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Repolarization abnormalities on admission predict 1-year outcome in COVID-19 patients

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ABSTRACT

Background: ECG abnormalities in COVID-19 have been widely reported, however data after discharge is limited. The aim was to describe ECG abnormalities on admission and following recovery of COVID-19, and their associated mortality.

Methods: All patients hospitalized in a tertiary care hospital between March 7th and July 1st 2020 with COVID-19 were included in a retrospective registry. The first ECG on admission was collected, together with an ECG after hospital discharge in the absence of acute pathology. Automated measures and clinical ECG interpretations were collected. Multivariate Cox regression analysis was performed to predict 1-year all-cause mortality.

Results: In total 420 patients were included, of which 83 patients (19.8%) died during the 1-year follow-up period. Repolarization abnormalities were present in 189 patients (45.0%). The extent of repolarization abnormalities was an independent predictor of 1-year all-cause mortality (HR per region 1.30, 95%CI 1.04–1.64) together with age (/year HR 1.06, 95%CI 1.04–1.08), heart rate (/bpm HR 1.02, 95%CI 1.01–1.03), neurological disorders (HR 2.41, 95%CI 1.47–3.93), active cancer (HR 2.75, 95%CI 1.57–4.82), CRP (per 10 mg/L HR 1.05, 95%CI 1.02–1.08) and eGFR (per 10 mg/L HR 0.90, 95%CI 0.83–0.98).

In 245 patients (68.1%) an ECG post discharge was available. New repolarization abnormalities were more frequent in patients who died after discharge (4.7% versus 41.7%, $p < 0.001$) and 8 (3.3%) had new ventricular conduction defects, none of whom died during follow-up.

Conclusions: The presence and extent of repolarization abnormalities predicted outcome in patients with COVID-19. New repolarization abnormalities after discharge were associated with post-discharge mortality.

1. Introduction

In March 2020 the World Health Organization declared a pandemic after a viral infection originating in Wuhan, China, spread worldwide [1]. The SARS-CoV-2 virus has put an enormous pressure on healthcare as 20% develops Coronavirus disease-2019 (COVID-19). COVID-19 has shown deleterious clinical outcomes, particularly in older populations with pre-existing comorbidities [2]. In the meantime several viral variants with increased transmissibility or virulence have emerged and continue to prolong the SARS-CoV-2 pandemic [3].

Myocardial involvement has been described extensively and the underlying pathophysiology include viral myocarditis, demand–supply ischemia due to shock and hypoxemia and microvascular pathology due to hypercoagulable state [4]. A routine 12-lead electrocardiogram (ECG) is an easily accessible tool to assess cardiac involvement and the presence of arrhythmias, and to monitor treatment-related side effects such

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as QTc prolongation [5]. ECG abnormalities in COVID-19 have been widely described, but literature on the predictive value of a 12-lead ECG and normalization of these abnormalities after infection is limited.

The aim of this study is to describe ECG abnormalities on admission and their potential to risk stratify patients for adverse outcomes, as well as assessing recovery of ECG abnormalities in COVID-19 survivors.

2. Methods

2.1. Study population

All adult patients aged 18 years or older who were admitted to the University Hospitals Leuven, Belgium, with SARS-CoV-2 infection during the first wave of the pandemic, between March 7th and July 1st, 2020, were included in a prospective registry and analyzed retrospectively. Diagnosis was based on a compatible clinical presentation, a positive polymerase-chain-reaction (PCR) assay of a nasopharyngeal, oropharyngeal or bronchoalveolar sample and/or computerized tomography (CT) findings indicative of COVID-19 pneumonia. Diagnoses were reviewed and confirmed by the Infectious Disease Department. The study was approved by the ethical committee of the University Hospitals of Leuven.

2.2. Electrocardiographic analysis

The index ECG was defined as the first ECG performed upon admission for COVID-19 and was collected using the MUSE Cardiology Information System (GE Medical Systems, Menomonee Falls, WI, USA). ECGs performed after hospital discharge and in the absence of acute pathology, were collected and classified as the post-COVID ECG. All ECGs were recorded using standard settings (25 mm/s paper speed, 10 mm/mV amplitude and 250 Hz sampling rate) and analyzed by the 'GE Marquette 12SL^{TM} ECG Analysis Program' (GE Medical Systems, Menomonee Falls, WI, USA). All ECGs were inspected visually for quality and rhythm, rejecting ECGs with missing leads and excessive noise potentially interfering with analysis. Manual over-reading of automated measurements and rhythm was performed by an experienced cardiologist (BV). Patients with ventricular pacing were excluded from this analysis.

The ECG Analysis Program automatically collected heart rate, PR-interval, QRS-duration and QT-interval. The QT-interval was measured in a median complex from the earliest detection of depolarization in any lead to the latest detection of repolarization in any lead. QT correction was performed using a previously described and validated patient-specific QT correction algorithm (QTcA) based on the superior heart rate of Fridericia's correction formula in patients without conduction delay, and Rautaharju's correction formula in patients with conduction delay [6]. Ventricular conduction delay was categorized as fascicular (left anterior and posterior fascicular block, LAFB and LPFB respectively), incomplete left (iLBBB) or right bundle branch block (iRBBB), left bundle branch block (LBBB), right bundle branch block (RBBB) and bifascicular block.

