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Reduced Hospitalizations and Mortality with COVID-19 Vaccination Amongst Patients with Heart Failure

--Manuscript Draft--

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Abstract:	Background: Patients with Heart Failure (HF) are at high risk for adverse outcomes with COVID-19. Reports of COVID-19 vaccine-related cardiac complications may contribute to vaccine hesitancy in patients with heart failure (HF). Methods: To analyze the impact of COVID-19 vaccine status on clinical outcomes in patients with HF, we conducted a retrospective cohort study on the association of COVID-19 vaccination status with hospitalizations, ICU admission, and mortality after adjustment for covariates. Inverse probability treatment weighted (IPTW) models were used to adjust for potential confounding. Results: Among 7094 patients with HF, 645 (9.1%) were partially vaccinated, 2,200 (31.0%) fully vaccinated, 1,053 vaccine-boosted (14.8%), and 3,196 remained unvaccinated (45.1%) by January 2022. The mean age was 73.3 ± 14.5 years, with 48% female. Lower mortality was observed among patients who were vaccine-boosted followed by those who were fully vaccinated experienced lower mortality (HRs 0.33 (CI 0.23, 0.48) and 0.36 (CI 0.30, 0.43), respectively, compared to unvaccinated individuals, $p<0.001$) over the mean follow up time of 276.5 ± 104.9 days, while no difference was observed between those who were unvaccinated or only partially vaccinated. Conclusion/Relevance: COVID-19 vaccination was associated with significant reduction in all-cause hospitalization rates and mortality, lending further evidence to support the importance of its implementation in the high-risk population of patients living with HF.
Response to Reviewers:	

Cover Letter

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May 13, 2022

Dear Dr. Pina,

Please find our attached revisions and comments for our Brief Report submission entitled: "Impact of COVID-19 Vaccination in Heart Failure Patients**"** for consideration of publication into the prestigious *Journal of Cardiac Failure (JCF).*

Thank you for consideration of our manuscript for publication and your review. We have addressed the reviewers' concerns and comments to the best of our ability, and hope that you will find them satisfactory. We believe our work has been strengthened by the excellent suggestions for improvement, and hope it will be found to be the case as well.

In light of the need for timely dissemination of these data as the COVID pandemic is curtailed, we kindly request an expedited re-consideration of our work.

We are indebted to you for your review and continued consideration.

Sincerely,

Anuradha Lala

JCF Reviewer Comments

Reviewer 1: **The authors of Reduced Hospitalizations and Mortality with COVID-19 Vaccination Amongst Patients with Heart Failure" (CARDFAIL-D-22-00243) provide the results of an analysis utilizing a single large healthcare system in New York City evaluating the relationship of vaccination status of patients with the diagnosis of heart failure and clinical outcomes of mortality, hospitalization and ICU admission. The investigators found that those patient fully vaccinated +/- booster had significantly better outcomes than unvaccinated and partially vaccinated patients. This is an important message, that although has been publicized for the general public, has not been disseminated for heart failure patients.**

Thank you for the thoughtful feedback and for taking the time to consider our manuscript for publication.

Summary Statement:
Major Concerns: Given the multiple avenues for obtaining a COVID vaccine, the investigators should include what they used to determine vaccine status- order for vaccine, specific visit for vaccination or clinical documentation of vaccination. Given that they were utilizing a single healthcare systems data, how did they identify vaccinations performed outside the health system?

We thank the reviewers for their thorough review of our work and for the opportunity to improve our manuscript. COVID vaccination status was derived by extracting structured documentation of immunization administrations. There are two workflows that lead to the specific structured documentation of COVID vaccination as examined in this study: 1) when the order is placed within Epic and the vaccine is administered within our large multi-site healthcare system across the New York City metro area, 2) when a patient reports to a clinician that they received the COVID vaccine. The health system's electronic health records prominently display an alert for the clinician to enter the patient's vaccination record information, which is typically obtained by asking the patient to provide their vaccination card or a similar official record of vaccination. The clinician then documents a historical administration of the COVID vaccine within Epic (the Electronic Health record) We have added this information to the manuscript.

We added the following under the methods section: "Vaccination status was obtained via two workflows: automatic EHR entry upon vaccine order or administration within the MSHS, or based on required clinician or staff documentation of COVID-vaccination status based on patient report and demonstration of vaccine card."

It would be helpful to know what treatments for COVID19 the patients received. Treatment options and protocols were changing during the study period and would likely benefit the vaccinated (+/- booster) cohort.

Unfortunately, due to data limitations and inability to abstract data given the large dataset,

determining and capturing the wide variety of drugs and treatment options used across our large and diverse health system, we were unable to incorporate the specific treatments of hospitalized patients into our analyses. We have added this as a limitation to our manuscript. We do note that our study period ended prior to the initiation of common outpatient therapies for COVID such as nirmatrelvir/ritonavir (Paxlovid).

We included the following under the discussion section: "Differing treatment strategies for heart failure or COVID-19 were not accounted for."

Minor Concerns:

The justification of the current analysis that patients with heart disease have vaccine hesitancy due to reports of myocarditis is not justified by the reference used, which highlights 2 cases of myocarditis in young patients. Although there is a significant amount of misinformation about the risk of myocarditis and there is well-described vaccine hesitancy, patients with chronic diseases have in general obtain vaccines more than the general population. It is unclear if the concern of myocarditis resonates more with patients who have underlying cardiovascular disease.

We thank the reviewers for the opportunity to revise manuscript and to provide a more substantiated reference as well as to soften the language here. We have since changed the reference to the CDC website which shows a heat map of vaccine hesitancy. We have also softened the language to be less declarative:

Abstract: Reports of COVID-19 vaccine-related cardiac complications may contribute to vaccine hesitancy in patients with heart failure (HF).

