Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Electrocardiology 75 (2022) 10–18

Contents lists available at ScienceDirect

Journal of Electrocardiology

journal homepage: www.jecgonline.com

The role of admission electrocardiogram in predicting outcome in patients hospitalized for COVID-19

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ARTICLE INFO

Keywords:
Electrocardiogram
COVID-19
Intensive care unit
Death

ABSTRACT

Background: Abnormal electrocardiogram (ECG) has been associated with poor outcome in patients hospitalized for COVID-19. However, the *independent* association between admission ECG and the risk of a poor outcome remains to be established. Our aim was to determine if abnormal admission ECG predicts treatment at intensive care unit or in-hospital death within 30 days in patients hospitalized for COVID-19.

Methods: We analyzed the propensity weighted association between abnormal admission ECG and outcome in patients hospitalized for COVID-19 (March to May 2020). All adult patients hospitalized for COVID-19 at the three centers of Sahlgrenska University Hospital (Gothenburg, Sweden) were eligible for inclusion ($N = 439$). Patients with available admission ECG within six hours from admission were included.

Results: 238 patients (age 62 ± 16 years, 74% male) were included. 103 patients had normal ECG and 135 patients had abnormal ECG. 99 patients were admitted to intensive care unit or died in-hospital within 30 days. Abnormal ECG was associated with increased risk of the outcome (odds ratio 2.11 [95% confidence interval 1.21–3.66]).

Conclusions: Abnormal admission ECG was associated with increased risk of treatment at intensive care unit or in-hospital death within 30 days; and could be considered a high-risk criterion in patients hospitalized for COVID-19.

Introduction

To date, the global Coronavirus disease 2019 (COVID-19) pandemic has resulted in over 588 million confirmed cases and caused over 6.4 million deaths worldwide [1]. Cardiovascular implications of COVID-19 has been observed since the earliest phases of the pandemic [2,3]. There are several suggested pathways to explain the cardiac involvement in COVID-19 but connection to the angiotensin-converting enzyme 2 receptor (ACE2) forms the basis of many theories [4].

Recent compiled research suggests myocardial injury (significantly elevated cardiac Troponin) to be common in COVID-19-patients and substantially more common for ACE2-binding viruses compared with non-ACE2-binding viruses [5]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, binds with high affinity to ACE2 in the process of entering the infected cell. Although mainly expressed in the lungs, ACE2 is also highly expressed in myocardial cells. Inhibition of ACE2, which leads to accumulation of angiotensin II, has been suggested as a pathway for direct cardiac involvement in COVID-19 [6–8]. Acute myocarditis caused by SARS-CoV-2 seems rare; and acute myocardial infarction (AMI) or pulmonary embolism has been observed in COVID-19, but also in association with other infections triggering substantial immune response [6].

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https://doi.org/10.1016/j.jelectrocard.2022.10.005

Available online 17 October 2022

In previous research, 12-lead electrocardiogram (ECG)-abnormalities have been associated with poor outcome in COVID-19 [9]. According to several previous studies, ECG predicted admission to intensive care unit (ICU) and/or death within 20–45 days from admission [10–14].

Previous studies have not presented details regarding time from admission to ECG, and the statistical adjustment has not thoroughly addressed the association between ECG per se and outcome [15–20]. Accounting for this, our aim was to investigate the independent association between abnormal admission ECG and ICU treatment or in-hospital death within 30 days, in patients hospitalized for COVID-19.

Methods

Study cohort

Adult (≥ 18 years of age) COVID-19 patients who were registered as admitted to any of the three centers of Sahlgrenska University Hospital (Gothenburg, Sweden) between March and May 2020 were identified using the International Classification of Disease-10 (ICD-10) code for positive SARS-CoV-2 PCR test (U07.1, $N = 439$). During the time-period of patient inclusion, all patients in Gothenburg with need of in-hospital care with/for COVID-19 were transferred to Sahlgrenska University Hospital; and therefore, all patients treated in-hospital for COVID-19 in Gothenburg were eligible for inclusion. After review of all patients' medical charts, we included patients who were hospitalized *for* COVID-19 (for clinical reasons) and had an available admission ECG within six hours from admission. Exclusion criteria were unconfirmed COVID-19 (negative SARS-CoV-2 PCR test), pacemaker rhythm on admission ECG or not requiring in-hospital care. Not *requiring* in-hospital care refers to clinically unaffected patients who were admitted to hospital only to prevent spread of SARS-CoV-2 (in the earliest phases of the pandemic). Patients were subdivided into those with normal or abnormal ECG *(*Fig. 1*)*. Medical charts and admission ECG were analyzed for all included patients.

Two independent physicians reviewed all included patients and extracted data to a pre-defined case report form. Information regarding baseline characteristics, co-morbidities, admission clinical variables, laboratory work-up, pre-admission medical treatment, in-hospital complications and outcomes were collected from the patients' medical charts.

ECG analysis

All 12-lead ECGs were recorded at a paper speed of 50 mm/s and an amplification of 10 mm/mV. ST-segment deviation was measured manually at the J-point from the isoelectric line to the nearest 0.5 mm. T-wave and Q-wave amplitudes were measured manually from the isoelectric line to peak or nadir to the nearest 0.5 mm. Electronically derived values for heartrate, QRS-duration, QRS-axis and QT-time were chosen if assessed manually as correct. The corrected QT interval (QTc) was calculated using Bazzet's formula. Definitions of all ECG-parameters are summarized in Supplementary Table 1.

Endpoints and definitions

The primary endpoint was the composite of treatment at ICU or in-hospital death within 30 days from admission, versus being discharged alive and not treated at ICU within 30 days. Abnormal ECG was defined as any of heart rate ≤ 50 beats per minute, QRS duration ≥120 milliseconds, QTc interval ≥ 500 milliseconds, abnormal QRS axis, abnormal QRS morphology, low voltage QRS, Q wave pathology, ST elevation ≥1 mm in any two continuous leads, or ST depression ≥1 mm in any two continuous leads, abnormal T wave inversion, non-sinus rhythm or AV block ≥2. An ECG without these abnormalities was defined as a normal ECG. As per routine at Sahlgrenska University Hospital, admission time is automatically registered in the patient's electronical medical chart. The time of admission was defined as at triage for patients admitted through the emergency department, and at admission to hospital ward for patients admitted directly to hospital ward.

