ORIGINAL ARTICLE

Characteristics and Outcomes of COVID-19 in Patients on Left Ventricular Assist Device Support

Edo Y. Birati[®], MD; Samer S. Najjar[®], MD; Ryan J. Tedford[®], MD; Brian A. Houston[®], MD; Supriya Shore[®], MD, MSCS; Esther Vorovich[®], MD; Pavan Atluri, MD; Kimberly Urgo[®], BSN, RN; Maria Molina, MSN, CRNP; Susan Chambers, MSN, CRNP; Nicole Escobar, BA; Eileen Hsich[®], MD; Jerry D. Estep, MD; Kevin M. Alexander[®], MD; Jeffrey J. Teuteberg, MD; Sunit-Preet Chaudhry[®], MD; Ashwin Ravichandran[®], MD, MPH; Adam D. DeVore[®], MD, MHS; Kenneth B. Margulies[®], MD; Thomas C. Hanff[®], MD, MPH; Ross Zimmer[®], MD; Arman Kilic[®], MD; Joyce W. Wald, DO; Himabindu Vidula[®], MD, MS; John Martens[®], MPH; Emily A. Blumberg[®], MD; Jeremy A. Mazurek, MD; Anjali T. Owens, MD; Lee R. Goldberg, MD, MPH; Jesus Alvarez-Garcia, MD, PhD; Donna M. Mancini[®], MD; Noah Moss[®], MD; Michael V. Genuardi[®], MD, MS

BACKGROUND: The coronavirus disease 2019 (COVID-19) pandemic continues to afflict millions of people worldwide. Patients with end-stage heart failure and left ventricular assist devices (LVADs) may be at risk for severe COVID-19 given a high prevalence of complex comorbidities and functional impaired immunity. The objective of this study is to describe the clinical characteristics and outcomes of COVID-19 in patients with end-stage heart failure and durable LVADs.

METHODS: The Trans-CoV-VAD registry is a multi-center registry of LVAD and cardiac transplant patients in the United States with confirmed COVID-19. Patient characteristics, exposure history, presentation, laboratory data, course, and clinical outcomes were collected by participating institutions and reviewed by a central data repository. This report represents the participation of the first 9 centers to report LVAD data into the registry.

RESULTS: A total of 40 patients were included in this cohort. The median age was 56 years (interquartile range, 46–68), 14 (35%) were women, and 21 (52%) were Black. Among the most common presenting symptoms were cough (41%), fever, and fatigue (both 38%). A total of 18% were asymptomatic at diagnosis. Only 43% of the patients reported either subjective or measured fever during the entire course of illness. Over half (60%) required hospitalization, and 8 patients (20%) died, often after lengthy hospitalizations.

CONCLUSIONS: We present the largest case series of LVAD patients with COVID-19 to date. Understanding these characteristics is essential in an effort to improve the outcome of this complex patient population.

Key Words: COVID-19 = heart failure = hospitalization = outcomes research = SARS-CoV-2 = ventricular assist device

Goronavirus disease 2019 (COVID-19), caused by the novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was officially recognized by the World Health Organization as a pandemic in March 2020.¹ It has now afflicted >30 millions of people worldwide, with >940000 confirmed deaths to date.² Elderly patients and those with comorbidities have a higher risk of severe disease and mortality, although the severity of the disease is also determined by the immunologic response of the host.^{3,4}

Mechanical circulatory assist devices have emerged as an important therapeutic option for patients with

Correspondence to: Edo Y. Birati, MD, Cardiovascular Division, Poriya Medical Center, Poriya, Israel, 1520800. Email ebirati@pmc.gov.il

This article was sent to Michael S. Kiernan, MD, MS, MBA, Guest Editor, for review by expert referees, editorial decision, and final disposition.

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.120.007957.

For Sources of Funding and Disclosures, see page 466.

^{© 2021} American Heart Association, Inc.

Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

WHAT IS NEW?

- Coronavirus disease 2019 (COVID-19) is known to be associated with a high risk of mortality or complication in certain high-risk populations, such as older individuals and those with preexisting comorbidities.
- The course and outcome of COVID-19 in patients with end-stage heart failure who are supported by durable left ventricular support devices was previously unknown.
- We describe a cohort of 40 patients with left ventricular support devices who were afflicted by COVID-19. The hospitalization and mortality rates were substantial at 60% and 20%, respectively.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Patients with left ventricular support devices represent a particularly high-risk subgroup with high resource utilization and poor outcomes following COVID-19.
- A minority of patients presented with fever during the course of illness. Other classic COVID-19 symptoms were not universal, suggesting a varied initial presentation which requires a high index of suspicion.
- Although we observed no cases of venous thromboembolism, 1 patient had a suspected left ventricular support device thrombosis.
- Among patients with available laboratory results, lymphopenia and elevated inflammatory markers were common.

