Association of Arrhythmia and Acute Cardiac Injury with COVID-19 Severity

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ABSTRACT

Background: Our study evaluates the published literature of the overall contribution of COVID-19 in the occurrence cardiac arrhythmia and acute cardiac injury in addition to their relation to COVID-19 severity.

Methods: The international web databases, including PubMed, Science Direct, and Scopus, were electronically searched between January 1, 2020, and August 18, 2020, to identify studies describing subjects with cardiac complications in COVID-19 infection in particular arrhythmia and acute cardiac injury. Studies that provided adequate details on cardiac arrhythmia and acute cardiac injury as outcomes complication in positivity diagnosed COVID-19 were included. The Joanna Briggs Institute (JBI) critical appraisal checklist for case series to assess the risk of bias. Random-effect models were used to estimate the pooled event rates of arrhythmia and acute cardiac injury.

Results: Relevant data regarding the event rate of cardiac manifestations particularly arrhythmia and acute cardiac injury in 4,355 patients with COVID-19 were collected from 13 studies. The pooled prevalence of arrhythmia as a complication of COVID-19 was 19% (95% CI: 12% to 29%), while the pooled prevalence of acute cardiac injury as a complication of COVID-19 was 9% (95% CI: 5% to 18%). Arrhythmia was found to increase the severity of COVID-19 about ten-folds significantly. In contrast, acute cardiac injury significantly increased the severity of COVID-19 with nearly 15-folds. No significant publication bias was indicated by either the visual symmetry or the Egger’s test.

Conclusion: In conclusion, cardiac arrhythmias and acute cardiac injury are highly associated with the severity and the mortality rate of COVID-19.

Keywords: Arrhythmia; Acute cardiac injury; COVID-19

Introduction

The indefatigable COVID-19 pandemic performs a significant public health threat to all populations worldwide (Alzoughool F and Alanagreh L, 2020; Alanagreh L, et al., 2020). As of February 02, 2021, the epidemic infected approximately 109 million people, including nearly 2.4 million patients who have died. Unluckily, the numbers keep increasing globally, indicating that the peak is far from near and putting the universal community on alert that the worst scenario is possible.

Cardiac manifestations in COVID patients including arrhythmia and acute cardiac injury have been reported in many case series (Hu L, et al., 2020; Mehrsa MR, et al., 2020; Si D, et al., 2020). Epidemiological studies have reported different mortality rates for COVID-19 patients with cardiac manifestations (Mishra AK, et al., 2020). Nevertheless, to what extend cardiac manifestations increase the risk of COVID-19 severity and fatality is unknown and should be investigated.

Arrhythmias can be triggered by myocardial dysfunction that results from severe systematic inflammation, severe inflammation conditions like sepsis and septic shock were reported to associate with several types of cardiac arrhythmias (Okazaki R, et al., 2019; Court O, et al., 2013; Huang C, et al., 2020). Several studies reported that most of the above inflammatory cytokines are associated with deadly arrhythmias (Sada EF, et al., 2017; Guo Y, et al., 2012). Although, a number of case series studies have reported the occurrence of arrhythmia as a cardiac manifestation of COVID-19 (Zhang J, et al., 2020; Lei S, et al., 2020; Goyal P, et al., 2020), however, to the best of our knowledge, no meta-analysis has quantified the pooled event rate of arrhythmia in COVID-19 patients and its association with disease severity.

COVID-19 can induce acute cardiac injury by several suggested pathways, including the myocarditis caused by the cytokine storm that mediated through the T cells and monocytes (Zhou Y, et al., 2020), the cardiac myocytes damage caused by hypoxemia and respiratory failure (Kubasiak LA, et al., 2002), and inhibition of the protective signalling pathways in cardiac myocyte as a result of the down regulation the expression of Angiotensin-converting enzyme 2 (ACE2), besides the induce of the hypercoagulability and micro vascular thrombosis (Han H, et al., 2020). Observational studies have studies the relationship between acute cardiac injury and COVID-19 disease outcome (Hu L, et al., 2020; Lei S, et al., 2020).

