Universidade do Minho
Escola de Engenharia

João Pedro Castro Coelho Oliveira Gomes

The independent effect of in-hospital adverse events on mortality and readmission in a heart failure population

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e a co-orientação da
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The independent effect of in-hospital adverse events on mortality and readmission in a heart failure population

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É AUTORIZADA A REPRODUÇÃO PARCIAL DESTA DISSERTAÇÃO APÓS PERÍODO DE EMBARGO DE 1 ANO, APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.

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Abstract

One of the metrics most commonly used to evaluate the quality of care in American hospitals is the frequency of in-hospital adverse events. They continue to be a major reason for concern as they pose significant harm to patients as well as tremendous financial consequences to healthcare institutions. However, despite the increased research about the incidence and consequences of in-hospital adverse events, there is a paucity of information regarding its independent effect on mortality and readmission in specific and homogenous populations.

The main objective of this thesis was to understand and determine the independent effect of adverse events on both mortality and readmission in a heart failure population, which would not only address a considerable gap in the literature, but also provide a quantification of the impact of adverse events on these outcomes, that could prove useful in the institutional and nationwide decision of how many resources to direct to their prevention.

In order to study the independent effect of adverse events on both outcomes, a homogenous population (heart failure) was chosen to reduce the issues of patient heterogeneity, and several confounding variables (patients' characteristics) were included in the statistical analyses.

Among a sample of 1,660 patients discharged from the hospital with a main diagnosis of heart failure, about 22% suffered at least on adverse event during their hospitalization. Results from the multivariate models obtained for each one of the outcomes showed an increased risk of in-hospital mortality (OR 4.47; $p = 0.001$) among the patients who had an adverse event during their hospitalization, while no association was found between adverse events and post-discharge 30-day mortality (OR 0.97; $p = 0.930$). Regarding 30-day readmissions, adverse events do not seem to be a predictor of an increased risk of readmission (OR 1.03; $p < 0.8644$).

In conclusion, to the best of our knowledge, this is the first study to consider the independent effect of adverse events on mortality and readmission on one specific population, by controlling for confounding variables. The risk of adverse events seems to be limited to in-hospital mortality only (OR = 4.47), and not to post-discharge 30-day mortality (OR = 0.97) or 30-day readmission (OR = 1.03).

Resumo

Um das métricas mais frequentemente usadas para avaliar a qualidade dos cuidados médicos prestado nos hospitais Americanos é a frequência dos eventos adversos. Estes continuam a ser uma fonte de preocupação, uma vez que causam danos significativos nos pacientes, assim como enormes consequências financeiras para as instituições de saúde. No entanto, apesar da contínua investigação acerca da incidência e consequências dos eventos adversos, o seu efeito independente na mortalidade e readmissão em populações homogéneas tem sido alvo de poucos estudos.

Esta dissertação teve como principal objectivo perceber e determinar o efeito independente dos eventos adversos na mortalidade e readmissão numa população com insuficiência cardíaca. Para além de acrescentar informação importante na literatura, fornece também uma quantificação sobre o impacto dos eventos adversos, que poderá vir a ser útil nas decisões acerca dos recursos a aplicar na sua prevenção a nível institucional e nacional.

O efeito independente dos eventos adversos na mortalidade e readmissão foi estudado através da escolha de uma população homogénea (insuficiência cardíaca), de modo a reduzir os problemas relacionados com a heterogeneidade dos pacientes, e também através da inclusão de variáveis de confusão (características do paciente) na análise estatística.

Numa amostra de 1660 pacientes diagnosticados com insuficiência cardíaca, cerca de 22% sofreram pelo menos um evento adverso durante o internamento. Os resultados obtidos através dos modelos multivariáveis para cada um dos estudos mostram um risco de mortalidade hospitalar acrescido entre os pacientes que sofreram eventos adversos (OR 4.47; $p < 0.001$), enquanto que nenhuma relação foi encontrada entre os eventos adversos e a mortalidade 30 dias após a alta médica (OR 0.97; $p = 0.930$). Relativamente à readmissão até 30 dias após a alta médica, os eventos adversos não se revelaram como um potencial factor de risco. (OR 1.03; $p = 0.8644$).

Tanto quanto sabemos, este é o primeiro estudo a considerar o efeito independente dos eventos adversos na mortalidade e readmissão numa população específica, através da inclusão de variáveis de confusão. Analisando todos os resultados, o risco dos eventos adversos parece estar circunscrito apenas à mortalidade hospitalar (OR = 4.47), e não à mortalidade e readmissão 30 dias após a alta médica (OR = 0.97 e OR = 1.03, respectivamente).

Preface

This dissertation represents part of the work accomplished during a nine-month internship on Mayo Clinic. During this internship, I had the opportunity to work in the Health Care Systems Engineering Program, part of the Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery. This dissertation is a result of a team-based project led by the Program's Medical Director, Dr. Jeanne Huddleston, which combined different areas of expertise, from medicine to engineering.

> "Nothing in the world can take the place of persistence. Talent will not; nothing is more common than unsuccessful men with talent. Genius will not; unrewarded genius is almost a proverb. Education will not; the world is full of educated derelicts. Persistence and determination alone are omnipotent. The slogan, 'press on' has solved, and always will solve, the problems of the human race."
>
> Calvin Coolidge

Publications and Communications

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List of abbreviations

ACA	Affordable Care Act
ACE	Angiotensin-Converting Enzyme
AE	Adverse event
ARB	Angiotensin II Receptor Blocker
BMI	Body Mass Index
COPD	Coronary obstructive pulmonary disease
CVA	Cerebrovascular accident
DNI	Do not Intubate
DNR	Do not Resuscitate
GTT	Global Trigger Tool
HF	Heart Failure
IOM	Institute of Medicine
IPFS	Inpatient Physiological Failure Score
LOS	Length of stay
MN	Minnesota
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
OR	Odds ratio
OSA	Obstructive sleep apnea
REDcap	Research Electronic Data Capture
TIA	Transient ischemic attack
U.S.	United States
UTI	Urinary track infection

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Chapter I.

General Introduction

1.1. The United States health care system and the Affordable Care Act

The United States (U.S.) health care system has been frequently characterized as one of the least functional among the most developed nations. According to the World Health Organization, the U.S. spend more on health care per capita than any other country in the world[1], despite its performance is not proportional to the money invested. The U.S. ranks fairly poor in terms of healthcare rankings, standing only in 48th among 222 countries for infant mortality rate[2] and ranking last out of 16 developed countries in regards to preventable mortality.[3] Furthermore, readmission rates have remained incredibly high over the last years (around 20%)[3,4] and access to medical care continues to be very difficult to uninsured people. As of 2010, around 49 million residents (accounting for 16% of the population) were uninsured, resulting in 45,000 possible avoidable deaths.[5]

A new perspective of health care has emerged since the implementation of the Affordable Care Act (ACA), the most significant reform in the U.S. health care system since 1965. This reform aims to improve the quality of health care delivery and targets many care gaps which urgently needed intervention: improving access to care by expanding insurance coverage and affordability; implementing a culture of continuous quality improvement by promoting patient safety; improving care coordination and outcomes by aiming for lower readmission, morbidity and mortality rates.

1.2. Quality and safety in healthcare

Quality is an integral principle of medical care, defined as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge".[6] Six different dimensions compose quality in healthcare: safety, effective, patient centered, timely, efficient and equitable. As a result, patient safety resides under the global concept of quality, and represents the foundation of all the other components. Florence Nightingale, founder of modern nursing, was the first to emphasize the concept of safety in healthcare. According to her book published in 1863, the very first requirement in a hospital should be "do the sick no harm".[7] More recently, the Institute of Medicine (IOM) defined patient safety as "the prevention of harm to patients".[8]

However, for a long period of time, quality in healthcare was devalued or simply forgotten by healthcare professionals and stakeholders, despite some late 1900s publications reporting innumerous cases of patients' injuries related with medical errors and system failures.[9-13] This issue only started to be nationally addressed in the early 2000s, when the IOM published a report named "To Err Is Human: Building a Safer Health System".[14] In this report, it was estimated that preventable medical errors could be associated with 44,000 to 98,000 deaths per year. Interestingly, this report was based on data from previous studies, which had received little attention. However, and since then, both the private and public sector have invested enormous resources and energy on improving the safety of healthcare delivery.

1.3. Adverse events

Adverse events (AEs) have been commonly used as an indicator of the safety of healthcare delivery. However, despite being used as a common metric, several authors have proposed different definitions of AEs[14-16] which has led to different interpretations and to a lack of consensus. As a result, there was a big discrepancy in the incidence rates of AEs found in some studies published in the late 1990s and early 2000s, where the rates reported varied from 2.9% to 16.6%[17-21]. More recently, due to new detection methods and to a standardization regarding the definition of AE, studies have reported incidence rates as high as 27%.[22,23]

From here forward, and for purposes of analysis, AEs will be defined as an "unanticipated illness or injury caused by medical evaluation and/or management rather than by the underlying disease or condition of the patient".[14] To be consistent with the published research, AEs were divided into four major groups: infection, medication errors, patient care and procedural. Distinction of preventability was not considered in this study.

1.4. Adverse events detection

Identifying AEs is a very challenging and complex task, except in the cases when they lead to serious harm or death. Traditionally, voluntary reporting has been the most common methodology adopted by hospitals to identify AEs. Reporting policies are required for all hospitals certified by Joint Commission. However, relying only on voluntary reporting can lead to inaccurate conclusions, as

studies have reported that only a small percentage of the events are really reported by the healthcare professionals (misses more than 90% of the events).[24,25] Moreover, most of the reports are made by nurses, and the majority of those reported events are usually harmless.[24]

Recently, hospitals have started to combine voluntary reporting with other detection methods in order to increase the yield of detection. The Institute for Healthcare Improvement's Global Trigger Tool[24] is a recent method developed for that purpose, and it is based on a trigger-review process. More specifically, the identification of AEs is made using triggers, which are sentinel conditions. These triggers are associated with the occurrence of AEs, allowing the reviewers to focus only on portions of the medical records near the time of the trigger. The reviewers are normally trained nurses, who proceed to the identification of the AE. On a second stage, the nurses' findings are validated by a trained physician, who makes the final determinations regarding the presence and the severity of the AEs. This new method has been increasingly used in U.S. hospitals and it was the tool used in the studies that found AEs' incidence to be the highest (22% - 27%),[22,25-27] suggesting greater sensitivity. The inter-rater reliability has also been previously reported to be good.[28] To be consistent with the most recent publications, the Global Trigger Tool (GTT) was the methodology used to identify AEs in this study.

1.5. Adverse events and mortality

The use of mortality indicators in developed countries has proven to be extremely reliable when assessing the quality of the healthcare provided in medical institutions.[29] Logically, death represents the ultimate condition that hospitals want to avoid, and on a global and simplified perspective, reduced mortality rates indicates a higher delivery of healthcare quality.

Normally, the majority of hospital-related deaths are a consequence of someone's underlying disease, which regardless of the undergoing treatment, was somehow unavoidable or untreatable. However, on some occasions, unexpected illnesses or injuries caused by medical evaluation and or management result in death. In these situations, adverse events are considered to be responsible for someone's death.

Some studies have tried to establish an association between adverse events and mortality,[23,25,27] but they only reported descriptive results. For example, one of the most recent studies[27] to have used the GTT for detecting AEs found that only 2.4% of the total AEs resulted or contributed to a patient´s death. However, the impact of AEs on mortality cannot be accurately measured if the

interaction of patients‘ characteristics with the occurrence of certain outcomes is not considered in the statistical analyses. In addition, these studies were conducted in general medical or surgical populations, which raises some issues of patient heterogeneity.

In addition to inpatient mortality, it is also pertinent to understand if AEs that occur during hospitalization can impact patients´ health condition after being discharge from the hospital. Some adverse events may have a longer lasting effect and its consequences may only be noticed after a patient´s discharge. Surprisingly, to the best knowledge, none of the studies found in the literature tried to determine the effect of AEs on mortality within 30-days of discharge, independently of patients‘ characteristics.

