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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Mayo Foundation for Medical Education and Research. Published by Elsevier Inc.
Characteristics, Treatment Patterns, and Clinical Outcomes After Heart Failure Hospitalizations in COVID-19 Pandemic, March – October 2020

Authors:
Mohammed Yousufuddin, MD, MSc1, Mohamad H. Yamani, MD2, Kianoush B. Kashani MD, MS3, Ye Zhu, MD, MPH, PhD4, Zhen Wang, PhD5, Ashok Seshadri, MD5, Katherine R. Blocker, DPT1, Jessica L. Peters, BSN3, Jewell M. Doss, BSN1, Dhauna Karam, MD1, Kanika Khandelwal, MD1, Umesh M. Sharma, MD6, Daniel V. Dudenkov, MD7, Tahir Mehmdov, MD4, Sandeep R. Pagali, MD, MPH8, Sanjeev Nanda, MD9, Ahmed D. Abdalrhim, MD9, Nichole Cummings, MD10, Sagar B. Bugani, MD, PhD8, Michael Smerina, MD7, Larry J. Prokop, MLS11, Lawrence R. Keenan, MD12, Sumit Bhagra, MD13, Arshad Jahangir, MD14, Philippe R. Bauer, MD, PhD15, Gregg C. Fonarow, MD16, Mohammad Hassan Murad, MD, MPH4.17

Affiliation:
1Division of Hospital Internal Medicine, Mayo Clinic Health System, Austin, Minnesota, USA
2Division of Cardiology, Mayo Clinic, Jacksonville, Florida, USA
3Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA
4Robert D. and Patricia E. Kern Center for the Science of Healthcare Delivery, Mayo Clinic, Rochester, Minnesota, USA
5Division of Psychiatry, Mayo Clinic Health System, Austin, Minnesota, USA
6Hospital Internal Medicine, Mayo Clinic, Phoenix, Arizona, USA
7Division of General Internal Medicine, Mayo Clinic, Jacksonville, Florida, USA
8Division of Hospital Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA
9Division of General Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA
10Division of Hospital Internal Medicine, St. Cloud Hospital, St. Cloud, Minnesota, USA
11Library and Public Services, Mayo Clinic, Rochester, Minnesota, USA
12Division of Cardiology, Mayo Clinic Health System, Austin, Minnesota, USA
13Division of Endocrinology, Mayo Clinic Health System, Austin, Minnesota, USA
14Aurora Cardiovascular and Thoracic Services, Aurora St. Luke’s Medical Center, Milwaukee, Wisconsin, USA
15Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota, USA
16Division of cardiology, University of California Los Angeles, Los Angeles, California, USA
17Preventive Medicine, Mayo Clinic, Rochester, Minnesota, USA

Address for Correspondence:
Mohammed Yousufuddin, MD, MSc
Mayo Clinic Health System
1000 First Drive NW
Austin, MN 55912
The United States
Yousufuddin.mohammed@Mayo.edu

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.
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).
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. 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), stroke, and even surgical emergencies 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. 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. 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.

**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. The study was approved by the Mayo Clinic Institutional Review Board, conforms to the Declaration of Helsinki and follows Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines 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\textsuperscript{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 defined as HF with preserved ejection fraction (EF) (HFP EF), HF with mid-range EF (HFM EF) or HF with borderline EF, and HF with reduced EF (HFR EF) based on LVEF ≥50%, 41%-49%, and ≤40%, respectively\textsuperscript{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\(^\text{20}\).

**Heart failure treatment pattern (Figure 1).** Divided into 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\(^\text{21-23}\), 2) guideline-directed pharmacological therapy\(^\text{17, 18}\), 3) guideline-directed non-pharmacological interventions, 4) discharge destination\(^\text{17, 24-26}\).

**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\(^\text{27}\). Search details were previously published\(^\text{28}\). 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\(^\text{29}\).

**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 $\chi^2$ 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
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-COVID-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, 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. These findings mirror similar trends in hospitalizations for all non-COVID hospitalizations in the United States and worldwide. 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 but contradictory to data from England 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. 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. 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.

