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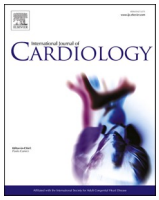

# Diagnostic utility of electrocardiogram for screening of cardiac injury on cardiac magnetic resonance in post-hospitalised COVID-19 patients: a prospective multicenter study

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ABSTRACT

*Background:* The role of ECG in ruling out myocardial complications on cardiac magnetic resonance (CMR) is unclear. We examined the clinical utility of ECG in screening for cardiac abnormalities on CMR among post-hospitalised COVID-19 patients.

*Methods:* Post-hospitalised patients ($n = 212$) and age, sex and comorbidity-matched controls ($n = 38$) underwent CMR and 12-lead ECG in a prospective multicenter follow-up study. Participants were screened for routinely reported ECG abnormalities, including arrhythmia, conduction and R wave abnormalities and ST-T changes (excluding repolarisation intervals). Quantitative repolarisation analyses included corrected QT (QTc), corrected QT dispersion (QTc disp), corrected JT (JTc) and corrected T peak-end (cTPe) intervals.

*Results:* At a median of 5.6 months, patients had a higher burden of ECG abnormalities (72.2% vs controls 42.1%, $p = 0.001$) and lower LVEF but a comparable cumulative burden of CMR abnormalities than controls. Patients with CMR abnormalities had more ECG abnormalities and longer repolarisation intervals than those with normal CMR and controls (82% vs 69% vs 42%, $p < 0.001$). Routinely reported ECG abnormalities had poor discriminative ability (area-under-the-receiver-operating curve: AUROC) for abnormal CMR, AUROC 0.56 (95% CI 0.47–0.65), $p = 0.185$; worse among female than male patients. Adding JTc and QTc disp improved the AUROC to 0.64 (95% CI 0.55–0.74), $p = 0.002$, the sensitivity of the ECG increased from 81.6% to 98.0%, negative predictive value from 84.7% to 96.3%, negative likelihood ratio from 0.60 to 0.13, and reduced sex-dependence variabilities of ECG diagnostic parameters.

*Conclusion:* Post-hospitalised COVID-19 patients have more ECG abnormalities than controls. Normal ECGs, including normal repolarisation intervals, reliably exclude CMR abnormalities in male and female patients.

**Nonstandard Abbreviations and Acronyms**

| | |
|---|---|
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus-2 |
| COVID-19 | Coronavirus disease |
| CMR | Cardiac magnetic resonance imaging |
| QTc | Corrected QT interval |
| QTPc | Corrected QT peak interval |
| JTc | Corrected JT interval |
| cTPe | Corrected T peak-to-T-end interval |
| LGE | Late gadolinium enhancement |
| AUROC | Area under the receiver operating characteristic curve |
| NPV | Negative predictive value |
| PPV | Positive predictive value |
| LR | Likelihood ratio |

## 1. Introduction

Cardiac injury is a known complication of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection [1] and portends high mortality, particularly in the context of moderate-to-severe coronavirus disease (COVID-19). Both direct (e.g. SARS-CoV-2 viral toxicity) and indirect mechanisms (e.g. cytokine storm and ischaemic injury) have been implicated as a source of cardiac injury [2].

The twelve-lead electrocardiogram (ECG) is the first-line test for assessing patients with suspected cardiac injury. Deviations in electrical activation and conduction, including pathology-induced abnormalities in myocardial electrical activities, may be inferred through a comprehensive evaluation of QRS, ST, and T wave morphology and various ECG intervals. ECG is inexpensive and widely accessible, making it an ideal screening tool for cardiac involvement secondary to infections. Although current guidelines recommend the use of ECG in post-COVID management [3], its diagnostic performance for pathological abnormalities is unclear. Additionally, despite an increased interest in exploring the impact of sex-based differences in ECG features, the sex-based diagnostic performance of ECG for cardiac abnormalities based on imaging modalities like cardiac magnetic resonance (CMR) is unknown.

In human hearts, physiological variations influencing the ECG features have been reported, with differences in expression linked to X- and Y-linked genes [4], and sex hormones [5]. Females generally show longer action potential (AP) duration, slower AP recovery, shorter PR interval, narrower QRS duration, and longer QT intervals than male patients [5]. In the setting of COVID-19, only a few of the sex-based studies reported on ECG findings for meaningful comparison, and their associations with CMR abnormalities were not explored [6,7].

CMR is the imaging gold standard modality for non-invasive assessment of myocardial injury following COVID-19 infection [8]. CMR imaging has several advantages over the 12-lead ECG, as it permits accurate assessment of cardiac structure, function, and pathology. Abnormal tissue characteristics on CMR, such as late gadolinium enhancement (LGE), high T1, and high T2 mapping, may indicate the presence of fibrosis and oedema, increasing its diagnostic confidence for infectious, inflammatory, and ischemic insults [9]. Despite these advantages, there is restricted access to CMR globally due to high costs, and limited domain expertise [10].

Although numerous studies have evaluated the burden of cardiac injury after COVID-19 with 12 leads ECG [11] or CMR [12], none have examined the diagnostic performance of 12 leads ECG in ruling out CMR abnormalities. This prospective multicenter study aimed to 1) examine the burden of ECG abnormalities in post-hospitalised COVID-19 patients relative to an age, risk factor and comorbidity-matched control group, 2) determine diagnostic utility of routinely reported ECG abnormalities and quantitative repolarisation ECG metrics for cardiac abnormalities on CMR, and 3) evaluate the impact of sex on ECG diagnostic performance.

## 2. Methods

### 2.1. Participants

In this multicenter observational cohort study, we included post-COVID-19 patients discharged from the hospital with a primary diagnosis of moderate-to-severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2 infection) according to the World Health Organisation (WHO) progression scale. Patients with clinical signs of pneumonia, such as respiratory rate > 30 breaths per minute, severe respiratory distress, SPO2 < 90% (on room air) and hospitalised for >48 h were considered to have moderate-to-severe COVID-19 infection [13] (**Supplemental Fig. 1**). Infection was confirmed by SARS-CoV-2 polymerase chain reaction (PCR) nasopharyngeal swab test, diagnosed between 1st March 2020 – 1st November 2021. Participants were prospectively recruited as part of a national UK-wide follow-up program called the Capturing MultiORgan Effects of COVID-19/ The Post-hospitalisation COVID-19 study (C-MORE/PHOSP-COVID). During the data collection period, alpha and delta were the predominant SARS-CoV-2 variants in the United Kingdom [14].

We excluded individuals with end-stage renal failure (eGFR<30 ml per 1·74 ml/min/kg) or other severe comorbidities –cardiac, liver, or neurological disease. Those with contraindications to MRI (e.g. claustrophobia, metal implant, implanted device like defibrillator) or who did not complete the MRI scan or had incomplete ECG, including having less than eight interpretable leads were also excluded from the study (Study Flow Diagram - Supplemental Fig. 2).

Uninfected individuals with no history of COVID-19 and tested negative for SARS-CoV-2 nucleocapsid antibody on screening blood tests from the community and outpatient clinics were prospectively recruited as controls and were matched for age, cardiac risk factors, comorbidities and body mass index (BMI). None of the control participants had any co-existing pulmonary infection or chronic lung disease. At least 30 controls were deemed sufficient based on the sensitivity of CMR for infection-induced pathological changes. Patients presented 3–7 months post-hospital discharge and had comprehensive multiorgan MRI, 12-lead ECG and blood sampling during the baseline visit. The study was approved by the Yorkshire & The Humber-Leeds West Research Ethics Committee (reference 20/YH/0225). and registered on ISRCTN Registry, ISRCTN10980107.