As a result, conducting a study on a homogenous population, with the inclusion of confounding variables, would allow for a more realistic quantification of the independent effect of AEs on mortality during hospitalization and within 30 days after discharge.

1.6. Adverse events and readmissions

In a push to improve the quality of healthcare delivery, both private and public providers have identified the reduction of hospital readmissions as one of their main priorities.[30] From a hospital perspective, reducing readmissions may be a very challenging goal. Some readmissions are just inherent to a treatment plan, while others may be a consequence of very low mortality rates: if very sick patients are kept alive, it is likely that they can be readmitted soon after discharge.[4,31] On the other hand, it is known that system failures can sometimes contribute for patients' readmissions, reflecting a poor and fragmented healthcare system.

Little improvement was made over the last decade, as 30-day readmission rates have remained practically unchanged from 2002 to 2009.[32] In 2009, nearly 20% of Medicare beneficiaries were readmitted within 30 days of discharge, with an annual cost higher than $17 billion.[4] Following the implementation of the ACA, hospitals are now starting to be financially penalized for excessive 30-day readmission rates. These penalties only apply for Medicare patients diagnosed with acute myocardial infarction, pneumonia and heart failure (HF). According to the most recent data, discharge from a heart failure hospitalization is followed by a readmission within 30 days of discharge in approximately 24% of the cases.

There has been a lot of research focusing on potential risk factors that may be predictors of readmissions.[33-35] Poor work environment,[36] nosocomial infections,[34] poor communication with patients

at discharge,[37,38] poor planning for transitions[37,38] or failure to reconcile medications[39] have been identified as potential causes for 30-day readmissions. However, most available models perform very poorly and are unable to consistently identify the main causes of 30-day readmission.[40]

There is still a considerable gap in the literature regarding the effects of AEs on readmissions. The ones that specifically discussed this issue focused only on the effect of some sub-types of AEs (such as infections or adverse drug-events), instead of including all the sub-types. For example, Emerson et al.[34] found that patients who had nosocomial infections during hospitalization had an increased hazard of readmission (HR 1.40, $p < 0.01$) after controlling for several confounders. Furthermore, these studies used either a major medical or surgical population, making it very difficult to adjust for patient variability, and in some cases did not control for confounders. Despite the difficulties in estimating the independent effect of AEs on readmissions, limiting the study population to a very specific population and including potential confounders to the study would certainly reduce some of these concerns.

1.7. Adverse events and heart failure

Most of the research involving AEs focused on general medical or surgical populations. However, performing these studies on such a general cohort makes it very difficult to control for all the confounding variables, given the very wide range of diseases found in these populations. However, the influence of these confounders could be reduced or eliminated if a homogeneous population was chosen. In this case, all patients would be restricted to the same medical diagnosis, which would automatically reduce the issues of patient heterogeneity.

Heart failure represents one of the most common causes of hospitalizations in the U.S., specially among the elderly.[41] According to the Center for Disease Control and Prevention, heart disease is also the leading cause of death in the U.S., accounting for more than 500,000 deaths in 2010.[42] Recognized the importance of this disease on the national panorama, choosing an HF population as the study cohort would certainly provide us a high volume of patients, when compared to other subclinical groups of patients. In addition, researching the effect of AEs on mortality and readmission in this specific population could be of particular relevance. Heart failure is a chronic disease, and normally patients diagnosed with this medical condition are considered to be more fragile, making the effects of AEs on mortality more noticeable. Concurrently, while the readmission rates

among HF failures patients have remained incredibly high over the last years, the possible contribution of AEs to this outcome remains unknown.

Chapter II.

Contextualization and Aims

2. Contextualization and Aims

Patient safety is a fundamental concept of quality in healthcare, which emphasizes the identification, analysis and prevention of potential harm. Several metrics can be used to measure safety, being the frequency of AEs a very commonly used indicator. Typically, most of the current research has focus on studying the incidence of AEs on medical institutions, providing estimations of how often these events tend to occur in the medical practice. However, and surprisingly, in spite of all the research surrounding AEs, there is a paucity of information in the literature regarding its true consequences on certain outcomes. More specifically, its independent effect on mortality and readmission remains uncertain, as studies published to date have not attempted to control for confounding variables in their analyses, which would provide a more realist quantification of the effect of AEs on the referred outcomes.

This thesis will focus on studying the independent effect of AEs on inpatient and post-discharge 30-day mortality (Chapter III), as well as on 30-day readmission (Chapter IV), by controlling for potential confounders (patients' characteristics). In order to limit the issues associated with patient heterogeneity, patient selection was limited to a single inpatient diagnosis, and therefore only patients discharged from the hospital with a primary diagnosis of heart failure were considered in this study. Additionally, AEs were identified using the Global Trigger Tool (GTT) and all sub-types of AEs were considered (medication, infections, procedural and patient care) in the statistical analyses.

Chapter III.

The Independent Effect of in-Hospital Adverse Events on Mortality

3.1. Abstract

Background: Previous studies have associated in-hospital adverse events with increased mortality rates. However, no published studies to date have focused on its independent effect on inpatient and post-discharge 30-day mortality.

Methods: A retrospective cohort study was conducted in hospitalized heart failure patients between 2005 and 2007 in Rochester, Minnesota. Adverse events were identified using the Institute for Healthcare Improvement's Global Trigger Tool. Multivariate models were used to assess the impact of adverse events on inpatient and post-discharge 30-day mortality.

Results: In a population of 1,660 patients, 371 (22.3%) suffered at least one adverse event during hospitalization. Overall mortality in the time period from admission to 30-days after discharge was 14.6% among patients who suffered an adverse event, compared to 5.4% among those without an adverse event. Inpatient mortality was substantially higher among patients who experienced an adverse event (8.9%), when compared to those without (1.3%). Post-discharge 30-day mortality (excluding inpatient death) was 4.5% overall, with no substantial differences between the two groups. After controlling for confounding variables, adverse events during hospitalization were independently associated with higher inpatient mortality (OR = 4.47; $p < 0.001$), but had no impact on post-discharge 30-day mortality (OR = 0.97; $p = 0.930$).

Conclusions: The presence of adverse events during hospitalization is independently associated with greater inpatient mortality rates. However, no association was found between adverse events and mortality after hospital discharge.

3.2. Introduction

Providing safe medical care continues to be a major challenge worldwide, receiving growing attention by hospitals and policy makers.[43-47] Despite all the efforts to improve healthcare quality, recent studies revealed that little progress has been made.[38,48,49] Adverse events are one important indicator of patient safety and healthcare quality, and can be defined as an "unanticipated illness or injury caused by medical evaluation and/or management rather than by the underlying disease or condition of the patient".[14] According to the most recent publications, the incidence of AEs in hospitals is reported to be between 22 and 33 per 100 admissions,[22,23,25-27] and they may be associated with 180,000 to 400,000 deaths a year in the U.S.[23,50]

While the incidence of AEs is well documented, their independent impact on mortality after controlling for patient characteristics has not been sufficiently explored in the literature. Furthermore, most studies were conducted in heterogeneous populations, which increases the risk of patient variability. One way to address this persistent uncertainty is to focus on a homogeneous population that allows evaluation of confounding patient characteristics. We decided to choose a heart failure population because it is a fragile medical population, where AEs are likely to have an effect on mortality. It is also a very common inpatient diagnosis,[41] thus ensuring a large volume of patients for this study.

We performed a retrospective cohort study in a homogeneous sample of heart failure patients and aimed to determine the independent effect of AEs on inpatient and post-discharge 30-day mortality, by controlling for confounding variables.

3.3. Methods

3.3.1. Study design

A retrospective cohort study was conducted in an academic, tertiary care medical center with two hospitals and 1,500 beds in Rochester, Minnesota. This study was based on administrative data and on the review of clinical records. It did not involve any direct contact with patients. Only patients who authorized the use of their medical record for clinical research were considered eligible. This project was first reviewed and approved by the Mayo Clinic Institutional Review Board.

3.3.2. Study population

We reviewed medical records of patients discharged from the hospital with a primary diagnosis of heart failure from January 1, 2005 through December 31, 2007. All hospitalizations were identified following diagnosis-related group (DRG) 127 (ICD9) codes: acute heart failure (428.9); combined systolic and diastolic failure (428.40-428.43); non-specified heart failure (428.00); hypertensive heart disease with heart failure (402.91); systolic heart failure (428.20-428.23); diastolic heart failure (428.30-428.33); and rheumatic heart failure (396.30). Only the subset of those who met the Framingham Criteria for HF[51] were included in the study. For patients with multiple HF hospitalizations, only the first was included in order to maintain statistical assumptions of independent observations. Individuals with congenital heart disease, severe leukopenia (absolute neutrophil count less than 500 WBC/mm^3), active chemotherapy or radiation, an admission for palliative care or a hospitalization less than 24 hours were excluded from this study. Patients that required a major surgery were also excluded. Examples of reasons for surgery include aortic valve replacement and coronary artery bypass grafting.

3.3.3. Study definition

Adverse events: In this study, AEs were defined as "an injury caused by medical management rather than by the underlying disease or condition of the patient".[14] Adverse events present at time of admission were excluded, as well as those who did not cause harm to patients. For that purpose, AEs were categorized according to the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP)[52] and only the ones classified as level E (temporary harm with documented patient symptoms or intervention) or higher were included (Figure 3.1). Adverse events were then divided into four categories: medication (e.g. hypotension, acute kidney injury), infection (e.g. catheter associated urinary tract infection (UTI), healthcare associated pneumonia), patient care (e.g. device failure or malfunction, fall), and procedure (e.g. hematoma, bleeding at the puncture site). Adverse events were not judged as preventable or non-preventable.

Mortality: Mortality was the primary outcome variable of this study. Deaths were identified through the clinical record and U.S. death registry.

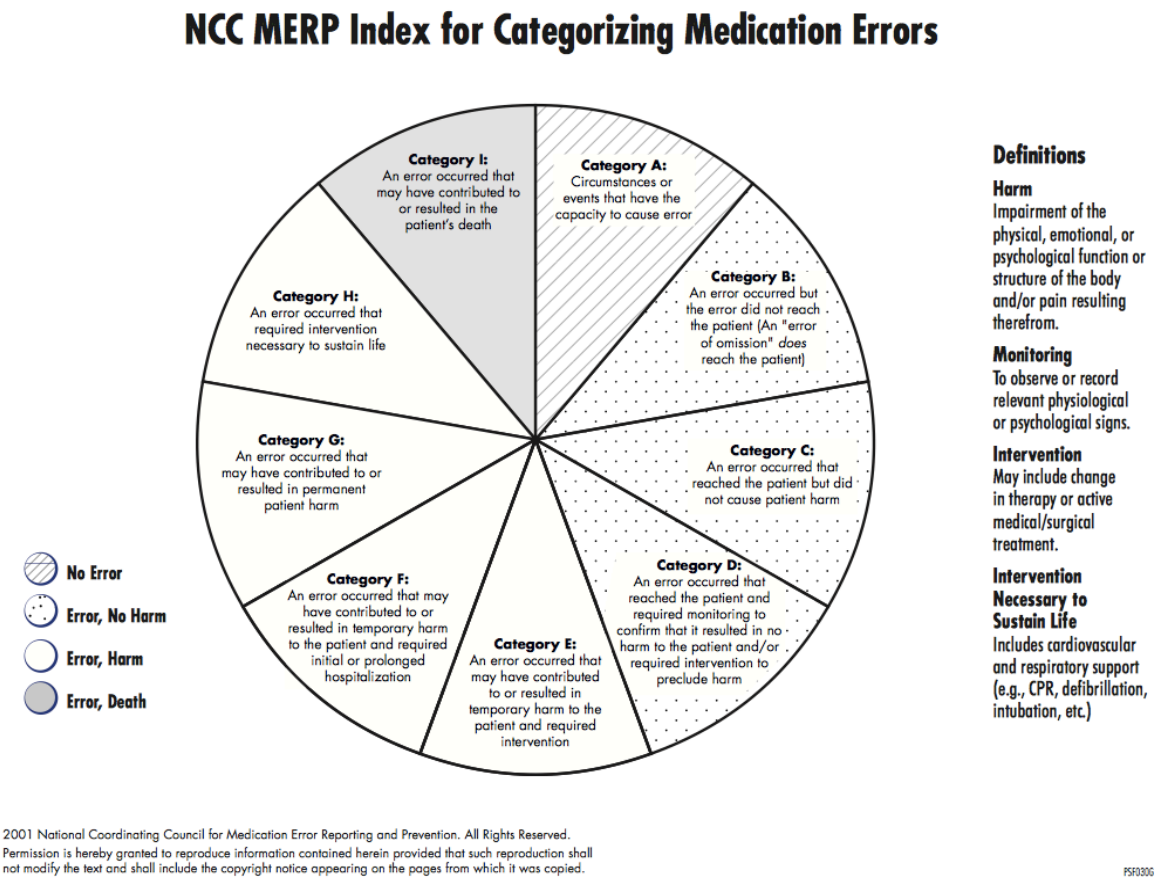


Figure 3.1 - National Coordinating Council for Medication Error Reporting and Prevention Index for categorizing medication errors.