QRS fragmentation (fQRS) was defined according to QRS-duration $\leq$ 120 ms or $>$ 120 ms. In patients with QRS-duration $\leq$ 120 ms fQRS was defined as the presence of any RSR' pattern, $\geq$1 R prime or notching of R or S wave [7]. In case of QRS-duration $>$ 120 ms, fQRS was defined as various RSR' patterns with or without a Q wave, with $>$ 2 R waves (R') or $>$ 2 notches in the R wave, or $>$ 2 notches in the downstroke or upstroke of the S wave [8]. fQRS was considered to be present when recorded in $\geq$ 2 contiguous leads as divided by coronary artery territory: anterior as V1 to V5, lateral as I, aVL and V6 and inferior as II, III and aVF [7].

For all ECGs the presence of atrial enlargement or ventricular hypertrophy was assessed. Left atrial enlargement (LAE) was defined as a widely notched P-wave ($\geq$40 ms) with a total duration $\geq$ 120 ms in lead II in combination with a biphasic P-wave in V1 with a terminal negative component [9]. Right atrial enlargement (RAE) was defined as a tall upright P-wave in lead II ($>$2.5 mm) in combination with a prominent upright first part of the P-wave in V1 ($\geq$1.5 mm) [9]. Biatrial enlargement was diagnosed if abnormalities with both left and right atrial enlargement were present [9]. Left ventricular hypertrophy (LVH) was defined using the Sokolov-Lyon criteria (S V1 + R V5 or V6 $>$ 35 mm), or if the R-wave in lead I was $>$ 15 mm or $>$ 11 mm in lead aVL [9]. Right ventricular hypertrophy (RVH) was defined as the strict combination of an increased R:S ratio in V1 ($>$1.0) and a reduced R:S ratio in V5 ($<$0.75) or V6 ($<$0.4) [9].

Repolarization abnormalities were categorized as minor or major. Minor abnormalities included *iso*-electric T-waves (excluding lead III and V1), and minor ST-depression $\leq$ 2 mm [10]. Isoelectric T-waves were defined as a T-wave amplitude between + 1 and −1 mm compared to the baseline [11]. Major repolarization abnormalities were significant ST-depression $>$ 2 mm, ST-elevation, biphasic T-waves and T-wave inversion (excluding lead III, aVR and V1). Inverted T-waves were defined as a T-wave amplitude $\leq$ −1 mm [11]. Findings were scored for each lead and similar coronary artery territories were used to define anterior, lateral and inferior regions as described above.

2.3. Clinical data and outcomes

Demographic and clinical data were collected by review of electronic medical records. Clinical data included the medical history, clinical presentation of SARS-CoV-2 infection, performed diagnostic tests, hospital admission and discharge dates. Heart failure was defined based on the electronic medical record or echocardiographic reports as a combination of heart failure with reduced, moderately reduced and preserved left ventricular function. The results of the first blood test upon admission were collected for complete blood count, C-reactive protein (CRP), estimated glomerular filtration rate (eGFR), D-dimers, high-sensitive Troponin T (hs-TnT) and arterial lactate. Further, admission to the intensive care unit (ICU) was registered, including extra-corporeal membrane oxygenation (ECMO) and the maximal need for ventilatory support assigned as high flow oxygen therapy, non-invasive and invasive mechanical ventilation. Patients were offered a follow-up outpatient clinic visit $\geq$ 6 weeks following discharge at the Pulmonology Department, including a 12-lead ECG, if they were admitted at the ICU or symptomatic, mobile patients aged $\leq$ 75 years of age.

The primary endpoints of the study were in-hospital all-cause mortality and 1-year all-cause mortality. Survival status was retrieved from the hospital's electronic medical record, which is linked with the national death registry, and last updated on July 4, 2021. Readmission rate for acute pathology was obtained by record review, excluding scheduled surgeries or ongoing treatments requiring admissions.

2.4. Statistical analysis

Continuous variables were tested for normal distribution by the -Kolmogorov-Smirnov test. As the majority of parameters showed a non-normal distribution, data are presented as medians with the 25th and 75th percentiles. Categorical variables are presented as number and percentages. Continuous variables were compared using non-parametric Mann-Whitney-U and Kruskal-Wallis testing when appropriate. Categorical variables were compared using Chi^2 testing. Kaplan–Meier analysis with log-rank testing was used to compare endpoint rates. Cox proportional-hazards regression modeling was performed presenting hazard ratios with the 95% confidence intervals. First, univariate analysis was performed for all variables. Subsequently, stepwise forward multivariate modelling was performed based on variables with a univariate p-value $<$ 0.100. Uni- and multivariate binary logistic regression using demographics, medical history and ECG information was performed in a similar way to identify independent predictors of repolarization abnormalities. A p-value $<$ 0.05 was considered significant. In case of missing data and a significant univariate p-value, for example

blood results, these parameters were selectively removed if the p-value for adding this parameter in the next step was not significant. This was repeated until a final model was obtained. Given the potential interaction between ventricular conduction delays and the presence of repolarization abnormalities, a sensitivity analysis was performed by excluding all patients with a QRS duration > 120 ms. All statistical analyses were performed using SPSS (IBM statistics, version 25).

3. Results

A total of 485 patients were hospitalized with COVID-19, of which 420 patients were included in the current analysis (Fig. 1). The median age on admission was 68.0 years (IQR 57.0–81.0) and 57% were male. A total of 83 patients (19.8%) died during the 1-year follow-up period, of which 60 (14.3%) during the initial hospital admission. The median hospital stay of the index admission was 11.0 days (IQR 6.0–19.8). Baseline characteristics according to survival status are presented in Table 1.A.

