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ORIGINAL RESEARCH CORONA EXPERIENCE

The relationship between morphological electrocardiographic characteristics and survival in critical COVID-19 patients

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ABSTRACT

Background: Myocardial damage is a sign of poor prognosis in coronavirus disease 2019 (COVID-19). Electrocardiography (ECG) would be useful to evaluate the effects of ECG findings on survival in severe COVID-19. We studied the relationship of pathological ECG findings in patients of COVID-19 admitted in ICU with other adverse physiological parameters as well as the mortality.

Methodology: The study population comprised critical COVID-19 patients in the intensive care unit (ICU). Patients with findings other than normal sinus rhythm, atrial extra beat, and ventricular extra beat were defined as patients with pathological ECG findings. Two groups were formed: patients with pathological ECG findings (n = 109) and patients without pathological ECG findings (n = 84). Data were compared and analysed between the groups. The relationship among the risk factors, and ECG findings with mortality was investigated.

Results: The presence of hypertension (69% vs. 40%, OR 5.49, CI 1.71-17.66, P = 0.004), peripheral oxygen saturation (SpO2) (88 vs. 95, OR 0.8, CI 0.7-0.9, P < 0.001) were found to be related to mortality in multivariable analyses. Patients with pathological ECG finding were older [74 (27-98) vs. 61 (22-89); P < 0.001], and more likely to have hypertension (68% vs. 44%, P = 0.001). Pathological ECG findings (66% vs. 51%, P = 0.02), atrial fibrillation (AF) (37% vs. 20%, P = 0.01), right branch bundle block (RBBB) (10% vs. 3%, P = 0.048) were associated with higher mortality in univariable analyses.

Conclusion: Although abnormal findings on ECG, especially AF and RBBB, are associated with a poor prognosis, they are not primary effective in increasing the mortality of critical COVID-19 patients**.**

Abbreviations: AF- Atrial Fibrillation; CRP- C-reactive protein; ICU- intensive care unit; RBBB- Right Bundle-Branch Block; RT-PCR- reverse-transcription polymerase chain reaction; VTE- venous thromboembolism

Key words: Atrial Fibrillation; Biomarkers; COVID-19; ECG; Mortality; Right Bundle-Branch Block

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1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) began in Wuhan, China in 2019.[1] Following the declaration of COVID-19 as a global pandemic by the World Health Organization (WHO) on 11 March 2020, knowledge of this disease has been continually updated.[2] Initially, it was thought that COVID-19 only affected the respiratory system. Over time, it was realized that cardiac events of viral origin directly affected survival.[3] Cardiac events were thought to be associated with the increased myocardial need for

oxygen associated with conditions such as the use of inotropic drugs, a severe inflammatory response/cytokine storm, and hypoxia resulting from respiratory failure, and consequently leading to the myocardial damage.[3,4] Previous studies have focused on different mechanisms. It has been reported that the virus genome has been found in the heart of 35% of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), along with direct myocardial damage, and an increase in the frequency of venous thromboembolism (VTE).[5,6] In addition to factors such as immobility and the presence of comorbidities, respiratory failure increases the risk of VTE associated with direct endothelial damage. It has been understood that this hypercoagulability status can create cardiac damage by causing microvascular thrombi in the myocardiovascular system.[6] It has also been reported that the inflammatory stress seen in COVID-19 can cause atherosclerotic plaque instability and plaque rupture, thereby resulting in the development of acute coronary syndrome (ACS).[7]

Cardiac arrhythmia is another important topic. It is known that especially in critical COVID-19 patients in the intensive care unit (ICU), sympathetic system activation resulting from severe infection, the use of vasopressors, metabolic dysfunction, myocardial damage, and arrhythmogenic drugs used in treatment cause cardiac arrhythmia.[8] Previous studies have reported that in many patients with COVID-19 infection, the presence of various abnormalities has been seen, including atrial fibrillation (AF) on ECG, ST-T segment changes, tachycardia, bradycardia, QTc prolongation, premature atrial contractions, intraventricular block, left branch bundle block (LBBB) and right branch bundle block (RBBB).[9–11] All these studies revealed that cardiac events in COVID-19 cases have a direct effect on mortality. However, the evaluation of cardiac risk factors, especially in patients in the ICU, has still not fully clarified points such as what should be done for the early detection of damage and the relationship with mortality. Sufficient awareness of the possible cardiac effects of COVID-19 in addition to respiratory effects could make a great contribution to increasing survival.

To improve the understanding of the prognosis of COVID-19-related cardiac damage of critically ill patients, this study aimed to assess the impact of ECG findings and prognostic biomarkers on the survival of COVID-19 patients and investigate the reasons for the pathological ECG findings that adversely affect survival.

2. METHODOLOGY

Ethical approval for this study (Project No. 2011-KAEK-27/2021-2100244844 and Decision No. 2022-(02)) was provided by the Clinical Research Ethics Committee of the University of Çanakkale, Çanakkale, Turkey on 19 January 2022. The study followed the principles of the Declaration of Helsinki. The requirement for informed consent was waived off as the anonymity of the data was maintained.

