Title

Relationship of Prehospital Clinical Biomarkers and New York Heart Association Classification in Management of Heart Failure Patients Infected with COVID-19 and long COVID

Author

Bakir, Maral

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Relationship of Prehospital Clinical Biomarkers and New York Heart Association Classification in Management of Heart Failure Patients Infected with COVID-19 and Long COVID

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Nursing

by

Maral Bakir

2024

ABSTRACT OF THE DISSERTATION

Relationship between Clinical Biomarkers and New York Heart Association Classification in Management of Heart Failure Patients Infected with COVID-19

by

Maral Bakir

Doctor of Philosophy in Nursing

University of California, Los Angeles, 2024

Professor Holli A. DeVon, Co-Chair

Professor Mary Rezk-Hanna, Co-Chair

Abstract

Background: Clinical management of coronavirus disease 2019 (COVID-19) requires understanding of the virus. Heart failure (HF) patients infected with COVID-19 have a higher risk for worse outcomes compared to those with no HF diagnosis. There is a critical gap in the scientific knowledge on COVID-19 outcomes and clinical management among HF patients. The physiological effects of COVID-19 among HF patients are still largely unknown. There is also a gap in the identification and clinical management of long COVID among HF patients.

Aims. The following research questions were explored: What are the outcomes seen from COVID-19 among HF patients? Is there a difference in prehospital clinical biomarker, NYHA classification and clinical outcome (mortality, hospital length of stay (LOS), and readmission)

among HF patients with and without COVID-19? Is there a difference in prehospital clinical biomarkers, NYHA classification, and clinical outcome (mortality, hospital LOS, and readmission) among HF patients with and without long COVID-19? Can prehospital clinical biomarkers and NYHA classification predict the development of long COVID among HF patients? Aim 1 is a review of the literature on the effects of the COVID-19 virus among HF population. Aim 2 compared the prehospital clinical biomarker, NYHA classification, and clinical outcomes (mortality, hospital LOS, and readmission) among HF patients with and without COVID-19. Aim 3 compared the prehospital clinical biomarker, NYHA classification, and clinical outcome among HF patients with and without long COVID and explored any predictive variables.

Methods. A retrospective electronic health record (EHR) review was conducted to answer the research questions. Only HF patients were included in the study and prehospital clinical biomarker as well as NYHA classification were utilized to assess differences among those with and without COVID-19 and to make predictions on the development of long COVID. Data were analyzed using bivariate and multivariate analyses.

Results. Two hundred adult HF patients with hospitalization between January 2020 and December 2023 (n=100) and without COVID-19 (n=100) were included in the study. Prehospital BNP (p=0.006) and mortality (p=0.03) showed significantly higher rates in the HF group without COVID-19. Prehospital BNP was the only marker predictive of mortality (p=0.029). There were no statistically significant differences in NYHA class data. Among HF patients with and without long COVID, there was no statistically significant difference in clinical biomarkers, NYHA classification, and clinical outcome data. No variable was predictive of developing long COVID.

Conclusions. Prehospital biomarkers and NYHA data do little to explain the risk of patients infected with COVID-19. There was no association with long COVID.

The dissertation of Maral Bakir is approved.

Mary-Lynn Brecht

Robert James Lucero

Holli A. DeVon, Committee Co-Chair

Mary Rezk-Hanna, Committee Co-Chair

University of California, Los Angeles

2024

Dedication

To my parents, for always being my biggest supporters and for standing by me through this wonderful and challenging journey. Their unwavering love and support have been influential in finalizing this journey.

To my mentor Dr. DeVon and professors/committee for their support and professional guidance. Their expertise has been instrumental in shaping my knowledge and skills in research and my final dissertation.

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List of Acronyms

BNP: Brain Natriuretic Peptide

COVID-19: coronavirus disease 2019

CRP: C-Reactive Protein

EHR: Electronic Health Record

HF: Heart Failure

LOS: Length of Stay

NYHA: New York Heart Association

PT: Prothrombin Time

WBC: White Blood Cell Count

Acknowledgments

Data Extraction

Clinical and Translational Science Institute at UCLA for required data extraction.

Vita/Biographical Sketch

Master's of Science, School of Nursing (MSN), 2020
Acute Care Nurse Practitioner, University of California Los Angeles
Practicum: Neurology
Fellowship: UCLA Graduate Division Fellowship 2018-2020

Bachelor of Science, School of Nursing (BS), 2015
University of California Los Angeles
Specialty: Nursing
Awards: Undergraduate Research Scholar Award (UCLA)
Scholarships: Jean C Cook and Helene Fuld Scholarships
Honors: Phi Beta Kappa Honor Society, Cum Laude Honors Student, Dean's List

Experience

2023-	Acute Care Nurse Practitioner, UCLA Ronald Reagan Hospital, Inpatient and Outpatient Neurology-Epilepsy
2021-2023	Acute Care Nurse Practitioner, Henry Mayo Hospital, Inpatient Neurology
2018-2021	Research Assistant Volunteer, UCLA David Geffen School of Medicine, Advanced Heart Failure
2017-2021	Registered Nurse, Neurology/Neurosurgery, UCLA Ronald Reagan Hospital
2013-2017	Research Assistant, UCLA David Geffen School of Medicine, Advanced Heart Failure

Licenses

Registered Nurse, State of California
Acute Care Nurse Practitioner, State of California
Adult Gerontology Acute Care Nurse Practitioner, Board Certified

Other Experience and Professional Memberships

2018- 2020	UCLA Medical Center Clinical Practice Council Member
2018- 2020	UCLA Medical Center Neurosurgery Patient Family Advisory Council Member
2017-2019	Unit Based Practice Council Member, UCLA Medical Center
2016	American Heart Association Member
2016	International Society of Heart and Lung Transplant, Nursing Committee
2016	International Nurses Association
2015	Phi Beta Kappa Honor Society- <5% of UCLA 2015 graduating class elected
2014	Sigma Theta Tau International, Honor Society of Nursing
2013	Alpha Gamma Sigma Honor Society

Honors

2021-2024	Ph.D. UCLA Graduate Division Registration Fee Award
2019	Donald T. Leahy Charitable Lead Trust Scholarship, Graduate Studies
2019	Audrienne H. Moseley Scholarship, Graduate Studies
2019	UCLA Graduate Division Award
2019	Delores Jones Scholarship by Kaiser Permanente for ACNP degree

2019	Invited to serve as a Judge at ISHLT Scientific Annual Conference
2018	UCLA Graduate Division Fellowship
2018	Benson Family Fellowship Fund. Graduate Studies
2018	Audrienne H. Moseley Scholarship, Graduate Studies
2018	Selected to review research abstract submissions to scientific conference
2017	Research and Evidence Based Practice Conference Poster Award, UCLA
2017	Nursing, Health Sciences and Allied Health Excellence in Research Award, ISHLT
2015	Cum Laude Latin Honors
2015	Phi Beta Kappa Honor Society- <5% of UCLA 2015 graduating class elected
2015	Undergraduate Research Scholar Award, UCLA
2014	Jean C Cook Scholarship UCLA
2014	Mangasarian Scholarship, UCLA
2014	Helene Fuld Scholarship, UCLA School of Nursing
2014	Undergraduate Research Fellow Award, UCLA

Presentations

2018	International Society of Heart and Lung Transplantation Conference, Nice -Poster presentation
2017	Research and Evidence Based Practice Conference, UCLA -Poster presentation
2017	Department of Medicine Cardiovascular Symposium, UCLA -Poster presentation
2017	International Society of Heart and Lung Transplantation Conference, San Diego -Oral presentation- Award Winner
2016	American Heart Association Conference, Orlando -Poster presentation
2016	Department of Medicine Cardiovascular Symposium, UCLA -Poster presentation
2016	International Society of Heart and Lung Transplantation Conference, Washington DC -Poster presentation
2015	International Society of Heart and Lung Transplantation Conference, Nice -Oral presentation

Publications

- Bondar, G., Cadeiras, M., Wisniewski, N., Maque, J., Chittoor, J., Chang, E., ... & Deng, M. (2014). Comparison of whole blood and peripheral blood mononuclear cell gene expression for evaluation of the perioperative inflammatory response in patients with advanced heart failure. PloS one, 9(12), e115097
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Chapter One: Introduction

COVID-19 Outcomes on Heart Failure

Heart failure (HF) is a serious condition that affects about 64 million individuals worldwide and 6.2 million in the U.S.[1–3]. HF is also associated with high death rates with 415,000 deaths seen in the U.S. in 2020[,3]. In 2012, the medical expenses associated with HF were $30.7 billion in the U.S. alone[2,3]. With the introduction of a novel virus, coronavirus disease 2019 (COVID-19), the world has faced a pandemic that conferred greater risk to those with HF[5,6]. HF patients have double the rate of hospitalizations and deaths from COVID-19 when compared to individuals without HF and similar demographic characteristics such as age and ethnicity[6].

COVID-19 is a serious threat to health with 1 million deaths seen through January 2023 in the U.S. alone[4]. Among the patients hospitalized with COVID-19, 16% had a HF diagnosis, and 8% of the patients had a hospital length of stay (LOS) of three months[21]. Among hospitalized patients, 15%, about 19,594 individuals, died from COVID-19, and among 106,543 patients that were discharged from the hospital, 9% (9,504) had hospital readmissions[21]. Research shows that 1 in 4 HF patients infected with COVID-19 that require hospitalization die from COVID-19[17,21,22]. Although there is increased knowledge about the effects of COVID-19 among HF patients, there is still a gap in the specific outcomes seen among COVID-19 infected HF patients. There is also a lack of knowledge on the reasons behind worse outcomes among HF patients and more studies are needed for risk stratification among this population[5,7,17,21,22]

NYHA Classification

New York Heart Association (NYHA) classification is used among HF patients for

the classification of cardiovascular disease based on their clinical severity and prognosis[28]. The NYHA classification is now used universally among HF patients to assess functional status and to guide clinical management[5,6,29]. NYHA allows for the identification of illness progression and provides a simple way to assess the extent of HF exacerbation[16]. The NYHA classification has high concordance rates among different providers with 75% to 90% agreement between randomly selected graders[24]. Higher NYHA classification is associated with increased hospitalizations, worse quality of life, and increased death rates[29,30].

Clinical Biomarkers

The immune system is needed to combat the virus. However, excessive activation of the inflammatory system and coagulation pathways can result in death or disability[9,12–14]. There is some evidence that COVID-19 can lead to new or worsening of existing cardiac injury through the mechanism of infiltration of inflammatory mononuclear cells in the myocardium[35]. This mechanism confirms the role of the immune system's involvement in cardiovascular damage in response to COVID-19 through both local and systemic inflammation [36,37].

Studies have identified associations between clinical biomarkers and COVID-19 progression[9–11,13,14,38]. The increased clinical biomarker levels are associated with symptom severity, progression of COVID-19, and worse clinical outcomes[13–1836]. There is a preliminary association of the prognostic ability of cardiac troponin (a biomarker with high sensitivity to myocardial injury) and D-dimer (protein for breakdown of blood clots) on poorer outcomes and in-hospital mortalities[11,12,14,16,39]. Studies also indicate that CRP, cardiac troponin, BNP (a biomarker of cardiac stress), PT, and D-dimer show an upward trend in those hospitalized with COVID-19 indicating myocardial damage and increased risk of clotting[7,9,10,13,38]. There are yet other studies showing that patients with elevated cardiac biomarkers during COVID-19 infection

have higher D-dimer ($p<0.001$), creatinine ($p<0.001$), and white blood cell count (WBC) ($p=0.007$), and specifically, CRP levels are found to be sensitive markers of acute COVID-19 disease.

Long COVID

Long COVID affects about 65 million individuals infected with COVID-19 in the U.S. alone[19,41]. Currently, there are no established diagnostic tests for the identification of long COVID[9,17,42]. Long COVID is defined and diagnosed through commonly seen symptoms that last for weeks, months, or even years after a COVID-19 infection[9,17,42]. These symptoms include fatigue, headache, dyspnea, anosmia, and numbness that are not attributable to underlying neurologic conditions[9,17,42]. Long COVID has been reported in about 10%-30% of the population infected with COVID-19 and is defined as having at least one long COVID symptom that lasted 30 days or more[9,17,19].

While preliminary evidence demonstrates a higher risk for adverse outcomes from long COVID among HF patients, there are significant gaps in science that persist. There is a limitation in diagnosing long COVID, treating symptoms of long COVID as well as whether HF exacerbation is correlated with increased risk of long COVID, and whether clinical biomarkers can predict high-risk HF patients that will develop long COVID.