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 during the pandemic other published studies corroborated our findings. 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 \textsuperscript{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
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 (HFrEF) displayed at the bottom, heart failure with mid-range ejection fraction (HfmrEF) in the middle, heart failure with preserved ejection fraction (HfpeF) 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).
References

1. House W. Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak. Vol 2020: White House; 2020.
2. Times TNY. See Which States and Cities Have Told Residents to Stay at Home. 2020.
3. De Rosa S, Spaccarotella C, Basso C, et al. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. *Eur Heart J.* 2020;41:2083-2088.
4. Garcia S, Albaghdadi MS, Meraj PM, et al. Reduction in ST-Segment Elevation Cardiac Catheterization Laboratory Activations in the United States during COVID-19 Pandemic. *J Am Coll Cardiol.* 2020;75(22):2871-2872
5. Uchino K, Kolikonda MK, Brown D, et al. Decline in Stroke Presentations During COVID-19 Surge. *Stroke.* 2020;51:2544-2547.
6. Bernstein L, Sellers F. Patients with Heart Attacks, Strokes and Even Appendicitis Vanish from Hospitals. https://www.washingtonpost.com/health/patients-with-heart-attacks-strokes-and-even-appendicitis-vanish-from-hospitals/2020/04/19/9ca3ef24-7eb4-11ea-9040-68981f488eed_story.html (accessed May 1, 2022)
7. Virani SS, Alonso A, Aparicio HJ, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation.* 2021;143:e254-e743.
8. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. National Burden of Heart Failure Events in the United States, 2006 to 2014. *Circ Heart Fail.* 2018;11:e004873.
9. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med.* 2009;360:1418-1428.
10. Agarwal MA, Fonarow GC, Ziaeian B. National Trends in Heart Failure Hospitalizations and Readmissions From 2010 to 2017. *JAMA Cardiol.* 2021;6:952-956.
11. Clark KAA, Reinhardt SW, Chouairi F, et al. Trends in Heart Failure Hospitalizations in the US from 2008 to 2018. *J Card Fail.* 2022;28(2):171-180.
12. Lin JS, Murad MH, Leas B, et al. A Narrative Review and Proposed Framework for Using Health System Data with Systematic Reviews to Support Decision-making. *J Gen Intern Med.* 2020;35:1830-1835.
13. Yousufuddin M, Bartley AC, Alsawas M, et al. Impact of Multiple Chronic Conditions in Patients Hospitalized with Stroke and Transient Ischemic Attack. *J Stroke Cerebrovasc Dis.* 2017.
14. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama.* 2013;310:2191-2194.
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandebroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med.* 2007;147:573-577.
16. Goodman RA, Posner SF, Huang ES, Parekh AK, Koh HK. Defining and measuring chronic conditions: imperatives for research, policy, program, and practice. *Prev Chronic Dis.* 2013;10:E66.
17. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;62:e147-239.
18. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016;37(27):2129-2200.
19. Bozkurt B, Coats AJ, Tsutsui H, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021;1:S1071-9164.

20. Fonarow GC, Adams KF, Jr., Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA. 2005;293:572-580.

21. Kapelios CJ, Canepa M, Benson L, et al. Non-cardiology vs. cardiology care of patients with heart failure and reduced ejection fraction is associated with lower use of guideline-based care and higher mortality: Observations from The Swedish Heart Failure Registry. Int J Cardiol. 2021;343:63-72.

22. Jong P, Gong Y, Liu PP, Austin PC, Lee DS, Tu JV. Care and outcomes of patients newly hospitalized for heart failure in the community treated by cardiologists compared with other specialists. Circulation. 2003;108:184-191.

23. Boom NK, Lee DS, Tu JV. Comparison of processes of care and clinical outcomes for patients newly hospitalized for heart failure attended by different physician specialists. Am Heart J. 2012;163:252-259.

24. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599-3726.

25. Writing C, Maddox TM, Januzzi JL, Jr., et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77:772-810.

26. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70:776-803.

27. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Bmj. 2009;339:b2700.

28. Yousufuddin M, Abdalrhim AD, Wang Z, Murad MH. Cardiac troponin in patients hospitalized with acute decompensated heart failure: A systematic review and meta-analysis. J Hosp Med. 2016;11:446-454.

29. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603-605.