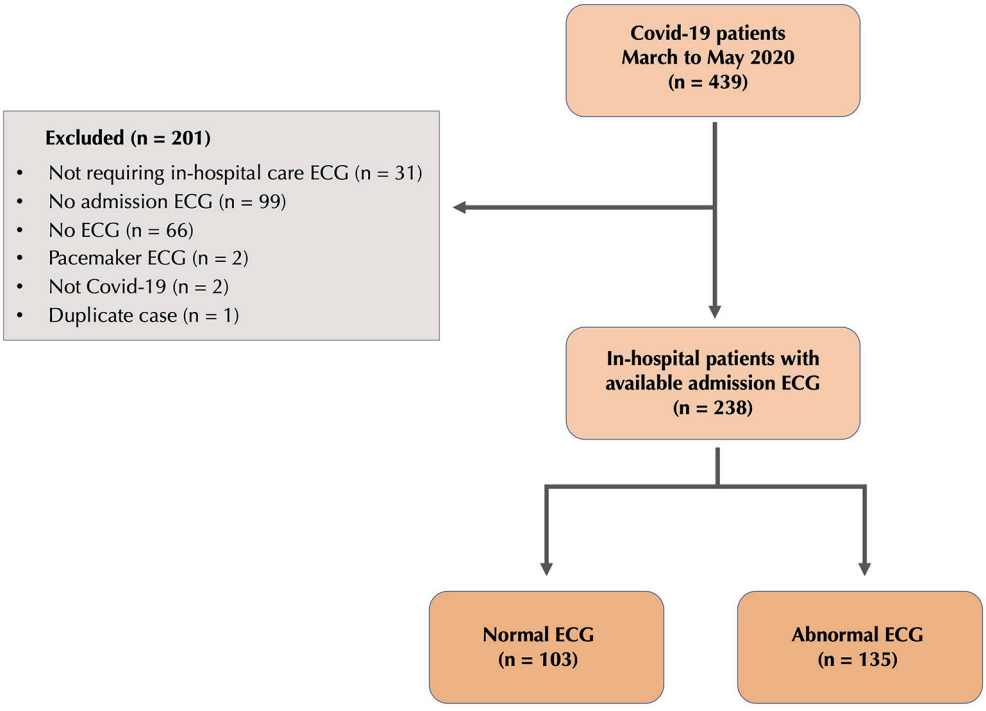

Fig. 1. Patient inclusion flowchart.
ECG = electrocardiogram.

Statistical analysis

Variables are presented as mean ± standard deviations, median and interquartile range, or percentages for categorical variables. Categorical variables were compared using Fischer's Exact test and continuous variables were compared using *t*-test for normally distributed variables and Mann-Whitney *U* Test for non-normally distributed variables.

We imputed missing values using non-parametric multivariate imputation by chained random forest (*missRanger* package in R). We then estimated the average treatment effect (ATE) using propensity scores, comparing those exhibiting an abnormal ECG to all others. We computed propensity scores using a gradient boost model (GBM), a tree-based ensemble method *(TWANG package in R)*. All baseline variables were used as covariates when calculating the propensity scores.

The following 55 baseline variables were used when estimating propensity scores: Age, sex, body mass index; history of diabetes, hypertension, hyperlipidaemia, ischemic heart disease, heart failure, atrial fibrillation, peripheral artery disease, chronic obstructive pulmonary disease, asthma and chronic kidney failure; prior acute myocardial infarction, stroke and venous thromboembolism; active cancer, any dementia, smoking; pre-admission treatment with beta-blockers, anti-arrhythmic agents, digoxin, aspirin, warfarin, direct-acting oral anti coagulants, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium antagonists, statins, P2Y12 inhibitors, mineralocorticoid receptor antagonists, diuretics, oral antidiabetics and oral cortisone; admission blood pressure, heart rate, respiratory rate and saturation without oxygen; oxygen at admission, admission cycle threshold value; presenting with fever, cough, dyspnea, sore throat, nasal congestion, loss of smell, loss of taste, headache, chest pain, abdominal pain, vomiting, diarrhea and disorientation.

Univariable and multivariable logistic regression, as well as propensity score adjusted and propensity score weighted regression models, were used to assess the association between abnormal ECG and the outcome. The regression models are presented as univariable analysis, Model A (adjusted for sex and age as covariates), Model B (adjusted for sex, age, diabetes, and hypertension as covariates), Model C (propensity score adjusted) and Model D (propensity score weighted). To calculate variable importance for age, sex and the ECG changes included in abnormal ECG, we used conditional random forests (*Party package in R)*. The level of significance was set at $P < 0.05$. All statistical analyses were performed using R-studio version 1.4.1103.

This study complies with the declaration of Helsinki. All data was collected retrospectively. No information that was not already available in the patients' medical charts was collected. The Swedish Ethical Review Authority approved the study and the need for individual informed consent was waived (registration number 2020–01569, amendment to 2019–02459).

Results

The study cohort consisted of 238 patients who were hospitalized for COVID-19 and had an available admission ECG. Admission ECG was obtained within two hours for 87% of patients and within four hours for 96% of patients. Of all patients, 103 had normal ECG and 135 had abnormal ECG at admission. Baseline characteristics and presenting symptoms are presented in Table 1.

Baseline characteristics and presenting symptoms

Overall, most patients were male, and patients with abnormal ECG were slightly older than patients with normal ECG. More patients with abnormal ECG than normal ECG had diabetes, hypertension, ischemic heart disease, heart failure with preserved ejection fraction, prior stroke, chronic kidney disease or a history of atrial fibrillation. Also, ongoing pre-admission treatment with beta-blockers, aspirin, direct acting anti coagulants, statins, P2Y12 inhibitors and diuretics were more common

Table 1
Baseline characteristics and presenting symptoms.

