Prognostic value of initial electrocardiography in predicting long-term all-cause mortality in COVID-19

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ABSTRACT

Background: The electrocardiography (ECG) has short-term prognostic value in coronavirus disease 2019 (COVID-19), yet its ability to predict long-term mortality is unknown. This study aimed to elucidate the predictive role of initial ECG on long-term all-cause mortality in patients diagnosed with COVID-19.

Methods: In this prospective cohort study, adults with COVID-19 who underwent ECG testing within a 17-hospital health system in Northeast Ohio and Florida between 03/2020-06/2020 were identified. An expert ECG reader analyzed all studies blinded to patient status. The associations of ECG characteristics with long-term all-cause mortality and intensive care unit (ICU) admission were assessed using Cox proportional hazards regression model and multivariable logistic regression models, respectively. Status of long-term mortality was adjudicated on 01/07/2022.

Results: Of 837 patients (median age 65 years, 51% female, 44% Black), 683 (81.6%) were hospitalized, 281 (33.6%) required ICU admission, 67 (8.0%) died in-hospital, and 206 (24.6%) died at final follow-up after a median (IQR) of 21 (9-103) days after ECG. Overall, 179 (20.7%) patients presented with sinus tachycardia, 12 (1.4%) with atrial flutter, and 45 (5.4%) with atrial fibrillation (AF). After multivariable adjustment, sinus tachycardia (E-value for HR=3.09, lower CI=2.2) and AF (E-value for HR=3.13, lower CI=2.03) each independently predicted all-cause mortality. At final follow-up, patients with AF had 64.5% probability of death compared with 20.5% for those with normal sinus rhythm (*P*<.0001).

Conclusions: Sinus tachycardia and AF on initial ECG strongly predict long-term all-cause mortality in COVID-19. The ECG can serve as a powerful long-term prognostic tool in COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) continues to impose a significant burden to individual and public health globally. The sequelae of acute and post-acute COVID-19 [1,2] have impacted the delivery of medical care, particularly as the disease evolves and remains heterogeneous in its mutations [3] and variable penetration across populations [4]. The multi-organ involvement of COVID-19 is well-documented [2], and there is strong evidence to suggest its deleterious effects extend to cardiovascular presentations [5,6] and their outcomes [7–9]. It is therefore imperative to employ standard risk stratification tools in order to help guide clinical decision-making and to optimally

prioritize care within an overburdened healthcare system [9,10].

Owing to its widespread availability, ease of use, and minimal cost, one such tool that has been applied for this purpose is electrocardiography (ECG). Several studies have utilized ECG to identify untoward prognostic markers in COVID-19, which include atrial fibrillation (AF)/flutter [11–15], right-heart strain [13,16], intraventricular conduction abnormalities [11,12,17–19], ST segment abnormalities [12–14], and ischemic T-wave inversions [11,17]. However, these investigations often included only hospitalized patients and failed to prognosticate beyond in-hospital or 30-day outcomes. No studies to date have assessed the prognostic value of ECG on long-term mortality. We aimed to elucidate the prognostic value of initial ECG on long-term mortality in patients diagnosed with COVID-19 who sought medical care within a 17-hospital health system.

Material and methods

Study design and population

The design and data source of this study have been previously reported [20]. In brief, this was a prospective cohort analysis of an institutional review board-approved COVID-19 registry of all patients who tested for COVID-19 within the Cleveland Clinic Health System in Ohio and Florida which comprises 17 hospitals. This registry was initiated in March 2020 and included data that were extracted from electronic medical records (EPIC; EPIC Systems Corporation) via both validated automated methods [21] as well as manual abstraction by a trained study team. Extracted data were managed in REDCap [22,23] and included demographics, baseline co-morbidities, medication use, initial laboratory values, in-hospital outcomes, discharge disposition, 30-day readmission, and long-term mortality.

We included patients aged 18 years or older who were diagnosed with COVID-19 after presenting to any facility within the Cleveland Clinic Health System in Ohio and Florida between March 2020 and June 2020. The diagnosis of COVID-19 was confirmed using real-time reverse-transcriptase polymerase chain reaction assays of nasopharyngeal swabs. We identified consecutive patients with an available ECG within 28 days of the COVID-19 diagnosis. Those without accessible or interpretable ECG on electronic health records were excluded. Otherwise, no exclusionary medical or ECG criteria were applied. The study protocol was approved by the Cleveland Clinic Institutional Review Board, and patient informed consent was waived.

Study data

Abstracted demographic data included age, sex, and self-reported race and ethnicity. Select baseline covariates included diabetes mellitus, hypertension, coronary artery disease, heart failure, chronic obstructive pulmonary disease, asthma, active tobacco use, inflammatory bowel disease, epilepsy, history of any cancer, and prior transplant. We further recorded the prevalence of home medication use including nonsteroidal anti-inflammatory drugs, steroids, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers. Laboratory data measured at the earliest time point from presentation included electrolytes, creatinine, albumin, lactate dehydrogenase, lactate, troponin T, ferritin, C-reactive protein, and D-dimer.

Recorded clinical outcomes included the need for hospitalization, therapeutics (remdesivir, hydroxychloroquine, tocilizumab, and steroids), non-invasive and invasive ventilation, tracheostomy, prone positioning, and dialysis during index hospitalization. Lengths of hospital and intensive care unit (ICU) stays, discharge disposition, and 30-day readmission rates were also identified.

