Outcomes of Heart Failure in COVID-19 Patients: An Appalachian Experience

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Abstract

Background: The Southeastern rural areas of the USA have a higher prevalence of heart failure (HF). Coronavirus disease 2019 (COVID-19) infection is associated with poor outcomes in patients with HF. Our study aimed to compare the outcomes of hospitalized HF patients with and without COVID-19 infection specifically in rural parts of the USA.

Methods: We conducted a retrospective cohort study of HF patients with and without COVID-19 hospitalized in Southeastern rural parts of the USA by using the Appalachian Regional Healthcare System. Analyses were stratified by waves from April 1, 2020 to May 31, 2021, and from June 1, 2021 to October 19, 2021.

Results: Of the 14,379 patients hospitalized with HF, 6% had concomitant COVID-19 infection. We found that HF patients with COVID-19 had higher mortality rate compared to those without COVID-19 (21.8% versus 3.8%, respectively, P < 0.01). Additionally, hospital resource utilization was significantly higher in HF patients with COVID-19 compared to HF patients without COVID-19 with intensive care unit (ICU) utilization of 21.6% versus 13.8%, P

< 0.01, mechanical ventilation use of 17.3% versus 6.2%, P < 0.01, and vasopressor/inotrope use of 16.8% versus 7.9%, P < 0.01. A lower percentage of those with COVID-19 were discharged home compared to those without a COVID-19 diagnosis (63.4% versus 72.0%, respectively). There was a six-fold greater odds of dying in the first wave and seven-fold greater odds of dying in the second wave.

Conclusions: Our study confirms previous findings of poor outcome in HF patients with COVID-19. There is a need for review of healthcare resources in rural hospitals which already face numerous healthcare challenges.

Keywords: Coronavirus; Heart failure; COVID-19; SARS-CoV-2; Cohort; Mortality; Survival

Introduction

Since December of 2019, coronavirus disease 2019 (COVID-19) has been a major cause of morbidity and mortality around the world. As of October 19, 2021, 242 million cases and 4.9 million deaths have been reported worldwide from COVID-19 [1]. Patients with comorbidities, especially cardiovascular diseases, are more susceptible to developing a severe form of disease [2]. Several studies have demonstrated that the cardiovascular risk factors such as advanced age, hypertension, diabetes, and obesity are also significant risk factors for severe COVID-19 infection [3]. Conversely, patients with COVID-19 are at increased risk of a broad range of cardiovascular disorders including cerebrovascular disorders, dysrhythmias, ischemic and nonischemic heart disease, pericarditis, myocarditis, heart failure (HF), and thromboembolic disease [4].

In an analysis of the Premier Healthcare database, which is a multi-center all-payer US database, Bhatt et al found that patients with preexisting HF hospitalized with COVID-19 had a higher mortality (24.2%) rates as compared to those hospitalized with HF without COVID-19 (2.6%) and those hospitalized for other reasons (4.6%) [5]. Further, a comparison study by Chatrath et al in London, UK found that patients hospitalized for HF with COVID-19 infection had a significantly higher rate of inpatient mortality as compared to those without
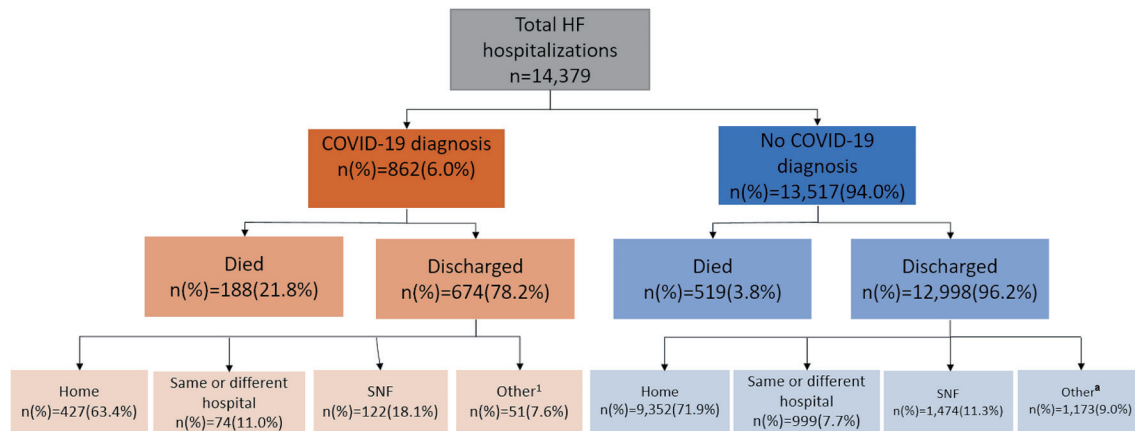
Figure 1. Summary of patients hospitalized with HF during the COVID-19 pandemic. [a]Includes intermediate care facilities, court/ law, hospice, rehabilitation facilities, and other stated locations. HF: heart failure; COVID-19: coronavirus disease 2019; SNF: skilled nursing facility.

