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Is Lactate Dehydrogenase An Important Mortality Predictor in Covid-19 Patients with Atrial Fibrillation?

Atrial Fibrilasyonlu Covid-19 Hastalarında Laktat Dehidrogenaz Mortalitenin Önemli Bir Göstergesi midir?

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Abstract

Introduction: Abnormal laboratory parameters can be detected in severe patients with COVID-19, which are associated with adverse outcomes. Increased lactate dehydrogenase (LDH) is usually associated with tissue damage. Cardiovascular disease is a common comorbidity in COVID-19 disease. In the current report, the objective was to examine the relationship between LDH levels and atrial fibrillation (AF) in COVID-19 patients.

Materials and Methods: This investigation involved a retrospective and cross-sectional study. A total of 195 consecutive COVID-19 [45 AF (+) and 150 AF (-)] subjects were enrolled in the study. COVID-19 cases were determined from analysis of an oropharyngeal/nasopharyngeal swab using RT-PCR. LDH, procalcitonin, and D-dimer were recorded from the hospital records.

Results: Fatal patients had higher LDH levels compared to non-fatal patients (470±144 vs 404±60). A significant positive association was determined for LDH and troponin, CRP, and procalcitonin in all study subjects and AF patients. An LDH level of 443 was identified as the cut-off point in mortality of AF patients with a sensitivity and specificity of 73% and 74% (AUC= 0.744), respectively. LDH (OR: 1.009) and age (OR: 1.238) were shown to independently predict mortality in COVID-19-AF patients.

Conclusions: Increased LDH levels were essential predictor of mortality in COVID-19 subjects with AF. High LDH levels need careful observation to help prevent potential complications in COVID-19 subjects presenting with AF.

Keywords: COVID-19; lactate dehydrogenase; atrial fibrillation.

Özet

Giriş: Ciddi COVID-19 hastalarında olumsuz olaylar ile ilişkili anormal laboratuvar parametreleri tespit edilebilmektedir. Yüksek laktat dehidrogenaz (LDH) düzeyleri genellikle doku hasarı ile ilişkilidir. Kardiyovasküler hastalık COVID-19 hastalarında yaygın bir komorbid durumdur. Bu çalışmanın amacı COVID-19 hastalarında LDH düzeyleri ile atriyal fibrilasyon (AF) arasındaki ilişkiyi incelemektir.

Yöntem ve Gereçler: Bu çalışma retrospektif ve kesitsel bir araştırmayı içermektedir. Çalışmaya ardışık 195 COVID-19 hastası [45 AF (+) ve 150 AF (-)] dahil edildi. COVID-19 tanısı RT-PCR kullanılarak bir orofarenks/nazofarenks sürüntü analizi ile belirlendi. LDH, prokalsitonin ve D-dimer düzeyleri hastane kayıtlarından kaydedildi.

Bulgular: Mortal hastalar, mortal olmayan hastalara kıyasla daha yüksek LDH seviyelerine sahipti (470±144'a karşı 404±60). Çalışmaya dahil edilen tüm hastalarda ve AF hastalarında LDH ile troponin, CRP ve prokalsitonin arasında anlamlı bir pozitif ilişki saptandı. AF hastalarının mortalitesinde 443 (U/l) LDH düzeyi sırasıyla %73 ve %74'lük bir duyarlılık ve özgüllükle (AUC= 0.744) sınır değer olarak saptandı. COVID-19-AF hastalarında LDH (OR: 1.009) ve yaş (OR: 1.238) mortalitenin bağımsız prediktörü olduğu belirlendi.

Tartışma ve Sonuç: Yüksek LDH düzeyleri COVID-19 AF hastalarında mortalitenin önemli bir prediktörüdür. AF ile başvuran COVID-19 hastalarında olası komplikasyonların önlenmesine yardımcı olmak için yüksek LDH düzeylerinin dikkatle gözlemlenmesi gerekmektedir.

Anahtar Kelimeler: COVID-19; laktat dehidrogenaz; atrial fibrilasyon.

