Journal Pre-proof

COVID-19 and Cardiac Arrhythmias

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PII: S1547-5271(20)30594-4

DOI: https://doi.org/10.1016/j.hrthm.2020.06.016

Reference: HRTHM 8445

To appear in: *Heart Rhythm*

Received Date: 17 May 2020

Revised Date: 14 June 2020

Accepted Date: 15 June 2020

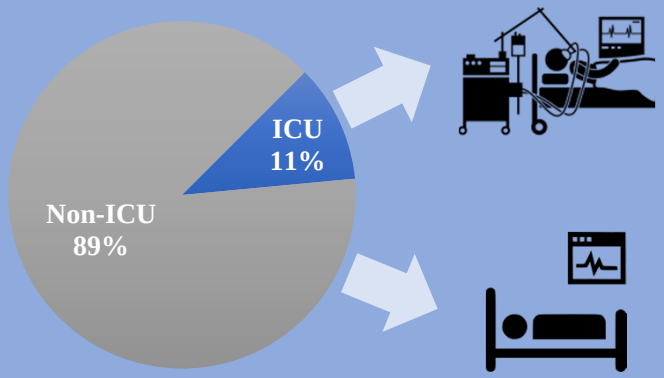
Please cite this article as: Bhatla A, Mayer MM, Adusumalli S, Hyman MC, Oh E, Tierney A, Moss J, Chahal AA, Anesi G, Denduluri S, Domenico CM, Arkles J, Abella BS, Bullinga JR, Callans DJ, Dixit S, Epstein AE, Frankel DS, Garcia FC, Kumareswaram R, Nazarian S, Riley MP, Santangeli P, Schaller RD, Supple GE, Lin D, Marchlinski F, Deo R, COVID-19 and Cardiac Arrhythmias, *Heart Rhythm* (2020), doi: https://doi.org/10.1016/j.hrthm.2020.06.016.

COVID-19 and Cardiac Arrhythmias

Study population

- N = 700 total patients
  - 50 years old
  - 45% male
  - 71% Black
- N = 79 ICU patients
  - Higher prevalence CVD
  - 23% died
- N = 621 non-ICU patients
  - 2% died

Admission status



	CARDIAC ARREST		Incident AF	Brady-arrhythmia	NSVT
	Non-shockable	Shockable			
ICU	8 events	1 events	14 events	5 events	6 events
Non-ICU	0 events	0 events	11 events	4 events	4 events

ICU admission = 10-fold increase arrhythmia risk

Cardiac arrest associated with in-hospital mortality

Severity of illness is an independent marker of cardiac arrest and arrhythmias.

COVID-19 and Cardiac Arrhythmias

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Brief Title: COVID-19 and Cardiac Arrhythmias

Total Word Count: 3601

Conflict of Interest: None

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ABSTRACT

Background: Early studies suggest that coronavirus disease 2019 (COVID-19) is associated with a high incidence of cardiac arrhythmias. SARS-CoV-2 infection may cause injury to cardiac myocytes and increase arrhythmia risk.

Objective: To evaluate the risk of cardiac arrest and arrhythmias including incident atrial fibrillation (AF), bradyarrhythmias, and nonsustained ventricular tachycardia (NSVT) in a large urban population hospitalized for COVID-19. We also evaluated correlations between the presence of these arrhythmias and mortality.

Methods: We reviewed the characteristics of all COVID-19 patients admitted to our center over a 9-week period. Throughout hospitalization, we evaluated the incidence of cardiac arrests, arrhythmias and in-patient mortality. We also used logistic regression to evaluate age, sex, race, body mass index, prevalent cardiovascular disease, diabetes, hypertension, kidney disease and ICU status as potential risk factors for each arrhythmia.

