ORIGINAL RESEARCH


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ABSTRACT
Background Coronavirus disease 2019 (COVID-19) has produced a significant health burden worldwide, especially in patients with cardiovascular comorbidities. The aim of this systematic review and meta-analysis was to assess the impact of underlying cardiovascular comorbidities and acute cardiac injury on in-hospital mortality risk.

Methods PubMed, Embase and Web of Science were searched for publications that reported the relationship of underlying cardiovascular disease (CVD), hypertension and myocardial injury with in-hospital fatal outcomes in patients with COVID-19. The ORs were extracted and pooled. Subgroup and sensitivity analyses were performed to explore the potential sources of heterogeneity.

Results A total of 10 studies were enrolled in this meta-analysis, including eight studies for CVD, seven for hypertension and eight for acute cardiac injury. The presence of CVD and hypertension was associated with higher odds of in-hospital mortality (unadjusted OR 4.85, 95% CI 3.07 to 7.70; I²=29%; unadjusted OR 3.67, 95% CI 2.31 to 5.83; I²=57%, respectively). Acute cardiac injury was also associated with a higher unadjusted odds of 21.15 (95% CI 10.19 to 43.94; I²=71%).

Conclusion COVID-19 patients with underlying cardiovascular comorbidities, including CVD and hypertension, may face a greater risk of fatal outcomes. Acute cardiac injury may act as a marker of mortality risk. Given the unadjusted results of our meta-analysis, future research are warranted.

INTRODUCTION
In the past two decades, the pandemic of severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012 have taken severe death tolls worldwide, with 916 and 800 deaths, respectively. In late 2019, another virus with lethal respiratory infection potential identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) emerged and heralded another global pandemic. Since the outbreak in Wuhan, more than 200 countries and regions have reported confirmed cases. The WHO coined COVID-19 to describe ‘coronavirus disease 2019’ and declared this outbreak as a public health emergency of international concern. As of 24 April 2020, there have been nearly 2750000 infections and over 192000 deaths worldwide.

Within less than 6 months, COVID-19 has registered a mortality record that is higher than that of SARS and MERS combined. Because of the overwhelming fatality cases caused by COVID-19, much concern has been raised to determine the risk factors for poor prognosis, such as advanced age and male sex. Previous research has reported that patients with underlying cardiovascular disease (CVD) were prone to viral infection and also had a greater risk of developing severe cases and being admitted to intensive care unit. SARS-CoV-2 can attack the respiratory system by targeting ACE2. However, with the high tissue-specificity of ACE2 expression in the cardiovascular system, cardiomyocytes may be particularly prone to damage. Several studies have reported a high incidence of elevated cardiac troponin in hospitalised patients, especially in those in critical conditions. Thus, patients with CVD complications may have poor prognosis when infected with SARS-CoV-2. Therefore, here we conducted a systematic review and meta-analysis on the available evidence to evaluate the association between underlying CVD and incident cardiac injury with in-hospital mortality risk in patients with COVID-19.

METHODS
This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and the Meta analysis of Observational Studies in Epidemiology statement.

Search strategy

Inclusion criteria
Studies were included for the meta-analysis if they met the following criteria: (1) exposure factor: CVD (coronary heart disease, cardiac disease and...
chronic cardiac disease), hypertension or acute cardiac injury; (2) outcome interest: in-hospital mortality; and (3) study population: adult patients with confirmed SARS-CoV-2 infection. To avoid duplication, we contacted the authors whose studies were conducted in the same hospital. If the same batch of patients were enrolled or no specific information identifying the patients could be provided, study with the largest sample size was included.

**Study selections**
Two researchers (XL and BG) independently screened the search results by titles and abstracts. Any potentially relevant studies were retrieved with full texts for further evaluation. Two authors (XL and BG) independently identified the eligible studies based on inclusion criteria. Any disagreements were resolved through discussion with another researcher (TS).

