Electrocardiographic Predictors of Disease Severity, Mortality, and Advanced Ventilatory Support Among Hospitalized COVID-19 Patients: A 2-Year Single-Center Retrospective, Cohort Study From January 2020 to December 2021

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Abstract

INTRODUCTION: For detecting myocardial injury in severe and critical COVID-19, the electrocardiogram (ECG) is neither sensitive nor specific, but in a resource-poor environment, it remains relevant. Changes in the ECG can be a potential marker of severe and critical COVID-19 to be used for predicting not only disease severity but also the prognosis for recovery.

METHODS: The admitting and interval ECGs of 1333 COVID-19 patients were reviewed in a 2-year, single-center, retrospective cohort study. Each was evaluated for 29 predefined ECG patterns under the categories of rhythm; rate; McGinn-White and right ventricular, axis, and QRS abnormalities; ischemia/infarct patterns; and atrioventricular blocks before univariate and multivariate regression analyses for correlation with disease severity, need for advanced ventilatory support, and in-hospital mortality.

RESULTS: Of the 29 ECG patterns, 18 showed a significant association with the dependent variables on univariate analysis. Multivariate analysis revealed that atrial fibrillation, heart rate greater than 100 beats per minute, low QRS voltage, QTc of 500 milliseconds or greater, diffuse nonspecific T-wave changes, and "any acute anterior myocardial infarction" ECG patterns correlate with disease severity, need for advanced ventilatory support, and in-hospital mortality. S1Q3 and S1Q3T3 increased the odds of critical disease and need for high oxygen requirement by 2.5- to 3-fold. Fractionated QRS increased the odds of advanced ventilatory support.

CONCLUSION: The ECG can be useful for predicting the severity and outcome of more than moderate COVID-19. Their use can facilitate rapid triage, predict disease trajectory, and prompt a decision to intensify therapy early in the disease to make a positive impact on clinical outcomes.

KEYWORDS: advanced ventilatory support, COVID-19 electrocardiographic predictors, disease severity, in-hospital mortality

INTRODUCTION

Unlike the other known human coronaviruses, including 229E, NL63, HKU1, OC43, MERS-CoV (Middle East respiratory syndrome–related coronavirus), and SARS-CoV (severe acute respiratory syndrome coronavirus), targeting the respiratory tract, SARS-CoV-2 shows marked tropism for the heart.[1] Most authorities currently accept the bidirectional relationship between COVID-19 (coronavirus disease 2019) infection and cardiac disease where a pre-existing cardiovascular disease increases the risk for worse outcomes in COVID-19 and the infection itself promotes cardiovascular complications.[2]

The pathologic processes associated with severe COVID-19 include cytokine storm, hypoxic injury, direct and indirect endothelial and myocardial injury, plaque rupture, coronary spasm, and microthrombi formation, all of which act in concert to extract a significant cardiovascular toll[3] that include thrombosis, ischemia, and heart failure. Utilizing the electrocardiogram (ECG) to screen for these problems is a practical diagnostic maneuver. There is much-published literature about ECG patterns in COVID-19, ranging from descriptive characterizations to studies that identified prognosticators.[4] However, there have been few studies that investigated if there is a correlation between the admitting and the interval ECGs and disease severity, in-hospital mortality, or the need for advanced ventilatory support. This article investigates this correlation by addressing the temporal pattern of the ECGs during the course of the disease in 1333 consecutive reverse transcriptase–polymerase chain reaction (RT-PCR)–confirmed COVID-19 patients admitted to one institution.

Several pathophysiologic mechanisms result in direct and indirect cardiac injury in more than moderate COVID-19. The direct cardiac injury was attributed to hemodynamic derangement, hypoxemia, inflammatory myocarditis, stress cardiomyopathy, microvascular dysfunction, thrombosis, hypercoagulability, and ischemia.[5] Indirect cardiac injury was attributed to the cytokine storm, sepsis, and right ventricular (RV) pressure overload during severe pneumonia, acute respiratory distress syndrome, and pulmonary thromboembolism.[6,7] There is international and local observational higher incidence of cardiac injury in severe and critical COVID-19.[8,9] The implication is that critical illness can be accompanied by significant ECG changes that have potential prognostic values and can predict disease trajectory.

In Nemati and colleagues'[4] 2020 systematic review of 31 articles (n = 2379) that investigated the ECG predictors of severe COVID-19 outcome, ST elevation, bradycardia, T-wave inversions (TWIs), QT prolongation, and atrial fibrillation (AF) predicted worse COVID-19 outcomes.[4]

Sinus tachycardia and AF were the most common rhythm abnormalities in severe COVID-19 with myocardial complications.[10] ST-segment shifts, especially elevation (STE) with or without associated T-wave changes, reflect myocardial injury from either myocarditis or ischemia/infarction and occasionally in Takotsubo syndrome.[11]

A systematic review of 20 studies and case reports on ECG and COVID-19 by Mehraeen et al[12] identified drug-induced and non–drug-induced changes. ST elevation was the most commonly observed change among the non–drug-induced changes, and this was associated with high fatality rate. QTc prolongation was the main finding for the drug-induced changes; this was likely related to the rampant use of chloroquine and hydroxychloroquine with azithromycin in the early days of the pandemic. However, although these drugs increased the risk for QTc prolongation, there were no arrhythmia-related deaths.[12]

Akhtar and colleagues[13] compared pre-COVID and COVID ECGs in their 293-patient cohort, reporting that QTc prolongation was more prevalent in the ECGs of patients who died, and they concluded that prolonged QTc was associated with increased mortality but not necessarily from arrhythmia.[13] Current evidence implicated alterations in the gene encoding K^+ channels by SARS-CoV-2 with subsequent dysregulation of the action potential and calcium handling in the cardiac muscle. Other problems were inflammatory cardiac channelopathies and QT prolongation.[14]

A study also reported on the absolute and relative diminution of the QRS amplitude in COVID-19 patients that preceded their clinical deterioration and often death and identified this feature as an independent predictor of mortality. [15]

Finally, the right ventricle takes the brunt of the severe pulmonary involvement in COVID-19, and a retrospective study was done by Raad et al[16] on 480 COVID-19 patients who had right-sided heart strain patterns in the presenting ECGs. These included new right axis deviation (RAD), S1Q3T3, or ST-segment depression with TWI in anterior or inferior leads; they occurred in 11% of patients and predicted both mortality and the need for mechanical ventilation.[16]

This study aimed to identify the ECG patterns correlating with COVID-19 disease severity, the need for more advanced ventilatory support, and in-hospital mortality.