Results: Among 700 patients (mean age 50±18 years, 45% men, 71% African American, and 11% received ICU care), there were 9 cardiac arrests, 25 incident AF events, 9 clinically significant bradyarrhythmias, and 10 NSVTs. All cardiac arrests occurred among patients admitted to the ICU. In addition, admission to the ICU was associated with incident AF (OR 4.68 [95% CI 1.66 – 13.18]) and NSVT (OR 8.92 [95% CI 1.73 – 46.06]) after multivariable adjustment. Also, age and incident AF (OR 1.05 [95% CI 1.02 – 1.09]); and prevalent heart failure and bradyarrhythmias (OR 9.75 [95% CI 1.95 – 48.65]) were independently associated. Only cardiac arrests were associated with acute, in-hospital mortality.

Conclusion: Cardiac arrests and arrhythmias are likely the consequence of systemic illness and not solely the direct effects of COVID-19 infection.

Keywords: COVID-19, cardiac arrest, arrhythmia, mortality

Abbreviations

1. COVID-19: Coronavirus disease 2019
2. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
3. ICU: intensive care unit
4. AF: atrial fibrillation
5. NSVT: nonsustained ventricular tachycardia
6. BNP: B-type natriuretic peptide

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a global pandemic, infecting more than one million patients in the United States as of early May 2020.[1] Early reports from China suggested an overall cardiac arrhythmia incidence of 17% in hospitalized COVID-19 patients. A higher arrhythmia rate (44%) was observed in COVID-19 patients admitted to the intensive care unit (ICU).[2] However, details of the type and burden of arrhythmias in this population have not been elucidated. Similarly, in another observational report from China that included 187 hospitalized patients, Guo et al reported an overall ventricular tachycardia (VT) / ventricular fibrillation (VF) incidence rate of 7% during hospitalization.[3] In addition, reports from Italy and New York City have described a concomitant increase in out-of-hospital cardiac arrests that are associated with the cumulative incidence of COVID-19.[4,5] These findings raise concerns that SARS-CoV-2 infection and secondary cardiac injury may increase the arrhythmia risk.

We sought to systematically evaluate the risk of cardiac arrest and arrhythmias including incident atrial fibrillation (AF), bradyarrhythmias, and nonsustained ventricular tachycardia (NSVT) in a large, urban patient population hospitalized for COVID-19. We also evaluated correlations between the presence of these arrhythmias and acute, in-hospital mortality.

Methods

Study Population

Our inpatient cohort included all COVID-19 patients admitted at the Hospital of the University of Pennsylvania between March 6, 2020 and May 19, 2020. In total, 700 patients had

confirmed SARS-CoV-2 infection by polymerase chain reaction testing of a nasopharyngeal sample. The study received expedited approval by the Institutional Review Board at the University of Pennsylvania.

Covariates

We systematically evaluated all clinical records to obtain demographics and medical comorbidities. In addition, we recorded the admission profile that included vitals, laboratory tests, and antiviral medications received during hospitalization. Demographics included age, sex, and race. Comorbid conditions included any history of coronary heart disease, which is defined as coronary artery disease or myocardial infarction, heart failure, hypertension, history of AF, diabetes, obstructive sleep apnea (OSA), chronic obstructive pulmonary disease (COPD), liver disease, and chronic kidney disease (CKD). We also evaluated any procedural history of implantable cardioverter-defibrillator (ICD) or permanent pacemaker placement.

Admission data included temperature, oxygen saturation on presentation, and body mass index (BMI). Basic laboratory measures included white blood cell count and electrolytes (potassium and magnesium). In addition, we recorded troponin, B-type natriuretic peptide (BNP), D-dimer, procalcitonin, and high sensitivity C-reactive protein (CRP).

Outcomes

We determined clinical outcomes (deceased, hospitalized, or discharged) for each patient by the time of censoring on May 24, 2020. Each patient's medical chart was also reviewed for

the presence of cardiac arrest or arrhythmias. Specifically, for all patients, we reviewed telemetry logs, nursing records, and physician notes for cardiac arrests and arrhythmias including incident AF, bradyarrhythmias, and NSVT. Patients with a history of AF were excluded from the incident AF analysis. We defined bradyarrhythmias as clinically significant episodes of bradycardia that were associated with hypotension. For these cases, we also confirmed that a medical intervention was performed. For cardiac arrests, we documented whether the initial rhythm recorded was VF, VT, sinus bradycardia, heart block, asystole, or pulseless electrical activity.