3.1. Index ECG

In 97.4% of patients the index ECG was obtained within 48 h after hospital admission. Upon admission, 371 patients (88.3%) were in normal sinus rhythm with a median heart rate of 84.0 bpm (IQR 72.0–96.0). A first-degree AV-block was present in 32 patients (7.6%). Ventricular conduction defects defined as QRS duration > 120 ms were present in 43 patients (10.2%), of which 12 LBBB (2.9%), 13 RBBB (3.1%) and 17 with bifascicular block (4.1%). fQRS was present in 85 patients (20.2%), most frequent in the inferior leads (17.4%) followed by lateral (3.8%) and anterior (2.9%). Only 14 patients (3.3%) fulfilled the strict criteria for RAE, whereas 37 patients (8.8%) had LAE and 17 (4.0%) had LVH. There were no patients with a QRS duration < 120 ms who fulfilled the criteria for RVH.

Abnormal repolarization was present in 189 patients (45.0%). In 81 patients (19.3%) this was limited to minor repolarization abnormalities, whereas in 108 patients (25.7%) major repolarization abnormalities were present. Two patients (0.5%) were admitted with an acute ST-elevated myocardial infarction. In 111 patients (26.4%) abnormal repolarization was limited to a single coronary artery territory, in 57 (13.6%) in 2 territories, and in 21 patients (5.0%) in each myocardial region. Table 1.B presents baseline characteristics according to the presence of repolarization abnormalities. A similar table comparing minor and major repolarization abnormalities can be found in Supplement 1. An older age (OR /year 1.02, 95% CI 1.01–1.04), history of coronary artery disease (OR 2.07, 95% CI 1.09–3.96), ventricular conduction defects on the index ECG (OR 3.30, 95% CI 1.53–7.10) and absence of sinus rhythm (OR 0.44, 95% CI 0.22–0.90) were independent predictors of repolarization abnormalities in binary logistic regression (Supplement 2).

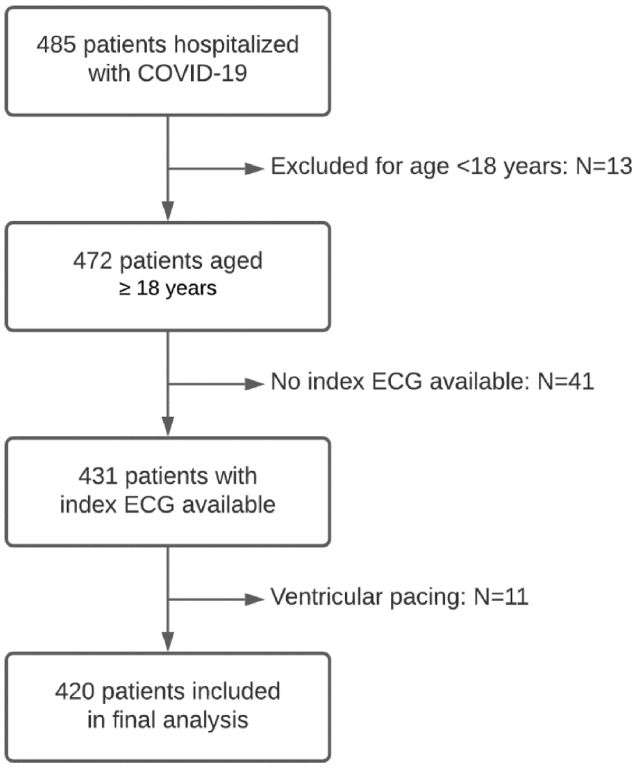

Fig. 1. Study flowchart.

3.2. All-cause mortality

The overall 1-year survival rate was 80.2% (Fig. 2.A). The electrocardiographic changes on index ECG, biochemistry results and differences in hospital stay according to survival status are presented in Table 1.A. In general, patients who had died during follow-up were significantly older, had a higher prevalence of cardiovascular medical history and a (recent) history of cancer. On the index ECG they presented less often with sinus rhythm, had a higher heart rate and a higher prevalence of abnormal repolarization, both minor and major abnormalities (Fig. 2.B). The extent of the repolarization abnormalities was also significantly larger in patients who had died during follow-up. Further, they had a lower hemoglobin, lower eGFR and higher D-dimers and hs-TnT levels on the first blood results after admission.

The in-hospital survival rate was 85.7%. A multivariate Cox regression model for in-hospital mortality identified the extent of repolarization abnormalities also as an independent predictor of in-hospital mortality with a HR of 1.47 (95% CI 1.13–1.90), together with an older age, history of neurological disorders and a reduced renal function (Table 2.A).

Multivariate Cox regression analysis identified a higher heart rate and the extent of repolarization abnormalities on the index ECG as independent predictors of 1-year all-cause mortality, together with an older age, history of neurological disorders, active cancer, a higher CRP and reduced renal function (Table 2.B). For each coronary artery territory with repolarization abnormalities, the risk of mortality increased by 30% (HR 1.30, 95% CI 1.04–1.64). The event rate after hospital discharge was too low to perform separate Cox regression modelling for mortality after hospital discharge.

Similar multivariate Cox regression models analyzing minor and major repolarization abnormalities separately resulted in borderline non-significant HR for both variables (1-year mortality: HR 1.66 (95% CI 0.94–2.95) for minor repolarization abnormalities; HR 1.60 (95% CI 0.93–2.76) for major repolarization abnormalities). The sensitivity analysis for ventricular conduction delays for in-hospital and 1-year mortality revealed similar findings and supports the association between repolarization abnormalities and mortality.

3.3. Electrocardiographic changes after hospital discharge

A total of 360 patients were followed after hospital discharge, of which 99 (27.5%) were readmitted with acute pathology during the 1-year follow-up. As described above, 23 patients (6.4%) died after hospital discharge, of which 14 (3.9%) died during a re-admission. The causes of mortality were infection (n = 7), oncological disease (n = 6), non-sudden cardiac death (n = 2), stroke (n = 1), end-stage liver disease (n = 1) and for 6 patients the cause of death was unknown.