Variable	Overall $N = 238$	Normal ECG $N = 103$	Abnormal ECG $N = 135$	SMD
Age (years)	62 ± 16	58 ± 15	65 ± 16	0.43
Age > 60	52% (123/238)	44% (45/103)	58% (78/135)	0.29
Age > 70	32% (76/238)	22% (23/103)	39% (53/135)	0.37
Age > 80	14% (33/238)	8.7% (9/103)	18% (24/135)	0.27
Age > 90	1.7% (4/238)	1.0% (1/103)	2.2% (3/135)	0.10
Male sex % (n/N)	74% (175/238)	74% (76/103)	73% (99/135)	0.010
BMI	28 (24–31)	28 (24–32)	28 (24–30)	0.20
Comorbidities % (n/N)				
Diabetes	23% (54/238)	17% (17/103)	27% (37/135)	0.27
Hypertension	45% (108/238)	36% (37/103)	53% (71/135)	0.34
Hyperlipidemia	16% (39/238)	13% (13/103)	19% (26/135)	0.18
IHD	12% (28/238)	6.8% (7/103)	16% (21/135)	0.28
Prior AMI	8.8% (21/238)	5.8% (6/103)	11% (15/135)	0.19
Prior stroke	14% (32/237)	8.7% (9/103)	17% (23/134)	0.25
Prior VTE	5.0% (12/238)	3.9% (4/103)	5.9% (8/135)	0.095
HFrEF	3.8% (9/237)	2.0% (2/102)	5.2% (7/135)	0.17
HFpEF	2.1% (5/238)	0% (0/103)	3.7% (5/135)	0.28
History of AF	14% (33/238)	6.8% (7/103)	19% (26/135)	0.38
Peripheral artery disease	1.3% (3/238)	0% (0/103)	2.2% (3/135)	0.21
COPD	5.5% (13/238)	4.9% (5/103)	5.9% (8/135)	0.047
Astma	5.9% (14/238)	6.8% (7/103)	5.2% (7/135)	0.068
CKD	5.5% (13/238)	1.0% (1/103)	8.9% (12/135)	0.37
Active cancer[a]	5.0% (12/238)	3.9% (4/103)	5.9% (8/135)	0.095
Any dementia[b]	2.9% (7/238)	1.9% (2/103)	3.7% (5/135)	0.11
Smoking[c]	43% (51/119)	40% (19/47)	44% (32/72)	0.081
Medication at admission % (n/N)				
Beta-blockers	25% (60/236)	18% (18/103)	32% (42/133)	0.33
Anti-arrhythmic agent[d]	0.8% (2/236)	0% (0/103)	1.5% (2/133)	0.18
Digoxin	0.8% (2/236)	0% (1/103)	1.5% (2/133)	0.18
Aspirin	11% (27/236)	6.8% (7/103)	15% (20/133)	0.27
Warfarin	2.5% (6/236)	1.0% (1/103)	3.8% (5/133)	0.18
DOAC	11% (27/237)	6.8% (7/103)	15% (20/132)	0.26
ACE inhibitor	21% (49/236)	17% (17/103)	24% (32/133)	0.19
ARB	13% (30/236)	12% (12/103)	14% (18/133)	0.057
Calcium antagonist	19% (44/236)	17% (17/103)	20% (27/133)	0.098
Statins	28% (65/236)	21% (22/103)	32% (43/133)	0.25
P2Y12 inhibitor				0.34

(*continued on next page*)

Table 1 (*continued*)

Variable	Overall $N = 238$	Normal ECG $N = 103$	Abnormal ECG $N = 135$	SMD
	6.4% (15/236)	1.9% (2/103)	9.8% (13/133)	
MRA	2.5% (6/236)	2.9% (3/103)	2.3% (3/133)	0.041
Diuretics	12% (29/236)	5.8% (6/103)	17% (23/133)	0.37
Oral antidiabetics	18% (43/237)	15% (15/103)	21% (28/134)	0.17
Oral cortisone	5.5% (13/237)	4.9% (5/103)	6.0% (8/134)	0.059
Symptoms and signs at admission				
Systolic BP (mmHg)	127 ± 21	126 ± 21	128 ± 22	0.083
Diastolic BP (mmHg)	77 ± 14	79 ± 13	76 ± 14	0.235
Heart rate (bpm)	97 (82–110)	93 (81–105)	100 (84–112)	0.261
Respiratory rate (brpm)	25 (20−30)	25 (21−30)	25 (20–30)	0.092
Saturation no oxygen %	91 (85–94)	91 (85–93)	92 (85–95)	0.028
Oxygen at admission[e]	71% (167/237)	76% (77/102)	67% (90/135)	0.196
Ct value (cycles)	27 (23−30)	28 (24–30)	27 (22−30)	0.110
Fever % (n/N)[f]	60% (138/232)	63% (63/100)	57% (75/132)	0.13
Cough	79% (188/238)	82% (84/103)	77% (104/135)	0.11
Dyspnea	69% (164/238)	70% (72/103)	68% (92/135)	0.038
Sore throat	14% (33/238)	16% (16/103)	13% (17/135)	0.085
Nasal congestion	3.0% (7/237)	2.0% (2/102)	3.7% (5/135)	0.11
Loss of smell	7.6% (18/238)	12% (12/103)	4.4% (6/135)	0.27
Loss of taste	7.1% (17/238)	9.7% (10/103)	5.2% (7/135)	0.17
Headache	10% (24/238)	12% (12/103)	8.9% (12/135)	0.091
Chest pain	11% (26/238)	16% (16/103)	7.4% (10/135)	0.26
Abdominal pain	3.4% (8/238)	3.9% (2/103)	3.0% (2/135)	0.051
Vomiting	8.0% (19/238)	8.7% (9/103)	7.4% (10/135)	0.049
Diarrhea	14% (33/238)	18% (18/103)	11% (15/135)	0.18
Disorientation[g]	10% (24/238)	5.8% (6/103)	13% (18/135)	0.26

ECG = electrocardiogram; SMD = standardized mean difference; BMI = body mass index; IHD = ischemic heart disease; AMI = acute myocardial infarction; VTE = venous thromboembolism: HFrEF = heart failure reduced ejection fraction; HFpEF = heart failure preserved ejection fraction; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; DOAC = Direct-acting oral anticoagulant; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist; BP = blood pressure; bpm = beats per minute; brpm = breaths per minute; Ct value = cycle threshold value.