METHODS OF THE STUDY

A. Study Design and Setting

This is a retrospective cohort study of the admitting and interval ECG tracings of RT-PCR–confirmed COVID-19 patients admitted to Perpetual Succour Hospital between January 1, 2020, and December 31, 2021.

B. Study Population and Sampling

All consecutively admitted COVID-19 patients during the prespecified period of 24 months were included, with the following inclusion and exclusion criteria:

Inclusion criteria:
1. Adult patients at least 18 years of age with available interpretable 12-lead ECG during admission
2. Confirmed COVID-19 infection with RT-PCR swab test

Exclusion criteria:
1. COVID probable/suspect
2. Confirmed COVID-19 patients with ventricular-based pace rhythms who manifested with Wolff-Parkinson-White ECG patterns because of the limitations of interpreting repolarization and ischemic changes
3. Confirmed COVID-19 patients who died within 24 hours of admission

C. Sample Size Calculation and Sampling Procedure
The sample size was based on the number of eligible case records of COVID-19 patients admitted between January 1, 2020, and December 31, 2021. There was no sampling technique.

D. Data Collection Procedure
The study proposal was approved by the technical committee of the Section of Adult Cardiology and Institutional Ethics Review Committee (IERB). Data collection began after IERB approval.

1. ECG Sampling and Analyses
   The cases were retrieved from the hospital's COVID-19 Registry; the admitting and interval ECGs of each were retrieved, printed out, and analyzed. Based on the medical case records, the interval ECGs were usually obtained during a patient's clinical deterioration. The interval ECG in patients with noncritical or benign course was their predischarge ECG.

   The primary investigator interpreted the ECGs before he retrieved the patients' charts to review the temporal course of their hospitalization and its outcome. After this, 2 cardiologists interpreted the retrieved ECG tracings independently. One of the 2 cardiologists was an electrophysiologist, and both were blinded to the patients' identities, condition during the hospitalization, temporal course, and outcome.

   The investigators and the ECG readers conferred to identify distinctive recurring ECG patterns and set these ECG patterns as the independent variables of the study. The interpretation of ECG was a consensus by two cardiologists and the principal investigators, with adjudication by the electrophysiologist.

2. Data Collection Tool
   After approval by IERB and the hospital administrator, each patient's chart was reviewed to extract detailed clinicodemographic profiles of the patients, including the presenting history, disease severity assessment, temporal course, and outcome.

   All data gathered were encoded in a Google Worksheet.

One thousand four hundred forty-two patients with confirmed COVID-19 infection were identified from the hospital COVID Registry from January 2020 to December 2021. After being screened according to predefined inclusion and exclusion criteria, a total of 1333 patients were eligible for the study. All their ECGs were retrieved, printed out, and analyzed for the ECG patterns. The chart review extracted the clinicodemographic profile, disease severity, O_2 requirement and

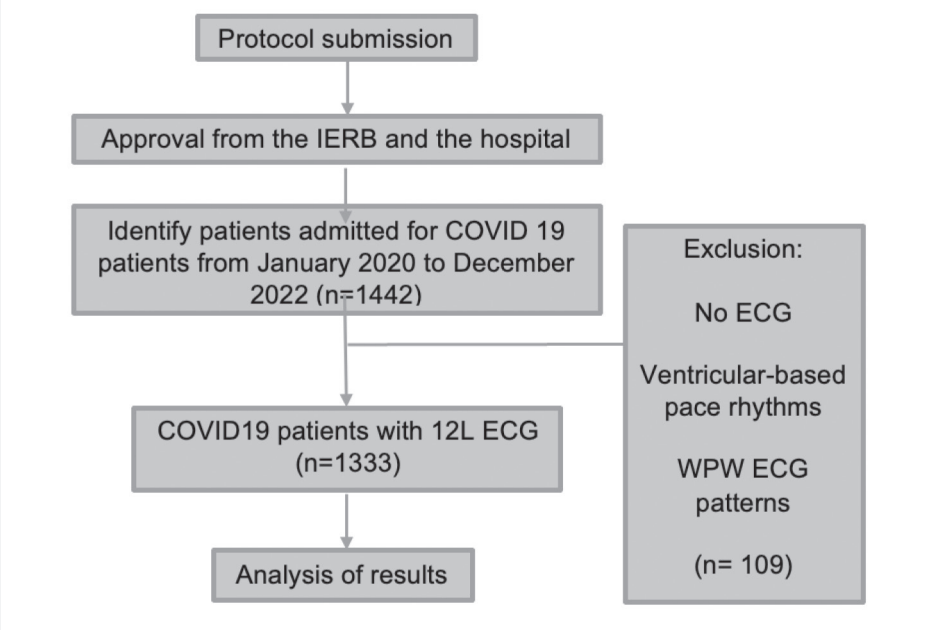

Figure 1. Flowchart of the study.

mode of delivery, and final discharge disposition. The Google Worksheet encoded the data of interest in a binary format to facilitate easy handling of event rate counts and logistic regression analyses. All data were collated, analyzed, and handled with the utmost confidentiality.