2.1. Study population

A retrospective examination was carried out on 519 patients treated for COVID-19 pneumonia in the ICU between March 15, 2020 to December 21, 2021. COVID-19 pneumonia was diagnosed using reverse-transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 on nasopharyngeal or tracheal swabs. A computerized tomography (CT) scan of the chest was performed. ECG was done at the baseline or during the course of hospitalization as indicated. Patients diagnosed with RT-PCR or with findings compatible with COVID-19 on chest CT were included in the study. The other conditions of participation in this study were: critically ill COVID-19 patients who were admitted to the ICU, over the age of 18, without known cardiac arrhythmia or pathological ECG findings, and having at least one ECG in their follow-up. Death of the patient after follow-up was not counted as an exclusion criterion. In this study, we evaluated the different rates of ECG abnormalities in patients who recovered and were successfully discharged, as well as in patients who died during their hospital stay, and to evaluate the prognostic effects of ECG changes. Patients were excluded from the study if they had no ECG record, had no severe lung involvement determined, or had known cardiac arrhythmia and ECG pathologies before admission to the ICU. Eventually a total of 193 patients were included in the study.

2.2. Data Sources

Demographic data, smoking status, body mass index (BMI), the use of invasive mechanical ventilation, the use of vasopressors, the presence of cytokine storm evaluated clinically by a hematologist, the Acute Physiology and Chronic Health Evaluation score (APACHE II), the Sequential Organ Failure Assessment (SOFA) score, the treatments applied, and the laboratory parameters were recorded from the hospital information system and patient records at the time of admission. The ECGs taken at any time during hospitalization were recorded from patient records.

The ECGs were evaluated by an independent cardiologist and anesthesiologist. The ECG findings were recorded as normal sinus rhythm, sinus tachycardia, atrial extra beat, AF, supraventricular tachycardia, atrioventricular (AV) block, findings of elevation or depression in the ST segment, T-wave inversion, RBBB, LBBB or ventricular ectopic beats. As supraventricular tachycardia and atrial tachycardia were seen at a low frequency in the patients included in the

Table 1: Patient characteristics and results according to the ECG findings

Parameter	Pathology on ECG (n = 106)	No pathology on ECG (n = 87)	Test	P value
Mortality	70 (66)	44 (51)	x2 = 5.434	0.020
Age (y)	74 (27-98)	61 (22-89)	z = -5.100	< 0.001
Male gender	67 (63)	53 (61)	x2 = 0.106	0.744
Length of stay in ICU (days)	10 (1-30)	10 (2-28)	z = -0.458	0.647
BMI (kg/m^2)	26.1 (17.3-46.8)	29.3 (17.3-50.8)	z = -1.613	0.107
Smoker	42 (40)	35 (40)	x2 = 0.007	0.932
Comorbidities				
- Hypertension	72 (68)	38 (44)	x2 = 11.461	0.001
- Diabetes Mellitus	60 (57)	40 (46)	x2 = 2.61	0.142
- Cardiovascular Disease*	36 (34)	20 (23)	x2 = 2.794	0.095
APACHE II Score	19 (5-40)	12 (3-36)	z = -4.049	< 0.001
SOFA Score	7 (2-19)	5 (2-17)	z = -4.133	< 0.001
SpO_2 (%)	92(62-100)	90 (72-99)	z = -1.602	0.109
Inotrope use	22 (21)	3 (3)	x2 = 12.693	< 0.001
Cytokine storm	41 (39)	26 (31)	x2 = 1.356	0.244
Invasive mechanical ventilation	60 (57)	29 (33)	x2 = 10.413	0.001

Data presented as n (%) or median (range): Mann Whitney U-test and Pearson Chi-Square test

ECG: Electrocardiogram, BMI: body mass index, SpO_2: peripheral oxygen saturation, APACHE II: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment

**Included coronary artery disease, heart failure, cardiac arrhythmias, heart valve diseases*

study, these tachycardias were collated and analyzed under the heading of atrial arrhythmia as tachycardia of supraventricular origin. As no ventricular fibrillation or ventricular tachycardia was seen on the ECG scans, these were not analyzed.

The diagnosis of macrophage activation syndrome (cytokine storm) was made based on the guide published by Turkish Public Health on November 7, 2020.[12] According to this guide, in patients with increased oxygen requirement, the diagnosis was made if five of the following findings were present: resistant fever, C-reactive protein (CRP) increase, ferritin increase, D-dimer increase, lymphopenia and neutrophilia, while having normal procalcitonin values.

2.3. Definition of the groups

Patients with findings other than normal sinus rhythm, atrial extra beat, and ventricular extra beat were defined as patients with pathological ECG findings. Two groups were formed: patients with pathological ECG findings (n = 109) and patients without pathological ECG findings (n = 84). Data were compared and analyzed between the groups. Statistical analysis was performed on AF and RBBB from the ECG findings as they were thought to have an effect on survival. While making these analyses, patients with both AF rhythm and RBBB rhythm (n = 5) were excluded. Missing data (n = 15) was excluded from analysis.

