OUTCOMES AND OPPORTUNITIES FOR REDUCING HEART FAILURE 30-DAY READMISSIONS AND MORTALITY FOR ACUTE CARE INTER-HOSPITAL TRANSFERS AT A MULTI-SITE HOSPITAL SYSTEM

A dissertation submitted
to Kent State University in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy

By

Stan Pokras

May 2020

Dissertation written by

Stan Pokras

B.A., Case Western Reserve University, 2010

M.P.H., Kent State University, 2016

Ph.D., Kent State University, 2020

Approved by

Melissa Zullo, PhD, Chair Doctoral Dissertation Committee

Lynette Phillips, PhD, Member, Doctoral Dissertation Committee

Jonathan VanGeest, PhD, Member, Doctoral Dissertation Committee

Richard Josephson, MD, Member, Doctoral Dissertation Committee

Joel Hughes, PhD, Graduate Faculty Representative, Doctoral Dissertation Committee

Accepted by

Jeffrey S. Hallam, PhD, Associate Dean for Research and Graduate Studies

Sonia Alemagno, PhD, Dean, College of Public Health

Table of Contents

Description **Page**

List of Tables

Table Number **Page**

Summary Abstract

Congestive heart failure is a growing epidemic within the American landscape with a prevalence of over six million patients with direct costs exceeding $32 billion annually. Post-discharge outcomes for patients with heart failure are poor and as high as 25% 30-day readmissions rates and 10% 30-day mortality rates. Inter-hospital transfer (IHT) of patients with heart failure is understudied and not well-known in the literature, although it is estimated to occur in 1.5%-4.5% of all inpatient encounters. The predictors of IHT of patients with heart failure from a community hospital to an academic medical center, post-discharge outcomes, and total cost outcomes within a multi-site hospital system were studied in this dissertation.

Multivariable logistic regression analysis found significant associations between higher severity of illness and odds of IHT from community hospitals to an academic medical center. Further analysis found 25% increased odds of 30-day mortality and 2.26 higher odds of 30-day readmissions of IHT patients compared to non-transfer patients. These poor post-discharge outcomes were also associated with higher severity of illness among patients with heart failure. IHT was associated with $2,015 in additional total costs compared to non-transfer patients, with those total cost increases associated with higher severity of illness and longer lengths of stay in the hospital. This research adds new information about the medical and economic aspects of IHT within a multi-site health system, while highlighting the need for future studies into these complex medical phenomena.

Chapter 1: Introduction

Background and Significance

There are approximately six million adults with heart failure in the United States, as of 2013 (Mayo Clinic, 2019). The five-year survival rate is only 50% and annual mortality from primary heart failure at 8%, and another 10% of mortality attributed to heart failure as a comorbidity (Feltner C, et al., 2014; CDC, 2017). Although heart failure is strongly associated with aging and worsening comorbidities, including diabetes, hypertension, obesity, and hypercholesteremia, the multifactorial disease process remains difficult to manage with 30-day post-discharge hospital readmissions reaching 25% and 30-day mortality as high as 10% (Feltner C, et al., 2014; Miro O, et al., 2017). Recent research has also shown that despite heart failure predominantly affecting the elderly, heart failure incidence has started to increase among adults ages 35-64, particularly minority groups (Glyn P, et al., 2019). Despite public reporting programs and ongoing national process improvement efforts, heart failure outcomes remain highly variable, although there is strong consensus that much improvement is needed to reduce both readmissions and mortality. In fact, reductions in readmissions have seen limited nationwide success, despite the Centers for Medicare and Medicaid Services (CMS) mandate of gradual reductions in heart failure readmissions (Glyn P, et al., 2019; Bergethon K, et al., 2016). Interestingly, the results have been mixed as reductions in heart failure readmissions have been associated with simultaneous increases in heart failure mortality (Dharmarajan K, et al., 2017; Wadhera R, et al., 2018; McIlvennen C, et al., 2015; Gorodeski E, et al., 2010; Krumholz H, et al., 2013). Although heart failure readmissions increase as the post-discharge timeframe increases, research has shown that 30 days post discharge is the opportune timeframe for evaluating treatment and improving outcomes (Feltner C, et al., 2014; CDC, 2017; Miro O, et al., 2017; Glyn P, et al., 2019; Bergethon K, et al., 2016; Dharmarajan K, et al., 2017; Wadhera R, et al., 2018; McIlvennen C, et al., 2015; Gorodeski E, et al., 2010; Krumholz H, et al., 2013; Epstein A, et al., 2011).

CMS CHF Population

CMS uses five primary inclusion criteria for defining the patients with heart failure (Centers for Medicare and Medicaid Services, 2018).

- Seventeen distinct ICD-10 principal diagnosis codes for heart failure: I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.9

Since the principal diagnosis is the highest coded diagnosis during an encounter episode, CMS only includes patients with the above seventeen principal diagnosis codes. Secondary diagnoses of heart failure are not used because of the focus on primary congestive heart failure as the main clinical factor affecting these patients. If secondary patients with heart failure are included, the patient population may become skewed due to more severe clinical conditions that are distinct from heart failure. Similarly, patients with heart failure are not included based on Medicare severity-diagnosis related group (MS-DRG). This methodology is used by CMS primarily because principal diagnoses are broader for capturing the heart failure population, where MS-DRGs are based on other comorbidities and have a significant role in reimbursement assessment (Centers for Medicare and Medicaid Services, 2016).

- Enrollment in Medicare Fee-For-Service or VA Beneficiaries due to available claims data – due to the availability of this publicly-reported data.

- Ages 65 and over – due to clinical distinctions between patients over and under 65 years of age.
- Discharged alive during the index encounter from acute hospital setting – deceased patients cannot be readmitted.
- Patients not transferred to another acute care hospital during encounter episode – CMS aggregates the encounter as one continuous episode of care.

Additionally, CMS uses four primary exclusion criteria for defining the heart failure patient population (Centers for Medicare and Medicaid Services, 2018).

- Lack of 30-day enrollment in Medicare Fee-For-Service or VA Beneficiaries post index discharge due to available claims data.
- Patients who were discharged/left against medical advice (LAMA).
- Subsequent heart failure admissions within 30 days that are considered part of the index admission.

The concept behind this exclusion is that a patient readmitted to an acute care facility cannot consider that readmission as an index discharge for another subsequent readmission. For example, if a heart failure patient is discharged on January 2, 2018 and readmitted on January 10, 2018 – that readmission on January 10th cannot be considered an index discharge for another 30-day window. The true readmission window for the index discharge runs from January 3, 2018 to February 2, 2018.

- Patients with procedure codes for left ventricular assist device (LVAD) implantation and heart transplantation.

Due to the complications and comorbidities associated with heart transplantation and LVAD, patients with the following ICD-10 principal or secondary procedure codes at the index discharge are excluded. Heart transplantation (02YA0Z0, 02YA0Z1, 02YA0Z2) and LVAD (02HA0QZ, 02HA0RS, 02HA0RZ, 02HA3QZ, 02HA3RS, 02HA3RZ, 02HA4QZ, 02HA4RS, 02HA4RZ).

CHF Treatment Guidelines

Despite extensive ongoing heart failure research, treatment guidelines for improving outcomes have remained high level for symptom and disease management, and there is a great deal of variability between hospitals and their programs, with most hospitals focusing on treatment and management of chronic conditions and acute hospitalizations (Feltner C, et al., 2014). This variability can, in part, be attributed to variability in continuity of care, clinical operations, hospital policies, and patient differences. Treatment issues can be compounded further if patients are transferred from one hospital to another for treatment – known as an inter-hospital transfer (IHT) (Tierney W, 2018). An acute inter-hospital transfer is generally defined as an encounter episode in which a patient is transferred from one acute care hospital to another acute care hospital for continuing treatment. From a methodological standpoint, this can occur as either a discharge from hospital A and subsequent admission to hospital B, or it can be a direct transfer without a technical discharge in the patient record. Either way, the patient is being physically transported from one hospital to another for treatment within the same encounter and continuum of care. Another term for IHT is contiguous hospitalizations, although this term is rarely utilized – generally, studies refer to this event as inter-hospital transfers (Avaldi V, et al., 2017). Studies have shown that IHT is an area of patient care that is heavily under-studied for all clinical care populations – not just heart failure (Herrigel D, et al., 2016).

Research suggests that about 1.5% of all hospital admissions include an inter-hospital transfer, but that recorded information is limited to Medicare claims data ages 65 and up, since these records are available for public reporting purposes (Mueller S, et al., 2017). These numbers increase to approximately 4.5% for critical care networks, involving severe acute illnesses, such as pneumonia and sepsis (Iwashyna T, et al., 2009). Despite the relatively small percentage of hospital admissions with IHT, the transfer of patients from one hospital to another needs additional research since the actual number may be much greater than 1.5% owing to the lack of complete and available inter-hospital data sets. It is also important to note the context of IHT and consider that there are over 36.5 million annual hospital admissions in the United States, which means that even at 1.5% rate of IHT, that number is over half a million patients. The number rises to over 1.5 million patients at an IHT rate of 4.5% (American Hospital Association, 2019).

It is common practice to evaluate clinical care at the discharge hospital – where the patient spends the majority of their inpatient treatment time, but as previously described, not all patients are directly admitted to their discharging hospital. In fact, previous studies aggregated IHT from one facility to another as a single continuous episode of care (Miro O, et al., 2017). Although this methodology for contiguous hospitalizations is also used by CMS, it may be misleading because the complex nature of heart failure is susceptible to variation and transfers of care that are inherent to contiguous hospitalizations. Such variations may frequently be attributed to socioeconomic status, including access to care, cost, location, and clinical limitations (McAlister F, et al., 2013). Patients with heart failure tend to frequently be admitted to local community hospitals that are more homogenously dispersed, even though such hospitals are less equipped to offer optimal care for heart failure treatment and attention. Larger academic hospitals offer higher levels of care and services necessary to treat heart failure, but the effect of IHT is unclear on the continuum of care, despite the frequent necessity of such transfers (Sokol-Hessner L, et al., 2016). Additionally, the sickest patients may be unfit for transfer depending on proximity, which would increase the risk of subsequent readmission and mortality, and so sufficient care needs to be taken to ensure the IHT is conducted within appropriate clinical guidelines (Kiss T, et al., 2017).

One study compared heart failure readmission outcomes at the original discharge hospital versus a different hospital and concluded that same-hospital readmissions had lower length of stay and lower risk of mortality than different-hospital readmissions due to better continuity of care resulting from less fragmentation of attention among multiple hospitals (Dharmarajan K, et al., 2017). Another study compared heart failure readmissions among teaching and non-teaching hospitals and concluded that despite similarities in readmissions and mortality rates at both types of hospitals, the cardiology service lines at teaching hospitals had distinct patient populations that were not as readily seen in non-teaching hospitals (Palacio C, et al., 2014). This result suggested that larger academic medical centers were more equipped to offer necessary heart failure care than smaller community hospitals. However, transport to the appropriate discharge hospital is susceptible to the IHT process. This should involve necessary considerations of transport communication and transfer, pre-transfer stabilization and preparation, peri-transport monitoring and also, documentation and handoff at the receiving hospital in order to ensure optimal transfer of the patient (Kulshrestha A & Singh J, 2016). Without proper IHT care, complications may occur resulting in patients becoming sicker as they are transferred based on three key parameters: distance between transfer hospitals, quality of care at the hospitals, and relationship between the hospitals in terms of continuity of care (Lu X & Lu F, 2017). Consider a closed hospital system, such as University Hospitals, the distance between hospitals is a major factor, while quality of care and clinical integration are more streamlined and structured due to the continuous hospital ecosystem.

A recent study has shown that IHT is associated with worse outcomes than direct admission to an academic medical center (European Society of Cardiology, 2019). Although this research is clinically meaningful, it is frequently impossible to directly admit a patient to the appropriate hospital given proximity, cost, and other logistical and clinical reasons. Therefore, the IHT needs to be carefully reviewed and advanced so that its contribution to adverse patient outcomes, if any, is reduced and mitigated as much as possible. Interestingly, heart failure is often treated as an operational complication in IHT studies, so it is even more clinically meaningful to study heart failure as a defining feature of a cohort rather than a covariate (Mueller S, et al., 2018). It should be noted that this study was exclusively from a Medicare population, and found worsened mortality outcomes for IHT, but the results varied differentially by disease grouping. The topic of IHT is complicated further because Medicare claims data across contiguous hospitalizations is limited to streamlined public reporting methods and populations of 65 years of age and older (Miro O, et al., 2017). This limitation within the data makes it difficult to study the effect and outcome of IHT, particularly since the Medicare data aggregates the entire encounter, including the IHT. However, a closed hospital ecosystem of IHT data would provide meaningful data on this under-studied topic that has not been done to date.

Other factors have been studied to understand readmission and mortality outcomes for patients with cardiovascular conditions. One study looking at post-discharge outcomes of stroke found higher 30-day readmissions and mortality for patients with stroke, but IHT was not assessed in this population (Nouh A, et al., 2016). A study focusing specifically on IHT for myocardial infarctions found that IHT was associated with longer post-discharge follow ups, which resulted in higher rates of 30-day readmissions without observable changes in mortality (Vora A, et al., 2016). The study authors concluded that “transfer patients face additional logistic barriers after discharge that may explain why they are less likely to have prompt follow up visits" (Sokol- Hessner L, et al., 2016). Conversely, patients with heart failure who visit their PCP within 30 days post discharge have been shown to have a reduced readmissions risk, but many patients do not consult their PCP within an appropriate window or are unable to follow up and thus suffer worsened outcomes (Misky G, et al., 2010). Outpatient cardiology consults have also been shown to have a significant reduction on heart failure readmissions and mortality (Koser K, et al., 2018; Edmonston D, et al., 2019).

Meanwhile, a previous study concluded that after adjusting for covariates, despite delays in percutaneous coronary intervention for myocardial infarction patients, there was no difference in outcomes for length of IHT time between hospitals (Diepen S, et al., 2012). One study used a readmission risk score model to determine the predictive value for heart failure readmissions but found no statistically-significant results – of note, their model did take into consideration IHT (Formiga F, et al., 2017). Patients treated by cardiologists during their inpatient hospital admission have also been shown to have lower readmission rates compared to patients treated by hospitalists, and more than half of patients with heart failure are already treated by cardiologists (Beresford L, 2013). These results broadly suggest that IHT has a poorly understood effect on outcomes, but due to the multifactorial natures of IHT and heart failure, there has not been a focused research study on this topic. Existing research has been more focused on the broad outcomes of heart failure patient, rather than the transfer effect of these patients between hospitals (Huynh Q, et al., 2018).

A recent study compared acute care IHT patients to emergency department transfer patients and found that IHT patients had a 36% higher chance of in-hospital death, even after adjusting for various risk factors (Sokol-Hessner L, et al., 2016). This study is meaningful because nearly 900,000 patients were included in the cohort population across 158 different academic medical centers. However, no data was collected on heart failure status and because the large sample size was across numerous hospitals, the nuances of continuity of care for patients were lost in the final results. As another study eloquently explained, "the transfer of patients between acute care hospitals is a common but non-standardized process leading to variable quality and safety" (Mueller S, et al., 2019). This variability is unavoidable within medical care, but the operational and clinical underlying decision-making needs to be as direct as possible for optimal patient outcomes. IHT for patients with heart failure definitely seems to be an area where this streamlining is much needed but heavily understudied, despite the large number of patients with heart failure.

In addition to the poor post-discharge outcomes faced by IHT patients with heart failure, the costs associated with hospitalizations and treatment of heart failure are staggering. Annual direct costs currently exceed $32 billion and are projected to reach $100 billion by 2030. The average lifetime cost of heart failure is $110,000 per patient per year, primarily comprised of hospitalization costs (Inamdar A & Inamdar A, 2016). With frequent multiple annual hospitalizations, it is unsurprising that heart failure costs are so high and continue to grow. Although there is evidence that patients who experienced an IHT had higher costs compared to non-transfers, the effect of IHT on cost outcomes remains unclear in the current literature (Tierney W, 2018; Mueller S, 2018).

The average cost of a single heart failure hospitalization is $23,077 per patient (Heidenreich P, et al., 2011; Titler M, et al., 2008; Wang G, et al., 2010). The costs can double for heart failure encounters with an IHT due, in part, to additional treatment, testing, and hospitalization costs (Sokol-Hessner L, et al., 2016). As a result, a heart failure IHT encounter could cost between $34,000 and $70,000 compared to $23,077 for a non-transfer case (Sokol-Hessner L, et al., 2016; Mohr N, et al., 2016). This difference in costs is particularly meaningful when considering that IHT does occur among patients with heart failure but the drivers of higher cost for these IHT encounters is understudied. Meaningful cost outcome data could optimize patient flow within and between hospitals, as well as resource allocation and treatment, to hopefully improve post-discharge outcomes.

Current State

Despite the various studies focusing on IHT for different populations, no study to date has reviewed coded heart failure and IHT from community hospitals to an academic medical center. One recent study did look at IHT for admitted and treated patients with heart failure at a core hospital and outcome of such transfers to collaborating hospitals (Yamaguchi T, et al., 2018). However, a search on PubMed using the key words "inter-hospital transfer" and "heart failure" returned only eight results. Of the eight search results, only three actually studied IHT as exposure variables and associations with either all-cause outcomes,[21] ECMO transfers (Dalmau M, et al., 2014), or primary angioplasty (Tarkin J, et al., 2015). Another study focused on acute myocardial infarctions for Medicare patients found that IHT rates exceeded 44%, and not all such transfers were to the ideal destination hospitals having the best outcomes (Iwashyna T, et al., 2010). All-cause outcomes have already been previously discussed, while ECMO transfers were shown to have comparable results with and without IHT (Mueller S, et al., 2018), and primary angioplasty delays due to IHT were concluded to be related more to the distinctness of that patient sub-population rather than failures in hospital operational systems (Vora A, et al., 2016).

Searching with keywords "contiguous hospitalization" and "heart failure" resulted in one tangentially-relevant paper about acute heart failure, which recommended rapid transfer of acute patients with heart failure to the nearest appropriate hospital with a cardiology department, particularly a cardiac intensive care unit (Mebazaa A, et al., 2015). This conclusion is important because it underlies the premise that IHT delay access to the appropriate cardiac care and increase patient lead times, which does concur with many other IHT study outcomes. Ultimately, no single study has focused on the proposed topic of this thesis, particularly within a closed hospital ecosystem of complete patient records and data over a continuous two year period to assess the predictors, outcomes, and costs of inter-hospital transfers from community hospitals to an academic medical center.

Specific Aims

The purpose of this study was to explore the predictors of IHT, post-discharge outcomes of IHT, and the cost-outcomes of IHT of patients with heart failure who are transferred from community hospitals to an academic medical center.

Specific aims included the following:

1) Determine the sociodemographic and clinical predictors of IHT of patients with heart failure from community hospitals to an academic medical center
2) Understand the effect of IHT of patients with heart failure on 1) 30-day unplanned readmissions and 2) 30-day mortality compared to academic medical center non-transfer patients
3) Conduct a cost analysis of IHT and total cost outcomes to determine the associated sociodemographic, clinical, and medical predictors of total costs

Chapter 2 Manuscript I

Sociodemographic and Clinical Predictors of Acute Care Inter-Hospital Transfer at a Multi-Site Hospital System

Abstract

Introduction: The sociodemographic, clinical, and medical predictors of inter-hospital transfers are not well known, and the association between IHT and post-discharge outcomes is unclear. No study has evaluated the sociodemographic and hospital level clinical predictors of IHT from community hospitals to an academic medical center in patients with heart failure. This study investigates the predictors of IHT patients with heart failure at community hospitals within a multi-site hospital system.

Methods: Data was collected from a multi-site hospital system in Cleveland, Ohio from 01/2017-12/2018 of patients with heart failure, including sociodemographic, clinical, and medical predictors and IHT outcome status. Multivariable logistic regression modeling evaluated the significant and potentially significant predictors of IHT of patients with heart failure to determine predictors of IHT among community hospital patients to an academic medical center.

Results: Significant predictors of IHT were primarily clinical and medical level predictors. Younger age, cancer, diabetes, lipid disease, blood pressure disorders, lack of dementia, evaluation by admitting cardiologist, emergency department patients, and patients arriving from a healthcare facility with previous history of admissions were all predictors of higher odds of IHT to an urban academic medical center from community hospitals.

Conclusion: This study is the first to determine the significant predictors of IHT from community hospitals to an academic medical center. These predictors may assist clinicians in a hospital setting to assess if patients with heart failure may need an IHT and thereby reduce lead time to transfer.

Introduction

Nearly 1.5 million patients are transferred annually from one hospital to another during their encounter in an inter-hospital transfer (IHT) process (American Hospital Association, 2019). This transfer may occur for many reasons, including medical necessity, limitations at the referring hospital, or availability of necessary resources at the destination hospital (Sokol-Hessner L, et al., 2016; Kiss T, et al., 2017; Palacio C, et al., 2014; Kulshrestha A & Singh J, 2016; Lu X & Lu F, 2017; European Society of Cardiology, 2019; Mueller S, et al., 2018). Multiple factors are necessary for appropriate IHT, including transport communication and transfer, pre-transfer stabilization and preparation, peri-transport monitoring, and documentation and handoff at the destination hospital (Kulshretha A & Singh J, 2016). Without proper IHT care, complications may occur resulting in patients becoming sicker as they are transferred based on three key parameters: distance between referring and destination hospitals, quality of care at the hospitals, and relationship between the hospitals in terms of continuity of care (Lu X & Lu F, 2017).

It is estimated that between 1.5% and 4.5% of all inpatient encounters involve an IHT from a referring to a destination hospital, and that higher severity of illness may be associated with overall higher likelihood of IHT (Iwashyna T, et al., 2009; American Hospital Association 2019). While previous studied have shown mixed results about the effect of IHT on mortality and readmissions, there is significant indication that IHT has an adverse effect on post-discharge outcomes (Mueller S, et al., 2017; European Society of Cardiology, 2019; Mueller S, et al., 2018; Dalmau M, et al., 2014). This association may have a differential impact based on patients' severity of illness, which would suggest that the context of IHT necessity is a combination of patient, hospital, and medical factors (Iwashyna T, et al., 2009). For patients suffering from congestive heart failure, IHT may be a necessary part of their continuum of care as exacerbations and complications occur that require treatment at hospitals offering higher levels of care. This reality for patients with heart failure highlights the importance of identifying and studying factors associated with heart failure outcomes, such as IHT.

Congestive heart failure affects over six million Americans, with recent studies indicating an increasing incidence among younger and minority populations (Glyn P, et al., 2019; Lee W, et al., 2019; McGregor A, et al., 2014; Dreyer R, et al., 2015). Both short and long-term outcomes for patients with heart failure are poor, and the multifactorial nature of heart failure complicates treatment and standardization, particularly among diverse populations that are differentially affected by heart failure (Knighton A, et al., 2018; Lu M, et al., 2016). The five-year survival rate is only 50%, 30-day mortality is as high as 10%, and 30-day readmissions are between 20-25% (Feltner C, et al., 2014; CDC, 2017; Miro O, et al., 2017; Gupta A, et al., 2018). These poor outcomes have remained despite all ongoing research and medical treatments available to patients with heart failure. There has not been a study specifically evaluating the effect of IHT from community hospitals to an academic medical center on 30-day mortality and readmissions outcomes in patients with heart failure, and the association between post-discharge outcomes based on IHT exposure is unclear. Patients with heart failure already have high mortality and readmissions rates, and it is important to study the predictors of IHT to find potential markers for improving heart failure outcomes.

Predictors of heart failure outcomes can be classified into two broad categories: patient level and hospital level factors. Patient level factors are the characteristics inherent to each specific patient, including age, race, ethnicity, sex, marital status, socioeconomic status (SES), and principal insurance payer. Additionally, medical characteristics of patients can be ascribed to patient level predictors, such as their chronic conditions and comorbidities (Inamdar A & Inamdar A, 2016; Shameer K, et al., 2017; Liu D, et al., 2019; Park C, et al., 2019). Due to the multifactorial nature of heart failure development and progression, there are many potential associated comorbidities, including blood pressure disorders (hypotension/hypertension), COPD, diabetes mellitus, kidney disease, liver disease, lipid diseases, stroke, smoking, alcohol, and previous history of major adverse cardiac events (Inamdar A & Inamdar A, 2016). Many of these predictors are based on the Charlson Comorbidity Index (CCI), which is a clinically-validated tool to aid in predicting 10-year mortality based on age and comorbidity status (Charlson M, et al., 1987; Quan H, et al., 2011; Radovanovic D, et al., 2014). In combination, these patient level factors comprise a significant portion of the sociodemographic and medical predictors commonly associated with heart failure study outcomes.

Hospital level predictors in heart failure studies are less standardized than patient level factors, partly because of the variability between hospitals and even within hospitals. One study included number of beds, specialists, nursing volume, location, teaching status, and occupancy rate (Kim S, et al., 2015). Another study only included hospital level factors of teaching status, heart failure clinic availability, and referral practices to other clinic programs (Gravely S, et al., 2012). While such hospital variables are of study outcome value, many of them are not applicable when assessing IHT necessity for clinicians in real time. In the UHHS integrated health system, patients with heart failure are frequently transferred to an academic medical center, which is an urban academic medical center. Thus, the hospital level factors that are important to the IHT process are associated with the patient encounter more so than the hospital facility itself, and include previous history of admissions, source of admission, admission unit, and physician specialty. Such predictors are more in line with IHT outcomes analysis because these are the variables that could be used to assess the need for IHT patients with heart failure who present at community hospitals.

