

# Arrhythmia in patients with severe coronavirus disease (COVID-19): a meta-analysis

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**Abstract. – OBJECTIVE:** Many studies have reported arrhythmia to be associated with coronavirus disease (COVID-19), but no meta-analysis has explored whether arrhythmia is related to COVID-19 severity. Therefore, the purpose of this study was to evaluate arrhythmia in patients with severe and non-severe COVID-19 during the current COVID-19 pandemic.

**MATERIALS AND METHODS:** We searched PubMed, Embase, Web of Science, and the Cochrane Library for case control studies that were published between January 1 and July 25, 2020, and that had data on arrhythmia in patients with COVID-19. Random effects model was used with the odds ratio as the effect size. The frequency of arrhythmia was compared between COVID-19 patients with and without the composite endpoint of severity. We also determined the pooled prevalence of arrhythmia in patients with COVID-19. Publication bias and heterogeneity were considered by using subgroup analyses, meta-regression, and the trim and fill method.

**RESULTS:** A total of 1553 patients with COVID-19 were included in the 5 articles we obtained. Of these, 349 cases (22.47%) and 1204 cases (77.53%) were severely ill and non-severely ill inpatients with COVID-19 pneumonia, respectively. There were 790 (50.87%) male patients. A total of 105 cases (30.09%) of severely ill inpatients with COVID-19 pneumonia had arrhythmia complications, and 34 cases (2.82%) of non-severely ill inpatients with COVID-19 pneumonia had arrhythmia complications. We found arrhythmia to be significantly associated with severely ill inpatients with COVID-19 pneumonia, with a pooled odds ratio of 17.97 (95% CI (11.30, 28.55),  $p < 0.00001$ ).

**CONCLUSIONS:** This study showed that the incidence of arrhythmia in patients with se-

vere COVID-19 was greater than that of those with non-severe COVID-19. Patients with severe COVID-19 had a higher risk of arrhythmia complications, which further showed that COVID-19 may be a risk factor for arrhythmia and that the incidence of arrhythmia may increase with the progression of the disease. More importantly, this meta-analysis graded the reliability of evidence for further basic and clinical research into arrhythmia in patients with COVID-19.

*Key Words:*

Arrhythmia, COVID-19, SARS-CoV-2, 2019-nCoV, Meta-analysis.

## Introduction

In December 2019, the world began to face a new pandemic, namely coronavirus disease (COVID-19), which is caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). This newly discovered infectious disease broke out in Wuhan, China, and it quickly spread to other provinces in China<sup>1</sup>. As of August 2, 2020, there have been 17,660,523 people infected worldwide, and 680,894 people have died<sup>2</sup>.

The main symptoms of COVID-19 patients in the early time were respiratory symptoms, such as cough, expectoration, dyspnea and so on. With the increase in confirmed COVID-19 cases and the accumulation of clinical data, the cardiovascular manifestations caused by infection with SARS-CoV-2 have attracted widespread atten-

tion in addition to the respiratory manifestations<sup>3</sup>. The cause of cardiac manifestations seems to be multifactorial, including direct viral myocardial injury, hypoxia, hypotension, increased inflammation, down-regulation of ACE-2 receptors, drug toxicity, and an endogenous catecholamine adrenergic state, and studies have shown that heart damage markers in patients with COVID-19 are associated with a poor prognosis<sup>4</sup>. More than 40% of heart disease symptoms are related to arrhythmia, and COVID-19 is related to a high incidence of arrhythmia. In addition to myocardial infarction and heart failure, arrhythmia is a major risk associated with viral infections. Arrhythmia is a common cardiovascular symptom in patients with COVID-19, with symptoms ranging from simple palpitations to arrhythmias that require treatment<sup>5</sup>. The risk of arrhythmia may increase with the development of a serious infection, the aggravation of infection, and/or systemic inflammatory response. Moreover, there is a correlation between significant myocardial damage, fulminant myocarditis, and arrhythmia<sup>6</sup>. An early report from Wuhan showed that the total incidence of arrhythmia among 138 hospitalized patients with COVID-19 was 16.7%, and the incidence of arrhythmia in those admitted to the intensive care unit (ICU) was 44%<sup>7</sup>. Another report of 700 patients with COVID-19 showed that 34 (43.04%) of 79 patients admitted to the ICU had arrhythmia, while only 19 (3.06%) of non-ICU patients had arrhythmia<sup>8</sup>. Therefore, we propose that the incidence of arrhythmia in patients with severe COVID-19 will be higher than that in those with non-severe COVID-19.