Nonstandard Abbreviations and Acronyms

COVID-19	coronavirus disease 2019
LVAD	left ventricular assist device
rt-PCR	reverse transcription-polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

end-stage heart failure,⁵ with >25000 patients having undergone implantation of a durable left ventricular assist device (LVAD) in the United States alone.⁶ Patients with end-stage heart failure may be at risk for severe COVID-19 given a high prevalence of complex comorbidities such as hypertension, diabetes, coronary artery disease, and older age.³⁷ Moreover, LVAD patients have functionally impaired immunity and may be prone to infection or infectious complications, for reasons that remain unclear.⁸

To date, 2 single-patient case reports have described complex clinical courses of COVID-19 in LVAD patients.^{9,10} While there have been several recent descriptions of the mortality rate and risk factors for COVID-19

in larger case series, none have included patients with durable LVADs. In this report, we describe the clinical characteristics, course, and outcomes of COVID-19 in a larger multi-center case series of patients on LVAD support.

METHODS

The Trans-CoV-VAD registry is a multi-center registry of LVAD and heart transplant patients with confirmed SARS-CoV-2 infection. Twelve advanced heart failure programs in the United States participated in this registry. Of these, the first 9 sites with complete data for LVAD patients participated in this case series: The University of Pennsylvania (Philadelphia, PA), Ascension St. Vincent Heart Center (Indianapolis, IN), the Cleveland Clinic (OH), the Medical University of South Carolina (Charleston, SC), MedStar Washington Hospital Center (Washington, DC), Mount Sinai Hospital (New York City, NY), Northwestern University (Chicago, IL), the University of Michigan (Ann Arbor, MI), and the University of Rochester (NY). Each site obtained approval from the local Institutional Review Board. Specific informed consent was waived due to the determination of minimal risk to included patients. Because of the sensitive nature of the data collected for this study, requests to access the data set and analysis code for reasons of reproducibility and data integrity made by qualified researchers trained in human subject confidentiality may be sent to the corresponding author.

Patients and Data Collection

We included all patients aged 18 years or older currently on durable LVAD support cared for by participating institutions who were diagnosed with SARS-CoV-2 infection. Patients were primarily diagnosed with reverse transcriptionpolymerase chain reaction (rt-PCR) assays after specimen collection via respiratory swab. In 2 cases, patients were diagnosed retrospectively with a SARS-CoV-2 antibody assay. As we were unable to properly attribute symptoms and details of presentation such as vital signs and laboratory results of these 2 patients, we did not include such details in this report. However, since both patients were diagnosed and remained in the ambulatory setting, we considered them in our accounting of the hospitalization and mortality rates. We also included these patients in our report of the demographics, baseline characteristics, and medical histories of patients described in this case series.

Clinical characteristics, need for admission, hospital course, laboratory results, treatment strategies, and outcomes were retrospectively extracted from the electronic medical records by each participant site. Anonymized data were reported to the central registry managed by the University of Pennsylvania Cardiovascular Clinical Research Unit.

We recorded laboratory values, when available, on the day of presentation and on day 3 after presentation. We allowed for a 24-hour grace period on both occasions to account for variability in when laboratory studies were sent and resulted. For laboratory values and vital signs, we defined the day of presentation as the day that the patient presented for evaluation of COVID-19-like symptoms. For purposes of survival analysis, we defined the start of the illness to be the start of symptoms (or the date of testing for asymptomatic patients). Note was made of patients with unresolved clinical courses at the time of preparation of this report in September, 2020.

Statistical Analysis

Continuous data are presented as medians with interquartile ranges, categorical data were expressed as n (%). Mortality was examined using a Kaplan-Meier survival analysis. To create a clinically useful analysis, patients who completed recovery from COVID-19, are asymptomatic, and are no longer receiving acute care related to the COVID-19 episode at the time of writing were projected to be alive through the follow-up time of the longest followed patient who died. Using this method, a total of 23 patients had at least 1 day imputed alive beyond their last known follow-up, averaging 45 days per imputed patient. Analyses were performed and figures created using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 40 patients were included in this cohort. Five (12%) patients were supported by a HeartMate 2 (Abbott, Chicago, IL), 9 (22%) by a HeartWare HVAD (Medtronic, Minneapolis, MN), and 26 (65%) by a Heart-Mate 3 (Abbott) device. Inclusion by participating center is presented in Table I in the Data Supplement. Descriptive characteristics of patients and medical histories are shown in Table 1. The median age was 56 years (interquartile range, 46–68), 14 (37%) were women, and 21 (53%) were Black. Ischemic cardiomyopathy was present in 9 patients (24%). The median time from LVAD implantation to COVID-19 diagnosis was 16 months (interquartile range, 7–37 months). The median body mass index of 28.3 kg/m² was notably above the normal range. No patients were on dialysis at baseline.

We compared the sex and race characteristics of the observed COVID-19 cases against the recent LVAD implantation activity at participating sites. As summarized in Table II in the Data Supplement, there were not significant differences in the racial or gender breakdown of COVID-19 cases compared with the total population receiving LVADs in the last 21 months at participating sites (N=955 patients).

