The association of cardiovascular disease and other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis

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Abstract

Importance. Exploring the association of coronavirus-2019 disease (COVID-19) mortality with chronic pre-existing conditions may promote the importance of targeting these populations during this pandemic in order to optimize survival.

Objective. To explore the association of pre-existing conditions with COVID-19 mortality.

Data Sources. MEDLINE, the OVID databases, SCOPUS, and Cochrane Register of Controlled Trials were searched for the period October 1, 2019 to May 1, 2020. Snowballing was used to identify additional studies.

Study Selection. Observational studies (n=19) reporting on 61,455 patients with relative risks (RR) or hazard ratios or odds ratios that reported the risk of mortality in patients with COVID-19 and comorbid conditions were included for the current study.

Data Extraction and Synthesis. Two independent reviewers extracted data and assessed the risk of bias. All analyses were performed using random-effects models and heterogeneity was quantified.

Main Outcomes and Measures The outcome of interest was the risk of COVID-19 mortality in patients with and without pre-existing conditions, reported as RR. Comorbidities explored were cardiovascular diseases (coronary artery disease, hypertension, cardiac arrhythmias, and congestive heart failure), chronic obstructive pulmonary disease, type 2 diabetes, cancer, chronic kidney disease, chronic liver disease, and stroke.

Results. Ten chronic conditions from 19 studies were included in the meta-analysis (n=61,455 patients with COVID-19; mean age, 61 years; 57% male). Any cardiovascular disease, coronary heart disease, hypertension, congestive heart failure, and cancer significantly increased the risk of mortality from COVID-19. Cardiovascular disease was associated with a 135% higher risk of COVID-19 mortality (RR=2.35, 95% CI 1.44-3.84, n=9). The risk of mortality from COVID-19 in patients with coronary heart disease was 2.4 times as high as those without coronary heart disease (RR=2.40, 95% CI 1.71-3.37, n=5) and twice as high in patients with hypertension as high as that compared to those without hypertension (RR=1.89, 95% CI=1.58-2.27, n=9). Patients with cancer also were at twice the risk of mortality from COVID-19 compared to those without cancer (RR=1.93, 95% CI 1.15-3.24, n=4), and those with congestive heart failure were at 2.5 times the risk of mortality compared to those without congestive heart failure (RR=2.66, 95% CI 1.58-4.48, n=3).

Conclusions and Relevance COVID-19 patients with all any cardiovascular disease, coronary heart disease, hypertension, congestive heart failure, and cancer have an increased risk of mortality. Tailored infection prevention and treatment strategies targeting this high-risk population are warranted to optimize survival.

Key Points

Question: Are COVID-19 patients with pre-existing chronic conditions at a significantly increased risk for death?

Findings: This meta-analysis found that COVID-19 patients with any cardiovascular disease, coronary heart disease, hypertension, congestive heart failure, and cancer have a significantly increased risk of mortality.

Meaning: An effective intervention is urgently needed in order to decrease this risk and to further optimize survival in these populations. Further research is necessary to conclusively explore this association.
Introduction

The number of total cases of the coronavirus-2019 disease (COVID-19) continues to rise quickly, threatening thousands to millions of individuals with preexisting chronic conditions who are disproportionately affected. To date, May 5, 2020, the John Hopkins coronavirus resource center reported that worldwide more than 180 countries have been affected with COVID-19 with more than three million confirmed cases and more than 250,000 deaths (https://coronavirus.jhu.edu/). As research related to potential risk factors for COVID-19 mortality continues, it is becoming clear that individuals with underlying conditions, such as cardiovascular disease (coronary artery disease, heart failure, hypertension, and cardiac arrhythmias), cancer, chronic obstructive pulmonary disease (COPD), type 2 diabetes, chronic kidney disease (CKD), and chronic liver disease (CLD), all may be at an increased risk of death. As the number of published studies increase, there is a widening gap due to inconsistent findings with respect to the influence that types of pre-existing comorbidities have on COVID-19 mortality. Some studies report an association between preexisting conditions and COVID-19 mortality, whereas others report no association. With this being said, it is clear that regions experiencing the highest mortality rates, such as the United States, Europe, and China, also have the greatest burden of these preexisting chronic conditions.

The novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, interacts with angiotensin-converting enzyme 2 (ACE2), a cellular receptor expressed in the heart, kidney, pulmonary alveolar type II cells. It has been postulated, though not confirmed, that preexisting use of angiotensin II type 1 receptor blockers (ARBs) may upregulate membrane-bound ACE2 hence increasing susceptibility to virus entry. Therefore, it is plausible that individuals with preexisting chronic conditions such as high blood pressure and
heart failure taking ARBs may be more susceptible to severity of SARS-CoV-2 including mortality.