E. Data Processing and Analysis

The descriptive analysis expressed the clinical and demographic profile of COVID-19 patients. Frequency and percentages were used for categorical variables, whereas the mean and standard deviation were used for continuous variables.

Univariate binomial logistic regression analysis assessed the association between ECG patterns and the dependent variables of disease severity, in-hospital mortality, and the need for more advanced ventilatory support.

Multivariate binomial logistic regression analysis was performed in all ECG patterns that reached statistically significant association with the dependent variables from the univariate logistic regression to determine the ECG predictors for disease severity, in-hospital mortality, and need for more advanced ventilatory support.

The independent ECG predictors of disease severity and outcome were subanalyzed using univariate binomial regression analysis according to their temporal observance to determine the predictive power of the admitting versus interval ECGs.

F. Ethical Considerations

The research proposal was approved by ethics review committee, and data collection began only after the approval. Patient privacy was protected with no personal identifiers in the case studies, and data were stored in secured password-protected files. There was no financial support from any company or individuals who may directly or indirectly benefit from the study results. The researchers declare no conflict of interest during the conduct of the study.

RESULTS

There was a slight male preponderance in the study population of 1333 (n = 710 [53%]), with the majority classified as noncritical illness (n = 826 [62%]). The patients ranged in age from 50 to 80 years, reflecting worldwide statistics. There were 507 critically ill patients, and 169 (23%) died. Hypertension, type 2 diabetes mellitus, and coronary artery disease (CAD) were the top comorbidities. Acute respiratory failure was the most common serious complication, with 38% of patients needing advanced ventilatory support. Acute kidney injury requiring renal replacement therapy occurred in 17%, and 3% developed acute coronary syndrome.

Univariate binomial regression analysis indicated that sinus rhythm and normal heart rate were prevalent among COVID-19 survivors, that is, those with noncritical disease. Electrocardiogram patterns that were associated with critical illness, high O_2 requirement, and mortality included AF, tachycardia, S1Q3, S1Q3T3, McG TWI, RAD, LoQRS, QTc ≥500 milliseconds, and all ischemia and infarct ECG patterns. Right bundle-branch block or RAD correlated with in-hospital mortality, whereas first-degree AV block and fragmented QRS (fQRS) correlated with critical disease and high O_2 requirements.

Some ECGs with PRWP (PRWP-to-QS or Qr pattern) evolved to QS/Qr pattern without accompanying ST-segment shifts on interval ECGs. This made it difficult to determine if the admitting anterior wall QS/Qr pattern was due to an old infarct or a PRWP-to-QS/Qr evolution. Nevertheless, this pattern showed a positive association with critical illness and poor outcomes. J-waves and bradycardia did not discriminate for the dependent variables.

After correction for confounders, AF, HR greater than 100 bpm, LoQRS, QTc ≥500 milliseconds, diffuse NSTWCs, and "any AMI" ECG emerged as independent predictors of disease severity and worse outcomes (Table 2).

Both the McGinn-White signs, S1Q3 and S1Q3T3, were independent predictors of disease severity and high O_2 (O_2) requirements. McG TWI predicted in-hospital mortality (odds ratio [OR], 4.73; 95% confidence interval [CI], 1.34–16.32; $P = 0.01$).

Significant reduction of QRS amplitude (LoQRS), either absolute (<5 mm in all limb leads and/or <10 mm in all precordial leads) or relative (interval decrease of QRS amplitude >50% from admitting ECG), was a prognosticator of all dependent variables.

The QTc prolongation was also a marker for critical disease (OR, 19.18; 95% CI, 10.34–35.59; $P = 0.0000$), need for advanced ventilatory support (OR, 17.64; 95% CI, 9.63-32.16; $P = 0.0000$), and mortality (OR, 1.82; 95% CI, 1.13-2.93; $P = 0.014$). A subanalysis on the temporal observance (admitting vs interval ECG) was performed using a univariate binomial logistic regression analysis to determine the predictive power of these parameters (Table 3).

Most of the ECG predictors detected on admission showed significant association with the predefined outcomes, providing support for the study hypothesis that the admitting ECG could predict COVID-19 disease trajectory.

When these ECG patterns appeared only during the course of the disease as documented in the interval ECGs, they consistently predict disease severity and outcomes with a higher OR and greater predictive power.

DISCUSSION

Atrial Fibrillation and Heart Rates >100 bpm

The prevalence of AF in our study population was 29% (383/1333). The presence of AF at time of admission (ADM AF) whether pre-existing or consequent of COVID disease conferred a 3- to 5-fold increase in likelihood for adverse outcomes. Most of AF cases reported here developed in the course of hospitalization as the disease worsened (281/345 [81%]), or

Table 1. Clinicodemographic Profile of COVID-19 Patients According to Gender, Disease Severity, Discharge Disposition, Need for Advance Respiratory Support, Age Group Distribution, Pre-existing Comorbidities, and Complications

PROFILE VARIABLES	N = 1333
GENDER	
MALE	710 (53)
FEMALE	623 (47)
DISEASE SEVERITY	
NON CRITICAL DISEASE	826 (62)
CRITICAL DISEASE	507 (38)
DISCHARGE DISPOSITION	
ALIVE	1164 (87)
EXPIRED	169 (13)
NEED FOR ADVANCE VENTILATORY SUPPORT	
LOW OXYGEN REQUIRING	822 (62)
HIGH OXYGEN REQUIRING	511 (38)