**Data extraction and quality assessment**
Two researchers (XL and BG) independently extracted data from the enrolled studies via a preset standardised form. The following information was extracted: first author, publication year, study design, location, patients enrolled period, age, sex, prevalence of comorbidities, exposure factors and level of adjustment. Newcastle-Ottawa Scale terms, with total score of nine stars, were applied to evaluate the quality of case series studies or cohort studies separately. The studies with 7 points or more were considered of high quality.

**Statistical analysis**
All analyses were performed using Stata V.12.0 software. The unadjusted ORs with 95% CIs were calculated as the common risk estimates and then were pooled due to the limited data on multivariable adjusted outcomes. The heterogeneity among studies was evaluated by Cochran’s Q-statistic and $I^2$ test. If $I^2 \leq 50\%$, a fixed effects model was adopted; otherwise, a random effects model was applied to meta-analysis. Meta-regression analysis was performed to test the potential sources of heterogeneity among studies. Sensitivity analyses were also performed by omitting one study at a time to evaluate the influence of individual study on the pooled results. Publication bias was evaluated by visual inspection of asymmetry in funnel plots.

**Patient and public involvement**
Patients or the public were not involved in the design, conduct, reporting, dissemination plans of our research.

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**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram of study selection.
RESULTS

Study selection

The initial database search yielded 1524 studies (figure 1). After removing duplicate publications, 825 studies were left and screened by title and abstract, and we identified 67 articles for full-text review. Of these, 57 studies were excluded due to no relevant outcome, no exposure of interest, duplicated publication, not a primary study or medical intervention study (online supplementary file 1). No additional studies met the inclusion criteria from screening reference lists. When several studies were published by the same institution, the authors were contacted to ensure that no overlapping cohorts were analysed as separate studies. Altogether, 10 studies comprising 3118 patients were included in this meta-analysis.

Study characteristics

The main characteristics of the included studies are summarised in table 1. Of all 10 studies, two were case series design15 16 and the remaining eight were cohort studies.17–24 All studies were conducted in Wuhan, China, except for one study that enrolled patients nationwide.17 The patients were all accrued from the end of December 2019 to February 2020. The mean age ranged from 49 years17 to 6819 years and the proportion of male patients ranged from 45%22 to 67%.21 The prevalence of CVD and hypertension ranged from 4%17 to 15%18 and from 17%17 to 44%,19 respectively, and from 15%24 to 44%15 of patients experienced cardiac injury during hospitalisation (table 2).

Table 1  Baseline characteristics of the included studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Location</th>
<th>Patients enrol period</th>
<th>Number of patients</th>
<th>Type of exposure</th>
<th>Adjustment level</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deng, 202016</td>
<td>Case series</td>
<td>Hankou and Caidian branch of Tongji Hospital; Hankou branch of Central Hospital, Wuhan, China.</td>
<td>1 January 2020–21 February 2020</td>
<td>225</td>
<td>Hypertension. Cardiac disease. Acute cardiac injury.</td>
<td>None.</td>
<td>6</td>
</tr>
<tr>
<td>Guo, 202018</td>
<td>Cohort</td>
<td>Seventh Hospital, Wuhan, China.</td>
<td>23 January 2020–23 February 2020</td>
<td>187</td>
<td>Cardiac injury.</td>
<td>None.</td>
<td>7</td>
</tr>
<tr>
<td>He, 202019</td>
<td>Cohort</td>
<td>Zhongfa Xincheng Hospital, Wuhan, China.</td>
<td>3 February 2020–24 February 2020</td>
<td>54</td>
<td>Hypertension. Coronary heart disease.</td>
<td>None.</td>
<td>7</td>
</tr>
<tr>
<td>ShiB, 202020</td>
<td>Cohort</td>
<td>Renmin Hospital, Wuhan, China.</td>
<td>20 January 2020–10 February 2020</td>
<td>416</td>
<td>Cardiac injury.</td>
<td>Multivariable-adjusted.</td>
<td>8</td>
</tr>
<tr>
<td>Yuan, 202022</td>
<td>Cohort</td>
<td>Central Hospital, Wuhan, China.</td>
<td>1 January 2020–25 January 2020</td>
<td>27</td>
<td>Cardiac disease.</td>
<td>None.</td>
<td>7</td>
</tr>
<tr>
<td>Zhou, 202023</td>
<td>Cohort</td>
<td>Jinyintan Hospital and Pulmonary Hospital, Wuhan, China.</td>
<td>29 December 2019–31 January 2020</td>
<td>191</td>
<td>Hypertension. Coronary heart disease.</td>
<td>Multivariable-adjusted for coronary heart disease.</td>
<td>8</td>
</tr>
<tr>
<td>Cao, 202024</td>
<td>Cohort</td>
<td>Zhongnan Hospital, Wuhan, China.</td>
<td>3 January 2020–1 February 2020</td>
<td>102</td>
<td>Hypertension. Cardiovascular disease. Acute cardiac injury.</td>
<td>None.</td>
<td>7</td>
</tr>
</tbody>
</table>