Electrocardiographic analysis

The initial ECG was defined as the first test within 28 days of the COVID-19 diagnosis. All standard 12-lead ECGs (speed 25 mm/s, voltage scale 10 mm/mV) were extracted from the electronic health records and analyzed off-line by the Medical Director of Electrocardiography at the Cleveland Clinic Main Campus (AB) using universally accepted criteria [24–31]. In order to standardize ECG analysis, the expert reader recorded the ECG findings using a scoring sheet as provided by the American Board of Internal Medicine for the purpose of ECG certification [32]. The expert reader was blinded to the clinical status and outcomes of all patients. No features on ECG were considered exclusionary criteria.

Analyzed ECG data included the following parameters: heart rate, atrial rhythm (normal sinus rhythm, sinus arrhythmia, sinus bradycardia, sinus tachycardia, sinus pause/arrest, atrial tachycardia, multifocal atrial tachycardia, supraventricular tachycardia, atrial flutter, and AF), ventricular rhythm (premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation), atrioventricular (AV) conduction abnormalities (first-degree, second-degree type I and II, and third-degree AV blocks, and shortened PR interval), changes in axes and voltage (low voltage, left and right axis deviation, and electrical alternans), chamber enlargement (left and right atrial enlargement), chamber hypertrophy (left and right ventricular hypertrophy), intraventricular conduction delays (complete and incomplete left and right bundle branch blocks and left anterior and posterior fascicular blocks), myocardial infarction (MI) (old and recent MI, by territory), changes in ST/T/U waves (prolonged QT interval and changes suggesting ischemia or myocardial injury), and pacemaker (atrial-paced, dual-chamber, malfunction/no capture, malfunction/no sensing, and biventricular or cardiac resynchronization therapy device).

Study outcomes

The primary study outcome was long-term all-cause mortality. The date of ECG was designated as the start of the observational period for incident deaths, and patients were followed until adjudication of mortality status on January 7, 2022. The secondary outcome was ICU admission during the index hospitalization. Both mortality status and need for ICU admission were determined by manual review of the electronic medical records by two physicians.

Statistical analysis

Categorical variables are summarized as counts (percentages) and compared using χ^2 or Fisher exact tests. Continuous variables are presented as mean (standard deviation) or median [interquartile range (IQR)], as appropriate, and assessed using 2-tailed Student *t*-tests or 2-sample Wilcoxon rank-sum tests according to the distribution of the data. In order to determine the associations of ECG characteristics with each long-term mortality and ICU admission, a Cox proportional hazards regression model and multivariable logistic regression model were employed, respectively, both of which incorporated all baseline clinical variables in Table 1 with statistical relevance designated as *P* value <.001. Of these variables, those with greater than 25% missing values were excluded from the present analysis to increase the robustness of the model. The clinical variables incorporated into the models included age, diabetes mellitus, hypertension, coronary artery disease, heart failure, chronic obstructive pulmonary disease, history of cancer, and any immunosuppressive disease. Likelihood ratio test and Akaike information criteria were employed to assess the fitness of the Cox proportional hazards regression model and multivariable logistic regression model, respectively. E-values were then calculated for all adjusted hazards and odds ratios in order to account for potential confounding by unmeasured factors in the study. An E-value is defined as the minimum strength of association on the risk ratio scale required of an unmeasured confounder with both the treatment and the outcome, conditional on the measured covariates, to invalidate a particular treatment-outcome association [33]. Landmark analysis at 30 days was performed as an additional

Table 1
Baseline characteristics and clinical outcomes of the study population.