To date, limited reviews only have studied cardiovascular disease and COVID-19 mortality alone, or only in China involving a few patients. We took a comprehensive approach and explored the association of major preexisting chronic conditions, including cardiovascular diseases such as coronary artery disease, heart failure, stroke, hypertension, and cardiac arrhythmia, type 2 diabetes, COPD, Asthma, cancer, HIV, chronic kidney, liver disease, and stroke and the risk of mortality from COVID-19. Although the majority of studies occurred in China, we identified additional studies involving patients from Europe and North America. We hypothesize that the risk of mortality in COVID-19 patients is higher in patients with preexisting chronic conditions. We believe that this set of meta-analyses will emphasize the increased risk within this population, in hopes of decreasing the burden that these individuals are actively experiencing.

**Methods**

We performed a systematic literature search of PubMed (MEDLINE), OVID (MEDLINE, HEALTHSTAR), SCOPUS, EMBASE, and Cochrane Library, using search criteria provided in the supplemental material ([Supplemental Document 1](https://doi.org/10.1101/2020.05.10.20097253)). We followed the standards of the Meta-analysis of Observational Studies in Epidemiology (MOOSE, Supplemental Table 1). This initial search was supplemented by scanning of the references lists of relevant publications, and identifying their citations through the Web of Sciences (snowballing). We identified all studies published between October 1, 2019 and May 1st, 2020 reporting the risk of mortality in patients with COVID-19. Our search criteria included the following keywords and MesH terms: (“COVID-19” OR “Coronavirus” or “Sars-cov-2”) AND (“Mortality”) AND (“cardiovascular
“disease” OR “chronic obstructive pulmonary disease” OR “asthma” OR “Coronary heart disease” OR “hypertension” OR “T2D” or “DM” or “diabetes” or “cancer” or “chronic kidney disease” or “chronic liver disease” or “comorbidities” or “chronic disease”). Two reviewers (ESH and AES) independently screened titles and abstracts of the studies for inclusion eligibility.

**Inclusion criteria**

Studies were included in the analysis if they met the following inclusion criteria: COVID-19 was diagnosed on the basis of the World Health Organization guidance; study examined the association of any of the preexisting comorbidities and COVID-19; the risk point estimates reported as odds ratios (ORs), relative risks (RRs), or hazard rations (HRs) or the data was presented such that the OR, (RR), or HR could be calculated; the 95% CI was reported, or the data were presented such that the 95% CI could be calculated. We excluded studies not conducted on humans, or not having reported the numbers or risk of mortality with any comorbidities. Studies not published in English were translated when possible. Review papers, meta-analyses, literature reviews, commentaries, and meeting abstracts were excluded as well. All excluded studies were documented with reasons for their exclusion.

**Quality Assessment and Data Extraction**

Since all of our studies were nonrandomized observational studies, we used the Newcastle-Ottawa Scale (NOS) for quality assessment (Supplemental Document 2 and 3). Studies were first screened based on titles and abstracts by AES and ESH. If they met the inclusion criteria, then full-text was obtained and they were screened. In the event of disagreement, a third researcher (PS) was recruited in order to reach a consensus. Information extracted from included studies included title, year of publication, country, number of participants with each comorbidity...
who died and did not die, the RR/OR/HR of mortality of COVID-19 with each underlying condition, the mean or median age, proportion that was male, and other findings of interest.

