Prognostic Value of T-wave Positivity in Lead aVR in COVID-19 Pneumonia

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SUMMARY

OBJECTIVE: T-wave positivity in the lead aVR is a marker of ventricular repolarization abnormality and provides information on short- and long-term cardiovascular mortality in heart failure patients, those with anterior myocardial infarction, and patients who underwent hemodialysis for various reasons. The aim of this study was to investigate the relationship between T-wave positivity in the lead aVR on superficial electrocardiogram and mortality from COVID-19 pneumonia.

METHODS: This study retrospectively included 130 patients who were diagnosed with COVID-19 and treated as an outpatient or in the thoracic diseases ward in a single center between January 2021 and June 2021. All patients included in the study had clinical and radiological features and signs of COVID-19 pneumonia. The COVID-19 diagnosis of all patients was confirmed by polymerase chain reaction detected from an oropharyngeal swab.

RESULTS: A total of 130 patients were included in this study. Patients were divided into two groups: survived and deceased. There were 55 patients (mean age: 64.76–14.93 years, 58.18 male, 41.12% female) in the survived group and 75 patients (mean age: 65–15 years, 58.67 male, 41.33% female) in the deceased group. The univariate and multivariate regression analyses showed that positive *transcatheter aortic valve replacement* (OR 5.151; 95%CI 1.001–26.504; p=0.0012), lactate dehydrogenase (OR 1.006; 95%CI 1.001–1.010; p=0.012), and ᴅ-dimer (OR 1.436; 95%CI 1.115–1.848; p=0.005) were independent risk factors for mortality.

CONCLUSION: A positive *transcatheter aortic valve replacement* is useful in risk stratification for mortality from COVID-19 pneumonia.

KEYWORDS: Electrocardiographic. SARS-CoV-2. Mortality

INTRODUCTION

Although the novel coronavirus 2019 (COVID-19) infection primarily affects the lungs and causes pneumonia, acute respiratory distress syndrome, and even death, various cardiovascular complications are also the leading causes of mortality[1]. Numerous studies and case series have reported that COVID-19 causes myocarditis[2-4], tamponade[5], acute heart failure[6], arrhythmia (tachycardia or bradycardia)[7], Brugada-like electrocardiographic (ECG) pattern[8], transient ST elevation, and sudden cardiac death[9,10].

Cardiac involvement is associated with a poor prognostic outcome, independent of other causes, with an incidence rate of 22–44% in cases of advanced and severe COVID-19 infection[11,12]. Cardiovascular damage can occur through a diverse range of pathways. In addition to the direct cardiotoxic effect, cardiovascular damage may be caused by inhibition of ACE-2 receptors, cytokine storm, coronary plaque rupture, coronary spasm, and microthromboembolism[13,14].

On a superficial ECG, the lead aVR is usually neglected. However, it provides prognostic information on many cardiovascular diseases. A positive T-wave amplitude in the lead aVR gives prognostic information on repolarization abnormality and provides diagnostic and prognostic information on many cardiovascular diseases such as in heart failure[15-17]. However, there is no information regarding its relationship with COVID-19 pneumonia. The aim of this study was to investigate the relationship between T-wave positivity in the lead aVR on superficial ECG and mortality from COVID-19 pneumonia.

METHODS

This study retrospectively included 130 patients who were diagnosed with COVID-19 and treated as an outpatient or in the thoracic diseases ward in a single center between January 2021 and June 2021 after the approval of the local ethics committee (permission dated October 21, 2021, and numbered

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2021/67) and the Ministry of Health of the Republic of Turkey. The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients included in the study had clinical and radiological features and signs of COVID-19 pneumonia. The COVID-19 diagnosis of all patients was confirmed by polymerase chain reaction (PCR) detected from an oropharyngeal swab. All patients were treated with hydroxychloroquine, azithromycin, and favipiravir. Patients with chronic kidney or liver failure; those with history of anti-arrhythmic drugs use; those living with pacemaker; and those with atrial fibrillation, coronary artery disease, heart failure (with preserved systolic function or systolic heart failure), and abnormal serum electrolyte values were not included in the study.

All patients were questioned in detail for hypertension, hyperlipidemia, diabetes mellitus, tobacco use, asthma, COPD (chronic obstructive pulmonary disease), and the drugs used. Hematological, biochemical, and serological values were obtained from the peripheral blood samples taken following 12 h of fasting and recorded. A troponin value above the 99th percentile upper reference limit value or newly developed ECG and echocardiographic change was considered myocardial damage. Chronic renal failure was defined as a glomerular filtration rate less than 60 mL/min/1.73 m^2, persisting for 3 months. The diagnosis of hypertension was defined as receiving antihypertensive therapy or having a systolic blood pressure above160 mmHg and diastolic blood pressure above 90 mmHg in at least three measurements. Diabetes was defined as the use of anti-diabetic drugs and having at least two postprandial blood glucose measurements above 126 mg/dL or an HbA1c level >6.5. The diagnosis of hyperlipidemia was considered as having a low-density lipoprotein (LDL) level >160 mg/dL or the use of statins.