2.4. Statistical Analysis

Data obtained in the study were analyzed statistically using IBM SPSS version 21.0 software. The Shapiro–Wilk test was used to evaluate the normality of the variables. In the comparisons of two groups of variables with normal distribution, the independent samples t-test was applied, and for data not showing normal distribution, the Mann–Whitney U test was used. To examine the relationships between categorical variables, the Pearson's chi-square test was used, and when the expected number of one of the four cells in the 2 x 2 table was < 5, Fisher's exact test was used. Logistic regression analysis was applied to variables with a statistically significant difference between the groups that were thought to have an effect on mortality. Logistic regression analyses were performed for ECG findings with a P value near 0.05 associated with mortality. Due to the limited sample size and the multiplicity of factors affecting mortality, multivariate analyses were adjusted

Table 2: Laboratory test results of the patients according to the ECG findings

Parameter	Pathology on ECG (n = 106)	No pathology on ECG (n = 87)	Test	P value
Glucose (mg/dl)	179 (69-449)	165 (60-616)	z = -0.557	0.578
Urea (mg/dl)	78 (7-379)	47 (5-309)	z = -5.357	**< 0.001**
Creatinine (mg/dl)	1.3 (0.4-8.1)	0.9 (0.5-5.4)	z = -5.211	**< 0.001**
Albumin (g/dl)	2.9 ± 0.5	3.2 ± 0.5	t = -3.324	**0.001**
Sodium (mmol/l)	139 (126-161)	140 (123-164)	z = -0.035	0.972
Potassium (mmol/l)	4.2 (2.7-8.2)	4.2 (2.9-6.1)	z = -0.495	0.621
Chloride (mmol/l)	101 (79-127)	102 (81-125)	z = -0.161	0.872
Phosphorus (mg/dl)	3.8 (0.8-13.0)	3.5 (1.3-7.7)	z = -1.386	0.166
Magnesium (mg/dl)	2.1 (1.2-4.5)	2.2 (1.3-2.9)	z = -1.006	0.314
CtCa (mg/dl)	8.9 (6.4-11.1)	8.9 (5.7-11.9)	z = -0.695	0.487
AST (U/L)	40 (8-4749)	36 (9-7711)	z = -1.164	0.244
ALT (U/L)	29 (5-2436)	26 (7-1756)	z = -0.694	0.488
LDH (U/L)	482 (174-3479)	505 (76-1045)	z = -0.039	0.969
Troponin T (ng/l)	58 (4-2939)	15 (3-1131)	z = -5.738	**< 0.001**
Ferritin (ng/ml)	588 (14-2000)	499 (20-2000)	z = -1.004	0.315
D-Dimer (µgFEU/ml)	0.83 (0.09-27.69)	0.79 (0.06-61.21)	z = -0.512	0.609
INR	1.2 (1.0-5.7)	1.1 (0.6-2.8)	z = -2.965	**0.003**
Hemoglobin (g/dl)	11.5 ± 2.1	12.1 ± 1.8	t = 2.092	**0.038**
Thrombocyte (x10^3/µl)	233 (26-580)	250 (43-607)	z = -1.716	0.086
Neutrophils (x10^3/µl)	9.9 (0.6-39.8)	9.3 (0.7-25.2)	z = -0.824	0.410
Lymphocytes (x10^3/µl)	0.51 (0.08-3.32)	0.73 (0.1-2.40)	z = -2.831	**0.005**
Neutrophil/lymphocyte	19 (4-97)	14 (3-97)	z = -2.418	**0.016**
CRP (mg/dl)	10.0 (0.3-38.0)	9.8 (0.2-35.0)	z = -0.543	0.587
Sedimentation (mm/s)	53 (2-140)	46 (2-140)	z = -0.264	0.792
Procalcitonin (ng/ml)	0.75 (0.05-134.00)	0.23 (0.02-34.00)	z = -3.750	**< 0.001**
PH	7.39 (6.83-7.56)	7.41 (7.00-7.54)	z = -1.669	0.095
PaO_2 (mmHg)	76 (39-289)	68 (42-205)	z = -1.841	0.066
$PaCO_2$ (mmHg)	40 (24-109)	37 (18-87)	z = -0.593	0.553
HcO_3 (mmol/l)	23 (5-50)	25 (7-39)	z = -2.341	**0.019**
Lactate (mmol/l)	1.7 (0.7-13.0)	1.7 (0.2-13.9)	z = -1.064	0.287
PaO_2/FiO_2	94 (39-410)	85 (51-460)	z = -1.659	0.097

Data presented as mean ± SD, or median (min-max); Mann Whitney U-test and Independent Samples t-test

ECG: Electrocardiogram, CtCa: corrected calcium, AST: Aspartate Aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, INR: international normalised ratio, CRP: C- reactive protein, PaO2: partial oxygen pressure in arterial blood, PaCO2: partial carbon dioxide pressure in arterial blood, PaO2/FiO2: ratio of partial oxygen pressure in arterial blood to the oxygen fraction in inspired gas mixture

only for the APACHE II score. Descriptive statistics were stated as mean ± standard deviation (SD), or median values with minimum–maximum values for continuous variables and as number (n) and percentage (%) for categorical variables. Results were reported with a 95% confidence interval, and the level of statistical significance was set at P = 0.05.

3. RESULTS

A total of 193 patients were evaluated. The patients had a mean age of 70 ± 15 years and a mean BMI of 29 ± 6 kg/m^2. The length of stay in the ICU had a mean of 11 ± 6 days. Hypertension was present in 57% (n = 110), diabetes in 52% (n = 100), cardiovascular disease in 29% (n = 56), and the need for invasive mechanical