### 2.2. Electrocardiography and analysis

ECG was conducted on the same day of the CMR visit. ECG was interpreted by two independent ECG analysts (AH, AA), blinded to the clinical data, in reference to the Minnesota Code of ECG findings. ECG quantitative repolarisation intervals were manually analysed (described in detail in Supplement, pg 16). Routinely reported ECG abnormalities in this study were defined as the presence of any arrhythmia (i.e. atrial fibrillation, atrial flutter, premature atrial and ventricular complexes, ventricular arrhythmias) or abnormal axis or heart block or abnormal R wave progression or fragmented QRS (fQRS) or bundle branch block (BBB) (including left bundle branch block (LBBB), right bundle branch block (RBBB), incomplete bundle branch block (IBBB) and non-specific intraventricular conduction delay (IVCD)) or ST-T changes, excluding all quantitative repolarisation intervals [15,16].

For the quantitative repolarisation intervals analysis, the terminal end of the T-wave was determined using the tangent method, defined as the intersection between the isoelectric line (TP segment or PR segment) and the line drawn along the steepest angle of the descending arm of the T-wave (Supplemental Fig. 3) [17]. Parameters measured among others included intervals such as corrected QT (QTc), QTc dispersion (QTc disp), corrected QT peak (QTPc), corrected JT (JTc) and corrected T-peak-to-T-end (cTPe). The longest QT interval of the 12 leads ECG was documented. The longest TPe interval was taken from the representative lead II and all the 6 precordial leads (V1-V6) [17]. Heart rate-corrected intervals were generated using the Bazett formula [18].

### 2.3. CMR and image analysis

Cardiac MRI was carried out on a 3 Tesla scanner (Siemens Healthineers, Erlangen, Germany or Philips Healthcare, The Netherlands). Cine imaging, T1 and T2 mapping (basal, mid and apical) and late gadolinium enhancement imaging were acquired (Supplement, pg 18). CMR abnormalities were defined as the presence of i) abnormal left ventricular ejection fraction (LVEF) < 52% and/or right ventricular ejection fraction (RVEF) < 48%, and/or ii) pathological pattern of late gadolinium enhancement (LGE) and/or iii) high T1 and T2 and/or iv) abnormal extracellular volume fraction (ECV) [19,20], (Supplement, pg 18). We defined high level of global T1 or T2 based on Z scores (number of standard deviations from the mean of our normal range) of the patients, a method recently described by Artico et al. [21] Abnormal Z score was defined as being >2 from a normal population, and above the 90th percentile of our entire population (cases and controls) [22]. Abnormal ECV was defined as the value above the 90th percentile of the entire population i.e., ECV > 0.32. A small number of cases were rejected in the sub-analysis of myocardial tissue characteristics due to poor image quality or missing data e.g. 3/212 (1.4%) for T1, 27/212 (12.7%) for T2 and 26/212 (12.3%) for ECV.

### 2.4. Statistical analysis

Continuous variables were summarised as mean ± standard deviation (SD) or median (interquartile range/IQR), and categorical variables as frequencies and percentages. Data distribution was assessed for normality using the Shapiro-Wilk 2-tailed test. Group differences were evaluated using Student's *t*-tests, Mann Whitney *U* tests, and one-way analysis of variance (ANOVA) with post-hoc Tukey Honest Significant Difference (HSD) analysis or Kruskal-Wallis adjusted with Bonferroni correction as appropriate. Chi-square test and the Fisher-Freeman-Halton exact tests were used for categorical variables and Pearsons's test to describe the correlation between CMR values and the ECG intervals. All *p*-values reported are from two-tailed tests. Discriminative ability of the repolarisation parameter to differentiate between two CMR outcome classes was evaluated using area under the receiver operating characteristic (AUROC) curve. Diagnostic performance of ECG repolarisation intervals and their sensitivities (SN), specificities (SP), predictive values (PV) and likelihood ratios (LR) were compared. Univariable and multivariable binary logistic regression models were used to estimate variables associated with CMR abnormalities. In the multivariable model, we tested each ECG parameter and adjusted for a clinical model (age and sex) [23]. Data are presented with 95% Confidence Intervals (CI). All statistical analysis was performed with SPSS version 27.0 (IBM, Armonk, NY, USA).

## 3. Results

### 3.1. Study population

Clinical data and baseline characteristics are summarised in Table 1. Two hundred and twelve post-hospitalised COVID-19 patients

**Table 1**
Clinical parameters of COVID-19 patients compared to controls.

| | COVID-19 $n$ = 212 | Control $n$ = 38 | $P$ values |
|---|---|---|---|
| Age (years) | 57.0 (49.0–65.0) | 52.0 (44.0–62.0) | 0.075[b] |
| Sex: female n (%) | 77 (36.3) | 17 (44.7) | 0.324[a] |
| Non-white ethnicity n (%) | 59/196 (30.1)* | 5 (13.2) | 0.032[c] |
| BMI kg/m$^2$ | 30.0 (26.7–34.5) | 28.0 (23.2–33.3) | 0.134[b] |
| Systolic pressure mmHg | 130 (118–143) | 132 (120–153) | 0.146[b] |
| Diastolic pressure mmHg | 78 (69–87) | 75 (63–88) | 0.589[b] |
| Duration of admission days | 6 (3–10) | NA | NA |
| Smoker and Ex-smoker n (%) | 57/194 (29.4) * | 7 (18.4) | 0.167[c] |
| Hypertension n (%) | 50/176 (28.4) * | 14/38 (36.8) | 0.303[c] |
| Diabetes Mellitus n (%) | 22/179 (12.3) * | 7 (18.4) | 0.313[c] |
| History of IHD n (%) | 6/178 (3.4) * | 1 (2.6) | 0.999[d] |
| Congestive heart failure n (%) | 2/175 (1.1) * | 0(0) | 0.999[d] |
| Oxygen supplementation n (%) | 150/192 (78.1) * | NA | NA |
| Invasive mechanical ventilation n (%) | 17/192 (8.9) * | NA | NA |
| Laboratory Results | | | |
| White cell count x 10$^9$/L | 6.6 (5.6–8.4) | 6.2 (5.2–7.8) | 0.182[b] |
| NT Pro-BNP, pg/mL | 39.0 (32.0–76.0) | 52.4 (22.8–84.1) | 0.367[b] |
| Troponin, ng/L | 6.4 (4.8–16.2) | 2.0 (2.0–2.0) | **<0.001**[b] |
| C-Reactive Protein, mg/L | 2.3 (0.0–5.0) | 0.9 (0.6–2.3) | 0.274[b] |

[a]Independent T-Test, [b]Mann-Whitney Test, [c]Chi-Square Test, [d]Fisher-Freeman-Halton Exact Test. Values are mean ± SD, median (IQR) or percentages. BMI = body mass index; IHD = ischaemic heart disease; NT Pro-BNP = N-terminal pro-B-type natriuretic peptide. *if denominator $n$ < 212.

(median age: 57 years (IQR 49–65), 36.3% female) and 38 age, sex and risk factor-matched controls (median age: 52 years (IQR 44–62), 44.7% female) were included in this study. Most patients (78.1%) required oxygen supplementation in hospital, with only a small proportion (8.9%) requiring escalation to mechanical ventilation. Twenty-eight percent of patients had underlying hypertension, 12.3% had diabetes, and <5% had a history of ischemic heart disease or congestive heart failure, comparable to the burden of cardiac comorbidities in controls.

### 3.2. ECG features in post-COVID-19 patients and controls

At a median of 5.6 [4.3–6.9] months post-hospitalisation, COVID-19 patients had a higher proportion of routinely reported ECG abnormalities than comorbidity-matched non-COVID controls (72.2% vs 42.1%, $p < 0.001$) (Table 2). Patients had a slightly higher resting heart rate versus controls (72 bpm IQR (62–84) vs 67 bpm, IQR (60–77), $p = 0.040$). Quantitative parameters such as cTPe interval ($p = 0.003$) were longer in patients. (See Table 3.)