Evaluating the overall contribution of cardiac manifestations to COVID-19 severity is important to improve treatment protocols. Therefore, the present meta-analysis study was performed to evaluate the association of both cardiac arrhythmia and acute cardiac injury with the severity of COVID-19 in patients.

Methods

Data search

The international web databases, including PubMed, Science Direct, and Scopus, were searched between January 1, 2020, and August 18, 2020. Several combined keywords were used for searching the databases including cardiac arrhythmias and COVID-19; arrhythmia and SAR-CoV-2; acute cardiac injury and SAR-CoV-2; and COVID-19. Besides, the lists of referenc-
es of all relevant studies were also manually checked to identify further studies. The protocol for this meta-analysis is registered at PROSPERO CRD42020191768. The meta-analysis was also conducted following the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) (Stroup DF, et al., 2000).

**Study selection**

Studies that provided adequate details on cardiac arrhythmia and acute cardiac injury as outcomes complication in positively diagnosed COVID-19 were included. Case reports, review articles, and editorials were excluded from this analysis. Studies that did not provide enough details on the number of cases with severe or fatal outcomes were excluded. The selection of the studies was limited to articles in English language.

**Data abstraction**

For studies that met the inclusion criteria, the following data were extracted from each one using a standardized form: the surname of the first author; the design of the study; ratios of clinical characteristics of interest; sample size, country, data relevant to arrhythmia and acute cardiac injury as an outcome, and the number of cases with severe and non-severe outcomes, and the number of survivors and non-survivors. The severity of the disease validation, as reported in the included studies, was identified if patients needed to be admitted to the intensive care unit, needed vital life support, or required mechanical ventilation. Two investigators (FA and MA) extracted the relevant data.

**Quality assessment**

The Joanna Briggs Institute (JBI) critical appraisal checklist for case series was used to assess the internal validity and the risk of bias (Munn Z, et al., 2019). The 10 items in JBI checklist deals with issues related to confounding, selection, and information bias to assess the internal validity of the case series. We presented the results of the quality assessment of the included studies in a table and not as a score (Munn Z, et al., 2019). The quality assessment of the included studies in this meta-analysis was carried out by SA.

**Quantitative data synthesis and analysis**

Data analysis was performed using Comprehensive Meta-Analysis V2 (Biostat, USA). A p-value of < 0.05 was considered statistically significant. The pooled event rates of pre-existing cardiovascular disease comorbidities as well as the Odds Ratio (OR) with 95% confidence intervals (95% CI) of disease severity and mortality associated with the exposures of interest were estimated using a random-effect model. Heterogeneity in any analysis was tested by using the I2 statistic (p-value of < 0.1), which estimates the percentage of variation in study results that is explained by between-study heterogeneity rather than sampling error. Usually, an I2 value > 50% indicates considerable heterogeneity (Higgins JP and Thompson SG, 2002). To assess the presence of publication bias, we used funnel plots as well as the Egger’s test.

**RESULTS**

**Search results and study characteristics**

A total of 650 articles were identified from the three examined databases examined. After excluding duplicated or overlapping articles and removing reviews and editorials, 36 articles met the primary searched criteria. For the quantitative part of our study, eight studies were included in the meta-analysis that reported arrhythmia as disease complications. On the other hand, ten studies were included in this meta-analysis that reported acute cardiac injury as disease complications (Figure 1). Studies were conducted mainly in China (n=9) and the United States of America (n=4).

**The proportions of cardiac manifestations in COVID-19 patients.**

Relevant data regarding the event rate of cardiac manifestations particularly arrhythmia and acute cardiac injury in 4,355 patients with COVID-19 were collected from 13 studies; eight studies reported arrhythmia and ten of them reported acute cardiac injury. The pooled prevalence of arrhythmia as a complication of COVID-19 among the 8 included studies (Table 1) was 19% (95%CI: 12% to 29%), as shown in Figure 2. Moreover, the pooled prevalence of acute cardiac injury as a complication of COVID-19 among the 10 included studies (Table 2) was 9% (95%CI: 5% to 18%), as shown in Figure 3.