Statistical Analysis

All data were included as study variables to characterize admitted patients. Baseline characteristics were compared between ICU and non-ICU patients using chi-squared, Student's t, Fisher's exact, or Mann-Whitney U-test. We then calculated the incidence of cardiac arrests and arrhythmic events: incident AF, bradyarrhythmias, and NSVT. We used logistic regression to evaluate the association between selected clinical characteristics including age, sex, race, BMI, history of heart failure, CHD, diabetes, hypertension, CKD and ICU status and each arrhythmia in univariate and multivariable models. In exploratory analysis, we also used logistic regression analysis to evaluate the association between each arrhythmia type and in-hospital mortality in both unadjusted and adjusted analyses. Multivariable models adjusted for age, sex, race, BMI, history of heart failure, CHD, diabetes, hypertension, CKD, ICU status on admission, and hydroxychloroquine use. SAS, version 9.4 (SAS Institute INC, Cary, North Carolina) was used for these analyses, and a p-value <0.05 was considered statistically significant.

Results

Our hospitalized cohort of 700 COVID-19 patients had a mean age of 50±18 years (Table 1), 45% were male, and 71% were African American. The majority of patients were admitted to a non-ICU setting that included cardiac telemetry. Only 11% of patients were admitted to the ICU. Compared to those admitted to a non-ICU setting, patients in the ICU were older, had a higher prevalence of cardiovascular disease, hypertension, diabetes, pulmonary disease including OSA and COPD, liver disease, and CKD. ICU patients also had a lower oxygen saturation on presentation than non-ICU patients. In terms of the biomarker profile, ICU patients were more likely to have an elevated troponin and greater concentrations of BNP, D-dimer, procalcitonin, and high sensitivity CRP on admission than patients admitted to the non-ICU setting. Further, ICU patients were more likely to be administered hydroxychloroquine or remdesivir than non-ICU patients. We did not observe any differences in sex or race according to ICU status. Only 6% of patients in our cohort had a history of AF, and 3% had a cardiac implantable electronic device that included either an ICD or permanent pacemaker. No differences were observed in any of these arrhythmic measures according to ICU status.

Outcomes

Among our cohort that included all COVID-19 inpatient admissions spanning a 74-day period, there were 30 patients (4% of the cohort) who died, 613 patients (88% of the cohort) who were discharged and 57 (8% of the cohort) who remained hospitalized at the time of study censor. Compared to those patients initially admitted to a non-ICU ward, the ICU patients were

more likely to die in-hospital (23% of the ICU group compared to 2% of the non-ICU group, p<0.001). Throughout hospitalization, there were 53 arrhythmic events. Specifically, 9 patients had a cardiac arrest including 6 cases of pulseless electrical activity (PEA), 2 asystole events, and 1 episode of torsades de pointes (Table 2). In addition, there were 25 incident AF events that required pharmacologic management with amiodarone and diltiazem, 9 clinically significant bradyarrhythmias, and 10 NSVT events (Figure 1). We did not observe any cases of heart block, sustained VT, or VF in our cohort of COVID-19 patients.

