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Complications of COVID-19: Correlation between Arrhythmia, Acute Cardiac Injury and COVID-19 Severity

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Abstract:

Occurrence of cardiac arrhythmias in COVID-19 patients with myocardial injuries is common, and it is potentially a life-threatening complication. The current study presents the published literature on cardiac arrhythmia occurrence in COVID-19 patients during 2020. We aimed to evaluate the association among cardiac arrhythmias, acute cardiac injury, and disease severity. Databases, including PubMed, Science Direct, and Scopus, were searched to find studies describing subjects with cardiac arrhythmias and COVID-19. In this study, we recruited 4,355 patients with COVID-19, collected from 13 studies. Relevant data were manually extracted and compared among two groups: arrhythmia as a complication of COVID-19 and cardiac injury as a complication of COVID-19. The pooled prevalence of cardiac arrhythmia was 19% (95%CI: 12% to 29%), compared to 9% (95%CI: 5% to 18%) in acute cardiac injury. Compared to patients without arrhythmias, the probability of developing severe symptoms was increased by ten folds in patients with arrhythmias. In addition, acute cardiac injury significantly increased the severity of COVID-19 by nearly 15-folds. No significant publication bias was indicated by either the visual symmetry or the Egger's test. In conclusion, the incidence of cardiac arrhythmias and acute cardiac injury is highly associated with the severity and the mortality rate of COVID-19.

Keywords: COVID-19, Arrhythmia, Acute cardiac injury

1. Background

The ongoing COVID-19 pandemic poses a significant threat to the health care systems around the globe [1, 2]. As of February 2nd, 2022, the epidemic infected approximately 382,296,709 million people, including nearly 5,706,691 million patients who have died. And the numbers keep increasing globally, indicating that the pandemic is far from the end.

Cardiac manifestations in COVID-19 patients, including arrhythmia and acute cardiac injury, have been reported since the pandemic's beginning [3-5, 37, 38]. Epidemiological studies have reported different mortality rates for COVID-19 patients with cardiac manifestations [6].

Arrhythmias can be triggered by myocardial dysfunction that results from severe systematic inflammation. Severe inflammation conditions like sepsis and septic shock were associated with several types of cardiac arrhythmias [7, 8, 9][9]. Several studies reported that most inflammatory cytokines are associated with deadly arrhythmias [10, 11]. Although many case series studies have reported the occurrence of arrhythmia as a cardiac manifestation of COVID-19 [12-14], fewer meta-analyses have quantified arrhythmia's pooled event rate in COVID-19 patients and its association with disease severity.

COVID-19 can induce acute cardiac injury through several suggested pathways: myocarditis which is caused by the cytokine storm mediated through the T cells and monocytes [15], the cardiac myocytes damage which is caused by hypoxemia and respiratory failure and the inhibition of the protective signaling pathways in cardiac myocytes as a result of the downregulation of Angiotensin-converting enzyme 2 (ACE2) expression [17].

Evaluating the contribution of cardiac manifestations to COVID-19 severity is essential 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.

2. Methods:

2.1. Data search

The international web databases, including PubMed, Science Direct, and Scopus, were searched between

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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 references 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) [18].

2.2. Study selection

Studies that provided adequate details on cardiac arrhythmia and acute cardiac injury as outcomes complications 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 the English language.

2.3. 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, the number of cases with severe and non-severe outcomes, and the number of survivors and non-survivors

As reported in the included studies, the severity of the disease validation 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,

2.4. Quality assessment

The Joanna Briggs Institute (JBI) critical appraisal checklist for the case series was used to assess the internal validity and the risk of bias [19]. The ten items in the JBI checklist deals with issues related to confounding, selection, and information bias to assess the internal validity of the case series. We presented the quality assessment results of the included studies in a table and not as a score [19]. SA carried out the quality assessment of the included studies in this meta-analysis.

2.5. 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 and 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 using the I2 statistic (p-value of <0.1), which estimates the percentage of variation in study results explained by between-study heterogeneity rather than sampling error. Usually, an I2 value >50% indicates considerable heterogeneity [20]. To assess the presence of publication bias, we used funnel plots as well as Egger's test.

3. Results

3.1. 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).

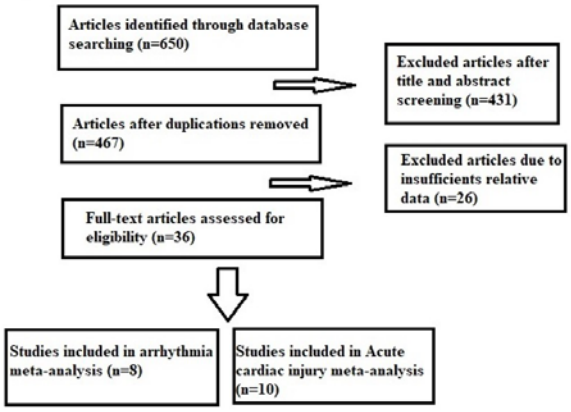

Figure 1. Flow chart of the literature search and study selection

3.2. 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 eight 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 ten included studies (Table 2) was 9% (95%CI: 5% to 18%), as shown in figure 3.

