Effects of pre-existing morbidities on occurrence of death among COVID-19 disease patients: A systematic review and meta-analysis

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Abstract

**Background:** Coronavirus disease 2019 (COVID-19), most hectic pandemic of the era, is increasing exponentially and taking thousands of lives, worldwide.

**Objective:** This study aimed to assess the prevalence of pre-existing morbidities among COVID-19 infected patients and their mortality risks against each type of pre-existing morbidity categories.

**Design:** Systematic review and meta-analysis

**Data sources:** Medline, Web of Science, Scopus, and CINAHL databases were searched using the following keywords: (COVID-19 or 2019-nCoV or Coronavirus or SARS-CoV-2) AND (Comorbidity or Morbidity) AND (Mortality or Death or Died) up to May 01, 2020. Further searches were conducted using the reference list of the selected studies, renowned pre-print servers (e.g., medRxiv, bioRxiv, SSRN), and relevant journal websites.

**Eligibility criteria:** Studies written in the English language included if those were conducted among COVID-19 patients with and without comorbidities and presented survivor vs. non-survivor counts or hazard/odds of deaths or survivors against types of pre-existing morbidities.

**Methods:** Comorbidities reported in the selected studies were grouped into eight categories. The pooled likelihoods of deaths in each category were estimated using a fixed or random-effect model, based on the heterogeneity assessment. Publication bias was assessed by visual inspection of the funnel plot asymmetry and Egger’s regression test. Trim and Fill method was used if there any publication bias was found.
**Results:** A total of 42 studies included in this study comprised of 39,398 samples. The most common pre-existing morbidities in COVID-19 infected patients were hypertension (36.5%), cardiovascular disease (11.9%), and diabetes (22.0%). The higher likelihood of deaths was found among COVID-19 patients who had pre-existing cardiovascular system diseases (OR: 3.32, 95% CI: 2.79-3.95), immune and metabolic disorders (OR: 2.39, 95% CI: 2.00-2.85), respiratory diseases (OR: 2.02, 95% CI: 1.80-2.26), cerebrovascular system diseases (OR: 4.12, 95% CI: 3.04-5.58), any types of cancers (OR: 2.22, 95% CI: 1.63-3.03), renal (OR: 3.02, 95% CI: 2.60-3.52), and liver system diseases (OR: 1.44, 95% CI: 1.21-1.71).

**Conclusions:** This study provides evidence of a higher likelihood of deaths among COVID-19 patients against morbidity categories. These findings could potentially help healthcare providers to sort out the most endangered COVID-19 patients by comorbidities, take precautionary measures during hospitalization, assess susceptibility to death, and prioritize their treatment, which could potentially reduce the number of fatalities in COVID-19 disease.

**Keywords:** Coronavirus; 2019-nCoV; COVID-19; SARS-CoV-2; Comorbidity; Mortality
Introduction

The coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2, a virus from the large coronavirus family, started in a seafood market in Wuhan, China, and is now a global pandemic. The virus is highly transmissible (reproductive number: 1.6-6.5, doubling time: 6.4 to 7.4 days) [1], which can mainly transmit through respiratory droplets (coughs or sneezes), close contact with the infected person [2, 3], and touching surfaces or objects that are touched by the infected person [2, 3]. As of May 08, 2020, 130 days since the virus was first detected on December 31, 2019, approximately 3.77 million people from 215 countries or territories have been infected with this virus [4]. Around 0.26 million of them have already died [4], and about 2% of currently infected people are now in critical conditions [5]. To date, there is no specific medicine or vaccine for COVID-19 disease; therefore, the majority of the affected countries are taking non-pharmaceutical interventions such as restriction in inhabitants' mobility, quarantine of suspected persons, isolation of infected persons, travel restrictions, and airport screening to reduce further infections [1, 6, 7].

The virus is equally transmissible in all ages; however, people who are now in critical conditions or who died were more likely to be in older age and found they had one or more morbidities [8-11]. Commonly reported morbidities among patients who died from COVID-19 were hypertension, diabetes, cardiovascular disease, and cerebrovascular disease [8, 12-14]. Notably, these comorbidities are independent causes of millions of annual deaths globally; 17.9 million deaths from cardiovascular system diseases, 9 million deaths from cancers, 3.9 million deaths from respiratory diseases, and 1.6 million deaths from diabetes, according to a report by World Health Organization (WHO) in 2018 [15]. People with one or more of these morbidities usually have poor immune systems, which increases their susceptibility to being infected, to reach in critical condition, and even died from a secondary disease like COVID-19 [1, 12, 16-19]. Precautionary measures following COVID-19 disease
among patients with one or more morbidities could be potential ways to combat its adverse outcomes and severities. Thus, we need to identify possible morbidities that are potentially increasing the risks of mortality, which are still lacking. Studies conducted among COVID-19 patients are highly varied with reported morbidities and the likelihood of mortality [8, 10, 20, 21]. To address these gaps, this study was conducted with two primary aims: (i) to summarize pre-existing morbidities in patients with a secondary disease, COVID-19 and (ii) to estimate the likelihood of mortality from COVID-19 against each category of pre-existing morbidities. The study findings could help healthcare providers to take appropriate measures to control fatalities from this pandemic.

