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SHORT COMMUNICATION

Surface electrocardiographic characteristics in coronavirus disease 2019: repolarization abnormalities associated with cardiac involvement

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Abstract

Aims The coronavirus disease 2019 (COVID-19) has spread rapidly around the globe, causing significant morbidity and mortality. This study aims to describe electrocardiographic (ECG) characteristics of COVID-19 patients and to identify ECG parameters that are associated with cardiac involvement.

Methods and results The study included patients who were hospitalized with COVID-19 diagnosis and had cardiac biomarker assessments and simultaneous 12-lead surface ECGs. Sixty-three hospitalized patients (median 53 [inter-quartile range, 43–65] years, 76.2% male) were enrolled, including patients with (n = 23) and without (n = 40) cardiac injury. Patients with cardiac injury were older, had more pre-existing co-morbidities, and had higher mortality than those without cardiac injury. They also had prolonged QTc intervals and more T wave changes. Logistic regression model identified that the number of abnormal T waves (odds ratio (OR), 2.36 [95% confidence interval (CI), 1.38–4.04], P = 0.002) and QTc interval (OR, 1.31 [95% CI, 1.03–1.66], P = 0.027) were independent indicators for cardiac injury. The combination model of these two parameters along with age could well discriminate cardiac injury (area the under curve 0.881, $P < 0.001$) by receiver operating characteristic analysis. Cox regression model identified that the presence of T wave changes was an independent predictor of mortality (hazard ratio, 3.57 [1.40, 9.11], P = 0.008) after adjustment for age.

Conclusions In COVID-19 patients, presence of cardiac injury at admission is associated with poor clinical outcomes. Repolarization abnormalities on surface ECG such as abnormal T waves and prolonged QTc intervals are more common in patients with cardiac involvement and can help in further risk stratification.

Keywords COVID-19; Heart injury; ECG; Repolarization; Clinical outcome

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has caused millions of infectious cases and considerable mortality.[1] Many studies have described the clinical characteristics of patients with COVID-19.[2–7] Cardiac injury has been observed as a common complication, ranging from 10% to 30% among hospitalized cases,[3,4,8,9] exacerbating severity and mortality of the disease. Monitoring of cardiac involvement in patients with COVID-19 is of utmost importance to evaluate the progression of disease and its prognosis.

Surface electrocardiographic (ECG) findings have not been systematically reported in COVID-19, except for in some case studies describing representative ECGs of special cases.[10–12] The evaluation of cardiac involvement by measuring serum cardiac biomarkers has often been reserved for high-risk individuals or suspected cases. An association between surface ECG characteristics and cardiac injury, if confirmed, can be of clinical relevance, because ECG can be used as a non-invasive monitoring strategy to reflect a possible cardiac involvement in patients with COVID-19. In the present study, we aimed to describe ECG characteristics of COVID-19 patients and to identify ECG parameters that are associated with cardiac involvement.

Methods

Study participants

This single-centre, observational study included laboratory confirmed COVID-19 patients who were treated at the Jinyintan Hopital in Wuhan, China, between 1 January 2020 and 27 February 2020. The cases who had no cardiac biomarker testing or surface ECG were excluded. This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of the Jinyintan Hospital. Written informed consent was provided from all patients.

Clinical data collection

The clinical data and 12-lead surface ECG were simultaneously collected during the hospitalization (by J. T., W. H., and P. Z.). Serum cardiac biomarkers were collected including high-sensitivity troponin I (hs-TnI), myohaemoglobin, and creatinine kinase-myocardial band at the time of ECG recordings for these patients. Cardiac injury was defined as at least one elevated cardiac biomarker (above the 99th percentile upper reference limit). The ECGs were evaluated by two experts (F. D. and M. C.) who were blinded to the patient groups. Abnormal T wave was defined as T wave inversion (TWI), isoelectric, or biphasic T wave. The degree of T wave abnormality was determined as prominent TWI, mild TWI, or isoelectric T wave. Treatment and outcome data were recorded during hospitalization (by N. H.). The clinical outcomes were defined as *hospital discharge* or *death*.