Introduction: While vaccination against COVID-19 has been proven highly effective for preventing adverse outcomes in the general population, concern over potential cardiovascular sequelae may contribute to vaccine hesitancy, particularly amongst patients with pre-existing cardiac disease

Reviewer 2:

1) **Unmeasured confounding is a major concern with this type of report. Reasons for hospitalization, ICU presentation, or death are not provided. If lower event rates observed in vaccinated individuals were driven by lower COVID-19 related events, that would be supportive and helpful to provide.**

We unequivocally agree that unmeasured confounding is a potential issue in all studies presenting data from non-randomized controlled trials due to the presence of possible unmeasured variables on the causal pathway.

In the present work, we undertook extensive efforts to attempt to mitigate this issue by conducting analyses using techniques drawn from body of modern statistical literature for causal inference on observational data–namely inverse probability of treatment weighting (IPTW) with propensity scores obtained from gradient-boosting machines using longitudinal data from the electronic health records. We used a relevant set of clinical, sociodemographic, and comorbidity variables to construct this IPTW model.

We also conducted a traditional statistical analysis (sensitivity analysis) without modeling for nonrandom treatment allocation, which yielded similar results. We intentionally presented the results from the IPTW model which were more conservative.

Many of the variables we used to model an individual's decision to get or receive COVID-19 vaccination may depend on traditional unmeasured confounders such as socioeconomic status or health literacy (insurance, race, chronic comorbid conditions which are overrepresented in underserved populations, etc.). Further information on the methodology used here could not be presented in the main manuscript due to space constraints but is provided in the supplementary material.

To ascertain whether the events of hospitalization, ED, ICU admission or mortality were COVID-19 related, we examined SARS-CoV-2 positivity at time of each encounter (hospitalization, ED, ICU, death). We now include results for SARS-CoV-2 test positivity during these adverse events as an interaction term with vaccination status in our regression models for hospitalization, ICU admission, and mortality. 1,767 patient encounters with at least one positive tests for SARS-CoV-2 were discovered. Respective estimates for the regression models including this interaction term are as follows:

Hospitalization (IRR):

- Fully vaccinated or boosted, 0.68 (0.66, 0.72) ($p<2x10^{-16}$)
- SARS-CoV-2 test positive, 1.67 (1.47, 1.89) ($p<2x10^{-16}$)
- Vaccine status x test positivity interaction term: 0.83 (0.78, 0.88) (p=0.02)

ICU admission (IRR)

- Fully vaccinated or boosted, 0.65 (0.61, 0.70) ($p<2x10^{-16}$)
- SARS-CoV-2 test positive, 2.01 (1.65, 2.44) ($p=3.67*10^{-12}$)
- Vaccine status x test positivity interaction term: 0.57 (0.372, 0.863) (p=0.009)

Mortality (HR):

- Fully vaccinated or boosted, 0.39 (0.33, 0.46) ($p<2x10^{-16}$)
- SARS-CoV-2 test positive, 3.39 (2.54, 4.50) ($p<2x10^{-16}$)
- Vaccine status x test positivity interaction term: 0.35 (0.12, 0.97) (p=0.045)

The interpretation of these regression models with interaction terms for SARS-CoV-2 PCR positivity and vaccination status is that vaccinated individuals, when SARS-CoV-2 positive, were significantly less likely to be hospitalized, be admitted to the ICU, or to die compared to

unvaccinated patients. These events were at least in part due to COVID-19 as demonstrated by the higher associated risk of SARS-CoV-2 positivity and hospitalizations, ICU admissions and mortality.

We have added these results to the manuscript in the methods, results, and discussion sections.

2) **Similarly, new positivity of SARS-COV-2 in this cohort would be helpful to again support prevention of infection in this high-risk cohort.**

We thank the reviewer for this suggestion to examine the possibility of new SARS-CoV-2 positivity after vaccination. However, due to the nature of our dataset being hospital-based, we could not reliably capture test positivity for COVID-19 outside the hospital : i.e. not accounting for the many tests conducted in the outpatient setting including non-PCR tests such as rapid antigen testing. Nonetheless, by addressing the first suggestion made by the reviewer, we were able to decipher that the protective association of vaccination with fewer adverse events were at least in part due to a reduction in COVID-19 related events as shown above. ,

This is shown in the limitations section as "Data was restricted to one albeit large hospital system, and thus seropositivity for SARS-CoV-2, hospitalization or death in other hospital systems would not have been recorded."

3) **The investigators uniquely define a vaccinated period and unvaccinated period for each individual patient. It would add robustness, to show that the instantaneous hazard of events was lower during the vaccinated periods. In this case, each patient serves as their own control, thus limiting confounding**

We thank the reviewer for this experimental design suggestion. We believe this is a close analogy of the analytic strategy we employed in the manuscript, intentionally examining individuals in their corresponding vaccinated and unvaccinated (or unvaccinated, partially vaccinated, fully vaccinated, and vaccine-boosted) time periods. Our presented hazard ratios thus do demonstrate the instantaneous hazards of individuals in the different time periods.

In our regression models, we allow for the non-independence of repeated measures to be incorporated into statistical testing by using robust standard errors incorporating the correlation between each patient's potential multiple measures from the different time periods. We thank the reviewer for pointing out our oversight and have added this to the methods section of the manuscript.

Below is our explanation of this strategy in the methods section as "Since vaccination status of patients changed over the study period, these inverse probabilities were used as weights in a Cox proportional hazards model with vaccination status as a time-dependent covariate to analyze the outcome of mortality while minimizing potential immortal time bias. Each patient's study time was divided into periods of unvaccinated time, partially vaccinated time (time period between dose 1 and dose 2 of mRNA-based vaccines or end of study period), fully vaccinated

time (time period following the second mRNA vaccination until receiving a booster vaccine or end of study period, and vaccine-boosted (time period between receiving the third vaccine until end of the study)."

