Prognostic Value of Electrocardiographic QRS Diminution in Patients Hospitalized With COVID-19 or Influenza

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During the clinical care of hospitalized patients with COVID-19, diminished QRS amplitude on the surface electrocardiogram (ECG) was observed to precede clinical decompensation, culminating in death. This prompted investigation into the prognostic utility and specificity of low QRS complex amplitude (LoQRS) in COVID-19. We retrospectively analyzed consecutive adults admitted to a telemetry service with SARS-CoV-2 (n = 140) or influenza (n = 281) infection with a final disposition—death or discharge. LoQRS was defined as a composite of QRS amplitude <5 mm or <10 mm in the limb or precordial leads, respectively, or a ≥50% decrease in QRS amplitude on follow-up ECG during hospitalization. LoQRS was more prevalent in patients with COVID-19 than influenza (24.3% vs 11.7%, p = 0.001), and in patients who died than survived with either COVID-19 (48.1% vs 10.2%, p <0.001) or influenza (38.9% vs 9.9%, p <0.001). LoQRS was independently associated with mortality in patients with COVID-19 when adjusted for baseline clinical variables (odds ratio [OR] 11.5, 95% confidence interval [CI] 3.9 to 33.8, p <0.001), presenting and peak troponin, D-dimer, C-reactive protein, albumin, intubation, and vasopressor requirement (OR 13.8, 95% CI 1.3 to 145.5, p = 0.029). The median time to death in COVID-19 from the first ECG with LoQRS was 52 hours (interquartile range 18 to 130). Dynamic QRS amplitude diminution is a strong independent predictor of death over not only the course of COVID-19 infection, but also influenza infection. In conclusion, this finding may serve as a pragmatic prognostication tool reflecting evolving clinical changes during hospitalization, over a potentially actionable time interval for clinical reassessment.   © 2021 Elsevier Inc. All rights reserved. (Am J Cardiol 2021;159:129 −137)

In some patients infected with SARS-CoV-2, localized viral replication progresses to a systemic inflammatory syndrome.[1−3] Myocardial injury has been reported in patients with COVID-19, yet the pathophysiologic mechanism has not been well defined.[4−6] There has likewise been little reported evidence of direct myocardial damage on the 12-lead electrocardiogram (ECG) despite myocardial injury occurring in 33.7% of hospitalized patients.[7] Low QRS amplitude (LoQRS) has been associated with both late gadolinium enhancement on magnetic resonance imaging and cardiac events in clinically suspected myocarditis.[8] We noted QRS amplitude diminution on the 12-lead ECG to be coincident with worsening clinical status and death while caring for patients with COVID-19, prompting investigation into the significance of QRS amplitude in a consecutive series of admitted patients.[9] Here, we expand the investigation to patients hospitalized with influenza to contextualize results and assess the specificity of any findings to COVID-19.

Methods

This single-center retrospective cohort study included consecutive adult patients (≥18 years old) with COVID-19 admitted to Mount Sinai Hospital (New York, NY) between March 7 and April 12, 2020 as part of a COVID-19 registry (NCT04358029). All patients had laboratory-confirmed COVID-19 based on a reverse transcriptase-polymerase chain reaction assay of nasal or pharyngeal swab specimens. Of 1,354 patients with COVID-19 screened using electronic medical records from March 7, 2020 to April 12, 2020, 800 patients were hospitalized. After exclusion of patients without telemetry data, retrievable ECGs, or a final

disposition (death or discharge), 140 patients were analyzed. The comparison group included a cohort of 1,420 patients with laboratory-confirmed Influenza A or Influenza B admitted to Mount Sinai Hospital between January 2, 2017 and January 5, 2020. A total of 281 consecutive influenza patients with retrievable ECGs from the electronic medical record from September 2017 through February 2020 were analyzed to allow for a 2:1 comparison to COVID-19 patients.

We manually extracted demographics, laboratory findings, ECG data, treatments received, and clinical outcomes from admission through hospitalization from electronic medical records. For patients with COVID-19, laboratory assessment consisted of complete blood count, assessment of liver and renal function including serum electrolytes, coagulation profile, troponin-I, d-dimer, C-reactive protein, lactate dehydrogenase, fibrinogen, interleukin-6, brain natriuretic peptide, and procalcitonin. Data for patients with influenza were obtained through automated extraction from the electronic medical record and included demographic, laboratory testing, ECG data, treatments received, and clinical outcomes. Telemetry and ECG data were obtained with the GE CARESCAPE B850 V2.0.8.213 telemetry system. ECGs at baseline and before admission were obtained with the GE Mac 5500 ECG system. Acquisition by either system utilized electrodes placed in the standard 12-lead ECG configuration. Follow-up ECG acquisition was routine in patients on the telemetry service.

