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## Heart failure in COVID-19 patients: Critical care experience

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### Abstract

Patients with heart failure (HF) may be at a higher risk of coronavirus disease 2019 (COVID-19) infection and may have a worse outcome due to their comorbid conditions and advanced age. In this narrative review, we aim to study the interaction between COVID-19 and HF from a critical care perspective. We performed a systematic search for studies that reported HF and critical care-related outcomes in COVID-19 patients in the PubMed and Medline databases. From a total of 1050 papers, we identified 26 that satisfied the eligibility criteria for our review. Data such as patient demographics, HF, intensive care unit (ICU) admission, management, and outcome were extracted from these studies and analyzed. We reported outcomes in heart-transplant patients with COVID-19 separately. In hospitalized patients with COVID-19, the prevalence of HF varied between 4% and 21%. The requirement for ICU admission was between 8% and 33%. HF patients with COVID-19 had an overall mortality rate between 20% and 40%. We identified that HF is an independent predictor of mortality in hospitalized COVID-19 patients, and patients with HF were more likely to require ventilation, ICU admission and develop complications. Patients with HF with reduced ejection fraction did worse than those with HF with midrange ejection fraction, and HF with preserved ejection fraction. COVID-19 patients with HF should be identified early and managed aggressively in an attempt to improve outcomes in this cohort of patients.

**Key Words:** Heart failure; COVID-19; Critical care; Intensive care; Mortality

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**Core Tip:** Heart failure (HF) can lead to worse outcomes in coronavirus disease 2019 (COVID-19). Moreover, critically ill patients with COVID-19 can develop *de novo* HF. Patients with COVID-19 and HF are more likely to require ventilation, ICU admission and develop complications. HF is an independent predictor of mortality in hospitalized COVID-19 patients and therefore, HF should be identified early and managed aggressively in an attempt to improve outcomes in critically ill patients.

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## INTRODUCTION

Coronavirus disease 2019 (COVID-19) emerged from China in December of 2019 and continues to be a public health emergency of international concern. As of March 12, 2021, more than 118 million cases have been diagnosed worldwide with 29.3 million patients reported from the United States. Patients with pre-existing comorbidities, cardiac dysfunction and immunocompromised status continue to be at high risk of morbidity and mortality. The literature on COVID-19 infection in patients with heart failure (HF) is limited. Patients with HF may be at higher risk of COVID-19 infection and have a worse outcome due to their comorbid conditions and advanced age.

The currently available literature regarding the role of critical care and a multidisciplinary approach in treating patients with HF and COVID-19 infection, remains scarce. In this narrative review, we aim to study the interaction between COVID-19 and HF from a critical care perspective. We also aim to explore the various outcomes as reported in the literature in this subgroup of patients and to provide a summary of the current evidence and practices in the management of HF in COVID-19 patients in the intensive care unit (ICU).

In this review, we have attempted to summarize all the articles published on the presentation and management of patients with COVID-19 and HF. We searched the PubMed and Medline database for the MeSH terms "COVID-19", "heart failure" and "critical care". Studies published in English, including adults with HF and COVID-19 infection were eligible to be included in this review (Figure 1). All studies published before March 2021 were included. Studies that provided details on patient demographics, HF, ICU admission, management, and outcome were analyzed. Various treatment details including medications such as beta blockers, angiotensin converting enzyme inhibitors (ACEi), aldosterone receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNi), automatic implantable cardioverter-defibrillator, permanent pace-maker and cardiac resynchronization therapy were included. Critical care details that were obtained were the type of organ dysfunction, the requirement of non-invasive and invasive ventilation, administration of vasopressor support, extra-corporeal membrane oxygenation (ECMO) and outcome. Articles that did not have the patient's details, opinions, comments, letters, and articles not published in English were excluded from the analysis. Studies that included cardiac transplant patients were analyzed separately. Two independent clinicians reviewed all articles.

As of March 2021, a total of 1050 papers were identified (Figure 1). Among these, 26 satisfied the eligibility criteria for our study. One study was a prospective cohort study, while all others were retrospective studies. Studies were principally published from North American and European nations. There were significant differences in the study design, data collection and measured outcomes among the studies which made the comparison of data difficult. Therefore, we divided the studies into four categories and reported the outcomes separately. The four categories were: (1) Studies highlighting prevalence of HF, requirement of ICU level of care and outcomes in hospitalized COVID-19 patients; (2) Studies reporting outcomes in COVID-19 patients admitted to ICU; (3) Studies reporting outcomes in HF patients with COVID-19; and (4) Studies reporting outcomes in heart-transplant patients with COVID-19 (Figure 2).



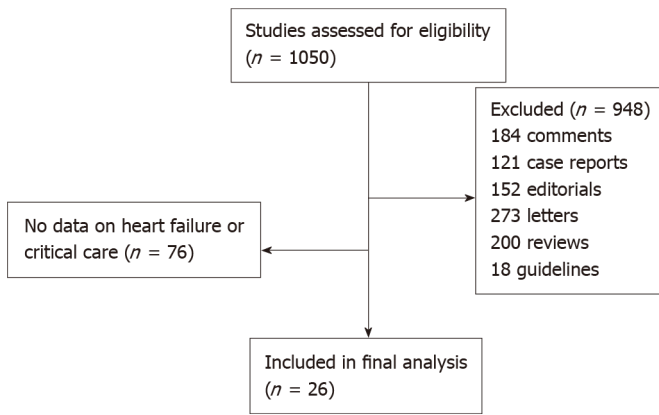


Figure 1 CONSORT diagram.