In 245 patients (68.1%) there was an ECG post hospital discharge available after a median of 53.0 days (IQR 38.0–72.5). New ECG abnormalities on the ECG post discharge when compared to the index ECG are summarized stratified by mortality in Supplement 3. A new first-

Table 1.A
Baseline characteristics for survival status.

		Survivors (N = 337, 80.2%)	In-hospital mortality (N = 60, 14.3%)	Post-discharge mortality (N = 23, 5.5%)	P-value
Baseline demographics and medical history	Age (y)	64.0 (54.0–76.0)	81.5 (72.0–88.0)	87.0 (72.0–90.0)	<0.001
	Female	146 (43.3%)	19 (31.7%)	14 (60.9%)	0.046
	BMI (kg/m^2)	26.4 (24.0–30.6)	27.4 (23.8–29.2)	23.8 (22.3–29.2)	0.074
	Arterial hypertension	166 (49.3%)	39 (65.0%)	16 (69.6%)	0.020
	Diabetes Mellitus	107 (31.8%)	22 (36.7%)	7 (30.4%)	0.739
	TIA / stroke	32 (9.5%)	11 (18.3%)	5 (21.7%)	0.039
	Atrial fibrillation	48 (14.2%)	22 (36.7%)	5 (21.7%)	<0.001
	Coronary artery disease	39 (11.6%)	14 (23.3%)	4 (17.4%)	0.043
	Heart failure	15 (4.5%)	10 (16.7%)	3 (13.0%)	0.001
	ILD / COPD / Asthma	40 (11.9%)	7 (11.7%)	6 (26.1%)	0.135
	Neurological disorders	57 (16.9%)	20 (33.3%)	3 (13.0%)	0.009
	Cancer: Previous	47 (13.9%)	7 (11.7%)	5 (21.7%)	<0.001
	Active	25 (7.4%)	8 (13.3%)	8 (34.8%)	
	Smoking: Never	158 (54.7%)	22 (51.2%)	8 (44.4%)	0.807
	Former	111 (38.4%)	19 (44.2%)	8 (44.4%)	
	Current	20 (6.9%)	2 (4.7%)	2 (11.1%)	
Electrocardiographic analysis	Sinus rhythm	312 (92.6%)	40 (66.7%)	19 (82.6%)	<0.001
	Heart rate (bpm)	83.0 (72.0–94.0)	91.0 (78.5–108.0)	83.0 (70.0–109.0)	0.005
	PR-interval (ms)	150.0 (136.0–168.0)	160.0 (139.0–183.5)	156.0 (145.0–176.0)	0.369
	QRS duration (ms)	88.0 (80.0–98.0)	87.0 (78.5–112.0)	86.0 (82.0–110.0)	0.827
	QTcA (ms)	415.5 (398.4–432.5)	421.3 (391.0–449.4)	427.5 (397.9–452.8)	0.226
	QRS > 120 ms	31 (9.2%)	9 (15.0%)	3 (13.0%)	0.355
	LAFB / LPFB	19 (5.6%)	9 (15.0%)	4 (17.4%)	0.011
	iRBBB	31 (9.2%)	3 (5.0%)	0 (0.0%)	
	RBBB	9 (2.7%)	4 (6.7%)	0 (0.0%)	
	iLBBB	0 (0.0%)	1 (1.7%)	0 (0.0%)	
	LBBB	11 (3.3%)	1 (1.7%)	0 (0.0%)	
	Bifascicular block	10 (3.0%)	4 (6.7%)	3 (13.0%)	
	fQRS	71 (21.1%)	12 (20.0%)	2 (8.7%)	0.360
	1 region	59 (17.5%)	10 (16.7%)	1 (4.3%)	0.812
	2 regions	11 (3.3%)	2 (3.3%)	1 (4.3%)	
	3 regions	1 (0.3%)	0 (0.0%)	0 (0.0%)	
	Right atrial enlargement	11 (3.5%)	2 (5.0%)	1 (5.3%)	0.843
	Left atrial enlargement	30 (9.6%)	4 (10.0%)	3 (15.8%)	0.680
	Left ventricular hypertrophy	11 (3.3%)	4 (6.8%)	2 (8.7%)	0.230
	Abnormal repolarization	134 (39.8%)	41 (68.3%)	14 (60.9%)	<0.001
	Minor	59 (17.5%)	15 (25.0%)	7 (30.4%)	<0.001
	Major	75 (22.3%)	28 (43.3%)	7 (30.4%)	
	Extent: 1 region	83 (24.6%)	19 (31.7%)	9 (39.1%)	<0.001
	2 regions	39 (11.6%)	15 (25.0%)	3 (13.0%)	
	3 regions	12 (3.6%)	7 (11.7%)	2 (8.7%)	
Biochemistry*	Hemoglobin (g/dL, 99.3%)	13.4 (12.0–15.0)	13.0 (10.6–14.5)	11.0 (9.6–12.2)	<0.001
	Platelets (10^9/L, 98.8%)	207.0 (159.0–284.5)	179.0 (137.5–235.8)	215.0 (145.0–299.0)	0.038
	WBC (10^9/L, 99.0%)	6.3 (4.6–8.0)	7.2 (5.3–10.9)	6.4 (4.6–11.0)	0.016
	CRP (mg/L, 99.3%)	59.5 (19.8–115.0)	75.3 (51.0–147.3)	55.8 (18.7–127.0)	0.013
	eGFR (mL/min, 99.0%)	79.0 (57.5–96.5)	44.5 (30.0–78.8)	54.0 (39.0–85.0)	<0.001
	D-dimers (ng/mL, 59.0%)	832.0 (540.3–1326.3)	1212.0 (695.5–3266.0)	1895.0 (1206.0–2738.0)	<0.001
	hs-TnT (μg/L, 91.0%)	0.013 (0.007–0.024)	0.040 (0.026–0.075)	0.035 (0.022–0.091)	<0.001
	Lactate (mmol/L, 71.0%)	1.0 (0.7–1.3)	1.3 (1.1–2.0)	1.1 (1.0–1.5)	<0.001
Outcome	Hospital stay (d)	12.0 (7.0–21.0)	8.0 (5.0–16.8)	11.0 (8.0–19.0)	0.046
	ICU admission	100 (29.7%)	15 (25.0%)	2 (8.7%)	0.082
	Ventilation: Optiflow	6 (1.8%)	1 (1.7%)	0 (0.0%)	0.266
	Non-invasive	21 (6.2%)	0 (0.0%)	0 (0.0%)	
	Invasive	58 (17.2%)	12 (20.0%)	2 (8.7%)	
	ECMO	9 (2.7%)	4 (6.7%)	0 (0.0%)	0.175

