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Characteristics, Treatment Patterns, and Clinical Outcomes After Heart Failure Hospitalizations During the COVID-19 Pandemic, March to October 2020

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Journal

Mayo Clinic Proceedings, 98(1)

ISSN

0025-6196

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Publication Date

2023

DOI

10.1016/j.mayocp.2022.09.005

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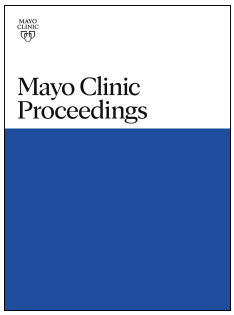

Characteristics, Treatment Patterns, and Clinical Outcomes After Heart Failure Hospitalizations in COVID-19 Pandemic, March – October 2020

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PII: S0025-6196(22)00540-7

DOI: https://doi.org/10.1016/j.mayocp.2022.09.005

Reference: JMCP 3942

To appear in: *Mayo Clinic Proceedings*

Received Date: 26 May 2022

Revised Date: 2 September 2022

Accepted Date: 13 September 2022

Please cite this article as: Yousufuddin M, Yamani MH, Kashani KB, Zhu Y, Wang Z, Seshadri A, Blocker KR, Peters JL, Doss JM, Karam D, Khandelwal K, Sharma UM, Dudenkov DV, Mehmood T, Pagali SR, Nanda S, Abdalrhim AD, Cummings N, Dugani SB, Smerina M, Prokop LJ, Keenan LR, Bhagra S, Jahangir A, Bauer PR, Fonarow GC, Murad MH, Characteristics, Treatment Patterns, and Clinical Outcomes After Heart Failure Hospitalizations in COVID-19 Pandemic, March – October 2020, *Mayo Clinic Proceedings* (2022), doi: https://doi.org/10.1016/j.mayocp.2022.09.005.

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Key words:
Heart failure, COVID-19 pandemic, readmissions, and mortality, quality metrics

Running title: Heart failure hospitalization in COVID-19 pandemic

Mayo Clinic IRB approval ID: 20-004920
PROSPERO ID: CRD42022310307
Funding source: Mayo Clinic Health System

A portion of the data related to the current study was presented as abstract at the Society of Hospital Medicine annual meeting, Nashville, TN, April 2022.

Dr Mohammad Hassan Murad, section editor of the journal, had no role in the editorial review of or decision to publish this article.

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Abstract

Objective

To compare clinical characteristics, treatment patterns, and 30-day all-cause readmission and mortality between patients hospitalized for heart failure (HF) before and during the COVID-19 pandemic.

Methods

The study was conducted at 16 hospitals across 3 geographically dispersed US states. The study included 6769 adults (mean age, 74 years; 56% men) with cumulative 8989 HF hospitalizations: 2341 hospitalizations in COVID-19 pandemic (Mar- Oct 2020) and 6648 in the pre-COVID-19 (Oct 2018 – Feb 2020) comparator group. We used Poisson regression, Kaplan-Meier estimates, multivariable logistic, and Cox regression analysis to determine whether pre-specified study outcomes vary by timeframes.

Results

The adjusted 30-day readmission rate decreased from 13.1% in pre-COVID-19 to 10.0% in the COVID-19 pandemic period (relative risk reduction 23%, number needed to avoid one additional readmission 33, hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.66 – 0.89). Conversely, all-cause mortality increased from 9.7% in pre-COVID-19 to 11.3% in the COVID-19 pandemic period (relative risk increase 16%, number of admissions needed for one additional death 62.5: HR 1.19, 95% CI 1.02 – 1.39). Despite significant differences in rates of index hospitalization, readmission, and mortality across the study timeframes, the disease severity, heart failure subtypes, and treatment patterns remained unchanged.

Conclusions

The findings of this large tristate multicenter cohort study of HF hospitalizations suggest lower rates of index hospitalizations and 30-day readmissions, but higher incidence of 30-day mortality with broadly

similar use of heart failure medication, surgical interventions, and devices during the COVID-19 pandemic compared with pre-COVID-19 timeframe.

Abbreviations and acronyms:

ADHF (acute decompensated heart failure), CI (confidence interval), COVID-19 (corona virus disease 2019), HF (heart failure), HR (hazard ratio), ICD-10 (International Classification of Diseases, tenth revision), OR (odds ratio), STROBE (Strengthening the Reporting of Observational Studies in Epidemiology).

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Introduction

On March 13, 2020, COVID-19 was declared as a national emergency in the United States. Subsequently several states enacted lockdown measures to slow the spread of SARS-CoV-2 [1, 2]. The effects of this proclamation were almost immediate for all disciplines of medicine with a sharp decline in emergency departments visits across the Nation for several life-threatening diagnostic categories and rates of hospitalizations for acute myocardial infarction (AMI) [3, 4], stroke [5], and even surgical emergencies [6]with no evidence of decrease in incidence of these conditions.

Heart failure (HF) patients are especially vulnerable for COVID-19-related disruptions in care process due to high-rates of hospitalizations, 30-day readmissions, and morality. [7-9] Before the pandemic, the trajectory was one of an increasing acute decompensated heart failure (ADHF) hospitalizations with higher comorbidity burden in association with a declining hospital mortality [10, 11]. A few prior studies reported data on patients with ADHF recruited early in the COVID-19 pandemic and raised concern for adherence to quality metrics and clinical outcomes. These studies were largely based on administrative data lacking granular clinical information. With multiple surges in COVID-19 activity, the collateral effect of COVID-19 pandemic on ADHF hospitalization and its outcome warrant further investigations.