Methods

This systematic review and meta-analysis was conducted by following the Preferred Reporting for Systematic Review and Meta-Analysis (PRISMA) consensus statement [22]. Studies relevant to the COVID-19 disease among people with pre-existing one or more morbidities were included.

Search strategy

Four databases: Medline, Web of Science, Scopus, and CINAHL were searched, concluded on May 01, 2020, using pre-specified search strategies for each database. The search strategy consists of keywords on COVID-19 disease (COVID-19, 2019-nCoV, Coronavirus, SARS-CoV-2), pre-existing morbidity (comorbidity, morbidity), and patients’ survival status (mortality, death, died) combined using the Boolean operators (AND, OR). Details of the search strategies are presented in the supplementary tables (Table 1-4). Additional searches were conducted using the reference list of the selected studies, relevant journal websites, and renowned pre-print servers (medRxiv, bioRxiv).
**Study selection criteria**

All peer-reviewed and pre-print (not-peer-reviewed) studies met the pre-specified inclusion, and exclusion criteria were included in this study.

**Inclusion criteria**

Studies met the following inclusion criteria were included if: (i) conducted for the patients infected with COVID-19 with or without pre-existing morbidities, (ii) presented survivor and non-survivor counts following COVID-19 disease among patients with or without preexisting morbidity or presented hazard/risk/odds ratio of deaths or survival following COVID-19 against the types of morbidities, and (iii) published in the English language. Studies without complete information but met our inclusion criteria were included in the narrative review.

**Exclusion criteria**

Studies excluded if COVID-19 was reported among pregnant women or children (aged <18 years) and written in languages other than English. We also excluded review papers, correspondence, viewpoints, editorials, commentaries, and studies where no information related to the previous morbidity was reported.

**Data extraction and quality assessment**

A data extraction form was designed, trialled, and modified to extract information from the selected studies. Two authors (MMAK and MGM) used the pre-designed form to extract information independently. The following information was extracted: study location, design, sample size, study population characteristics (e.g., age, gender), and survivor vs. non-survivor counts among COVID-19 patients with or without specific morbidity. If available, the odds/risk/hazard ratio of deaths among COVID-19 patients with comorbidities were extracted.
against the types of morbidity. Disagreements reported in data extraction were reviewed and solved by the corresponding and senior authors (MNK and MIK). The modified Newcastle-Ottawa scale, as part of the data extraction strategy, was used to assess the quality of selected studies.

**Statistical analysis**

Pre-existing one or more morbidities among COVID-19 disease patients reported in the selected studies were grouped into eight broad categories based on the type of morbidities. These were cardiovascular system diseases (hypertension, cardiovascular disease, arrhythmia, heart failure), immune and metabolic disorders (diabetes, immunosuppression, autoimmune disease, immunodeficiency, metabolic disorder), respiratory system diseases (chronic lung diseases, Chronic Obstructive Pulmonary Disease (COPD), acute respiratory distress syndrome, tuberculosis, etc.), cancer (malignancy, cancer, and tumor), cerebrovascular diseases (cerebrovascular disease, peripheral vascular disease), renal system diseases (chronic kidney disease, urinary disease), liver system diseases (chronic liver disease, cirrhosis, hyperlipidemia, Hepatitis B, etc.), and gastrointestinal system diseases (chronic digestive disorder, gastrointestinal disease). The odds ratios (ORs) of deaths with 95% confidence interval (95% CI) for the people exposed to a particular category of morbidity as compared to people unexposed to any specific morbidity was estimated from the extracted raw data or reported ORs. We first used the Haldane correction (add constant 0.5 to each cell) for the studies in which the sample included in the exposed or unexposed group was zero (such as all exposed patients died or vice versa) [23-25]. We then used either a fixed effect or random effect model to estimate ORs, selected based on heterogeneity assessment. When the test of heterogeneity ($I^2$ statistics) was moderate (50-74%) or high ($\geq$75%), the pooled estimates of ORs were computed using the random-effects model [26]. Subgroup and meta-regression analyses were conducted for the groups where moderate or higher heterogeneity was
reported. For this, pre-specified subgroups (types of morbidities, study country, study design, mean age of the total sample, mean age of death sample) were used. Publication bias was assessed by visual inspection of the funnel plot asymmetry and Egger’s regression test [27]. When evidence of publication bias was found, the Trim and Fill method was used to estimate and adjust potentially missing studies, and the effect size was recalculated accordingly [28]. Stata software version 15.1 (StataCorp. LP, College Station, TX, USA) was used for all analyses.

Results

A total of 247 articles were identified from the databases searched, and the additional 15 articles were identified by checking the reference list of the selected articles and the selected journal’s websites (Figure 1). Around 1273 articles were also initially identified from the aforementioned pre-prints servers. Of the selected articles, 1341 articles were excluded after screening titles and abstracts, leaving 114 articles for full-text review for possible inclusion in this study. Of these, 55 articles were excluded based on the inclusion and exclusion criteria for the study sample (e.g., excluded pregnant or children), and 11 articles were excluded for study types (e.g., review papers, correspondence, viewpoints, editorials, commentaries), and six articles were excluded for fully incomplete data. A total of 42 articles were finally selected for this study; 36 articles were included in the meta-analysis, and the remaining six articles were synthesized narratively.