**Table 2**
ECG and CMR findings of COVID-19 patients compared to controls.

| **ECG** | | | |
|---|---|---|---|
| | **COVID-19 n = 212** | **Control n = 38** | **P values** |
| Abnormal ECG n (%) | 153 (72.2) | 16 (42.1) | **<0.001**[c] |
| Atrial Fibrillation/Flutter n (%) | 1 (0.5) | 0 (0) | 0.999[d] |
| Bundle Branch Block n (%) | 21 (9.9) | 0 (0) | 0.051[d] |
| LBBB n (%) | 2 (1.9) | 0 (0) | 1.000[d] |
| RBBB n (%) | 8 (3.8) | 0 (0) | 0.615[d] |
| ILBBB/IRBBB/IVCD | 11 (5.2) | 0 (0) | 0.381[d] |
| Abnormal axis (BBB excluded) n (%) | 42/191 (22) | 8 (21.1) | 0.898[c] |
| ST-T changes (BBB excluded) n (%) | 79/191 (41.4) | 11 (28.9) | 0.152[c] |
| Abnormal R wave progression n (%) | 38 (17.9) | 6 (15.8) | 0.750[c] |
| Fragmented QRS (BBB excluded) n (%) | 51/191 (26.7) | 5 (13.2) | 0.076[c] |
| Heart block (First degree AV block) n (%) | 14 (6.8) | 0(0) | 0.135[d] |
| PVC/PAC n (%) | 10 (4.7) | 0 (0) | 0.372[d] |
| Heart rate (bpm) | 72 (62–84) | 67 (60–77) | **0.040**[b] |
| | **COVID-19 n = 212** | **Control n = 38** | **P values** |
| PR interval ms | 158.0 (142.8–174.0) | 152.5 (142.5–173.3) | 0.221[b] |
| QRS ms | 92.0 (85.3–98.0) | 87.5 (81.8–93.3) | 0.050[b] |
| QTc ms | 428.0 ± 34.6 | 422.2 ± 30.3 | 0.166[a] |
| QTc disp ms | 54.8 (41.5–69.0) | 50.3 (36.6–65.2) | 0.082[b] |
| QTPc ms | 347.4 ± 32.6 | 351.2 ± 27.8 | 0.506[a] |
| JTc ms | 331.7 ± 28.6 | 332.9 ± 22.4 | 0.820[a] |
| cTPe ms | 99.1 (90.2–109.5) | 90.9 (84.2–99.2) | **0.003**[b] |
| **CMR** | | | |
| | **COVID-19 n = 212** | **Control n = 38** | **P values** |
| CMR abnormal n (%) | 49 (23.1) | 7 (18.4) | 0.592[b] |
| LVEDV ml | 151 (127–170) | 147 (127–173) | 0.935[b] |
| LVESV ml | 59 (46–74) | 54 (48–66) | 0.213[b] |
| LVSV ml | 90(77–100) | 91(78–107) | 0.424[b] |
| LV mass g | 111 ± 26 | 110 ± 28 | 0.948[a] |
| LV mass index g/m$^2$ | 52 (46–59) | 52 (48–61) | 0.601[b] |
| LVEF (%) | 60.3 ± 5.8 | 63.0 ± 6.0 | **0.007**[a] |
| LVEF <52% n (%) | 11 (5.2) | 1 (2.6) | 0.699[d] |
| LVCI L/min/m2 | 3.0 (2.6–3.4) | 3.1 (2.8–3.4) | 0.267[b] |
| RVEDV ml | 151 (126–171) | 160 (130–190) | 0.207[b] |
| RVESV ml | 60 (46–76) | 63 (48–85) | 0.300[b] |
| RVSV ml | 89 (75–99) | 87 (80–102) | 0.402[b] |
| RVEF (%) | 59.4 ± 6.6 | 59.5 ± 6.5 | 0.876[a] |
| RVEF <48% n (%) | 10 (4.7) | 1 (2.6) | 0.999[d] |
| RVCI L/min/m$^2$ | 2.8 (2.5–3.3) | 3.0 (2.5–3.5) | 0.412[b] |
| **Myocardial Tissue Charcterisation** | | | |
| T1 normalized Z score | 0.08 (−1.05–1.27) | 0.02 (−1.30–2.3) | 0.637[b] |
| T2 normalized Z score | 0.63 (−0.07–1.32) | 0.82 (0.17–1.61) | 0.219[b] |
| ECV (%) | 0.28 ± 0.03 | 0.29 ± 0.03 | 0.096[a] |
| High ECV (>0.32) (%) | 15/186 (8.1) | 1 (14.8) | 0.274[d] |
| Pathological LGE n (%) | 27/195 (13.8) | 4 (10.5) | 0.581[d] |
| LGE mass (g) | 4.3 ± 3.7 | 1.1 ± 3.2 | **0.008**[a] |
| Non pathological LGE n (%) | 16/195 (8.2) | 2 (5.3) | 0.745[d] |
| RV insertion LGE n (%) | 5/195 (2.6) | 1 (2.6) | 1.000[d] |
| Basal subvalvular LGE n (%) | 8/195 (4.1) | 1 (2.6) | 1.000[d] |
| Ischemic LGE n (%) | 12/195 (6.2) | 1 (2.6) | 0.699[d] |
| Myocarditis LGE n (%) | 17/195 (8.7) | 4 (10.5) | 0.757[d] |
| Mixed LGE n (%) | 2 /195 (1.0) | 0 (0) | 1.000[d] |
| Cardiomyopathy LGE n (%) | 3/195 (1.5) | 0 (0) | 0.585[d] |
| Pleural effusion n (%) | 2/195 (1.0) | 0 (0) | 1.000[d] |

[a]Independent T-Test, [b]Mann-Whitney Test, [c]Chi-Square Test, [d]Fisher's Exact Test. Values are given as mean ± SD, n (%) or median (IQR), unless otherwise indicated. BBB = bundle branch block; BMI = body mass index; CMR = cardiac magnetic resonance; ECG = electrocardiography; ECV = Extracellular volume; disp = dispersion; LGE = late gadolinium enhancement; LV = left ventricular; LVEDV = left ventricular end- diastolic volume; LVESV = left ventricular end-systolic volume; LVSV = left ventricular systolic volume; LVEF = left ventricular ejection fraction; LVCO = left ventricular cardiac output; LVCI = left ventricular cardiac index; QTc = corrected QT; QTPc = corrected QT peak; RV = right ventricular; PAC = premature atrial complex; PVC = premature ventricular complex; RVEDV = right ventricular end-diastolic volume; RVESV = right ventricular end-systolic volume; RVSV = right ventricular systolic volume; RVEF = right ventricular ejection fraction; RVCO = right ventricular cardiac output; RVCI = right ventricular cardiac index; cTPe = corrected T-peak- to-T-end.

### 3.3. CMR findings between patients and controls

About a quarter of patients had cardiac abnormalities on CMR (Table 2). Relative to risk-factor-matched uninfected controls, patients had a comparable burden of CMR abnormalities, although patients did have lower LV systolic function (60.3 ± 5.8% vs 63.0 ± 6.0%, $p$ = 0.007) and higher LGE mass (4.3 ± 3.7 g vs 1.1 ± 3.2 g, $p$ = 0.008). Myocardial T1, T2 and ECV were similar across patients and controls (Table 2).

### 3.4. ECG features in patients with CMR abnormalities

Overall, patients with CMR abnormalities displayed a higher frequency of commonly reported ECG and repolarisation abnormalities (81.6%) than patients without CMR abnormalities (69.3%) and controls (42.1%, $p < 0.001$) (Fig. 1). Even after excluding patients and controls with comorbidities, routinely reported ECG abnormalities and repolarisation parameters such as QTc, QTPc and cTPe were higher among patients with than without CMR abnormalities and controls (Supplemental Table 1).

### 3.5. ECG features in patients with reduced LVEF and high myocardial T1, T2, ECV and LGE

Comparisons of quantitative ECG parameters among patients with and without individual CMR abnormalities versus controls are summarised in Supplemental Table 2.