Statement of Study Purpose

Although preliminary research studies are addressing the impact of COVID-19 among HF patients, the critical problem is that there is still a large gap in our knowledge of the factors associated with poorer outcomes[7]. Current data show that patients with HF overall have worse outcomes when infected with COVID-19[5,7,8]. However, the extent of worse outcomes as well as underlying clinical factors that place HF patients at high risk are largely unknown[5–7]. This lack of

knowledge also makes it difficult to allocate resources appropriately[5–7]. This dissertation adds to the state of the science by contributing a review of the literature and exploring the effects of prehospital NYHA classification and clinical biomarkers on outcomes seen among HF patients infected with COVID-19 and those that develop long COVID.

Specific Aims

1. To conduct a systematic review to explore the current state of outcomes seen among HF patients infected with COVID-19 for the development of effective interventions.
2. To determine if prehospital clinical biomarkers and NYHA classification vary between patients with HF at initial hospitalization with COVID-19 compared to age and sex matched HF patients hospitalized without COVID-19.
3. To determine if prehospital clinical biomarkers and NYHA classification are associated with the development of long COVID among patients with HF 6 months following hospitalization for COVID-19.

Content of the Dissertation: Three Manuscripts

The content of the dissertation features three manuscripts, which are as follows:

1. Chapter Two: Heart Failure and COVID-19 Clinical Outcomes: A Systematic Review.

   This chapter features a systematic review of the literature from 2020 to 2023 including HF patients infected with COVID-19 to understand the outcomes seen among this patient population. The review included outcomes on mortality, hospital readmissions, and hospital length of stay (LOS). The review also provided pertinent information on risk factors that increase the risk for worse outcomes seen among HF patients. The main results showed that HF patients infected with COVID-19 experienced increased death

rates, hospital readmissions, and hospital LOS. Older age and admission to skilled nursing facilities were found to be risk factors for worse outcomes.

2. Chapter Three: Effect of Prehospital Clinical Biomarkers and NYHA Classification on Outcomes among Heart Failure Patients Infected with COVID-19. This chapter describes a retrospective study with EHR data comparing two groups of HF patients with and without COVID-19 infection admitted to the hospital. A total of 200 HF patients were included in the analysis with 100 in the COVID-19 positive group and 100 in COVID-19 negative group. A significant difference was found in the BNP levels and deaths which were higher in the HF group without COVID-19 when compared to the HF group with COVID-19.
3. Chapter Four: Effect of Prehospital Clinical Biomarkers and NYHA Classification on Development of Long COVID among Heart Failure Patients. This chapter describes a retrospective study design including EHR data. Prehospital clinical biomarkers and NYHA classification data were used to analyze any association with the development of long COVID. The results showed no significant difference between those with and without long COVID.
4. Chapter Five: Dissertation Summary. The dissertation summary provides a summary of the study significance as well as recommendations for future research.

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Chapter Two: Literature Review (First Manuscript)

Patients with Heart Failure and COVID-19 Clinical Outcomes: A Systematic Review

Abstract

Background: Coronavirus disease 2019 (COVID-19) has led to a pandemic that conferred greater risks for those with a heart failure (HF) diagnosis. The reasons behind worse outcomes among those with an HF diagnosis infected with COVID-19 are unknown. The purpose of this systematic review was to determine death rates, hospital length of stay (LOS), and hospital readmissions among HF patients hospitalized with confirmed COVID-19.

Methods: PubMed and CINAHL databases were searched using the keywords heart failure, mortality, COVID-19, hospital readmission, and hospital LOS. Inclusion criteria were: (1) HF patients with hospitalization and confirmed COVID-19 through polymerase chain reaction testing, (2) articles published between 2020-2023, and (3) English-language and full-text articles. The Crowe Critical Appraisal Tool was used to evaluate the quality of the articles.

Results: A total of 388 full-text articles were identified from the keyword search. Fifteen articles met the inclusion criteria. Most studies (n=8) showed a significant association with HF diagnosis and increased mortality from COVID-19 (2-fold higher risk of death). Most articles (n=9) also found that concomitant HF and COVID-19 diagnoses were associated with an increased risk of readmission between one to 60 days after discharge (30-day readmission: OR 3.81, 95% CI:1.41-10.31, $p<0.008$). Two studies showed a HF diagnosis to be associated with longer hospital LOS compared to those without HF (8 days vs. 6 days; $p < 0.001$).

Conclusion: A HF diagnosis increased the risk for mortality, hospital readmissions, and hospital LOS for those with COVID-19.

Background

Heart failure (HF) is a progressive disease with 26 million individuals diagnosed worldwide and 6.2 million individuals diagnosed in the U.S[1–3]. It is estimated that HF will increase about 1% to 3% by 2030 worldwide[4]. Heart Failure is also associated with high death rates. Heart Failure was the contributing cause of 415,922 deaths in the U.S. in 2020 alone, and it is expected that about 50% of individuals diagnosed with HF will face death within five years and about 90% within 10 years[4,5]. Heart Failure is also known to be the leading cause of hospitalizations among adults[6]. The cost of HF was $30.7 billion in 2012 in the U.S. alone and is estimated to increase to $70 billion by 2030[4,7].

With the emergence of the Coronavirus disease 2019 (COVID-19) virus, clinicians faced increased challenges in their clinical management of patients with HF. COVID-19 contributed to an estimated 345,323 deaths in 2020, and with more than one million deaths between February 2020 and January 2023 in the U.S.[8] During this period, COVID-19 was among the top three causes of deaths in the U.S.[1] COVID-19 led to increased mortality, hospital readmission rates, and long term medical problems specifically among those with multiple baseline comorbidities[9–12]. One in four HF patients infected with COVID-19 that required hospitalization died from COVID-19[13,14].

COVID-19 conferred greater risks to those with HF diagnosis[15,16]. Individuals with HF diagnosis infected with COVID-19 were more likely to be hospitalized and have higher death rates from COVID-19 compared to those without HF adjusting for demographic factors[15,17]. However, there is still a large gap in the scientific knowledge of COVID-19 infection, particularly the risks associated with COVID-19 infection on patients with HF. The purpose of

this systematic review was to determine death rates, hospital readmission rates, and hospital length of stay (LOS) for patients with HF who contracted COVID-19.

Methods

Data Sources

This systematic review was conducted using PRISMA guidelines (Figure 1). The PubMed and CINAHL databases were searched for original, peer-reviewed articles published between 2020 and 2023. The following search terms were used in different combinations to identify the articles: heart failure, cardiomyopathy, COVID-19, hospital readmission, hospital LOS, and mortality (Table 1). The years 2020-2023 were chosen to retrieve articles as COVID-19 was first identified in the U.S. in January 2020.

Study Selection

A total of 388 articles were identified in the search process by the author as being potentially relevant after utilizing the search terms listed in Table 1. Duplicates were removed and the following inclusion criteria were applied: (1) HF diagnosis and confirmed COVID-19 through polymerase chain reaction testing (PCR), (2) articles published between 2020-2023, (3) English-language and full-text articles, (4) articles with full text availability, and (5) articles that included patients greater than 17 years of age. This resulted in 25 articles. The articles were further reviewed to include HF patients with hospitalization and outcome data of interest (death rates, hospital readmissions, and hospital LOS). This further narrowed down the number of articles that were available and resulted in 15 articles which were included in this review.

Quality Appraisal

The Crowe Critical Appraisal Tool (CCAT) was used to assess the quality of the included articles. CCAT was developed by Crowe and colleagues[18] and consists of eight categories

including preliminaries (title, abstract, and text with sufficient detail), introduction, design, sampling, data collection, ethical matters, results, and discussion[18,19]. Each category is scored from zero to five, with a range of scores from 0-40, and a higher score indicating higher quality[18,19]. The summary score was computed by the authors and requires subjective judgment. The summary score was used to compare the quality of the articles (Table 3).

Results

Study Characteristics

All 15 of the articles were published between 2020 and 2023 and were retrospective observational studies. Each article included data abstracted from the electronic health record (EHR) and some were based on large registries. All studies included data on HF and COVID-19 outcomes[9,10,13–16,20–28]. The majority of the articles were multicenter studies and were performed in the United States[9,13–15,20]. Four articles were conducted in Europe (one in London, one in Germany, and three in Spain), one article was conducted in Australia, and one article was a registry study that included data across 13 countries including the U.S., Germany, Italy, Switzerland, Spain, Belgium, United Kingdom, Bosnia, Turkey, Austria and Herzegovina[10,16,21,24,26,27].

Demographic and clinical data including age, gender, and ethnicity, body mass index (BMI), heart rhythm, medical comorbidities, medications, and ejection fraction (EF) percentages were included in all 15 studies[9,10,13–16,20–26,26–28]. Additional biological data included creatinine, blood urea nitrogen (BUN), and brain natriuretic peptide (BNP) levels. The majority of articles used predictive modeling such as multivariate logistic regression analyses to report outcomes and to define the impact of risk factors[10,13,14,16,20,22,23].

Studies were rated on the 8 categories established by the CCAT by the primary author. Total scores ranged from 19 to 36 (mean, 26.93 ± 4.91). Most studies scored relatively high in ethics, and sampling. A majority of the studies lacked the necessary depth in preliminaries, introduction, design, data collection, results, and discussion[14,20–22,24,25].

Participant Characteristics

Study sample sizes ranged from 134 to 132,312 patients; of those, the number with an HF diagnosis ranged from 16 to 20,182[10,16,24–26]. The mean ages of the patients in the studies were from 56 to 65 years[10,13,14,16,22,23,25,26,28]. The majority of articles included relatively equal numbers of males and females[9,10,13–16,20,23–26,28]. Eleven of the articles included patients with multiple comorbidities including diabetes, chronic kidney disease (CKD), and hypertension[9,10,13,14,16,21–23,25–27].

Heart Failure patients hospitalized with COVID-19 were more likely to be older (76.2 ± 14.6 years vs. 55.4 ± 19.6 years, $p < 0.001$), with a significantly higher incidence of hypertension (71.9% vs. 34.2%, $p < 0.001$), hypercholesterolemia (48.2% vs. 21.9%, $p < 0.001$), diabetes (35.4% vs. 19.8%, $p < 0.001$), and CKD (19.1% vs. 4.3%, $p < 0.001$)[26]. Heart failure patients with COVID-19 had a more severe presentation to the hospital with higher systolic blood pressures (126 mmHg vs 119 mmHg, $p<0.001$) and lower oxygen saturations (91% vs 94%, $p<0.001$) compared to those without HF diagnosis[28]. Heart failure patients also had three times higher risk for mechanical ventilation and having a history of HF diagnosis was an independent risk factor for intensive care unit (ICU) admission (OR: 1.71; 95% CI: 1.25 to 2.34; p¼0.001), mechanical ventilation use (OR: 3.64;95% CI: 2.56 to 5.16; $p<0.001$), and in-hospital deaths (OR: 1.88; 95% CI: 1.27 to 2.78; $p=0.002$)[15,28].

Death Rates

Death rates from COVID-19 were higher among those with an HF diagnosis[10,15,24–26]. Heart Failure was significantly associated with greater 180-day all-cause death rates (odds ratio [OR]=1.35; 95% confidence interval [CI]= 1.18-1.54; $p<0.01$)[10]. One article concluded that a history of HF was associated with a two-fold increase in deaths from COVID-19 while another found that one in four patients hospitalized with COVID-19 died during hospitalization[15,28]. When comparing COVID-19 infected patients with and without an HF diagnosis, one article showed a 46.8% death rate among the HF group compared to a 19.7% death rate in the non-HF group ($p<0.001$)[25]. Another study compared HF patients hospitalized with COVID-19 infection to HF patients hospitalized for non-COVID related reasons such as an HF exacerbation[15]. According to Bhatt et al.[15], death rates were 24.2% (n=2,026) for in-patient deaths among those with COVID-19, 2.6% (n=617) among acute HF exacerbation patients, and 4.6% (n=4,542) among those hospitalized for any other reason during the same time period[15].

HF diagnosis also nearly doubled the risk of death after adjusting for comorbid conditions[28]. Linschoten et al.[27] concluded that severe HF (NYHA class III and IV) was strongly associated with in-hospital mortality across a spectrum of different types of heart diseases in unadjusted analyses[27]. After adjusting for age, sex, BMI, diabetes, hypertension, CKD, and chronic obstructive pulmonary disease (COPD) there were no differences in mortality[27].

Interestingly, two of the studies did not find a statistically significant difference in death rates and the need for ICU admission and intubation among patients based on ejection fraction (EF)[15,28]. However, one study concluded that those who died from COVID-19 were more likely to be older (mean age 87), be of white race, and have preserved EF (90%) with high comorbid conditions[20].