Variables	No. (%)			
	Overall (n = 837)	Alive (n = 631)	Dead (n = 206)	P value
Age, median (IQR)	65 (52.9-76.6)	61.2 (49.8-71.2)	77.7 (67.9-84.7)	<.001
Sex				
Female	424 (50.7)	324 (51.3)	100 (48.5)	0.65
Male	413 (49.3)	307 (48.7)	106 (51.5)	
Race/ethnicity				
White	403 (48.1)	288 (45.6)	115 (55.8)	
Black	366 (43.7)	287 (45.4)	79 (38.3)	.02
Hispanic	42 (5.0)	38 (6.0)	4 (1.9)	
Asian	11 (1.3)	9 (1.4)	2 (1.0)	
Multiracial	37 (4.4)	31 (4.9)	6 (2.9)	
Comorbidities				
Diabetes mellitus	323 (38.6)	225 (35.6)	98 (47.6)	<.001
Hypertension	605 (72.3)	423 (67.0)	182 (88.3)	<.001
Coronary artery disease	205 (24.5)	125 (19.8)	80 (38.8)	<.001
Heart failure	185 (22.1)	102 (16.2)	83 (40.3)	<.001
COPD	111 (13.3)	66 (10.4)	45 (21.8)	<.001
Asthma	188 (22.5)	147 (23.3)	41 (19.9)	.33
History of cancer	150 (17.9)	92 (14.6)	58 (28.2)	<.001
Prior transplant	21 (2.5)	15 (2.4)	6 (2.9)	.68
Inflammatory bowel disease	42 (5.0)	29 (4.6)	13 (6.3)	.32
Epilepsy	63 (7.5)	39 (6.2)	24 (11.6)	.005
Any immunosuppressive disease	180 (21.5)	118 (18.7)	62 (30.1)	<.001
Tobacco use				
Current	81 (9.7)	62 (9.8)	19 (9.2)	.21
Former	321 (38.3)	232 (36.8)	89 (43.2)	
Home medications				
Nonsteroidal anti-inflammatory drugs	275 (32.8)	221 (35.0)	54 (26.2)	.05
Steroids	135 (16.1)	195 (30.9)	40 (19.4)	.07
Angiotensin-converting enzyme	132 (15.8)	98 (15.5)	34 (16.5)	.54
Angiotensin-receptor blocker	88 (10.5)	69 (10.9)	19 (9.2)	.62
Biomarkers on initial medical contact				
Sodium, mmol/L	137 (134-139)	137 (134-139)	137 (134-140)	.10
Potassium, mmol/L	4 (3.7-4.4)	4 (3.7-4.3)	4.2 (3.8-4.5)	<.001
Chloride, mmol/L	99 (95-102)	99 (95-102)	99 (95-103)	.23
Blood urea nitrogen, mg/dL	19 (13-31)	16 (11-26)	26 (18-44)	<.001
Creatinine, mg/dL	1.1 (0.8-1.6)	1.0 (0.8-1.4)	1.3 (0.89-2)	<.001
Albumin, g/dL	3.7 (3.3-4.0)	3.7 (3.4-4.0)	3.5 (3.0-3.9)	<.001
Lactate dehydrogenase, U/L	310 (234-411)	309 (229-404)	319.0 (250-433)	.14
Lactate, mmol/L	1.4 (1.1-2.0)	1.3 (1.0-1.8)	1.6 (1.2-2.1)	.007
Troponin T, ng/mL	0.05 (0.02-0.3)	0.05 (0.02-4.7)	0.06 (0.02-0.2)	.17
Ferritin, ng/mL	515 (229-1046)	499 (221-994)	548 (242-1265)	.27
C-reactive protein, mg/dL	7.1 (3.1-12.3)	7.2 (2.6-12.0)	7.0 (4.3-13.6)	.06

Table 1 (*continued*)

Variables	No. (%)			
	Overall (n = 837)	Alive (n = 631)	Dead (n = 206)	P value
D-dimer, ng/mL	950 (515-1835)	870 (488-1560)	1370 (690-3050)	<.001
Outcomes				
Hospitalized	683 (81.6)	487 (77.2)	196 (95.1)	<.001
ICU admission	281 (33.6)	166 (26.3)	115 (55.8)	<.001
Remdesivir	10 (1.2)	10 (1.6)	0	.04
Hydroxychloroquine	215 (25.7)	160 (25.4)	55 (26.7)	.24
Tocilizumab	58 (6.9)	43 (6.8)	15 (7.3)	.66
Steroids	163 (19.5)	97 (15.4)	66 (32.0)	<.001
Non-invasive ventilation	195 (23.3)	126 (20.0)	69 (33.5)	.005
Invasive ventilation	168 (20.1)	93 (14.7)	75 (36.4)	<.001
Tracheostomy	14 (1.7)	9 (1.4)	5 (2.4)	.63
Prone position	56 (6.7)	34 (5.4)	22 (10.7)	.68
Dialysis	38 (4.5)	15 (2.4)	23 (11.2)	.06
Length of hospitalization, days	7 (4-13)	7 (4-12)	8 (5-16)	.02
Length of ICU stay, days	6 (3-12)	6 (3-13)	5 (2-11)	.14
In-hospital mortality	67 (8.0)	-	67 (32.5)	-
Any mortality	206 (24.6)	-	206 (100.0)	-
30-day readmission	76 (9.1)	51 (8.1)	25 (12.1)	.40
Disposition				
Home	308 (36.8)	286 (45.3)	22 (10.7)	<.001
Home health care	45 (5.4)	40 (6.3)	5 (2.4)	.007
Skilled nursing facility	118 (14.1)	82 (13.0)	36 (17.5)	.64
Long-term acute care facility	18 (2.2)	9 (1.4)	9 (4.4)	.04
Hospice	22 (2.6)	0	22 (10.7)	<.001

Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

sensitivity analysis in order to strengthen the interpretation of the relationship between ECG features and long-term outcomes. Significance was set at $P<.05$, and all P values were 2-sided. All statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 5,310 consecutive adult patients were diagnosed with COVID-19 during the study period, with 1781 (33.5%), 177 (3.3%), and 3352 (63.1%) subjects undergoing diagnostic testing via emergency department, hospital, and outpatient/drive-through services, respectively. Of these, 874 individuals underwent initial ECG testing. Among this cohort, 37 were excluded due to an inability to access ECG via electronic medical records (n=13) or owing to ≥ 28 days between COVID-19 diagnosis and ECG testing (n=24). Of the 837 patients who met the final inclusion criteria, 565 (67.5%), 81 (9.7%), and 191 (22.8%) underwent COVID-19 testing via emergency department, hospital, and outpatient/drive-through services, respectively. Overall, the median (IQR) age was 65 (53-77) years, 424 (51%) were female, and 366 (44%) were Black. With 77.2% of included patients undergoing hospital-based COVID-19 testing, the median (IQR) time from COVID-19 diagnosis to ECG was 0 (0-2) days. Among survivors at final follow-up, the median (IQR) time from ECG to follow-up was 582 (496-659) days. All demographic data, clinical characteristics, and unadjusted outcomes are detailed in Table 1. The overall cohort comprised a high prevalence of baseline co-morbidities: diabetes mellitus (324 [39%]), hypertension (606 [72%]), coronary artery disease (205 [25%]), heart failure (186 [22%]), asthma or chronic obstructive pulmonary disease (300 [36%]), and history of any cancer (150 [18%]). Overall, 683 (81.6%) patients

were hospitalized, 281 (33.6%) required ICU admission, 168 (20.1%) required mechanical ventilation, and 67 (8.0%) died in-hospital. Among the 206 (24.6%) patients who died during the study period, 139 (67.5%) died after hospital discharge, with a median (IQR) time to death of 21 (9-103) days after ECG.