PROFILE VARIABLES	N = 1333
COMORBIDITIES/RISK FACTORS	
HYPERTENSION	999 (75)
DIABETES	751 (56)
CORONARY ARTERY DISEASE	425 (32)
SMOKER	272 (20)
BRONCHIAL ASTHMA	155 (12)
CHRONIC KIDNEY DISEASE	131 (10)
ESRD	58 (4)
MALIGNANCIES	127 (10)
DYSLIPIDEMIA	35 (3)
PREVIOUS STROKE	30 (2)
HYPOTHYROIDISM	32 (2)
HYPERTHYROIDISM	25 (2)
BETA THALASSEMIA	4 (0.3)

PROFILE VARIABLES	N = 1333
AGE DISTRIBUTION (years old)	
< 20	7 (0.53)
21-30	66 (5)
31-40	121 (9)
41-50	189 (14)
51-60	312 (23)
61-70	334 (25)
71-80	183 (14)
>80	121 (9)

PROFILE VARIABLES	N = 1333
COMPLICATIONS	
ACUTE RESPIRATORY FAILURE	350 (26)
ACUTE KIDNEY INJURY	232 (17)
ACUTE CORONARY SYNDROME	45 (3)
CVD INFARCT	25 (2)
CVD BLEED	8 (0.6)
PULMONARY EMBOLISM	40 (3)
DEEP VENOUS THROMBOSIS	8 (0.6)

when the patient developed a need for higher O_2 support, and prior to death (94/133 [71%]).

In a meta-analysis[17] of 19 observational studies involving 21,653 COVID-19 patients, the prevalence of atrial fibrillation was 11%, and in all these studies, both pre-existing and new-onset atrial fibrillation increased all-cause mortality.[17] We identified AF as a strong predictor for mortality, with 30-fold increase in critical disease and a 6-fold increase in odds for high O_2 requirements.

Our evaluation of tachycardia includes both sinus tachycardia and AF with a rapid ventricular response, and HR greater than 100 bpm emerged as a strong predictor for the prespecified outcomes. The patients who developed any of these three outcomes were already tachycardic on admission, underscoring the prognostic utility of ADM HR greater than 100 bpm.

McGinn-White and RV Overload ECG Patterns

Historically, the McGinn-White signs, S1Q3 and S1Q3T3, became the morphologic criteria for acute cor pulmonale due to pulmonary embolism,[18] and the S1Q3 pattern is reported to be more common in confirmed pulmonary embolism with hemodynamic deterioration.[19] Because of this, we analyzed S1Q3 and S1Q3T3 separately to determine their individual

Table 2. Univariate and Multivariate Binomial Logistic Regression Analyses: ECG patterns versus Disease Severity, In-hospital Mortality and Advance Ventilatory Support