COVID-19 infection (50.0% vs. 10.6%; P < 0.001) [6].

The rural parts of the USA have higher rates of mortality due to HF as compared to other parts of the USA [7, 8]. We aimed to compare the outcomes of HF patients hospitalized with concomitant COVID-19 infection as compared to those without COVID-19 in the rural healthcare system of USA.

Materials and Methods

This is a multi-center retrospective cohort study of hospitalized patients with a primary or secondary diagnosis of HF between April 1, 2020 and October 19, 2021. The study was approved by the Appalachian Regional Healthcare Institutional Review Board (IRB). As per IRB requirements, written consent was waived for this project as it is a retrospective study that includes the abstraction of data from medical records. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

The data were extracted from 13 facilities in the Appalachian Regional Healthcare System in Southeastern parts of Kentucky and in West Virginia that share the same electronic health record. The principal admitting diagnosis of HF using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes in patients 18 years or older was identified. The primary exposure of interest was COVID-19 diagnosis. The primary outcome was in-hospital mortality and secondary outcomes included intensive care unit (ICU) stay, mechanical ventilation, length of stay (LOS), re-admittance between 1 and 30 days, and re-admittance between 31 and 60 days. Records were excluded from patients that were < 18 years old or were missing information on COVID-19 diagnosis, age, or discharge status. A readmission was defined as a subsequent hospital admission for any cause a specified time interval following an initial index admission.

Descriptive statistics were utilized to compare demographic characteristics, comorbidities, discharge status, and resource utilization between those hospitalized with HF that had a COVID-19 diagnosis and those that did not have a COV-ID-19 diagnosis using Chi-square analyses for categorical variables. Fisher exact was used instead of Chi-square analyses when expected cell counts were < 5. Independent t-tests were used to compare the average age and body mass index (BMI) between HF patients with and without a COVID-19 diagnosis.

Outcomes among HF patients with and without a COV-ID-19 diagnosis were compared using adjusted and unadjusted regression models. Mixed-effects logistic regression was used for all binary outcomes (mortality, ICU stay, mechanical ventilation, re-admittance between 1 and 30 days, and re-admittance between 31 and 60 days) and mixed linear regression was used for LOS. A random intercept for hospital (n = 13) was included in all models to adjust for shared variance at the hospital level. Adjusted analyses were adjusted for age, gender, marital status, obesity, diabetes mellitus, hypertension, pulmonary disease, kidney disease, and smoking. Analyses were stratified by waves, which were identified as wave 1 (April 1, 2020 to May 31, 2021) and wave 2 (June 1, 2021 to October 19, 2021) using histograms of the case count over time.

Additional models were built among HF patients to identify demographic and comorbidity risk factors associated with the primary and secondary outcomes among those with a COV-ID-19 diagnosis. Risk factors included age, gender, marital status, obesity, diabetes mellitus, hypertension, pulmonary disease, kidney disease, smoking, and wave. For mixed linear regression models and t-tests, normality and homoscedasticity of residuals were checked using residual plots. LOS and BMI did not follow a normal distribution; therefore, they were transformed by the logarithm function. Model results were back-transformed to their original scale for ease of interpretation.

Results

In total, 14,408 records were downloaded from the database. After exclusion criteria (< 18 years old or missing age (n = 14), missing COVID-19 diagnosis information (n = 0), missing discharge data (n = 15)), 14,379 records remained. Out of the total hospitalized with HF, 6.0% were diagnosed with COVID-19 (Fig. 1).

