Acute Cardiac Injury in Coronavirus Disease 2019 and Other Viral Infections—A Systematic Review and Meta-Analysis

OBJECTIVES: Severe acute respiratory syndrome–related coronavirus-2 binds and inhibits angiotensin-converting enzyme-2. The frequency of acute cardiac injury in patients with coronavirus disease 2019 is unknown. The objective was to compare the rates of cardiac injury by angiotensin-converting enzyme-2–binding viruses from viruses that do not bind to angiotensin-converting enzyme-2.

DATA SOURCES: We performed a systematic review of coronavirus disease 2019 literature on PubMed and EMBASE.

STUDY SELECTION: We included studies with ten or more hospitalized adults with confirmed coronavirus disease 2019 or other viral pathogens that described the occurrence of acute cardiac injury. This was defined by the original publication authors or by: 1) myocardial ischemia, 2) new cardiac arrhythmia on echocardiogram, or 3) new or worsening heart failure on echocardiogram.

DATA EXTRACTION: We compared the rates of cardiac injury among patients with respiratory infections with viruses that down-regulate angiotensin-converting enzyme-2, including H1N1, H5N1, H7N9, and severe acute respiratory syndrome–related coronavirus-1, to those with respiratory infections from other influenza viruses that do not bind angiotensin-converting enzyme-2, including Influenza H3N2 and influenza B.

DATA SYNTHESIS: Of 57 studies including 34,072 patients, acute cardiac injury occurred in 50% (95% CI, 44–57%) of critically ill patients with coronavirus disease 2019. The overall risk of acute cardiac injury was 21% (95% CI, 18–26%) among hospitalized patients with coronavirus disease 2019. In comparison, 37% (95% CI, 26–49%) of critically ill patients with other respiratory viruses that bind angiotensin-converting enzyme-2 (p = 0.061) and 12% (95% CI, 7–22%) of critically ill patients with other respiratory viruses that do not bind angiotensin-converting enzyme-2 (p < 0.001) experienced a cardiac injury.

CONCLUSIONS: Acute cardiac injury may be associated with whether the virus binds angiotensin-converting enzyme-2. Acute cardiac injury occurs in half of critically ill coronavirus disease 2019 patients, but only 12% of patients infected by viruses that do not bind to angiotensin-converting enzyme-2.

KEY WORDS: cardiovascular disease; coronavirus disease 2019; severe acute respiratory syndrome–related coronavirus 2

BACKGROUND

As the coronavirus disease 2019 (COVID-19) pandemic grows, numerous randomized controlled trials (RCTs) are evaluating vaccines and novel antivirals...
to inhibit severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) directly. However, the critical illness complications of COVID-19 are caused in part by the binding (1) and inhibition (1, 2) of angiotensin-converting enzyme-2 (ACE2) by SARS-CoV-2, which increases angiotensin II. ACE2 is expressed in lung, heart, kidney, and endothelium, potentially explaining the frequent involvement of lung, cardiac, and kidney injury in COVID-19. ACE2 cleaves a terminal peptide from angiotensin II, converting it to angiotensin (1–7), a vasodilating and anti-inflammatory protein. The binding of SARS-CoV-2 to ACE2 may prevent ACE2 conversion of angiotensin II to angiotensin 1–7, leading to unopposed angiotensin II accumulation, which can be blocked by angiotensin II type 1 receptor blockers (ARBs).

Influenza A viruses, as well as the severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), also down-regulate ACE2. Upon viral ACE2 binding, its function is down-regulated in H1N1, H5N1, H7N9, and SARS-CoV-1 (3–6) leading to increased angiotensin II. Angiotensin II worsens lung injury in influenza models (3–6). Angiotensin II levels are increased in human influenza and are associated with influenza viral load, disease progression, and mortality (7). In murine H7N9 influenza lung injury, the ARB losartan decreased viral replication and lung injury (8) and attenuated lung injury in a two-hit model of lung injury induced by acid instillation and injection of SARS-CoV-1 spike protein (5). ACE2 may be even more important in COVID-19 than in SARS-CoV-1 because SARS-CoV-2 binds to ACE2 10–20 times more avidly than does SARS-CoV-1 (1).

The objectives of this article were first to synthesize the current literature and perform a meta-analysis regarding underlying cardiovascular disease and the frequency of acute cardiac injury. Second, we compared SARS-CoV-2–induced acute cardiac injury frequency with that in other respiratory viruses that do and do not bind ACE2 to determine whether acute cardiac injury is unique to SARS-CoV-2 or is a common feature of viruses that bind ACE2.