Table 3: Analysis of odds ratio for death of ECG findings. *

ECG features	Survived (n = 80)	Died (n = 113)	Total (n = 193)	Univariable analysis		Multivariable analysis***	
				OR (95% CI)	P	OR (95% CI)	P
ECG abnormality	36 (45)	70 (62)	106 (55)	1.99 (1.11-3.56)	**0.020**	1.14 (0.59-2.23)	0.694
Normal sinus rhythm	43 (54)	40 (35)	82 (43)	0.47 (0.26-0.85)	**0.012**	0.56 (0.29-1.08)	0.082
Sinus tachycardia	14 (18)	20 (18)	35 (18)	1.01 (0.48-2.15)	0.971		
Atrial fibrillation	16 (20)	42 (37)	58 (30)	2.36 (1.21-4.61)	**0.011**	1.57 (0.74-3.34)	0.245
Atrial arrhythmias **	16 (20)	45 (40)	61 (32)	2.65 (1.36-5.15)	**0.004**	1.65 (0.78-3.51)	0.193
Atrial extra beat	2 (3)	6 (5)	8 (4)	2.19 (0.43-11.13)	0.346		
AV block	1 (1)	1 ()	2 (1)	0.71 (0.04-11.45)	0.806		
ST depression	2 (3)	4 (4)	6 (3)	1.43 (0.26-8.01)	0.683		
ST elevation	3 (4)	5 (4)	8 (4)	1.19 (0.28-5.12)	0.817		
T wave inversion	8 (10)	12 (10)	18 (10)	1.07 (0.42-2.75)	0.889		
Long QT	24 (34)	21 (23)	45 (28)	0.58 (0.29-1.51)	0.118		
Left bundle branch block	8 (10)	11 (10)	19 (10)	0.97 (0.37-2.53)	0.951		
Right bundle branch block	2 (3)	11 (10)	13 (7)	4.2 (0.91-19.5)	0.067	4.33 (0.85-21.9)	0.077
Ventricular extra beat	12 (15)	12 (11)	24 (13)	0.67 (0.29-1.59)	0.366		

** More than one ECG finding was present in some patients; Data presented as n (%) or OR (95% CI)*

***Atrial tachycardia was seen at a low frequency in the patients included in the study (n:0 survived, n:3 died) for this reason, these patients were included in the analysis as atrial arrhythmias with atrial fibrillation.*

****Multivariable analysis performed for ECG findings with univariable analysis's; P < 0.07 and adjusted for APACHE II.*

ECG: Electrocardiography, AV: atrioventricular, APACHE II: Acute Physiology and Chronic Health Evaluation.

ventilation at admission was present in 46% (n = 89) of the patients. The mean APACHE II score was 17 ± 9 and the mean SOFA score was 7 ± 4 (Table 1). Mortality developed in 59% of the patients included in the study.

Pathological ECG findings were present in 109 patients, and these patients were seen to be older (median age 74 years, min–max 27–98 vs. 61 years, min–max 22–89; P < 0.001). The probability of in-hospital death (66% vs. 51%; P = 0.02), the frequency of hypertension (68% vs.

44%; P = 0.001), the use of vasopressors (21% vs. 3%; P < 0.001) and invasive mechanical ventilation (57% vs. 33%; P = 0.001) were determined to be greater in this group (Table 1).

Various physiological and pathological parameters including APACHE II score, SOFA score, urea, creatinine, troponin T, international normalized ratio (INR), neutrophil–lymphocyte ratio (NLR), procalcitonin, bicarbonate (HCO_3) values were determined to be higher and lymphocyte count was lower in the patients with pathological ECG findings (Tables 1 and 2).

AF was observed to be the most common pathological ECG finding (30%), and the detection of AF (P = 0.011)

Table 4: Atrial fibrillation and Heart Block

Parameters	Survivors (n = 80)	Non-survivors (n = 113)	Total (n,%)	Test	P value
Atrial fibrillation*	16(20)	42(37)	58 (30)	$X^2 = 6.568$	**0.01**
Right branch block*	2(3)	11(10)	13 (7)	$x^2 = 3.902$	**0.048**
Only atrial fibrillation	10 (13)	30 (27)	40 (21)	$x^2 = 5.627$	**0.018**
Only right branch block	0	7 (6)	7 (4)	$x^2 = 5.142$	**0.043**
Atrial fibrillation + right branch block	2 (3)	3 (3)	5 (3)	$x^2 = 0.004$	1
Atrial fibrillation + left branch block	4 (5)	9 (8)	13 (7)	$x^2 = 0.655$	0.418
Atrial fibrillation + branch block	6 (8)	12 (11)	18 (9)	$x^2 = 0.539$	0.463

**More than one ECG finding was present in some patients; ECG: Electrocardiography.*

Table 5: Comparison of plasma laboratory values and organ support during intensive care unit admission between patients with NSR, and AF or RBBB respectively.

Parameter	NSR (n = 83)	Atrial fibrillation (n = 58)	P-value	RBBB (n = 13)	P
Age (y)	68 (22-93)	76 (51-98)	**< 0.001**	73 (53-85)	0.118
Hypertansion	36 (43)	44 (76)	**< 0.001**	10 (77)	**0.024**
Diabetes mellitus	34 (41)	36 (62)	**0.014**	10 (77)	**0.016**
Invasive mechanical ventilation	31 (37)	34 (59)	**0.013**	6(46)	0.544
Vasoactive treatment	4 (5)	16 (28)	**< 0.001**	4 (31)	**0.011**
Creatinine	1 (0.5-5.4)	1.3 (0.4-8.1)	**0.001**	1.3 (0.5-6)	0.092
Troponin-t	24 (3-1225)	59 (4-2939)	**0.002**	42 (8-243)	0.214
Ferritin	425 (34-2000)	565 (14-2000)	0.264	654 (287-2000)	0.08
D-dimer	0.73 (0.06-61.21)	0.9 (0.2-19.88)	0.240	1.13 (0.2-9.1)	0.427
INR	1.13 (0.55-2.83)	1.21 (1-5.7)	**0.01**	1.23 (1-1.7)	0.349
Hemoglobin	12 ± 1.7	11.1 ± 2	**0.009**	11.8±2.4	0.730
Lymphocyte	0.64 (0.17-2.87)	0.5 (0.08-3.27)	**0.046**	0.33 (0.2-3.3)	0.073
N/L	16 (3-97)	19 (5-97)	0.073	29 (5.1-94)	**0.023**
CRP	10 (0.2-31)	10 (0.3-35)	0.865	8.7 (0.6-38)	0.740
Procalcitonin	0.3 (0.05-134)	0.8 (0.06-100)	**0.005**	0.6 (0.08-56)	0.230
PaO_2/FiO_2	92 (46-460)	94 (39-410)	0.332	90 (62-360)	0.744
Lactat	1.7 (0.2-14)	1.8 (0.7-12.4)	0.349	1.5 (1-13)	0.637