Among the assessment of selected variables that included age, sex, race, BMI, history of heart failure, CHD, diabetes, hypertension, CKD, and ICU status on admission, only ICU status emerged as having an association with each arrhythmia category. In unadjusted analysis, admission to the ICU was associated with a greater than 10-fold odds of developing each arrhythmia (Figure 2). All cardiac arrest patients had been admitted to the ICU on initial presentation and prior to the development of cardiac arrest. Further, after adjustment for age, sex, race, BMI, prevalent cardiovascular disease, diabetes, hypertension, CKD, and hydroxychloroquine treatment, ICU status remained independently associated with incident AF and NSVT; however, the odds for bradyarrhythmias was rendered nonsignificant (Figure 2). An increase in 1-year of age was associated with incident AF (OR 1.06 [95% CI 1.04 – 1.09]), bradyarrhythmia (OR 1.03 [95% CI 1.00 – 1.06]), and NSVT (OR 1.04 [95% CI 1.01 – 1.08]) in univariate analysis. After multivariable adjustment, only age and incident AF remained independently associated (OR 1.05 [95C CI 1.02 – 1.09]). Further, heart failure was associated with incident AF (OR 5.61 [95% CI 2.37 – 13.25]) and bradyarrhythmias (OR 9.16 [95% CI 2.41 – 34.79]) in univariate analysis. After multivariable adjustment, prevalent heart failure remained independently associated with bradyarrhythmias (OR 9.75 [95% CI 1.95 – 48.65]). No

associations were observed between sex, race, BMI, diabetes, hypertension, and CKD and any of the arrhythmia categories in either univariate or multivariable analyses.

In exploratory analysis, our findings demonstrate that cardiac arrest is associated with in-hospital mortality (OR 20.47 [95% CI 5.19 – 80.69]) even after controlling for age, sex, race, prevalent cardiovascular disease, ICU status, and hydroxychloroquine treatment (OR 34.99 [95% CI 3.49 – 350.69]). In addition, AF was associated with in-hospital mortality (OR 6.73 [95% CI 2.52 – 17.98]) but was attenuated to nonsignificance after multivariable analysis. No association was observed between bradyarrhythmias, NSVT and acute mortality (Figure 3).

Discussion

In our analysis of 700 COVID-19 patients admitted over a 2.5 month period, 30 patients died in-hospital. The overall acute mortality was over 10-fold higher in ICU patients compared with non-ICU patients. We identified 53 arrhythmia-related events including 9 cardiac arrests, 25 incident AF cases, 9 clinically significant bradyarrhythmias, and 10 NSVTs. With the exception of the cardiac arrest cases, none of the 3 arrhythmia types were independently associated with acute mortality.

Our findings suggest that the incidence of cardiac arrests and arrhythmias in COVID-19 patients corresponds to the severity of illness and is not the sole consequence of the viral infection. The acute, in-hospital mortality rates in both our ICU population and the recent

studies from New York are similar and slightly more than 20%.[6,7] The cardiac arrest rate of 11% observed in our ICU population approximates the 13% cardiac arrest rate observed across New York.[6] The slightly higher rate in New York may be explained by combination treatment with hydroxychloroquine and azithromycin – medications that result in QT prolongation and independently increase the risk of cardiac arrest.[6] None of the patients in our center were treated with azithromycin. Our findings also expand on these initial observations by specifying that nearly all of the cardiac arrests in our COVID-19 population included non-shockable rhythms such as PEA or asystole. Only 1 case of torsades de pointes was present. We did not observe the burden of sustained VT/VF that was reported from the early experiences in Wuhan.[2,3] Our findings support that non-cardiac causes such as systemic infection, inflammation and illness are likely to contribute more to the etiology of cardiac arrest than direct myocardial infection with or necrosis due to the viral infection. Further support is also provided by our study's non-ICU population of 621 patients, who had a much lower rate of acute mortality. No cardiac arrests were observed in this group, which comprised nearly 90% of our COVID-19 population.

Patients with more severe systemic illness as evidenced by ICU admission also had a greater likelihood of developing cardiac arrhythmias. The association with bradyarrhythmias could be explained after accounting for demographic and clinical differences such as underlying cardiovascular risk factors and disease between ICU and non-ICU patients. However, unmeasured factors that relate to the severity of illness likely explain the ongoing, independent association between ICU admission and incident AF and NSVT. Recent findings from the University of Alabama Birmingham also support the higher likelihood of observing atrial arrhythmias in the ICU versus non-ICU population.[8] These consistent findings should highlight

considerations for long-term anticoagulation therapy. COVID-19 can present with thrombotic complications including arterial and venous thrombosis.[9] SARS-Cov-2 infection of endothelial cells is postulated to result in a cytokine response with release of inflammatory mediators that lead to endothelial and hemostatic activation.[10,11] This inflammatory state may increase risk of thromboembolic complications especially when atrial fibrillation is present. Future studies will need to evaluate the most effective and safest strategies for long-term anticoagulation and rhythm management in this population.