Our similar strategy for the IPTW model construction is detailed in the supplementary material.

We intentionally did not only include individuals who had both unvaccinated and vaccinated time periods to avoid immortal time bias. Patients who survived to become vaccinated by definition did not die during their period of unvaccinated time. In fact, since they could only possibly die (or have other events) during their vaccinated period (simply because of such a study specification), the outcome in this would actually show a paradoxical result where events could only possibly happen in the vaccinated period. Thus, in these patients, vaccination would by default only be harmful. Similarly, it would not be valid to measure hospitalizations or ICU admissions in this subset of patients, as the immortal period would bias the counts of hospitalizations and ICU admissions by serving as an unintended stratifier since these metrics are correlated. Our overall analytic strategy was thus designed and carried out to account for this immortal time bias by inclusion of vaccination status as a time-dependent covariate.

4) **Please remove all causal language (such as "confers") and instead use association language given the study design. This is especially important for the Abstract conclusion**

We appreciate this feedback and have in response removed all causal language and replaced it with association language. In the abstract conclusion, we changed "confers" to "is associated with."

5) **In the Abstract and Results, please add confidence limits to HR and IRR reporting**

We thank the reviewers for highlighting this point. We have added confidence intervals to the HR and IRR reporting throughout the paper. Under abstract results, we included "lower mortality (HRs 0.33 (CI 0.23, 0.48) and 0.36 (CI 0.30, 0.43)." Under the results paragraph 4, we included "fully vaccinated period (HR 0.36 (0.30, 0.43) and 0.33 (0.23, 0.48) respectively)." Under the results paragraph 4, we have also included "unvaccinated (HR=0.87 (0.68, 1.12), p=0.28)." Under paragraph 4, we have also included "(IRR 0.68 (0.65, 0.71), p<0.001) or admitted to the ICU (IRR 0.63 (0.58, 0.68), p<0.001)."

6) **The tables are broken across multiple pages in the PDF thus making it very difficult to read**

We appreciate the feedback and as a result have reformatted our tables to fit on one page. This may possibly have resulted from issues encountered during conversion to PDF during submission and apologize.

7) **Common medical therapies for HF (including ACEI/ARB/ARNI, BB, MRA, SGLT2i) would be helpful to account for in multivariable modeling**

We thank the reviewer for this suggestion. Unfortunately, it was not feasible to incorporate common medical therapies for heart failure given the multiple time points of data capture.

Title: Association of Reduced Hospitalizations and Mortality Among COVID-19 Vaccinated Patients with Heart Failure

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Abstract

Background: Patients with Heart Failure (HF) are at high risk for adverse outcomes with COVID-19. Reports of COVID-19 vaccine-related cardiac complications may contribute to vaccine hesitancy in patients with heart failure (HF).

Methods: To analyze the impact of COVID-19 vaccine status on clinical outcomes in patients with HF, we conducted a retrospective cohort study on the association of COVID-19 vaccination status with hospitalizations, ICU admission, and mortality after adjustment for covariates. Inverse probability treatment weighted (IPTW) models were used to adjust for potential confounding.

Results: Among 7094 patients with HF, 645 (9.1%) were partially vaccinated, 2,200 (31.0%) fully vaccinated, 1,053 vaccine-boosted (14.8%), and 3,196 remained unvaccinated (45.1%) by January 2022. The mean age was 73.3 ± 14.5 years, with 48% female. Lower mortality was observed among patients who were vaccine-boosted followed by those who were fully vaccinated experienced lower mortality (HRs 0.33 (CI 0.23, 0.48) and 0.36 (CI 0.30, 0.43), respectively, compared to unvaccinated individuals, $p<0.001$) over the mean follow up time of 276.5 ± 104.9 days, while no difference was observed between those who were unvaccinated or only partially vaccinated.

Conclusion/Relevance: COVID-19 vaccination was associated with significant reduction in all-cause hospitalization rates and mortality, lending further evidence to support the importance of its implementation in the high-risk population of patients living

with HF.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic constitutes a major public health crisis, especially with the emergence and spread of new variants of disease. Observational data highlight increased risk of severe complications, including death among patients with heart failure (HF) hospitalized with COVID-19.[1-4] While vaccination against COVID-19 has been proven highly effective for preventing adverse outcomes in the general population, concern over potential cardiovascular sequelae may contribute to vaccine hesitancy, particularly amongst patients with pre-existing cardiac disease.[5-9] We sought to evaluate the impact of COVID-19 vaccination among patients with HF on all-cause hospitalization and mortality across a large New York City health system.

Methods

All patients with a HF diagnosis, identified via electronic health record (EHR) phenotyping and followed within a large NYC health system with visits from January 1st, 2021 to January 24th, 2022 were included. Using ICD-10 codes (hospitalization billing or encounter diagnosis of HF) in the preceding two years (January 2019- December 2020), HF patients were identified with elevated natriuretic peptide levels (NT-proBNP ≥ 500 pg/mL or BNP ≥ 150 pg/mL).[10] Patients with a history of mechanical circulatory support or orthotopic heart and other solid organ transplant were excluded (Supplementary Material).