Study characteristics

A summary of the 42 selected articles is represented in Table 1. A total of 23 of the selected 42 articles were published in peer-reviewed journals, and 18 articles were published in pre-print servers. One of the selected studies was a national report for Australia. The majority of these studies were retrospective in nature (26) along with 7 prospective studies. The selected
studies comprised 36,398 COVID-19 patients, 7,558 (42.5%) of them had preexisting one or more morbidities, 38.4% of patients had undergone critical care, and 5,310 (14.6%) of them died. Their average age was 60.5 ± 8.0 years, and 60.1% of them were male. The mean age at death was 69.9 ± 5.6 for the patients who died in COVID-19 disease. Total 36 of the selected studies presented death counts following COVID-19 disease among patients with or without specific one or more morbidities. Four included studies (Du et al. [29], Zhang et al. [30], Kim et al. [31] and Yao et al. [32]) were conducted only for dead COVID-19 patients and reported the status of pre-existing morbidities before their deaths. All studies were of moderate to high quality (Supplementary Table 6-7).

**Prevalence of preexisting morbidity among COVID-19 patients**

Distribution of the type of morbidity presented in Table 2. Approximately 36.5% of the total COVID-19 disease patients reported that they had hypertension, 22.0% had diabetes, 11.9% had cardiovascular disease, 4.1% had chronic lung disease, 2.3% had COPD, 11.0% had hyperlipidemia, and 3.0% had chronic kidney disease.

**Effects of preexisting morbidity on deaths in COVID-19 disease patients**

The pooled ORs of deaths for each category of preexisting morbidities among COVID-19 disease patients, publication bias, and Trim and Fill estimates are presented in Table 3. COVID-19 disease patients with preexisting cardiovascular system disease were 3.32 times more likely to die (OR: 3.32, 95% CI: 2.79-3.95; $I^2 = 83.8\%$) than the patients who had no cardiovascular system diseases. The odds of death among COVID-19 disease patients with immune and metabolic disorders were also found to be 239% higher (OR: 2.39, 95% CI: 2.00-2.85; $I^2 = 64.5\%$) than among COVID-19 patients without such disorders. The incidence of COVID-19 disease among people with respiratory system disease increases mortality risk around two times (OR: 2.02, 95% CI: 1.80-2.26; $I^2 = 71.2\%$) than COVID-19 disease patients.
without respiratory system diseases. Similarly, we found higher mortality risk among COVID-19 disease patients who had pre-existing any types of cancers (OR: 2.22, 95% CI: 1.63-3.03, $I^2 = 67.7\%$) and cerebrovascular system diseases (OR: 4.12, 95% CI: 3.04-5.58) than their counterparts. Moreover, the incidence of COVID-19 disease among patients with preexisting renal system disease and chronic liver disease increased mortality risk by about three times (OR: 3.02, 95% CI: 2.60-3.51) and one and half times (OR: 1.44, 95% CI: 1.21-1.71), respectively compared to the COVID-19 disease patients who did not mention such comorbidities.

We found evidence of publication bias for the three categories of preexisting morbidities: any type of cancer, cerebrovascular diseases, and liver system diseases (Figure 1a to 8a). We then used Trim and Fill methods to impute the number of missing studies, which hypothetically imputed two studies for cardiovascular system diseases, three studies for renal system diseases, and three studies for liver system diseases. The pooled analysis, including these missing studies, showed almost similar results to the summary estimates presented earlier without these missing studies.

Evidence of higher deaths among COVID-19 disease patients with preexisting one or more morbidities were also demonstrated in the narrative review (Supplementary Table 5). In two of the three articles reviewed in this study, researchers reported that each of the patients who died following COVID-19 disease had preexisting morbidities, mostly had any types of cardiovascular system diseases and immune and metabolic disorders [29, 30]. Researchers in one study found around 38% of the COVID-19 disease patients with hypertension died [33] and one study reported higher odds for deaths in kidney injury [34].

**Stratified analysis**
We found evidence of high heterogeneity ($I^2 > 75\%$) for cardiovascular system diseases (83.8%). To examine the sources of heterogeneity, we conducted stratified analysis across types of comorbidities, study design (cross-sectional vs. retrospective cohort vs. prospective cohort), sample size (divided based on mean sample size of the included studies and classified as $\leq 1134$, $>1134$), age of the total sample (divided based on mean age and classified as $\leq 60$ years and $>60$ years), and age at death (divided based on mean age and classified as $\leq 69$ vs. $>69$) (Table 4). We found odds of death varied across specific types of preexisting morbidities included to generate cardiovascular system diseases category. For instance, in the cardiovascular system diseases category, the odds of mortality were found higher for COVID-19 disease patients with preexisting heart failure (OR: 3.98, 95% CI: 2.96-5.35), cardiovascular disease (OR: 3.35, 95% CI: 2.53-4.42), hypertension (OR: 3.28, 95% CI: 2.53-4.24), than for COVID-19 disease patients with pre-existing arrhythmia (OR: 3.00, 95% CI: 1.96-4.57).