Hospital Readmissions

Readmission rates after primary hospitalization with COVID-19 infection were higher among HF patients across multiple articles[9,14,16,21,23]. Most readmissions occurred between one and 60 days after initial discharge from the hospital[9,10,13,14,16,20–23]. Eight articles concluded that a HF diagnosis was associated with an increased risk for readmissions within two months of discharge (OR=1.6; CI=1.48–1.67; p<0.001), and the overall risk for readmissions was 4 times greater (OR= 4.09; 95% CI= 1.35-12.46; p=0.013)[16]. Another study showed that among those with HF (n=22), seven patients had readmission within four months of discharge[9]. Three articles concluded that 30-day readmission rates after a COVID-19 infection were associated with HF diagnosis, and HF patients had significantly higher 30-day readmission rates compared to non-HF patients (20.6% vs 19.1% respectively; p<0.001)[21,23].

Two articles analyzed the comorbidities and the increased risk of readmissions among patients infected with COVID-19[14,23]. Heart Failure exacerbation and acute coronary syndrome were the most common reasons for readmissions among COVID-19 infected patients[22]. Another study showed a previous diagnosis of cancer (p = 0.025) and HF (p = 0.001) to be associated with readmissions[16]. Verna et al. found that COVID-19 infected patients discharged to skilled nursing facilities (SNF) had overall higher readmissions[13].

Hospital Length of Stay

Patients with HF, hospitalized with COVID-19, had longer hospital LOS during their primary hospitalization[28]. A history of HF among COVID-19 patients was associated with a three times greater risk for longer hospital LOS during initial hospitalization with COVID-19 after adjustment for relevant clinical factors[28]. A study by Kirkegaard et al. found that the median LOS during initial hospitalization for COVID-19 and HF was 9 days[16]. The authors

concluded that an increase in hospital LOS during initial hospitalization was significantly associated with hospital readmissions (20 days vs 9 days, $p<0.001$)[16]. A hospital LOS of 13 days or more during primary hospitalization with COVID-19 was associated with hospital readmission (OR 2.39; 95% CI 1.21-6.12; p=0.015) in a study by Kirkegaard and colleagues[16].

Discussion

This systematic review aimed to determine death rates, hospital length of stay (LOS), and hospital readmissions among HF patients hospitalized with confirmed COVID-19. CCAT was used to assess the quality of the articles included in the systematic review. The majority of the articles lacked the necessary depth in preliminaries, introduction, design, data collection, results, and discussion[14,20–22,24,25]. The systematic review showed that most of the studies had significant associations with presence of HF diagnosis and increased death rates, hospital readmissions, and hospital LOS when hospitalized with COVID-19.

Articles included a diverse sample from different ethnic and racial backgrounds and sexes. The ages of the patients included in the studies ranged from 18 to 85 years while the mean ages were from 56 to 65 years which was an expected outcome given that the majority of HF patients are older, and older age is associated with worse outcomes when infected with COVID-19[13,20,28]. It is also known that HF patients are also more likely to have other comorbidities such as hypertension, diabetes, and kidney disease[14,20,24,26]. Articles included a sample of individuals with numerous comorbidities, and several authors adjusted for comorbidities in their statistical analyses[27,28]. Overall, HF was still significantly associated with higher death rates after adjusting for age, sex, and comorbidities such as diabetes, hypertension, and kidney disease[24,27,28].

There was a strong association between the presence of HF and the number of deaths from COVID-19[15,20,27,28]. Results ranged from a 25% increase in death rates to a 2-fold increased

risk of death among HF patients[15,28]. Those with acute HF compared to chronic HF also had a worse clinical presentation to the hospital with lower oxygen saturation and a greater need for supplementary oxygen. This was also associated with increased resource utilization with higher rates of ICU admissions, need for central venous catheter insertion, and mechanical ventilation[15,25,28]. Patients' more severe condition may be related to the severity of HF exacerbation as a consequence of COVID-19 infection. Those with chronic HF at baseline were more likely to develop acute HF after a COVID-19 infection[25]. One study found that severe HF as measured by NYHA class III or IV, was most strongly associated with in-hospital mortality[27].

Some studies included other cardiovascular diagnoses such as acute coronary syndrome, valvular heart disease, and HF had the most significant association with in-hospital deaths from COVID-19[27]. No other diagnosis was associated with in-hospital mortality after adjusting for confounding factors such as age, sex, BMI, diabetes hypertension, and CKD[27]. Of note, hospitalized HF patients faced an increased risk of death regardless of their EF[28]. There was no difference among hospitalized HF patients and LOS, ICU admission, intubation, and the need for ventilation based on their EF. However, those with reduced EF overall had significantly higher HF-related 30-day readmissions compared to those with preserved EF (47.1% vs 8.6%)[28].

Hospital readmissions and hospital LOS during initial hospitalization were also significantly worse among those with an HF diagnosis[14,16,21–23]. A HF diagnosis and HF related exacerbation were the most common reasons for hospital readmissions and LOS[13,16,21,22]. It is important to note, however, that of the nine articles that analyzed hospital readmission outcomes among HF patients with COVID-19, two of them excluded patients that did not have readmission to the same hospital as their initial hospitalization[9,10,14,22]. Two articles excluded patients that did not have readmission within 30 days after initial discharge from the hospital with COVID-

19[13,21,24,25]. Therefore, some patients were lost to follow-up and not included in the overall analysis. High hospital LOS and readmission rates that are seen among HF patients infected with COVID-19 were associated with poor quality of lives. This lead to increased hospital costs given that hospitals do not receive reimbursement for HF patients with a readmission within 30 days of discharge[29].

Strengths and Limitations

Most of the articles in this review had large sample sizes and included multiple institutions in the U.S., and international locations. Many studies included patients with different ethnic and racial backgrounds, and there was nearly an equal inclusion of both women and men. This is important since studies have found sex differences in COVID-19 sequela. Finally, most articles included those with multimorbidity in addition to HF. This is important to account for potential confounding factors. Weaknesses included the lack of data on the severity of illness such as NYHA classification and EF values. The articles were selected and reviewed by the primary author alone which is a limitation to our study. Most of the articles analyzing hospital readmission rates did not count hospital readmissions that took place in a different institution than the initial hospitalization.

Implications for Practice and Future Research

There is a need for more research studies with a focus on understanding the reasons behind poorer outcomes for patients with HF who contract COVID-19. This will allow for early identification of high-risk HF patients to improve clinical outcomes. It is critical to determine if a HF exacerbation further increases the risk for poor outcomes following COVID-19.

Conclusion

A HF diagnosis was significantly associated with poorer outcomes among those that required hospitalization for COVID-19 including higher death rates, longer hospital LOS, and higher hospital readmissions. Scientific studies on COVID-19 and HF have the potential to improve the lives of those with HF and to decrease hospital burden through better allocation of resources.

Table 1: Search Strategy Terms

Database	Search Strategy Terms
PubMed and CINAHL	(heart failure[Title/Abstract]) OR (heart failure[MeSH Terms])) OR (cardiomyopathy[Title/Abstract])) AND (covid-19[Title/Abstract])) OR (covid-19[MeSH Terms])) OR (coronavirus[Title/Abstract])) OR (sars-cov-2[Title/Abstract])) AND (mortality[Title/Abstract])) OR (mortality[MeSH Terms])) OR (death rate[Title/Abstract])) AND (readmission[Title/Abstract])) OR (readmission[MeSH Terms])) OR (readmission rate[Title/Abstract])) AND (length of stay[Title/Abstract])) OR (length of stay[MeSH Terms])

Table 2: Characteristics and Results of Included Studies (n=15)

Author (Year)	Purpose	Sample Characteristics	Outcome	Results
Caraballo et al (2020)	To characterize the prevalence and outcomes of COVID-19 in a live registry of heart failure patients across an integrated health care system in Connecticut.	n=201 HF with PCR confirmed COVID-19 Mean age/%Female: 73 vs 50.5% Data collected in April 2020- Connecticut, USA Multicenter (n=6)	Mortality	Older age, multiple comorbidities, black race more likely to be hospitalized and have higher mortality. Age associated with increased risk of death [OR 1.92 95% CI (1.33–2.78); P<0.001].
Lavery et al (2020)	To assess the characteristic of hospitalized COVID-19 patients that are discharged and were readmitted into the hospital.	n=126,317 PCR confirmed COVID-19 n=20,182 HF diagnosis Mean age/%Female: 73 vs 47.9% Data collection March-July 2020. Multicenter, U.S. hospitals (n=865)	Hospital readmission	Heart failure diagnosis was significantly associated with increased risk for readmissions. Odds of readmission HF: (OR = 1.6)
Chatrath et al (2020)	To quantify the impact of COVID-19 infection on mortality in hospitalized	n=134 hospital admitted patients with chronic HF n=40 COVID-19 positive with HF	Mortality	COVID-19 associated with significantly increased mortality in patients admitted with HF.

	patients known to have HF.	Mean age/%Female: 79.4 vs 55% Data collection March-May 2020 London- single center		Death rate + COVID vs - COVID HF patients: 50% vs. 10.6%, RR 4.70 (95%CI2.42–9.12), P < 0.001]
Sritharan et al (2023)	To analyze the relationship between pre-existing cardiovascular disease, mortality and cardiovascular outcomes in patients hospitalized with COVID-19	1,567 PCR confirmed COVID-19 patients. HF (n=106) Mean age/%Female: 60.7 vs 46.6% Data collection April 2021 – Nov 2022 Australia (n=21 hospitals). Multicenter	Mortality	HF identified as a high-risk cohort with poorer outcomes from COVID-19 11.2% mortality
Guarin et al (2021)	To identify factors associated with readmission after an index hospital admission for coronavirus disease 2019 (COVID-19)	n=275 PCR confirmed hospitalized COVID-19 patients HF (n=40) Mean age/%Female: 64.7 vs 48% Data collection March 2020- October 2020 Philadelphia, single center	Hospital readmission	HF exacerbation and acute coronary syndrome were the most common reasons for readmission. n=14 hospital readmissions with HF
Kirkegaard et al (2021)	To assess risk factors related to early readmission in previous hospitalized patients with COVID-19	N=629 PCR confirmed COVID-19 patients HF (n=26) Mean age/%Female: 60 vs 49.4% Data Collection March 2020- May 2020 Barcelona, Spain- single center	Hospital readmission Hospital LOS	HF diagnosis was significantly associated with increased risk for readmissions. Risk factors for readmissions: prior HF diagnosis (OR 4.09; 95% CI 1.35–12.46; p = 0.013), LOS >13 days (OR 2.39; 95% CI 1.21–6.12; p = 0.015)

Ramos-Martínez et al (2021)	To determine the proportion of patients with COVID-19 who were readmitted to the hospital and the most common causes and the factors associated with readmission	8392 PCR confirmed COVID-19 patients. HF (N=16) with readmission Mean age/%Female: 74 vs 42% Data collection March - April 2020 Spain, multicenter (n=147 hospitals)	Hospital readmission	HF was among the common causes of hospital readmission. HF (5%) readmission
Yeo et al (2021)	To examine the rate, timing, causes, predictors, and outcomes of 30-day readmission after COVID-19 hospitalization	1062 PCR confirmed COVID-19 patients. HF (N=35) Mean age/%Female: 56.5 vs 40.5% Data collection March-April 2020 New York, USA- single center	Hospital readmission	HF was a risk factor for hospital readmissions 30 days after discharge. HF 30-day readmission: OR 3.81 (95% CI:1.41-10.31) p<0.008
Alvarez-Garcia et al (2020)	To describe the clinical profile and associated outcomes among patients with HF hospitalized with COVID-19	6,439 PCR confirmed COVID-19 patients. HF (n=422, 6.6%) Mean age/%Female: 63.5 vs 45% February 27 and June 26, 2020. New York, USA- Multicenter (n=5 hospitals in NYC)	Mortality (40%) Hospital LOS	History of HF associated with nearly 2-fold higher risk of death, >3times higher risk of mechanical ventilation, and longer LOS. mortality risk among HF twice that of those without HF (40.0% vs. 24.9%; OR: 2.02; 95% CI: 1.65 to 2.48; p<0.001)
Linschoten et al (2021)	To evaluate heterogeneity in associations between various heart disease	16,511 PCR confirmed COVID-19 patients. HF (n=1,314)	Mortality	HF and in particular severe HF (NYHA class III/IV) most strongly associated with in-hospital mortality across the