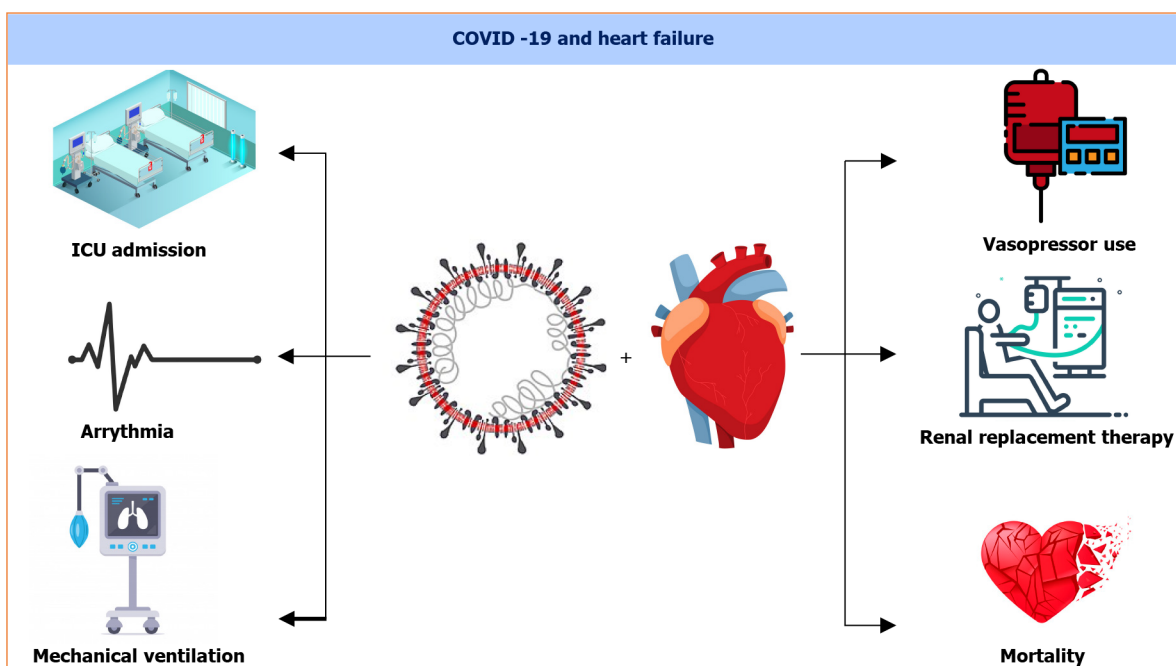


Figure 2 Coronavirus disease 2019 and heart failure.

## INCREASED RISK OF HEART FAILURE IN COVID-19 PATIENTS

Among studies that reported outcomes in hospitalized patients with COVID-19, we found 11 studies that provided data on HF and ICU admission (Table 1)[1-11]. The total number of patients in this group was 9420, with studies from the United States contributing the maximum number of patents. The diagnosis of COVID-19 was uniformly established with reverse transcription polymerase chain reaction (RT-PCR) in all of the patients. The proportion of patients with pre-existing HF varied from 1% to 21%, which was almost ten times the community prevalence of HF, as reported by the Framingham study[12]. This suggests that patients with HF are more likely to require hospitalization for COVID-19. Zylla *et al*[3] reported that 3% of patients developed newly diagnosed (*de novo*) left ventricular (LV) dysfunction after admission, while Zhou *et al*[9] and Chen *et al*[10] reported a number close to 25%. This highlights the fact that HF can be both a risk factor, as well as a complication of COVID-19. Most studies reported a male preponderance with a mean age above 60 years. The requirement for ICU admission was between 8% and 33%. Patients with HF were more likely to require mechanical ventilation and develop complications such as thromboembolism, sepsis, stroke and acute kidney injury. The overall mortality rate for hospitalized patients with COVID-19 was between 4% and 40%. Inciardi *et al*[1] noted that chronic therapy with an ACEi, ARB, or ARNI had to be discontinued in 77% of cases

**Table 1 Studies highlighting prevalence of heart failure, requirement of intensive care unit level of care and outcomes in hospitalized coronavirus disease 2019 patients, *n* (%)**

No.	1	2	3	4	5	6	7	8	9	10	11
Ref.	Inciardi <i>et al</i> [1]	Singer <i>et al</i> [2]	Zylla <i>et al</i> [3]	Russo <i>et al</i> [4]	Bhatla <i>et al</i> [5]	Peltzer <i>et al</i> [6]	Lala <i>et al</i> [7]	Shi <i>et al</i> [8]	Zhou <i>et al</i> [9]	Chen <i>et al</i> [10]	Jarrett <i>et al</i> [11]
Country	Italy	United States	Germany	Italy	United States	United States	United States	China	China	China	United States
Total number of patients	99	737	166	414	700	1053	2736	416	191	274	2634 (all patients died)
Patients with chronic heart failure	21 (21)	39 (5)	-	46 (11.1)	88 (13)	79 (7.5)	276 (10.1)	17 (4.1)	-	1 (< 1)	291 (11.1)
Newly diagnosed LV dysfunction	-	-	5 (3)	-	-	-	-	-	44 (23)	43/176 (24)	-
Study type	RC, single centre	RC, single centre	RC,multicenter	RC, multicenter	RC, single centre	RC, multicenter	RC, multicenter	RC, single centre	RC, multicenter	RC, single center	RC of in-patients who died of COVID-19 in a single center
Age (mean $\pm$ SD)	67 $\pm$ 12	60 $\pm$ 18	64.1 $\pm$ 16.7	66.9 $\pm$ 15.0	50 $\pm$ 18	62 $\pm$ 17	66.4 (median)	64 (range: 21-95)	56 (IQR: 46-67)	62 (IQR: 44-70)	Range: 21-107
Male	8 (81)	423 (57)	108 (65.1)	253 (61.1)	315 (45)	653 (62)	1630 (59.5)	205 (49.3)	119 (62)	171 (62)	1664 (63.2)
LVEF, % (mean $\pm$ SD)	48 $\pm$ 14	-	53.0 $\pm$ 12.3	-	-	HFrEF: 41 (3.8)	-	-	-	-	-
ICU admission	12 (12)	59 (8)	65 (39.2)	-	79 (11.28)	349 (33.14)	-	-	50 (26)	-	1299 (49.3)
NIV	18 (19.1)	40 (5)	39 (23.5)	-	-	-	-	32 (7.7)	26 (14)	102 (37)	-
IV	2 (2)	149 (20.2)	37 (22.3)	-	-	327 (31.05)	307 (11.2)	51 (12.3)	32 (17)	17 (6)	140 (53.2)
ECMO/ICD/CRT/PPM	-	-	PPM:3 (1.8), ICD:2 (1.2), ECMO:3 (1.8)	-	-	-	-	-	ECMO: 3 (2)	ECMO: 1 (<m1)	-
Vasopressor	-	-	30 (18.1)	-	-	323 (30.67)	-	-	-	-	-
Hospital LOS, d, (mean $\pm$ SD)	11.4 $\pm$ 6.5	4.7 $\pm$ 3.0	10.5 (IQR 5-22 d)[ICU stay: 8 (IQR 4-22.5)]	-	-	-	5.75 (IQR :3.36-9.56)	-	11 (7-14) [ICU stay: 8 (4-12)]	-	-
Complications	Venous thrombo-embolism: 12 (12),	-	-	-	-	Bacteremia:100 (9.5), VTE: 54 (5.13),	Hospitalized at time of study	CRRT: 2 (0.5), ARDS: 97 (23.3), Coagulation	RRT: 10 (5), sepsis:112 (59), respiratory failure: 103 (54),	AKI: 29 (11), CRRT: 3 (1),	-

