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Prior left ventricular systolic dysfunction is an independent predictor of in-hospital mortality in patients with COVID-19

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ABSTRACT

Objectives: This study aims to examine the effect of left ventricular systolic dysfunction (LVSD) on in-hospital mortality in patients hospitalized for novel coronavirus disease 2019 (COVID-19).

Patients and methods: Between June 2020 and December 2020, a total of 847 patients (423 males, 424 females; median age: 68 years; range, 58 to 77 years) who had echocardiography and had positive real-time reverse transcriptase-polymerase chain reaction were retrospectively analyzed. A left ventricular ejection fraction (LVEF%) of <50% was defined as LVSD.

Results: In 138 patients, LVEF was <50% and in 709 patients LVEF was >50% (non-LVSD). Of the patients with LVSD, 89 had mid-range LVEF (40 to 49%), and 49 had reduced LVEF (LVEF <40%). Intensive care unit admission (p<0.001), myocardial injury (p<0.001), and mechanical ventilation (p<0.001) were more frequent in patients with LVSD, and LVSD was found to significantly increase the risk of and in-hospital mortality (odds ratio=2.57, 95% confidence interval, 1.43-4.60, p=0.002). Among patients with LVSD, no significant difference was observed in terms of in-hospital mortality between patients with mid-range LVEF and patients with reduced LVEF.

Conclusion: Our study results showed that LVSD significantly increased the risk of in-hospital mortality in patients hospitalized for COVID-19. In addition, an increased risk of in-hospital mortality was present in both the mid-range LVEF and the reduced LVEF group, separately.

Keywords: COVID-19, in-hospital mortality, left ventricular systolic dysfunction.

Novel coronavirus disease 2019 (COVID-19) remains an important cause of mortality.[1] It may cause mild respiratory tract infection, as well as severe pneumonia and acute respiratory distress syndrome. Besides, it can cause failure in many organs such as the heart, kidney, and liver, and can cause death.[2,3] Complications such as myocarditis, heart failure (HF), arrhythmias, and myocardial ischemia can occur, and high mortality can be seen in these patient groups.[4-6]

Cardiovascular (CV) disease and classical CV risk factors are common comorbidities in COVID-19 patients and have been associated with poor outcomes.[2] Heart failure, one of these comorbidities, is one of the leading causes of death in the world. Respiratory infections are one of the most common factors that trigger decompensation in HF patients and are independently associated with hospital mortality.[7,8] Also, COVID-19 patients with HF have been found to have a predisposition to acute decompensation.[9] Small-scale studies evaluating left ventricular (LV) functions with echocardiography in COVID-19 patients found that the disease was more severe, and mortality was higher in patients with decreased LV functions.[6,10]

In the literature, there are not sufficient data regarding the prognosis of COVID-19 in patients with previously known LV systolic dysfunction (LVSD). In this study, we aimed to examine the effect of prior LVSD on in-hospital mortality in patients hospitalized with COVID-19.

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PATIENTS AND METHODS

This single-center, retrospective, observational study was conducted at University of Health Sciences Diyarbakır Gazi Yaşargil Education and Research Hospital, Department of Cardiology between June 1st, 2020 and December 31st, 2020. Patients aged >18 years hospitalized for COVID-19 pneumonia were evaluated. Patients who had transthoracic echocardiography and had positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) were screened for the study. Patients who had negative RT-PCR results were excluded from the study. Patients who did not have echocardiography and those hospitalized for reasons that may affect LV ejection fraction (LVEF), such as myocardial infarction (MI) and myocarditis after the date of echocardiography were excluded from the study. Also, patients who developed new LVSD due to MI, stress cardiomyopathy, and myocarditis while being followed with COVID-19 were excluded from the study. A total of 5,920 patients were screened for the study, and 847 patients (423 males, 424 females; median age: 68 years; range, 58 to 77 years) were included in the study. The study flow chart is shown in Figure 1. The study protocol was approved by the University of Health Sciences Diyarbakır Gazi Yaşargil Education and Research Hospital Ethics Committee (date/no: 26.03.2021/737). The study was conducted in accordance with the principles of the Declaration of Helsinki.