**Arrhythmia and the risk of severity outcomes in COVID-19**

Relevant data regarding the association of arrhythmia with severity in 4,355 patients with COVID-19 were collected from five included studies. The OR of arrhythmia in severe compared to non-severe cases of COVID-19 was significantly higher (OR=9.9, 95% CI: 4.8 to 20.4), which means that arrhythmia increases the severity of COVID-19 about ten folds as shown in Figure 4.

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**Figure 1: Flow chart of the literature search and study selection**
Table 1: Arrhythmia outcomes complication in COVID-19 patients

<table>
<thead>
<tr>
<th>Study’s Author</th>
<th>Country</th>
<th>Condition</th>
<th>Sample size</th>
<th>Events (n)</th>
<th>Non-events (n)</th>
<th>Severe cases ratio</th>
<th>Non-sever cases ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang G, et al. [22]</td>
<td>China</td>
<td>Arrhythmia</td>
<td>221</td>
<td>24</td>
<td>197</td>
<td>22/55</td>
<td>2/166</td>
</tr>
<tr>
<td>Hu L, et al. [3]</td>
<td>USA</td>
<td>Arrhythmia</td>
<td>323</td>
<td>98</td>
<td>225</td>
<td>80/172</td>
<td>18/151</td>
</tr>
<tr>
<td>Du Y, et al. [23]</td>
<td>China</td>
<td>Arrhythmia</td>
<td>85</td>
<td>51</td>
<td>34</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rosenberg E, et al. [24]</td>
<td>USA</td>
<td>Arrhythmia</td>
<td>1438</td>
<td>240</td>
<td>1198</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Enzmann M, et al. [25]</td>
<td>USA</td>
<td>Arrhythmia</td>
<td>150</td>
<td>14</td>
<td>136</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 2: Pooled event rate of arrhythmia as a complication in patients with COVID-19

Table 2: Acute cardiac injury outcomes complication in COVID-19 patients

<table>
<thead>
<tr>
<th>Study’s Author</th>
<th>Country</th>
<th>Condition</th>
<th>Sample size</th>
<th>Events (n)</th>
<th>Non-events (n)</th>
<th>Severe cases ratio</th>
<th>Non-sever cases ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang G, et al. [22]</td>
<td>China</td>
<td>Acute Cardiac injury</td>
<td>221</td>
<td>17</td>
<td>204</td>
<td>16/55</td>
<td>1/166</td>
</tr>
<tr>
<td>Hu L, et al. [3]</td>
<td>USA</td>
<td>Acute Cardiac injury</td>
<td>323</td>
<td>24</td>
<td>299</td>
<td>22/172</td>
<td>2/151</td>
</tr>
<tr>
<td>Du Y, et al. [23]</td>
<td>China</td>
<td>Acute cardiac injury</td>
<td>85</td>
<td>38</td>
<td>47</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lei S, et al. [13]</td>
<td>China</td>
<td>Acute cardiac injury</td>
<td>34</td>
<td>5</td>
<td>29</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Huang C, et al. [9]</td>
<td>China</td>
<td>Acute cardiac injury</td>
<td>41</td>
<td>5</td>
<td>36</td>
<td>Apr-13</td>
<td>Jan-28</td>
</tr>
<tr>
<td>Wan S, et al. [25]</td>
<td>China</td>
<td>Acute cardiac injury</td>
<td>135</td>
<td>10</td>
<td>125</td>
<td>Feb-40</td>
<td>Aug-95</td>
</tr>
<tr>
<td>Zhou F, et al. [26]</td>
<td>China</td>
<td>Acute Cardiac injury</td>
<td>191</td>
<td>33</td>
<td>158</td>
<td>32/54</td>
<td>1/137</td>
</tr>
<tr>
<td>Wang D, et al. [27]</td>
<td>China</td>
<td>Acute Cardiac injury</td>
<td>107</td>
<td>12</td>
<td>95</td>
<td>Aug-19</td>
<td>Apr-88</td>
</tr>
</tbody>
</table>
Acute cardiac injury and the risk of severity outcomes in COVID-19