30. Andersson C, Gerds T, Fosbøl E, et al. Incidence of New-Onset and Worsening Heart Failure Before and After the COVID-19 Epidemic Lockdown in Denmark: A Nationwide Cohort Study. Circ Heart Fail. 2020;13:e007274.

31. Blecker S, Jones SA, Petrilli CM, et al. Hospitalizations for Chronic Disease and Acute Conditions in the Time of COVID-19. JAMA Intern Med. 2021;181:269-271.

32. Bodilsen J, Nielsen PB, Søgaard M, et al. Hospital admission and mortality rates for non-covid diseases in Denmark during covid-19 pandemic: nationwide population based cohort study. Bmj. 2021;373:n1135.

33. Bollmann A, Hohenstein S, König S, Meier-Hellmann A, Kuhlen R, Hindricks G. In-hospital mortality in heart failure in Germany during the Covid-19 pandemic. ESC Heart Fail. 2020;7:4416-4419.
34. Bromage DI, Cannatà A, Rind IA, et al. The impact of COVID-19 on heart failure hospitalization and management: report from a Heart Failure Unit in London during the peak of the pandemic. *Eur J Heart Fail.* 2020;22:978-984.

35. Cannatà A, Bromage DI, Rind IA, et al. Temporal trends in decompensated heart failure and outcomes during COVID-19: a multisite report from heart failure referral centres in London. *Eur J Heart Fail.* 2020;22:2219-2224.

36. Cox ZL, Lai P, Lindenfeld J. Decreases in acute heart failure hospitalizations during COVID-19. *Eur J Heart Fail.* 2020;22:1045-1046.

37. Doolub G, Wong C, Hewitson L, et al. Impact of COVID-19 on inpatient referral of acute heart failure: a single-centre experience from the south-west of the UK. *ESC Heart Fail.* 2021;8(2):1691-1695.

38. Frankfurter C, Buchan TA, Kobulnik J, et al. Reduced Rate of Hospital Presentations for Heart Failure During the COVID-19 Pandemic in Toronto, Canada. *Can J Cardiol.* 2020;36:1680-1684.

39. Jayagopal PB, Abdullakutty J, Sridhar L, et al. Acute decompensated heart failure (ADHF) during COVID-19 pandemic-insights from South India. *Indian Heart J.* 2021;73:464-469.

40. Jiménez-Blanco Bravo M, Cordero Pereda D, Sánchez Vega D, et al. Heart Failure in the Time of COVID-19. *Cardiology.* 2020;145:481-484.

41. König S, Hohenstein S, Meier-Hellmann A, Kuhlen R, Hindricks G, Bollmann A. In-hospital care in acute heart failure during the COVID-19 pandemic: insights from the German-wide Helios hospital network. *Eur J Heart Fail.* 2020;22:2190-2201.

42. Severino P, D'Amato A, Saglietto A, et al. Reduction in heart failure hospitalization rate during coronavirus disease 19 pandemic outbreak. *ESC Heart Fail.* 2020;7:4182-4188.

43. Shoaib A, Van Spall HGC, Wu J, et al. Substantial decline in hospital admissions for heart failure accompanied by increased community mortality during COVID-19 pandemic. *Eur Heart J Qual Care Clin Outcomes.* 2021;7:378-387.

44. Sokolski M, Gajewski P, Zymliński R, et al. Impact of Coronavirus Disease 2019 (COVID-19) Outbreak on Acute Admissions at the Emergency and Cardiology Departments Across Europe. *Am J Med.* 2021;134:482-489.

45. Ta Anyu A, Badawy L, Cannata A, et al. Long-term outcomes after heart failure hospitalization during the COVID-19 pandemic: a multisite report from heart failure referral centers in London. *ESC Heart Fail.* 2021;8(6):4701-4704.

46. Toner L, Koshy AN, Ko J, Driscoll A, Farouque O. Clinical Characteristics and Trends in Heart Failure Hospitalizations: An Australian Experience During the COVID-19 Lockdown. *JACC Heart Fail.* 2020;8:872-875.