Exposure History and Clinical Presentation

Exposure history, presenting symptoms, and vital signs are shown in Tables 2 and 3. The majority of patients did not report a history of travel to an endemic area, and most patients did not have contact with a known or suspected positive case. Two cases were diagnosed in inpatients over 14 days after hospital admission and likely represent health care-acquired infections. The most common presenting symptom was cough (endorsed by 41% of patients), followed by fever and fatigue (both endorsed by 38%). Notably, a minority (43%) of patients had a self-reported or measured fever during the course of illness. Additionally, only 7 of 27 patients (26%) had a fever (\geq 38 °C) measured at presentation (11 patients did not have a temperature available at presentation). Other common COVID-19 symptoms included dyspnea (35%) and gastrointestinal symptoms (24%). Most patients (68%) had 2 or more symptoms at presentation. Only 8% reported dysgeusia or anosmia at presentation; during the course of illness, an additional 2 patients developed anosmia for a total symptom prevalence of 14%. Interestingly, 7 patients (18%) were asymptomatic at the time of testing. Of these, 1 patient subsequently developed symptoms. The other 6 remained asymptomatic for at least 2 weeks of follow-up post rt-PCR result. One patient presented with abdominal pain and fatigue with reduced LVAD flows and was found to have partial occlusion of the outflow graft which required percutaneous stenting. This patient remained afebrile and without respiratory symptoms despite positive SARS-CoV-2 rt-PCR test.

Laboratory Results

A total of 34 patients had partial or complete laboratory data available, as shown in Figure 1. At time of presentation, 13% of patients had leukocytosis (≥10.0×10⁹ cells/L) and 17% had leukopenia ($<4.0\times10^9$ cells/L). At both presentation and on day 3, lymphopenia $(<1.0\times10^9 \text{ cells/L})$ was common, occurring in 67% and 71% of patients, respectively. Mild elevations in alanine aminotransferase and aspartate aminotransferase to 1 to 3× upper limit of normal were seen in several patients; however, 6 patients had elevations of either >3× upper limit of normal (all were hospitalized; 3 of these patients died). Of note, of the patients with the 6 highest presenting total bilirubin values (range, 1.3-3.2 μ mol/L), 5 had died and 1 remains hospitalized. Ferritin was >400 ng/mL in 44% of cases, however, was only available in 18 patients. Lactate dehydrogenase was greater than the laboratory upper limit of normal in 78% and >2× upper limit of normal in 30% of patients with laboratory results available. For reference, 8 of the 9 participating sites used similarly scaled assays with an upper limit of normal of ≈220 U/L; the mean lactate dehydrogenase level 24 months postimplant was 252 U/L in the HeartMate 3 and 344 U/L in the HeartMate II in the largest comparator trial of the 2 devices.¹¹ The 18 patients with a C-reactive protein value available had an exceptionally high median of 60.0 mg/dL (case range, 1.01-327 mg/dL; typical reference range, ≤ 0.80 mg/dL). Supratherapeutic international normalized ratio was common on presentation with 46% having an international normalized ratio >3.0 on presentation. By day 3, 37% remained supratherapeutic.

	Ambulatory (N=14)	Hospitalized (N=26)	Total (N=40)
Age, y (IQR)	47 (38–65)	57 (50-68)	56 (46-68)
Female, n (%)	8/14 (57)	6/26 (23)	14/40 (35)
Race, n (%)			
White	5/14 (36)	14/26 (54)	19/40 (48)
Black	9/14 (64)	12/26 (46)	21/40 (52)
Body mass index, kg/m ² (IQR)	29.0 (24.7–38.0)	28.6 (25.1–34.6)	28.6 (25.0–37.3)
Time since implant, mo (IQR)	16 (7–29)	16 (9–39)	16 (8–38)
Ischemic cardiomyopathy, n (%)	*	*	9/40 (22)
Hypertension, n (%)	9/14 (64)	20/26 (77)	29/40 (72)
Diabetes, n (%)	6/14 (43)	12/26 (46)	18/40 (45)
History of stroke (preimplant), n (%)	*	*	10/40 (25)
Chronic obstructive pulmonary disease, n (%)	*	*	≤3/40*
History of atrial fibrillation, n (%)	4/14 (29)	11/26 (42)	15/40 (38)
Obstructive sleep apnea, n (%)	*	*	10/40 (25)
History of smoking, n (%)	4/14 (29)	16/26 (62)	20/40 (50)
Postimplant history, n (%)			
Postimplant stroke	*	*	6/40 (15)
Major gastrointestinal bleeding	*	*	12/40 (30)
Right ventricular failure	4/14 (29)	10/26 (38)	14/40 (35)
Medical therapy, n (%)			
Renin angiotensin system inhibitors	6/14 (43)	16/26 (62)	22/40 (55)
β-blockers	6/14 (43)	13/26 (50)	19/40 (48)
Mineralocorticoid receptor antagonist	9/14 (64)	12/26 (46)	21/40 (52)
Aspirin	12/14 (86)	16/26 (62)	28/40 (70)
Oral anticoagulation	14/14 (100)	25/26 (96)	39/40 (98)
Phosphodiesterase type 5 inhibitor	*	*	≤3/40*
Statin	6/14 (43)	14/26 (54)	20/40 (50)

Table 1	Detiont Characteristics by	Monogoment Location	(Ambulatory vs Inpatient)
	Patient Characteristics D		(Ampulatory vs impatient)

Figures shown are median (IQR) or n/total (%). Right ventricular failure is defined as symptomatic heart failure due to right ventricular dysfunction requiring treatment or intervention. IQR indicates interquartile range.

