Review Article: Cardiac Arrhythmia among Hospitalized COVID-19 Patients

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ABSTRACT

Cardiac arrhythmia is one of the common complications among hospitalized COVID-19 patients. The incidence of arrhythmia in COVID-19 varies from 5.9% to 16.7%. This literature review to explore the epidemiology, risk factors, clinical manifestation, pathophysiology, outcomes, and management of hospitalized COVID -19 patients with cardiac arrhythmia. The literature search and review of the literature was performed on PubMed and Google Scholar from January 2020 to July 2021.

Age, comorbidities, and COVID-19 disease severity may increase the risk to develop arrhythmia. Hypertension, coronary artery disease, heart failure, diabetes mellitus, and renal disease are more frequently observed patients with arrhythmia. The proposed pathophysiology of arrhythmia in COVID-19 are myocardial injury, hypoxia, cytokine storm, and drugs side effects. In addition, comorbidity, pre-existing scar or conduction defect, history of previous arrhythmia, electrolyte abnormalities may play a role in the pathophysiology of tachyarrhythmia and bradyarrhythmia. The in-hospital mortality, need of intensive care unit, need of mechanical ventilation or non-invasive ventilation, hypotension, and thromboembolic event were higher in hospitalized COVID-19 patients with arrhythmia. The general managements were to treat the underlying COVID-19 infection and to tackle the hemodynamic disturbances due to tachyarrhythmia or bradyarrhythmia.

Cardiac arrhythmia is a common complication among hospitalized COVID-19 patients. Hospitalized COVID-19 patients with tachyarrhythmia or bradyarrhythmia had worse in-hospital outcomes compared with patients without arrhythmia.

BACKGROUND

Coronavirus disease 2019 (COVID-19), first identified in Wuhan during December 2019, has various complications, including cardiac arrhythmia.[1, 2] There are no specific symptoms regarding arrhythmia in COVID-19. Patients may present with symptoms related to tachy- or bradyarrhythmia.[3] The presentation of cardiac arrhythmia varies from sinus tachycardia to malignant ventricular arrhythmia (VA) or complete heart block (CHB).[4-7]

The incidence of cardiac arrhythmia among hospitalized COVID-19 patients varies from 5.9% to 16.7%.[8, 9] In addition, patients with more severe forms of disease may have a higher risk of developing cardiac arrhythmia. The same study from Wuhan reported 44.4% hospitalized COVID-19 patients in the ICU had cardiac arrhythmia.[8] Atrial fibrillation (AF) was the most common tachyarrhythmia (21%) reported in hospitalized COVID-19 patients. The reported incidence varies from 5.6% to 21%.[10, 11] Sinus bradycardia and complete heart block were also reported in 8% hospitalized COVID-19 patients.[10]

Despite the high incidence of cardiac arrhythmia among hospitalized COVID-19 patients, there is a paucity and variability regarding the exact nature and outcome of hospitalized COVID-19 patients with cardiac arrhythmia. Direct viral infection to the heart was commonly reported as the pathophysiology of arrhythmia among COVID-19 patients. However, other potential mechanisms are also described among many studies.[4,12-15] Furthermore, patient comorbidities and certain drugs that were used to treat COVID-19 may be involved in the mechanism of arrhythmia in COVID-19.[14, 15] Therefore, we performed this literature review to explore the epidemiology, risk factors, clinical manifestation, pathophysiology, outcomes, and management of hospitalized COVID-19 patients with cardiac arrhythmia.

MAIN TEXT

Data Sources

The literature search was performed on PubMed and Google Scholar from January 2020 to July 2021 and updated on 3rd February 2023. We included the search terms: “arrhythmia” OR “supraventricular tachycardia” OR “atrial fibrillation” OR “atrial flutter” OR “atrioventricular nodal re-entry tachycardia” OR “atrioventricular re-entry tachycardia” OR “sinus tachycardia” OR “ventricular arrhythmia” OR “ventricular tachycardia” OR “ventricular fibrillation” OR “premature ventricular complex” OR “premature atrial complex” OR “sinus bradycardia” OR “atrioventricular block” OR “sinus pause” OR “sinus arrest” AND “COVID-19” OR “coronavirus disease 2019” OR “coronavirus” AND “hospitalization” OR “hospitalized”. The inclusion criteria were: 1) Confirmed COVID-19 patients with polymerase chain reaction 2) Age ≥18 years old; 3) Studies reported the outcomes of confirmed COVID-19 patients with arrhythmia. Search was limited only to English language manuscripts. Citations in each included article during the main search were reviewed for potential relevance.

Epidemiology

The early study from Wuhan reported the incidence of arrhythmia among hospitalized COVID-19 patients was 16.7% and may reach as high as 44.4% in patients admitted to the ICU.[7] This discrepancy in arrhythmia incidence between non-ICU and ICU population was due to the high population of ICU patients in the study. To date, many studies have reported various incidences of arrhythmia. Tachyarrhythmia was more commonly reported compared with bradyarrhythmia. However, the true incidence of

tachyarrhythmia and bradyarrhythmia may be underestimated since not every study used continuous electrocardiography (ECG) monitoring for every hospitalized patient.[16-30]

Tachyarrhythmia can manifest as sinus tachycardia, atrial fibrillation (AF), atrial flutter (AFL), atrial tachycardia, and atrioventricular nodal re-entrant tachycardia (AVNRT).[10, 24] Sinus tachycardia was reported in 24.44-64.8% from hospitalized COVID-19 patients.[11, 18, 25] Atrial fibrillation /Atrial flutter was reported in 4%-15.8% hospitalized patients.[19, 24, 31] The incidence of pre-existing AF, new-onset AF, and new-onset AFL were 9.64%, 6.63% and 0.77%, respectively.[16, 17] Atrial tachycardia was reported 0.2% hospitalized patients.[22] On the other hand, the incidence of AVNRT remains scarce since patients with AVNRT are typically younger and lack significant comorbidities.[32]

The incidence of Ventricular Tachycardia (VT)/Ventricular Fibrillation (VF) varied from 1.28%-17.5%.[11, 17, 18, 21] The reported incidence of VT/VF was higher in patients with elevated troponin level compared to normal troponin level, 17.3% and 1.5% respectively.[33]