Given the multifactorial nature of heart failure in a diverse patient population and the limited knowledge of exposure variable data for IHT patients, it is important to determine which predictors are associated with IHT as an outcome. The effect of IHT on post-discharge outcomes is unclear but may be dependent upon sociodemographic, medical, and hospital level clinical predictors. However, the exact nature of this relationship is unknown, although it is likely that medical predictors are important exposures. There is a need to study the specific predictors of IHT among patients with heart failure, and this research is limited. This type of study would assist clinicians in streamlining the determinative need of IHT based on the patient populations presenting at community hospitals, which could have positive downstream effects on post-discharge outcomes, such as readmissions, mortality, or costs. Such data would be particularly meaningful for clinicians to use in their real-time evaluation of patients with heart failure in the emergency department or immediately post-admission. These evaluations could improve treatment lead times among community hospitals by optimizing heart failure care or expediting the IHT process.

Short and long-term outcomes for patients with heart failure are poor with a 30-day mortality rate upwards of 10% (Miro O, et al., 2017; Lindennauer P, et al., 2013). In comparison, the 30-day mortality rate for COPD, another chronic and frequently concomitant disease in heart failure, is lower at around 8.6%. Such differences in mortality highlights that need for predictors of heart failure mortality to be studied in an effort to reduce the odds of death in this patient population. The association between IHT and 30-day mortality and readmissions is unclear, particularly in patients with heart failure, and the specific predictors associated with patients with heart failure experiencing IHT are unknown. By focusing specifically on the patient level (sociodemographic and medical) and hospital level (clinical) predictors of IHT, this study will examine potential predictors of IHT in patients with heart failure from community hospitals to an academic medical center.

Methods

Overview

This was a retrospective cohort study consisting of patients with heart failure admitted as inpatient encounters within seven integrated inpatient medical hospitals at University Hospitals Health System (UHHS). The study population consisted of patients with a principal diagnosis of congestive heart failure discharged between January 1, 2017 and December 30, 2018. This study was approved by UHHS of Cleveland, Ohio and the Kent State University Institutional Research Boards (IRB).

Study Population

Patients were eligible for study inclusion if they had an International Statistical Classification of Diseases and Related Health Problems (ICD-10) principal diagnosis code of heart failure (I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.9) and did not have a principal or secondary ICD-10 procedure code for heart transplantation (02YA0Z0, 02YA0Z1, 02YA0Z2) or left ventricular assist device (LVAD) implantation (02HA0QZ, 02HA0RS, 02HA0RZ, 02HA3QZ, 02HA3RS, 02HA3RZ, 02HA4QZ, 02HA4RS, 02HA4RZ). All patients were adults ages 25-103 who were 1) admitted and discharged from one of six community hospitals or 2) admitted but transferred from one of six community hospitals to an academic medical center and discharged during the study period. Only inpatient encounters were included to maintain consistency of care among patients with heart failure since observation/short stay encounters were almost exclusively shorter than 24 hours. Of note, less than 100 patients annually were admitted as observation/short stay patients with heart failure, while over 1,500 were admitted annually as inpatients with heart failure at community hospitals. Patients who were admitted to the hospital from jail/police/court of law (n=2) were excluded from the study population due to the unique differences of this subgroup – all other admission sources, statues, and locations were included for analysis. Patients who were discharged from the destination hospital as left against medical advice (n=48) were excluded because their medical care was incomplete, and attributing their post-discharge outcomes to previous clinical care could be misleading and inconclusive.

Data Source

Medical record data for all eligible patients were reported from UHCare Inpatient (Allscripts) – the inpatient EMR used by integrated hospitals within UHHS. The seven hospitals were selected due to their integrated clinical care pathways and information technology (IT) architecture among registration, coding, billing, and inpatient and outpatient electronic medical records (EMR). Additional data were collected from Midas+ Care Manager (Conduent) – a Quality Institute data entry and reporting application for coded patient-level registration, encounter, and discharge information.

Study Predictors

There was no single exposure variable in this study since the aim was to understand potential predictors of IHT outcomes. Thus, a total of 23 different potential predictors were evaluated as possible exposure variables. Due to the complex nature of heart failure and the generally higher severity of illness of heart failure, the following predictors were included in data collection and analysis and were also examined for potential confounding and interaction effects.

Age was coded as an ordinal categorical variable to assess the impact of increasing years of age on IHT outcome. A continuous variable was considered but not used because a single value increase in age would have been difficult to apply in a clinical setting, whereas stratified age was more applicable. Age groups were 25-59 (reference group), 60-69, 70-79, 80-89, and 90-103. The youngest patient was 25 years of age, and the oldest patient was 103 years of age.

Race was dichotomized as white (reference group) and non-white. The non-white group included black, Asian, Native American, Pacific Islander, Alaskan, and no data available. Ethnicity was not consistently available in the medical records and was not examined.

Sex was defined as male (reference group) vs. female.

Marital status was dichotomized as married (reference group) vs. unmarried. The married group included married and partnered. The unmarried group included single, widowed, divorced, separated, and no data available.

Principal payer/insurance type was used as a proxy for socioeconomic status (SES) and dichotomized as managed care/Medicare/traditional indemnity/HMO (high SES – reference group) vs. dual eligible/Medicaid/self-pay/other (low SES). Since Medicare eligibility broadly applies to adults 65 and older, the Medicare payer was aggregated with managed care, traditional indemnity and HMO, which all required payment by patients to maintain coverage of service. Similarly, patients with Medicaid, dual eligibility of Medicaid and Medicare, self-pay/indigent/charity care were considered as having low socioeconomic status based on their payer groups.

Previous admission history was dichotomized as no (reference group) vs. yes. This variable was defined as each unique patient who had at least one non-elective/unplanned admission to one of the seven integrated UHHS hospital during the July 2016-December 2016 pre-study period or multiple admissions during the study period of 2017-2018 that were not considered a readmission encounter. The purpose of this variable was to adjust for patients who had more frequent hospital admissions either during the pre-study period or during the actual study period;

however, to avoid multicollinearity with the 30-day readmissions outcome, only encounters that were not readmissions and within the 30-day readmissions window were included in this variable. Due to unavailable data outside the UHHS system, only patient encounters to the seven integrated hospitals were eligible for this covariate.

Admitting physician specialty was defined as the specialty of the physician who treated/evaluated the patient upon pre-admission or admission. The admitting physician was primarily responsible for evaluating if the patient should be admitted at the community hospital or transferred from the emergency department to an academic medical center. The groups were dichotomized as specialties of cardiovascular medicine (reference group) vs. other. The other group included lower volume divisions, such as emergency medicine, hematology oncology, and pulmonology due to their small patient populations.

Admission unit type was defined as the type of hospital unit the patient first entered when coming to the hospital. For IHT patients, this was the first admission unit at the referring hospital. Groups were dichotomized as emergency department (reference group) vs. inpatient units. Patients that started at urgent care and went to the emergency department were included in the emergency department data. Intensive care unit (ICU) patients were included in the inpatient unit data, since these are technically inpatient units. Additionally, most community hospitals do not have distinct ICUs for specific patient subgroups, and so stratifying ICU populations would not have been clinically meaningful.

Admitting source was defined as where the patient arrived from when coming to the UH hospital. Due to the variability of healthcare, patients were dichotomized as arriving to the hospital from home (reference group) vs. healthcare facility. Healthcare facilities included hospice, long-term acute care (LTAC), skilled nursing facility (SNF), psychiatric, intermediate rehab, or Veteran's healthcare facility.

Cluster Description

While sociodemographic and hospital level data was obtained from coded encounter data, medical comorbidities were collected using medical chart abstraction. The medical conditions of interest were defined based on the Charlson Comorbidity Index (CCI) disease groupings due to the existing literature validating this tool. However, since CCI was used to predict the risk of 10-year mortality, a composite variable was not created as the study outcome was IHT and not mortality (Charlson M, et al., 1987; Quan H, et al., 2011; Radovanovic D, et al., 2014). All patient medical data was abstracted using ICD-10 diagnostic coding, and each patients' top 25 diagnoses were chart abstracted for inclusion in disease groups referred to as clinical clusters. Each cluster was considered a dichotomous variable coded as the presence or absence of each disease group in the medical record.

Since each medical record included 25 available diagnoses, and the principal diagnosis for each patient was coded heart failure, 24 secondary diagnoses were manually reviewed for coded clinical clusters. If the presence of any disease grouping was coded in the medical record, the cluster was coded as yes for the specific disease group, regardless of the diagnosis number in the chart or how many times the diagnosis was listed in the medical record.

Clusters included 1) blood pressure defined as hypertension, hypotension, essential hypertension, or orthostatic hypertension; 2) cancer defined as active/recurrent leukemia, lymphoma, or tumor mass; 3) chronic obstructive pulmonary disease (COPD) defined as COPD and/or exacerbations; 4) connective tissue disease defined as lupus, scleroderma, arthritis, granulomatosis, myositis, polyangiitis, and/or Churg-Strauss Syndrome; 5) dementia defined as dementia or mild cognitive impairment; 6) diabetes defined as Type 1 diabetes, Type 2 diabetes, prediabetes, and/or any diabetic conditions; 7) kidney disease defined as renal disease, use of dialysis, uremia, and/or creatinine abnormality; 8) lipid disease defined as dyslipidemia and/or cholesterolemia; 9) liver disease defined as any liver condition, portal hypertension, hepatitis, and/or cirrhosis; 10) myocardial infarction (MI) defined as acute MI and/or history of MI; 11) peripheral vascular disease defined as peripheral vascular and/or peripheral arterial disease; 12) stroke defined as cerebrovascular infarction, transient ischemia attack (TIA), and/or hemiplegia; 13) alcohol defined as alcohol use, abuse, and/or alcohol-induced conditions; and 14) tobacco/Nicotine defined as tobacco/nicotine use, abuse, or tobacco/nicotine-induced conditions (Inamdar A & Inamdar A, 2016).

Study Outcome

The outcome variable was a dichotomous variable defined as the presence or absence of IHT from one of six community hospitals to an academic medical center during the encounter episode. Community hospital patients were either treated at the community hospital they presented at or were transferred directly to an academic medical center for treatment.

Sample Size Calculation

Due to the lack of consistent data on IHT frequency and status in the general population among studies, effect size estimation was limited. An estimated incidence of 4.5% in the overall population was used along with 3.0% incidence of IHT in the study sample based on preliminary data review (Hsieh F, et al., 1998; Llonzo N, et al., 2015; Hernandez-Boussard T, et al., 2017). The resulting minimum sample size was 1,344 patients in the study sample yielding 80% power with a 95% type one error rate (Rosner B, 2011). This estimation was in line with other studies using a crude sample size estimation of minimum 1,250 cases based on 23 possible predictors in this current study (Bujang M, et al., 2018). The final study sample included 3,248 cases and a 2.58% incidence rate of IHT.

Statistical Analysis

Sociodemographic, clinical and medical predictors were collected on all patients for 23 predictors. All predictors were stratified as categorical variables by IHT outcome. All analysis were conducted using SAS 9.3 (SAS Institute, Cary, NC, USA). Descriptive statistics were generated for covariates using frequency summaries for categorical variables. Differences between the groups were examined with chi-square tests for categorical variables and Fisher Exact Tests for categorical variables with frequencies of less than five patients for specific factors.

Univariate logistic regression was conducted with predictors using a p-value cutoff of 0.20. Significant predictors were entered into a multivariable logistic regression model and predictor levels were compared to reference groups (for categorical predictors) to determine significant adjusted odds ratios ($p<0.05$) based on IHT outcome. Multicollinearity was assessed using variance inflation factors and a cutoff of 10 or higher was used as an indication of high correlation. The final multivariable model did not include any predictors that exceeded the threshold. Using the significant predictors of the multivariable models, interaction terms were fit and tested based on possible and clinically-meaningful interaction effects between predictors. A cutoff of $p<0.05$ was considered a significant interaction term for potential predictors. The final multivariable model included one statistically-significant interaction term.

Results

A total of 3,250 patients were included in the study sample with 84 patients (2.58%) experiencing IHT to an academic medical center, and 3,166 patients (97.42%) being treated directly at their admitting community hospital. Patient ages ranged from 25-103 years of age. The mean age of IHT patients was 67.68 years (standard deviation: 14.80 years), and the mean age of non-transfer patients was 74.54 years (standard deviation: 13.81 years); p-value<0.0001.

Table 1 includes the frequency counts and percentages of the five sociodemographic predictors based on IHT outcome. Age (p=0.0003), sex (p=0.08), and SES (p=0.013) were significantly different between the two groups using a cutoff p-value=0.20. For the IHT patients, the majority were younger with increasing age being less frequent, while non-transfer patients were predominantly older with the majority above 70 years of age. While the majority of IHT patients were male, this relationship was opposite for non-transfer patients with the majority being female. The vast majority of patients in the study sample were high SES although a higher percentage of IHT patients were low SES compared to the non-transfer group.

Table 1: Sociodemographic characteristics by IHT outcome, n=3,248

		IHT		No IHT		
Characteristic		Number	Percent	Number	Percent	P-Value
Age in Years						0.0003
	25-59	24	28.57%	458	14.47%	
	60-69	21	25.00%	615	19.44%	
	70-79	21	25.00%	764	24.15%	
	80-89	14	16.67%	898	28.38%	
	90-103	4	4.76%	429	13.56%	
Race						0.90
	White	51	60.71%	1,943	61.41%	
	Non-White	33	39.29%	1,221	38.59%	
Sex						0.08
	Male	46	54.76%	1,426	45.07%	
	Female	38	45.25%	1,738	54.93%	
Marital Status						0.37
	Married	27	32.14%	1,168	36.92%	
	Unmarried	57	67.86%	1,996	63.08%	
Socioeconomic Status						0.13
	High SES	71	84.52%	2,837	89.66%	
	Low SES	13	15.48%	327	10.34%	

Table 2 includes the frequency counts and percentages of the four hospital clinical predictors based on IHT outcome. Previous admissions (p=0.07), admitting specialty (p=0.001), admit source (p<0.0001), and admit unit type (p=0.03) were significantly different between the two groups using a cutoff p-value=0.20. Although more than half of the IHT and non-transfer groups had a history of previous admissions, a larger percentage of IHT patients had previous admissions compared to non-transfer patients. Admitting specialty was highly different between the two groups with the majority of IHT patients evaluated by cardiovascular medicine, whereas the majority of non-transfer patients were evaluated by other specialties. Similarly, the admission source for IHT patients was almost exclusively from healthcare facilities, while less than 20% of the non-transfer patients were admitted to the hospital from healthcare facilities. The majority of patients in the study population were first admitted to the hospital in the emergency department, although a much higher percentage of non-transfer patients were first admitted to the emergency department than IHT patients.

Table 2: Clinical characteristics by IHT outcome, n=3,248

	IHT		No IHT		
Characteristic	Number	Percent	Number	Percent	P-Value
Previous Admissions					0.07
No	33	39.29%	1,558	49.24%	
Yes	51	60.71%	1,606	50.76%	
Admitting Specialty					0.001
Cardiovascular Medicine	69	82.14%	689	21.78%	
Other	15	17.86%	2,475	78.22%	
Admit Source					<0.0001
Home	5	5.95%	2,545	80.43%	
Healthcare Facility	79	94.05%	619	19.57%	
Admit Unit Type					0.03
Emergency Department	51	60.71%	2,686	84.49%	
Inpatient Unit	33	39.29%	416	15.11%	

Table 3 includes the frequency counts and percentages of the 14 medical predictors based on IHT outcome. Blood pressure (p=0.04), cancer (p=0.03), dementia (p=0.04), diabetes (p=0.02), lipid disease (p=0.0002), and myocardial infarction (p=0.20) were significantly different between the two groups using a cutoff p-value=0.20. Although the majority of study sample patients had blood pressure disease, a higher percentage had blood pressure diseases among the IHT patients than the non-transfer cases. The rate of cancer was similarly low among all patients, although twice as many non-transfer patients had cancer compared to IHT patients. The dementia rate was low in the study sample, but nearly three times as many non-transfer patients had dementia compared to IHT patients. Diabetes was observed in more than half of the study sample, but more patients had diabetes in the IHT group than the non-transfer group. Lipid disease was much more frequent in the non-transfer group with nearly two-thirds of non-transfer patients having lipid disease compared to less than one-half of IHT patients. Although the majority of study sample patients did not have a history of MI, the rate of MI was higher in the IHT group compared to non-transfers.

Table 3: Medical comorbidities by IHT outcome, n=3,248

Characteristic		IHT Number	IHT Percent	No IHT Number	No IHT Percent	P-Value
Blood Pressure						0.04
	No	26	30.95%	1,209	38.21%	
	Yes	58	69.05%	1,955	61.79%	
Cancer						0.03
	No	75	89.29%	2,523	79.74%	
	Yes	9	10.71%	641	20.26%	
COPD						0.80
	No	55	65.48%	2,029	64.13%	
	Yes	29	34.52%	1,135	35.87%	
Connective Tissue Disease						0.28
	No	70	83.33%	2,481	78.41%	
	Yes	14	16.67%	683	21.59%	
Dementia						0.04
	No	81	96.43%	2,829	89.41%	
	Yes	3	3.57%	335	10.59%	
Diabetes						0.02
	No	34	40.48%	1,510	47.72%	
	Yes	50	59.52%	1,654	52.28%	
Kidney Disease						0.68
	No	28	33.33%	1,123	35.49%	
	Yes	56	66.67%	2,041	64.51%	
Lipid Disease						0.0002
	No	47	55.95%	1,142	36.09%	
	Yes	37	44.05%	2,022	63.91%	
Liver Disease						0.81
	No	79	94.05%	2,989	94.47%	
	Yes	5	5.95%	175	5.53%	
Myocardial Infarction						0.20
	No	46	54.76%	1,952	61.69%	
	Yes	38	45.24%	1,212	38.31%	
Peripheral Vascular Disease						0.79
	No	79	94.05%	2,953	93.33%	
	Yes	5	5.95%	211	6.67%	
Stroke						0.29
	No	78	92.86%	3,016	95.32%	
	Yes	6	7.14%	148	4.68%	
Alcohol						0.43
	No	79	94.05%	3,022	95.91%	
	Yes	5	5.95%	142	4.49%	
Tobacco						0.74
	No	38	45.24%	1,373	43.39%	
	Yes	46	54.76%	1,791	56.61%	

Table 4 lists the seven sociodemographic and hospital-level predictors with a p-value of 0.20 or lower that were subsequently analyzed using univariate logistic regression analysis. Reference groups were coded in the model for all categorical predictors of IHT. Predictors of age, previous admissions, admitting specialty, admit source, and admit unit type were significant predictors in the unadjusted model. Although increasing age was associated with lower odds of IHT, the confidence intervals overlapped suggesting the association was not simply related to 10-year increases in age. Females had 32% lower odds of experiencing IHT than males, while low SES was associated with 59% higher odds of IHT than high SES, previous admissions increased odds of IHT by 50%, admitting physician specialty of other reduced the odds of IHT by 94% compared to cardiovascular medicine, admissions from healthcare facilities increased the odds of IHT by 6.5 times compared to home, and patients first admitted directly to an inpatient unit had 2.29 times the odds of IHT compared to emergency department patients.

Table 4: Univariate analysis of unadjusted odds ratios of sociodemographic and clinical predictors with p-value cutoff of 0.20

Variable (Level)		Unadjusted Odds Ratio	95% CI
Age			
	18-60	REF	
	60-69	0.65	0.36-1.19
	70-79	0.53	0.29-0.95
	80-89	0.30	0.15-0.58
	90-103	0.18	0.06-0.52
Sex			
	Male	REF	
	Female	0.68	0.44-1.05
Socioeconomic Status			
	High SES	REF	
	Low SES	1.59	0.87-2.90
Previous Admissions			
	No	REF	
	Yes	1.50	1.02-2.14
Admitting Specialty			
	Cardiovascular Medicine	REF	
	Other	0.06	0.03-0.11
Admit Source			
	Home	REF	
	Healthcare Facility	6.50	2.62-16.17
Admit Unit Type			
	Emergency Department	REF	
	Inpatient Unit	2.29	1.56-9.37

Table 5 lists the six medical predictors with a p-value of 0.20 or lower that were subsequently analyzed using univariate logistic regression analysis. Reference groups were coded in the model for all categorical predictors of IHT. Predictors of blood pressure, cancer, dementia, diabetes, and lipid disease were significant predictors in the unadjusted model. Blood pressure was associated with 38% higher odds of IHT, cancer was associated with 47% higher odds of IHT, dementia was associated with 69% lower odds of IHT, diabetes was associated with

68% higher odds of IHT, history of MI was associated with 33% higher odds of IHT, and lipid disease was associated with 45% higher odds of IHT.

Table 5: Univariate analysis of unadjusted odds ratios of medical predictors with p-value cutoff of 0.20

Variable (Level)		Unadjusted Odds Ratio	95% CI
Blood Pressure			
	No	REF	
	Yes	1.38	1.07-1.76
Cancer			
	No	REF	
	Yes	1.47	1.24-1.77
Dementia			
	No	REF	
	Yes	0.31	0.10-0.90
Diabetes			
	No	REF	
	Yes	1.68	1.19-1.96
Myocardial Infarction			
	No	REF	
	Yes	1.33	0.86-2.06
Lipid Disease			
	No	REF	
	Yes	1.45	1.29-1.69

The final multivariable model (Table 6) was analyzed using backwards logistic regression and resulted in a parsimonious multivariable model that converged, including age, cancer, diabetes, blood pressure, dementia, lipid disease, admitting specialty, admit unit, and an interaction term of admit source and previous admits as significant predictors of IHT to an academic medical center.

Table 6: Multivariable logistic regression model for predictors associated with IHT

Variable (Level)		Adjusted Odds Ratio	95% CI
Age			
	18-60	REF	
	60-69	0.68	0.34-1.35
	70-79	0.53	0.26-0.96
	80-89	0.34	0.16-0.73
	90-103	0.23	0.07-0.73
Cancer			
	No	REF	
	Yes	1.87	1.31-2.56
Diabetes			
	No	REF	
	Yes	1.97	1.55-2.68
Lipid Disease			
	No	REF	
	Yes	1.49	1.30-1.81
Blood Pressure			
	No	REF	
	Yes	1.40	1.16-1.82
Dementia			
	No	REF	
	Yes	0.47	0.08-0.95
Admitting Specialty			
	Cardiovascular Medicine	REF	
	Other	0.07	0.04-0.13
Admit Source*Previous Admits			
	Home without Previous Admissions	REF	
	Healthcare Facility with Previous Admissions	11.75	10.04-13.15
Admit Unit Type			
	Emergency Department	REF	
	Inpatient Unit	0.37	0.21-0.65

Discussion

This study provided the first evidence of significant associations between predictors of patients with heart failure and IHT from a community hospital to an urban academic medical center. These associations remained significant after adjusting for patient level and hospital level differences, as well as medical comorbidities. The inclusion of patient level sociodemographic

(Table 1) and hospital level clinical (Table 2) predictors was extremely important because the adjusted multivariable model indicated the predictors of patients who were at higher odds of IHT after adjustment for effect modification and study sample differences. These associations using the significant predictors of IHT in this multivariable model may help determine which patients are at higher odds of IHT, and this information could be used by clinicians to assess in near real-time which patients with heart failure should be transferred to an academic medical center and which patients should continue receiving care at the respective community hospitals.

The adjusted multivariable logistic regression model (Table 6) included eight predictors and one interaction term that were significantly associated with odds of IHT to an academic medical center. Eight of those predictors were associated with increased odds of IHT, while the presence of dementia was associated with lower odds of IHT. These associations were temporally unsurprising due to medical cogence in transferring sicker patients from a community hospital to an academic medical center for higher levels of care and treatment. The significant predictors are clinically meaningful because the effect of IHT on patient outcomes remains unclear, but there is indication that the association may be adverse. Thus, there may be an association between predictors of IHT and patient outcomes. As a result, the significant predictors of IHT in this multivariable model may subsequently aid clinicians in determining which patients with heart failure are at higher odds of poor outcomes.

The current study found that for every 10 years of increase in age for patients 60 years and older, there was approximately 15% lower odds of IHT to an academic medical center from a community hospital. However, due to the crossing of the confidence intervals, this stratification was not significant, and this may indicate that although increasing age is associated with lower odds of IHT, there is no meaningful difference between age ranges, although this predictor should still be considered when assessing need for IHT. It is possible that clinicians are less likely to transfer older patients due to concerns about the IHT process and patients' ability to withstand the transfer without deterioration in their medical state. This conclusion is supported by existing evidence that older patients tend to have higher severity of illness and fragility, which may be exacerbated more severely via IHT (Abraham W, et al., 2008). Additionally, clinicians may believe that younger patients with heart failure need more aggressive treatments to maintain care that is not available at community hospitals, whereas older patients require more maintenance-based care which can be provided at the community hospitals. Due to the extensive resources and services that are more widely available at an academic medical center, younger patients may simply benefit more extensively from IHT, where the IHT risk-benefit tradeoff is much higher for older patients who are treated at community hospitals instead.

