Malignant Arrhythmias in Patients with COVID-19: Incidence, Mechanisms and Outcomes

Running title: *Turagam & Musikantow et al.; Malignant Arrhythmias in COVID-19*

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Abstract:

Background - Patients with coronavirus disease 2019 (COVID-19) who develop cardiac injury are reported to experience higher rates of malignant cardiac arrhythmias. However, little is known about these arrhythmias – their frequency, the underlying mechanisms, and their impact on mortality.

Methods - We extracted data from a registry (NCT04358029) regarding consecutive inpatients with confirmed COVID-19, were receiving continuous telemetric ECG monitoring, and had a definitive disposition of hospital discharge or death. Between patients who died versus discharged, we compared a primary composite endpoint of cardiac arrest from ventricular tachycardia/fibrillation or bradyarrhythmias such as atrio-ventricular block.

Results - Among 800 COVID-19 patients at Mount Sinai Hospital with definitive dispositions, 140 patients had telemetric monitoring and either died (52) or were discharged (88). The median (IQR) age was 61 years (48 – 74); 73% men; and ethnicity was Caucasian in 34%. Comorbidities included hypertension in 61%, coronary artery disease in 25%, ventricular arrhythmia history in 1.4%, and no significant comorbidities in 16%. Compared to discharged patients, those who died had elevated peak troponin I levels (0.27 vs 0.02 ng/mL), and more primary endpoint events (17% vs 4%, p = 0.01), a difference driven by tachyarrhythmias. Fatal tachyarrhythmias invariably occurred in the presence of severe metabolic imbalance, while atrioventricular block was largely an independent primary event.

Conclusions - Hospitalized COVID-19 patients who die experience malignant cardiac arrhythmias more often than those surviving to discharge. However, these events represent a minority of cardiovascular deaths, and ventricular tachyarrhythmias are mainly associated with severe metabolic derangement.

Registration - clinicaltrials.gov; Unique Identifier: NCT04358029

Key words: arrhythmia; ventricular fibrillation; all-cause death; myocardial infarction; atrioventricular block; Coronavirus, COVID-19

Nonstandard Abbreviations and Acronyms

COVID-19: Coronavirus disease 2019

RT-PCR: Reverse-transcriptase-polymerase-chain-reaction

AMCAs: Acute malignant cardiac arrhythmias

VT: Ventricular tachycardia

VF: Ventricular fibrillation

MI: Myocardial infarction

PEA: Pulseless electrical activity

ECMO: Extracorporeal membrane oxygenation

Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic caused by a novel enveloped RNA betacoronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1-3] As of May 23, 2020, the infection has been confirmed in ~5 million individuals worldwide, and the United States was most affected, with over 1.5 million cases.[4]

In addition to severe clinical symptoms, COVID-19 is associated with a substantial risk for death. The worldwide case-fatality ratio is currently estimated at 6.5% and 6% in the United States.[4] Indeed, as of May 23, 2020, over 340,000 individuals have died worldwide, of whom ~97,000 have died in the U.S., in turn of whom nearly one-fifth are from New York City alone.[4]

These staggering numbers obligate a better understanding of how COVID-19 culminates in death. Early reports identified demographic characteristics predicting poor outcomes,

including older age and comorbidities such as hypertension, diabetes and cardiovascular disease.[5-9] While these general risk factors don't provide much mechanistic information, a relationship has been observed between elevated levels of certain biomarkers and COVID-19 related mortality.[5-10] These observations have provoked intense speculation as to the nature and significance of this cardiac injury.[9, 11]

Intriguingly, there is a reported interaction between disease severity and cardiac arrhythmias, with the latter reportedly ranging in frequency from 16.7% to 30.3%, and even higher rates (44.4% to 74.6%) reported in critically ill COVID-19 patients. Indeed, "malignant" ventricular arrhythmias were reported in 17.3% of COVID-19 patients with abnormal troponin levels.[5, 12] However, the exact nature and frequency of these malignant arrhythmias have not been well-characterized.[13] Accordingly, we conducted a rigorous patient-level analysis to determine whether acute malignant cardiac arrhythmias (AMCAs), such as tachy- or bradyarrhythmias, are major contributors to the demise of hospitalized Covid-19 patients. Furthermore, we characterized whether these arrhythmic events were the primary incitements or merely epiphenomena of the severe hypoxic and metabolic stress of this critical illness.

Methods

Study Population and Data Collection

The data that support the findings of this study are available from the corresponding author upon reasonable request. This single-center retrospective cohort study included consecutive adult patients (≥18 years old) with laboratory-confirmed COVID-19 infection admitted to Mount Sinai Hospital (New York, NY) between March 7 and April 12, 2020 as part of a COVID-19 registry (NCT04358029). Patients were diagnosed with COVID-19 infection based on a reverse-

transcriptase-polymerase-chain-reaction (RT-PCR) assay of a nasal or pharyngeal swab specimen.

Laboratory confirmed COVID-19 patients were included provided they received i) at least 24 hours of continuous inpatient telemetric electrocardiographic monitoring, and ii) reached a final disposition –death or hospital discharge. The decision to receive telemetry was partially based on the physician assessment of acuity of illness, but mostly on the availability of telemetry in a resource-constrained environment (that is, allocation based on first available bed). Patients who remained hospitalized for ongoing treatment, pregnant women, and children (age <18 years) were excluded. Patients readmitted during the study period were also excluded from analysis. A successful hospital discharge comprised of near-complete resolution of clinical symptoms with resolution of fever and improvement in blood inflammatory markers.