	DISEASE SEVERITY				IN-HOSPITAL MORTALITY				ADVANCE VENTILATORY SUPPORT			
ECG PARAMETERS	UNIVARIATE BINOMIAL LOGISTIC REGRESSION ANALYSIS OR (95% CI)	p value	MULTIVARIATE BINOMIAL LOGISTIC REGRESSION ANALYSIS OR (95% CI)	p value	UNIVARIATE BINOMIAL LOGISTIC REGRESSION ANALYSIS OR (95% CI)	p value	MULTIVARIATE BINOMIAL LOGISTIC REGRESSION ANALYSIS OR (95% CI)	p value	UNIVARIATE BINOMIAL LOGISTIC REGRESSION ANALYSIS OR (95% CI)	p value	MULTIVARIATE BINOMIAL LOGISTIC REGRESSION ANALYSIS OR (95% CI)	p value
RHYTHM												
SINUS RHYTHM	0.29 (0.19, 0.44)	0.0000	1.83 (0.73 -3.60)	0.09	0.18 (0.11-0.28)	0.0000	0.65 (0.53, 1.78)	0.63	0.28 (0.18, 0.44)	0.0000	1.76 (0.75, 3.02)	0.23
ATRIAL FIBRILLATION	38.68 (26.55, 56.35)	0.0000	35.92 (23.35, 55.25)	0.0000	10.08 (6.98, 14.55)	0.0000	6.41 (4.19, 9.81)	0.0000	36.48 (25.21, 52.77	0.0000	33.15 (21.78, 50.46)	0.0000
HEART RATE												
HR >100 BPM	3.29 (2.60, 4.18)	0.0000	4.37 (2.30, 8.30)	0.0000	5.16 (3.66,7.27)	0.0000	2.95 (1.48,5.90)	0.002	3.23 (2.55, 4.10)	0.0000	3.94 (2.10, 7.38)	0.0000
HR 60-99 BPM	0.36 (0.29, 0.45)	0.0000	1.63 (0.88 -3.02)	0.12	0.20 (0.14, 0.29)	0.0000	0.79 (0.38, 1.63)	0.52	0.36 (0.29, 0.46)	0.0000	1.54 (0.84, 2.81)	0.16
HR < 60 BPM	0.86 (0.60, 1.26)	0.44			0.84 (0.48, 1.47)	0.54			0.87 (0.60, 1.26)	0.46		
McGINN WHITE SIGN												
S1Q3	2.76 (1.95, 3.93)	0.0000	3.35 (1.97-5.67)	0.0000	2.19 (1.43, 3.36)	0.0003	1.57 (0.88, 2.78)	0.12	2.79 (1.96, 3.95)	0.0000	3.26 (1.93, 5.50)	0.0000
S1Q3T3	2.76 (1.86, 3.40)	0.0000	2.54 (1.44, 4.49)	0.001	2.65 (1.70, 4.13)	0.0000	1.59 (0.84, 2.98)	0.15	2.75 (1.88, 4.03)	0.0000	2.53 (1.45, 4.54)	0.001
McG + ANY RV Overload ECG PATTERNS	1.25 (0.88-1.79)	0.22			1.60 (1.00, 2.55)	0.05			1.26 (0.88, 1.80)	0.20		
RV OVERLOAD ECG PATTERNS												
PERSISTENT S V5-V6	0.97 (0.74, 1.26)	0.81			1.19 (0.82, 1.73)	0.35			0.98 (0.75, 1.27)	0.86		
TALL R IN V1	1.18 (0.97, 1.56)	0.25			1.15 (0.77, 1.72)	0.50			1.19 (0.90, 1.58)	0.23		
McG TWI	2.30 (1.48, 3.57)	0.0002	1.40 (0.46, 4.25)	0.55	2.36 (1.40, 3.97)	0.001	4.73 (1.34-16.32)	0.01	2.32 (1.49, 3.60)	0.0002	1.73 (0.57, 5.33)	0.33
BUNDLE BRANCH BLOCK												
CRBBB/IRBBB	1.31 (0.97, 1.77)	0.08			1.90 (1.29, 2.82)	0.001	1.35 (0.80, 2.26)	0.26	1.29 (0.95, 1.74)	0.10		
CLBBB/ILBBB	5.69 (1.18, 27.51)	0.03	3.78 (0.51, 28.05)	0.19	3.49 (0.86, 14.08)	0.08			3.26 (0.81,13.11)	0.09		
ABNORMAL AXIS												
RAD	2.01 (1.27, 3.17)	0.003	1.08 (1.36-2.69)	0.82	4.07 (2.47, 6.68)	0.0000	3.7 (1.87, 7.32)	0.0002	2.02 (1.28, 3.19)	0.002	1.11 (0.56, 2.21)	0.76
INDETERMINATE	2.08 (0.94, 4.61	0.07			1.32 (0.45, 3.89)	0.61			2.09 (0.94, 4.64)	0.07		
LAD	1.08 (0.66, 1.76)	0.77			1.16 (0.58, 2.32)	0.68			1.08 (0.66, 1.77)	0.75		
QRS ABNORMALITIES												
LoQRS	3.09 (2.46,3.89)	0.0000	1.91 (1.36, 2.69)	0.0002	3.22 (2.27, 4.57)	0.0000	1.78 (1.16, 2.72)	0.008	3.05 (2.43, 3.84)	0.0000	1.89, (1.35, 2.65)	0.0002
J WAVES	1.25 (0.86, 1.81)	0.24			0.78 (0.43, 1.42)	0.42			1.26 (0.87, 1.82)	0.23		
fQRS	1.75 (1.16-2.63)	0.007	1.78 (0.97, 3.28)	0.06	1.34 (0.77, 2.53)	0.30			1.76 (1.17, 2.65)	0.007	1.90 (1.05, 3.44	0.03
QTc ≥ 500 msec	19.09 (11.53, 31.59	0.0000	19.18 (10.34, 35.59)	0.0000	3.49 (2.38, 5.11)	0.0000	1.82 (1.13, 2.93)	0.01	18.04 (11.02, 29.53)	0.0000	17.64 (9.63,32.16)	0.0000
ISCHEMIA/INFARCT ECG PATTERNS												
DIFFUSE NSTWC	2.19 (1.55, 3.09)	0.0000	2.05 (1.20, 3.51)	0.008	2.32 (1.52, 3.54)	0.0001	2.39 (1.40, 4.08)	0.001	2.21 (1.56, 3.11)	0.0000	2.11 (1.24, 3.57)	0.006
PRWP	1.81 (1.33, 2.48)	0.0002	1.02 (0.60, 1.76)	0.92	2.06 (1.38, 3.06)	0.0004	0.87 (0.47, 1.59)	0.64	1.83 (1.34, 2.49)	0.0001	1.04 (0.61,1.77)	0.89
PRWP-TO-QS	4.26 (1.95, 9.28)	0.0003	1.40 (0.34, 5.82)	0.64	8.57 (4.19, 17.5)	0.0000	2.89 (0.84, 9.89)	0.09	4.29 (1.97, 9.34)	0.0002	1.33 (0.32, 5.43)	0.69
ADM Anterior QS or Qr	3.70 (2.31, 5.93)	0.0000	1.34 (0.53, 3.44)	0.54	5.30 (3.30, 8.49)	0.0000	1.87 (0.74, 4.72)	0.18	3.72 (2.32,5.97)	0.0000	1.40 (0.55, 3.55)	0.48
NOT McG TWI	2.47 (1.70, 3.60)	0.0000	1.98 (0.0- inf)	0.98	2.07 (1.30, 3.28)	0.002	1.99 (0.0-inf)	0.98	2.40 (1.65, 3.48)	0.0000	1.56 (0.21, 11.44)	0.66
ANY AMI ECG	8.17 (3.78, 17.79)	0.0000	2.82 (1.03, 7.73)	0.04	15.49 (8.23, 29.13)	0.0000	8.37 (3.90, 17.93)	0.0000	8.23 (3.81, 17.79)	0.0000	2.82 (1.03,7.68)	0.04
AV BLOCKS												
FIRST DEGREE AVB	1.80 (1.13, 2.88)	0.01	1.63 (0.80, 3.32)	0.18	1.34 (0.70, 2.53)	0.37			1.82 (1.14, 2.90)	0.01	1.63 (0.81,3.29)	0.17

ADM=admitting; fQRS=fragmented QRS; LAD=left axis deviation; LoQRS=low-voltage QRS complexes; McG=McGinn-White signs; NSTWC=nonspecific T-wave changes; PRWP=poor R wave progression; PRWP-to-QS=PRWP evolution to QS wave; RAD=right axis deviation; TWI=T-wave inversion.

Highlighted are the ECG patterns found to have significant association with (by univariate binomial regression analysis) and identified as independent predictors of (by multivariate binomial regression analysis) severe disease, in-hospital mortality, and need for advance ventilatory support after multivariate logistic regression analysis.

impact on prognosis; and S1Q3 was found to have a slightly higher predictive power (OR, 3.3 vs 2.5) for the adverse outcomes than S1Q3T3.