47. Editorial: The miners. A special case? *Lancet.* 1974;1:81.

48. Shoaib A, Van Spall HGC, Wu J, et al. Substantial decline in hospital admissions for heart failure accompanied by increased community mortality during COVID-19 pandemic. *Eur Heart J Qual Care Clin Outcomes.* 2021;7:378-387.

49. Hammad TA, Parikh M, Tashtish N, et al. Impact of COVID-19 pandemic on ST-elevation myocardial infarction in a non-COVID-19 epicenter. *Catheter Cardiovasc Interv.* 2020;97(2):208-214.

50. Connolly NP, Simpkin A, Mylotte D, et al. Impact on percutaneous coronary intervention for acute coronary syndromes during the COVID-19 outbreak in a non-overwhelmed European healthcare system: COVID-19 ACS-PCI experience in Ireland. *BMJ Open.* 2021;11:e045590.

51. Solomon MD, Nguyen-Huyhn M, Leong TK, et al. Changes in Patterns of Hospital Visits for Acute Myocardial Infarction or Ischemic Stroke During COVID-19 Surges. *Jama.* 2021;326:82-84.
52. Wu J, Mamas MA, de Belder MA, Deanfield JE, Gale CP. Second Decline in Admissions With Heart Failure and Myocardial Infarction During the COVID-19 Pandemic. *J Am Coll Cardiol.* 2021;77:1141-1143.

53. Sharma A, Zhao X, Hammill BG, et al. Trends in Noncardiovascular Comorbidities Among Patients Hospitalized for Heart Failure: Insights From the Get With The Guidelines-Heart Failure Registry. *Circ Heart Fail.* 2018;11:e004646.

54. Stewart KA, Blue L, Kranker K, et al. Hospital Use for Myocardial Infarction and Stroke Among Medicare Beneficiaries From March to December 2020. *JAMA Cardiol.* 2021;6(11):1340-1342.

55. Kwok CS, Gale CP, Curzen N, et al. Impact of the COVID-19 Pandemic on Percutaneous Coronary Intervention in England: Insights From the British Cardiovascular Intervention Society PCI Database Cohort. *Circ Cardiovasc Interv.* 2020;13:e009654.

56. Primessnig U, Pieske BM, Sherif M. Increased mortality and worse cardiac outcome of acute myocardial infarction during the early COVID-19 pandemic. *ESC Heart Fail.* 2020;8:333-343.

57. De Luca G, Algowhary M, Uguz B, et al. COVID-19 pandemic, mechanical reperfusion and 30-day mortality in ST elevation myocardial infarction. *Heart.* 2022;108(6):458-466.

58. Gale R, Eberlein S, Fuller G, Khalil C, Almario CV, Spiegel BMR. Public Perspectives on Decisions About Emergency Care Seeking for Care Unrelated to COVID-19 During the COVID-19 Pandemic. *JAMA Netw Open.* 2021;4:e2120940.

59. Afonso Nogueira M, Ferreira F, Raposo AF, et al. Impact of telemedicine on the management of heart failure patients during coronavirus disease 2019 pandemic. *ESC Heart Fail.* 2021.

60. Schwamm LH, Chumber N, Brown E, et al. Recommendations for the Implementation of Telehealth in Cardiovascular and Stroke Care: A Policy Statement From the American Heart Association. *Circulation.* 2017;135:e24-e44.

61. Olsen SJ, Winn AK, Budd AP, et al. Changes in Influenza and Other Respiratory Virus Activity During the COVID-19 Pandemic - United States, 2020-2021. *MMWR Morb Mortal Wkly Rep.* 2021;70:1013-1019.

62. Chan PS, Girotra S, Tang Y, Al-Araji R, Nallamothu BK, McNally B. Outcomes for Out-of-Hospital Cardiac Arrest in the United States During the Coronavirus Disease 2019 Pandemic. *JAMA Cardiol.* 2021;6:296-303.

63. Lai S. Cancer related fatigue and cancer cachexia are the consequence of endocrine failure caused by persistent stress. *Med Hypotheses.* 2019;123:60-62.