An explanatory theory of the relationship between COVID-19 and cardiovascular disease is that chronic cardiovascular disease may become unstable in light of viral infection due to increased metabolic demand caused by the infection and decreased cardiac reserve. This imbalance, accompanied by inflammation and myocardial damage, would increase the risk of arrhythmia<sup>8</sup>. With the increase in confirmed COVID-19 cases, there are several reports of arrhythmia, but actual data on the incidence of new arrhythmia in patients infected with SARS-CoV-2 is still lacking, and there is no systematic description analyzing arrhythmia in patients with severe and non-severe COVID-19. Further, there are few reports on the incidence of COVID-19-related arrhythmia. Finally, there are no reports on effective treatments for arrhythmia in patients with COVID-19. Hence,

this meta-analysis was conducted to systematically analyze and compare the specific conditions of patients with severe and non-severe COVID-19 and arrhythmia so as to better treat patients with COVID-19 complicated with arrhythmia.

## Materials and Methods

### Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for this research. We included studies involving SARS-CoV-2, COVID-19, or arrhythmia.

We performed a comprehensive retrieval of arrhythmia in PubMed, Embase, Web of Science, and the Cochrane Library using the following terms: “COVID-19,” “SARS-CoV-2,” “Wuhan virus,” “Chinese virus,” “novel coronavirus,” “novel coronavirus 2019,” “2019-nCoV,” “Wuhan coronavirus,” “Wuhan pneumonia,” “the 2019 coronavirus,” “cardiac arrhythmia,” “dysrhythmia,” and “arrythmia.” We searched the databases for all papers dated through July 25, 2020, with no restrictions of language. We also reviewed reference lists to find additional eligible studies based on the recognized literature.

### Study Selection

The following information was collected from each study: publication year, first author’s name, sample size, and comorbidity. We first screened the titles and abstracts of the articles that might involve data concerning COVID-19, SARS-CoV-2, or arrhythmia. If the title and abstract of an article reported the number and proportion of patients with severe and non-severe COVID-19 and arrhythmia, we made a record and marked it as temporarily available. If the title or abstract did not clearly state the relevant content, it was marked as unclear literature. After the preliminary screening, we screened the full text of the well-labeled literature and further screened the literature that could be included.

### Inclusion and Exclusion Criteria

Inclusion criteria were: (1) duplicated studies, letters, case reports, abstracts, or reviews and (2) research focusing on morbidity rather than mortality.

Exclusion criteria were: (1) an article irrelevant to the research direction, (2) an article without data related to arrhythmia in severely ill patients