Our study has several limitations. This analysis was from a single center serving a large urban population. As such, our findings may not be generalizable to COVID-19 patients from across the world. In addition, some patients in the non-ICU ward were taken off telemetry during their hospitalization. As such, our ability to detect subclinical arrhythmias in these patients would be limited. Finally, our analysis was restricted to inpatient follow-up only. As such, we are unable to assess whether the presence of arrhythmic events have long-term health effects on our treated COVID-19 patients.

Conclusion

In summary, 11% of the hospitalized COVID-19 patients at our center were admitted to the ICU. Cardiac arrest and arrhythmias were more likely to occur in the ICU population compared to the non-ICU population even after controlling for underlying demographic and clinical factors. As such, cardiac arrests and arrhythmias are likely the consequence of systemic illness and not solely the direct effect of COVID-19 infection.

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Funding Source: Partial support for this project was provided by the Winkelman Family Fund in Cardiovascular Innovation.

Table 1. Baseline characteristics of COVID-19 patients at time of admission				
Characteristics	**Overall**	**ICU patients**	**Non-ICU patients**	**P value***
Number of patients	700	79	621	-
Demographics				
Age (years) ± SD	50 ± 18	63 ± 16	48 ± 18	<.0001
Male, n (%)	314 (45)	40 (51)	274 (44)	0.27
African American, n (%)	486 (71)	51 (68)	435 (72)	0.52
Comorbidities				
Coronary heart disease, n (%)	76 (11)	21 (27)	55 (9)	<.0001
Heart failure, n (%)	88 (13)	22 (28)	66 (11)	<.0001
Hypertension, n (%)	347 (50)	62 (78)	285 (46)	<.0001
Atrial fibrillation history, n (%)	39 (6)	5 (6)	34 (5)	0.79
ICD/PPM, n (%)	20 (3)	5 (6)	15 (2)	0.064
Diabetes mellitus, n (%)	182 (26)	35 (44)	147 (24)	<.0001
Obstructive sleep apnea, n (%)	124 (18)	23 (29)	101 (16)	0.0048
COPD, n (%)	63 (9)	14 (18)	49 (8)	0.0040
Liver disease, n (%)	67 (10)	14 (18)	53 (9)	0.0089
Chronic kidney disease, n (%)	80 (11)	16 (20)	64 (10)	0.0089
Current tobacco, n (%)	51 (9)	4 (7)	47 (10)	0.49
Admission profile				
Temperature (˚F) ± SD	98.6 ± 1.0	98.9 ± 1.6	98.6 ± 0.9	0.14
Oxygen saturation on presentation (%), ± SD	92.2 ± 11.7	89.4 ± 10.3	92.5 ± 12.0	0.0006
BMI (kg/m2) ± SD	31 ± 9	33 ± 12	31 ± 8	0.14
Baseline laboratory values				
WBC count (cells/μl) ± SD	7.3 ± 3.9	9.9 ± 6.3	6.9 ± 3.2	<.0001
Potassium (mmol/L) ± SD	4.1 ± 0.5	4.3 ± 0.8	4.0 ± 0.5	0.0178
Magnesium (mmol/L) ± SD	1.9 ± 0.4	2.1 ± 0.5	1.9 ± 0.3	0.0992
Non-elevated troponin†, n (%)	291 (78)	44 (62)	247 (82)	0.0003
BNP (pg/mL) ± SD	2940 ± 7962	5347 ± 10381	2214 ± 6950	<.0001
D-dimer (ng/mL) ± SD	3.3 ± 10.9	7.2 ± 21.1	2.2 ± 5.1	0.0005
Procalcitonin (ng/mL) ± SD	1.7 ± 9.9	2.8 ± 10.8	1.4 ± 9.6	<.0001
High sensitivity CRP (mg/L) ± SD	85.3 ± 55.3	112.3 ± 52.1	75.1 ± 53.1	<.0001
Medications during hospitalization				
Hydroxychloroquine, n (%)	172 (25)	53 (67)	119 (19)	<.0001
Remdesivir, n (%)	57 (8)	20 (25)	37 (6)	<.0001

BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ICD, implantable cardioverter defibrillator; ICU, intensive care unit; PEA, pulseless electrical activity; PPM, permanent pacemaker; NSVT, non-sustained ventricular tachycardia;

RA, room air; WBC, white blood cell

* P-value comparisons for ICU versus non-ICU patients

† Non-elevated troponin on admission is defined as less than 0.010 ng/mL.

Table 2. Characteristics of cardiac arrests in COVID-19 patients				
Patient No.	**Cardiac arrest on hospital day no.**	**Cardiac arrest rhythm**	**Background / etiology**	**Outcome**
1	1	Asystole	85 yo nursing home resident presenting with respiratory distress	ROSC; eventually WOC
2	5	PEA	59 yo h/o systemic scleroderma and recent hospitalization for ILD. Pt presented with pneumonia and hypoxia.	ROSC; remains hospitalized
3	2	PEA	35 yo elective C-section and diagnosed with COVID-19 per routine screening. Suspected amniotic fluid embolism.	ROSC; discharged with baby
4	18	PEA	41 yo h/o obesity, CHD, diabetes presented with respiratory distress.	ROSC; remains hospitalized
5	5	PEA	55 yo with mitral valve endocarditis and developed acute stroke. Recovering from mechanical thrombectomy and became non-responsive.	Deceased
6	5	PEA	50 yo with h/o scleroderma post-double lung transplantation 2.5 years prior presented with respiratory failure.	Deceased
7	45	Asystole	74 yo presented with respiratory failure. Complicated hospitalization including multi-organ dysfunction.	Deceased
8	1	TdP	42 yo presented with respiratory failure. Complicated hospitalization including left ventricular dysfunction and ECMO.	ROSC; remains hospitalized
9	1	PEA	43 yo h/o morbid obesity presented with fevers and respiratory distress.	ROSC; discharged

Abbreviations: yo, years old; CHD, coronary heart disease; ECMO, extracorporeal membrane oxygenation; h/o, history of; HTN, hypertension; ILD, interstitial lung disease; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; TdP, torsades de pointes; WOC, withdrawal of care

Figure Legend

Figure 1. Arrhythmic Events by ICU Status

The number of cardiac arrests and arrhythmias are depicted in the entire cohort of COVID-19 patients (dark blue), those admitted to the ICU (light blue), and those admitted to non-ICU wards (orange).

Figure 2. Association of ICU Status and Cardiac Arrhythmias

The odds ratios (and 95% CIs) of ICU admission and specified cardiac arrhythmias are depicted. The dashed, vertical red line represents an odds ratio = 1. Unadjusted models have a blue marker. Multivariable models (black marker) adjusted for age, sex, race, body mass index, heart failure, coronary heart disease, diabetes, hypertension, chronic kidney disease, and hydroxychloroquine treatment.

Figure 3. Cardiac Arrhythmias and Death

The percent of deceased and alive patients in each arrhythmia category is depicted.