Table 1. Baseline Characteristics of a Sample of Hospitalized HF Patients Stratified by COVID-19 Diagnosis Status (N = 14,379)

Baseline characteristics	No COVID-19 (n = 13,517)		COVID-19 (n = 862)		Total (n = 14,379)		P value
	N	% (within row)	N	% (within row)	N	% (of total)	
Age (years)							
18 - 39	206	94.9	11	5.1	217	1.5	0.02
40 - 49	784	96.2	31	3.8	815	5.7	-
50 - 64	3,567	94.5	207	5.5	3,774	26.3	-
65 - 74	4,205	96.7	283	6.3	4,488	31.2	-
74 and older	4,755	93.5	330	6.5	5,085	35.4	-
Marital status							
Married	5,501	93.8	364	6.2	5,865	41.1	0.10
Single	2,149	93.3	154	6.7	2,303	16.1	-
Divorced/separated/widowed	5,782	94.5	339	5.5	6,121	42.8	-
White							
No	373	93.3	27	6.8	400	2.8	0.52
Yes	13,144	94	835	6	13,979	97.2	-
Gender							
Male	6,147	93.4	433	6.6	6,580	45.8	0.01
Female	7,369	94.5	429	5.5	7,798	54.2	-
Insurance							
Medicaid/Medicare	12,320	94.1	778	5.9	13,098	91.1	0.37
Other	1,197	93.4	84	6.6	1,281	8.9	-
Weight status							
Underweight	541	95.6	25	4.4	566	4.1	0.09
Normal weight	2,850	94.4	170	5.6	3,020	21.7	-
Overweight	3,136	93.8	209	6.3	3,345	24.1	-
Obese	2,576	94.5	151	5.5	2,727	19.6	-
Morbidly obese	3,967	93.3	284	6.7	4,251	30.6	-
Asthma							
No	13,331	94	854	6	14,185	98.7	0.27
Yes	186	95.9	8	4.1	194	1.4	-
Diabetes							
No	6,357	94.3	385	5.7	6,742	46.9	0.18
Yes	7,160	93.8	477	6.3	7,637	53.1	-
Hypertension							
No	2,356	93.6	162	6.4	2,518	17.5	0.31
Yes	11,161	94.1	700	5.9	11,861	82.5	-
Anemia							
No	12,620	94	812	6.1	13,432	93.4	0.34
Yes	897	94.7	50	5.3	947	6.6	-
Hepatitis							
No	946	88.3	125	11.7	1071	88.7	0.32
Yes	124	91.2	12	8.8	136	11.3	-
Valvular heart disease							
No	12,528	93.9	812	6.1	13,340	92.8	0.10

Table 1. Baseline Characteristics of a Sample of Hospitalized HF Patients Stratified by COVID-19 Diagnosis Status (N = 14,379) - *(continued)*

Baseline characteristics	No COVID-19 (n = 13,517)		COVID-19 (n = 862)		Total (n = 14,379)		P value
	N	% (within row)	N	% (within row)	N	% (of total)	
Yes	989	95.2	50	4.8	1,039	7.2	-
Pulmonary disease							
No	5,676	93.3	409	6.7	6,085	42.3	< 0.01
Yes	7,841	94.5	453	5.5	8,294	57.7	-
Kidney disease							
No	9,526	93.9	624	6.2	10,150	70.6	0.23
Yes	3,991	94.4	238	5.6	4,229	29.4	-
End-stage renal disease							
No	12,713	94	807	6	13,520	94	0.60
Yes	804	93.6	55	6.4	859	6	-
Malignancy							
No	12,888	93.9	835	6.1	13,723	95.4	0.04
Yes	629	95.9	27	4.1	656	4.6	-
Smoking							
No	7,968	93	599	7	8,567	59.6	<0.01
Yes	5,549	95.5	263	4.5	5,812	40.4	-

HF: heart failure; COVID-19: coronavirus disease 2019.

Patients with a COVID-19 diagnosis had a higher mortality rate compared to those without a COVID-19 diagnosis (21.8% versus 3.8%, respectively, P < 0.01). Of those that were discharged, a lower percentage of those with a COVID-19 diagnosis were discharged home compared to those without a COVID-19 diagnosis (63.4% versus 72.0%, respectively) and remaining were referred to skilled nursing facilities, rehabilitation facilities, hospice, and other locations.