The data regarding incidence of bradyarrhythmia is limited.[11, 12, 17, 18, 22, 34-38] Sinus bradycardia, relative sinus bradycardia, and atrioventricular (AV) block was reported among hospitalized COVID-19 patients.[17, 34, 35, 37, 38] Sinus bradycardia and relative bradycardia may occur in 4.9% and 36% of hospitalized COVID-19 patients.[11, 37] Severe bradyarrhythmia such as high grade AV block and complete heart block (CHB) was also reported during admission or during hospitalization.[11, 16, 34] The incidence of high grade AV block and CHB was 0.26% and 0.26-1.4% respectively.[11, 16] A study also reported 15 patients with 2:1 AV block and CHB (1 with 2:1 AV block; 14 with CHB) in which 13 out of 15 patients presented with CHB during initial admission.[34]

Clinical presentation

The clinical presentations of tachyarrhythmias and bradyarrhythmias among COVID-19 patients are the same as the usual presentations. The clinical presentations are summarized in Table 1. To date, there is no single specific pattern for arrhythmia in SARS-CoV-2 infection.[39] Respiratory symptoms such as fever, altered sensorium, and cough may also present during initial admission to the hospital.[16, 34] In tachyarrhythmia, palpitations and/or syncope was commonly reported.[16] In bradyarrhythmia patients presenting with high grade AV block or CHB, syncope was the most common symptom.[34] Less common symptoms such as fatigue and dyspnea are quite common in patients with high grade AV block or CHB.[34]

TABLE 1. AGE, SYMPTOMS, AND REPORTED COMORBIDITIES

Comorbidities and risk factor of developing arrhythmia

The age and comorbidities were summarized in Table 1. Patients with arrhythmias were older and had more comorbidities than those without.[16, 17, 19, 22, 40] Age was significantly associated with incident arrhythmia during hospitalization.[17, 40] An increase in 1 year of age was independently associated with new-onset AF (adjusted OR 1.05;95% CI 1.02-1.09).[23] Hypertension, diabetes mellitus, coronary artery disease, heart failure, renal disease, prior stroke, past arrhythmia, and prior history of AF were more commonly observed in patients with arrhythmia compared with patients without arrhythmia.[16, 17, 19, 22, 23]

There were some risk factors associated with new-onset arrhythmia among COVID-19 patients. One study reported disease severity was associated with higher probability to develop new-onset arrhythmia.[16] Patients with moderate, severe, and critical disease severity had a higher probability to develop new-onset arrhythmia compared with mild severity, with OR of 4.81, 8.86, and 15.79 respectively.[16] Another study also reported cardiovascular disease (OR 3.307,;95% CI 1.329-8.232;*P*=0.01) was significantly associated with incident arrhythmia in COVID-19.[17] The presence of heart failure (HF) as comorbidity was associated with new-onset tachyarrhythmia (OR 4.78;95% CI 1.31-17.48;*P*=0.018)[16] and was associated with bradyarrhythmia (adjusted OR 9.75;95% CI 1.95-48.65).[23]

Biomarker of Cytokine Storm and Myocardial Injury

During cytokine storms, the level of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-2 (IL-2), and tumour necrosis factor-α (TNFα) are markedly elevated.[4, 41] Also, the level of inflammatory markers such as c-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin are markedly elevated.[40, 42] Indeed, hospitalized patients with arrhythmia have significantly higher IL-6, LDH, CRP, and ferritin levels compared with hospitalized patients without arrhythmia.[17, 19, 22] Interestingly, patients with four times elevated level of IL-6 had a higher chance of developing atrial arrhythmias compared with patients with less than two times elevated level of IL-6 (*P*=0.05).[22]

Other than elevated cytokines and inflammatory markers, the level biomarkers of myocardial injury were significantly higher in patients with arrhythmia than those without arrhythmia.[11, 17, 19, 22] Patients with arrhythmia had significantly elevated level of high-sensitivity troponin T (hsTnT), high-sensitivity troponin I (hsTnI), creatinine kinase-MB fraction (CK-MB), brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP).[17, 19, 22] Specific arrhythmia, such as new-onset AF, AFL, and NSVT was more common in patients with elevated troponin levels.[11]

Proposed pathophysiology of cardiac arrhythmia

The COVID-19 has 3 phases of clinical evolution, but the phases can overlap each other. The first is a mild phase occurring in the first 7 days of infection indicated by constitutional symptoms with about 80% cases are resolved.[39, 41] SARS-CoV-2 enters the target cell by using angiotensin converting enzyme 2 (ACE2) receptor. ACE2 receptor is expressed on the small intestine, kidney, heart, epicardial adipose tissue, pericytes, blood vessel, and lung.[43-46] Direct myocardial injury may occur in this stage.[47] If the infection is worsening, the patient will develop the second phase or moderate pneumonia. Approximately, 15% patients will develop the second stage or moderate pneumonia. In this phase, acute lung injury may cause hypoxemia and oxygen demand-supply mismatch in which further development of anaerobic metabolic will eventually start metabolic derangements.[4, 41, 47] Finally, the third phase or severe pneumonia occurs in approximately 5% patients.[41] This phase is marked by cytokine storm and is associated with severe systemic inflammation and multiorgan failure.[47] The level of pro-inflammatory cytokines (IL-6, IL-2, and TNFα) and inflammatory markers (CRP, LDH, ferritin) are markedly elevated.[4, 41] Myocardial injury, which happened in 12% of COVID-19 patients with or without cardiovascular comorbidity, [41] may cause arrhythmia exacerbation as explained in Figure 1. The injury can disrupt cardiac electrical conduction system.[48] However, troponin level was not elevated in every COVID-19 patient with arrhythmia, suggesting other mechanism may be involved during the arrhythmia occurrence.[4, 15, 49]

