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ORIGINAL RESEARCH ARTICLE

Worsening of heart failure by coronavirus disease 2019 is associated with high mortality

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Abstract

Aims Patients with advanced heart failure (HF) with reduced left ventricular ejection fraction (HFrEF) and concurrent coronavirus disease 2019 (COVID-19) might have a higher risk of severe events.

Methods and results We retrospectively studied 16 patients with advanced HFrEF who developed COVID-19 between 1 March and 29 May 2020. Follow-up lasted until 30 September. Ten patients previously hospitalized with decompensated HFrEF were infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during hospitalization. Six patients undergoing ambulatory care at initiation of COVID-19 symptoms were hospitalized because of advanced HFrEF. All patients who experienced worsening of HFrEF due to COVID-19 required higher doses or introduction of additional inotropic drugs or intra-aortic balloon pump in the intensive care unit. The mean intravenous dobutamine dose before SARS-CoV-2 infection in previously hospitalized patients (n = 10) and the median (inter-quartile range) peak intravenous dobutamine dose during SARS-CoV-2 infection in all patients (n = 16) were 2 (0–7) μg/kg/min and 20 (14–20) ($P < 0.001$), respectively. During follow-up, 56% underwent heart transplantation (n = 2) or died (n = 7). Four patients died during hospitalization from mixed shock consequent to severe acute respiratory syndrome with inflammatory storm syndrome associated with septic and cardiogenic shock during COVID-19. After COVID-19 recovery, two patients died from mixed septic and cardiogenic shock and one from sustained ventricular tachycardia and cardiogenic shock. Five patients were discharged from hospital to ambulatory care. Four were awaiting heart transplantation.

Conclusion Worsening of advanced HF by COVID-19 is associated with high mortality. This report highlights the importance of preventing COVID-19 in patients with advanced HF.

Keywords Heart failure; COVID-19; SARS-CoV-2; Inotropic drugs; Decompensated heart failure

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [coronavirus disease 2019 (COVID-19)] was reported as the aetiology of viral pneumonia and caused a worldwide outbreak.[1] As of 30 September 2020, 33 502 430 confirmed coronavirus disease-19 (COVID-19) cases with 1 004 421 deaths (3%) have been reported in 216 countries, areas, or territories around the world.[2] The risk of worse outcome with COVID-19 is increased in those who are ageing and obese and have cardiovascular disease, diabetes mellitus, cerebrovascular disease, co-morbidities, and heart failure (HF).[3] Also, COVID-19 has been associated with cardiovascular complications, including myocarditis, myocardial injury, HF, arrhythmias, and acute myocardial infarction.[3]

It is expected that patients with advanced HF with reduced left ventricular ejection fraction (HFrEF) and concurrent COVID-19 might have a higher risk of suffering severe events. However, data regarding effects of SARS-CoV-2 infection on

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outcomes of patients with advanced HF are scarce. The present report describes the outcomes of 16 patients with advanced HF affected by COVID-19.

Methods

A retrospective single-centre analysis of patients with advanced HFrEF who developed COVID-19 was conducted in the heart failure clinic of a tertiary cardiology centre. HF patients with a diagnosis of COVID-19 between 1 March and 29 May 2020 were included and followed up until 30 September 2020. We studied two groups of patients: first, patients with advanced HFrEF hospitalized because of decompensated HF (DHF) who were infected with COVID-19 during hospitalization, and second, those who underwent hospitalization due to worsening of advanced HFrEF after COVID-19 infection. Clinical data were initially obtained through of electronic medical records. Data were reviewed and also were checked by telephone calls to patients or their families as necessary. Outcomes and follow-up were recorded for all patients through 30 September 2020. Written informed consent was not obtained based on the retrospective nature of the study without any intervention. Also, a waiver of consent was granted to protect the safety of the staff, because consent would have required direct exposure while patients were infected with COVID-19. The patients were treated according to Brazilian guideline-directed medical therapy for HFrEF. Patients were continuously non-invasively monitored during hospitalization concerning heart rhythm. Electrocardiography was performed when rhythm abnormalities occurred during monitoring. In the treatment of HF patients with COVID-19, use of a Swan–Ganz catheter was not a standard procedure. Inotropic drug doses were decided upon based on concurrent assessment of decreased peripheral perfusion, skin mottling, cold sweatiness, altered mental status, oliguria, and macrohaemodynamics using the inotropic dose required to maintain a mean systemic arterial pressure ≥65 mmHg. Adequate cardiac output (by EVMI0) and laboratory values were maintained as normal as possible (e.g. arterial lactate levels, central/mixed venous oxygen saturation, central venous to arterial carbon dioxide tension gap, bicarbonate levels, and base deficit).