**Discussion**

This study aimed to summarize preexisting morbidities among COVID-19 disease patients, which increases their incidence of deaths and their corresponding likelihoods. A total of 42 studies were included that comprised 36,398 samples, and 7,558 (42.5%) of them had preexisting morbidities. The most frequently reported morbidities were hypertension (36.5%), diabetes (22.0%), and cardiovascular disease (11.9%). The likelihood of death was higher among COVID-19 patients who had comorbidities like cardiovascular and cerebrovascular diseases, respiratory diseases, renal diseases, immune and metabolic disorders, hepatic diseases, and cancer. This evidence will guide physicians to take precautionary measures, which could reduce the number of fatalities following secondary infection with COVID-19.
Among the total positive COVID-19 disease cases included in this systematic review study, around 43% had preexisting one or more morbidities, mostly cardiovascular system diseases and immune and metabolic disorders. Importantly, patients with these diseases are more likely to have a higher neutrophil-lymphocyte ratio [35, 36], higher D-dimer level [37], and higher C-reactive protein [38]. These increased parameters lead to multiple organ failure [39, 40], severe pneumonia, hypoxia, respiratory failure, myocardial damage, and circulatory failure [18]. These non-communicable diseases independently elevate the risk of death and increase further if patients are infected with COVID-19 disease [21, 40-42]. COVID-19 disease also damages patients’ myocardial cells by destabilizing coronary plaque in pre-existing cardiovascular conditions and previous history of myocardial infarct [43, 44]. Similar higher risks of mortality were reported among SARS-CoV and MERS-CoV patients with cardiovascular diseases [41, 43, 45, 46]. These two diseases are considered as ancestors of current COVID-19 disease, which were reported in 2003 and 2012, respectively [41, 43, 45, 46]. Evidence also validates that the occurrence of influenza, along with cardiovascular diseases and diabetes, could increase the risk of death [47, 48].

Pooled likelihoods in this study provide evidence of higher deaths among COVID-19 disease patients who had preexisting chronic respiratory diseases or any type of cancers. Chronic respiratory diseases like COPD and asthma are well-established risk factors for pneumonia [49], which also increase the susceptibility to COVID-19 disease infection [50]. Once patients are infected with COVID-19 disease, these further affect the patient’s respiratory system and progress to severe hypoxemia [51]; therefore, the cumulative effects lead to events of death [18, 50]. Cancer patients are more likely to report a systemic immunosuppressive state and progress to severe clinical events, such as require intensive care (ICU) or death [52, 53]. Secondary infection with COVID-19 disease, which has its own
adverse consequences on the human body, could, therefore, boost serve clinical events as well as deaths among patients with these pre-existing morbidities.

This study also suggests that patients with cerebrovascular, liver and renal diseases are more vulnerable to mortality following the second incidence of COVID-19 disease than the patient does not have such diseases. The results are comparable to deaths among previously reported SARS patients [54]. Comorbidities such as, cardio-cerebrovascular diseases, liver damage, or renal diseases accelerate an abrupt loss of kidney function [55, 56], tissue damage that causes hypoxia, shock, and rhabdomyolysis [34, 57], and increased occurrence of thrombocytopenia (reduced platelet counts) [21, 58]. These could independently elevate the risk of death and add to the adverse effects on the human body being infected with COVID-19 disease. Together, these increase occurrences of deaths. Moreover, elevated alanine aminotransferase (ALT) levels and reduced albumin levels are found to be associated with higher mortality in COVID-19 disease [21, 58], which can be caused by chronic liver and kidney diseases [58-62]. Thus, it indicates an urgency of early precautions to prevent deaths among COVID-19 disease patients with pre-existing morbidities.

**Strengths and limitations**

This study has several strengths and limitations that should be reported. To our knowledge, this is the first of its kind that summarizes all morbidities among COVID-19 disease patients that lead to death. Moreover, morbidities reported among COVID-19 disease patients were classified into board groups based on their characteristics, and the likelihood of death was estimated separately for each group. This evidence informs healthcare providers about the risk of death among COVID-19 disease patients with different groups of pre-existing morbidities. Thus, they will be able to take precautionary measures early targeting to prevent deaths. However, this study reported the odds of death for COVID-19 disease patients with
one preexisting morbidity only. Many COVID-19 disease patients may have multi-morbidities (COVID-19 disease with pre-existing two or more morbidities) and a higher risk of death. However, the studies included in this review considered each morbidity separately; for instance, if COVID-19 patients had both hypertension and diabetes, they were included in both groups. None of the included studies considered COVID-19 disease with two or more morbidities together; therefore, we failed to provide the likelihood of deaths for COVID-19 disease patients with two or more preexisting morbidities. Moreover, the likelihoods presented in this study were mostly unadjusted (31 of the 36 articles included) calculated from the extracted raw data. This may overestimate or underestimate the actual likelihood of deaths in COVID-19 disease patients because age and other socio-demographic characteristics are potential confounders of their deaths, which should be adjusted for getting unbiased estimates. Despite these limitations, this study is unique and beneficial for healthcare providers to handle COVID-19 disease patients with preexisting morbidities.