Patient-specific variables: Patient-specific variables were the confounding variables used in this study. They were grouped in four distinct groups: demographics, functional status, medical history and medications at time of admission and discharge (Table 3.1 - 3.4).

Table 3.1 - List and definition of the variables grouped in the category "demographics".

Covariate	Definition
Age	Continuous variable represented in years.
Gender	Categorical variable of gender (male vs female).
Race	Categorical variable of race (Caucasian vs others).
BMI	Body mass index: measure of body fat based on height and weight. BMI = [mass (kg) / height $(m)^2$]
Geographical residence	Categorical variable describing patients' primary residence at time of admission (southeastern MN vs others). Patients were categorized as southeastern MN if they lived in Olmsted, Dodge, Fillmore, Freeborn, Goodhue, Houston, Mower, Rice, Steele, Wabasha, and Winona counties at time of admission. The remaining patients were categorized as "others".
Length of Stay	Continuous variable referring to the duration of hospitalization, represented in days.

Table 3.2 - List and definition of the variables grouped in the category "functional status".

Covariate	Definition
Living arrangements	Categorical variable describing the living situation at time of admission and discharge (skilled nursing facility vs others).
Ejection fraction	Measure of the total amount of blood pumped by the left ventricle with each contraction. Measurement under 40 may be evidence of heart failure or cardiomyopathy. EF (%) = [stroke volume (ml) / end-diastolic volume (ml)] * 100
Mobility status	Categorical variable reflecting the level of assistance required for basic movement of ambulation (walk independently vs others). Patients who were able to walk without any assistance were labeled as "walk independently". Patients who depended on devices to walk or move were categorized as "others".
Personal hygiene	Categorical variable describing patients' capacity to perform personal hygiene tasks (bathing, dressing and toileting) with or without assistance.
Housekeeping	Categorical variable referring to patients' ability to perform daily housekeeping tasks with or without assistance.
Code Status	Categorical variable describing the type of intervention that the healthcare team conducts in the case of cardio-respiratory arrest (full code: resuscitate/intubate; DNR/DNI: do not resuscitate/do not intubate).
IPFS[53]	Inpatient Physiological Failure Score: Weighted index of acute illness derived and validated as a mortality prediction tool in elderly medical patients, including patients with HF. Each of the 12 physiological measurements included were given a point value of 6, 4, 3, or 2 based upon the adjusted odds ratio of the variable's association with inpatient mortality. All measurements are taken within the first 48 hours of admission.

IPFS[53]	These variables (point values assigned for abnormal results) include: level of consciousness*(6), highest bilirubin (4), O2 saturation* (4), highest blood urea nitrogen (4), lowest glucose (3), lowest albumin (3), lowest sodium (3), diastolic blood pressure* (3), highest white blood cell count (3), highest glucose (2), systolic blood pressure* (2), highest creatinine (2). Maximum raw score is 39 points. Higher values indicate elevated severity of acute illness at time of presentation to the hospital. [*only the first value recorded within 48 hours of admission]
Charlson Index[54]	Weighted index of comorbidity used to predict the risk mortality in longitudinal studies. Clinical conditions and associated score include history of the following: myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, ulcer, diabetes, hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any malignancy, leukemia, malignant lymphoma, moderate or severe liver disease, AIDS.

Table 3.3 - List of the variables grouped in the category "medical history".

Medical History		
Dementia	CVA/TIA	Peripheral vascular disease
OSA	Severe aortic stenosis	Cancer
Diabetes	Coronary artery disease	Renal insufficiency
Atrial arrhythmia	Ventricular arrhythmia	Depression
Asthma, COPD, other pulmonary disease		

CVA/TIA: cerebrovascular accident/transient ischemic attack; OSA: obstructive sleep apnea; COPD: coronary obstructive pulmonary disease; Cancer: any tumor, metastasis, lymphoma, or leukemia.

Table 3.4 - List of the variables grouped in the category "medications".

Medications		
Statin	Diuretic	ACE/ARB
Beta blockers	Calcium channel blockers	Digitalis preparations
Anti-platelets	Amiodarone	Coumadin
Insulin	Home O2 prior to admission*	

* medication only at admission; diuretic: = loop, thiazide-like, or potassium sparing.

3.3.4. Study procedure

Adverse events were identified using the Institute for Healthcare Improvement's Global Trigger Tool.[24] A two-stage review process was adopted. First, two trained nurses independently reviewed the medical records of the sampled patients looking for triggers. These triggers were defined as sentinel conditions, which could be associated with the occurrence of AEs, allowing reviewers to focus only on portions of the medical records. A trigger could be an abnormal lab value, medications, patient symptoms or infections (e.g., antiemetic use, which can be the result of drug toxicity or overdose; *C. difficile* positive stool, which represents an AE if history of antibiotic use is present). In cases where an AE was identified, the medical record was exhaustedly reviewed near the time the trigger occurred. All the nurses' findings were then reviewed and confirmed by trained physicians, who made the final determinations regarding the presence and severity of an AE, according to the NCC MERP index.[52]

3.3.5. Statistical methods

All qualifying patients discharged from the hospital with a primary diagnosis of HF between January 1, 2005 and December 31, 2007 were included in the analyses. Participants were classified into one of two groups: with adverse event(s) and without adverse event(s). The rate of AEs was estimated using the number of patients who experienced an AE as the numerator and all study participants as the denominator. Inpatient, post-discharge and overall 30-day mortality rates were compared between both groups. Baseline characteristics were grouped into demographics, functional status, medical history and medications at time of admission and discharge. These were presented as frequencies for categorical variables and means with standard deviations for continuous variables.

To assess the independent effect of AEs on inpatient and post-discharge 30-day mortality, a separate multivariate logistic regression model was created for each one of the outcomes. First, a

univariate analysis was performed to identify possible confounders (excluding AEs) and only variables with a level of significance $p < 0.1$ were retained. These variables were then entered into a multivariate model. Second, a backward elimination method was performed and variables were eliminated one at a time, until obtaining a final model where all covariates were significant at $p < 0.05$. Finally, AEs were forced into each model in order to assess their independent effect on mortality after controlling for all confounding variables. As a result, a multivariate odds ratio model was obtained with 95% confidence interval (CI) for each outcome: inpatient and post-discharge 30-day mortality. A separate Kaplan-Meier analysis was also performed to estimate the overall 30-day mortality rate curve for patients who suffered one or more AEs during hospitalization.

All data was collected and managed using the Research Electronic Data Capture (REDcap)[55] tool hosted at Mayo Clinic. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

3.4. Results

3.4.1. Study cohort analysis

The final study cohort consisted of 1,660 patients hospitalized for HF between 2005 and 2007. The mean age of patients was 75.9 ± 12.5 years, 54.7% were male and mostly Caucasian (96.7%). More than half of the patients lived in southeastern Minnesota (58.7%). Mean length of stay was 5.1 ± 4.6 days; mean Charlson Index was 4.0 ± 2.7 and mean IPFS was 4.2 ± 3.7. One hundred sixty-five patients (9.9%) were admitted from a skilled nursing facility, while 350 (21.1%) were discharge to that same living arrangement after their hospitalization. Only 27.4% of patients required assistance with their personal hygiene activities (bathing, dressing and toileting), while 45.5% depended on someone to do their housekeeping. The most common medication at admission and discharge was diuretics (73.6% and 84.6%, respectively). According to the past medical history, coronary artery disease was the only comorbidity present in more than half of the patients (56.0%).

3.4.2. Adverse events and mortality outcomes

Among the 1,660 participants considered in this study, 371 (22.3%) patients met the criteria for an AE. Of those 371 patients, 33 (8.9%) died in the hospital. For the remaining patients without an AE, inpatient mortality was 1.3% ($p < 0.001$). Post-discharge 30-day mortality for patients who had an AE was 6.2% and for those who did not was 4.1% ($p = 0.095$). Overall 30-day mortality for all participants was 7.4%. Mortality during the same time period (unadjusted) for patients who experienced an AE was 14.6% and for those who did not was 5.4% ($p < 0.001$).

On an univariate and unadjusted analysis (Table 3.5), the occurrence of an AE during hospitalization was strongly associated with an increased risk of in-hospital mortality (OR 7.31; 95% CI; 4.02 to 13.28; $p < 0.001$). On the other hand, post-discharge 30-day mortality did not differ between those who experienced an AE and those who did not (OR 1.43; 95% CI, 0.85 to 2.40; $p = 0.095$).

Table 3.5 - Unadjusted results of inpatient, post-discharge and overall 30-day mortality for patients with and without adverse events.

	Total N = 1660	With AEs **N = 371** (22.3%)	Without AEs **N = 1289** (77.7%)	p value	Unadjusted Odds Ratio **(95% CI)**
Inpatient mortality	50 (3.0%)	33 (8.9%)	17 (1.3%)	$p < 0.001$	7.31 (4.02, 13.28)
Post-discharge 30-day mortality	73 (4.5%)	21 (6.2%)	52 (4.1%)	$p = 0.095$	1.43 (0.85, 2.40)
Overall 30-day mortality	123 (7.4%)	54 (14.6%)	69 (5.4%)	$p < 0.001$	3.01 (2.06, 4.39)

The multivariate logistic regression model performed to evaluate the effect of AEs on inpatient death confirmed that patients who experienced AEs faced an increased risk of in-hospital death, after adjusting for confounding variables (Figure 3.2). Adverse events were independently associated with an increased inpatient mortality risk (OR 4.47; 95% CI; 2.28 to 8.78; $p < 0.001$). Severe aortic stenosis was the most significant risk factor associated with inpatient mortality (OR 4.68; $p < 0.001$). On the other hand, male gender was found to reduce the risk of death during hospitalization (OR 0.48; $p < 0.05$).