Unadjusted study outcomes are summarized in Table 1. Relative to patients who survived, those who died during the study period were more frequently admitted to the hospital (77.2% vs 95.1%, *P*<.001) and ICU (26.3% vs 55.8%, *P*<.001) with a greater length of hospitalization. Compared with survivors, patients who died had significantly greater requirements for non-invasive ventilation (20.0% vs 33.5%, *P*=.005) and invasive ventilation (14.7% vs 36.4%, *P*<.001), with statistically similar rates of tracheostomy (1.4% vs 2.4%, *P*=.63), prone positioning (5.4% vs 10.7%, *P*=.68), and dialysis initiation (2.4% vs 11.2%, *P*=.06). There was no difference in 30-day readmission rate between patients who survived and died (8.1% vs 12.1%, *P*=.4), and all patients discharged to hospice (n=25) eventually died.

Descriptive ECG characteristics

Table 2 describes the electrocardiographic features of the study population. Overall, 179 (21%) patients presented with sinus tachycardia, 22 (2.6%) with sinus bradycardia, 12 (1.4%) with atrial flutter, and 45 (5.4%) with AF of which 36 (80%) were considered pre-existing. In total, 35 (4.1%) patients presented with first-degree AV conduction block and none with more advanced heart block. Left and right axis deviation were found in 74 (8.8%) and 12 (1.4%) individuals, respectively. The overwhelming majority of the population had no atrial enlargement (817 [98%]) and no ventricular hypertrophy (765 [91%]). A total of 47 (5.6%) and 14 (1.7%) patients had complete right and left bundle branch blocks, respectively. No patients presented with acute MI, and only 16 (1.9%) ECGs had ST and/or T wave abnormalities suggestive of ischemia. Prolonged QTc was observed in 38 (4.5%) patients.

ECG predictors of clinical outcomes

On univariate analysis, patients who died had significantly greater atrial and ventricular rhythm disturbances as well as intraventricular conduction abnormalities relative to those who survived (Table 2). After adjusting for age and various baseline co-morbidities, the primary ECG findings that independently predicted all-cause mortality were sinus tachycardia (HR=2.44; 95% CI [1.67-3.57]; E-value for HR=3.09 and lower CI=2.2) and AF (HR=2.47; 95% CI [1.54-3.94]; E-value for HR=3.13 and lower CI=2.03) (Table 3, Fig. 1). On 30-day landmark analysis, the presence of AF remained associated with higher mortality compared with normal sinus rhythm (HR=2.45; 95% CI [1.14-5.30], *P*=0.02) (Supplementary Fig. 1). Additional ECG predictors of all-cause mortality included right axis deviation (HR=4.45; 95% CI [1.79-11.06]; E-value for HR=4.93 and lower CI=2.35), left ventricular hypertrophy (HR=1.78; 95% CI [1.09-2.92]; E-value for HR=2.34 and lower CI=1.32), and left anterior fascicular block (HR=2.07; 95% CI [1.04-4.11]; E-value for HR=2.69 and lower CI=1.2) (Table 3, Supplementary Fig. 2). Further, on multivariable logistic regression analysis, sinus tachycardia (OR=2.30; 95% CI [1.53-3.46]; E-value for OR=2.4 and lower CI=1.78) and AF (OR=2.31; 95% CI [1.11-4.86]; E-value for OR=2.41 and lower CI=1.29) significantly predicted the need for ICU admission (Supplementary Table 1). At 1 year and at final follow up, patients with AF had 55.6% and 64.5% probability of death, respectively, compared with 18.9% and 20.5% probability of death for those with normal sinus rhythm, respectively (*P*<.0001 for both comparisons).

Discussion

The present study is the first to utilize ECG to predict long-term mortality in patients diagnosed with COVID-19. In this prospective

Table 2
Electrocardiographic features of the study population.