**Conclusion**

About 46% of the sample included in this systematic review had one or more preexisting morbidities and get COVID-19 as a secondary infection. The most common preexisting morbidities were hypertension, diabetes, and cardiovascular disease. The likelihood of death was higher among COVID-19 disease patients who had pre-existing cardiovascular and cerebrovascular system diseases, respiratory system diseases, renal diseases, immune and metabolic disorders, liver diseases, and any types of cancer. These findings will help healthcare providers to sort COVID-19 patients by comorbidities, take precautionary measures during hospital admission, assess susceptibility to death, and prioritize their treatment. These could potentially reduce the number of fatalities from secondary infection with COVID-19 disease.
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Authors Contribution

Conceptualization: MMAK, NMK, MIK

Research design: MMAK and MNK

Data curation: MMAK and MGM

Analysis: MNK and MMAK

Draft preparation: MMAK, MNK, and MGM

Supervision: MNK

Critical review: JR, MIK and MSI,

Conflicts of interest

The authors have no competing interests to declare.

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Availability of data and materials

Data related to this study are available upon request to the corresponding author.
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Table 1. Background characteristics of the selected studies and hospitalized sample (n = 36,398).

| Sl | Authors | Article type | Study country | Publication date | Study type | Total Sample (n) | Total death Sample, n (%) | Mean age (±SD, or confidence interval) | Mean age at death (±SD, or confidence interval) | Male sample (%) | Female sample (%) | Prevalence of any forms of pre-existing morbidities among COVID-19 disease a, n (%) | ICU admission following COVID-19 disease b (%) |
|----|---------|-------------|---------------|------------------|------------|-----------------|--------------------------|-----------------------------------------|---------------------------------------------|----------------|----------------|--------------------------------------------------------------------------------|------------------------------------------------|
| 1. | Guan et al. [8] | Peer reviewed | China | 26 Mar 2020 | Retrospective | 1590 | 50 (3.1) | 48.9 ± 16.3 | - | 57.3 | 42.7 | 399 (25.1) | 6.2 |
| 2. | Cao et al. [63] | Peer reviewed | China | 2 Apr 2020 | Prospective | 102 | 17 (16.7) | 54 (37-67) | 72 (63-81) | 52.0 | 48.0 | 47 (46.1) | 17.6 |
| 3. | Chen et al. [64] | Peer reviewed | China | 31 Mar 2020 | Retrospective | 274 | 113 (41.2) | 62 (44-70) | 68 (62-77) | 62.0 | 38.0 | 133 (48.5) | - |
| 4. | Deng et al. [65] | Peer reviewed | China | 20 Mar 2020 | Retrospective | 225 | 109 (48.4) | 54 | 69 (62-74) | 55.1 | 44.9 | 127 (56.4) | - |
| 5. | Yang et al. [10] | Peer reviewed | China | 24 Feb 2020 | Retrospective | 52 | 32 (61.5) | 59.7 ± 13.3 | 64.6 ± 11.2 | 67.0 | 33.0 | 21 (40.4) | 38.5 |
| 6. | Wu et al. [66] | Peer reviewed | China | 13 Mar 2020 | Retrospective | 201 | 44 (21.9) | 51 (43-60) | 63.7 | 36.3 | - | 26.4 |
| 7. | Chen et al. a [20] | Peer reviewed | China | 11 Apr 2020 | Retrospective | 55 | 19 (34.5) | 74 | 77 | 61.8 | 38.2 | 37 (67.3) | - |
| 8. | Zhou et al. [21] | Peer reviewed | China | 9 Mar 2020 | Retrospective | 191 | 54 (28.3) | 56 (46-67) | 69 (63-76) | 62.0 | 38.0 | 91 (47.6) | 26.0 |
| 9. | Yuan et al. [67] | Peer reviewed | China | 19 Mar 2020 | Retrospective | 27 | 10 (37.0) | 60 (47-69) | 68 (63-73) | 45 | 55 | 13 (48.1) | - |
| 10. | Chen et al. [68] | Preprint | China | 30 Mar 2020 | Retrospective | 123 | 5 (4.1) | 51 (35-66) | - | 40.7 | 59.3 | 15 (12.2) | - |