We extracted patient demographics, laboratory findings, imaging results, EKG/telemetry data, treatments received, and clinical outcomes on admission and during hospitalization from the electronic medical records. All available imaging scans, electrocardiographic and telemetry data were reviewed by experienced cardiologists, and differences in interpretation were reconciled by consultation with a senior electrophysiologist. Telemetry data were obtained by General Electric (GE) monitoring systems (GE Healthcare, Waukesha, WI) from 191 inpatient beds and 101 critical care beds and stored at 240 hz with 12-bit magnitude using BedMasterEx V5.1.2 (Excel Medical Electronics LLC., Jupiter, FL). Allocation to these units was based on acuity of illness, physician discretion and bed availability. During high patient volumes, ICU rooms housed two patients in which case, one patient's data was not recorded. Available autopsy reports were also examined.

The study was approved by the institutional review board governing research in human subjects at the Icahn School of Medicine at Mount Sinai, which waived informed consent. Extracted data were secured in a computerized database and missing data clarified by revisiting the electronic medical records. Patient level data were de-identified prior to analysis. The authors had full access to the data and take responsibility for the integrity of the data. All authors have read and agree to the findings in the manuscript as written.

Study Outcomes

The composite primary endpoint was acute malignant cardiac arrhythmias (AMCAs) as defined by either ventricular tachycardia (VT) or fibrillation (VF) or bradyarrhythmias such as atrioventricular block causing hemodynamic compromise or cardiac arrest. The secondary endpoint was acute ST-elevation myocardial infarction (MI).

Study Definitions

Cardiac arrest from VT/VF or AV block was defined as sudden loss of consciousness with no signs of systemic circulation. Acute MI was defined by chest pain (if conscious) and new ST-elevation in two or more contiguous electrocardiographic leads (when available).[14] Similarly, myocardial injury was defined by a rise and/or fall of blood troponin values with at least 1 value above the 99th percentile upper reference limit. Pulseless electrical activity (PEA) was defined by organized or semi-organized cardiac electrical activity other than ventricular tachycardia or ventricular fibrillation resulting in hemodynamic compromise and/or death.

Acute respiratory distress syndrome[15], acute kidney injury, and septic shock were defined according to the standard guidelines.[16] Cardiovascular mortality was defined as death attributable to acute myocardial infarction, decompensated heart failure, cerebrovascular accident or cardiac

arrest from primary VT or VF. Mortality due to other causes was categorized as non-cardiovascular deaths.

Laboratory Confirmation

Clinical specimens were obtained and diagnostic testing for COVID-19 performed as recommended by the Centers for Disease Control and Prevention (CDC) in patients who met clinical and epidemiological criteria. The RT-PCR tests were performed using the Roche's cobas 6800 System (Basel, Switzerland) which targets ORF1 gene (Target 1) and SARS-CoV-2 E gene (Target 2).[17] If both targets were detected, the assay was reported as positive; detection of Target 2 without Target 1 was interpreted as a presumptively positive.

Statistical Analyses

Based on previous reports demonstrating a high prevalence of arrhythmias, as well as elevated troponin levels in 1 of 5 COVID-19 patients, we hypothesized that COVID-19 patients who die would have a substantially higher incidence of AMCAs (VT/VF or AV block) than those surviving to discharge. Because the relative rate of accrual of consecutive telemetry patients varied between groups, a sample size curve was derived based on an 80% chance of detecting, as significant at the 5% level, an increase in the primary outcome from 3% in the Discharged group to 17% in the Mortality group.[5] Based on the ratio of Discharged:Mortality subjects, between 139 and 160 total patients were required (see **Supplement** for details). At the manifest discharge: mortality ratio of 1.7, the sample size of 140 patients provided sufficient power for the primary endpoint.

Continuous variables were summarized as median and interquartile range (IQR) or means and standard deviations, as appropriate. Categorical variables were summarized as counts or percentages. No imputation was made for missing data. Mann-Whitney U test, Fisher's exact

test or χ^2 test was used to compare data between dead and discharged patients where appropriate. Poisson linear regression model was used to analyze the composite primary outcomes and calculate the incidence rate ratios between the patients who died or survived hospitalization. A multivariable binary logistic regression analysis was performed to calculate the odds ratio to estimate the association of risk between mortality and various covariates. A model was created including various risk factors which were significant on univariable analysis and had ≥10 events. A p-value ≤0.05 (2-tailed) was considered statistically significant. Statistical analysis was performed using SPSS version 25.0 (IBM Corp, Armonk, NY).

Results

Demographics and Clinical Characteristics

A total of 1,354 patients were screened using electronic medical records from March 7, 2020 to April 12, 2020, of whom 800 patients were hospitalized for treatment of Covid-19. Among these 670 were discharged and 130 died. No telemetry data were available from 78 patients who died and 582 patients who were discharged, leaving 140 consecutive patients (Mortality group=52 and Discharge group=88) for final analysis (Supplemental Figure 1).