QRS complex amplitudes were measured individually to the nearest 0.5 mm and recorded as the sum of 2 peak-to-peak QRS complexes (peak of the R wave to the nadir of the Q or S wave, whichever was larger) in the limb leads (leads I, II, III, aVR, aVL, aVF) and for leads V1-V3 and V4-V6 which are reported respectively in aggregate such that the sum of the limb lead voltage is comprised of 12 QRS complexes and V1-V3 and V4-V6 each are comprised of 6 QRS complexes. If artifact precluded interpretation, 2 QRS complexes least impacted by the artifact in a given lead (e.g., V2) were reported. The sum of precordial QRS complex amplitude was obtained by adding the sum obtained for V1-V3 to that of leads V4-V6. To capture relative changes in QRS amplitude, the sum of the QRS amplitudes on the last available ECG were subtracted from the sum in the respective leads on the presenting (admission) ECG and the baseline ECG (ECG obtained within the past year). QRS amplitudes were considered to have met threshold cutoffs if all the QRS complexes in a given group were below the respective cutoff. Therefore, if the cutoff is <5 mm, then all leads to which that threshold applies must each individually demonstrate QRS amplitudes <5 mm.

LoQRS was defined by a composite of either: (1) QRS amplitude <5 mm in the limb leads odds ratio [OR] <10 mm in the precordial leads (a composite of V1-V3 and V4-V6), V1-V3 independently, or V4-V6 independently; (2) QRS amplitude decrease by ≥50% compared with the baseline or admission ECG in the limb leads or precordial leads; or (3) meeting the aforementioned criteria with a "limited interpretability" QRS morphology due to changes in rhythm origin or new bundle branch block. Stable QRS amplitude was defined by a failure to meet criteria for LoQRS. If a patient met the disposition outcome of death

and met LoQRS criteria on the last available ECG, all ECGs were reviewed from the last available ECG until the first ECG with LoQRS identified. We recorded the interval from the day of presentation to the first ECG showing LoQRS, and calculated the time to death from the time stamp on the first ECG showing LoQRS until the clinically documented time of death. We likewise calculated the time interval from the last available ECG to the time of final disposition. Before data collection, the study was approved by the Institutional Review Board. The primary outcome was death. Secondary outcomes included the composite criteria of LoQRS and individual components of the composite.

Continuous variables are reported as the median and interquartile range (IQR), and were compared using the Wilcoxon rank-sum test. Categorical variables are reported as percentages and were compared using the chi-square test. Multivariable logistic regression models were performed to evaluate the association between LoQRS and in-hospital mortality for patients hospitalized with Covid-19 or Influenza. Model 1 accounted for baseline demographic and clinical characteristics that differed significantly between the COVID-19 and influenza groups and included the following covariates: age, body mass index, current/former smoking, and history of chronic kidney disease, liver disease, and hypertension. Model 2 included the same covariates as Model 1, with the addition of LoQRS. Using the same covariates as in Model 2, we performed formal interaction testing to determine how the type of viral infection, COVID-19 versus influenza, influenced the association of LoQRS with in-hospital mortality. Model 3, performed only in the COVID-19 group, additionally controlled for significant laboratory differences in admission troponin, peak troponin, peak D-dimer, C-reactive protein, and last available albumin levels. Lastly, Model 4 additionally controlled for patients who required intubation or inotropic or vasopressor medications.

We assessed discrimination of the predictive models by receiver operating characteristic analysis for each model. Improvement in model discrimination was assessed by calculating the integrated discrimination improvement index (IDI) of adding LoQRS to the baseline clinical variables adjusted for in Model 1. All analyses were performed with the use of Stata software version 14.2. A 2-sided p value <0.05 was deemed statistically significant.

Results

The study population included 140 patients hospitalized with COVID-19 and 281 patients hospitalized with influenza A or B. Clinical characteristics at baseline among COVID-19 patients are shown in Table 1. Additional characteristics specific to COVID-19 patients are listed in the Appendix (Tables S1 through S7). Compared with patients with influenza, the patients with COVID-19 were younger and had a higher prevalence of diabetes, hypertension, sleep apnea, and female sex (Table 2). Patients admitted with COVID-19 had higher levels of C-reactive protein and lower levels of brain natriuretic peptide.

QRS amplitudes in the limb leads, composite precordial leads, leads V1-V3, and leads V4-V6 were all significantly lower on the last available ECG in patients who died

Table 1
Patient demographics, clinical, and laboratory characteristics in patients with COVID-19