Statistical analysis

Continuous variables were presented as median (inter-quartile range [IQR]) values. Comparisons between two groups were performed by Mann–Whitney *U* test or Fisher's exact test, as appropriate. Paired Student's *t*-test was used to compare paired samples between the two groups. Spearman test was used for correlation analysis between hs-cTnI and number of abnormal T waves. Logistic regression analysis with odds ratio (OR) and 95% confidence intervals (CIs) was used to determine the independent factors reflecting cardiac injury. Receiver operating characteristic (ROC) with area the under curve (AUC) analyses were used to assess the prediction value with optimal sensitivity and specificity. Multivariable Cox regression with hazard ratio (HR) and 95% CI was used to evaluate the predictors for mortality.

Results

Patient characteristics and laboratory findings

The study included 63 patients (53 [IQR, 43–65] years, 15 [23.8%] female) including 23 patients (36.5%) with cardiac injury and 40 patients (63.5%) without cardiac injury. The patient characteristics were presented in *Table 1*. Compared with patients without cardiac injury, patients with cardiac injury were older and more often had baseline co-morbidities such as hypertension, coronary heart disease, arrhythmias, and cancer. In addition to significantly elevated cardiac biomarkers, patients with cardiac injury also showed higher leukocytes count, aspartate transaminase, high-sensitivity C-reaction protein, D-dimer, serum ferritin, and lactic dehydrogenase. Renal function, lipid, and interleukin 6 (IL6) were comparable between two groups (*Table 1*).

Clinical course and outcomes

Table 2 shows the treatment, complications, and clinical outcomes. Compared with patients without cardiac injury, patients with cardiac injury required more glucocorticoids and non-invasive ventilation and showed more frequent hypoproteinaemia and acute respiratory distress syndrome, and more often progressed to severe condition. As a consequence, the mortality rate was higher among patients with vs. without cardiac injury (12 [52.2%] vs. 5 [12.5%], $P = 0.001$).

Electrocardiographic characteristics

Most patients with COVID-19 showed abnormal ECG features, such as sinus tachycardia (17.5%), abnormal T waves (48.3%), and ST segment changes (7.9%) (*Table 3*). Compared with patients without cardiac injury, patients with cardiac injury showed prolonged QTc interval (452 [423, 479] vs. 428 [407.5, 439.5], $P = 0.006$), more abnormal T wave leads (2 [1, 2] vs. 0 [0, 1], $P < 0.001$), and more severe T wave

Table 1 Baseline characteristics and laboratory findings of 63 patients with coronavirus disease 2019