Table 1. Arrhythmia outcomes complication in COVID-19 patients.

Study's Author	Country	Condition	Sample size	Events (n)	Non-events (n)	Severe cases ratio	Non-sever cases ratio
Wang D, et al [21]	China	Arrhythmia	138	23	115	16/36	7/102
Goyal P, et al [14]	USA	Arrhythmia	393	29	364	24/130	5/263
Zhang G, et al [22]	China	Arrhythmia	221	24	197	22/55	2/166
Hu L, et al [3]	USA	Arrhythmia	323	98	225	80/172	18/151
Du Y, et al [23]	China	Arrhythmia	85	51	34		
Rosenberg E, et al [24]	USA	Arrhythmia	1438	240	1198		
Lei S, et al [13]	China	Arrhythmia	34	8	26	5/15	3/19
Enzmann M, et al [25]	USA	Arrhythmia	150	14	136		

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

Study's Author	Country	Condition	Sample size	Events (n)	Non-events (n)	Severe cases ratio	Non-sever cases ratio
Wang D, et al [21]	China	Acute cardiac injury	138	10	128	8/36	2/102
Zhang G, et al [22]	China	Acute Cardiac injury	221	17	204	16/55	1/166
Hu L, et al [3]	USA	Acute Cardiac injury	323	24	299	22/172	2/151
Du Y, et al [23]	China	Acute cardiac injury	85	38	47		
Lei S, et al [13]	China	Acute cardiac injury	34	5	29		
Guan W, et al [26]	China	Acute cardiac injury	1099	6	1093	5/926	1/962
Huang C, et al [9]	China	Acute cardiac injury	41	5	36	4/13	1/28
Wan S, et al [27]	China	Acute cardiac injury	135	10	125	2/40	8/95
Zhou F, et al [28]	China	Acute Cardiac injury	191	33	158	32/54	1/137
Wang D, et al [29]	China	Acute Cardiac injury	107	12	95	8/19	4/88

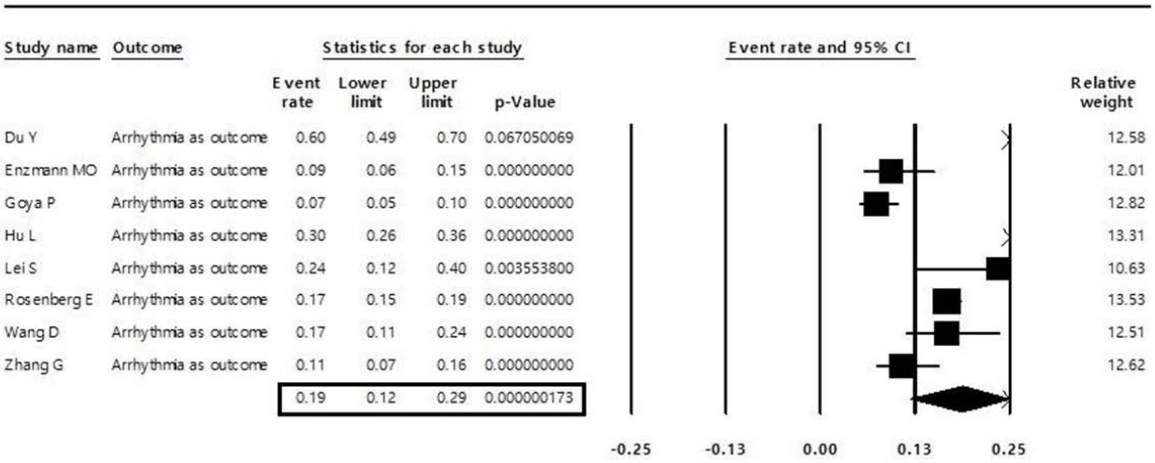

Figure 2: Pooled event rate of arrhythmia as a complication in patients with COVID-19.