Demographics (age, sex, self-declared race/ethnicity, insurance status), comorbidities, as well as vaccination status (none, partially vaccinated, fully vaccinated, and vaccine-boosted), and clinical outcomes (hospitalizations, intensive care unit (ICU) admissions, and mortality) were abstracted from EHR. Comorbidities at study entry were extracted using ICD-10 codes and included pulmonary disease (asthma, chronic obstructive pulmonary disease, obstructive sleep apnea), other cardiovascular disease (coronary artery disease, history of myocardial infarction, atrial fibrillation, and peripheral vascular disease), autoinflammatory diseases (ulcerative colitis, Crohn's disease, rheumatoid arthritis), history of liver disease including chronic viral hepatitis or nonalcoholic steatohepatitis, history of cerebrovascular accident, obesity, hypertension, type II diabetes mellitus, and chronic kidney disease. Vaccination status was obtained via two workflows: automatic EHR entry upon vaccine order or administration within the MSHS, or based on required clinician or staff documentation of COVID-vaccination status based on patient report and demonstration of vaccine card.

To minimize potential systematic differences between patients who elected to or were recommended to receive vaccination and those who were not, inverse probability treatment weighted (IPTW) models were used. Since vaccination status of patients changed over the study period, these inverse probabilities were used as weights in a Cox proportional hazards model with vaccination status as a time-dependent covariate to analyze the outcome of mortality while minimizing potential immortal time bias. Each patient's study time was divided into periods of unvaccinated time, partially vaccinated time (time period between dose 1 and dose 2 of mRNA-based vaccines or end of study period), fully vaccinated time (time period following the second mRNA vaccination until

receiving a booster vaccine or end of study period, and vaccine-boosted (time period between receiving the third vaccine until end of the study). Patients who received a viral vector vaccine were considered fully vaccinated after the first dose, and vaccine-boosted if they subsequently received a second dose or an mRNA booster.

To analyze hospitalizations and ICU admissions, negative binomial regression models were constructed with counts of hospitalizations and ICU admissions as the dependent variable. To adjust for differential follow-up between patients who were ultimately vaccinated and patients who were not, an offset term was included in the regression model consisting of the log of the observation period for each patient. Observation period was constructed as the interval from the initiation of the study period to the last contact with the health system. Further details are provided within the Supplemental Material. The Mount Sinai Institutional Review Board approved this research.

Statistical analyses were performed using R version 4.1 (R Foundation). Negative binomial models were fit using the glm.nb function from the MASS R package, and Cox proportional hazards models were fit using the Survival R Package.[11-12] Regression coefficients were exponentiated to obtain incidence rate ratios (IRRs, negative binomial models) and Hazard Ratios (HRs, Cox models). Robust standard errors modeling for clustering by patient were used in all regression models. To ascertain whether the events of hospitalization, ICU admission or mortality were COVID-19 related, we examined SARS-CoV-2 positivity at time of each adverse event encounter as an interaction term in regression models.

Results

Among 7,094 patients with a history of HF within the health system, 645 patients (9.1%) were partially vaccinated, 2,200 (31.0%) were fully vaccinated, and 1,053 (14.8%) were vaccine-boosted (Table 1), leaving 3,196 patients (45.1%) were unvaccinated. Patients who received their first vaccination before the beginning of the study period on January 1st, 2021 (n=78) were excluded from analysis.

Overall, the mean age was 73.3 ± 14.5 years, 48% were women, and 63.3% of patients had Medicare insurance. Other cardiovascular diseases (as previously defined) (77.9%), hypertension (58.3%), and type II diabetes (32.0%) were the most frequent comorbidities.

Compared to the unvaccinated and partially vaccinated cohorts, the vaccine-boosted and fully vaccinated cohorts were slightly older, more likely to be of White race, with Medicare insurance, had higher rates of other cardiovascular disease ($p<0.001$), obesity ($p=0.008$), hypertension, pulmonary disease, and diabetes, and had more former smokers ($p<0.001$).

Overall, 904 of 7,094 total patients died over the mean follow up time of 276.5 ± 104.9 days (12.7%). Of these, 73.4% were unvaccinated or only partially vaccinated. Patients in the vaccine-boosted period were observed to experience the lowest mortality followed by patients in fully vaccinated period (HR 0.36 (0.30, 0.43) and 0.33 (0.23, 0.48) respectively) compared to unvaccinated individuals, all $p<0.001$) (Table 2). There was

no significant associated difference in mortality amongst patients who were partially vaccinated vs. unvaccinated (HR = 0.87 (0.68, 1.12), p=0.28) (Figure 1). Fully vaccinated or boosted patients were also significantly less likely to be admitted to the hospital (IRR 0.68 (0.65,0.71), p<0.001) or admitted to the ICU (IRR 0.63 (0.58, 0.68), p<0.001) than unvaccinated or partially vaccinated individuals (Table 2).

In secondary analyses examining whether adverse events were COVID-19 related, SARS-CoV-2 test positivity was indeed associated with higher rates of hospitalization (IRR 1.67 (1.47, 1.89), p<0.001), ICU admission (IRR 2.01 (1.65, 2.44), p<0.001), and mortality (HR 3.39 (2.54, 4.50, p<0.001). Among patients with SARS-CoV-2 positive tests, vaccination status was associated with lower rates of adverse events compared to unvaccinated status: hospitalization HR 0.83 (0.78, 0.89), p=0.02); ICU admission IRR 0.57 (0.37, 0.86), p=0.009, and mortality HR 0.35 (0.12, 0.97), p=0.045.

Discussion

Patients with HF constitute a high-risk population for adverse outcomes with COVID-19. To our knowledge, this is one of the largest studies to examine the association between COVID-19 vaccination status and clinical outcomes specifically amongst patients with HF, wherein vaccine hesitancy attributed to perceived cardiac side effects may be encountered. Full vaccination and vaccine-boosted status was associated with a significantly lower incidence of hospitalizations, ICU admissions, and mortality than partially vaccinated or unvaccinated status. These adverse events were at least in part COVID-19 related (as SARS-CoV-2 test positivity was associated with higher risk) and

among patients who tested positive for SARS-CoV-2, fully vaccinated and boosted vaccine status was associated with fewer hospitalizations and lower mortality.