Variable	Full cohort (n = 140)	Death (n = 52)	Discharge (n = 88)	p value
Median age in years (IQR)	61 (48.5-74)	71 (59-78)	58 (45-71)	<0.01
Women	38/140 (27%)	14/52 (27%)	24/88 (27%)	0.96
Race				0.69
White	47/140 (34%)	20/52 (39%)	27/88 (31%)	
Black	21/140 (15%)	8/52 (15%)	13/88 (15%)	
Hispanic	32/140 (23%)	12/52 (23%)	20/88 (23%)	
Asian	0/140 (0%)	0/52 (0%)	0/88 (0%)	
Other/unknown	40/140 (29%)	12/52 (23%)	28/88 (32%)	
Weight (kg)	84 (69-95)	85 (73-96)	82 (67-94)	0.45
Body mass index in kg/m^2 (IQR)	28 (25-33)	30 (27-35)	28 (25-32)	0.08
Comorbidities of interest				
Diabetes mellitus	54/140 (39%)	21/52 (40%)	33/88 (38%)	0.74
Heart failure	22/140 (16%)	11/52 (21%)	11/88 (13%)	0.17
Hypertension	86/140 (61%)	35/52 (67%)	51/88 (58)	0.27
Asthma	18/140 (13%)	8/52 (15%)	10/88 (11%)	0.49
Chronic kidney disease	20/140 (14%)	12/52 (23%)	8/88 (9%)	0.02
Liver disease	5/140 (4%)	4/52 (8%)	1/88 (1%)	0.04
HIV	8/140 (6%)	2/52 (4%)	6/88 (7%)	0.46
Obesity	52/140 (37%)	25/52 (48%)	27/88 (31%)	0.04
Smoker	32/124 (26%)	16/42 (38%)	16/82 (20%)	0.03
Alcohol abuse	8/140 (6%)	4/52 (8%)	4/88 (5%)	0.44
Sleep apnea	18/140 (13%)	9/52 (17%)	9/88 (10%)	0.23
Coronary artery disease	35/140 (25%)	13/52 (25%)	22/88 (25%)	0.99
Prior revascularization	27/140 (19%)	10/52 (19%)	17/88 (19%)	0.99
PTCA/PCI	21/27 (78%)	8/10 (80%)	13/17 (77%)	0.83
CABG	4/27 (15%)	1/10 (10%)	3/17 (18%)	0.59
Atrial fibrillation or flutter	19/140 (14%)	8/52 (15%)	11/88 (13%)	0.37
Prior ventricular arrhythmias	3/140 (2%)	1/52 (2%)	1/88 (1%)	0.69
Ischemic stroke	6/140 (4%)	2/52 (4%)	4/88 (5%)	0.84
Laboratory characteristics (IQR)				
White blood cell count ($\times 10^3$/uL)	6.7 (4.9-10.2)	8.1 (5.1-10.2)	6.3 (4.9-9.8)	0.4
Neutrophil count ($\times 10^3$/uL)	5.0 (3.4-8.0)	6.2 (3.4-8.0)	4.6 (3.4-8.1)	0.43
Lymphocyte count ($\times 10^3$/uL)	0.9 (0.6-1.2)	0.9 (0.5-1.3)	0.9 (0.6-1.2)	0.45
Hemoglobin (g/dl)	13.1 (11.0-14.0)	12.1 (9.6-14.0)	13.5 (12.3-14.7)	<0.01
Platelets ($\times 10^3$/dl)	199 (161-256)	187 (132-245)	219 (170-257)	0.03
Creatinine (mg/dl)	1.1 (0.8-1.5)	1.5 (1.0-2.7)	1.0 (0.8-1.3)	<0.01
Aspartate aminotransferase (AST) (U/L)	38 (27-56)	46 (27-69)	36 (27-50)	0.06
Alanine transaminase (ALT) (U/L)	28 (17-46)	30 (17-48)	28 (17-44)	0.68
Albumin (g/dl)	3.3 (2.9-3.6)	3.1 (2.7-3.5)	3.3 (3.0-3.6)	0.02
D-Dimer (ug/ml)	1.4 (0.6-3.1)	2.3 (0.9-4.1)	1.1 (0.5-2.3)	0.01
International normalized ratio (INR)	1.1 (1.0-1.3)	1.2 (1.1-1.4)	1.1 (1.0-1.2)	<0.01
Troponin-I (ng/ml)	0.02 (0.01-0.07)	0.03 (0.01-0.20)	0.01 (0.01-0.04)	<0.01
Lactate dehydrogenase (LDH) (U/L)	400 (296-544)	481 (331-835)	369 (292-494)	<0.01
Brain natriuretic peptide (pg/ml)	48 (10-205)	71 (15-579)	34 (10-167)	0.12
Erythrocyte sedimentation rate (mm/h)	59 (24-85)	67 (33-101)	51 (18-77)	0.25
C-reactive protein (mg/L)	105 (46-185)	146 (62-219)	87 (31-143)	<0.01
Fibrinogen (mg/dl)	556 (438-685)	558 (420-685)	554 (453-667)	0.82
Interleukin-6 (pg/ml)	111 (42-234)	160 (85-327)	55 (26-148)	<0.01
Lactate (mmol/L)	1.5 (1.1-2.0)	1.5 (1.0-2.1)	1.6 (1.2-2.0)	0.37
Procalcitonin (ng/ml)	0.17 (0.08-0.61)	0.51 (0.13-1.39)	0.12 (0.06-0.30)	<0.01
Baseline medications				
ACE inhibitor	28/140 (20%)	9/52 (17%)	19/88 (22%)	0.54
Angiotensin receptor blocker	21/140 (15%)	8/52 (15%)	13/88 (15%)	0.92
Aspirin	41/140 (29%)	14/52 (27%)	27/88 (31%)	0.64
Anticoagulant	21/140 (15%)	10/52 (19%)	11/88 (13%)	0.28
Warfarin	7/21 (33%)	2/10 (20%)	5/11 (46%)	0.22
DOAC	14/21 (67%)	8/10 (80%)	6/11 (55%)	0.22
Antiarrhythmic	6/140 (4%)	4/52 (8%)	2/88 (2%)	0.13