Introduction

COVID-19 started in Wuhan, China, and rapidly spread worldwide, and was declared a pandemic at the end of 2019. The etiological agent of this atypical pneumonia was "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2). SARS-CoV-2 or COVID-19 is very transmissible, spreading directly from person to person (1). However, most patients are asymptomatic; some complain of dry cough, fever, nausea, and myalgia. The viral evasion of cellular immune responses and inflammatory cytokine storm play an essential role in COVID-19 disease severity (2). Patients suffering from COVID-19 are at risk for ARDS and often need ventilatory support. Risk factors for the progression of severe disease in subjects contracting COVID-19 are increased age, male, and at higher risk for confounding factors such as cardiovascular disease (3). Abnormal laboratory parameters have been identified in severe COVID-19 subjects, and have been associated with adverse outcomes. The ferritin, C-reactive protein (CRP), procalcitonin, lymphocyte, D-dimer, troponin, and LDH have been reported to

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be abnormal parameters in COVID-19 disease severity (4,5). LDH is an enzyme that is located in almost every tissue. Increased LDH is usually associated with tissue damage. LDH levels have been associated with increased fatality rates COVID-19 subjects (6). Shi et al. indicated that LDH levels are essential risk factors for progression in mild COVID-19 patients (7). Cardiovascular disease is a common comorbidity in COVID-19 disease. Cardiac arrhythmia has been related to increased fatality COVID-19 patients (8). Previous reports have shown that atrial fibrillation (AF) and heart failure have been showed in patients with COVID-19 (9). Italian National Institute of Health was registered that one-fourth of patients who died had AF, and it was the most frequently observed comorbidity in non-surviving COVID-19 patients (10). Here, the objective was to examine the relationship of LDH levels and atrial fibrillation (AF) in 195 COVID-19 patients. Secondly, we assessed whether LDH levels predicted mortality in fatal COVID-19-AF patients.

Materials and Methods

The investigation was an observational and cross-sectional study. Ethics committee approval was obtained from Adıyaman University (Ethic committee no: 2020/8-12/ 22.09.2020). From April 2020 to August 2020, a total of 195 consecutive COVID-19 [45 AF (+) and 150 AF (-)] subjects, who were admitted to the hospital ward and ICU, were registered for the study. The real-time reverse transcription–polymerase chain reaction (RT-PCR) on nasal swabs from these patients complaining of COVID-19 related symptoms including cough, fever, shortness of breath, gastrointestinal illness, fatigue, clinician concern, or known exposure to a coronavirus positive patient. According to the WHO, the determination of COVID-19 is based on the RT-PCR assay. COVID-19 positivity was determined following the outcome of the RT-PCR assay. Critical illness was defined for those who needed admittance to the ICU, those who needed mechanical ventilation, or those who died. Inclusion of severe status demonstrated the following: respiratory rate ≥30 times/minute, respiratory distress; below-resting rate, O_2 saturation of less than or equal to 93 percent; (PaO_2/FiO_2) in arterial blood less than or equal to 300 mmHg (11). Exclusion criteria were refusal to participate in the study: known malignancy, age < 18 years, pregnancy, systemic inflammatory disorders, and negative PCR tests. Electronic health records were used to obtain age, gender, smoking status, medical history (e.g., hypertension (HT), diabetes mellitus (DM), AF, hyperlipidemia (HL), chronic kidney disease (CKD), coronary artery disease (CAD), and COPD. Besides, past medication history (anti-hypertensive, anti-diabetic, oral anticoagulant (OAC) was obtained from medical records. Atrial fibrillation was defined at least 30 s of atrial fibrillation documented by telemetry, as a history of atrial fibrillation, or electrocardiography (ECG) in 12 leads. For the ECG, AF arrhythmia was diagnosed using regular P wave substitution with f-waves (irregular and fast wavelets) (12). Medical laboratory results, including the numbers of lymphocytes, neutrophil, platelets, ALT, AST, CKMB, serum LDH, serum creatinine, serum glucose, sodium, potassium, blood urea nitrogen, cardiac troponin I, concentrations of D-dimer, CRP, procalcitonin, were collected for each patient from electronic medical recorded data. This study was reviewed by our institutional IRB and performed under the ethical standards of the Declaration of Helsinki.

