The electrocardiographic manifestations and derangements of 2019 novel coronavirus disease (COVID-19)

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ABSTRACT

Electrocardiographic (ECG) findings in patients admitted with COVID-19 and a decision tree to predict their survival were assessed. 145 consecutive patients with severe COVID-19 infection were selected. Patient demographics, ECG variables, peak troponins, use of standard medications, and clinical outcomes were analyzed using descriptive and inferential statistics, and a predictive model of survival was developed using classification tree analysis. Of the 145 admitted patients, 38 (26%) died. Deceased patients were more likely to have a significantly higher incidence of poor R-Wave progression [6 of 37 (16.2%) Vs. 0 of 104 (0%), p < 0.001] as well as prolonged QTc values [24 of 37 (64.9%) Vs. 38 of 99 (38.4%), p 0.006]. Significant ST segment depressions were found in 5 of 37 (13.5%) of the deceased category compared to 0% in the non-deceased (p < 0.01). Right and/or left atrial enlargement was more prevalent in the deceased cohort [7 of 37 (18.9%) Vs. 4 of 104 (3.8%), p = 0.03]. Bundle branch blocks were more prevalent in the deceased group [9 of 35 (25.8%) Vs. 7 of 104 (6.7%), p 0.002]. Peak troponins were significantly higher in the deceased group (1.0 Vs 0.07 ng/ml, p < 0.001) A prediction tree built utilizing age, PACs, troponins and QTc had an accuracy of 85.5%. 65 of 74 patients (87.8%) were correctly predicted to survive, while 23 of 29 (79.3%) were correctly predicted to become deceased. Among patients hospitalized with Covid-19, the parameters of age, QT interval, troponin and PACs are useful for prognostication and help predict survival with reasonable accuracy.

1. Introduction

The recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused a nearly unprecedented rush to understand and combat the disease processes. Although the 2019 novel coronavirus disease (COVID-19) primarily causes dysfunction and injury of the respiratory system, severe compromise of the cardiovascular system has been reported in a growing number of patients [1,2]. Indeed, patients with existing cardiac disease seem to be particularly susceptible to symptomatic infection. A meta-analysis of six published studies from China including 1527

patients with COVID-19 reported a prevalence of 16.4% of underlying cardio-cerebrovascular disease, and an associated 3-fold greater risk of severe disease or requiring intensive care unit (ICU) admission [3]. In addition, acute cardiac injury, defined as significant elevation of cardiac troponins, has been reported to occur in approximately 8—12% of all infected patients [3].

Given the high prevalence and alarming consequences of cardiovascular damage in COVID-19 patients, it becomes clear why the precise mechanisms of cardiac disruption must be understood. To date, however, there has been no research specifically investigating the cardiac electrical effects of SARS-CoV-2, and the little cardiac data that are available is insufficient to build a comprehensive clinical picture. Both tachy- and brady-arrhythmias are known to occur. A study describing clinical profile and outcomes in 138 Chinese patients with COVID-19 reported a 16.7% incidence of arrhythmia [2], but the authors failed to provide any classification

or definition of these arrhythmias. Another study of 187 patients in Wuhan reported a prevalence of ventricular tachycardia/fibrillation of 5.9% [4], but no other data relating to cardiac rhythm. One case report described the development of torsade-de-pointes in an 84-year-old COVID-19 patient as an apparent result of hydroxy-chloroquine use [5]. A recent effort to improve cardiac telemetry in 524 COVID-19 patients reports the prevalence of QT prolongation at 19.7% [6].

It remains that reliable, comprehensive data regarding the prevalence of COVID-19 cardiac electrophysiologic effects and sequelae have yet not been reported, a gap in knowledge addressed by this research project. The EKG derangements provoked by the COVID-19 virus have not been well researched in the current literature.

2. Methods

The research vehicle is a case-control retrospective analysis of data obtained from the ECGs and telemetry information of laboratory-confirmed COVID-19 positive patients admitted to our center. This study includes data from 145 patients admitted to The Medical Center hospital in Bowling Green, Kentucky, between March 18, 2020 and June 9, 2020. Primary analyses were conducted utilizing data from patients' first ECG, taken near the time of hospital admission; additional ECGs were conducted on most patients during the course of their hospitalization; these data were used to examine the level of variability in ECG parameters over time.