	Arterial thrombo-embolism: 3 (3), septic shock/sepsis: 6 (6)					stroke/TIA:18 (1.71), AKI requiring RRT: 34 (3.23)	publication: 1098 (40.1)	disorders: 12 (2.9), hospitalized at end of study period:319 (76.7)	ARDS: 59 (31), septic shock: 38 (20), coagulopathy: 37 (19), secondary infection:28 (15)	sepsis: 179 (65), DIC: 21 (8), shock: 46 (17), ALI: 13 (5)	
Mortality	26 (26)	68 (9)	26 (15.7)	107 (25.8)	30 (4)	184 (17.47)	506 (18.5)	57 (13.7)	54 (28.2)	113 (40)	2634 (100)

- Signifies that the variable was not reported in the study.

LV: Left ventricle; RC: Retrospective cohort; LVEF: Left ventricle ejection fraction; HFrEF: Heart failure with reduced ejection fraction; ICU: Intensive care unit; NIV: Non-invasive ventilation; IV: Invasive ventilation; ECMO: Extracorporeal membrane oxygenation; ICD: Implantable cardiovascular-defibrillator; CRT: Cardiac resynchronisation therapy; PPM: Permanent pacemaker; LOS: Length of stay; IQR: Inter-quartile range; VTE: Venous thrombo-embolism; TIA: Transient ischemic attack; AKI: Acute kidney injury; CRRT: Continuous renal replacement therapy; RRT: Renal replacement therapy; ARDS: Acute respiratory distress syndrome; ALI: Acute liver injury; DIC: Disseminated intravascular coagulation.

because of severe hypotension, and patients who died were more likely to have a history of HF. In the same study, the mortality rate remained higher in patients with cardiac disease compared to those without (26% *vs* 9%;  $P = 0.039$ ), even after excluding patients who were denied intubation due to comorbidities or age. Another study used multivariate regression modelling to identify an increased risk of atrial fibrillation among COVID-19 patients with HF (RR 1.88;  $P = 0.023$ ), which in-turn increased the odds of ICU or intermediate care ward admission (OR 2.37; 95%CI: 1.10-5.09;  $P = 0.03$ ) [4,5]. HF was also linked to brady-arrhythmias (OR 9.75; 95%CI: 1.95-48.65) by a separate group of investigators[5]. Three separate meta-analysis identified that HF was independently associated with an increased risk of mortality in patients with COVID-19[13-15].

## NEED FOR INTENSIVE CARE UNIT LEVEL OF CARE

We found six studies that reported HF data in COVID-19 patients who were admitted to the ICU, while excluding patients who were hospitalized without requiring ICU care (Table 2)[5,16-20]. These studies had a total patient number of 6539, with a major patient population contributed from the United States. The mean age in this group of patients was above 60 years and there were more men than women. Between 10% and 43% of these patients had pre-existing HF. This range was higher than what was observed among hospitalized patients overall. It was also noted that more patients developed *de-novo* HF in this group (up to 33%)[16]. The average ICU length of stay was between 2 to 5 weeks and a majority of patients required ventilatory assistance. In addition, advanced life-sustaining supportive interventions such as ECMO were also utilized by 3% to 15% of these patients. As a group, these patients had a higher mortality rate, which was as high as 52%. A cross-sectional observational multi-centre nationwide survey in Italy identified that obesity, chronic kidney disease and



**Table 2 Studies reporting outcomes in coronavirus disease 2019 patients admitted to intensive care unit, *n* (%)**

No.	1	2	3	4	5	6
Ref.	Zeng <i>et al</i> [16]	Petrilli <i>et al</i> [17]	Bhatla <i>et al</i> [5]	Hayek <i>et al</i> [18]	Iaccarino <i>et al</i> [19]	Arentz <i>et al</i> [20]
Country	China	United States	United States	United States	Italy	United States
Total number of patients in ICU	35	990	79	5019	395	21
Patients with chronic heart failure	NR	189 (19.1)	22 (28)	512 (10.20)	60 (15.2)	9 (42.9)
Newly diagnosed LV dysfunction/acute heart failure	5 (14)	-	-	166 (3.3)	-	7 (33.3)
Study type	Retrospective cohort, single centre	Prospective cohort, single centre	Retrospective cohort, single centre	Retrospective cohort, multicenter	Cross-sectional study, multicenter	Retrospective cohort, single centre
Age, (mean $\pm$ SD)	64.00 (59.50–68.00)	68 (58–78)	63 $\pm$ 16	60 $\pm$ 15, 63 $\pm$ 14 <sup>1</sup>	68.9 $\pm$ 0.7	70 (43–92) range
Male	23 (66)	656 (66.3)	40 (51)	3165 (63.06)	291 (73.7)	11 (52)
Risk factors	Hypertension: 13 (37), coronary artery disease: 2 (6), arrhythmia: 2 (6), valvular disease:1 (3), diabetes: 10 (29), COPD: 1 (3)	Diabetes: 389 (39.3), asthma or COPD: 169 (17.1), chronic kidney disease: 259 (26.2), cancer: 138 (13.9)	Coronary heart disease: 21 (27), diabetes mellitus :35 (44), hypertension: 62 (78), atrial fibrillation history: 5 (6), obstructive sleep apnea: 23 (29), COPD: 14 (18), liver disease: 14 (18), chronic kidney disease: 16 (20), current tobacco: 4 (5)	Current or former tobacco use: 2174 (43.31), diabetes mellitus: 2110 (42.04), hypertension:3086 (61.48), coronary artery disease:676 (13.46), chronic obstructive pulmonary disease: 43 (0.85), chronic or end stage kidney disease: 819 (16.31), active malignancy:227 (4.52)	Hypertension: 256 (65.3), obesity: 49 (12.4), diabetes: 90 (22.8), COPD: 41 (10.4), CKD: 34 (8.6), coronary artery disease: 62 (15.7)	Asthma: 2 (9.1), chronic obstructive pulmonary disease: 7 (33.3), diabetes: 7 (33.3), obstructive sleep apnea: 6 (28.6), chronic kidney disease: 10 (47.6), end-stage kidney disease: 2 (9.5), history of solid organ transplant: 2 (9.5), cirrhosis: 1 (4.8), immunosuppression: 3 (14.3)
HFrEF,	5 (14)	-	-	-	-	-
HFpEF	0 (0)	-	-	-	-	-
Drugs	-	-	-	-	ACE-inhibitors: 97 (24.6), ARB: 66 (16.7), beta-blockers: 96 (24.3), calcium-antagonists: 31 (7.8), diuretics: 58 (14.7), alpha-blockers: 7 (1.8)	-
ICD	-	-	5 (6)	-	-	-
Ventilation	35 (100)	647 (65.35)	-	-	-	19 (90.5)
NIV	17 (49)	-	-	-	-	4 (19)
IV	18 (51)	647 (65.35)	-	3663 (72.98)	-	15 (71)
ECMO	5 (15)	-	-	176 (3.51)	-	-
Vasopressor	NR	-	-	1617 (32.22)	-	14 (67)
ICU stay duration in days	38 (33–47)	36 (32–40)	-	17 (9–30), 6 (4–10) <sup>1</sup>	-	-
Organ dysfunction	NR	-	-	Acute kidney injury requiring RRT: 1003	-	AKI: 4 (19.1), ALI: 3 (14.3)
Morbidity	acute cardiac injury: 21 (60), atrial or ventricular tachyarrhythmia:3 (9)	86 (8.68) patients being ventilated and 74 (7.47) patients still	-	Still in hospital 30 days after ICU admission: 169	-	Admitted in ICU at end of study: 8 (38.1)