NOS, Newcastle-Ottawa Scale.

Table 2  Characteristics of patients in included studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Total number</th>
<th>Mean age (years)</th>
<th>Sex (male,% )</th>
<th>Cardiovascular disease (%)</th>
<th>Hypertension (%)</th>
<th>Cardiac injury (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen, 202015</td>
<td>113</td>
<td>161</td>
<td>68</td>
<td>51</td>
<td>73</td>
<td>55</td>
</tr>
<tr>
<td>Deng, 202016</td>
<td>109</td>
<td>116</td>
<td>69</td>
<td>40</td>
<td>67</td>
<td>44</td>
</tr>
<tr>
<td>Guan, 202017</td>
<td>50</td>
<td>1540</td>
<td>48.9</td>
<td>57.3</td>
<td>16.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Guo, 202018</td>
<td>43</td>
<td>144</td>
<td>58.5</td>
<td>48.7</td>
<td>15.5</td>
<td>0.3</td>
</tr>
<tr>
<td>He, 202019</td>
<td>26</td>
<td>28</td>
<td>70.0</td>
<td>66.5</td>
<td>61.5</td>
<td>64.3</td>
</tr>
<tr>
<td>ShiB, 202020</td>
<td>57</td>
<td>359</td>
<td>64</td>
<td>49.3</td>
<td>14.7</td>
<td>30.5</td>
</tr>
<tr>
<td>Yang, 202021</td>
<td>32</td>
<td>20</td>
<td>64.6</td>
<td>51.9</td>
<td>66</td>
<td>70</td>
</tr>
<tr>
<td>Yuan, 202022</td>
<td>10</td>
<td>17</td>
<td>68</td>
<td>55</td>
<td>40</td>
<td>47</td>
</tr>
<tr>
<td>Zhou, 202023</td>
<td>54</td>
<td>137</td>
<td>69</td>
<td>52</td>
<td>70</td>
<td>59</td>
</tr>
<tr>
<td>Cao, 202024</td>
<td>17</td>
<td>85</td>
<td>72</td>
<td>53</td>
<td>76.5</td>
<td>47.1</td>
</tr>
</tbody>
</table>

NA, not available.
Primary outcomes

Eight studies15–17 19 21–24 reported the relationship between underlying CVD and in-hospital mortality risk (2515 patients and 127 deaths) in unadjusted model. Five studies15–17 21 22 24 consistently revealed a significantly higher death risk in the CVD group and the remaining three studies19 21 22 reported no significant relationship between CVD and in-hospital mortality (figure 2). Overall, the summary estimate demonstrated that patients with CVD had an approximately fivefold higher risk of mortality compared with non-CVD patients (unadjusted OR 4.85, p<0.001; 95% CI 3.06 to 7.70). The heterogeneity across the studies was non-significant (I²=29.3%, p=0.194).