Cases were defined as COVID-19 by clinical, laboratory, and imaging [X-ray or computed tomography (CT)] criteria. This analysis is part of the study approved by the Institutional Ethical Committee of the Heart Institute (InCor) under Number CAAE 28188620.9.0000.0068. All patients were previously chronically followed in the heart failure clinic ambulatory department or in the heart institute (InCor) except for one who was referred.

Statistical analysis

Continuous data are presented as mean ± 1 standard deviation or median [inter-quartile range (IQR)]. In the statistical analyses for comparison of intravenous peak dobutamine doses, a non-parametric two-tailed Wilcoxon signed-rank test was used for paired comparison. Statistical analysis was performed using SPSS v.18.0 (SPSS Inc., Chicago, IL). *P* value less than 0.05 was considered statistically significant. Shapiro–Wilk test was used for normality.

Results

Baseline characteristics are reported in *Table 1*. From 1 March to 29 May 2020, 16 patients fulfilled the criteria for inclusion in the analysis. Before hospitalization due to DHF or hospitalization consequent to COVID-19 worsening HF, patients were receiving the following daily doses of drugs for HF treatment: beta-blockers (carvedilol *n* = 15, mean dose 22.5 ± 18.5 mg; metoprolol succinate *n* = 1, dose 200 mg); enalapril (*n* = 11, mean dose 9.7 ± 11 mg); losartan (*n* = 2, dose 100 mg); angiotensin receptor neprilysin inhibitor (sacubitril/valsartan, *n* = 2, dose 97/103 and 24/26 mg); spironolactone (*n* = 10, mean dose 13.3 ± 15 mg); and furosemide (*n* = 16, mean dose 72.5 ± 46 mg).

All patients tested positive during real-time polymerase chain reaction nasopharyngeal swab for SARS-CoV-2, except one who had positive real-time polymerase chain reaction for SARS-CoV-2 in sputum samples. Ten patients had initial symptoms and signals of typical SARS-CoV-2 infection. Worsening dyspnoea was reported in 15 patients, fever in 10 patients, lower than 92–93% oxygen arterial saturation in 7 patients, rhinorrhea/nasal congestion in 4 patients, frequent cough in 3 patients, pulmonary oedema in 2 patients, anosmia/ageusia in 1 patient, and hemoptysis, headache, delirium, myalgia, and nausea/vomiting in 1 patient. Eight patients out of 16 underwent chest CT that showed bilaterally peripheral and central ground glass opacities (*n* = 8), consolidations (*n* = 3), and reticular pattern (*n* = 8) in lung parenchyma predominantly in the upper lobes. Six of 16 had pleural effusions. Eight patients underwent chest X-ray that showed bilateral reticular infiltrates. The choice between chest CT and X-ray was based on the severity of the case, according to the decision of the assisting physician.

Six patients were hospitalized because of advanced HFrEF that worsened with COVID-19 (*Table 2*). Ten patients previously hospitalized due to DHF were infected with SARS-CoV-2 in the hospital. These patients were previously hospitalized during 129 ± 52 days before initiation of COVID-19 symptoms. Eight of the previously hospitalized patients with decompensated HFrEF and one of those admitted with COVID-19 were awaiting heart transplantation.