Missing data in continuous variables: BMI 44.5%; systolic BP 4.6%; diastolic BP 20%; heart rate 1.7%; respiratory rate 8%; saturation no oxygen 5%; Ct value 18%.

[a] Any active cancer.

[b] Any dementia diagnosis prior to admission.

[c] Current or ex-smoker.

[d] Non beta-blocker anti-arrhythmic medication.

[e] Treated with oxygen or not treated with oxygen at admission.

[f] Body temperature ≥ 38 degrees Celsius.

[g] New disorientation aggravated previous disorientation.

for patients with abnormal ECG. Presenting symptoms and signs were similar between groups, but patients with abnormal ECG had higher heart rate and were disoriented more frequently than patients with normal ECG. Lastly, patients with abnormal ECG presented with loss of smell or chest pain less frequently compared with patients with normal ECG.

Propensity score model

The achieved balance through propensity score weighting is presented in Table 2 as unweighted and weighted baseline variables. The propensity scores for abnormal and normal ECG showed overlap which is presented in Supplementary Fig. 1.

Clinical outcomes

In-hospital complications and outcome are presented in Supplementary Table 2. Of 238 patients, 39 died and 74 were treated at ICU within 30 days. A total of 99 patients met the primary clinical endpoint of ICU treatment or in-hospital death within 30 days. The remaining 139 patients were discharged alive and not treated at ICU within 30 days.

In-hospital complications were similar between patients with abnormal and normal ECG, with the exception that atrial fibrillation was more common in patients with abnormal ECG. The frequency of ICU treatment was similar but in-hospital death, and ICU treatment or in-hospital death within 30 days, were more common in patients with abnormal compared with normal ECG. Acute myocardial infarction was rare, with no significant difference between abnormal and normal ECG, and no patients were diagnosed with myocarditis in-hospital. When analyzed, elevation of Troponin T (TnT) and N-terminal prohormone brain natriuretic peptide (NTproBNP) was common without significant differences between groups. However, TnT and NTproBNP was not analyzed in the majority of patients.

In univariable and multivariable analysis, as well as in propensity score adjusted and propensity score weighted analysis, abnormal ECG was associated with an increased risk of ICU treatment or in-hospital death within 30 days *(*Table 3*)*.

Abnormal ECG was more common than normal ECG in patients who were treated at ICU or died within 30 days compared with those who were not treated at ICU and were discharged alive within 30 days. However, there were no differences in the separate ECG changes between the groups *(*Table 4*)*. Although the respective variables did not predict outcome alone, among the ECG variables included in abnormal ECG, abnormal T wave inversion, followed by abnormal QRS axis, had the largest relative importance for the outcome (i.e. ECG changes as investigated in relation to each as well as in relation to age and sex) *(*Fig. 2*)*.

Pre-admission comorbidities and ongoing medical treatment were similar between patients who were treated at ICU or died or were within 30 days compared with those who were not treated at ICU and were discharged alive within 30 days. The only significant differences were that patients who were treated at ICU or died within 30 days were more likely to be male or to have ongoing treatment with beta blockers, and less likely to have ongoing treatment with any oral cortisone *(*Supplementary Table 3*)*. When investigating the same variables according only to in-hospital death within 30 days, almost half of the variables were more common (and the majority of variables were numerically higher) among patients who died within 30 days *(*Supplementary Table 4*)*.

Discussion

The main finding in this study was that in patients hospitalized for COVID-19, abnormal ECG remained associated with an increased risk of ICU treatment or in-hospital death within 30 days in propensity score analysis.

The major strength of our study compared to previous research was the propensity score model. Several previous studies investigating ECG as a tool for risk assessment in COVID-19 did not sufficiently adjust their

Table 2
Unweighted and propensity score weighted baseline characteristics.