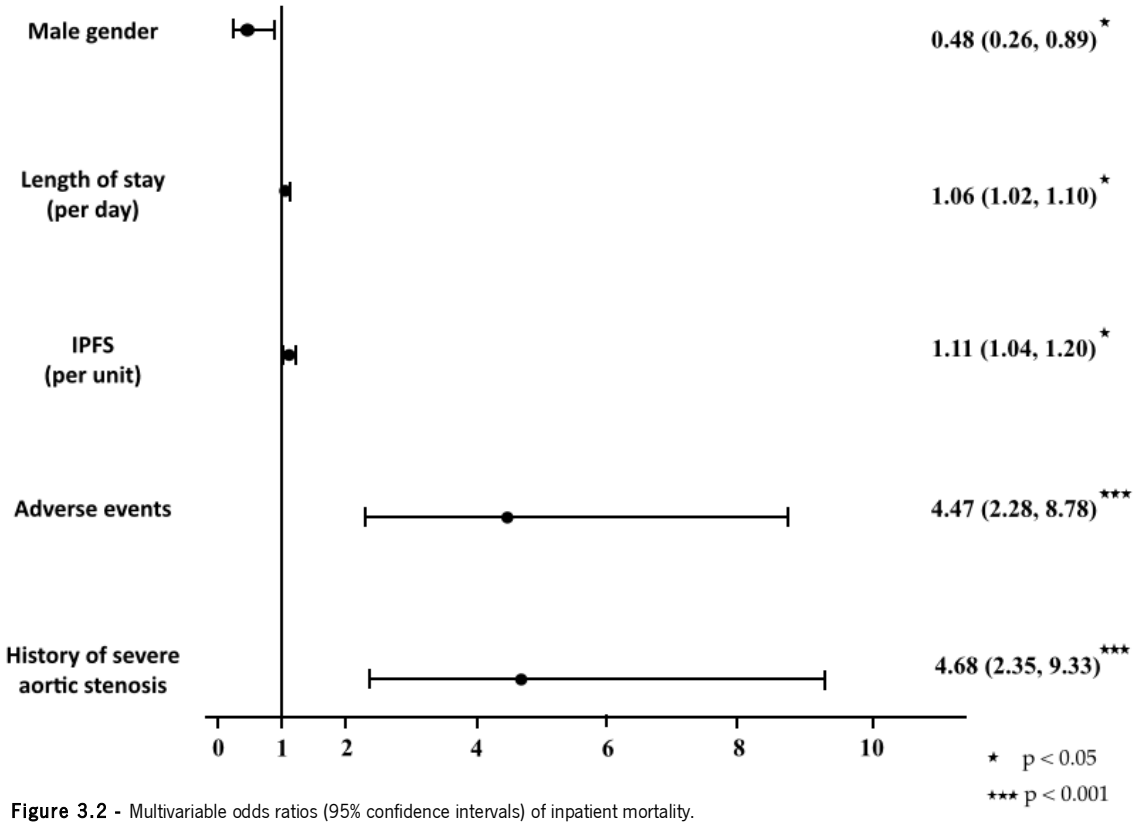


Figure 3.2 - Multivariable odds ratios (95% confidence intervals) of inpatient mortality.

Regarding post-discharge 30-day mortality (Figure 3.3), no significant differences were found among those who experienced an AE and those who did not, after adjusting for confounders (OR 0.97; 95% CI; 0.52 to 1.81; $p = 0.930$). History of depression (OR 1.83; $p < 0.05$) was found to significantly increase the risk of death after discharge, while full code status (OR 0.19; $p < 0.001$) and ACE/ARB medications at discharge (OR 0.52; 95% CI; $p < 0.01$) were associated with a decreased risk of death.

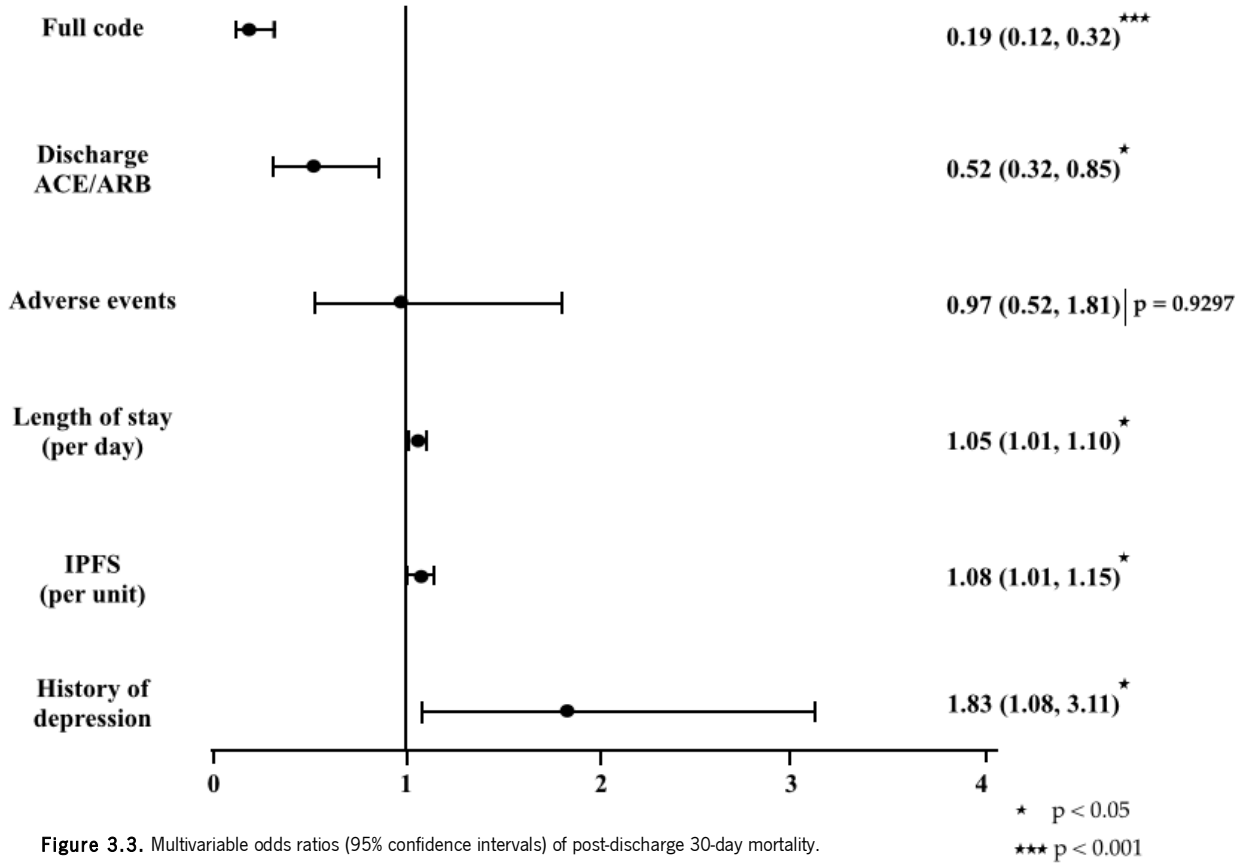


Figure 3.3. Multivariable odds ratios (95% confidence intervals) of post-discharge 30-day mortality.

Figure 3.4 represents a Kaplan-Meier analysis for overall 30-day mortality rate from the time of admission based on experiencing an AE. Mortality rates were higher among patients who suffered an AE during hospitalization.

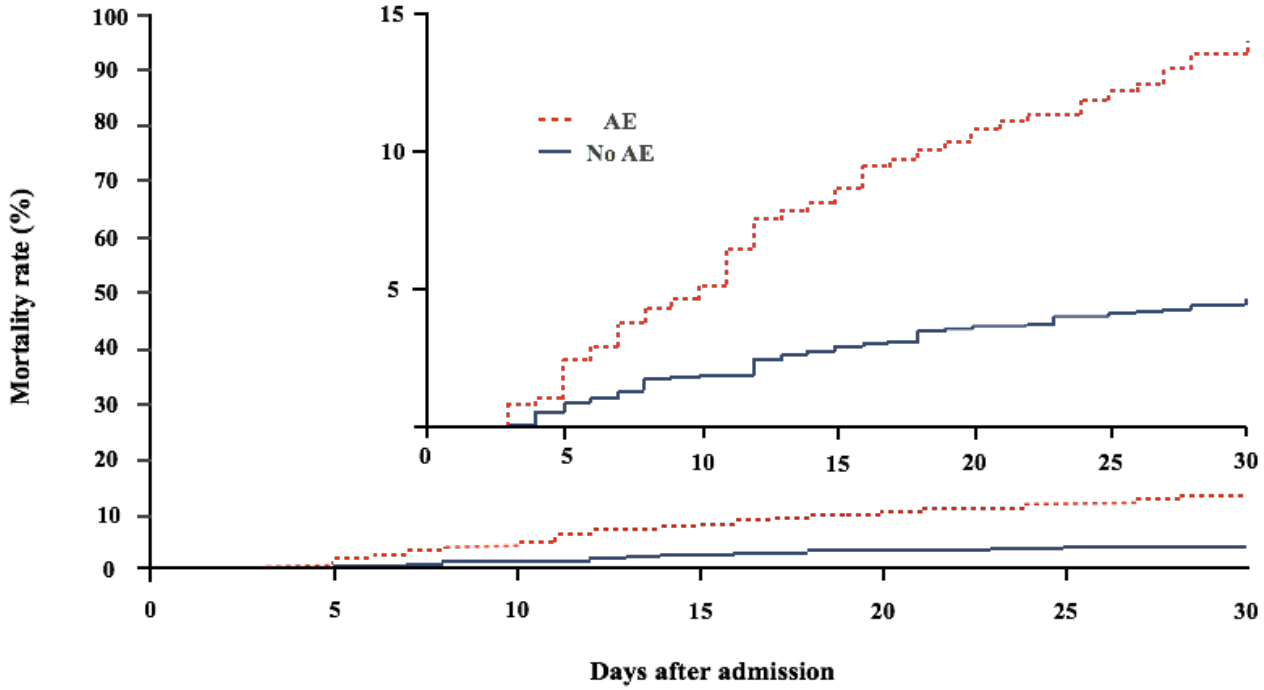


Figure 3.4 - Kaplan-Meier overall 30-day mortality curve for patients with and without adverse events.

3.5. Discussion

3.5.1. Independent effect of adverse events on mortality

To our knowledge, this is the first study to address the independent effect of AEs on both inpatient and post-discharge 30-day mortality after controlling for patients' characteristics. Two previous studies tried to estimate the independent effect of AEs on mortality, but focused only on inpatient mortality.[32,33] According to our findings, patients who experienced an AE had an increased risk of death during hospitalization (OR = 4.47; $p < 0.001$), after controlling for all confounding variables. However, no association was found between AEs and post-discharge 30-day mortality (OR = 0.97; P = 0.930). The rate of AEs found in our study (21%) is consistent with the most recent publications that used the GTT to identify AEs, where its incidence was reported to be between 21 and 33 per 100 admissions.[22,23,25,27] This study provides evidence to support the importance of improving patient safety in hospitals, as it presents an estimation of the independent impact of AEs on mortality.

The two previous studies[56,57] that estimated the independent effect of AEs on mortality focused only on inpatient mortality and used different definitions and methodologies to identify AEs. One of the studies[56] focused on the effect of AEs in patients who underwent radical cystectomy for bladder cancer. Adverse events were identified using hospital claims. According to their findings, patients who suffered an AE had an 8-fold increased risk of death during their hospitalization, after controlling for confounding variables (OR = 8.07; $p < 0.001$). The second study[57] focused on the impact of AEs on mortality and length of stay in the ICU. After adjusting for specific variables, they concluded that AEs were not significantly associated with time to in-hospital death (OR = 0.93). However, the ICU is known for having higher mortality rates than the general hospital floors, as patients hospitalized in this unit are normally in a very critical condition. Furthermore, this study used a very small sample of patients (N = 207), which may be insufficient in detecting true associations between AEs and the proposed outcomes.

Our findings suggest that AEs may be a significant predictor of in-hospital mortality, but not of post-discharge mortality. These findings may be explained by the time to occurrence of AEs. It has been reported that most AEs occur in the first 48 to 72 hours after admission[26] and most patients will probably develop clinically evident symptoms as a result from AEs during their hospitalization.

Our findings also present higher mortality rates than estimations reported by other studies which also used the GTT to identify AEs.[23,25,27] Inpatient mortality found in those studies varied between

1.5% and 2.5%. First, unlike the other studies, we chose a very specific and fragile population. Patients hospitalized with a primary diagnosis of HF face a 17 times higher risk of death in the month after hospitalization when compared to the general Medicare-age population.[58] Furthermore, the mean age at admission in our study was approximately 76 years old, while in the study by Classen et al.[25] the average age was 52 years old. Additionally, these studies included a heterogeneous mix of patients and did not attempt to control for potential confounders.