Table 2
Patient demographics, clinical, and laboratory characteristics in patients with COVID-19 or influenza

Characteristic	COVID-19 (n = 140)	Influenza (n = 281)	p value
Median age in years (IQR)	61 (49-74)	69 (57-80)	<0.01
Women	38 (27%)	157 (56%)	<0.01
Race			<0.01
White	47 (34%)	77 (28%)	
Black	21 (15%)	79 (28%)	
Hispanic	32(23%)	89 (32%)	
Asian	0 (0%)	8 (3%)	
Other/unknown	40 (29%)	27 (10%)	
Median body mass index in kg/m^2 (IQR)	28 (25-33)	27 (23-32)	0.01
Comorbidities of interest			
Diabetes mellitus	54 (39%)	64 (23%)	0.01
Heart failure	22 (16%)	61 (22%)	0.15
Hypertension	86 (61%)	121 (43%)	<0.01
Asthma	18 (13%)	45 (16%)	0.39
Chronic kidney disease	20 (14%)	59 (18%)	0.36
Liver disease	5 (4%)	11 (4%)	0.86
HIV	8 (6%)	15 (5%)	0.87
Obesity	52 (37%)	97 (35%)	0.60
Smoker	32 (26%)	129 (46%)	<0.01
Sleep apnea	18 (13%)	14 (5%)	<0.01
Ischemic stroke	6 (4%)	13 (5%)	0.87
Baseline laboratory characteristics			
White blood cell count ($\times 10^3$/uL)	6.7 (4.9-10.2)	7.9 (5.9-10.7)	0.03
Neutrophil count ($\times 10^3$/uL)	5.0 (3.4-8.0)	6.0 (4.2-8.6)	0.04
Lymphocyte count ($\times 10^3$/uL)	0.9 (0.6-1.2)	0.9 (0.6-1.1)	0.45
Hemoglobin (g/dl)	13.1 (11.0-14.4)	12.3 (10.8-14.0)	0.05
Platelets ($\times 10^3$/dl)	199 (161-256)	195 (147-246)	0.34
Creatinine (mg/dl)	1.1 (0.8-1.5)	1.0 (0.8-1.5)	0.14
Aspartate aminotransferase (AST) (U/L)	38 (27-56)	34 (22-53)	0.09
Alanine transaminase (ALT) (U/L)	28 (17-46)	22 (15-38)	0.03
Albumin (g/dl)	3.3 (2.9-3.6)	3.5 (2.9-3.8)	0.02
D-Dimer (ug/ml)	1.4 (0.6-3.1)	0.9 (0.5-4.0)	0.91
International normalized ratio (INR)	1.1 (1.0-1.3)	N/A	N/A
Troponin-I (ng/ml)	0.02 (0.01-0.07)	0.03 (0.01-0.06)	0.32
Lactate dehydrogenase (LDH) (U/L)	400 (296-544)	353 (260-530)	0.30
Brain natriuretic peptide (pg/ml)	48 (10-205)	188 (51-812)	<0.01
Erythrocyte sedimentation rate (mm/h)	59 (24-85)	42 (28-70)	0.54
C-reactive protein (mg/L)	105 (46-185)	49 (11-106)	0.04
Fibrinogen (mg/dl)	556 (438-685)	N/A	N/A
Interleukin-6 (pg/ml)	111 (42-234)	N/A	N/A
Lactate (mmol/L)	1.5 (1.1-2.0)	N/A	N/A
Procalcitonin (ng/ml)	0.2 (0.1-0.6)	0.6 (0.1-3.7)	<0.01
Baseline medications no. (%)			
ACE inhibitor	28 (20%)	47 (17%)	0.43
Angiotensin receptor blocker	21 (15%)	41 (15%)	0.92
Aspirin	41 (29%)	89 (32%)	0.60

N/A = not available.

compared with those surviving to hospital discharge (Table 3). There were no significant differences in QRS amplitude measurements between the baseline and admission ECGs. A representative ECG demonstrating LoQRS is shown in Figure 1.