Characteristics	Total (n = 63)	Without cardiac injury (n = 40)	With cardiac injury (n = 23)	P value
Female	15 (23.8)	9 (22.5)	6 (26.1)	0.750
Age, years	53 (43, 65)	48 (39, 62)	61 (49, 75)	0.007
Systolic pressure, mmHg	124 (115, 140)	125.5 (119, 141.5)	120 (110, 136)	0.123
Diastolic pressure, mmHg	77 (70, 85)	78.5 (70, 84)	72 (66, 87)	0.597
Signs and symptoms at admission, n (%)				
Fever	56 (88.9)	34 (85)	22 (95.7)	0.199
Cough	47 (74.6)	28 (70)	19 (82.6)	0.272
Chest tightness	29 (46)	19 (47.5)	10 (43.5)	0.760
Palpitation	1 (1.6)	1 (2.5)	0 (0)	1.000
Dyspnoea	25 (39.7)	14 (35)	11 (47.8)	0.320
Fatigue	18 (28.6)	9 (22.5)	9 (39.1)	0.163
Sputum	18 (28.6)	11 (27.5)	7 (30.4)	0.805
Muscle ache	5 (7.9)	3 (7.5)	2 (8.7)	0.867
Diarrhoea	8 (12.7)	5 (12.5)	3 (13)	1.000
Chest pain	2 (3.2)	2 (5)	0 (0)	0.529
Headache	3 (4.8)	3 (7.5)	0 (0)	0.293
Sore throat	4 (6.3)	4 (10)	0 (0)	0.287
Hypertension	17 (27)	7 (17.5)	10 (43.5)	0.027
Diabetes	11 (17.5)	6 (15)	5 (21.7)	0.732
Coronary heart disease	4 (6.3)	0 (0)	4 (17.4)	0.015
Arrhythmias	5 (7.9)	1 (2.5)	4 (17.4)	0.055
COPD	4 (6.3)	2 (5)	2 (8.7)	0.566
Cancer	3 (4.8)	0 (0)	3 (13)	0.045
Laboratory findings at admission, median (IQR)				
SpO_2 (%)	95 (89, 98)	97 (94, 98)	92 (84, 95)	0.001
Leukocytes, /μL	6.36 (4.16, 9.83)	5.63 (3.44, 8.12)	8.69 (5.14, 11.26)	0.008
Erythrocytes, /μL	4.41 (4.02, 4.74)	4.44 (4.04, 4.92)	4.26 (3.92, 4.61)	0.558
Haemoglobin, g/dL	132 (122, 141)	131.5 (123, 141)	132 (118, 142)	0.869
Platelets, /μL	176 (133, 272)	187 (134.5, 278.5)	166 (132, 229)	0.617
Lymphocytes, /μL	0.84 (0.59, 1.25)	0.88 (0.56, 1.33)	0.83 (0.63, 1.08)	0.842
Creatine, μmol/L	71.9 (64, 84.6)	77.7 (66.3, 87)	68.7 (52.5, 84.2)	0.109
eGFR, ×mL/(min × 1.73 m^2)	103.52 (86.37, 123.33)	101.79 (84.42, 121.87)	113.15 (86.51, 148.21)	0.226
Albumin, g/L	33.3 (29.2, 37.4)	35.75 (31.65, 38.9)	31.4 (28.6, 35.3)	0.036
Total bilirubin, μmol/L	13.05 (9.9, 17.3)	13.2 (10, 17)	12.9 (9.5, 18)	0.965
AST, U/L	40 (26, 49)	34.5 (25.5, 43.5)	45 (30, 55)	0.012
ALT, U/L	32.5 (23, 43)	32 (23, 43)	33 (20, 53)	0.748
Total cholesterol, mmol/L	3.88 (3.15, 4.63)	3.98 (3.18, 4.55)	3.73 (3.01, 4.68)	0.743
Triglyceride, mmol/L	1.17 (0.96, 1.76)	1.14 (0.96, 1.76)	1.21 (0.94, 1.86)	0.867
LDL-C, mmol/L	2.29 (1.75, 2.65)	2.36 (1.91, 2.68)	2.21 (1.51, 2.61)	0.173
HDL-C, mmol/L	0.98 (0.81, 1.17)	0.96 (0.82, 1.13)	1.13 (0.78, 1.26)	0.526
hs-CRP, mg/L	26.7 (7.35, 69.7)	17.1 (4, 71.5)	47.1 (21.9, 67.9)	0.027
PaO_2, kPa	9.36 (7.81, 14.08)	9.12 (7.75, 13.57)	9.36 (8.24, 14.16)	0.605
D-dimer, μg/mL	0.79 (0.36, 2.97)	0.48 (0.26, 1.66)	2.11 (0.55, 22.47)	0.002
Serum ferritin, ng/mL	757.85 (420.33, 1280.95)	523.65 (300.83, 808.35)	1035.7 (787.29, 2000)	0.001
ESR, mm/h	41 (28, 53.7)	39.25 (27.65, 48.05)	48.2 (31, 66)	0.075
Interleukin 6, pg/mL	8.68 (6.65, 11.2)	8.68 (6.73, 11.92)	8.73 (6.32, 10.93)	0.706
hs-TnI, pg/mL	6.1 (2.6, 14.4)	3.55 (1.1, 8.75)	13.1 (5.7, 79)	<0.001
Myohaemoglobin, ng/mL	71 (34.7, 139.7)	52.1 (30.8, 76.6)	147.65 (77.7, 230.1)	<0.001
BNP, pg/mL	36.3 (12.6, 85)	27.4 (3, 50.9)	73.6 (32.1, 324.25)	0.007
Creatinine kinase, U/L	96 (67, 175)	80.5 (65.5, 133.5)	139 (67, 349)	0.074
CK-MB, U/L	15 (12, 19)	15 (11, 17)	18 (14, 26)	0.005
Lactic dehydrogenase, U/L	352 (236, 473)	276.5 (217, 417)	416 (327, 631)	0.001

ALT, alanine aminotransferase; AST, aspartate transaminase; BNP, B-type natriuretic peptide; CK-MB, creatinine kinase-myocardial band; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; HDL-C, high density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reaction protein; LDL-C, low density lipoprotein cholesterol

alterations (P = 0.002). In addition, sinus tachycardia (7 [30.4%] vs. 4 [10.0%], P = 0.041) and Q wave (4 [17.4%] vs. 1 [2.5%], P = 0.037) were more often observed among patients with vs. without cardiac injury. *Figure 1A* shows representative ECGs from patients with and without cardiac injury.