This current study found no significant associations between sex and IHT outcome, although sex has been shown to have an effect on heart failure outcomes with females having better short and long-term outcomes than males (Savarese G & D'Amario D, 2018). Although more males than females experienced IHT in this current study sample, the non-transfer outcome group had more females than males, and the predictor was not significant in multivariable analysis (p=0.08). Similarly, no association was observed between race and IHT outcome in this current study with no observable differences in race based on IHT outcome. The lack of associations between these sociodemographic predictors and IHT may indicate that IHT decisions are clinically and operationally motivated, despite the variable outcome data in the literature of sex and race differences (Eisenberg E, et al., 2018; Mehta P & Cowie M, 2006). Given the likely conclusion that IHT was based on medical risk factors, sociodemographic risk factors were potential mediators of IHT rather than actual markers of IHT transfer necessity. For example, race had been previously shown to have differential effects on heart failure outcomes, but race was not a significant predictor of IHT in this current study (Chamberlain R, et al., 2018; Latafa J, et al., 2004; Huckfeldt P, et al., 2019; Chaiyachati K, 2018). This result may suggest that although there are underlying mediation effects of potential predictors, such as sex and race, these variables are not necessarily markers or predictors of IHT. Rather the patient level differences may be accounted for more meaningfully through medical predictors due to the lack of observed interaction effects between sociodemographic predictors and IHT outcomes.

Due to the complex nature of heart failure, numerous medical comorbidities are significantly associated with heart failure outcomes, including blood pressure disorders, kidney disease, diabetes, lipid disorders, etc. (Yancy C, 2013). This current study found a significant difference in the study sample of blood pressure, cancer, diabetes, lipid disease, and dementia between IHT and non-transfer outcome cases, but it is important to note that there are many other comorbidities that may be clinically relevant to heart failure outcomes. For example, kidney disease is associated with poor heart failure outcomes, but this current study found no association between kidney disease and IHT (Tuegel C & Bansal N, 2017; Grande D, et al., 2018). This result suggests that some chronic medical conditions, like kidney disease, may be mediators of heart failure but not predictors of IHT due to the frequency of disease in the heart failure population and presence of concomitant medical conditions. Diabetes is also a frequent comorbidity with heart failure, and patients with diabetes are frequently on medication, such as metformin (Inamdar A & Inamdar A, 2016). A recent systematic review evaluating metformin use including patients with heart failure concluded differential effects on outcomes, which may be supported by this current study indicating a 68% increase in odds of IHT for diabetic patients (Crowley M, et al., 2017). This increase in transfer odds of diabetics may suggest that patients with diabetes and heart failure have higher severity of illness, which mediates heart failure outcomes since more than half of the study sample was diabetic.

Patients with heart failure frequently have concomitant lipid disorders, such as hyperlipidemia or dyslipidemia (Inamdar A & Inamdar A, 2016). This current study found a 45% increased odds of IHT transfer for patients with lipid disease, which may indicate that there is an underlying pathophysiology with lipid disorders that mediate heart failure outcomes, or it may be the medications that these patients are prescribed. Due to lack of medication data available in this study, no clear conclusion was available as to this observation. Unsurprisingly, blood pressure disorders were associated with a 38% increase in odds of IHT, and this result was in line with previous studies indicating that majority of the patients with heart failure also suffered from some form of hypertension (Yancy C, et al., 2015). Cancer was associated with 47% increased odds of IHT in this current study, but the topic is currently actively researched with heart failure being studied as both an exposure and outcome of cancer (Bertero E, et al., 2018). Although some community hospitals offer cancer treatment, these services are limited, and clinicians may be reluctant to treat patients with heart failure with active or history of cancer due to the limited services available at these community hospitals. Thus, it may be operationally more practical and clinically safer to transfer this group of patients to an academic medical center to treat heart failure while monitoring cancer status in an environment that is better suited to mitigating potential risks and complications.

Lastly, presence of dementia among patients with heart failure was associated with reduced odds of IHT by 69%. This result was in line with previous studies indicating the increased prevalence of dementia and mild cognitive impairment in patients with heart failure (Adelborg K, et al., 2017). In a clinical setting where physicians are in need of determining IHT status, dementia may pose an operational challenge for some patients with heart failure who may be ill-suited for a transfer to another hospital. Clinicians may be hesitant to transfer a dementia patient who is likely living unmarried and has limited caregivers available at home. Although such scenarios may explain the lower odds of IHT for dementia, more research is needed to assess the impact of dementia on transfer status.

The medical predictors in this current study are relevant by suggesting differential effects of comorbidity treatment and management on heart failure IHT outcomes. All four medical predictors of increased odds of IHT (blood pressure, cancer, diabetes, and lipid disease) are chronic conditions that have both short and long-term effects on health outcomes, and so they should be studied carefully in the context of IHT status. Although dementia is associated with reduced odds of IHT, concomitant medical comorbidities require clinician assessment and evaluation in totality when assessing transfer need. Furthermore, a chronic medical condition may be more indicative of a mediator of transfer status rather than a true marker simply because these predictors are systemic and should be reviewed holistically by a clinician when determining the need for an IHT.

Over 80% of patients with heart failure who were treated solely at community hospitals arrived from home, whereas over 94% of transfer patients arrived from another healthcare facility. Patients with heart failure living at healthcare facilities are generally sicker and thus undergoing more consistent and routine medical care. Therefore, it was unsurprising that patients admitted to the hospital from another healthcare facility had higher odds of transfer to an academic medical center likely due to higher severity of illness ($p<0.0001$). More importantly, this admission source predictor was found to have an interaction effect with previous admission history indicating that patients admitted to the hospital from a healthcare facility with a history of previous admission had 11.75 times the odds of IHT (95% CI: 10.04-13.15) compared to patients arriving from home without a history of previous admissions. This association may be interpreted as patients with higher severity of illness having higher odds of transfer to an academic medical center based on their admission from a healthcare facility and previous history of admission to the hospital – two independent predictors of IHT with an interaction effect. From a clinician's perspective, it is possible that such high severity patients are also at higher risk of mortality and readmissions, and so the operational decision to transfer to an academic medical center for treatment is more pronounced and immediate for this group of high severity of illness patients with heart failure.

Physician specialty has been shown to have a significant effect on heart failure outcomes in previous studies (Palacio C, et al., 2014; Beresford L, 2013). In this current study, the specialty of the admitting physician was evaluated because that physician was integral in the IHT decision-making process. In other words, the admitting physician was either evaluating the patient to make the decision to transfer to an academic medical center in the emergency department or actually evaluating the patient for treatment upon admission at the community hospital prior to potential transfer to an academic medical center at some point later in the encounter. For encounters in which a physician with a specialty of cardiovascular medicine did not evaluate the patient, the odds of IHT to an academic medical center were 93% lower compared to cardiovascular medicine physicians. Since all the patients in this study had heart failure as their principal diagnosis, evaluation by a cardiologist could have been a recommendation, but this may could pose logistical or operational challenge due to staffing issues and volume. As a result, it could have been necessary for non-cardiologists to evaluate patients with heart failure, and such cases were significantly less likely to be transferred to an academic medical center. This was not a reflection of clinician skill or expertise, but rather an observation of the variability in services offered between smaller community hospitals and a large academic medical center that is fully equipped with all levels of cardiovascular services and care. There may also be a predisposition among community hospital cardiologists to preferentially transfer patients with heart failure to an academic medical center for treatment, but this could not be evaluated from the given data.

In line with admitting physician specialty, the admission unit was a significant predictor of IHT with patients first presenting to inpatient units having 63% lower odds of IHT to an academic medical center. This scenario is logistically reasonable since inpatient admissions are able to receive more prompt and expeditious care compared to emergency department patients where staffing and volume may adversely impact treatment and triage times. As a result, patients were more likely to be transferred to an academic medical center when presenting to the emergency department rather than an inpatient unit at the community hospital, and this effect did not vary depending on the type of inpatient unit (Fish-Trotter H, et al., 2018). Interestingly, no interaction effect was observed between admission unit and admitting physician specialty even though emergency department patients were being assessed by varying physicians depending on staffing.

One limitation in this current study was the lack of available data on patient income or household financial situation. Principal insurance payer was used as a proxy for socioeconomic status (SES) with a dichotomous categorization of high and low SES. High SES patients were those who could afford to pay for traditional indemnity/commercial insurance, managed care plans, health maintenance organizations (HMOs), and/or had qualifying Medicare from CMS. Conversely, patients on Medicaid, dual eligibility for Medicare and Medicaid, other forms of governmental financial insurance assistance based on poverty level, or self-pay patients were considered low SES. Previous studies had shown that low SES was associated with poor heart failure outcomes, particularly among disparate minority groups (Glyn P, et al., 2019; Lee W, et al., 2019; Groeneveld P, et al., 2019). In this current study, there was no significant difference in SES between IHT and non-transfer patients, and the predictor was also not significant in the multivariable model. Although payer is a limited proxy measure for SES, the lack of association with IHT may indicate that patients with heart failure are treated and transferred based on their severity of illness rather than ability to pay for treatment and transfer. More research is needed into the effect of payer as a proxy for SES on IHT outcomes.

In summary, younger age, cancer, diabetes, lipid disease, blood pressure disorders, lack of dementia, evaluation by admitting cardiologist, emergency department patients, and patients arriving from a healthcare facility with previous history of admissions were all significant predictors of higher odds of IHT to an academic medical center from community hospitals. One of the major strengths of this current study was that it had appropriate statistical power and sample size to determine any meaningful associations in multivariable logistic regression. Additionally, use of a continuous data set over two years of in-house UHHS data ensured a high level of precision within the data and complete medical records for the study population. As a result, all clinical data occurring within UHHS was complete to the best ability of the health system and clinical operations. Of note, two of the community hospitals are critical access hospitals, which offered limitations of certain services available to patients, but this was a feature of the hospitals rather than a limitation of the study design or analysis. Overall, due to the stringent inclusion and exclusion criteria, the heart failure population was homogenous and clinically-distinct, and the results had temporal and clinical meaningfulness.

Although this study was appropriately powered with adequate sample size, IHT was still an infrequent occurrence in the acute hospital setting. More studies with larger data sets, particularly among IHT groups, would be beneficial to further evaluate the associations observed in this study. Additionally, residual confounding was possible due to variables that were not able to be included in the analysis. For example, ethnicity has been associated with heart failure and race, but concise data on ethnicity was not available in the data set for analysis and adjustment (Inamdar A & Inamdar A, 2016; Latafa J, et al., 2004). The admitting physician specialty was abstracted from the medical record, and if there were multiple evaluations by different specialties, only the most recent specialty was recorded in the chart. This process may could have affected certain patients due to the holistic IHT decision-making process, but there was no way to assess this possibility based on the available data. Although in-house data from UHHS was used, such data was still limited by missing external hospital encounter data, such as if a patient visited another hospital system for medical care or provided incorrect self-reported information. There may have also been errors in the medical record from data entry at the encounter level, although data validation was performed to mitigate as many errors as possible.

Binary coding via manual chart reviews for clinical clusters was performed to capture medical diagnoses, and this process was susceptible to errors, including determination of which ICD-10 diagnoses qualified for inclusion. Generalizations were made for the dichotomous presence or absence of clinical clusters irrespective of duration or onset; however, in a chronically-ill heart failure population, it was reasonable for multiple comorbidities to be present. Lastly, less than 3% of the study population had more than 25 diagnoses in their medical record, but those other diagnoses were unable to be extracted from the medical record, and so only the top 25 diagnoses were reviewed for inclusion. The medical predictors used in this study were based on the Charlson Comorbidity Index but could also be modeled in future studies in other ways, including different comorbidities that factor into accounting for severity of illness. Different acuity scores or indices could provide additional evidence of associations between medical predictors and IHT outcomes.

Future studies could focus on geographic analysis using comprehensive data sets of patient commute times and distances to assess the impact of access to care for patients with heart failure based on their location. Additional research using more refined variables for SES, rather than just payer type, could also have meaningful clinical implications. The current study results should also be evaluated using more diverse medical populations or different groups of patients with heart failure. Heart failure is a very complex chronic condition that is associated with numerous patient and hospital level predictors, and it is possible that other predictors differentially affect IHT, and so these findings should be generalized among patients with caution. Larger analyses that are outcome, rather than exposure driven, may provide additional insights into the effects of IHT on the general population. Due to the unique study population of homogenous patients with heart failure within UHHS, these results may not be externally generalizable to other health systems across the United States, and so care needs to be taken to understand the results in context. Further studies should be done to compare other health systems or multiple health systems in aggregate data sets.

Chapter 3 Manuscript II

Heart Failure 30-Day Readmissions and Mortality Outcomes for Acute Care Inter-Hospital Transfers at a Multi-Site Hospital System

Abstract

Introduction: Heart failure 30-day mortality rates may reach 10%, while 30-day readmissions rates may exceed 25%. The five-year survival rate is only 50%. Treatment and coordination of care among patients with heart failure is complex, expensive, and results are mixed about the best strategies for improving outcomes. Inter-hospital transfer (IHT) between hospitals occurs when patients with heart failure need to be transferred to destination hospital for treatment, but the effects of IHT on 30-day outcomes are not well known.

Methods: Data was collected from a multi-site hospital system in Cleveland, Ohio from 01/2017 to 12/2018 of patients with heart failure, including IHT exposure, sociodemographic, clinical, and medical covariates, and 30-day mortality and readmissions outcomes. Two separate multivariable logistic regression models evaluated the associations between IHT from community hospitals to an academic medical center and 30-day mortality and 30-day readmissions to determine the effects of IHT on outcomes.

Results: IHT from community hospitals to an academic medical center was associated with increased odds of 30-day mortality (AOR: 1.25, 95% CI: 1.08-1.41) and 30-day readmissions (AOR: 2.26, 95% CI: 1.32-3.89) among patients with heart failure after adjustment for population differences.

Conclusion: This study is the first to specifically evaluate the associations of IHT with 30-day mortality and 30-day readmissions in patients with heart failure. The increased odds of adverse post-discharge outcomes for IHT patients with heart failure highlight the need for more research into the IHT process to improve these outcomes for this high-risk population.

Introduction

Congestive heart failure (CHF) is a growing epidemic in the United States affecting over six million adults, and that number has been increasing in recent years (Mayo Clinic, 2019; Feltner C, et al., 2014). Patients with heart failure suffer from poor long-term outcomes, including a 50% 5-year survival rate, with over 18% of all annual mortality in the United States attributed to heart failure complications (CDC, 2017). Short-term outcomes are also poor for patients with heart failure with 30-day readmissions as high as 25%, and 30-day mortality as high as 10% (Feltner C, et al., 2014; Miro O, et al., 2017). Although traditionally considered a chronic disease of the elderly, a new study indicates that the incidence of heart failure in the younger population under age 65 is steadily increasing, particularly among minority groups (Glyn P, et al., 2019). These poor outcomes and increasing prevalence of heart failure underscore the importance of improving survival and decreasing readmissions, but studies are mixed about which factors associated with heart failure are primary drivers of poor outcomes (Dharmarajan K, et al., 2017; Wadhera R, et al., 2018).

Treating patients with heart failure is complex because of frequent hospitalizations and reliance on advanced medical care, and many hospitals are simply not equipped to handle the complications and comorbidities associated with heart failure (Palacio C, et al., 2014; European Society of Cardiology, 2019; Mebazaa A, et al., 2015). Therefore, some patients with heart failure must be transferred from a referring hospital to a destination hospital via inter-hospital transfer (IHT), also referred to as contiguous hospitalizations (Tierney W, 2018; Avaldi V, et al., 2017). It is estimated that between 1.5% and 4.5% of all inpatient admissions in the United States involve an IHT, and IHT rates tend to increase in frequency with greater severity of illness upon admission (Mueller S, et al., 2017; Iwashyna T, et al., 2009; American Hospital Association, 2019). However, IHT is significantly understudied in the literature, and there are few available studies examining IHT exposure and heart failure outcomes. A Japanese study evaluated the one-year mortality and readmissions outcomes of heart failure patients who were stabilized and subsequently transferred from an academic medical center to community hospitals for long-term care. That study found no worsened outcomes for transferred patients compared to non-transferred patients (Yamaguchi T, et al, 2018). Yamaguchi's study, however, focused on patients with heart failure who were already stabilized and treated before IHT, whereas IHT typically occurs during initial assessment or when the need is determined post-initial admission making comparisons to the United States system difficult (McAlister F, et al., 2013; Sokol-Hessner L, et al., 2016; Yamaguchi T, et al., 2018). No study has focused specifically on post-discharge outcomes of patients with heart failure who were transferred from community hospitals to an academic medical center. Given the high prevalence of heart failure in the population and the much greater number of potentially less-equipped community hospitals than large academic medical centers, the effects of IHT on heart failure outcomes is an important relationship to study (Sokol-Hessner L, et al., 2016).

Although IHT should be evaluated holistically based on patient and hospital-level variables, other factors are part of the decision-making process. For example, patients may be unable to physically go to the destination hospital of medical necessity due to proximity or practical reasons, such as transportation, cost, or severity of illness. Hospitals may not have the necessary resources to treat certain patients with heart failure who are otherwise unable to travel other hospitals on their own. There may also exist policies or procedures that affect physician-decision making, and sometimes, patient preference may override all of these variables. Unfortunately, most of these operational variables are difficult to accurately quantify, whereas post-discharge outcomes of mortality and readmissions are ubiquitous for all patients with heart failure, regardless of IHT status.

Heart failure outcome studies are frequently focused on readmissions and/or mortality, although there is significant variability between which covariates are evaluated in study populations (Mueller S, et al., 2018; Nouh A, et al., 2017; Vora A, et al., 2016; Misky G, et al., 2010; Koser K, et al., 2018; Edmonston D, et al., 2019). Such variations in risk factors and methodologies complicate post-discharge guidelines because of the difficulty in standardizing recommendations given the highly diverse medical issues affecting patients with heart failure. Despite the plethora of ongoing heart failure research and national efforts to reduce heart failure readmissions since the implementation of the Hospital Readmission Reduction Program (HRRP) in 2012, heart failure readmissions have remained among the highest readmission populations (Feltner C, et al., 2014; McIlvennen C, et al., 2015). This difficulty in improving outcomes may indicate that additional research is needed into previously under-studied phenomena, such as IHT of patients with heart failure.

A recent study reviewed various patient-level and hospital-level factors associated with heart failure readmissions and mortality and concluded that patient-level characteristics explained significantly more of the variation than hospital-level factors. In fact, hospital-level factors did not account for any significant variation in that study, although the study authors were careful to point out that such findings should not be generalized to all hospitals and health systems (Park C, et al., 2019). While patient-level variables are certainly important factors for decision-making in heart failure treatment programs, hospital-level program variables, such as case management, and multidisciplinary interventions, have also had positive effects on heart failure outcomes (Charlson M, et al., 1987). It is important to include relevant covariates that may be associated with IHT and post-discharge outcomes in order to effectively study the heart failure population. IHT is likely a combination of patient and hospital-level variables, and so the evaluation of IHT exposure on heart failure outcomes would fill a fundamental gap in the literature. This study will examine the association between IHT status and 30-day mortality and 30-day readmissions outcomes for patients with heart failure transferred from community hospitals to an academic medical center, an urban academic medical center.

Methods

Overview

This was a retrospective cohort study consisting of patients with heart failure discharged as inpatient encounters from an academic medical center. All patients were transferred from one of six community hospitals within University Hospitals Health System (UHHS) or admitted directly to an academic medical center. The study population consisted of patients with a principal diagnosis of congestive heart failure discharged between January 1, 2017 and December 30, 2018. This study was approved by UHHS of Cleveland, Ohio and the Kent State University Institutional Research Boards (IRB).

Study Population

Patients were eligible for study inclusion if they had a current International Statistical Classification of Diseases and Related Health Problems (ICD-10) principal diagnosis code of heart failure (I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, or I50.9) and did not have a principal or secondary ICD-10 procedure code for heart transplantation (02YA0Z0, 02YA0Z1, 02YA0Z2) or left ventricular assist device (LVAD) implantation (02HA0QZ, 02HA0RS, 02HA0RZ, 02HA3QZ, 02HA3RS, 02HA3RZ, 02HA4QZ, 02HA4RS, 02HA4RZ). All patients were adults ages 22-100 who were 1) initially admitted to one of six community hospitals and experienced IHT to an academic medical center or 2) admitted and discharged entirely from an academic medical center during the study period. Only inpatient encounters were included to maintain consistency of care among patients with heart failure since observation/short stay encounters were almost exclusively less than 24 hours. Of note, less than 80 patients annually were admitted as observation/short stay patients with heart failure, while over 900 were admitted annually as inpatient encounters with a principal diagnosis of heart failure at an academic medical center. Patients who were discharged from the destination hospital as left against medical advice (n=26) were excluded because their medical care was incomplete, and attributing their post-discharge outcomes to previous clinical care could be misleading and inconclusive. Patients who died in the hospital during their inpatient encounter (n=38) were excluded because they were ineligible for any post-discharge outcomes. The final study sample included 1,880 patients.

Data Source

Medical record data for all eligible patients were reported from UHCare Inpatient (Allscripts) – the inpatient EMR used by integrated hospitals within UHHS. The seven hospitals were selected due to their integrated clinical care pathways and information technology (IT) architecture among registration, coding, billing, and inpatient and outpatient electronic medical records (EMR). Additional data were collected from Midas+ Care Manager (Conduent) – a Quality Institute data entry and reporting application for coded patient-level registration, encounter, and discharge information.

Readmissions data was obtained from Midas+ Care Manager using a reporting query called the Readmission Toolpack. Mortality data was obtained from the UHHS IT Department using the Ohio Department of Health's monthly Ohio Death Data (ODD) files provided through a secure server. The ODD files are downloaded monthly by the IT Department and cross-linked to patient encounters within UHCare Inpatient to identify the date of death of UHHS patients. The ODD files are available for download within 2-3 weeks after the end of a month, and this short lead time ensures that records are as concise and current as possible. Each ODD file includes additional mortality data that may not have been available during previous months to ensure historical data is complete and accurate.

Study Exposure

The study exposure was dichotomized as the absence or presence of IHT for patients with heart failure from community hospitals to an academic medical center. There were 79 patients who experienced IHT to an academic medical center during the study period, while 1,801 patients were non-transfer patients admitted and discharged directly from an academic medical center. The total study sample included 1,880 patients.

Covariates

Due to the complex nature of heart failure and the high severity of illness of patients, the following 26 covariates were included in data collection and examined in analysis to adjust for potential confounding and interaction effects.

Age was coded as an ordinal categorical variable to assess the impact of increasing years of age on outcomes. Age groups were 22-59 (reference group), 60-69, 70-79, 80-89, and 90-100. The youngest patient was 22 years of age, and the oldest patient was 100 years of age.

Total length of stay (LOS) was defined as the aggregate number of days the patient was in the hospital and coded as an ordinal categorical variable to assess the impact of longer hospital length of stay on outcomes. For IHT patients, total LOS was calculated as LOS at the community hospital, the time between transfer from the community hospital and an academic medical center, and the LOS at an academic medical center from arrival to discharge. A continuous variable was considered but not used due to the difficulty in applying a single value increase in LOS to retrospective evaluation of outcomes associated with IHT, as well as to adjust for outliers. LOS groups were 1-3 days (reference), 4-10 days, and 11-98 days. The shortest LOS was 1 day, and the longest LOS was 98 days. Of the 313 patients with LOS of 11-98 days, less than 10% were outliers with LOS exceeding 25 days. The total LOS value was rounded to the nearest whole day upon calculation due to the reporting methods of the data source supplying this information.

Race was dichotomized as white (reference group) and non-white. The non-white group included black, Asian, Native American, Pacific Islander, Alaskan, and no data available. Ethnicity was not consistently available in the medical records and was not examined.

Sex was defined as male (reference group) vs. female.

Marital status was dichotomized as married (reference group) vs. unmarried. The married group included married and partnered. The unmarried group included single, widowed, divorced, separated, and no data available.

Principal payer/insurance type was used as a proxy for socioeconomic status (SES) and dichotomized as managed care/Medicare/traditional indemnity/HMO (high SES – reference group) vs. dual eligible/Medicaid/self-pay/other (low SES). Since Medicare eligibility broadly applies to adults 65 and older, the Medicare payer was aggregated with managed care, traditional indemnity and HMO, which all required payment by patients to maintain coverage of service. Similarly, patients with Medicaid, dual eligibility of Medicaid and Medicare, self-pay/indigent/charity care were considered as having low socioeconomic status based on their payer groups.

Previous admission history was dichotomized as no (reference group) vs. yes. This variable was defined as each unique patient who had at least one non-elective/unplanned admission to one of the seven integrated UHHS hospital during the July 2016-December 2016 pre-study period or multiple admissions during the study period of 2017-2018 that were not considered a readmission encounter. The purpose of this variable was to adjust for patients who had more frequent hospital admissions either during the pre-study period or during the actual study period; however, to avoid multicollinearity with the 30-day readmissions outcome, only encounters that were not readmissions and within the 30-day readmissions window were included in this variable. Due to unavailable data outside the UHHS system, only patient encounters to the seven integrated hospitals were eligible for this covariate.