3.5.2. Patient-specific risk factors for mortality

Results from the multivariate models identified potential variables that may increase or decrease the risk of death, either during hospitalization or after discharge. Regarding inpatient mortality, severe aortic stenosis was the most significant predictor of death during hospitalization (OR = 4.68; $p < 0.001$). This is not surprising once mortality rates for untreated symptomatic severe aortic stenosis are extremely high. According to the literature, mortality varies between 50% and 60% at 2 years and 70% at 3 years.[59] On the other hand, male gender was found to significantly reduce the risk of death during hospitalization (OR = 0.48; $p < 0.05$). Normally, cardiovascular diseases tend to develop later in women, but usually with more severe consequences when compared to men.[60] Even though heart disease is the leading cause of death for women in the United States[61], it is sometimes misdiagnosed and underestimated which results in delays in treatment and in less aggressive therapies.[62,63]

The risk factors identified for the post-discharge 30-day mortality were different that the ones found for in-hospital mortality. As previously referred, AEs were no longer associated with an increased risk of death after discharge. History of depression was found to increase the risk of mortality within 30 days of discharge (OR = 1.83; $p < 0.05$). Depression has already been identified as a potential risk factor for mortality in patients with heart disease in previous studies.[64,65] Depressed patients are less likely to adjust their behavior and lifestyle (diet, stress, regular exercise) after being diagnosed with heart failure. Furthermore, it has been reported that patients with major depression do not always take the medication as prescribed, which can have a significant effect on mortality. On the other hand, full code status (OR = 0.19; $p < 0.001$) and ACE/ARB medication at time of discharge (OR = 0.52; $p < 0.05$) were related with a reduced risk of post-discharge 30-day mortality. Patients are classified as full code by default, meaning that medical intervention (resuscitation/intubation) is authorized in case of cardio-pulmonary arrest. However, very sick patients who do not expect to live much longer sometimes

change their status to DNR/DNI. Therefore, patients who are full code are normally healthier patients who do not expect to die, while patients that change their code status are usually expecting to die soon. This could be a reason for full code status appearing as a protective factor, as probably most of the patients who were DNR/DNI died within 30 days after discharge. ACE and ARB are medications used to lower blood pressure,[66] and known to reduce the risk of HF related problems.[66]

3.5.3. Limitations of the study

The methodology used in this study to identify AEs was the GTT.[67] This method has been used in previous studies finding AEs' incidence to be the highest, when compared to other methods of identifying AEs, suggesting greater sensitivity.[22,25-27,67] However, it has been reported that the GTT still misses some events that are identified by other methods,[22,68] which may lead to an underestimation of the total number of AEs. Furthermore, the GTT identifies an AE from the resulting signs and symptoms of that event. It is possible that we are also underestimating the number of AEs in less frail populations. These resilient patients may experience an AE but not develop clinically evident signs or symptoms, let alone death.

Another limitation of this study is that approximately 97% of all participants are Caucasian. The results found in our study may not be generalizable to the entire population, as African Americans have been reported to have both a higher incidence of HF[69,70] and AEs.[71] Furthermore, by choosing only HF patients in order to limit issues of patient heterogeneity, our results may not be representative of the entire hospital population.

Finally, as we controlled for confounding variables, there is the possibility that some important variables were not captured. Future studies could try to replicate our findings in a different patient population, combining different detection tools or including more confounding variables.

3.6. Conclusion

Our study suggests that AEs during HF hospitalizations are associated with inpatient mortality. According to our findings, patients who had an AE during hospitalization faced a 4-fold increase in inpatient mortality risk, after controlling for confounding variables. On the other hand, no association was found between AEs and post-discharge 30-day mortality. More research is needed to consolidate and generalize our findings to other hospital populations.

This study adds to the literature an estimation of the independent effect of AEs on inpatient mortality, thereby improving the understanding of the potential gains to be achieved by improving patient safety in U.S. hospitals.

Chapter IV.

The Independent Effect of in-Hospital Adverse Events on Readmission

4.1. Abstract

Background: Previous studies have associated adverse events with an increased risk of readmission. However, these studies focused only on certain sub-types of adverse events and were performed in heterogonous populations.

Methods: A retrospective cohort study was conducted in hospitalized heart failure patients between 2005 and 2007 in Rochester, Minnesota. Adverse events were identified using the Institute for Healthcare Improvement's Global Trigger Tool. A multivariate model was used to assess the impact of adverse events on 30-day readmission.

Results: In a population of 1,610 patients, a total of 290 patients (18.0%) were readmitted within 30 days after discharge. The readmission rate among the 307 patients (19.1%) that suffered at least one adverse event during hospitalization was 19.9%. Among the remaining 1303 patients, 17.6% were readmitted within 30 days after discharge. After controlling for confounding variables, adverse events were not independently associated with an increased risk of readmission within 30 days of discharge (OR, 1.03; $p = 0.8644$).

Conclusion: The occurrence of adverse events during heart failure hospitalizations was not associated with an increased risk of 30-day readmission.

4.2. Introduction

Hospital readmissions are a chronic and costly problem for U.S. hospitals, affecting millions of patients every year[4] and accounting for billions in spending.[72] While some readmissions are inherent to treatment, others are unplanned and result from poor quality care, with consequences to patients, physicians and institutions.[4,73] In a perspective of reducing hospital readmissions, the ACA established the implementation of the Hospital Readmission Reduction Program, which requires hospitals to reduce avoidable readmissions among Medicare patients for conditions of acute myocardial infarction, pneumonia and heart failure.

Adverse events are a common metric used to evaluate the quality of healthcare and can be defined as "unanticipated illness or injuries caused by medical evaluation and/or management rather than by the underlying disease or condition of the patient".[14] Some previous studies have identified some sub-types of AEs, such medication errors or infections, as potential predictors of readmissions.[33,34,74] However, these studies were performed in heterogeneous populations, making it difficult to adjust for patient variability. A study conducted on a specific population would allow for a better understanding about the independent effect of AEs on readmission.

In order to address this considerable gap in the literature, this study aimed to evaluate the independent effect of AEs on 30-day readmission in a homogenous population of heart failure patients, by controlling for confounding variables.

4.3. Methods

4.3.1. Study Design

The study design is the same as that described in the mortality study.

4.3.2. Study Population

The study population is the same as that described in the mortality study, except that in this study patients who died during hospitalization were also excluded from the statistical analysis.

4.3.3. Study Definition

This study aimed to analyze the independent effect of AEs on 30-day readmission in a HF population. Adverse events were identified using the GTT. Statistical analysis was performed to assess the impact of AEs on 30-day mortality readmission, by controlling for confounding variables. Patient-specific variables considered in this study were the same as the ones described in the methods section for the mortality study. Patients who were discharged from the hospital and rehospitalized within 30 days were identified as readmissions.

4.3.4. Study Procedure

The study procedure is the same as that described in the mortality study. However, given that a variable may not be simultaneously both an outcome (readmission is our primary outcome) and a predictor (readmission could also be an adverse event), we excluded all the events identified as readmissions from the primary statistical analysis (N = 31). Simultaneously, a secondary statistical analysis was conducted where those 31 adverse events were included. For purposes of discussion, the primary analysis was considered the most conservative and statically most correct approach.

4.3.5. Statistical Methods

All qualifying patients discharged from the hospitals with a primary diagnosis of HF between January 1, 2005 and December 31, 2007 were included. Participants were classified into one of two

groups: with adverse event(s) and without adverse event(s). The rate of AEs was estimated by using the number of patients who experienced an AE as the numerator and all study participants as the denominator. Thirty-day readmission rate was compared for those who experienced an AE and for those who did not experience an AE.

To assess the independent impact of AEs with confounding variables on 30-day readmission, a multivariate logistic regression model was created. Potential confounders were grouped into demographics, functional status, medical history and medication at admission and discharge. These were presented as frequencies for categorical variables and means with standard deviations for continuous variables and calculated separately for those who had an AE and for those who did not have an AE, as well as for the entire study population. Bivariate logistic analyses were performed in which all models with candidate confounders were also adjusted for geographical residence at admission to account for potential referral bias. Variables with a level of significance of $p < 0.1$ were retained and entered into a multivariable model. A backward selection method was then performed, eliminating variables one at a time, until obtaining a model where all covariates were significant at $p < 0.05$. Finally, we forced AEs into the model to assess their independent effect on readmissions. A secondary multivariable model was performed where the AEs identified by the readmission trigger were included in the statistical analyses.

All data was collected and managed using REDcap electronic data capture tool[55] hosted at Mayo Clinic. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

4.4. Results

4.4.1. Study cohort analysis

The final study cohort consisted of 1,610 patients hospitalized for HF between 2005 and 2007. The mean age of patients was 76 ± 12.5 years; 55.2% were male and 96.8% were Caucasian. More than half of the patients lived in southeastern Minnesota (58.7%). Mean length of stay was 4.9 ± 4.5 days; mean Charlson Index was 4.0 ± 2.7 with a mean IPFS of 4.1 ± 3.6. One hundred fifty-seven patients (9.8%) were admitted from a skilled nursing facility, while 350 (21.7%) were discharge to that same living arrangement after hospitalization. Only 27% of patients required assistance with their personal hygiene activities (bathing, dressing and toileting), while 44.8% depended on someone to do their housekeeping. The most common medication at admission and discharge was diuretics (73.6% and 86.2%, respectively). According to the past medical history, coronary artery disease was the only comorbidity present in more than half of the patients (56.0%).

4.4.2. Adverse events and mortality outcomes

A total of 1,722 patients were diagnosed and hospitalized for HF between January 2005 and December 2007. Among those patients, 62 went to surgery and were consequently excluded from this study, while 50 died during hospitalization. Among the remaining 1,610 patients, overall 30-day readmission rate was 18%. A total of 307 patients (19.1%) developed an AE during hospitalization, and 61 of those patients (19.9%) were readmitted to the hospital within 30 days of discharge; for the remaining 1,303 patients, 229 (17.6%) were rehospitalized in the same period of time ($p = 0.3885$).

On a bivariate analysis (Table 4.1), AEs were not related with an increased risk of readmission within 30 days of discharge (OR 1.15; 95% CI, 0.84 to 1.58; P = 0.3885).

Table 4.1. Unadjusted results of 30-day readmission for patients with and without adverse events.

	Total N = 1610	With AEs N = 307 (19.1%)	Without AEs N = 1303 (80.9%)	*p value*	Unadjusted Odds Ratio (95% CI)
30-day readmission	290 (18.0%)	61 (19.9%)	229 (17.6%)	$p = 0.3885$	1.15 (0.84, 1.58)

Results from the multivariable logistic regression model performed in the primary statistical analysis are illustrated in Figure 4.1. In a multivariate analysis, after adjusting for confounding variables, AEs did not represent a risk factor for 30-day readmission (OR 1.03; 95% CI; 0.74 to 1.42; P = 0.8644). Dependent housekeeping was found to increase the risk of readmission within 30 days of discharge (OR 1.49; 95% CI; 1.13 to 1.96; $p < 0.05$), while past dementia (OR 0.43; 95% CI; 0.78 to 0.96; $p < 0.05$), ACE/ARB medications at time of discharge (OR 0.71; 95% CI; 0.54 to 0.94; $p < 0.05$) and age (OR 0.86; 95% CI; 0.21 to 0.88; $p < 0.01$) were related with a reduced risk of readmission.