To address these knowledge gaps, we aimed to compare pre-pandemic (October 2018 – February 2020) to during the pandemic (March – October 2020) hospitalizations for HF severity and types, treatment patterns, in-hospital clinical outcomes, and 30-day readmissions and mortality. To examine the strength of the main analysis, a sensitivity analysis was performed using a second comparator cohort of ADHF admissions in the matched calendar months in 2019 (March – October 2019). Considering the potential geographical variations in these outcomes, we conducted a mixed study design that included a cohort of

HF population from a large healthcare system (16 centers across three geographically dispersed US states) as well as a systematic review that provides data from other locations and places the findings of the present study in the context of previously published studies. This mixed study follows the framework by Lin and colleagues and can provide stronger conclusions and improved applicability [12].

METHODS

Data source

Data were abstracted from the inpatient database of the Mayo Clinic, one of the largest integrated healthcare networks in the United States, with three tertiary care centers and 13 community hospitals dispersed across Arizona, Florida, and Minnesota, from October 2018 to October 2020.

Study design and population

The unit of analysis was hospitalization for ADHF for at least 1 night. The diagnosis of ADHF was defined by the *International Classification of Diseases, tenth revision* (ICD-10) codes and subsequently verified by manual review of electronic medical records. The ICD-10 codes for these conditions are described in Supplement Table 1. Further details of data extraction were published previously [13]. The study was approved by the Mayo Clinic Institutional Review Board, conforms to the Declaration of Helsinki[14] and follows Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[15] for observational studies. A STROBE flow-diagram for study cohort selection is shown in Supplement Figure 1. A 12 item STROBE checklist is provided in Supplement Table 2. The objectives were to compare patients hospitalized for ADHF in the COVID-19 pandemic (March-October 2020) with two pre-COVID-19 control groups: ADHF patients hospitalized between October 2018-February 2020 for main analysis and those hospitalized in matched-calendar months, March-October 2019 for sensitivity analysis.

Baseline covariates

The following data were abstracted from electronic medical records (EMR).

Socio-demographic indicators. Data-related to age, sex at birth (male and female), race (white and non-white), marital status (married and others), and body mass index (BMI).

Physiological and laboratory measures. Values for systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, blood urea nitrogen (BUN), and creatinine on the day of admission. An average of 3 consecutive measurements of SBP, DBP, or heart rate were used for data analysis.

Measure of comorbidities. A total of 16 of 20 comorbidities (Figure 1), specified by the Office of the Assistant Secretary for Health [16] were identified from the list of secondary diagnoses. The obstructive sleep apnea (OSA) was incorporated as a comorbidity due to increasing prevalence in heart failure population.

Outcome measures

PRIMARY OUTCOMES

30-day readmissions. 30-day all-cause readmission was defined as repeat hospitalization from any condition occurring within 30 days from the date of discharge.

30-day mortality. 30-day all-cause mortality was defined as death from any cause occurring within 30 days from the date of admission.

SECONDARY OUTCOMES

Time trends in rates of hospitalization**.** Hospitalizations for ADHF were all counted by calendar month from October 2018 through October 2020.

Heart failure-specific measures**.** ADHF diagnosis was based on physician's documentation. Left ventricular ejection fraction (LVEF)-derived from transthoracic echocardiogram, performed within the preceding 18 months or during index hospitalization. Types of HF were defned as HF with preserved ejection fraction (EF) (HF*p*EF), HF with mid-range EF (HF*mr*EF) or HF with borderline EF, and HF with reduced EF (HF*r*EF) based on LVEF ≥50%, 41%-49%, and ≤40%, respectively [17-19]. Patients were risk

stratified as low, intermediate, and high-risk categories using Acute Decompensated Heart Failure National Registry (ADHERE) risk prediction model, which was modified [20].

Heart failure treatment pattern (Figure 1). Divided in to four categories: 1) admission services: cardiology, internal medicine, family medicine, critical care, and other specialty services based on the premise that clinical outcome vary with hospitalization by sub-specialty service [21-23], 2) guideline-directed pharmacological therapy [17, 18], 3) guideline-directed non-pharmacological interventions, 4) discharge destination [17, 24-26].

In-hospital clinical outcomes. Incident acute myocardial infarction (AMI), shock, or all-cause death.

Follow-up

All patients were followed up until readmission, death, or censoring at 30-days after discharge whichever occurred first.

Systematic review

The systematic review protocol was registered with PROSPERO (CRD42022310307) and conducted in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [27]. Search details were previously published [28]. Briefly, we searched multiple databases with no language restriction through October 11, 2021, for studies that compared ADHF hospitalizations between COVID-19 and pre-COVID periods and reported following outcomes: trends in ADHF hospitalization, treatment patterns, in-hospital mortality, readmissions or 30-day mortality. The detailed search strategy is described in the Supplement. Two investigators (MY, AS), independently screened search results, selected studies, abstracted data, and assessed the risk of bias by the Newcastle-Ottawa Scale for cohort studies [29].

Statistical analysis

APPROACHES FOR MAIN ANALYSES

Descriptive statistics We described continuous variables with normal distribution as mean and standard deviation (SD), variables with non-normal distribution as median and interquartile range, and categorical variables as number of patients and percentages. We used unpaired t-test for parametric data, Wilcoxon rank-sum test for non-parametric data, and χ^2 and Fisher exact tests for categorical variable to compare demographics, social indicators, anthropometric measure, physiological data, and key laboratory measures between time periods.

***Logistic regression models*.** Separate logistic regression models were developed to evaluate whether odds of comorbidities, measures of treatment patterns, or clinical outcomes differed by time frame accounting for patient-level characteristics. Due to large number of independent variables and the features of some of the variables, we customized each regression to include the most relevant variables only.

