Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letters

TO THE EDITOR

Staring Points in Heart Failure Drug Development

Future Outlook

Fiuzat et al. (1) eloquently summarized the endpoints used for heart failure drugs approved in the United States. As discussed by the authors, a focus on symptomatic, functional, and quality of life endpoints is much needed to meaningfully advance heart failure therapeutics (1). On the other end of the spectrum of drug development, issues of safety and efficacy account for a sizable percentage of the phase I and II clinical trial failures, driven in part by inadequate in vitro modeling of target tissues (2,3). It would be pertinent to reconcile the future outlook of drug development starting points.

Microphysiological systems, frequently referred to as "organs-on-chips," hold the promise of improving target identification, high-throughput screening, lead optimization, and preclinical pharmacokinetic and pharmacodynamic testing (3). Cardiac microphysiological systems capable of quantifying the functional impact of extracellular matrix remodeling may lead to new therapeutic targets and treatment strategies in heart failure (4). The National Center for Advancing Translation Sciences through its Tissue Chip for Drug Screening program is aiming to accelerate the translation of basic discoveries (2). Advances in systems biology and machine learning may offer novel translational frameworks by humanizing computational models derived from animal experiments (5).

Evolution of preclinical models of drug discovery will require multidisciplinary collaboration across the spectrum of biomedicine. The ultimate test of these models' efficacy will be a comparison of the results with patient outcomes. Optimizing clinical endpoints has the potential to advance heart failure drug discovery through all phases of development. Fiuzat et al. (1) are to be congratulated for enlightening the path forward.

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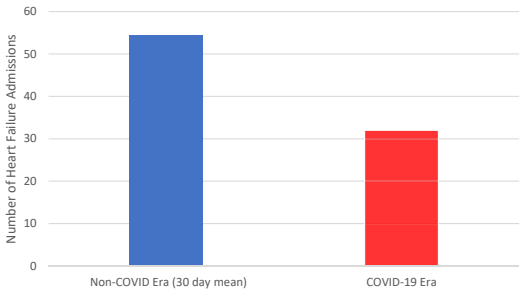
Clinical Characteristics and Trends in Heart Failure Hospitalizations

An Australian Experience During the COVID-19 Lockdown

Heart failure (HF) is a leading cause of morbidity, mortality, and use of health care resources. The coronavirus-2019 (COVID-19) pandemic presents novel challenges at the patient level as dyspnea is a cardinal symptom of both conditions. The unprecedented challenges to health care systems have led to implementation of rapid ambulatory telehealth services. The consequences of COVID-19 and associated public health regulatory changes may adversely impact patients with HF due to patient avoidance of medical care (1). The secondary impact of the COVID-19

FIGURE 1 Heart Failure Hospitalizations in the COVID-19 Era Compared to a 30-Day Mean Sampled From 2013 to 2017



Data show the number of heart failure hospitalizations in the COVID-19 era (March 16, 2020 to April 14, 2020) compared to a historical 30-day mean sampled from 2013 to 2017.

lockdown on the incidence and acuity of HF hospitalizations has not been studied.

We sought to compare the number of HF hospitalizations, patient characteristics on presentation, and key HF quality metrics across the COVID-19 and non-COVID-19 eras. Key metrics assessed included inpatient mortality, length of stay, and use of guideline-directed medical therapy. Cases were identified after comprehensive review of records of all patients hospitalized under the cardiology and internal medicine teams. HF in the COVID-19 era has been defined as the first 30-day period from the beginning of lockdown in Australia (March 16, 2020 to April 14, 2020). This period coincided with the peak of the COVID-19 epidemic curve in Australia. These data were compared to historic data at our hospital from the VCOR-HF (Victorian Cardiac Outcomes Registry-HF), which was collected prospectively over a 30-day period each year from 2014 to 2017. The methodology and results of the VCOR-HF project were described previously (2). This registry was coordinated by the independent Center of Cardiovascular Research and Education in Therapeutics at Monash University (Clayton, Victoria, Australia) with periodic quality control audits that demonstrated a data accuracy of 97% (2). Data from 2018 to 2019 had not been collated by the registry at the time of the study and was excluded. Data were collected at Austin Health, a major quaternary hospital with a catchment population of 1.14 million people.