There are several limitations to this study related to the rapid, ongoing spread of COVID-19 and its different variants during the assessed study period. Data was restricted to one, albeit large, hospital system, and thus seropositivity for SARS-CoV-2, hospitalization, or death in other hospital systems were not captured. Individuals were not distinguished based on type or stage of HF (HF with preserved ejection fraction vs. HF with reduced ejection fraction) nor cause of hospitalization. Although analyses were adjusted for relevant confounding factors, unmeasured variables such as social determinants of health, health literacy, and access to care may have contributed to between-group differences. Data as to specific treatment for HF or COVID-19 were not available.

Conclusion

In a large New York City cohort of patients with HF, vaccination against COVID-19 was associated with a lower likelihood of all-cause hospitalizations and mortality. Benefit of vaccination was observed in a graded fashion as vaccine-boosted status was associated with the lowest rates of hospitalization and mortality followed by fully, and partially vaccinated status, with the worst outcome association observed among unvaccinated individuals. These findings underscore the profound protective effect of vaccination against COVID-19 amongst patients with HF.

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Figure Captions

Figure 1: Cumulative incidence curve for mortality stratified by vaccination status

Table Captions

Table 1: Baseline Characteristics, overall and stratified by vaccination period

Table 2: Summary of regression models for hospitalization, ICU admission, and mortality

Conflict of Interest Disclosures:

Dr. Lala has received personal fees from Zoll, outside the submitted work. All other authors report no relationships relevant to the contents of this paper to disclose.

Funding/Support:

This study was internally funded.

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To the Mount Sinai Data Warehouse for data query. To all of the nurses, physicians, and providers who contributed to the care of these patients. To the patients and their family members who were affected by this pandemic.

Abstract

Background: Patients with Heart Failure (HF) are at high risk for adverse outcomes with COVID-19.~~-~~ Reports of COVID-19 vaccine-related cardiac complications may~~have~~ contribute~~d~~ to vaccine hesitancy in patients with heart failure (HF).

Methods: To analyze the impact of COVID-19 vaccine status on clinical outcomes in patients with HF, we conducted a retrospective cohort study on the association of COVID-19 vaccination status with hospitalizations, ICU admission, and mortality after adjustment for covariates. Inverse probability treatment weighted (IPTW) models were used to adjust for potential confounding~~. in outcomes by patient choice to receive vaccinations.~~

Results: Among 7094 patients with HF, 645 (9.1%) were partially vaccinated, 2,200 (31.0%) fully vaccinated, 1,053 vaccine-boosted (14.8%), and 3,196 remained unvaccinated (45.1%) by January 2022. The mean age was 73.3 ± 14.5 years, with 48% female. Lower mortality was observed among p~~P~~atients who were vaccine-boosted followed by those who were fully vaccinated experienced lower mortality (HRs 0.33 (CI 0.23, 0.48) and 0.36 (CI 0.30, 0.43), respectively, compared to unvaccinated individuals, p<0.001) over the mean follow up time of 276.5 ± 104.9 days, while no difference was observed between those who were unvaccinated or only partially vaccinated.

Conclusion/Relevance: COVID-19 v~~V~~accination ~~confers~~ was associated with significant reduction in all-cause hospitalization rates and mortality, lending further

evidence to support the importance of its implementation in the high-risk population of patients living with HF.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic constitutes a major public health crisis, especially with the emergence and spread of new variants of disease. Observational data highlight increased risk of severe complications, including death among patients with heart failure (HF) hospitalized with COVID-19.[1-4] While vaccination against COVID-19 has been proven highly effective for preventing adverse outcomes in the general population, concern over potential cardiovascular ~~myocarditis and other cardiovascular~~ sequelae ~~has led to~~ may contribute to vaccine hesitancy, particularly amongst patients with pre-existing cardiac disease.[5-~~9~~8] We sought to evaluate the impact of COVID-19 vaccination among patients with HF on all-cause hospitalization and mortality ~~in~~ across a large New York City health system.

Methods

All patients with a HF diagnosis, identified via electronic health record (EHR) phenotyping and followed within ~~the Mount Sinai Health System (MSHS)~~ a large NYC health system with visits from January 1st, 2021 to January 24th, 2022 were included. ~~HF patients were identified~~ Uusing ICD-10 codes (hospitalization billing or encounter diagnosis of HF) ~~n~~ in the preceding two years (January 2019- December 2020), HF patients were identified ~~and~~ with elevated natriuretic peptide levels (NT-proBNP ≥ 500 pg/mL or BNP ≥ 150 pg/mL).[10~~9~~6] ~~.~~ Patients with a history of mechanical circulatory

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support or orthotopic heart and other solid organ transplant were excluded (Supplementary Material).

Demographics (age, sex, self-declared race/ethnicity, insurance status), comorbidities, as well as vaccination status (none, partially vaccinated, fully vaccinated, and vaccine-boosted), and clinical outcomes (hospitalizations, intensive care unit (ICU) admissions, and mortality) were abstracted from ~~electronic health records~~EHR. Comorbidities at study entry were extracted using ICD-10 codes and included pulmonary disease (asthma, chronic obstructive pulmonary disease, obstructive sleep apnea), other cardiovascular disease (coronary artery disease, history of myocardial infarction, atrial fibrillation, and peripheral vascular disease), autoinflammatory diseases (ulcerative colitis, Crohn's disease, rheumatoid arthritis), history of liver disease including chronic viral hepatitis or nonalcoholic steatohepatitis, history of cerebrovascular accident, obesity, hypertension, type II diabetes mellitus, and chronic kidney disease. Vaccination status was obtained ~~from~~via ~~-~~two workflows:~~:~~ automatic EHR entry upon vaccine order or administration within the MSHS, or based on required clinician or staff documentation of COVID-vaccination status based on patient report and demonstration of vaccine card.~~First, automatically when the vaccine was ordered or administered within the context of the present study's health system. Second, when a clinician or other provider or staff documenteds COVID-vaccination status at the time of patient presentation in the electronic health records via a prominently displayed alert in the EHR sidebar.~~