Poisson regression models. Incidence rate ratios (IRR) and 95% confidence interval (CI) were estimated to assess time trends in hospitalizations. we included both age and exposure of months as covariates in the Poisson model. Hospitalizations were included as an offset variable.

Kaplan-Meier analyses. Cumulative event rates were evaluated with censoring time 30 days and differences were assessed by log-rank test.

Cox proportional hazard models. Separate multivariable Cox proportional hazard models were generated to estimate hazard ratio (HR) and 95% CI for readmission (all-cause and HF-specific readmission) and all-cause mortality for patients hospitalized in COVID-19 pandemic vs pre-COVID-19 period. Three sequential Cox regression models were fitted: model 1 adjusted for age, sex, race, marital status, and body mass index (BMI), model 2 controlled for the variables in model 1 and additional adjustment for 17 comorbidities, finally model 3 incorporated variables of model 2 with additional adjustment for guideline-directed pharmacological and non-pharmacological interventions.

OTHER ANALYSIS

Sensitivity analysis. A sensitivity analysis that included only the matched calendar months in 2019 as a second comparator cohort was performed to examine the strength of the main analysis.

Results

Study population

From October 2018 to October 2020, a combined total of 8989 ADHF hospitalizations occurred among 6769 unique patients including 2341 ADHF hospitalizations in the COVID-19 pandemic, 6648 in pre-pandemic, and 3094 in the matched calendar months in 2019.

Baseline characteristics (Table 1)

Overall mean age was 74 (±14.7) years with 5033 (56%) men, 8270 (92%) white, and 4584 (51%) married. Patients who were hospitalized during COVID-19 pandemic were not different from those hospitalized in baseline or matching comparison periods in sex, race, marital status, BMI, heart failure types, SBP, and heart rate. Although age, BUN, and creatinine showed between group significant statistical differences due to the size of the population and may have no clinical relevance and the directionality of the data. However, ADHF patients hospitalized during COVID-19 pandemic, compared to pre-pandemic timeframe had lower prevalence of atrial fibrillation, chronic kidney disease (CKD), cancer, dementia, dyslipidemia, hypertension, and other psychiatric illnesses as shown in Figure 1.

Time trend in hospitalizations (Figure 2A). The mean monthly ADHF hospitalization rate was 293 in the COVID-19 pandemic compared with 383 in pre-COVID-19 period. With first surge in COVID-19, the predicted age-adjusted monthly HF hospitalizations decreased by 68% (IRR, 0.32; 95% CI 0.31 – 0.34) with no 2nd dip with 2nd surge in COVID-19 activity.

Heart failure-specific characteristics (Figure2B and Figure 2C). We found no between timeframe differences in proportions of hospitalizations by risk categories (*P*=.35) or HF types by LVEF (*P*=.84).

In-hospital outcome (Figure 1). we found no between timeframe differences in the incidence of AMI or shock. However, in-hospital mortality was lower in COVID-19 pandemic than in pre-COVID-19 period.

Treatment patterns (Figure 1). Proportions of patients directly admitted to services other than internal medicine, cardiovascular medicine, critical care, and family medicine were increased during the COVID-19 pandemic vs. pre-pandemic period. Conversely, patients who were discharged home with home care, nursing home, hospice, or long-term acute care were decreased compared to those dismissed home with self-care during the COVID-19 pandemic vs. pre-pandemic periods. Except for statin and anticoagulants, the prescription of which were increased in pandemic vs. pre-pandemic period, exposure to other guideline-directed therapy remained unchanged across the timeframes.

30-day outcome measures (Figure 3)

Upper panels in Figure 3 show Kaplan-Meier estimates for all-cause readmissions and all-cause mortality by timeframes. Multivariable Cox regression analysis (lower panel in Figure 3) demonstrated that all-cause readmission was lower during COVID-19 pandemic (10.0%) than in the pre-pandemic period (13.1%), which implied a 3.1% absolute risk reduction, 23% relative risk reduction (RRR), and number needed to avoid one additional readmission was 33.3. Conversely, all-cause mortality was higher in the COVID-19 pandemic (11.3%) than in pre-pandemic period (9.7%), which translated to a 1.6% absolute and 16% RRR increased risk of death, and number of index admissions needed for one additional death was 62.5.

Competing risk analysis

Of 8989 patients 65 (0.72%) A 0.72% had both 30-day readmission and deaths. The rate was too low that a competing analysis might not be required.

Assessment of possible collinearity

We conducted correlation analysis between key variable with most variables had a weak correlation as shown in Supplement Table 3. The problems related to collinearity and overfitting were limited.

Furthermore, the model selection was also strongly based on clinical significance and clinical knowledge with clinician's opinion incorporated into the model design to enhance the model's clinical validity.

Sensitivity analysis

Results of main analysis were consistently replicated in sensitivity analysis. Kaplan-Meir estimates with log-Rank *P* value for sensitivity analysis are displayed as insets in the left upper quadrants of the upper panels of Figure 3. Similarly, results of Cox-proportional regression models with adjusted HRs and 95% CI are presented in the lower panels of the Figure 3.