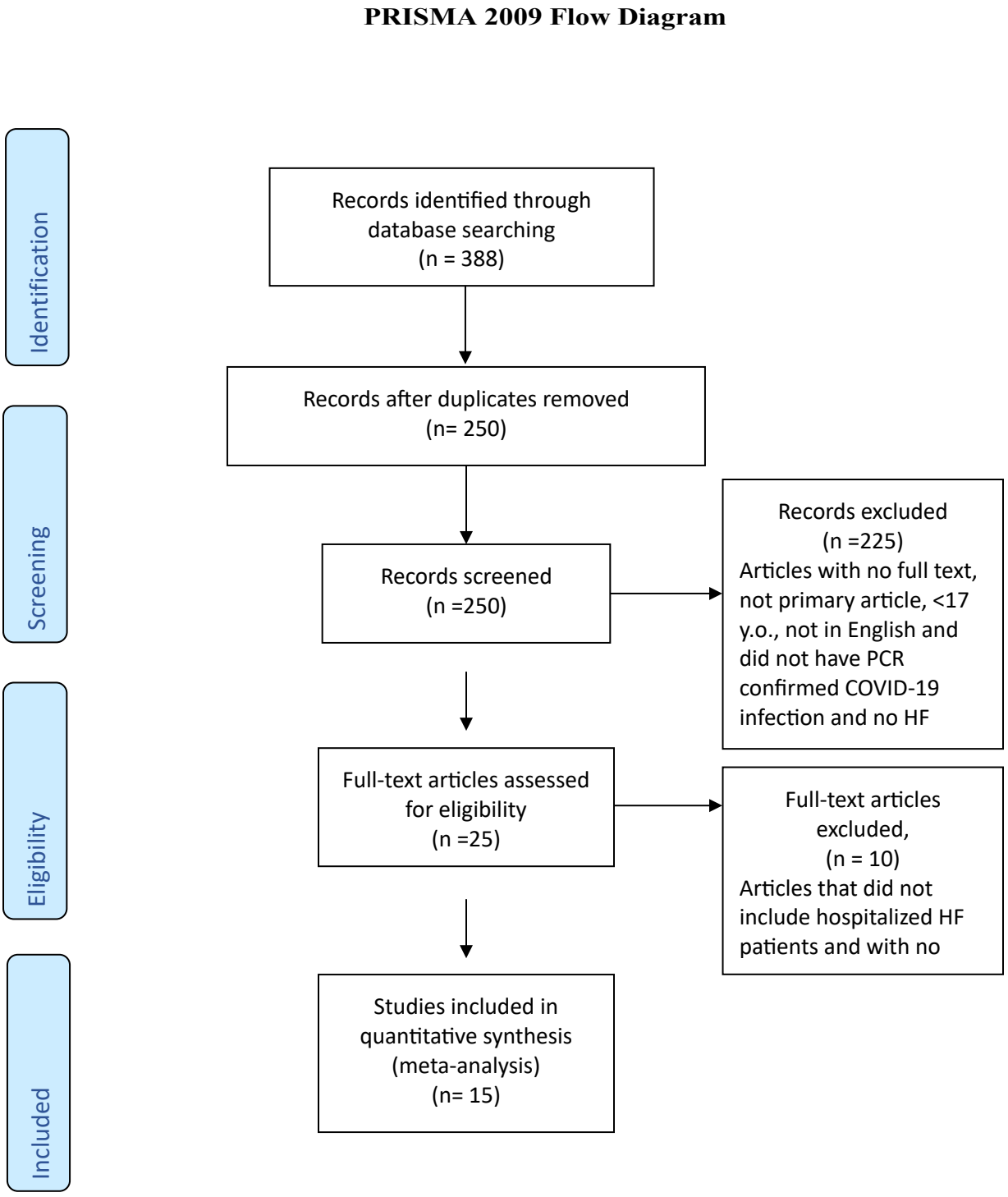
	subtypes and in-hospital mortality.	Age/%Female: 66-75 years/40.2% Data collection March 2020 – May 2021 Multicenter (18 countries including the U.S.)		spectrum of different heart disease subtypes. In-hospital mortality highest significantly among HF (RR 1.19, 95% CI 1.10-1.30; p<0.018) and severe NYHA III/IV HF (RR 1.41, 95% CI 1.20-1.64; p<0.018)
Clark et al (2021)	To characterize these reencounters and factors associated with reencounters	466 PCR confirmed COVID-19 patients. HF (n=22) Mean age/%Female: 57.4 vs 46.4% Data collection March 2020- April 2020 Chicago, USA single center	Hospital readmission	HF was among the list of comorbidities among readmitted patients within 4 months. HF (n=22) n=7 had readmission within 4 months of discharge
Verna et al (2021)	To estimate the rate of readmission among patients discharged with confirmed COVID-19, and identify risk factors for readmission to target for intervention	29,659 PCR confirmed COVID-19 patients. HF (n=755) Mean age/%Female: 54.3 vs 49.5% Data collection February - June 2020 U.S.- Multicenter study (n=297 hospitals across 40 states)	Hospital readmission	Baseline comorbidity including HF significantly associated with readmission. N=69 hospital readmissions among HF; (6.4% readmitted vs 2.4% not admitted; p<0.0001)
Günster et al (2021)	to provide a detailed account of hospitalized COVID-19 patients up to 180 days after their initial hospital admission	8,679 PCR confirmed COVID-19 patients. HF (n=1,652) Median age/%Female: 72 vs 46.5% February - April 2020 Germany	Mortality Hospital readmission	HF second highest increase in 180-day mortality and coagulopathy is the primary reason. HF associated with higher readmissions. HF all cause 180-day hospital mortality OR 1.35

				95% CI (1.18-1.54) p<0.001
Rey et al (2020)	To study characteristics, cardiovascular outcomes, and mortality in patients with confirmed COVID-19 infection and a prior diagnosis of HF	3,080 PCR confirmed COVID-19 patients. HF (n=152) Mean age/%Female: 62.3 vs 45.2% Data collection March - April 2020 Madrid, Spain, multiple hospitals from Spain	Mortality	Those with previous HF had higher death rates (48.7% vs. 19.0%; P < 0.001). Acute HF had more severe presentations of COVID-19, with lower levels of oxygen saturation on admission (89.3 ± 7.6% vs. 92.3 ± 6.2%; P < 0.001) and a higher need for supplementary oxygen (20.8% vs. 8.9%; P = 0.001),
Bhatt et al (2021)	To evaluate in-hospital outcomes among patients with a history of HF hospitalized with COVID-19	132,312 patients with history of HF n=8,383 (HF with COVID-19 infection) Mean age/%Female: 71.7 vs 50.2% Data collection April 2020 – September 2020 U.S.- multicenter (1,041 health entity included)	Mortality	One in four HF patients hospitalized with COVID-19 died during hospitalization, corresponding to 14-fold greater odds of dying in April and 10-fold greater odds of dying in subsequent months. HF with COVID 24.2% mortality (n=2,026), 2.6%(n=617) mortality for acute HF hospitalization, 4.6% (n=4,542) mortality in hospitalized for other reasons

Table 3: Quality of Articles Using the Crowe Critical Appraisal Tool (n=15)

Author	Total CCAT	Preliminaries	Introduction	Design	Sampling	Data Collection	Ethical Matters	Results	Discussion
Caraballo et al (2020)	24	3	3	4	2	3	4	2	3
Lavery et al (2020)	19	2	2	2	3	2	4	2	2
Chatrath et al (2020)	23	3	2	3	3	3	4	2	3
Sritharan et al (2023)	29	4	3	3	4	4	4	3	4
Guarin et al (2021)	19	2	2	2	3	3	3	2	2
Kirkegaard et al (2021)	28	3	4	3	4	3	4	4	3
Ramos-Martínez et al (2021)	23	2	2	3	3	2	5	3	3
Yeo et al (2021)	27	3	3	4	3	3	4	3	4
Alvarez-Garcia et al (2020)	34	4	4	4	5	5	4	4	4
Linschoten et al (2021)	36	4	4	4	5	5	4	5	5
Clark et al (2021)	27	4	3	3	3	3	4	3	4
Verna et al (2021)	30	4	4	3	4	4	4	4	3
Günster et al (2021)	29	4	3	3	4	3	4	4	4
Rey et al (2020)	25	3	4	3	3	2	4	3	3
Bhatt et al (2021)	31	4	3	3	5	5	4	4	3
Mean	26.93	3.27	3.07	3.13	3.60	3.33	4.00	3.20	3.33
SD	4.91	0.80	0.80	0.64	0.91	1.05	0.38	0.94	0.82

Figure.1



Note: © PRISMA

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Chapter Three: Clinical Biomarkers and COVID-19 (Second Manuscript)

Relationship between Prehospital Clinical Biomarkers and New York Heart Association Classification on Outcomes among Heart Failure Patients Infected with COVID-19

Abstract

Background: Heart Failure (HF) patients infected with coronavirus disease 2019 (COVID-19) have higher risks for adverse outcomes. A critical problem is the lack of scientific knowledge on the effects of COVID-19 on cardiovascular function that may be associated with poor outcomes such as higher death rates, longer hospital length of stay (LOS), and hospital readmissions. The purpose of this study was to determine if prehospital clinical biomarkers and NYHA classification differed between hospitalized HF patients with and without COVID-19 and if they could predict mortality, LOS, and hospital readmissions.

Methods: We conducted a retrospective medical record review among HF patients hospitalized with and without COVID-19 infection between January 2020 and December 2023. We analyzed prehospital biomarkers of brain natriuretic peptide (BNP), troponin, prothrombin time, platelet count, creatinine, and c-reactive protein, and NYHA data from age and sex matched hospitalized HF patients with (Cohort A; n=100) and without (Cohort B; n=100) COVID-19. Data were analyzed using bivariate and multivariate analyses.

Results: Prehospital BNP levels and mortality were significantly different between the two cohorts with Cohort B (non-COVID group) having higher BNP values (700 vs. 401.9, p=0.006) and higher death rates (47% vs. 31%, p=0.03) compared to Cohort A. There were no significant differences between groups on prehospital NYHA classification.

Conclusion: Our results demonstrate that prehospital biomarkers and NYHA classification do little to explain the added risk for patients with HF who become infected with COVID-19.

Prospective studies are needed to examine biomarkers of the patients with HF prior to and at the time of COVID-19 infection to determine variables that may predict worse outcomes.

Background

Heart failure (HF) is a serious and progressive condition affecting more than 64 million individuals worldwide with an estimated prevalence of 6.2 million individuals in the U.S.[1–3]. It was estimated that the prevalence of HF would increase by 24% accounting to about 8.5 million individuals by 2030[2]. Heart failure accounted for high death rates with 415,000 deaths seen in the U.S. in 2020[1,4,5]. Heart failure was also associated with estimated direct and indirect costs of $43.6 billion in 2020 in the U.S. and a projected increase to $69.7 billion by 2030[1,2].

Globally the emergence of coronavirus disease 2019 (COVID-19) led to a serious threat to health with 470 million COVID-19 cases and 6 million deaths seen from January 2020 to March 2022[6]. In the U.S. alone, there were an estimated one million deaths from COVID-19 between February 2020 to January 2023[7]. For those hospitalized with COVID-19, 16% had an HF diagnosis, and 8% had a hospital length of stay (LOS) of three months[8]. Overall, one in four HF patients with COVID-19 that required hospitalization died from COVID-19[8–10].

The physiological effects of the COVID-19 on an already weakened heart are not well understood[11–13]. The New York Heart Association (NYHA) classification is a standardized tool that is universally used among HF patients to categorize the severity of HF, assess functional status, and to guide clinical management[11,14,15]. NYHA classification is composed of four categories (I-IV) that address functional capacity (Table 1). The classification helps identify illness progression and provides a simple way to assess the extent of HF exacerbation[16]. The NYHA classification has a fairly high concordance rate among providers with 75% to 90% agreement between randomly selected graders[11]. Higher NYHA classification is associated with

increased hospitalizations, worse quality of life, and increased death rates[11,17]. NYHA classes III and IV are also associated with increased hospital LOS[18].

Studies have compared NYHA classification among HF patients infected with COVID-19 for the assessment of outcomes such as death rates and COVID-19 severity[13]. However, these studies lacked NYHA classification data prior to hospital admission, so it was not possible to determine if the patient's functional status had decreased. Thus, current research is limited in its ability to identify high-risk HF patients before infection to make predictions about the risk for poor clinical outcomes[11–13]. There is some literature analyzing the deleterious effects of COVID-19 infection on preexisting HF as well as new diagnoses of HF secondary to COVID-19[19]. However, a major limitation of these studies is the lack of prehospital NYHA classification prior to COVID-19 infection. Therefore, it is not feasible to conclude whether worse HF exacerbation as measured by NYHA classification at the time of hospitalization is a result of COVID-19 infection, overall worsening of HF symptoms independent of the infection, or a new HF symptom seen secondary to acute COVID-19 infection[20].

Clinical biomarkers may be important predictors of outcomes for HF patients with COVID-19. While the precise mechanism of action between elevated clinical biomarkers and mortality in COVID-19 is unknown, there is some evidence that cardiac biomarkers reflect myocardial injury, inflammation, and remodeling[21,22]. There are preliminary studies that identified associations between clinical biomarkers and COVID-19 at the time of hospitalization. Elevated levels of biomarkers were associated with symptom severity, progression of COVID-19, and overall worse clinical outcomes[23,24,25,26,27]. The biomarkers included brain natriuretic peptide (BNP), cardiac troponin, creatinine, biomarkers of coagulation; prothrombin time (PT) and platelet count[23–28]. There are also studies establishing an association between COVID-19

severity and inflammatory biomarkers such as C-reactive protein (CRP)[16,24,26,27]. However, these studies lacked prehospital clinical biomarker data, and they only reported biomarkers at the time of hospitalization with COVID-19 infection.