Data analysis

We adopted a narrative approach to describe the number of studies, study settings, diagnoses criteria for COVID-19, and the proportion of gender and race from each study. Our primary outcome was the risk of mortality in COVID-19 associated with preexisting chronic diseases. According to the previous study, if the outcome is rare in all populations and subgroups, the distinctions among different measures of RRs (e.g., odds ratios, rate ratios, and risk ratios) can be ignored, thus we combined RRs and HRs with ORs in the present meta-analysis and reported the pooled effect size as RRs as common risk estimates for all studies. We used the reported ORs, RRs, or HRs as the measures of the association between preexisting chronic conditions and the risk of mortality in COVID-19. For studies without measures of associations, we used generalized linear mixed model to calculate the odds ratios using number of events and the sample size of each study group. We combined RRs and HRs with ORs in the present meta-analysis and reported the pooled effect size as RRs as common risk estimates for all studies. We first log-transform all the reported effect size data to normalize the distributions. We calculated standard errors (SEs) via the following equations. Lower = log (lower 95% CI) and upper = log (upper 95% CI), and SE = (upper - lower)/3.92. To assess the associations between preexisting conditions and the risk of mortality, we pooled the RR estimates for the presence versus absence of preexisting conditions from each study, weighted by the inverse of their variances (inter-study plus intra-study variances). We applied the metagen function from the R package meta to calculate the pooled effect estimates using random-effects models. We invoked random-effects models to pool study results for the association between preexisting
chronic conditions and the risk of mortality. Because of the few studies we identified, we did not conduct any meta-regressions or subgroup analyses. We applied the DerSimonian and Laird (DL) random-effects method to estimate the pooled inter-study variance (heterogeneity). We graphically displayed individual and pooled estimates with forest plots. We assessed inter-study heterogeneity using $I^2$ statistics, expressed as % (low (25%), moderate (50%), and high (75%)) and Cochrane’s $Q$ statistic (significance level < 0.05). We assessed potential ascertainment bias (as might be caused by publication bias) with funnel plots, by plotting the study effect size against standard errors of the effect size, and Egger’s test. We performed all statistical analyses with R software, version 3.4.3 (R, College Station, TX).

**Results**

As shown in Figure 1, we identified a total of 261 studies from Scopus, OVID, PubMed, and Joana Briggs International EBF database. We excluded a total of 57 studies because they were duplicate, leaving 204 studies to explore for inclusion. Based on the title and abstracts, we excluded another 98 studies based on titles and abstracts and another 87 studies based on full text, which left us with 19 studies for the quantitative analysis. This yielded a total of 61,455 patients for the quantitative analysis, with 17 studies performed in China, in Italy, and 1 in 11 countries from North America, Europe and Asia. (Table 1).

**The risk of mortality from COVID-19 in patients with any cardiovascular disease**

The risk ratio of mortality from COVID-19 and cardiovascular disease ranged from 0.72 to 5.99 (Figure 2A). Cardiovascular disease made patients significantly more likely to die from Covid-
19. Those with cardiovascular disease had twice the risk of mortality from COVID-19 as compared to those without cardiovascular disease (risk ratio: RR: 2.35 95%CI 1.44-3.84).

**The risk of mortality from COVID-19 in patients with chronic obstructive pulmonary disease (COPD)**

Three of seven studies found that patients with COPD were at a significantly higher risk of mortality from COVID-19 compared to patients without COPD (figure 2B). The risk ratio ranged from 0.37 to 5.40. The pulled risk of mortality from Covid-19 in patients with COPD was 1.76 (95% CI 0.92-3.36), indicating that these patients were not at significantly increased risk of mortality from COVID-19.

**The risk of mortality from COVID-10 in patients with coronary artery disease**

Coronary artery disease significantly increased patient’s risk of mortality from COVID-19 (Figure 2C). Five studies reported the risk ratio of dying from COVID-19 with underlying coronary heart disease. Four studies were from China and one international study including patients from the USA. The risk of dying from COVID-19 with coronary heart disease ranged from 1.3 to 3.2. The overall risk was significant, indicating that patients with coronary heart disease were about 2 times as likely to die from COVID-19 compared to patients without coronary heart disease (RR=1.89 95%CI= 1.58-2.27). The between study heterogeneity was very low, with I²= 0%. 


The risk of mortality from COVID-10 in patients with hypertension

Eight studies from China, and one from Italy, reported the risk of mortality from COVID-19 in patients with hypertension (Figure 3A). Patients with hypertension were twice as likely to die from COVID-19 compared to patients without hypertension (RR= 1.89 95%CI 1.58-2.27). The between study heterogeneity, $I^2$ was equal to 0%.

The risk of mortality from COVID-10 in patients with type 2 diabetes

Twelve studies reported the risk of mortality from COVID-19 in patients with type 2 diabetes (Figure 3B). However, only four studies found that patients with type 2 diabetes were at a significantly higher risk of mortality. Using random-effect models in our pooled analysis, we found that those with type 2 diabetes were not at an increased risk of mortality from COVID-19 (RR=1.37, 95%CI =0.85-2.20).

The risk of mortality from COVID-10 in patients with cancer

Four studies reported the COVID-19 mortality risk in patients with cancer (Figure 3C). Feng and colleagues and Guan and colleagues found that those with cancer were 2.5-3.5 times as likely to die from COVID-19 compared to those without cancer, however other studies found that there was no significant difference in the COVID-19 mortality risk. Our pooled analysis using the random effects model found that those with cancer were 2 times as likely to die from COVID-19 compared to those without (RR=1.93, 95%CI – 1.15-3.24).
The risk of mortality from COVID-10 in patients with chronic kidney disease (CKD)

Four studies reported the risk of mortality from COVID-19 in patients with chronic kidney disease (Figure 4A). One of these studies found that patients with chronic kidney disease were at increased of mortality from COVID-19. However, our pooled analysis on 2172 patients with CKD indicated that these patients were not at a significantly higher risk of COVID-19 mortality (RR=2.36 95%CI 0.97-5.77).