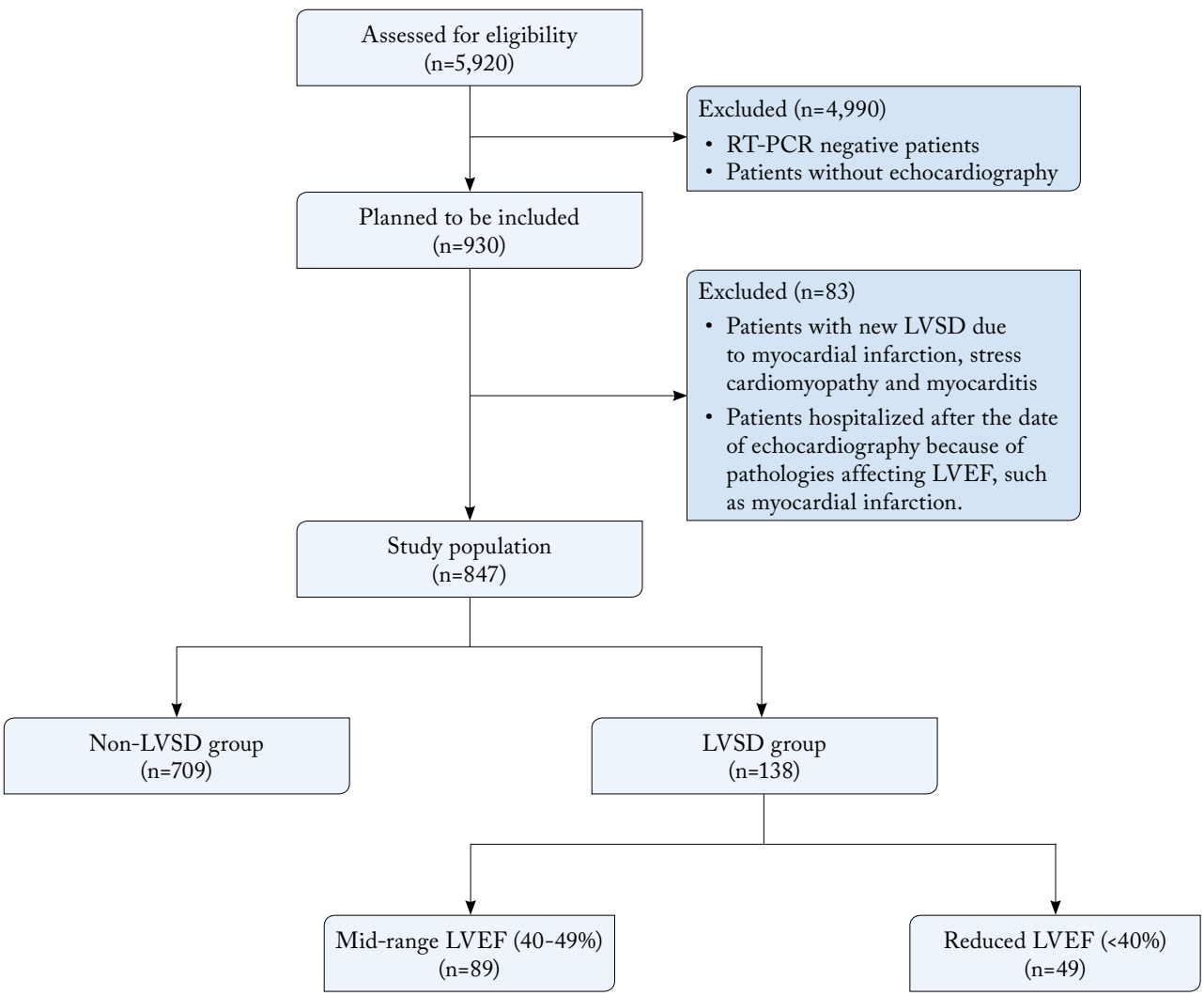

Figure 1. Study flow chart.

RT-PCR: Real-time reverse transcriptase-polymerase chain reaction; LVSD: Left ventricular systolic dysfunction; LVEF: Left ventricular ejection fraction.