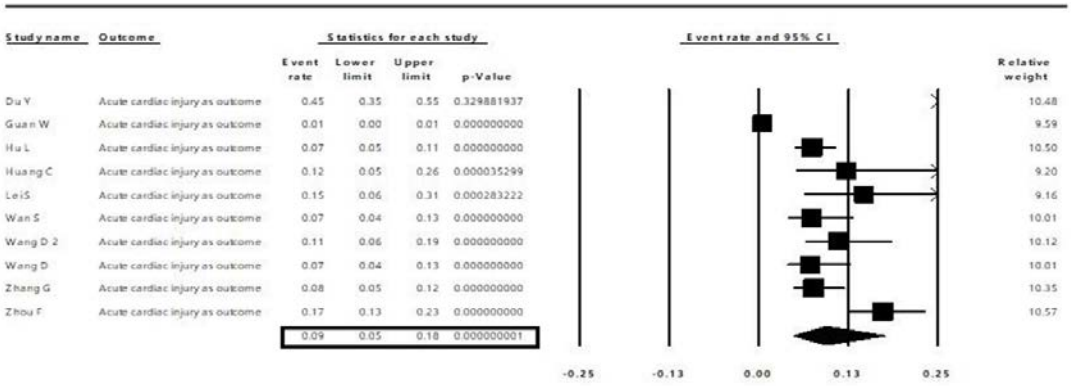

Figure 3: Pooled event rate of acute cardiac injury as a complication in patients with COVID-19.

3.3. 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.

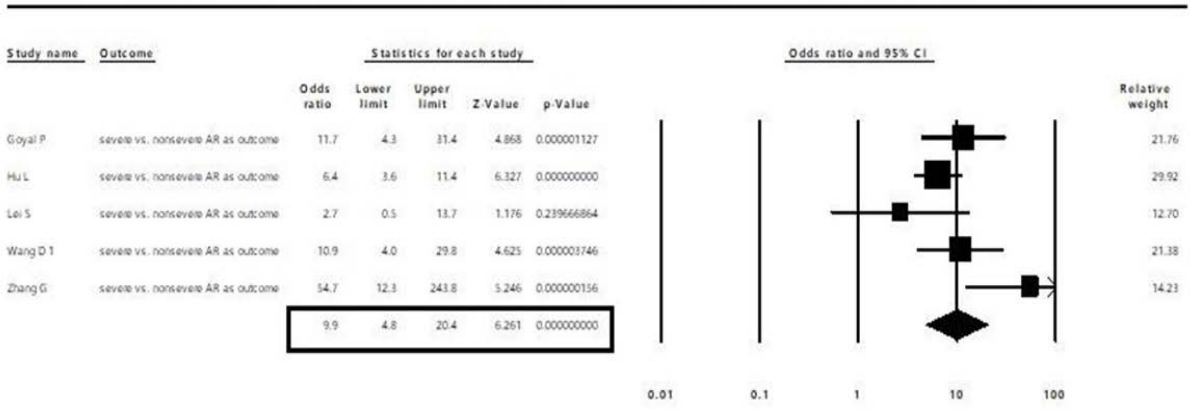

Figure 4: Forest plot of the odd ratios of arrhythmia in severe compared to non-severe COVID-19 cases.

3.4. 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.

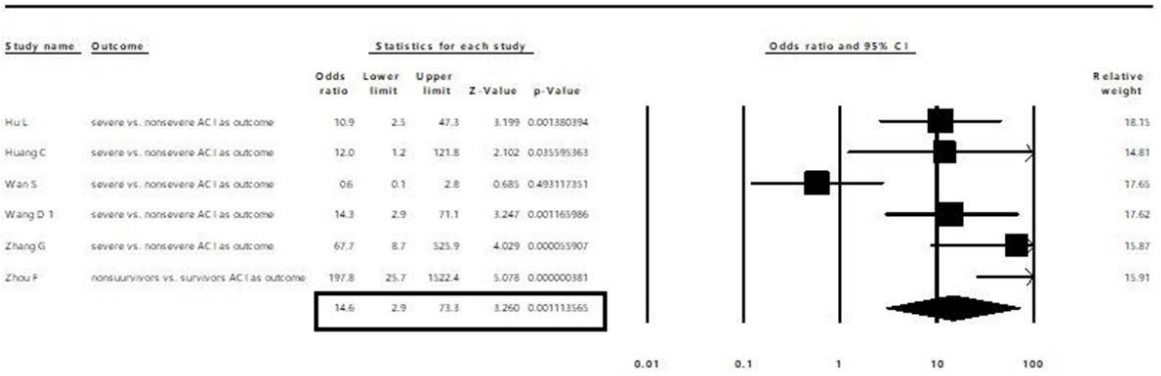

Figure 5: Forest plot of the odd ratios of acute cardiac injury in severe compared to non-severe COVID-19 cases.

3.5. Quality of the included studies

Supplementary Table S1 summarizes the quality assessment of the included studies. All included studies in this analysis reported the demographic and clinical characteristics and 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. Most of the studies diagnosed COVID-19 disease and outcome of interests using valid and reliable methods and used appropriate statistical analysis.

3.6. Assessment of publication bias

As shown, figures 6 and 7 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).