Relevant data regarding the association of acute cardiac injury severity rate in patients with COVID-19 were collected from six studies. The OR of acute cardiac injury in severe compared to non-severe cases of COVID-19 was significantly higher with nearly 15-fold risk of poor outcomes (OR=14.6, 95% CI: 2.9 to 73.7) as it is shown in Figure 5.

Quality of the included studies

Supplementary (Table S1) summarizes the quality assessment of the included studies. All included studies in this analysis clearly reported the demographic and the clinical characteristics as well as the outcomes of the participants. However, most of the studies did not have defined participants’ eligibility criteria. In addition, it was unclear whether most of the studies had consecutive inclusion of the participants and whether it was a complete inclusion. The majority of the studies diagnosed COVID-19 disease and outcome of interests using valid and reliable methods and used appropriate statistical analysis.

Assessment of publication bias

As shown in Figures 6 and 7 that evaluate publication bias using a funnel plot based on the event rate of arrhythmia and acute cardiac injury outcomes, a visual symmetry indicates the absence of publication bias. Also, the Egger’s test revealed no significant publication bias (Egger’s test: p=0.5124, and 0.30009 respectively).

DISCUSSION

In the present meta-analysis, we examined 18 independent studies, eight of these studies were included in the meta-analysis that reported arrhythmia as disease complications and ten studies were included in this meta-analysis that reported acute cardiac injury as disease complications. The pooled studies reporting clinical data on 4,355 patients with COVID-19 worldwide. Our results add values to the literature as it summarized the prevalence of arrhythmia and acute cardiac injury as a disease outcome among COVID-19 patients.

Arrhythmias are well known to occur in COVID-19. Our result indicates that the incidence of arrhythmia occurrence in COVID-19 patients was 19% compared to a study describing the outcomes in 138 Chinese patients with COVID-19 reported 16.7% incidence of arrhythmia (Wang D, et al., 2020). For the acute cardiac injury, a meta-analysis of the Chinese studies (Li B, et al., 2020) reported an 8% incidence of acute cardiac injury, while our study indicates a 9% incidence of acute cardiac injury. Our study included more studies and thus larger sample size from different countries compared to the previous meta-analysis. Hence, our pooled analysis is the most comprehensive and updated analysis. Severe systemic inflammation associated with COVID-19 can trigger myocardial dysfunction, which leads to arrhythmia (Okazaki R, et al., 2009; Court O, et al., 2003). Many evidence reported that the pro-inflammatory cytokines are associated with arrhythmia (Guo Y, et al., 2012; van den OJA, et al., 2014). Several studies have suggested the
### Figure 5: Forest plot of the odd ratios of acute cardiac injury in severe compared to non-severe COVID-19 cases

<table>
<thead>
<tr>
<th>Study name</th>
<th>Outcome</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu L</td>
<td>severe vs. nonsevere ACI as outcome</td>
<td>10.9</td>
<td>2.3</td>
<td>47.3</td>
<td>3.199</td>
<td>0.001380294</td>
</tr>
<tr>
<td>Huang C</td>
<td>severe vs. nonsevere ACI as outcome</td>
<td>12.0</td>
<td>1.2</td>
<td>121.5</td>
<td>2.102</td>
<td>0.033709386</td>
</tr>
<tr>
<td>Wan S</td>
<td>severe vs. nonsevere ACI as outcome</td>
<td>0.6</td>
<td>0.1</td>
<td>5.8</td>
<td>0.685</td>
<td>0.49317351</td>
</tr>
<tr>
<td>Wang D 1</td>
<td>severe vs. nonsevere ACI as outcome</td>
<td>14.3</td>
<td>2.9</td>
<td>71.3</td>
<td>3.247</td>
<td>0.001669896</td>
</tr>
<tr>
<td>Zheng B</td>
<td>severe vs. nonsevere ACI as outcome</td>
<td>67.7</td>
<td>5.7</td>
<td>520.9</td>
<td>4.029</td>
<td>0.000013507</td>
</tr>
<tr>
<td>Zhou F</td>
<td>non-survivors vs. survivors ACI as outcome</td>
<td>997.8</td>
<td>257.7</td>
<td>11224</td>
<td>6.078</td>
<td>0.000003481</td>
</tr>
</tbody>
</table>