Many other pulmonary conditions are associated with the McGinn-White signs, and today, they are considered neither pathognomonic nor sensitive or specific for pulmonary embolism.[20] However, other investigators such as Raad et al[16] also found S1Q3T3 and RV overload ECG patterns (new-onset RAD, RBBB, precordial or inferior wall TWI) to be predictors of critical COVID-19. One example is the case of a 38-year-old woman who manifested RV overload ECG patterns of S1Q3 as she deteriorated before she died.

Although the McGinn-White signs predicted critical disease and high O_2 requirements, the concomitant precordial and/or inferior wall TWI (McG TWI) or RAD (McG RAD) increased the likelihood of death by 5-fold.

Low QRS Voltage Complexes

The severity of QRS voltage diminution (LoQRS) progressed with time, and this dynamic diminution preceded clinical deterioration and predicted eventual demise.

Lampert and colleagues[21] observed this dynamic LoQRS in their study cohorts correlating low QRS voltage and COVID-induced myocardial injury (troponin elevations >0.03 ng/mL). In that study, LoQRS was an independent predictor for mortality, and the median time from its first appearance until death was only 52 hours.[21] Our data showed a similar correlation between LoQRS and disease severity and death regardless of their temporal observance (ADM LoQRS vs INT LoQRS) or location (frontal, precordial, or diffuse), but dynamic INT LoQRS that progresses to diffuse LoQRS portends a grimmer prognosis with an OR of 13.

Impaired voltage generation (myocardial injury from myocarditis or ischemia/infarction) and altered transmission from the myocardium to skin electrode (eg, pneumonic consolidation, pericardial or pleural effusion, and pulmonary hyperinflation) are possible mechanisms of low QRS voltage.[22] Low QRS voltage in the frontal plane has been associated with both ischemic and

Table 3. Univariate Regression Analysis of ECG Predictors of COVID-19 Disease Severity and Outcomes According to Their Temporal Observance (Admitting vs Interval ECG)

