: 1.44-9.13 *I2*: 15.7%) and observational (OR 2.77 95% CI: 1.80-4.27 *I2:* 48.3%) studies showed higher odds of COVID-19 severity among CVD patients. The overall estimated 95% PI (1.07-7.80) indicating 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 (Figure 4). However, we cannot ignore the impact of small study effects (Eggers regression test p-value=0.050).

*Association between cardiovascular disease and mortality*

The analysis considering mortality due to COVID-19 retrieved 6 studies evaluating 4110 individuals being 441 with cardiovascular disease. The random-effects analysis resulted a pooled OR of 3.00 (95% CI 1.67-5.39 *I2*: 68.5%) (Figure 3). We also estimated the mortality by 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 *I2:* 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 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. While the risk of mortality due to COVID-19 was found 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]) whereas comorbidities such as chronic liver disease, HIV, hyperlipidemia and hepatitis B were not found statistically significant with the severity outcome (Table 2). and COPD, malignancy and hepatitis B were not significant with the mortality outcome.

**DISCUSSION**

Recent evidence on SARS-CoV-2 suggest that the presence of comorbidities increase mortality risk in COVID-19 patients8. Cardiac disease and diabetes are the most important components to predict adverse outcomes12. Thus, the present systematic review was conducted to assess the association of cardiovascular disease 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 or 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 cardiovascular disease as one of the most prevalent comorbidities (5±4, 95%CI 4-7%) in COVID-19 patients. Significant difference was found in cardiovascular disease between severe and non-severe group13[11]. Another similar meta-analysis demonstrated the pooled prevalence of cardiovascular disease to be 12.11% (95%CI 4.40%-22.75%)14. A meta-analysis reported the proportions of cardiovascular disease in patients with COVID-19 to be 17.1%. The incidences of cardia-cerebrovascular disease were about threefolds higher in ICU/severe cases than in their non-ICU/severe counterparts12. A retrospective study showed that 85.54% of severe patients had diabetes or cardiovascular diseases, which was significantly higher than that of the mild group24. A cohort study demonstrated that COVID-19 patients with comorbid chronic hypertension were higher in deceased group as compared to the recovered group3–11.

Although the pathophysiology involved in this comorbidity remains unexplained, several hypotheses have been hypothesized. It is suggested 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-CoV4. Human pathogenic coronaviruses, SARS-CoV and SARSCoV-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 vessels12.A pre-clinical 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 expression25. The expression of ACE2 is significantly increased in patients being treated with ACE inhibitors and angiotensin II type-I receptor blockers. Use of thiazolidinediones and ibuprofen can also be increased ACE2. Consequently, the increased expression of ACE2 would facilitate infection with COVID-1926. Hypoxaemia can be also an important cause of cardiac injury. Severe 2019-nCoV 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-1β, IFN-γ, IP-10 and MCP-1 has been detected in COVID-19 patients, which may cause activated T-helper-1 (Th1) cell responses. Studies suggest that 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 damage12.

The present study revealed significant association of diabetes, hypertension, COPD, malignancy and CKD with severity of COVID-19. The results also demonstrate significant association of diabetes, hypertension, CLD, CeVD 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‑1915. A retrospective study showed hypertension, diabetes, cardiovascular disease, 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 and cardiovascular disease and cerebrovascular disease27. Another meta-analysis revealed the presence of comorbid cerebrovascular and cardiovascular diseases to be associated with increased risk for poor outcome in COVID-1917. A meta-analysis revealed that patients with comorbid cardiovascular disease, hypertension, diabetes, congestive heart failure, chronic kidney disease and cancer have a greater risk of mortality compared to those without these comorbidities18.

Diseases such as hypertension, diabetes and cardiovascular diseases, 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 admission13. Major gaps in the knowledge of the origin, duration of human transmission, epidemiology, and clinical spectrum of disease need to be fulfilled by future studies28. COVID-19 has had a crippling effect on the health care 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 staying away from accident and emergency departments and reaching out for urgent medical conditions such as heart, cancer illnesses29.

**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 cases 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 that 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 of relevant studies. People with cardiovascular diseases 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 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 magnitude of these concerning comorbidities. Extensive studies are required to fill the major gaps in understanding of the disease to establish risk stratification of the patients.

**DECLARATION**

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Table-1 Demographic characteristics