NSR: Normal sinus rhythm, AF: Atrial fibrillation, RBBB: Right bundle branche block, INR: international normalised ratio, N/L: Neutrophil-to-lymphocyte ratio, CRP: C reactive protein, PaO_2/FiO_2: ratio of oxygen pressure in arterial blood to the oxygen fraction in inspired gas mixture; Data presented as mean ± SD or median (min-max)

Table 6: Evaluation of the mortality status

Parameters	Survivors (n = 80)	Non-survivors (n = 113)	Test	p
Age (y)	65 (22-89)	72 (25-98)	z = -3.403	**0.001**
Male gender	43 (54)	77 (68)	$x^2 = 4.125$	**0.042**
Length of stay (days)	9 (2-30)	11 (1-28)	z = -1.564	0.118
BMI (kg/m^2)	27.4 (19.2-50.8)	27.3 (17.3-50.7)	z = -1.004	0.316
Smoker	35 (44)	42 (37)	$x^2 = 0.846$	0.358
Comorbidities				
- Hypertension	32 (40)	78 (69)	$x^2 = 16.101$	**< 0.001**
- Diabetes Mellitus	35 (44)	65 (58)	$x^2 = 3.558$	0.059
- Cardiovascular Disease*	26 (33)	30 (27)	$x^2 = 0.805$	0.369
APACHE II Score	10 (3-33)	20 (4-40)	z = -6.929	**< 0.001**
SOFA Score	5 (2-12)	8 (3-19)	z = -6.356	**< 0.001**
SpO_2 (%)	95(80-100)	88 (62-100)	z = -6.356	**< 0.001**
Inotrope use	2 (3)	23 (20)	$x^2 = 13.242$	**< 0.001**
Cytokine storm	15 (19)	52 (47)	$x^2 = 16.116$	**< 0.001**
Invasive mechanical ventilation	28 (35)	61 (54)	$x^2 = 6.792$	**0.009**

Data presented as n (%) or median (min-max); Mann Whitney U-test and Pearson Chi-Square test

*BMI: body mass index, APACHE II: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment; *Included coronary artery disease, heart failure, cardiac arrhythmias, heart valve diseases*

Table 7: Evaluation of the mortality status

Parameters	Survivors (n = 80)	Non-survivors (n = 113)	Test	p
Glucose (mg/dl)	162 (69-616)	182 (60-602)	z = -1.427	0.154
Urea (mg/dl)	46 (5-213)	79 (7-379)	z = -5.738	**< 0.001**
Creatinine (mg/dl)	0.9 (0.4-5.4)	1.2 (0.5-8.1)	z = -4.418	**< 0.001**
Albumin (g/dl)	3.3 ± 0.5	2.9 ± 0.5	t = 4.821	**< 0.001**
Sodium (mmol/l)	139 (123-157)	140 (126-164)	z = -1.590	0.112
Potassium (mmol/l)	4.1 (2.9-6.1)	4.3(2.7-8.2)	z = -0.910	0.363
Chloride (mmol/l)	101 (79-123)	102 (89-127)	z = -2.022	**0.043**
Phosphorus (mg/dl)	3.6 (1.3-7.2)	3.6 (0.8-13)	z = -0.800	0.423
Magnesium (mg/dl)	2.0 (1.4-4.0)	2.2 (1.2-4.5)	z = -3.029	**0.002**
CtCa (mg/dl)	8.9 (7.6-11)	8.8 (5.7-11.9)	z = -0.763	0.446
AST (U/L)	30 (8-703)	45 (9-7711)	z = -3.547	**< 0.001**
ALT (U/L)	26 (5-201)	29 (5-2436)	z = -1.733	0.083
LDH (U/L)	402 (94-1124)	564 (76-3479)	z = -4.762	**< 0.001**
Troponin T (ng/l)	24 (3-1131)	35 (3-2939)	z = -2.510	**0.012**
Ferritin (ng/ml)	372 (20-2000)	652 (14-2000)	z = -4.336	**< 0.001**
D-Dimer (µgFEU/ml)	0.65 (0.06-61.21)	1.09 (0.16-27.68)	z = -3.957	**< 0.001**
INR	1.15 (0.55-2.49)	1.17 (0.96-5.72)	z = - 0.988	0.323
Hemoglobin (g/dl)	12.0 ± 2.0	11.6 ± 2.0	t = 1.407	0.161
Thrombocyte (x10^3/µl)	249 (43-607)	228 (26-573)	z = -0.859	0.390
Neutrophils (x10^3/µl)	8.5 (2.8-39.8)	10.9 (0.6-34.2)	z = -2.822	**0.005**
Lymphocytes (x10^3/µl)	0.7 (0.2-2.9)	0.5 (0.1-3.3)	z = -4.583	**< 0.001**
Neutrophil/lymphocyte	12 (3-54)	23 (4-97)	z = -6.089	**< 0.001**
CRP (mg/dl)	6.3 (0.2-34.0)	11.6 (0.3-38.0)	z = -3.520	**< 0.001**
Sedimentation (mm/s)	46 (2-140)	53 (2-140)	z = -0.954	0.340
Procalcitonin (ng/ml)	0.21 (0.02-100.00)	0.60 (0.05-134.00)	z = -3.888	**< 0.001**
PH	7.41 (7.04-7.56)	7.39 (6.83-7.54)	z = -1.998	**0.047**
PaO_2 (mmHg)	80 (42-198)	67 (39-289)	z = -3.641	**< 0.001**
$PaCO_2$ (mmHg)	39 (18-109)	38 (21-81)	z = -0.345	0.730
HCO_3 (mmol/l)	26 (8-50)	23 (5-37)	z = -3.668	**< 0.001**
Lactate (mmol/l)	1.6 (0.4-5.1)	2.1 (0.2-13.9)	z = -3.166	**0.002**
PaO_2/FiO_2	124 (62-460)	82 (39-410)	z = -5.085	**< 0.001**