The composite endpoint of LoQRS occurred in 24.3% of COVID-19 patients (Table 4). LoQRS occurred more frequently in patients who died compared with those who survived to hospital discharge (48.1% vs 10.2%, p <0.001). A ≥50% decrease in QRS amplitude occurred in 17.1% of patients (36.5% in the mortality group vs 5.7% in the

discharged group, p <0.001). QRS amplitude met a threshold <5 mm in the limb leads or <10 mm in the precordial leads in 15.7% of patients and was more prevalent in those who died (28.9% vs 8.0%, p = 0.001). Estimates of survival by LoQRS are demonstrated in the Appendix (Figure S1).

Mortality occurred in 37.1% of the COVID-19 cohort, but was 73.5% in patients with LoQRS compared with 25.5% of patients without LoQRS (p <0.001). There was no significant difference in the median length of stay between groups (7 days, IQR 4 to 10, p = 0.89). More

Table 3
Quantitative QRS amplitude characteristics by patient disposition in COVID-19 patients

Median voltage in mm (IQR)	Full cohort (n = 140)	Death (n = 52)	Discharge (n = 88)	p value
Baseline QRS amplitude				
Sum of all leads	258 (208-292)	240 (209-294)	259 (202-291)	0.95
Sum of limb leads	98 (80-129)	104 (73-135)	96 (81-115)	0.27
Sum of precordial leads	149 (115-179)	133 (112-175)	164 (119-180)	0.36
Sum of V1-V3	75 (52-88)	72 (52-89)	76 (53-87)	0.52
Sum of V4-V6	73 (50-97)	70 (50-96)	74 (50-98)	0.72
Admission QRS amplitude				
Sum of all leads	242 (205-303)	249 (208-294)	241 (203-307)	0.61
Sum of limb leads	100 (80-128)	99 (75-126)	100 (82-131)	0.48
Sum of precordial leads	141 (116-177)	138 (110-176)	143 (117-181)	0.49
Sum of V1-V3	73 (57-89)	70 (57-86)	74 (58-89)	0.42
Sum of V4-V6	69 (53-93)	69 (45-94)	69 (56-93)	0.44
Last available QRS amplitude				
Sum of all leads	224 (174-287)	200 (151-274)	231 (192-297)	<0.01
Sum of limb leads	95 (70-124)	86 (63-124)	98 (81-129)	0.02
Sum of precordial leads	129 (94-166)	107 (78-157)	140 (106-176)	<0.01
Sum of V1-V3	67 (48-90)	58 (40-79)	73 (54-96)	<0.01
Sum of V4-V6	58 (42-85)	52 (34-82)	62 (46-86)	0.03

QRS complex amplitudes reflect the sum of 2 peak-to-peak QRS complexes per lead presented in aggregate.

patients with LoQRS required both intubation (61.8% vs 30.2%, p = 0.001) and administration of inotropic or vasopressor medications (58.8% vs 25.5%, p <0.001). Among patients who died, the median time to the first ECG with LoQRS was 5.3 days (IQR 2.1 to 11.1), and the median time to death from the first ECG with LoQRS was 52 hours (IQR 18 to 130). No significant difference in timing from the last available ECG to disposition between LoQRS and stable QRS amplitude groups was noted (Supplement, Table S15).

When adjusted for baseline clinical variables, LoQRS was independently associated with mortality (OR 11.5, 95% confidence interval [CI] 3.9 to 33.8, p <0.001) and improved discrimination of the logistic regression model (Table 5). The area under the receiver operating characteristic curve increased from 0.79 to 0.87 when LoQRS was added to the multivariable model and the IDI was 0.15, with a p value of <0.001, indicating that the mean

difference of predicted risk between patients who died or survived increased by 15%.

The strong association between LoQRS and mortality (Figure 2) persisted after adjustment for presenting troponin, peak troponin, peak d-dimer, C-reactive protein, and last available albumin in addition to baseline clinical covariates [OR 6.0 (95% CI 1.3 to 27.6), p = 0.021] with an area under the receiver operating characteristic curve of 0.91 and when intubation and inotrope or vasopressor requirement were added to the model (OR 13.78 (1.31 to 145.46), p = 0.029). No interaction between myocardial injury (troponin level >0.03 ng/ml) and LoQRS was demonstrated by multivariable analysis (p interaction 0.179). When mortality was stratified by LoQRS and presence of myocardial injury, there was a significant trend towards increased mortality not only in those who exhibited LoQRS without myocardial injury but even more so in patients with
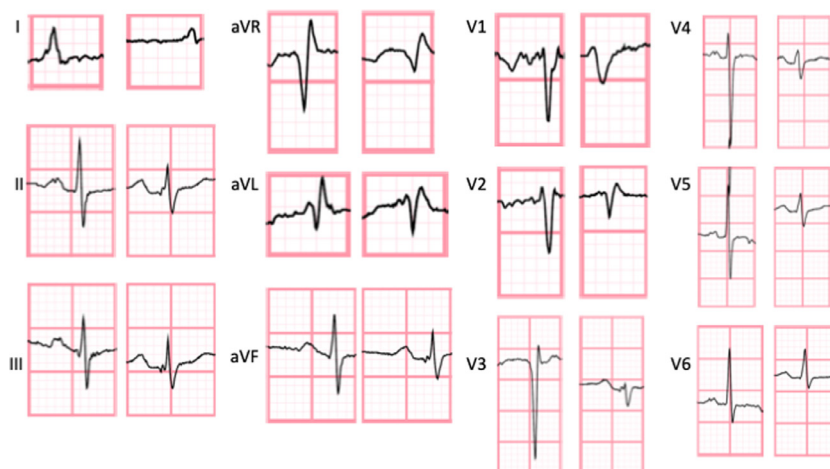

