

## **Outcomes of patients with left ventricular assist device infected with SARS-CoV-2**

*SARS-CoV-2 ile enfekte sol ventrikül destek cihazı olan hastaların sonuçları*

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### **ABSTRACT**

**Background:** The aim of this study was to describe clinical characteristics, course, and outcomes of the novel coronavirus disease 2019 (COVID-19) in heart failure patients with left ventricular assist device.

**Methods:** Between November 2020 and August 2021, a total of 20 patients (18 males, 2 females; mean age: 57.0±10.0 years; range, 30 to 71 years) with left ventricular assist device and who were diagnosed by the COVID-19 polymerase chain reaction testing were included. For each patient, disease-related factors were evaluated including presence of hospitalization, home quarantine, presence of lung damage, antiviral medication strategy, symptomatology and complications following COVID-19.

**Results:** Seven patients (35% patients died in our cohort following the COVID-19. All these patients experienced variety of complications following COVID-19 including subarachnoid hemorrhage and right heart failure. Three patients were already hospitalized due to COVID-19 and decompensated progressively, resulting in death on Days 14, 4, and 7 after the initial diagnosis.

**Conclusion:** COVID-19 seems to be an important cause of mortality in patients with LVAD who have borderline cardiopulmonary function. Great care should be taken to avoid interruption in routine follow-ups with these patients, since they present a more sensitive population.

**Keywords:** COVID-19, left ventricular assist device, SARS-CoV-2, transplantation.

### **ÖZ**

**Amaç:** Bu çalışmada sol ventrikül destek cihazlı kalp yetmezliği olan hastalarda koronavirüs hastalığı 2019'un (COVID-19) klinik özelliklerini, seyri ve sonuçları tanımladı.

**Çalışma planı:** Kasım 2020 - Ağustos 2021 tarihleri arasında COVID-19 ile enfekte sol ventrikül destek cihazı olan ve polimeraz zincir reaksiyon testi ile COVID-19 tanısı konan. toplam 20 hasta 18 erkek, 2 kadın; ort. yaş: 57.0±10.0 yıl; dağılım, 30-71 yıl çalışmaya alındı. Her hasta için hastanede yataş varlığı, ev karantinası, akciğer hasarı varlığı, antiviral ilaç stratejisi, semptomatoloji ve COVID-19 sonrası komplikasyonlar dahil olmak üzere hastalık ile ilişkili faktörler değerlendirildi.

**Bulgular:** COVID-19 sonrası kohortumuzda yedi hasta (%35) kaybedildi. Bu hastaların tümünde subaraknoid kanama ve sağ kalp yetmezliği dahil olmak üzere COVID-19 sonrası çeşitli komplikasyonlar izlendi. Üç hasta COVID-19 nedeniyle hastanede yatıyordu ve giderek kötüleşti ve ilk tanıdan 14, 4 ve 7 gün sonra kaybedildi.

**Sonuç:** COVID-19 sırında kardiyopulmoner fonksiyonlara sahip sol ventrikül destek cihazlı hastalarda ciddi mortalite nedeni olarak görülmektedir. Bu hastaların daha hassas bir popülasyon olduğundan rutin izlemlerinin aksatılmaması için özel ihtimam gösterilmelidir.

**Anahtar sözcükler:** COVID-19, sol ventrikül destek cihazı, SARS-CoV-2, nakil.

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On February 11<sup>th</sup>, 2020, the International Committee on Taxonomy of Viruses identified 2019-nCoV as a virus of severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2). The outbreak was declared as pandemic by the World Health Organization (WHO) on March 11<sup>th</sup>, 2020.<sup>[1,2]</sup>

Patients with cardiovascular comorbidities are exposed to higher morbidity and mortality.<sup>[3]</sup> In particular, heart failure patients with left ventricular assist device (LVAD) support are prone to novel coronavirus disease 2019 (COVID-19) due to their comorbidities and impaired immune systems.<sup>[4]</sup> Thus, they need a regular connection with heart teams, particularly in pandemic circumstances. With the COVID-19 outbreak, most of the elective surgeries have been postponed and majority of the outpatient clinic activities have suspended. Also, in-person interaction between LVAD patients and transplant coordinators was interrupted and the contact was possible only by remote telecommunication. Thus, routine follow-ups were obstructed and management of LVAD-related complications became harder. Diagnosis of COVID-19 in LVAD patients also became complicated and management strategies remained uncertain. To date, characteristics, clinical course, and treatment strategies of COVID-19 in LVAD patients have not been clearly described and outcomes studies are limited.<sup>[5-7]</sup>

In this study, we aimed to describe the clinical characteristics, course, and outcomes of the COVID-19 in LVAD patients.