**METHODS**

We performed a systematic review of COVID-19 literature on PubMed and EMBASE. One independent reviewer searched these databases using combinations of the following terms and their associated clusters: COVID, COVID-19, 2019-nCoV, SARS-nCoV-2, cardiac injury, troponin, cardiovascular, myocardium, and cardiac. Two independent reviewers screened the articles, first by title and then by abstract. Potentially relevant studies underwent a full article evaluation and were assessed for eligibility. Articles were searched from database inception to August 29, 2020. No language restrictions were applied. When needed, we translated articles using Google translate. Other studies were identified from the references in review articles and meta-analyses.

We included cohorts with at least 10 hospitalized adults (≥ 18 yr old) with COVID-19. Acute cardiac injury was defined by the original publication authors or by 1) myocardial ischemia, 2) new cardiac arrhythmia on electrocardiogram, or 3) new or worsening heart failure on echocardiogram. Studies were required to report cardiac biomarkers (cardiac troponin) inferring cardiac injury. Critical illness was defined as ICU admission or the need for invasive mechanical ventilation. When the number of patients with acute cardiac injury who died were reported, we considered that patients who died were critically ill. Data were extracted with a standardized form and were then double entered in databases and cross-referenced to minimize data entry errors. Participant data included number of patients, basic demographics, comorbidities, number of critically ill cases, and number of cases with acute cardiac injury overall and in critically ill patients. Exclusion criteria were policy briefs, commentaries, case reports, review papers, unpublished data, research posters, and retracted articles. Manuscripts that did not undergo peer review were excluded as they were felt to have an important risk of bias. Studies of pediatric patients were also excluded.

For control patients, we defined viruses that down-regulate ACE2 including H1N1, H5N1, H7N9, and SARS-CoV-1. We compared them with other influenza viruses that do not bind ACE2, including influenza H3N2 (9) and influenza B (10–12). We systematically searched PubMed and EMBASE from database inception until August 29, 2020, using combinations of the following terms: troponin, cardiac injury, cardiovascular, myocardium, clinical characteristics, or clinical features, SARS, severe acute respiratory distress syndrome, Middle East Respiratory Syndrome, MERS,
influenza, flu, H1N1, H5N1, and H7N9. We extracted studies with similar methodology and similar inclusion criteria to the COVID-19 studies. We also identified references from review articles and meta-analyses. We compared rates of acute cardiac injury between patients with COVID-19 and patients with respiratory viral illnesses that do or do not bind ACE2. Pooled estimates for the proportion of acute cardiac injury within each virus group and comparison of rates between groups were obtained using random-effects (REs) meta-analysis based on the generalized linear mixed effects model framework.

Pooled estimates for the proportion of acute cardiac injury within each virus group and comparison of rates between groups were obtained using REs meta-analysis based on a random intercept logistic regression model with logit link (13, 14) and covariate being virus group. Analyses were performed within critically ill patients and then repeated for the overall population (critically ill and noncritically ill combined). Pairwise comparisons between virus groups were done by testing the appropriate regression coefficient using Wald-type test from the estimated model, and omnibus test for group of viruses (i.e., test for the null hypothesis for all viruses being the same) was based on an F-distribution. Meta-analysis was performed using the meta package in R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). The risk of bias in each study was determined by a validated assessment tool that was adapted for this project (15). A detailed assessment regarding the risk of bias for all included studies is available in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/G255), Supplemental Table 2 (Supplemental Digital Content 2, http://links.lww.com/CCM/G256), and Supplemental Table 3 (Supplemental Digital Content 3, http://links.lww.com/CCM/G257).

Included Publications—Other Respiratory Viruses

We identified 1,422 articles based on screening abstracts and titles, after which 319 full-text articles were reviewed. For viruses that bind or do not bind ACE2, 23 studies and nine studies met the specified inclusion criteria, respectively (Fig. 1B).

Presence of Comorbidities in COVID-19

Patients (n = 34,072) in the included publications were hospitalized, 33% had hypertension, 18% diabetes, 10% cardiovascular disease, and 6% chronic kidney disease (Supplemental Table 4, Supplemental Digital Content 4, http://links.lww.com/CCM/G258). Of studies who reported critical illness, 18% of patients (n = 6,202) were critically ill.

Acute Cardiac Injury in COVID-19

The pooled rate of acute cardiac injury among critically ill COVID-19 patients based on meta-analysis was 50% (95% CI, 44–57%), and it was 21% (95% CI, 18–26%) for the overall population of patients with COVID-19 (Supplemental Fig. 1, Supplemental Digital Content 5, http://links.lww.com/CCM/G259; legend, Supplemental Digital Content 7, http://links.lww.com/CCM/G261). Visual inspection of the funnel plot revealed no publication bias which was confirmed by the Begg rank correlation test. Statistical heterogeneity was assessed by I² and Cochran’s Q test.