Systematic review

A systematic review identified 17 relevant studies [30-46] with 67039 participants (n = 22078 exposure and n = 44961 comparator arm) from 1682 citations (Supplement Figure 2 shows PRISMA flow diagram). The PRISPMA check list is provided in Supplement Table 4. We classified 5 studies with low, 7 studies as moderate, and 5 studies as high risk of bias. Seven studies provided data on in-hospital mortality, 30-day mortality, and/or 30-day readmission [32, 37-39, 41, 42, 46-48]. The descriptive summary of the included studies is provided in supplement Tables 5.1, 5.2, and 5.3. Supplement Table 5 shows risk bias assessment using Newcastle-Ottawa scale. The studies showed variations in classifying disease severity and distribution of HF types by LVEF. Two studies reported admission by specialty service [45,34] and one study focused on discharge destination [46]. Three studies reported guideline-directed medication therapy results[34, 43, 46].

Overall, most identified studies had incomplete data and moderated to high-risk of bias in multiple domains, prohibiting synthesis of meta-analysis. However, the data from previous studies on in-hospital mortality (6 studies[38, 39, 41-43, 46]), 30 readmission (one study[41]), and 30-day mortality (two studies[37, 43]) in

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comparison with the current study are presented as risk ratios with corresponding confidence intervals in Figure 4.

Discussion

Main findings

This large, tristate, multicenter cohort study that compared 2341 ADHF hospitalizations in the COVID-19 pandemic with 6648 hospitalizations in pre-COVID-19 era, provides following key findings. First, a decline in index ADHF hospitalizations and fewer 30-day all-cause readmissions occurred concomitant with increased 30-day mortality during the COVID-19 pandemic compared with pre-pandemic control periods. Our findings imply that 3.1% fewer rehospitalizations occurred during the study COVID-19 pandemic period than would have admitted to hospital in pre-pandemic time. Conversely, an additional 1.6% HF patients died in 8 months through COVID-19 pandemic than would have died in pre-COVID-19 times. Second, decline in HF hospitalizations were consistent across HF subtypes by LVEF and HF severity ADHERE grading, and particularly evident in older adults with higher comorbidity burden. Third, admission to critical care unit, treatment patterns including drugs, surgical interventions and devices, incident AMI, shock, and in-hospital death did not vary across the pre-pandemic and pandemic timeframes. Lack of statistical significance in variables such as incident heart transplant between pre-COVI-19 and during the COVID-19 pandemic groups should be viewed with circumspection due to fewer events and a large 95 CI that may lead to a larger margin of error and less precise estimation. Fourth, a higher proportion of patients were admitted to services other than internal medicine, cardiology, and critical care or discharged home with self-care during the COVID-19 pandemic compared to pre-

pandemic period. Finally, sensitivity analysis comparing hospitalizations in COVID-19 to those admitted in matched calendar months in 2019 (n = 3049) replicated findings of main analysis.

Clinical perspective

Trends in heart failure hospitalization during COVID-19 pandemic. In the United States, time-trends in HF hospitalizations, which showed a steady rise since 2014 [10, 11], demonstrated a precipitous decline in the early months of COVID-19 pandemic, a phenomenon observed across all regions regardless of level of COVID-19 activity [41, 49, 50]. These findings mirror similar trends in hospitalizations for all non-COVID hospitalizations in the United States and worldwide. (4-6, 62-65, 85) After initial decline and subsequent partial reversal of the ADHF hospitalizations trend, we did not observe a second dip concomitant with second wave in COVID-19 activity, a finding consistent with a report from California in AMI or stroke [51] but contradictory to data from England [52] attributable to geographical differences.

Patient and heart failure characteristics. HF patients have become progressively more complex over time due to increased accumulation of non-cardiovascular comorbidities based on pre-pandemic data [53]. In reversal of this course, patients hospitalized for ADHF in COVID-19 pandemic tend to have lower comorbidity burden in our cohort consistent with findings in AMI or stroke [54]. Previous studies revealed mixed results regarding HF severity and HF types among HF patients hospitalized before and during the COVID-19 pandemic probably reflect differences in measurement of disease severity and LVEF cutoff used for classifying HF subtypes [34, 35, 38, 41-43, 46].

Treatment patterns. Analysis of receipt of in-hospital guideline-directed interventions according to pre-COVID and COVID-19 timeframes yielded comparable results in the present study. Except for an isolated report showing a reduction in angiotensin converting enzyme inhibitor prescription [46] during the pandemic other published studies corroborated our findings. [34, 38, 39]. The valve repair surgery was less frequently performed in patients with heart failure during the COVID-19 pandemic compared to pre-pandemic period. On the contrary, the frequency of pacemaker or ICD implantation, coronary artery

revascularization by PCI or CABG, placement of LVAD, and heart transplantation were comparable across COVID-19 pandemic and pre-pandemic time frames, a finding in agreement with previous reports [38, 41, 43] These findings are contradictory to previous studies in AMI that showed a substantial reduction in adherence to quality care metrics, increased complications, and in-hospital mortality during the pandemic. [49, 55, 56]

Readmissions and mortality. Decreases in hospital readmissions and in-hospital mortality in COVID-19 pandemic compared with pre-pandemic times observed in the present cohort study did not reach statistical significance in the accompanying meta-analysis. However, the present cohort study together with meta-analysis clearly demonstrated increased 30-day all-cause mortality following index ADHF hospitalization in the COVID-19 pandemic compared with pre-pandemic period, consistent with a recent report in AMI. [57] Increased mortality may persist beyond 30 days among patients with HF hospitalized during the COVID-19 pandemic. [45]

A systematic review. The systematic review critically appraised published studies through October 2021 that evaluated in-hospital mortality, 30-day readmission, and 30-day mortality in AHDF patients hospitalized in COVID-19 pandemic compared to those admitted in pre-pandemic period. The increased 30-day mortality[37, 43] among patients hospitalized during the pandemic were consistent with our findings. the results associated with in-hospital mortality and 30-day readmission were divergent from those of the present study attributed to differences in study design, population, and geography.