Patients with LV dysfunction (LVEF <52%) had a longer QRS duration, and cTPe intervals relative to controls. Patients with a high myocardial T1 had significantly longer QTc and JTc intervals relative to those without high T1 and controls (Supplemental Fig. 4), whereas patients with high T2, had longer QTc intervals relative to patients without high T2 and controls (Supplemental Fig. 5). Patients with high ECV had significantly longer QTPc and JTc intervals compared to patients without high ECV, whereas patients with pathological LGE demonstrated longer PR intervals than patients without pathological LGE and controls (Supplemental Table 2).

### 3.6. Association of ECG features and CMR abnormalities in regression analysis

The univariable and multivariable analysis of ECG parameters among patients, with composite and individual CMR abnormalities after adjusting for age and sex, are summarised in Supplemental Tables 3 and 4. The odds of an abnormal CMR increased by 2% ($p$ = 0.004) for every unit increase in QTc disp after age and sex adjustments. For individual CMR abnormalities, QTc disp was significantly associated with LV dysfunction and high T1 whereas, the QTc and JTc interval were significantly associated with high T1 and T2. There were no associations seen between ECG parameters and LGE or ECV in the age and sex adjusted model ($p > 0.05$).

### 3.7. Diagnostic performance of ECG parameters for CMR abnormalities

Routinely reported ECG abnormalities had a weak AUROC curve for CMR abnormalities of only 0.56 (95% CI 0.47–0.65, $p$ = 0.185). The SN was 82%, SP 31%, NPV 85% and negative -LR of 0.60 (Table 4). The discriminative ability of routinely reported ECG features for abnormal CMR when stratified based on the severity of infection, was poor for both moderate and severe COVID-19 groups with AUROC 0.61 (95% CI 0.0.51–0.72,$p$ = 0.066) and 0.52 (95% CI 0.33–0.71, $p$ = 0.845), respectively. Individual repolarisation interval showed a poor-to-moderate AUROC ranging from 0.48 to 0.61. For each repolarisation interval, the optimal cut-off value was determined [24] and generated into a categorical variable (e.g. QTc ≥ 450, JTc ≥ 340 ms, cTPe ≥100 ms) for the analysis of the diagnostic performance (SN, SP, NPV, PPV, and LR) (Table 4). Adding the JTc interval with/out QTc disp to the routinely reported ECG features, marginally increased the AUROC from 0.56 to 0.62–0.64, $p < 0.05$. Specifically, when JTc ≥ 340 ms with/out QTc disp ≥55 ms were added, the SN increased from 82% to 96–98%, NPV from 85% to 95–96% (Table 4) and -LR improved nearly by 50 folds from 0.60 to 0.19–0.13 (Fig. 2). No significant improvement in SP and PPV was observed. The diagnostic performance of routinely reported ECG abnormalities with and without the repolarisation parameter for detecting individual CMR abnormalities are summarised in Supplemental Table 5 and 6).

### 3.8. Diagnostic performance of ECG for CMR abnormalities stratified by patients' sex

The discriminative ability of routinely reported ECG abnormalities for CMR abnormalities was worse in women than men, with AUROC of 0.49 vs 0.60, respectively (Fig. 3). In women, routinely reported ECG abnormalities had a SN of 67% and SP of 32% for detecting CMR abnormalities, while in men, such parameters had a SN of 90%, SP of 30%. In other words, out of 100 male or female patients, 10 male patients and

**Table 3**
ECG comparisons of patients with and without CMR abnormalities and control.

| | COVID-19 with CMR abnormalities ($n$ = 49) | COVID-19 without CMR abnormalities ($n$ = 163) | Control (n = 38) | P values |
|---|---|---|---|---|
| Age years | 62.0 (53.5–70.5) | 56.0 (47.0–63.3) | 52.0 (44.0–62.0) | **0.008**[b] |
| Abnormal ECG n (%) | 40 (81.6) | 113 (69.3) | 16 (42.1) | **<0.001**[c] |
| Atrial fibrillation/flutter | 1 (2.0) | 0 (0) | 0 (0) | 0.128[d] |
| Bundle branch block n (%) | 9 (18.4) | 12 (7.4) | 0 (0) | **0.007**[d] |
| ST-T abnormalities n (%) | 28 (57.1) | 52 (31.9) | 11 (28.9) | **0.003**[c] |
| Abnormal axis n (%) | 16 (32.7) | 33 (20.2) | 8 (21.1) | 0.185[c] |
| Fragmented QRS n (%) | 18 (36.7) | 46 (28.2) | 5 (13.2) | **0.049**[c] |
| Abnormal R wave progression n (%) | 11 (22.4) | 27 (16.6) | 6 (15.8) | 0.606[c] |
| Heart block n (%) | 6 (12.2) | 8 (4.9) | 0 (0) | **0.039**[d] |
| PAC/ PVC) n (%) | 6 (12.2) | 4 (2.5) | 0 (0) | **0.004**[d] |
| | **COVID-19 with CMR abnormalities (n = 49)** | **COVID-19 without CMR abnormalities (n = 163)** | **Control (n = 38)** | **P values** |
| PR interval ms | 164.0 (150.0–178.0) | 158.0 (142.0–173.0) | 152.5 (142.5–173.3) | 0.151[b] |
| QRS ms | 92.0 (85.0–103.0) | 91.0 (85.0–98.0) | 87.5 (81.8–93.3) | 0.098[b] |
| QTc ms | 434.3 ± 39.2 | 426.1 ± 33.0 | 422.2 ± 30.3 | 0.211[a] |
| QTc disp ms | 65.1 ± 27.0 | 54.0 ± 18.0 | 51.6 ± 18.2 | **0.001**[a] |
| QTPc ms | 355.1 ± 35.2 | 345.1 ± 31.5 | 351.2 ± 27.8 | 0.124[a] |
| JTc ms | 340.1 ± 33.5 | 329.2 ± 26.5 | 332.4 ± 22.4 | 0.052[a] |
| cTPe ms | 97.1 (86.9–113.2) | 99.6 (90.2–109.2) | 91.0 (84.2–99.2) | **0.013**[b] |

[a]ANOVA, [b]Kruskal-Wallis Test, [c]Chi-Square Test, [d]Fisher-Freeman-Halton Test. Values are given as mean ± SD, n (%) or median (IQR), unless otherwise indicated. BBB = bundle branch block; CMR = cardiac magnetic resonance; ECG = electrocardiography; PAC = premature atrial complex; PVC = premature ventricular complex; QTc = corrected QT; QTPc = corrected QT peak; cTPe = corrected T-peak- to-T-end; disp = dispersion.