The research project considers the following cardiac and patient parameters in its analysis:

Rhythm	Age	Gender
Heart rate	Medications	Ventilator status
Health outcomes	Peak troponin level	P-wave duration
P-wave amplitude	PR interval	QRS duration
Bundle branch blocks	QTc	QRS axis
Left/right ventricular hypertrophy	ST elevation	Dysrhythmias
Poor R wave progression	T-wave inversion	Serum potassium
Serum magnesium		

All ECG parameters were independently reviewed by two board certified cardiologists. All statistical analyses were conducted using SYSTAT, version 13. We compared patient demographics, ECG variables and cardiac states of hospitalized COVID-19 patients who survived versus those who did not survive. Continuous variables were tested for normality within groups using a Shapiro-Wilk test. Because several deviated from normality, variables were subsequently tested for significant differences between groups using Mann-Whitney U-tests. Discrete variables were tested for significant differences among groups using chi-square tests of association. Significance was assessed using the Bonferroni correction applied within each family of tests (demographics, ECG variables, cardiac states, troponin level, and cardiac states outside of normal range).

Early in the pandemic, many patients in our study (n = 68) were treated with hydroxychloroquine, which is known to potentially increase QTc and/or QT interval. To examine the potential confounding effects of hydroxychloroquine in our study, we tested for significant differences in QTc and QT Interval as a function of treatment with hydroxychloroquine, and the relationship between hydroxychloroquine and survival. Similarly, a Spearman correlation comparison was done to assess the potential impact of serum potassium and magnesium on QT prolongation. Mann-Whitney U-

tests were conducted to assess the relationship between levels of these electrolytes and survival.

A classification tree approach based on the Gini index was used to partition individual patients into predicted 'survived' and 'deceased' groups based on combinations of demographic, ECG, and cardiac ischemia biomarker variables. This approach uses a recursive splitting process to partition groups of individuals that are as homogeneous as possible with respect to the outcome variable [7]. One or more predictor variables contribute to establishing the splitting criterion at each node. The process continues until there is little improvement in the relative error of the model. The resulting decision tree can be used as a basis for judging the accuracy of the model in predicting the outcome variable, as well as serving as a clinical predictive framework for new cases.

To test for significance of independent predictors of survival/mortality, a logistic regression was conducted using those variables initially identified as important through the classification tree analysis. In this model, these variables were used to predict the probability of mortality, while survival served as the default (reference) state.

To examine the level of variation in serial ECGs conducted on patients over the course of their hospitalization, and thus the utility of first ECGs in predicting outcomes, data for each patient were converted to z-scores. For each variable, the percentage of individual values differing by more than ±2 standard deviations from the within-patient mean was determined as used as an indicator of statistically-significant variation.

3. Results

Deceased patients were significantly older, less likely to be female, had higher QTc values and higher peak troponin levels than those who survived (Table 1). Deceased patients were characterized by a significantly higher incidence of right or left atrial enlargement, ST depression, poor R-Wave progression, and QTc values outside the normal range (Table 1). Bundle branch blocks were also significantly-more frequent in deceased patients (Table 1); 14 of 16 blocks occurred as right bundle branch morphology. The incidences of PACs as well as QRS duration values outside the normal range were also proportionally higher in deceased patients, though these differences were not significant based on Bonferroni-adjusted criteria (Table 1). All other variables were very similar between groups.

While hydroxychloroquine is known to lengthen QTc and/or QT interval, such effects were not seen within the study population. There was no significant difference in either QTc (U = 2.025.0, df = 1, p = 0.26) or QT interval (U = 1,547.5, df = 1, p = 0.19) based on whether patients received hydroxychloroquine as part of their treatment. Similarly, there was no strong association between survival and treatment with hydroxychloroquine; while a higher percentage of patients receiving hydroxychloroquine survived (68.0% vs. 43.3%), this difference was significant (x [2] = 6.0 df = 1, p = 0.01), but is largely accounted for by the fact that patients who received hydroxychloroquine were significantly younger than those who did not (U = 2513.5, df = 1, p = 0.03); in fact, logistic regression of survival versus age and hydroxychloroquine status indicates that only age is a significant predictor.

Serum magnesium and potassium levels were also investigated and recorded. Hypomagnesemia and hypokalemia are known to prolong the QT interval. To rule out confounding prolonged QT interval from electrolyte derangements, Spearman correlations were compiled. Serum magnesium and potassium likewise showed no relationship with either QTc or QT interval. Spearman correlation coefficients were not significant (magnesium: r = −0.13 and −0.12, potassium: 0.05 and 0.06 for QTc and QT Interval,

Table 1
Characteristics of COVID-19 patients who survived vs. those who were deceased. p-values for continuous variables were determined via Mann-Whitney U-tests, and for discrete variables using chi-square tests of association.