Electrocardiographic and cardiac injury

We enrolled a logistic regression model to identify indicators of cardiac injury among ECG features as well as routine laboratory blood tests (*Table 4*). After adjustment for age,

Table 2 Treatment, complications, and clinical outcome of patients with coronavirus disease 2019

Characteristics	Total (n = 63)	Without cardiac injury (n = 40)	With cardiac injury (n = 23)	P value
Treatment				
Antiviral drugs	57 (90.5)	35 (87.5)	22 (95.7)	0.402
Antibiotics	60 (95.2)	38 (95)	22 (95.7)	1.000
Glucocorticoids	33 (52.4)	17 (42.5)	16 (69.6)	0.040
Immunoglobulin therapy	14 (22.2)	8 (20)	6 (26.1)	0.579
Oxygen inhalation	37 (73.0)	27 (67.5)	19 (82.6)	0.197
Non-invasive ventilation	17 (27)	6 (15)	11 (47.8)	0.005
Invasive ventilation	1 (1.6)	0 (0)	1 (4.3)	0.365
Complications				
ARDS	15 (23.8)	7 (17.5)	8 (34.8)	0.124
Acute kidney injury	2 (3.2)	1 (2.5)	1 (4.3)	1.000
Hypoproteinaemia	18 (28.6)	7 (17.5)	11 (47.8)	0.011
Anaemia	4 (6.3)	2 (5)	2 (8.7)	0.619
Hypoxaemia	23 (36.5)	12 (30)	11 (47.8)	0.160
Outcome				
Critical condition	32 (50.8)	13 (32.5)	19 (82.6)	<0.001
Death	17 (27)	5 (12.5)	12 (52.2)	0.001

Table 3 Electrocardiographic characteristics of patients with coronavirus disease 2019

Characteristics	Total (n = 63)	Without cardiac injury (n = 40)	With cardiac injury (n = 23)	P value
Heart rate, b.p.m.	80 (71, 89)	77 (68, 86.5)	85 (77, 101)	0.018
PR interval, ms	150 (139, 165)	155 (139, 164)	147 (139, 166)	0.597
QRS duration, ms	92 (86, 99)	92 (87, 100)	89 (84, 95)	0.155
QT interval, ms	372 (354, 402)	373 (355, 403)	369 (354, 402)	0.911
QTc, ms	432.5 (413, 452)	428 (407.5, 439.5)	452 (423, 479)	0.006
Sinus tachycardia	11 (17.5)	4 (10.0)	7 (30.4)	0.041
Branch bundle block	5 (7.9)	4 (10)	1 (4.3)	0.644
ST segment changes	5 (7.9)	3 (7.5)	2 (8.7)	1.000
Q wave	5 (7.9)	1 (2.5)	4 (17.4)	0.037
Abnormal T waves (≥1 lead)	29 (48.3)	11 (28.9)	18 (81.8)	<0.001
Severity of abnormal T wave[a]				0.002
Prominent T wave	9 (15)	4 (10.5)	5 (22.7)	
Mild TWI	10 (16.7)	4 (10.5)	6 (27.3)	
Isoelectric T wave	10 (16.7)	3 (7.9)	7 (31.8)	
Normal	31 (51.7)	27 (71.1)	4 (18.2)	
No. of abnormal T waves	0 (0, 2)	0 (0, 1)	2 (1, 2)	<0.001

[a]Abnormal T wave was defined as T wave inversion (TWI), isoelectric, or biphasic T wave.

baseline co-morbidities, leukocyte counts, albumin, and aspartate transaminase, both number of abnormal T waves (OR, 2.36 [95% CI, 1.38–4.04], P = 0.002) and QTc intervals (OR, 1.31 [95% CI, 1.03–1.66], P = 0.027) were independent predictors for cardiac injury. Spearman test validated positive correlation between number of leads with abnormal T waves and hs-cTnI levels among patients with COVID-19 (r = 0.66, $P < 0.0001$), which suggests the extent of abnormal T waves leads reflecting the severity of cardiac injury (*Figure 1B*). ROC curve analysis confirmed that both QTc and number of leads with abnormal T waves could discriminate cardiac injury with AUC of 0.716 (P = 0.006) and 0.798 ($P < 0.001$), respectively (*Figure 1C, D*). The discrimination reached 0.881 (AUC) as we used a combined model of age, number of leads with abnormal T waves, and QTc interval ($P < 0.001$), with a sensitivity of 77.3% and specificity of 83.3% (*Figure 1E*).