ECG characteristic	No. (%)			
	Overall (n = 837)	Alive (n = 631)	Dead (n = 206)	*P* value
Atrial rhythm				
Normal sinus rhythm	560 (66.9)	445 (70.5)	115 (55.8)	
Sinus arrhythmia	14 (1.7)	12 (1.9)	2 (1.0)	
Sinus bradycardia	24 (2.9)	16 (2.5)	8 (3.9)	
Sinus tachycardia	179 (20.7)	131 (20.8)	48 (23.3)	
Sinus pause/arrest	0	0	0	
Atrial tachycardia	1 (0.1)	0	1 (0.5)	<.001
Multifocal atrial tachycardia	0	0	0	
Supraventricular tachycardia	2 (0.2)	2 (0.3)	0	
Atrial flutter	12 (1.4)	9 (1.4)	3 (1.4)	
Atrial fibrillation	45 (5.4)	16 (2.5)	29 (14.1)	
Ventricular rhythm				
None	790 (94.4)	602 (95.4)	188 (91.3)	
Premature ventricular complex	46 (5.5)	29 (4.6)	17 (8.2)	.03
Ventricular tachycardia	1 (0.1)	0	1 (0.5)	
Ventricular fibrillation	0	0	0	
Atrioventricular conduction				
No abnormalities	802 (95.8)	606 (96.0)	196 (95.1)	
First-degree AV block	35 (4.2)	25 (4.0)	10 (4.8)	
Second/third-degree AV block	0	0	0	.58
Shortened PR interval	0	0	0	
Axes and voltage				
No abnormalities	698 (83.4)	533 (84.5)	165 (80.1)	
Low voltage waves	53 (6.3)	42 (6.7)	11 (5.3)	
Left axis deviation	74 (8.8)	49 (7.8)	25 (12.1)	.11
Right axis deviation	12 (1.4)	7 (1.1)	5 (2.4)	
Electrical alternans	0	0	0	
Chamber enlargement				
No chamber enlargement	818 (97.7)	619 (98.1)	199 (96.6)	
Left atrial enlargement	12 (1.4)	8 (1.3)	4 (1.9)	.41
Right atrial enlargement	7 (0.8)	4 (0.6)	3 (1.5)	
Chamber hypertrophy				
No ventricular hypertrophy	765 (91.4)	583 (92.4)	182 (88.3)	
Left ventricular hypertrophy	69 (8.2)	47 (7.4)	22 (10.7)	.08
Right ventricular hypertrophy	3 (0.3)	1 (0.2)	2 (1.0)	
Intraventricular conduction				
No abnormalities	737 (88.1)	571 (90.5)	166 (80.6)	
Complete RBBB	47 (5.6)	27 (4.3)	20 (9.7)	
Incomplete RBBB	15 (1.8)	9 (1.4)	6 (2.9)	
Complete LBBB	14 (1.7)	10 (1.6)	4 (1.9)	
Incomplete LBBB	1 (0.1)	1 (0.2)	0	.005
Left anterior fascicular block	23 (2.7)	13 (2.1)	10 (4.9)	
Left posterior fascicular block	0	0	0	
Myocardial infarction				
None	811 (96.9)	613 (97.1)	198 (96.1)	
Recent, any territory	0	0	0	.46
Old, any territory	26 (3.1)	18 (2.8)	8 (3.9)	
Changes in QTc				
Normal QTc	799 (95.5)	602 (95.4)	197 (95.6)	.89
Prolonged QTc	38 (4.5)	29 (4.6)	9 (4.4)	
Changes in ST/T/U waves				
Suggestive of ischemia	16 (1.9)	13 (2.1)	3 (1.4)	<.001
Suggestive of myocardial injury	2 (0.2)	0	2 (1.0)	
Pacemaker				
None	813 (97.1)	616 (97.6)	197 (95.6)	
Atrial-paced	4 (0.5)	2 (0.3)	2 (1.0)	
Dual-chamber (DDD)	19 (2.3)	13 (2.1)	6 (2.9)	.17
No capture/sensing	0	0	0	
Bi-ventricular/CRT	1 (0.1)	0	1 (0.5)	

Abbreviations: AV, atrioventricular; CRT, cardiac resynchronization therapy; ECG, electrocardiography; RBBB, right bundle branch block; LBBB, left bundle branch block.

cohort analysis of 837 patients from a large health system, we found that in comparison with survivors, patients who died had a higher burden of ECG abnormalities, predominantly atrial and ventricular rhythm disturbances as well as intraventricular conduction delays. The presence of sinus tachycardia and AF strongly and independently predicted long-term all-cause mortality. Mortality in patients with COVID-19 and AF was 3-fold higher relative to those with normal sinus rhythm, with nearly two-thirds of this population dead at long-term follow-up. Our study demonstrates the prognostic value of ECG in predicting long-term mortality and supports the important role for this fundamental diagnostic test in the early risk stratification of COVID-19 patients.

This study is unique in designating long-term mortality as the clinical outcome of interest. While a large proportion of individuals in our analysis were hospitalized or required ICU-level care, greater than two-thirds of deaths occurred after hospital discharge. Patients with COVID-19 are at particularly increased risk of clinical deterioration during the vulnerable period after hospitalization [34–36], which may be a consequence of persistent inflammation [37], the sequela of acute thrombotic complications [38], or a gradual decline due to neuro-cognitive impairments [35]. Mounting evidence demonstrates that a significant proportion of patients who survive to hospital discharge are readmitted or die within 60 days [34], 6 months [35], and 12 months [36] after hospitalization. Notably, Mainous and colleagues demonstrated that the 12-month mortality risk in hospitalized COVID-19 patients < 65 years of age is 233% greater than COVID-19-negative controls, with most deaths attributed to indirect insults of COVID-19 [36]. These studies suggest that the mortality risk of COVID-19 persists beyond the initial encounter, and consistent with our findings, supports the ongoing need to monitor and investigate longer-term outcomes in this high-risk cohort.