The risk of mortality from COVID-10 in patients with chronic liver disease (CLD)

Two reports explored whether chronic liver disease (CLD) increased patients’ risk of mortality from COVID-19 (Figure 4B). Both studies found that patients with CLD were not at an increased risk of mortality. Our pooled analysis confirmed these findings (RR=1.57 95%CI 0.70-3.50). More studies are urgently needed to further explore this relationship.

The risk of mortality from COVID-10 in patients with congestive heart failure (CHF)

We found that patients with congestive heart failure had 2.7 times the risk of mortality from COVID-19 compared to those without CHF (Figure 4C, RR=2.66, 95%CI 1.58-4.48). Among the three studies reporting the risk of mortality from COVID-19 in patients with CHF, the risk ratio ranged from 2.44 to 3.89. The between-study heterogeneity was 0%.

The risk of mortality from COVID-10 in patients with stroke
Three studies from China explored whether patients with a history of stroke were at an increased risk of COVID-19 mortality (Figure 4D). Two of the three studies found that patients with stroke were at a significantly higher risk of mortality, resulting in a pooled RR of 2.72, 95% CI 0.90-8.21.

Lastly, one study reported the association of arrhythmia and COVID-19 mortality.1 Those with arrhythmia were 95% more likely to die compared to those without. OR: (1.95 (1.33–2.86)
Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to include COVID-19 cases from across Europe, Asia and North America, while also having the largest sample size (N=61,455) and number of studies (n=19). This meta-analysis was based on data from 19 studies with laboratory-confirmed COVID-19. Our findings suggest that patients with preexisting chronic conditions had a higher risk of death from COVID-19, particularly any cardiovascular disease, hypertension, coronary heart disease, congestive heart failure and cancer. Our findings further highlight two important points. First, the failure of allostasis caused by preexisting conditions may in part explain the increased risk of mortality among COVID-19 patients. Second, a need for optimization of COVID-19 survival and limited health resources by employing focused vaccination for individuals with cardiovascular disease, chronic kidney disease, and cancer.

A probable hypothesis of the pathophysiological mechanism related to the increased risk of mortality among COVID-19 patients may be explained by the allostatic load imposed on the body by cardiovascular and other preexisting conditions. Chronic conditions cause dysregulation of major physiological systems, including the hypothalamic–pituitary–adrenal axis, the sympathetic nervous system, and the immune system. The chronic nature of such conditions induces the ‘‘wear and tear’’ on body’s regulatory systems, leading to accumulation of pro-inflammatory cytokines and effect of the cellular immune system. As a result of the reduced immunity, these individuals become very susceptible to severe complications of SARS-CoV-2 and death. However, such an association with this type of virus is not relatively new. Seasonal influenza, SARS-CoV, and Middle Eastern respiratory syndrome (MERS)-CoV, have also been associated with increased severity and mortality in patients with preexisting conditions.
As the race towards acquiring a vaccination against COVID-19 intensifies, the question remains as to which group of individuals should be prioritized for this vaccine. Our findings suggest that those with preexisting cardiovascular disease, hypertension and cancer may benefit from vaccination to optimize both survival and limited resources. Targeted public health vaccination intervention strategy for influenza vaccination are recommended by the Advisory Committee on Immunization Practices against seasonal influenza.\textsuperscript{36} In the population with chronic comorbidities, annual influenza vaccination significantly reduces mortality and morbidity.\textsuperscript{37} It is postulated that SARS-CoV-2 may become seasonal requiring annual vaccination.

Lastly, although the specific mechanisms are uncertain, SARS-CoV-2 is thought to infect host cells through ACE2 to cause COVID-19, while also causing damage to the myocardium.\textsuperscript{38} Majority of patients with preexisting cardiovascular disease use renin-angiotensin system (RAS) blockers, which are postulated to increase the risk of developing a severe and fatal SARS-CoV-2 infection.\textsuperscript{39} In animal studies, Ferrario and colleagues reported ACE inhibitors or ARBs increased the levels of Ace2 mRNA compared with placebo.\textsuperscript{40} Particularly, cardiac levels of Ace2 mRNA increased by 4.7-fold or 2.8-fold with either lisinopril (an ACE inhibitor) or losartan (an ARB), respectively. However, it remains a controversial whether patients with COVID-19 and pre-existing cardiovascular disease who are taking an ACE inhibitor or ARB should switch to another antihypertensive drug.\textsuperscript{6} Nevertheless, particular attention should be given to cardiovascular protection during treatment for COVID-19.