## PATIENTS AND METHODS

This single-center, retrospective, observational cohort study was conducted at Ege University Faculty of Medicine, Department of Cardiovascular Surgery between November 2020 and August 2021. A total of 20 LVAD patients (18 males, 2 females; mean age: 57.0±10.0 years; range, 30 to 71 years) diagnosed with COVID-19 by SARS-CoV-2 as confirmed by polymerase chain reaction (PCR) test were included in the study. The patients with LVAD but no history of COVID-19 were not included in this study. All SARS-CoV-2 tests were reverse transcriptase PCR (rt-PCR) assays obtained via nasopharyngeal and oropharyngeal swabs. Demographic and clinical data were collected for all patients including age, sex, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) score, etiology of heart failure, type of ventricular assist device and comorbidities. For each patient, COVID-19-related factors were evaluated and included presence of hospitalization, home quarantine, presence of lung

damage, antiviral medication strategy, symptomatology and complications following COVID-19. Laboratory results were also collected at the time of diagnosis and included D-dimer, lactate dehydrogenase, international normalized ratio, fibrinogen, hemoglobin levels.

## Statistical analysis

Statistical analysis was performed using the R software version 4.0.5 (<http://r-project.org>). Continuous data were expressed in mean ± standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. Categorical variables were compared using the Fisher exact test, while numerical variables were compared using the t-test or Wilcoxon rank-sum test (or Mann-Whitney U test) between the groups with and without hospitalization. An exact *p* value of Wilcoxon rank-sum test was computed, if there were no ties.

## RESULTS

Only the patients who were diagnosed by the COVID-19 PCR testing were included in the study. Clinical profiles of the patients are presented in Table 1.

Two patients had a D-dimer value higher than 2,000 µg/L (1,139.3, 675.6%). Seven patients had a fibrinogen level >1,000 mg/dL (415.5, 149.1%). Five patients had international normalized ratio (INR) higher than 3 (2.3, 0.9%). Four patients had lactate dehydrogenase level greater than 400 U/L (375.1, 305.5%). Twelve patients had hemoglobin level less than 10 g/dL (11.1, 2.4%).

The most common presenting symptoms at presentation were cough, fatigue, dyspnea and fever seen in five, six, four, and four patients, respectively. They remained being most common throughout the disease course. Five patients were asymptomatic both at the presentation and throughout the course. Those are the patients underwent PCR testing for routine screening.

Of 20 patients, 11 (55%) were hospitalized and nine (45%) remained in home quarantine. The comparison of laboratory results and clinical features between hospitalized and non-hospitalized patients are shown in Table 2. Of 11 hospitalized patients, three were in intensive care unit (ICU) and eight were followed on the ward. The mean length of stay in hospital was 10.2±5.07 (5.07%) days. Six (54.5%) patients were treated with supplemental oxygen. Three (27.7%) patients were on mechanical ventilatory support and three were on inotropic support. Ten (90.9%) patients received favipiravir as an antiviral therapy.

**Table 1. Demographics, clinical characteristics, and laboratory results of LVAD patients infected by SARS-CoV-2 (n=20)**

	n	%	Mean±SD	Median	Range
Age (year)			57.0±10.0	58.0	30.0-71.0
Sex					
Female	2	10.0			
Male	18	90			
Body mass index			29.1±5.5	29.5	17.9-38.3
INTERMACS score					
Profile 1	1	5.0			
Profile 2	7	35.0			
Profile 3	9	45.0			
Profile 4	3	15.0			
Etiology					
Dilated cardiomyopathy	9	45			
Ischemic cardiomyopathy	11	55.0			
Assist device type					
HeartMate 2 (Abbott)	1	5.0			
HeartMate 3 (Abbott)	6	30.0			
HeartWare HVAD (Medtronic)	13	65.0			
Echocardiographic measurements			37.9±5.9	<b>35.0</b>	30.0-53.0
right ventricular ejection fraction					
Aortic valve regurgitation					
Mild	12	60.0			
Moderate	5	25.0			
Severe	3	15.0			
Mitral valve regurgitation					
Mild	11	55.0			
Moderate	8	40.0			
Severe	1	5.0			
Tricuspid valve regurgitation					
Mild	8	40.0			
Moderate	7	35.0			
Severe	5	25.0			
Comorbidities					
Hypertension	8	40.0			
Chronic obstructive pulmonary disease	1	5.0			
Diabetes mellitus	4	20.0			
Carotid arterial disease	2	10.0			
Hyperlipidemia	3	15.0			
Cancer	0	0.0			
Medication					
Beta blockers	10	50.0			
Acetylsalicylic acid	17	85.0			
Warfarin	15	75.0			
Low molecular weight heparin	9	45.0			
Statin	11	55.0			
ACE-inhibitors	11	55.0			

LVAD: Left ventricular assist device; SARS-CoV-2: Severe acute respiratory syndrome-related coronavirus 2; SD: Standard deviation; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; ACE: Angiotensin-converting enzyme.