Statistical analysis: Data were analyzed statistically using SPSS software version 25.0 for Windows (SPSS, Chicago, IL, USA). The Kolmogorov-Smirnov test was used to test whether the data were distributed normally. Continuous normally distributed variables are expressed by their mean ± standard deviation (SD), while non-normally distributed variables are expressed as median with interquartile range (IQR). The categorical variables are presented as number (percentage). Normally distributed data were analyzed using Student's t-tests. Moreover, not normally distributed data were tested non-parametrically using the Mann-Whitney U test. Dichotomous or nominal variables were compared using the chi-square test or Fisher's exact test. Pearson correlation coefficient analyses was used for all correlation tests. A Receiver-operating characteristic (ROC) curve analysis was used to determine the optimum cut-off level for the LDH value that best predicted mortality in COVID-19 patients. A multiple logistic regression model was used for analysis to determine the independent predictors of mortality in COVID-19-AF patients. The level of statistical significance was determined as $p<.05$.

Results

Demographic and clinical findings are shown in Table 1. Patients with AF were older than subjects without AF (71.9 ± 11.9 vs. 62.3 ± 14.4).

Table 1: The demographic and clinical data of the AF and non-AF patients.

	Total (n=195)	Non-AF (n=150)	AF (n=45)	p
Age (years)	64.5±14.4	62.3±14.4	71.9±11.9	<0.001
Male, n (%)	111(57)	87(58)	24(53)	0.57
Hypertension, n (%)	113(58)	82(55)	31(67)	0.09
Diabetes mellitus, n (%)	78(40)	62(41)	16(36)	0.48
Hyperlipidemia, n (%)	50(26)	41(27)	9(20)	0.32
Coronary artery disease, n (%)	54(28)	34(23)	20(45)	0.004
Smoking, n (%)	84(43)	63(42)	21(47)	0.57
COPD, n (%)	45(23)	24(16)	11(24)	0.33
Chronic kidney disease, n (%)	28(14)	17(11)	11(24)	0.02
Beta-blocker, n (%)	66(34)	38(25)	28(62)	<0.001
ACE inhibitor, n (%)	37(19)	25(17)	12(27)	0.13
Calcium channel blocker, n (%)	54(28)	41(27)	13(29)	0.83
Acetylsalicylic acid, n (%)	49(25)	39(26)	10(23)	0.59
Oral anticoagulant, n (%)	37(19)	2(1)	35(80)	0.001
Oral antidiabetic, n (%)	64(32)	50(33)	14(31)	0.78
Insulin, n (%)	25(13)	19(12)	6(13)	0.90
Mortality, n (%)	45(23)	30(20)	15(33)	0.06
Troponin (ng/mL)	12.5 (6.5-40.0)	11.0 (5.7-33.6)	24.0 (12.0-126.0)	0.001
D-Dimer (ng/mL)	78.0 (40.0-750.0)	84.5 (35.0-836.8)	73.0 (41.0-619.5)	0.97
Creatine Kinase MB (ng/mL)	2.0 (1.0-8.0)	1.8 (1.0-7.4)	2.7 (1.0-14.0)	0.08
Creatinine (mg/dl)	0.9 (0.7-1.3)	0.9 (0.7-1.3)	1.0 (0.8-1.6)	0.03
Urea (mg/dL)	40.0 (27.0-70.0)	37.0 (26.0-66.3)	43.0 (32.5-82.0)	0.18
Sodium (mEq/L)	137.3±7.2	137.8±7.5	135.6±6.0	0.07
Potassium (mEq/L)	4.2±0.7	4.2±0.7	4.3±0.9	0.25
Serum glucose (mg/dl)	153.7±80.8	157.7±84.6	139.6±64.4	0.20
C-reactive protein (mg/L)	90.0 (49.0-142.0)	97.5 (55.0-146.8)	72.0 (31.0-130.0)	0.08
Procalcitonin (ng/mL)	0.2 (0.1-0.6)	0.2 (0.1-0.5)	0.2 (0.1-1.1)	0.83
White blood cell count ($10^3/mm^3$)	6.5 (5.2-10.0)	6.5 (5.2-9.7)	7.4 (4.9-10.8)	0.75
Hemoglobin (g/dL)	12.7±1.9	12.7±1.8	13.0±2.0	0.34
Neutrophil ($10^3/mm^3$)	5.1 (3.4-8.1)	5.0 (3.6-8.1)	5.7 (2.7-8.3)	0.90
Lymphocyte ($10^3/mm^3$)	1.1 (0.7-1.4)	1.0 (0.7-1.4)	1.1 (0.8-1.6)	0.38
Platelet count ($10^3/mm^3$)	215.1±86.9	222.0±87.0	192.2±83.6	0.04
Aspartate transaminase (U/l)	38.0 (28.0-58.0)	38.0 (29.0-55.8)	36.0 (23.0-66.0)	0.86
Alanine transaminase (U/l)	25.0 (18.0-42.5)	26.0 (18.0-43.5)	25.0 (16.0-39.0)	0.57
Lactate dehydrogenase (U/l)	420.4±90.0	399.5±56.0	485.1±142.0	0.001
Follow-up, (days)	9.0 (5.0-14.0)	10.5 (6.0-15.0)	7.0 (2.0-11.0)	0.003