Table 1. Age, symptoms, and comorbidities

First Author (Years) (citation)	Mean/median age of patients with cardiac arrhythmias (years)	Symptoms of patients with cardiac arrhythmias (%)	Comorbidities of patients with cardiac arrhythmias (%)
Peltzer et al (2020) (19)	74.5±13	-	Hypertension (68.7%), prior history of AF (39.2%), diabetes (30.1%), CAD (27.1%), pulmonary disease (26.5%), renal disease (17.5%), CHF (13.9%), prior stroke (12.6%), cirrhosis (1.2%)
Rav-Acha et al (2020) (16)	77 (62.5-87.25)	Respiratory symptoms (85.7%), palpitations/syncope (7.1%), palpitations (3.6%), syncope (3.6%)	Hypertension (53.6%), DM (42.9%), IHD (25%), CHF (21.4%), VHD (14.3%), past arrhythmia (25%), lung disease (7.1%)
Shrivastava et al (2020) (34)	62 (52-68)	Syncope (80%), fatigue 11 (73.3%), dyspnea (40%), cough (33.3%), fever (26.7%), presyncope/ giddiness (20%), URTI (13.2%), altered sensorium (6.67%)	CAD (20%), DM (60%), hypertension (40%)
Zareini et al (2020) (24)	69.5 (61.1-79.7)	-	Stroke/TIA (14.8%), IHD (18.5%), PAD (3.7%), hypertension (44.4%), diabetes (25.9%), chronic HF (14.8%), asthma (7.4%), COPD (16.7%), history of DVT/PE (11.1%), VHD (14.8), CKD (13%), rheumatic disease (9.3%), active cancer (18.5%), AF (11.1%)
Guan et al (2021) (22)	70 (63-75)	-	Hypertension (50.6%), coronary heart disease (24.7%), diabetes (23.5%), AF (4.7%), HF (3.55%), cardiomyopathy (2.4%)
Patel et al (2021) (49)	79 (66-91)	-	Type 2 DM (36%), CAD (19%), systemic hypertension (41%), CKD (7%), congestive HF (31%), peripheral vascular disease (22%), prior atrial arrhythmia (26%)
Yarmohammadi et al (2021) (59)	76±13	-	DM (51%), hypertension (84%), HF (28%), CAD (35%), CKD/ESRD (20%)
Zylla et al (2021) (17)	73.6±12.8	-	Hypertension (76.5%), cardiovascular disease (41.2%), obesity (23.3%), diabe7es (20.6%), pulmonary disease (17.6%), immunodeficiency (7.6%), cardiomyopathy (2.9%)
Aghajani et al (2022)	62.18±17.83	-	Hypertension (54.7%), cardiovascular disease (60.9%), DM (52.4%), CKD (50.5%)
Cozzolino et al (2022) (40)	74.5 (68-80.5)	-	DM (30%), CKD (17.5%), chronic liver disease (11.3%), hyperlipidemia (10%), arterial hypertension (68.7%), CAD (27.5%), heart failure (15%), any previous arrhythmia (42.5%)
Lopes et al (2022) (57)	67	-	Hypertension (73.5%), hyperlipidemia (52.9%), diabetes (17.6%), CAD (11.8%), heart failure (17.6%), stroke (5.9%), CKD (8.9%)
Maloberti et al (2022) (27)	73 (64-81)	-	History of AF (6.2%), chronic coronary syndrome (9.1%), HF (4.5%), peripheral vascular disease (6.6%), previous stroke (8.3%), DM (17%)
Naeem et al (2022) (60)	72.4±13.8	-	DM (41.7%), hypertension (54.2%)
Offerhaus et al (2022) (28)	74 (54-74)	-	Heart failure (12.7%), hypertension (60.2%), type 1 or 2 DM (27.6%), PAD (9.8%), renal impairment (17.9%)
Rahimi et al (2022) (29)	70.7±14.1	-	Hypertension (50.3%), diabetes (27.2%), dyslipidemia (23.8%), HF (29.9%), CAD (31.9%), prior stroke/TIA (9.5%), VHD (12.9%), peripheral vascular disease (4.1%), CKD (14.9%)
Rosenblatt et al (2022) (54)	73 (64-82)	-	Prior cardiovascular disease (32.6%), cerebrovascular accident (11.9%), PAD (3.4%), congestive HF (17.4%), hypertension (72.5%), diabetes (38.2%), hyperlipidemia (44.4%), DVT (4.3%), PE (2.6%), renal disease (18.7%)
Argawal et al (2023) (31)	75.9±0.06	-	Congestive heart failure (43.7%), VHD (11.5%), prior MI (8.2%), peripheral vascular disorders (10.3), hypertension (84.2%), diabetes (43.7%), renal failure (34.9%)
Wang et al (2023) (58)	76.52±11.3	-	Hypertension (76.4%), diabetes (39.1%), CAD (35.1%), CKD/ESRD (24.7%), HF (28.2%), history of stroke (14.4%)

AF = atrial fibrillation; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease; DM = diabetes mellitus; DVT = deep vein thrombosis; ESRD = end stage renal disease; HF = heart failure; IHD = ischemic heart disease; PAD = peripheral artery disease; PE = pulmonary embolism; TIA = transient ischemic attack; VHD = valvular heart disease

Hypoxia due to ARDS in COVID-19 infection may cause electrolyte imbalance and further precipitate arrhythmia. Hypoxia activates anaerobic glycolysis, reduces intracellular pH, and increases cytosolic calcium levels. Moreover, increased cytosolic calcium levels can facilitate early and late depolarisations, as well as temporal alterations in the action potential duration.[4] Furthermore, hypoxia reduces the rapid delayed rectifier potassium (I_{Kr}), resulting in the increased extracellular potassium levels.[7, 50] This can decrease the threshold for depolarization and accelerates electrical conduction.[50] On the other hand, hypoxia can increase the number of late sodium current (I_{NaL}) along with I_{Kr} reduction can prolong ventricular repolarization which lead into re-entrant arrhythmia.[7, 50]

Cytokine storm may increase the risk of developing arrhythmia.[4, 47] Cytokine storms affect potassium and calcium channels, which may prolong ventricular action potential.[3] Pro-inflammatory cytokine such as IL-6 can cause hyperactivation of cardiac sympathetic system and trigger malignant arrhythmia in patients with long QT interval.[50] Furthermore, IL-6 is thought to be the central mediator of pro-inflammatory cytokine and organizes its responses from immune cells.[48] Higher viral load expressed higher levels of pro-inflammatory cytokines.[15]