Our findings underscore the additive value of ECG for long-term prognostication in COVID-19. There is sufficient evidence citing the prognostic role of varying laboratory biomarkers [39–41] and imaging parameters, including those on echocardiography [43] and chest computed tomography [43], in COVID-19. Yet, these tools are limited by several factors; for laboratory markers, these include vascular access and time to sample analysis; with respect to imaging modalities, these include availability of technology, preclusive patient characteristics such as large body habitus and clinical instability, need for competent study operators and readers, time to image interpretation, and in cases of computed tomography, radiation exposure. In contrast, the ECG largely avoids these limitations. In particular, the primary advantages of ECG in COVID-19 include its ease in use, nominal labor intensiveness, minimal COVID-19 exposure risk, and wide availability and accessibility throughout hospitals, emergency departments, and outpatient clinics. Its short-term prognostic utility in COVID-19 has previously been described [11–19], further supporting its clinical application in this population. In light of an ongoing pandemic, we believe that the fundamental role of ECG extends beyond its diagnostic capacity to immediately detect time-sensitive conditions to include the powerful prediction of long-term mortality in patients with COVID-19.

As sinus tachycardia independently predicted long-term mortality in our COVID-19 population, its presence on ECG provides critical, actionable information for practitioners to rapidly risk-stratify patients on initial contact. Relying on objective and efficient data for care prioritization and allocation is vital as the disease burden of the pandemic continues to overcrowd hospitals, strain infrastructures, and necessitate rationing of resources [9,10]. Healthcare professionals should maintain heightened awareness of the presence of sinus tachycardia on ECG, even in the absence of abnormal additional vital signs and antecedent to receiving laboratory results which may delay clinical decision-making. Sinus tachycardia represents a physiological cardiac response to

Table 3

Cox proportional hazards regression analysis on the electrocardiographic predictors of long-term mortality[a] in patients diagnosed with COVID-19.

ECG characteristic[b]	HR (95% CI)[c,d]	E-value for HR	E-value for lower CI
Atrial rhythm			
Sinus arrhythmia	0.43 (0.06-3.16)	2.97	1
Sinus bradycardia	1.80 (0.86-3.75)	2.37	1
Sinus tachycardia	2.44 (1.67-3.57)	3.09	2.2
Sinus pause/arrest	-	-	-
Atrial tachycardia	-	-	-
Multifocal atrial tachycardia	-	-	-
Supraventricular tachycardia	-	-	-
Atrial flutter	0.94 (0.23-3.84)	1.26	1
Atrial fibrillation	2.47 (1.54-3.94)	3.13	2.03
Ventricular rhythm			
Premature ventricular complex	1.26 (0.74-2.16)	1.63	1
Ventricular tachycardia	1.47 (0.20-10.96)	1.94	1
Ventricular fibrillation	-	-	-
Atrioventricular conduction			
First degree AV block	0.67 (0.34-1.32)	1.97	1
Second/third degree AV block	-	-	-
Shortened PR interval	-	-	-
Axes and voltage			
Low voltage waves	0.95 (0.50-1.81)	1.23	1
Left axis deviation	1.02 (0.64-1.65)	1.13	1
Right axis deviation	4.45 (1.79-11.06)	4.93	2.35
Electrical alternans	-	-	-
Chamber enlargement			
Left atrial enlargement	1.19 (0.37-3.80)	1.51	1
Right atrial enlargement	3.98 (0.96-16.44)	4.54	1
Chamber hypertrophy			
Left ventricular hypertrophy	1.78 (1.09-2.92)	2.34	1.32
Right ventricular hypertrophy	3.08 (0.71-13.36)	3.74	1
Intraventricular conduction			
Complete RBBB	1.13 (0.68-1.89)	1.4	1
Incomplete RBBB	1.70 (0.68-4.25)	2.24	1
Complete LBBB	0.49 (0.12-2.00)	2.65	1
Incomplete LBBB	-	-	-
Left anterior fascicular block	2.07 (1.04-4.11)	2.69	1.2
Left posterior fascicular block	-	-	-
Myocardial infarction			
Recent, any territory	-	-	-
Old, any territory	0.72 (0.31-1.63)	1.82	1
Changes in QTc			
Prolonged QTc	0.84 (0.39-1.80)	1.51	1
Changes in ST/T/U waves			
Suggestive of ischemia	1.34 (0.42-4.31)	1.75	1
Suggestive of myocardial injury	-	-	-
Pacemaker			

Table 3 (*continued*)

ECG characteristic[b]	HR (95% CI)[c,d]	E-value for HR	E-value for lower CI
Atrial-paced	0.68 (0.16-2.87)	1.94	1
Dual-chamber (DDD)	0.44 (0.18-1.11)	2.91	1
No capture/sensing	-	-	-
Bi-ventricular/CRT	3.29 (0.44-24.91)	3.93	1

Abbreviations: AV, atrioventricular; CI, confidence interval; CRT, cardiac resynchronization therapy; ECG, electrocardiography; HR, hazard ratio; LBBB, left bundle branch block; RBBB, right bundle branch block.

[a] Long-term mortality was determined by adjudication of mortality status (dead or alive) on January 7, 2022 by physician review of the electronic medical records.

[b] Normal sinus rhythm was the reference group for rhythm abnormalities, otherwise the absence of stated electrocardiographic characteristics served as the reference group for the remaining variables.

[c] Cox proportional hazards regression model adjusted for all variables with *P* value <.001 in Table 1, excluding those with more than 25% missing values to increase the robustness of the model.