		admitted at the end of study period				
Mortality	3 (9)	485 (49)	-	2043 (40.71)	-	11 (52.4)

<sup>1</sup>Baseline characteristics of patients who did not have cardiac arrest and those who had cardiac arrest respectively.

- Signifies that the variable was not reported in the study.

ICU: Intensive care unit; LV: Left ventricle; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; ICD: Implantable cardiovascular-defibrillator; NIV: Non-invasive ventilation; IV: Invasive ventilation; ECMO: Extra-corporeal membrane oxygenation; ECMO: Extra-corporeal membrane oxygenation; RRT: Renal replacement therapy; AKI: Acute kidney injury; ALI: Acute liver injury.

hypertension in men, and obesity (OR 2.564; 95%CI: 1.336-4.920;  $P < 0.0001$ ) and HF (OR 1.775; 95%CI: 1.030-3.057) in women were associated with higher rate of ICU admission[19]. Similar observations were made from a single academic medical centre in New York City and Long Island which found that the strongest risk factors for critical illness besides age were HF (OR 1.9; 95%CI: 1.4-2.5), BMI > 40 (OR 1.5; 95%CI: 1.0-2.2), and male sex (OR 1.5; 95%CI: 1.3-1.8)[17].

## OUTCOMES IN CRITICALLY ILL COVID-19 PATIENTS WITH PREEXISTING HEART FAILURE

There were five studies (from North America and Europe) that focused on the outcomes of COVID-19 infection in patients with pre-existing HF (Table 3)[21-25]. Three of them were from the United States, one was from Italy and the last one was from Denmark. Together, these studies included 9191 patients. Maximum number of patients were contributed by the study by Bhatt *et al*[21]. The mean age of patients in these studies were above 70 years, which was about 10 years higher than what was observed in the two previous groups. Two out of the five studies had more women than men. This was in contrast to the uniform male predominance observed in the two previous groups. ICU admission rates were reported by two studies and ranged between 23% and 29%. ECMO was used by three patients in one study[21]. An overall mortality rate between 20% to 40% was observed. Overall mortality variation in multinational studies have ranged from close to 30 % to over 90 %. There was also a significant inter-hospital variability in the outcome of critically ill patients which could not be attributed to the location or performance of the treating facility[26]. Tomasoni *et al*[24] reported more in-hospital complications such as acute HF (33.3% vs 5.1%,  $P < 0.001$ ), acute renal failure (28.1% vs 12.9%,  $P < 0.001$ ), multiorgan failure (15.9% vs 5.8%,  $P = 0.004$ ) and sepsis (18.4% vs 8.9%,  $P = 0.006$ ) in COVID-19 patients with a prior history of HF. This suggests that patients with HF and COVID-19 have a poorer outcome than the general population. When compared to hospital admissions for other causes, HF patients admitted for COVID-19 were older, more likely to identify as Black and/or Hispanic, had higher rates of diabetes and kidney disease and used more healthcare resources such as ICU beds (29% vs 15%), mechanical ventilation (17% vs 6%), and central venous catheter insertion (19% vs 7%;  $P < 0.001$  for all)[21]. They also had higher in-hospital mortality (24.2% vs 2.6%) as well as higher skilled-nursing and rehabilitative care requirement among survivors (13% vs 41%)[21]. Similar conclusions were drawn by Alvarez-Garcia *et al*[22], who noted that the history of HF was an independent risk factor for the need for ICU care (adjusted OR 1.71; 95%CI: 1.25-2.34;  $P = 0.001$ ), intubation and mechanical ventilation (adjusted OR 3.64; 95%CI: 2.56 -5.16;  $P < 0.001$ ), and in-hospital mortality (adjusted OR 1.88; 95%CI: 1.27-2.78;  $P = 0.002$ ). Furthermore, the former was the only study to look at outcomes stratified by left ventricular ejection fraction (LVEF) and found that cardiogenic shock (7.8% vs 2.3% vs 2%;  $P = 0.019$ ) and HF-related causes for 30-day readmission (47.1% vs 0% vs 8.6%) were significantly higher in patients with HF with reduced ejection fraction (HFrEF) than in those with HF with midrange ejection fraction (HFmrEF) or HF with preserved ejection fraction (HFpEF)[22]. Multivariate cox regression identified older age, more severe HF [baseline New York Heart Association (NYHA) functional classes III and IV], previous mitral regurgitation, lower systolic blood pressure, lower oxygen saturation, lower lymphocyte count, and increased troponin concentrations as risk factors for in-hospital mortality in COVID-19 patients with HF[22].