Data presented as mean ± SD or median (min-max); Mann Whitney U-test and Independent Samples t-test

ECG: Electrocardiogram, CtCa: corrected calcium, AST: Aspartate Aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, INR: international normalised ratio, CRP: C- reactive protein, PaO2: partial oxygen pressure in arterial blood, PaCO2: partial carbon dioxide pressure in arterial blood, PaO2/FiO2: ratio of partial oxygen pressure in arterial blood to the oxygen fraction in inspired gas mixture

on ECG was found to be associated with mortality in univariate analysis (Table 3). Other ECG findings were not determined to affect mortality in univariate analysis. According to the results of the multivariate analysis performed for ECG findings with a $P < 0.07$ of the univariable analysis and adjusted according to APACHE II, there was no significant association with mortality (Table 3). The association of isolated AF and bundle branch blocks with mortality was examined. Branch block with AF had no effect on mortality. The presence of isolated AF ($P = 0.018$) and RBBB ($P = 0.043$) were found to be associated with mortality (Table 4). Patients with AF at ICU were seen to be older compared to patients who had normal sinus rhythm ($P < 0.001$). The

Table 8: Variables which could have an effect on survival- model 2 (P = 0.023, Nagelkerke R Square = 0.719)

Independent variables	Exp(β)	95% confidence interval		P value
		Lower limit	Upper limit	
Age	1.01	0.97	1.06	0.540
Gender	0.75	0.25	2.22	0.601
Hypertension	5.49	1.71	17.66	**0.004**
First day SpO_2	0.80	0.71	0.91	**< 0.001**
First day use of vasopressor	67.14	4.00	1128.16	**0.003**
Invasive mechanical ventilation	2.37	0.76	7.34	0.135
First day urea	1.00	0.99	1.02	0.558
First day albumin	0.57	0.16	2.01	0.381
First day chloride	1.04	0.94	1.15	0.426
First day magnesium	3.81	0.96	15.18	0.058
First day AST	1.00	1.00	1.00	0.279
First day LDH	1.00	1.00	1.01	**0.036**
First day troponin-t	1.00	1.00	1.01	0.145
First day ferritin	1.00	1.00	1.00	0.855
First day d-dimer	1.00	1.00	1.00	0.496
First day neutrophil	1.00	1.00	1.00	0.416
First day lymphocyte	1.00	1.00	1.00	0.424
First day N/L	1.06	0.99	1.13	0.106
First day CRP	1.00	0.93	1.07	0.903
First day procalcitonin	0.98	0.94	1.03	0.501
First day PaO_2/FiO_2	1.00	0.99	1.00	0.310
First day lactate	0.72	0.39	1.33	0.295
First day HCO_3	1.01	0.87	1.16	0.946

Logistic regression analysis; N/L: neutrophil / lymphocyte ratio, ECG: Electrocardiography

frequency of hypertension (P < 0.001), diabetes (P = 0.014), the use of vasoactive treatment (P < 0.001) and invasive mechanical ventilation (P = 0.013) on admission were determined to be greater in AF compared to patients who had normal sinus rhythm. Patients with AF had higher plasma values of creatinine (P = 0.001), troponin-t (P = 0.002), INR (P = 0.01) and procalcitonin (P = 0.005) compared to patients who had normal sinus rhythm. Additionally, these patients had lower plasma values of hemoglobin (P = 0.009) and lymphocyte (P = 0.046). The frequency of hypertension (P = 0.024) and diabetes (P = 0.016) and the use of vasoactive treatment (P = 0.011) on admission were determined to be greater in RBBB compared to patients who had normal sinus rhythm. Additionally, patients with RBBB had higher plasma values of N/L (P = 0.023) compared to patients with normal ECG (Table 5).