Attending physician specialty was defined as the specialty of the physician who primarily treated/evaluated the patient during the inpatient encounter. The attending physician was primarily responsible for treatment and medical decision-making at an academic medical center for the patients. The groups were dichotomized as specialties of cardiovascular medicine (reference group) vs. other. The other group included lower volume divisions, such as emergency medicine, hematology oncology, and pulmonology due to their small patient populations.

Discharge unit type was defined as the type of hospital unit the patient was discharged from at an academic medical center. Since all study patients were ultimately discharged from an academic medical center, groups were dichotomized as an academic medical center units of inpatient units (reference group) vs. intensive care units (ICU).

Admitting source was defined as the location the patient arrived from when coming to the UH hospital. Due to the variability of healthcare, patients were dichotomized as arriving to the hospital from home (reference group) vs. another healthcare facility. Healthcare facilities included hospice, long-term acute care (LTAC), skilled nursing facility (SNF), psychiatric, intermediate rehab, or Veteran’s healthcare facility.

Discharge disposition was defined as the status of the patient when leaving the hospital and coded as discharged to home (reference group) vs. discharged to other healthcare facility.

Outpatient care utilization was defined as patients who went to see an outpatient physician for medical care or evaluation within 30 days post index discharge from an academic medical center. This variable was dichotomized as no (reference group) vs. yes. Due to the complex care needs and comorbidities of heart failure, no specific outpatient care limitations were placed on which physician specialties were seen, but all study patients had at least one qualifying outpatient visit with a physician associated with their heart failure treatment and care. The qualifying outpatient encounter had to occur prior to potential readmissions to avoid misleading associations with outpatient care utilization post-readmission. Due to unavailable data outside the UHHS system, only outpatient encounters to the seven integrated hospitals were eligible for this covariate.

Cluster Description

Medical comorbidities were collected using medical chart abstraction and defined based on the Charlson Comorbidity Index (CCI) disease groupings due to the existing literature validating this tool. However, since CCI was used to predict the risk of 10-year mortality, a composite variable was not created as the study outcome was IHT and not mortality (Charlson M, et al., 1987; Quan H, et al., 2011; Radovanovic D, et al., 2012). All patient medical data was abstracted using ICD-10 diagnostic coding, and each patients' top 25 diagnoses were chart abstracted for inclusion in disease groups referred to as clinical clusters. Each cluster was considered a dichotomous variable coded as the presence or absence of each disease group in the medical record.

Since each medical record included 25 available diagnoses, and the principal diagnosis for each patient was coded heart failure, 24 secondary diagnoses were manually reviewed for coded clinical clusters. If the presence of any disease grouping was coded in the medical record, the cluster was coded as yes for the specific disease group, regardless of the diagnosis number in the chart or how many times the diagnosis was listed in the medical record.

Clusters included 1) blood pressure defined as hypertension, hypotension, essential hypertension, or orthostatic hypertension; 2) cancer defined as active/recurrent leukemia, lymphoma, or tumor mass; 3) chronic obstructive pulmonary disease (COPD) defined as COPD and/or exacerbations; 4) connective tissue disease defined as lupus, scleroderma, arthritis, granulomatosis, myositis, polyangiitis, and/or Churg-Strauss Syndrome; 5) dementia defined as dementia or mild cognitive impairment; 6) diabetes defined as Type 1 diabetes, Type 2 diabetes, prediabetes, and/or any diabetic conditions; 7) kidney disease defined as renal disease, use of dialysis, uremia, and/or creatinine abnormality; 8) lipid disease defined as dyslipidemia and/or cholesterolemia; 9) liver disease defined as any liver condition, portal hypertension, hepatitis, and/or cirrhosis; 10) myocardial infarction (MI) defined as acute MI and/or history of MI; 11) peripheral vascular disease defined as peripheral vascular and/or peripheral arterial disease; 12) stroke defined as cerebrovascular infarction, transient ischemia attack (TIA), and/or hemiplegia; 13) alcohol defined as alcohol use, abuse, and/or alcohol-induced conditions; and 14) tobacco/Nicotine defined as tobacco/nicotine use, abuse, or tobacco/nicotine-induced conditions (Inamdar A & Inamdar A, 2016).

Study Outcomes

Two outcome variables were analyzed independently: 30-day mortality and 30-day readmissions. Each outcome was a dichotomous variable defined as the presence or absence of the outcome of interest. Mortality was defined as any patient with heart failure who experienced all-cause within 30 days of discharge from an academic medical center based on ODD data. Readmissions was specifically defined as any patient with heart failure who experienced all-cause non-elective/unplanned readmission back to the seven integrated hospitals within 30 days of discharge from an academic medical center. This definition for readmissions also aligned with CMS's Hospital Readmission Reduction Program (HRRP) definition.

Sample Size Calculation

Two sample size calculations were performed due to the different mortality and readmissions analyses. Effect size estimation was based on 30-day heart failure mortality in the general population. An estimated incidence of 9% in the overall population was used along with 7% incidence of 30-day heart failure mortality in the study sample based on preliminary data review (Hsieh F, et al., 1998; Llonzo N, et al., 2015; Hernandez-Boussard T, et al., 2017). The resulting minimum sample size was 1,504 patients in the study sample yielding 80% power with a 95% type one error rate (Rosner B, 2011). This estimation was in line with other studies using a crude sample size estimation of minimum 1,400 cases based on 26 covariates in this current study (Bujang M, et al., 2018). The final mortality analysis included 1,880 cases and a 5.43% 30-day mortality rate.

For the readmissions analysis, an estimated incidence of 25% in the overall population was used along with 22% incidence of 30-day readmissions in the study sample based on preliminary data review (Hsieh F, et al., 1998; Llonzo N, et al., 2015; Hernandez-Boussard T, et al., 2017). The resulting minimum sample size was 1,593 patients in the study sample yielding 80% power with a 95% type one error rate (Rosner B, 2011). This estimation was in line with other studies using a crude sample size estimation of minimum 1,400 cases based on 26 possible covariates in this current study (Bujang M, et al., 2018). The final readmissions analysis included 1,880 cases and a 22.34% 30-day readmissions rate.

Statistical Analysis

Data was collected on IHT exposure, 30-day mortality and 30-day readmissions outcomes, and 26 covariates on all patients. All covariates were stratified as categorical variables by outcomes and two separate analyses were conducted based on outcome of interest. All analysis were conducted using SAS 9.3 (SAS Institute, Cary, NC, USA). Descriptive statistics were generated for covariates using frequency summaries for categorical variables. Differences between the groups were examined with chi-square tests for categorical variables and Fisher's Exact Test for categorical variables with frequencies of less than five patients for specific factors.

For the 30-day mortality analysis, univariate logistic regression was conducted with covariates using a p-value cutoff of 0.20. Significant predictors were entered into a multivariable logistic regression model and predictor levels were compared to reference groups (for categorical predictors) to determine significant adjusted odds ratios ($p<0.05$) based on mortality outcome using backwards logistic regression. Multicollinearity was assessed using variance inflation factors and a cutoff of 10 or higher was used as an indication of high correlation. The final multivariable model did not include any variables that exceeded the threshold. Using the significant predictors of the multivariable models, interaction terms were fit and tested based on possible and clinically-meaningful interaction effects between predictors. A cutoff of $p<0.05$ was considered a significant interaction term for potential predictors. This analysis process was repeated for the 30-day readmissions analysis.

Results

30-Day Mortality Analysis

A total of 1,880 patients were included in the study sample with an overall 5.43% 30-day mortality rate (n=102). The IHT rate among the study sample was 4.20% (n=79). When stratified by outcome, 11.39% of IHT patients experienced mortality vs. 5.16% non-transfer mortality (p=0.03). The average age of mortality patients was 73.10 (standard deviation: 14.35) years compared to 65.41 (standard deviation: 15.07) years for surviving patients (p<0.0001). The average length of stay of patients who died was 10.36 (standard deviation: 8.53) days compared to 6.51 (standard deviation: 6.04) days for surviving patients (p<0.0001).

Table 7 includes the frequency counts and percentages of the sociodemographic and clinical covariates stratified by IHT exposure status. IHT patients were slightly younger than non-transfer patients, although approximately 20% of each subgroup included the oldest patients aged 80-100 (p=0.06). Over 63% of IHT patients were white compared to only 31% of non-transfer patients (p<0.0001). Although the majority of study patients were high SES, over 83% of IHT patients were high SES compared to 71% of non-transfer patients (p=0.02). IHT patients had a slightly higher rate of previous admissions than non-transfer patients, but both groups exceeded 61% (p=0.05). 58% of non-transfer patients had a cardiologist attending physician compared to over 72% of IHT patients (p=0.01). While nearly 94% of IHT patients were admitted to the hospital from another healthcare facility, over 77% of non-transfer patients were admitted to the hospital from home (p<0.0001). Nearly 51% of both IHT and non-transfer patients had LOS between 4 and 10 days, while twice the rate of IHT patients had LOS between

11-98 days compared to non-transfer patients (p=0.0002). Over 79% of non-transfer patients were discharged to home compared to nearly 71% of IHT patients (p=0.08). Only 35% of IHT patients visited an outpatient physician post-discharge compared to 44% of non-transfer patients (p=0.12).

Table 7: Sociodemographic and clinical characteristics by IHT exposure, n=1,880

Characteristic	IHT Number	IHT Percent	No IHT Number	No IHT Percent	P-Value
Age in Years					0.06
22-59	22	27.85%	599	33.35%	
60-69	20	25.32%	476	26.50%	
70-79	21	26.58%	353	19.65%	
80-89	12	15.19%	278	15.48%	
90-100	4	5.06%	95	5.29%	
Race					<0.0001
White	50	63.29%	553	30.79%	
Non-White	29	36.71%	1,248	69.21%	
Sex					0.36
Male	44	55.70%	909	50.61%	
Female	35	44.30%	892	49.39%	
Marital Status					0.41
Married	27	34.18%	538	29.96%	
Unmarried	52	65.82%	1,263	70.04%	
Socioeconomic Status					0.02
High SES	66	83.54%	1,281	71.33%	
Low SES	13	16.46%	520	28.67%	
Previous Admissions					0.05
No	51	64.56%	1,100	61.25%	
Yes	28	35.44%	701	38.75%	
Attending Specialty					0.01
Cardiovascular Medicine	57	72.15%	1,050	58.46%	
Other	22	27.85%	751	41.54%	
Admit Source					<0.0001
Home	5	6.33%	1,388	77.28%	
Healthcare Facility	74	93.67%	413	22.72%	
Total LOS (days)					0.0002
1-3	13	16.46%	594	33.07%	
4-10	41	51.90%	919	51.17%	
11-98	25	31.64%	288	16.04%	
Discharge Disposition					0.08
Home	56	70.89%	1,424	79.29%	
Healthcare Facility	23	29.11%	377	20.71%	
Outpatient Utilization					0.12
No	51	64.56%	1,005	55.96%	
Yes	28	35.44%	796	44.04%	
Discharge Unit Type					0.26
Inpatient Unit	67	84.81%	1,601	89.14%	
Intensive Care Unit	12	15.19%	200	10.86%	

Table 8 includes the frequency counts and percentages of the medical covariates stratified by IHT exposure status. Over 68% of IHT patients had blood pressure disorders compared to 57% of non-transfer patients (p=0.05). 11% of IHT patients had a history of cancer compared to nearly 17% of non-transfer patients (p=0.20). 9% of non-transfer patients had a connective tissue disease compared to over 16% of IHT patients (p=0.03). The diabetes rates were high in both groups, but 60% of IHT patients had diabetes compared to 52% of non-transfer patients (p=0.14). Over 44% of IHT patients had a history of myocardial infarction compared to 28% of non-transfer patients (p=0.0003).

Table 8: Medical comorbidities by IHT exposure status, n=1,880

Characteristic		IHT Number	IHT Percent	No IHT Number	No IHT Percent	P-Value
Blood Pressure						0.05
	No	25	31.65%	767	42.71%	
	Yes	54	68.35%	1,034	57.29%	
Cancer						0.20
	No	70	88.61%	1,496	83.30%	
	Yes	9	11.39%	305	16.70%	
COPD						0.86
	No	53	67.09%	1,225	68.21%	
	Yes	26	32.91%	576	31.79%	
Connective Tissue Disease						0.03
	No	66	83.54%	1,635	91.04%	
	Yes	13	16.46%	166	8.98%	
Dementia						0.63
	No	76	96.20%	1,689	94.04%	
	Yes	3	3.80%	112	5.96%	
Diabetes						0.14
	No	31	39.24%	859	47.83%	
	Yes	48	60.76%	942	52.17%	
Kidney Disease						0.37
	No	28	35.44%	553	30.79%	
	Yes	51	64.56%	1,248	69.21%	
Lipid Disease						0.46
	No	45	56.96%	950	52.90%	
	Yes	34	43.04%	851	47.10%	
Liver Disease						0.55
	No	74	93.67%	1,653	92.04%	
	Yes	5	6.33%	148	7.96%	
Myocardial Infarction						0.0003
	No	44	55.70%	1,282	71.38%	
	Yes	35	44.30%	519	28.62%	
Peripheral Vascular Disease						0.90
	No	74	93.67%	1,687	93.93%	
	Yes	5	6.33%	114	6.07%	
Stroke						0.26
	No	73	92.41%	1,715	95.49%	
	Yes	6	7.59%	86	4.51%	
Alcohol						0.73
	No	74	93.67%	1,703	94.82%	
	Yes	5	6.33%	98	5.18%	
Tobacco						0.62
	No	36	45.57%	770	42.787%	
	Yes	43	54.43%	1,031	57.13%	

Table 9 includes the univariate and multivariable logistic regression analysis models including IHT exposure status, sociodemographic, clinical, and medical predictors of 30-day mortality. Univariate analysis included all significant predictors with their unadjusted odds ratio and 95% confidence intervals. IHT was associated with 2.36 (95% CI: 1.15-4.88) times the odds of 30-day mortality compared to non-transfers in univariate analysis. The final multivariable model of 30-day mortality was analyzed using backwards logistic regression and resulted in a parsimonious multivariable model that converged, including SES, outpatient utilization, discharge unit, blood pressure, cancer, and liver disease as significant covariates associated with IHT and 30-day mortality outcomes. The multivariable model also included two significant interaction terms between age and total length of stay and between admit source and discharge disposition. Multivariable analysis resulted in an adjusted odds ratio of 1.25 (95% CI: 1.08-1.41) higher odds of 30-day mortality compared to non-transfers. The asterisks indicate covariates that were significant in univariate but not multivariable analysis. Additionally, multivariable interaction terms were not assessed in univariate analysis, as indicated by the asterisks.

Table 9: Univariate and multivariable analysis of odds ratios of covariates of 30-day mortality

Covariate (Level)	Unadjusted Odds Ratio	95% CI	Adjusted Odds Ratio	95% CCI
IHT				
No	REF		REF	
Yes	2.36	1.15-4.88	1.25	1.08-1.41
Age*Total LOS (days)	*	*		
22-59 years*11-98 days			REF	
60-69 years*11-98 days			2.87	1.86-4.42
70-79 years*11-98 days			4.32	2.92-6.41
80-89 years*11-98 days			3.50	2.13-5.76
90-100 years*11-98 days			11.05	5.12-23.82
Race			*	*
White	REF			
Non-White	0.38	0.26-0.57		
Marital Status			*	*
Married	REF			
Unmarried	0.52	0.35-0.78		
Socioeconomic Status				
High SES	REF		REF	
Low SES	0.23	0.12-0.46	0.32	0.15-0.67
Discharge Disposition			*	*
Home	REF			
Healthcare Facility	5.23	3.52-7.97		
Outpatient Utilization				
No	REF		REF	
Yes	0.22	0.13-0.38	0.23	0.13-0.40
Discharge Unit Type				
Inpatient Unit	REF		REF	
Intensive Care Unit	2.93	1.83-4.69	3.53	2.07-6.04
Admit Source*Discharge Disposition	*	*		
Home*Home			REF	
Healthcare Facility*Healthcare Facility			2.88	2.21-3.76
Blood Pressure				
No	REF		REF	
Yes	0.69	0.46-1.02	0.63	0.41-0.97
Cancer				
No	REF		REF	
Yes	1.87	1.18-2.96	1.57	1.09-2.62
Kidney Disease			*	*
No	REF			
Yes	2.50	1.46-4.31		
Liver Disease				
No	REF		REF	
Yes	2.23	1.27-3.91	2.21	1.18-4.12

30-Day Readmissions Analysis

A total of 1,880 patients were included in the readmissions analysis with a 22.34% 30-day readmissions rate (n=420). The IHT rate among the readmissions sample was 4.20% (n=79). When stratified by outcome, 31.65% of IHT patients experienced readmissions vs. 21.93% non-transfer readmissions (p=0.04). Univariate logistic regression analysis resulted in an unadjusted odds ratio of 1.65 (95% confidence interval: 1.01-2.69) of 30-day readmissions for IHT patients compared to non-IHT patients. The average age of readmissions patients was 64.81 (standard deviation: 15.24) years compared to 66.12 (standard deviation: 15.24) years for non-readmissions patients (p=0.11). The average length of stay of readmissions patients was 7.44 (standard deviation: 8.00) days compared to 6.52 (standard deviation: 5.65) days for non-readmissions patients (p=0.01).

Table 10 includes the univariate and multivariable logistic regression analysis models including IHT exposure status, sociodemographic, clinical, and medical predictors of 30-day readmissions. Univariate analysis included all significant predictors with their unadjusted odds ratio and 95% confidence intervals. IHT was associated with 1.65 (95% CI: 1.01-2.69) times the odds of 30-day readmissions compared to non-transfers in univariate analysis. The final multivariable model of 30-day readmissions was analyzed using backwards logistic regression and resulted in a parsimonious multivariable model that converged, including COPD, diabetes, kidney disease, tobacco, attending specialty, outpatient utilization, and admit source as significant covariates associated with IHT and 30-day readmissions outcomes. Multivariable analysis resulted in an adjusted odds ratio of 2.26 (95% CI: 1.32-3.89) higher odds of 30-day readmissions compared to non-transfers. The asterisks indicate covariates that were significant in univariate but not multivariable analysis.

Table 10: Univariate and multivariable analysis of odds ratios of covariates of 30-day readmissions

Covariate (Level)		Unadjuste d Odds Ratio	95% CI	Adjusted Odds Ratio	95% CCI
IHT					
	No	REF		REF	
	Yes	1.65	1.01-2.69	2.26	1.32-3.89
Total LOS (days)				*	*
	1-3 days	REF			
	4-10 days	0.87	0.68-1.11		
	11-98 days	1.24	0.90-1.69		
Race				*	*
	White	REF			
	Non-White	1.53	1.20-1.95		
Marital Status				*	*
	Married	REF			
	Unmarried	1.38	1.08-1.77		
Admit Source					
	Home	REF		REF	
	Healthcare Facility	0.76	0.58-0.98	0.70	0.52-0.94
Attending Specialty					
	Cardiovascular Medicine	REF		REF	
	Other	1.57	1.27-1.96	1.38	1.10-1.73
Outpatient Utilization					
	No	REF		REF	
	Yes	0.56	0.45-0.70	0.63	0.50-0.80
Blood Pressure				*	*
	No	REF			
	Yes	0.71	0.57-0.89		
COPD					
	No	REF		REF	
	Yes	1.58	1.26-1.97	1.44	1.14-1.83
Diabetes					
	No	REF		REF	
	Yes	1.34	1.08-1.67	1.16	1.12-1.46
Kidney Disease					
	No	REF		REF	
	Yes	1.62	1.26-2.09	1.49	1.13-1.96
Stroke				*	*
	No	REF			
	Yes	1.56	0.99-2.46		
Tobacco					
	No	REF		REF	
	Yes	1.36	1.09-1.70	1.22	1.09-1.55

Discussion

This study provided the first evidence of significant associations between IHT exposure from community hospitals to an academic medical center and increased odds of 30-day mortality (1.25, 95% CI: 1.08-1.41) and 30-day unplanned readmissions (2.26, 95% CI: 1.32-3.89) of patients with heart failure. The inclusion of statistically-significant sociodemographic, clinical, and medical covariates during analysis resulted in two separate multivariable models that accounted for effect modification and study sample differences. The significantly increased odds of adverse post-discharge outcomes of mortality and readmissions associated with IHT from community hospitals may indicate that destination hospitals, such as an academic medical center, should place careful focus on treating IHT patients in an effort to improve outcomes. This study also offers insight into the covariates that may be associated with these worsened outcomes that clinicians should take into consideration when treating patients with heart failure.

IHT patients with heart failure had 25% higher odds of 30-day mortality than non-transfer patients who were admitted and discharged from an academic medical center, and six covariates were found to be significantly associated in this model, including two interaction effects between increasing age and longer lengths of stay (LOS) and between admit source and discharge disposition. Blood pressure, cancer, and liver disease were associated with higher odds of mortality. Low SES was associated with lower odds of mortality compared to high SES patients. Post-discharge outpatient utilization was also associated with lower odds of mortality compared to no outpatient care. Patients discharged from the hospital from an ICU had higher odds of mortality compared to patients who were discharged from an inpatient unit.

IHT patients with heart failure had 2.26 times higher odds of 30-day unplanned readmissions than non-transfer patients who were admitted and discharged from an academic medical center, and seven covariates were found to be significantly associated in this model. COPD, diabetes, and kidney disease were associated with higher odds of readmissions, as well tobacco/nicotine usage. Patients who were treated by attending physicians other than cardiologists also had higher odds of readmissions. Patients who visited an outpatient physician post-hospital discharge had lower odds of readmissions. Interestingly, patients who were admitted to the hospital from a healthcare facility had lower odds of readmissions than patients admitted from home. Among both outcome models, kidney disease was associated with higher odds of adverse outcomes, while outpatient utilization was associated with lower odds of adverse outcomes. Patients admitted from a healthcare facility had higher odds of mortality but lower odds of readmissions than patients admitted from home.

The interaction effect of increasing age and lengths of stay of 11 days or more was significant, despite some overlapping of confidence intervals, suggesting that increasing stratified age was not directly associated with increased odds of mortality. However, among patients with LOS of 11-98 days in the hospital, patients aged 60-69 had 2.87 (95% CI: 1.86-4.42) times the odds of mortality while patients aged 90-100 had 11.05 (95% CI: 5.12-23.82) times the odds of mortality. These associations indicate that IHT of patients who have longer LOS and are aged 60-69 and 90-100 may be among the highest odds of mortality groups. Increasing age has previously been shown to be associated with higher risk of adverse post-discharge outcomes, while longer LOS has similarly been associated with poor outcomes (Abraham W, et al., 2008; Van der Wal H, et al., 2017; Sud M, et al., 2017). From a clinical standpoint, these associations are unsurprisingly because older patients generally have higher severity of illness and thus require longer and more frequent hospital stays for treatment and medical care. This current study adds further evidence to such associations through the interaction effect of age and LOS being associated with mortality of IHT patients with heart failure.

Cancer was associated with 57% (95% CI: 1.09-2.62) higher odds of mortality, and this result was unsurprising because cancer as a comorbidity increases the risk of mortality in an already high-risk heart failure population. Unfortunately, the relationship between cancer and heart failure is complex, and there is extensive ongoing research as to the exposure-outcome relationship between the two medical conditions (Bertero E, et al., 2018). Thus, it is difficult to isolate specific guidelines for cancer patients with concomitant heart failure, although clinicians should exercise caution when treating such patients, particularly if patients are being transferred for treatment from a community hospital, where both cancer and heart failure treatment options may be limited in availability.

Kidney disease was associated with 49% higher odds of readmissions (95% CI: 1.13-1.96), but not significantly associated with mortality in the multivariable models. There is already a high prevalence of kidney disease among the elderly (Inamdar A & Inamdar A, 2016). However, among heart failure patients, this association is supported by multiple studies, and it is temporally meaningful that IHT patients with kidney disease also experienced higher odds of readmissions but not mortality (Tuegel C & Bansal N, 2017; Grande D, et al., 2018). Thus, kidney disease may be a predictor of readmissions but a mediator of mortality outcomes. Other medical conditions were differentially associated with poor outcomes of patients with heart failure, including blood pressure disorders, diabetes, COPD, liver disease, and tobacco usage.

Blood pressure disorders were associated with 27% (95% CI: 0.41-0.97) lower odds of mortality but had no significant association with readmissions. Since blood pressure disorders, particularly hypertension, are frequent comorbidities among heart failure, this reduced odds of mortality may indicate that patients with both heart failure and blood pressure disorders are high risk and manage their conditions actively in such a way that reduces odds of mortality (Inamdar A & Inamdar A, 2016; Yancy C, et al., 2015). This would also provide a basis for IHT of such patients for higher levels of care at an academic medical center, as indicated in Chapter 2. Diabetes was associated with 16% (95% CI: 1.12-1.46) higher odds of readmissions of IHT patients, but had no association with mortality. Diabetes is a manageable condition with medications and diet, and so patients with diabetes may be readmitted for treatment more frequently with diabetes as a comorbidity, but they are not at higher odds of death due to associated diabetes (Inamdar A & Inamdar A, 2016; Crowley M, et al., 2017). This current study supports those results with IHT being a major exposure for patients with diabetes presenting to the hospital.