Overall, 249 patients were included in the study analysis. There were 32 HF hospitalizations in the COVID-19 era, which represents a 41% reduction from our historical monthly mean of 54 hospitalizations (range, 44% to 74%; $p < 0.001$) (Figure 1). Baseline clinical characteristics and burden of chronic disease were similar across the COVID-19 and non-COVID era. The proportion of patients with HF diagnosis with reduced ejection fraction did not vary. Infection remained the most common precipitant for acute HF in both the COVID and non-COVID eras (Table 1). Of note, 31% of HF hospitalizations in the COVID era were managed initially in a COVID-19 medical unit due to a high index of suspicion for infection with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Among these patients, there were no confirmed cases of SARS-CoV-2.

Patients admitted during the COVID-19 era were significantly more symptomatic on presentation and there was a higher proportion with New York Heart Association (NYHA) functional class III/IV symptoms (96.9%/71.0%, respectively; $p = 0.001$). No major differences in HF quality metrics, including intensive care admission or in-hospital mortality, were recorded (Table 1). Length of hospital stay was numerically lower in the COVID-19 era, although this was not statistically significant (median, 4.0 vs. 6.0 days, respectively; $p = 0.16$). With regard to goal-directed medical therapy, prescription rates of beta-blockers and mineralocorticoid receptor antagonists were similar across the eras. However, there was a significant reduction in the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) in the COVID-19 era (35.7% vs 57.1%, respectively; $p = 0.03$).

In this study, evaluating early data for acute HF hospitalizations during the COVID-19 era, 3 key findings merit attention. First, there was a 41% reduction in hospitalizations due to HF. Second, patients hospitalized during the COVID-19 era had significantly higher NYHA functional classification. Third, despite comparable clinical characteristics of the patients across the eras, there was a significant reduction in the prescription of ACE inhibitors/ARBs in the COVID era.

Although some anecdotal reports have indicated a reduction in acute HF presentations, no data to date have been presented to support this notion. The significant reduction in HF hospitalizations in this study mirrors observations in the presentation of patients with ST-segment elevation myocardial infarction (3). The exact reasons for this remain unclear, but the following are possible explanations. Self-isolation and social distancing may have lowered the overall rate of respiratory infections that are known to be common triggers for clinical decompensation. Additionally, improved patient vigilance with both medication and dietary adherence may also have played a role. These factors coupled with patients' reticence in seeking medical care due to perceptions

TABLE 1 Baseline Characteristics, Presentation Details, and Clinical Outcomes

	Overall (N = 249)	COVID-19 Era (n = 32)	Non-COVID-19 Era (n = 217)	p Value
Age, yrs	79.9 ± 11	80.2 ± 14	79.8 ± 11	0.85
Males	217 (50)	14 (44)	113 (52)	0.18
Charlson comorbidity index	7.5 ± 2.2	7.7 ± 1.7	7.5 ± 2.0	0.52
Diabetes	115 (46)	18 (56)	97 (45)	0.70
Hypertension	197 (79)	23 (72)	174 (80)	0.28
Stroke	55 (22)	5 (16)	50 (23)	0.39
CIED	50 (20)	8 (25)	42 (19)	0.45
Chronic kidney disease	172 (69)	18 (56)	154 (71)	0.09
Dementia	26 (10)	2 (6.3)	24 (11)	0.35
Active malignancy	23 (9.2)	4 (13)	19 (9.0)	0.18
COPD	76 (31)	5 (16)	71 (33)	0.05
Cause of heart failure				
Ischemia	68 (27)	9 (28)	59 (27)	0.88
Hypertension	24 (9.5)	4 (13.0)	19 (8.8)	0.37
Valvular heart disease	16 (6.5)	2 (6.5)	11 (5.1)	0.69
Ejection fraction, %				0.25
≥50	113 (45.0)	16 (51.0)	96 (44.2)	
45-49	28 (11.0)	2 (6.3)	28 (12.0)	
35-44	52 (21)	5 (16)	48 (22)	
≤35	56 (23)	9 (29)	45 (21)	
Presentation characteristics				
Systolic BP, mm Hg	137 ± 26	144 ± 29	136 ± 26	0.06
Diastolic BP, mm Hg	75 ± 15	77 ± 12	74 ± 16	0.26
Admission under cardiology	80 (32)	7 (22)	75 (34)	0.09
NYHA functional class on admission				0.009
II	71 (29)	1 (3)	70 (32)	
III	120 (48)	21 (66)	99 (46)	
IV	58 (23)	10 (31)	48 (22)	
III/IV	178 (71)	31 (97)	147(68)	0.01
Precipitant for decompensation				
Ischemia	26 (10.0)	2 (6.5)	24 (11.0)	0.36
Medication nonadherence	20 (8.0)	6 (18.0)	14 (6.4)	0.04
Infection	84 (34)	8 (25)	78 (36)	0.22
Arrhythmia	54 (22)	5 (15)	50 (23)	0.24
Unknown/other	65 (26)	11 (34)	51 (24)	0.35
Admissions				0.01*
2014	45	-	-	
2015	44	-	-	
2016	74	-	-	
2017	54	-	-	
2020 (COVID-19)	32	-	-	
Quality metrics				
Length of stay	5.5 (3-9)	4.0 (3-8)	6.0 (3-10)	0.16
% of inpatient weight loss	3.3 ± 5.2	2.9 ± 5.5	3.4 ± 5.1	0.66
In-hospital mortality	16 (6.4)	3 (9.4)	13 (5.9)	0.47
ICU admission	16 (6.4)	3 (9.0)	13 (6.0)	0.47
ICU length of stay, days	3.9 ± 2	5.3 ± 4	3.6 ± 2	0.32
Non-invasive ventilation	46 (18.0)	1 (3.1)	45 (21.0)	0.02
Discharge to Home	202 (81)	25 (78)	178 (82)	0.86
Discharge medications				
ACE inhibitor/ARB	136 (55)	10 (35)	124 (57)	0.033
Beta-blockers	170 (68)	25 (79)	145 (67)	0.20
MRA	86 (35)	11 (36)	74 (34)	0.88