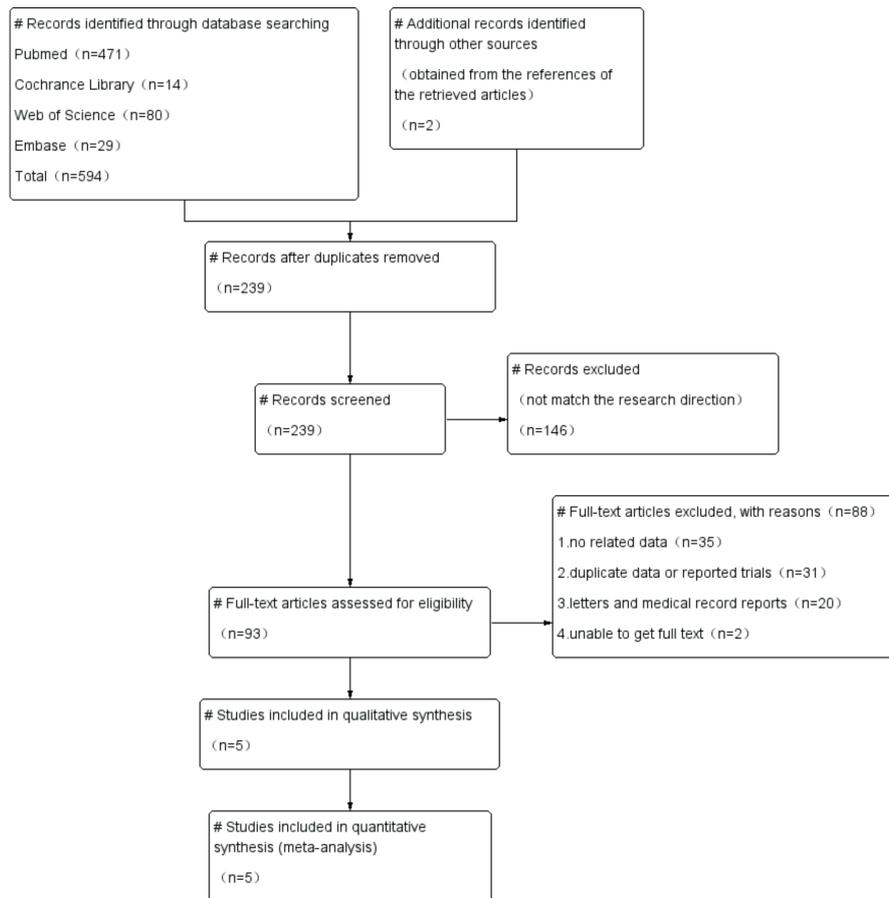


Figure 1. Flow chart of article screening.

with COVID-19, (3) a letter or medical record report, (4) duplicate data, (5) duplicate article, and (6) unobtainable full text.

### Data Extraction

This study included 5 valid COVID-19 articles. The collected data included the name of the study's first author, the study's publication year, the age and sex of the patients, the total sample size, the number of patients with severe and non-severe COVID-19 and arrhythmia, and the incidence of arrhythmia in patients with severe and non-severe COVID-19 (Table I).

### Statistical Analysis

All statistical analyses were performed using Review Manager 5.2 software. We used a binary classification method and a fixed effects model to calculate and compare the 95% confidence interval (CI) and odds ratio (OR) of patients with mild and severe COVID-19 complicated by arrhythmia.

## Results

### Data Collection

The initial search result was 596 articles, with 2 obtained from the references of the retrieved articles. There were 357 duplicate articles; 35 articles without data related to arrhythmia in severely ill patients with COVID-19; 31 articles with duplicate data or repeated trials; 20 letters and medical record reports; and 146 articles that did not match the research direction after reading the title and abstract. These were all excluded. There were also 2 articles that could not be obtained in full that were excluded. In the end, 5 articles were included in our study, with a total of 1553 patients with COVID-19; of these cases, 349 were severe (22.47%), and there were 790 male patients (50.87%) (Figure 1).

### Characteristics of the Included Studies

The characteristics of the included studies are shown in Table I.

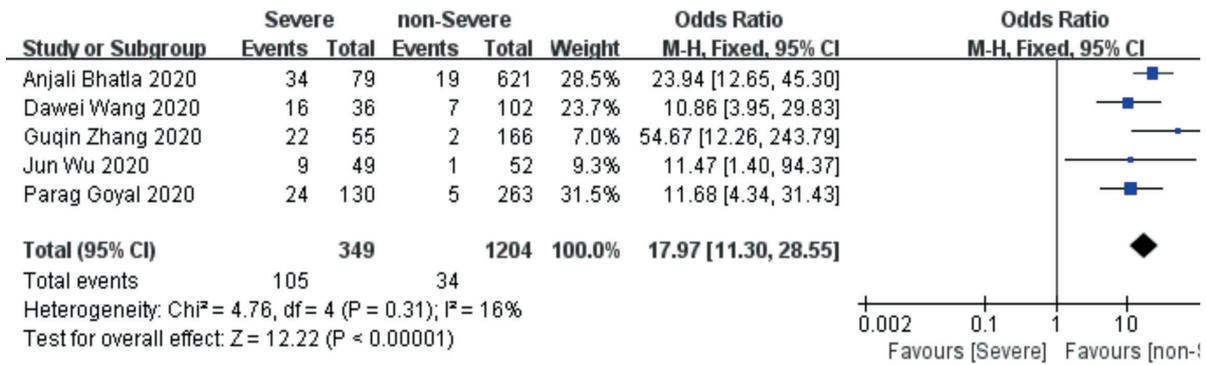


Figure 2. Forest map of arrhythmia in severe and non-severe covid-19 patients was compared.