COPD is a chronic condition that affects both quality of life and necessitates extensive hospital care due to exacerbations and complications (Inamdar A & Inamdar A, 2016). COPD mortality rates may soon exceed cardiovascular disease mortality rates, and these patients require frequent medical care, generally resulting in emergency room visits and inpatient admissions (Diaz-Guzman E & Mannino D, 2014). This current study found 44% (95% CI: 1.14-1.83) higher odds of readmissions for COPD patients indicating that COPD patients with concomitant heart failure are being readmitted more frequently, presumably for treatment due to severity of illness. However, it is difficult to ascribe the admissions to specific diseases or conditions because of the holistic nature of medical illness, and so it is likely that COPD is a mediator of readmissions outcomes, rather than a marker.

Similarly to COPD, liver disease may be a mediator of mortality outcomes associated with IHT rather than a marker of outcomes. Liver disease is a frequent comorbidity among patients with heart failure, and the presence of liver disease was associated with 2.21 (95% CI: 1.18-4.12) higher odds of mortality (Inamdar A & Inamdar A, 2016). Although manageable with some medications, liver diseases are serious illnesses that have poor mortality outcomes, as observed in this current study.[80] Interestingly, no association or interaction was observed between liver disease and alcohol use in the study sample, which may indicate that alcohol use was not a major factor in the medical histories of these patients. However, it was possible that alcohol use was not consistently or accurately coded in the medical charts of patients.

Tobacco/nicotine was associated with 22% (95% CI: 1.09-1.55) higher odds of readmissions, which was unsurprising since tobacco users experience frequent medical issues associated with tobacco use, and the effects of smoking on heart disease are well-known (Suskin N, et al., 2001). However, smoking is generally associated with poor long-term outcomes, and mortality risk increases over the course of years, whereas in this current study, only 30-day mortality was evaluated as an endpoint (CDC, et al., 2010). The 22% higher odds of readmissions may indicate that smoking is a mediator of disease in patients with heart failure, which requires more frequent hospital admissions for treatment and management. Of note, this current study did not differentiate between past and current tobacco use. No interaction was observed between tobacco use and COPD in this current study, even though smoking is a common cause of COPD (Diaz-Guzman E & Mannino D, 2014).

Admission source was differentially associated with outcomes, possibly due to the interaction effect among the mortality analysis. Patients admitted from a healthcare facility had 30% lower odds of readmissions (95% CI: 0.52-0.94) than patients admitted from home associated with IHT. However, patients admitted from a healthcare facility and discharged to another healthcare had 2.88 (95% CI: 2.21-3.76) times the odds of mortality compared to patients who were admitted and discharged from home. Patients who are actively being treated at another healthcare facility, such as a long-term acute care facility, psych hospital, or Veterans facility, generally require more ongoing care due to higher severity of illness. These patients are at higher odds of IHT likely due to more complex care needs that are unavailable at community hospitals. Therefore, due to the higher severity of illness necessitating stays at healthcare facilities, the IHT to an academic medical center indicates these patients are also more likely to die because of the higher severity of illness, as was seen in this current study. The higher odds of mortality aligned with lower odds of readmissions because these patients were at higher risk of death than they were able to be readmitted since mortality was a terminal endpoint and readmission could reoccur or be followed by subsequent mortality. This mortality association was particularly meaningful among patients who arrived to the hospital from a healthcare facility, received treatment, and were discharged back to a healthcare facility, which indicated that although medically-stable, these patients remained severely ill.

Patients treated by attending physicians who were not cardiologists had 38% (95% CI: 1.10-1.73) higher odds of readmissions than patients treated by cardiologists. These results in no way indicated quality of treatment, rather they suggested that patients with heart failure may have benefited from attending physicians who specialized in cardiology. Previous studies have shown associations between physician specialty and heart failure outcomes, and these results align with this current study in that physician specialty is a relevant factor with cardiologists being associated with lower readmissions among patients with heart failure (Palacio C, et al., 2014; Beresford L, 2013). Nevertheless, operational issues may make it difficult for all patients with heart failure to be treated by cardiologists, although such a scenario may improve both IHT outcomes and reduce readmissions by optimizing patient care.

Outpatient physician utilization was associated with 77% (95% CI: 0.13-0.40) lower odds of mortality and 37% (95% CI: 0.50-0.80) lower odds of readmissions. Outpatient physician care has been shown to improve heart failure outcomes, regardless of whether patients were seeing their cardiologist or primary care physician (Koser K, et al., 2018; Edmonston D, et al., 2019; Latafa J, et al., 2004). The results of this current study aligned with other studies indicating that outpatient utilization is a significant factor in improving outcomes. The 77% lower odds of mortality indicated outpatient care was an important factor in maintaining medical treatment post-hospital discharge, while the 37% reduction in odds of readmissions indicated that although these patients had chronic and severe illnesses, they were able to mitigate that by seeking outpatient physician care. Limitations of this covariate were that the type of outpatient care and frequency of visits pre-readmissions and/or mortality were not evaluated in this current study.

Low socioeconomic status (SES) was associated with 68% (95% CI: 0.15-0.67) lower odds of mortality than high SES, but this covariate was challenging to interpret in context. Payer was used as a proxy for SES due to the lack of available data on other socioeconomic variables, and this was definitely a limitation. However, previous studies had found associations between low SES and poor outcomes (Glyn P, et al., 2019; Lee W, et al., 2019; Groeneveld P, et al., 2019). The results of this current study may indicate that SES is a mediator of mortality outcomes, and the results may differ when using more long-term endpoints. The fact that no association was observed between SES and readmissions suggests that patients with heart failure are receiving comparable care regardless of their ability to pay, and so the higher odds of mortality among high SEs patients may be mediating severity of illness. More research on SES and heart failure outcomes is warranted.

Patients discharged from intensive care units (ICU) had 3.53 (95% CI: 2.07-6.04) times the odds of mortality than patients discharged from an inpatient unit at an academic medical center. Since inpatient units are generally used for long-term patient care and treatment, it is reasonable ICU patients had higher severity of illness and were more likely to die after being discharged from the ICU. However, from a clinical perspective, it is important to note that the ICU discharge was considered the medically-appropriate unit of discharge for the patient, rather than the most convenient. Operationally, patients were likely discharged from an ICU, rather than an inpatient unit, because the next level of care for them was either another healthcare facility or home. Interestingly, the location that the patient went to after discharge from the hospital (known as discharge disposition) was not a significant covariate in either model. These results may indicate that patients with heart failure who are being considered for discharge while in an ICU may benefit from additional inpatient treatment rather than discharge from the hospital. Other studies may support these conclusions by observing similar associations between ICU utilization and poor outcomes (Lee D, et al., 2016; Valley T, et al., 2017).

By comparing the predictors of IHT from community hospitals to an academic medical center in Chapter 2, and the associations between IHT and increased odds of poor outcomes for patients with heart failure in this current study, it may be possible to assess which factors are key drivers of both. From Chapter 2, cancer was associated with 87% (95% CI: 1.31-2.56) higher odds of IHT to an academic medical center, and cancer was also associated with 57% higher odds of 30-day mortality in this current study. Thus, patients with heart failure presenting with cancer may warrant higher necessity of IHT upon presenting to community hospitals to improve survival odds. Similarly, from Chapter 2, diabetes was associated with 97% (95% CI:1.55-2.68) higher odds of IHT, as well 16% higher odds of readmissions in this current study. Thus, concomitant diabetes and heart failure may also benefit from expeditious IHT to an academic medical center. Blood pressure disorders were associated with 40% higher odds of IHT to an academic medical center in Chapter 2, but blood pressure was also associated with 27% lower odds of mortality indicating that patients may be receiving the appropriate and timely treatment via IHT. Physician specialty was also relevant in both IHT outcome and post-discharge outcomes as Chapter 2 found 93% (95% CI: 0.04-0.13) lower odds of IHT to an academic medical center for non-cardiologists, but this current study found 38% higher odds of readmissions for non-cardiology treated patients with heart failure. Thus, IHT may help streamline the medical care process by effectively pairing patients with heart failure with cardiovascular medicine specialists.

Additional areas of study should focus on admission source and the interaction of this covariate with other variables. Chapter 2 found 11.75 (95% CI: 10.04-13.15) higher odds of IHT for patients admitted from a healthcare facility with previous history of admissions compared to patients admitted from home without such a history. These results are somewhat aligned with this current study in which patients admitted from a healthcare facility had 30% lower odds of readmissions but 2.88 timers the odds of mortality when admitted and discharged back to another healthcare facility. One conclusion may be that such patients are severely ill, and inpatient care simply does not have a strong effect on improving their overall health. More research is warranted into these observations and complex interactions. Similarly, the associations of age, IHT, and outcomes are complex and difficult to clearly discern based on the study data. While age had been shown in previous studies to be associated with increasing severity of illness and poorer general health, Chapter 2 found reduced odds of IHT to an academic medical center for older patients, although the association was complex.[69,85] In this current study, age was associated with higher odds of mortality among patients with longer lengths of stay (11 days or greater) for patients ages 60-69 and 90-100. Thus, there is an opportunity for future research as to the lower IHT odds of older patients, despite the higher mortality odds for such patients.

Multivariable modeling of IHT from community hospitals and non-IHT patients treated at an academic medical center, an academic medical center, found 25% higher odds (95% CI: 1.08-1.41) of 30-day mortality and 2.26 (95% CI: 1.32-3.89) times the odds of 30-day unplanned readmissions. The elevated mortality odds are temporally meaningful because mortality is a terminal endpoint for all patients and no subsequent outcomes can be observed. Thus, patient mortality is a non-repeatable risk event, while readmissions can continue to occur, until the likely occurrence of subsequent mortality. As a result, the higher readmissions odds are based on the high readmissions rates of patients with heart failure. Such conclusions were supported after adjustment of sociodemographic, clinical, and medical covariates among the study sample. It is important to note that many different studies with varying conclusions regarding heart failure risk factors and outcomes have been published over the years, and this current study is only one such analysis and should be evaluated in context.

One of the major strengths of this study was appropriate statistical power and sample size to determine meaningful associations in both multivariable logistic regression outcome models. However, IHT was still an infrequent occurrence in the acute hospital setting, and more studies with larger data sets, particularly among IHT groups, would be beneficial to further evaluate the associations with outcomes. The use of a continuous data set over two years of in-house UHHS data ensured a high level of precision within the data and complete medical records for the available study population. Overall, due to the stringent inclusion and exclusion criteria, the heart failure population was homogenous and clinically-distinct, and the results had temporal and clinical meaningfulness.

Another strength of the study data included all adults ages 18 and up, which provided a more robust data set than the traditional Medicare population of the HRRP ages 65 and up (Centers for Medicare and Medicaid Services, 2018). Including younger adults increased the generalizability of the results, particularly for a younger heart failure population (Glyn P, et al., 2019). Additionally, inclusion of all payers, compared to the Medicare-only beneficiaries of the HRRP, further increased the diversity of the study sample and generalizability of study results (Centers for Medicare and Medicaid Services, 2018). These two factors are important because including all ages and all payers provides new insight into previously understudied outcomes for patients who are not traditionally considered among the HRRP patient population.

Heart failure is a complex chronic condition, and despite the homogeneity of this study population, there are other methods to define such a population, instead of the ICD-10 diagnosis codes that were modelled after the HRRP. Although similar associations would be expected in such an analysis, there may be other variables that become relevant in such a model. Additionally, residual confounding is possible due to variables that were not able to be included in the analysis. For example, ethnicity is associated with heart failure and race, but concise data on ethnicity was not available in the data set for analysis and adjustment (Inamdar A & Inamdar A, 2016; Chamberlain R, et al., 2018). Although in-house data from UHHS was used, such data is still limited by missing external hospital encounter data, such as if a patient visited another hospital system or provided incorrect medical information. There may have also been errors in the medical record from data entry at the encounter level, although data validation was performed to catch as many errors as possible.

While UHHS provided all available medical record data for this study, post-discharge mortality was only available through the Ohio Department of Health (ODH), and their data processes were independent of UHHS. Thus, there was no way to validate the ODH data. Other data integrity issues could have included deceased patients in another state, ODH reporting issues, and issues within UHHS record databases that prevented matching of patients, since ODH death records are partially de-identified.

Binary coding via chart abstraction for clinical clusters was performed to capture medical diagnoses, and this process was susceptible to errors, including determination of which ICD-10 diagnoses qualified for inclusion. Generalizations were made for the dichotomous presence or absence of clinical clusters irrespective of duration or onset; however, in a chronically-ill heart failure population, it was reasonable for multiple comorbidities to be present. Lastly, less than 5% of the study population had more than 25 diagnoses in their medical record, but those other diagnoses were unable to be extracted from the medical record, and so only the top 25 diagnoses were reviewed for inclusion. The medical predictors used in this study were based on the Charlson Comorbidity Index but could also be modeled in future studies in other ways, including different comorbidities that factor into accounting for severity of illness and disease conditions. Different acuity scores or indices could provide additional covariates for evaluation of associations between IHT and mortality and readmissions outcomes.

Future studies should attempt to replicate these findings using more diverse medical populations or different groups of patients with heart failure. It is possible that IHT differentially affects other disease conditions, and so these findings cannot be extrapolated broadly among other medical groups of patients. Larger population analyses may provide additional insights into the effects of IHT on post-discharge outcomes. Also, due to the unique study population of homogenous patients with heart failure within UHHS, the current results may not be generalizable to other health systems across the United States, and so care needs to be taken to interpret and apply the results in context. Additional studies should be performed to compare other health systems or multiple health systems in an aggregate data set. Lastly, this current study utilized two separate endpoints of 30-day mortality and 30-day readmissions, but using an aggregate endpoint of readmissions/mortality could yield different results. The decision to use 30-days as the risk period for mortality and readmissions was based on the HRRP, but there is no national gold standard for this risk period, and future studies could include different time points as study outcomes.

Chapter 4 Manuscript III

Cost Analysis of Acute Care Inter-Hospital Transfers at a Multi-Site Hospital System

Abstract

Introduction: Over six million Americans suffer from congestive heart failure with average treatment costs of $110,000 annually. This healthcare utilization equates to approximately $32 billion in direct costs, and that number is projected to reach $100 billion by 2030. Three-quarters of those costs are associated with hospitalizations. One-quarter of patients with heart failure are readmitted within 30 days, while 10% die within 30 days. This study investigates inter-hospital transfers (IHT) and predictors of total cost outcomes of patients with heart failure within a multi-site hospital system.

Methods: Data was collected from a multi-site hospital system in Cleveland, Ohio from 01/2017-12/2018 of patients with heart failure, including IHT status and sociodemographic, clinical, and medical predictors of total costs. Multivariable generalized linear modeling evaluated the potential predictors associated with IHT of patients with heart failure and differences in total cost outcomes between patients transferred from a community hospital to an academic medical center and non-transfer patients.

Results: IHT patients with heart failure had $2,015 (95% CI: $1,039-$5,071) higher total costs than non-transfer patients. Younger age, longer lengths of stay, and higher severity of illness were also differentially associated with higher total costs.

Conclusions: This study provided a cost analysis of aggregated total costs of IHT patients with heart failure transferred from a community hospital to an academic medical center compared to

non-transfer patients. Higher total costs were associated with IHT and predictors of hospital utilization and severity of illness.

Introduction

Heart failure affects over six million Americans - approximately 2% of the population in the United States (Feltner C, et al., 2014; CDC, 2017). The annual financial costs of heart failure on the United States healthcare system are approximately $32 billion in direct costs (Mayo Clinic, 2019; Inamdar A & Inamdar A, 2016). With a 5-year survival rate of 50%, the average lifetime cost of heart failure for a patient is $110,000 per year (Inamdar A & Inamdar A, 2016). By comparison, the average annual per capita cost of healthcare in the United States is $10,500 per person (AHRQ, 2019). Thus, the annual cost of heart failure is ten times greater than the average cost of healthcare per capita. By 2030, the direct costs of heart failure are expected to triple to nearly $100 billion annually in the United States, and those costs will continue to grow as the prevalence of heart failure increases (Inamdar A & Inamdar A, 2016).

A new study has shown an increase in the prevalence of heart failure among minorities and younger adults under age 65 (Glyn P, et al., 2019). While traditionally a chronic disease associated with aging, particularly adults ages 65 and over, heart failure incidence is increasing in patients between ages 35 and 64 (Glyn P, et al., 2019). Although only 16% of the United States population is ages 65 and over, this group accounts for 36% of all healthcare spending costs. Ages 35-64 account for 38% of the population, but only 43% of all healthcare spending costs (AHRQ, 2019). Thus, not only are there numerous segments of the population that are at risk of heart failure, but these groups also comprise the majority of healthcare spending on heart failure care and treatment. If these trends continue, it may be difficult to maintain optimal care due to skyrocketing spending costs that become unmanageable for both patients and the United States healthcare system. Of note, medical costs are the monies hospitals spend on patient care and not the charges that are passed on to patients and their payers.

Healthcare spending costs also vary significantly by sociodemographic factors. Whites spend an annual average of $6,020 vs. $4,009 for African Americans ($p<0.05$). Adult females also consistently spend more than adult males on healthcare costs ($p<0.05$). Healthcare spending costs also significantly increase with age regardless of race and sex ($p<0.05$) (AHRQ, 2019). The increasing incidence of heart failure in the younger population is strongly associated with minority groups, and African American males are at an increasing risk of developing heart failure (Glyn P, et al., 2019). However, research demonstrates that this group of the population is among the lowest healthcare spending group, although their actual healthcare needs may be among the highest (AHRQ, 2019). This disparity underscores the need to better evaluate the healthcare costs of heart failure within the populations, and which factors are affecting these rapidly increasing costs.

Due to the complex nature of heart failure, numerous variables are associated with healthcare costs, including treatment, testing, and hospitalizations. Studies have shown that hospitalizations account for nearly three-quarters of the total heart failure costs (Inamdar A & Inamdar A, 2016; Dunlay S, et al., 2011). In perspective, the average cost of a heart failure hospitalization is $23,077 per patient with 83% of patients with heart failure experiencing at least one hospitalization, and 43% experiencing at least four hospitalizations during their post-diagnosis lifetime (Heidenreich P, et al., 2011; Titler M, et al., 2008; Wang G, et al., 2010). These numbers are unsurprising given the high readmissions rate for this patient population, which equates to nearly five million patients with heart failure needing at least one inpatient admission, and over two and a half million needing at least four inpatient admissions during their lifetimes. Since most of these patients are over 65 and qualify for Medicare, Medicaid, or have dual eligibility, these costs are often absorbed directly by the healthcare system that is struggling to balance and reduce such costs (Inamdar A & Inamdar A, 2016).

Inter-hospital transfer (IHT) from a referring to destination hospital of a heart failure patient can occur as frequently as 4.5% of all encounters, although the actual numbers may be higher (Mueller S, et al., 2017; Iwashyna T, et al., 2009). Multivariable logistic regression models in Chapter 3 found increased odds of 30-day mortality (1.25, 95% CI: 1.08-1.41) and 30-day readmissions (2.26, 95% CI: 1.32-3.89) among patients with heart failure who were transferred from community hospitals to an academic medical center. However, there has not been an analysis of the total costs associated with IHT encounters of patients with heart failure, rather the data is frequently aggregated among a broad range of patients and disease conditions.

A recent study concluded that not only was IHT care more expensive than non-transfer care, but IHT encounters were almost twice as costly as non-transfers (Sokol-Hessner L, et al., 2016). A separate study of IHT and severe sepsis found that IHT costs were three times higher than non-transfers. Interestingly, the sepsis study also found an association between IHT and increased odds of in-hospital mortality (Mohr N, et al., 2016). Comprising only a portion of the overall cost, the IHT does increase cumulative total costs during the encounter episode of care. The sepsis study attributed $890 for each ambulance transfer cost in their IHT model, although Medicare patients may pay less because the government has a fee schedule for ambulance transfer costs. On average, Medicare patients pay $389 ($324-$453) plus $7.29 per mile for an ambulance transfer (Government Accountability Office, 2012). These costs are generally higher for private insurers, although a significant number of patients with heart failure have Medicare as their principal payer (Office of Inspector General, 2015). These numbers skyrocket to $8,500-$15,200 plus $26-$133 per mile for an air ambulance (Murdo P, 2015). Overall, there is a lot of high-level variability in the costs of IHT based on region, principal payer, and hospital operational policies.

Another important aspect of IHT is that cost aggregation can vary depending on the health system and payer policies. For example, a patient transferred from a referring to a destination hospital is still financially responsible for the costs at the referring hospital, the transfer to the destination hospital, and whatever costs are incurred at the destination hospital. Thus, for an average heart failure encounter costing $23,077, an $890 IHT cost may not seem like a cost-prohibitive amount, but considering that IHT patients also have referring hospital costs, the total IHT encounter costs likely include thousands more dollars. Thus, the average heart failure IHT encounter may cost between $34,000 and $70,000 depending on estimates (Sokol-Hessner, et al., 2016; Mohr N, et al., 2016). It is important to note that no such cost analysis has been performed on heart failure IHT costs to date, and so these are high-level estimates based on other high acuity disease groupings and limited Medicare claims data.

Another point of consideration is that IHT costs may not be available within claims data due to cost absorption by the referring and/or destination hospitals. Hospitals generally aggregate their costs at the encounter level, and the IHT can be costed to the referring hospital, destination hospital, or potentially split up between the two hospitals. Additionally, IHT costs can be outsourced to third-party transport companies with their own billing policies (Bailey M, 2017). Other hospital factors, such as intensive care unit (ICU) utilization, have also been frequently shown to increase total costs, particularly if patients were admitted to an ICU pre-IHT (Bernad A, et al., 1996; Lauerman M, et al., 2016). The available research suggests that the IHT process is highly variable with a wide range of costs and little standardization across the American healthcare landscape.

This current study aims to perform a cost analysis of patients with heart failure undergoing IHT within a multi-site hospital system to evaluate the total cost outcomes of IHT for patients and hospitals. Since both short and long-term heart failure outcomes are poor, and the cost of healthcare for these patients is so expensive, it is important to understand the financial implication of this subset of the population knowing that IHT can add to the cost of care while adversely affecting outcomes, as shown in Chapter 3.

Methods

Overview

This was a retrospective cohort study consisting of patients with heart failure who were either admitted and discharged from a community hospital, admitted and discharged from an academic medical center, or admitted to a community hospital and then transferred to an academic medical center. All patients received were admitted and discharged within seven integrated hospitals within University Hospitals Health System (UHHS). The study population consisted of patients with a principal diagnosis of congestive heart failure discharged between January 1, 2017 and December 30, 2018. This study was approved by UHHS of Cleveland, Ohio and the Kent State University Institutional Research Boards (IRB).

Study Population

Patients were eligible for study inclusion if they had a current International Statistical Classification of Diseases and Related Health Problems (ICD-10) principal diagnosis code of heart failure (I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, or I50.9) and did not have a principal or secondary ICD-10 procedure code for heart transplantation (02YA0Z0, 02YA0Z1, 02YA0Z2) or left ventricular assist device (LVAD) implantation (02HA0QZ, 02HA0RS, 02HA0RZ, 02HA3QZ, 02HA3RS, 02HA3RZ, 02HA4QZ, 02HA4RS, 02HA4RZ). All patients were adults ages 22-103 who were 1) admitted and discharged from one of seven hospitals, including six community hospitals and one urban academic medical center, or 2) initially admitted to one of six community hospitals experienced IHT to an urban academic medical center during the study period. Patients were stratified as either IHT from community hospital to an academic medical center or non-transfers.

Only inpatient encounters were included to maintain consistency of care among patients with heart failure since observation/short stay encounters were almost exclusively less than 24 hours. Of note, less than 180 patients annually were admitted as observation/short stay patients with heart failure, while nearly 2,500 were admitted annually as inpatient encounters with a principal diagnosis of heart failure within UHHS hospitals. Patients who had missing or incomplete total cost data (n=220) were excluded from analysis due to inability to conduct cost analysis. Patients who were admitted to the hospital from jail/police/court of law (n=2) were excluded from the study population due to the unique differences of this subgroup – all other admission sources, statues, and locations were included for analysis. Patients who were discharged from the destination hospital as left against medical advice (n=48) were excluded because their medical care was incomplete, and attributing their post-discharge outcomes to previous clinical care could be misleading and inconclusive. The final study population included 4,862 patients.

Data Source

Medical record data for all eligible patients were reported from UHCare Inpatient (Allscripts) – the inpatient EMR used by integrated hospitals within UHHS. The seven hospitals were selected due to their integrated clinical care pathways and information technology (IT) architecture among registration, coding, billing, and inpatient and outpatient electronic medical records (EMR). Additional data were collected from Midas+ Care Manager (Conduent) – a Quality Institute data entry and reporting application for coded patient-level registration, encounter, and discharge information.

Total cost data was reported from EPSi Financial Analytics (Allscripts) – the financial reporting tool used by all integrated UHHS hospitals. Total cost data was automatically extracted from EPSi on a rolling quarterly basis and imported into Midas+ Care Manager and associated with each patient encounter, thus ensuring accurate and complete records. Total cost data through December 2018 was finalized and available for reporting in April 2019 due to the rolling data submission process. Total costs, also known as full costs, included fixed costs and direct variable costs. Fixed costs were the total direct costs, such as nursing service and diagnostic equipment costs, and indirect costs, such as administrative and information technology costs, associated with the episode of care. Direct variable costs included costs of medications, supplies, and imaging. Physician billing and cost data were not available for inclusion in this data. Of note, all total costs were the financial amounts spent by the hospital on patient care, and not the charges that were subsequently passed on to patients and their associated payers.