As shown in Table 1, the median age of the patient cohort was 61 years (range 23-97 years), 102 (73%) patients were men and only 47 (38%) were Caucasian. Among the overall population, 84% had at least one coexisting illness. Compared with patients in the Discharge group, patients in the Mortality group were older (median [IQR] 71 (58-78) vs 58 (45-71) years; p<0.0001), and more likely to have chronic kidney disease (25% vs 10%, p=0.03) and obesity (body mass index≥30). There were no significant differences between groups in the frequency

of other chronic comorbidities including hypertension, diabetes, coronary artery disease, chronic obstructive airway disease or heart failure. (Table 1)

Laboratory and Radiological Findings

Table 1 details the laboratory and radiological findings upon admission and during hospitalization. On admission, when compared with the Discharge group, patients in the Mortality group presented with significantly elevated inflammatory markers such as C-reactive protein, procalcitonin, and interleukin (IL)-6.

Patients in the Mortality group also had significantly higher D-dimer levels at admission (median 2.4 vs 1.2, p=0.001), peak (5.2 vs 1.8, p<0.0001) and last known (3.8 vs 1.1, p<0.0001) timepoints compared with the Discharge group. Furthermore, both admission (0.03 vs 0.01 ng/mL, p<0.0001) and peak (0.27 vs 0.02 ng/mL, p<0.0001) troponin I levels were significantly elevated in the Mortality group compared with Discharge group.

Treatments and Complications

Admission to the ICU (42% vs 20%) and initiation of invasive mechanical ventilation (40% vs 7%) during admission occurred more often in the Mortality group than Discharge group. (Table 2).

Twenty patients (14%) were admitted with severe hypotension requiring vasopressors, occurring more often in the Mortality group (15 patients, 29%) than the Discharge group (5 patients, 6%). A higher percentage of patients who died received class III antiarrhythmic drugs than those who survived (23% vs 4%). There were no significant differences in the proportions of patients who received hydroxychloroquine, tocilizumab, sirolumab and remdesivir in the two groups.

During hospitalization, 47% had a diagnosis of myocardial injury, followed by shock (33%) and acute respiratory distress syndrome (ARDS) (30%) – all significantly higher among patients in the Mortality group.

Clinical Outcomes

In the overall cohort, primary endpoint events occurred in 12 patients (9%) – 7 patients (5%) with VT/VF and 5 patients (3.5%) with AV block (***Table 3***). This primary composite endpoint occurred more frequently in the Mortality *vs* Discharge group (17% vs 4%; Incidence rate ratio 5.1, 95% CI 1.4 -18.7, p=0.01). The difference was mainly driven by the higher incidence of VT or VF in the Mortality group (11%) compared with the Discharge group (1%; p=0.01). The secondary outcome of acute ST-elevation MI occurred in 6 patients (4%); there was no significant difference between groups.

Among the 52 deaths in the Mortality group, only 6 (12%) were categorized as cardiovascular deaths, of which 4 (8%) were attributed to myocardial infarction and 2 (4%) to decompensated heart failure. None of the deaths were directly attributed to either VT/VF or AV block. The rest of the 48 (88%) deaths were categorized as non-cardiovascular deaths. The arrhythmia at the time of death in these patients was PEA in 46 (89%) patients and VT/VF in 6 (11%) patients, respectively.

In the Mortality cohort, 20 patients (38%) received care focusing on palliative/comfort measures. The median time to death after withdrawing aggressive treatments was only 19 hours (interquartile range [IQR] 6-84 hours). The higher rate of primary composite endpoint event in the Mortality group was also observed (19% vs 4%; p=0.02) when comparing the 32 patients who died unexpectedly (without a decision to implement palliative care) with those patients who survived, again mainly driven by VT or VF. However, among these 32 patients, only 4 (12.5%)

deaths were categorized as cardiovascular deaths, 3 deaths due to myocardial infarction and 1 death due to congestive heart failure.

To reduce potential bias related to selective application of telemetry monitoring, we investigated primary outcome events occurring in the 78 patients who died but *without* telemetric monitoring (Supplemental Table S1). In that population, there were only 1 (1%) primary outcome events and only 2 (3%) cardiovascular deaths respectively.

Relationship of Malignant Cardiac Arrhythmias and Mortality

To better distinguish whether the *cause* of mortality was cardiovascular or non-cardiovascular death, we explored associated clinical conditions (Supplemental Tables S2). All 6 patients with ventricular tachyarrhythmias in the Mortality group had VF (Figure 1A), and five of them had either metabolic or hypoxic abnormalities or extremely high vasopressor requirements at the time of death. None of the 6 deaths were categorized as cardiovascular deaths. Furthermore, autopsy data was available for two patients, and both demonstrated large lobar pulmonary emboli. Only one other patient, in the Discharge group, with a history of non-ischemic cardiomyopathy (LVEF 35%) and a biventricular implantable cardioverter pacemaker had monomorphic VT, apparently of outflow tract origin which resolved with medications.