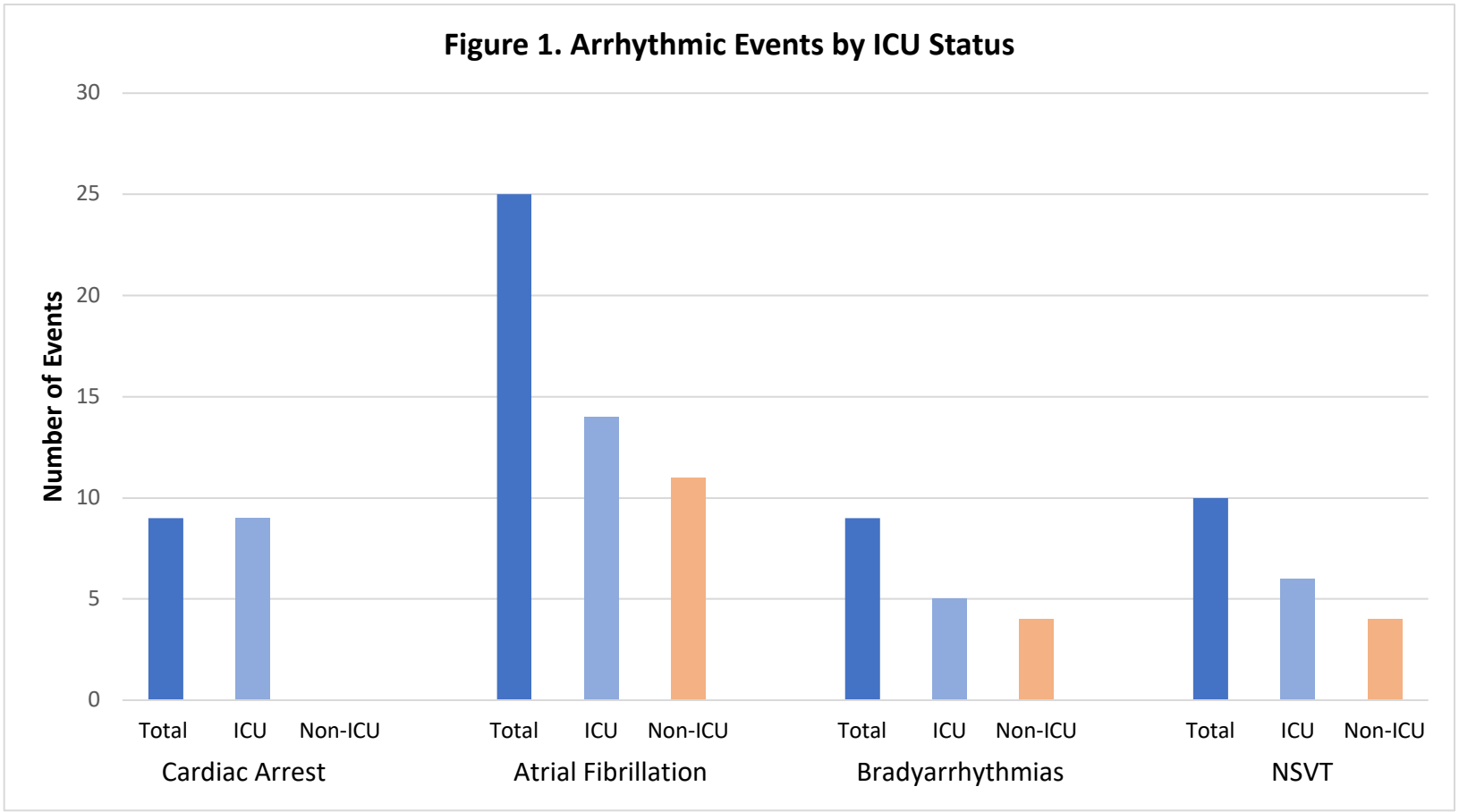
Figure 1. Arrhythmic Events by ICU Status
Number of Events
30
25
20
15
10
5
0
Total
ICU
Non-ICU
Cardiac Arrest
Atrial Fibrillation
Bradyarrhythmias
NSVT