**Table 2. Laboratory results and clinical differences between hospitalized and non-hospitalized patients**

Laboratory	Hospitalization						<i>p</i>	
	No (n=9)			Yes (n=11)				
	n	%	Mean±SD	Median	Range	n		
Lung damage on CT	3	33.3			7	63.6	0.370 <sup>1</sup>	
COVID-19 medication								
Favipiravir	8	88.9			10	90.9	1.000 <sup>1</sup>	
Hydroxychloroquine	1	11.1			0	0.0	0.450 <sup>1</sup>	
Immune plasma	0	0.0			1	9.1	1.000 <sup>1</sup>	
Dexamethasone	0	0.0			5	45.5	0.094 <sup>1</sup>	
Colchicine	0	0.0			1	9.1	1.000 <sup>1</sup>	
Vitamin-C	1	11.1			1	9.1	1.000 <sup>1</sup>	
Interval from LVAD implant to COVID (days)								
	815.3±708.0		<b>457.0</b>	21.0-1929.0		1,681.3±761.2	<b>1651.0</b>	
Lactate dehydrogenase	402.6±415.3		<b>255.0</b>	197.0-1495.0		352.7±195.2	<b>240.0</b>	
International normalized ratio	2.6±0.9		<b>2.8</b>	0.9-3.7		2.1±0.8	<b>2.0</b>	
D-dimer	1,219.3±697.8		<b>1070.0</b>	411.0-2323.0		1,083.3±691.6	<b>893.5</b>	
Fibrinogen	392.6±80.7		<b>413.0</b>	304.0-489.0		429.8±183.8	<b>397.5</b>	
Hemoglobin levels	11.0±2.4		<b>12.0</b>	7.8-15.0		11.1±2.6	<b>10.0</b>	

SD: Standard deviation; CT: Computed tomography; LVAD: Left ventricular assist device; <sup>1</sup>Fisher exact test for count data; <sup>2</sup>T-test; <sup>3</sup>Wilcoxon rank sum test or Mann Whitney U test; <sup>4</sup>Wilcoxon rank sum exact test.

**Table 3. Clinical course and characteristics of LVAD patients who were hospitalized due to COVID-19 (n=11)**

	n	%	Mean±SD
Intensive care unit stay	3	27.7	
Supplemental oxygen	6	54.5	
Mechanical ventilation	3	27.7	
Inotropic support	3	27.7	
Renal replacement therapy	0	0	
Treatment strategy			
Favipiravir	10	90.9	
Acetyl salicylic acid	9	81.1	
Warfarin	8	72.7	
Low-molecular-weight heparin	7	63.6	
Vitamin-C	2	18.1	
Immune plasma	1	9.0	
Dexamethasone	5	45.5	
Colchicine	1	9.0	
N-acetyl cysteine	4	36.3	
Complications			
Secondary pneumonia	1	9.0	
Cardiac arrest	3	27.7	
New onset stroke	0	0	
Pump thrombosis	0	0	
Outcome			
Hospital stay (days in mean)			10.2±5.1
Death	7	63.6	

LVAD: Left ventricular assist device; SD: Standard deviation.

**Table 4. Clinical features and causes of mortality in patients following COVID-19**

	Patient						
	1	2	3	4	5	6	7
Interval from COVID to death (days)	28	21	120	14	150	4	7
Medication	FPV, DXT	None	FPV, DXT	FPV, IP, V-C, DXT	None	FPV, DXT COL	FPV, DXT
Lung damage on CT	No	Yes	Yes	Yes	Yes	Yes	Yes
Discharge after diagnosis	Yes	Yes	Yes	No	Yes	No	No
Complications							
Intracranial hemorrhage	No	No	No	No	Yes	No	No
Right heart failure	Yes	No	No	No	No	Yes	No
General decompensation	No	Yes	No	No	No	No	Yes
SIADH	No	No	Yes	No	No	No	No
Device malfunction	No	No	No	Yes	No	No	No

FPV: Favipiravir; DXT: Dexamethasone; IP: Immune plasma; V-C: Vitamin-C; COL: Colchicine; CT: Computed tomography; SIADH: Syndrome of inappropriate secretion of antidiuretic hormone.