*Specific values suppressed due to low numbers.

Course of COVID-19 and Outcomes

Eight patients were placed on supplemental oxygen at the time of initial presentation, and 6 patients required mechanical ventilation during their hospital course (2 patients who required mechanical ventilation did not require supplemental oxygen at presentation). Three patients developed serious secondary infections: one with acalculous cholecystitis, bacteremia, and fungemia; one with bacteremia from an unclear source; and one with gram-negative pulmonary superinfection. Two of these patients died; the other was critically ill but recovered.

Most patients (26/40, 60%) were managed inpatient. Ten (25%) developed critical illness (defined as a need for mechanical ventilation, vasopressors, or initiation of renal replacement therapy) and 8 (20%) died. Detailed clinical characteristics and outcomes are shown in Figure 2. Overall mortality is shown in Figure 3. No patients had venous thromboembolism complicating their illness. One patient had a suspected LVAD thrombosis that was medically managed. Deaths occurred a median of 22 days (range, 8–122) after admission. Deaths were attributable to shock with multisystem organ failure (4), hypoxemic respiratory failure (3), and hemorrhagic stroke (1). At the time of preparation of article submission in September 2020, 5 patients (12%) had unresolved clinical courses and had ongoing symptoms at home (2) or remained hospitalized (3).

Disease-Specific Therapy

Few patients received therapies intended to be specific to SARS-CoV-2 at the time. Among the hospitalized patients, aside from supplemental oxygen, the most common therapies were hydroxychloroquine (6 patients), convalescent plasma (3), tocilizumab (2), remdesivir (1), lopinavir-ritonavir (1), and dexamethasone (1). In addition, 6 patients received at least moderate dose (20 mg prednisone equivalents/d) of a nondexamethasone steroid for at least 1 day of their hospital course.

Table 2. Presentation of COVID-19

	Ambulato-	Hospi- talized	Total
	ry (N=12)	(N=26)	(N=38)
Contact with known COVID-19 case			
Confirmed	5/12 (42)	5/26 (19)	10/38 (26)
Probable	1/12 (8)	4/26 (15)	5/38 (13)
None	6/12 (50)	16/26 (62)	22/38 (58)
Unknown	0/12 (0)	1/26 (4)	1/38 (3)
Vital signs on presentation			
Mean blood pressure, mm Hg			
<70	0/2 (0)	5/22 (23)	5/24 (21)
70–89	0/2 (0)	7/22 (32)	7/24 (29)
≥90	2/2 (100)	10/22 (45)	12/24 (50)
Respiratory rate, min ⁻¹			
12-19	2/2 (100)	14/22 (64)	16/24 (67)
≥20	0/2 (0)	8/22 (36)	8/24 (33)
Oxyhemoglobin saturation, %			
<90	0/4 (0)	3/23 (13)	3/27 (11)
90-94	0/4 (0)	5/23 (22)	5/27 (19)
≥95%	4/4 (100)	15/23 (65)	19/27 (70)
O ₂ delivery device			
Room air	4/4 (100)	12/20 (60)	16/24 (67)
1–3 L/min nasal cannula	0/4 (0)	5/20 (25)	5/24 (21)
4–6 L/min nasal cannula	0/4 (0)	1/20 (5)	1/24 (4)
Positive airway pressure	0/4 (0)	2/20 (10)	2/24 (8)
Temperature			
<36 °C (<96.8°F)	0/2 (0)	0/25 (0)	0/27 (0)
36-37.9 °C (96.8-100.3°F)	2/2 (100)	18/25 (72)	20/27 (74)
≥38°C (≥100.4°F)	0/2 (0)	7/25 (28)	7/27 (26)

Not all values could be obtained on all patients. Two patients diagnosed retrospectively via antibody testing and managed in the ambulatory setting are not included in this table due to inability to properly time and attribute symptoms. COVID-19 indicates coronavirus disease 2019.