Advanced age (P = 0.001), male gender (P =0.042) and hypertension (P < 0.001) were found to be associated with mortality (Table 6). In the patients who developed mortality, the APACHE II (P < 0.001) and SOFA scores (P < 0.001) were higher, the SpO_2 (P < 0.001) values were lower, and the frequency of cytokine storm (P < 0.001), vasopressor use (P < 0.001) and the need for invasive mechanical ventilation (P = 0.009) were greater (Table 6). The urea (P < 0.001), creatinine (P < 0.001), chloride (P < 0.001), magnesium (P = 0.002), aspartate aminotransferase (AST) (P < 0.001), lactate dehydrogenase (LDH) (P < 0.001), troponin T (P = 0.012), ferritin (P < 0.001), D-dimer (P < 0.001), neutrophil count (P = 0.005), NLR (P < 0.001), CRP (P < 0.001), procalcitonin (P < 0.001) and lactate (P = 0.002) values were determined to be higher in the patients with mortality, and the albumin (P < 0.001), lymphocyte count (P < 0.001), partial oxygen pressure in

arterial blood (PaO_2) (P < 0.001), HCO_3 (P < 0.001) and ratio of PaO_2 to the oxygen fraction in inspired gas mixture (PaO_2 /FiO_2) (P = 0.01) values were found to be lower (P < 0.01) (Table 7).

The results of the logistic regression analysis performed on the variables that could have an effect on ICU mortality and were statistically significant in the univariate analysis (Nagelkerke R Square = 0.719; P = 0.023). Results from the multivariable analyses indicated that the presence of hypertension (P = 0.004), use of vasopressor (P < 0.001), peripheral oxygen saturation (SpO_2) (P < 0.001) and LDH value (P = 0.036) were found to be related to mortality (Table 8).

4. DISCUSSION

In this study, it was found that abnormal findings on ECG in univariate analyses, especially AF and RBBB, were associated with a poor prognosis. No significant results were obtained in multivariate analyses. Although ECG findings are not the primary effect on increasing the mortality of critical COVID-19 patients in ICU, they have an indication of the worsening prognosis.

Cardiac events associated with COVID-19 usually accompany severe disease and have poor prognostic characteristics. In a meta-analysis by Dalia et al.[13] it was shown that there was an increased risk of cardiac damage and cardiac arrhythmia in patients with severe COVID-19 and those who died. It has been reported in previous studies that mortality is increased in patients with pathological findings seen on ECG.[14,15] In a study by Yuan et al., any ECG abnormality was an independent predictor of death.[16] A study that described ECG findings at hospitalization,+ in 431 patients who later died or underwent invasive ventilation reported abnormal ECG in 93% of patients.[17] Similar to these studies, it was found that pathological ECG findings were associated with death and invasive ventilation at ICU admission.

It is thought that the ECG changes in COVID-19 patients could be associated with various issues, such as cardiac damage, hypoxia, worsening coronary perfusion, direct tissue damage, hyperacute systemic inflammatory response syndrome, renal failure, overwhelming critical illness or the effects of drugs used.[18] In our study, higher troponin-T values of patients with abnormal ECG findings may be associated with COVID-19-related cardiac damage. The need for a vasopressor may occur after cardiogenic shock, and the use of a vasopressor can induce cardiac damage by increasing cardiac oxygen consumption and reducing oxygen supply. In a study by Koeppen et al., the most common cardiac complication in critical COVID-19 patients in the ICU was the shock (39%); vasopressor was needed in 74% of patients, and heart damage developed in 30%.[19] In our study, vasoactive treatment rates were found to be high in patients with abnormal ECG findings (21% vs. 3%). In a previous study, higher plasma creatinine values were observed in patients with abnormal ECG, and these patients had a higher incidence of continuous kidney replacement therapy compared to patients with normal ECG.[20] In our study, plasma creatinine values were higher in patients with ECG abnormalities. Various ECG findings such as atrial and ventricular arrhythmias, conduction abnormalities, ischemic changes or long QTc have been associated with COVID-19.[21] In the current study, sinus tachycardia (18%), AF (30%), T negativity (9%), ventricular extra beats (10%), LBBB (10%), RBBB (7%) and long QTc (23%) were the more common ECG findings. In many studies, previous MI findings, acute ST and T changes, LBBB, intraventricular block, premature atrial beats, RBBB, right ventricle loading findings, fragmented QRS, long QT and fatal arrhythmias have been associated with severe disease or increased mortality in COVID-19 patients.[11,22-27] In our study, AF and RBBB were associated with mortality only in univariate analyses. This difference can be explained, at least in part, by the fact that the current study included elderly patients, consisted of severe or critical COVID-19 patients and had a limited sample size.