| 11. | Caramelo et al. a [69] | Preprint | China | 25 Feb 2020 | Retrospective | - | - | - | - | 51.4 | 48.6 | - | - |
| 12. | Ren et al. a [70] | Peer reviewed | China | 11 Feb 2020 | Retrospective | 5 | 1 (20.0) | 53.6 | 61 | 60.0 | 40.0 | 2 (40.0) | 100 |
| 13. | Australian Govt. a [71] | Report | Australia | 5 Apr 2020 | Retrospective | 817 | 69 (5.3) | 59.5 | 79 (74-84) | - | - | - | 13 |
| 14. | Shi et al. [41] | Peer reviewed | China | 25 Mar 2020 | Retrospective | 416 | 57 (13.7) | 64 (21-95) | - | 49.3 | 50.7 | - | - |
| 15. | Zhang et al. [11] | Peer reviewed | China | 15 Apr 2020 | Retrospective | 663 | 25 (3.8) | 56 (44-69) | 67.1 (61-78) | 48.4 | 51.6 | - | 14.2 |
| 16. | Du et al. [72] | Peer reviewed | China | 8 Apr 2020 | Prospective | 179 | 21 (11.7) | 57.6 ± 13.7 | 70.2 ± 7.7 | 54.2 | 45.8 | - | - |
| 17. | Wang et al. a [73] | Peer reviewed | China | 15 Mar 2020 | Retrospective | 339 | 65 (19.2) | 71 ± 8 | 76 (70-83) | 49.0 | 51.0 | - | 23.6 |
| 18. | Fu et al. [74] | Preprint | China | 16 Mar 2020 | Retrospective | 200 | 34 (17.0) | - | 49.5 | 50.5 | 161 (80.5) | 25.5 |
| 19. | Paranjpe et al. [75] | Preprint | USA | 26 Apr 2020 | Prospective | 889 | 310 (34.9) | 65 (54-76) | 75 (64-85) | 70.5 | 29.5 | - | 43.3 |
| 20. | Cummings et al. a [76] | Preprint | USA | 20 Apr 2020 | Prospective | 257 | 86 (33.5) | 62 (51-72) | - | 66.1 | 33.9 | - | 100.0 |
| 21. | Guo et al. a [77] | Preprint | China | 14 Apr 2020 | Retrospective | 118 | 51 (43.2) | 71.6 | 73.1 ± 7.3 | 44.9 | 55.1 | - | - |
| 22. | Zhu et al. [78] | Preprint | China | 8 Apr 2020 | Retrospective | 325 | 17 (5.2) | 45 (34-61) | 63 (57-76) | 42.2 | 57.8 | 69 (21.2) | 18.5 |
| 23. | Yin et al. a [79] | Preprint | China | 7 Apr 2020 | Retrospective | 112 | 52 (46.4) | 66 (56-76) | 70 (62-78) | 68.7 | 31.3 | 71 (63.4) | 100.0 |
| 24. | Sun et al. a [80] | Preprint | China | 6 Apr 2020 | Retrospective | 69 | 57 (82.6) | 66 (59-73) | 66 (62-77.5) | 67.0 | 33.0 | 40 (58) | 100.0 |
| 25. | Luo et al. [81] | Preprint | China | 24 Mar 2020 | Retrospective | 403 | 100 (24.8) | 56 (39-68) | 71 (65-80) | 47.9 | 52.1 | 175 (43.4) | 50.9 |
| 26. | Zhang et al. [82] | Preprint | China | 23 Mar 2020 | Retrospective | 315 | 47 (14.9) | 57 (44-66) | 66 (61-72) | 55.6 | 44.4 | 103 (32.7) | 56.5 |
| Study (Reference) | Study Type | Country | Date | Study Design | Patients (Age) | Mortality (%) | Age (Mean ± SD) | Comorbidities |
|------------------|------------|---------|------|--------------|----------------|---------------|----------------|---------------|
| Solis et al. [83] | Preprint   | Mexico  | 25 Apr 2020 | Cross-sectional | 7497 | 650 | 46 | - |
| Yao et al. [84]  | Peer reviewed | China  | 24 Apr 2020 | Retrospective | 108 | 12 (11.1) | 52 (37-58) | 65 (51-73.5) |
| Zangrillo et al. [85] | Peer reviewed | Italy | 23 Apr 2020 | Prospective | 73 | 17 (23.3) | 61 (54-69) | - |
| Yan et al. [86]  | Peer reviewed | China  | 06 Apr 2020 | Retrospective | 193 | 108 (56.0) | 64 (49-73) | 70 (62-78) |
| Tedeschi et al. [87] | Peer reviewed | Italy | 27 Apr 2020 | Prospective | 609 | 174 (28.6) | 68 (55-80) | - |
| Nikpouraghdam et al. [88] | Peer reviewed | Iran | 21 Apr 2020 | Retrospective | 2878 | 55.5 ± 7.9 | 66.0 ± 7.6 | 32.0 ± 11.7 |
| Benelli et al. [89] | Preprint | Italy | 30 Apr 2020 | Retrospective | 72 | 17 (17.5) | 66.8 ± 16.4 | 81.1 ± 16.4 |
| Levy et al. [90]  | Preprint | USA    | 30 Apr 2020 | Retrospective | 4933 | 1185 (24.0) | - | - |
| Sneep et al. [91] | Preprint | UK     | 29 Apr 2020 | Retrospective | 200 | 28 (14.0) | 63.4 ± 17.8 | 76 ± 14 |
| Mehra et al. [9]  | Peer reviewed | Asia, Europe, and North America | 01 May 2020 | Prospective | 8910 | 515 (5.8) | 48.7 ± 16.6 | 55.8 ± 15.1 |