Variable	Overall		Survived		Deceased		p-value
Age (years) — mean ± SE	n = 145	63.8 ± 1.3	n = 106	60.6 ± 1.6	n = 38	73.3 ± 2.0	<0.001*
Female — no. (%)	n = 144	70 (48.6)	n = 106	57 (53.8)	n = 38	13 (34.2)	0.04
Heart Rate (bpm) - mean ± SE	n = 136	89.6 ± 2.0	n = 99	90.2 ± 2.2	n = 37	87.8 ± 4.0	0.95
PR Interval (ms) — mean ± SE	n = 123	155.2 ± 2.4	n = 91	154.0 ± 2.5	n = 32	158.7 ± 5.9	0.55
QRS Duration (ms) — mean ± SE	n = 136	93.9 ± 1.9	n = 99	92.5 ± 1.7	n = 29	97.6 ± 5.4	0.14
QT Interval (ms) — mean ± SE	n = 136	383.6 ± 5.0	n = 99	376.8 ± 5.1	n = 37	401.6 ± 12.0	0.12
QTc (ms) — mean ± SE	n = 136	455.1 ± 3.7	n = 99	451.9 ± 3.1	n = 37	463.6 ± 10.8	0.006*
QRS Axis - mean ± SE	n = 134	12.8 ± 4.3	n = 98	14.8 ± 4.0	n = 36	7.3 ± 11.6	0.30
Peak Troponin (ng/ml) - mean ± SE	n = 110	0.3 ± 0.1	n = 79	0.07 ± 0.02	n = 31	1.0 ± 0.4	<0.001*
LBBB/RBBB — no. (%)	n = 139	16 (11.5)	n = 104	7 (6.7)	n = 35	9 (25.8)	0.002*
Non-Specific IVCD — no. (%)	n = 126	6 (4.7)	n = 100	5 (5.0)	n = 26	1 (3.8)	0.81
RAE/LAE — no. (%)	n = 141	11 (7.8)	n = 104	4 (3.8)	n = 37	7 (18.9)	0.003*
LVH/RVH — no. (%)	n = 141	14 (9.9)	n = 104	11 (10.6)	n = 37	3 (8.1)	0.67
ST Depression — no. (%)	n = 141	5 (3.5)	n = 104	0 (0.0)	n = 37	5 (13.5)	<0.001*
T-Wave Inversion	n = 141	14 (9.9)	n = 104	8 (7.7)	n = 37	6 (16.2)	0.14
Atrial Fibrillation — no. (%)	n = 141	9 (6.4)	n = 104	7 (6.7)	n = 37	2 (5.4)	0.78
Atrial Tachycardia — no. (%)	n = 141	1 (0.7)	n = 104	0 (0.0)	n = 37	1 (2.7)	0.09
NVST — no. (%)	n = 141	1 (0.7)	n = 104	1 (1.0)	n = 37	0 (0.0)	0.55
PVC — no. (%)	n = 141	6 (4.3)	n = 104	4 (3.8)	n = 37	2 (5.4)	0.69
PAC — no. (%)	n = 141	7 (5.0)	n = 104	3 (2.9)	n = 37	4 (10.8)	0.06
Poor R-Wave Progression — no. (%)	n = 141	6 (4.3)	n = 104	0 (0.0)	n = 37	6 (16.2)	<0.001*
Heart Rate > 100 — no. (%)	n = 136	34 (25.0)	n = 99	27 (27.3)	n = 37	7 (18.9)	0.32
PR Interval > 120 — no. (%)	n = 123	112 (91.1)	n = 91	84 (92.3)	n = 32	28 (87.5)	0.41
QRS Duration > 100	n = 136	39 (28.7)	n = 99	23 (23.2)	n = 37	16 (43.2)	0.02
QTc > 460 — no. (%)	n = 136	62 (45.6)	n = 99	38 (38.4)	n = 37	24 (64.9)	0.006*
Non-Sinus Rhythm — no. (%)	n = 136	30 (22.1)	n = 99	19 (19.2)	n = 37	11 (29.8)	0.19

* Indicates p-values that are significant based on Bonferroni-adjusted criteria applied within the family of tests.

respectively; p 0.13 to 0.49). There was also no relationship between levels of magnesium (U = 703.0, df = 1, p = 0.76) or potassium (U = 1298.0, df = 1, p = 0.08) and survival.