Among the five patients manifesting atrioventricular block, two were associated with myocardial infarction (Figure 1B), two had either metabolic abnormalities or high pressor requirements, suggesting that refractory shock was primarily responsible for conduction block and one patient had AV block in the setting of NSTEMI and newly depressed left ventricular ejection fraction. (Supplemental Table S3)

Univariable analysis demonstrated age>65 years, obesity, myocardial injury, admission IL-6>100 pg/ml, vasopressors during hospitalization, ARDS and composite primary outcomes were significantly different between the death and discharged groups. (Supplemental Table S4)

Predictors of mortality by multivariable binary logistic regression analysis were age>65 years (odds ratio [OR] 3.10 (1.10-9.37), P=0.05), vasopressor during hospitalization (OR 4.97 (1.44-17.10), p=0.01) and ARDS (OR 12.93 (3.20 – 52.17, p<0.0001) but not myocardial injury, obesity or admission IL-6>100 pg/mL ; Supplemental Table S5)

12-Lead Electrocardiographic and Telemetric Monitoring

The 12-lead electrocardiographic findings during admission and prior to death of discharge were benign. Overall, the electrocardiographic intervals, including the QTc interval, remained within normal limits and there were no significant differences between groups (Supplemental Table S6).

The most common rhythm at the time of death/demise was PEA (pulseless electrical activity) which occurred in 46 patients (88%), followed by VF in 6 patients (12%). Importantly, none of these episodes of VF were preceded by other non-sustained ventricular arrhythmias. There were also no instances of QT prolongation culminating in *torsade de pointes*.

Discussion

In this study, patients who died experienced more primary endpoint events of acute malignant arrhythmias including VT/VF or AV block (17% vs 4%, p=0.01) than compared with those discharged. There was no significant difference in the secondary endpoint of ST-elevation myocardial infarction (8% vs 2%, p=0.2).Only a small proportion (12%) of deaths was categorized as cardiovascular deaths, and most of these deaths (67%) occurred in the setting of ST-elevation myocardial infarction. Tachyarrhythmias such as VT/VF invariably occurred in the

setting of severe metabolic stress, while bradyarrhythmias were not necessarily related to metabolic derangements, but could instead be primary inciting events contributing to mortality.

Cardiovascular complications have been reported with the two other major coronaviruses that have caused major epidemics: severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), including reports of left ventricular dysfunction, acute myocarditis, and cardiac arrest.[18] However, the data pale next to the plethora of reports purporting various cardiac arrhythmias in COVID-19. "Arrhythmia" was poorly defined in most of these studies, but one clearly defined "malignant arrhythmia" as rapid ventricular tachycardia lasting more than 30 seconds, inducing hemodynamic instability and/or ventricular fibrillation.[5] They reported malignant arrhythmias in 17.3% of COVID-19 patients with abnormal troponin values, versus only 1.5% for patients with low troponin values.[5] A recent review postulated that this propensity for developing malignant ventricular arrhythmias was related to the hyper-abnormal systemic immune-inflammatory response elicited by the SARS-CoV-2 virus.[19]

Indeed, in the mortality group, we observed significantly higher levels of both the cardiac injury biomarker, troponin I, and the inflammation-related biomarkers, C-reactive protein, procalcitonin and interleukin-6. And using a strict definition of malignant ventricular arrhythmias, and a chart review including a comprehensive review of continuous ECG telemetry, we identified ventricular tachyarrhythmias as the terminal event in 11% of the mortality cohort. But it is important to recognize that these arrhythmias were not preceded by non-sustained ventricular tachyarrhythmia episodes, and all these events were ventricular fibrillation, not ventricular tachycardia. This is more consistent with a nonspecific arrhythmia in the context of a toxic milieu of hypoxemia and metabolic disarray atop a pro-arrhythmogenic environment of catecholamine and inflammatory stress.

Furthermore, careful review of the 12-lead electrocardiograms failed to identify other critical proarrhythmic factors like prolonged QT intervals. Recent data has suggested that 30% of patients treated with hydroxychloroquine/azithromycin for COVID-19 exhibited QT interval prolongation by 40 ms, with 11% increasing to >500 ms.[20] In our study, hydroxychloroquine was used in 76% of our patients for a median duration of 4 days (interquartile range [IQR] 1-5 days), and a QT_c increase by ≥50 ms occurred in 9% of patients. Together, these data suggest that while ventricular arrhythmias *are* more common with severe COVID-19, it is likely that the mechanism is not a specific myocardial inflammatory or coronary vascular process related to SARS-CoV-2, but rather a generalized response to a pulmonary and metabolic catastrophe.

On the other hand, while some instances of atrioventricular block were similarly related to metabolic disarray, it appeared to be the primary cause of cardiac arrest in other patients, including some that survived hospitalization. Similarly, ST-elevation myocardial infarction was also a primary inciting factor in the cardiac arrest. An association of acute coronary syndrome with COVID-19 has been reported.[21,22] However, this connection would not be surprising given the hyper-intense inflammatory response attendant with COVID-19 and associated thrombogenicity. Indeed, the mortality cohort did exhibit markedly elevated levels of the various inflammatory biomarkers. Furthermore, acute myocardial infarction has been frequent during other respiratory infections, particularly H1N1 influenza.[23]

Taken together, these data indicate that AMCAs *do* contribute to the ultimate demise of a small proportion of COVID-19 patients, some involving specific mechanisms potentially amenable to targeted interventions such as pacemaker implantation or revascularization. But the majority may occur as a generalized response to acute critical illness and may not prove amenable to antiarrhythmic interventions.