Side effects of certain drugs may also trigger cardiac arrhythmia in COVID-19 patients.[4] Hydroxychloroquine and azithromycin are known for their effects in prolonging QT interval by inhibiting the I_{Kr}.[3] The net effect of QT prolongation to the I_{Kr} by multiple QT prolonging drugs is synergistic.[51] Therefore, special attention must be put on patients receiving multiple drugs that can block I_{Kr}, such as those who receive chloroquine or hydroxychloroquine combined with other antiviral drugs (lopinavir/ritonavir) or even antibiotics (macrolides and fluoroquinolones).[51, 52] In addition, COVID-19 patients may have prolonged QT interval due to hypokalemia or hypomagnesemia precipitated by either diarrhea or diuretic agents.[15] Furthermore, IL-6 inhibits cytochrome P450 (CYP) 3A4, which in turn increases the bioavailability of QT-prolonging drugs.[15]

FIGURE 1. PROPOSED PATHOPHYSIOLOGY OF CARDIAC ARRHYTHMIA

Proposed pathophysiology of tachyarrhythmia

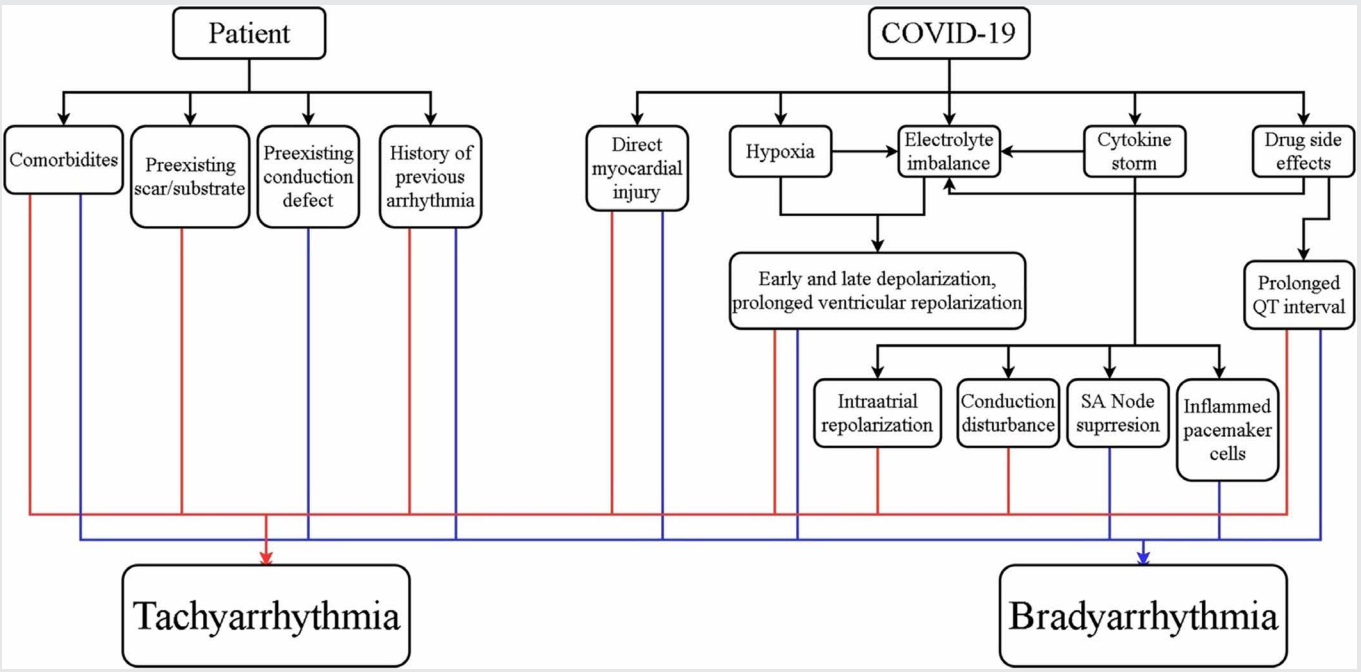
Multiple mechanisms are involved in the pathophysiology of tachyarrhythmia in COVID-19. Myocardial injury, renal failure, electrolyte abnormalities, cytokine storm, and use of certain drugs may trigger tachyarrhythmia.[9, 10, 15, 28, 45, 53]

Supraventricular tachycardia (SVT) in COVID-19 can manifest as sinus tachycardia, AF, AFL, atrial tachycardia, and AVNRT.[3, 10, 11, 32] The presence of sinus tachycardia, AF, and AFL in COVID-19 was frequently reported. However, AVNRT is uncommon due to population in studies consist of mainly younger age and lack significant comorbidities.[32]

The development of sinus tachycardia in COVID-19 patients represent acute course of illness that usually cause by hypovolemia, hypoperfusion, hypoxia, fever, and fear/anxiety during COVID-19.[15, 32, 53] Meanwhile, AF which is the second most common type of supraventricular arrhythmia after sinus tachycardia occur during hospitalization (new-onset, recurrence of previous dysrhythmia, or AF with persisting rapid ventricular response) and post recovery.[10, 32, 46] In most cases, new onset AF in COVID-19 patients occurred in the older population and with at least 1 pre-existing risk factor.[28, 45, 54] The incubation period of COVID-19 is relatively short and is not enough to develop fibrosis as a substrate for AF. Therefore, the patients may have had a pre-existing substrate and acute COVID-19 infection triggered the new onset AF.[45, 54] Other factor such as pro-inflammatory cytokine for instance TNF-α may increase risk of AF vulnerability by triggering pulmonary cardiomyocyte vein activity that results in increased activity of sodium-calcium exchanger (NCX) and impaired sarcoplasmic reticulum (SR) ATPase.[9]

Malignant arrhythmia, defined as rapid ventricular tachycardia lasting >30s, inducing hemodynamic instability, or ventricular fibrillation, occurred in 17.3% patients with myocardial injury.[15]

Figure 1: Proposed pathophysiology of cardiac arrhythmia



Factors that may precipitate this process including the elevation of troponin and CRP level, hyperadrenergic state in the scarring myocardium, and inflammation.[15, 41, 48] Myocardial inflammation is reported to have the potential in prolonging ventricular action potential duration, cause severe necrosis, and create a re-entry area that triggers VT and VF.[15, 48] Myocardial inflammation may persist in approximately 60% patients who recently recovered from COVID-19 infection, irrespective of pre-existing condition, severity of acute COVID-19 infection, and the course of COVID-19 infection.[55]