\textbf{Strengths and Limitations}
As COVID-19 is still a relatively new phenomenon, there has been a limited number of comprehensive and conclusive studies related to mortality in diverse populations. Therefore, data from Africa and Australia were not included in this meta-analysis. We are hopeful that in the future, further research will be published that explores the association between COVID-19 mortality and preexisting chronic conditions in these regions. In addition to this, we were unable to explore the influence that cancer, HIV, and asthma may have on COVID-19 mortality. As mentioned above, further research is necessary to conclusively determine if individuals with these preexisting chronic conditions in these regions are at an increased risk for death from COVID-19.

As previously mentioned, this meta-analysis employed a large number of studies, which allowed for a relatively large sample size \( (n=61,455) \). By doing this, we were able to explore a broad scope of chronic conditions, with over seven comorbidities included. This allows our meta-analysis to comprehensively cover a multitude of prevalent conditions throughout populations.

**Conclusion**

Our findings suggest that of the major comorbidities analyzed, **cardiovascular disease**, coronary heart disease, hypertension, congestive heart failure, and cancer carry the strongest risk of death from COVID-19. This research highlights the importance of conducting further research related to the association between preexisting chronic conditions and COVID-19 mortality, in order to explore potential mechanisms to decrease this burden.
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| AUTHOR          | YEAR | COUNTRY | CONTINENT                    | SAMPLE SIZE (N) | STUDY TYPE | STUDY PERIOD         | MEAN AGE | MALE (%) | COVARATES CONTROLLED                                                                 | STATISTICAL MODEL FOR THE ANALYSIS | SCORE |
|-----------------|------|---------|-------------------------------|-----------------|------------|----------------------|----------|----------|-------------------------------------------------------------------------------------|-------------------------------------|--------|
| MEHRA ET AL     | 2020 | 11 countries in Asia, USA, and Europe | North America, Asia, and Europe | 8910          | Cohort     | 12/15/19-3/15/20    | 48.7 ± 16.6 | 60       | >65 yr of age, female sex, coronary artery disease, congestive heart failure, arrhythmia, COPD, current smoker, receiving ACE inhibitor, receiving ARB, receiving statin | OR                                  | 9      |
| DU ET AL        | 2020 | China   | Asia                          | 179            | Cohort     | 12/25/19-2/07/20    | 57.6 ± 15.7 | 54.2     | Age ≥ 65 years, cardiovascular or cerebrovascular disease, CD3+CD8+ T cells < 75 cells/μL, Cardiac troponin I > 0.06 ng/mL | OR                                  | 9      |
| ZHOU ET AL      | 2020 | China   | Asia                          | 191            | Cohort     | 12/29/19-1/31/20    | 56        | 62       | Age, coronary heart disease, SOFA score, lymphocyte county x 109 per L, D-dimer μg/mL > 0.05, D-dimer μg/mL > 1 | OR                                  | 9      |
| SHI ET AL       | 2020 | China   | Asia                          | 416            | Cohort     | 1/20/20-2/20/20     | 64        | 49.3     | Age, cardiovascular diseases, cerebrovascular diseases, diabetes, chronic obstructive pulmonary disease, renal failure, cancer, acute respiratory distress syndrome, cardiac injury, creatinine ≥ 15 mg/dL, N-terminal pro-B-type natriuretic peptide ≥ 500 pg/mL | HR                                  | 9      |
| LI ET AL        | 2020 | China   | Asia                          | 548            | Cohort     | 1/26/20-2/05/20     | 60        | 50.9     | Age ≥65 vs <65, sex, blood leukocyte count, LDH >445 U/L vs ≤445 U/L, complications (cardiac injury, hyperglycemia), corticosteroids (low dose, high dose), Lopinavir/Ritonavir, Umifenovir | HR & OR                             | 9      |
| GUO ET AL       | 2020 | China   | Asia                          | 187            | Cohort     | 1/23/2022/23/20     | 58.5      | 48.7     | -                                                                                   | Calculated                          | 9      |
| GRASSELLI ET AL | 2020 | Italy   | Europe                        | 1591           | Cohort     | 2/20/20-3/18/20     | 63        | 82       | -                                                                                   | Calculated                          | 6      |
| CHEN ET AL      | 2020 | China   | Asia                          | 799            | Cohort     | 1/13/20-2/12/20     | 62        | 62       | -                                                                                   | Calculated                          | 7      |
| FU ET AL        | 2020 | China   | Asia                          | 200            | Case-cohort | 1/01/20-1/30/20     | -         | 49.5     | Liver function indexes (alanine aminotransferase, total bilirubin), renal function (creatinine, urea nitrogen, uric acid), myocardial function (creatinine kinase, myoglobin, lactate dehydrogenase, aspartate aminotransferase, aspartate aminotransferase/alanine aminotransferase ratio) | OR                                  | 9      |
| GU ET AL        | 2020 | China   | Asia                          | 275            | Nested case-control | 12/18/19-3/08/20    | 66.4      | 62.9     | Age, male, before 01/11/20, coronary heart disease, cerebral infarction, COPD, renal failure | HR & OR                             | 9      |
| YANG ET AL      | 2020 | China   | Asia                          | 52             | Cohort     | 12/24/20-1/26/20    | 59.7      | 67       | -                                                                                   | Calculated                          | 9      |
| DENG ET AL      | 2020 | China   | Asia                          | 225            | Cohort     | 1/01/20-2/21/20     | -         | -        | -                                                                                   | Calculated                          | 7      |
| YUAN ET AL      | 2020 | China   | Asia                          | 27             | Cohort     | 1/01/20-1/25/20     | 60        | 45       | -                                                                                   | Calculated                          | 7      |
| WANG ET AL      | 2020 | China   | Asia                          | 339            | Cohort     | 1/01/20-2/06/20     | 71±8      | 49       | Age, cardiovascular disease, cerebrovascular disease, COPD, acute cardiac injury, arrhythmia, AKI, ARDS, cardiac insufficiency, bacterial infection | HR                                  | 9      |
| LI ET AL        | 2020 | China   | Asia                          | 1,178          | Cohort     | 1/15/20-3/15/20     | 66        | 52.2     | -                                                                                   | Calculated                          | 7      |
| ZHANG ET AL     | 2020 | China   | Asia                          | 28             | Cohort     | 1/13/20-2/26/20     | 65        | 60.7     | Sex, age, antitumor ≤14 days, patchy consolidation                                    | HR                                  | 9      |
| FENG ET AL      | 2020 | China   | Asia                          | 44,672         | Cohort     | Through 2/11/2020   | -         | 51.4     | -                                                                                   | Calculated                          | 7      |
| ZHANG ET AL     | 2020 | China   | Asia                          | 48             | Cohort     | 12/25/20-2/15/20    | 70.58 ± 8.31 | 68.7 | Age, SpO2%, Serum Cr value, d-dimer value, le-CTn elevation | HR                                  | 9      |
| GUAN ET         | 2020 | China   | Asia                          | 1580           | Cohort     | 12/11/20-1/31/20    | 48.9      | 57.3     | Type of comorbidity (COPD, diabetes, hypertension, malignant)                       | HR                                  | 9      |
Figure 1: Flow Diagram