COPD, HT, DM, HL, and smoking rates were similar between COVID-19-non-AF patients and COVID-19-AF patients. CAD and CKD were significantly increased in COVID-19-AF subjects compared to the COVID-19-non-AF group ($p < 0.05$). Thirty-seven patients were taking OAC (n=32, COVID-19-AF and n=2, COVID-19-non-AF).

Table 2: The demographic and clinical data of the fatal and non-fatal patients.

	Non-Fatal (n=150)	Fatal (n=45)	p value
Age (years)	61.7±14.0	74.0±11.4	0.001
Male, n (%)	82(55)	29(65)	0.24
Hypertension, n (%)	81(54)	32(71)	0.04
Diabetes mellitus, n (%)	60(40)	18(41)	0.95
Hyperlipidemia, n (%)	40(27)	10(22)	0.54
Coronary artery disease, n (%)	33(22)	21(47)	0.001
Smoking, n (%)	62(43)	22(49)	0.36
COPD, n (%)	22(15)	12(27)	0.06
Chronic kidney disease, n (%)	19(13)	9(20)	0.21
Beta-blocker, n (%)	47(30)	19(42)	0.17
ACE inhibitor, n (%)	28(19)	9(20)	0.84
Calcium channel blocker, n (%)	37(25)	17(38)	0.08
Acetylsalicylic acid, n (%)	34(23)	15(33)	0.15
Oral anticoagulant, n (%)	25(17)	12(27)	0.13
Oral antidiabetic, n (%)	50(33)	14(30)	0.78
Insulin, n (%)	21(14)	4(9)	0.36
Atrial fibrillation, n (%)	30(20)	15(33)	0.06
Troponin (ng/mL)	5.7 (3.2-24.0)	36.0 (11.9-139.5)	0.001
D-Dimer (ng/mL)	62.5 (33.8-437.3)	269.0 (60.5-2250.0)	0.001
Creatine Kinase MB (ng/mL)	1.4 (0.9-8.0)	3.3 (2.0-7.8)	0.001
Creatinine (mg/dl)	0.9 (0.7-1.2)	1.1 (0.8-2.2)	0.001
Urea (mg/dL)	35.5 (24.8-59.3)	66.0 (40.5-118.0)	0.001
Sodium (mEq/L)	137.0±6.6	138.5±8.9	0.22
Potassium (mEq/L)	4.2±0.7	4.2±0.9	0.78
Serum glucose (mg/dl)	147.9±73.3	171.6±99.6	0.08
C-reactive protein (mg/L)	77.0 (39.8-122.5)	128.0 (89.9-229.0)	0.001
Procalcitonin (ng/mL)	0.1 (0.1-0.3)	0.8 (0.2-1.9)	0.001
White blood cell count ($10^3/mm^3$)	6.3 (4.9-8.8)	9.5 (6.2-14.1)	0.001
Hemoglobin (g/dL)	12.7±1.9	12.9±1.8	0.44
Neutrophil ($10^3/mm^3$)	4.8 (3.2-6.9)	7.2 (4.6-11.8)	0.001
Lymphocyte ($10^3/mm^3$)	1.1 (0.9-1.5)	0.8 (0.5-1.1)	0.002
Platelet count ($10^3/mm^3$)	212.9±81.5	222.4±103.8	0.52
Aspartate transaminase (U/l)	37.0 (27.8-52.3)	47.0 (32.0-73.5)	0.01
Alanine transaminase (U/l)	25.0 (18.0-42.0)	28.0 (15.5-51.0)	0.78
Lactate dehydrogenase (U/l)	404.0±60.0	470.0±144.0	0.001
Follow-up, (days)	10.0 (5.0-14.0)	9.0 (6.0-15.0)	0.89