64. Wadhera RK, Joynt Maddox KE, Wasfy JH, Haneuse S, Shen C, Yeh RW. Association of the Hospital Readmissions Reduction Program With Mortality Among Medicare Beneficiaries Hospitalized for Heart Failure, Acute Myocardial Infarction, and Pneumonia. *Jama.* 2018;320:2542-2552.
Table 1. Baseline characteristics of hospitalized patient with acute decompensated heart failure by time periods.

| Demographics | Mar – Oct 2020, n = 2341 | Mar – Oct 2019, n = 3094 | Oct 2018 – Feb 2020, n = 6648 | Pa | Pb |
|--------------|--------------------------|--------------------------|-------------------------------|----|----|
| 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) | .1 | .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/m², mean (SD) | 31.7 (9.3) | 31.4 (9.5) | 31.5 (9.5) | .65 | .90 |
| Heart failure types | | | | | |
| HFrEF, LVEF ≤ 40%, n (%) | 729 (32) | 959 (32) | 2088 (33) | .67 | .84 |
| HFmrEF, LVEF 41 – 49%, n (%) | 277 (12) | 342 (12) | 762 (12) | | |
| HFP 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; HFmrEF, heart failure with mid-range ejection fraction; HFP EF, heart failure with preserved ejection fraction; HFrEF, 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 \textsuperscript{a} Comparison, COVID-19 pandemic period (Mar-Oct 2020) vs 2019 pre-COVID matched historic control period
P \textsuperscript{b} Comparison, COVID-19 pandemic period (Mar-Oct 2020) vs pre-COVID-19 baseline period
Kaplan-Meier estimates for readmission and mortality

COVID-19 pandemic, 2020
COVID-19 pandemic
Pre-COVID-19 baseline, Oct 2018-Feb 2020
Pre-COVID-19 matched historic controls, 2019

Log-Rank P<.001
aHR 0.77 (95% CI 0.66-0.89)

Probability of 30-day all-cause rehospitalisations, %
0.0 0.1 0.2
0 5 10 15 20 25 30

Days after the date of discharge

2341 2297 2247 2206 2168 2139 2110
6648 6478 6294 6137 6044 5869 5794

Log-Rank P<.05
aHR 1.22 (95% CI 1.02-1.46)

Probability of 30-day all-cause death, %
0.0 0.1 0.2
0 5 10 15 20 25 30

Days after the date of discharge

2341 2276 2218 2181 2138 2113 2081
6648 6529 6388 6263 6168 6095 6013

Adjusted Cox regression analysis for readmission and mortality

|               | COVID-19 Events (%) | Pre-COVID-19 Events (%) | HR    | 95% CI    | P   |
|---------------|---------------------|-------------------------|-------|-----------|-----|
|               | (n=)                | (n=)                    |       |           |     |
| 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   | 0.65-0.88 | <.001 |
|                 | Model 2:            |                         |     0.76   | 0.66-0.88 | <.001 |
|                 | Model 3:            |                         |     0.77   | 0.66-0.89 | <.001 |
| All-cause deaths | 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 | 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  |
### In-hospital mortality, COVID-19 vs pre-COVID-19

#### Study or subgroup

| 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%  | 0.69 (0.50, 0.94) |
| 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, 4.22) |
|                   | Frankfurt 2020 | 16   | 107    | 11     | 196    | 5.8%  | 2.80 (1.26, 6.28) |
|                   | Jayagoal 2021 | 54   | 526    | 86     | 1,056  | 16.2% | 1.29 (0.90, 1.85) |
|                   | Kong 2020    | 296   | 3,501  | 288    | 4,799  | 24.4% | 1.24 (1.04, 1.47) |
|                   | Shoab 2021   | 1,000 | 9,791  | 2,752  | 27,183 | 27.6% | 1.01 (0.94, 1.09) |

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

#### Study or subgroup

| 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     | 2,341 | 645    | 6,648 | 36.3%  | 1.18 (1.02, 1.38) |
| Previous Studies  | Dussoit 2021 | 25   | 119    | 18     | 164    | 3.7%  | 2.16 (1.12, 4.17) |
|                   | Shoab-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

| 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     | 2,341 | 872    | 6,648 | 50.4%  | 0.76 (0.66, 0.87) |
| Previous Studies  | Kong 2020    | 280   | 3,501  | 336    | 4,799  | 49.6% | 1.14 (0.98, 1.33) |

Favors COVID Favors Pre-COVID