Attributes for decreased hospitalizations and increased mortality

Lower rates of readmissions might be attributable to restraints in seeking care for perceived threat of contracting COVID-19 in healthcare environment [58], transition to telemedicine and device monitoring [59, 60], reduced triggers for decompensation due to a historic low level of influenza and other non-COVID viruses activity [61]. Plausible explanations for increased mortality in COVID-19 era are competing COVID-19 infection [37], rise in out-of-hospital cardiac arrest [62, 63], an inverse association between readmissions

and 30-day mortality [64], missed opportunity to avert premature death, insufficient post-discharge care, and worsening socio-economic disparity in healthcare access due to COVID-19.

Strengths and limitations

Strengths of the study include large sample size of real-world patients from academic and rural community hospitals across three geographically dispersed states, comprehensive data collection especially of comorbidities and treatment patterns, sensitivity analysis, and data integration with that of published data in systematic review and metanalysis to support the robustness of our analysis. One of the main limitations of the study is incomplete acquisition of readmission data with those readmitted to non-Mayo Clinic sites were not accounted for. However, focus on timeframe comparison among same participant sites minimize relevance of unavoidable incomplete acquisition of readmission data. Other limitations included retrospective design with possibility of unmeasured confounders, predominant non-Hispanic white patient population with lower Gini coefficient. Small percentage of non-white patient population precluded subgroup analysis by minorities who were disproportionately affected with COVID-19. The significant difference in sample size between pre-COVID-19 (n=6648) and COVID-19 pandemic (n=3094) groups may influence rates of 30-day readmissions and mortality in main analysis. The robustness of these findings was assessed in sensitivity analysis by comparing COVID-19 pandemic group with a more restricted time-matched historical control group in 2019 (n=3094) and the results had been consistent.

Implications for clinical practice

Patients with heart failure are at increased risk of death if they inadvertently avoid hospitalizations during the COVID-19 pandemic, particularly those with advanced age and higher comorbidity burden. Our results indicate that treatment patterns have been consistent during COVID-19 pandemic vs pre-pandemic periods among hospitalized patients with ADHF with no decline in rates of provision of even

specific advanced cardiovascular procedures. These results have important implications for shared decision for advanced heart failure and not to miss an opportunity to improve quality of care even during times, as challenging as COVID-19 pandemic.

We emphasize continued adherence to quality metrics, improved post-discharge care, and a broader patient education and behavioral interventions to promote timely access of care at the community level. The study was performed during the pre-pandemic period; therefore, the value of COVID-19 vaccination could not be determined.

Implications for research

Further studies are needed to extend our findings in minority population and to determine what factors drive reductions in rates of heart failure hospitalization and readmissions and increase in mortality during COVID-19 pandemic requires further research.

Conclusions

This large tri-state multisite cohort study of ADHF hospitalizations together with meta-analysis suggest lower rates of 30-day readmission but higher rates of 30-day mortality with similar use of heart failure medication, surgical interventions, and devices during the COVID-19 pandemic compared with pre-COVID-19 times. Our findings conceptualize a COVID-19 HF phenotype with younger age, fewer comorbidities, and increased 30-day mortality.

Funding source

The study was funded by the Mayo Clinic Health System. The funding source had no role in the study design, data collection, data analysis, or manuscript drafting.

Declaration of Competing interest

Professor Fonarow disclosed consulting for Abbott, Amgen, AstraZeneca, Bayer, Cytokinetics, Edwards, Janssen, Medtronic, Merck, and Novartis, Dr. Sagar Dugani is being supported by the National Institute

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of Health/National Institute on Minority Health and Health Disparities (K23 MD016230). The remaining others have none to disclose.

Figure legends

Figure 1.

Title

Results of comparative multivariable logistic regression analysis of patient- and hospital- level characteristic of hospitalized patients for acute decompensated heart failure presented as Forest plot with point estimates in odds ratio (OR) and corresponding 95% confidence intervals (CI).

Text at the bottom of the Figure 1

Comparisons of distribution of comorbidities, treatment patterns, hospital-level characteristics, and in-hospital clinical outcomes between COVID-19 and pre-COVID-19 timeframes. *Comorbidities were adjusted to age, sex, race, marital status, and body mass index (BMI) and **variables in other categories were adjusted to age, sex, race, marital status, BMI, and comorbidities.

Figure 2.

Title

Bar diagram of hospitalizations for acute decompensated heart failure by calendar month from October 2018 through October 2020.

Text at the bottom of the Figure 2

Part A illustrates trends in cumulative hospitalizations for acute decompensated heart failure by calendar month (October 2018-October 2020) with each bar stacked to represent monthly aggregate of study population by study state. Trend line (black line on the top) was constructed using multivariate time-series estimation with age-adjusted rate as dependent variable and the calendar month as independent variable. The superimposed curved orange line displays trends in COVID-19 cases from March – October 2020 in the United States reported to Centers for Disease Control and Prevention.

Part B represent stacked bar diagram of % distribution of acute decompensated heart failure patients by three risk categories: low- (bottom), intermediate- (middle), and high-risk (top)

categories for adverse in-hospital events in accordance with modified Acute Decompensated Heart Failure National Registry (ADHERE) risk stratification. No timeframes differences in proportions of hospitalizations by low-, intermediate-, or high-risk categories (*P*=0.35)
Part C shows stacked bar diagram of % distribution of acute decompensated heart failure patients by three heart failure types: heart failure with reduced ejection fraction (HF*r*EF) displayed at the bottom, heart failure with mid-range ejection fraction (HF*mr*EF) in the middle, heart failure with preserved ejection fraction (HF*p*EF) in the top. No timeframes differences in proportions of hospitalizations by heart failure types (*P*=0.84)

Figure 3.