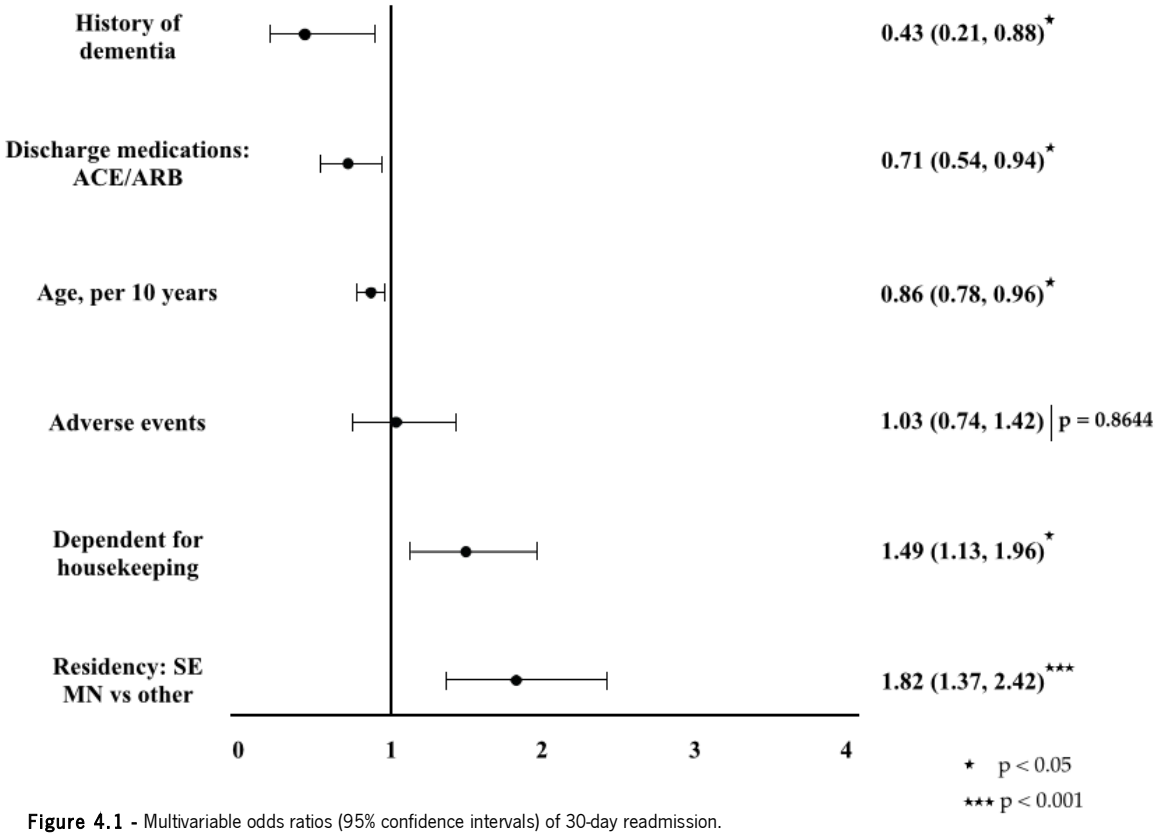


Figure 4.1 - Multivariable odds ratios (95% confidence intervals) of 30-day readmission.

Figure 4.2 represents the multivariate model obtained from the secondary statistical analysis, which includes the readmission adverse events identified by the readmission trigger (N = 31) In this secondary model, with the inclusion of these 31 events, it is possible to observe that AEs now have a strong effect on 30-day readmission after adjusting for confounders (OR = 1.75, $p < 0.001$). All the others covariates remained unchanged.

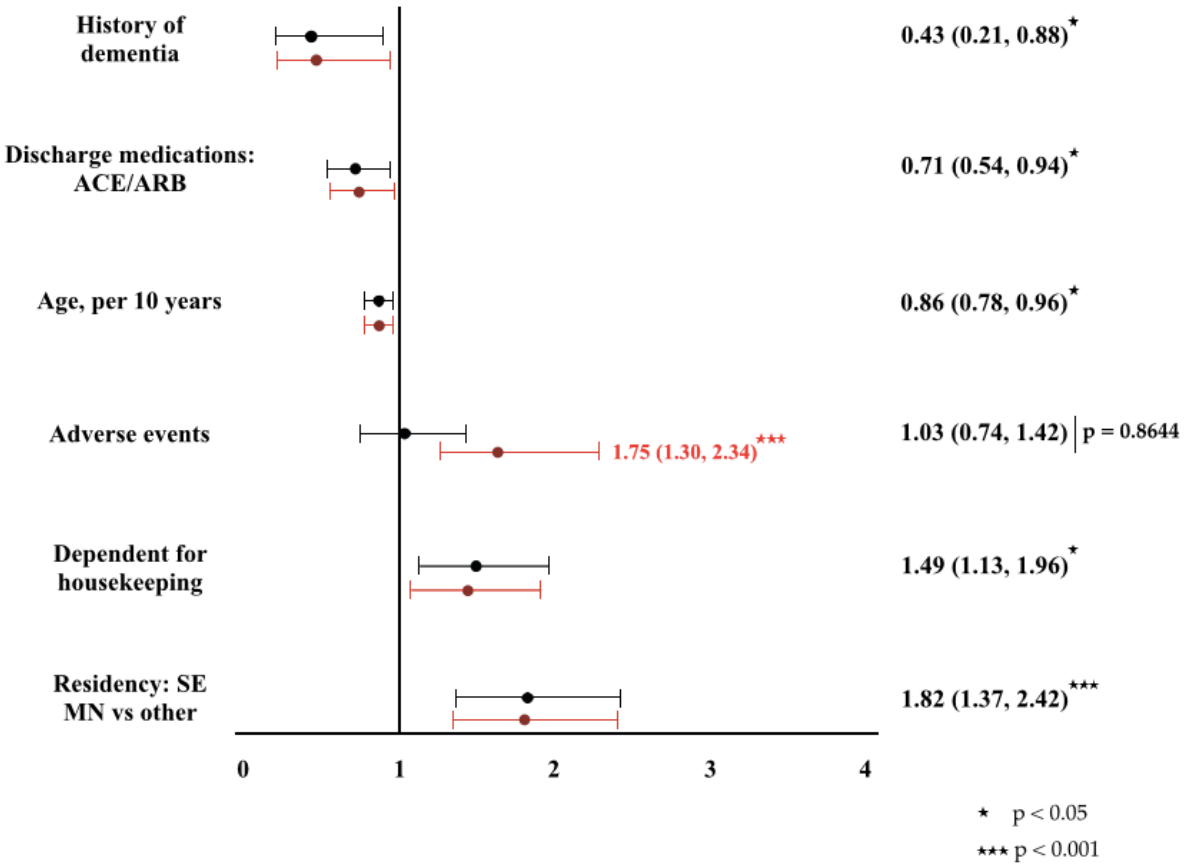


Figure 4.2 - Multivariable odds ratios (95% confidence intervals) of 30-day readmission with the inclusion of readmission adverse events. The first multivariate model is represented with black colored lines, while the secondary model, which includes the readmission events, is represented with red colored lines.

Figure 4.3 represents a Kaplan-Meier analysis for overall 30-day readmission rate based on experiencing an AE. Readmission rates were slightly higher among patients who suffered an AE during hospitalization.

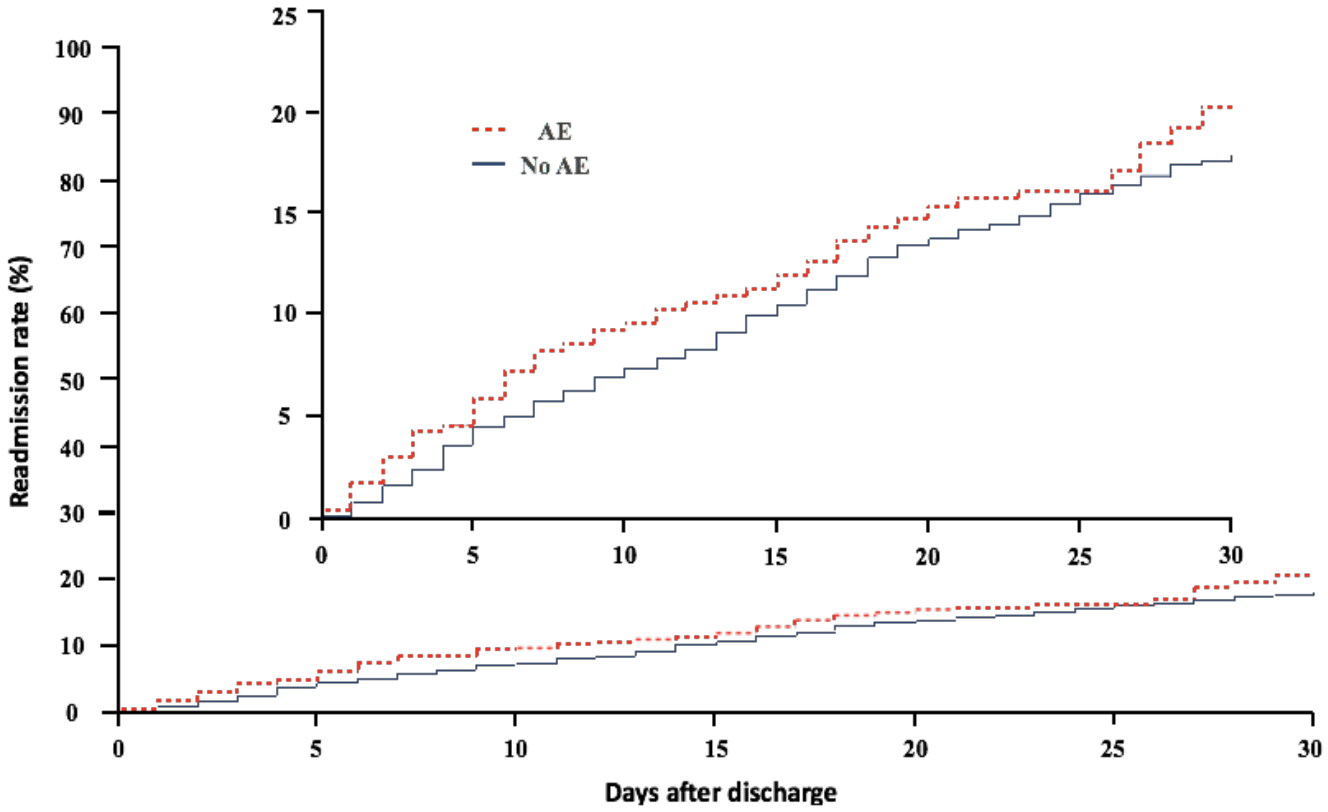


Figure 4.3 - Kaplan-Meier overall 30-day readmission curve for patients with and without adverse events.

4.5. Discussion

4.5.1. Independent effect of adverse events on readmission

To our knowledge, this is the first study to address the independent effect of AEs (considering all the sub-types) on 30-day readmission in a specific population. Our study suggests that AEs do not independently increase the risk of readmission within 30 days after discharge in HF patients, after controlling for confounding variables (OR = 1.03; 95% CI, 0.74 to 1.42; p = 0.8644).

The 30-day readmission rate (18.0%) found in our study is consistent with the rate following Medicare medical discharges reported for our hospital in 2008 (17.1%),[27] but lower than the U.S. average rate reported in 2008 and 2010 (21.4% and 21.1% respectively)[27] for Medicare HF patients. The rate of AEs found in our study (18.9%) is also similar to rates found in the most recent publications that used the GTT to identify AEs (22- 33 per 100 admissions).[22,25-27]

There is a recent body of literature focusing on potential risk factors that can contribute to hospital readmissions. However, and to the best of our knowledge, our study is the first to try to estimate the independent effect of AEs on 30-day readmission. Previous studies have identified some sub-types of AEs (nosocomial infections, adverse drug-events)[33-35] as potential risk factors for readmission in different populations. One of the studies[34] found that patients who developed nosocomial infections during hospitalization had a greater hazard of readmission within one year of admission (OR = 1.40), after adjusting for some confounders (sex, age, LOS, ICU stay, Charlson comorbidity index and year of admission). Another study[35] found a 33% increase in the odds of being readmitted within 30 days after discharge in patients who had a vascular catheter-associated infection during hospitalization.

However, unlike those studies, we did not find an association between AEs and 30-day readmissions in our primary statistical analyses. One potential cause for the disparity between our findings and the literature could be a possible referral bias. It is possible that some of the patients admitted to our hospital were then readmitted to other medical care units closer to their geographical residence. These readmissions were not captured in this study, but we tried to limit this bias by controlling for area of geographical residence. Another possible reason is that we considered all sub-types of AEs and used a homogenous population, unlike the other studies that focused only on certain sub-types and used heterogeneous samples of patients. It is possible that AEs affect readmissions differently for patients with different primary diagnoses.