Table 1 shows the baseline characteristics of HF patients with and without COVID-19 infection. HF patients hospitalized with a COVID-19 diagnosis were older (70.5 years versus 69.2 years, P < 0.01), more likely to be male (50.2% versus 45.5%, P < 0.01), had a higher mean BMI (32.6 kg/m^2 versus 31.8 kg/m^2,

P = 0.03), less likely to have a pulmonary disease (52.6% versus 58.0%, P < 0.01), malignancy (3.1% versus 4.7%, P = 0.04), and were less likely to smoke (30.5% versus 41.1%, P < 0.01) compared to the patients without COVID-19 diagnosis.

Overall, resource use as defined as the percent utilization over total HF hospitalizations was lower in HF hospitalizations with COVID-19 compared to HF hospitalizations without COVID-19 (Fig. 2). However, the percent of HF hospitalization with COVID-19 that required an arterial catheter (1.3% versus 0.6%, P = 0.01), ICU utilization (21.6% versus 13.8%, P < 0.01), mechanical ventilation (17.3% versus 6.2%, P < 0.01), and vasopressor/inotrope use (16.8% versus 7.9%, P < 0.01) was significantly higher compared to HF hospitaliza-
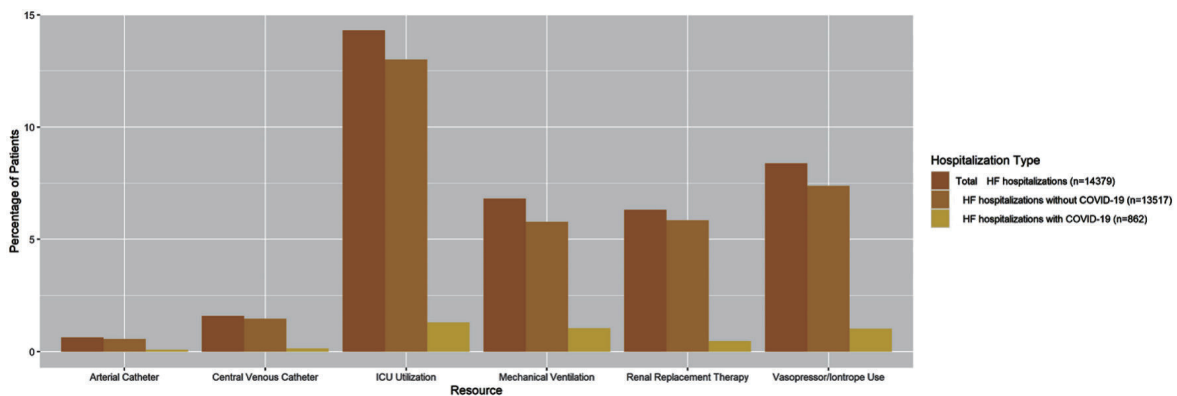

Figure 2. Hospital resource use of as a percentage of total HF patients by COVID-19 diagnosis status (n = 14,379). HF: heart failure; COVID-19: coronavirus disease 2019; ICU: intensive care unit.

Table 2. Adjusted and Unadjusted Results for the Association of COVID-19 Diagnosis and Multiple Outcomes in a Sample of Hospitalized HF Patients (N = 14,379)

	Wave 1 (April 1, 2020 to May 31, 2021)	Wave 2 (June 1, 2021 to October 19, 2021)
Mortality		
Unadjusted OR (95% CI)	6.55 (5.21 - 8.23)*	7.04 (5.04 - 9.85)*
Adjusted OR (95% CI)[a]	6.21 (4.88 - 7.91)*	7.47 (5.27 - 10.60)*
Mechanical ventilation		
Unadjusted OR (95% CI)	2.98 (2.34 - 3.78)*	3.93 (2.78 - 5.56)*
Adjusted OR (95% CI)[a]	3.40 (2.63 - 4.34)*	3.78 (2.63 - 5.41)*
ICU stay		
Unadjusted OR (95% CI)	1.57 (1.26 - 1.94)*	1.71 (1.26 - 2.31)*
Adjusted OR (95% CI)[a]	1.62 (1.30 - 2.02)*	1.66 (1.22 - 2.26)*
1 - 30 days re-admittance		
Unadjusted OR (95% CI)	1.18 (0.96 - 1.45)	1.12 (0.82 - 1.52)
Adjusted OR (95% CI)[a]	1.25 (1.01 - 1.54)*	1.18 (0.86 - 1.60)
31 - 60 days re-admittance		
Unadjusted OR (95% CI)	0.65 (0.50 - 0.84)*	0.44 (0.27 - 0.71)*
Adjusted OR (95% CI)[a]	0.66 (0.51 - 0.86)*	0.46 (0.28 - 0.75)*
Length of stay in days		
Unadjusted beta coefficient (95% CI)	1.59 (1.49 - 1.69)*	1.42 (1.30 - 1.55)*
Adjusted beta coefficient (95% CI)[a]	1.56 (1.47 - 1.66)*	1.42 (1.30 - 1.55)*