**Table 3 Studies reporting outcomes in heart failure patients with coronavirus disease 2019, *n* (%)**

No.	1	2	3	4	5
Ref.	Bhatt <i>et al</i> [21]	Alvarez-Garcia <i>et al</i> [22]	Caraballo <i>et al</i> [23]	Tomasoni <i>et al</i> [24]	Andersson <i>et al</i> [25]
Country	United States	United States	United States	Italy	Denmark
Patient number	8383	422	206	90	90
Study type	Retrospective cohort, multicentre	Retrospective cohort, multicentre	Retrospective cohort, multicentre	Retrospective cohort, multicentre	Retrospective cohort, multicentre
Age, (mean±SD)	71.7 ± 13.2	72.5 ± 13.3	78 (IQR: 65-87)	73.0 ± 11.4	
Male	4178 (49.8)	236 (55.9)	93 (45.1)	66 (73.3)	
Risk factors	Obesity: 2461 (29.4), morbid obesity: 1425 (17.0), hypertension: 6997 (83.5), diabetes: 5107 (60.9), history of arrhythmia: 4548 (54.3), valvular disease: 1417 (16.9), kidney disease: 5020 (59.9), ESKD: 1689 (20.1), smoking: 3665 (43.7), pulmonary disease: 3539 (42.2), asthma: 628 (7.5), anemia: 628 (7.5), malignancy: 290 (3.5)	Obesity: 169 (40.0), hypertension: 382 (90.5), diabetes mellitus: 269 (63.7), dyslipidemia: 228 (54.0), CAD: 235 (55.7), stroke: 114 (27.0), atrial fibrillation: 160 (37.9), CKD: 177 (41.9), COPD: 94 (22.3), asthma: 58 (13.7), OSA: 57 (13.5)	Hypertension: 164 (79.6)COPD: 67 (32.5)CAD: 73 (35.4)Renal disease: 79 (38.3)	Smoker: 42 (55.3), hypertension: 68 (75.6), dyslipidaemia: 56 (62.2), diabetes: 37 (41.1), atrial fibrillation: 42 (46.7), coronary artery disease: 55 (61.1), COPD: 22 (24.4), CKD: 49 (54.4)	
LVEF (%), (mean ± SD)	-	-	-	42.1 ± 13.1	-
HFrEF	3318 (39.6)	128 (30.3)	36 (17.5)	64 (71)	-
HFmrEF	-	44 (10.4)	-	-	-
HFpEF	3486 (41.6)	250 (59.3)	-	26 (29)	-
RV dysfunction	-	-	-	16 (28.6)	-
Drugs prior to hospitalization	-	RAAS inhibitors: 260 (61.6), beta-blockers: 354 (83.9), MRA: 60 (14.2), loop diuretics: 318 (75.4), thiazides: 64 (15.2), antiplatelet: 327 (77.5), anticoagulant: 175 (41.5), statins: 351 (83.2)	ACEi/ARB: 58 (28.2), beta-blocker: 94 (45.6), CCB: 69 (33.5), SGLT2i: 1 (0.5), warfarin: 16 (7.8), NOAC: 47 (22.8), diuretic: 99 (48.1), statin: 117 (56.8)	ACEi/ARBs/ARNI: 42 (50.0), MRAs: 23 (34.8), beta-blockers: 69 (81.2), direct oral anticoagulants: 17 (20.5), warfarin: 18 (21.6), statins: 47 (56.0)	-
ICD/CRT	-	-	-	ICD: 20 (22.2), CRT: 8 (8.9) (both prior to hospitalization)	-
ICU	2431 (29)	98 (23.2)	-	-	-
Ventilation	-	96 (22.8)	-	-	-
NIV	-	-	-	28 (31.1)	-
IV	-	96 (22.8)	-	5 (5.6)	-
ECMO	3 (0.04)	-	-	-	-
ICU stay duration	-	5 (2-11)	-	-	-
Mortality	2026 (24.2)	169 (40.0)	41 (20)	37 (41.1)	33 (27)

- Signifies that the variable was not reported in the study.

ESKD: End stage kidney disease; CAD: Coronary artery disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; OSA: Obstructive sleep apnea; LVEF: Left ventricle ejection fraction; HFrEF: Heart failure with reduced ejection fraction; HFmrEF: Heart failure with mid-range ejection fraction; HFpEF: Heart failure with preserved ejection fraction; RV: Right ventricle; RAAS: Renin angiotensin aldosterone system; MRA: Mineralocorticoid receptor antagonist; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker; SGLT: Sodium-glucose linked transporter; NOAC: Novel oral anticoagulants; ARNI: Angiotensin receptor II blocker – neprilysin inhibitor; ICD: Implantable cardiovascular-defibrillator; CRT: Cardiac resynchronisation therapy; ICU: Intensive care unit; NIV: Non-invasive ventilation; IV: Invasive ventilation; ECMO: Extra-corporeal membrane oxygenation.

## DATA ON CARDIAC TRANSPLANT PATIENTS WITH COVID-19

We analyzed studies that included heart transplant patients separately because they are a distinct subset of patients who are likely to be on immunosuppressive therapy. We found five retrospective studies with a total of 99 patients (Table 4)[27-31]. This was a group of predominantly male patients with a mean age above 55 years and a wide variation in requirements for ICU level of care; ranging from 10.5% to 100%. The patients who were admitted to ICU were sicker as evidenced by increased requirement of vasopressors, mechanical ventilation, and renal replacement therapy (83% *vs* 38%) [28]. The mortality rate was between 18% and 37%. In one study, all patients who required ICU admission died[29]. This was higher than the mortality rate in the general population, but not much more than non-transplanted HF patients or patients in ICU. Bottio *et al*[31] reported that older age ( $P = 0.002$ ), diabetes mellitus ( $P = 0.040$ ), extracardiac arteriopathy ( $P = 0.040$ ), previous percutaneous coronary intervention ( $P = 0.040$ ), cardiac allograft vasculopathy score ( $P = 0.039$ ), lower glomerular filtration rate ( $P = 0.004$ ), and higher NYHA functional classes ( $P = 0.023$ ) were all significantly associated with in-hospital mortality among heart-transplant patients with COVID-19 [31]. We know that steroids are beneficial in severe COVID-19, and cardiac transplant patients are often on multiple immunosuppressive medications that include steroids, calcineurin inhibitors and anti-metabolites[32]. Whether these immunosuppressive medications protected these patients from severe disease is a question that warrants further investigation.