Electrocardiographic evaluation

Superficial 12-lead ECGs of all patients (Nihon Kohden Cardiofix V Model ECG-1550K device 25 mm/s and standard 1 mV/10 mm) were recorded before the treatment of COVID-19 infection and were evaluated by two independent cardiologists who were blinded to the characteristics of the patients. Heart rate, P-R interval, QT and QTc intervals, and QRS duration were recorded. The P-R interval was measured as the time from the beginning of the P wave to the beginning of the QRS complex in milliseconds. The QRS duration was measured from the beginning of the Q or R wave to the end of the R or S wave in milliseconds. The QT interval was measured from the beginning of the QRS complex to the end of the T wave in milliseconds. The QT-corrected distance was measured using

Bazett's formula. The depression or elevation of the ST segment in the lead aVR from the isoelectric line was measured numerically (STaVR). According to the T-wave amplitude in the lead aVR, patients with a positive peak (>0 mV) from the isoelectric line were recorded as positive (positive TAVR), while patients with a negative peak (<0 mV) from the isovolumetric line were recorded as negative (negative TAVR). The amplitude of the T wave (TPaVR) was recorded by calculating its negative or positive deflection from the isoelectric line. The TPaVR/STaVR ratio was obtained by dividing whichever value is greater by the other (large value/small value).

Statistical analysis

The study data were evaluated using the SPSS version 21.0 statistical software. Normality distribution of continuous variables was investigated using visual (histogram and probability charts) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). The descriptive statistics of the study were presented as mean and standard deviation for normally distributed data and as median, minimum, and maximum for non-normally distributed data. The chi-square test was used to show whether there was a difference between categorical variables. The Student's t-test was used to compare the continuous variables with parametric properties in independent groups, while the Mann-Whitney U test was used to compare continuous variables with non-parametric properties in independent groups. The level of statistical significance was set at a p-value less than 0.05. There was no study that could be referenced in the sample calculation when the literature was searched; medium-effect size of the chi-square test was taken in the calculation and it was decided to recruit 117 participants in 90% power, 0.05 margin of error, 1 degree of freedom, and 129 participants with 10% reserve.

RESULTS

A total of 130 patients were included in this study. Patients were divided into tw o groups: survived and deceased. There were 55 patients (mean age 64.76–14.93 years, 58.18 male, 41.12% female) in the survived group and 75 patients (mean age 65–15 years, 58.67 male, 41.33% female) in the deceased group. There was no difference between the groups in terms of age and gender. The baseline clinical and laboratory characteristics of the groups are shown in Table 1.

The comparison of laboratory characteristics showed that the deceased group had higher CK-MB (60.88±46.99 vs. 30.55±21.77, p=0.000), troponin (106±64.02 vs. 39.87±14.36, p=0.000), lactate dehydrogenase (LDH) (554.61±209.22 vs. 365.2±155.47 p=0.000), C-reactive protein (CRP) (127±75.32 vs. 87.4±68.24,

Table 1. Baseline characteristics and electrocardiographic findings.

| | | Group | | | | p |
| | | Deceased | | Living | | |
		n	%	n	%	
Sex	Male	44	58.67	32	58.18	0.956
	Female	31	41.33	23	41.82	
Hypertension	No	28	37.33	15	27.27	0.228
	Yes	47	62.67	40	72.73	
DM	No	52	69.33	38	69.09	0.976
	Yes	23	30.67	17	30.91	
Cerebrovascular disease	No	75	100.00	52	94.55	0.073
	Yes	0	0.00	3	5.45	
COPD	No	41	54.67	44	80.00	0.003
	Yes	34	45.33	11	20.00	
TAVR positive	No	47	62.67	50	90.91	0.000
	Yes	28	37.33	5	9.09	
TAVR negative	No	29	38.67	18	32.73	0.486
	Yes	46	61.33	37	67.27	

DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; TAVR: T-wave amplitude in the lead aVR.

p=0.001), leukocyte (13.01±4.87 vs. 8.82±4.84, p=0.000), and D-dimer values (25.29±23.09 vs. 1.18±1.06, p=0.000).

The laboratory, ECG, and echocardiographic characteristics are shown in Table 2. Positive TAVR (p=0.000) and STaVR (0.15±0.6 vs. 0.19±0.12, p=0.002) were statistically significant in the deceased group. The univariate and multivariate regression analyses showed that positive TAVR (OR 5.151; 95%CI 1.001–26.504, p=0.0012), LDH (OR 1.006; 95%CI 1.001–1.010, p=0.012), and D-dimer (OR=1.436, 95%CI 1.115–1.848, p=0.005) were independent risk factors for mortality (Table 3).