Multivariate Cox regression analysis indicated that age and cardiac injury were independent predictors of mortality in patients with COVID-19. When we included age and ECG parameters into the Cox regression model, presence of T wave changes was still an independent predictor (HR = 3.57 [1.40, 9.11], P = 0.008) for mortality when adjusted by age (*Table 5*).

Dynamic alterations of electrocardiogram

In order to investigate the dynamic alterations of ECG along with the progression of cardiac injury among patients with COVID-19, we enrolled a subgroup of eight patients who developed cardiac injury during hospitalization and had serial ECG examinations from baseline to the time of cardiac injury. Our results showed that QTc intervals and the number of leads with abnormal T waves were significantly increased (P = 0.001 and P = 0.001, respectively), along with elevation of cardiac injury biomarkers hs-TnI and myohaemoglobin, in parallel to the progression of cardiac involvement (*Figure*

Figure 1 T wave changes associated with cardiac injury among patients with coronavirus disease 2019 (COVID-19). (A) Representative electrocardiogram (ECG) from patients with (upper panel, female, 70 years old, QTc 459 ms) and without (lower panel, 30 years, QTc 423 ms) cardiac injury. (B) Spearman correlation analysis between number of abnormal T waves and serum high-sensitivity troponin I (hs-TnI) concentrations. Receiver operating characteristic (ROC) curve in discriminating cardiac injury by number of abnormal T waves (C), QTc interval (D), and combined model of age, number of abnormal T waves and QTc interval with a sensitivity of 77.3% and specificity of 83.3% (E).

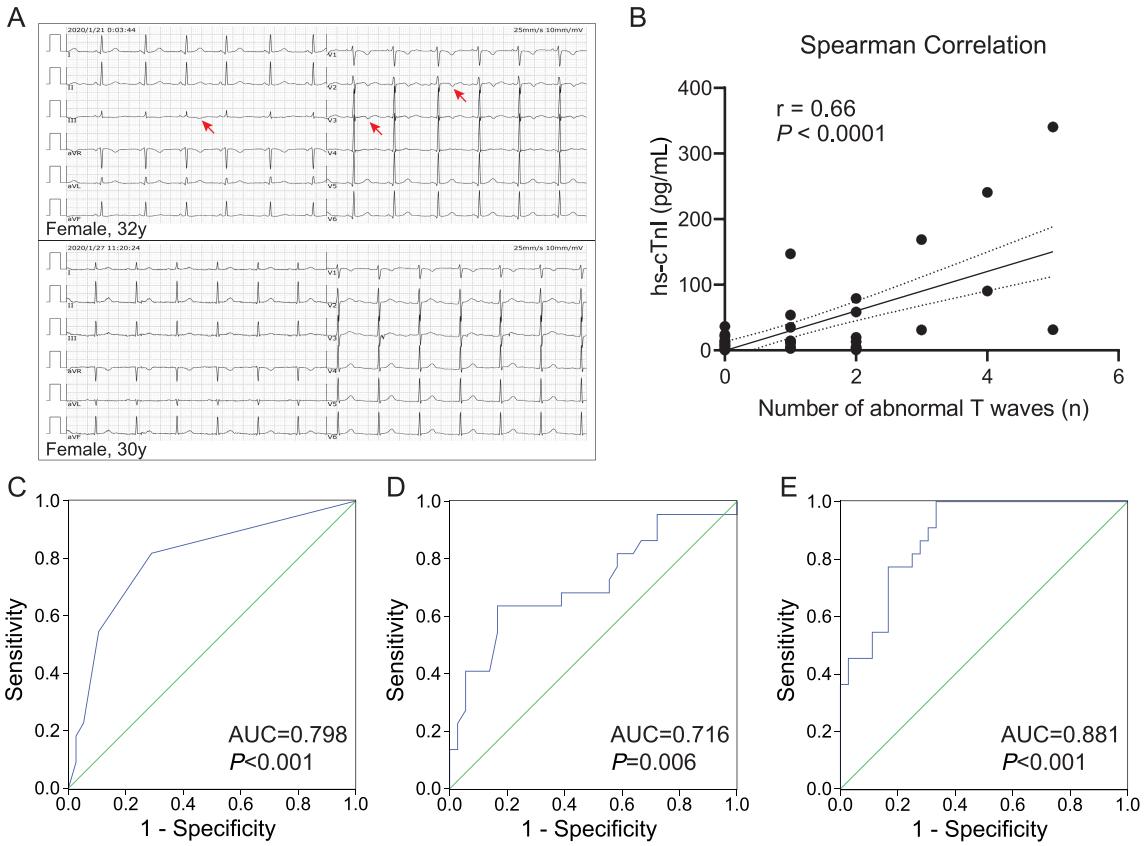


Table 4 Logistic regression to identify cardiac injury using electrocardiographic features and routine laboratory parameters