To minimize potential systematic differences between patients who elected to or were recommended to receive vaccination and those who ~~did~~ were not, inverse probability

treatment weighted (IPTW) models were used. Since vaccination status of patients changed over the study period, these inverse probabilities were used as weights in a Cox proportional hazards model with vaccination status as a time-dependent covariate to analyze the outcome of mortality while minimizing potential immortal time bias. Each patient's study time was divided into periods of unvaccinated time, partially vaccinated time (time period between dose 1 and dose 2 of mRNA-based vaccines or end of study period), fully vaccinated time (time period following the second mRNA vaccination until receiving a booster vaccine or end of study period, and vaccine-boosted (time period between receiving the third vaccine until end of the study). Patients who received a viral vector vaccine were considered fully vaccinated after the first dose, and vaccine-boosted if they subsequently received a second dose or an mRNA booster.

To analyze hospitalizations and ICU admissions, negative binomial regression models were constructed with counts of hospitalizations and ICU admissions as the dependent variable. To adjust for differential follow-up between patients who were ultimately vaccinated and patients who were not, an offset term was included in the regression model consisting of the log of the observation period for each patient. Observation period was constructed as the interval from the initiation of the study period to the last contact with the health system. Further details are provided within the Supplemental Material. The Mount Sinai Institutional Review Board approved this research.

~~We also examined the effect SARS-CoV-2 test positivity at the time of patient encounter in the health system to examine if there was a relationship between observed outcomes~~

~~and SARS-CoV-2 infection, as well as if vaccination moderated the risk of adverse outcomes given SARS-CoV-2 test positivity.~~

Statistical analyses were performed using R version 4.1 (R Foundation). Negative binomial models were fit using the glm.nb function from the MASS R package[7], and Cox proportional hazards models were fit using the Survival R Package.[11-120 118.] Regression coefficients were exponentiated to obtain incidence rate ratios (IRRs, negative binomial models) and Hazard Ratios (HRs, Cox models). Robust standard errors modeling for clustering by patient were used in all regression models. To ascertain whether the events of hospitalization, ICU admission or mortality were COVID-19 related, we examined SARS-CoV-2 positivity at time of each adverse event encounter as an interaction term in regression models.

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Results

Among 7,094 patients with a history of HF within the health system~~MSHS~~, 645 patients (9.1%) were partially vaccinated, 2,200 (31.0%) were fully vaccinated, and 1,053 (14.8%) were vaccine-boosted (Table 1), leaving~~,~~ 3,196 patients (45.1%) were unvaccinated. P~~78 p~~atients who received their first vaccination before the beginning of the study period on January 1st, 2021 (n=78) were ~~dropped~~ excluded from analysis.

Overall, the mean age was 73.3 ± 14.5 years, 48% were women, and 63.3% of patients had M~~m~~edicare insurance. Other cardiovascular diseases (as previously defined)

(77.9%), hypertension (58.3%), and type II diabetes (32.0%) were the most frequent comorbidities.

Compared to the unvaccinated and partially vaccinated cohorts, the vaccine-boosted and fully vaccinated cohorts were slightly older, more likely to be of White race, with Medicare insurance, had higher rates of other cardiovascular disease ($p<0.001$), obesity ($p=0.008$), hypertension, pulmonary disease, and diabetes, and had more former smokers ($p<0.001$).

Overall, 904 of 7,094 total patients died over the mean follow up time of 276.5 ± 104.9 days (12.7%). Of these, 73.4% were unvaccinated or only partially vaccinated. Patients in the vaccine-boosted period were observed to experience the lowest mortality followed by patients in fully vaccinated period- (HR 0.36 (0.30, 0.43) and 0.33 (0.23, 0.48) respectively) compared to unvaccinated individuals, all $p<0.001$) (Table 2). There was no significant associated difference in mortality amongst patients who were partially vaccinated vs. unvaccinated (HR = 0.87 (0.68, 1.12), $p=0.28$) (Figure 1). Fully vaccinated or boosted patients were also significantly less likely to be admitted to the hospital (IRR 0.68 (0.65,0.71), $p<0.001$) or admitted to the ICU (IRR 0.63 (0.58, 0.68), $p<0.001$) than unvaccinated or partially vaccinated individuals (Table 2).

In secondary analyses examining whether adverse events were ~~-~~COVID-19 related, SARS-CoV-2 test positivity~~ during the patient encounter, positivity~~ was indeed associated with higher rates of ~~, there was a higher associated risk of was associated with higher rates of~~ hospitalization (IRR 1.67 (1.47, 1.89), p<0.001), ICU admission (IRR 2.01 (1.65, 2.44), p<0.001), and mortality (HR 3.39 (2.54, 4.50, p<0.001). Among patients with SARS-CoV-2 positive tests, ~~among patients who tested positive compared to those who did not test positive.~~ v~~V~~accination status was associated with~~ted pPatients who tested positive for SARS-CoV-2 but were vaccinated had comparativelyhad~~ lower rates of adverse ~~the same three~~ events compared to ~~those~~ unvaccinated ~~patients who tested positive~~status ~~but were not vaccinated~~: h~~H~~ospitalization HR 0.83 (0.78, 0.89), p=0.02); ICU admission IRR 0.57 (0.37, 0.86), p=0.009, and mortality HR 0.35 (0.12, 0.97), p=0.045.