Seven studies15–17 22–24 (2463 patients and 535 deaths) were included for the pre-existing hypertension and in-hospital mortality analysis with unadjusted ORs. Six studies15–17 22–24 reported a significantly higher mortality risk in patients with previous hypertension, and the remaining study19 showed no significant association (figure 3). The pooled unadjusted effect of hypertension on mortality risk was 3.67 (95% CI 2.31 to 5.83, p<0.001) with moderate heterogeneity (I²=57.4%, p=0.029).

For cardiac injury, all eight studies15 16 18–21 23 24 (1429 patients and 374 deaths) except one23 reported that acute cardiac injury was significantly associated with a high mortality risk in unadjusted model (figure 4). The pooled effect of these studies (unadjusted OR 21.15, 95%CI 10.19 to 43.94, p<0.001; heterogeneity: I²=70.5%, p=0.001) showed that patients with elevated troponin levels had a significant higher mortality risk than those with normal troponin levels.

Publication bias, sensitivity analysis and meta-regression

Visual inspection of the funnel plots did not show significant asymmetry (online supplementary file 2). Sensitivity analyses were conducted by systematically excluding one study at a time, and the results remained consistent with the primary analyses (online supplementary file 3). To explore potential sources of heterogeneity, meta-regression was applied to test the influence of study design, sample size, mean age and male proportion. None of these factors contributed significantly to the observed heterogeneity (online supplementary file 4).

DISCUSSION

Our study evaluated the impact of underlying CVD, hypertension and acute cardiac injury on in-hospital mortality in patients with COVID-19. Our results showed a positive association between previous CVD and hypertension with fatal outcomes, with unadjusted ORs and 95% CIs of 4.85 (3.06 to 7.70) and 3.67 (2.31 to 5.83) and a significant relationship between acute cardiac injury and in-hospital mortality (unadjusted OR 21.15, 95%CI 10.19 to 43.94).

The 2019 novel coronavirus (2019-nCoV) is a single-strand RNA virus that shares several similarities with SARS-CoV and MERS-CoV in genetic sequencing and clinical presentation but is equipped with a more robust capacity for human-to-human transmission.25 26 From the outset, the capacity of 2019-nCoV to spread and infect people in Wuhan, China, was alarming, and the infection has rippled throughout the rest of the world, causing severe morbidity and mortality.27 Therefore, there is a pressing need to identify risk factors for poor prognosis among patients with COVID-19.

Patients with cardiovascular comorbidities were found to be more vulnerable to coronavirus infection and may have poor prognoses.2 Previous meta-analyses systematically tested the relationship between CVD and severity of the disease but with non-uniform definitions of clinical outcome.28 29 The meta-analysis by Zuin et al30 included three studies and reported a positive association between hypertension and mortality risk in patients with COVID-19. Our study reinforced their conclusion and found that patients with CVD history also had an almost fivefold higher risk of mortality comparing with non-CVD patients. However, since our results were obtained using unadjusted ORs, the exact role of CVD in the risk stratification of patients with COVID-19 remains uncertain.
COVID-19 is still undetermined. There may be several mechanisms that account for the high mortality risk of COVID-19 patients with CVD history. First, patients with underlying CVD are more likely to decline into an unstable haemodynamic status when infected with 2019-nCoV. Severe pneumonia places a considerable workload on cardiac ventricles, which may exacerbate pre-existing left ventricular dysfunction, even causing cardiogenic shock. Second, inflammatory reactions caused by 2019-nCoV infection might convert chronic coronary artery disease into acute coronary syndrome. A profound systemic inflammation wave along with local inflammatory infiltration may lead to a hypercoagulable state and atherosclerotic plaque rupture, which may culminate in thrombotic events. Third, the priority of treatments, in favour of limiting nosocomial viral transmission while neglecting other medical issues, might predispose CVD patients to unfavourable clinical outcomes. The current interim guidelines suggest that patients with ST-segment elevation myocardial infarction should consider thrombolysis first in the COVID-19 era. Severe adverse effects such as cerebral haemorrhage and insufficient and undesignated coronary revascularisation caused by thrombolysis can increase the risk of death.