DISCUSSION

This multi-center study represents the largest published case series of patients with SARS-CoV-2 infection on durable LVAD support. The current literature describing the course of COVID-19 in LVAD patients is limited to 2 single case reports.^{9,10}

Morbidity and Mortality of COVID-19

Overall, the case fatality rate was high in our study with a lower bound of 20%. We describe 8 fatalities in 40 patients, occurring as soon as 11 days after first symptom (8 days after hospital admission) but often occurring after a lengthy hospitalization. At the time of this article submission, 3 more patients remain in the hospital. The overall hospitalization rate was high at 60%. The high mortality and hospitalization rates may be explained by the complexity and medical comorbidities of this patient

Table 3. Symptoms of COVID-19 in Patients With LVADs

	At/before presentation	At any time
Any symptom	31/38 (79)	32/38 (84)
Fever (reported or measured)	14/37 (38)	16/37 (43)
Cough	15/37 (41)	17/37 (46)
Shortness of breath	13/37 (35)	15/37 (41)
Fatigue	14/37 (38)	15/37 (41)
Change in taste or smell	≤3/37*	5/37 (14)
Nausea, vomiting, or diarrhea	9/37 (24)	10/37 (27)

Symptoms may be patient-reported or directly observed. One patient in the cohort was hospitalized at an outside institution and full symptomatology was not available. Two patients were diagnosed retrospectively via antibody testing and were not included.

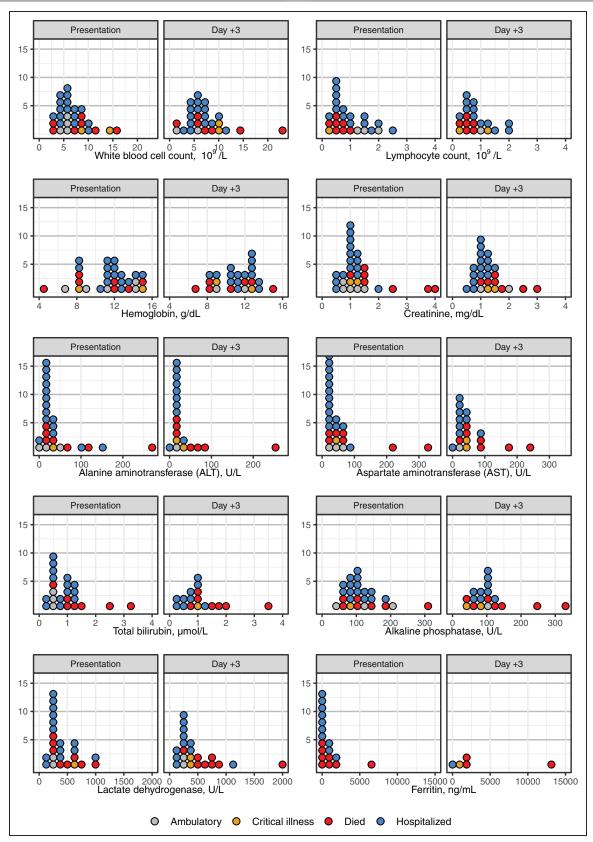
*Specific value suppressed due to low numbers.

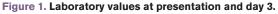
population. It is possible that the high hospitalization rate might be attributable to a low threshold to admit an LVAD patient compared with a non-LVAD patient. However, given the overall in-hospital mortality of 31%, a low admission threshold would not be inappropriate. We note that the outcomes among these LVAD patients are similar to outcomes seen among very elderly adults with COVID-19. An early report found that for patients aged \geq 85 years, the hospitalization rate was 31% to 70%, and the mortality rate was 10% to 27%.12 However, this report summarized cases diagnosed in the early phase of the US epidemic (February and March 2020), when testing was more limited and many mild cases were likely undiagnosed. Data updated through May 2020 indicate that our mortality rate is comparable to those aged 70 to 79 years. Our hospitalization rate is similar to the 62% reported for patients in the oldest age group (\geq 80) with medical comorbidities in that report.13

Symptomatology

Almost 1-in-5 cases in this cohort were discovered through screening and were asymptomatic at the time of diagnosis. This is at the higher end of the 8% to 20% typical reported prevalence of asymptomatic individuals among patients who are tested via rt-PCR.^{14,15} This would require a larger sample to confirm; however, we hypothesize that a higher rate of asymptomatic diagnosis might be seen in LVAD patients due to (1) the high rate of medical resource utilization among LVAD patients¹⁶ and (2) increasing uptake of routine COVID-19 screening for patients accessing cardiac care.¹⁷ Our quoted rate of patients who were asymptomatic at the time of testing (7/38) includes only patients diagnosed via rt-PCR thus are unlikely to include false-positive test results.

Interestingly, only 38% of patients in this case series had a fever (objective or subjective) by the time of diagnosis, and only 43% developed a fever during the course of illness. Of symptomatic patients in our series, 45% had a fever reported by time of presentation, compared with





Selected laboratory values for patients in series. Each circle represents one patient. Color represents severity of illness: red denotes died; orange, critical illness; blue, hospitalized without critical illness; and gray, ambulatory.