Syndemic Theory

This study is grounded in the Syndemic theory which helps explain the rationale for investigating the combined effects of a HF diagnosis and COVID-19 infection on individuals. The purpose of the Syndemic theory is to describe the effects of co-occurring diseases (HF and COVID-19) that may increase the severity of each condition and outcomes[29,30]. Syndemic theory provides an explanation for generating new hypotheses by focusing on synergies and co-occurring diseases[30,31]. It also provides a rationale for how disease processes interact with each other.

Purpose/Aims

The purpose of this study was to determine if prehospital clinical biomarkers and NYHA classification as measured 2 weeks to 3 months before hospitalization differed between age and sex matched HF patients with and without COVID-19 and to determine if biomarkers, NYHA classification, and COVID-19 could predict the outcomes of mortality, LOS, and readmissions.

Methods

Design, Sample, and Setting

Data were obtained retrospectively using electronic health records (EHR) from the University of California, Los Angeles Health System. A total of 200 patients hospitalized with a HF diagnosis between January 2020 and December 2023 were included. One hundred patients (Cohort A- HF with COVID-19) had COVID-19 which was identified through a positive polymerase chain reaction (PCR) test while one hundred (Cohort B- HF without COVID-19)

patients had HF alone without a COVID-19 infection. The cohorts were age and sex matched. A heterogeneous sample of both males and females with racially diverse backgrounds was included.

The sample was composed of patients with the following inclusion criteria, having a HF diagnosis, PCR confirmed COVID-19 infection, and having hospitalization between January 2020 to December 2023. Prehospital NYHA classification and clinical biomarkers including BNP, troponin, PT, platelet count, creatinine, and CRP were included 2 weeks to 3 months before hospital admission. The prehospital clinical biomarker and NYHA classification data were obtained from the patients' outpatient clinic visits that took place within the same institution prior to their hospital admissions. The 2 weeks to 3 months timeframe was selected to ensure recent biomarker and NYHA classification data were available *prior* to the COVID-19 infection for comparison purposes. Given that COVID-19 infection generally takes 14-15 days to resolve, 2 weeks before admission was selected to ensure the clinical biomarker data included in the study was reflective of the patient's prehospital baseline (prior to COVID-19 infection)[37]. Given that HF patients generally have 3 month follow up, 3 month was selected as the distant time point. Exclusion criteria included: (1) anyone who was less than 17 years of age and (2) had any organ transplants.

Protocol

The data were extracted from the EHR through a deidentified data query service available from the institution. To extract the data, a request was made which included the HF diagnosis and COVID-19 infection, specific date ranges, list of clinical biomarkers, NYHA classification, death rates, admissions dates, and discharge dates for each patient. The data extraction was done

according to the protocol set in place for this study which required detailed criteria to be set by the statisticians to allow for accurate query of data.

For cohort A, HF and COVID-19 were identified based on ICD-9 codes. The data were extracted based on those that had hospital admissions and available prehospital clinical biomarker data (2 weeks to 3 months before admission) between January 2020 and December 2023. Following this, Cohort B was identified based on those with HF diagnosis as identified by ICD-9 codes, hospital admissions, and available clinical biomarker data (2 weeks to 3 months before admission) between January 2020 and December 2023. Available patients were then age and sex matched to Cohort A. Patients with prehospital clinical biomarker data, both for Cohort A and Cohort B, were included in the analysis. None of the patients had all the clinical biomarkers available for data extraction. Patients that were missing one biomarker alone were selected first for inclusion in the data extraction then those that had two missing biomarkers and so on until n=100 was reached for both cohorts. The analysis was focused on deidentified data, and it was exempted by the University of California, Los Angeles Institutional Review Board.

Measures

NYHA classification and clinical biomarker data which included BNP, troponin, PT, creatinine, and CRP were collected for each patient before hospitalization. BNP is a marker of cardiac stress with normal levels that are less than 100 pg/mL, and troponin is a measure of a protein in the blood that is indicative of damage to heart muscle (normal troponin <0.04 ng/mL)[24,32–34]. PT and platelet count are measures of clotting factors in the blood with normal levels that are between 11.1 to 13.1 seconds and 150 to 350 x10E3/uL respectively[33,35]. Creatinine is a marker of kidney function with normal levels that are less than 1.5mg/dl[35]. CRP is

a protein that is made in the liver, and it is a marker of systemic inflammation (normal CRP <1.0mg/dL)[36].

To identify prehospital biomarkers, each patient's hospital admission date was identified in the EHR, and the clinical biomarkers that fell 2 weeks to 3 months before hospital admission were included in the dataset. If patients had several measures of the same biomarker available before hospital admission, the closest measure to the hospital admission was included for analysis. The availability of the NYHA data that fell within the 2 weeks to 3-month timeframe was limited given that our sample included some HF patients that were stable and had longer follow up periods than 3 months. Therefore, any available NYHA data before hospital admission for both cohorts were included for analysis.

Clinical Outcomes

The outcome measures included death rates, hospital LOS, and hospital readmissions. The data query included available mortalities, hospital admission, and discharge data for each patient. For the mortality data, mortality at the time of hospitalization and during post discharge period until December 2023 were included in the analysis. For Cohort A, the admission dates with COVID-19 infection were used for analysis. Hospital LOS was calculated by the admission and discharge dates for each patient. Hospital readmissions were analyzed based on 30-day, 60-day, and 90-day hospitalizations after the primary admission for each patient. Those who had emergency department visits without any hospitalization were not counted in the analysis as hospital readmissions.

Power Analysis

A sample size of 100 per cohort (HF with COVID-19 and HF without COVID-19), will have 80% power to detect a d=0.4 difference in biomarkers and NYHA classification between

Cohorts A and B with a 2-tailed alpha < 0.05 using independent samples t-test[38]. Based on the power analysis, nearly half standard deviation (SD) class difference for NYHA and half unit difference for clinical biomarkers would be needed for a detectable effect size which would entail half class difference for NYHA classification[11,17,25,27,39].

Data Analysis

To characterize the study sample and to make comparisons between groups, descriptive statistics (means, medians, minimum and maximum ranges) were used to analyze demographic and clinical information. The differences between the two cohorts (A vs. B) were characterized using bivariate analysis. The continuous variables were compared with Wilcoxon's rank-sum test, and the categorical variables were compared with the chi-square test. The variables in the bivariate analysis that were determined to have a level of significance of $p<0.20$ were included in the multivariate analysis to identify predictors of the outcomes. All biomarkers except troponin were log-scaled for inclusion in the multivariate analysis. For LOS, residuals were plotted which suggested a relatively normal distribution of data. Three models were estimated for each outcome (mortality, hospital LOS, and readmission) in the multivariate analysis, and linear regression was used for the LOS outcome while logistic regression was used for the mortality and readmission outcomes. We did not impute values for missing data since the numbers of missing prehospital biomarker and NYHA classification data were large.

Results

Baseline Characteristics

Of the total of 200 HF patients included in the study, 51% were male with a mean age of 74.5 years. Cohort A (n=100) was composed of 43% White, 19% Hispanic or Latino, 13% Black or African American, and 4% Asian ethnicities. Cohort B (n=100) was composed of 48% White,

13% Hispanic or Latino, 20% Black or African American, and 7% Asian ethnicities. The demographic and clinical characteristics of the sample are summarized in Table 2.

NYHA Classification and Clinical Biomarkers

Bivariate analysis was used to determine if there were differences in clinical biomarkers between Cohort A and Cohort B. Prehospital dates of 2 weeks to 3 months were required for biomarker inclusion in the study, and unexpectedly, there were large amounts of missing data (a total of 120 patients had missing NYHA classification data). The mean prehospital BNP was 401.9 (SD 728.5) pg/ml in Cohort A and 700.0 (SD 916.0) pg/ml, in Cohort B (p=0.006). There were 23.4% (n=11) patients with positive troponin (>0.04ng/ml) in Cohort A, and 43.9% (n=18) patients with positive troponin in Cohort B (p=0.07) (Table 3).

The categories for NYHA classification for Cohort A were Class I, 17.1% (n=7) patients; Class II, 48.8% (n=20), Class III, 29.3% (n=12), and Class IV, 4.9% (n=2). The proportion of patients in Cohort B was Class I, 12.8% (n=5); Class II, 41.0% (n=16); Class III, 35.9% (n=14), and Class IV, 10.3% (n=4) (p=0.196). There were no significant differences in other biomarkers as summarized in Table 3.

Mortality, Length of Stay, and Readmission Outcomes

There were 31% (n=31) and 47% (n=47) deaths that took place in Cohort A and Cohort B respectively (p=0.03). The mean hospital LOS was 8.3 (SD 9.4) days in Cohort A and 6.6 (SD, 7.4) days in Cohort B (p=0.196). Hospital readmissions were 35% and 40% in Cohorts A and B respectively (p=0.56). See Table 4.

We sought to determine if any of the variables of interest were predictors of mortality, LOS, or readmissions. Those variables significant in bivariate analyses as identified by variables with $p<0.2$ (Ethnicity/Race; p=0.188; BNP, p=0.006 & Troponin, p=0.07) were included as

potential predictors in a multivariate model. Although CRP also fit the criteria (p=0.11), it was not included in the multivariate analysis due to large numbers of missing data. Three models were created including data from Cohort A and Cohort B for each outcome. BNP was the only variable that was predictive of mortality (model 2) after adjusting for ethnicity/race, troponin, and COVID-19 (Odds ratio (OR):1.69, 95% CI=1.05-2.71, p=0.029). Hospital LOS (model 1) and readmissions (model 3) were not statistically significant (Table 5).

Discussion

Key findings from this study showed that HF patients without COVID-19 infection had higher prehospital BNP levels and higher deaths compared to HF patients with COVID-19. BNP was also the single predictor of mortality even after adjusting for potential confounders of ethnicity, troponin, and COVID-19. We hypothesized that hospitalized HF patients with COVID-19 would have higher prehospital biomarkers compared to those without COVID-19 and poorer outcomes, however, our results did not support these hypotheses.

Several studies concluded that COVID-19 patients had high BNP and troponin levels during hospitalization, and these were determined to be prognostic of 28-day all-cause mortality from COVID-19[21,32,33]. Other studies that identified BNP and troponin to be higher in the HF patients with COVID-19 group[26,40]. In a study of 152 HF patients, Rey et al. found that those infected with COVID-19 had significantly higher BNP levels (16 802 ± 30 726 pg/mL vs. 4726 ± 13 530 pg/mL; $p < 0.001$), and troponin levels (4331 ± 23 952 ng/L vs. 306 ± 2646 ng/L; $p < 0.001$) at the time of hospital admission compared to patients without a HF diagnosis[26]. However, it is important to note that these studies measured biomarkers at the time of hospitalization, prior to hospitalization as we did, and the HF patients were not compared to other HF patients without COVID-19 infection.

The results from our study indicating significantly higher BNP levels in the HF group without COVID-19 (Cohort B) could be explained by high BNP levels seen in other studies that were due to HF diagnosis alone, COVID-19 infection alone, or the synergistic effect of both[26,33,40]. BNP is also known to be a biomarker of HF[41]. However, it is also usual for BNP levels to normalize as HF is treated and stabilized[41]. Therefore, our results may be explained by Cohort B having more severe HF. This would be confirmed by NYHA classification; however, we were unable to validate this in our study due to the large number of missing data for NYHA classification. We had 120 patients with missing NYHA data. These patients were clinically stable and had longer than 3-month follow ups. Given our inclusion criteria of 2 weeks to 3 months before hospitalization, data from these patients were not obtained.

Our multivariate models also show that BNP was the only predictor associated with mortality even after adjusting for ethnicity/race, troponin, and COVID-19. There were no variables predictive of hospital LOS and readmissions in our study. This suggests that high BNP levels in HF contribute to additional risk associated with COVID-19. More studies are needed to confirm the additive risk associated with COVID-19 for patients with HF.

Death was the only clinical outcome that was significantly different between the two cohorts with patients in Cohort B having higher death rates compared to Cohort A. According to Ma et al., higher NYHA classification was associated with higher death rates and higher BNP levels among HF patients[42]. Although our results supported this for Cohort B, we were unable to validate the NYHA classification due to having a large number of missing data.

Our study raises some important questions about the added risk associated with COVID-19 for patients with HF. However, due to large numbers of missing data, our results need to be replicated in a larger study of prehospital clinical biomarkers and NYHA classification data. It is

also important to compare biomarkers of HF before hospital admission to biomarkers during COVID-19 hospitalization to determine if changes in biomarkers predict poorer patient outcomes.