Figure 1. Precordial electrocardiographic QRS diminution. QRS amplitudes are demonstrated meeting criteria for precordial LoQRS. From left to right in each column, an ECG QRS complex on admission is compared with an ECG QRS complex on the last available ECG.

Table 4

Categorical electrocardiographic QRS amplitude changes in COVID-19 by patient disposition

Voltage characteristic no. (%)	Death (n = 52)	Discharge (n = 88)	p value
Composite low QRS amplitude (LoQRS)*	25 (48.1)	9 (10.2)	<0.01
QRS amplitude <5 mm in limb leads AND <10 mm in precordial leads	0 (0.0)	0 (0.0)	0.99
≥50% decrease in QRS amplitude	19 (36.5)	5 (5.7)	<0.01
QRS amplitude <5 mm limb OR <10 mm precordial in precordial leads	15 (28.9)	7 (8.0)	0.001
LoQRS in limb leads	7 (13.5)	3 (3.4)	0.026
LoQRS in precordial leads	18 (34.6)	6 (6.8)	<0.01
LoQRS in leads V1-V3	10 (19.2)	5 (5.7)	0.01
LoQRS in leads V4-V6	14 (26.9)	4 (4.6)	<0.01
LoQRS with LIQRS morphology[†]	5 (9.6)	2 (2.3)	0.05
Any QRS amplitude increase (baseline to admission ECG)	8 (15.4)	8 (9.1)	0.26
Any QRS amplitude increase (baseline to last ECG)	4 (7.7)	11 (12.5)	0.37
Any QRS amplitude increase (admission to last ECG)	4 (7.7)	12 (13.6)	0.29

* Low QRS amplitude (LoQRS) is a composite of relative QRS amplitude reduction by ≥50% from baseline or admission ECG or meeting a threshold of QRS amplitude <5 mm in the limb leads or <10 mm in the precordial leads or in V1-V3 or V4-V6.

[†] Limited interpretablity QRS morphology due to change from sinus rhythm, new bundle branch block, or pacing.

both LoQRS and concomitant myocardial injury (Figure 2).

Compared with Covid-19, LoQRS occurred less frequently in the influenza cohort (11.0% vs 24.3%, p = 0.001).

Table 5

Multivariable sensitivity analysis in COVID-19

Significant covariates	Odds ratio (95% CI)	p value	AUC
Model 1: Baseline characteristics without LoQRS			0.79
Age	1.07 (1.04-1.11)	<0.01	
BMI	1.10 (1.03-1.18)	<0.01	
Liver disease	12.01 (1.09-132.76)	0.04	
Model 2: Baseline characteristics and LoQRS			0.87
LoQRS	11.51 (3.92-33.81)	<0.01	
Age	1.08 (1.04-1.12)	<0.01	
BMI	1.13 (1.05-1.22)	0.01	
Model 3: Baseline characteristics, labs, and LoQRS			0.91
LoQRS	6.01 (1.31-27.63)	0.02	
Age	1.07 (1.01-1.13)	0.03	
BMI	1.16 (1.05-1.29)	<0.01	
Peak D-dimer	1.14 (1.02-1.28)	0.02	
Last available albumin	0.12 (0.02-0.62)	0.01	
Model 4: Baseline characteristics, labs, LoQRS, and need for inotropes, vasopressors, or mechanical ventilation			0.98
LoQRS	13.78 (1.31-145.46)	0.03	
Age	1.08 (1.00-1.16)	0.04	
Mechanical ventilation	90.32 (2.82-2893.11)	0.01	

Model 1 included the following covariates: Age, BMI, CKD, smoker (current or former), liver disease, HTN. Model 2 included the covariates in Model 1, in addition to low QRS amplitude (LoQRS). Model 3 included the covariates of Model 2, presenting and peak troponin, peak d-dimer, presenting C-reactive protein, and last available albumin. Model 4 included all covariates in Model 3, need for mechanical ventilation, and need for inotropes or vasopressors. AUC = area under the receiver operating characteristic curve.