Variables, mean ± standard deviation	Unweighted, N = 238			Weighted, N = 238		
	Normal ECG *N* = 103	Abnormal ECG N = 135	KS *p*-value	Normal ECG N = 103	Abnormal ECG N = 135	KS p-value
Age (years)	58 ± 15	65 ± 16	0.0050	59 ± 15	63 ± 16	0.22
Male sex (binary)	0.74 ± 0.44	0.73 ± 0.44	0.94	0.73 ± 0.45	0.75 ± 0.45	0.68
BMI	28 ± 6.6	27 ± 5.1	0.45	28 ± 6.4	27 ± 5.1	0.69
Comorbidities (binary, yes)						
Diabetes	0.17 ± 0.37	0.27 ± 0.45	0.048	0.16 ± 0.37	0.26 ± 0.44	0.072
Hypertension	0.36 ± 0.48	0.53 ± 0.50	0.011	0.37 ± 0.48	0.50 ± 0.50	0.061
Hyperlipidemia	0.13 ± 0.33	0.19 ± 0.39	0.17	0.13 ± 0.34	0.13 ± 0.39	0.31
IHD	0.068 ± 0.25	0.16 ± 0.36	0.040	0.079 ± 0.27	0.14 ± 0.35	0.16
Prior AMI	0.058 ± 0.23	0.11 ± 0.31	0.16	0.067 ± 0.25	0.10 ± 0.31	0.35
Prior stroke	0.087 ± 0.28	0.17 ± 0.38	0.065	0.10 ± 0.30	0.15 ± 0.35	0.30
Prior VTE	0.039 ± 0.19	0.059 ± 0.24	0.48	0.038 ± 0.19	0.061 ± 0.24	0.43
HFrEF	0.019 ± 0.14	0.052 ± 0.22	0.20	0.024 ± 0.15	0.047 ± 0.21	0.37
HFpEF	0	0.037 ± 0.19	0.048	0	0.032 ± 0.18	0.036
History of AF	0.068 ± 0.25	0.19 ± 0.39	0.0060	0.077 ± 0.27	0.17 ± 0.37	0.048
Peripheral artery disease	0	0.022 ± 0.15	0.13	0	0.022 ± 0.15	0.10
COPD	0.049 ± 0.22	0.059 ± 0.24	0.72	0.051 ± 0.22	0.056 ± 0.23	0.85
Astma	0.068 ± 0.25	0.052 ± 0.22	0.60	0.062 ± 0.24	0.055 ± 0.23	0.80
CKD	0.01 ± 0.10	0.089 ± 0.29	0.0080	0.011 ± 0.10	0.073 ± 0.26	0.030
Active cancer[a]	0.039 ± 0.19	0.059 ± 0.24	0.48	0.047 ± 0.21	0.058 ± 0.23	0.72
Any dementia[b]	0.019 ± 0.14	0.037 ± 0.19	0.43	0.024 ± 0.15	0.037 ± 0.19	0.62
Smoking[c]	0.53 ± 0.50	0.56 ± 0.50	0.88	0.54 ± 0.50	0.55 ± 0.50	0.99
Medication at admission (yes)						
Beta-blockers	0.18 ± 0.38	0.33 ± 0.47	0.0090	0.20 ± 0.40	0.30 ± 0.46	0.084
Anti-arrhythmic agent[d]	0	0.015 ± 0.12	0.22	0	0.011 ± 0.10	0.19
Digoxin	0	0.022 ± 0.15	0.13	0	0.021 ± 0.14	0.11
Aspirin	0.068 ± 0.25	0.15 ± 0.36	0.055	0.077 ± 0.27	0.14 ± 0.35	0.14
Warfarin	0.01 ± 0.098	0.037 ± 0.19	0.19	0.0080 ± 0.088	0.033 ± 0.18	0.15
DOAC	0.068 ± 0.25	0.15 ± 0.36	0.055	0.079 ± 0.27	0.13 ± 0.34	0.21
ACE inhibitor	0.17 ± 0.37	0.24 ± 0.43	0.14	0.17 ± 0.38	0.23 ± 0.42	0.26
ARB	0.12 ± 0.32	0.13 ± 0.34	0.70	0.12 ± 0.33	0.13 ± 0.33	0.91
Calcium antagonist	0.17 ± 0.37	0.20 ± 0.40	0.49	0.17 ± 0.38	0.19 ± 0.40	0.71
Statins	0.21 ± 0.41	0.33 ± 0.47	0.057	0.23 ± 0.42	0.30 ± 0.46	0.24
P2Y12 inhibitor	0.019 ± 0.14	0.096 ± 0.30	0.017	0.022 ± 0.15	0.083 ± 0.28	0.058
MRA	0.029 ± 0.17	0.022 ± 0.15	0.74	0.033 ± 0.18	0.021 ± 0.14	0.57
Diuretics	0.058 ± 0.23	0.17 ± 0.38	0.010	0.068 ± 0.25	0.15 ± 0.36	0.061
Oral antidiabetics	0.15 ± 0.35	0.22 ± 0.41	0.18	0.14 ± 0.35	0.20 ± 0.40	0.22
Oral cortisone	0.049 ± 0.22	0.059 ± 0.24	0.72	0.056 ± 0.23	0.052 ± 0.22	0.90
Symptoms and signs at admission						
Systolic BP (mmHg)	126 ± 21	128 ± 22	0.69	126 ± 21	127 ± 22	0.81
Diastolic BP (mmHg)	77 ± 13	75 ± 13	0.24	77 ± 13	76 ± 13	0.58
Heart rate (bpm)	95 ± 18	100 ± 23	0.13	95 ± 18	99 ± 22	0.45
Respiratory rate (brpm)	27 ± 8.4	26 ± 8.0	0.96	27 ± 8.2	26 ± 8.0	0.96
Saturation no oxygen %	88 ± 8.2	88 ± 12	0.37	88 ± 8.6	88 ± 11	0.87
Oxygen at admission % (n/N)[e]	0.76 ± 0.43	0.67 ± 0.47	0.13	0.74 ± 0.44	0.68 ± 0.47	0.30
Ct value (cycles)	28 ± 5.7	27 ± 5.9	0.35	27 ± 5.7	27 ± 5.6	0.65
Fever % (n/N)[f]	0.64 ± 0.48	0.58 ± 0.49	0.33	0.63 ± 0.48	0.58 ± 0.49	0.43
Cough	0.82 ± 0.39	0.77 ± 0.42	0.40	0.80 ± 0.40	0.78 ± 0.42	0.66
Dyspnea	0.70 ± 0.46	0.68 ± 0.47	0.77	0.69 ± 0.46	0.68 ± 0.47	0.81
Sore throat	0.16 ± 0.36	0.13 ± 0.33	0.52	0.15 ± 0.35	0.14 ± 0.34	0.83
Nasal congestion	0.019 ± 0.14	0.037 ± 0.19	0.43	0.022 ± 0.15	0.031 ± 0.17	0.688
Loss of smell	0.12 ± 0.32	0.044 ± 0.21	0.039	0.10 ± 0.30	0.048 ± 0.21	0.11
Loss of taste	0.097 ± 0.30	0.052 ± 0.22	0.18	0.083 ± 0.28	0.059 ± 0.24	0.47
Headache	0.12 ± 0.32	0.089 ± 0.29	0.49	0.11 ± 0.32	0.092 ± 0.29	0.58
Chest pain	0.16 ± 0.36	0.074 ± 0.26	0.048	0.14 ± 0.35	0.080 ± 0.27	0.13
Abdominal pain	0.039 ± 0.19	0.030 ± 0.17	0.70	0.040 ± 0.20	0.029 ± 0.17	0.65
Vomiting	0.087 ± 0.28	0.074 ± 0.26	0.71	0.087 ± 0.28	0.072 ± 0.26	0.68
Diarrhea	0.18 ± 0.38	0.11 ± 0.31	0.16	0.17 ± 0.37	0.12 ± 0.32	0.28
Disorientation[g]	0.058 ± 0.23	0.13 ± 0.34	0.058	0.077 ± 0.27	0.12 ± 0.32	0.33

ECG = electrocardiogram; KS = Kolmogorov-Smirnov; BMI = body mass index; IHD = ischemic heart disease; AMI = acute myocardial infarction; VTE = venous thromboembolism: HFrEF = heart failure reduced ejection fraction; HFpEF = heart failure preserved ejection fraction; AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; DOAC = Direct-acting oral anticoagulant; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist; BP = blood pressure; bpm = beats per minute; brpm = breaths per minute; Ct value = cycle threshold value.