In this review, we summarized the relationship between HF, COVID-19 and the role of intensive care in patients with COVID-19 and HF. Our review of literature revealed many interesting observations. The evidence suggests that patients with HF are more likely to be hospitalized after COVID-19 infection. Exact quantification of risk will require community-level studies and cannot be derived from the hospital-based studies included in this review. Also, patients with COVID-19 are at increased risk of developing *de novo* HF after admission to the hospital; a risk that increases substantially with admission to the ICU. The reversibility and long-term morbidity of COVID-19 related *de novo* HF is unclear at this point and will require future studies with longer durations of follow up. Patients with COVID-19 and HF had increased chance of requiring ICU admission, mechanical ventilation, vasopressors and renal replacement therapy. They also had more complications and a higher mortality rate when compared to non-HF patients. These differences may be due to the effect of additional organ injury and decreased physiologic reserve leading to faster decompensation. This may also be an indirect marker for variation in practices. While it is expected that patients admitted to the ICU are at increased risk for development of complications and mortality, what is interesting is that the presence of HF represents an additional independent risk factor for the same. Furthermore, due to the similarity in clinical presentation, HF in COVID-19 patients is probably underdiagnosed. Therefore, it stands to reason that the risk estimate from the studies reported thus far are lower than the true risk estimate. It was noteworthy that the outcomes in critically ill heart transplant patients with COVID-19 was not very different from critically ill non-heart transplant patients. Whether the immunosuppressive medications that heart transplant patients are on, provides them with a selective advantage in combating the 'cytokine storm' seen in COVID-19 is a question worth asking. What is clear from our analysis of the existing literature is that HF is inextricably linked with the outcomes of COVID-19 infection. What is not known is the exact mechanisms by which they are linked and therefore, this is a field with immense scope for future research. There are many reasons to study HF in COVID-19 patients. Heart-lung interactions dictate that insult to one organ, affects the other. Acute respiratory distress syndrome (ARDS) is the most common manifestation of severe COVID-19 disease. While hypoxia and positive pressure ventilation stresses the right heart, the left heart has to compensate for increased metabolic demand. These problems are compounded in patients with pre-existing HF. Therefore, it is vital that we investigate the interaction between HF and COVID-19 so that we have a better understanding of its pathophysiology, optimal management and outcome.

## PATHOGENESIS OF HF IN COVID-19

Cardiac troponins were elevated in 8%-12% of COVID-19 cases and the percentage rose up to 23%-33% in critically ill patients[1,33,34]. COVID-19 is theorized to injure the myocardium indirectly and directly. The systemic inflammatory response and

**Table 4 Studies reporting outcomes in heart-transplant patients with coronavirus disease 2019, n (%)**

No.	1	2	3	4	5
Ref.	Latif <i>et al</i> [27]	Ketcham <i>et al</i> [28]	Singhvi <i>et al</i> [29]	Lima <i>et al</i> [30]	Bottio <i>et al</i> [31]
Country	United States	United States	United States	United States	Italy
Patient number	28	6	22	5	38
Study type	Retrospective observational	Retrospective observational	Retrospective observational	Retrospective observational	Retrospective observational
Age, (mean $\pm$ SD)	64 (53.5-70.5)	57 (34-73) <sup>1</sup>	58.6 (49.1-71.2) <sup>2</sup>	62 $\pm$ 9.8	64.9 $\pm$ 12.0
Male	22 (79)	6 (100)	14 (63.6)	4 (80)	31 (82)
Risk factors	Hypertension:20 (71), diabetes:17 (61), lung disease: 10 (36), malignancy: 5 (18), chronic kidney disease: 10 (36)	Chronic heart failure: 4 (67), chronic kidney disease: 4 (67), Chronic anemia: 3 (50), coronary artery disease: 4 (67), former tobacco smoker: 1 (17), diabetes mellitus: 4 (67), hypertension: 6 (100), obesity: 3 (50), obstructive sleep apnea: 3 (50)	Hypertension: 21 (95.5), diabetes: 12 (54.5), lung disease: 3 (13.6), chronic kidney disease stage $\geq$ III: 14 (63.6), end stage renal disease on dialysis: 3 (13.6), malignancy (excluding non-melanoma skin cancers): 6 (27.3), HIV: 1 (4.5), current smoker: 1 (4.5), former smoker: 7 (31.8), permanent pacemaker: 3 (13.6), charlson comorbidity index $\geq$ 5: 12 (54.5)	Ischemic cardiomyopathy (pre-HTx): 2 (40), hypertension: 5 (100), hyperlipidemia: 3 (60), diabetes mellitus: 1 (20), obesity: 2 (40), post-transplant renal insufficiency: 2 (40)	Obesity: 7 (18), arterial hypertension: 25 (66), dyslipidemia: 18 (47), diabetes mellitus: 7 (18), former smoker: 8 (21), peripheral vascular disease: 8 (21), COPD: 3 (8), stroke: 1 (2), malignancy: 3 (8), previous PCI: 11 (29)
NYHA class	-	-	-	-	I:27 (71), II:8 (21), III:3 (8), IV:0 (0)
ICU	7 (25)	6 (100)	4 (18.18)	2 (40)	4 (10.5)
Ventilation	7 (25)	5 (83)	7 (31.81)	2 (40)	17 (44)
NIV	-	0	3 (13.63)	0	15 (39.4)
IV	7 (25)	5 (83)	4 (18.18)	2 (40)	2 (5.2)
ECMO	-	0	-	0	0 (0)
Vasopressor	-	5 (83)	3 (13.63)	-	3 (7.9%)
ICU stay duration in days	-	8.25 (4-12.5)	7 (4-9)	-	-
Organ dysfunction	HD: 3 (10.71)	AKI requiring CRRT: 5 (83)	RRT: 3 (13.63)	AKI requiring HD: 1 (20)	-
Morbidity	4 (18) patients remained hospitalized at the end of study period	2 (33) patients still admitted at the end of the study period	-	One patient developed mild acute cellular rejection	Bacterial coinfection:5 (13), sepsis: 4 (10.5), neurological complication: 1 (2.6), gastrointestinal complication: 1 (2.6)
Mortality	7 (25)	2 (33)	4 (18.18)	0 (0)	14 (36.8)

<sup>1</sup>Range.<sup>2</sup>IQR.

- signifies that the variable was not reported in the study. All patients had COVID-19 confirmed by RT-PCR.