Limitations

First, this is a retrospective, non-randomized analysis of hospitalized patients with no long-term follow-up data. However, in contrast with many previous COVID-19 studies, all patients in our analysis had a definitive disposition of either hospital discharge or death, and the chart and data review were rigorous. Second, while the power analysis indicated sufficient sample size to test the study hypothesis, the study was not powered to assess for differences in the individual components of the composite endpoint. However, it is unlikely that including more patients would appreciably change any important conclusions. Third, not all hospitalized patients with COVID-19 received telemetry, as allocation of telemetry beds was based partially on medical acuity, and largely upon bed availability at a time of constrained resources, rather than chronic comorbidities. Therefore, we cannot verify the frequency of arrhythmic events in patients who did not receive telemetry monitoring. Fourth, systematic echocardiography and other cardiovascular imaging data are lacking due to the logistic challenges posed by isolation units. But we did have echocardiography results on 9 of our patients, revealing normal ventricular function in most patients (7 of 9; Supplemental Table S7). Fifth, the COVID-19 patients included in the study were admitted earlier during this epidemic in NYC; hence there is some variation in treatments received during hospitalization; however, the efficacy of these treatments is uncertain. Finally, virtually all the patients we studied had normal ventricular function preceding hospitalization. It is possible, indeed likely, that monomorphic VT would have occurred with greater frequency in patients who had preexisting structural heart disease and ventricular scarring.

Conclusions

As COVID-19 rages across the world, there is a pressing need to better understand the mechanisms of mortality in this deadly disease. Our data indicate that malignant arrhythmic events contribute to a minority of deaths in these patients. While ventricular tachyarrhythmias appear largely secondary to metabolic derangement, there are some patients who sustain acute myocardial infarction and/or atrioventricular block that may be amenable to treatment.

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Table 1: Demographics, Clinical Characteristics & Laboratory Data

Characteristics	All Patients		Patient Disposition		p-value
	No. with Available Data	Value	Death (N=52)	Discharged (N=88)	
Median age (range, IQR) – year	140	61 (48 – 74)	71 (58 – 78)	58 (45 – 71)	<0.0001
Male gender (%)	140	102 (73)	38 (73)	64 (73)	0.56
Ethnicity (%)	123				
Caucasian		47 (38)	20 (43)	27 (36)	0.22
African-American		21 (17)	8 (17)	13 (17)	1.00
Hispanic		32 (26)	12 (25)	20 (26)	1.00
Other		23 (19)	7 (15)	16 (21)	0.64
Body mass-index, median (IQR)	139	28.4 (25.3 – 32.8)	29.7 (26.7 – 35.2)	28.1 (24.7 – 32.3)	0.08
Blood Type – O (%)	118	49 (42)	18 (35)	31 (35)	1.00
Comorbidities – no. (%)					
No Comorbidities	140	23 (16)	4 (8)	19 (21)	**0.035**
Hypertension	140	86 (61)	35 (67)	51 (58)	0.29
Diabetes mellitus	140	54 (39)	21 (40)	33 (38)	0.43
Coronary artery disease	140	35 (25)	13 (25)	22 (25)	1.00
Prior Coronary artery bypass surgery	140	4 (3)	1 (2)	3 (3)	1.00
Prior percutaneous coronary intervention	140	20 (14)	8 (15)	12 (14)	0.86
Congestive heart failure	140	22 (16)	11 (21)	11 (13)	0.23
Asthma	140	28 (20)	8 (15)	10 (11)	0.6
Obesity (Body mass-index ≥30)	140	52 (37)	25 (48)	27 (31)	**0.047**
Chronic kidney disease	140	21 (15)	13 (25)	9 (10)	**0.03**
Chronic dialysis	140	6 (4)	4 (8)	2 (2)	0.19
Chronic obstructive pulmonary disease	140	6 (4)	4 (8)	2 (2)	0.19
Obstructive Sleep Apnea	140	18 (13)	9 (17)	9 (10)	0.30
Immunocompromised	140	18 (13)	8 (15)	8 (9)	0.28
Human immunodeficiency virus	140	8 (6)	2 (4)	6 (7)	0.71
History of atrial arrhythmias	140	19 (14)	8 (15)	11 (13)	0.62
History of ventricular arrhythmias	140	2 (1)	1 (2)	1 (1)	1.00
Pacemaker	140	5 (4)	2 (4)	3 (3)	1.00
Implantable Cardioverter Defibrillator	140	4 (3)	1 (2)	3 (3)	1.00
Current or former smoker	138	40 (29)	18 (35)	22 (25)	0.24
Medications – no. (%)					
Angiotensin Converting Inhibitors	140	28 (20)	9 (17)	19 (22)	0.66
Angiotensin Receptor Blockers	140	21 (15)	8 (15)	13 (15)	1.00
Non-steroidal anti-inflammatory drugs	140	6 (4)	2 (4)	4 (5)	1.00
Class I/III Antiarrhythmics	139	6 (4)	4 (8)	2 (2)	0.20