RESULTS

Included Publications—COVID-19

After screening abstracts and titles, 949 publications were identified, and the full texts of 292 articles were ultimately reviewed, including articles published in languages other than English (Fig. 1A). Duplicate studies were removed. A total of 57 publications cohorts met inclusion criteria. We acknowledge that there may be some overlap in reported cases, that is, the same patients reported in multiple articles (16). The risk of bias was felt to be low for most included studies, particularly those regarding COVID-19. A detailed assessment regarding the risk of bias for all included studies is available in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/G255), Supplemental Table 2 (Supplemental Digital Content 2, http://links.lww.com/CCM/G256), and Supplemental Table 3 (Supplemental Digital Content 3, http://links.lww.com/CCM/G257).
p < 0.001 for both) and had fewer cardiac injury results (Table 1). In publications regarding critically ill patients with infections by respiratory viruses for which ACE2 plays a central role (H1N1 [17], severe acute respiratory syndrome [SARS] [5] and H7N9 [8]), the raw rates of acute cardiac injury in critically ill patients were 53%, 30%, and 49% respectively, for meta-analysis, a pooled frequency of 37% (95% CI: 26%, 49%), not significantly different from COVID-19 (p = 0.061) (Supplemental Fig. 1, Supplemental Digital Content 5, http://links.lww.com/CCM/G259; legend, Supplemental Digital Content 7, http://links.lww.com/CCM/G261). The pooled cardiac injury rates for H1N1, SARS, and H7N9 were 39% (95% CI, 25–55%), 27% (95% CI, 12–51%), and 40% (95% CI, 19–65%), respectively, for critically ill and 28% (95% CI, 15–47%), 13% (95% CI, 2–47%), and 32% (95% CI, 16–55%) for overall. These rates were not significantly different from each other (omnibus test p = 0.65 and 0.51 for critically ill and overall, respectively) nor significantly different from COVID-19 (omnibus test p = 0.48 and 0.17 for critically ill and overall, respectively).

Visual inspection of the funnel plot again revealed no publication bias nor did the Begg test (Supplemental Fig. 2, Supplemental Digital Content 6, http://links.lww.com/CCM/G260; legend, Supplemental Digital Content 7, http://links.lww.com/CCM/G261).

Acute Cardiac Injury in Viruses That Do Not Bind to ACE2

Publications regarding other respiratory viruses that do not bind to ACE2 were smaller and were also heterogeneous (Table 2) (I²: 90.8% and 98.4% for critically ill and overall, respectively; p < 0.001 for both). The meta-analysis pooled rate of acute cardiac injury among critically ill patients was 12% (95% CI, 7–22%), significantly lower than for COVID-19 (p < 0.001) and other respiratory viruses that bind to ACE2 (p = 0.001) (Supplemental Fig. 1, Supplemental Digital Content 5, http://links.lww.com/CCM/G259; legend, Supplemental Digital Content 7, http://links.lww.com/CCM/G261). There were too few studies for viruses that do not bind ACE2 to create a funnel plot.

For the overall populations, there were no statistically significant differences in acute cardiac injury rates between groups: COVID-19 versus viruses that bind ACE2 p value equals to 0.44; COVID-19 versus viruses that do not bind ACE2 p equals to 0.077; viruses that bind ACE2 versus viruses that do not bind ACE2 p value equals to 0.054.

DISCUSSION

We found that the risk of acute cardiac injury was high in COVID-19 (50% of critically ill patients, 21% of the overall population of the included studies) as well as
TABLE 1. Acute Cardiac Injury in Cohorts of Hospitalized Patients Who Had Respiratory Viral Infection With Viruses That Bind Angiotensin-Converting Enzyme 2 as Receptor