**Studies included in the narrative review**

| Study (Reference) | Study Type | Country | Date | Study Design | Patients (Age) | Mortality (%) | Age (Mean ± SD) | Comorbidities |
|------------------|------------|---------|------|--------------|----------------|---------------|----------------|---------------|
| Grasselli et al. [33] | Peer reviewed | Italy | 6 Apr 2020 | Retrospective | 1591 | 405 (25.6) | 63 (56-70) | - |
| Du et al. [29]    | Peer reviewed | China | 7 Apr 2020 | Prospective | 109 | 109 (100) | 70.7 ± 10.9 | 67.9 |
| Zhang et al. [30] | Preprint | China | 27 Feb 2020 | Retrospective | 82 | 82 (100) | 72 (65-80) | 65.9 |
| Kim et al. [31]   | Preprint | Korea | 20 Apr 2020 | Retrospective | 101 | 101 (100) | 76 ± 10.3 | 52.5 |
| Yao et al. [32]   | Preprint | China | 13 Mar 2020 | Retrospective | 55 | 55 (100) | 70.7 ± 13.5 | 67.0 |
| Cheng et al. [34] | Peer reviewed | China | 20 Mar 2020 | Prospective | 701 | 113 (16.1) | 63 (50-71) | - |

**Total or average**

|               |           |         |       |               |                |               |                |               |
|---------------|-----------|---------|-------|---------------|----------------|---------------|----------------|---------------|
| Total patients | 36398     | 5310 (14.6) | 60.5 ± 8.0 | 69.9 ± 5.6 | 60.1 | 39.9 | 7558 (42.5) | 38.4 |

**Note:** Sample with missing value were excluded from percentage calculation; Complete data available for 17794 patients, and missing sample had incomplete information or directly indicated the likelihood of mortality or did not report people count with any forms of existing comorbidities; Included only the patients in ICU or in critical condition with or without pre-existing morbidities, and data was available for 10154 patients; Included only aged or elderly people as sample; Not included in total calculation as the study was a secondary data analysis; Included only the patients in ICU or in critical condition; this study included only hospitalized patients; Sample included only death patients; Study of Tedeschi et al [87] had all patients more than one comorbidities.
Table 2. Percentage distribution of comorbidities among patients reported in admission COVID-19 infection.

| Pre-existing morbidities | Distribution of comorbidities for total patients | (%) |
|--------------------------|-----------------------------------------------|-----|
| **Cardiovascular system disease** | 12760 | 51.2 |
| Hypertension             | 9085  | 36.5 |
| Cardiovascular Disease \(a\) | 2957  | 11.9 |
| Arrhythmia               | 393   | 1.6  |
| Heart failure            | 325   | 1.3  |
| **Immune and metabolic disorders** | 5966 | 23.9 |
| Diabetes                 | 5478  | 22.0 |
| Immunosuppression        | 406   | 1.6  |
| Autoimmune disease       | 8     | 0.03 |
| Immunodeficiency         | 3     | 0.01 |
| Metabolic disorder       | 4     | 0.02 |
| **Respiratory system diseases** | 1975 | 7.9 |
| Chronic lung disease     | 1010  | 4.1  |
| Chronic obstructive pulmonary disease (COPD) | 577 | 2.3 |
| Asthma                   | 355   | 1.4  |
| Acute respiratory distress syndrome (ARDS) | 11 | 0.04 |
| Chronic bronchitis       | 10    | 0.04 |
| Tuberculosis             | 9     | 0.04 |
| Pulmonary emphysema      | 3     | 0.01 |
| **Any types of cancer** | 224   | 0.9  |
| Malignancy               | 33    | 0.1  |
| Cancer                   | 92    | 0.4  |
| Tumor                    | 16    | 0.1  |
| Carcinoma                | 4     | 0.02 |
| **Cerebrovascular system diseases** | 198 | 0.8 |
| Cerebrovascular disease \(b\) | 189 | 0.8 |
| Peripheral vascular disease | 9 | 0.04 |
| **Renal system diseases** | 779 | 3.1 |
| Chronic kidney disease   | 758   | 3.0  |
| Urinary disease          | 21    | 0.1  |
| **Liver system diseases** | 2844 | 11.4 |
| Chronic liver disease    | 45    | 0.2  |
| Cirrhosis                | 25    | 0.1  |
| Fatty liver disease      | 15    | 0.1  |
| Hepatitis B              | 21    | 0.1  |
| Hyperlipidemia           | 2732  | 11.0 |
| Inflammatory disease     | 6     | 0.02 |
| **Gastrointestinal system diseases** | 61 | 0.2 |
| Chronic digestive disorder | 21 | 0.1 |
| Gastrointestinal disease | 40    | 0.2  |
| **Others \(c\)**         | 109   | 0.4  |
| **Grand total**          | 24916 | 100.0 |

Note: Patients with more than one comorbidity were missing. Calculated in column percentage format; One study (Caramelo et al.) was excluded from prevalence calculation as the study had not reported frequency of comorbidities; Malnutrition and dementia was skipped from the analysis as we found only one patient (Yang et al.); \(a\) Included all types of cardiovascular diseases like coronary heart diseases or artery disease; \(b\) Included Cerebral infarction; \(c\) anemia, bowel disease, tissue disease, etc.
Table 3. Summary effects of type of morbidity categories on death among patients infected with COVID-19 disease, publication bias, and Trim and Fill estimates

| Characteristics                       | Number of studies | Number of times morbidity reported | Summary estimates | Egger bias test p-value | Trim and Fill estimates | Egger bias test p-value |
|---------------------------------------|-------------------|-----------------------------------|-------------------|-------------------------|-------------------------|-------------------------|
|                                       | OR (95% CI)       | Heterogeneity Index (I²)          | Missing studies no. | OR (95% CI)             |                         |                         |
| Cardiovascular system diseases        | 33                | 64                                | 3.32 (2.79-3.95)   | 83.8%                   | 0.001                   | 13                      | 2.82 (2.38-3.34)       |
| Immune and metabolic disorders        | 31                | 38                                | 2.39 (2.00-2.85)   | 64.5%                   | 0.019                   | 6                       | 2.14 (1.78-2.57)       |
| Respiratory system diseases           | 28                | 33                                | 2.02 (1.80-2.26)   | 71.2%                   | 0.031                   | 3                       | 2.36 (1.79-3.11)       |
| Any types of cancer                   | 20                | 20                                | 2.22 (1.63-3.03)   | 67.7%                   | 0.891                   | 0                       | 2.22 (1.63-3.03)       |
| Cerebrovascular system diseases       | 15                | 16                                | 4.12 (3.04-5.58)   | 25.7%                   | 0.048                   | 2                       | 3.94 (2.92-5.31)       |
| Renal system diseases                 | 21                | 21                                | 3.02 (2.60-3.51)   | 56.0%                   | 0.024                   | 4                       | 2.86 (2.47-3.32)       |
| Liver system diseases                 | 14                | 17                                | 1.44 (1.21-1.71)   | 0.0%                    | 0.001                   | 6                       | 1.38 (1.16-1.63)       |
| Gastrointestinal system diseases      | 5                 | 5                                 | 1.33 (0.56-3.19)   | 0.0%                    | 0.170                   | 0                       | 1.33 (0.56-3.19)       |