[a] Any active cancer.

[b] Any dementia diagnosis prior to admission; [c]current or ex-smoker; [d]Non beta-blocker anti-arrhythmic medication.

[e] Treated with oxygen or not treated with oxygen at admission.

[f] Body temperature ≥ 38 degrees Celsius.

[g] New disorientation aggravated previous disorientation.

Table 3
The adjusted association between abnormal ECG and ICU/in-hospital death within 30 days.

Variable	OR (95%CI)	p-value
Univariable	2.03 (1.20–3.46)	0.0094
Model A[a]	2.13 (1.22–3.74)	0.0081
Model B[b]	2.04 (1.16–3.62)	0.014
Model C[c]	2.80 (1.20–6.70)	0.018
Model D[d]	2.11 (1.21–3.66)	0.0084

Baseline variables = Age, sex, body mass index; history of diabetes, hypertension, hyperlipidaemia, ischemic heart disease, heart failure, atrial fibrillation, peripheral artery disease, chronic obstructive pulmonary disease, asthma and chronic kidney failure; prior acute myocardial infarction, stroke and venous thromboembolism; active cancer, any dementia, smoking; pre-admission treatment with beta-blockers, anti-arrhythmic agents, digoxin, aspirin, warfarin, direct-acting oral anti coagulants, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium antagonists, statins, P2Y12 inhibitors, mineralocorticoid receptor antagonists, diuretics, oral antidiabetics and oral cortisone; admission blood pressure, heart rate, respiratory rate and saturation without oxygen; oxygen at admission, admission cycle threshold value; presenting with fever, cough, dyspnea, sore throat, nasal congestion, loss of smell, loss of taste, headache, chest pain, abdominal pain, vomiting, diarrhea and disorientation.

[a] Adjusted for age and sex.
[b] Adjusted for age, sex, diabetes and hypertension.
[c] Propensity score adjusted for all baseline variables.
[d] Propensity score weighted with all baseline variables.

analyses [15–20]. Furthermore, most previous studies have used "univariable prefiltering", that is including those variables that were significantly different in univariable analysis as covariates in their multivariable analysis [11–14,21–24], which is an approach that is generally not recommended [25,26]. Other studies have adjusted their analysis with a large number of potential covariates in different regression models [27,28]. However, it is difficult to assess and manually choose which variables should be included in such models. Propensity scores, especially when estimated using GBM, has been suggested to better estimate possible causal associations in these situations [29,30].

Our main finding that abnormal ECG remained associated with an increased risk of poor outcome in COVID-19 after statistical adjustment is important for several reasons. First, ECG is non-invasive an easily accessible tool immediately when a patient arrives to an emergency department or to a hospital ward. An abnormal ECG may be the first sign that a patient has an increased risk of poor outcome during hospitalization. ECG could therefore be an *add-on* in the decision to admit a COVID-19 patient to in-hospital care, or to decide which level of care is necessary. Second, our results are in line with previous research of ECG in the risk assessment in COVID-19 [9,15,18,21,28], and or findings further highlight the relevance of early ECG in COVID-19. Third, our results indicated that an abnormal ECG predicted an increased risk of poor outcome irrespective of prior cardiac burden, which emphasizes the need of further investigating the relevance of direct cardiac injury in COVID-19.

Although none of the respective ECG variables predicted outcome alone, among the ECG changes included in abnormal ECG; relative to each other as well as to age and sex; T wave inversion and QRS axis abnormality had the largest importance for the outcome. Previous research has indicated that, among other ECG changes, QRS axis deviation or T wave changes predicted worse outcome in COVID-19 [12,13,31]. QRS axis deviation (mainly right axis deviation) and T wave inversion can arise from right ventricular strain in patients suffering from acute respiratory failure, and right ventricular strain pattern on ECG has previously been associated with poor outcome in COVID-19 [32,33]. However, we cannot draw any conclusions regarding the precise cause of ECG changes based on the present study.

Comorbidities and pre-admission ongoing medical treatment were similar when comparing patients who were admitted to ICU or died in-hospital within 30 days with those who were not admitted to ICU and were discharged alive within 30 days. Only male sex and ongoing treatment with beta blockers were significantly more common in the ICU/in-hospital death group. However, some risk factors were numerically higher in the ICU/in-hospital death group and the absence of significant differences may be due to lack of power. This is further supported by the fact that several comorbidities incorporated in this analysis are known risk factors for poor outcome in COVID-19 [34]. That said, our propensity score adjusted analysis suggest that an abnormal ECG predicts admission to ICU or in-hospital death within 30 days irrespective of pre-existing co-morbidities. Previous research has suggested that COVID-19 can cause cardiac injury [5] and some ECG abnormalities could possibly be caused by COVID-19 per se. However, in the present study, baseline ECG *before* the COVID-19 event was not available. Therefore it was not possible to assess cardiac injury as an explanation for any ECG changes.

The mean age of the present cohort was 62 years. The mean age of patients hospitalized with COVID-19 in Sweden overall the corresponding time period (March to May 2020) was 63.8 years, and the mean age of patients hospitalized with COVID-19 in the Region Västra Götaland (where Gothenburg is situated) was 63.3 years [35]. Therefore, the age of the present cohort corresponds well to the age of the overall COVID-19 population during the corresponding time-period. Because patients who died within 30 days were older than those who survived (mean age 71 ± 14 vs 60 ± 16 years, $p \leq 0.0001$), whereas patients who were treated at ICU within 30 days were younger compared to those who were not (56 ± 13 vs 64 ± 17 years, $p = 0.0003$), there was no difference in age between groups regarding the composite endpoint of ICU or death within 30 days.