Table 1
Demographic, clinical characteristics, laboratory findings and outcomes of the study population

	Total (n=847)				Non-LVSD (n=709)				LVSD (n=138)				
	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	*p*
Age (year)			68	58-77			66	57-75			73	67-82	<0.001
Sex													
Female	424	50.1			368	51.9			56	40.1			0.015
Comorbidities													
Hypertension	521	61.5			405	57.1			116	84.1			<0.001
Diabetes mellitus	270	31.9			215	30.3			55	39.9			0.028
Coronary artery disease	334	39.4			222	31.3			112	81.2			<0.001
Chronic obstructive pulmonary disease	115	13.6			86	12.1			29	21			0.008
Chronic renal failure	46	5.4			34	4.8			12	8.7			0.100
Atrial fibrillation	50	5.9			32	4.5			18	13			<0.001
Stroke	56	6.6			46	6.5			10	7.2			0.888
Malignancy	47	5.5			44	6.2			3	2.2			0.091
Ejection fraction (%)			60	55-60			60	58-63			43	36-45	
Myocardial injury	84	9.9			56	7.9			28	20.3			<0.001
Symptoms													
Weakness/fatigue	395	46.6			322	45.4			73	52.9			0.107
Cough	400	47.2			343	48.4			57	41.3			0.128
Shortness of breath	671	79.2			554	78.1			117	84.8			0.078
Fever	275	32.5			224	31.6			51	37			0.218
Clinical finding													
Oxygen saturation (%)			88	82-91			88	82-91			86	80-90	0.024
Heart rate (beat/min)			85	76-95			85	76-95			85	76-96	0.768
Temperature (°C)			36.7	36.5-37.0			36.7	36.4-37.0			36.7	36.5-37.1	0.006
Systolic blood pressure (mmHg)			120	110-130			120	110-127			120	110-130	0.083
Diastolic blood pressure (mmHg)			70	60-80			70	60-80			70	61-80	
Laboratory													
White blood cell (10^3/uL)			7.52	5.50-10.65			7.28	5.49-10.24			8.53	6.10-13.41	0.004
Neutrophil (10^3/uL)			5.80	3.95-8.77			5.59	3.88-8.16			6.87	4.35-11.42	0.001
Lymphocyte (10^3/uL)			1.03	0.71-1.49			1.05	0.72-1.49			0.97	0.65-1.46	0.061
Hemoglobin (g/dL)			13.1	11.914.4			13.2	12.0-14.4			12.7	11.0-14.2	0.012
Platelet (10^3/uL)			212	168-265			213	170-259			210	152-282	0.484
C-reactive protein (mg/L)			84	41-144			84	41-141			83	40-155	0.674
D-dimer (ng/mL)			303	196-611			289	190-538			395	249-878	<0.001
Ferritin (µg/L)			433	214-871			433	214-865			458	215-879	0.845
Lactate dehydrogenase (IU/L)			327	256-434			330	257-435			307	253-431	0.338
Procalsitonin (ng/mL)			0.12	0.07-0.33			0.11	0.07-0.29			0.21	0.10-0.64	<0.001
Troponin (ng/mL)			0.1	0.1-0.1			0.1	0.1-0.1			0.1	0.1-0.12	<0.001
Creatinine (mg/dl)			1.00	0.79-1.43			0.93	0.78-1.34			1.35	0.98-2.03	<0.001
Alanin transaminaz (U/L)			22	15-36			23	15-37			18	13-30	0.001
Albumin (g/L)			31	28-35			32	28-35			29	27-32	<0.001
Sodium (mmol/L)			136	133-139			136	134-139			135	133-139	0.096
Total calcium (mg/dL)			8.2	7.8-8.6			8.2	7.8-8.6			8.1	7.7-8.5	0.064
Potassium (mmol/L)			4.21	3.87-4.66			4.18	3.86-4.62			4.47	4.00-4.90	<0.001

Table 1
Continued

	Total (n=847)				Non-LVSD (n=709)				LVSD (n=138)				
	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	*p*
Pre-hospitalization medications													
Beta-blockers	366	43.2			263	37.1			103	74.6			<0.001
RAAS inhibitors	480	56.7			372	52.5			108	78.3			<0.001
Calcium channel blockers	276	32.6			225	31.7			51	37			0.231
Thiazide	278	32.8			223	31.5			55	39.9			0.054
Mineralocorticoid receptor antagonist	37	4.4			14	2			23	16.7			<0.001
Loop diuretic	86	10.2			34	4.8			52	37.7			<0.001
Antiplatelet	411	48.5			306	43.2			105	76.1			<0.001
Oral anticoagulant	41	4.8			22	3.1			19	13.8			<0.001
Statin	182	21.5			132	18.6			50	36.2			<0.001
In-hospital medication													
Anticoagulant	766	90.4			640	90.3			126	91.3			0.825
Favipiravir	759	89.6			637	89.8			122	88.4			0.723
Tocilizumab	49	5.8			44	6.2			6	4.3			0.321
Steroids	602	71.1			504	71.1			98	71			0.986
Vasopressor	114	13.5			85	12			29	21			0.007
IV diuretic	135	15.9			66	9.3			69	50			<0.001
Nasal oxygen	652	77			542	76.4			110	79.7			0.405
Outcomes													
Intensive care unit admission	299	35.3			227	32			72	52.2			<0.001
Length of stay hospital (day)			8	6-12			8	6-12			9	6-13	0.181
Mechanical ventilation	218	25.7			154	21.7			64	46.4			<0.001
All cause in-hospital mortality	187	22.1			129	18.2			58	42			<0.001