Note: Person survived from COVID-19 infection is considered as reference category; CI, confidence interval; OR, odds ratio.

*a The trim-and-fill method simulates studies that are likely to be missing from the literature due to publication or other forms of bias. The trim-and-fill OR estimates what the pooled OR would be if these missing studies were included in the analysis; b Summary estimates were based on fixed-effects methods; c Summary estimates were based on random-effects methods.
**Table 4.** Stratified analysis of the likelihood of death among patients with cardiovascular system diseases infected with COVID-19 diseases

| Characteristics        | Pooled OR (95% CI) | P     | Heterogeneity | Meta-regression |
|------------------------|--------------------|-------|---------------|-----------------|
|                        |                    |       |               |                 |
| **Type of diseases**   |                    |       |               |                 |
| Cardiovascular diseases| 3.35 (2.53-4.42)   | <0.01 |               | 0.95            |
| Hypertension           | 3.28 (2.53-4.24)   | <0.01 |               |                 |
| Heart failure          | 3.98 (2.96-5.34)   |       | 0.348         |                 |
| Arrhythmia             | 3.00 (1.96-4.57)   |       | 0.192         |                 |
| **Study country**      |                    |       |               |                 |
| Australia              | 3.68 (2.06-6.57)** | NA    | <0.01         |                 |
| Italy                  | 3.95 (2.82-5.54)   |       | 0.239         |                 |
| China                  | 4.36 (3.40-5.58)   | <0.01 |               |                 |
| United State of America| 2.74 (2.00-3.75)   | <0.01 |               |                 |
| Asia, Europe, and North America | 1.98 (1.16-3.38) | <0.01 |               |                 |
| Iran                   | 1.75 (0.95-3.22)   |       | 0.685         |                 |
| UK                     | 2.73 (1.17-6.35)** | NA    | <0.05         |                 |
| Mexico                 | 1.12 (0.71-1.75)   |       | <0.05         |                 |
| **Study design**       |                    |       |               |                 |
| Cross-sectional        | 3.79 (2.86-5.03)   | <0.01 |               | <0.05           |
| Prospective cohort     | 3.15 (2.25-4.41)   | <0.01 |               |                 |
| Retrospective cohort   | 1.82 (0.71-1.75)   | <0.05 |               |                 |
| **Adjustment factor**  |                    |       |               |                 |
| Unadjusted             | 3.94 (3.24-4.80)   | <0.01 |               | <0.05           |
| Adjusted               | 1.81 (1.30-2.53)   | <0.01 |               |                 |
| **Sample size**        |                    |       |               |                 |
| >1134                  | 2.19 (1.59-3.02)   | <0.01 |               | <0.01           |
| ≤1134                  | 3.78 (3.14-4.56)   | <0.01 |               |                 |
| **Mean age of total sample** |            |       |               |                 |
| ≤60                    | 3.70 (2.70-5.07)   | <0.01 |               | 0.593           |
| >60                    | 3.14 (2.60-3.80)   | <0.01 |               |                 |
| **Mean age of death sample** |          |       |               |                 |
| ≤69                    | 4.39 (3.05-6.32)   | <0.01 |               | 0.100           |
| >69                    | 3.00 (2.46-3.66)   | <0.01 |               |                 |
Records identified through database (Medline, Web of Science, Scopus, and CINAHL) searching after duplicates were removed (n = 247)

Additional records identified through checking references in selected articles and selected journals or from other sources (n = 15)

Preprints were selected through searching the preprint database of medRxiv, bioRxiv, and SSRN (n = 1273)

Records identified for title and abstract screening (n = 1535)

Records excluded based on title and abstract. (n = 1341)

Records assessed for eligibility further screening (n = 114)

Records excluded due to those had different outcomes (n = 55)

Records assessed for eligibility to full-text preview (n = 59)

Full-text articles assessed for eligibility, (n = 42)
- 23 peer-reviewed articles, 18 preprints, and 1 national report
- 26 studies were retrospective cohort
- 7 studies were prospective cohort
- 1 study were cross-sectional study

Full-text articles excluded, with reasons:
- Wrong study design (n=11)
- Incomplete data (n=6)

Studies included in quantitative synthesis (meta-analysis) (n = 36)

Studies included in qualitative synthesis (n = 6)

**Figure 1.** Schematic representation of studies included in the systematic review and meta-analysis using PRISMA checklist and flow diagram