To the best of our knowledge, our study provides the earliest ECG recordings and the most distinct definition of *admission* ECG to date. Almost all previous studies investigating ECG as a risk assessment tool in COVID-19 have omitted to state the time from admission to ECG [11,13–20,22–24,27,28]. Three previous studies included patients with ECG recordings within 24–48 h as admission ECG [10,12,24]. As far as we know, only one previous study had an earlier cut-off time (six hours from admission, as in the present study) than 24 h from admission to ECG, however, no further details are presented regarding time to ECG in this particular study [21]. In the present study, nine out of ten patients' admission ECG was recorded within two hours from admission. The timing of ECG is important because changes can develop over time due to emerging cardiac pathology [36].

Our cohort was larger than most previous studies investigating ECG as a risk assessment tool in COVID-19 [13,16,18–20,23,24,27]. In all larger studies except two [10,21] the time from admission to ECG was not stated at all [11,12,14,17,22,28]. Therefore, these studies did not have a sufficient definition of admission ECG. Without a clear definition of admission ECG, the findings are less applicable in clinical reality since it is not possible to know which ECG in to interpret as the "predictor ECG". For the purpose of investigating ECG as a risk assessment tool in COVID-19, our study is the second largest to date with a clear definition of admission ECG within 24 h, and the only study providing details of when each ECG was recorded in relation to admission.

Limitations

Our study has several limitations. The study investigated 30-day *in-hospital* mortality during the first wave of COVID-19 and data on out-of-hospital death was not available. However, discharge of severely ill

Table 4
ECG characteristics at admission.

Variable	Overall N = 238	Discharged alive and not treated at ICU within 30 days *N* = 139	Dead in-hospital or treated at ICU within 30 days *N* = 99	*p*-value
Heart rate (bpm)	92 (80–107)	91 (81–106)	92 (80–109)	0.562
Heart rate < 50 bpm % (n/N)	0.4% (1/238)	0% (0/139)	1.0% (1/99)	0.416
Sinus rhythm	89% (212/238)	89% (124/139)	89% (88/99)	>0.99
Atrial fibrillation	9.7% (23/238)	8.6% (12/139)	11% (11/99)	0.657
Atrial flutter	0.4% (1/238)	0.7% (1/139)	0% (0/99)	>0.99
Other rhythm	0.4% (1/238)	0.7% (1/139)	0% (0/99)	>0.99
QRS axis (degrees)	21 (−7.0–56)	26 (−4.3–59)	16 (−16–53)	0.346
Abnormal QRS axis[a] % (n/N)	20% (48/238)	17% (24/139)	24% (24/99)	0.194
QRS duration (ms)	92 (85–102)	90 (84–102)	94 (86–102)	0.174
QRS duration >120 ms	9.7% (23/238)	10% (14/139)	9.1% (9/99)	>0.99
QTc interval (ms)	433 (417–450)	431 (415–445)	437 (421–451)	0.091
Long QTc % (n/N)	29% (70/238)	25% (35/139)	35% (35/99)	0.112
QTc > 500 ms	0.8% (2/238)	0.7% (1/139)	1.0% (1/99)	>0.99
Normal AV conduction	87% (206//238)	87% (121/139)	86% (85/99)	0.848
First-degree AV block	2.5% (6/238)	2.2% (3/139)	3.0% (3/99)	0.695
Second-degree AV block Mobitz I	0% (0/238)	0% (0/139)	0% (0/99)	NA
Second-degree AV block Mobitz II	0% (0/238)	0% (0/139)	0% (0/99)	NA
Third-degree AV block	0% (0/238)	0% (0/139)	0% (0/99)	NA
Q wave pathology[b]	6.7% (16/238)	5.8% (8/139)	8.1% (8/99)	0.601
Abnormal QRS morphology[c]	11% (26/238)	11% (15/139)	11% (11/99)	>0.99
QRS morphology RBBB	5.9% (14/238)	5.8% (8/139)	6.1% (6/99)	>0.99
QRS morphology LBBB	2.5% (6/238)	2.9% (4/139)	2.0% (2/99)	>0.99
QRS morphology LAH or LPH	2.5% (6/238)	2.2% (3/139)	3.0% (3/99)	0.695
Low voltage QRS[d]	7.1% (17/238)	6.5% (9/139)	8.1% (8/99)	0.799
ST elevation[e]	5.0% (12/238)	4.3% (6/139)	6.1% (6/99)	0.562
ST depression[f]	4.2% (10/238)	5.0% (7/139)	3.0% (3/99)	0.528
T wave inversion[g]	24% (58/238)	21% (29/139)	29% (29/99)	0.168
Abnormal ECG[h]	57% (135/238)	50% (69/139)	67% (66/99)	0.012

ECG = electrocardiogram; ICU = intensive care unit; bpm = beats per minute; ms = milliseconds; QTc = corrected QT interval; AV = atrioventricular; NA = not applicable: RBBB = right bundle branch block; LBBB = left bundle branch block; LAH = left anterior hemiblock; LPH = left posterior hemiblock.

[a] QRS axis < minus 30 degrees or >90 degrees.

[b] Negative deflection preceding R-wave with duration >40 ms or > 2 mm deep or >25% of QRS amplitude in two anatomically consecutive leads.

[c] Right/left bundle branch block or left anterior/posterior hemiblock.

[d] QRS complex with amplitude ≤5 mm in all limb leads or ≤10 mm in all precordial leads.

[e] ≥1 mm ST elevation in any two anatomically consecutive leads.

[f] ≥1 mm ST depression in any two anatomically consecutive leads.

[g] Negative T-wave with depth >1 mm in any lead except for minus aVR or V1.