	DISEASE SEVERITY				IN-HOSPITAL MORTALITY				ADVANCE VENTILATORY SUPPORT			
ECG PARAMETERS	UNIVARIATE BINOMIAL LOGISTIC REGRESSION ANALYSIS OR (95% CI)	p value	MULTIVARIATE BINOMIAL LOGISTIC REGRESSION ANALYSIS OR (95% CI)	p value	UNIVARIATE BINOMIAL LOGISTIC REGRESSION ANALYSIS OR (95% CI)	p value	MULTIVARIATE BINOMIAL LOGISTIC REGRESSION ANALYSIS OR (95% CI)	p value	UNIVARIATE BINOMIAL LOGISTIC REGRESSION ANALYSIS OR (95% CI)	p value	MULTIVARIATE BINOMIAL LOGISTIC REGRESSION ANALYSIS OR (95% CI)	p value
RHYTHM												
SINUS RHYTHM	0.29 (0.19, 0.44)	0.0000	1.83 (0.73 -3.60)	0.09	0.18 (0.11-0.28)	0.0000	0.65 (0.53, 1.78)	0.63	0.28 (0.18, 0.44)	0.0000	1.76 (0.75, 3.02)	0.23
ATRIAL FIBRILLATION	38.68 (26.55, 56.35)	0.0000	35.92 (23.35, 55.25)	0.0000	10.08 (6.98, 14.55)	0.0000	6.41 (4.19, 9.81)	0.0000	36.48 (25.21, 52.77	0.0000	33.15 (21.78, 50.46)	0.0000
HEART RATE												
HR >100 BPM	3.29 (2.60, 4.18)	0.0000	4.37 (2.30, 8.30)	0.0000	5.16 (3.66,7.27)	0.0000	2.95 (1.48,5.90)	0.002	3.23 (2.55, 4.10)	0.0000	3.94 (2.10, 7.38)	0.0000
HR 60-99 BPM	0.36 (0.29, 0.45)	0.0000	1.63 (0.88 -3.02)	0.12	0.20 (0.14, 0.29)	0.0000	0.79 (0.38, 1.63)	0.52	0.36 (0.29, 0.46)	0.0000	1.54 (0.84, 2.81)	0.16
HR < 60 BPM	0.86 (0.60, 1.26)	0.44			0.84 (0.48, 1.47)	0.54			0.87 (0.60, 1.26)	0.46		
McGINN WHITE SIGN												
S1Q3	2.76 (1.95, 3.93)	0.0000	3.35 (1.97-5.67)	0.0000	2.19 (1.43, 3.36)	0.0003	1.57 (0.88, 2.78)	0.12	2.79 (1.96, 3.95)	0.0000	3.26 (1.93, 5.50)	0.0000
S1Q3T3	2.76 (1.86, 3.40)	0.0000	2.54 (1.44, 4.49)	0.001	2.65 (1.70, 4.13)	0.0000	1.59 (0.84, 2.98)	0.15	2.75 (1.88, 4.03)	0.0000	2.53 (1.45, 4.54)	0.001
McG + ANY RV Overload ECG PATTERNS	1.25 (0.88-1.79)	0.22			1.60 (1.00, 2.55)	0.05			1.26 (0.88, 1.80)	0.20		
RV OVERLOAD ECG PATTERNS												
PERSISTENT S V5-V6	0.97 (0.74, 1.26)	0.81			1.19 (0.82, 1.73)	0.35			0.98 (0.75, 1.27)	0.86		
TALL R IN V1	1.18 (0.97, 1.56)	0.25			1.15 (0.77, 1.72)	0.50			1.19 (0.90, 1.58)	0.23		
McG TWI	2.30 (1.48, 3.57)	0.0002	1.40 (0.46, 4.25)	0.55	2.36 (1.40, 3.97)	0.001	4.73 (1.34-16.32)	0.01	2.32 (1.49, 3.60)	0.0002	1.73 (0.57, 5.33)	0.33
BUNDLE BRANCH BLOCK												
CRBBB/IRBBB	1.31 (0.97, 1.77)	0.08			1.90 (1.29, 2.82)	0.001	1.35 (0.80, 2.26)	0.26	1.29 (0.95, 1.74)	0.10		
CLBBB/ILBBB	5.69 (1.18, 27.51)	0.03	3.78 (0.51, 28.05)	0.19	3.49 (0.86, 14.08)	0.08			3.26 (0.81,13.11)	0.09		
ABNORMAL AXIS												
RAD	2.01 (1.27, 3.17)	0.003	1.08 (1.36-2.69)	0.82	4.07 (2.47, 6.68)	0.0000	3.7 (1.87, 7.32)	0.0002	2.02 (1.28, 3.19)	0.002	1.11 (0.56, 2.21)	0.76
INDETERMINATE	2.08 (0.94, 4.61	0.07			1.32 (0.45, 3.89)	0.61			2.09 (0.94, 4.64)	0.07		
LAD	1.08 (0.66, 1.76)	0.77			1.16 (0.58, 2.32)	0.68			1.08 (0.66, 1.77)	0.75		
QRS ABNORMALITIES												
LoQRS	3.09 (2.46,3.89)	0.0000	1.91 (1.36, 2.69)	0.0002	3.22 (2.27, 4.57)	0.0000	1.78 (1.16, 2.72)	0.008	3.05 (2.43, 3.84)	0.0000	1.89, (1.35, 2.65)	0.0002
J WAVES	1.25 (0.86, 1.81)	0.24			0.78 (0.43, 1.42)	0.42			1.26 (0.87, 1.82)	0.23		
fQRS	1.75 (1.16-2.63)	0.007	1.78 (0.97, 3.28)	0.06	1.34 (0.77, 2.53)	0.30			1.76 (1.17, 2.65)	0.007	1.90 (1.05, 3.44	0.03
QTc ≥ 500 msec	19.09 (11.53, 31.59	0.0000	19.18 (10.34, 35.59)	0.0000	3.49 (2.38, 5.11)	0.0000	1.82 (1.13, 2.93)	0.01	18.04 (11.02, 29.53)	0.0000	17.64 (9.63,32.16)	0.0000
ISCHEMIA/INFARCT ECG PATTERNS												
DIFFUSE NSTWC	2.19 (1.55, 3.09)	0.0000	2.05 (1.20, 3.51)	0.008	2.32 (1.52, 3.54)	0.0001	2.39 (1.40, 4.08)	0.001	2.21 (1.56, 3.11)	0.0000	2.11 (1.24, 3.57)	0.006
PRWP	1.81 (1.33, 2.48)	0.0002	1.02 (0.60, 1.76)	0.92	2.06 (1.38, 3.06)	0.0004	0.87 (0.47, 1.59)	0.64	1.83 (1.34, 2.49)	0.0001	1.04 (0.61,1.77)	0.89
PRWP-TO-QS	4.26 (1.95, 9.28)	0.0003	1.40 (0.34, 5.82)	0.64	8.57 (4.19, 17.5)	0.0000	2.89 (0.84, 9.89)	0.09	4.29 (1.97, 9.34)	0.0002	1.33 (0.32, 5.43)	0.69
ADM Anterior QS or Qr	3.70 (2.31, 5.93)	0.0000	1.34 (0.53, 3.44)	0.54	5.30 (3.30, 8.49)	0.0000	1.87 (0.74, 4.72)	0.18	3.72 (2.32,5.97)	0.0000	1.40 (0.55, 3.55)	0.48
NOT McG TWI	2.47 (1.70, 3.60)	0.0000	1.98 (0.0- inf)	0.98	2.07 (1.30, 3.28)	0.002	1.99 (0.0-inf)	0.98	2.40 (1.65, 3.48)	0.0000	1.56 (0.21, 11.44)	0.66
ANY AMI ECG	8.17 (3.78, 17.79)	0.0000	2.82 (1.03, 7.73)	0.04	15.49 (8.23, 29.13)	0.0000	8.37 (3.90, 17.93)	0.0000	8.23 (3.81, 17.79)	0.0000	2.82 (1.03,7.68)	0.04
AV BLOCKS												
FIRST DEGREE AVB	1.80 (1.13, 2.88)	0.01	1.63 (0.80, 3.32)	0.18	1.34 (0.70, 2.53)	0.37			1.82 (1.14, 2.90)	0.01	1.63 (0.81,3.29)	0.17

ADM=admitting ECG; AFIB=atrial fibrillation; ECG=electrocardiogram; fQRS=fragmented QRS; INT=interval ECG; LoQRS=low-voltage QRS complexes; NSTWC=nonspecific T-wave changes; RAD=right axis deviation; TWI McG=T-wave inversion + McGinn-White signs.

Highlighted in yellow are the significant ECG predictors of critical disease, in-hospital mortality, and advance ventilatory according to the predictive power of the admitting or interval ECGs.

nonischemic heart failure and LV systolic dysfunction.[23]

Ischemic/Infarction ECG Patterns

Myocardial ischemia in COVID-19 can be due to microvascular dysfunction, small vessel vasculitis, endothelitis, and epicardial CAD.[24] The univariate regression analysis correlated all our outcomes with the prespecified ischemia/infarction ECG patterns. However, after multivariate regression analysis, only the "any AMI ECG" pattern and the diffuse NSTWC were true predictors.

The AMI occurred during the course of the disease, and ST-elevation MI was the most common phenotype observed. Most of the patients were critically ill, and reperfusion therapies (primary PCI & thrombolytics) were refused by responsible parties after an informed discussion about risks and benefits, and this could have contributed to the high (8-fold increased odds) mortality.