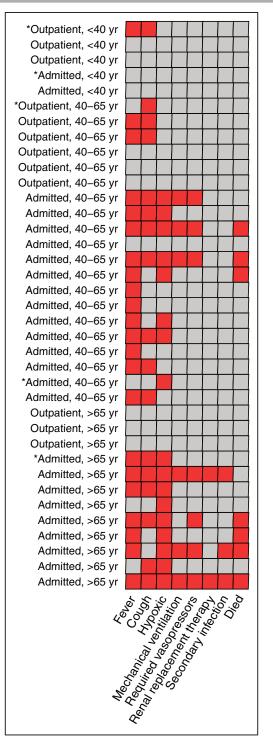


Figure 2. Course of coronavirus disease 2019 (COVID-19) in patients with durable left ventricular assist device (LVAD). Findings of fever, cough, and hypoxia are considered present when apparent at any point during the patient's illness course. *Patient remains symptomatic or is undergoing continued acute care at the time of writing.

57% of a general population. Additionally, 9% reported anosmia or dysgeusia, less than the 56% percent in the general COVID-19 afflicted population.¹⁵ Admittedly, the design of this case series did not permit structured

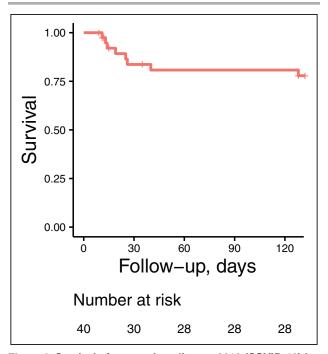


Figure 3. Survival of coronavirus disease 2019 (COVID-19) in patients with durable left ventricular assist devices. Survival of the entire cohort from time of first symptom of COVID-19. Patients who completed full recovery from COVID-19 are projected to be alive through 128 days from first symptom (the time of death of the patient with the longest time to death). Patients are censored if

they are still symptomatic or have acute clinical care ongoing at the time of writing. interviews to comprehensively assess symptoms and relied on retrospective evaluation of contemporaneous

medical documentation, possibly resulting in underre-

porting of certain symptoms. Inflammatory Response and Thrombotic Complications

Previous case series of hospitalized patients with COVID-19 have found initial laboratory results consistent with a viral syndrome with elevated acute-phase reactants.^{18,19} Lymphopenia with normal white blood cell count is common, as are elevations in aminotransferases, lactate dehydrogenase, ferritin, and C-reactive protein. In our cohort, lymphopenia (<1.0×10⁹ cells/L) was present at either day 1 or 3 in 16/20 (80%) of patients with available data. Based on our results, it also appears that similar patterns of acute-phase reactant and inflammatory marker elevation are evident between LVAD and non-LVAD patients. Bilirubin may be a particularly important early marker of severe disease given our observed mortality among the patients with highest initial values; however, more data are necessary.

High rates of thrombotic and thromboembolic events have been described in patients with COVID-19.²⁰ We observed no venous thromboembolic events, but one patient had an episode of suspected pump thrombosis. Additionally, one patient was found to have reduced LVAD flow and a partial outflow graft obstruction that required percutaneous stenting after being diagnosed with SARS-CoV-2 infection. It is not clear that the obstruction was thrombotic in nature, but this is a possibility. At the time of submission of this article, to the knowledge of the co-authors, no patients were felt to have a confirmed or likely device thrombosis other than the 2 cases currently described in the text. Our opinion is that the elevated lactate dehydrogenase values reported here are likely in the setting of systemic inflammation or perhaps endothelial injury due to COVID-19,²¹ rather than a device-related thrombosis.

Clinical Context

Our experience with COVID-19 in LVAD patients reflects the realities of the early phase of the ongoing epidemic in the United States. The patients included in this case series largely presented before July 2020 and were treated according to practice patterns in use at the time. Specifically, the low use of remdesivir and steroids in our cohort underscores the fact that most patients were treated before the public release of large-scale randomized studies of those therapies demonstrating efficacy in shortening duration of illness and reducing mortality, respectively.^{22,23} Underscoring this point, most of patient who received steroids in this study received intravenous hydrocortisone or methylprednisolone in the setting of septic shock, not for COVID-19 specifically.

Finally, many patients in our case series required prolonged hospitalizations. Among the 15 patients hospitalized for COVID-19 who were discharged alive, the mean length of stay was 14 days. The length of stay was 29 days on average for the 8 patients who died. An additional 3 patients remaining hospitalized. While the geography of the epidemic and the accepted therapeutics may change, it is likely that LVAD patients afflicted with COVID-19 will continue to require high degrees of health care utilization relative to the general population.

Limitations

Limitations of our study include the retrospective nature of this case series and the inability to systematically collect laboratories nor conduct structured interviews looking for symptoms or case features. Some laboratory results and vital signs may have been missed if collected outside of the major center's hospital system. Additionally, 5 patients have unresolved clinical courses that do not allow for more conclusive mortality or hospitalization rate estimates. The multi-center approach of this collaboration may also be susceptible to disparate data collecting and reporting practices. However, the variables collected were defined in advance of data collection, with input and consent from the entire group to minimize variation. Finally, mild or asymptomatic cases of COVID-19 might go undiagnosed, as in the general population. We note that all sites had similar screening practices (testing all patients before invasive procedures and testing almost all patients in the emergency department or before admission). Use of antibody testing to diagnose retrospective disease was exceedingly rare across all sites. We speculate that LVAD patients, being highly engaged with the nurse coordinators and physicians on the LVAD team, may have easier access to resources such as outpatient testing compared with the general population. Indeed, we observed slightly more asymptomatic cases than might be expected compared with the general population, as previously discussed. In this context, our observed hospitalization and mortality rates would be even more striking.