Proposed pathophysiology of bradyarrhythmia

Bradyarrhythmia are less commonly reported in hospitalized COVID-19 patients.[34-36, 38, 43, 56] It may manifest as sinus bradycardia, relative bradycardia, AV block, high grade AV block, or CHB. New onset bradycardia during hospitalization may be a marker of worsening cytokine storm.[36, 53]

Various mechanisms are involved in the pathophysiology of bradyarrhythmia.[38, 56] Myocardial injury may cause transient AV block because of the affected electrical conduction system.[41] This was supported by the presence of SARS-CoV-2 RNA in cardiac myocytes and endothelial cells from autopsies of COVID-19 patients.[34, 56] In addition, severe hypoxia, inflamed cardiac pacemaker cells, worsening of pre-existing conduction disease, reaction to the systemic inflammation, and inappropriate drug response may also trigger bradyarrhythmia.[34, 36, 38, 49] However, bradyarrhythmia due to reversible causes, e.g. in patients with AV block related to acute coronary syndrome and metabolic abnormalities, are less likely induced by COVID-19.[21] Pro-inflammatory cytokines such as IL-6 is highly associated with relative bradycardia and may directly supress Sinoatrial (SA) Node, increase vagal tone, and reduce heart rate variability.[36, 43] Increasing level of CRP and ferritin was also reported to have association with CHB and high grade AV block.[34]

Electrocardiographic monitoring, QT prolonging drugs, and QTc interval

Hospitalized COVID-19 patients may develop arrhythmia at the time of hospital admission or during hospitalization period.[11, 16-30, 34, 57] Continuous electrocardiographic (ECG) monitoring for every hospitalized COVID-19 patient is required to evaluate arrhythmic events.[24] ECG monitoring is also performed during brady- and tachyarrhythmia therapy.[48] Other than that, ECG monitoring provides QT corrected (QTc) interval measurement.[39]

The QTc interval >450 milliseconds in males and >460 milliseconds in females can be defined as prolonged QTc interval. Lead II or V5 is the preferable lead to measure QTc interval and bazett's correction is the most commonly used formula to calculate the QTc interval.[53] Sometimes, the combination of QT prolonging drugs is inevitable. Since the QT prolongation effect is synergistic,[51] the combination of azithromycin, chloroquine, or hydroxychloroquine can prolong QTc interval and may induce arrhythmia.[36, 39, 43] The combination of dual antiviral therapy was independent predictors of QT prolongation (OR 12.46;95% CI 2.09-74.20;*P*<0.01).[20]

Ideally, monitoring of QTc interval in patients receiving QT prolonging drugs is mandatory, especially in patients admitted to the ICU.[53] But, single-lead electrocardiography (ECG) devices tend to underestimate the QTc interval. Twelve-lead ECG devices provide more accurate and reliable QT interval measurement compared with single-lead ECG,[39] however this situation puts a considerable strain on medical personnel during the COVID-19 pandemic. Therefore, contactless monitoring and telemetry systems may be preferred and act as an alternative. Smart watches, smartphones, and smart beds can provide wireless monitoring for in-hospital QTc interval monitoring.[53]

In-hospital outcomes

The outcomes of hospitalized COVID-19 patients with arrhythmia were summarized in Table 2. Overall, hospitalized COVID-19 patients with arrhythmia had worse outcomes compared with hospitalized COVID-19 patients without arrhythmia.[17, 19, 22, 40] The overall duration of hospitalization and duration of hospitalization in the ICU/intermediate care unit (IMC) was longer in hospitalized COVID-19 patients.[17] Patients with arrhythmia had a higher rate of ICU or IMC admission (OR 2.37;95% CI 1.10-5.09;*P*=0.03), mechanical ventilation due to severe respiratory failure (OR 6.69;95% CI 2.92-15.35;*P*<0.001), vasopressors (47.1% vs. 10.6%;*P*<0.001), and high-flow nasal cannula (HFNC) / non-invasive ventilation (NIV) (41.2% vs. 19.1%;*P*=0.01) compared with patients without arrhythmia.[17] In terms of cardiac events, patients with arrhythmia were more likely to develop myocardial infarction (8.8% vs. 0.8%;*P*=0.021) or heart failure (34.12% vs. 8.73%;*P*<0.001) during hospitalization compared with patients without arrhythmia.[17, 22] The in-hospital mortality was significantly higher in patients with arrhythmia during hospitalization than patients without arrhythmia (OR 3.02;95% CI 1.22-7.46;*P*=0.02).[17] In addition, patients with arrhythmia during initial presentation had increased risk of death compared with patients without arrhythmia (*P*<0.001).[22] Furthermore, elevated troponin level was associated with higher in-hospital mortality compared with normal troponin level (34.8 vs. 16.7%;*P*=0.014).[11]

TABLE 2. IN-HOSPITAL OUTCOMES FROM THE STUDIES

Association between type of arrhythmia and in-hospital outcome

Sinus tachycardia, the most common tachycardia, was associated with increased in-hospital mortality (58.3% in non-survivors vs. 33.6% in survivors; *P*=0.009).[11] In AF/AFL, the in-hospital mortality was significantly higher in patients with AF/AFL compared with patients without AF/AFL.[19, 28] Also, both new-onset and pre-existing AF were associated with higher rate of in-hospital mortality, need of ICU, need for mechanical ventilation, and shock compared to patients without AF.[26, 57-60] Compared to non-major arrhythmias (sinus tachycardia, premature atrial complexes, premature ventricular complexes), patients with major arrhythmia (SVT, new AF/AFL, sinus pause, and VT) had higher in-hospital mortality rate and higher rate incidence of pulmonary embolism/deep vein thrombosis.[24] Furthermore, VT significantly increased the risk of in-hospital mortality (RR=2.55;*P*=0.003).[61]

Bradyarrhythmia has been considered with worse outcome and more severe disease compared with tachyarrhythmia.[43] The in-hospital mortality of bradyarrhythmia in hospitalized COVID-19 patients was 18.8% to 57%, despite being treated with pacemaker.[34, 35, 38] Self-reverted rhythm back to sinus was reported in patients with CHB with narrow and wide complex escape rhythm.[34] Moreover, broad QRS complex escape rhythm may predict worse inflammatory state and poorer rhythm recovery compared with narrow QRS complex escape rhythm.[34]