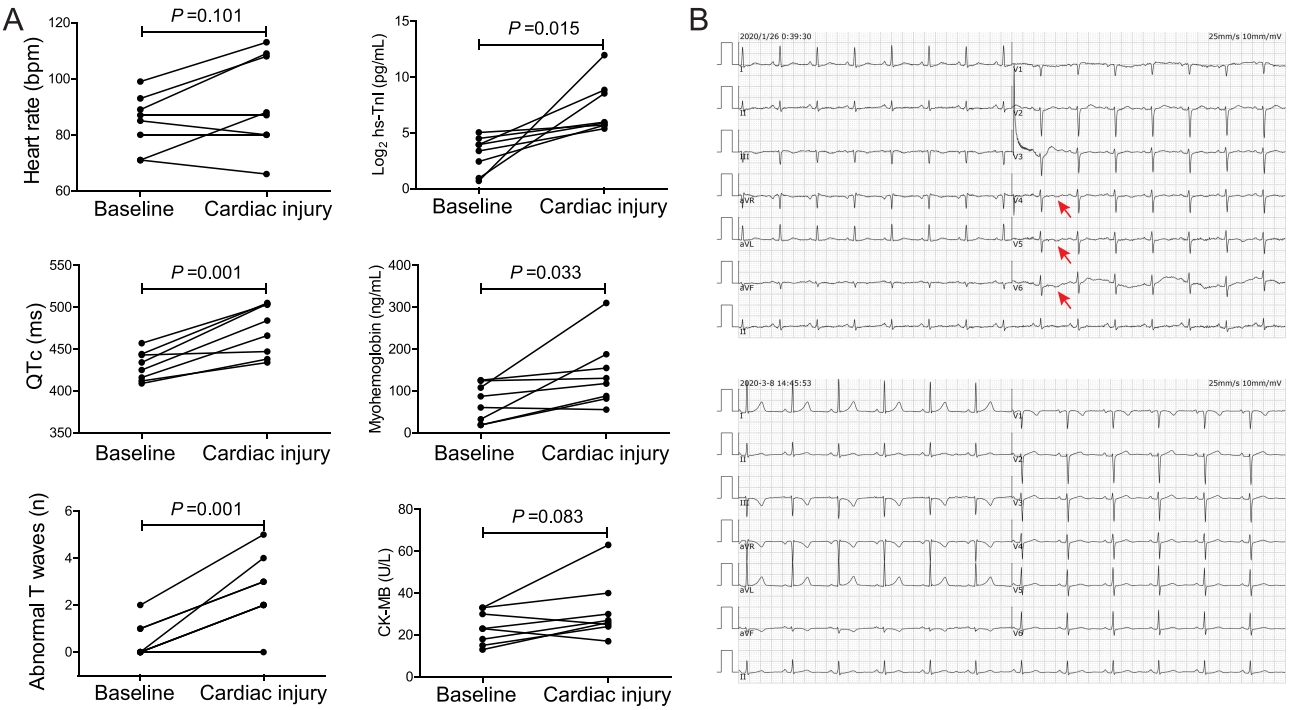
Variables	OR (95% CI)	*P* value
Age (per 10 years)	1.64 (1.09–2.47)	0.017
No. of abnormal T waves	2.36 (1.38–4.04)	0.002
QTc (per 10 ms)	1.31 (1.03–1.66)	0.027
Q wave	—	0.059
Sinus tachycardia	—	0.740
Hypertension	—	0.275
Coronary heart disease	—	0.199
Leukocytes	—	0.349
Albumin	—	0.859
Aspartate transaminase	—	0.204

2A). In addition, after patients completely recovering, the abnormal T waves of some patients were able to return back to normal as shown in one patient with comparable ECGs at admission and discharged from hospital (*Figure 2B*). These

Table 5 Multivariable Cox regression prediction of mortality in patients with coronavirus disease 2019