DISCUSSION

This study has examined the effects of superficial ECG and laboratory findings on mortality in patients with SARS-CoV-2 infection and found several important results. First, the positive T wave in lead aVR is an independent risk factor for mortality. Second, D-dimer and LDH values are also independent risk factors for mortality.

Although SARS-CoV-2 infection primarily affects the lungs and causes pneumonia and/or acute respiratory distress syndrome, it leads to complications such as myocarditis, cardiac tamponade, transit ST elevation, acute heart failure, arrhythmia (tachycardia or bradycardia), and sudden cardiac death[18].

Cardiac damage can occur through a diverse range of pathways. While it may be directly related to cardiac damage, it may cause myocardial inflammation and edema by inhibiting ACE-2 receptors and impairing the cellular defense mechanism. Another mechanism of action is the cytokine storm, which results from excessive cytokine release from type 1 and type 2 T-helper cells and leads to immunopathological events. These factors may cause direct myocyte damage as well as coronary spasm, plaque rupture, and microthromboembolism, leading to vascular inflammation and hypercoagulopathy[19].

Although the lead aVR is often neglected on a superficial 12-lead ECG, it provides diagnostic and prognostic information for many cardiovascular diseases. Lead aVR is a unique superficial ECG lead derived from near leads V1 and D1, providing information about right heart upper basal and viewing the left ventricle from the full brow. Since the lead aVR is a unipolar right extremity lead, represents the cavity of the heart, and is the opposite of the main cardiac vector, all positive deflection waves are negative in the lead aVR. A positive T wave in the lead aVR is usually an uncommon finding. According to the most common and valid hypothesis, the T wave is thought to be positive after vectorial deviation caused by damage to the left ventricular apical, inferior and inferior lateral wall due to various reasons. In another study, in patients with anterior myocardial infarction, positive T wave in lead aVR showed global left ventricular ischemia. Recent

Table 2. Basıc laboratory parameters and electrocardiographic findings to deceased and living groups.

	Group										p
	Deceased (n=75)					Living (n=55)					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
AGE	64.76	14.93	68.00	31.00	98.00	64.31	16.00	65.00	20.00	95.00	0.930*
CREATININE	1.35	0.87	1.06	0.20	4.30	1.30	1.50	0.90	0.38	9.00	0.066*
CK-MB	60.88	46.49	45.00	14.00	300.00	30.50	21.76	23.00	11.00	121.00	0.000*
LDH	554.61	209.02	467.00	172.00	950.00	365.24	155.47	321.00	152.00	1052.00	0.000*
SODIUM	136.25	6.73	137.00	140.00	150.00	133.13	5.60	134.00	116.00	142.00	0.12
POTASSIUM	4.21	0.94	4.10	2.90	4.14	4.34	0.68	4.30	3.10	4.80	0.14
CRP	127.09	75.32	103.00	36.00	390.00	87.21	68.24	77.60	2.30	270.00	0.001*
WBC	13.01	4.87	13.20	4.03	29.70	8.82	4.84	8.30	2.30	26.10	0.000*
Hg	11.47	2.10	12.10	7.80	16.10	12.28	1.67	12.20	8.20	15.40	0.062
D-DIMER	25.29	23.09	9.33	0.28	136.00	1.18	1.06	0.65	0.14	8.60	0.000*
TROPONIN	106.28	64.02	74.00	5.00	1031.00	39.87	14.36	12.60	3.00	527.00	0.000*
TPaVR	-0.07	0.26	-0.21	-0.41	0.29	-0.16	0.12	-0.18	-0.40	0.22	0.06
STaVR	0.15	0.06	0.12	0.10	0.39	0.19	0.12	0.15	0.01	0.50	0.002*
HR	83.21	19.10	88.00	45.00	111.00	86.51	17.06	90.00	55.00	125.00	0.290*
PR INTERVAL	107.51	7.30	110.00	89.00	125.00	109.56	23.42	102.00	80.00	200.00	0.173*
QRS INTERVAL	110.52	5.71	111.00	95.00	125.00	112.15	9.42	112.00	95.00	160.00	0.333*
LVEF	64.77	1.58	65.00	60.00	68.00	64.73	2.02	65.00	50.00	65.00	0.147*
QT INT	393.73	42.85	398.00	320.00	490.00	382.22	27.63	386.00	320.00	440.00	0.101*
QTC INT	439.79	46.14	427.00	349.00	521.00	429.47	43.69	430.00	320.00	513.00	0.388*
TPaVR/STaVR	1.58	0.79	1.60	0.00	3.46	1.62	0.62	1.38	0.00	3.20	0.739*

CK-MB LDH: lactate dehydrogenase; CRP: C-reactive protein; WBC: white blood cell; Hg: hemoglobın; TPaVR: amplitude of the T wave; STaVR: The depression or elevation of the ST segment in the lead aVR from the isoelectric line; HR: heart rate; LVEF: left ventricular ejection fraction; QT INT: QT interval; QTc INT: corrected QT interval. *

Table 3. Effects of various variables on COVID-19 mortality in univariate and multivariate logistic regression analyses.