* Biochemistry values with availability in percentage.
Abbreviations: BBB: bundle branch block BMI: body mass index COPD: chronic obstructive pulmonary disease CRP: C-reactive protein ECMO: extracorporeal membrane oxygenation eGFR: estimated glomerular filtration rate fQRS: fragmented QRS hs-TnT: high-sensitive troponin T ICU: intensive care unit ILD: interstitial lung disease QTcA: corrected QT interval with validated algorithm TIA: transient ischemic attack WBC: white blood cell count

degree AV-block was present in 1 patient (0.4%), whereas new ventricular conduction defects were present in 8 patients (3.3%), of which 1 new RBBB and 1 new LBBB. New fQRS was present in 10 patients (4.1%), none of whom died during follow-up. New repolarization abnormalities were present in 16 patients (6.5%), 5 of whom had died ($p < 0.001$). Kaplan-Meier analysis showed no association between repolarization abnormalities on the index ECG and post-discharge mortality ($p = 0.638$, Supplement 4). Whereas new repolarization abnormalities on the post-discharge ECG were associated with post-discharge mortality ($p < 0.001$), however only 12 (52.2%) of patients with post-discharge

Table 1.B
Baseline characteristics for repolarization abnormalities.

		Normal repolarization (N = 231, 55.0%)	Abnormal repolarization (N = 189, 45.0%)	P-value
Baseline demographics and medical history	Age (y)	63.0 (54.0–75.0)	74.0 (62.0–85.0)	<0.001
	Female	94 (40.7%)	85 (45.0%)	0.377
	BMI (kg/m^2)	26.3 (23.9–29.9)	26.6 (23.8–31.2)	0.489
	Arterial hypertension	109 (47.2%)	112 (59.3%)	0.014
	Diabetes mellitus	71 (30.7%)	65 (34.4%)	0.426
	TIA / stroke	18 (7.8%)	30 (15.9%)	0.010
	Atrial fibrillation	26 (11.3%)	49 (25.9%)	<0.001
	Coronary artery disease	17 (7.4%)	40 (21.2%)	<0.001
	Heart failure	8 (3.5%)	20 (10.6%)	0.004
	ILD / COPD / Asthma	28 (12.1%)	25 (13.2%)	0.734
	Neurological disorders	43 (18.6%)	37 (19.6%)	0.803
	Cancer: Previous	34 (14.7%)	25 (13.2%)	0.314
	Active	18 (7.8%)	23 (12.2%)	
	Smoking: Never	105 (53.8%)	83 (53.5%)	0.263
	Former	73 (37.4%)	65 (41.9%)	
	Current	17 (8.7%)	7 (4.5%)	
Electrocardiographic analysis	Sinus rhythm	217 (93.9%)	154 (81.5%)	<0.001
	Heart rate (bpm)	83.0 (73.0–94.0)	85.0 (70.0–98.0)	0.519
	PR-interval (ms)	150.0 (136.0–170.0)	153.0 (138.0–172.0)	0.459
	QRS duration (ms)	86.0 (80.0–96.0)	90.0 (82.0–110.5)	0.007
	QTcA (ms)	412.8 (398.8–433.5)	420.4 (396.9–438.4)	0.264
	QRS > 120 ms	10 (4.3%)	33 (17.5%)	<0.001
	LAFB / LPFB	12 (5.2%)	20 (10.6%)	<0.001
	iRBBB	22 (9.5%)	12 (6.3%)	
	RBBB	4 (1.7%)	9 (4.8%)	
	iLBBB	0 (0.0%)	1 (0.5%)	
	LBBB	0 (0.0%)	12 (6.3%)	
	Bifascicular block	5 (2.2%)	12 (6.3%)	
	fQRS	42 (18.2%)	43 (22.8%)	0.246
	1 region	35 (15.2%)	35 (18.5%)	0.504
	2 regions	7 (3.0%)	7 (3.7%)	
	3 regions	0 (0.0%)	1 (0.5%)	
	Right atrial enlargement	10 (4.6%)	4 (2.6%)	0.311
	Left atrial enlargement	20 (9.2%)	17 (11.0%)	0.578
	Left ventricular hypertrophy	7 (3.0%)	10 (5.3%)	0.246
Biochemistry*	Hemoglobin (g/dL, 99.3%)	13.6 (12.0–15.0)	13.0 (11.5–14.5)	0.046
	Platelets (10^9/L, 98.8%)	204.0 (161.5–280.0)	200.5 (152.0–286.8)	0.535
	WBC (10^9/L, 99.0%)	6.3 (4.6–8.4)	6.5 (4.7–9.0)	0.657
	CRP (mg/L, 99.3%)	60.2 (20.8–127.5)	62.0 (27.8–110.0)	0.559
	eGFR (mL/min, 99.0%)	81.5 (59.0–98.0)	64.0 (40.8–87.3)	<0.001
	D-dimers (ng/mL, 59.0%)	940.0 (562.0–1518.0)	950.0 (576.0–1516.0)	0.652
	hs-TnT (μg/L, 91.0%)	0.013 (0.007–0.024)	0.020 (0.011–0.043)	<0.001
	Lactate (mmol/L, 71.0%)	1.0 (0.7–1.3)	1.1 (0.7–1.6)	0.579
Outcome	Hospital stay (d)	11.0 (7.0–18.0)	12.0 (6.0–21.0)	0.808
	ICU admission	65 (28.1%)	52 (27.5%)	0.887
	Ventilation: Optiflow	4 (1.7%)	3 (1.6%)	0.900
	Non-invasive	10 (0.3%)	11 (5.8%)	
	Invasive	41 (17.7%)	31 (16.4%)	
	ECMO	8 (3.5%)	5 (2.6%)	0.630
	Mortality	28 (12.1%)	55 (29.1%)	<0.001
	In-hospital	19 (8.2%)	41 (21.7%)	<0.001
	Post-discharge	9 (3.9%)	14 (7.4%)	