*P ≤ 0.05. [a]Adjusted for age, gender, marital status, obesity status, diabetes, hypertension, pulmonary disease, kidney disease, and smoking. HF: heart failure; COVID-19: coronavirus disease 2019; ICU: intensive care unit; OR: odds ratio; CI: confidence interval.

tions without a COVID-19 diagnosis.

In Table 2, unadjusted and adjusted analyses indicate that HF patients with a COVID-19 diagnosis had higher odds of inpatient mortality, mechanical ventilation use, and requiring ICU care compared to those without a COVID-19 diagnosis. In addition, patients with a COVID-19 diagnosis had greater LOS compared with patients without a COVID-19 diagnosis. Results were inconstant for re-admittance between 1 and 30 days as HF patients with COVID-19 had significantly higher odds of being re-admitted between 1 and 30 days with odds ratio (OR): 1.25, confidence interval (CI): 1.01 - 1.54, P value < 0.05 during the first wave in adjusted analyses, compared with OR: 1.18, CI: 0.86 - 1.60 in second wave. HF patients with COVID-19 had lower odds of being re-admitted between 31 and 60 days compared with HF patients without COVID-19 during both waves. Results were consistent across both the waves for most of the outcomes as shown in the Table 2.

Among HF patients with a COVID-19 diagnosis, there were no significant demographic or comorbidity risk factors identified for needing mechanical ventilation or ICU care (Fig. 3). However, patients that were 75 or older had approximately twice the odds of mortality compared to those who were < 65 years old (OR (95% CI): 2.05 (1.28 - 3.28)).

Patients that had kidney disease had about twice the odds of being re-admitted between 1 to 30 days compared to those without kidney disease (1.92 (1.30 - 2.84)) (Fig. 4). Being fe-

male and having diabetes were associated with higher odds of being re-admitted between 31 and 60 days (1.93 (1.18 - 3.16)). Patients in the second wave had about 50% lower odds of being re-admitted between 31 and 60 days (0.49 (0.28 - 0.86)). On average, patients aged 75 and older spent approximately 2 more days in the hospital compared with those < 65 years old. Patients with diabetes spent approximately 1 more day in the hospital compared to those without diabetes.

Discussion

To our knowledge, this is the first study to compare the clinical outcomes in HF patients with and without COVID-19 in rural areas of the USA. In this analysis of 14,379 patients with HF hospitalized during the pandemic, 6% had concomitant COVID-19 infection, and one in five HF patients with COVID-19 died.