Table 1 Baseline characteristics of patients at hospitalization and clinical status and laboratory values at initiation of symptoms of COVID-19

Patient characteristics	
Age (years)	50 ± 16
Male/female (pts)	11/5
Time of HF diagnosis (months)	63 ± 43
Aetiology (*n*)	
Ischaemic	5
Idiopathic dilated CMP	2
Chagas disease	3
Others	6
LVEF (%)	24 ± 7
Ambulatory HFrEF chronic treatment of all patients at hospitalization, *n* (%)	
Beta-blockers (carvedilol/metoprolol)	16 (100%) (15 pts with carvedilol)
ACEI/ARB	11 (69%)/2 (12.5%)
Sacubitril/valsartan	2 (12.5%)
Diuretics	
Furosemide	16 (100%)
Hydrochlorothiazide	2 (12.5%)
MRA	10 (64%)
Digoxin	2 (12.5%)
Ivabradine	2 (12.5%)
Amiodarone	3 (19%)
Hydralazine/nitrates	3 (19%)
Anticoagulants	5 (31%)
Cardiac resynchronization therapy	1 (6.3%)
NYHA functional class before HF worsening by COVID-19 in patients under ambulatory care	
I/II/III/IV	0/2/2/2
INTERMACS profile of already hospitalized patients by DHF before being SARS-CoV-2 infected in the hospital	
INTERMACS 1/2/3/3/4	0/0/8/2
Laboratory at COVID-19 diagnosis[a]	
BNP (pg/mL)	870 ± 704
Creatinine (mg/dL)	1.2 ± 0.5
Sodium (mEq/L)	138 ± 3.9
Haemoglobin (g/dL)	13 ± 2.3
Lymphocytes (mL)	1830 ± 658

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist; BNP, brain natriuretic peptide; CMP, cardiomyopathy; COVID-19, coronavirus disease 2019; DHF, decompensated heart failure; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IABP, intra-aortic balloon pump; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVEF, left ventricular ejection fraction; MRA mineralocorticoid receptor antagonists; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; pt, patient; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Values in mean ± standard deviation.

All patients developed worsening of HFrEF in the context of COVID-19, requiring higher doses or introduction of new inotropic drugs or intra-aortic balloon pump (IABP) with admission to or permanence in the intensive care unit. The median (IQR) peak intravenous dobutamine dose before SARS-CoV-2 infection in previously hospitalized patients (n = 6) and the median (IQR) peak intravenous dobutamine dose during SARS-CoV-2 infection in all patients (n = 16) were 2 (0–7) μg/kg/min and 20 (14–20) ($P < 0.001$), respectively. The peak of worsening haemodynamic status data in *Table 2* illustrates the inotropic support for HFrEF and COVID-19 patients. Also, vasopressin or sodium nitroprusside intravenous infusion was prescribed in some patients.

Initially, after the hospitalization, the assisting physicians tried to maintain the drugs used for chronic HF treatment, according to guideline-directed medical therapy in lower doses. However, facing the severity of the shock and the necessity for high doses of inotropic drugs, the chronic HF treatment was stopped in all patients except for furosemide use. Before discharging five patients from the hospital, the drugs were reintroduced. Nine patients received anticoagulation, 14 antibiotics, and 7 corticosteroids, according to decisions of assisting physicians. Patients did not receive any specific treatment for SARS-CoV-2 infection because reduction in mortality was not demonstrated in trials (e.g. hydroxychloroquine, chloroquine, clarithromycin, azithromycin, antiviral therapy, convalescent plasma, and immunomodulatory agents). Many concerns exist regarding the safety of hydroxychloroquine in the treatment of COVID-19.[4] Treatment for HF individuals with COVID-19

Table 2 Treatment of heart failure and shock at the time of initiation of COVID-19 symptoms and during COVID-19, and outcome