[d] Likelihood ratio test was employed to assess the fitness of the model.

underlying pathological processes that compromise metabolic supply to vital organs, which may be related to reduced stroke volume, arterial tone, or arterial oxygenation. In COVID-19, sinus tachycardia may act as a surrogate for any combination of these underlying pathologic mechanisms resulting from a range of potential etiologies, including hypovolemia from poor oral intake or insensible losses due to high-grade fever, cardiac dysfunction after acute cardiac injury, pulmonary embolism in the setting of a pro-thrombotic state, sepsis from the virus itself or a bacterial coinfection, or hypoxia of various etiologies. Tachycardia is an independent negative risk factor for several of these conditions [44,45], has been incorporated into prognostic models in varying patient populations [46,47], and is associated with excess cardiovascular mortality [48,49] irrespective of pre-existing cardiac damage [50]. The excess long-term risk associated with sinus tachycardia extends to patients with COVID-19 and should serve to alert both patients and practitioners alike of an underlying pathologic process.

Our study is the first to reveal the long-term increase in risk of mortality in patients with COVID-19 and AF. This strong relationship has substantial public health implications with an ongoing pandemic and as AF remains the most common sustained arrhythmia in both the general population worldwide and in hospitalized COVID-19 patients [51,52], with extensive associated morbidity and mortality [53–55]. Building on the findings of prior work [51,55–59], there are both direct and indirect ramifications of AF linked to all-cause mortality in COVID-19. As pre-existing AF comprised the predominant AF type in this study, it is especially plausible that AF represents a marker of structural heart disease and cardiomyopathy, its permanence impressing a progressive susceptibility to subsequent deleterious effects. The long-standing, sustained presence of AF may have led to worse long-term survival via atrial structural remodeling in which interstitial and myocyte alterations cause irreversible cardiac damage, which manifests as a loss of atrial contractile force and can serve as a self-perpetuating arrhythmogenic substrate [60,61]. Additionally, in light of the pro-thrombotic state of both conditions [38,51,59,62,63], the risks related to AF itself such as cardiac injury and stroke may be acutely responsible for the poor prognosis especially in those with new-onset AF. We cannot exclude contributions from contextual factors such as absent or suboptimal anticoagulation, as demonstrated by Peltzer and colleagues who found that 80% of strokes or transient ischemic attacks in COVID-19 patients occurred while off therapeutic anticoagulation [51]. Furthermore, AF is directly linked to multiple co-morbidities and inflammatory markers, including C-reactive protein [41] and lactate dehydrogenase [40], which themselves are prognostic of adverse outcomes in COVID-19

[51,59]. AF may therefore be a marker of disease severity as evidenced by the degree of inflammatory response. As an independent risk factor for long-term mortality in COVID-19, a diagnosis of AF should further prompt clinicians to vigorously urge for infection prevention measures in these patients by means of vaccination, social distancing, and use of personal protection equipment by those with exposure risk.

Our inclusion of a diverse study population with a notably high percentage of African American/Black patients adds to our understanding of prognostic risk factors in patients who are disproportionally impacted by COVID-19. Akin to public health patterns of various conditions, the COVID-19 pandemic has exposed health disparities among socially vulnerable racial and ethnic communities. In particular, African American/Black patients have experienced higher rates of hospitalization, ICU admission, and death from COVID-19 compared with non-Hispanic white individuals [64,65]. While socioeconomic status, infectious exposure, and health care access are large contributors to these disparities, the disproportionate burden of underlying co-morbid conditions among minority populations has further been implicated [64–67]. In addition to these sources of disparities, we provide novel evidence of ECG determinants of long-term mortality in COVID-19 among a diverse patient population.

Limitations

Several study limitations are worth noting. First, although patients were identified prospectively, this analysis was subject to the inherent biases of an observational study. Second, the study cohort represented those who sought medical care, and as such, our findings may not be generalizable to individuals who are asymptomatic or less acutely ill. The overwhelming majority of included patients underwent diagnostic testing prompted by symptoms. Our study was performed during the early stages of the pandemic, prior to the introduction of vaccines or therapeutics and at a time of global shortages of PPE and ventilators, and therefore, the high rates of hospitalization, ICU admission, and mortality are not unexpected. Third, as a function of the study design in which a single initial ECG was identified, the true prevalence of ECG findings including sinus tachycardia and AF may have been underreported. This single ECG approach was pursued to reflect its efficient and practical use in clinical practice. Fourth, most patients in the initial COVID-19 registry did not undergo an initial ECG. This is largely due to the majority of registry patients undergoing diagnostic COVID-19 testing in the outpatient setting or via drive-through services. Further, this likely reflects the caution exercised in the early stages of the pandemic with regard to diagnostic testing that required hands-on patient contact, yet this may be less clinically relevant in our AF cohort given the high prevalence of pre-existing arrhythmia. Fifth, we were unable to differentiate the association with outcomes between pre-existing and new-onset AF owing to the extremely limited sample of those with new-onset AF. Nonetheless, the aim of this study centered on identifying high-risk ECG features overall. Sixth, given an absence of available data and the breadth of potential sources for sinus tachycardia, which is a relatively non-specific finding, it was not feasible to definitively identify etiologies of sinus tachycardia. Seventh, the risk of residual confounding by covariates unaccounted for within our COVID-19 registry cannot be fully eliminated; we attempted to mitigate this by use of multivariate adjustment with E-values in our statistical model. Lastly, cause-specific mortality was not delineated, although all-cause mortality is a well-validated and objective endpoint [68].