Discussion

Patients with HF constitute a high~~-~~-risk population for adverse outcomes with COVID-19. To our knowledge, this is one of the largest studies to examine the association between COVID-19 vaccination status and clinical outcomes specifically amongst patients with HF, wherein vaccine hesitancy attributed to perceived cardiac side effects may be encountered ~~high~~. Full~~y~~ vaccination~~ed~~ and vaccine-boosted status was associated with ~~patients had~~ a significantly lower incidence of hospitalizations, ICU admissions, and mortality than partially vaccinated or unvaccinated status~~individuals~~. These adverse events were at least in part ~~In both vaccinated and unvaccinated~~

~~individuals,~~COVID-19 related (as SARS-CoV-2 ~~-SARS-CoV-2~~ test positivity was associated with higher risk) ~~ates of hospitalization, ICU admission, and mortality~~and ~~,~~ ~~implying COVID-19 related increases in adverse events. that COVID-19 was a major component of the observed elevations in hospitalizations, ICU admissions, and mortality. HoweverNonetheless, ~~among patients who tested positive for SARS-CoV-2, ~~rates of these outcomes were lower among vaccinated individuals~~ fully vaccinated and boosted vaccine status was associated with ~~who tested positive for COVID-19 than unvaccinated individuals who tested positive for COVID-19.experienced~~ fewer hospitalizations and lower mortality.

There are several limitations to this study related to the rapid, ongoing spread of ~~covid~~COVID-19 and its different variants during the assessed study period.~~this analysis~~. Data was restricted to one, albeit large, hospital system, and thus seropositivity for SARS-Co-
V-2, hospitalization, or death in other ~~patients hospitalized in other~~ hospital systems ~~or died outside of New York State would not have been recorded~~were not captured. ~~I~~Also, ~~i~~ndividuals were not distinguished based on type or stage of HF (HF with preserved ejection fraction vs. HF with reduced ejection fraction) nor cause of hospitalization. ~~Different eras and variants of COVID-19 were not taken into account.~~ Although ~~we~~ analyses were adjusted for relevant confounding factors, unmeasured variables such as social determinants of health, health literacy, and access to care ~~among others~~ may have contributed to between-~~-~~group differences.~~- D~~Finally, due to smaller patient counts, fewer event outcomes, and shorter follow-up periods for vaccine-boosted patients, we~~

~~lacked statistical power to directly compare fully vaccinated and vaccine-boosted individuals~~ was lacking~~. Finally , due to difficulty modeling varied and heterogeneous therapeutic options, Wwe were not able to include the effect of D~~differing~~Data as to specific~~ent~~ treatment ~~strategies~~ for ~~heart failure~~HF or COVID-19 ~~in our analysis~~were not available. ~~accounted for and will also be an important area of future research. Finally, in our analyses of SARS-CoV-2 test positivity and its association with outcomes, we could only capture the results of tests that occurred within or were ordered by a clinician within our healthcare system and thus our infection rates are likely an underestimate of true infection rates.~~

Conclusion

In a large New York City~~YC~~ cohort of patients ~~living~~ with HF, vaccination against COVID-19 was associated with a lower likelihood of all-cause hospitalizations and mortality. Benefit of vaccination was observed in a graded fashion as vaccine-boosted status was associated with the~~patients experienced~~ lowest~~r~~ rates of hospitalization and mortality followed by fully, and partially vaccinated ~~individuals~~status, with the worst outcome association ~~s~~observed ~~-~~among unvaccinated individuals. These findings ~~, though observational,~~ underscore the profound protective effect of vaccination against COVID-19 amongst patients with HF.

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Figure Captions

Figure 1: Cumulative incidence curve for mortality stratified by vaccination status

Table Captions

Table 1: Baseline Characteristics, overall and stratified by vaccination period

Table 2: Summary of regression models for hospitalization, ICU admission, and mortality

Conflict of Interest Disclosures:

Dr. Lala has received personal fees from Zoll, outside the submitted work. All other authors report no relationships relevant to the contents of this paper to disclose.