Patient number Sex Age in years	Infection acquirement	HF or shock treatment at initiation of COVID-19 symptoms	HF and shock treatment during COVID-19	Treatment support during COVID-19	Outcome during COVID-19	Outcome follow-up after COVID-19 recovery
1 Male 59 years old	Hospital	Dobutamine 20 μg/kg/min (peak dose) IV furosemide as needed	Dobutamine 20 μg/kg/min (peak dose) IV furosemide as needed IABP	NIMV Anticoagulation (continuous non-fractional heparin)	Alive	Death from sepsis18 days after COVID-19 recovery RRT
2 Female 45 years old	Hospital	Dobutamine 6.7 μg/kg/min (peak dose) IV furosemide as needed	Dobutamine 20 μg/kg/min (peak dose) Norepinephrine 0.9 μg/kg/min (peak dose) IV furosemide as needed	IMV Antiarrhythmic (amiodarone) Corticosteroids (low-dose dexamethasone 6 mg/day) Antibiotics (meropenem plus azithromycin) Anticoagulation (continuous non-fractional heparin)	Death	
3 Female 28 years old	Hospital	Dobutamine 6.0 μg/kg/min (peak dose) IV furosemide as needed	Dobutamine 15 μg/kg/min (peak dose) IV furosemide as needed	NIMV Anticoagulation (continuous non-fractional heparin)	Alive	Heart transplant after 71 days of COVID-19 recovery
4 Male 45 years old	Community	Furosemide oral (40 mg/day) Beta-blocker (carvedilol 25 mg/day) ACEI (enalapril 10 mg/day) MRA (25 mg/day)	Dobutamine 20 μg/kg/min (peak dose) Norepinephrine 1.2 μg/kg/min (peak dose) IV furosemide as needed	IMV Corticosteroids (hydrocortisone 50 mg q6h) Antibiotics (meropenem plus azithromycin) Anticoagulation (continuous non-fractional heparin)	Death	
5 Female 34 years old	Hospital	Dobutamine 4.0 μg/kg/min (peak dose) IV furosemide as needed	Dobutamine 20 μg/kg/min (peak dose) IV furosemide as needed	Oxygen catheter Antibiotics (piperacillin–tazobactam plus azithromycin) Anticoagulation (continuous non-fractional heparin)	Alive	Alive awaiting heart transplant at ambulatory care
6 Male 34 years old	Hospital	Dobutamine 5.0 μg/kg/min (peak dose) IV furosemide as needed	Dobutamine 20 μg/kg/min (peak dose) IV furosemide as needed	NIMV Antibiotics (ceftriaxone plus azithromycin)	Alive	Heart transplant after 114 days of COVID-19 recovery infection
7 Male 57 years old	Hospital	Dobutamine 6.6 μg/kg/min (peak dose) IV furosemide as needed	Dobutamine 20 μg/kg/min (peak dose) Norepinephrine 1.3 μg/kg/min (peak dose) IV furosemide as needed	IMV Corticosteroids (hydrocortisone 50 mg q6h) Antibiotics (meropenem plus azithromycin)	Death	
8 Male 79 years old	Community	Furosemide oral (80 mg/day) Beta-blocker (carvedilol 6.25 mg/day)	Dobutamine 19 μg/kg/min (peak dose) Norepinephrine 1.0 μg/kg/min (peak dose)	IMV Corticosteroids (low-dose dexamethasone) Antibiotics (piperacillin–tazobactam plus	Death	

(*Continues*)

Table 2 (continued)