Conclusions

We present the largest case series of LVAD patients with COVID-19. The rates of mortality and hospitalization are relatively high in this patient population, likely as a result of their medical complexity and high rate of comorbidities. Further understanding of these characteristics is essential to improve outcomes in this complex patient population.

ARTICLE INFORMATION

Received September 18, 2020; accepted February 18, 2021.

Affiliations

Cardiovascular Division, Department of Medicine (E.Y.B., K.U., M.M., S.C., N.E., K.B.M., T.C.H., R.Z., J.W.W., J.A.M., A.T.O., L.R.G., M.V.G.), Perelman School of Medicine and Cardiovascular Outcomes, Quality, and Evaluative Research Center (E.Y.B.), Department of Cardiothoracic Surgery (P.A.), and Division of Infectious Diseases (E.A.B.), University of Pennsylvania, Philadelphia. MedStar Washington Hospital Center, Washington, DC (S.S.N.). Cardiovascular Division, Poriya Medical Center, Bar-Ilan University, Israel. (E.Y.B.) Medical University of South Carolina, Charleston, SC (R.J.T., B.A.H.). Cardiovascular Division, University of Michigan, Ann Arbor (S.S.). Division of Cardiology, Northwestern University, Chicago, IL (E.V.). Heart and Vascular Institute at the Cleveland Clinic and Cleveland Clinic Lerner College of Medicine of Case Western Reserve University School of Medicine, OH (E.H., J.D.E.). Division of Cardiovascular Medicine and the Stanford Cardiovascular Institute, Stanford University School of Medicine, CA (K.M.A., J.J.T.). St Vincent Medical Group, St Vincent Heart Center, Indianapolis, IN (S.-P.C., A.R.). Duke Clinical Research Institute and Department of Medicine, Duke University School of Medicine, Durham, NC (A.D.D.). Division of Cardiac Surgery, University of Pittsburgh Medical Center, PA (A.K.). Division of Cardiology, University of Rochester School of Medicine and Dentistry, NY (H.V., J.M.). Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, NY (J.A.-G., D.M.M., N.M.).

Acknowledgments

We would like to express our deep gratitude to all of the left ventricular assist device coordinators at our institutions for their exceptional dedication to these complex patients.

Sources of Funding

None.

Disclosures

Dr DeVore reports research funding through his institution from the American Heart Association, Amgen, AstraZeneca, Bayer, IntraCellular Therapies, American Regent, Inc, the NHLBI, Novartis and PCORI; consulting services for Amgen, AstraZeneca, Bayer, CareDx, InnaMed, LivaNova, Mardil Medical, Novartis,

Procyrion, scPharmaceuticals, Story Health, and Zoll; and nonfinancial support for Abbott for educational activities. Dr Kilic reports medical advisory board for Medtronic. Dr Ravichandran is a speaker honoraria for Abbott and Medtronic. Dr Houston reports research grant, outside submitted work for Medtronic. Dr Birati reports research support paid to the University for Medtronic and Impulse Dynamics Ltd. Dr Vorovich reports speaker's bureau for Abiomed. Dr Vidula reports research grant for Abbott. Dr Teuteberg is a consultant for Abbott; speaking/ advisory board for Medtronic and CareDx; advisory board for Abiomed; and speaker for Paragonix. Dr Mazurek is a speaker for Abbott. Dr Estep is a consultant for Abbott; medical advisor for Medtronic; and consultant for Getinge Group. Dr Margulies sponsored research support for Sanofi-Aventis USA and GlaxoSmithKline; and consulting fees for MyoKardia and Pfizer. Dr Alexander reports advisory boards for Alnylam, Eidos, and Pfizer; and funding for American Heart Association-Amos Medical Faculty Development Program (AHA-AMFDP). K. Urgo is a speaker, subject matter expert for Abbott. Dr Goldberg reports consulting fees and research grants for Respircardia; consulting fees for Abbott. Dr Atluri is a speaker for Edwards Lifesciences and Abbott; advisory board for Medtronic. Dr Tedford reports Consulting relationships: Medtronic, Aria CV Inc, Acceleron, Arena Pharmaceuticals and United Therapeutics; steering committee for Medtronic; and research advisory board for Abiomed. He also does hemodynamic core lab work for Actelion and Merck. Dr Najjar reports institutional research support and consultant for Abbott and Medtronic. The other authors report no conflicts.