* Biochemistry values with availability in percentage.
Abbreviations: BBB: bundle branch block; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; ECMO: extracorporeal membrane oxygenation; eGFR: estimated glomerular filtration rate; fQRS: fragmented QRS; hs-TnT: high-sensitive troponin T; ICU: intensive care unit; ILD: interstitial lung disease; QTcA: corrected QT interval with validated algorithm; TIA: transient ischemic attack; WBC: white blood cell count.

mortality had a post-discharge ECG available.

4. Discussion

In this retrospective cohort of patients from the first wave of the COVID-19 pandemic in Belgium, the index ECG obtained on admission was predictive of clinical outcome. Repolarization abnormalities were present in almost half of the patients, and both minor and major repolarization abnormalities were associated with mortality. The extent of repolarization abnormalities was an independent predictor of in-hospital and 1-year all-cause mortality. Furthermore, following hospital discharge readmission rate for acute pathology was high, and new repolarization abnormalities on ECG after discharge were associated with post-discharge mortality.

The main novelties of this study are the worse outcome associated with minor repolarization abnormalities and the extended 1-year follow-up, including the readmission rate. The predictive value of major repolarization abnormalities has been described extensively in cohort studies of variable size. The presence of repolarization abnormalities on admission ranged from 10.9% to 41.0%, depending on the inclusion criteria and definitions of repolarization abnormalities [12–15]. Whereas Ghio et al. reported a rate of 10.9% in 340 patients, however they did not define the criteria to assess cardiac repolarization [13]. Whereas Poterucha et al. reported a rate of 38% in patients with normal

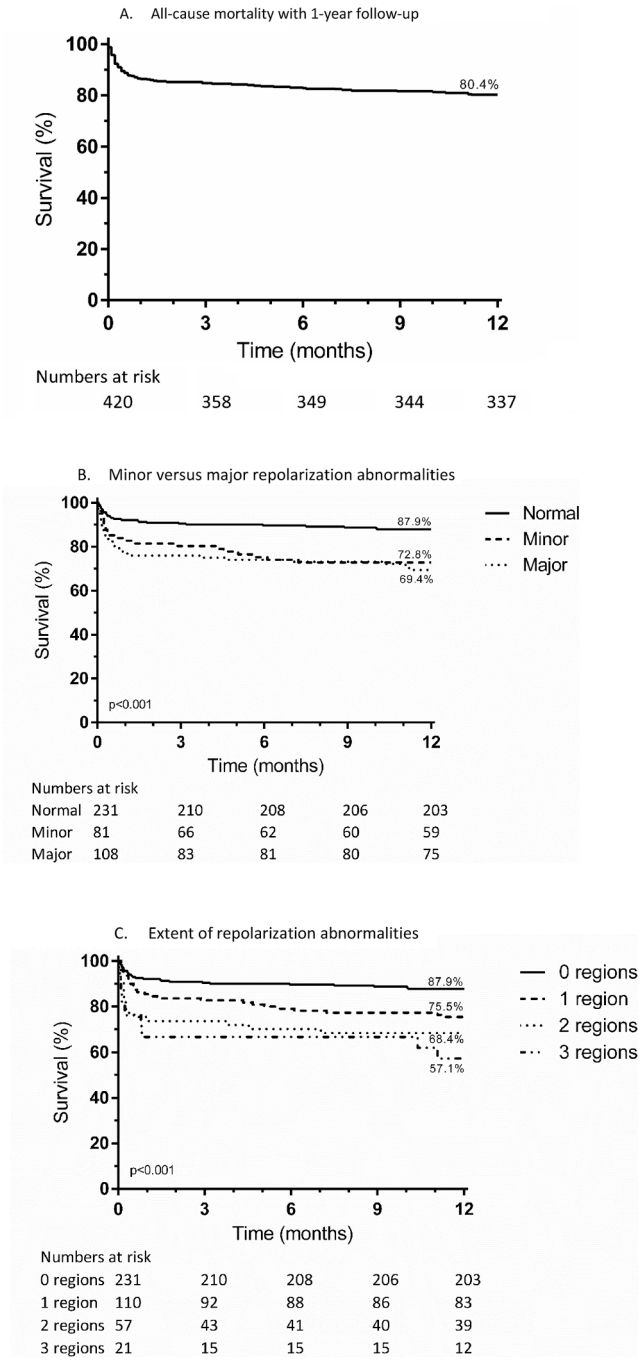

Fig. 2. Kaplan-Meier graphs with log-rank analysis.