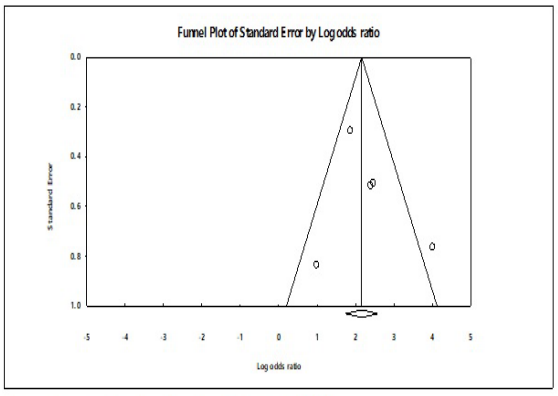

Figure 6: Funnel plot for publication bias based on arrhythmia

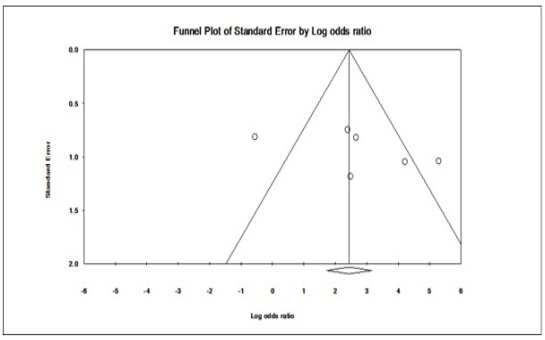

Figure 7: Funnel plot for publication bias based on acute cardiac injury

4. Discussion

In the present meta-analysis, we examined 18 independent studies. Eight of these studies discussed arrhythmia as a COVID-19 disease complication, and ten studies were included in this meta-analysis of acute cardiac injury as disease complications. Pooled studies were reporting clinical data on 4,355 COVID-19 patients. Results added value to the literature as it summarized the prevalence of arrhythmia and acute cardiac injury as a disease outcome among COVID-19 patients.

Our results showed that 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 [21]. A recent study reported the incidence of arrhythmia at 6.9% in hospitalized patients [38]. For acute cardiac injury, a meta-analysis of the Chinese studies reported an 8% incidence of acute cardiac injury, while our study indicates a 9% incidence of acute cardiac injury [30].

Severe systemic inflammation associated with COVID-19 can trigger myocardial dysfunction, which leads to arrhythmia [7, 8]. Many studies reported that pro-inflammatory cytokines are associated with arrhythmia [11, 31]. Pro-inflammatory cytokines like C-reactive protein (CRP), TNF-a, and IL6 played a role in inducing the synthesis of several coagulation markers, including tissue factor (TF) [31, 32]. Moreover, these markers have been extremely investigated in the association with atrial fibrillation (AF) [11].

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 1β (IL-1β), 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 inducing ischemic heart disease. Many inflammatory markers are shown to be increased locally at ischemia, such as; IL-6 [33] and TNF-a [34]. 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 be associated with several types of cardiac arrhythmias[7, 8]. Another important indirect potential pathway of how systematic inflammation induces arrhythmia is the activation of systematic coagulation response. Even though there are not fully established clinical settings that prove the association between systemic inflammation and cardiac arrhythmias, several studies shed light on the potential association between atrial fibrillation and systemic inflammation due to its high incidence[11, 35, 36].

Our results showed that the incidence of arrhythmia was associated with ten folds increase in disease severity. Patients with the more severe systemic disease also had a higher probability of promoting cardiac arrhythmias, as evidenced by ICU admissions. Therefore, clinical protocols should pay attention to preventing and managing arrhythmia in COVID-19 patients. Future studies should investigate whether arrhythmia management in COVID-19 patients reduces disease severity.

The most common cardiovascular disease complication is acute cardiac injury. Our results reported that the incidence of acute cardiac injury was 14 folds higher in patients with severe complications than in 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, cardiac myocytes damage, inhibition of the protective signaling pathways in cardiac myocyte, and increased hypercoagulability and microvascular thrombosis suggested mechanisms of induced acute cardiac injury among COVID-19 patients. Future studies should look at risk factors for developing cardiac injury in COID-19 patients.

Our study rigorously analyzed the number of patients with arrhythmia outcomes and acute cardiac injury outcomes collected from a large sample of patients with COVID-19; advantageously, 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 concern in the included studies. Other biases in the included studies are less likely since all studies address sufficiently other points in the JBI tool.

5. Conclusion

In summary, present evidence showed that cardiac arrhythmias and acute cardiac injury are highly associated with the severity and the mortality rate of COVID-19. Early cardiac arrhythmias and acute cardiac injury management may considerably improve COVID-19 prognosis.

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Conflicts of Interest

The authors declare no conflict of interest.

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