Patient number Sex Age in years	Infection acquirement	HF or shock treatment at initiation of COVID-19 symptoms	HF and shock treatment during COVID-19	Treatment support during COVID-19	Outcome during COVID-19	Outcome follow-up after COVID-19 recovery
			Vasopressin 0.06UI/min (peak dose) IV furosemide as needed	vancomycin plus azithromycin) Anticoagulation (continuous non-fractional heparin)		
9 Male 46 years old	Community	Furosemide oral (40 mg/day) Beta-blocker (carvedilol 25 mg/day) ACEI (enalapril 10 mg/day)	Dobutamine 20 μg/kg/min (peak dose) Sodium nitroprusside 1 .1 μg/kg/min (peak dose) IV furosemide as needed	NIMV Antibiotics (ceftriaxone plus azithromycin)	Alive	Alive in rehabilitation (polyneuropathy of critical illness)
10 Male 66 years old	Hospital	IV furosemide as needed	Dobutamine 10 μg/kg/min (peak dose) IV furosemide as needed	NIMV Antibiotics (ceftriaxone plus azithromycin)	Alive	Alive awaiting heart transplant in ambulatory care
11 Male 44 years old	Hospital	Dobutamine 14 μg/kg/min (peak dose) Milrinone 0.4 μg/kg/min (peak dose) IV furosemide as needed	Dobutamine 20 μg/kg/min (peak dose) Norepinephrine 0.6 μg/kg/min (peak dose) Vasopressin 0.06 UI/min (peak dose) IABP IV furosemide as needed	IMV Inhaled nitric oxide 8 ppm Neuromuscular blockade Corticosteroids (low-dose dexamethasone) Antibiotics (meropenem plus azithromycin) Anticoagulation (continuous non-fractional heparin) Renal replacement therapy	Alive	Death from sustained ventricular tachycardia and cardiogenic shock after 38 days of COVID-19 recovery
12 Male 68 years old	Hospital	Dobutamine 6.0 μg/kg/min (peak dose) Milrinone 0.3 μg/kg/min (peak dose) IV furosemide as needed	Dobutamine 20 μg/kg/min (peak dose) Norepinephrine 0.05 μg/kg/min (peak dose) IABP IV furosemide as needed	IMV Corticosteroids (low-dose dexamethasone) Antibiotics (meropenem plus colistin) Anticoagulation (continuous non-fractional heparin) Renal replacement therapy	Alive	Death from pulmonary infection, sepsis, and cardiogenic shock after 33 days of COVID-19 recovery
13 Female 37 years old	Hospital	IV furosemide as needed	Dobutamine 20 μg/kg/min (peak dose) Norepinephrine 0.05 μg/kg/min (peak dose) IABP IV furosemide as needed	IMV Corticosteroids (low-dose dexamethasone) Antibiotics (meropenem plus colistin) Anticoagulation (continuous non-fractional heparin) Renal replacement therapy	Alive	Alive in rehabilitation (polyneuropathy of critical illness) RRT
14 Female 36 years old	Community	Furosemide oral (40 mg/day)	Dobutamine 14 μg/kg/min (peak dose)	IMV Antibiotics (ceftriaxone plus azithromycin)	Alive	Alive awaiting heart transplant at ambulatory care centre

(*Continues*)

Table 2 (continued)

Patient number Sex Age in years	Infection acquirement	HF or shock treatment at initiation of COVID-19 symptoms	HF and shock treatment during COVID-19	Treatment support during COVID-19	Outcome during COVID-19	Outcome follow-up after COVID-19 recovery
		Beta-blocker (carvedilol 12.5 mg/day) Enalapril 10 mg/day MRA 25 mg/day	Norepinephrine 0.2 μg/kg/min (peak dose) IV furosemide as needed	Renal replacement therapy		
15 Male 42 years old	Community	Furosemide oral (40 mg/day) Beta-blocker (carvedilol 25 mg/day) ARNI (sacubitril–valsartan 97/103 mg twice per day) MRA (25 mg/day)	Dobutamine 8.0 μg/kg/min (peak dose) Norepinephrine 0.15 μg/kg/min IV furosemide as needed	NIMV Antibiotics (ceftriaxone plus azithromycin)	Alive	Alive awaiting heart transplant at ambulatory care centre
16 Male 78 years old	Community	Furosemide oral (80 mg/day) Beta-blocker (carvedilol 50 mg/day) ARB (losartan 50 mg/day) MRA (25 mg/day)	Dobutamine 5.0 μg/kg/min IV furosemide as needed	NIMV Antibiotics (piperacillin–tazobactam)	Alive	Alive under ambulatory care