Late Repolarization Abnormalities

QTc prolongation represents late repolarization abnormalities, and its genesis in COVID-19 is multifactorial. In the early days of the pandemic, rampant use of hydroxychloroquine and azithromycin was attributed to the observed QT prolongation. In a large cohort study on COVID-19 therapeutics[25] at the start of the pandemic, there was an independent association between COVID-19 and QT prolongation. A quarter of their study population had QTc ≥500 milliseconds even without hydroxychloroquine or azithromycin, suggesting a direct relation between infection and prolonged QT interval.[25]

Some viruses, including SARS-CoV-2, can encode their own ion channels and even regulate or utilize the ion channels expressed by host cells. An emerging concept is that of viral channelopathies that link viral infection with dysregulation of the ion channel function with resultant QT prolongation.[26] This downregulation of the potassium channels along with abnormal calcium handling cause the repolarization abnormalities that manifest electrographically as QTc prolongation.[27]

In our study, QTc ≥500 milliseconds was a marker for increasing disease severity, high O_2 requirements, and

increased in-hospital mortality, findings that are consistent with other studies.[28]. It is interesting to note that the ADM QTc ≥500 milliseconds (even without hydroxychloroquine and azithromycin exposure) can already predict the likelihood of these adverse events. Prolonged QTc implies higher arrhythmogenic risk, but arrhythmic deaths are not the major cause of COVID-19 fatality. Several studies[29,30] correlated increased mortality in COVID-19–related QTc prolongation with elevated immune-inflammatory markers, suggesting that it is due to myocyte inflammation.

Cytokine-mediated effects on the potassium channel are also implicated in QT prolongation of HIV-, hepatitis C virus–, and West Nile virus–associated inflammation.[31–33] The cytokine storm in severe COVID-19 provides the same inflammatory milieu for QTc prolongation, and Chen et al[34] found QT prolongation as an independent predictor of the SARS-CoV-2–induced myocardial injury. Because the extent of myocardial injury reflects severity and subsequent higher mortality, QT prolongation in COVID-19 can be an early predictor of poor outcome. Our data supported this as INT QTc ≥500 milliseconds parallel (with higher OR) the progression to critical disease and mortality.

Early Repolarization Abnormalities
The late positive deflection resembling a "hump" at the junction between the QRS and ST segment is the "J" wave. Accentuated J waves are associated with hypothermia, hypercalcemia, and ischemia. A spontaneous accentuation of this wave may predispose to polymorphic ventricular tachycardia and ventricular fibrillation. They are also associated with the "J-wave syndromes" that include Brugada syndrome and early repolarization syndrome, both representing a spectrum of pathologic early repolarization abnormalities predisposing to ventricular tachyarrhythmias.[35]

Accentuated J waves were seen in 121 of 1333 (9%) of our study population, primarily occurring in the inferior leads. Data from prior studies reported high arrhythmic risks with the inferior, inferolateral, and global wall location, whereas the lateral wall location conferred low arrhythmic risk. In one study, the presence of J waves (12% prevalence in the study by Zagidullin et al[37]) was a predictor of 28-day mortality among COVID-19 cohorts.

However, our data did not show demonstrable association between J waves and the outcomes of interest after univariate regression analysis. Despite the inferior and inferolateral wall location of the J waves in our study subjects, there were only three ventricular tachyarrhythmia events and only one led to death.

Fragmented QRS
Fragmented QRS are abnormal complexes with an additional R' or notch in the nadir of the R or S wave that resemble "fragmentations," and they should appear in at least two contiguous leads that correspond to a coronary artery territory (anterior, lateral, or inferior) in a routine 12-lead ECG (0.5–150 Hz). Both narrow and wide QRS (eg, bundle-branch block, premature ventricular contractions, V-paced rhythms, and ventricular tachycardia) can display fragmentation as exemplified from the ECGs of two of our patients. The fQRS is a marker of myocardial damage from a variety of disorders.[38] In CAD, fQRS positively correlates with the myocardial scar, mortality, and arrhythmic events.[39]

Yildirim et al[41] reported fQRS in 42 (36.8%) of their 114 COVID-19 patients, and in that subset of patients, there was a longer duration of hospitalization with greater need for intensive care unit level care as well as all-cause and cardiac mortality. In our study, there were few observed events (100/1333 [7.5%]) associated with fQRS after multivariate regression analysis, and fQRS was validated only as a predictor for high O_2 requirement.

Because this was a single-center research that relied on retrieved medical records, there is a risk of misclassification bias and population selection bias. The confounding factors utilized in the study were not measured but were precisely defined.

The ECG analyses were done on available 12-lead ECG tracings obtained at the attending physician's discretion; this might underestimate the magnitude of association, but we hope a larger population will compensate for this. The pre-COVID ECG was unavailable for the majority of patients, making it almost impossible to determine if the rhythm or conduction abnormalities were pre-existing. And in many cases, the interpretation of the ECG lacked corroboration with cardiac imaging and cardiac biomarkers.

CONCLUSION

This study confirms the prognostic value of atrial fibrillation, HR >100 bpm, S1Q3, S1Q3T3, LoQRS, McG TWI, McG RAD, diffuse NSTWC, and any AMI ECG pattern for COVID-19 severity and/or mortality and worse outcomes.

Our data also verified the prognostic power of the admitting ECG: that recognition and identification of these patterns at the emergency room predict disease trajectory and facilitate rapid triage. When these ECG predictors appear during the interval ECGs, they indicate worsening disease and worse outcomes at consistently higher OR.

As soon as these ECG patterns are recognized, a more aggressive and intensive strategy for treatment should be instituted to improve the clinical outcomes in COVID-19.

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