IQR: Interquartile range; LVSD: Left ventricular systolic dysfunction; RAAS: Renin-angiotensin-aldosterone system; Renin-angiotensin-aldosterone system inhibitors.

The demographic, clinical characteristics and laboratory parameters, comorbidities, hospitalization time of the patients during hospitalization were collected from the electronic medical records of the hospital and national electronic medical record system. We have obtained other hospital admissions from these national records.

The LVEF% was measured by the biplane Simpson method or Teicholz method.[11] In addition, LVSD was calculated as an LVEF of <50%. Mid-range LVEF (40 to 49%) and reduced LVEF (<40%) were calculated according to the European Society of Cardiology (ESC) Heart failure guidelines.[12] Myocardial injury was defined as the presence of at least one cardiac troponin value above the 99th percentile upper reference limit.[13] The study outcome was in-hospital mortality.

The primary outcome measure of the study was in-hospital mortality.

Statistical analysis

Statistical analysis was performed using the "rms", "Hmisc", and "ggplot2" packages with R studio version 4.02 (R Project, Vienna, Austria). Continuous variables were presented in median and interquartile range (IQR, 25th-75th). Categorical variables were presented in number and frequency. The chi-square test was used to compare categorical variables between groups. Continuous variables were compared using the Mann-Whitney U tests. A p value of <0.05 was considered statistically significant.

We used the logistic regression method to investigate the relationship between primary outcome and candidate predictors. Effects of individual

Table 2
Univariate and multivariate logistic regression analyses for predictors of in-hospital mortality

	Univariable analysis			Multivariable analysis		
Variables	OR	95% CI	p	OR	95% CI	p
Age (year)	1.05	1.04-1.07	<0.001	1.05	1.03-1.07	<0.001
Sex						
Male	1.24	0.89-1.71	0.201			
Hypertension	1.48	1.05-2.09	0.027	0.98	0.59-1.62	0.934
Diabetes mellitus	1.55	1.10-2.17	0.011	2.08	1.29-3.36	0.003
Coronary artery disease	1.77	1.28-2.46	0.001	1.21	0.75-1.98	0.437
Left ventricular systolic dysfunction	3.30	2.34-4.87	<0.001	2.57	1.43-4.60	0.002
Atrial fibrillation	1.90	1.03-3.49	0.039	1.12	0.50-2.51	0.790
Chronic obstructive pulmonary disease	1.43	0.918-2.23	0.113			
Chronic renal failure	1.77	0.93-3.35	0.081			
Myocardial injury	5.810	3.63-9.31	<0.001	3.30	1.68-6.45	<0.001
Creatinine (mg/dL)	1.11	1.01-121	0.023	1.02	0.89-1.16	0.785
White blood cell (10^3/uL)	1.09	1.05-1.12	<0.001	0.97	0.94-1.03	0.555
Lymphocyte (10^3/uL)	0.65	0.71-2.43	0.003	0.89	0.66-1.20	0.461
D-dimer (ng/mL) (per 100 units increase)	1.02	1.01-1.03	<0.001	1.01	1.00-1.02	0.013
LDH (U/L) (per 10 units increase)	1.03	1.02-1.04	<0.001	1.01	1.00-1.02	0.194
CRP (mg/L) (per 10 units increase)	1.07	1.05-1.09	<0.001	0.99	0.96-1.03	0.696
Oxygen saturation (%)	0.84	0.82-0.87	<0.001	0.85	0.82-0.87	<0.001
Heart rate (beat/min)	1.03	1.01-1.04	<0.001	1.02	1.00-1.03	0.012
Malignancy	1.22	0.67-2.40	0.561			
Cerebrovascular event	1.31	0.71-2.43	0.384			
Systolic blood pressure (mmHg)	1.07	1.00-1.02	0.248			

OR: Odds ratio; CI: Confidence interval; LDH: Lactate dehydrogenase; CRP: C-reactive protein.

predictors were reported using odds ratio [OR] and 95% confidence interval [CI].