In our secondary statistical analyses, we found an increased risk of readmission among patients who had an AE during hospitalization (OR = 1.75, $p < 0.001$). In this case, the adverse events identified by the readmission trigger were also included in the statistical analyses, which substantially increased the risk of readmission. The adverse events identified by the readmission trigger are referent to the day of discharge, and may include episodes of premature discharge, medication change, or others.

However, the purpose of a trigger-based review process is to look closely in the area of the chart review where the trigger was identified to determine if an AE is also present. As a result, the patients with a readmission trigger had an increased level of scrutiny by reviewers on the last day of hospitalization. This unbalanced degree of attention to the last day of hospitalization for only those with the readmission trigger could lead to AEs being missed on other cases where a readmission trigger was not noted. On the other hand, summarily dismissing events related to the readmission trigger automatically discounts the relevancy of the last day's AEs on a study investigating risk of readmission. This is a complex methodological issue. We opted for considering the primary statistical analysis as the most conservative and correct approach, given the statistical necessity of not including a variable which is both an outcome and a predictor.

4.5.2. Patient-specific risk factors for 30-day readmissions

Geographical residence in SE Minnesota at time of admission and dependent housekeeping were the only significant risk factors predictors of 30-day readmission, after controlling for all variables. It is possible that some of the patients admitted to our hospital were then readmitted to other medical care units closer to their geographical residence, factor that would explain why patients from SE Minnesota are more prone to be readmitted within 30 days of discharge (referral bias). Both dependent housekeeping and dependent personal-hygiene were related to an increased risk of readmission on a bivariate analysis, but only dependent housekeeping remained independently significant in the multivariate model. A previous study had already identified difficulty in performing activities of daily living (housekeeping and personal-hygiene) as the second most common cause for readmissions.[75] Patients with housekeeping dependence are more likely to have trouble following doctor's recommendation for diet and exercises due to their physical and cognitive impairments, which may increase their risk of readmission.

On the other hand, dementia, ACE/ARB medications at time of discharge and increased age were found to reduce the risk of readmission, while renal insufficiency did not remain significant after adjusting for potential confounders. Patients suffering from dementia are less likely to sense and communicate post-discharge complications such as chest pain, due to their cognitive impairment.[76] Furthermore, family and nurses may sometimes underestimate their symptoms. ACE and ARB are medications used to lower the blood pressure[66] and are known to reduce the risk of HF related problems,[66] which explains its protective factor. Interestingly, increased age was found to reduce the risk of 30-day readmission in this study. Elderly patients are frequently discharged to skilled nursing facilities where they have access to some degree of medical care, avoiding potential readmissions. Previously reported risk factors of readmission in HF patients such as diabetes or male gender[77,78] were not found to be significant in our study, after controlling for all the confounding variables.

4.5.3. Limitations of the study

This study has some limitations. First, as previously mentioned, we probably underestimated the number of AEs by dismissing the events that were identified through the readmission trigger in the primary statistical analyses. However, this was the most conservative and statistically most correct approach, given the necessity of not including a variable which was both an outcome and a predictor.

Second, it has been reported that the GTT misses some events that are identified by other methods,[22] which may lead to an underestimation of the total number of AEs. Furthermore, the GTT identifies an AE from the resulting signs and symptoms of that event. It is likely that less frail patients do not develop clinically evident signs or symptoms from potential AEs, which could result in a possible underestimation of AEs in more resilient populations.

Third, we only identified patients who were readmitted to our hospital. It is possible that some patients were readmitted to other hospitals, which may have led to an underestimation of the total number of readmissions. Covariates were adjusted for geographical residence at admission to try to account for potential referral bias, but it might still be present. Finally, it is possible that some variables were not captured in our analysis, as this was a non-randomized study.

Future studies could combine different detection tools in order to equally evaluate the day of discharge on all patients, instead of focusing only on those identified through the readmission trigger. In addition, our findings could be consolidated if this study was conducted on other hospital populations.

4.6. Conclusion

Our findings suggest that AEs before the day of discharge do not increase the risk of readmission within 30-days of discharge in HF patients, after controlling for confounding variables. However, the events that occurred on the day of discharge were dismissed from the primary statistical analyses, due to a complex methodological issue.

Reducing hospital readmissions is a challenging task that requires the intervention and effort of all stakeholders. Its accomplishment would translate not only into financial savings for hospitals, but would also represent a step forward in improving the value of healthcare. However, and so far, models trying to predict readmissions have shown to perform poorly, and no single intervention was found to regularly reduce them.

Chapter V.

Concluding Remarks

5. Concluding Remarks

In this work, adverse events were identified in a population of heart failure patients and its independent effect of was studied on two different outcomes: mortality (inpatient and post-discharge 30-day mortality) and readmission (30-day readmission).

In respect of the mortality study, it was verified that adverse events substantially increase the risk of mortality during the hospitalization, independently of the patients' characteristics. On the other hand, it was found that adverse events are not related with an increased risk of post-discharge 30-day mortality, after controlling for confounders. In conclusion, the effect of adverse events seems to be limited to in-hospital mortality.

By analysing the primary multivariate model created for the readmission study, it was possible to observe that adverse events do not seem to increase the risk of readmission after discharge. However, the events that occurred on the day of discharge were not considered in the primary statistical analysis due to a complex methodological issue, what automatically discounted the relevancy of the last day's AEs on readmission. On the secondary multivariate model, which included the events that occurred on the day of discharge, it was found an increased risk of readmission among the patients who had an AE during their hospitalization. However, given the fact that the day of discharge was not equally evaluated among all patients, this model can be under or overestimating the effect of AEs on readmission. In summary, adverse events before the day of discharge do not seem to be related with an increased risk of readmission, while the effect of last day's AEs on readmission remains unknown.

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APPENDICES

Appendix A – Summary of mortality outcomes and patient-specific variables regarding the mortality study

Table A.1 – Descriptive results of mortality outcomes and summary of patients' characteristics for patients with and without adverse events during hospitalization.

	Total (N = 1660)†	With adverse event(s) N = 371 (22.3%)	Without adverse event(s) N = 1289 (77.7%)	*p value*
Mortality outcomes				
Inpatient death	50 (3.0%)	33 (8.9%)	17 (1.3%)	*p < 0.*001
Within 30 days post-discharge, including inpatient death	123 (7.4%)	54 (14.6%)	69 (5.4%)	*p < 0.*001
Within 30 days post-discharge, excluding inpatient death (NMISS=50)	73 (4.5%)	21 (6.2%)	52 (4.1%)	*p = 0.*095
Age at admission*				
Mean (SD)	75.9 (12.5)	75.9 (12.1)	76.0 (12.6)	*p = 0.*786
Median (range)	78.1 (20.6-101.5)	78.2 (25.8-101.5)	78.1 (20.6-99.3)	
Male gender	908 (54.7%)	190 (51.2%)	718 (55.7%)	*p = 0.*126
Caucasian race (NMISS=5)	1600 (96.7%)	359 (96.8%)	1241 (96.7%)	*p = 0.*914
BMI*				
Mean (SD)	30.6 (8.1)	31.6 (9.1)	30.3 (7.8)	*p = 0.*034
Median (range)	29.2 (13.9-94.8)	30.0 (15.4-84.4)	29.0 (13.9-94.8)	
Length of stay*				
Mean (SD)	5.1 (4.6)	9.0 (7.1)	4.0 (2.8)	*p < 0.*001
Median (range)	4.0 (1.0-55.0)	7.0 (1.0-55.0)	3.0(1.0-25.0)	
Geographical residence: southeastern MN‡	975 (58.7%)	232 (62.5%)	743 (57.6%)	*p = 0.*092
Full code status (NMISS=8)	1312 (79.4%)	289 (78.3%)	1023 (79.7%)	*p = 0.*554
Admit mobility status (NMISS=10)				
Walk independently	864 (52.4%)	154 (41.8%)	710 (55.4%)	*p < 0.*001
Admission living arrangements: Skilled nursing facility	165 (9.9%)	56 (15.1%)	109 (8.5%)	*p < 0.*001
Discharge living arrangements: Skilled nursing facility	350 (21.1%)	132 (35.6%)	218 (16.9%)	p < 0 001
Dependent personal hygiene‡ (NMISS=1)	454 (27.4%)	152 (41.1%)	302 (23.4%)	*p < 0.*001
Dependent housekeeping (NMISS=2)	754 (45.5%)	221 (59.7%)	533 (41.4%)	p < 0 001
Past medical history:				

	Total (N = 1660)†	With adverse event(s) N = 371 (22.3%)	Without adverse event(s) N = 1289 (77.7%)	*p value*
Dementia	89 (5.4%)	18 (4.9%)	71 (5.5%)	p = 0.621
CVA/TIA	322 (19.4%)	85 (22.9%)	237 (18.4%)	p = 0.052
Peripheral vascular disease	311 (18.7%)	82 (22.1%)	229 (17.8%)	p = 0.059
OSA	286 (17.2%)	73 (19.7%)	213 (16.5%)	p = 0.157
Severe aortic stenosis	152 (9.2%)	35 (9.4%)	117 (9.1%)	p = 0.834
Asthma, COPD, other pulmonary disease	469 (28.3%)	110 (29.6%)	359 (27.9%)	p = 0.498
Diabetes	616 (37.1%)	155 (41.8%)	461 (35.8%)	p = 0.035
Coronary artery disease	930 (56.0%)	207 (55.8%)	723 (56.1%)	p = 0.920
Renal insufficiency	631 (38.0%)	153 (41.2%)	478 (37.1%)	p = 0.146
Atrial arrhythmia	873 (52.6%)	199 (53.6%)	674 (52.3%)	p = 0.646
Ventricular arrhythmia	121 (7.3%)	29 (7.8%)	92 (7.1%)	p = 0.657
Depression	310 (18.7%)	75 (20.2%)	235 (18.2%)	p = 0.387
Cancer‡	403 (24.3%)	86 (23.2%)	317 (24.6%)	p = 0.576
Charlson Index*				
Mean (SD)	4.0 (2.7)	4.2 (2.8)	3.9 (2.6)	p = 0.059
Median (range)	3.0 (0.0-16.0)	4.0 (0.0-14.0)	3.0 (0.0-16.0)	
IPFS*				
Mean (SD)	4.2 (3.7)	5.2 (4.0)	3.9 (3.5)	p < 0.001
Median (range)	4.0 (0.0-19.0)	4.0 (0.0-19.0)	4.0 (0.0-18.0)	
Admission medications:				
Home oxygen prior to admission	231 (13.9%)	60 (16.2%)	171 (13.3%)	p = 0.154
Diuretic‡	1221 (73.6%)	292 (78.7%)	929 (72.1%)	p = 0.011
ACE/ARB (NMISS=1)	976 (58.8%)	203 (54.7%)	773 (60.0%)	p = 0.068
Beta blockers (NMISS=1)	1142 (68.8%)	240 (64.7%)	902 (70.0%)	p = 0 .050
Calcium channel blockers	371 (22.3%)	75 (20.2%)	296 (23.0%)	p = 0.263
Digitalis preparations (NMISS=1)	416 (25.1%)	108 (29.1%)	308 (23.9%)	p = 0.042
Anti-platelets (NMISS=1)	194 (11.7%)	44 (11.9%)	150 (11.6%)	p = 0.910
Amiodarone (NMISS=1)	112 (6.8%)	33 (8.9%)	79 (6.1%)	p = 0.062

	Total (N = 1660)†	With adverse event(s) N = 371 (22.3%)	Without adverse event(s) N = 1289 (77.7%)	*p value*
Coumadin (NMISS=1)	654 (39.4%)	157 (42.3%)	497 (38.6%)	p = 0.195
Statin (NMISS=1)	760 (45.8%)	167 (45.0%)	593 (46.0%)	p = 0.727
Insulin (NMISS=1)	325 (19.6%)	91 (24.5%)	234 (18.2%)	p = 0.007
Discharge medications:				
Diuretic‡	1405 (84.6%)	295 (79.5%)	1110 (86.1%)	p = 0.002
ACE/ARB	1123 (67.7%)	205 (55.3%)	918 (71.2%)	p < 0.001
Beta blockers	1296 (78.1%)	268 (72.2%)	1028 (79.8%)	p = 0.002
Calcium channel blockers	374 (22.5%)	67 (18.1%)	307 (23.8%)	p = 0.019
Digitalis preparations	562 (33.9%)	126 (34.0%)	436 (33.8%)	p = 0.961
Anti-platelets	211 (12.7%)	50 (13.5%)	161 (12.5%)	p = 0.615
Amiodarone	123 (7.4%)	33 (8.9%)	90 (7.0%)	p = 0.215
Coumadin	690 (41.6%)	161 (43.4%)	529 (41.0%)	p = 0.417
Statin	816 (49.2%)	167 (45.0%)	649 (50.3%)	p = 0.070
Insulin	350 (21.1%)	102 (27.5%)	248 (19.2%)	p < 0.001

***** Results are reported as "n (percentage)", except for variables marked with an *, where "mean (standard deviation)" and "median (range)" are reported.