Title

Kaplan-Meier estimates and Cox regression analysis for 30-day readmission and mortality.

Text at the bottom of the Figure 3

Upper panels illustrate Kaplan-Meier estimates of probability of 30-day all-cause readmission (left upper) and all-cause mortality (right upper) by timeframes. The larger figure shows comparison between COVID-19 pandemic (March-October 2020) and pre-pandemic baseline (October 2018-February 2020) control whereas insets represent comparison between COVID-19 pandemic (March-October 2020) and pre-pandemic matched historic control (March-October 2019).

Lower panel shows Hazard ratios (HR) and 95% confidence intervals (CI) for 30-day all-cause readmission and all-cause mortality associated with patients hospitalized in COVID-19 pandemic (March-October 2020) vs those hospitalized in pre-pandemic periods COVID-19 pandemic baseline (October 2018-February 2020) control vs those hospitalized in matched pre-pandemic historic control (March-October 2019)
Model 1 adjusted for age, sex, race, marital status, and body mass index
Model 2 adjusted for variables of Model 1 plus additional adjustment for 17 comorbidities
Model 3 adjusted for variable of Model 2 plus additional adjustments for pharmacological therapy and non-pharmacological interventions.

Figure 4.

Title

In-hospital, and 30-day mortality, and 30-day readmissions in the current study in comparison with reports.

Text at the bottom of the Figure 4

In these studies patients hospitalized with acute decompensated heart failure in the COVID-19 pandemic were compared with those in the pre-pandemic period for in-hospital mortality (A), 30-day mortality (B), and 30-day readmissions and the results are displayed in forest plot with point estimates and 95% confidence intervals (CI).

Journal Pre-proof

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Table 1. Baseline characteristics of hospitalized patient with acute decompensated heart failure by time periods.

	Mar – Oct 2020, n = 2341	Mar – Oct 2019, n = 3094	Oct 2018 – Feb 2020, n = 6648	P[a]	P[b]
Demographics					
Age, mean (SD), y	73.7 (14.1)	74.4 (14.9)	74.3 (14.9)	<.01	.01
Male, n (%)	1319 (56)	1714 (55)	3742 (56)	.49	.96
Race					
White, n (%)	2136 (91)	2860 (92)	6124 (92)	.11	.27
Non-white, n (%)	205 (9)	234 (8)	524 (8)		
Marital status					
Married, n (%)	1181 (50)	1605 (52)	3418 (51)	.30	.55
Other status	1160 (50)	1489 (48)	3230 (49)		
Anthropometric measures					
BMI kg/m^2, mean (SD)	31.7 (9.3)	31.4 (9.5)	31.5 (9.5)	.65	.90
Heart failure types					
HF*r*EF, LVEF ≤ 40%, n (%)	729 (32)	959 (32)	2088 (33)	.67	.84
HF*mr*EF, LVEF 41 – 49%, n (%)	277 (12)	342 (12)	762 (12)		
HF*p*EF, ≥ 50%, n (%)	1234 (55)	1650 (56)	3488 (55)		
Vitals					
SBP mmHg, mean (SD)	133 (28)	132 (28)	132 (28)	.32	.40
DBP mmHg, mean (SD)	78 (19)	76 (18)	76 (18)	.01	.01
Heart rate, beats/min, mean (SD)	84 (21)	85 (21)	85 (21)	.57	.58
Laboratory measures					
Blood urea nitrogen, mg/dl, mean (SD)	34 (22)	32 (21)	33 (21)	<.01	.08
Creatinine mg/dl, mean (SD)	1.67 (1.3)	1.56 (1.1)	1.6 (1.2)	<.01	.06
Heart Failure by risk categories					
High risk, n = (%)	66 (3)	72 (2)	185 (3)	.20	.35
Intermediate risk, n = (%)	985 (43)	1243 (41)	2791 (41)		
Low risk, n = (%)	1244 (54)	1701 (56)	3777 (56)		

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HF*mr*EF, heart failure with mid-range ejection fraction; HF*p*EF, heart failure with preserved ejection fraction; HF*r*EF, heart failure with reduced ejection fraction; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation.

Mar-Oct 2020 represents COVID-19 pandemic period
Mar-Oct 2019 Pre-COVID matched historic control period
October 2018-Feb 2020 indicates pre-COVID-19 baseline comparison period
P[a] Comparison, COVID-19 pandemic period (Mar-Oct 2020) vs 2019 pre-COVID matched historic control period
P[b] Comparison, COVID-19 pandemic period (Mar-Oct 2020) vs pre-COVID-19 baseline period