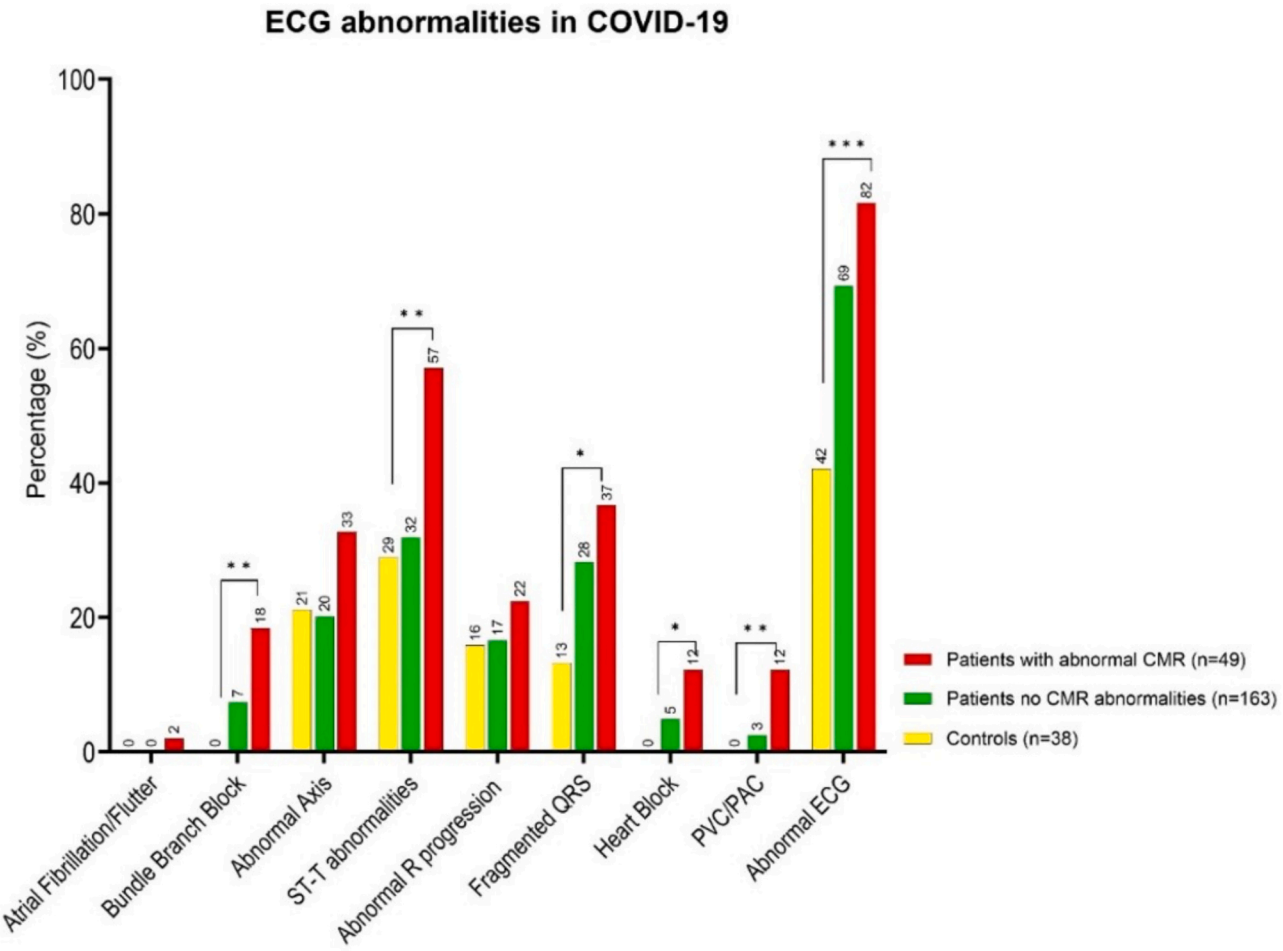


**Fig. 1.** ECG abnormalities in COVID-19 patients with CMR abnormalities (red bar), without CMR abnormalities (green bar) and control (yellow).
COVID-19 with CMR abnormalities demonstrate a higher frequency of ECG abnormalities relative to controls. The most common abnormalities include ST-T abnormalities and fragmented QRS (P value * < 0.05, ** < 0.01 or *** < 0.001). Abnormal ECG is defined as the composite of the routinely reported ECG features (Atrial fibrillation/flutter, bundle branch block, abnormal axis, ST-T abnormalities, abnormal R progression, fragmented QRS complex, heart block and premature ventricular (PVC)/atrial complexes (PAC)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 4**
Diagnostic performance of ECG for CMR abnormalities.

| CMR abnormalities | C- statistic | 95% CI | P value | ECG parameters | SN (%) | SP (%) | PPV (%) | NPV (%) | +LR | -LR |
|---|---|---|---|---|---|---|---|---|---|---|
| ECG abnorm | 0.56 | 0.47–0.65 | 0.185 | ECG abnorm | 81.6 | 30.7 | 26.1 | 84.7 | 1.18 | 0.60 |
| **Individual replarisation parameters** | | | | | | | | | | |
| QTc | 0.56 | 0.46–0.65 | 0.240 | QTc ≥ 450 | 32.7 | 76.1 | 29.1 | 79.0 | 1.37 | 0.88 |
| QTc disp | 0.61 | 0.51–0.71 | **0.019** | QTc disp ≥55 | 55.1 | 52.1 | 25.7 | 79.4 | 1.15 | 0.86 |
| QTPc | 0.58 | 0.48–0.67 | 0.105 | QTPc ≥366 | 34.7 | 70.6 | 26.2 | 78.2 | 1.18 | 0.92 |
| JTc | 0.59 | 0.50–0.69 | **0.048** | JTc ≥ 340 | 49.0 | 66.9 | 30.8 | 81.3 | 1.48 | 0.76 |
| cTPe | 0.48 | 0.38–0.57 | 0.590 | cTPe ≥100 | 44.9 | 50.9 | 21.6 | 75.5 | 0.91 | 1.08 |
| **ECG abnorm + repolarisation parameters** | | | | | | | | | | |
| ECG abnorm + QTc disp | 0.59 | 0.49–0.69 | 0.095 | ECG abnorm + QTc disp ≥55 | 91.8 | 17.8 | 25.1 | 87.9 | 1.12 | 0.46 |
| ECG abnorm + JTc | 0.62 | 0.53–0.71 | **0.011** | ECG abnorm + JTc ≥ 340 | 95.6 | 23.3 | 27.3 | 95.0 | 1.25 | 0.19 |
| ECG abnorm + QTc disp + JTc | 0.64 | 0.55–0.74 | **0.002** | ECG abnorm + QTc disp ≥55 + JTc ≥ 340 | 98.0 | 16.0 | 25.9 | 96.3 | 1.17 | 0.13 |

Abnorm = abnormalities CMR = cardiac magnetic resonance; ECG = electrocardiography; QTc = corrected QT; QTPc = corrected QT peak; cTPe = corrected T-peak-to-T-end; disp = dispersion; LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value; SN = sensitivity; SP = specificity.

33 female patients can be falsely diagnosed (false negative) based only on the routinely reported ECG criteria (Fig. 4). To optimise the diagnostic performance of ECG parameters for excluding cardiac abnormalities across both sexes, adding QTc disp and JTc interval to the routinely reported parameters led to an improvement in the AUROC from 0.60 to 0.62 in men and 0.49 to 0.66 in women (Fig. 3). Likewise, there was a substantial increase in SN and NPV of the ECG for detecting abnormal CMR in women (SN 67% to 94%; NPV 76% to 91%) while matching the SN and NPV in men (sensitivity 90% to 99.9%; negative predictive value 91% to 99.9%). The SP and PPV remained poor across

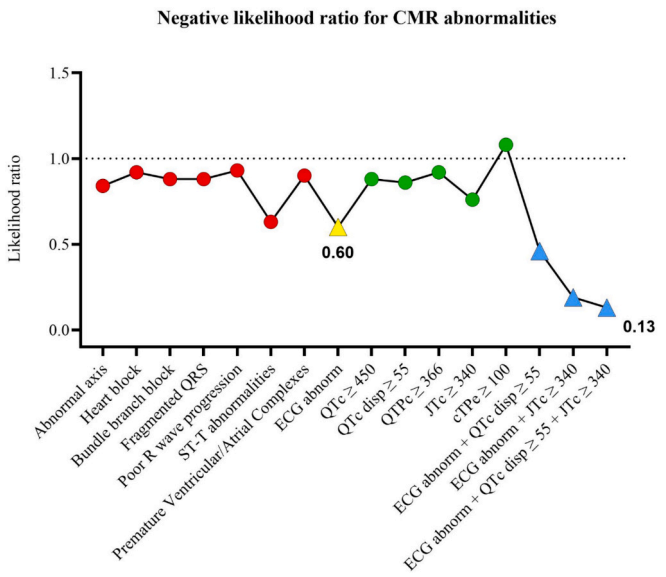


**Fig. 2.** Overall negative likelihood ratios of routinely reported ECG parameters and repolarisation intervals for composite CMR abnormalities.
Individual ● or composite △ routinely reported ECG parameters were poor in ruling out CMR abnormalities (negative likelihood ratio (−LR) ranged between 0.63 and 0.96). Likewise, the -LR of individual repolarisation interval ● was equally poor (−LR ranged between 0.63 and 1.08). Combining the composite routinely reported ECG abnormalities with the repolarisation interval △ substantially enhanced the overall -LR values of ECG to exclude CMR abnormalities. Notably, the addition of repolarisation intervals QTc disp ≥55 ms and JTc ≥ 340 ms to the routinely reported ECG features improved the -LR from 0.60 to 0.13. (ECG abnorm, composite routinely reported ECG features; JTc, corrected JT interval; JTPc, corrected JT peak; QTc disp, QTc dispersion; QTc, corrected QT interval; cTPe, corrected T peak T end interval).
LR of **1.0** indicates no difference in the probability of positive or negative test between those with and without CMR abnormalities.
LR approaching **0** indicates higher probability of a negative test in those without CMR abnormalities.