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; COVID-19, coronavirus disease 2019; COVID-19 recovery, negative real-time polymerase chain reaction associated to lack of clinical or laboratory manifestation of COVID-19; HF, heart failure; IABP, intra-aortic balloon pump; IMV, invasive mechanical ventilation; IV, intravenous infusion; MRA, mineralocorticoid receptor antagonist (spironolactone); NIMV, non-invasive mechanical ventilation; RRT, renal replacement therapy.

included best practices for supportive management of acute hypoxic respiratory failure, haemodynamics, organ failures, and general clinical status.

Eight patients progressed to SARS requiring invasive pulmonary mechanical ventilation, seven needed non-invasive pulmonary ventilation, and one patient received supplemental oxygen by catheter. Severe ventricular arrhythmias were reported in one patient during COVID-19 and in other patients after COVID-19 recovery (*Table 2*). During COVID-19, the patient experienced an electrical storm with recurrent episodes of sustained ventricular tachycardia needing cardioverter–defibrillator shocks. The patient did not have characteristics of polymorphic ventricular tachycardia or long Q-T (torsades de pointes). Acute kidney injury needing renal replacement therapy was observed in four patients.

In the follow-up until 30 September, two patients underwent heart transplantation, and four patients died during the hospitalization from mixed shock (cardiogenic and septic) with SARS and inflammatory storm. After COVID-19 recovery, two patients died from sepsis and cardiogenic shock, and one patient died from sustained ventricular tachycardia and cardiogenic shock. The rate of death or heart transplantation was 56% with a total mortality rate of 44%. The mortality rate during COVID-19 was 25% (n = 4) during a mean follow-up of 10 ± 3.2 days after the diagnosis of COVID-19. The mean follow-up of survival patients (n = 7) excluding heart transplant was 153 ± 134 days after COVID-19 diagnosis. Two patients remain hospitalized in a rehabilitation programme, five patients were discharged to ambulatory care, and four are waiting heart transplant. Before discharging these patients from hospital, the drugs for chronic treatment of HF were reintroduced.

Laboratory data during COVID-19 are shown in *Table 3*. High-sensitivity troponin T, D-dimer, brain natriuretic peptide, high-sensitivity C-reactive protein, lactate dehydrogenase, and ferritin were increased in 100% of patients, respectively (n = 16), 94% (n = 15), 94%, 94%, 94%, and 63% (n = 10).

Discussion

We report the first series of hospitalized patients with concurrent advanced HF and COVID-19. Our main findings showed worsening of advanced HF by COVID-19 with a high mortality rate. Also, most of the clinical presentation of COVID-19 on top of advanced HF was worsening of haemodynamic status and dyspnoea instead of fever and other signs and symptoms of infection. Based on our findings of predominant cardiac symptoms, COVID-19 on top of HF should be suspected in a pandemic area with DHF. All patients with DHF should be tested for SARS-CoV-2. Likewise, discriminating between cardiac or respiratory aetiology of worsening symptoms can be challenging because each cause may

Table 3 Laboratory peak data of advanced heart failure patients during hospitalization due to COVID-19