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	Overall	Unvaccinated Period	Partially Vaccinated Period	Vaccinated Period	Vaccine-Boosted Period	P Value*
Patients in Vaccine Period, N	7094	7094	3898	3253	1053	
Total Patient-Days in Vaccine Period	1,977,412	1,062,752	185,506	651,706	77,448	
Days in Vaccination Period (mean (SD))	276.46 (104.89)	149.81 (115.44)	47.59 (62.61)	200.34 (77.01)	73.55 (69.64)	
Mortality (N (%))	904 (12.7)	598 (8.4)	75 (1.9)	197 (6.1)	36 (3.4)	<0.001
Age (mean (SD))	73.27 (14.48)	73.27 (14.48)	73.90 (13.84)	74.19 (13.58)	75.91 (12.23)	<0.001
Sex (Male %)	3719 (52.4)	3719 (52.4)	2021 (51.8)	1671 (51.4)	559 (53.1)	0.68
Race/Ethnicity (N (%))						<0.001
White	2360 (33.3)	2360 (33.3)	1308 (33.6)	1106 (34.0)	432 (41.0)	
Asian	353 (5.0)	353 (5.0)	208 (5.3)	179 (5.5)	53 (5.0)	
Black / African American	1826 (25.7)	1826 (25.7)	998 (25.6)	821 (25.2)	237 (22.5)	
Hispanic	1571 (22.1)	1571 (22.1)	962 (24.7)	816 (25.1)	237 (22.5)	
Other / Multiracial	741 (10.4)	741 (10.4)	345 (8.9)	272 (8.4)	79 (7.5)	
Unknown	243 (3.4)	243 (3.4)	77 (2.0)	59 (1.8)	15 (1.4)	
Insurance (N (%))						<0.001
Private	994 (14.0)	994 (14.0)	584 (15.0)	512 (15.7)	159 (15.1)	
Medicaid	704 (9.9)	704 (9.9)	328 (8.4)	241 (7.4)	49 (4.7)	
Medicare	4493 (63.3)	4493 (63.3)	2568 (65.9)	2165 (66.6)	758 (72.0)	
Other	903 (12.7)	903 (12.7)	418 (10.7)	335 (10.3)	87 (8.3)	
Smoking Status (N, (%))						<0.001
Non-smoker	4198 (59.2)	4198 (59.2)	2145 (55.0)	1791 (55.1)	557 (52.9)	
Former smoker	2380 (33.5)	2380 (33.5)	1513 (38.8)	1272 (39.1)	447 (42.5)	
Current smoker	516 (7.3)	516 (7.3)	240 (6.2)	190 (5.8)	49 (4.7)	
Past Medical History (N, (%))						
Pulmonary Disease (%)	1255 (17.7)	1255 (17.7)	787 (20.2)	657 (20.2)	244 (23.2)	<0.001
Immunological Disease (N (%))	169 (2.4)	169 (2.4)	123 (3.2)	102 (3.1)	38 (3.6)	0.018
Cerebrovascular Disease (N (%))	958 (13.5)	958 (13.5)	568 (14.6)	476 (14.6)	165 (15.7)	0.132
Cardiovascular Disease (N (%))	5529 (77.9)	5529 (77.9)	3227 (82.8)	2707 (83.2)	923 (87.7)	<0.001
Liver Disease (N (%))	206 (2.9)	206 (2.9)	125 (3.2)	103 (3.2)	47 (4.5)	0.06
Obesity (N (%))	738 (10.4)	738 (10.4)	477 (12.2)	387 (11.9)	132 (12.5)	0.008
Hypertension (N (%))	4139 (58.3)	4139 (58.3)	2529 (64.9)	2122 (65.2)	739 (70.2)	<0.001
Chronic Kidney Disease (N (%))	1789 (25.2)	1789 (25.2)	1108 (28.4)	947 (29.1)	344 (32.7)	<0.001
Diabetes (N (%))	2272 (32.0)	2272 (32.0)	1376 (35.3)	1149 (35.3)	399 (37.9)	<0.001

*P values from comparisons between patients between time periods, not including overall column

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2272 (32.0)	1376 (35.3)	1149 (35.3)

ding overall column

Vaccine-Boosted Period	P Value*
1053	
77,448	
73.55 (69.64)	
36 (3.4)	<0.001
75.91 (12.23)	<0.001
559 (53.1)	0.68
	<0.001
432 (41.0)	
53 (5.0)	
237 (22.5)	
237 (22.5)	
79 (7.5)	
15 (1.4)	
	<0.001
159 (15.1)	
49 (4.7)	
758 (72.0)	
87 (8.3)	
	<0.001
557 (52.9)	
447 (42.5)	
49 (4.7)	
244 (23.2)	<0.001
38 (3.6)	0.018
165 (15.7)	0.132
923 (87.7)	<0.001
47 (4.5)	0.06
132 (12.5)	0.008
739 (70.2)	<0.001
344 (32.7)	<0.001
399 (37.9)	<0.001

Table 2. Multivariable Regression Analyses for Vaccine Efficacy

	Statistic	Reference Level	Coefficient	Estimate (95% CI)	P Value
Model 1: Mortality*	*Hazard Ratio (HR)*	*Unvaccinated*	*Partially Vaccinated*	*0.87 (0.68, 1.12)*	*0.28*
			Fully Vaccinated	*0.36 (0.30, 0.43)*	*<0.001*
			Boosted	*0.33 (0.23, 0.48)*	*<0.001*
Model 2: Hospitalization Count†	*Incidence Rate Ratio (IRR)*	*Unvaccinated or Partially Vaccinated*	*Fully Vaccinated or Vaccine-Boosted*	*0.68 (0.65, 0.71)*	*<0.001*
Model 3: ICU Admission Count††	*Incidence Rate Ratio (IRR)*	*Unvaccinated or Partially Vaccinated*	*Fully Vaccinated or Vaccine-Boosted*	*0.63 (0.58, 0.68)*	*<0.001*

** IPTW model with time-dependent covariate for vaccination*

† Negative binomial regression model for count of hospitalizations

†† Negative binomial regression model for count of ICU admissions

Adjustment covariates: age, sex, race/ethnicity, insurance, smoking, pulmonary disease, immunological disease, liver disease, obesity, HTN, CKD, diabetes

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	Statistic
Model 1: Mortality*	*Hazard Ratio (HR)*
Model 2: Hospitalization Count†	*Incidence Rate Ratio (IRR)*
Model 3: ICU Admission Count††	*Incidence Rate Ratio (IRR)*

** IPTW model with time-dependent covariate for vaccination*

† Negative binomial regression model for count of hospitalizations

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Adjustment covariates: age, sex, race/ethnicity, insurance, smoking, pulmonary c

y	
Reference Level	**Coefficient**
Unvaccinated	*Partially Vaccinated* *Fully Vaccinated* *Boosted*
Unvaccinated or Partially Vaccinated	*Fully Vaccinated or Vaccine-Boosted*
Unvaccinated or Partially Vaccinated	*Fully Vaccinated or Vaccine-Boosted*

lisease, immunological disease, liver disease, obesity, HTN, CKD, diabetes

Estimate (95% CI)	P Value
0.87 (0.68, 1.12)	*0.28*
0.36 (0.30, 0.43)	*<0.001*
0.33 (0.23, 0.48)	*<0.001*
0.68 (0.65, 0.71)	*<0.001*
0.63 (0.58, 0.68)	*<0.001*