Table 2. In-hospital outcomes from the studies

First Author (Years) (citation)	Number of patients (number of patients with cardiac arrhythmia)	Type of cardiac arrhythmia	In-hospital mortality, mortality during follow-up, the need of ICU, the need of CPAP/NIV/mechanical ventilation, hypotension requiring vasopressor, major bleeding, and thromboembolic event associated with arrhythmia
Bhatla et al (2020) (23)	700 (53)	9 patients had cardiac arrest (6 with PEA, 2 with asystole, and 1 with TdP), 25 patients had AF, 9 patients had clinically significant bradyarrhythmias, and 10 patients had NSVT	The mortality rate in AF, bradyarrhythmias, and NSVT groups were 24%, 11%, and 10% Cardiac arrest was associated with in-hospital mortality (adjusted OR 34.99, 95% CI 3.49-350.69)
Cho et al (2020) (11)	143 (143)	57 patients had sinus tachycardia, 7 patients had sinus bradycardia, 11 patients had PAC, 41 patients had PVC, 8 patients had SVT, 17 patients had AF as a baseline ECG, 8 patients had new-onset AF, 3 patients had AFL, 22 patients had NSVT, 2 patients had VT, 1 patient had VF, 2 patients had CHB, and 1 patient had sinus arrest	Patients with sinus tachycardia had increased mortality compared with patients without sinus tachycardia. (58.3% in non-survivors vs. 33.6% in survivors, *P*=0.009)
Mohammadyari et al (2020) (18)	45 (45)	2 patients had PAC, 9 patients had PVC, 9 patients had AF, 2 patients had PSVT, 2 patients had VT, 1 patient had VF, 1 patient had AV block	The mortality rate in COVID-19 patients with arrhythmia was 17.7%
Peltzer et al (2020) (19)	1053 (166)	166 patients had AF/AFL	Patients with AF/AFL had a higher in-hospital mortality (39.2% vs. 13.4%, *P*<0.001) compared with patients without AF/AFL. Patients with AF/AFL (adjusted OR 1.93, 95% CI 1.20-3.11, *P*=0.07) and with newly detected AF/AFL (adjusted OR 2.87, 95% CI 1.74-4.74, *P*<0.001) were independently associated with increased mortality Patients with AF/AFL had a higher risk for ICU admission (60.2% vs. 28.1%, *P*<0.001), to develop hypotension requiring vasopressor therapy (60.2% vs.25.6%, *P*<0.001), to develop respiratory failure requiring mechanical ventilation (60.2% vs. 25.6%, *P*<0.001), and to develop stroke/TIA (6% vs. 0.9%, *P*<0.001) compared with patients without AF/AFL The incidence of venous thromboembolism did not differ between groups (*P*=0.085)
Rav-acha et al (2020) (16)	390 (28)	1 patient with CHB, 1 patient with high degree AV block, 1 patient with extreme sinus bradycardia with slow ventricular escape rhythm, 1 patient with SVT, 19 patients with AF, 1 patient with atypical AFL, 2 patients with AFL, 1 patient with AF and VF, 1 patient with VT storm	Mechanical ventilation was performed in 21.4% patients. Hemodynamic shock was developed in 25% patients. The mortality rate was 32.1%.
Russo et al (2020) (61)	414 (90)	50 patients had new-onset AF, 21 patients with recurrent AF, 14 patients had VT, and 5 patients had SVT	Incident VT (RR=2.55, *P*=0.003) was a strong independent predictor of in-hospital mortality
Shrivastava et al (2020) (34)	15 (15)	14 patients with CHB and 1 patients with 2:1 AV Block	In-hospital mortality rate was 33.3% patients despite being treated with pacing. Admission to the ICU occurred in 26.67% patients. Vasopressors were given to 20% patients.
Turagam et al (2020) (21)	140 (12)	6 patients with VF, 1 patient with VT, and 5 patients with AV block	There were statistically significant differences of malignant cardiac arrhythmia (VT/VF/AV block) between the deceased group with VT or VF compared with the survived group (17% vs. 4%, *P*=0.01) and the difference was driven by tachyarrhythmias
Zareini et al (2020) (24)	54 (54)	27.8% (15 patients) with major arrhythmias (SVT, new AF/AFL, sinus pause, AV block, VT) and 72.2% (39 patients) with non-major arrhythmias (sinus tachycardia, PAC, PVC)	In-hospital mortality (*P*=0.03), admission to the ICU (*P*=0.05), and PE/DVT (*P*=0.02) was higher in the major arrhythmias group compared with non-major arrhythmias The need for CPAP/NIV (*P*=0.07) and the incidence of ARDS (*P*=0.4) was not statistically significant between groups