	Unadjusted OR	95%CI	p-value	Adjusted OR	95%CI	p-value
TAVR positive	5.957	2.124-16.713	0.001	5.151	1.001-26.504	0.0012
COPD	3.317	1.487-7.397	0.003	1.431	0.306-6.696	0.649
Troponin	1.009	1.002-1.016	0.014	1.005	0.997-1.014	0.221
CK-MB	1.040	1.020-1.059	0.000	1.021	0.996-1.047	0.104
LDH	1.006	1.003-1.009	0.000	1.006	1.001-1.010	0.012
CRP	1.008	1.003-1.014	0.004	1.006	0.996-1.017	0.210
WBC	1.211	1.108-1.324	0.000	1.155	0.958-1.392	0.131
D-Dimer	1.647	1.254-2.163	0.000	1.436	1.115-1.848	0.005
STaVR	0.005	0.000-0.422	0.019	0.000	0.000-8.308	0.092

TAVR: T-wave amplitude in the lead aVR; COPD: chronic obstructive pulmonary disease; CK-MB: Creatine kinase and its MB isoenzyme; LDH: lactate dehydrogenase; CRP: C-reactive protein; WBC: whıte blood cell. STaVR: The depression or elevation of the ST segment in the lead aVR from the isoelectric line. Bold indicates significant p-value.

studies have shown that the T-wave positivity in the lead aVR is a marker of ventricular repolarization abnormality and provides information on short- and long-term cardiovascular mortality in patients with heart failure, patients with anterior myocardial infarction, and those who receive hemodialysis for various reasons[15-17]. In their long-term follow-up study of male individuals, Tan et al. showed that the T-wave positivity is an independent risk factor for cardiovascular events[20]. The 33-month follow-up study of 93 patients with heart failure and narrow QRS ECG by Okuda et al. showed that the T-wave positivity provided long-term prognostic information, independent of other causes[21]. The 31-month follow-up study of 93 patients with ICD (implantable cardioverter defibrillation) and ischemic and non-ischemic cardiomyopathy by Tanaka et al. showed that a positive T wave in the lead aVR was an independent risk factor for long-term mortality[22]. The study of 86 cases by Donmez et al. showed that the occurrence of the T-wave positivity in the lead aVR after transaortic valve implantation (TAVI) procedure was an independent risk factor for postoperative short- and long-term mortality[23]. In our study, the examination of the ECG findings of the lead aVR in patients with COVID-19 infection revealed that positive TAVR alone was an independent indicator for mortality. This suggests that a positive TAVR wave provides information on the entire myocardial tissue rather than the apical, inferior, and inferior lateral wall. Even if ejection fraction is same in the two groups, univariate analysis has showed that troponin values are significantly higher in the deceased group. Thus, there is marked subclinical ischemia of global left ventricle without any effect of ejection fraction. For this reason, T-wave positivity in the lead aVR may occur in the deceased group.

İn our study, higher LDH and D-dimer value are independent risk factors of mortality, as shown in previous study. Recent studies and meta-analysis showed that D-dimer value higher 3–4

times in the early stage of COVID-19 infection associated with independent risk for mortality and higher vascular complications. High LDH levels were found to be 6 times more related to the progression of COVID-19 pneumonia and 16 times to mortality compared to patients with normal LDH levels[24,25].

Limitations of the study

This study has several limitations. First, the sample size was small, and the study had a retrospective design. Second, the values such as CRP and troponin, which are associated with subclinical myocardial damage, were not followed up. Third, ECGs of the patients at initial diagnosis were examined, while positive or negative T wave changes on ECGs were not examined. Finally, the medical treatments of the patients were not questioned in detail and their post-treatment ECG changes were not investigated. A prospective study with a large number of patients is needed to validate the results of this study.

CONCLUSION

This study demonstrated that positive T wave in the lead aVR was a significant and independent risk factor for mortality from COVID-19 infection. This unique ECG parameter, which is often overlooked, provides information on the mortality of patients even when other ECG parameters are normal. We recommend that a positive TAVR wave not be neglected when evaluating high-risk patients.

AUTHORS' CONTRIBUTIONS

FS: Conceptualization, Data curation, Formal Analysis, Writing – original draft. **BÖ:** Formal Analysis. **MMÇ:** Formal Analysis. **FA:** Formal Analysis. **BA:** Formal Analysis.

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