We selected predictive candidate variables based on existing studies and known or plausible associations with COVID-19 infection morbidity and mortality.[14,15] Variables (age, sex, cerebrovascular event, malignancy, hypertension, diabetes mellitus [DM], coronary artery disease, atrial fibrillation, chronic renal failure, chronic obstructive pulmonary disease, myocardial injury, systolic blood pressure, heart rate, oxygen saturation, white blood count, lymphocytes, creatinine, lactate dehydrogenase, C-reactive protein, D-dimer) were used in regression analysis. Univariate and multivariate logistic regression analyses were performed to determine the effect of LVSD on in-hospital mortality. Variables with a p value of <0.05 in the univariate analysis were added to the model in the multivariate analysis. Furthermore, LVSD was added to the full model first as two groups (LVSD and non-LVSD) and, then, as three groups (mid-LVEF, reduced LVEF, and non-LVSD). Adjusted variable three-dimensional (3D) plot of the model was performed to predict outcome (mortality) probabilities according to age scores and LVSD.

RESULTS

A total of 847 patients, including 709 (83.8%) non-LVSD and 138 (16.2%) LVSD patients, were included in the study. Intensive care unit admission (52.1% *vs.* 32%), myocardial injury (20% *vs.* 8%), mechanical ventilation (46% *vs.* 22%), and death (42% *vs.* 18%) were higher in the LVSD group. The demographic, clinical characteristics, laboratory findings, and outcomes of the study population are given in Table 1.

Mortality was significantly higher in the LVSD group than in the non-LVSD group, and LVSD significantly increased the risk of in-hospital mortality in the multivariate logistic regression analysis (OR=2.57, 95% CI: 1.43-4.60, p=0.002). When LVSD was added to the model as two separate groups, both mid-range LVEF and reduced LVEF was observed as independent predictors of in-hospital mortality (OR= 2.66, 95% CI: 1.38-5.14 p=0.004, OR=2.39 95% CI: 1.02-5.62, p=0.046, respectively). Age, myocardial injury, DM, D-dimer, heart rate, and oxygen saturation were other parameters that significantly increased in-hospital mortality risk. Univariate and multivariate logistic regression analyses were performed to evaluate the effect of LVSD on in-hospital mortality (Table 2). Figure 2 shows adjusted variable 3D plots of the full model, predicted probabilities of mortality according to age and LVSD presence.

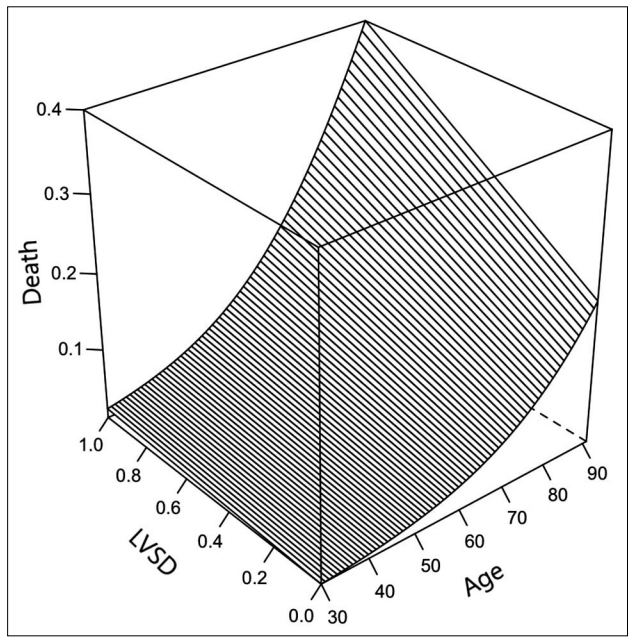

Figure 2. Three-dimensional plot showing the effect of age and LVSD on in-hospital mortality after adjustment with clinical predictors.
LVSD: Left ventricular systolic dysfunction.

DISCUSSION

According to the results of this study, LVSD was associated with poor outcomes and it was found to be an independent predictor of in-hospital mortality and an approximately 2.6-fold increase in risk was observed, after adjustment with multivariate analysis. No significant difference was observed in mid-range LVEF and reduced LVEF groups in terms of in-hospital mortality, and the mortality risk increased significantly in both groups in the regression analysis, compared to the non-LVSD group.