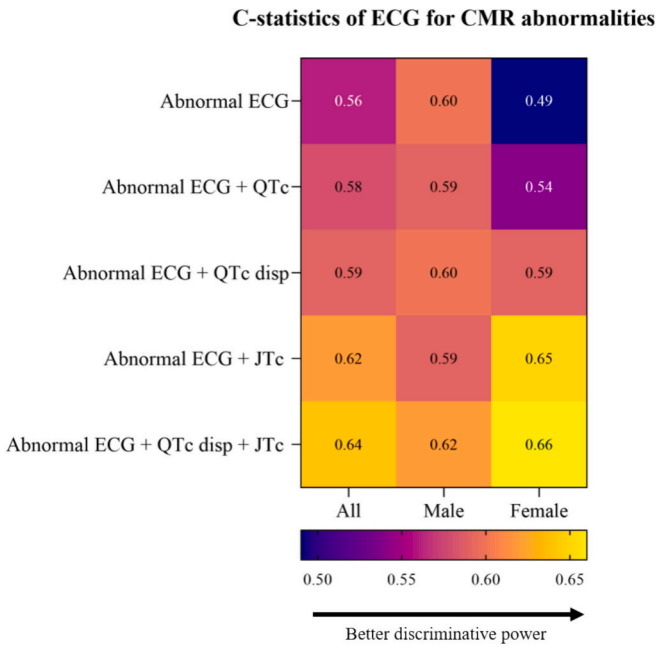


**Fig. 3.** Heat map demonstrating the c-statistic values of various ECG intervals to discriminate composite CMR abnormalities stratified by sex.
(A value below 0.5 (dark blue) indicates poor model; 0.5 indicates discriminative ability that is no better than classifying outcomes randomly by chance; and values approaching 1.0 (bright yellow) indicate excellent discriminative ability). (CMR abnormalities indicate composite cardiac magnetic resonance imaging abnormalities; disp dispersion. Abnormal ECG is defined as the composite of the routinely reported ECG features (Atrial fibrillation/flutter, bundle branch block, abnormal axis, ST-T abnormalities, abnormal R progression, fragmented QRS complex, heart block and premature ventricular (PVC)/atrial complexes (PAC)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

both sexes (Supplemental Table 7). Overall, the diagnostic power of ECG for CMR abnormalities was optimised, and the sex-based variabilities were minimised when the routinely reported, and the quantitative ECG features were both analysed.

Similarly, when evaluating the impact of repolarisation parameters like QTc, QTc disp, and JTc on the diagnostic performance of routinely reported ECG readouts for individual CMR abnormalities, we observed better c-statistics in both sexes for individual CMR abnormalities, particularly in discriminating patients with abnormal myocardial tissue characteristics (high T1 or high T2), and in female patients for discriminating impaired LVEF (i.e.,< 52%) (Supplemental Fig. 6).

## 4. Discussion

The main findings from our study are as follows: First, post-hospitalised COVID-19 patients have a high burden of ECG abnormalities relative to comorbidity-matched uninfected non-COVID-19 controls. Second, at a median of 5.6 months post-discharge, patients had lower left ventricular systolic function and higher LGE mass relative to matched controls, but overall CMR abnormalities were comparable across groups. Third, the ECG diagnostic performance to detect CMR abnormalities displayed significant sex-based variability. Importantly, we demonstrated that utilizing the routinely reported ECG abnormalities without quantitative repolarisation intervals led to a higher risk of misdiagnosis, especially among female patients. The diagnostic performance improved, and the rate of false negative was minimised by adding the repolarisation intervals to the ECG criteria making ECG a potentially good rule-out test for CMR abnormalities post-COVID-19 in both male and female patients. Fourth, repolarisation parameters (particularly the QTc disp and JTc intervals) were significant predictors of abnormal CMR even after adjusting for age and sex as covariates.

### *4.1. ECG abnormalities were common in post-hospitalised COVID-19 patients*

Numerous studies have examined the prevalence of ECG abnormalities in the acute COVID-19 period, and only a few have described this among post-hospitalised individuals, and none have evaluated its diagnostic accuracy for CMR abnormalities [25,26]. In our study, we noted significant ECG abnormalities among patients with abnormal CMR findings including ST-T changes, BBB, fQRS and premature atrial or ventricular complexes. Remarkably, even patients without CMR abnormalities had an abnormal ECG suggesting that severe infections with COVID-19 and potentially other respiratory viruses may be associated with ionic remodelling despite an absence of overt structural changes. Our findings are consistent with previous research, which has also noted a high frequency of ECG abnormalities (50–61%) at 3–12 months in a large prospective study of 594 post-COVID patients in Wuhan, although CMR was not performed in that study [27].

### *4.2. Role of 12-lead ECG in screening individuals with structural cardiac abnormalities on CMR*

At a median of 5.6 months after infection, post-hospitalised patients had mildly lower LV systolic function and higher LGE volume than controls, but the overall burden of CMR abnormalities was comparable between patients and controls consistent with other studies [21,28].

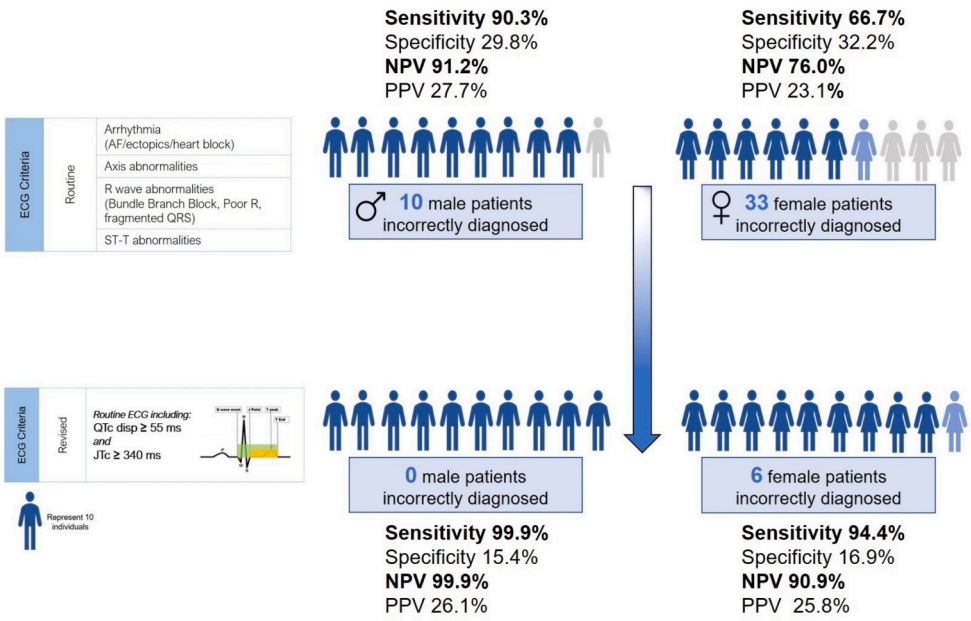


**Fig. 4.** Sex-based improvement in the rate of misdiagnosis (false negative) of ECG for CMR abnormalities.
This figure illustrates the magnitude of change in the diagnostic performance of ECG to rule out CMR abnormalities among post-hospitalised COVID-19 male and female patients. Adding quantitative repolarisarion ECG parameters, specifically JTc ≥ 340 ms and QTc dispersion ≥55 ms into the routinely reported ECG criteria, substantially reduced the rate of misdiagnosis (false negative) in both sexes, particularly females.