57 studies identified from OVID & Joana Briggs
97 studies identified from PUBMED
67 studies identified from SCOPUS
40 studies identified from snowballing

57 duplicate studies excluded

204 abstracts screened for inclusion

- 98 studies excluded
- 39 Studies were review articles, meta-analyses, editorials, or commentaries
- 54 Studies did not report on COVID-19
- 5 Studies included non-human subjects

106 full-text articles screened for inclusion

- 87 studies excluded
- 2 Studies were case studies
- 79 Studies looked at other outcomes of interest
- 6 Studies did not look at chronic pre-existing conditions

19 studies eligible for inclusion
2A. Any cardiovascular disease

| Author, Publication Year, Country | Risk Ratio  | RR    | 95% CI   | Weight |
|----------------------------------|-------------|-------|----------|--------|
| Fu et al, 2020, China            |             | 0.72  | [0.34; 1.51] | 12.7%  |
| Yang et al, 2020, China          |             | 0.93  | [0.33; 2.64] | 9.9%   |
| Shi et al, 2020, China           |             | 1.51  | [0.79; 2.89] | 13.6%  |
| Du et al, 2020, China            |             | 2.46  | [0.85; 7.11] | 9.8%   |
| Wang et al, 2020, China          |             | 2.87  | [1.38; 5.94] | 12.8%  |
| Chen et al, 2020, China          |             | 2.94  | [1.31; 6.59] | 12.0%  |
| Feng et al, 2020, China          |             | 4.96  | [2.26; 10.90] | 12.2%  |
| Guan et al, 2020, China          |             | 5.56  | [1.64; 18.89] | 8.5%   |
| Guo et al, 2020, China           |             | 5.99  | [1.77; 20.31] | 8.5%   |