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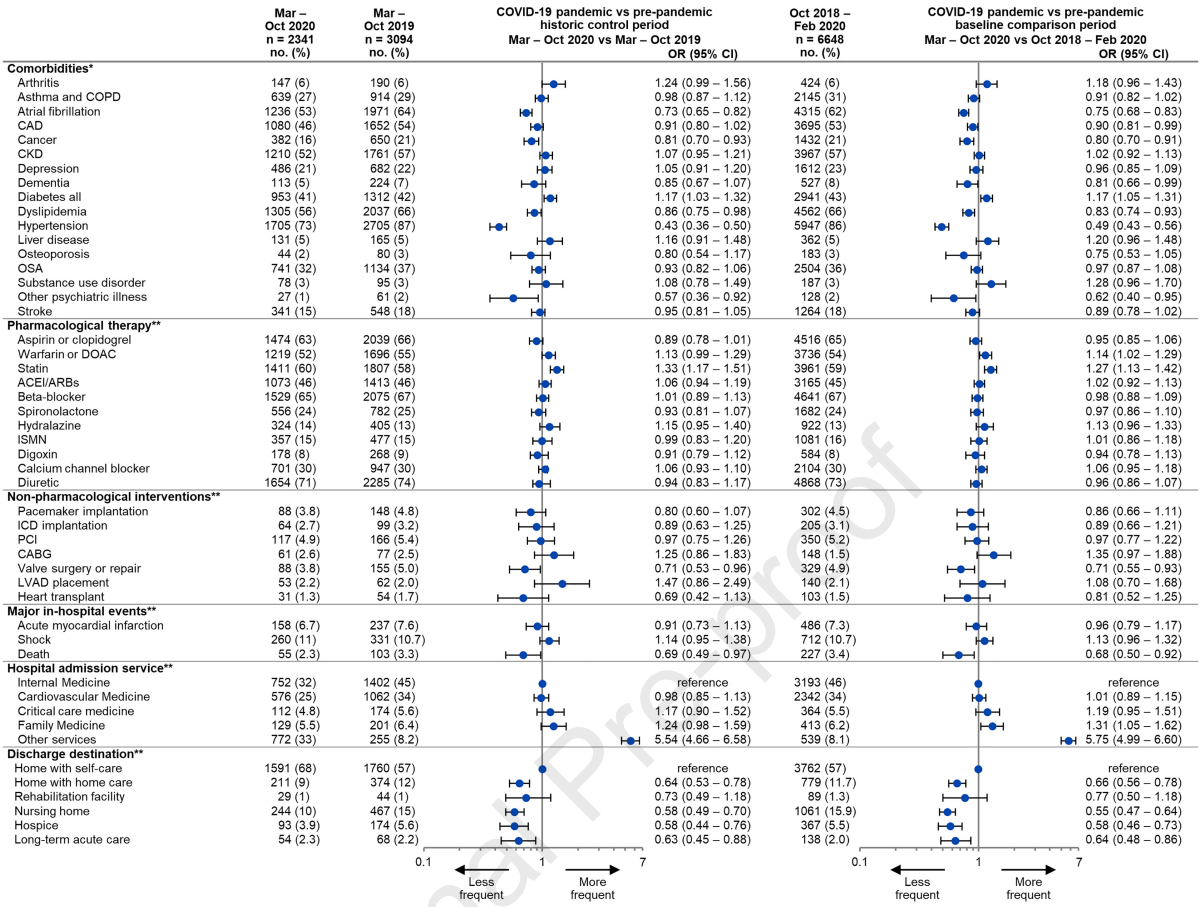

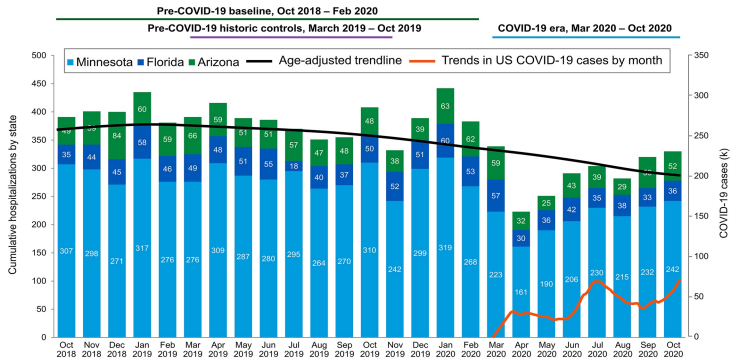

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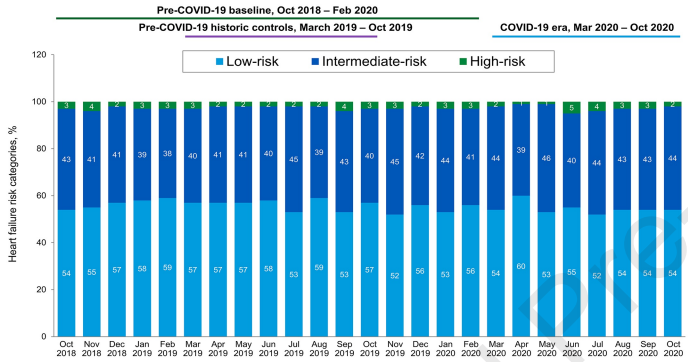

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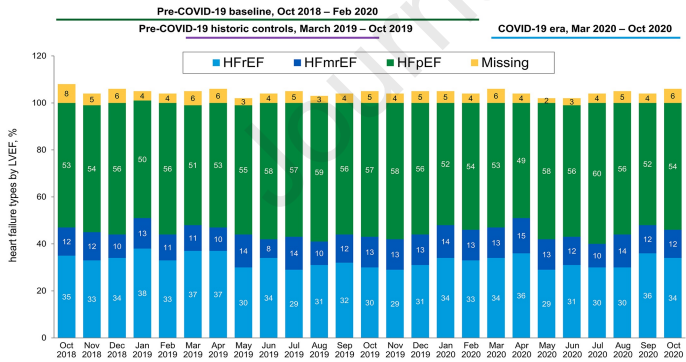