Strengths

Determining potential markers that explain the additional risk for poor outcomes associated with COVID-19 for patients with preexisting HF is important. Meeting these aims may result in improved outcomes as well as more precise care based on the patient's unique status. Prior studies have not examined the influence of clinical biomarkers on risk for poor outcomes before hospitalization with COVID-19 and prior studies did not compare HF patients with COVID-19 to other HF patients without COVID-19.

Limitations

Our results were limited by large amounts of missing clinical biomarkers and NYHA classification data. This may also be a limitation of abstracting data from the EHR. We do not know if the data were absent in the EHR or were not properly reported in the records given to the researcher. Patients were asked to stay at home in the beginning of the pandemic and the sample from 2020 to 2021 may not be a valid representation of the general HF population. However, we included HF hospital admissions from 2020 to 2023 to account for the beginning of the pandemic. We did not acquire the vaccination status of our patients included in the study because vaccines did not become readily available until late winter 2021. Given our study inclusion dates, we expect our data to be representative of an HF sample with and without COVID-19 vaccination.

Conclusions

Prehospital BNP levels and mortality were significantly different between the two cohorts with Cohort B (non-COVID group) having higher BNP values and significantly higher death rates. There were no significant differences between groups on prehospital NYHA classification. Our results demonstrate that biomarkers and NYHA classification do little to explain the added risk for patients with HF who become infected with COVID-19. Prospective studies are needed to examine biomarkers of patients with HF prior to COVID-19 infection to determine variables that may predict worse outcomes.

Table 2.1: New York Heart Association (NYHA) Classification

Class	Description	Symptoms
Class I	No limitation of physical activity	Ordinary physical activity does not cause symptoms
Class II	Slight limitation of physical activity	Comfortable at rest, but ordinary physical activity results in HF symptoms as: • Palpitations • Fatigue • Shortness of breath
Class III	Marked limitation of physical activity	Comfortable at rest, but less than ordinary activity results in HF symptoms Common symptoms include: • Shortness of breath • Fatigue • Pain
Class IV	HF symptoms present, even at rest	Discomfort with any physical activity. Unable to carry on any physical activity without symptoms of HF Symptoms increase during any activity including: • Persistent cough • PND • Swelling • Cognitive change

Table 2.2: Characteristics of Cohorts

Characteristic		Cohort		
		A (n=100)	B (n=100)	p-value
Age[1]				0.789
	Mean (SD)	74.5 (13.3)	74.0 (13.4)	
	Median (Q1-Q3)	75.0 (67.0-83.2)	74.5 (66.8-83.0)	
	Min-Max	33.0-99.0	33.0-100.0	
Sex[2]				1
	Female	49 (49.0%)	49 (49.0%)	
	Male	51 (51.0%)	51 (51.0%)	
Race/Ethnicity[2]				0.188
	Asian	4 (4.0%)	7 (7.0%)	
	Black or African American	13 (13.0%)	20 (20.0%)	
	Hispanic or Latino	19 (19.0%)	13 (13.0%)	
	White or Caucasian	43 (43.0%)	48 (48.0%)	
	Other/Unknown	21 (21.0%)	12 (12.0%)	
Language[2]				0.207
	English	80 (80.0%)	89 (89.0%)	
	Spanish	10 (10.0%)	6 (6.0%)	
	Other Language	10 (10.0%)	5 (5.0%)	

Note. 1.Continuous variables were compared with Wilcoxon's rank-sum test
2.Categorical variables were compared with chi-square test. SD: Standard Deviation
Total sample size: 200. Cohort A: HF with COVID-19; Cohort B: HF with no COVID-19

Table 2.3: NYHA and Clinical Biomarkers

Clinical Biomarkers & NYHA		Cohort		
		A (n=100)	B (n=100)	p-value
Brain Natriuretic Peptide (pg/ml)[1]		*n=64*	*n=72*	0.006
	Mean (SD)	401.9 (728.5)	700.0 (916.0)	
	Median (Q1-Q3)	216.0 (95.0-381.2)	308.0 (189.0-785.0)	
	Min-Max	21.0-4953.0	25.0-4200.0	
	Missing	36	28	
Creatinine (mg/dL)[1]		*n=76*	*n=77*	0.499
	Mean (SD)	1.5 (1.2)	1.3 (0.9)	
	Median (Q1-Q3)	1.2 (0.9-1.7)	1.2 (0.9-1.4)	
	Min-Max	0.4-7.6	0.5-8.1	
	Missing	12	10	
CRP (mg/dL)[1]		*n=24*	*n=23*	0.107
	Mean (SD)	5.4 (7.1)	2.4 (3.0)	
	Median (Q1-Q3)	2.7 (0.9-7.4)	1.5 (0.5-2.8)	
	Min-Max	0.3-32.1	0.3-13.2	
	Missing	76	77	
		n=87	*n=88*	
Platelet Count (10E3/uL)[1]	Mean (SD)	228.8 (103.5)	222.6 (97.2)	0.961
	Median (Q1-Q3)	214.0 (164.0-253.5)	215.0 (169.2-268.2)	
	Min-Max	38.0-625.0	22.0-547.0	
	Missing	13	12	
Prothrombin Time (sec)[1]		*n=51*	*n=62*	0.275
	Mean (SD)	14.8 (2.0)	17.2 (5.7)	
	Median (Q1-Q3)	14.4 (13.4-15.4)	14.6 (13.4-18.1)	
	Min-Max	9.8-22.3	12.1-34.7	
	Missing	49	38	
Troponin[2]		*n=47*	*n=41*	0.07
	Negative (<0.04)	36 (76.6%)	23 (56.1%)	
	Positive (>0.04)	11 (23.4%)	18 (43.9%)	
	Missing	53	59	
NYHA Class[2]		*n=41*	*n=39*	0.703
	1	7 (17.1%)	5 (12.8%)	
	2	20 (48.8%)	16 (41.0%)	
	3	12 (29.3%)	14 (35.9%)	
	4	2 (4.9%)	4 (10.3%)	
	Missing	59	61	

Note. 1.Continuous variables: Compared with Wilcoxon's rank-sum test. 2.Categorical variables: Compared with chi-square test. SD: Standard Deviation Cohort A: HF with COVID-19; Cohort B: HF with no COVID-19

Table 2.4: Patient Outcomes

Outcomes		Cohort		
		A (n=100)	B (n=100)	p-value
Length of Stay[1]				0.196
	Mean (SD)	8.3 (9.4)	6.6 (7.4)	
	Median (Q1-Q3)	5.0 (2.0-10.0)	4.0 (2.0-8.0)	
	Min-Max	0.0-59.0	0.0-40.0	
	Missing	0	1	
Readmission[2]				0.559
	No	65 (65.0%)	60 (60.0%)	
	Yes	35 (35.0%)	40 (40.0%)	
Readmission Type[2]				0.714
	30-day	24 (68.6%)	24 (60.0%)	
	60-day	9 (25.7%)	12 (30.0%)	
	90-day	2 (5.7%)	4 (10.0%)	
	Missing	65	60	
Mortality[2]				0.03
	Known Deceased	31 (31.0%)	47 (47.0%)	
	Survived	69 (69.0%)	53 (53.0%)	

Note. 1.Continuous variables were compared with Wilcoxon's rank-sum test
2.Categorical variables were compared with chi-square test SD- Standard Deviation: Readmissions within 90 days. Cohort A: HF with COVID-19; Cohort B: HF with no COVID-19

Table 2.5: Multivariate Models for Outcome Variables

Multivariate Models **All biomarkers except troponin are on log scale**					
Outcome: Length of Stay					
Predictor	Estimate	95% CI Lower	95% CI Upper	p-value	n=76
Cohort A vs. B	2.19	-2.72	7.09	0.385	
Ethnicity/Race					
Asian vs. White/Caucasian	0.24	-10.71	11.18	0.966	
Black/African American vs. White/Caucasian	3.37	-3.61	10.36	0.348	
Hispanic/Latino vs. White/Caucasian	4.41	-1.96	10.78	0.179	
Other/Unknown vs. White/Caucasian	-3.55	-12.85	5.75	0.457	
BNP (pg/ml)	-0.32	-2.40	1.75	0.760	
Troponin (Positive vs. Negative)	-0.33	-6.34	5.67	0.913	
Outcome: Mortality					
Predictor	OR	95% CI Lower	95% CI Upper	p-value	n=76
Cohort A vs. B	0.70	0.24	2.04	0.512	
Asian vs. White/Caucasian	0.17	0.01	2.04	0.164	
Black/African American vs. White/Caucasian	0.41	0.08	2.01	0.274	
Hispanic/Latino vs. White/Caucasian	0.34	0.09	1.30	0.115	
Other/Unknown vs. White/Caucasian	0.20	0.02	2.00	0.169	
BNP (pg/ml)	1.69	1.05	2.71	0.029	
Troponin (Positive vs. Negative)	1.93	0.51	7.31	0.331	
Outcome: Readmission					
Predictor	OR	95% CI Lower	95% CI Upper	p-value	n=72
Cohort A vs. B	1.15	0.43	3.08	0.774	
Black/African American vs. White/Caucasian	1.29	0.33	5.05	0.715	
Hispanic/Latino vs. White/Caucasian	1.19	0.35	4.06	0.786	
Other/Unknown vs. White/Caucasian	1.32	0.22	7.89	0.761	
BNP (pg/ml)	0.96	0.64	1.46	0.861	
Troponin (Positive vs. Negative)	0.99	0.29	3.40	0.991	

Note: BNP: Brain Natriuretic Peptide.OR: Odds Ratio. Cohort A: HF with COVID-19; Cohort B: HF with no COVID-19

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Chapter Four: Heart Failure and Long COVID (Third Manuscript)

Relationship of Prehospital Clinical Biomarkers and New York Heart Association Classification on Development of Long COVID among Heart Failure Patients

Abstract

Background: There is a critical gap in the identification and management of long COVID among those with heart failure (HF). This study aimed to determine if: (1) there was a difference in prehospital clinical biomarkers and New York Heart Association (NYHA) classification in the development of long COVID among those hospitalized with HF and coronavirus disease 2019 (COVID-19), (2) biomarkers, NYHA, and long COVID could predict mortality, hospital length of stay (LOS), and readmissions, and (3) biomarkers and NYHA could predict long COVID.

Method: A retrospective medical record review was conducted among 100 HF patients at an academic medical center in Southern California. Patients hospitalized with COVID-19 between January 2020 and December 2023 were included. Thirteen of our sample of 100 developed long COVID. Biomarkers of brain natriuretic peptide (BNP), troponin, prothrombin time, platelet count, creatinine, and c-reactive protein were abstracted. Data were analyzed using bivariate and multivariate analyses.

Results: There were no differences between biomarkers and NYHA class between those with and without long COVID (p values 0.04 – 1.00). Biomarkers, NYHA, and long COVID did not predict mortality, LOS, and readmissions (p values 0.06-0.94). Finally, biomarkers and NYHA classification did not predict the development of long COVID (p 0.21-0.65).

Conclusions: There was no difference between biomarkers and NYHA classification in the development of long COVID or poor outcomes. However, our findings were limited by missing data and a small percentage of patients who developed long COVID.

Background

Long COVID is a growing problem worldwide. It is known that long COVID accounts for about 5.4 to 17.9 million individuals globally and 700,000 of these are seen in the U.S. alone[1]. It is estimated that about 7.5% of adults in the U.S. are experiencing persistent symptoms three or more months after COVID-19 infection[2]. In addition, about 10% to 30% of those infected with COVID-19 experience long-term symptoms[1,3–5]. While long COVID is seen among all ages, the highest percentage of diagnoses are made between the ages of 36 to 50 years[3–5] .

Long COVID is associated with COVID-19 infection severity, and there is also evidence that increased age and presence of comorbidities are risk factors for developing long COVID[6–9]. Among individuals that tested positive for COVID-19, those that had five or more symptoms in the first week of infection were significantly more likely to experience long COVID after 28 days (odds ratio (OR) 3.95, confidence interval (CI) 95% 3.10–5.04)[6]. There is some growing knowledge that certain long COVID symptoms, mostly those associated with systemic and neurologic conditions including cognitive changes, can last for years [5,10]. A study found that fatigue and intermittent headaches were the most commonly reported symptoms of long COVID persisting for 28 days or more with a prevalence of 97.7% and 91.2% respectively[6]. Other common symptoms of long COVID include dyspnea, anosmia, and numbness that are not attributable to underlying neurologic conditions[6,11,12].