Earlier in the pandemic from April to September, 2020, a study from a larger sample of multi-center US healthcare showed similar results, with 6% hospitalized HF patients having concomitant COVID-19 infection and a mortality rate of 24.2% among HF patients with concomitant COVID-19 [5]. The increase in mortality in HF patients with COVID-19 is due to the bidirectional relationship between HF and COVID-19 infection [9-12]. The virus enters the cells through angioten-
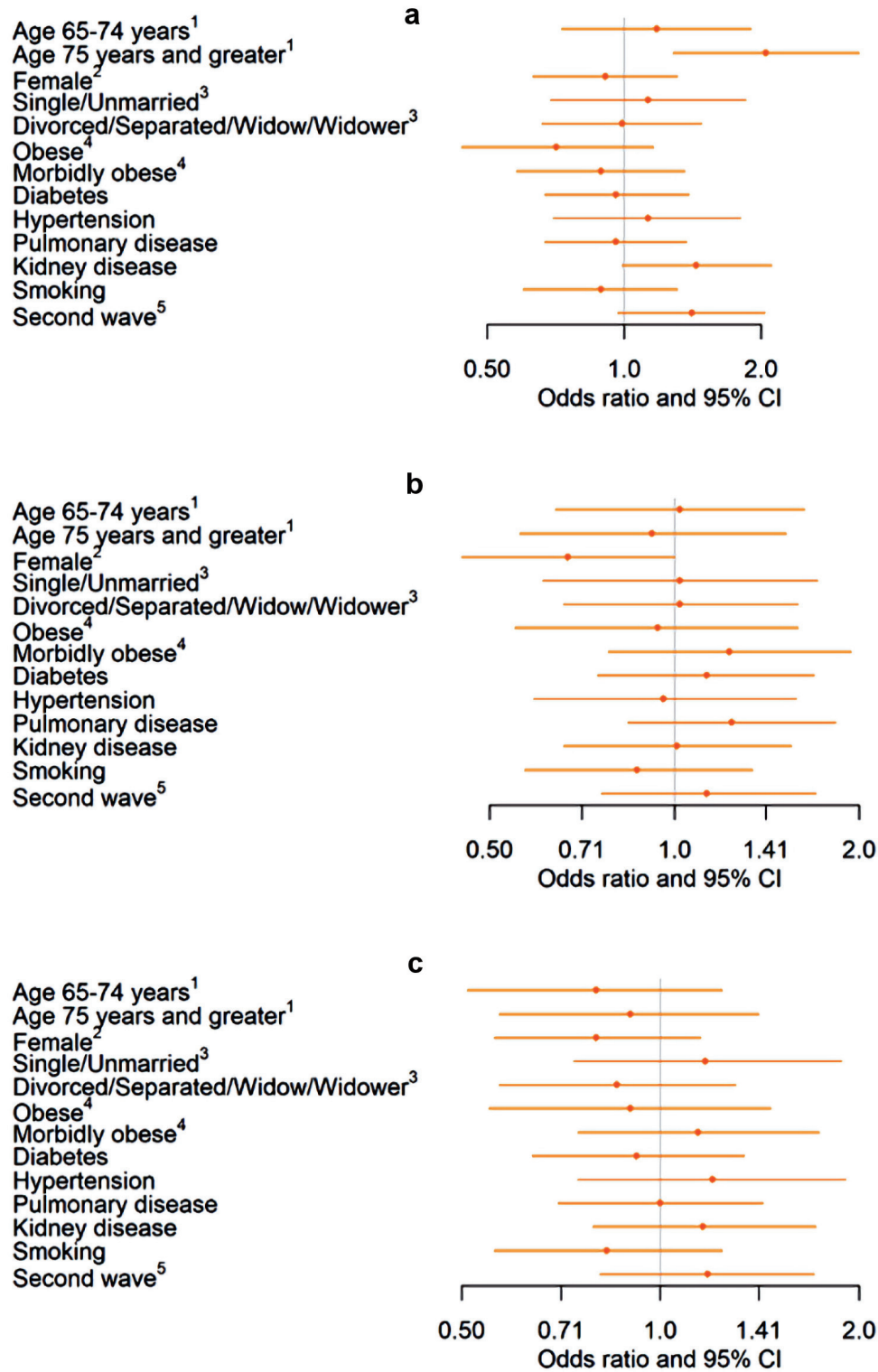
Figure 3. Association of demographics and comorbidities with mortality, mechanical ventilation, and ICU stay in a sample of HF patients diagnosed with COVID-19 (n = 862). (a) Association between demographics and comorbidities and mortality among hospitalized COVID-19 patients. (b) Association between demographics and comorbidities and mechanical ventilation among hospitalized COVID-19 patients. (c) Association between demographics and comorbidities and ICU stay among hospitalized COVID-19 patients. [1]Reference: age < 65 years. [2]Reference: male. [3]Reference: married. [4]Reference: not obese. [5]Reference: first wave. HF: heart failure; COVID-19: coronavirus disease 2019; ICU: intensive care unit; CI: confidence interval.
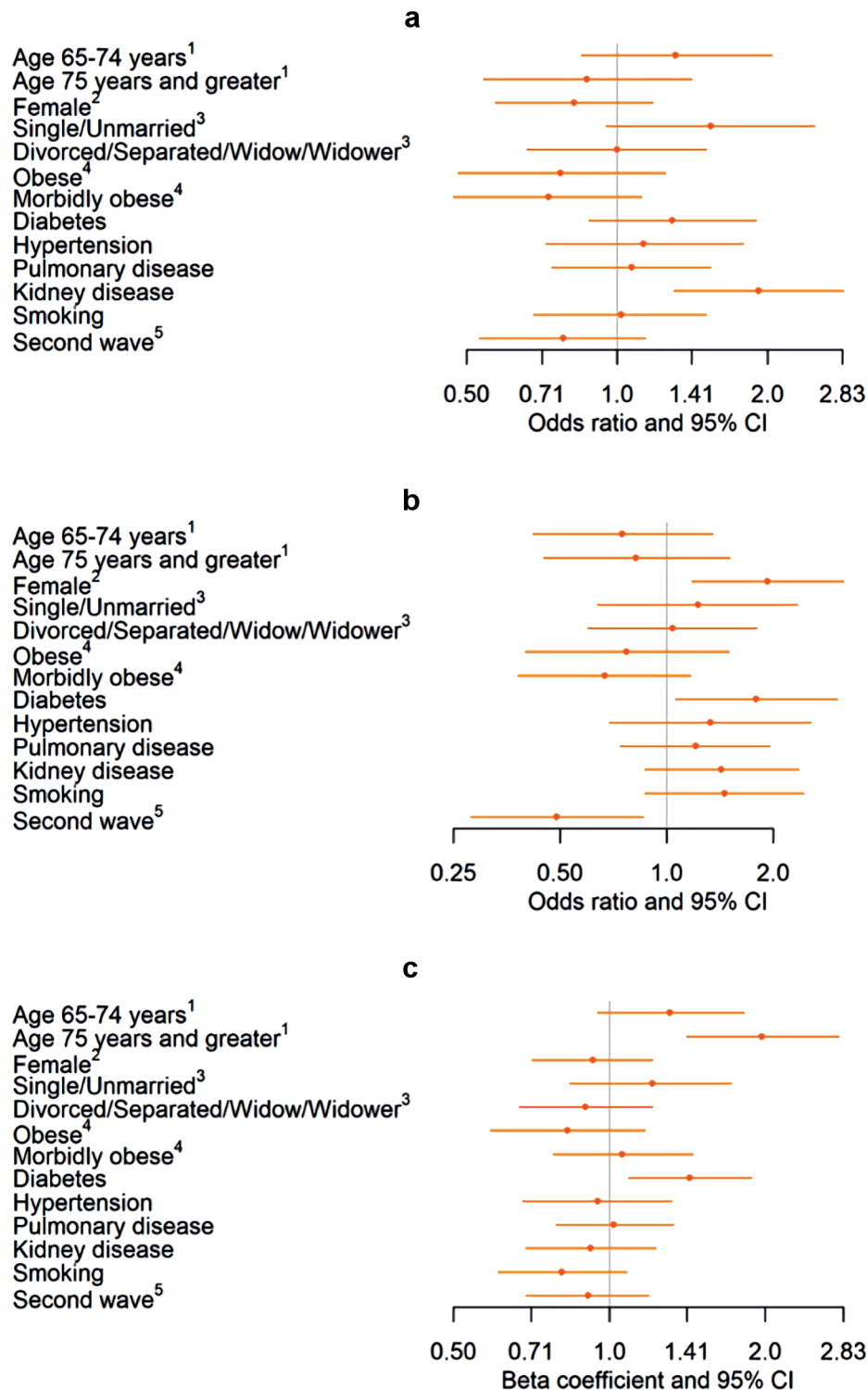
Figure 4. Association of demographics and comorbidities with re-admittance between 1 and 30 days, re-admittance between 31 and 60 days, and length of stay in a sample of HF patients diagnosed with COVID-19 (n = 862). (a) Association between demographics and comorbidities and re-admittance between 1 and 30 days among hospitalized COVID-19 patients. (b) Association between demographics and comorbidities and re-admittance between 31 and 60 days among hospitalized COVID-19 patients. (c) Association between demographics and comorbidities and length of stay among hospitalized COVID-19 patients. Values back-transformed from log10 scale. [1]Reference: age < 65 years. [2]Reference: male. [3]Reference: married. [4]Reference: not obese. [5]Reference: first wave. HF: heart failure; COVID-19: coronavirus disease 2019; CI: confidence interval.