Study Predictors

There was no single exposure variable in this study since the aim was to understand potential predictors of IHT outcomes. Thus, a total of 25 different potential predictors were evaluated as possible exposure variables. Due to the complex nature of heart failure and the generally higher severity of illness of heart failure, the following predictors were included in data collection and analysis and were also examined for potential confounding and interaction effects.

Age was coded as an ordinal categorical variable to assess the impact of increasing years of age on IHT outcome. A continuous variable was considered but not used because a single value increase in age would have been difficult to apply in a clinical setting, whereas stratified age was more applicable. Age groups were 22-59, 60-69, 70-79, 80-89, and 90-103 (reference group). The youngest patient was 22 years of age, and the oldest patient was 103 years of age.

Total length of stay (LOS) was defined as the aggregate number of days the patient was in the hospital and coded as an ordinal categorical variable to assess the impact of longer hospital length of stay on outcomes. For IHT patients, total LOS was calculated as LOS at the community hospital, the time between transfer from the community hospital and an academic medical center, and the LOS at an academic medical center from arrival to discharge. A continuous variable was considered but not used due to the difficulty in applying a single value increase in LOS to retrospective evaluation of outcomes associated with IHT, as well as to adjust for outliers. LOS groups were 1-3 days (reference), 4-10 days, and 11-98 days. The shortest LOS was 1 day, and the longest LOS was 98 days. Of the 482 patients with LOS of 11-98 days, approximately 1% were outliers with LOS exceeding 20 days. The total LOS value was rounded to the nearest whole day upon calculation due to the reporting methods of the data source supplying this information.

Race was dichotomized as white (reference group) and non-white. The non-white group included black, Asian, Native American, Pacific Islander, Alaskan, and no data available. Ethnicity was not consistently available in the medical records and was not examined.

Sex was defined as male vs. female (reference group).

Principal payer/insurance type was used as a proxy for socioeconomic status (SES) and dichotomized as managed care/Medicare/traditional indemnity/HMO (high SES – reference group) vs. dual eligible/Medicaid/self-pay/other (low SES). Since Medicare eligibility broadly applies to adults 65 and older, the Medicare payer was aggregated with managed care, traditional indemnity and HMO, which all required payment by patients to maintain coverage of service. Similarly, patients with Medicaid, dual eligibility of Medicaid and Medicare, self-pay/indigent/charity care were considered as having low socioeconomic status based on their payer groups.

Previous admission history was dichotomized as no vs. yes (reference group). This variable was defined as each unique patient who had at least one non-elective/unplanned admission to one of the seven integrated UHHS hospital during the July 2016-December 2016 pre-study period or multiple admissions during the study period of 2017-2018 that were not considered a readmission encounter. The purpose of this variable was to adjust for patients who had more frequent hospital admissions either during the pre-study period or during the actual study period; however, to avoid multicollinearity with the 30-day readmissions outcome, only encounters that were not readmissions and within the 30-day readmissions window were included in this variable. Due to unavailable data outside the UHHS system, only patient encounters to the seven integrated hospitals were eligible for this covariate.

Attending physician specialty was defined as the specialty of the physician who primarily treated/evaluated the patient during the inpatient encounter. The attending physician was primarily responsible for treatment and medical decision-making at an academic medical center for the patients. The groups were dichotomized as specialties of cardiovascular medicine vs. other (reference group). The other group included lower volume divisions, such as emergency medicine, hematology oncology, and pulmonology due to their small patient populations.

Admission unit type was defined as the type of hospital unit the patient first entered when coming to the hospital. Groups were dichotomized as emergency department (reference group) vs. inpatient units. Since IHT patients were ineligible to be admitted to an academic medical center emergency department or inpatient unit, no distinction was made between community hospital and an academic medical center units. Instead, for IHT patients, this unit was the admission unit at the community hospital. Patients that started at urgent care and went to the emergency department were included in the emergency department data. Intensive care unit (ICU) patients were included in the inpatient unit data, since these are technically inpatient units. Additionally, most community hospitals do not have distinct ICUs for specific patient subgroups, and so stratifying ICU populations would not have been clinically meaningful.

Discharge unit type was defined as the type of hospital unit the patient was discharged from at the end of the episode of care. Groups were dichotomized as inpatient units (reference group) vs. intensive care units (ICU) since no patients were discharged from the emergency department. Since IHT patients were ineligible to be discharged from a community inpatient unit or ICU, no distinction was made between community hospital and an academic medical center units.

Admitting source was defined as where the patient arrived from when coming to the UH hospital. Due to the variability of healthcare, patients were dichotomized as arriving to the hospital from home (reference group) vs. healthcare facility. Healthcare facilities included hospice, long-term acute care (LTAC), skilled nursing facility (SNF), psychiatric, intermediate rehab, or Veteran's healthcare facility.

Cluster Description

While sociodemographic and hospital level data was obtained from coded encounter data, medical comorbidities were collected using medical chart abstraction. The medical conditions of interest were defined based on the Charlson Comorbidity Index (CCI) disease groupings due to the existing literature validating this tool. However, since CCI was used to predict the risk of 10-year mortality, a composite variable was not created as the study outcome was IHT and not mortality (Charlson M, et al., 1987; Quan H, et al., 2011; Radovanovic D, et al., 2014). All patient medical data was abstracted using ICD-10 diagnostic coding, and each patients' top 25 diagnoses were manually reviewed for inclusion in disease groups referred to as clinical clusters. Each cluster was considered a dichotomous variable coded as the presence or absence of each disease group in the medical record.

Since each medical record included 25 available diagnoses, and the principal diagnosis for each patient was coded heart failure, 24 secondary diagnoses were chart abstracted for coded clinical clusters. If the presence of any disease grouping was coded in the medical record, the cluster was coded as yes for the specific disease group, regardless of the diagnosis number in the chart or how many times the diagnosis was listed in the medical record.

Clusters included 1) blood pressure defined as hypertension, hypotension, essential hypertension, or orthostatic hypertension; 2) cancer defined as active/recurrent leukemia, lymphoma, or tumor mass; 3) chronic obstructive pulmonary disease (COPD) defined as COPD and/or exacerbations; 4) connective tissue disease defined as lupus, scleroderma, arthritis, granulomatosis, myositis, polyangiitis, and/or Churg-Strauss Syndrome; 5) dementia defined as dementia or mild cognitive impairment; 6) diabetes defined as Type 1 diabetes, Type 2 diabetes, prediabetes, and/or any diabetic conditions; 7) kidney disease defined as renal disease, use of dialysis, uremia, and/or creatinine abnormality; 8) lipid disease defined as dyslipidemia and/or cholesterolemia; 9) liver disease defined as any liver condition, portal hypertension, hepatitis, and/or cirrhosis; 10) myocardial infarction (MI) defined as acute MI and/or history of MI; 11) peripheral vascular disease defined as peripheral vascular and/or peripheral arterial disease; 12) stroke defined as cerebrovascular infarction, transient ischemia attack (TIA), and/or hemiplegia; 13) alcohol defined as alcohol use, abuse, and/or alcohol-induced conditions; and 14) tobacco/Nicotine defined as tobacco/nicotine use, abuse, or tobacco/nicotine-induced conditions (Inamdar A & Inamdar A, 2016).

Study Outcome

The outcome variable was a continuous variable defined as the total costs per episode of care of patients with heart failure to determine if there was a total cost difference between IHT and non-transfer patients. Total costs included fixed costs (direct and indirect costs) and direct variable costs. Individual transfer costs of IHT and physician costs were not available in the data. For IHT patients, total costs were aggregated from both the referring community hospital and an academic medical center in order to account for the total costs associated with the entire encounter episode of care. Due to the integrated total cost data reporting in EPSi, the individual costs attributed to IHT from a community hospital to an academic medical center were unavailable. Several assumptions were made about the IHT cost to account for this limitation. IHT costs were assumed to be aggregated into the total cost data as a combination of fixed and direct variable costs. All IHT was assumed to have been conducted by ground ambulance transport, rather than air flight, which was much more expensive. To account for this, an average cost of $700 was assigned to each IHT patient for the transfer amount based on IHT ambulance costs from similar studies and the reduced ambulance costs that Medicare patients pay.[43,94] Therefore, a $700 IHT cost was subtracted from each IHT encounter total cost to adjust for comparison costs with non-transfer patients.

Sample Size Calculation

Since the study outcome was a continuous variable of total costs, sample size calculation included the average total costs and standard deviation of non-transfer patients and IHT patients. The average total cost of non-transfer patients was $13,303 with a standard deviation of $17,503. The average total cost of IHT patients, after adjusting for an estimated $700 ambulance transfer cost, was $26,582. The resulting minimum sample size was 28 IHT and 28 non-transfer patients in the study sample yielding 80% power with a 95% type one error rate (Rosner B, 2011). The final study sample included 4,862 cases and a 1.71% incidence rate of IHT.

Statistical Analysis

Sociodemographic, clinical and medical predictors were collected on all patients for 25 predictors. All predictors were stratified as categorical variables by IHT status. All analysis were conducted using SAS 9.3 (SAS Institute, Cary, NC, USA). Descriptive statistics were generated for covariates using frequency summaries for categorical variables. Differences between the groups were examined with chi-square tests for categorical variables and Fisher Exact Tests for categorical variables with frequencies of less than five patients for specific factors.

Univariate generalized linear modelling was conducted with predictors of total costs using a p-value cutoff of 0.20. Significant predictors were entered into a multivariable generalized linear model and predictor levels were compared to reference groups (for categorical predictors) to determine significant adjusted odds ratios ($p<0.05$) based on total cost outcomes using backwards elimination. This methodology was based on a similar approach by Mohr et al. using generalized linear modeling validated by general estimating equations – with both methods yielding similar results.[43] Multicollinearity was assessed using variance inflation factors and a cutoff of 10 or higher was used as an indication of high correlation. The final multivariable generalized linear model did not include any variables that exceeded the threshold. Using the significant predictors of the multivariable generalized linear model, interaction terms were fit and tested based on possible and clinically-meaningful interaction effects between predictors. A cutoff of $p<0.05$ was considered a significant interaction term for potential predictors. Two such interaction terms were included in the final model.

Results

A total of 4,862 patients were included in the study sample with 83 patients (1.71%) experiencing IHT to an academic medical center, and 4,779 non-transfer patients (98.29%). Patient ages ranged from 22-103 years of age. The mean age of IHT patients was 67.46 years (standard deviation: 14.75 years), and the mean age of non-transfer patients was 71.10 years (standard deviation: 14.98 years); p=0.03. The average total length of stay of IHT patients was 9.73 days (standard deviation: 6.64 days, and the average total length of stay of non-transfer patients was 5.37 days (standard deviation: 4.79 days); p<0.0001). The mean total cost of IHT patients was $26,581.70 (standard deviation: $26,661.00), and the mean total cost of non-transfer patients was $13,032.50 (standard deviation: $17,502.80); p<0.0001).

Table 11 includes the frequency counts and percentages of the sociodemographic and clinical covariates stratified by IHT status. IHT patients were slightly younger than non-transfer patients, with nearly 80% of IHT patients under age 80, while less than 67% of non-transfer patients were under age 80 (p=0.14). 60% of IHT patients were white compared to 48% of non-transfer patients (p=0.03). Nearly 47% of non-transfer patients had a history of previous admissions compared to less than 39% of IHT patients (p=0.13). While nearly 69% of IHT patients were treated by a cardiologist, only 24% of non-transfer patients were treated by a cardiologist (p<0.0001). Nearly 94% of IHT patients were admitted to the hospital from another healthcare facility compared to only 21% of non-transfer patients (p<0.0001). Over 84% of IHT patients had total LOS of at least 4 days, while only 59% of non-transfer had similarly long total lengths of stay (p<0.0001). A lower percentage of IHT patients were discharged to home with a higher rate of in-hospital mortality, while a higher percentage of non-transfer patients were discharged home with fewer in-house deaths ($p=0.03$). The majority of study patients were admitted to an ED at the hospital, but over 77% of non-transfer patients presented at the ED compared to 61% of IHT patients ($p=0.0006$). While only 7% of non-transfer patients were discharged from a hospital ICU, over 15% of IHT patients were discharged from an ICU ($p=0.007$).

Table 11: Sociodemographic and clinical characteristics by IHT status, n=4,862

	IHT		No IHT		
Characteristic	Number	Percent	Number	Percent	P-Value
Age in Years					0.14
22-59	24	28.92%	1,045	21.87%	
60-69	21	25.30%	1,070	22.39%	
70-79	21	25.30%	1,062	22.22%	
80-89	13	15.66%	1,099	23.00%	
90-100	4	4.82%	503	10.53%	
Race					0.03
White	50	60.24%	2,304	48.21%	
Non-White	33	39.76%	2,475	51.79%	
Sex					0.23
Male	45	54.22%	2,272	47.54%	
Female	38	45.78%	2,507	52.46%	
Socioeconomic Status					0.65
High SES	70	84.34%	3,938	82.40%	
Low SES	13	15.66%	841	17.60%	
Previous Admissions					0.13
No	32	38.55%	2,242	46.91%	
Yes	51	61.45%	2,537	53.09%	
Attending Specialty					<0.0001
Cardiovascular Medicine	57	68.67%	1,150	24.06%	
Other	26	31.33%	3,629	75.94%	
Admit Source					<0.0001
Home	5	6.02%	3,774	78.97%	
Healthcare Facility	78	93.98%	1,005	21.03%	
Total LOS (days)					<0.0001
1-3	13	15.66%	1,967	41.16%	
4-10	42	50.60%	2,358	49.34%	
11-98	28	33.73%	454	9.50%	
Discharge Disposition					0.03
Home	56	67.47%	3,461	72.42%	
Healthcare Facility	22	26.51%	1,227	25.67%	
Expired	5	6.02%	91	1.90%	
Admit Unit Type					0.0006
Emergency Department	51	61.45%	3,698	77.38%	
Inpatient Unit	32	38.55%	1,081	22.62%	
Discharge Unit Type					
Inpatient Unit	70	84.34%	4,411	92.30%	
Intensive Care Unit	13	15.66%	368	7.70%	0.007

Table 12 includes the frequency counts and percentages of the medical covariates stratified by IHT status. The majority of study patients had blood pressure disorders, but the rate was 10% higher among IHT patients (p=0.06). Non-transfer patients had nearly double the rate of cancer at 18% compared to 9% of IHT patients (p=0.03). The rate of dementia among non-transfer patients was 8% compared to only 3% of IHT patients (p=0.10). 60% of IHT patients had diabetes compared to 52% of non-transfer patients (p=0.14). Nearly 57% of non-transfer patients had lipid disease compared to 44% of IHT patients (p=0.02). Over 44% of IHT patients had a history of myocardial infarction compared to less than 35% of non-transfer patients (p=0.07).

Table 12: Medical characteristics by IHT status, n=4,862

Characteristic		IHT		No IHT		
		Number	Percent	Number	Percent	P-Value
Blood Pressure						0.06
	No	25	30.12%	1,932	40.43%	
	Yes	58	69.88%	2,847	59.27%	
Cancer						0.03
	No	75	90.36%	3,879	81.54%	
	Yes	8	9.64%	900	18.46%	
COPD						0.83
	No	54	65.06%	3,164	66.21%	
	Yes	29	34.94%	1,615	33.79%	
Connective Tissue Disease						0.98
	No	69	83.13%	3,978	83.24%	
	Yes	14	16.87%	801	16.76%	
Dementia						0.10
	No	80	96.39%	4,362	91.27%	
	Yes	3	3.61%	417	8.73%	
Diabetes						0.14
	No	33	39.76%	2,294	48.00%	
	Yes	50	60.24%	2,485	52.00%	
Kidney Disease						0.92
	No	28	33.73%	1,586	33.19%	
	Yes	55	66.27%	3,193	66.81%	
Lipid Disease						0.02
	No	46	55.42%	2,058	43.06%	
	Yes	37	44.58%	2,721	56.94%	
Liver Disease						0.78
	No	78	93.98%	4,454	93.20%	
	Yes	5	6.02%	325	6.80%	
Myocardial Infarction						0.07
	No	46	55.42%	3,109	65.06%	
	Yes	37	44.58%	1,670	34.94%	
Peripheral Vascular Disease						0.89
	No	78	93.98%	4,473	93.60%	
	Yes	5	6.02%	306	6.40%	
Stroke						0.31
	No	77	92.77%	4,549	95.19%	
	Yes	6	7.23%	230	4.81%	
Alcohol						0.61
	No	78	93.98%	4,544	95.05%	
	Yes	5	6.02%	235	4.92%	
Tobacco						0.62
	No	38	45.78%	2,058	43.06%	
	Yes	45	54.22%	2,721	56.94%	

Table 13 includes the univariate analysis of IHT, sociodemographic, and clinical predictors of total cost outcomes. IHT was associated with $13,549 (95% CI: $9,708-$17,390) higher total costs compared to non-transfer patients. Despite overlapping of confidence intervals, increasing decades of age were associated with lower total costs. The two significant differences in age and cost outcomes were between patients aged 22-59 and 80-89 compared to a reference group of patients aged 90-103. The 80-89 years of age group had the lowest total costs at $2,108, while the youngest patients ages 22-59 had the highest total costs at $7,796. Increasing total length of stay was directly associated with higher total costs with patients of LOS 4-10 days costing $7,813, while LOS 11-98 were associated with the highest total costs at $18,554. Males had slightly higher total costs ($1,829) than females, while patients without a history of previous admissions had slightly higher total costs ($1,126) than those with a history of previous admissions. Low SES patients had $3,064 higher total costs than high SES patients. Patients with heart failure treated by a cardiologist had $5,868 higher total costs than patients who were not treated by a cardiologist. Patients discharged to another healthcare facility had $5,738 higher total costs compared to patients who were discharged home, but the highest total cost was among patients who died in the hospital with total costs of $17,213. Patients first admitted to an inpatient unit had $8,454 higher total costs than patients first admitted to an emergency department. Patients who were discharged from the hospital from an ICU had $11,889 higher total costs than patients who were discharged from an inpatient unit. Patients who were admitted to the hospital from another healthcare facility had $3,820 higher total costs than patients admitted to the hospital from home.

Table 13: Univariate analysis of IHT, sociodemographic, and clinical predictors of total cost outcomes

Predictor (Level)		Total Cost Difference	95% CI
IHT			
	No	REF	
	Yes	$13,549	$9,708-$17,390
Age			
	22-59 Years	$7,796	$5,933-$9,658
	60-69 Years	$5,653	$3,797-$7,509
	70-79 Years	$4,546	$2,687-$6,404
	80-89 Years	$2,108	$257-$3,959
	90-103 Years	REF	
Total LOS (days)			
	1-3 Days	REF	
	4-10 Days	$7,813	$6,976-$8,649
	11-98 Days	$18,554	$17,153-$19,954
Sex			
	No	$1,829	$830-$2,829
	Yes	REF	
Previous Admissions			
	No	$1,126	$125-$2,128
	Yes	REF	
Socioeconomic Status			
	High SES	REF	
	Low SES	$3,064	$1,753-$4,375
Attending Specialty			
	Cardiovascular Medicine	$5,868	$4,722-$7,013
	Other	REF	
Discharge Disposition			
	Home	REF	
	Healthcare Facility	$5,738	$4,610-$6,866
	Expired	$17,213	$13,669-$20,756
Admit Unit Type			
	Emergency Department	REF	
	Inpatient Unit	$8,454	$7,306-$9,602
Discharge Unit Type			
	Inpatient Unit	REF	
	ICU	$11,889	$10,059-$13,719
Admit Source			
	Home	REF	
	Healthcare Facility	$3,820	$2,623-$5,017

Table 14 includes the univariate analysis of medical predictors of total cost outcomes. Absence of dementia was associated with $1,952 lower total costs. Kidney disease was associated with $4,542 higher total costs. Absence of lipid disease was associated with $1,705 lower total costs. Liver disease was associated with $6,978 higher total costs. Peripheral vascular disease was associated with $3,390 higher total costs. Stroke was associated with $2,445 higher total costs. Alcohol-related conditions were associated with $5,379 higher total costs. Tobacco/nicotine usage were associated with $1,830 higher total costs.

Table 14: Univariate analysis of medical predictors of total cost outcomes

Predictor (Level)		Total Cost Difference	95% CI
Dementia			
	No	$1,952	$173-$3,731
	Yes	REF	
Kidney Disease			
	No	REF	
	Yes	$4,542	$3,488-$5,596
Lipid Disease			
	No	$1,705	$697-$2,713
	Yes	REF	
Liver Disease			
	No	REF	
	Yes	$6,978	$5,000-$8,956
Peripheral Vascular Disease			
	No	REF	
	Yes	$3,390	$1,349-$5,431
Stroke			
	No	REF	
	Yes	$2,445	$119-$4,770
Alcohol			
	No	REF	
	Yes	$5,379	$3,075-$7,682
Tobacco			
	No	REF	
	Yes	$1,830	$822-$2,839

Table 15 is the final multivariable model of total cost outcomes analyzed using backwards elimination via adjusted generalized linear modeling. This model included stratified age, stratified total LOS, previous admissions, kidney disease, liver disease, peripheral disease, and tobacco/nicotine usage as significant predictors also associated with IHT and total cost outcomes of patients with heart failure. The multivariable model also included two significant interaction terms between admission unit and discharge unit and between admission source and discharge disposition. Multivariable analysis resulted in an adjusted total cost difference of $2,015 (95% CI: $1,039-$5,071) associated with IHT from community hospitals to an academic medical center. The parentheses indicate negative total cost estimates – predictors that were associated with reduced total costs, rather than increased total costs.

Table 15: Multivariable generalized linear model of predictors associated with total cost outcomes

Predictor (Level)		Adjusted Total Cost Difference	95% CI
IHT			
	No	REF	
	Yes	$2,015	$1,039-$5,071
Age (Years)			
	22-59 Years	$4,148	$2,652-$5,645
	60-69 Years	$2,706	$1,232-$4,179
	70-79 Years	$1,432	-($25)-$2,890
	80-89 Years	$394	-($1,038)-$1,827
	90-103 Years	REF	
Total LOS (days)			
	1-3 Days	REF	
	4-10 Days	$7,238	$6,409-$8,066
	11-98 Days	$15,925	$14,487-$17,363
Previous Admissions			
	No	$1,409	$633-$2,186
	Yes	REF	
Admission Unit*Discharge Unit			
	ED*Inpatient Unit	REF	
	ED *ICU	$6,311	$4,098-$8,524
	Inpatient Unit*Inpatient Unit	$4,612	$3,410-$5,815
	Inpatient Unit*ICU	$13,376	$11,419-$15,333
Admit Source*Discharge Disposition			
	Home*Home	REF	
	Healthcare Facility*Home	-($2,534)	-($3,956)-($1,113)
	Home*Healthcare Facility	$1,291	$186-$2,397
	Home*Expired	$12,126	$7,214-$15,551
Kidney Disease			
	No	REF	
	Yes	$1,313	$479-$2,148
Liver Disease			
	No	REF	
	Yes	$2,341	$815-$3,867
Peripheral Vascular Disease			
	No	REF	
	Yes	$1,524	$100-$3,867
Tobacco			
	No	REF	
	Yes	$1,141	$357-$1,925

Discussion

This study provided insights into the total costs associated with IHT of patients with heart failure from community hospitals to an academic medical center. IHT was associated with an adjusted total cost difference of $2,015 (95% CI: $1,039-$5,071) compared to non-transfer patients who were treated solely at one hospital, rather than transferred for treatment. However, nine other predictors, including two interaction terms, were also associated with higher total costs of IHT of patients with heart failure. Multivariable generalized linear modeling indicated that, although IHT was a driver of higher total costs, IHT was not the only factor associated with total costs, and the full model was complex and included severity of illness, length of stay in the hospital, and medical utilization predictors. These results are clinically and temporally meaningful since the ambulance transfer cost was excluded from analysis to minimize artificial cost inflation associated with transferring a patient from one hospital facility to another during a continuous episode of care.

Univariate analysis determined that IHT was associated with $13,549 higher total costs compared to non-transfer patients, which was in line with $13,486 higher total cost results from a previous study (Mohr N, et al., 2016). However, in multivariable modeling, only $2,015 in total costs were attributed to IHT in this current study compared to $6,897 in Mohr's study. This difference may be attributed to several factors, particularly since Mohr studied severe sepsis and septic shock patients, rather than heart failure, as well as differences in analytical approaches. Additionally, the lack of specifically attributable cost data in this current study limited multivariable adjustment of other potential cost variables. Nevertheless, the results of this current study align with literature indicating that IHT patients have higher total costs than non-transfer patients, and part of that cost is associated with the IHT itself (Sokol-Hessner L, et al., 2016; Mohr N, et al., 2016; Bernard A, et al., 1996).