Table 2. In-hospital outcomes from the studies

First Author (Years) (citation)	Number of patients (number of patients with cardiac arrhythmia)	Type of cardiac arrhythmia	In-hospital mortality, mortality during follow-up, the need of ICU, the need of CPAP/NIV/mechanical ventilation, hypotension requiring vasopressor, major bleeding, and thromboembolic event associated with arrhythmia
Guan et al (2021) (22)	463 (85)	17 patients had AF, 3 patients had AFL, 1 patient had AT, 1 patients had SVT, 1 patient had VT, 7 patients had 1st degree AV block	Patients with arrhythmia had a higher all-cause mortality compared to patients without arrhythmia, 25.9% (22 patients) and 10.1% (38 patients), respectively. (*P*<0.001) Atrial arrhythmias (adjusted OR 3.51, 95% CI 1.74-7.08) and ventricular arrhythmias (adjusted OR 3.41, 95% CI 1.13-10.24) was significantly associated with death during hospitalization
Lao et al (2021) (38)	200 (11)	7 patients had 1st degree AV block, 1 patients had 1st degree AV block that turned into transient 2nd degree AV block, 2 patients had 1st degree AV block that turned into AF with rapid ventricular response, 1 patient had high degree AV block	Patients who developed new-onset AV block had similar in-hospital mortality (18.18% vs. 16.49%, *P*=1.00) and mechanical ventilation (0% vs. 15.43%, *P*=0.3724) rate compared to patients who didn't develop new-onset AV block.
Patel et al (2021) (30)	173 (27)	10 patients had NOAF, 1 patient had new-onset AFL, 2 patients had new SVT, 6 patients had new PAC, 5 patients had new monomorphic VT, 1 patient had new VF, and 2 patients had new PVC	Patients with arrhythmia significantly had higher in-hospital mortality rate (41% vs. 10%, *P*=0.0002) compared to patients without arrhythmia.
Yarmohammadi et al (2021) (59)	1029 (82)	82 patients had atrial arrhythmia	Patients with atrial arrhythmia had significantly higher mortality rate (65% vs. 21%, *P*<0.0001) compared to patients without atrial arrhythmia.
Zylla et al (2021) (17)	166 (34)	NS	Patients with arrhythmia had a longer hospitalization period (24 [10.0-33.0] days vs. 9 [5.0-15.0] days, *P*<0.001), a higher mortality rate (29.4% vs. 12.1%, *P*= 0.026), a higher risk for ICU admission (55.9% vs. 24.8%, *P*= 0.025), a higher risk for requiring mechanical ventilation (52.9% vs. 14.4%, *P* <0.001), and a higher risk for requiring vasopressor therapy (47.1% vs. 10.6%, *P*<0.001) compared to patients without arrhythmia
Aghajani et al (2022) (25)	893 (486)	315 patients had sinus tachycardia, 56 patients had AF, 55 patients had sinus bradycardia, 24 patients had PVC, 23 patients had PAC	Patients who developed cardiac dysrhythmias during admission significantly had higher in-hospital mortality (70% vs. 30%, *P*<0.001) compared to patients without cardiac dysrhythmias during admission. After multivariable analysis, male sex (RR 1.16, 95% CI 1.02-1.31, *P*=0.018), underlying cardiovascular disease (RR 1.16, 95% CI 1.02-1.31, *P*=0.017), and presence of QT interval prolongation (RR 1.18, 95% CI 1.03-1.35, *P*=0.017) were independently associated with increased risk of cardiac dysrhythmias on admission.
Aydemir et al (2022) (26)	5577 (368)	286 patients had PEAF and 82 patients had NOAF	Patients with NOAF had higher in-hospital mortality (58.5% vs. 10.1%, *P*<0.001), need for ICU (63.4% vs. 14.7%, *P*<0.001), need for intubation (48.8% vs. 7.9%, *P*<0.001), and longer hospitalization period (17 [9-26] days vs. 8 [5-13] days, *P*<0.001) compared to patients without AF. NOAF was also associated with increased in-hospital mortality (OR 12.56, 95% CI 8.02-19.68, *P*<0.001), need for ICU (OR 10.05, 95% CI 6.37-15.86, *P*<0.001), and need for intubation (OR 11.14, 95% CI 7.14-17.38, *P*<0.001). Patients with PEAF had higher in-hospital mortality (18.5% vs. 10.1%, *P*<0.001), need for ICU (27.6% vs. 14.7%, P<0.001), and need for intubation (15% vs. 7.9%, *P*<0.001) compared to patients without AF. PEAF was also associated with increased in-hospital mortality (OR 2.02, 95% CI 1.48-2.76, *P*<0.001), need for ICU (OR 2.21, 95% CI 1.68-2.90, P<0.001), and need for intubation (OR 2.07, 95% CI 1.47-2.90, *P*<0.001).
Cozzolino et al (2022) (40)	200 (80)	NS	Patients with arrhythmia significantly had higher in-hospital mortality rate (25% vs. 0.8%, *P*<0.0001) compared to patients without arrhythmia. Arrhythmia was associated with increased in-hospital mortality (OR 39.66, 95% CI 5.20-302.51, *P*=0.0004).

Table 2. In-hospital outcomes from the studies

First Author (Years) (citation)	Number of patients (number of patients with cardiac arrhythmia)	Type of cardiac arrhythmia	In-hospital mortality, mortality during follow-up, the need of ICU, the need of CPAP/NIV/mechanical ventilation, hypotension requiring vasopressor, major bleeding, and thromboembolic event associated with arrhythmia
Lopes et al (2022) (57)	278 (34)	34 patients had NOAF	Patients with NOAF significantly had higher rate of MACE (composite of ICU all-cause mortality, new-onset heart failure, myocardial infarction, stroke, PE, myocarditis, stroke, and ventricular arrhythmia) (67.6% vs. 29.1%, *P*<0.001) compared to patients without NOAF.
Maloberti et al (2022) (27)	3435 (145)	145 patients had incident AF	Patients with incident AF had longer hospitalization period [22 (13-41) days vs. 12 (7-21) days, *P*<0.001], higher ICU admission (39.3% vs. 12.4%, *P*<0.001), and higher all-cause death (37.2% vs. 16.9%, *P*<0.001) compared to patients without incident AF.
Naeem et al (2022) (60)	149 (24)	24 patients had AF	Patients with AF had significantly higher rate of in-hospital mortality (83.3% vs. 40.8%, *P*<0.001) and mechanical ventilation (91.7% vs. 41.6%, *P*<0.001) compared to patients without AF.
Offerhaus et al (2022) (28)	5782 (692)	692 patients had new-onset or recurrent AF/AFL	After multivariable analysis, new-onset AF and/or AFL were associated with increased in-hospital mortality (adjusted OR 3.80, 95% CI 0.03-84.86).
Rahimi et al (2022) (29)	1764 (147)	147 patients had NOAF	Patients with NOAF significantly had higher cerebral infarction (1.4% vs. 0.2%, *P*<0.001), pulmonary embolism (14.3% vs. 7.5%, *P*=0.004), bleeding events (26.5% vs. 20.7%, *P*=0.004), ICU admission (19.7% vs. 12.2%, *P*=0.002), and in-hospital mortality rates (17.7% vs. 6.4%, *P*<0.001) compared to patients without NOAF.
Rosenblatt et al (2022) (54)	27,632 (1517)	1517 patients had NOAF	Patients with NOAF significantly had higher rate of in-hospital mortality (45.2% vs. 11.9%, *P*<0.001) and in-hospital MACE (composite of cardiovascular mortality, myocardial infarction, stroke, cardiogenic shock, and new-onset heart failure) (23.8% vs. 6.5%, *P*<0.001) compared to patients without NOAF. After adjustment, NOAF was associated with higher risk of MACE (HR 1.3, 95% CI 1.14-1.50).
Argawal et al (2023) (31)	1050,045 (155,407)	155,407 patiens had AF	Patients with AF had higher in-hospital mortality (22.0% vs. 9.3%, *P*<0.01), ischemic stroke (1.3% vs. 0.6%, *P*<0.01), haemorrhagic stroke (0.5% vs. 0.3%, P<0.01), major bleeding requiring blood transfusion (6.4% vs. 4.7%, *P*<0.01), and cardiogenic shock (0.9% vs. 0.3%, *P*<0.01) compared to patients without AF. After adjustment, patients with AF was associated with higher probability of in-hospital mortality (adjusted OR 1.59, 95% CI 1.53-1.65, *P*<0.01), ischemic stroke (adjusted OR 1.55, 95% CI 1.33-1.80, *P*<0.01), haemorrhagic stroke (adjusted OR 1.31, 95% CI 1.04-1.64, *P*<0.01), major bleeding requiring transfusion (adjusted OR 1.31, 95% CI 1.23-1.40, P<0.01), and cardiogenic shock (adjusted OR 2.72, 95% CI 2.24-3.31, *P*<0.01) compared to patients without AF. Patients with AF also significantly had longer hospitalization period (8.8±0.05 days vs. 7.2±0.02 days, *P*<0.01) compared to patients without AF.
Wang et al (2023) (58)	2732 (174)	28 patient had NOAF and 146 patients had PEAF	AF was significantly associated with MACE (composite of heart failure exacerbation, cardiac tamponade, pericardial effusion, myocarditis, pericarditis, myocardial infarction, stroke, PE/DVT, or shock) (46% vs. 26.2, RR 1.753, 95% CI 1.473-2.085, *P*<0.001) compared to sinus rhythm.