COPD, Chronic obstructive pulmonary disease ACE, Angiotensin Converting Enzyme.

In the hematological analysis, platelet counts were significantly lower in the COVID-19-AF group compared to the COVID-19-non-AFcohort. At the time of admission, LDH was increased in COVID-19-AF subjects compared to COVID-19-non-AF subjects (485.1±142.0 vs. 399.5±56.0; $p<0.001$). The clinical and demographics findings for fatal and non-fatal patients are shown in Table 2. Non-fatal patients were younger than fatal patients (61.7±14.0 vs. 74.0±11.4).

Table 3: Correlation analyzes between the Lactate dehydrogenase and clinical parameters.

	All patients		AF patients	
	r	p	r	P
Troponin	0.267	<0.001	0.404	0.006
D-Dimer	0.096	0.184	0.372	0.012
C-reactive protein	0.218	0.002	0.454	0.002
Procalcitonin	0.281	<0.001	0.392	0.008
Lymphocyte	0.011	0.875	-0.273	0.073
Platelet count	-0.079	0.275	0.008	0.960

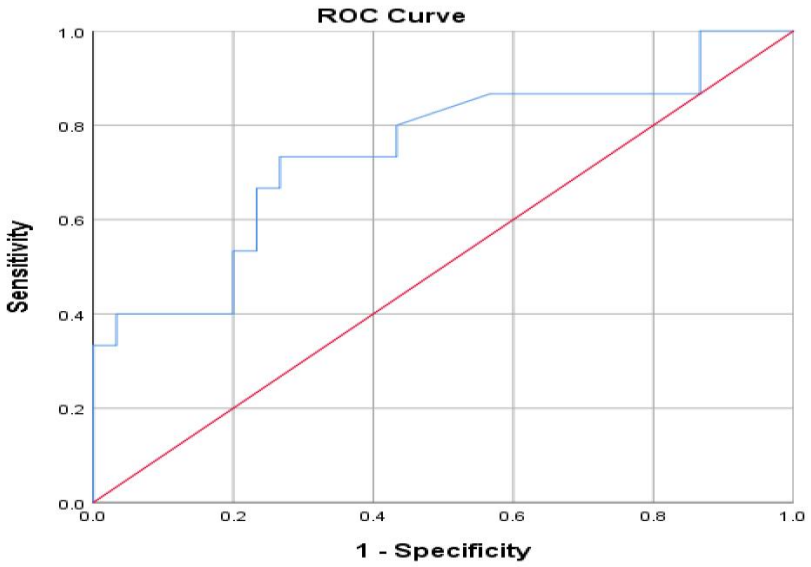

Figure 1. In ROC curve analyses, lactate dehydrogenase of 400 was determined as an effective cut-off point in COVID-19 mortality with a sensitivity of 64% and specificity of 63% (LDH; AUC= 0.646, p<0.001; 95% CI (0.552- 0.740)).