HIV: Human immunodeficiency virus; Htx: Heart transplant; PCI: Percutaneous coronary intervention; COPD: Chronic obstructive pulmonary disease; NYHA: New York Heart Association; ICU: Intensive care unit; NIV: Non-invasive ventilation; IV: Invasive ventilation; ECMO: Extra-corporeal membrane oxygenation; HD: Hemodialysis; AKI: Acute kidney injury; CRRT: Continuous renal replacement therapy; RRT: Renal replacement therapy; AKI: Acute kidney injury.

cytokine storm increases blood viscosity and coagulability, which causes endothelial dysfunction[35,36]. The sympathetic activation, tachycardia, increased myocardial oxygen consumption and energy expenditure can also injure the myocardium. More cases of takotsubo cardiomyopathy are being diagnosed in patients with severe COVID-19[37]. Elevated positive end-expiratory pressure during mechanical ventilation in COVID-19 patients with severe ARDS increases right ventricular wall stress and can further reduce the cardiac output in a failing heart[38]. In a series of consecutive autopsy cases, Lindner and colleagues documented SARS-CoV-2 in 24 of



39 patients (61.5%), suggesting that direct viral myocardial damage is also possible [39]. SARS-CoV-2 attaches to human cells after binding with its spikes to the ACE2, which are upregulated in patients with cardiovascular disease, diabetes, and those treated with ACEi or ARB[40-42]. In light of this observation, role of ACE2 and ACEi in the pathogenesis of COVID-19 related myocardial injury has also been investigated from a therapeutic point of view.

While there are multiple factors contributing to HF in COVID-19, the incidence of true 'myocarditis' in COVID-19 is unclear[43]. Some authors estimate that myocarditis may account for up to 7% of COVID-19 deaths[44]. This estimate is fundamentally flawed because the diagnosis cannot be confirmed in a vast number of cases. Also, the presentation of acute coronary syndrome, sepsis-related cardiomyopathy and takotsubo cardiomyopathy can mimic myocarditis, making this a challenging diagnosis. Myocarditis, even when subclinical, can worsen patient outcomes. In the short term, it can increase the risk of arrhythmias and precipitate decompensated HF, especially in patients with pre-existing chronic HF[45]. In the long term, the resultant myocardial fibrosis and negative remodeling can accelerate the decline of systolic function leading to a limitation of physical activity. Therefore, in the ICU, it is important to screen patients for subclinical myocarditis, by following the AHA recommendation of testing patients with signs consistent with myocarditis with one or more cardiac imaging methods such as echocardiogram or cardiovascular magnetic resonance[46].

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## SCREENING FOR HF IN THE ICU

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Up to one-third of COVID-19 patients admitted to the ICU develop cardiomyopathy, and cohort studies from Wuhan have estimated the proportion of COVID-19 patients with cardiac injury to be between 20% and 28%[8,47]. Therefore, it would be prudent to screen all COVID-19 patients admitted to the ICU for HF. Critically ill patients in the ICU, are not able to communicate their complaints, and physical examination findings are often limited. A screening algorithm such as the one suggested by the Cardiac Society of Australia and New Zealand can be employed in the ICU[48]. Incorporation of such a screening algorithm into the treatment protocol will help identify more patients with HF and optimize treatment.

Although major society guidelines recommend the measurement of natriuretic peptides when the diagnosis of HF is uncertain, they should be interpreted in the context of other clinical information due to their high sensitivity and limited specificity [49,50]. In addition to its diagnostic value, natriuretic peptides also have prognostic significance with higher pro-brain natriuretic peptide (pro-BNP) values associated with increased mortality[51,52]. Therefore, natriuretic peptides can be used for risk stratification of COVID-19 patients with HF. Elevations in cardiac troponins have also been observed in COVID-19 patients and may indicate both coronary and non-coronary disease[53]. Acute coronary syndrome, microvascular ischemia, myocarditis, takotsubo cardiomyopathy and arrhythmia are some of the reasons for an elevated troponin in COVID-19 patients[54]. While this makes the measurement of cardiac troponins less useful from the point of view of diagnosing HF, an elevated troponin level cannot be ignored as it may point towards underlying heart disease in an asymptomatic COVID-19 patient.

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## ROLE OF CARDIAC POINT OF CARE ULTRASOUND

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The American Society of Echocardiography defines cardiac point of care ultrasound (POCUS) as 'focused exams with specific imaging protocols based upon suspicion of a specific disease' and differentiates it from ultrasound assisted physical examination [55]. POCUS has multiple uses in the diagnosis and management of HF in COVID-19 patients in the ICU. POCUS has the added benefit of reducing risk of exposure to the health-care worker, when compared to the use of stethoscopes[56]. Adhering to a set-protocol such as the one described by Huang *et al*[57], will reduce inter and intra-observer variability. Documenting POCUS findings is important and if possible, the images should be stored on the device or on a central server. As this technology is relatively new, using mannequins for standardized training in image acquisition and interpretation may be helpful[58].



## ECHOCARDIOGRAPHY

The American Society of Echocardiography, in a statement endorsed by the American College of Cardiology, recommends that Transthoracic echocardiography should be performed if it is expected to provide clinical benefit[59]. In the ICU, this can be done at the bedside, with adequate airborne precautions[59]. Echocardiography (ECHO) can provide more information when compared to cardiac POCUS and can also be used to risk stratify patients to aid in follow up. A study of 75 hospitalized patients with COVID-19 showed a significant association between lower LVEF and mortality[60]. The mortality among the patients with LVEF < 50% was 65% compared to 26% in the group with LVEF ≥ 50%. The patients with LVEF < 50% also had higher troponin T and pro-BNP levels[60]. Stepwise modelling demonstrated that mechanical ventilation (OR 22.6; 95%CI: 3.0-170.4), LVEF < 50% (OR 8.2; 95%CI: 1.4-46.9), and pro-BNP above the cohort median value (OR 5.8; 95%CI: 1.4-23.9) were the strongest predictors of mortality[60]. Similar findings were reported by Alvarez-Garcia *et al*[22], as mentioned previously. Both left ventricular global longitudinal strain (HR 1.39; 95%CI: 1.11-1.76) and right ventricular longitudinal strain (HR 1.33; 95%CI: 1.15-1.53) were associated with increased mortality in COVID-19[61,62]. ECHO also allows for more detailed evaluation of right heart function, including tricuspid annular plane systolic excursion/pulmonary artery systolic pressure ratio (HR 0.026; 95%CI: 0.01-0.579; *P* = 0.019) which was an independent predictor of mortality in one study[63].