QRS duration, and Bertini et al. reported a rate up to 41% in 431 patients who had died or required mechanical ventilation [12,14]. The underlying pathophysiology of repolarization abnormalities includes a spectrum of possible etiologies, such as cytokine storm, myocardial ischemia (including both myocardial infarction and demand ischemia), electrolyte abnormalities, microthrombi, and direct endothelial or myocardial injury [16]. Hence, it is not unexpected that even minor repolarization abnormalities predict outcome in this study, together with well-known predictors such as increasing age, heart rate, renal function and CRP. Although hs-TnT on admission was significantly higher in patients with repolarization abnormalities, as well as in patients who died during hospital admission and after discharge, it was not retained in the Cox regression models. Troponin is easily accessible and can be monitored over time; it is however a generic marker of myocardial damage

Table 2
Cox regression analysis for mortality.

A. In-hospital mortality

	Univariate		Multivariate	
	P-value	HR (95% CI)	P-value	HR (95% CI)
Age (/y)	<0.001	1.07 (1.04–1.09)	<0.001	1.05 (1.02–1.07)
Male sex	0.240	1.39 (0.80–2.41)		
BMI (/kg/m^2)	0.977	1.00 (0.95–1.05)		
Arterial hypertension	0.062	1.67 (0.97–2.86)		
Diabetes mellitus	0.641	1.14 (0.67–1.93)		
TIA / stroke	0.232	1.52 (0.77–3.03)		
Atrial fibrillation	0.001	2.42 (1.41–4.16)		
Coronary artery disease	0.023	2.01 (1.10–3.68)		
Heart failure	0.001	3.22 (1.62–6.40)		
ILD / COPD / Asthma	0.824	0.91 (0.41–2.02)		
Neurological disorders	<0.001	2.68 (1.56–4.62)	<0.001	2.73 (1.58–4.71)
Active cancer	0.273	1.52 (0.72–3.21)		
Sinus rhythm	<0.001	0.26 (0.15–0.44)		
Heart rate (/bpm)	<0.001	1.02 (1.01–1.04)		
PR-interval (/ms)	0.207	1.00 (0.99–1.00)		
QRS duration (/ms)	0.637	1.00 (0.99–1.01)		
QTcA (/ms)	0.869	1.00 (0.99–1.01)		
QRS > 120 ms	0.396	1.36 (0.67–2.78)		
fQRS	0.987	1.01 (0.53–1.90)		
Abnormal repolarization	0.001	2.44 (1.41–4.22)		
Extent of abnormal repolarization (/region)	<0.001	1.66 (1.30–2.11)	0.004	1.47 (1.13–1.90)
Hemoglobin (/g/dL)	0.177	0.93 (0.84–1.03)		
Platelets (/100^9/L)	0.058	0.97 (0.94–1.00)		
WBC (/10^9/L)	0.250	1.01 (1.00–1.01)		
CRP (/10 mg/L)	0.283	1.02 (0.99–1.04)		
eGFR (/10 mL/min)	<0.001	0.80 (0.73–0.88)	0.009	0.87 (0.79–0.97)
D-dimers (/1000 ng/mL)	0.045	1.02 (1.00–1.03)		
hs-TnT (/μg/L)	0.020	1.29 (1.04–1.59)		
Lactate (/mmol/L)	0.052	1.14 (1.00–1.31)		

B. All mortality within 1 year of admission.

	Univariate		Multivariate	
	P-value	HR (95% CI)	P-value	HR (95% CI)
Age (/y)	<0.001	1.07 (1.05–1.08)	<0.001	1.06 (1.04–1.08)
Male sex	0.501	1.16 (0.75–1.81)		
BMI (/kg/m^2)	0.230	0.97 (0.93–1.02)		

(*continued on next page*)

Table 2 (*continued*)

B. All mortality within 1 year of admission.

	Univariate		Multivariate	
	P-value	HR (95% CI)	P-value	HR (95% CI)
Arterial hypertension	0.007	1.88 (1.19–2.96)		
Diabetes mellitus	0.560	1.14 (0.73–1.80)		
TIA / stroke	0.012	2.01 (1.16–3.46)		
Atrial fibrillation	<0.001	2.54 (1.60–4.02)		
Coronary artery disease	0.012	1.95 (1.16–3.29)		
Heart failure	<0.001	3.14 (1.74–5.69)		
ILD / COPD / Asthma	0.399	1.29 (0.71–2.33)		
Neurological disorders	0.015	1.82 (1.12–2.94)	<0.001	2.41 (1.47–3.93)
Active cancer	0.002	2.42 (1.40–4.17)	<0.001	2.75 (1.57–4.82)
Sinus rhythm	<0.001	0.25 (0.16–0.41)		
Heart rate (/bpm)	<0.001	1.03 (1.01–1.04)	<0.001	1.02 (1.01–1.03)
PR-interval (/ms)	0.252	1.00 (0.99–1.00)		
QRS duration (/ms)	0.177	1.01 (0.99–1.02)		
QTcA (/ms)	0.163	1.00 (0.99–1.01)		
QRS >120 ms	0.145	1.58 (0.86–2.91)		
fQRS	0.448	0.80 (0.45–1.42)		
Abnormal repolarization	<0.001	2.66 (1.69–4.19)		
Extent of abnormal repolarization (/region)	<0.001	1.66 (1.35–2.04)	0.024	1.30 (1.04–1.64)
Hemoglobin (/g/dL)	0.005	0.88 (0.81–0.96)		
Platelets (/100^9/L)	0.044	0.98 (0.95–1.00)		
WBC (/10^9/L)	0.580	1.00 (0.99–1.01)		
CRP (/10 mg/L)	0.036	1.03 (1.00–1.05)	0.001	1.05 (1.02–1.08)
eGFR (/10 mL/min)	<0.001	0.79 (0.73–0.85)	0.020	0.90 (0.83–0.98)
D-dimers (/1000 ng/mL)	0.002	1.02 (1.01–1.04)		
hs-TnT (/μg/L)	0.004	1.34 (1.10–1.62)		
Lactate (/mmol/L)	0.002	1.21 (1.07–1.36)		

confounded by age and renal function amongst others. Moreover, it is considered a screening tool; unlike a routine ECG, it does not provide insight in the underlying pathophysiology.