[h] Any of heart rate ≤50 beats per minute, QRS duration ≥120 milliseconds, QTc interval ≥500 milliseconds, abnormal QRS axis, abnormal QRS morphology, low voltage QRS, Q wave pathology, ST elevation ≥1 mm in any two continuous leads, or ST depression ≥1 mm in any two continuous leads, abnormal T wave inversion, non-sinus rhythm or AV block ≥2.

patients (for the purpose of palliative care) in the first wave of COVID-19 is highly unlikely due to infection control measures, and therefore COVID-19-specific death likely occurred in-hospital. In 165 of 439 patients, admission ECG was not available. Therefore, it was not possible to investigate the association between ECG and outcome in these patients. However, available admission ECG within six hours was an inclusion criterion in the present study and clinical variables were only investigated in relation to ECG. In all previous studies presenting the total number of COVID-19 patients, as opposed to those only presenting the number of patients with available ECG, the lack of admission ECG has been a challenge to some degree [12,14,16,18,20,21,27,28]. Furthermore, our cohort was predominately male which makes our results mainly applicable to male patients with COVID-19. However, previous research has indicated that male patients are more likely to suffer from severe COVID-19 compared with women [37], and therefore our results are probably representative for the real-life clinical population of patients with COVID-19. Also, the present study was based on a sample of patients with COVID-19 in Gothenburg, Sweden, and may not be representative for all patients with COVID-19. Another limitation of the present study, and other previous studies in relation to each other, is the varying definition of "abnormal ECG". In the present study, we had a high detail level of the ECG analysis, which allowed a clinically applicable definition of abnormal ECG which is close to the definitions of studies with comparable detail level [11,15,21]. It is also important to note that mutations of SARS-CoV-2 resulting in new variants, immunization and vaccination have altered the natural clinical course of COVID-19. Consequently, more research is needed to confirm if ECG abnormalities are associated with worse outcome in new variants COVID-19 or after immunization. The study was also limited by a high degree of missing data in the central variable BMI (44.5% missing). However, we carefully addressed missing data with a meticulous approach to imputation, using multivariable imputation by chained random forests including all variables in the dataset. Lastly, although the mean age of our cohort corresponds well to the overall age of patients hospitalized with COVID-19 during the first wave in Sweden, the overall age distribution differs in relation to all COVID-19 patients from the start of the pandemic to present time (52% vs 62% over 60 years; 32% vs 46% over 70 years; 14% vs 25% over 80 years; and 1.7% vs 6.5% over 90 years old, with the numbers from the present study followed by overall numbers in Sweden from start of the pandemic to present time [35]). This may hypothetically make our results less representable to the present overall hospitalized COVID-19 population). However, the overall numbers of patients hospitalized with COVID-19 from the start of the pandemic to present time reflect patients hospitalized during and *between* waves of COVID-19, and may not be representative for the populations *during* waves of COVID-19.

Conclusion

In propensity score adjusted and propensity score weighted analysis accounting for 55 patient characteristics, an abnormal ECG at admission was strongly associated with ICU admission or in-hospital death within 30 days in patients hospitalized for COVID-19. Admission ECG could therefore have value as an add-on in the clinical decision making for patients presenting with COVID-19.

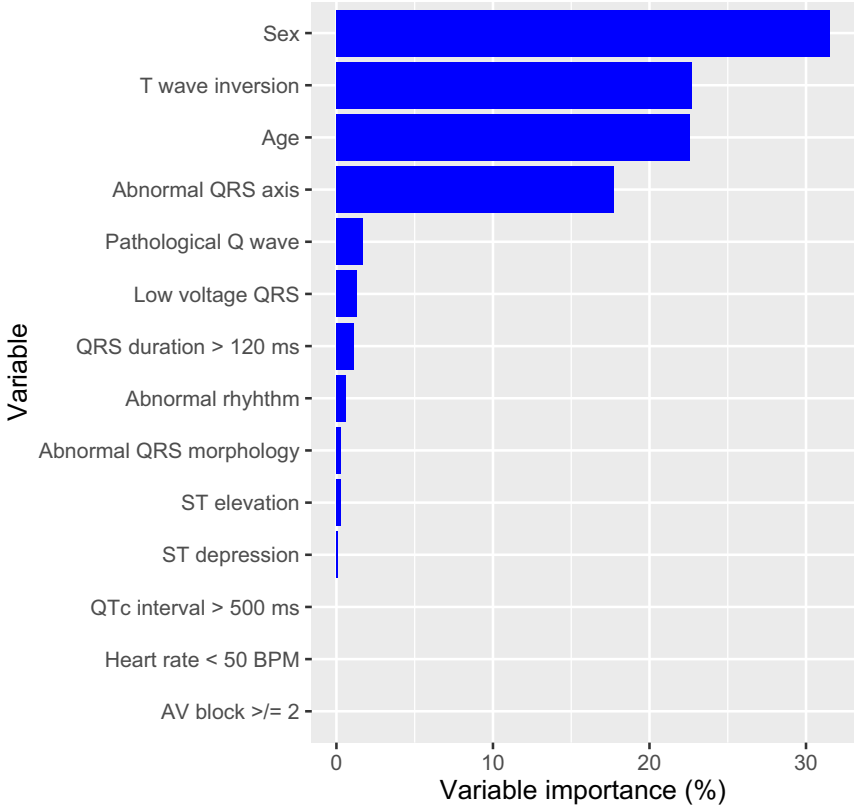

Fig. 2. Variable importance of outcome (ICU treatment or death within 30 days) for age, sex and ECG changes included in abnormal ECG. ms = milliseconds; BPM = beats per minute.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2022.10.005.

Funding

This work was supported by the Swedish Heart-Lung Foundation [20180555].

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Rickard Zeijlon: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration. **Peter Hällgren:** Conceptualization, Methodology, Investigation, Writing – review & editing, Project administration. **Vina Le:** Conceptualization, Investigation, Writing – review & editing. **Jasmina Chamat:** Conceptualization, Investigation, Writing – review & editing. **Johan Wågerman:** Conceptualization, Investigation, Writing – review & editing. **Israa Enabtawi:** Conceptualization, Investigation, Writing – review & editing. **Araz Rawshani:** Conceptualization, Formal analysis, Investigation, Writing – review & editing. **Sten Unenge:** Conceptualization, Investigation, Writing – review & editing. **Sandeep Jha:** Conceptualization, Investigation, Writing – review & editing. **Elmir Omerovic:** Conceptualization, Resources, Writing – review & editing, Supervision. **Björn Redfors:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgements

The authors are grateful to Peter Thorsson for assisting the authors in identifying patients through ICD-10 codes.

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