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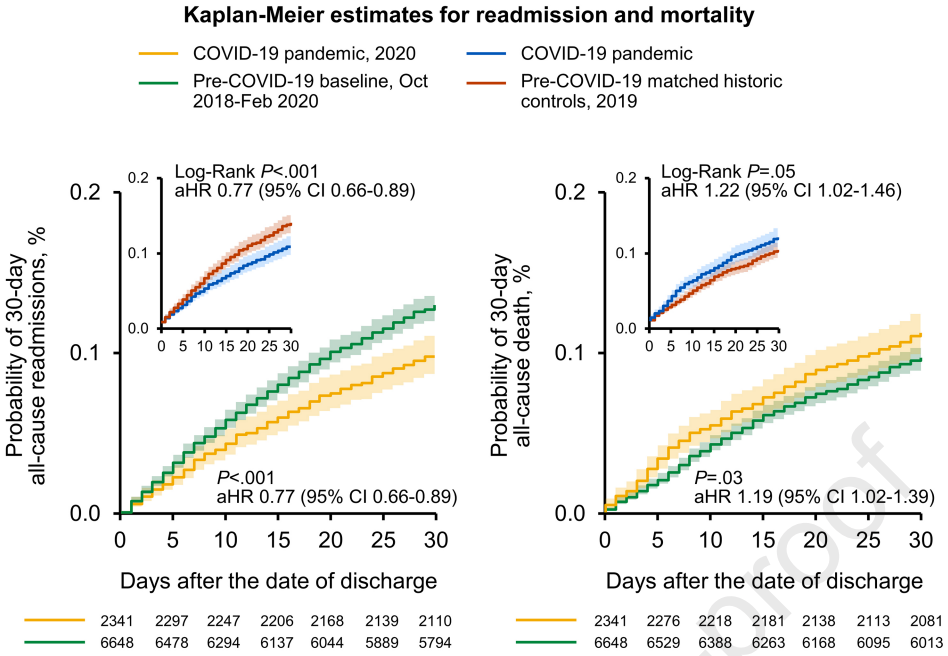
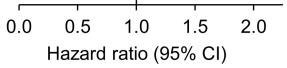
Kaplan-Meier estimates for readmission and mortality



Adjusted Cox regression analysis for readmission and mortality

		COVID-19 Events (%)/n=	Pre-COVID-19 Events (%)/n=	HR	95% CI	P
COVID-19 pandemic vs. pre-pandemic baseline						
All-cause readmissions						
All three states	Model 1	234 (10.0)/2341	872 (13.1)/6684	0.75	0.65-0.86	<.001
	Model 2			0.76	0.66-0.88	<.001
	Model 3			0.77	0.66-0.89	<.001
All-cause deaths						
All three states	Model 1	264 (11.3)/2341	645 (9.7)/6648	1.21	1.05-1.40	.01
	Model 2			1.20	1.04-1.39	.01
	Model 3			1.19	1.02-1.39	.03
COVID-19 pandemic vs. matching historical control in 2019						
All-cause readmissions						
All three states	Model 1	234 (10.0)/2341	401 (13.0)/3094	0.76	0.65-0.89	<.001
	Model 2			0.77	0.65-0.91	.01
	Model 3			0.79	0.67-0.93	.01
All-cause deaths						
All three states	Model 1	234 (11.3)/2341	300 (9.6)/3094	1.22	1.03-1.44	.02
	Model 2			1.20	1.01-1.42	.04
	Model 3			1.22	1.02-1.46	.03



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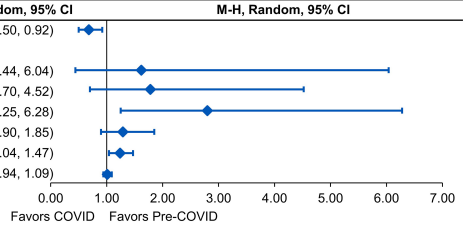
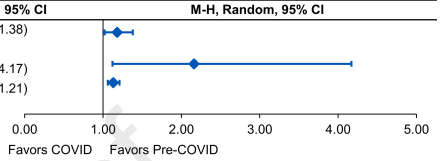
In-hospital mortality, COVID-19 vs pre-COVID-19

Study or subgroup	During COVID		Pre-COVID			Odds Ratio	Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Current Study	55	2,341	227	6,648	17.7%	0.68 (0.50, 0.92)	
Previous Studies							
Toner 2020	3	32	13	217	2.5%	1.62 (0.44, 6.04)	
Severino 2020	10	112	9	172	4.6%	1.78 (0.70, 4.52)	
Frankfurter 2020	16	107	11	186	5.8%	2.80 (1.25, 6.28)	
Jayagopal 2021	54	526	86	1,056	16.2%	1.29 (0.90, 1.85)	
Konig 2020	256	3,501	288	4,799	24.4%	1.24 (1.04, 1.47)	
Shoaib 2021	1,000	9,791	2,752	27,183	27.9%	1.01 (0.94, 1.09)	



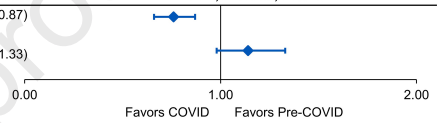
In-hospital mortality, COVID-19 vs pre-COVID-19

Study or subgroup	During COVID		Pre-COVID			Odds Ratio	Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Current study	264	2341	645	6,648	36.3%	1.18 (1.02, 1.38)	
Previous Studies							
Doolub 2021	25	119	18	164	3.7%	2.16 (1.12, 4.17)	
Shoaib-b 2021	1,439	9,791	3,594	27,183	60.0%	1.13 (1.06, 1.21)	



In-hospital mortality, COVID-19 vs pre-COVID-19

Study or subgroup	During COVID		Pre-COVID			Odds Ratio	Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Current study 2021	234	2341	872	6648	50.4%	0.76 (0.66, 0.87)	
Previous Studies							
Konig 2020	280	3501	336	4799	49.6%	1.14 (0.98, 1.33)	



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