4. Survival analysis

We subsequently studied a potential algorithm to predict survival. Eighty-two (82) patients had complete data for all variables and thus served as the basis for the classification analysis. The resulting optimal decision tree contained three terminal nodes across two hierarchical splitting criteria (Fig. 1). The first split partitioned individuals based on the presence of PACs and peak troponin level; individuals with values of (PAC and/or Peak Troponin <0.057) formed a terminal node containing individuals with a predicted outcome of 'survived.' The remaining individuals were subsequently partitioned into two nodes based on QT Interval and Age; individuals with values of (QT interval + Age < 419) were placed into a terminal node with a predicted outcome of 'survived.' The remaining individuals formed a terminal node with a predicted outcome of 'deceased.'

Both splits were characterized by significant differences in the mean of the associated predictor variables of (PAC and/or Peak Troponin) and (QT Interval + Age) (p = 0.003 and p < 0.001, respectively).

To examine the predictability of the decision tree, all patients with complete data for the predictor variables associated with each split (n = 103) were classified, and the predicted outcomes compared to actual outcomes.

The overall accuracy of prediction of the decision tree was 85.5%. Sixty-five of 74 patients (87.8%) were correctly predicted to survive, while 23 of 29 (79.3%) were correctly predicted to become deceased. Nine patients were incorrectly predicted to become deceased, while six were incorrectly predicted to survive. This level of accuracy led to a positive predictive value of 91.5% for the

outcome of 'survived,' and 71.8% for 'deceased. A clinical decision-making flow chart is provided in Table 2.

Logistic regression indicated that age (b = 0.06, Z = 3.15, p = 0.002) and peak troponin level (b = 2,76, Z = 2.43, p = 0.016) were significant predictors of mortality; neither QT Interval (p = 0.28) nor the presence of PACs (p = 0.50) were significant in this model (Table 3). However, the classification efficiency of the logistic regression model was lower than that of the classification tree analysis both overall (85/105 correct, 80.9%) and for 'survived' (72 of 89, 80.9%); the classification efficiency for 'deceased' was slightly better using the logistic model (13 of 16, 81.3%) (see Table 4).

One-hundred nine (109) of 145 patients received multiple ECGs over the course of their hospitalization. Among these, the number of individual ECGs conducted ranged from 2 to 12, with a mean of 4.6 ± 0.2. For each of the seven variables examined, the level of within-patient variability was very low; fewer than 1.5% of values differed from the within-patient mean by more than +2 standard deviations (Table 3). Only 10 patients showed multiple values exceeding this threshold, and only one patient who showed values both greater than and less than 2 standard deviations. There was also very limited association between ECG variability and misclassification based on the decision tree; none of the patients with individual ECG values ± 2 standard deviations from the within-patient mean were incorrectly predicted to survive based on the first ECG, and only one such patient was incorrectly predicted to become deceased (and this misclassification was based on a high peak troponin level as opposed to her/his ECG characteristics.

5. Discussion

The SARS-CoV-2 pandemic has not only impacted the US but the entire world. Despite various medical therapies including hydroxychloroquine, convalescent plasma, anticoagulation such as
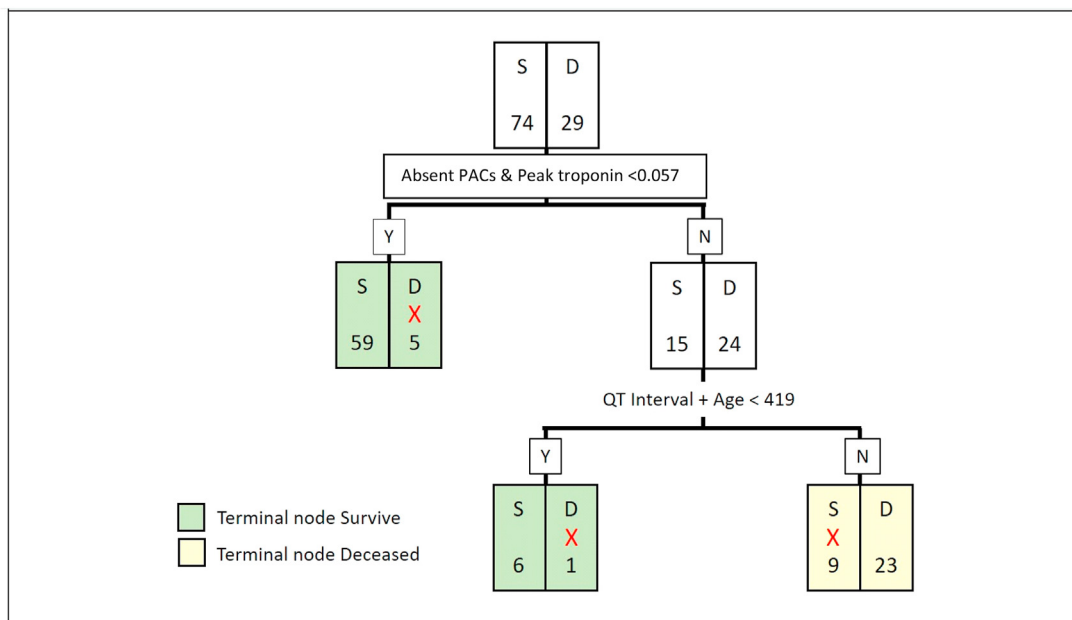
Fig. 1. Optimal decision tree for survival based on patient demographics, ECG variables, and cardiac states. All patients with complete data for splitting variables were classified. Incorrect classifications are indicated by red Xs. Note that, at the first node, survival ('Y') is predicted by the absence of PACs and a Peak Troponin level < 0.057.