Oral anticoagulants	138	21 (15)	10 (19)	11 (13)	0.33
Laboratory Data – On Admission					
White blood cell count, × 10^9 per L	140	6.6 (4.9 – 10.1)	8.1 (5.0 – 10.2)	6.3 (4.9 – 9.8)	0.4
Lymphocyte count, × 10^9 per L	133	0.9 (0.6 – 1.2)	0.9 (0.5 – 1.3)	0.9 (0.6 – 1.2)	0.45
Hemoglobin, g/L	140	13.1 (11 – 14.4)	12.1 (9.4 – 14.0)	13.4 (12.2 – 14.7)	**0.002**
Platelet count, median (IQR) – × 10^9 per L	140	199 (161 – 256)	187 (131 – 246)	219 (169 – 257)	**0.03**
Albumin, g/L	137	3.3 (2.9 – 3.6)	3.1 (2.7 – 3.5)	3.3 (3.0 – 3.6)	**0.05**
ALT, U/L	139	38 (27 – 56.5)	30 (17 – 48)	28 (17 – 45)	0.68
AST, U/L	140	28 (17 – 46)	46 (26 – 73)	36 (27 – 50)	**0.02**
Lactate, mmol/liter	128	1.6 (1.1 – 2.1)	1.6 (1.0 – 2.1)	1.6 (1.2 – 2.1)	0.77
Lactate dehydrogenase, U/L	128	400 (295 – 545)	481 (331 – 835)	369 (287 – 499)	**0.008**
Serum creatinine, mg/dL	138	1.04 (0.8 – 1.5)	1.45 (0.96 – 2.7)	0.99 (0.8 – 1.3)	**<0.0001**
D-dimer					
On admission, µg/mL	126	1.5 (0.7 – 3.1)	2.4 (1.0 – 4.2)	1.2 (0.5 – 2.3)	**0.001**
Peak level, µg/mL	117	2.9 (1.1 – 6.7)	5.2 (3.3 – 15.9)	1.8 (0.8 – 3.7)	**<0.0001**
Last known value, µg/mL	118	1.8 (0.8 – 3.6)	3.8 (2.6 – 10.4)	1.1 (0.6 – 2.2)	**<0.0001**
Troponin-I					
On admission, ng/mL	133	0.02 (0.01 – 0.07)	0.03 (0.01 – 0.21)	0.01 (0.01 – 0.03)	**<0.0001**
Peak level, ng/mL	120	0.05 (0.01 – 0.38)	0.27 (0.06 – 2.1)	0.02 (0.01 – 0.05)	**<0.0001**
Brain natriuretic peptide					
On admission, pg/mL	86	56 (13 – 218)	75 (16 – 580)	35 (10 – 167)	**0.046**
Peak level, pg/mL	61	87 (21 – 414)	224 (44 – 742)	57 (10 – 233)	**0.009**
Fibrinogen					
On admission, mg/dL	76	557 (443 – 685)	563 (435 – 694)	556 (453 – 685)	0.97
Peak level, mg/dL	73	632 (501 – 761)	639 (526 – 866)	629 (496 – 746)	0.61
Last known value, mg/dl	60	494 (402 – 580)	499 (326 – 643)	480 (425 – 566)	0.85
Serum ferritin, µg/mL	130	715 (340 – 2103)	787 (413 – 2807)	616 (287 – 1858)	0.14
Prothrombin time, sec	115	1.1 (1.00 – 1.30)	1.2 (1.0 – 1.4)	1.1 (1.1 – 1.2)	0.26
C-reactive protein, mg/L	134	105 (46 – 187)	146 (61.2 – 219.3)	87 (31 – 145)	**0.001**
Procalcitonin, ng/mL	132	0.16 (0.08 – 0.6)	0.51 (0.13 – 1.3)	0.12 (0.06 – 0.30)	**<0.0001**
IL-6, pg/mL	91	111 (42 – 234)	160 (82 – 370)	55 (26 – 150)	**<0.0001**
Erythrocyte sedimentation rate, mm/hr	55	59 (24 – 85)	67 (33 – 101)	51 (17 – 77)	0.24
Chest radiography – no./total no. (%)	140				
Bilateral pulmonary infiltrates		97 (69)	42 (81)	55 (62)	**0.015**
Unilateral pulmonary infiltrates		25 (18)	3 (6)	22 (25)	
Clear		18 (13)	7 (13)	11 (13)	
Baseline Transthoracic echocardiography – mean (IQR)					
Left ventricular ejection fraction (%)	82	57 (53 – 65)	55 (51 – 64)	60 (55 – 65)	0.38

All values are expressed as median (IQR), unless otherwise specified.
Values are on admission unless otherwise specified.