Values are mean ± SD, n (%), or mean (interquartile range). Ejection fraction was measured using the Simpson biplane method. Chronic kidney disease was defined as baseline eGFR <60 ml/min/1.73 m^2. *The p value for the average number of admissions in the non-COVID-19 era were compared to those in the COVID-19 era.

ACEI = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CIED = cardiac implantable-electronic device; COPD = chronic obstructive pulmonary disease; COVID = corona virus; eGFR = estimated glomerular filtration rate; ICU = intensive care unit; MRA = mineralocorticoid agonist; NYHA = New York Heart Association.

of contracting COVID-19 in the hospital environment might have lowered HF presentation rates (1).

The Australian government commenced lockdown restrictions on March 16, 2020, to reduce the spread of COVID-19. Over the next 30 days, the number of cases in Australia rose from 310 to 6,400, and the first deaths were recorded (4). Fortunately, this was followed by a reduction in the number of new cases due to successful lockdown restrictions as there were only 588 new cases in the following 30 days. As such, the period of data collection reflects the peak of the Australian COVID-19 epidemic curve. These authors speculate that, as lockdown restrictions are eased, these social impacts will lessen and that HF admissions will return to levels observed in the pre-COVID era. The long-term sequelae of this interruption remains to be seen.

It is notable that the present cohort demonstrated a significant reduction in prescriptions for ACE inhibitors/ARBs in the COVID era. Lower use may be due to the widely publicized concerns regarding upregulation of the ACE2 receptor by these drug classes, given that this receptor is known to mediate SARS-CoV-2 cellular entry (5). However, in light of the strong evidence supporting use of these agents in patients with HF, underutilization of these therapies is not medically justifiable (6).

A limitation of these data reporting trends in hospitalizations is the variation in the timing of data sampling across the years. Seasonality may account for a variation of at most 20% in HF admissions (7).

In conclusion, this paper reports a 41% reduction in HF hospitalizations and a significant increase in the proportion of patients presenting with NYHA functional class III/IV symptoms in the COVID-19 era. Despite restructuring of management pathways, in-hospital clinical outcomes in patients admitted with HF remained unchanged. Underuse of ACE inhibitor and ARBs is of concern and may translate to adverse clinical outcomes. Examining reasons for the reduced hospital presentations and enhancing integrated multidisciplinary outpatient models of care in this pandemic may mitigate the collateral impact of COVID-19 in patients with HF.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Heart Failure* author instructions page.

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Ethnicity, Health Literacy, and Outcomes in Heart Failure

We were interested to read the study by Fabbri et al. (1), a meta-analysis which investigated the association between health literacy and outcomes in heart failure patients. The study demonstrated an increased risk of death (risk ratio [RR]: 1.41; 95% confidence interval [CI]: 1.06 to 1.88) and hospitalization (RR: 1.12; 95% CI: 1.01 to 1.25) in those with poor health literacy compared to those with adequate health literacy. Although the outcomes were adjusted for age, sex, education, and clinical confounders such as comorbidities, ethnicity was not included as one of the main demographic confounders.

This is of particular concern because there is evidence of lower health literacy rates associated with