Conclusions

This is the first study to assess the long-term incremental prognostic value of ECG in adult all-comers with COVID-19. In this prospective analysis, the presence of sinus tachycardia and atrial fibrillation on initial ECG strongly and independently predicted long-term all-cause mortality. As COVID-19 endures and adversely impacts individual
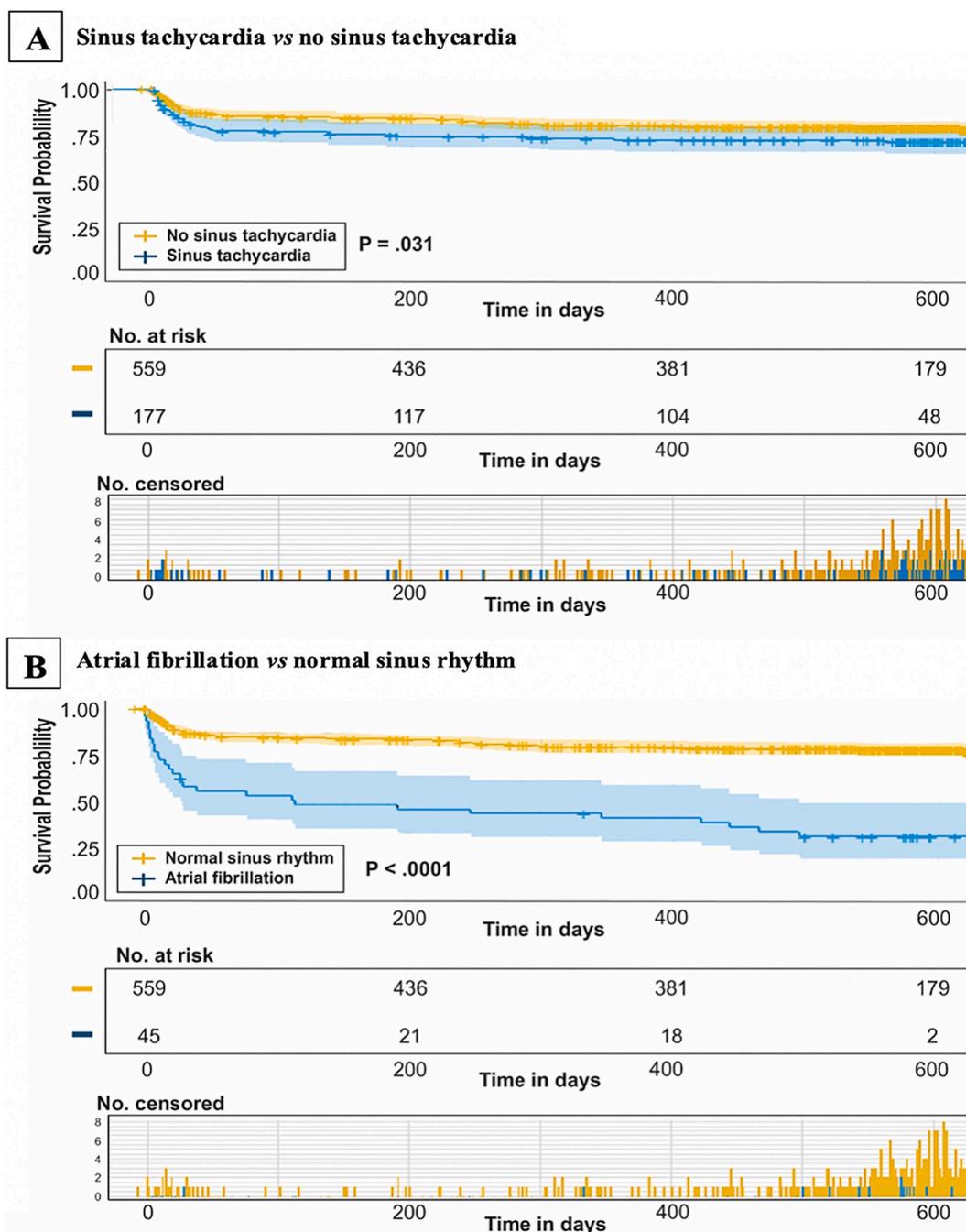
Fig. 1. Association of Sinus Tachycardia (A) and Atrial Fibrillation (B) on Initial Electrocardiography with Long-Term Survival in Patients with COVID-19. After adjusting for age and various baseline co-morbidities, (A) sinus tachycardia (HR=2.44; 95% CI [1.67-3.57]; E-value for HR=3.09 and lower CI=2.2), and (B) atrial fibrillation (HR=2.47; 95% CI [1.54-3.94]; E-value for HR=3.13 and lower CI=2.03) each independently predicted long-term all-cause mortality.

health and the surrounding medical infrastructure, the medical community must discover novel applications of foundational tools in order to risk-stratify patients, prioritize care, and allocate resources. The ECG can serve as a powerful diagnostic test to help predict long-term mortality in COVID-19 patients.

Data availability

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Nicholas Kassis: Conceptualization, Data curation, Investigation, Methodology, Project administration, Visualization, Writing – original

draft, Writing – review & editing. **Ashish Kumar:** Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Writing – original draft, Writing – review & editing. **Shravani Gangidi:** Data curation, Formal analysis, Investigation, Methodology, Resources. **Alex Milinovich:** Data curation, Formal analysis, Investigation, Methodology, Resources, Software. **Ankur Kalra:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Ajay Bhargava:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Venu Menon:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **Oussama M. Wazni:** Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **John Rickard:** Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Umesh N. Khot:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None.

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None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2022.10.003.

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