## MANAGEMENT OF ACUTE HEART FAILURE IN THE ICU

Management of acute HF in COVID-19 patients in the ICU should be done according to established guidelines and protocols. Although questions have been raised about the potential deleterious effects of ACEi and ARBs in COVID-19, a joint statement from the Heart Failure Society of America and American College of Cardiology/American Heart Association recommends continuation of these medications in patients with HF, if hemodynamics allow[64]. An effort must be made to identify HF due to takotsubo cardiomyopathy, which may masquerade as an acute coronary syndrome, but is increasingly being recognized in the context of COVID-19[37]. Since catecholamine-excess is considered to be part of the pathogenesis behind takotsubo cardiomyopathy, this subset of patients may benefit from restricting the use of catecholamine-inotropes such as dobutamine and dopamine and replacing them with non-catecholamine inotropes such as levosimendan and milrinone[65-67]. In patients who develop HF refractory to inotrope support, mechanical circulatory support, *e.g.*, veno-arterial ECMO or other cardiac assistive devices such as Impella (Abiomed, Danvers, MA, United States) may be used. These interventions are resource intensive and may not be available in all centres. In patients with suspected myocarditis or cytokine mediated injury, high dose corticosteroids, intravenous immunoglobulin and even selective cytokine blockade are options that can be considered on an experimental basis, given the absence of strong evidence of their benefit[68].

## EXTRA-CORPOREAL MEMBRANE OXYGENATION

The World Health Organization has recommended that ECMO can be used in experienced centres for the management of critically ill COVID-19 patients with ARDS with or without HF[69]. The Extracorporeal Life Support Organization has emphasized that ECMO should be judiciously used as a rescue strategy in severely ill patients since it is a resource-intensive, highly specialized, and expensive form of life support with the potential for significant complications[70]. Key considerations while implementing ECMO include proper patient assessment and selection, personnel assignment, infection control measures before and during ECMO initiation as well as devising protocols for ECMO weaning, decannulation and rehabilitation[71]. Given the resource intensive nature of ECMO, some authors have raised the question of whether it is worth using during a pandemic[72]. Barbaro *et al*[73] used the data from the ELSO registry and determined that the mortality in COVID-19 patients who required ECMO was less than 40%. This shows that in the appropriate setting, ECMO is indeed beneficial in critically ill COVID-19 patients.

The role of ECMO after CPR (E-CPR) is unclear at this point, and as of February 3, 2021, the Extracorporeal Life Support Organization registry has reported 32 COVID-19 patients who underwent E-CPR[74]. Current guidelines recommend judicious use of

E-CPR and only in centres that already have experience in its use[70,75,76]. Candidate selection should be done with due consideration of the patients comorbidities, other organ function, short and long-term life expectancy, availability of ECMO resources and risk of infectious exposure during cannulation and bed-side management[71].

## LEFT-VENTRICULAR ASSIST DEVICES

Literature on left ventricular assist devices and COVID-19 are scant. LVADs have been used with varying success in the management of HF in COVID-19. Valchanov *et al*[77] have described a case of a 43-year patient with severe COVID-19 ARDS and HF who was managed with veno-arterial ECMO and an Impella 5.0 ventricular assist device. The patient, however, succumbed to his illness after a 3-wk period. There are case-reports and case-series of patients on long-term LVAD who developed COVID-19[78-82]. It is important to recognize that COVID-19 patients with LVADs are particularly prone to thrombotic complications. This requires intensivists to walk a fine line between potential complications of bleeding and thrombosis. In recipients with COVID-19 infection, daily interrogation of LVAD parameters can help in the early recognition of early signs of hemodynamic compromise, pump thrombosis, right ventricular failure, vasoplegia associated with secondary infection, or innate device malfunction[83].

## REHABILITATION OF HF PATIENTS WITH COVID-19 AFTER ICU DISCHARGE

Rehabilitation of COVID-19 survivors who were in the ICU is critical. In those who developed HF, this becomes even more important. COVID-19 survivors who were critically ill often develop respiratory sequelae, cognitive sequelae, deconditioning, critical-illness related myopathy and neuropathy, dysphagia, joint stiffness and pain and psychiatric problems[84,85]. An early physical medicine and rehabilitation consultation, will help identify and address these issues early on. Rehabilitation can be initiated while the patient is still in ICU. However, more holistic rehabilitation will require assessment of respiratory capacity, muscle strength, exercise capacity, gait speed, balance and activities of daily living[86]. This is preferably done in a dedicated rehabilitation facility, after the patient is discharged home[82]. A graded exercise-based cardiac rehabilitation strategy can be prescribed, in accordance with standard HF guidelines[87].

Home based cardiac rehabilitation programs with telemonitoring methods can also be considered[88]. Few authors have reported promising results with remote cardiac care during the COVID-19 pandemic with telemonitoring devices such as the V-LAP™ (Vectorious Medical Technologies, Ltd) device for monitoring left atrial pressure as well as the HeartLogic platform (Boston Scientific, Marlborough, Massachusetts)[89, 90]. Although this technology is relatively new, we may soon see its integration into rehabilitation protocols for patients with HF, after ICU discharge.

## LIMITATIONS

We identified that only very few studies discussed the medical management of sick patients with COVID-19 in the background of HF. While many studies reported prevalence of 'cardiovascular disease' and 'cardiac injury' (usually defined as troponin I above the 99<sup>th</sup> percentile upper reference limit or new abnormalities shown on electrocardiography and echocardiography) in COVID-19 patients, the number of studies that reported chronic and *de novo* HF in this cohort was limited. Part of the reason may be the similarity in presentation of severe COVID-19 ARDS and acute decompensated HF. This is particularly challenging in the ICU patients, in whom both conditions often coexist. Moreover, HF is both a risk factor and a complication of COVID-19. Moreover, studies included in this review were retrospective and lack granular details on the severity of the disease, medical treatment, comorbidities, drug interactions, and outcome. Details of COVID-19 infection on the management of HF and vice versa were also not uniformly addressed. Outcomes in different studies were different. Details of treatment of COVID-19, duration of therapy, length of hospital stay, the long-term outcome were not uniformly available. Details of intensive care

treatment, including mode of ventilation, pressors of choice, renal replacement therapies, the role of sedatives and paralytics on this subgroup of populations were also not discussed in all studies. However, the strength of the studies was that it included studies with patients having COVID-19 in the background of HF from all over the world. We also tried to identify the predictors of morbidity and the role of intensive care therapy in these patients, from the literature. More research focusing on this subset of patients is necessary to clarify the pathogenesis, improve screening methods and identify optimal therapeutic strategies.

## CONCLUSION

In this review, we identified that HF is an independent predictor of mortality in hospitalized COVID-19 patients. Patients with HF were more likely to require ventilation, ICU admission and develop complications. Patients with HF<sub>r</sub>EF did worse than those with HF<sub>m</sub>rEF and HF<sub>p</sub>EF. COVID-19 patients with HF should be identified early and managed aggressively in an attempt to improve outcomes in this cohort of patients.

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