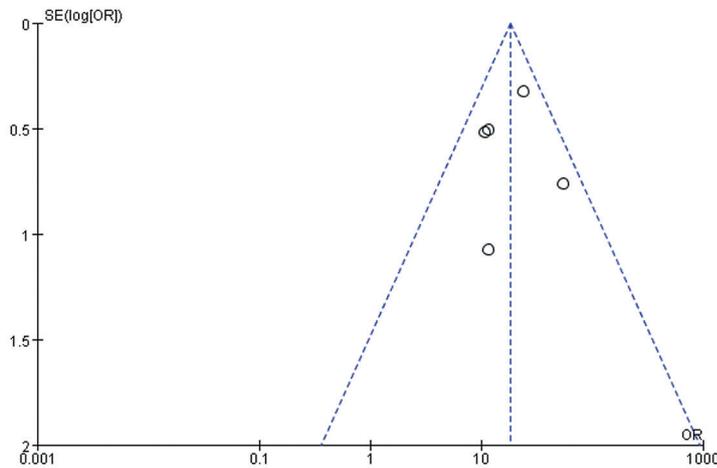


Figure 3. Funnel map analysis of publication bias of included literature.

The sample size in the included articles was between 101 and 700 cases, and the proportion of severely ill patients with COVID-19 was between 11.29% and 48.51%. We defined severely ill patients with COVID-19 as those needing invasive mechanical ventilation, those admitted to the ICU, and those needing hemodialysis.

Of the included literature, two articles described concurrent arrhythmia in ICU and non-ICU patients<sup>7,9</sup>. The third article clearly showed the conditions of severely and non-severely ill patients with COVID-19<sup>10</sup>. The fourth article explained the conditions of patients requiring or not requiring hemodialysis<sup>11</sup>, and the fifth article interpreted the need for invasive and non-invasive mechanical ventilation<sup>12</sup>.

**Meta-Analysis**

In the 5 included articles, there were a total of 1553 patients with COVID-19. Of these patients,

349 were severely ill (22.47%), and 1204 were not (77.53%). Initially, we used a random effects model to analyze the research. However, due to the low level of heterogeneity observed in the research ( $I^2=16\%$ ,  $p=0.31$ ), the model was changed to a fixed effects model. As shown in Figure 2, there were 105 cases (30.09%) of severely ill patients with arrhythmia and 34 cases (2.82%) of mildly ill patients with arrhythmia. The OR of severely ill patients and non-severely ill patients was 17.97 (95% CI (11.30, 28.55),  $p<0.00001$ ), and the upper and lower limits of the 95% CI were both greater than 1. The horizontal line did not intersect the invalid vertical line, and the horizontal line was located at the invalid line on the right, showing that the incidence of arrhythmia in severely ill patients with COVID-19 in this study was greater than that of non-severely ill patients with COVID-19. It may be that severely ill patients with COVID-19 were at higher risk of arrhythmia complications,

**Table I.** Basic information of included literature.

Literatures	Severe								
	Age	Male N (%)	Total	Number of arrhythmias N (%)	Hypertension	Cardiovascular diseases	Diabetes	CHD	HF
Bhatla et al 2020 <sup>7</sup>	63 ± 16	40 (51)	79	34 (43.0)	62 (78)	/	35 (44)	21 (27)	22 (28)
Wang et al 2020 <sup>9</sup>	66 (57-78)	22 (61.1)	36	16 (44.4)	21 (58.3)	9 (25.0)	8 (22.2)	/	/
Zhang et al 2020 <sup>10</sup>	62.0 (52.0–74.0)	35 (63.6)	55	22 (40.0)	26 (47.3)	13 (23.6)	7 (12.7)	/	/
Wu et al 2020 <sup>11</sup>	62 (54-71)	31 (63)	49	9 (18.4)	45 (92)	10 (20)	10 (20)	/	/
Goyal et al 2020 <sup>12</sup>	64.5 (51.7-73.6)	92 (70.8)	130	24 (18.5)	70 (53.8)	/	36 (27.7)	25 (19.2)	/

Literatures	Non-Severe								
	Age	Male N (%)	Total	Number of arrhythmias N (%)	Hypertension	Cardiovascular diseases	Diabetes	CHD	HF
Bhatla et al 2020 <sup>7</sup>	48 ± 18	274 (44)	621	19 (3.1)	285 (46)	/	147 (24)	55 (9)	66 (11)
Wang et al 2020 <sup>9</sup>	51 (37-62)	53 (52.0)	102	7 (6.9)	22 (21.6)	11 (10.8)	6 (5.9)	/	/
Zhang et al 2020 <sup>10</sup>	51.0 (36.0–64.3)	73 (44.0)	166	2 (1.2)	28 (16.9)	9 (5.4)	15 (9.0)	/	/
Wu et al 2020 <sup>11</sup>	62 (47-73)	24 (46)	52	1 (1.9)	23 (44)	5 (10)	10 (19)	/	/
Goyal et al 2020 <sup>12</sup>	61.5 (47.0–75.0)	146 (55.5)	263	5 (1.9)	127 (48.3)	/	63 (24.0)	29 (11.0)	/

which further indicating that COVID-19 could be associated with arrhythmia. This finding also suggests that the risk factors and the incidence of arrhythmia would increase with the development of COVID-19. In addition, as shown in Figure 3, all the 5 included articles are within the dotted line, basically concentrated in the upper part and roughly symmetrical, indicating that the publication bias is small.