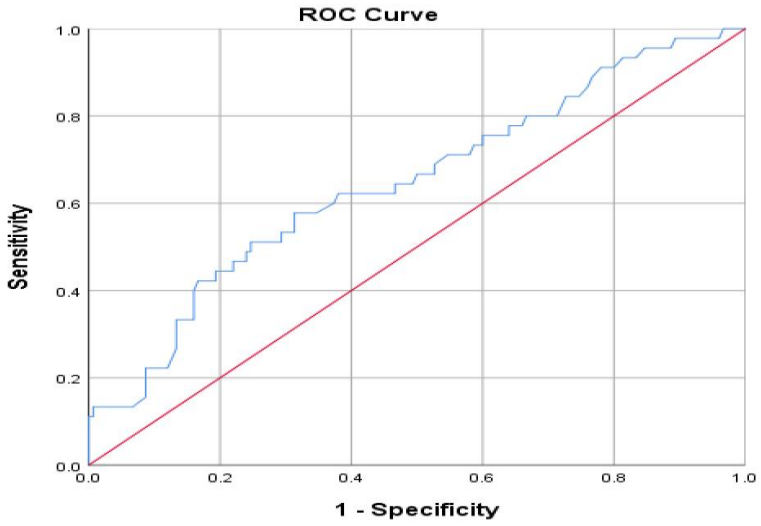

Figure 2. In ROC curve analyses, lactate dehydrogenase of 443 was determined as an effective cut-off point in mortality of COVID-19 patients with atrial fibrillation with a sensitivity of 73% and specificity of 74% (LDH; AUC= 0.744, p<0.001; 95% CI (0.581- 0.908)).

Table 4: Multiple logistic regression analysis to determine the independent predictors of mortality in COVID-19 patients with atrial fibrillation.

	OR	95% CI	p
Age	1.238	1.068-1.434	0.005
Coronary artery disease	1.292	0.114-3.058	0.836
Chronic kidney disease	2.733	0.215-3.718	0.438
Troponin	0.998	0.998-1.001	0.129
D-Dimer	1.002	1.000-1.003	0.087
Creatine Kinase MB	1.004	0.953-1.059	0.871
Platelet count	1.003	0.992-1.015	0.575
Lactate dehydrogenase	1.009	1.002-1.019	0.039

Although comorbidities were generally similar between the groups, CAD was increased for the fatal cohort. Hematological analyses for neutrophils and white blood cell counts were significantly increased for the fatal COVID-19 subjects in comparison to non-fatal COVID-19 subjects. Conversely, lymphocyte levels were lower in the fatal group. In the biochemical analysis, troponin, procalcitonin, and CRP were increased in the fatal group compared to the non-fatal group. Moreover, fatal COVID-19 patients had higher LDH levels compared to non-fatal patients (470.0±144.0 vs 404.0±60.0; $p<0.001$). Table-3 presents the correlation analyzes between the LDH and clinical parameters. There was a positive and significant correlation between the LDH and troponin, CRP, and procalcitonin in all patients and AF patients. In ROC analysis, lactate dehydrogenase of 400 was determined as an effective cut-off point in COVID-19 mortality with a sensitivity of 64% and specificity of 63% (AUC= 0.646, $p<0.001$; 95% CI; 0.552-0.740) (Figure-1). Moreover, LDH of 443 was determined as an effective cut-off point in mortality of AF patients with a sensitivity of 73% and specificity of 74% (AUC= 0.744, $p<0.001$; 95% CI; 0.581-0.908) (Figure-2). Multiple logistic regression analyses of the association between the mortality and multiple parameters are listed in Table 4. In multivariate analyses, LDH (OR: 1.009, CI: 1.002-1.019, p=0.039) and age (OR: 1.238, CI: 1.068-1.434, p=0.005) were independent predictors of mortality in COVID-19 patients with AF.