Chapter 2 studied the predictors of IHT from community hospitals to an academic medical center, and included several predictors that were also associated with higher total costs, including age, admission unit, admission source, and history of previous admissions. Increasing age was associated with reduced odds of IHT among older patients, and increasing age was also associated with reduced total costs among older patients. While difficult to interpret in the context of medical care and treatment, these results may indicate that, from a clinician or patient perspective, elderly patients may not benefit as much from IHT and the associated costs. This conclusion is supported by data from Chapter 3 indicating that increasing age is associated with higher odds of 30-day mortality among IHT patients. Aging is an inevitable process, and the cost-benefit of treatment at a certain stage, particularly among chronically and severely ill patients with heart failure, may simply elicit diminishing returns that clinicians and/or patients believe are not justified (Abraham W, et al., 2008).

An interaction effect was observed between admission and discharge units. Patients who were discharged from an ICU had much higher total costs, which was compounded by admission to an inpatient unit, rather than through the emergency department. In fact, compared to ED patients discharged from an inpatient unit, ED patients discharged from an ICU had $6,311 higher total costs, and this number ballooned to $13,376 for patients admitted to an inpatient unit and discharged from an ICU. From a clinical perspective, this association is reasonable since most patients presenting at the hospital are admitted through the emergency department, and so direct admissions to inpatient units warrant higher severity of illness and necessity of higher levels of care. Similarly, patients discharged from an ICU have higher total costs due to the high operating costs of ICU stays (Lauerman M, et al., 2016; Valley T, et al., 2017). The associated disease burden with such patients suggests that they are severely ill and this require more and longer care at inpatient and ICU units, which drives increases in total costs among severely ill patients (Lee D, et al., 2016; Valley T, 2017). In context, these interactions are clinically-meaningful since ED's are triage and assessment units where patient time spent is limited, while inpatient units are longer length of stay units which have costs exceeding thousands of dollars per day (Dunlay S, et al., 2011; Titler M, et al., 2008; Wang G, et al., 2010).

Another interaction effect was observed between admission source and discharge disposition in this current study. Compared to patients admitted and discharged back to home, admissions from a healthcare facility that resulted in discharges to home actually had $2,534 lower total costs. This reduction is challenging to interpret because it suggests that sicker patients had improvements in their medical status in the hospital, which permitted them to go home, but the associated cost reductions could have been absorbed by the referring healthcare facility. Unsurprisingly, patients admitted from home and discharged to a healthcare facility had $1,291 higher total costs, and total costs increased to $12,126 for patients admitted from home who died in the hospital. These cost increases suggest that higher severity of illness, particularly among IHT patients who are at 25% increased odds of mortality (Chapter 3), is a key driver of higher total costs.

Patients who did not have a history of previous admissions had $1,409 higher total costs than patients with a previous history of admissions, and this association can be interpreted multiple ways. It is possible this group of patients has lower severity of illness, and thus their hospital visits occur when they are sicker, which would increase total costs. Alternatively, these patients may have some logistical or personal predisposition that reduces their likelihood of going to a hospital, and so when they do go to the hospital, utilization increases for other comorbid and chronic conditions. No association was found in Chapter 3 among IHT patients and 30-day readmissions or mortality based on previous admission history. However, an interaction effect was found with 11.75 times higher odds of IHT to an academic medical center of patients admitted from a healthcare facility with history of previous admissions compared to patients admitted from home without a history of previous admissions in Chapter 2. Thus, it is possible that lack of previous admissions drives costs because patients do not make it to the hospital until their severity of illness becomes higher than they can independently manage, which would drive up hospital total costs.

Unsurprisingly, increased total lengths of stay were major drivers of higher total costs. Compared to patients who stayed in the hospital for 1-3 days, patients with 4-10 days of stay had $7,238 higher total costs, and this number increased to $15,925 for patients with lengths of stay of 11 days and above. Long lengths of stay were associated with increased odds of mortality among increasing age groups in Chapter 3, which aligned with other studies associating older patients with longer hospital stays and poor outcomes.[69,85,86] Similarly, these long lengths of stay drove up total costs due to all the hospital costs associated with treating patients, particularly since every single day that a patient spends in the hospital increases total costs, regardless of the amount or level of care they receive (Lesyuk W, et al., 2018; Salem K & ElKhateeb O, 2017).

Aside from length of stay, severity of illness is major driver of utilization across the healthcare ecosystem because sicker patients require more complex care, which is also more expensive (Silverstein M, et al., 2008). This applies more so to chronic conditions, such as kidney disease, liver disease, peripheral vascular disease, and tobacco usage – all of which were associated with higher total costs. Interestingly, none of those four chronic conditions were predictors of IHT from community hospitals to an academic medical center in Chapter 2, although these predictors were drivers of higher total costs associated with IHT in this current study. Thus, it may be concluded that the factors affecting IHT are not necessarily associated with higher total costs, but rather severity of illness as a whole. The IHT process should be operationally based on clinical necessity and care, rather than cost drivers, and this current study supports that conclusion.

Kidney disease is a common comorbidity among patients with heart failure and accounted for $1,313 in higher total costs (Inamdar A & Inamdar A, 2016). From Chapter 3, kidney disease was also associated with 49% higher odds of 30-day readmissions, and so this condition chronically increases total costs due to the long-term treatment that kidney disease mandates (Tuegel C & Bansal N, 2017; Grande D, et al., 2018). Liver disease was associated with $2,341 in higher total costs, and Chapter 3 found that IHT patients with liver disease have 2.21 higher odds of 30-day mortality. Thus, this increase in total costs may indicate that extensive resources are being dedicated for patients with liver disease to maintain their medical care and treatment (Inamdar A & Inamdar A; 2016; Crowley M, et al., 2017).

Peripheral vascular disease (PVD) was associated with $1,524 higher total costs. A recent study found associations between PVD and heart failure, but also indicated that diabetes and tobacco usage wee additional concomitant risk factors (Inglis S, et al., 2013). These associated increases in total costs with PVD were unsurprising given the comorbidities frequently present with PVD. No interaction effects were observed in this current study with PVD and any other medical predictors. Tobacco use was associated with $1,141 in higher total costs, and the effects of smoking on heart disease and overall health indicate this association was unsurprising (Suskin N, et al., 2001; Centers for Disease Control and Prevention, et al., 2010). Interestingly, tobacco use was also associated with 22% higher odds of 30-day readmissions in Chapter 3, and like kidney disease, tobacco use may exacerbate medical severity of patients and require more frequent and costly hospitalizations. Of note, no interaction effects were observed between history of previous admissions and any other study predictors.

In summary, IHT was associated with higher total costs of patients with heart failure compared to non-transfer patients, but this association was affected by clinical and medical predictors. Longer lengths of stay in the hospital and predictors associated with higher severity of illness were associated with higher total costs. The predictors of IHT from community hospitals to an academic medical center, studied in Chapter 2, were not necessarily the same ones driving total cost increases. However, in both instances, higher severity of illness was associated with higher odds of IHT and higher total costs – indicating that despite variabilities in patients with heart failure, operational and clinical decision-making for patients with heart failure was largely medically-driven. Similarly, higher odds of both 30-day mortality and 30-day readmissions were associated with higher severity of illness, irrespective of the total costs of hospital stay and treatment. Sicker patients were more likely to be transferred from a community hospital to an academic medical center for treatment, which was associated with higher total costs for patients, but post-discharge outcomes remained poor with increased odds of readmissions and mortality due to higher severity of illness.

One of the major strengths of this study was appropriate statistical power and sample size that exceeded the minimum sample size needed to determine meaningful associations in multivariable generalized linear modeling. However, IHT was an infrequent occurrence in the acute hospital setting, and more studies with larger data sets, particularly among IHT groups, would be beneficial to further evaluate the associations with outcomes. The use of a continuous data set over two years of in-house UHHS data ensured a high level of precision within the data and complete medical records for the available study population. Overall, due to the stringent inclusion and exclusion criteria, the heart failure population was homogenous and clinically-distinct, and the results had temporal and clinical meaningfulness.

Other strengths of the study data included all adults ages 18 and up, which provided a more robust data set than the traditional Medicare population of the HRRP ages 65 and up (Centers for Medicare and Medicaid Services, 2018). Including younger adults increased the generalizability of the results, particularly for a younger heart failure population (Glyn P, et al., 2019). Additionally, inclusion of all payers, compared to the Medicare-only beneficiaries of the HRRP, further increased the diversity of the study sample and generalizability of study results (Centers for Medicare and Medicaid Services, 2018). These two factors are important because including all ages and all payers provides new insight into previously understudied outcomes for patients who are not traditionally considered among the HRRP patient population.

Heart failure is a complex chronic condition, and despite the homogeneity of this study population, there are other methods to define such a population, instead of the ICD-10 diagnosis codes that were modelled after the HRRP. Although similar associations would be expected in such an analysis, there may be other variables that become relevant in such a model. Additionally, residual confounding is possible due to variables that were not able to be included in the analysis. For example, ethnicity is associated with heart failure and race, but concise data on ethnicity was not available in the data set for analysis and adjustment (Inamdar A & Inamdar A, 2016; Chamberlain R, et al., 20181). Although in-house data from UHHS was used, such data is still limited by missing external hospital encounter data, such as if a patient visited another hospital system or provided incorrect medical information. There may have also been errors in the medical record from data entry at the encounter level, although data validation was performed to catch as many errors as possible.

While UHHS provided all available medical record data for this study, total cost data was only available from EPSi after automatic uploading into Midas+ Care Manager. This resulted in 220 encounters that were excluded due to missing total cost data. Although the data sets were all internal to UHHS, it is possible that data aggregation issues could have occurred when linking EPSi financial data and encounter data. Furthermore, lack of individual cost data was a major limitation of this study since only total costs were available for study. Thus, it was not possible to attribute specific costs, other than modeling the differences in total costs associated with various predictors. Detailed cost data would add additional information for analysis that was not available. Similarly, the cost of IHT was not available in this data set, and estimates from previous studies were used for statistical adjustment. Having the actual IHT costs would provide additional data that was not currently available for analysis. Lastly, physician billing data was not available for analysis, and this data could have provided additional data for outcomes analysis.

Binary coding via chart abstraction for clinical clusters was performed to capture medical diagnoses, and this process was susceptible to errors, including determination of which ICD-10 diagnoses qualified for inclusion. Generalizations were made for the dichotomous presence or absence of clinical clusters irrespective of duration or onset; however, in a chronically-ill heart failure population, it was reasonable for multiple comorbidities to be present. Lastly, less than 5% of the study population had more than 25 diagnoses in their medical record, but those other diagnoses were unable to be extracted from the medical record, and so only the top 25 diagnoses were reviewed for inclusion. The medical predictors used in this study were based on the

Charlson Comorbidity Index but could also be modeled in future studies in other ways, including different comorbidities that factor into accounting for severity of illness and disease conditions.

Future studies should attempt to replicate these findings using more diverse medical populations or different groups of patients with heart failure. It is possible that IHT differentially affects other disease conditions and severity of illness, and so these findings cannot be extrapolated broadly among other medical groups of patients. Larger population analyses may provide additional insights into other predictors of total cost outcomes. Also, due to the unique study population of homogenous patients with heart failure within UHHS, the current results may not be generalizable to other health systems across the United States, and so care needs to be taken to interpret and apply the results in context, particularly since cost data varies so significantly both within and between healthcare institutions. Additional studies should be performed to compare other health systems or multiple health systems in an aggregate data set using different cost outcome endpoints to determine meaningful clinical associations.

Chapter 5: Discussion

IHT is a multifactorial occurrence that involves coordination between two hospitals in an attempt to streamline and optimize medical resources and care for acutely ill patients (Tierney W, 2018; Avaldi V, et al., 2017; Herrigel D, et al., 016). This complexity is overshadowed by the relative infrequency of IHT among inpatient encounters. With an average 1.5%-4.5% of all inpatient episodes of care involving an IHT, there are still many unclear aspects of IHT, including the predictors of transfer, post-discharge patient outcomes, and cost outcomes of transfer patients (Mueller S, et al., 2017; Iwashyna T, et al., 2009; American Hospital Association, 2019). Heart failure is a chronic medical condition associated with many comorbidities and poor post-discharge outcomes, including high rates of readmissions, mortality, and costs expenditures (Mayo Clinic, 2019; Feltner C, et al., 2014; CDC, 2017; Miro O, et al., 2017). The role of IHT from community hospitals to an academic medical center among patients with heart failure has not previously been studied, and this dissertation provides new insights into this unique population and outcomes.

One of the key drivers of the Centers for Medicare and Medicaid Services' 2012 Hospital Readmission Reduction Program (HRRP) was reducing 30-day readmission rates among diseases, and heart failure was a primary target of the program (Feltner C, et al., 2014). With 30-day heart failure readmission rates as high as 25%, the HRRP saw some national success, despite high readmission rates remaining (Feltner C, et al., 2014; McIlvennen C, 2015). However, an unintended consequence of the reduced readmissions of the HRRP may have been associated increases in mortality among severely ill patients with heart failure. The general consensus among these studies was that patients with heart failure were being readmitted less frequently, but their severity of illness was not substantively improving, and so their mortality was either increasing or having no meaningful improvement (Wadhera R, et al., 2018; McIlvennen C, 2015; Gupta A, et al., 2018). With 30-day heart failure mortality rates as high as 10%, these studies were major cause for concern (CDC, 2017; Miro O, et al., 2017; Gupta A, et al., 2018). These associations remain an area of study due to the relatively recent inception of the HRRP, but in the meantime, more studies have focused on factors associated with actionable aspects of patient care, including IHT of acute care patients (Mueller S & Schnipper J, 2019; Yamaguchi T, et al., 2018; Dalmau M, et al., 2014). Of note, CMS does not stratify encounters with an IHT into separate episodes of care, but aggregates the data into one encounter for reporting purposes (Centers for Medicare and Medicaid Services, 2018). This methodology makes IHT studies more complicated among Medicare data sets. As a result, it is even more important to study the predictors of IHT and post-discharge outcomes of IHT patients, as well as the cost drivers of IHT because heart failure treatment and care is very expensive (Inamdar A & Inamdar A, 2016; Heidenreich P, et al., 2011; Titler M, et al., 2008; Wang G, et al., 2010).

Chapter 2 studied the predictors associated with IHT of patients with heart failure from community hospitals to an academic medical center. From a clinical perspective, predictors that were indicative of higher severity of illness were associated with significant increases in odds of IHT to an academic medical center. Blood pressure disorders, cancer, diabetes, and lipid disease were all predictors of IHT, as well as patients admitted to a community hospital from another healthcare facility and discharged back to a healthcare facility after treatment. In aggregate, these predictors reflected higher severity of illness among patients with heart failure having higher odds of IHT to an academic medical center, presumably for medical care and treatment. It is also likely that these associated disease were mediating IHT outcomes due to varying severity of illness. For example, a patient with heart failure who also has controlled diabetes may have lower severity of illness compared to a similar patient but with uncontrolled type 2 diabetes. However, data regarding severity of specific illnesses were not available in the current study.

Further evidence of IHT operationalization was seen with reduced odds IHT for older patients compared to younger patients, which may have indicated that clinician discretion was used to assess the relative benefits of transfer for older and more severely ill patients who potentially stood to benefit less from transfer. The higher odds of mortality and readmissions for IHT patients in Chapter 3 certainly added validity to this conclusion, as well as the increased total costs studied in Chapter 4. Several other predictors were associated with reduced odds of IHT to an academic medical center, including dementia, patient evaluation by non-cardiologists, and direct admissions to an inpatient unit rather than an ED. These results suggested that clinicians may have been less likely to recommend transfer for psychiatric patients due to difficulties in operationalizing inter-hospital coordination and care processes of dementia patients (Kulshrestha A & Singh J, 2016; Adelborg K, et al., 2017). Cardiologists are ideally the physicians of choice for treating heart failure due to their specialized training, but operationally, this is not always possible. Community hospitals are generally smaller and have fewer staffed specialists, and the reduced odds of IHT for non-cardiologists may have indicated that cardiologists were the most comfortable with assessing IHT necessity compared to their peers (Palacio C, et al., 2014; Beresford L, 2013).

Admission unit was a complex predictor to interpret, but generally patients first presented to the hospital via an ED, where they were triaged and assessed for admission. Direct admission to an inpatient unit indicated either a higher severity of illness or arrival at the hospital through a vector that bypassed the ED, such as ambulance or air transport (Fish-Trotter H, et al., 2018). Since arrival vector was not a predictor available in the study, the assessment of higher severity of illness was determined based on direct admission to an inpatient unit. Such patients were found to have lower odds of IHT to an academic medical center, which indicated that admitted patients at community hospitals were more likely to receive treatment at that hospital, and that the ED played an important role in IHT assessment and determination. In summary, younger age, predictors reflective of higher severity of illness, and evaluation by cardiologists were associated with higher odds of IHT from community hospitals to an academic medical center.

In Chapter 3, IHT patients were shown to experience worst post-discharge outcomes, including 25% higher odds of 30-day mortality and 2.26 higher odds of unplanned 30-day readmissions. Once again, higher severity of illness was associated with higher odds of poor outcomes, but the covariates differed somewhat between the mortality and readmissions multivariable models. Increasing age and longer lengths of stay in the hospital were associated with significantly higher odds of mortality, but had no associations with readmissions. These results indicated that elderly patients with long lengths of stay may have been predisposed to mortality, and there may not have been any meaningful interventions to improve their outcomes, including IHT (Abraham W, et al., 2008; Van der Wal H, et al., 2017; Sud M, et al., 2017). Patients admitted and discharged from a healthcare facility had higher odds of mortality, indicating a higher severity of illness among those patients, while discharges from an ICU were also associated with higher odds of mortality (Lee D, et al., 2016; Valley T, et al., 2017). As with predictors of IHT, cancer and liver disease were also associated with higher odds of mortality. Chronic conditions, including COPD, diabetes, kidney disease, and tobacco usage, were associated with higher odds of readmissions but not with mortality. Such associations indicated frequent utilization of medical care that likely drove medical costs and poor outcomes (Inamdar A & Inamdar A, 2016; Tuegel C & Bansal N, 2017; Grande D, et al., 2018; Crowley M, et al., 2017; Bertero E, et al., 2018; Diaz-Guzman E & Mannino D, 2014; Suskin N, et al., 2001; Centers for Disease Control and Prevention, et al., 2010). However, as in Chapter 2, these comorbid conditions were likely acting as mediators of severity, although no such data was available for assessment.

Patients with lower SES had lower odds of mortality, which may have reflected a higher utilization of subsidized medical care, and the lack of association with readmissions among low SES patients added validity to this conclusion, although it was difficult to determine due to limited socioeconomic data on study patients. More research is recommended into socioeconomic status variables to understand the IHT process and outcomes. As expected, patients with outpatient care utilization post-discharge had reduced odds of both mortality and readmissions, likely due to more active maintenance of their health status after discharge (Glyn P, et al., 2019; Lee W, et al., 2019; Groenveld P, et al., 2019). Patients with heart failure treated by cardiologists had higher odds of readmissions, and this association was interpreted in two potential ways. Firstly, these patients were more severely ill and had a higher predisposition toward readmissions, which is why they were being treated and monitored by outpatient physicians. Second, these patients may have been receiving more relevant outpatient education about their health status and were more likely to seek a readmission encounter due to perceived medical complications based on their outpatient education from physicians (Palacio C, et al., 2014; Beresford L, 2014). Interestingly, despite having no association with readmissions, blood pressure disorders were associated with lower odds of mortality. Although blood pressure disorders are complicated and dangerous medical conditions, they are chronic and frequently manifest as precursors to other high-mortality conditions (Inamdar A & Inamdar A, 2016; Yancy C, et al., 2013; Crowley M, et al., 2017). Thus, patients with heart failure are less likely to die from blood pressure complications, although it is a factor in their overall medical profile.

In summary, IHT of patients with heart failure was associated with higher odds of post-discharge mortality and readmissions based on severity of illness and hospital utilization. These results are specific in context to patients transferred from community hospitals to an academic medical center, as a previous study has shown that patients transferred from an academic medical center to community hospitals do not have worse outcomes (Yamaguchi T, et al., 2018). These study associations are temporally meaningful because transfer from a hospital with lower levels of care to higher levels of care is indicative of patient severity of illness and healthcare needs. The patients with heart failure would stand to benefit from advanced medical services but would remain at higher odds of mortality and readmissions because their medical care could be ameliorated but not resolved due to the chronic nature of heart failure. The multivariable models provided support for these conclusions of IHT patient outcomes in post-discharge settings.

In addition to the medical and operational aspects of IHT from community hospitals to an academic medical center, the cost outcomes associated with transfers are meaningful for evaluation due to resource utilization and ubiquitous cost management issues facing the American healthcare system (Sokol-Hessner L, et al., 2016; Inamdar A & Inamdar A, 2016; Mohr N, et al., 2016). Chapter 4 found that the unadjusted total cost difference of IHT of patients with heart failure was $13,549 per encounter episode of care. This amount was nearly identical to the unadjusted $13,486 total cost difference of IHT of patients with severe sepsis or septic shock from a similar study of cost outcomes (Mohr N, et al., 2016). However, multivariable adjustment in Chapter 4 found the adjusted IHT cost was actually $2,015, and the remaining cost difference was largely attributable to severity of illness and length of stay in the hospital – two key drivers of hospital costs within the healthcare ecosystem (Inamdar A & Inamdar A, 2016; Dunlay S, et al., 2011; Heidenreich P, et al., 2011; Titler M, et al., 2008; Wang G, et al., 2010). These associations may add further evidence to the conclusions in Chapter 2 that severity of illness is both a driver of IHT from community hospitals to an academic medical center and of increasing costs associated with IHT patients.

As with increasing age and lower odds of IHT in Chapter 2, increasing age was also associated with lower total costs among IHT patients. The youngest patients with heart failure aged 22-59 had higher total costs compared to the oldest patients aged 90-103. This association may be attributed to differential cost spending and clinicians' decisions to allocate resources to maximize health benefits while reducing inefficient spending. In words, it is possible that clinicians may believe that an IHT of a younger patient will have more meaningful medical impact than a much older patient, and the associated total costs may reflect these scenarios occurring at community hospitals (Abraham W, et al., 2008).

Unsurprisingly, patients admitted to an inpatient unit and discharged from an ICU had higher total costs compared to ED admissions. Despite the interaction effect, the discharge unit may be the primary driver of these costs since ICU care is among the most expensive care accommodative offered by hospitals (Bernard A, et al., 1996; Lauerman M, et al., 2016). These costs are compounded further based on total hospital length of stay with lengths of stay of 4-10 days costing $7,238 more than lengths of stay of 1-3, while lengths of stay of 11 days or greater cost twice as much at $15,925. These associations are clinically-meaningful because total costs directly increase as the time patients spend in the hospital increases (Lesyuk W, et al., 2018; Salem K & ElKhateeb O, 2017). The costs will fluctuate depending on variable cost utilization and unit-specific lengths of stay, but since that specific data was not available, meaningful estimates of IHT cost outcomes were based on total costs (Lee D, et al., 2016; Valley T, et al., 2017).

In addition to unit-specific admissions and discharges driving costs, admission source and discharge disposition had an interaction effect on total cost outcomes of IHT patients. Patients admitted from a healthcare facility were assumed to have higher severity of illness, and such patients who were discharged from a healthcare facility had higher total costs than patients discharged to home. Total costs were highest among patients admitted from a healthcare facility who died in the hospital. Such outcomes indicated a higher severity of illness among IHT patients as a significant driver of total cost increases based on utilization of treating more severely ill patients, including those who died in the hospital. Interestingly, severity of illness as a driver of total costs may have been counter-indicated among patients without a history of previous hospital admissions. This predictor was associated with higher total costs for patients who did not frequently utilize inpatient services, thus indicating potentially lower severity of illness. However, it was also possible these patients had more limited access to services or could only utilize them sparingly, and so costs were driven up when patients finally presented to the hospital.

Medical predictors of higher severity of illness, including kidney disease, liver disease, peripheral vascular disease, and tobacco usage, were all associated with higher total costs among IHT patients. These results were unsurprising since all four chronic conditions have high costs of care with long duration (Inamdar A & Inamdar A, 2016; Crowley M, et al., 2017; Suskin N, et al., 2001; Centers for Disease Control and Prevention, et al., 2010). Although none of the four medical predictors were associated with IHT in Chapter 2, liver disease was also associated with higher odds of mortality and both kidney disease and tobacco usage were associated with higher odds of readmissions in Chapter 3. It is likely that these medical predictors are also mediating costs based on disease severity and complexity of care. These costly medical care pathways all indicate that additional research is needed into IHT among acute care patients with chronic medical conditions, such as heart failure, in order to understand optimal treatment strategies and improve post-discharge outcomes while aiming to reduce total costs of care.

This study had several important limitations pertaining to data outcomes and variables of interest. Socioeconomic patient-level variables, such as income, household size, commute availability, etc., could not be evaluated because this information was not available in the data sets. Although insurance payer was used as a proxy for SES, the predictors were not interchangeable, and future analysis with SES data could be meaningful as potential predictors. The use of other post-discharge outcomes, including different periods besides 30-days, may be useful to study shorter- or longer-term effects of IHT since patients with heart failure already experience high rates of 30-day mortality and readmissions. Survival analysis using time to readmission and/or mortality as endpoints could also be conducted to study differences in time-to-event for IHT patients compared to non-transfers. Due to the overall infrequency of IHT in the general population, larger studies of IHT-specific patients could yield additional data about associations and outcomes that would have meaningful implications for clinicians treating these patients in an acute-care inter-hospital setting. However, it is important to note that the current study may have limited generalizability to other IHT chronic-disease sub-populations, such as COPD or liver disease, due to differences in disease pathophysiology and treatment options. Acutely-ill sub-populations, such as pneumonia or sepsis, may be even more clinically-distinct, and these differences between chronic and acute medical conditions could result in further differential outcomes and associations.