Among patients, individuals with high myocardial T1 and T2 (markers sensitive to myocardial fibrosis and oedema) had significantly longer repolarisation intervals (including QTc, QTPc, JTc, and cTPe) than those with normal tissue characteristics and controls. Additionally, repolarisation parameters (QTc, QTPc, and JTc interval) were significantly associated with global myocardial T1 among patients and had a reasonable diagnostic performance for tissue abnormalities. One possible explanation for this finding is that some patients may have residual fibrosis or oedema, which might alter myocardial conduction [29]. Another possibility is that patients may have persistently raised cytokines like IL-1, IL-6, TNF-α as previously demonstrated by us [30], which could inturn induce ionic remodelling and myocardial capillary dilatation and increase permeability, resulting in alteration in both myocardial tissue properties on CMR and electrical conduction [31]. Specifically, these cytokines may result in transient outward flux of K+, which will prolong phases II and III of myocardial action potential duration, both of which correspond to the QT interval and TPe segment of the ECG [32]. The finding that patients had greater QT disp also indicates a heterogeneous response reflecting the complex interaction of structural and humoral factors that induce ionic remodelling. It is worth noting that such heterogeneity in ventricular repolarisation is a well-known risk factor for increased arrhythmogenicity and sudden cardiac death [33]. In support of this, two large retrospective cohort studies from the UK and USA that looked at follow-up data from patients up to 1 year after hospitalisation for COVID-19 have shown that patients who were previously hospitalised with COVID-19 face a notably elevated risk of major adverse cardiovascular events, including cardiac death [34,35].

### *4.3. Sex-based differences in the diagnostic performance of ECG for CMR abnormalities*

The diagnostic performance of routinely reported ECG abnormalities was poor, with differences seen in AUROC between male and female participants (0.49 in females, 0.60 in males). This difference was attenuated when two repolarisation parameters (QTc disp and/or JTc interval) were added to routinely reported ECG abnormalities, significantly improving the SN and NPV. Sex-based differences in ECG measures particularly after puberty are a well known phenomenon. This have been attributed to physiological variations on gene expression linked to ionic channel distribution on myocardium [4], systemic inflammation [31] and sex hormones [36]. Women typically demonstrate shorter and lower QRS amplitude, lower ST-T wave amplitude [5] and longer repolarisation intervals such as QT and JT intervals [36] commonly leading to misclassification of ECGs. In the present study, we showed that by adding quantitative repolarisation interval thresholds to the ECG criteria we minimise the risk of false negatives particularly among women. This is important as women are more likely to report post-COVID symptoms after severe infection highlighting the potential for us to improve the diagnostic utility of the 12-lead ECG in Long COVID.

### *4.4. Clinical implications of the study findings*

The 12-lead ECG may provide a pragmatic screening solution for clinicians, especially in centres with limited CMR services. Our study has, for the first time, comprehensively evaluated the sex-based diagnostic utility of ECG as a screening tool among post-hospitalised COVID-19 patients for cardiac abnormalities defined by CMR. We demonstrated that, although routinely reported features on ECG have a poor sex-dependent diagnostic performance for CMR abnormalities, the sensitivity of a 12-lead ECG can be enhanced by additionally evaluating quantitative repolarisation parameters (JTc, QTc disp), making it potentially an effective screening test to rule out significant cardiac disease post-COVID-19 in both men and women. These findings may allow clinicians to reassure certain patients (such as those with normal ECG) that cardiac structural or functional involvement is likely to be minimal or absent, enabling early discharge and freeing up resources for others in need of such services.

### *4.5. Study limitations*

The lack of CMR and ECG data during pre-COVID, initial COVID hospitalisation and serial analysis of post-hospitalisation limit our ability to establish a clear causal relationship between SARS-CoV-2 infection and cardiac abnormalities. Prolonged follow-up time may also contribute to the dynamic changes of ECG and CMR, and the

correlation between them. Furthermore, patients were recruited from multiple sites across the UK with only a few centers utilizing electronic ECG, hence artificial intelligence (AI) assisted analysis was not possible, limiting further AI-driven insights. Nonetheless, our pragmatic approach can be viewed as a strength of this study, as the parameters measured were manually ascertained and can be inferred from computer-assisted measurements (QRS and QT intervals) on ECG, which should allow for more widespread adoption. Although the present study does not provide external validation of the proposed cut-offs for ECG intervals, its multicenter study design has potential advantages for the robustness of our findings.

## 5. Conclusion

Among post-hospitalised COVID-19 patients, a normal 12-lead ECG may serve as a reliable screening tool to rule out significant cardiac damage on CMR in both male and female patients. The relationship between specific ECG measures and tissue properties on CMR offers biological insights into potential mechanisms for arrhythmias in post-hospitalised COVID-19 patients.

## CRediT authorship contribution statement

**Azlan Helmy Abd Samat:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mark P. Cassar:** Writing – review & editing, Data curation. **Abid M. Akhtar:** Writing – review & editing, Formal analysis. **Celeste McCracken:** Writing – review & editing, Resources. **Zakariye M. Ashkir:** Writing – review & editing. **Rebecca Mills:** Investigation. **Alastair J. Moss:** Writing – review & editing. **Lucy E.M. Finnigan:** Writing – review & editing. **Adam J. Lewandowski:** Writing – review & editing, Supervision. **Masliza Mahmod:** Writing – review & editing, Supervision. **Godwin I. Ogbole:** Writing – review & editing. **Elizabeth M. Tunnicliffe:** Writing – review & editing. **Elena Lukaschuk:** Formal analysis. **Stefan K. Piechnik:** Methodology. **Vanessa M. Ferreira:** Writing – review & editing. **Chrysovalantou Nikolaidou:** Writing – review & editing. **Najib M. Rahman:** Writing – review & editing. **Ling-Pei Ho:** Writing – review & editing. **Victoria C. Harris:** Resources, Project administration. **Amisha Singapuri:** Resources, Project administration. **Charlotte Manisty:** Writing – review & editing. **Declan P. O'Regan:** Writing – review & editing, Investigation. **Jonathan R. Weir-McCall:** Writing – review & editing, Investigation. **Richard P. Steeds:** Writing – review & editing, Investigation. **Krisnah Poinasamy LLM:** Writing – review & editing. **Dan J. Cuthbertson:** Writing – review & editing, Investigation. **Graham J. Kemp:** Writing – review & editing, Investigation. **Alexander Horsley:** Writing – review & editing, Investigation. **Caitlin O'Brien:** Writing – review & editing, Investigation. **Amedeo Chiribiri:** Writing – review & editing, Investigation. **Susan T. Francis:** Writing – review & editing. **James D. Chalmers:** Writing – review & editing. **Sven Plein:** Writing – review & editing. **Ana-Maria Poener:** Writing – review & editing. **James M. Wild:** Writing – review & editing. **Thomas A. Treibel:** Writing – review & editing, Investigation. **Michael Marks:** Writing – review & editing. **Mark Toshner:** Writing – review & editing. **Louise V. Wain:** Writing – review & editing. **Rachael A. Evans:** Writing – review & editing, Resources, Investigation. **Christopher E. Brightling:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition. **Stefan Neubauer:** Writing – review & editing, Supervision, Investigation. **Gerry P. McCann:** Writing – review & editing, Resources, Investigation. **Betty Raman:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.132415.