Overall (Random-Effect Model)  
Heterogeneity: $I^2 = 65\%$, $I^2 = 0.3531$, $p < 0.01$

2.35 [1.44; 3.84] 100.0%

2B. Chronic obstructive pulmonary disease

| Author, Publication Year, Country | Risk Ratio  | RR    | 95% CI   | Weight |
|----------------------------------|-------------|-------|----------|--------|
| Shi et al, 2020, China           |             | 0.37  | [0.14; 0.96] | 14.2%  |
| Yang et al, 2020, China          |             | 0.60  | [0.22; 1.61] | 13.9%  |
| Gu et al, 2020, China            |             | 1.90  | [0.95; 3.80] | 16.5%  |
| Guan et al, 2020, China          |             | 2.68  | [1.24; 5.81] | 15.8%  |
| Mehra et al, 2020, International  |             | 2.96  | [1.54; 5.70] | 16.9%  |
| Wang et al, 2020, China          |             | 3.72  | [1.46; 9.46] | 14.3%  |
| Zhou et al, 2020, China          |             | 5.40  | [0.98; 29.79] | 8.4%   |

Overall (Random-Effect Model)  
Heterogeneity: $I^2 = 73\%$, $I^2 = 0.5358$, $p < 0.01$

1.76 [0.92; 3.36] 100.0%

2C. Coronary Heart Disease

| Author, Publication Year, Country | Risk Ratio  | RR    | 95% CI   | Weight |
|----------------------------------|-------------|-------|----------|--------|
| Deng et al, 2020, China          |             | 1.61  | [0.77; 3.36] | 21.4%  |
| Zhou et al, 2020, China          |             | 2.14  | [0.49; 9.36] | 5.3%   |
| Li et al, 2020, China            |             | 2.23  | [0.68; 7.29] | 8.2%   |
| Mehra et al, 2020, International  |             | 2.70  | [1.62; 4.50] | 44.2%  |
| Gu et al, 2020, China            |             | 3.00  | [1.43; 6.30] | 20.9%  |

Overall (Random-Effect Model)  
Heterogeneity: $I^2 = 0\%$, $I^2 = 0$, $p = 0.79$

2.40 [1.71; 3.37] 100.0%
3A. Hypertension

| Author, Publication Year, Country | Risk Ratio | RR  | 95% CI  | Weight |
|----------------------------------|------------|-----|---------|--------|
| Zhang et al, 2020, China         | 1.32       | 1.50| [0.55; 3.16] | 4.2% |
| Wang et al, 2020, China          | 1.49       | 1.57| [0.94; 2.37] | 14.9%|
| Guan et al, 2020, China          | 1.57       | 1.78| [1.05; 2.37] | 19.4%|
| Chen et al, 2020, China          | 1.78       | 1.80| [1.09; 2.90] | 13.5%|
| Fu et al, 2020, China            | 1.80       | 2.24| [0.96; 3.36] | 8.2% |
| Grasselli et al, 2020, Italy     | 2.24       | 2.29| [1.44; 3.48] | 16.5%|
| Feng et al, 2020, China          | 2.29       | 3.05| [1.43; 3.67] | 14.4%|
| Zhou et al, 2020, China          | 3.05       | 3.16| [1.30; 7.13] | 4.4% |
| Deng et al, 2020, China          | 3.16       |     | [1.35; 7.38] | 4.5% |

Overall (Random-Effect Model)
Heterogeneity: $I^2 = 0\%$, $\chi^2 = 0$, $p = 0.81$

| Risk Ratio | RR  | 95% CI  | Weight |
|------------|-----|---------|--------|
|            | 1.89| [1.58; 2.27] | 100.0%|