Future research should aim to study predictors of IHT and associated post-discharge outcomes among different disease conditions using other predictors and different hospital settings. Detailed clinical data, including laboratory values and acuity scores, would be meaningful to elucidate the potential mediation effects of disease severity of IHT and associated outcomes. For example, assessing kidney disease as a marker of health status is meaningful from a medical context, but there are inherent differences in patient health status when comparing end-stage renal disease to a more moderate kidney disorder. However, disease-specific severity was not evaluated as a key driver of IHT and outcomes in this study – rather the totality of health status of patients with heart failure was shown to be significant towards IHT, post-discharge, and total cost outcomes. This scenario is amplified when considering that patients with heart failure frequently have multiple comorbidities of varying disease severity. Such analysis could provide additional layers of information for IHT modelling, but the analysis would likely have limited impact on results since individual disease severity may act as an effect modifier rather than a statistically-significant and meaningful clinical predictor of outcomes.

Age is another predictor of outcomes that has been shown to have differential effects on outcomes, as older patients were less likely to be transferred (Chapter 2), but those patients were more likely to experience poor post-discharge outcomes (Chapter 3) and have lower total costs as age increased (Chapter 4). Therefore, opportunities for improvement and next steps could include holistic evaluation of the health status of patients with heart failure presenting at community hospitals in order to either expeditiously determine the need for IHT or reduce lead time at community hospitals to start aggressive treatment for heart failure and other associated comorbidities. These assessments would entail intensive screenings of all medical and clinical issues, including age, of patients with heart failure presenting at community hospitals – not just heart failure as the principal reason for the hospitalization.

For example, a patient with heart failure presenting to a community hospital from a healthcare facility, such as skilled nursing or long-term acute care, is generally sicker than a patient presenting from home, as evidenced by the intensive medical care these healthcare facilities offer that are not available to patients at home. Similar conclusions can be drawn from patients first admitted to an inpatient unit compared to an emergency department, and patients discharged from an ICU compared to an inpatient unit, as well as longer lengths of stay of patients in the hospital for care and treatment. These types of clinical predictors are indicative of sicker patients who need more complex and coordinated care, and part of that care includes an IHT to an academic medical center with higher acuity of care, resources, and clinical staffing. In context, disease-specific severity is suggested to have a mediation effect that could not be evaluated in this current study, but the clinical markers of overall patient health status and severity were evaluated and shown in Chapters 2-4 as being associated with IHT, poor post-discharge outcomes, and higher total costs.

Since this study was conducted within an integrated multi-site hospital system, no data on medical care was available from other institutions, and so a larger study involving other hospitals with randomized data sets would increase the external validity and generalizability of these results. Unfortunately, this may be challenging since non-integrated health systems may complicate patient-level data linkage, especially when including other external agencies, such as Departments of Health and CMS. Detailed cost data would also provide a more robust analysis of specific drivers among inpatient IHT costs of care. Since only total cost data, comprised of fixed and direct variable costs, was available for study, no analysis was able to be performed on individual-level costs, such as medications, procedures, or disease evaluation. Thus, another limitation of the cost analysis was inability to attribute specific costs to disease-specific severity due to lack of such data. It is reasonable to conclude that sicker patients will have higher total costs, but specific disease conditions could drive costs differentially compared to other comorbidities due to disease-specific severity. For example, costs for end-stage renal disease would be expected to be much higher due to dialysis care compared to a mild kidney disorder manageable by medications alone. Such cost analyses could not be conducted in the current study because only total cost data at the encounter level was available.

The lack of physician billing data compounded this limitation further since physician costs can have high increases on cost outcomes depending on how much clinician involvement is necessary for treatment. One next step using the available data could include expanding service availability at community hospitals so that patients with heart failure who have comorbidities could benefit from additional services offered at community hospitals, which would reduce their need for IHT and subsequent poor post-discharge outcomes. A byproduct of this service expansion would be potential benefits to other patient sub-populations who are also in need of similar services at community hospitals. Thus, there would be downstream benefits for multiple patient populations, as well as IHT patients who are not necessarily benefiting from transfers to an academic medical center.

From a clinical perspective, IHT is often unavoidable, and so the results of this current study must be evaluated and applied in context. Clinicians should evaluate patients presenting to community hospitals with heart failure in the totality of their health status as expeditiously as possible to determine whether IHT may or may not be beneficial. Optimizing the decision to transfer to an academic medical center based on health status, as indicated by socioeconomic, clinical, and medical predictors, can lead to improved patient outcomes by streamlining the holistic evaluation and treatment of patients with heart failure at community hospitals, so that these patients receive the appropriate aggregate level of care for all their health conditions, rather than just heart failure being the primary focus. Such decision-making and evaluation could lead to opportunities for reducing 30-day readmissions and mortality for acute care patients experiencing IHT within an integrated hospital system.

References

Abraham W, Fonarow G, Albert N, et al. (2008). Predictors of in-hospital mortality in patients hospitalized for heart failure. *J Am Coll Cardiol*. 52(5) 347-356.

Adelborg K, Horváth-Puhó E, Ording A, et al. (2017). Heart failure and risk of dementia: a Danish nationwide population-based cohort study. *European Journal of Heart Failure.* 19(2):253-260.

AHRQ. (2019). KFF analysis of medical expenditure panel survey. *U.S. Department of Health & Human Services*.

American Hospital Association. (2019). Fast facts on U.S. hospitals, 2019. *American Hospital Association*.

Avaldi V, Lenzi J, Urbinati S, et al. (2017). Effect of cardiologist care on 6-month outcomes in patients discharged with heart failure: results from an observational study based on administrative data. *BMJ Open*. 7(11):e018243.

Bailey, M. (2017). Taken for a ride? Ambulances stick patients with surprise bills. *Kaiser Health News*.

Beresford L. (2013). Cardiologists help lower readmission rates for hospitalized patients with heart failure. *The Hospitalist*. 2.

Bergethon K, Ju C, DeVore A, et al. (2016). Trends in 30-day readmission rates for patients hospitalized with heart failure: finding from the get with the guidelines-heart failure registry. *American Heart Association: Circulation: Heart Failure*. 9(6)10.1161/CIRCHEARTFAILURE.115.002594 e002594.

Bernard A, Hayward R, Rosevear J, et al. (1996). Comparing the hospitalizations of transfer and non-transfer patients in an academic medical center. *Acad Med*. 71:262–266.

Bertero E, Canepa M, Maack C, et al. (2018). Linking heart failure to cancer. *Circulation*. 10.1161.

Bujang M, Sa'at N, Joo L, et al. (2018). Sample size guidelines for logistic regression from observational studies with large population: emphasis on the accuracy between statistics and parameters based on real life clinical data. *Malaysian Journal of Medical Sciences*. 10.21315/mjms2018.25.4.12.

CDC. (2017). Underlying cause of death. *CDC Wonder*. CDC.

Centers for Disease Control and Prevention, et al. (2010). How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the surgeon general. *Atlanta (GA): Centers for Disease Control and Prevention (US).* 6, Cardiovascular Diseases.

Centers for Medicare and Medicaid Services. (2018). 2018 Condition-specific measures updates and specifications report hospital-level 30-day risk-standardized readmission measures. *Center for Medicare & Medicaid Services*.

Centers for Medicare and Medicaid Services. (2016). ICD-10-CM/PCS MS-DRG v34.0 Definitions manual. *Centers for Medicare and Medicaid Services*.

Chaiyachati K, Qi M, Werner R. (2018). Changes to racial disparities in readmission rates after medicare's hospital readmissions reduction program within safety-net and non-safety-net hospitals. *JAMA Netw Open*. 1(7):e184154.

Chamberlain R, Sond J, Mahendraraj K, et al. (2018). Determining 30-day readmission risk for patients with heart failure: The readmission after heart failure scale. *International Journal of General Medicine*. 11:127-141.

Charlson M, Pompei P, Alex K, et al. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases*. 40(5):373-383.

Crowley M, Diamantidis C, McDuffie J, et al. (2017). Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronicle disease: A systematic review. *Ann Intern Med*. 166(3):191-200.

Dalmau M, Beiras- Fernández A, Keller H, et al. (2014). Initiation of an inter-hospital ECMO transfer program for patients suffering from severe acute heart and/or pulmonary failure. *Revista Española de Cardiología.* 67(4):329-330.

Dharmarajan K, Wang Y, Lin Z, et al. (2017). Association of changing hospital readmission rates with mortality rates after hospital discharge. *Journal of the American Medical Association*. 318(3)270-278.

Diaz-Guzman E, Mannino D. (2014). Epidemiology and prevalence of chronic obstructive pulmonary disease. *Clinical Chest Med*. 35(1):7-16.

Diepen S, Widimský P, Lopes R, et al. (2012). Transfer times and outcomes in patients with st-segment-elevation myocardial infarction undergoing interhospital transfer for primary percutaneous coronary intervention. *American Heart Association: Circulation: Cardiovascular Quality and Outcomes.* 5: 437-444.

Dreyer R, Ranasinghe I, Wang Y, et al. (2015). Sex differences in the rate, timing, and principle diagnoses of 30-day readmissions in younger patients with acute myocardial infarction. *American Heart Association: Circulation*. 132(3):158-166.

Dunlay S, Shah N, Shi Q, et al. (2011). Lifetime costs of medical care after heart failure diagnosis. *Circ. Cardiovasc. Qual. Outcomes.* 4:68–75.

Edmonston D, Wu J, Matsouaka R, et al. (2019). Association of post-discharge specialty outpatient visits with readmissions and mortality in high-risk patients with heart failure. *American Heart Journal.* 212:101-112.

Eisenberg E, Di Palo K, Piña I. (2018). Sex differences in heart failure. *Clin Cardiol.* 41:211–6.

Epstein A, Jha A, Orav E. (2011). The relationship between hospital readmission rates and rehospitalizations. *New England Journal of Medicine*. 365:2287-2295.

European Society of Cardiology. (2019). Heart attack patients taken directly to heart centres have better long-term survival: heart attacks in young people and women may be unrecognised by paramedics and patients. *European Society of Cardiology. Press Release.*

Feltner C, Jones C, Cene C, et al, (2014). Transitional care interventions to prevent readmissions for persons with heart failure: A systematic review and meta-analysis. *Annals of Internal Medicine.* 160 (11): 774-784.

Fish-Trotter H, Collins S, Danagoulian S, et al. (2018). Design and rationale of a randomized trial: Using short stay units instead of routine admission to improve patient centered health outcomes for acute patients with heart failure (SSU-AHF). *Contemp Clin Trials.* 72:137-145.

Formiga F, Masip J, Chivite D, et al. (2017). Applicability of the heart failure readmission risk score: A first European study. *International Journal of Cardiology*. 236:304-309.

Glyn P, Lloyd-Jones D, Feinstein M. (2019). Disparities in cardiovascular mortality related to heart failure in the United States. *Journal of the American College of Cardiology*. doi: 10.1016/j.jacc.2019.02.042.

Gorodeski E, Starling R, Blackstone E. (2010). Are all readmissions bad readmissions? *New England Journal of Medicine*. 363:297-298.

Government Accountability Office. (2012). Costs and medicare margins varied widely; transports of beneficiaries have increased. *U.S. GAO.* 13-6.

Grande D, Gioia MI, Terlizzese P, et al. (2018). Heart failure and kidney disease. *Adv Exp Med Biol.* 1067:219-238.

Gravely S, Ginsburg L, Stewart D, et al. (2012). Cardiac Rehabilitation Care Continuity through Automatic Referral Evaluation (CRCARE) Investigators. Referral and use of heart failure clinics: what factors are related to use? *Can J Cardiol.* 28(4):483–489.

Groeneveld P, Medvedeva E, Walker L, et al. (2019). Association between spending and survival of chronic heart failure across veterans affairs medical centers. *JAMA Netw Open.* 2(7):e197238.

Gupta A, Allen L, Bhatt D, et al. (2018). Association of the hospital readmissions reduction program implementation with readmission and mortality outcomes in heart failure. *Journal of the American Medical Association Cardiology*. 3(1):44-53.

Heidenreich P, Trogdon J, Khavjou O, et al. (2011). Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation.* 123: pp. 933-944.

Hernandez-Boussard T, Davies S, McDonald K, et al. (2017). Interhospital transfers in the United States: A nationwide outcomes study. *Journal of Patient Safety.* 13(4):187-191.

Herrigel D, Carroll M, Fanning C, et al. (2016). Interhospital transfer handoff practices among U.S. Tertiary Care Centers: A descriptive survey. *Journal of Hospital Medicine.* 11(6):413-417.

Hsieh F, Bloch D, Larsen M. (1998). A simple method of sample size calculation for linear and logistic regression. Print. *Stanford. Statistics in Medicine.* 17(14):1623-1634.

Huckfeldt P, Escarce J, Sood N, et al. (2019). Thirty-day postdischarge mortality among Black and White patients 65 years and older in the medicare hospital readmissions reduction program. *JAMA Netw Open.* 2(3):e190634.

Huynh Q, Negishi K, De Pasquale C, et al. (2018). Validation of predictive score of 30-day hospital readmission or death in patients with heart failure. *American Journal of Cardiology.* 121(3):322-329.

Inamdar A, Inamdar A. (2016). Heart failure: diagnosis, management and utilization. *Journal of Clinical Medicine.* 5(7):62.

Inglis S, Hermis A, Shehab S, et al. (2013). Peripheral arterial disease and chronic heart failure: a dangerous mix. *Heart Failure Review.* 18(4):457-464.

Iwashyna T, Kahn J, Hayward R, et al. (2010). Interhospital transfers among medicare beneficiaries admitted for acute myocardial infarction at nonrevacsularization hospitals. *American Heart Association: Circulation: Cardiovascular Quality and Outcomes.* 3:468-475.

Iwashyna T, Christine J, Moody J, et al. (2009). The structure of critical care transfer networks. *Medical Care.* 47:787-793.

Kim S, Park E, Kim T, et al. (2015). Mortality, length of stay, and inpatient charges for patients with heart failure at public versus private hospitals in South Korea. *Yonsei Med J.* 56(3):853–861.

Kiss T, Bölke A, Spieth PM. (2017). Interhospital transfer of critically ill patients. *Minerva Anestesiol.* doi:10.23736/S0375-9393.17.11857-2.

Knighton A, Savitz L, Benuzillo J, et al. (2018). It takes a village: exploring the impact of social determinants on delivery system outcomes for patients with heart failure. *Healthcare (Amst).* 6(2):112-116.

Koser K, Ball L, Homa J, et al. (2018). An outpatient heart failure clinic reduces 30-day readmission and mortality rates for discharged patients: process and preliminary outcomes. *Journal of Nursing Research*. 26(6)393-398.

Krumholz H, Lin Z, Keenan P, et al. (2013). Relationship between hospital readmission and mortality rates for patients hospitalized with acute myocardial infarction, heart failure, or pneumonia. *Journal of the American Medical Association*. 309:587-593.

Kulshrestha A, Singh J. (2016). Inter-hospital and intra-hospital patient transfer: recent concepts. Indiana Journal of Anaesthesia. 60(7):451-457.

Latafa J, Pladevall M, Divine G, et al. (2004). Are there race/ethnicity differences in outpatient congestive heart failure management, hospital use, and mortality among an insured population? *Medical Care.* 42(7):680-689.

Lauerman M, Herrera A, Chen H, et al. (2016). Double jeopardy? Transfers, readmissions, and charges in emergency general surgery ICU patients. *Critical Care Medicine.* 44(12):201.

Lee D, Ross H, Stelfox T, et al. (2016). Outcomes of heart failure (HF) patients admitted to the Intensive Care Unit (ICU): Impact of early or late ICU admission. American Heart Association: Circulation. *Circulation*. 134(1):A13175.

Lee W, Serag H, Ohsfeldt R, et al. (2019). Racial disparities in type of heart failure and hospitalization. *Journal of Immigrant and Minority Health.* 21(1):98-104.

Lesyuk W, Kriza C, Kolominsky-Rabas P. (2018). Cost-of-illness studies in heart failure: a systematic review 2004–2016. *BMC Cardiovascular Disorders.* 18(74).

Lindenauer P, Grosso L, Wang C, et al. (2013). Development, validation, and results of a risk-standardized measure of hospital 30- day mortality for patients with exacerbation of chronic obstructive pulmonary disease. *Journal of Hospital Medicine*. 8(8):428-435.

Liu D, Lei L, Ruan T, et al. (2019). Constructing large scale cohort for clinical study on heart failure with electronic heart record in regional healthcare platform: challenges and strategies in data reuse. *Chinese Medical Sciences Journal.* 34(2):90-102.

Llonzo N, Egorova N, Nowygrod R. (2015). Interhospital transfer and seadmissions, mortality, and failure to rescue for elective abdominal aortic aneurysm repair. *Journal of Vascular Surgery.* 61(6)53S.

Lu M, Davila C, Shah M, et al. (2016). Marital status and living condition as predictors of mortality and readmissions among African Americans with heart failure. *International Journal of Cardiology.* 222:313-318.

Lu X, Lu F. (2017). Distance, quality, or relationship? Interhospital transfer of heart attack patients. *Production and Operations Management.* 27(12). doi:10.1111/poms.12711.

Mayo Clinic. (1998-2019). Heart failure. *Mayo Clinic*.

McAlister F, Au A, Majumdar S, et al. (2013). Post discharge outcomes in heart failure are better for teaching hospitals and weekday discharges. *American Heart Association: Circulation: Heart Failure*. 6(5):922-999.

McGregor A, Peacock F, Chang A, et al. (2014). Sex and gender specific research priorities for the emergency management of heart failure and acute arrhythmia: proceedings from the 2014 academic emergency medicine consensus conference cardiovascular research workgroup. *Academic Emergency Medicine.* 21(12):1361-1369.

McIlvennen C, Eapen Z, Allen L. (2015). Hospital readmissions reduction program. *American Heart Association: Circulation*. 131(20):1796-1803.

Mebazaa A, Yilmaz B, Levy P, et al. (2015). Recommendations on pre-hospital and early hospital management of acute heart failure: A consensus paper from the heart failure association of the European society of cardiology, the European society of emergency medicine and the society of academic emergency medicine – short version. *European Heart Journal.* 36(30):1958-1966.

Mehta P, Cowie M. (2006). Gender and heart failure: a population perspective. *Heart.* 92 Suppl 3(Suppl 3):iii14–iii18.

Miro O, Rossello X, Gil V, et al. (2017). Predicting 30-day mortality for patients with acute heart failure in the emergency department: A cohort study. *Annals of Internal Medicine.* (167):698-705.

Misky G, Wald H, Coleman E. (2010). Post-hospitalization transitions: examining the effects of timing of primary care provider follow-up. *Journal of Hospital Medicine*. 7:392-397.

Mohr N, Harland K, Shane D, et al. (2016). Inter-hospital transfer is associated with increased mortality and costs in severe sepsis and septic shock: An instrumental variables approach. *J Crit Care.* 36:187–194.

Mueller S, Zheng J, Orav E, et al. (2018). Inter-hospital transfer and patient outcomes: A retrospective cohort study. *BMJ Quality and Safety.* doi:10.1136/bmjqs-2018-008087.

Mueller S, Schnipper J. (2019). Physician perspectives on interhospital transfers. *Journal of Patient Safety*. 15(2):86-89.

Mueller S, Zheng j, Orav E, et al. (2017). Rates, predictors, and variability of interhospital transfers: A national evaluation. *Journal of Hospital Medicine.* 6:435-442.

Murdo P. (2015). Survey responses from (most) air ambulances serving Montana. *Economic Affairs Interim Committee.*

Nouh A, McCormick L, Modak J, et al. (2017). High mortality among 30-day readmission after stroke: predictors and etiologies of readmission. *Frontiers in Neurology.* 8:632. Doi:10.3389/fneur.2017.00632.

Office of Inspector General. (2015). Inappropriate payments and questionable billing for medicare Part B ambulance transports. *U.S. Department of Health and Human Services.* OEI-09-12-00351.

Palacio C, House J, Ibrahim S, et al. (2014). A comparison of congestive heart failure readmissions among teaching and nonteaching hospital services. *Southern Medical Journal.* 107(8)501-507.

Park C, Park J, Mebazaa A, et al. (2019). Characteristics, outcomes, and treatment of heart failure with improved ejection fraction. *J Am Heart Assoc.* 8(6):e011077.

Quan H, Li B, Couris C, et al. (2011). Updating and validating the Charlson Comorbidity Index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *American Journal of Epidemiology.* 173(6):676-682.

Radovanovic D, Seifert B, Urban P, et al. (2014). Validity of Charlson Comorbidity Index in patients hospitalized with acute coronary syndrome. Insights from the nationwide AMIS plus registry 2002-2012. *BMJ Heart.* 100(4):288-294.

Rosner B. (2011). *Fundamentals of Biostatistics.* 7th ed. Boston, MA: Brooks/Cole.

Salem K, ElKhateeb O. (2017). Gender-adjusted and age-adjusted economic inpatient burden of congestive heart failure: cost and disability-adjusted life-year analysis. *ESC Heart Fail.* 4(3):259–265.

Savarese G, D'Amario D. (2018). Sex differences in heart failure. *Adv Exp Med Biol.* 1065:529-544.

Shameer K, Johnson K, Yahi A, et al. (2017). Predictive modeling of hospital readmission rates using electronic medical record-wide machine learning: A case-study using Mount Sinai heart failure cohort. *Pacific Symposium on Biocomputing 2017.* 22:276-287.

Silverstein M, Qin H, Mercer S, et al. (2008). Risk factors for 30-day hospital readmission in patients ≥65 years of age. *Proc (Bayl Univ Med Cent).* 21(4):363–372.

Sokol-Hessner L, White A, Davis K, et al. (2016). Interhospital transfer patients discharged by academic hospitalist and general internists: characteristics and outcomes. *Journal of Hospital Medicine.* 4:245-250.

Sud M, Yu B, Wijeysundera H. (2017). Associations between short or long associations between short or long length of stay and 30-day readmission and mortality in hospitalized patients with heart failure ay and 30-day readmission and mortality in hospitalized patients with heart failure. *Journal of American College of Cardiology: Heart Failure.* 5(8):578-588.

Suskin N, Sheth T, Negassa A, et al. (2001). Relationship of current and past smoking to mortality and morbidity in patients with left ventricular dysfunction. *Journal of the American College of Cardiology.* 37(6):1677–82.

Tarkin J, Malhotra A, Apps A, et al. (2015). Inter-hospital transfer for primary angioplasty: delays are often due to diagnostic uncertainty rather than systems failure and universal time metrics may not be appropriate. *EuroIntervention: Journal of EuroPCR in Collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology.* 11:511-517.

Tierney W. (2018). Breakdowns on the information highway during inter-hospital patient transfers. *Journal of General Internal Medicine.* 33(9):1415-1416.

Titler M, Jensen G, Dochterman J, et al. (2008). Cost of hospital care for older adults with heart failure: medical, pharmaceutical, and nursing costs. *Health Serv Res 2008*; 43: pp. 635-655.

Tuegel C, Bansal N. (2017). Heart failure in patients with kidney disease. *Heart.* 103(23):1848-1853.

Valley T, Sjoding M, Ryan A, et al. (2017). Intensive Care Unit admission and survival among older patients with chronic obstructive pulmonary disease, heart failure, or myocardial infarction. *Annals of American Thoracic Society.* 14(6)943-951.

Valley T, Sjoding M, Ryan A, et al. (2017). Intensive Care Unit admission and survival among older patients with chronic obstructive pulmonary disease, heart failure, or myocardial infarction. *Annals of American Thoracic Society.* 14(6)943-951.

Van der Wal H, Van Deursen V, Van der Meer P, et al. (2017). Comorbidities in heart failure. *Handbook of Experimental Pharmacology.* 243:35-55.

Vora A, Peterson E, Hellkamp A, et al. (2016). Care transitions after acute myocardial infarction for transferred-in versus direct-arrival patients. *American Heart Association: Circulation: Cardiovascular Quality and Outcomes.* 9(2):109-116.

Wadhera R, Joynt Maddox K, Wasfy J, et al. (2018). Association of the hospital readmissions reduction program with mortality among medicare beneficiaries hospitalized for heart failure, acute myocardial infarction, and pneumonia. *Journal of the American Medical Association.* 320(24):2542-2552.

Wang G, Zhang Z, Ayala C, et al. (2010). Costs of heart failure-related hospitalizations in patients aged 18 to 64 years. *Am J Manag Care.* 16: pp. 769-776.

Yamaguchi T, Miyamoto T, Sekigawa M, et al. (2018). Early transfer of patients with acute heart failure from a core hospital to collaborating hospitals and their prognoses. *Int Heart J.* 59: 1026-1033.

Yancy C, Jessup M, Bozkurt B, et al. (2015). 2013 ACCF/AHA guideline for the management of heart failure. *Journal of the American College of Cardiology.* 62(16):e147-e239.