## References

[1] T. Guo, Y. Fan, M. Chen, et al., Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (covid-19), JAMA Cardiol. 5 (2020) 811–818.
[2] E. Driggin, V. Madhavan Mahesh, B. Bikdeli, et al., Cardiovascular considerations for patients, health care workers, and health systems during the covid-19 pandemic, J. Am. Coll. Cardiol. 75 (2020) 2352–2371.
[3] D.R. Lakkireddy, M.K. Chung, T.F. Deering, et al., Guidance for rebooting electrophysiology through the covid-19 pandemic from the heart rhythm society and the american heart association electrocardiography and arrhythmias committee of the council on clinical cardiology, Circ. Arrhythm. Electrophysiol. 13 (2020) e008999.
[4] P. Krisai, G. Cheniti, T. Takagi, et al., Sex differences in ventricular arrhythmia: epidemiology, pathophysiology and catheter ablation, Rev. Cardiovasc. Med. 23 (2022) 14.
[5] V. Carbone, F. Guarnaccia, G. Carbone, et al., Gender differences in the 12-lead electrocardiogram: clinical implications and prospects, J. Sex Gender Specific Med. 6 (2020) 126–141.
[6] L.M. Montaño, B. Sommer, H. Solís-Chagoyán, et al., Could lower testosterone in older men explain higher covid-19 morbidity and mortalities? Int. J. Mol. Sci. 23 (2022).
[7] T. Omar, M. Karayakalı, G. Perincek, Do cardiological characteristics explain the mortality rate disparity between genders in covid-19? E J. Cardiovasc. Med. (2021) 9.
[8] S.E. Petersen, M.G. Friedrich, T. Leiner, et al., Cardiovascular magnetic resonance for patients with covid-19, JACC Cardiovasc. Imaging 15 (2022) 685–699.

[9] V.M. Ferreira, S.K. Piechnik, E. Dall'Armellina, et al., Non-contrast t1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to t2-weighted cardiovascular magnetic resonance, J. Cardiovasc. Magn. Reson. 14 (2012) 1–12.
[10] G.I. Ogbole, A.O. Adeyomoye, A. Badu-Peprah, Y. Mensah, D.A. Nzeh, Survey of magnetic resonance imaging availability in west africa, Pan Afr. Med. J. 30 (2018) 240.
[11] M.Y. Alsagaff, Y.H. Oktaviono, B.B. Dharmadjati, et al., Electrocardiography on admission is associated with poor outcomes in coronavirus disease 2019 (covid-19) patients: a systematic review and meta-analysis, J Arrhythm. 37 (2021) 877–885.
[12] V.O. Puntmann, M.L. Carerj, I. Wieters, et al., Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (covid-19), JAMA Cardiol. 5 (2020) 1265–1273.
[13] J.C. Marshall, S. Murthy, J. Diaz, et al., A minimal common outcome measure set for covid-19 clinical research, Lancet Infect. Dis. 20 (2020) e192–e197.
[14] W.S. Hart, E. Miller, N.J. Andrews, et al., Generation time of the alpha and delta sars-cov-2 variants: an epidemiological analysis, Lancet Infect. Dis. 22 (2022) 603–610.
[15] B. Long, W.J. Brady, R.E. Bridwell, et al., Electrocardiographic manifestations of covid-19, Am. J. Emerg. Med. 41 (2021) 96–103.
[16] A. Yıldırım, İ.O. Karaca, F.K. Yılmaz, H.M. Güneş, B. Çakal, Fragmented qrs on surface electrocardiography as a predictor of cardiac mortality in patients with sars-cov-2 infection, J. Electrocardiol. 66 (2021) 108–112.
[17] T.M. Rosenthal, D. Masvidal, F.M. Abi Samra, et al., Optimal method of measuring the t-peak to t-end interval for risk stratification in primary prevention, Ep Europace. 20 (2018) 698–705.
[18] H. Bazett, An analysis of the time-relations of Heart 7, 1920, p. 353.
[19] S.E. Petersen, N. Aung, M.M. Sanghvi, et al., Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (cmr) in caucasians from the Uk biobank population cohort, J. Cardiovasc. Magn. Reson. 19 (2017) 18.
[20] X. Li, H. Wang, R. Zhao, et al., Elevated extracellular volume fraction and reduced global longitudinal strains in participants recovered from covid-19 without clinical cardiac findings, Radiology 299 (2021) E230–e240.
[21] J. Artico, H. Shiwani, J.C. Moon, et al., Myocardial involvement after hospitalization for covid-19 complicated by troponin elevation: a prospective, multicenter, observational study, Circulation 147 (2023) 364–374.
[22] I.A. Popescu, K. Werys, Q. Zhang, et al., Standardization of t1-mapping in cardiovascular magnetic resonance using clustered structuring for benchmarking normal ranges, Int. J. Cardiol. 326 (2021) 220–225.
[23] S.K. Piechnik, V.M. Ferreira, A.J. Lewandowski, et al., Normal variation of magnetic resonance t1 relaxation times in the human population at 1.5 t using shmolli, J. Cardiovasc. Magn. Reson. 15 (2013) 1–11.
[24] K. Hajian-Tilaki, Receiver operating characteristic (roc) curve analysis for medical diagnostic test evaluation, Caspian J. Intern. Med. 4 (2013) 627.
[25] J. Starekova, D.A. Bluemke, W.S. Bradham, et al., Evaluation for myocarditis in competitive student athletes recovering from coronavirus disease 2019 with cardiac magnetic resonance imaging, JAMA Cardiol. 6 (8) (2021) 945–950.
[26] R. Eiros, M. Barreiro-Pérez, A. Martín-García, et al., Pericardial and myocardial involvement after sars-cov-2 infection: a cross-sectional descriptive study in healthcare workers, Rev Esp Cardiol (Engl Ed). 75 (2022) 734–746.
[27] T. Liu, D. Wu, W. Yan, et al., Twelve-month systemic consequences of coronavirus disease 2019 (covid-19) in patients discharged from hospital: a prospective cohort study in Wuhan, China, Clin. Infect. Dis. 74 (2021) 1953–1965.
[28] M.P. Cassar, E.M. Tunnicliffe, N. Petousi, et al., Symptom persistence despite improvement in cardiopulmonary health – insights from longitudinal cmr, cpet and lung function testing post-covid-19, EClinicalMedicine 41 (2021) 101159.
[29] P.E. Lazzerini, F. Laghi-Pasini, I. Bertolozzi, et al., Systemic inflammation as a novel qt-prolonging risk factor in patients with torsades de pointes, Heart 103 (2017) 1821–1829.
[30] R.A. Evans, O.C. Leavy, M. Richardson, et al., Clinical characteristics with inflammation profiling of long covid and association with 1-year recovery following hospitalisation in the UK: a prospective observational study, Lancet Respir. Med. 10 (2022) 761–775.
[31] P.E. Lazzerini, F. Laghi-Pasini, M. Boutjdir, P.L. Capecchi, Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies, Nat. Rev. Immunol. 19 (2019) 63–64.
[32] C. Antzelevitch, J. Fish, Electrical heterogeneity within the ventricular wall, Basic Res. Cardiol. 96 (2001) 517–527.
[33] A. Riza Demir, Ö. Celik, S. Sevinç, et al., The relationship between myocardial fibrosis detected by cardiac magnetic resonance and tp-e interval, 5-year sudden cardiac death risk score in hypertrophic cardiomyopathy patients, Ann. Noninvasive Electrocardiol. 24 (2019) e12672.
[34] Y. Xie, E. Xu, B. Bowe, Z. Al-Aly, Long-term cardiovascular outcomes of covid-19, Nat. Med. 28 (2022) 583–590.
[35] Z. Raisi-Estabragh, J. Cooper, A. Salih, et al., Cardiovascular disease and mortality sequelae of covid-19 in the UK biobank, Heart 109 (2023) 119–126.
[36] J. Vicente, L. Johannesen, L. Galeotti, D.G. Strauss, Mechanisms of sex and age differences in ventricular repolarization in humans, Am. Heart J. 168 (749–756) (2014) e743.