Table 2
Decision-making flow chart for predicting survival of hospitalized COVID-19 patients based on ECG, biochemical, and cardiac states.

Node 1.a. Absence of PACs and peak troponin <0.057 ng/ml…....…………………………….	Survive
b. Presence of PACs and/or peak troponin ≥ 0.057 ng/ml…….…….………………………….	Next node (2)
Node 2.a. QT interval + age <419...……………………………………………………	Survive
b. QT interval + age ≥ 419………………………………………………………..	Deceased

Table 3
Results of logistic regression of variables identified through the classification tree analysis as important predictors of survival/mortality. The overall regression model predicting mortality was highly significant (log-likelihood = −45.838, x^2 = 33.960, df = 4, p < 0.001); approximately 27% of the probability of survival/mortality was accounted for by the model (R^2 = 0.276).

Parameter	Estimate (b ± SE)	z-value	P -value	Odds Ratio (±SE)
PAC = 0	−0.603 ± 0.886	−0.681	0.496	0.547 ± 0.485
Peak Troponin	2.755 ± 1.136	2.425	0.015	15.723 ± 17.863
QT Interval	0.005 ± 0.005	1.072	0.284	1.005 ± 0.005
Age	0.063 ± 0.020	3.148	0.002	1.065 ± 0.024

heparin or enoxaparin, steroids, antibody infusions and remdesivir, we are still do not have a universal evidence-based medical approach. New literature is now surfacing with FDA emergency use criteria on the rise. Our objective was to identify high risk electrocardiography features that may develop as the severity of the disease increases or progresses.

The prevalence of the various significant variables identified on the ECGs have been established in the literature. The Health 2000 Survey was a population cohort in Finland between 2000 and 2001 that looked at the prevalence of poor R wave progression in the population and that was found to be present in 7% of women and 2.7% of men [8]. The QTc in the general population is distributed normally with up to 10–20% of otherwise healthy individuals exhibiting values that are beyond the normal range [9]. QTc prolongation as measured by the Bazett formula, among deceased patients was independent of the use of hydroxychloroquine. In our patient sample, use of hydroxychloroquine did not lead to significant QTc prolongation, nor any difference in survival not otherwise attributable to patient age. QTc prolongation and sudden cardiac death have been linked. An increase in death among individuals with prolonged QTc intervals has been established [11].

The presence of poor R wave progression and prolonged QTc were found to be statistically significant when looking at mortality for those patients hospitalized with COVID-19. Poor R wave progression was not seen in the patient cohort who survived while 16.2% of those deceased demonstrated such on EKG.

Table 4
Summary of within-patient variability in ECG variables. Individual values ± 2 SDs from the within-patient mean were considered to represent statistically significant variation.