AF = atrial fibrillation; AFL = atrial flutter; ARDS = acute respiratory distress syndrome; AV = atrioventricular; CKMB = creatinine kinase-MB; CPAP = continuous positive airway pressure; CRP = c-reactive protein; ICU = intensive care unit; MACE = major adverse cardiovascular events; MI = myocardial infarction; NIV = noninvasive ventilation; NOAF = new-onset atrial fibrillation; NS = not specified; OR = odds ratio; PAC = premature atrial complex; PEA = pulseless electrical activity; PEAF = pre-existing atrial fibrillation; PSVT = paroxysmal supraventricular tachycardia; PVC = premature ventricular complex; RR = risk ratio; SVT = supraventricular tachycardia; TdP = torsades des Pointes; VT = ventricular tachycardia; VF = ventricular fibrillation

Management of arrhythmia from real world data

Several studies reported real world data regarding the management of arrhythmia in hospitalized COVID-19 patients.[16, 17, 19-21, 34-37, 56, 62] The general approach is to treat the underlying COVID-19 infection and is to treat hemodynamic disturbances due to tachyarrhythmia or bradyarrhythmia. Antiviral, antibiotic, and supportive treatment can be administered for COVID-19.[8, 20] Caution must be used regarding the combination of antiviral and antibiotic that may result in QTc prolongation.[20] In addition, lopinavir and ritonavir can cause PR prolongation, QRS widening, and QT prolongation.52 Hemodynamic disturbances in form of hypotension and desaturation can be treated with inotropes and non-invasive or invasive ventilation.[16, 21, 34]

The management of tachyarrhythmia in COVID-19 from available data mostly followed the recommendation from advanced cardiac life support (ACLS) algorithm. Electrical cardioversion can be performed in AF with hemodynamic instability.[17, 57, 63] Pharmacological cardioversion using amiodarone can be administered to convert AF, AFL, and AT to sinus rhythm.[17] Intravenous beta blocker may be administered to treat NSVT.[20] In case of pulseless VT, torsades des pointes (TdP), or VF, the management was performed according to ACLS algorithm.[20, 64] One compelling finding was the anticoagulant treatment to prevent stroke or transient ischemic attack (TIA) in COVID-19 with AF or AFL. Therapeutic or prophylaxis dose of low-molecular weight heparin (LMWH) or non-vitamin K oral anticoagulant (NOAC) can be administered as anticoagulant treatment in hospitalized COVID-19 patients with AF or AFL.[17, 19] Approximately, 80% of stroke or TIA occurred in hospitalized COVID-19 with AF or AFL who were not on therapeutic dose of anticoagulant.[19] Therefore, therapeutic dose of anticoagulant may be preferred over prophylaxis dose of anticoagulant in COVID-19 with new-onset AF without contraindication to anticoagulant treatment.[19]

In COVID-19 with bradycardia, the initial treatment also followed the recommendation from ACLS algorithm. There were several reports of sinus bradycardia and relative bradycardia related to COVID-19 infection and no specific treatment was reported.[36, 37] Temporary pacemaker may be required to treat hemodynamic disturbances due to sinus pause, sinus sick syndrome, or high grade or CHB.[34, 35, 56] Self-reverted from narrow complex escape rhythm in high grade or CHB to sinus rhythm was reported in 42.9% patients.[34] In contrast, no self-reverted from wide complex escape rhythm to sinus rhythm was reported and permanent pacemaker was implanted.[34] The need of permanent pacemaker due to sinus pause and high grade or CHB was between 46.7% and 57.1%.[34, 35] Permanent pacemaker implantation can be performed after clinical recovery or 14 days after COVID-19 infection.[34] Asystole and pulseless electrical activity (PEA) can be treated according to the ACLS algorithm.[20, 64]

CONCLUSIONS

Based on this literature review, cardiac arrhythmia is a common complication in COVID-19 and the true incidence is not fully appreciated. To date, there were no specific symptoms or signs to alert the physician regarding the presence of tachyarrhythmia or bradyarrhythmia. The occurrence of arrhythmia among hospitalized COVID-19 patients may be predictor of worse in-hospital outcomes. Furthermore, larger studies are needed to fully understand the exact nature of arrhythmia in COVID-19 and to understand the effect of arrhythmia in COVID-19 in relation to in-hospital outcomes.

Keywords: arrhythmia, COVID-19, supraventricular arrhythmia, ventricular arrhythmia

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