3B. Type 2 Diabetes

| Author, Publication Year, Country | Risk Ratio | RR  | 95% CI  | Weight |
|----------------------------------|------------|-----|---------|--------|
| Chen et al, 2020, China          | 0.15       | 0.79| [0.09; 0.26] | 8.8% |
| Shi et al, 2020, China           | 0.79       | 1.09| [0.51; 1.23] | 9.2% |
| Wang et al, 2020, China          | 1.09       | 1.12| [0.67; 1.77] | 9.0% |
| Gu et al, 2020, China            | 1.12       | 1.50| [0.72; 1.74] | 9.2% |
| Fu et al, 2020, China            | 1.50       | 1.59| [0.81; 2.78] | 8.5% |
| Guan et al, 2020, China          | 1.59       | 1.94| [1.02; 2.47] | 9.2% |
| Du et al, 2020, China            | 1.94       | 2.15| [0.80; 4.68] | 7.4% |
| Li et al, 2020, China            | 2.15       | 2.17| [1.18; 3.92] | 8.6% |
| Zhang et al, 2020, China         | 2.17       | 2.20| [0.70; 6.71] | 6.4% |
| Deng et al, 2020, China          | 2.20       | 2.85| [0.96; 5.03] | 7.7% |
| Zhou et al, 2020, China          | 2.85       | 3.35| [1.19; 6.81] | 7.5% |
| Feng et al, 2020, China          | 3.35       |     | [1.85; 6.06] | 8.6% |

Overall (Random-Effect Model)
Heterogeneity: $I^2 = 87\%$, $\chi^2 = 0.5895$, $p < 0.01$

| Risk Ratio | RR  | 95% CI  | Weight |
|------------|-----|---------|--------|
|            | 1.37| [0.85; 2.20] | 100.0%|

3C. Cancer

| Author, Publication Year, Country | Risk Ratio | RR  | 95% CI  | Weight |
|----------------------------------|------------|-----|---------|--------|
| Zhang et al, 2020, China         | 1.06       | 1.75| [0.47; 2.39] | 29.8%|
| Shi et al, 2020, China           | 1.75       | 2.46| [0.62; 4.95] | 20.3%|
| Feng et al, 2020, China          | 2.46       | 3.50| [1.05; 5.78] | 27.7%|
| Guan et al, 2020, China          | 3.50       |     | [1.31; 9.37] | 22.2%|

Overall (Random-Effect Model)
Heterogeneity: $I^2 = 22\%$, $\chi^2 = 0.0601$, $p = 0.28$

| Risk Ratio | RR  | 95% CI  | Weight |
|------------|-----|---------|--------|
|            | 1.93| [1.15; 3.24] | 100.0%|
4A. Chronic Kidney Disease

| Author, Publication Year, Country | Risk Ratio | RR  | 95% CI | Weight |
|----------------------------------|------------|-----|--------|--------|
| Shi et al, 2020, China           | 1.10       | 1.10| [0.62; 1.95] | 37.2%  |
| Wang et al, 2020, China          | 1.73       | 1.73| [0.76; 3.96] | 31.9%  |
| Chen et al, 2020, China          | 5.87       | 5.87| [0.80; 43.01] | 13.8%  |
| Guan et al, 2020, China          | 10.58      | 10.58| [1.97; 56.81] | 17.2%  |

Overall (Random-Effect Model)

Heterogeneity: $I^2 = 63\%, \tau^2 = 0.4728, p = 0.04$

4B. Chronic Liver Disease

| Author, Publication Year, Country | Risk Ratio | RR  | 95% CI | Weight |
|----------------------------------|------------|-----|--------|--------|
| Fu et al, 2020, China            | 1.33       | 1.33| [0.56; 3.16] | 85.7%  |
| Wang et al, 2020, China          | 4.27       | 4.27| [0.51; 35.84] | 14.3%  |

Overall (Random-Effect Model)

Heterogeneity: $I^2 = 0\%, \tau^2 = 0, p = 0.32$

4C. Congestive Heart Failure

| Author, Publication Year, Country | Risk Ratio | RR  | 95% CI | Weight |
|----------------------------------|------------|-----|--------|--------|
| Chen et al, 2020, China          | 2.44       | 2.44| [0.38; 15.66] | 7.9%   |
| Mehra et al, 2020, International  | 2.48       | 2.48| [1.36; 4.51] | 76.2%  |
| Li et al, 2020, China            | 3.89       | 3.89| [1.05; 14.40] | 15.9%  |

Overall (Random-Effect Model)

Heterogeneity: $I^2 = 0\%, \tau^2 = 0, p = 0.82$

4D. Stroke

| Author, Publication Year, Country | Risk Ratio | RR  | 95% CI | Weight |
|----------------------------------|------------|-----|--------|--------|
| Shi et al, 2020, China           | 1.12       | 1.12| [0.60; 2.09] | 40.2%  |
| Wang et al, 2020, China          | 3.26       | 3.26| [1.34; 7.91] | 35.5%  |
| Guan et al, 2020, China          | 9.02       | 9.02| [1.92; 42.28] | 24.3%  |

Overall (Random-Effect Model)

Heterogeneity: $I^2 = 75\%, \tau^2 = 0.6920, p = 0.02$