Currently, there are no established diagnostic tests for the identification of long COVID[6,11,12]. Persistent symptoms in those with a history of COVID-19 infection that last beyond three months, and symptoms that cannot be explained by an alternative diagnosis, are defined as long COVID[13]. There are studies showing that a large percentage of long COVID

symptoms take place within three to six months after a COVID-19 infection[14–16]. Some long COVID symptoms can last for weeks, months, or even years after a COVID-19 infection[6,11,12].

There is a large gap in the scientific knowledge among long COVID in heart failure (HF) patients. The number of long COVID studies that include individuals with HF are scarce[17,18]. There are currently no validated effective treatments for long COVID, and clinical management of long COVID patients is challenging given that providers are not equipped to identify and treat long COVID[1,5,6,10,11,19].

Clinical biomarkers may be important predictors of outcomes for HF patients with COVID-19 and resulting long COVID. There are preliminary studies that identified associations between certain clinical biomarkers and COVID-19 at the time of hospitalization, and elevated levels of these clinical biomarkers were associated with symptom severity, progression of COVID-19, and overall worse clinical outcomes[1,6,11,20,21]. These biomarkers include brain natriuretic peptide (BNP), cardiac troponin, creatinine, prothrombin time (PT), platelet count, and C-reactive protein (CRP)[1,6,21–23]. Studies show that patients with elevated cardiac biomarkers during COVID-19 infection have higher creatinine ($p<0.001$), and specifically, CRP levels were found to be sensitive markers of acute COVID-19 disease [37,39].

There is initial evidence that elevation in cardiac troponin, CK-MB and BNP levels during hospitalization and at time of hospital admission to be prognostic of 28 day all-cause mortality of COVID-19 including mortalities soon after admission [36,39]. Among patients that died from COVID-19, cardiac troponin had the highest sensitivity for predicting death: standardized mean difference (SMD= 0.96, 95% CI= 0.71-1.22, $p<0.001$) and NT-proBNP (SMD = 1.15, 95% CI= 0.83-1.48, $P<0.001$)33. Innovative approaches such as the use of prehospital (2 weeks to 3

months prior to hospital admission) clinical biomarkers may provide a viable approach to identification of individuals with HF at high-risk for the development of long COVID.

New York Heart Association (NYHA) classification is a standardized tool utilized universally among HF patients to assess functional status and to guide clinical management. NYHA classification allows for the identification of illness progression and provides a simple way to assess the extent of HF exacerbation[21,24–26].

Preliminary evidence demonstrates a higher risk for adverse outcomes from long COVID among HF patients, and there are significant gaps in science including: diagnosing long COVID, effectively treating symptoms of long COVID, identifying whether HF exacerbation is correlated with increased risk of long COVID, and identifying whether clinical biomarkers can predict high risk HF patients to develop long COVID[24,27,28].

Syndemic Theory

This study is grounded in the Syndemic theory which helps explain the rationale for investigating the combined effects of a HF diagnosis and long COVID. The purpose of the Syndemic theory is to describe the effects of co-occurring diseases (HF and long COVID) that may increase the severity of each condition and outcomes[19,29]. Syndemic theory provides an explanation for generating new hypotheses by focusing on synergies and co-occurring diseases[12,29]. It also provides a rationale for how disease processes interact with one another.

Purpose/Aim

The purpose of this study was to determine if: (1) there was a difference in prehospital clinical biomarkers and NYHA classification in the development of long COVID among hospitalized HF patients with COVID-19, (2) prehospital biomarkers, NYHA, and long COVID

could predict mortality, hospital length of stay (LOS), and readmissions, and (3) prehospital biomarkers and NYHA could predict long COVID.

Methods

Design, Sample, and Setting

This was a retrospective study using electronic health record (EHR) data from the University of California, Los Angeles Health System. A total of 100 HF patients hospitalized between January 2020 and December 2023 with positive polymerase chain reaction (PCR) for COVID-19 infection were included. Of these, 13 patients were diagnosed with long-COVID after hospital admission between the dates set for the study (January 2020- December 2023). Prehospital clinical biomarkers and NYHA classification data were compared between those with HF and COVID-19 (n=87) and the HF patients who developed long COVID (n=13). Inclusion criteria were women and men with racially diverse backgrounds.

Participant inclusion criteria were: having a HF diagnosis, PCR confirmed COVID-19 infection, presence of long COVID as determined by international classification of diseases (ICD)-9 codes, and hospitalization between January 2020 and December 2023. Prehospital NYHA classification and clinical biomarkers including BNP, troponin, platelet count, PT, creatinine, and CRP were included 2 weeks to 3 months before hospital admission. The prehospital clinical biomarker and NYHA classification data were obtained from patients' outpatient clinic visits that took place within the same institution prior to their hospital admissions. The 2 weeks to 3 months timeframe was selected to ensure the biomarker and NYHA classification data were measured prior to COVID-19 infection. Given that COVID-19 infection generally takes 14-15 days to resolve, 2 weeks before admission was selected to ensure the clinical biomarker data were reflective of the patient's prehospital baseline (prior to COVID-

19 infection)[37]. Given that HF patients generally have 3 month follow up, 3 month was selected as the distant time point. Exclusion criteria were patients less than 18 years of age and the presence of any organ transplants.

Protocol

The data were extracted from the EHR through a deidentified data query service available from the institution. To extract the data, a request was made to include patients with HF diagnosis and COVID-19 infection between January 2020 and December 2023 and to include a list of clinical biomarkers, NYHA classification, death rates, admissions dates, and discharge dates for each patient. The data extraction was done according to the protocol set in place for this study which required detailed criteria to be set by the statisticians to allow for accurate query of data.

None of the patients had all the clinical biomarkers available for data extraction. Patients that were missing one biomarker alone were selected first for inclusion in the data then those that had two missing biomarkers and so on until n=100 was reached. The University of California, Los Angeles Institutional Review Board approved the study as exempt given that the design was an analysis of deidentified EHR.

Measures

NYHA classification and clinical biomarker data including BNP, troponin, PT, platelet count, creatinine, and CRP were collected for each patient before hospitalization. BNP is a marker of cardiac stress with normal levels that are less than 100 pg./mL, and troponin is a measure of a protein in the blood that is indicative of damage to the heart muscle (normal troponin <0.04 ng/mL)[35–38]. PT and platelet count are measures of clotting factors in the blood with normal levels that are between 11.1 to 13.1 seconds and 150 to 350 x10E3/uL

respectively[36,39]. Creatinine is a marker of kidney function with normal levels that are less than 1.5mg/dl while CRP is a protein that is made in the liver, and it is a marker of systemic inflammation (normal CRP <1.0mg/dL)[39,40].

To identify prehospital biomarkers, each patient's hospital admission and clinical biomarkers that fell 2 weeks to 3 months before hospital admission were included. If patients had several of the same biomarker data available before hospital admission, the closest biomarker date to the hospital admission was included for analysis. The availability of the NYHA data that fell within the 2 weeks to 3-month timeframe was limited given that our sample included some HF patients that were stable and had longer follow up periods than 3 months. Therefore, any available NYHA classification data before hospital admission were included for analysis.

Clinical Outcomes

The outcome measures included death rates, hospital LOS, and hospital readmissions. All mortality data from the time of hospitalization until December 2023 were included in the analysis. Hospital LOS was calculated by the admission and discharge dates for each patient. Hospital readmissions were analyzed based on 30-day, 60-day, and 90-day hospitalizations after the primary admission for each patient. Those who had emergency department visits without hospitalization were not counted as hospital readmissions.

Data Analysis

Power analysis indicated that a sample size of 100 HF patients resulted in 80% power to detect a d=0.8 difference in biomarkers and NYHA classification between the two groups (with and without long COVID) with a 2-tailed alpha < 0.05 using independent samples t-test[30]. Based on the power analysis, nearly one standard deviation (SD) class difference for NYHA and one unit difference for clinical biomarkers would be needed for a detectable effect size[26,31–34].

To characterize the study population and to make comparisons between groups, descriptive statistics (means, medians, minimum and maximum ranges) were used for baseline demographic and clinical information. The differences between HF patients with COVID-19 (n=87) and those that developed long COVID (n=13) were characterized by using bivariate analysis. The continuous variables were compared with Wilcoxon's rank-sum test, and the categorical variables were compared with the chi-square test.

The clinical biomarkers and long COVID were then included in the multivariate analysis to identify predictors of the three outcome variables. Three separate models were estimated for each outcome: mortality, hospital LOS, and hospital readmission. Data was not normally distributed and all biomarkers except troponin were log transformed for inclusion in the multivariate analysis. Linear regression was used for LOS outcome while logistic regression was used for the mortality and readmission outcomes. Another multivariate model, using logistic regression, was tested to identify predictors of long COVID.

None of the prehospital clinical biomarkers and NYHA classification were found to be significant in our bivariate analysis. Therefore, we included most of the prehospital biomarker variables in Model 1 given the linear nature of LOS outcomes which provided more statistical power with a different method of estimation. For Model 2 and Model 3 (binary outcomes), the number of predictors that could be included was limited due to sample size and number of events. C-reactive protein and NYHA class were excluded from these models due a large amount of missing data. Due to having large numbers of missing prehospital biomarker and NYHA classification data, missing data were not imputed.

Results

Baseline Characteristics

Data were collected from 100 hospitalized adult HF patients with COVID-19 of which 13 developed long COVID after hospitalization with COVID-19. Patients with COVID-19 (n=87) had a mean age of 75 years, were 50.6% (n=44) male, 44.8% White, 17.2% Hispanic or Latino, 11.5% Black or African American, and 4.6% Asian. Patients who developed long COVID had a mean age of 71.4 years and were 53.8% (n=7) male, 30.8% White, 30.8% Hispanic or Latino, and 23.1% Black or African American. The demographic and clinical characteristics of the sample are summarized in Table 2.

NYHA Classification and Clinical Biomarkers

Bivariate analysis was used to determine any differences in clinical biomarkers and NYHA classification among HF patients with and without long COVID. Prehospital dates of 2 weeks to 3 months were required for biomarker inclusion in the study, and there were large amounts of missing data. We do not know if the data were missing from the record or were not abstracted as requested. The mean prehospital BNPs for those with and without long COVID were 208.0 (SD 145.4) pg./ml and 425.7 (SD 767.8) pg./ml, p=0.621 respectively. The mean prehospital CRP was 1.6 (SD 2.2) mg/L for patients with long COVID and 5.9 (SD 7.4) mg/L for those without long COVID p= 0.15 (Table 3).

Patients' NYHA classification for patients with long COVID were 20.0% (n=2) in Class I, 50.0% (n=5) in Class II, 30.0% (n=3) in Class III, and no patients in Class IV. For those without long COVID-19 were: 16.1% (n=5) in Class I, 48.4% (n=15) in Class II, 29.0% (n=9) in Class III, and 6.5% (n=2) in Class IV (p=1.0). The remaining clinical biomarkers are summarized in Table 3.

Mortality, Length of Stay, and Readmission Outcomes

Patients with and without long COVID had 23.1% (n=3) and 32.2% (n=28) deaths in Cohort A and Cohort B respectively (p=0.75). The mean hospital LOS was 7.5 (SD 7.6) days for those with long COVID and 8.4 (SD 9.7) days for those without long COVID (p=0.69). Hospital readmissions for patients with and without long COVID were 38.5% (n=5) and 34.5% (n=30) respectively (p=0.77) (Table 4).

The variables from the bivariate analysis were then included in the multivariate analyses to identify any variables that could be predictors of our outcomes of interest and long COVID. While more variables were included in the hospital LOS model, only BNP and troponin markers and Ethnicity/Race were included in the mortality and readmission models because of small numbers of data. A model was constructed for each outcome; hospital LOS (Model 1), mortality (Model 2), and readmissions (Model 3). BNP was the only variable that approached significance as a predictor of mortality after adjusting for ethnicity/race, troponin, and long COVID (OR:1.98, 95% CI, 0.97-4.01, p=0.059). Hospital LOS (Model 1) and readmissions (Model 3) were not statistically significant (Table 5).

Finally, we sought to determine if any of the prehospital biomarkers and NYHA classification could predict the development of long COVID (Model 4). This model was limited by the large number of missing biomarker data. Therefore, only BNP and creatinine biomarkers and NYHA classification were included for analysis. The model was not significant (Table 6).

Discussion

The findings from this study were negative and only BNP approached significance as a predictor of mortality (p=0.059). In the general population, the data suggest that 10% to 30% of COVID-19 infected patients develop long term COVID-19 effects, long COVID[1]. Our study included a total of 100 HF patients who were hospitalized with COVID-19. Of these, 13 patients

developed long COVID. While 13% is similar to the reported statistics of those that develop long COVID, a sample size of 13 was likely too small, and thus our study was underpowered. Furthermore, we had many missing data for prehospital clinical biomarkers and NYHA classification within the period of 2 weeks to 3 months before hospital admission.