Laboratory data	Mean peak (±1 DP)
White blood cell count (per microlitre) (nl range 3500–10 500)	6796 ± 3193
n (%) of pts with peak value > upper nl value	3 (19%)
Lymphocyte count (per microlitre) (nl range 900–2900)	856 ± 366
n (%) of pts with lower number < nl value	8 (50%)
White blood cell/lymphocyte count (range 3.62–3.89)	14 ± 24
n (%) of pts with peak > upper nl value	13 (81%)
High-sensitivity troponin T peak level (ng/mL)	0.27 ± 0.23
n (%) of pts with peak value >0.014 ng/mL	16 (100%)
High-sensitivity C-reactive protein (<5 or 0.5 mg/dL)	91 ± 50
n (%) of pts with peak > upper nl value	15 (94%)
D-Dimer (μg/mL) (nl < 500 ng/mL)	4877 ± 6900
n (%) of pts with peak value > upper normal value	15 (94%)
Serum creatinine levels (mg/dL) (nl man <1.3, woman <1.02)	1.49 ± 1.03
n (%) of pts with peak > nl upper value	7 (44%)
Brain natriuretic peptide (pg/mL) (nl < 100)	4040 ± 5680
n (%) of pts with peak > nl upper value	15 (94%)
Aspartate aminotransferase (U/L) (nl 15–37)	47 ± 52
n (%) of pts with peak > nl upper value	5 (31%)
Alanine aminotransferase (U/L) (nl 14–57)	47 ± 76
n (%) of pts with peak > nl upper value	3 (1%)
Ferritin (ng/mL) (nl value man 22–322, woman 15–190)	516 ± 385
n (%) of pts with peak > upper nl value	10 pts (63%)
Fibrinogen (nl 200–400 mg/dL)	423 ± 172
n (%) of pts with peak > upper nl value	7 (44%)
Platelet count (per microlitre) (nl 150 000–450 000)	187 733 ± 55 769
n (%) of pts with lower value < nl	5 (31%)
Lactate dehydrogenase (U/L) (nl 81–234)	510 ± 248
n (%) of pts with peak > upper nl value	15 (94%)

DP, standard deviation; *n*, number; nl, normal; pts, patients.

present predominantly with dyspnoea. The high percentage of abnormalities is remarkable in laboratory biomarkers of myocardial injury, inflammation, coagulopathies, renal function, HF, and tissue lesions.

The cause of COVID-19 worsening advanced HF in our patients may be multifactorial. Some mechanisms can be proposed, such as systemic infection effects on HF haemodynamics and mechanisms related to COVID-19. Infection is a common cause of acute DHF (ADHF).[5] Pulmonary infection was one of the most prevalent factors precipitating ADHF and was reported to be independently associated with hospital mortality.[6,7] Although the exact cause is still unclear, activation of inflammatory and immunological pathways may lead to systemic effects and myocardial dysfunction. Cardiac dysfunction was observed in patients with H1N1 influenza infections.[8] Inflammation diagnosed by C-reactive protein during pneumonia was independently associated with in-hospital and long-term mortality.[6] Experimental data indicated that pulmonary congestion may facilitate the growth of bacteria commonly seen in pneumonia.[6] Also, pulmonary congestion was identified as an independent predictor of pneumonia.

Multiple mechanisms following COVID-19 could determine cardiac function worsening in advanced HF. Myocarditis, myocyte necrosis, and myocardial injury based on elevated troponin levels were reported in COVID-19.[9,10,11] Ischaemic and non-ischaemic mechanisms can be involved in myocardial injury. Microvascular dysfunction secondary to heart pericyte infection by SARS associated or not with thrombosis or inflammation-induced destabilization of previous coronary artery plaque was proposed.[12,13] Non-ischaemic causes of injury in COVID-19 include elevated systemic inflammatory cytokine/chemokine responses (cytokine storm),[13,14] neurohormonal activation (mainly catecholamine and renin–angiotensin–aldosterone system), myocardial strain, and altered calcium handling secondary systemic condition. However, increased troponin levels were also reported in both chronic and decompensated HFrEF and HF with preserved EF with independent prognostic value.[15]