Among influenza patients, LoQRS was more prevalent in those who died than in those who survived to discharge (38.9% vs 9.1%, p <0.001; Supplement, Table S13). QRS amplitude met a threshold of <5 mm in limb leads AND <10 mm in the precordial leads in 5.2% of patients, which was significantly more common in patients who died (22.2% vs 4.0%, p = 0.001). QRS amplitudes that decreased by at least 50% from baseline or admission ECG occurred in 5.3% of the influenza cohort and were also more frequent in patients who died (27.8% vs 3.8%, p <0.001). Similarly, QRS amplitudes that met a threshold of <5 mm in the limb leads OR <10 mm in the precordial leads were noted in 7.8% of the influenza group and were significantly more prevalent in patients who died (27.8% vs 6.5%, p = 0.001).

Mortality was lower in patients with influenza than in those with COVID-19 (6.4% vs 37.1%, p <0.01) and the length of hospital stay was shorter with influenza (5 days vs 7 days, p = 0.002). However, length of stay among those who died was shorter in COVID-19 patients (7 days [IQR 4 to 11]) than in those who succumbed to influenza (9.5 days [IQR 7 to 26], p = 0.01). For influenza patients with LoQRS who died, the median time to death from the first ECG meeting LoQRS criteria was 144 hours (IQR 48 to 144). The median time from admission to the first ECG that met LoQRS criteria was 55 days (IQR 11 to 65). LoQRS was also an independent predictor of mortality in influenza when adjusted for baseline clinical variables (OR 10.71, 95% CI 3.01 to 38.16, p <0.001; Table 6). The IDI was 0.09 (p = 0.03). A significant interaction between LoQRS and type of viral infection (i.e., SARS-CoV-2 or Influenza) on mortality was noted (p = 0.038).

Discussion

This study demonstrates that LoQRS is an independent predictor of mortality in hospitalized patients with either COVID-19 or influenza. QRS amplitude diminution is dynamic during the course of illness and underscores the utility of both a relative reduction in QRS amplitude of at least 50% or meeting a threshold in QRS amplitude.

Low QRS complex amplitude on the ECG has been described in conditions that decrease net myocardial action

Table 6
Multivariable sensitivity analysis in influenza

Significant covariates	OR (95% CI)	p value	AUC
Model 1: Baseline characteristics without LoQRS			0.78
Hypertension	0.13 (0.03-0.63)	0.01	
Model 2: Baseline characteristics with LoQRS			0.85
LoQRS	10.71 (3.01-38.16)	<0.01	
BMI	0.89 (0.81-0.98)	0.02	
Hypertension	0.10 (0.02-0.53)	<0.01	

Model 1 included the following covariates: Age, BMI, CKD, smoker (current or former), liver disease, HTN. Model 2 included the covariates in Model 1, in addition to low QRS amplitude (LoQRS).

potential generation or attenuate recorded surface voltage.[10]−[18] In a variety of disease processes, low ECG voltage portends adverse outcomes.[12,13,19,20] A recent multicenter analysis noted low QRS voltage in only 5% of COVID-19 patients, highlighting the potential importance of dynamic QRS amplitude diminution during the course of illness. A median time of 52 hours from the first ECG with LoQRS until death in COVID-19 may provide an opportunity to focus clinical reassessment such as escalating the level of care or medical therapy when LoQRS is identified.

The absence of imaging and autopsy data limits definitive conclusions regarding the mechanism of LoQRS. Recovered COVID-19 patients who underwent cardiac MRI exhibited myocardial edema in 54% to 60% of cases with 31% demonstrating late gadolinium enhancement.[21,22] This parallels findings in patients with myocarditis and ECG abnormalities.[8] LoQRS tracks with the incidence of influenza-associated myocarditis, which has been reported in over 10% of patients and was prevalent in 11% of patients in our influenza cohort.[23] We found that inflammatory markers in the COVID-19 cohort were higher in those with LoQRS, suggesting inflammation-mediated myocardial edema as a plausible mechanism. Myocardial injury alone does not explain LoQRS as initial and peak troponin levels were not significant in the multivariable model, while

patients with the highest mortality exhibited coincident myocardial injury and LoQRS (Figure 2).

Alternative mechanisms such as lung parenchymal disease can explain LoQRS by extracardiac voltage attenuation. Low voltage in leads V4-V6 has been attributed to the relative contribution of underlying lung parenchymal volume to those unipolar leads.[24] This contrasts with our observation that all leads demonstrated significant decreases in QRS amplitude, suggesting a more diffuse process. Given that LoQRS remained independently predictive of mortality adjusted for intubation requirement, which would be expected to track with lung disease severity, this singular etiology is less likely but could plausibly contribute to the findings.