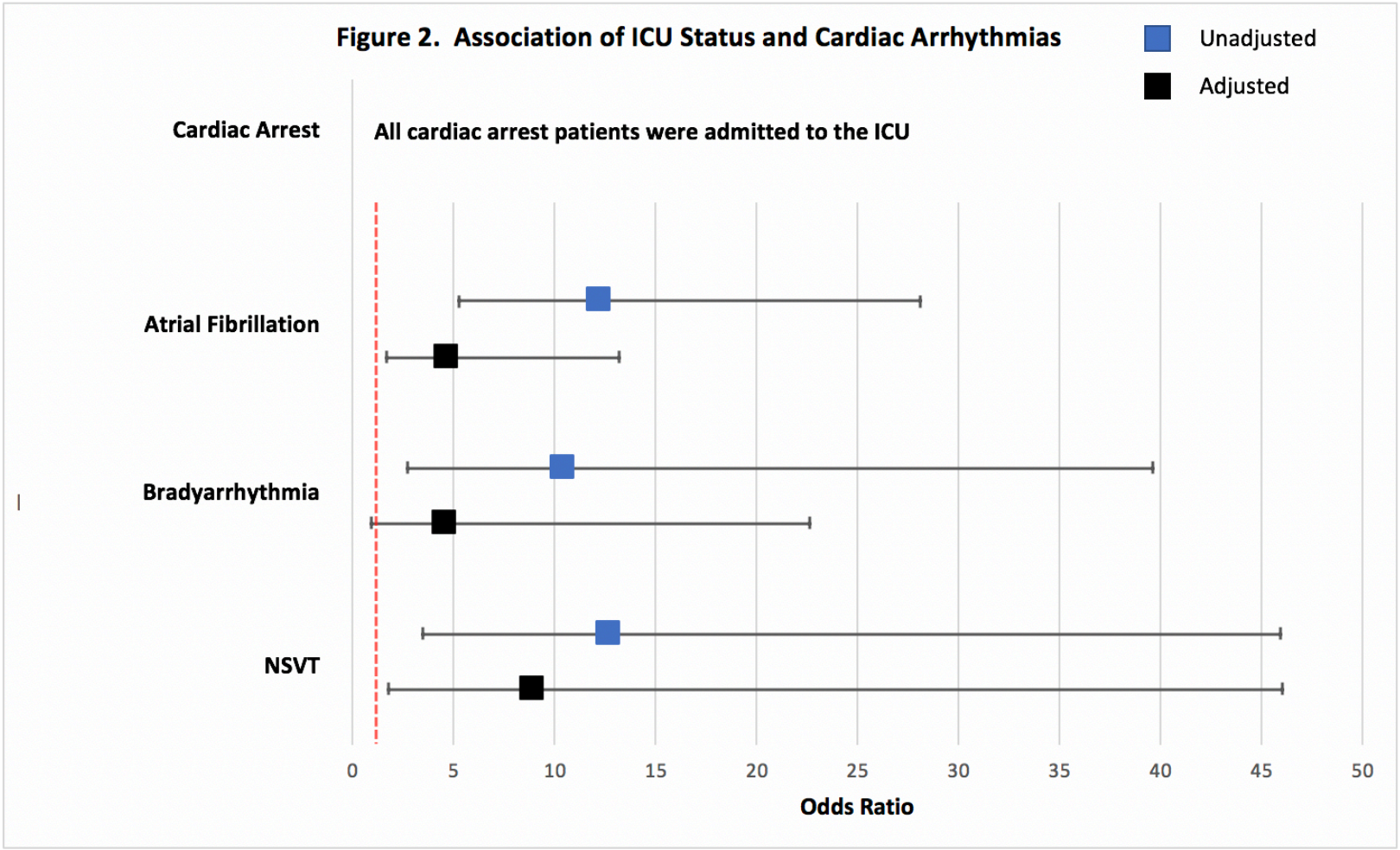
Figure 2. Association of ICU Status and Cardiac Arrhythmias
Unadjusted
Adjusted
Cardiac Arrest
All cardiac arrest patients were admitted to the ICU
Atrial Fibrillation
Bradyarrhythmia
NSVT
0
5
10
15
20
25
30
35
40
45
50
Odds Ratio

Figure 3. Cardiac Arrhythmias and Death