Although COVID-19 infection begins as a respiratory tract infection, pathological findings can often occur in many organs and tissues, such as the heart. In the studies conducted, the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) was seen in macrophages, endothelial cells, and pericytes, and in the autopsy series, evidence of viral replication in myocardial cells was obtained.[16] Conditions such as the increased risk of MI, fulminant

myocarditis, arrhythmias, venous thromboembolism, and Takotsubo cardiomyopathy are the most common CV complications identified in COVID-19 patients.[17] In addition to direct myocardial damage caused by the virus by binding to the angiotensin-converting enzyme 2 (ACE-2) receptor, which is important for cardiac functions, causing ACE-2 receptor downregulation, the release of inflammatory mediators, endothelial dysfunction, and myocardial damage due to micro- and macro-thrombi may play a role in the occurrence of these complications.[18-20] Myocardial injury, defined by the increased troponin levels, presented mortality greater than those without myocardial injury, is an independent risk factor for mortality.[15] In our study, the myocardial injury was observed as the independent predictor of mortality (OR=3.30, p<0.001). Arterial and venous thrombosis can be seen in COVID-19.[21] Studies have found that elevated D-dimer increases the risk of mortality.[22] In our study, a significant increase was observed in-hospital mortality risk with elevated D-dimer. Also, age, DM, heart rate, and oxygen saturation were other factors that significantly increased the risk of in-hospital mortality.

Cardiovascular diseases are among the most common comorbidities in patients hospitalized with COVID-19 and are associated with poor outcomes.[2] Heart failure is one of the important causes of morbidity and mortality, particularly in advanced ages. Conditions such as upper respiratory tract infection and pneumonia may cause decompensation in these patient groups.[7,8] It has been observed that COVID-19 infection, which is a respiratory tract infection, also predisposes to decompensation.[9] In a small-scale study comparing the patients hospitalized due to HF with and without COVID-19 infection, mortality was approximately five times higher in those with COVID-19 infection.[23] Again, in a study by Alvarez-Garcia et al.,[14] the effect of HF on in-hospital death in COVID-19 patients was examined and HF increased mortality significantly, regardless of LVEF, and mortality was observed at a rate of approximately 40% in the group with HF. In our study, LVSD (both in the mid-range LVEF and reduced LVEF groups) was found to be an independent predictor of in-hospital mortality, with a 2.6-fold increase in risk with LVSD, and 42% of patients died during in-hospital follow-up. According to the results of our study, the frequency of myocardial injury was observed more in the LVSD group, which is one of the predictors of mortality. The SARS-CoV-2 may predispose to stress cardiomyopathy and cytokine-induced myocardial dysfunction and, as a result, acute decompensation of congestive heart failure may worsen subclinical pre-existing injury in well-compensated patients.[24] The increase in mortality in these patient groups may be due to myocardial damage caused by the direct effect of the virus, inflammatory response, hypoxia, and endothelial dysfunction worsening LV systolic functions and decompensation.

Heart failure patients are the groups that require special care during hospitalization. Mortality was found to be significantly higher in COVID-19 patients with HF, both with the results of other studies and the results of our study. Perhaps due to the density of hospitals caused by the pandemic, the inability to pay close attention to these patients may have contributed to the increase in mortality. Among LVSD patients included in the study, the number of patients who did not have optimal HF treatment during hospitalization was not small. A study showed that discontinuation of HF treatment during hospitalization caused a significant increase in in-hospital mortality.[9] Therefore, close follow-up of patients hospitalized for COVID-19 with LVSD and providing optimal treatment may reduce high mortality rates.

This study has some limitations, including the small number of LVSD patients from a single center with a retrospective design. Another limitation is that obesity and New York Heart Association (NYHA) classes cannot be included in the multivariate analysis due to insufficient data. As brain natriuretic peptide levels were not studied and diastolic dysfunction parameters were not evaluated in detail in most patients, HF patients with preserved ejection fraction could not be excluded from the study. The inability to determine the intensive care admissions as the outcome is another limitation. This is because severe patients cannot be taken into intensive care due to the lack of enough beds during the peak periods of the disease.

In conclusion, LVSD was an independent predictor of in-hospital mortality in our study. An increased risk of in-hospital mortality was present in both the mid-range LVEF and the reduced LVEF group, separately. In addition, myocardial injury, older age, DM, D-dimer, oxygen saturation, and heart rate were other independent predictors of in-hospital mortality.

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