Echocardiographic data were not available to eliminate pericardial effusion as a contributing factor, but imaging studies have found pericardial effusion to be infrequent in patients with COVID-19.[25,26] Barotrauma and pleural effusions have likewise been reported in only 15% and 5% of cases, respectively, and similarly cannot account for the observed prevalence of LoQRS in this study.[27,28] Prone positioning was not standard practice in the absence of mechanical ventilation during the study period, which might entail posterior ECG lead placement. Mechanical ventilation does not appear to cause significant changes in QRS amplitude and LoQRS remained independently predictive even when adjusted for intubation.[29] Telemetry electrodes were placed in a standard 12-lead configuration from which ECGs during admission were obtained, thus improving reliability between acquisitions. As LoQRS was predictive of mortality after adjusting for serum albumin levels and weight, it is unlikely that volume accumulation or body habitus explain the findings.

Treatment differences do not explain the association between LoQRS and mortality (Supplement, Table S7). More patients in the mortality group received glucocorticoids, which were reserved for the most critically ill patients during the study period and have subsequently demonstrated a mortality benefit in a randomized trial.[30] LoQRS may ultimately reflect a spectrum of accumulated
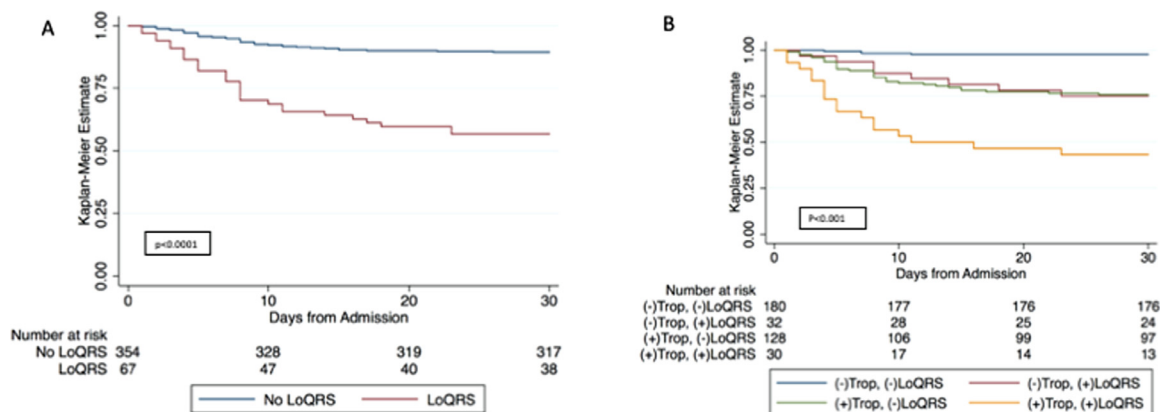

Figure 2. In-hospital survival in COVID-19 and influenza. (A) In-hospital survival by presence of LoQRS. In this Kaplan-Meier analysis, patients discharged from the hospital were considered to have survived (not censored). (B) In-hospital survival by presence of LoQRS and troponin positivity. Trop = troponin level. A positive troponin level (+) is demarcated by a troponin-I level by the Abbot architect methodology exceeding 0.03 ng/ml.

insults resulting in a cardiotoxic milieu, including edema, hypoxia, and metabolic disarray.

This study is limited by its retrospective design and lack of corroborating imaging or autopsy data. Inclusion of hospitalized patients on a telemetry service may compromise generalizability to other populations or raise potential for selection bias, possibly overestimating the magnitude of association between LoQRS and mortality. Alternatively, the data were manually extracted at a patient level—buttressing data quality. Lastly, this study did not include outpatient follow-up in survivors with LoQRS to assess long-term outcomes or QRS amplitude recovery.

LoQRS is a dynamic finding associated with mortality in patients with both COVID-19 and influenza infections, underscoring the importance of both a reduction in QRS amplitude below an absolute threshold and the prognostic utility of a relative reduction in QRS amplitude over time. Further studies should address the optimum intervals at which QRS amplitude should be assessed and whether intensification of therapy in individuals manifesting LoQRS would improve clinical outcomes.

Authors' Contributions

Joshua Lampert: Data curation, conceptualization, data curation, methodology, writing, review, and editing. Michael Miller: Formal Analysis, methodology, writing. Jonathan L. Halperin: Methodology, writing conceptualization, supervision. Connor Oates: data acquisition. Gennaro Giustino: methodology, formal analysis. Kyle Nelson: data acquisition. Jason Feinman: data acquisition. Nikola Kocovic: data acquisition. Matthew Pulaski: data acquisition. Daniel Musikantow: review and editing, writing. Mohit K. Turagam: review and editing, writing, formal analysis. Aamir Sofi: review and editing, writing. Subbarao Choudry: review and editing, writing. Marie-Noelle Langan: review and editing, writing. Jacob S. Koruth: review and editing, writing. William Whang: review and editing, writing. Marc A. Miller: conceptualization, review and editing, writing. Srinivas R. Dukkipati: review and editing, writing, conceptualization. Adel Bassily-Marcus: data acquisition. Roopa Kohli-Seth: data acquisition. Martin E. Goldman: conceptualization, review and editing, supervision. Vivek Y. Reddy: conceptualization, review and editing, methodology, writing, supervision.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.07.048.

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