Many small studies have shown associations between ECG abnormalities and outcome. In a retrospective study including 114 patients with COVID-19, QRS duration and presence of fQRS were associated with all-cause and cardiac mortality [17]. Using the same criteria they reported fQRS in 36.8% of patients, whereas in our population fQRS was present in 20.2%. However, even binary fQRS scoring with clear definitions is prone to observer variability [18]. In our study, QRS duration and the presence of ventricular conduction delays were not predictive of mortality. However, the proportion of patients with a QRS duration > 120 ms was only 10.2%. Although this proportion was equal or higher when compared to other studies, these results should be interpreted with caution due to small samples [15,19]. Other studies have assessed the predictive value of right ventricular overload. In the study by Bertini et al., 30% of patients who had died or required mechanical ventilation had signs of right ventricular overload [14]. In a study by Elias et al., which included 1258 patients, right ventricular overload was present in 4% on admission and right ventricular overload was an independent predictor of death or mechanical ventilation within 48 h [20]. In our study no patients fulfilled the strict criteria of right ventricular hypertrophy or S1Q3T3 on admission. Also, ECG findings upon admission may not be very specific for COVID-19 infection as every acute pathology may cause similar changes. De Vita et al. compared the ECG on admission of 324 patients with COVID-19 with these of 232 patients with other acute respiratory infections [19]. The prevalence of ECG abnormalities was similar between groups with 37.0% versus 43.5%, respectively ($p = 0.13$).

So far, only a few studies have reported long-term outcome after COVID-19 infection with rate depending on the population selected and the follow-up period. Huang et al. reported 6 months outcome form a large cohort of 1733 patients discharged after COVID infection from a hospital in the Wuhan province, China [21]. The mortality rate after hospital discharge was 1.3% at 6 months, whereas in our registry the corresponding rate was 3.9%. Maestrini et al. reported a 1-year outcome in patients with confirmed cardiovascular involvement [22]. Of the 120 COVID-19 survivors who were discharged from the hospital, 47.5% reported symptoms, 9.3% were readmitted and none had died. Their readmission rate was much lower compared to the 27.5% in our registry. Although the median age was comparable, the prevalence of atrial fibrillation and neurological disorders was higher in our population.

The true long-term cardiovascular outcome after COVID-19 should preferably be assessed with prospective, observational, longitudinal cohort studies. An excellent example is the COVID-HEART study which is a multi-center study including patients with confirmed COVID-19 and elevated troponin levels [23]. Baseline assessment in the COVID-HEART study will include cardiac magnetic resonance imaging, serial ECG, biomarkers, genetics and quality of life assessment.

5. Limitations

The main limitation of this study is its single-center retrospective design including patients from the first COVID-19 wave only. The analysis was intentionally restricted to the index ECG on first admission with COVID-19. Although it would be of interest to correlate ECG changes and arrhythmias during the index admission, the latter would require continuous ECG monitoring to avoid underestimation of the incidence of arrhythmias. Moreover, studying ECG changes during admission would require adjustment for potential confounders, such as QT-prolonging medication, inclusion in clinical trials, sedation or ventilation. Only a limited number of patients had an ECG prior to the index admission, but some patients might have had pre-existing repolarization abnormalities. There might be a value for echocardiography to assess myocardial involvement, however during the first COVID-19 wave these were not easily accessible. Different studies have used different ECG criteria which may limit their comparability. The cut-off 2 mm for ST-depression was chosen as this cut-off has been shown to be a better predictor of myocardial ischemia during exercise testing [10].

6. Conclusion

The 12-lead ECG obtained on admission for COVID-19 can be used to risk stratify patients for mortality. Repolarization abnormalities were common, and both minor and major abnormalities were associated with mortality. The extent of repolarization abnormalities was an independent predictor of both in-hospital and 1-year all-cause mortality. Also, new repolarization abnormalities after hospital discharge were associated with poor outcome during further follow-up. Therefore, baseline ECG upon hospital admission and serial ECGs during follow-up after COVID-19 infections would be recommended.

Authorship statement

All authors should have made substantial contributions to the manuscript and all authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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CRediT authorship contribution statement

Bert Vandenberk: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Matthias M. Engelen:** Methodology, Investigation, Writing – review & editing. **Greet Van De Sijpe:** Methodology, Investigation, Writing – review & editing. **Jonas Vermeulen:** Conceptualization, Resources, Writing – review & editing, Supervision. **Stefan Janssens:** . **Thomas Vanassche:** Conceptualization, Writing – review & editing. **Peter Verhamme:** Conceptualization, Resources, Writing – review & editing. **Paul De Munter:** Conceptualization, Resources, Writing – review & editing. **Natalie Lorent:** Conceptualization, Resources, Writing – review & editing. **Rik Willems:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision.

Declaration of Competing Interest

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Appendix A. Supplementary data

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