Table 2: Treatments & Complications

Characteristics	All Patients (N=140)	Death (N=52)	Survived (N=88)	p-value
Treatments				
Admit to intensive care unit – no. (%)	40 (28)	22 (42)	18 (20)	**0.007**
Invasive mechanical ventilation on Day 1 – no. (%)	27 (19)	21 (40)	6 (7)	**<0.0001**
Invasive mechanical ventilation during hospitalization – no. (%)	52 (37)	41 (79)	11 (12)	**<0.0001**
Non-invasive ventilation during hospitalization – no. (%)	44 (31)	24 (46)	20 (23)	**0.005**
Vasopressor requirement on Day 1 – no. (%)	20 (14)	15 (29)	5 (6)	**<0.0001**
Maximum vasopressor support during hospitalization – mean (SD)	0.54±0.8	1.2±1.0	0.11±0.3	**<0.0001**
Therapeutic anticoagulation – no. (%)	25 (18)	11 (21)	14 (16)	0.5
Hydroxychloroquine – no. (%)	107 (76)	40 (77)	67 (76)	1.0
Azithromycin – no. (%)	62 (44)	24 (46)	38 (43)	0.8
Immunomodulators – no. (%)				
Sirolumab – no. (%)	7 (5)	4 (8)	3 (3)	0.4
Tocilizumab – no. (%)	11 (8)	5 (10)	6 (7)	0.5
Remdesivir – no. (%)	1 (1)	0	1 (1)	1.0
Glucocorticoids – no. (%)	7 (5)	4 (8)	3 (3)	0.4
Antiarrhythmics – no. (%)	15 (11)	12 (23)	3 (4)	**<0.0001**
Class I antiarrhythmics – no. (%)	0	0	0	-
Class III antiarrhythmics – no. (%)	15 (11)	12 (23)	3 (4)	**<0.0001**
Extracorporeal membrane oxygenation – no. (%)	0	0	0	-
Days on mechanical ventilator, median (IQR) – no. (%)	2±3.5	2.3±3.2	2.0±3.5	0.14
Hospital length of stay, median (IQR) – no. (%)	7 (4 – 10)	7 (4 – 11)	7 (4 – 10)	0.8
Complications				
Acute respiratory distress syndrome – no. (%)	43 (30)	34 (65)	8 (9)	**<0.0001**
Myocardial injury – no. (%)	66 (47)	39 (75)	27 (31)	**<0.0001**
Acute kidney injury requiring renal replacement therapy – no. (%)	14 (10)	12 (53)	2 (2)	**<0.0001**
Shock, requiring pressors – no. (%)	46 (33)	36 (69)	10 (11)	**<0.0001**
Ischemic Stroke – no. (%)	6 (4)	2 (4)	4 (4)	1.0
Diabetic ketoacidosis – no. (%)	7 (5)	2 (4)	5 (6)	1.0
Palliative Care – no. (%)	20 (14)	20 (38)	0	**<0.0001**

All values are expressed as median (IQR), unless otherwise specified*

Table 3: Primary Composite Outcome

Characteristics	All Patients (N=140)	Death (N=52)			Survived (N=88)	p-value	
		All Death (N=52)	Comfort Care (N=20)	Not Comfort Care (N=32)		All Death *vs* Survived	Not Comfort Care *vs* Survived
Composite Primary Outcome							
Total – no. (%)	12 (9)	**9 (17)**	3 (15)	6 (19)	**3 (4)**	0.01 *	0.02 †
Ventricular Tachycardia or Fibrillation – no. (%)	7 (5)	**6 (11)**	2 (10)	4 (12)	**1 (1)**	0.01	0.02
Atrioventricular block – no. (%)	5 (3.5)	**3 (6)**	1 (5)	2 (6)	**2 (2)**	0.4	0.3
Secondary Outcome							
Acute myocardial infarction – no. (%)	6 (4)	**4 (8)**	2 (5)	2 (6)	**2 (2)**	0.2	0.3

* Poisson Regression Analysis shows a Incidence rate ratios 5.1, 95% CI (1.4 -18.7), p=0.01
† Poisson Regression Analysis shows a Incidence rate ratios 5.5, 95% CI (1.4 -21.9), p=0.02

Figure Legends:

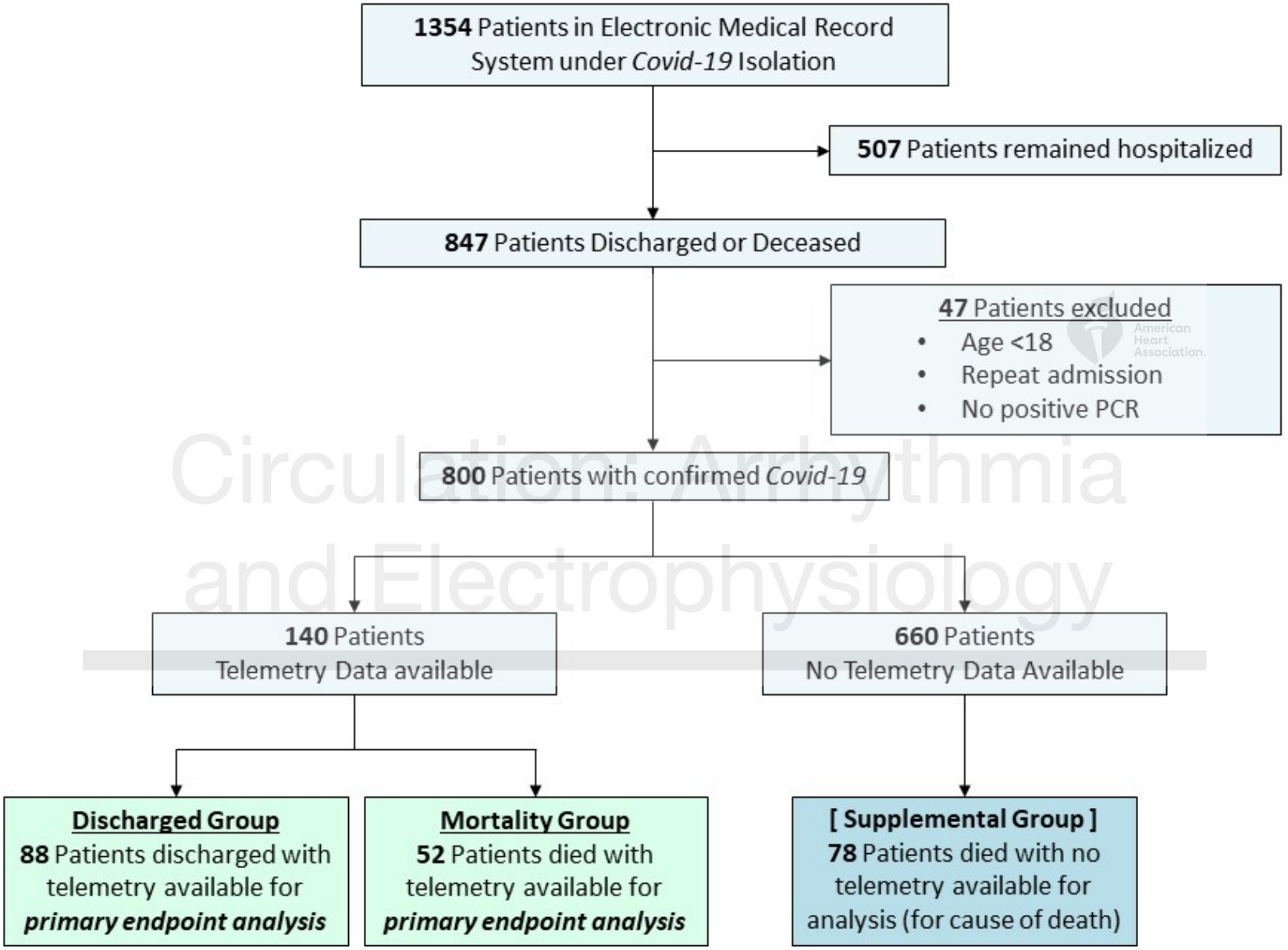
Figure 1: Cardiac Arrhythmias.