## Discussion

We reported the number of patients with COVID-19 and arrhythmia as well as the incidence of arrhythmia in patients with severe and non-severe COVID-19 and conducted a meta-analysis. Our results showed that 105 patients (30.09%) of 349 patients with severe COVID-19 (22.47%) had arrhythmia complications and 34 (2.82%) of 1204 patients with non-severe COVID-19 (77.53%) had arrhythmia complications. In this study, the incidence of arrhythmia in severely ill patients with COVID-19 was significantly greater than that of non-severely ill patients with COVID-19. The correctness of our hypothesis has thus been verified. Patients with severe COVID-19 are at higher risk of developing arrhythmia complications, which also indicates that COVID-19 is a risk factor for arrhythmia and that the incidence of arrhythmia will increase as the infection progresses. From the findings of this study, we put forward two possible conclusions. First, it can be seen from Table I that the age of the patients with severe COVID-19 in the 5 articles included in this study was slightly higher than that of patients with non-severe COVID-19. A cross-sectional survey on the incidence of arrhythmia in patients with COVID-19 indicated that most patients with severe COVID-19 are older and have potential comorbidities, that is, atrial fibrillation<sup>13</sup>. In this regard, we suspect that age may be a risk factor for arrhythmia in patients with severe COVID-19. In addition, according to Figure 2, we found that the incidence of patients with severe COVID-19 and underlying diseases in the literature was significantly higher than that of patients with non-severe COVID-19. We believe that underlying diseases may be another risk factor of severe arrhythmia in patients with COVID-19. For patients with underlying cardiovascular diseases, including hypertension, coronary heart disease, and cardiomyopathy, viral diseases can further damage cardiomyocytes through multiple mechanisms,

including direct viral damage, systemic inflammation, coronary plaque instability, and increased hypoxia<sup>4</sup>. The various mechanisms associated with COVID-19 can lead to an increase in the incidence of slow and rapid arrhythmias. The development of arrhythmia may be secondary to direct myocardial infarction and injury, and severe hypoxic lung disease caused by COVID-19 can cause atrial arrhythmia<sup>14</sup>. In addition, the increase in the incidence of viral infection and its related metabolic requirements and cytokine activation may trigger atrial and ventricular arrhythmias in patients with acute myocarditis or inflammatory response, as well as potential coronary heart disease or other structural heart disease<sup>15</sup>. Our research shows that the severity of COVID-19 is highly correlated with the incidence of arrhythmia, prompting us to pay more attention to the incidence of arrhythmia when studying pathophysiology, clinical manifestations, and treatment of new coronary pneumonia cases in the future. We strongly recommend strengthening the monitoring of the vital signs of patients with COVID-19 and performing electrophysiological examinations to prevent the disease from worsening so as to avoid serious adverse consequences.

Our research had some shortcomings. First, we only included 5 valid articles and did not find more relevant literature on the incidence of arrhythmia in patients with severe and non-severe COVID-19. In addition, the sample size of the included literature was not very large, and there may be a risk of bias or error in the process of the meta-analysis. In addition, we only studied the incidence of arrhythmia in patients with severe COVID-19. No clear literature was found on the specific types of arrhythmia in patients with severe COVID-19, so no analysis was made.

## Conclusions

Our research showed that the occurrence of arrhythmia in patients with severe COVID-19 was greater than that of patients with non-severe COVID-19. Further, patients with severe COVID-19 were at higher risk of arrhythmia complications, indicating that COVID-19 was a risk factor for arrhythmia. The occurrence of arrhythmia may increase with the progression of the infection. In this regard, we must be vigilant and strengthen the electrophysiological monitoring and cardiac function examinations of patients with COVID-19 to prevent the

spread of the virus and reduce the number of patients with arrhythmia.

### Conflict of Interest

The authors declare that they have no conflicts of interest. All listed authors contributed to the planning, performing, and reporting of this work.

### Acknowledgment

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