Relative weight

No significant publication of bias (Egger’s test: p=0.5124)

### Figure 6: Funnel plot for publication bias based on arrhythmia

### Figure 7: Funnel plot for publication bias based on acute cardiac injury
COVID-19, as a viral infection, can trigger a hyper-inflammatory state with a fatal storm of cytokine and arrhythmogenic potential. Interleukin 1 (IL-1), interleukin 2 (IL-2), interleukin 1 β (IL-1 β), IL-7, granulocyte colony-stimulating factor (G-CSF), interferon-γ, inducible protein 10, monocyte chemoattractant protein 1 (mcp1), and tumor necrosis factor-α (TNF-α) are cytokines reported to increase in COVID-19 patients One of the possible mechanisms of triggering arrhythmia by systematic inflammation is via inducing ischemic heart disease, where many are inflammatory markers shown increased locally at the site of ischemia such as; IL-6 (Maier W, et al., 2005) and TNF-a (Satoh M, et al., 2008). Arrhythmias can also be triggered by myocardial dysfunction that results from severe systematic inflammation, severe inflammation conditions like sepsis and septic shock were reported to associate with several types of cardiac arrhythmias (Okazaki R, et al., 2009; Court O, et al., 2009). Another important indirect potential pathway of how systematic inflammation induces arrhythmia is via the activation of systematic coagulation response. Even though there are not fully established clinical setting proved the association between systemic inflammation and cardiac arrhythmias, several studies shed light on the potential association between atrial fibrillation with systematic inflammation due to its high incidence (Guo Y, et al., 2012; Liew R, et al., 2013; Kenan Y, et al., 2013). Unfortunately, the studies did not report enough information on the blood levels of various pro-inflammatory cytokines nor on type of drugs used in COVID-19 patients. More studies are needed to investigate the main cause of arrhythmia in COVID-19 patients.

Our meta-analysis is the first to report that the incidence of arrhythmia was associated with 10 folds’ increase in disease severity. Our result means that patients with more severe systemic disease as evidenced by ICU admission also had a higher probability of promoting cardiac arrhythmias. Therefore, clinical protocols should pay attention to prevention and management of arrhythmia in COVID-19 patients. Future studies should investigate whether arrhythmia management in COVID-19 patients reduce disease severity.

The most common cardiovascular disease complication is the acute cardiac injury; our result reported that acute cardiac injury incidence was 14 folds higher in patients with severe complication compared to non-severe patients. Early cardiac interventional protocols in COVID-19 patients may aid in reducing the disease severity and mortality. The myocarditis caused by the cytokine storm, the cardiac myocytes damage, inhibition of the protective signalling pathways in cardiac myocyte, in addition, to increase the hypercoagulability and micro vascular thrombosis; all are suggested mechanism of induced the acute cardiac injury among COVID-19 patients. Future studies should look at risk factors for developing cardiac injury in COVID-19 patients.

Our study rigorously analysed the number of patients with arrhythmia outcomes, and acute cardiac injury outcome collected from a large sample of patients with COVID-19, advantageous, a visual symmetry indicates the absence of publication bias. Most studies did not report the eligibility criteria and whether participants were recruited consecutively. Therefore, selection bias is likely a concern in the included studies. Other biases in the included studies are less likely since all studies addresses sufficiently other points in the JBI tool.