Variables	Hazard ratio (95% confidential interval)	*P* value
Age + clinical variables		
Age (per 10 years)	1.77 (1.27, 2.47)	0.001
Cardiac injury	8.77 (2.41, 31.95)	0.001
Hypertension	—	0.537
Coronary artery disease	—	0.469
COPD	—	0.193
Cancer	—	0.897
SpO_2	—	0.114
Age + ECG parameters		
Age (per 10 years)	1.86 (1.37, 2.53)	<0.001
Abnormal T waves ≥ 2	3.57 (1.40, 9.11)	0.008
QTc ≥ 448 ms	—	0.090
ST segment changes	—	0.885
Bundle branch block	—	0.924
Q wave	—	0.407
Heart rate	—	0.723

Figure 2 Dynamic changes of electrocardiogram (ECG). (A) The ECG parameters and cardiac biomarker alterations from baseline to the time of cardiac injury (compared by paired Student's *t*-test). (B) Representative ECG from one patient (male, 65 years old) during cardiac injury (upper panel) and recovery state (lower panel).



results validated that ECG alterations in patients with COVID-19 were associated with the presence of cardiac injury, and there were dynamic changes during disease progression.

Discussion

Cardiac injury associated with prognosis

Cardiac injury was commonly reported in patients with COVID-19, with a prevalence ranging from 10% to 30% at hospital admission.[8,9] Patients with cardiac injury had a considerably high mortality rate (more than 50%), compared with the ~2.3% among the overall disease population.[8,9,13] Our study has also revealed a similar mortality rate in patients with cardiac injury (52.2%), much higher than the mortality rate in patient without cardiac injury (12.5%). Our Cox regression analysis also demonstrated the independent role of cardiac injury in predicting mortality. Therefore, it is of utmost importance to detect cardiac involvement in patients with COVID-19 and a 12-lead surface ECG can help for identifying these patients. Other clinical conditions such as old age and the presence of chronic obstructive pulmonary disease were also reported to be associated with higher mortality in patients with COVID-19.[9]

Surface electrocardiogram and cardiac injury

Abnormal ECG features such as ST segment changes and presence of Q wave and bundle branch block were observed in a minority of cases in our cohort, which were also reported by previous case series.[10,14] In contrast, T wave changes were common findings with a prevalence of 48.3% in the whole study cohort. The number of leads with abnormal T waves was significantly higher among patients with vs. without cardiac injury, and this was also significantly correlated with serum hs-cTnI levels. In addition, patients with cardiac injury had longer QTc intervals, and none of these patients received chloroquine or hydroxychloroquine therapy that might have induced QT prolongation.[15] We further demonstrated that T wave changes along with QTc interval and age could be used as a substantial predictor of cardiac injury with good discrimination. Therefore, considering that cardiac biomarkers are not routinely tested in clinical practice, ECG can be of clinical importance in determining cardiac involvement in COVID-19 patients. As old age with presence of cardiovascular co-morbidities may be a confounder for QTc and T wave changes, the dynamic alterations of ECG from baseline to

progressive disease are clinically more applicable for monitoring cardiac involvement in patients with COVID-19.

Potential mechanism underlying cardiac injury

The mechanisms underlying cardiac injury caused by SARS-CoV-2 remain unknown. A newly proposed theory has focused on endothelial involvement causing microvascular dysfunction across different organ systems.[16] Our recent study has revealed that cardiac pericytes (a perivascular cell type that wrap around capillaries) have high expression of angiotensin-converting enzyme 2 (ACE2), the putative viral receptor and, therefore, may serve as the target cell of SARS-CoV-2,[17] which was later validated by an independent study.[18] Therefore, pericyte injury due to virus infection may result in capillary endothelial dysfunction, thus inducing microvascular dysfunction.[17] The representative signature of T wave alterations among COVID-19 patients with cardiac injury was also previously demonstrated to be a predictor of coronary microvascular dysfunction in patients with non-obstructive disease.[19]

This study was a retrospective, observational study and included only a limited number of cases. ECG findings from larger multicentre cohorts are warranted to investigate the role of ECG in predicting cardiac injury and prognosis in COVID-19.

In summary, presence of cardiac injury in COVID-19 patients is associated with poor clinical outcome. ECG repolarization abnormalities such as abnormal T waves and prolonged QTc intervals are more common in patients with cardiac involvement and can help in identifying these patients. Larger multicentre cohorts are warranted to investigate the role of ECG findings in predicting cardiac injury in COVID-19.

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Conflict of interest

None declared.

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