<table>
<thead>
<tr>
<th>Virus Type</th>
<th>References</th>
<th>n, Total</th>
<th>n, Critically III</th>
<th>Frequency of Cardiac Injury, n (% of Critically III)</th>
<th>Frequency of Cardiac Injury Overall, n (% of overall)</th>
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<tr>
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<td></td>
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<td>84</td>
<td>84</td>
<td>37 (44)</td>
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<tr>
<td></td>
<td>Nin et al (25)</td>
<td>96</td>
<td>96</td>
<td>22/49 (45)</td>
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<td>585</td>
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<td>12 (2)</td>
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<td>3 (10)</td>
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<td></td>
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<td>37</td>
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<td>24 (9)</td>
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<td>H1N1 subtotals that evaluated cardiac injury</td>
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<td>1,876</td>
<td>1,059</td>
<td>520 (53)</td>
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<td>SARS</td>
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<td></td>
<td>Chen et al (43)</td>
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<td>8</td>
<td>5 (63)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>H7N9 subtotals that evaluated acute cardiac injury</td>
<td></td>
<td>853</td>
<td>485</td>
<td>236 (49)</td>
<td>270 (44)</td>
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<td></td>
<td>2,988</td>
<td>1,682</td>
<td>798 (50)</td>
<td>869 (32)</td>
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SARS = severe acute respiratory syndrome.
in respiratory infections caused by viruses that also bind ACE2. The pooled acute cardiac injury rates were 39%, 27%, and 40% in critically ill patients with H1N1, SARS, and H7N9 infections, respectively, for a combined pooled frequency of 37%. In contrast, for respiratory viruses that do not bind ACE2, the rate of acute cardiac injury among critically ill patients was significantly lower (12%) than in COVID-19 and other respiratory viruses that bind ACE2.

The novel features of our study are that we tested a sound biological hypothesis focused on ACE2 binding, by comparing SARS-CoV-2 with other respiratory viruses that do or do not bind ACE2, and found that the rates of acute cardiac injury align with viral ACE2 binding.

We found that about 10% and 33% of COVID-19 patients had underlying cardiovascular disease or hypertension respectively. Patients with underlying cardiovascular disease have a higher risk of acute cardiac injury (18) in part because patients with heart failure have increased ACE2 expression in the heart (19) and that could increase direct SARS-CoV-2 myocardial injury.

The mechanisms of the increased rate of acute cardiac injury in COVID-19 and in other viruses that bind ACE2 are not determined but could include virus binding (1) and inhibiting ACE2 (2), which likely increases serum levels of angiotensin II. Angiotensin II is a potent vasoconstrictor that could limit coronary blood flow, accounting in part for frequent signs of myocardial ischemia in COVID-19 as suggested by increased troponin levels. Another mechanism of acute cardiac injury is direct viral infection of endothelial cells (20) and cardiomyocytes. There are case reports of myocardial ischemia with open coronary arteries in COVID-19 (21) indicating excessive coronary artery vasoconstriction as another plausible mechanism of acute cardiac injury in COVID-19; this phenomenon could be due to excessive angiotensin II. Finally, there are reports of arterial and venous thrombosis (31% frequency in one study) (22), pulmonary emboli (22), and elevated D-dimers (23). These thromboembolic events may present as acute cardiovascular collapse that has therapeutic implications. There are ongoing RCTs evaluating therapeutic anticoagulation in COVID-19 for this reason (e.g., NCT04372589).

There are several larger implications of our findings. First, the high rate of acute cardiac injury could be a class effect of viruses that bind ACE2 because we found similarly high rates of acute cardiac injury in patients with COVID-19 and patients infected with ACE2-binding viruses. Our results must be interpreted in the context of our study’s characteristics. Some limitations of our

### TABLE 2.
Acute Cardiac Injury in Cohorts of Hospitalized Patients Who Had Respiratory Viral Infection That Do Not Bind Angiotensin-Converting Enzyme 2 as Receptor

<table>
<thead>
<tr>
<th>References</th>
<th>n, Overall</th>
<th>n, Critically III</th>
<th>Frequency of Cardiac Injury, n (% of Critically III)</th>
<th>Frequency of Cardiac Injury Overall, n (% of Overall)</th>
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<td>264</td>
<td>97</td>
<td>26 (27)</td>
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<td>336</td>
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<td>17 (5)</td>
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<td>3 (16)</td>
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<td>9,046 (11)</td>
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<td>583</td>
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<td>83,279</td>
<td>16,978</td>
<td>2,952 (17)</td>
<td>9,432 (11)</td>
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</table>
study include that acute cardiac injury does not have a standard definition in the literature, so we applied our definition to achieve consistency in our reviews. We only included studies of hospitalized patients, which limits the generalizability of our results. There was no severity-matching of viruses that do or do not bind ACE2 with the COVID-19 studies, which would be a concern if the COVID-19 patients were sicker. We were unable to address potential overlap of patients, which has been raised as a concern regarding COVID-19 scientific reports (16).

Nonetheless, we included all publications that met our inclusion criteria. Although included studies are at risk of bias due to their observational nature, the overall risk of bias was felt to be low, particularly among COVID-19 studies.

In conclusion, cardiovascular conditions are common comorbidities in COVID-19, increasing risk of acute cardiac injury and death. Acute cardiac injury may be associated with ACE2-binding viruses such as SARS-CoV-2. Strategies to identify and mitigate this complication are warranted.

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REFERENCES