Supplemental Materials

Tables I–II

REFERENCES

- World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. https://www.who.int/dg/ speeches/detail/who-director-general-s-opening-remarks-at-the-mediabriefing-on-covid-19---11-march-2020. Accessed July 4, 2020.
- World Health Organization. Coronavirus disease (COVID-19) World Health Organization. https://www.who.int/emergencies/diseases/novelcoronavirus-2019. Accessed November 2, 2020.
- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395:1054– 1062. doi: 10.1016/S0140-6736(20)30566-3
- Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest.* 2020;130:2620–2629. doi: 10.1172/JCI137244
- Y Birati E, Jessup M. Left ventricular assist devices in the management of heart failure. *Card Fail Rev.* 2015;1:25–30. doi: 10.15420/CFR. 2015.01.01.25
- Kormos RL, Cowger J, Pagani FD, Teuteberg JJ, Goldstein DJ, Jacobs JP, Higgins RS, Stevenson LW, Stehlik J, Atluri P, et al. The society of thoracic surgeons intermacs database annual report: evolving indications, outcomes, and scientific partnerships. *Ann Thorac Surg.* 2019;107:341–353. doi: 10.1016/j.athoracsur.2018.11.011
- DeFilippis EM, Reza N, Donald E, Givertz MM, Lindenfeld J, Jessup M. Considerations for heart failure care during the COVID-19 pandemic. *JACC Heart Fail.* 2020;8:681–691. doi: 10.1016/j.jchf.2020.05.006
- Kimball PM, Flattery M, McDougan F, Kasirajan V. Cellular immunity impaired among patients on left ventricular assist device for 6 months. *Ann Thorac Surg.* 2008;85:1656–1661. doi: 10.1016/j.athoracsur.2008.01.050
- Singh R, Domenico C, Rao SD, Urgo K, Prenner SB, Wald JW, Atluri P, Birati EY. Novel coronavirus disease 2019 in a patient on durable left ventricular assist device support. *J Card Fail*. 2020;26:438–439. doi: 10.1016/j.cardfail.2020.04.007

- Chau VQ, Oliveros E, Mahmood K, Singhvi A, Lala A, Moss N, Gidwani U, Mancini DM, Pinney SP, Parikh A. The imperfect cytokine storm: severe COVID-19 with ARDS in a patient on durable LVAD support. *JACC Case Rep.* 2020;2:1315–1320. doi: 10.1016/j.jaccas.2020.04.001
- Mehra MR, Uriel N, Naka Y, Cleveland JC Jr, Yuzefpolskaya M, Salerno CT, Walsh MN, Milano CA, Patel CB, Hutchins SW, et al; MOMENTUM 3 Investigators. A fully magnetically levitated left ventricular assist device - Final report. *N Engl J Med.* 2019;380:1618–1627. doi: 10.1056/NEJMoa1900486
- CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:343–346. doi: 10.15585/mmwr.mm6912e2
- Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, Felix SEB, Tie Y, Fullerton KE. Coronavirus Disease 2019 Case Surveillance – United States, January 22–May 30, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69:759–765. doi: 10.15585/mmwr.mm6924e2
- World Health Organization. Transmission of SARS-CoV-2: implications for infection prevention precautions. 2020. https://www.who.int/publications/i/ item/modes-of-transmission-of-virus-causing-covid-19-implications-foripc-precaution-recommendations. Accessed July 14, 2020.
- Tenforde MW, Billig Rose E, Lindsell CJ, Shapiro NI, Files DC, Gibbs KW, Prekker ME, Steingrub JS, Smithline HA, Gong MN, et al; CDC COVID-19 Response Team. Characteristics of adult outpatients and inpatients with COVID-19 - 11 academic medical centers, United States, March-May 2020. MMWR Morb Mortal Wkly Rep. 2020;69:841–846. doi: 10.15585/ mmwr.mm6926e3
- Smedira NG, Hoercher KJ, Lima B, Mountis MM, Starling RC, Thuita L, Schmuhl DM, Blackstone EH. Unplanned hospital readmissions after Heart-Mate II implantation: frequency, risk factors, and impact on resource use and survival. JACC Heart Fail. 2013;1:31–39. doi: 10.1016/j.jchf.2012.11.001
- Wood DA, Mahmud E, Thourani VH, Sathananthan J, Virani A, Poppas A, Harrington RA, Dearani JA, Swaminathan M, Russo AM, et al. Safe reintroduction of cardiovascular services during the COVID-19 pandemic: from the North American Society Leadership. *J Am Coll Cardiol*. 2020;75:3177– 3183. doi: 10.1016/jjacc.2020.04.063
- Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP, Becker LB, Chelico JD, Cohen SL, et al; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020;323:2052–2059. doi: 10.1001/ jama.2020.6775
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–1069. doi: 10.1001/jama.2020.1585
- Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian C, Ageno W, Madjid M, Guo Y, et al; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75:2950–2973. doi: 10.1016/j.jacc.2020.04.031
- Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol. 2021;17:46–64. doi: 10.1038/s41581-020-00357-4
- 22. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19 Preliminary report. *N Engl J Med.* 2020;384:693–704. doi: 10.1056/NEJMoa2021436
- Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, et al. Remdesivir for the treatment of COVID-19 – Final report. *N Engl J Med.* 383:1813-1826. doi: 10.1056/NEJMoa2007764.