	HR	PR-Interval	QRS Duration	QT-Interval	QTC	QRS Axis
Num Patients	108	98	105	109	109	109
Num ECGs	504	460	497	506	506	505
Num ECGs ±2 SD	6	5	6	4	5	7
% ECGs ±2 SD	1.2	1.1	1.2	0.8	1.0	1.4

In addition to these prevalent features of the COVID EKGs, the presence of premature atrial contractions, age, and peak troponin levels allowed for additional predictability of survival from the virus use a risk prediction approach. Using standard cut-off values of 460 msec, a troponin I elevation cut off value of 0.057 ng/ml, and presence or absence of PACs found on telemetry or EKG, allowed us to develop a clinical decision flow chart that yielded positive predictive values for survival and deceased outcomes, respectively. Our risk prediction decision algorithm may help future providers risk-stratify patients for prognostic implications using readily available information, regardless of the treatment plan in place. Unfortunately for those inflicted, older age, elevated troponin, prolonged QT interval, and the presence PACs, were found to increase the risk of demise.

The increased presence of PACs has not been well established as to the underlying pathophysiology. Increased ventricular filling pressures and transient cardiac dysfunction throughout the cardiac cycle have both been postulated. This may also lead to atrial enlargement due to increased volume and/or pressure overload. Severe left atrial enlargement has also been linked to further atrial dysrhythmias, in particular a 4-fold increase in atrial fibrillation in the non-COVID-19 population [15].

Premature atrial contractions (PACs) have been highly linked with additional atrial arrhythmias including atrial fibrillation. The burden of PACs has been shown to increase with age, presence of CV disease, abnormal levels of natriuretic peptide and dyslipidemia/hyperlipidemia. Frequent PACs may be early warning signs of atrial fibrosis. PACs have shown to increase composite events with ischemic stroke and may adversely affect the sinus node and/or AV nodes, and can also lead to remodeling of the atrium furthering the risk for atrial arrhythmias. In addition, PACs have been shown in 10 year follow up study to potentially be associated with CV hospitalizations, atrial fibrillation, and possible permanent pacemaker implantation, independent of risk factors [12,13].

Elevated troponin levels, regardless of the cause of the elevation, are thought to put patients at higher overall risk of morbidity and mortality. The majority of patients with elevated troponin have higher ischemia burden. The BMJ published a study looking at 250,000 patients over 8 years and found that the positive troponin was 3x mortality risk with the most at risk patients for long term outcomes being in the younger population [8]. A Swedish study with nearly 20,000 patients found that 3 year mortality increased with an increase in the level of troponin detected [10]. Increased troponin levels regardless of the cause is implicated in a worse long-term prognosis.

The biomarkers released may be an indication of underlying subendocardial ischemia especially in the setting of those with underlying coronary artery disease, whether it be from a type two non-ST segment elevation myocardial infarction from supply demand mismatch through severe hypoxia, microcirculatory thrombotic events, or direct endothelial injury or from a type one NSTEMI pathology. Other causes may include underlying viral myocarditis through direct cytotoxicity or cytokine release. This correlates with the significantly higher incidence of ST depression also supports the idea of subendocardial ischemia, rather than transmural infarction in the setting of COVID-19 infection.

Conduction abnormalities identified as left and right bundle branch blocks were also significantly-more frequent in deceased patients (Table 1); 14 of 16 blocks occurred as right bundle branch morphology. The incidences of QRS duration values outside the normal range were also proportionally higher in deceased patients, though these differences were not significant. Increased pulmonary vascular resistance, pulmonary vasoconstriction, endothelial dysfunction, cytokine storm, hypoxemia, and a pro-coagulopathic state with microvascular thrombi have all been implicated in RV

dysfunction and RV distension [14]. The RV distension may also reflect the predilection for right bundle branch block morphology over a left bundle branch block morphology.

Age has also been identified as a significant risk factor for the development of future cardiovascular events. Older adults are defined as greater than or equal to 65 years of age by the ACC/AHA. Age may convey risk especially if frailty, cognition, social factors, and mobility limitations are present. As age increases the risk of comorbid diagnoses also increases. In this study, age alone did not produce a statistically significant risk without additional comorbidities with regards to survival outcomes.

6. Conclusions

The presence of PACs, higher QT interval values, troponin biomarkers, and age, when combined, were able to yield a positive predictive value of 91.5 for the outcome of 'survived,' and 71.8% for 'deceased. Repeating EKGs during the hospitalization of COVID-19 patients may provide more useful information that previously expected. With the low sample size from a single study site, the results are susceptible to bias and overestimation of the predictive value. Further studies should be considered to verify the findings provided for reproducibility. This study can be useful when trying to risk stratify COVID-19 patients that are acutely ill requiring hospitalization to help risk stratify patients during the current pandemic.

Declaration of competing interest

No conflicts of interest, personal financial gain, or relationships with industry to be reported.

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