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author and year** | **Study design** | **Location** | **Sample size** | **Mean age (Range)** | **Gender****N (%)** | **Current smoker (%age)** | **Comorbidities** | **Outcome (%age)** | **Quality Index** |
|  |  |  |  |  | **Male** | **Female** |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Huang et al, 202030 | Prospectivecase-series | China | 41 | 49 (41–58) | 30 (73) | 11 (27) | 7 | DIA, HTN, COPD, CLD, Malignancy | Severity(31.7) | Good |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Wang D et al, 202027 | Retrospectivecase-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, 202028 | Retrospectivecohort | China | 140 | 57 (25-87) | 71 (50.7) | 69 (49.3) | 1.4 | DIA, HTN, COPD, Hyperlipidemia | Severity(41.42) | Fair |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| Wan et al, 202031 | Retrospectivecase-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, 202032 | Retrospectivecohort | China | 1099 | 47 (35–58) | 637 (58.1)\* | 459 (41.9)\* | 12.6^ | DIA, HTN, COPD, Malignancy, CeVD, CKD, Hep-B | Severity(15.74) | Fair |
|  |  |  |  |  |  |  |  |  |  |  |
| Li et al, 202012 | Retrospectivecohort | China | 312 | 69.2±7.3 | 187 | 125 | 10.3 | DIA, HTN, COPD, Malignancy, CLD, CKD, CeVD | Severity(33.65) | Fair |
|  |  |  |  |  |  |  |  |  |  |  |
| Buckner et al, 20209 | Retrospectivecohort | USA | 105 | 69 (23-97) | 53 (50) | 52 (50) | NA | DIA, HTN, COPD, Malignancy, CKD, HIV | Severity(48.57) | Fair |
|  |  |  |  |  |  |  |  |  |  |  |
| Cao et al, 202010 | Retrospectivecohort | China | 80 | 53±20 | 38 (47.5) | 42 (52.5) | NA | DIA, HTN, COPD | Severity(33.75) | Fair |
|  |  |  |  |  |  |  |  |  |  |  |
| Jiang et al, 202033 | Retrospectivecohort | China | 59 | 64 (56-72) | 29 (49) | 30(51) | NA | DIA, HTN, COPD, Malignancy, CLD | Severity(74.57) | Fair |
|  |  |  |  |  |  |  |  |  |  |  |
| Zhao et al, 202034 | Retrospectivecohort | China | 29 | 56 (31.5–66) | 14 (48.3) | 15 (51.7) | NA | DIA, HTN | Severity(72.41) | Fair |
|  |  |  |  |  |  |  |  |  |  |  |
| Colombi et al, 202035 | Retrospectivecohort | Italy | 236 | 68 (66-70) | 177 (75) | 59 (25) | 3 | DIA, COPD, Malignancy, CLD, CKD | Severity(45.76) | Fair |
|  |  |  |  |  |  |  |  |  |  |  |
| Deng et al, 202036 | Retrospectivecohort | China | 112 | 65 (49–70.8) | 57 (50.9) | 55 (49.1) | NA | DIA, HTN, Malignancy | Severity(59.82) | Fair |
|  |  |  |  |  |  |  |  |  |  |  |
| Wei et al, 202037 | Retrospectivecohort | China | 276 | 51 (41–58) | 155 (56.2) | 121 (43.8) | NA | DIA, HTN, COPD, MALIGNACY, CeVD | Severity(5.07) | Fair |
|  |  |  |  |  |  |  |  |  |  |  |
| Chen et al, 202011 | Retrospectivecase-series | China | 274 | 62 (44-70) | 171 (62) | 103 (38) | 4 | DIA, HTN, Hep-B Malignancy, CLD, CeVD, CKD, HIV,  | Mortality(58.75) | Good |
|  |  |  |  |  |  |  |  |  |  |  |
| Zhou et al, 202038 | Retrospectivecohort | China | 191 | 56 (46–67) | 119 (62) | 72 (38) | 6 | DIA, HTN, COPD, Malignancy, CKD | Mortality(71.72) | Fair |
|  |  |  |  |  |  |  |  |  |  |  |
| Wang L et al, 202039 | Retrospectivecohort | 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, 202040 | Case-control | China | 124 | 68 (61-75) | 85 (68.5) | 39 (31.5) | NA | DIA, HTN, COPD | Mortality(28.22) | Good |
|  |  |  |  |  |  |  |  |  |  |  |
| Rastad et al , 202041 | Retrospectivecohort | Iran | 2957 | 54.8 (16.9) | 53.7 (1589) | 46.3 (1368) | NA | DIA | Mortality(89.82) | Fair |
|  |  |  |  |  |  |  |  |  |  |  |
| Deng et al, 202042 | Retrospectivecohort | China | 225 | NA | 124 (55.1) | 101 (44.9) | NA | NA | Mortality(51.55) | Fair |

Data is presented as Median (IQR) or number (%). 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

No., number; ICU, intensive care unit; NA, not available; IQR, inter quartile range.

\*Out of 1096, \*\*Out of 923, ^Out of 1085, ^^Out of 913, ^^^Out of 172

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Co-morbidity** | **Severity outcome** |  | **Mortality outcome** |
| No of reports | n/N | OR [95%CI] | P-value | PI | *I2*(%) | No of reports | n/N | OR [95%CI] | P-value | PI | *I2*(%) |
| 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

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

Records excluded by screening title/abstract
(n = 1450 )

 )

Studies included in quantitative synthesis (meta-analysis)
(n = 19 )

Studies included in qualitative synthesis
(n = 19 )

Full-text articles assessed for eligibility
(n = 698 )

Records screened
(n = 2148 )

Records after duplicates removed
(n = 2148 )

Additional records identified through other sources
(n = 5 )

## Identification

## Eligibility

## Included

## Screening

Records identified through database searching
(n = 3040 )

Full-text articles excluded,

with reasons (n = 679 )

Review/Systematic Review/Meta-analysis (n=363)

Study not reporting the desired data/outcome (n=257)

Case reports (n=59)

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