What Is Known?

- A significant elevation in cardiac troponin, a marker of myocardial injury is present in ~20% of hospitalized COVID-19 patients and portends a poor clinical prognosis particularly in the presence of coexisting cardiovascular disease.
- There is a reported interaction between disease severity and cardiac arrhythmias, particularly in critically ill COVID-19 patients. However, the exact nature and frequency of “malignant arrhythmias” have not been well-characterized, and more importantly, whether they contribute to death.

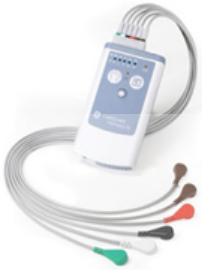
What the Study Adds?

- Hospitalized COVID-19 patients who die experience acute malignant cardiac arrhythmias more often than those surviving to discharge.
- Acute malignant cardiac arrhythmias do contribute to the ultimate demise of a small proportion of COVID-19 patients, some involving specific mechanisms potentially amenable to targeted interventions such as pacemaker implantation or revascularization. However, the majority appear to occur as a generalized response to acute critical illness and may not prove amenable to antiarrhythmic interventions.

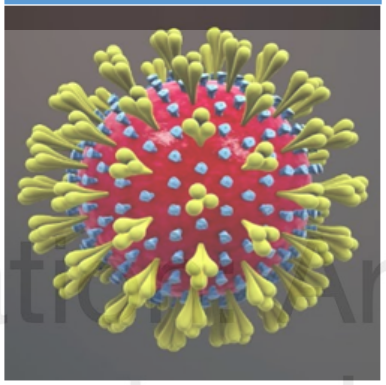


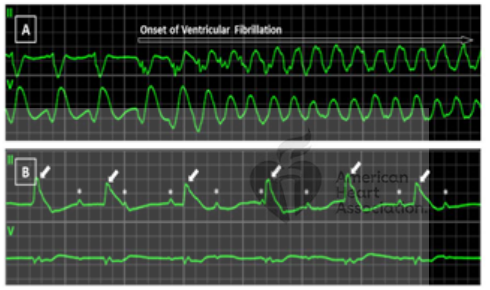
Graphic Abstract

Acute Malignant Cardiac Events in Hospitalized COVID-19 Patients

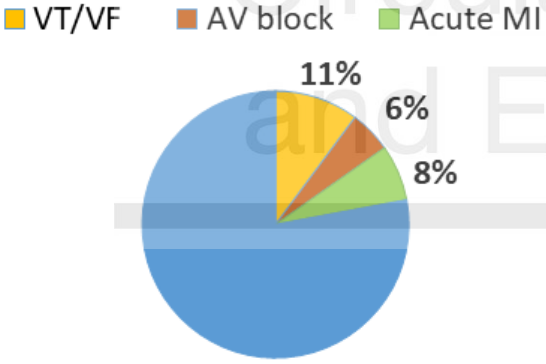


SARS-CoV-2

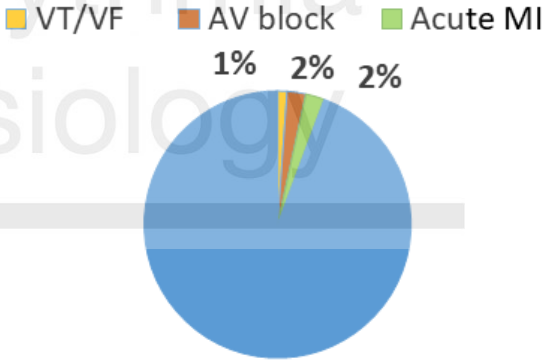




Death Group (N=52)



Discharged Group (N=88)



120 HOURS OF TELEMTRY

- Malignant arrhythmias occur more commonly in patients who die from COVID-19
- But overall, a minority of deaths in COVID-19 are caused by malignant arrhythmias