Acute cardiac injury is commonly recorded in patients with COVID-19. The incidence of cardiac injury among our enrolled studies ranged from 15% to 44%, which was higher than the prevalence of CVD (5%–15%). This suggested that 2019-nCoV might attack cardiomyocytes through different pathways, other than exacerbating the already compromised cardiovascular system. 2019-nCoV infection may lead to cardiac injury secondary to conditions causing oxygen supplement insufficiency, such as severe pneumonia, anaemia, hypotension and bradycardia. Furthermore, by attacking myocardium via the highly expressed ACE2 directly, 2019-nCoV precipitated the release of cytokine and chemokine waves and caused myocardial inflammation, even leading to fulminant myocarditis in severe cases. Meanwhile, our results compiled with Guo et al., who reported that the death risk of cardiac injury was much higher than that of pre-existing CVD. Their study revealed that patients with copresence of CVD and cardiac injury registered the highest mortality rate of 69.4%, while those with only underlying CVD had a relatively favourable prognosis (mortality rate of 13.3%). Furthermore, elevated troponin was reported to be associated with a high risk of acute respiratory distress syndrome, hepatic dysfunction and acute renal injury in patients with COVID-19. The study by Shi et al. demonstrated that elevated troponin was an independent risk factor for death after adjusting other confounders. Thus, this index may be considered as a biomarker to predict the mortality risk of patients with COVID-19. More studies are warranted to confirm this finding and provide probable suggestions on the risk stratification of patients with COVID-19.

To the best of our knowledge, our study is the first systematic review and meta-analysis to investigate the association of underlying CVD and acute cardiac injury with mortality risk in patients with COVID-19. This meta-analysis may provide insights into the prognosis stratification of patients with COVID-19. However, there are some important limitations that should be mentioned. First, our meta-analysis was conducted on unadjusted ORs due to the limited data on multivariable-adjusted outcomes. The observed association of CVD and cardiac injury with mortality might be confounded by other risk factors, such as advanced age, and confounder adjustment may distort our meta-analysis results towards a less significant risk. Thus, large cohort studies with multivariate analysis are needed to provide more evidence on this issue. Second, our study could not determine the causal effects of cardiovascular comorbidities on mortality due to the inherent limitations of observational studies. Future studies aiming to investigate this causal association are warranted. Third, the heterogeneity among studies for cardiac injury was significantly high, which may be caused by the study design and patient inclusion criteria. However, the meta-regression exploring the potential sources did not find significant results, and the results remained consistent in sensitivity analyses. Finally, most of the studies enrolled were conducted in Wuhan, China. Therefore, these results should be treated with caution when extrapolated to other populations. Since Wuhan was the initial epicentre of the outbreak, these early evidence may provide clinical implications and insights for researchers and clinicians in other parts of the world.

CONCLUSION

COVID-19 patients with underlying cardiovascular comorbidities, including CVD and hypertension, may face a greater risk of fatal outcomes. Acute cardiac injury may act as a marker of in-hospital mortality risk. Given the unadjusted results of our meta-analysis, future well-designed studies with multivariate analysis are warranted to confirm these findings.

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Contributors XL and BG performed the main research. TS and MC analysed the data. WL and KBW prepared the tables and figures. XL and XG wrote the main article. TG and ZZ critically reviewed and revised the article.

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Competing interests None declared.

What is already known on this subject?
- Previous studies showed that COVID-19 patients with pre-existing cardiovascular disease (CVD) were more likely to be admitted to intensive care unit, and in-hospital cardiac injury was commonly seen in critically ill patients. However, the relationship between CVD and cardiac injury with fatal outcomes has not been fully elucidated.

What might this study add?
- In this systematic review and meta-analysis, we found that in-hospital mortality risk was significantly higher in COVID-19 patients with underlying CVD or hypertension, and patients with acute cardiac injury had a worse prognosis.

How might this impact on clinical practice?
- Among patients with COVID-19, those with established cardiovascular comorbidities and acute myocardial injury should be recognised earlier, and more aggressive treatment may be warranted. Elevated troponin may be considered as an important predictor for mortality risk.

Key messages
Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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