After sinus tachycardia, AF is the second most commonly seen arrhythmia in patients with severe COVID-19.[21] In a previous study, AF was observed in 21% of patients with COVID-19 infection.[28] It has also been reported that AF was observed in 42% of patients who died because of COVID-19 and in 36% of patients with cardiovascular disease.[29] Although new onset of AF has been the subject of few studies, the incidence has been reported to vary between 5-14.9% in published studies.[30–32] AF was seen at the rate of 30% in the current study. This significantly higher rate than has been reported in previous literature was thought to be due to the fact that the study population comprised severe and critical COVID-19 patients of advanced age with comorbidities. It has been previously suggested that AF is associated with myocardial damage and poor outcomes in COVID-19.[21] A study of 171 COVID-19 patients showed that the AF increased mortality.[33] Abdullahman et al.[31] found that mortality was higher in patients admitted to the ICU who developed new-onset AF. Similarly, Spironi et al.[34] also reported higher mortality rates in hospitalized COVID-19 patients with AF. In the current study, mortality was higher in the patients with AF, and 72% of the patients with AF developed mortality. Several mechanisms that are thought to be effective in AF development have been the focus of research. One of these is that the virus binding to ACE2 receptors on the cell surface causes a systemic effect as a result of reduced ACE2. This reduction of ACE2 causes increased vulnerability to AF by causing cardiac hypertrophy, vasoconstriction, tissue fibrosis and oxidative stress in the heart.[35] That the troponin T values of the patients with AF in the current study were seen to be higher than those of patients with normal sinus rhythm suggests that underlying cardiac damage could trigger AF. By changing sodium transport, thereby causing kidney damage and hypertension, reduced ACE2 may also increase the risk of AF development.[36] That elevated creatinine values and the increase in the incidence of hypertension were observed in the current study's patients with AF supports the view that AF is triggered by kidney damage. Another mechanism is thought to be caused by systemic inflammation and the over-activation of immune cells. Strong expression of proinflammatory cytokines can lead to apoptosis or necrosis of myocardial cells, and it is thought that this could cause intra-atrial repolarization and signaling impairments.[37,38] The procalcitonin values of the patients in the current study with AF were determined to be significantly high. Kelesoğlu et al.[30] also found that infection markers were high in patients with AF. Secondary infections and sepsis can be considered to

trigger AF. Another mechanism that is thought to cause AF is injury to cardiomyocytes and the development of apoptosis because of hypoxia in patients with severe COVID-19.[30,34] Previous studies have shown that the severity of acute respiratory distress syndrome (ARDS) is greater in patients with AF, and there is a greater need for invasive mechanical ventilation.[30,32-38] The greater need for invasive mechanical ventilation in the current study with AF showed that AF was triggered by hypoxemia and the more severity of ARDS.[39] It is also known that vasopressor support increases the risk of AF in patients in the ICU.[39] Moreover, activation of the sympathetic system in these patients increases the risk of AF. Consistent with the literature, the use of vasopressors was greater in patients with AF in the current study. As a result, advanced age and the presence of comorbidities in COVID-19, primarily hypertension, increase the risk of AF development. AF is triggered by cytokine storm, kidney damage, sepsis, and cardiac damage forming after severe COVID-19. Maintaining hemodynamic stability in patients with AF may reduce mortality. The prognostic biomarkers of troponin T, and lymphocytes must be followed up closely in patients with AF.

Right heart failure can develop secondary to pulmonary embolism and pulmonary hypertension due to ARDS with hypoxia in COVID-19 patients.[40] In a cohort of 105 COVID-19 patients hospitalized for treatment right ventricle dilatation was observed in 31% of intubated patients, and right ventricular hypokinesia was observed in 66% of the COVID-19 patients with it and in 5% of the COVID-19 patients with no right ventricle dilatation.[41] In a meta-analysis of 29 studies by Corica et al.,[42] the rate of right ventricle dysfunction in COVID-19 patients was 20.4%, and this was shown to be associated with mortality.

RBBB is seen on ECG as a finding of right heart loading. Barman et al.[43] examined the right ventricle loading findings on ECG, including RBBB, in a study of 324 COVID-19 patients, and found that right ventricle loading findings were associated with mortality. In another meta-analysis of 6 studies including 1904 patients, Zuin et al.[44] reported that RBBB was present on the ECG of 7.8% of the patients, and the finding of RBBB was shown to be associated with mortality. In the current study, RBBB was seen at the rate of 6.8%, which was similar to the findings of other studies. In addition, the mortality rate was found to be high in the current study's patients with the finding of RBBB on ECG, and mortality developed in 84.6% of the patients with RBBB. Therefore, correlation analysis was applied to RBBB. As a result of the analyses, the NLR value in patients with RBBB was found to be higher. COVID-19 triggers a hyperinflammatory condition that is responsible for some life-threatening conditions and death.[45] Previous studies have shown that the NLR is increased in severe disease and is associated with a poor prognosis.[46,47] As severe COVID-19 leads to a severe ARDS condition, it is thought to increase mortality by exacerbating right heart failure.

5. LIMITATIONS

Primarily it was a retrospective study conducted at a single center. Although patients with previously known arrhythmia were excluded from the study, it can be considered that because of the higher age group of the patients, there could have been some with undiagnosed cardiac arrhythmia. Another limitation could be that advanced cardiac examinations were not made on the patient group, as the ECG findings of cardiac damage could have been better identified on ECHO. Finally, the number of patients in the study population was insufficient for a detailed analysis of all the pathological ECG findings.

6. CONCLUSION

The results of this study demonstrated the importance of ECG in the detection of COVID-19-related cardiac events. In addition to pathological ECG findings showing a poor prognosis, they should be a warning to the clinician of shorter survival of patients with AF and RBBB on ECG. When necessary, further cardiac investigations should be performed.

7. Data availability of supporting data

The datasets used and analyzed during the current study are available from the corresponding author on a reasonable request.

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9. Conflict of interests

The authors have no conflict of interests to declare.

10. Disclosure statement

This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the Anesthesia, Pain & Intensive Care. We attest that the article is the authors' original work, has not received prior publication and is not under consideration for publication elsewhere. On behalf of all co-authors, the corresponding Author shall bear full responsibility for the submission. All the authors declare that they have no competing interests.

11. Authors contribution

AHB: Constructing an idea or hypothesis for manuscript; Organising and supervising; Reviewing the final draft

SM: Planning methodology to reach the conclusion; literature search; drafting the manuscript; statistical analysis

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