Discussion

Here, we presented that fatal COVID-19 patients had significantly higher LDH levels compared to non-fatal patients at the admission. LDH levels were significantly and positively correlated with troponin, CRP, and procalcitonin in COVID-19-AF patients. Besides, LDH levels were independently related to mortality in COVID-19-AF patients (OR: 1.009, p = 0.039). The clinical COVID-19 symptoms has been identified as mildly asymptomatic and severe ARDS, which is the most common cause of death (13). LDH levels are a marker for the poor prognosis of patients with ARDS (14). LDH levels have been shown to be high following other viral infections including MERS-CoV and H7N9 (15,16). Increased LDH levels can be observed in more than 40% of COVID-19 patients (4). Moreover, it is known that LDH is related to increased mortality following SARS-CoV2 infection (6). LDH is an enzyme involved in energy production, and it is present in almost all tissue cells. LDH has been identified as five separate isozymes in human subjects. LDH is considered an inflammatory biomarker, which indicates tissue damage (17). Moreover, LDH isoenzymes test may help to locate damaged organs. Interestingly, increased LDH levels have been found in acute and severe pulmonary injury (18). In addition, augmented LDH levels have also been reported in patients with thrombotic angiopathy, which is associated with myocardial damage and renal failure (19,20). Increased LDH levels indicate the inflammatory status and pulmonary damage in COVID-19 patients (21). Han et al. showed that LDH could be powerful predictor for early determination of lung injury in critically ill COVID-19 subjects (22). Also, Cai et al. evaluated 432 COVID-19 patients and presented that severe COVID-19 subjects had increased LDH levels in comparison to mild COVID-19 cases (23). The correlation between LDH and CRP levels shows the inflammatory conditions and tissue damage in COVID-19 subjects. Nine studies showed that there was a greater than 16-fold higher all-mortality odds and

a greater than 6-fold higher odds of severe disease in COVID-19 subjects with elevated LDH. The authors also showed that high LDH was found in >95 percent of fatal subjects in comparison to the greater than 60 percent of survivors (24). Besides, a previous study indicated that there was a strong and negative association between respiratory performance (PaO_2 / FiO_2) and LDH levels in COVID-19 patients (r = 0.62, p-value <0.0001) (25). ICU subjects had increased LDH compared to non-ICU unit patients, and was directly proportional to the length of ICU stay (26). AF patients have higher levels of ACE-2 activity. The severe course of COVID-19 disease can be explained by the increased ACE-2 activity in AF patients. A previous study reported that 51 (60%) of 85 fatal COVID-19 cases had cardiac arrhythmia, and it was associated with increased mortality in these patients (8). Inciardi et al. evaluated cardiac diseases in COVID-19 patients, and they showed that 20 of 53 patients had AF (9). In our study, the AF rate was 23% in all patients and 33% in fatal cases. A previous study proposed that LDH > 245 U/L can predict the progress of COVID-19 (21). Besides, we indicated that LDH> 346 U/L could predict the mortality in COVID-19 patients with AF. Han et al. demonstrated that LDH positively associated with CRP and cardiac troponin I, and negatively associated with lymphocyte counts. The authors also reported that LDH was positively and significantly associated with SOFA, APACHE-II, PSI, and CT scores (22). In our study, similar to previous data, LDH positively correlated with CRP, D-Dimer, procalcitonin troponin I, and negatively correlated with lymphocytes in COVID-19-AF patients.

Limitations: This study has limitations. The number of cases was small because of the single-center design of the study and the more patient numbers are needed to strengthen the results and findings in this study. Another limitation is that only patients with AF were included, and other cardiac arrhythmias were not analyzed. LDH isoenzymes were not tested due to limited resources. The lack of a CT score is another limitation of this study. Against the limits, our research is essential as it provides a significant result for further studies about LDH levels in fatal COVID-19-AF patients.

Conclusion

We showed that increased LDH has the potential capability to predict all-cause mortality in COVID-19-AF subjects. High LDH levels need careful observation to prevent the possible development of adverse events in COVID-19-AF patients. Therefore, our findings could guide physicians to identify the critically ill COVID-19-AF patients.

Ethics Approval: Ethics committee approval was obtained from Adıyaman University (Ethic committee no: 2020/8-12/ 22.09.2020).

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