sin-converting enzyme 2 (ACE-2) receptors which are abundant on heart, kidney, and lung alveolar epithelial cells [13]. In turn, dysregulation of the renin-angiotensin-aldosterone system (RAAS) as in patients with HF play a role in the severity of COVID-19 infection [14-16]. It has been hypothesized earlier in the pandemic that patients taking ACE inhibitors or angiotensin receptor blockers would be at a higher risk of adverse clinical outcomes; however, later studies have refuted this hypothesis [17, 18]. In addition, COVID-19 is associated with myocardial injury [19, 20], thrombocytopenia [21, 22], and liver dysfunction [23-27] which predicts higher mortality in the general population and in patients with HF [28, 29].

In our study, HF patients with COVID-19 were likely to be male and recent studies have shown that ACE-2 levels are 50% higher in males with HF [30, 31]. Our study showed that patients with HF and COVID-19 were less likely to be smokers, have pulmonary disease and malignancy as compared to those without COVID-19. In our sample of HF patients, those who were current smokers had a lower incidence of COVID-19 infection as compared to those who were non-smokers (Table 1). Studies relating to COVID-19 and smoking have shown a similar inverse association [32, 33]. There is biological plausibility for this relationship such as nicotine binds to ACE-2 receptors, the binding sites for COVID-19, and also downregulates them in multiple organs [34, 35]. However, previous studies have also shown that smokers who get COVID-19 have overall poor outcomes and increased mortality compared to non-smokers [36].

We found that there was six-fold greater odds of dying in the first wave from April 2020 to May 2021, and seven-fold greater odds of dying in the second wave from June 2021 to October 2021 in HF patients with COVID-19 compared to those hospitalized without concomitant COVID-19 infection (Table 2). The reason for this increase in mortality in HF patients with COVID-19 compared to those without COVID-19 is multifold. First, as shown in a study before the onset of the pandemic there is a higher mortality rate from HF in rural areas as compared to urban areas with occurrence of "heart failure belt" in Southeastern USA [8]. Second, as the COVID-19 mortality has declined nationally, this decline is only seen in urban areas whereas in rural areas the mortality from COVID-19 has doubled [37, 38]. This is due to multiple factors as the vaccination rates for COVID-19 is lower in rural than urban areas [37, 39, 40], and prevalence of obesity is higher in rural than in urban areas [41]. Additionally, healthcare facilities in rural areas are typically less-resourced with reduced access to ventilators and ICU beds which are the key aspects of care for critically ill COVID-19 patients [42, 43]. In addition, rural areas are associated with poor compliance and follow-up that complicate care [29, 44]. Our study shows that there was increased use of resources during and after hospitalization such as mechanical ventilation, ICU stays, skilled nursing and rehabilitation as well as a prolonged hospital stay among HF patients with COVID-19.

Limitations

This study has several limitations, most of which are inherent to the analysis of administrative databases. Since the data are collected based on administrative codes, it is not possible to establish whether a complication was present on admission or developed during the hospital stay. Rare complications of COVID-19 were not reported in this study [45, 46]. Second, laboratory data and metrics like SOFA score, APACHE II, and SAPS III that have been validated to predict mortality in critically ill patients were not evaluated in our study [47]. We were not able to examine the effect of different treatments on the population [44, 48-50]. We were unable to compare outcomes based on medications that the patients were prescribed for HF prior to admission, thereby, we were unable to determine the effects of guideline-directed medical therapy on the severity of COVID-19 infection. Lastly, this study did not distinguish between stages or subcategories of HF. Despite these limitations, this study addresses a significant knowledge gap as a contemporary epidemiological study of COVID-19 in rural regions.

Conclusions

Our study shows that COVID-19 represents a clinical challenge in patients with HF in the setting of rural facilities [51]. This study highlights the need for a review of healthcare challenges in rural areas posed by the concurrence of these two illnesses.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

The study was approved by the Appalachian Regional Healthcare institutional review board (IRB). As per IRB requirements, written consent was waived for this project as it is a retrospective study that includes the abstraction of data from medical records.

Author Contributions

HB, AA, ND, AH, VM, LW and AMKM contributed to study design, literature review, statistical analysis, and drafting manuscript. SSD, A. Kolodziej, GV, A. Kulkarni, JP, SG and AB contributed to final approval, mentorship, manuscript revision and intellectual revisions. NM contributed to mentorship and drafting.

Data Availability

The data used in this study can be made available to researchers collaborating with Appalachian Regional Healthcare under a research agreement. However, the data are not publicly available due to the need to preserve privacy of patient health information.

Abbreviations

BMI: body mass index; HF: heart failure; COVID-19: coronavirus disease 2019; ICU: intensive care unit; IRB: Institutional Review Board; LOS: length of stay

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