Conflicting results were reported regarding incidental AHF during COVID-19 in patients without a history of HF. HF was reported in 50% of patients with hypertension or cardiovascular disease who died. In a retrospective multicentre cohort study, HF occurred in 52% of non-survivors and in 12% of survivors, being the fourth most frequent complication of COVID-19 after sepsis, respiratory failure, and severe acute respiratory distress syndrome.[16] However, other studies have not reported HF as a common complication of COVID-19.[17]

Limitations

This study has limitations including the small number of patients from a single centre and its retrospective design. Some patients had incomplete documentation of laboratory testing. Our patients may be a selected HF population because missed asymptomatic and mild COVID-19 patients may have stayed at home for fear of being infected with COVID-19 in the hospital. Sometimes, diagnosing COVID-19 pneumonia and its consequences in patients with ADHF is challenging because clinical symptoms are very difficult to discriminate between being caused by ADHF or pneumonia; the interpretation of chest radiographs regarding infiltrates is difficult in congested patients, and C-reactive protein may also be elevated due to the inflammatory state of ADHF alone. The brain natriuretic peptide and N-terminal prohormone brain natriuretic peptide are useful for the exclusion of clinically relevant congestive HF; however, increase in natriuretic peptides has also been reported in COVID-19.[18]

The lack of use of higher levels of mechanical circulatory support, such as extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD) therapy in our HF patients, could be considered a limitation. IABP was the first-line mechanical support instead of other more effective haemodynamic devices. IABP requires the least maintenance from medical support staff. However, in COVID-19 patients with cardiac involvement, important questions remain regarding the use and efficacy of mechanical circulatory support.[19] The high incidence of mixed shock (cardiogenic and infectious shock) and cytokine storm syndrome with hyperinflammation leading also to progressive shock and multiorgan failure in our patients may be an unfavourable scenario for indication of ECMO and VAD. Also, ECMO and VAD maintenance requires significant equipment, blood products, and personnel. Health systems may have limited resources to support these therapies mainly with other co-morbidities. According to the ELSO Guidance Document, ECMO in younger patients with minor or no co-morbidities has the highest priority while resources are limited. The use of ECMO in patients with a combination of multiple co-morbidities or multiple organ failure should be rare.[20]

Concerning limitations in pharmacological treatment of our patients, the low indication of dexamethasone could be considered a limitation of our study. Dexamethasone was not prescribed routinely because of the lack of evidence at the time of patient hospitalizations. In the RECOVERY trial, dexamethasone significantly reduced the absolute risk of death by 2.8% in hospitalized patients with COVID-19.[21] However, the RECOVERY trial was published after the hospitalization of our patients. Also, the dexamethasone trial has the limitation of being an open-label trial. In addition, steroid bursts were significantly associated with increments in HF rates within 5 to 30 days after steroid therapy initiation.[22] Another concern could be the non-use of antiviral drugs, convalescent plasma, and immune modulators in our patients and the lack of indication for anticoagulation in most patients. However, ongoing trials are still testing antiviral therapies, immune modulators, and anticoagulants in COVID-19.

Unfortunately, there is still no definite drug for COVID-19 that is capable of reducing either short-term or long-term mortality.[23,24] Many concerns exist regarding the safety of hydroxychloroquine in the treatment of COVID-19. Concerning remdesivir, this antiviral drug was not associated with statistically significant clinical benefits except for the reduction in time to clinical improvement and recovery.[25,26]

Conclusion and take-home message

This report of high mortality in HFrEF made worse by COVID-19 highlights the importance of preventing COVID-19 in patients with advanced HFrEF. SARS-CoV-2 infection always should be suspected in patients with HFrEF who experience DHF in pandemic areas even in the absence of fever or cough. COVID-19 can cause severe decompensation in underlying advanced HF and frequent severe acute respiratory syndrome. Furthermore, the COVID-19 pandemic creates a challenge for the management of HF patients on a heart transplant waiting list. The rapid evaluation and diagnosis of COVID-19 in advanced HF patients may be crucial for early management to improve HF outcome.

Conflict of interest

None declared.

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