Eight (72.7%) patients were already on warfarin therapy and seven (63.6%) were started low-molecular-weight heparin during the course of the disease. One patient was already on low-molecular-weight due to prior history of gastrointestinal bleeding. Five

patients had dexamethasone and one patient were given immune plasma. Two patients received vitamin C and one patient received colchicine therapy. Four patients were given N-acetyl cysteine during the course of the disease.

Amongst hospitalized patients, eight of them survived to discharge and three died during the hospitalization period as a result of cardiac arrest. One of the patients developed a secondary pneumonia and was started on sulfamethoxazole and trimethoprim following *stenotrophomonas maltophilia* isolation from a sputum culture. There was no new onset of stroke or pump thrombosis as a complication (Table 3).

Seven patients died in our cohort following COVID-19 disease and each of them had unique clinical courses (Table 4). Among them, three patients did not survive to discharge after being hospitalized for COVID-19. They decompensated progressively and died on 4, 7 and 14 after the diagnosis. Other four patients were discharged after receiving initial treatment for COVID-19. However, they were re-hospitalized due to different complications which resulted in death. One patient presented with subarachnoid hemorrhage and hydrocephalus in emergency department five months after COVID-19. He was followed in ICU where he decompensated progressively and died within five days. One patient presented with low flow alarm on device four months after COVID-19. He developed fatigue, weakness, and hyponatremia and he gradually lost the function of his kidneys. Pre-diagnosis for syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was made. Unfortunately, he died after four days in ICU following a respiratory arrest and further diagnostic tests were unfeasible. One presented with symptoms of right heart failure, fatigue and lethargy a month after COVID-19. The patient was intubated and vasopressor therapy was started. However, he gradually decompensated in six days and died after a cardiac arrest. One represented with respiratory problems and malaise three weeks after COVID-19. He was followed in ICU and died after a respiratory arrest.

## DISCUSSION

With the spread of COVID-19, patients and the healthcare professionals experience challenges that may affect their ability to maintain optimal self and patient care.

Clinical symptoms of the COVID-19 are mostly respiratory; however, the cardiovascular system is particularly affected.<sup>[8]</sup> Patients with advanced heart failure, including those with LVAD support, have severely reduced functional capacity<sup>[9,10]</sup> and impaired ability to increase cardiac output to physiological stressors. These factors decrease the cardiopulmonary reserve.

Albeit different in cohort sizes, overall mortality was slightly higher in our cohort (35%) than what is reported (32%) in another single center study by Zakrzewski et al.<sup>[11]</sup> The hospitalization rate was 11 (55%) in our study. Similarly, the hospitalization rate was high at 60% in a multi-center study by Birati et al.<sup>[5]</sup> It can be concluded that higher rates of mortality and hospitalization of this patient population could be explained by the comorbidities, impaired immune system, and lower cardiovascular reserve.

Although the COVID-19 has been associated with thromboembolic complications in the literature,<sup>[12]</sup> we did not experience thromboembolic events in our patient cohort. The main cause may be optimal antiplatelet and anticoagulant therapy for LVAD before and during COVID-19. The heterogeneity of responses between individuals indicates host characteristics with a range of different clinical presentations.

The results from the RECOVERY trial indicated that the use of steroids in COVID-19 patients was associated with increased survival.<sup>[13]</sup> Seven patients died in our cohort, and the medication strategies were different for each. Among them, two patients did not receive any medication due to elevated kidney functional tests. Remaining five had favipiravir and dexamethasone, one patient received colchicine and one other received immune plasma and vitamin C in combination to an antiviral therapy. In a study from Zakrzewski et al.,<sup>[11]</sup> it was reported that patients who received systemic steroids showed increased mortality rate. Further studies regarding the utility of steroid use in LVAD patients with COVID-19 are needed.

The main limitations of the study include the retrospective nature, documentation of patient information from the electronic medical records, and small number of patients and variable treatment strategies which precluded to indicate specific conclusions. Some of the laboratory results were also missing due to data outside of our hospital system.

In conclusion, left ventricular assist device patients have borderline cardiopulmonary functions and comorbidities and COVID-19 may be an important cause of mortality in this group. Great care should be taken to avoid interruption in patient follow-up and education about the ongoing pandemic.

**Ethics Committee Approval:** The study protocol was approved by the Medicine Faculty of Ege University Ethics Committee (No: 21-9T/22). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from each patient.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Ü.K., D.G.E., carried out literature survey and analyzed the data and wrote the manuscript; B.Y., participated in the analysis of the data; Ç.E., T.Y., S.N., M.Ö., supervised the study and participated in critical revision, technical and material support.

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