This was an exploratory study of long COVID among HF patients infected with COVID-19. Our study compared HF patients without long COVID-19 to patients with long COVID to identify any differences in biomarkers that could explain the development of long COVID and result in worse clinical outcomes (death, readmissions, and longer LOS). This is a clinically important difference given that not every HF patient develops long COVID. Our study aims were important in that we needed to identify predictors of long COVID, and the outcomes for patients with long COVID. While our results did not show significance, the study aims are justified by its exploratory nature and should be repeated in a fully powered study.

Strengths

The aims of the study were conceptually grounded and supported by a comprehensive literature review. Our study was one of the first to utilize clinical biomarkers to study long COVID among HF population. Other studies also did not compare HF patients to each other to account for the effects contributed by COVID-19 infection compared to HF exacerbation.

Limitations

Our study was limited by the small sample size, missing prehospital clinical biomarker data, and NYHA data resulting in a lack of power. Another limitation is the modest number of patients who developed long COVID. Long COVID patients were identified through ICD-9 codes. We expect that some patients in the early stages of the COVID-19 pandemic may have been missed because the diagnosis was not recorded in the list of ICD-9 codes. Additionally,

there are currently no established criteria to diagnose long COVID among providers, and the long COVID symptoms are subjective which may have resulted in some patients with chronic COVID symptoms not being diagnosed. Additionally, this is a retrospective study design involving medical record review which may lead to measurement error. We did not acquire the COVID-19 vaccination status of the patients included in the study because the vaccine was not available until late winter 2021. Given our study inclusion dates (2020-2023), we expect our data to be representative of an HF sample with and without COVID-19 vaccination.

Implications

Long COVID continues to reduce the quality of life among patients with HF. Long COVID causes debilitating symptoms and may lead to the inability to work and suffer from disability[42,43]. The studies among HF patients with long COVID are scarce. There is a need to determine potential markers that explain the additional risk for poor outcomes associated with COVID-19 and long COVID for patients with preexisting HF. Identifying factors that increase the risk of developing long COVID among vulnerable HF patients can aid in timely detection, diagnosis, and treatment which can improve outcomes.

Conclusions

We did not detect a statistically significant difference in prehospital biomarkers and NYHA classification for HF patients with and without long COVID. Given the premise of our aims were grounded in the literature, we recommend larger, fully powered studies to identify predictors of long COVID for patients with HF.

Table 3.1: New York Heart Association (NYHA) Classification

Class	Description	Symptoms
Class I	No limitation of physical activity	Ordinary physical activity does not cause symptoms
Class II	Slight limitation of physical activity	Comfortable at rest, but ordinary physical activity results in HF symptoms as: • Palpitations • Fatigue • Shortness of breath
Class III	Marked limitation of physical activity	Comfortable at rest, but less than ordinary activity results in HF symptoms Common symptoms include: • Shortness of breath • Fatigue • Pain
Class IV	HF symptoms present, even at rest	Discomfort with any physical activity. Unable to carry on any physical activity without symptoms of HF Symptoms increase during any activity including: • Persistent cough • PND • Swelling • Cognitive change

Table 3.2: Characteristics of the Sample

Characteristic		Groups		p-value
		HF without Long COVID (n=87)	HF with Long COVID (n=13)	
Age[1]				0.31
	Mean (SD)	75.0 (13.2)	71.4 (13.7)	
	Median (Q1-Q3)	76.0 (68.5-83.5)	72.0 (63.0-82.0)	
	Min-Max	33.0-99.0	52.0-93.0	
Sex[2]				1
	Female	43 (49.4%)	6 (46.2%)	
	Male	44 (50.6%)	7 (53.8%)	
Race/Ethnicity[2]				0.456
	Asian	4 (4.6%)	0 (0.0%)	
	Black or African American	10 (11.5%)	3 (23.1%)	
	Hispanic or Latino	15 (17.2%)	4 (30.8%)	
	White or Caucasian	39 (44.8%)	4 (30.8%)	
	Other/Unknown	19 (21.8%)	2 (15.4%)	
Language[2]				0.099
	English	72 (82.8%)	8 (61.5%)	
	Spanish	7 (8.0%)	3 (23.1%)	
	Other Language	8 (9.2%)	2 (15.4%)	

Note. 1.Continuous variables were compared with Wilcoxon's rank-sum test
2.Categorical variables were compared with chi-square test. SD: Standard Deviation
Total sample size: 100

Table 3.3: NYHA Classification and Clinical Biomarkers

Clinical Biomarkers & NYHA		HF without Long COVID (n=87)	HF with Long COVID (n=13)	p-value
BNP (pg./ml)[1]		*n=57*	*n=7*	0.621
	Mean (SD)	425.7 (767.8)	208.0 (145.4)	
	Median (Q1-Q3)	229.0 (95.0-397.0)	148.0 (119.5-291.5)	
	Min-Max	21.0-4953.0	31.0-455.0	
	Missing	30	6	
Creatinine (mg/dL)[1]		*n=76*	*n=12*	0.127
	Mean (SD)	1.6 (1.2)	1.0 (0.3)	
	Median (Q1-Q3)	1.2 (0.9-1.8)	1.0 (0.9-1.2)	
	Min-Max	0.4-7.6	0.7-1.6	
	Missing	11	1	
CRP (mg/dL)[1]		*n=21*	*n=3*	0.149
	Mean (SD)	5.9 (7.4)	1.6 (2.2)	
	Median (Q1-Q3)	2.8 (1.0-7.7)	0.4 (0.3-2.2)	
	Min-Max	0.3-32.1	0.3-4.1	
	Missing	66	10	
Platelet Count (10E3/uL)[1]		*n=75*	*n=12*	0.487
	Mean (SD)	228.1 (108.4)	232.8 (68.2)	
	Median (Q1-Q3)	208.0 (163.0-246.0)	226.5 (168.8-283.0)	
	Min-Max	38.0-625.0	132.0-340.0	
	Missing	12	1	
Prothrombin Time (sec)[1]		*n=46*	*n=5*	0.536
	Mean (SD)	14.8 (2.1)	14.1 (1.7)	
	Median (Q1-Q3)	14.5 (13.4-15.4)	14.3 (13.9-14.3)	
	Min-Max	9.8-22.3	11.6-16.3	
	Missing	41	8	
Troponin[2]		*n=43*	*n=4*	0.56
	Negative	32 (74.4%)	4 (100.0%)	
	Positive	11 (25.6%)	0 (0.0%)	
	Missing	44	9	
NYHA Class[2]		*n=31*	*n=10*	1
	1	5 (16.1%)	2 (20.0%)	
	2	15 (48.4%)	5 (50.0%)	
	3	9 (29.0%)	3 (30.0%)	
	4	2 (6.5%)	0 (0.0%)	
	Missing	56	3	

Note. 1.Continuous variables were compared with Wilcoxon's rank-sum test 2.Categorical variables were compared with chi-square test. SD: Standard Deviation. Total sample size: 100

Table 3.4 Patient Outcomes

Outcomes		Groups		p-value
		HF without Long COVID (n=87)	HF with Long COVID (n=13)	
Length of Stay[1]				0.685
	Mean (SD)	8.4 (9.7)	7.5 (7.6)	
	Median (Q1-Q3)	5.0 (2.0-10.0)	5.0 (1.0-9.0)	
	Min-Max	0.0-59.0	0.0-25.0	
Readmission[2]				0.765
	No	57 (65.5%)	8 (61.5%)	
	Yes	30 (34.5%)	5 (38.5%)	
Readmission Type[2]				0.04
	30-day	23 (76.7%)	1 (20.0%)	
	60-day	6 (20.0%)	3 (60.0%)	
	90-day	1 (3.3%)	1 (20.0%)	
	Missing	57	8	
Mortality[2]				0.749
	Known Deceased	28 (32.2%)	3 (23.1%)	
	Not Known Deceased	59 (67.8%)	10 (76.9%)	

Note. 1.Continuous variables were compared with Wilcoxon's rank-sum test
2.Categorical variables were compared with chi-square test. SD: Standard Deviation
Readmissions within 90 days.

Table 3.5 Multivariate Models for Outcome Variables

Model 1. Outcome: Length of Stay					
Model: Linear Regression					
Predictor	Estimate	95% CI Lower	95% CI Upper	p-value	n=36
Long COVID	2.37	-13.60	18.35	0.774	
Encounter Age	0.06	-0.35	0.46	0.788	
Male vs. Female	-2.61	-14.12	8.90	0.661	
Other Language vs. English	2.78	-13.95	19.52	0.748	
Spanish vs. English	-17.47	-38.61	3.66	0.120	
Asian vs. White/Caucasian	-5.07	-25.29	15.15	0.628	
Black/African American vs. White/Caucasian	-0.78	-22.79	21.23	0.945	
Hispanic/Latino vs. White/Caucasian	15.87	-5.15	36.90	0.154	
Other/Unknown vs. White/Caucasian	-11.56	-31.52	8.40	0.269	
BNP (pg/ml)	-0.69	-4.85	3.47	0.748	
Creatinine (mg/dL)	8.31	-1.33	17.94	0.106	
Platelet Count (10E3/uL)	-0.79	-9.00	7.43	0.853	
Prothrombin Time (sec)	5.81	-45.27	56.89	0.826	
Troponin (Positive vs. Negative)	-2.31	-15.56	10.94	0.736	
Model 2. Outcome: Mortality					
Model: Logistic Regression					
Predictor	OR	95% CI Lower	95% CI Upper	p-value	n=41
Long COVID	2.49	0.23	27.25	0.456	
Asian vs. White/Caucasian	0.75	0.03	16.84	0.856	
Black/African American vs. White/Caucasian	0.78	0.06	10.08	0.846	
Hispanic/Latino vs. White/Caucasian	0.34	0.06	2.09	0.247	
Other/Unknown vs. White/Caucasian	0.34	0.03	4.30	0.405	
BNP (pg/ml)	1.98	0.97	4.01	0.059	
Troponin (Positive vs. Negative)	1.99	0.30	13.12	0.475	

Model 3. Outcome: Readmission					
Model: Logistic Regression					
Predictor	OR	95% CI Lower	95% CI Upper	p-value	n=39
Long COVID	4.09	0.34	48.78	0.265	
Black/African American vs. White/Caucasian	0.51	0.04	6.97	0.612	
Hispanic/Latino vs. White/Caucasian	2.30	0.46	11.39	0.308	
Other/Unknown vs. White/Caucasian	1.15	0.12	11.38	0.907	
BNP (pg/ml)	1.03	0.56	1.89	0.936	
Model 4. Outcome: Long COVID					
Model: Logistic Regression					
Predictor	OR	95% CI Lower	95% CI Upper	p-value	n=31
BNP (pg/ml)	0.68	0.14	3.46	0.647	
Creatinine (mg/dL)	0.21	0.02	2.36	0.208	
NYHA Class	1.71	0.37	7.94	0.496	

Note: BNP: Brain Natriuretic Peptide. OR: Odds Ratio

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Chapter Five: Dissertation Summary

Significance of the Study

This systematic review and research illustrate the value of prehospital clinical biomarkers and NYHA classification levels. Gaps were identified through a systematic literature review concerning the lack of use of clinical biomarkers before hospitalization with COVID-19 infection. The review also identified gaps in having studies that compare HF patients to other HF patients with and without COVID-19. Instead, the available literature compared clinical biomarkers of HF patients only at the time of hospitalization with COVID-19 to non-HF patients with COVID-19. Therefore, it is not feasible to conclude whether worse outcomes seen among the HF population from COVID-19 are a result of COVID-19 infection, overall worsening of HF symptoms independent of the infection, or a new HF symptom seen secondary to acute COVID-19 infection.

The first database research study showed that there were statistically significant differences in prehospital BNP levels and deaths among HF patients with and without COVID-19 with higher levels seen in the HF group without any COVID-19 infection. The prehospital BNP was also the only variable that was predictive of mortality after adjusting for ethnicity/race, troponin, and COVID-19. The second database research study showed no statistically significant differences between HF patients with and without long COVID.

The dissertation revealed the importance of having prehospital clinical biomarkers and NYHA classification levels. The results also revealed the importance of comparing HF patients with COVID-19 to other HF patients without COVID-19 to account for the effects of the HF diagnosis itself on the outcomes seen.

Directions for Future Research

This dissertation revealed some directions for future research. Continued research comparing HF patients with and without COVID-19 is needed to answer the question of whether outcomes among the HF population infected with COVID-19 are due to HF diagnosis, COVID-19 infection, or combined effects of both. Future research is also needed to compare prehospital clinical biomarkers and NYHA classification before COVID-19 infection to clinical biomarkers and NYHA classification at the time of infection with COVID-19 to rule out the effects seen by HF diagnosis alone and COVID-19 alone among this population. This research should be repeated in larger samples with complete prehospital clinical biomarker data to determine variables that may be predictive of poor outcomes seen among the HF population.