† N=62 of 1722 patients diagnosed and hospitalized for heart failure were discharged to the operating room and excluded from this analysis.

‡ Risk factor was considered as a grouped variable. **Southeastern Minnesota** = Olmsted, Dodge, Fillmore, Freeborn, Goodhue, Houston, Mower, Rice, Steele, Wabasha, and Winona counties; **Dependent personal hygiene** = bathing, dressing, or toileting; **Cancer** = any tumor, metastasis, lymphoma, or leukemia**; Diuretic** = loop, thiazide-like, or potassium sparing.

BMI = Body mass index; **CVA/TIA** = Cerebrovascular accident / transient ischemic attack; **OSA** = Obstructive sleep apnea; **IPFS** = Inpatient physiological failure score; **COPD** = Chronic obstructive pulmonary disease**; ACE/ARB** = Angiotensin-Converting Enzyme/Angiotensin II Receptor.

Chi-square tests were performed for categorical variables; Wilcoxon Rank Sum tests were performed for continuous variables.

Appendix B – Summary of readmission outcomes and patient-specific variables regarding the readmission study

Table B.1 – Descriptive results of readmission outcomes and summary of patients' characteristics for patients with and without adverse events during hospitalization.

	Adverse Event(s) During Hospitalization:		Total	Outcome: 30-day Readmission	
	Y (N=307)	N (N=1303)	(N=1610)†	OR (95% CI)	*p* value
Readmission within 30 days post-discharge	61 (19.9%)	229 (17.6%)	290 (18.0%)	1.15 (0.84, 1.58)	0.3885
Age at admission				0.89 (0.80, 0.99)$^{\Delta}$	0.0281
Mean (SD)	76.1 (12.3)	76.0 (12.6)	76.0 (12.5)		
Median (range)	78.6 (25.8-101.5)	78.0 (20.6-99.3)	78.3 (20.6-101.5)		
Male gender	159 (51.8%)	730 (56.0%)	889 (55.2%)	1.13 (0.87, 1.46)	0.3753
Caucasian race (NMISS=5)	298 (97.1%)	1255 (96.7%)	1553 (96.8%)	0.93 (0.46, 1.88)	0.8327
BMI				1.00 (0.98, 1.02)	0.9922
Mean (SD)	31.4 (9.4)	30.3 (7.7)	30.5 (8.1)		
Median (range)	29.8 (15.4-84.4)	29.0 (13.9-94.8)	29.2 (13.9-94.8)		
Length of stay				1.00 (0.98, 1.03)	0.7710
Mean (SD)	9.2 (7.1)	3.9 (2.7)	4.9 (4.5)		
Median (range)	7.0 (2.0-55.0)	3.0 (1.0-25.0)	4.0 (1.0-55.0)		
Geographical Residence: southeastern MN*	187 (60.9%)	758 (58.2%)	945 (58.7%)	1.65 (1.26, 2,16)	0.0003
Full code status (NMISS=8)	239 (78.4%)	1036 (79.9%)	1275 (79.6%)	1.15 (0.83, 1.58)	0.4133
Admission Ejection Fraction: <40 (NMISS=13)	139 (45.3%)	577 (44.7%)	716 (44.8%)	0.85 (0.66, 1.11)	0.2284
Admission mobility status: Walk independently (NMISS=9)	125 (41.1%)	722 (55.7%)	847 (52.9%)	0.92 (0.71, 1.19)	0.5306
Admission living arrangements: Skilled Nursing Facility	45 (14.7%)	112 (8.6%)	157 (9.8%)	0.86 (0.56, 1.33)	0.4941
Discharge living arrangements: Skilled Nursing Facility	126 (41.0%)	224 (17.2%)	350 (21.7%)	0.95 (0.70, 1.30)	0.7620
Dependent personal hygiene* (NMISS=1)	125 (40.8%)	309 (23.7%)	434 (27.0%)	1.33 (1.01, 1.76)	0.0421
Dependent housekeeping (NMISS=2)	183 (59.8%)	538 (41.3%)	721 (44.8%)	1.32 (1.02, 1.71)	0.0327
Past medical history:					

	Adverse Event(s) During Hospitalization:		Total	Outcome: 30-day Readmission	
	Y (N=307)	N (N=1303)	(N=1610)†	OR (95% CI)	*p* value
Dementia	16 (5.2%)	69 (5.3%)	85 (5.3%)	0.47 (0.23, 0.96)	0.0379
CVA/TIA	67 (21.8%)	245 (18.8%)	312 (19.4%)	1.14 (0.83, 1.56)	0.4230
Peripheral vascular disease	69 (22.5%)	232 (17.8%)	301 (18.7%)	1.14 (0.83, 1.56)	0.4340
OSA	61 (19.9%)	217 (16.7%)	278 (17.3%)	1.00 (0.71, 1.40)	0.9804
Severe aortic stenosis	25 (8.1%)	113 (8.7%)	138 (8.6%)	1.38 (0.90, 2.12)	0.1427
Asthma, COPD, other pulmonary disease	94 (30.6%)	365 (28.0%)	459 (28.5%)	1.27 (0.97, 1.67)	0.0847
Diabetes	126 (41.0%)	469 (36.0%)	595 (37.0%)	1.14 (0.88, 1.48)	0.3361
Coronary artery disease	169 (55.0%)	732 (56.2%)	901 (56.0%)	0.98 (0.76, 1.26)	0.8643
Renal insufficiency	125 (40.7%)	483 (37.1%)	608 (37.8%)	1.35 (1.04, 1.75)	0.0234
Atrial arrhythmia	169 (55.0%)	681 (52.3%)	850 (52.8%)	1.04 (0.81, 1.35)	0.7416
Ventricular arrhythmia	24 (7.8%)	94 (7.2%)	118 (7.3%)	1.03 (0.62, 1.70)	0.9173
Depression	64 (20.8%)	238 (18.3%)	302 (18.8%)	0.83 (0.59, 1.17)	0.2902
Cancer *	74 (24.1%)	318 (24.4%)	392 (24.3%)	0.84 (0.62, 1.14)	0.2640
Charlson Index				1.02 (0.97, 1.07)	0.5186
Mean (SD)	4.2 (2.9)	3.9 (2.6)	4.0 (2.7)		
Median (range)	4.0 (0.0-14.0)	3.0 (0.0-16.0)	3.0 (0.0-16.0)		
IPFS				1.04 (1.00, 1.08)	0.0335
Mean (SD)	5.2 (3.9)	3.8 (3.5)	4.1 (3.6)		
Median (range)	4.0 (0.0-16.0)	4.0 (0.0-18.0)	4.0 (0.0-18.0)		
Admission medications:					
Home O2 prior to admission	50 (16.3%)	172 (13.2%)	222 (13.8%)	1.02 (0.70, 1.47)	.9303
Diuretic*	241 (78.5%)	944 (72.4%)	1185 (73.6%)	0.99 (0.74, 1.32)	0.9341
ACE/ARB (NMISS=1)	171 (55.7%)	781 (60.0%)	952 (59.2%)	0.89 (0.69, 1.15)	0.3684
Beta blockers (NMISS=1)	203 (66.1%)	908 (69.7%)	1111 (69.0%)	0.85 (0.65, 1.12)	0.2469
Calcium channel blockers	67 (21.8%)	296 (22.7%)	363 (22.5%)	1.02 (0.75, 1.38)	0.9226
Digitalis preparations (NMISS=1)	89 (29.0%)	318 (24.4%)	407 (25.3%)	1.00 (0.75, 1.35)	0.9842
Antiplatelets (NMISS=1)	36 (11.7%)	153 (11.8%)	189 (11.7%)	0.88 (0.58, 1.32)	0.5356

	Adverse Event(s) During Hospitalization:		Total	Outcome: 30-day Readmission	
	Y (N=307)	N (N=1303)	(N=1610)†	OR (95% CI)	*p* value
Amiodarone (NMISS=1)	26 (8.5%)	81 (6.2%)	107 (6.7%)	1.36 (0.83, 2.23)	0.2232
Coumadin (NMISS=1)	132 (43.0%)	504 (38.7%)	636 (39.5%)	1.09 (0.84, 1.42)	0.5229
Statin (NMISS=1)	140 (45.6%)	603 (46.3%)	743 (46.2%)	0.92 (0.71, 1.18)	0.4993
Insulin (NMISS=1)	74 (24.1%)	240 (18.4%)	314 (19.5%)	1.26 (0.92, 1.71)	0.1467
Discharge medications:					
Diuretic*	255 (83.1%)	1133 (87.0%)	1388 (86.2%)	0.83 (0.58, 1.19)	0.3075
ACE/ARB	182 (59.3%)	939 (72.1%)	1121 (69.6%)	0.70 (0.53, 0.91)	0.0084
Beta blockers	239 (77.9%)	1043 (80.0%)	1282 (79.6%)	0.94 (0.69, 1.29)	0.6906
Calcium channel blockers	61 (19.9%)	309 (23.7%)	370 (23.0%)	1.03 (0.76, 1.39)	0.8578
Digitalis preparations	108 (35.2%)	446 (34.2%)	554 (34.4%)	0.83 (0.63, 1.09)	0.1840
Antiplatelets	41 (13.4%)	168 (12.9%)	209 (13.0%)	0.93 (0.63, 1.37)	0.7159
Amiodarone	29 (9.4%)	93 (7.1%)	122 (7.6%)	1.34 (0.84, 2.14)	0.2162
Coumadin	145 (47.2%)	543 (41.7%)	688 (42.7%)	1.25 (0.96, 1.62)	0.0935
Statin	147 (47.9%)	664 (51.0%)	811 (50.4%)	0.87 (0.67, 1.12)	0.2762
Insulin	86 (28.0%)	257 (19.7%)	343 (21.3%)	1.24 (0.92, 1.68)	0.1554

†The initial cohort consisted of 1,722 unique subjects diagnosed and hospitalized for heart failure. Among these 1,722 subjects, a total of 1,610 were analyzed for this outcome after excluding N=62 discharged to the operating room and N=50 who died during their hospitalization.

‡ Odds ratios, 95% confidence intervals, and p values from logistic regression models evaluating the risk of readmission within 30 days of discharge for each baseline risk factor. Each model is adjusted for residency at the time of admission (SE MN vs. other) to account for possible referral bias, except for geographical residence which represents the only univariate analysis.

ΔAge was analyzed per 10-year increase.

*Risk factor was considered as a grouped variable as follows: **Southeastern Minnesota** = Olmsted, Dodge, Fillmore, Freeborn, Goodhue, Houston, Mower, Rice, Steele, Wabasha, and Winona counties; **Dependent personal hygiene** = bathing, dressing, or toileting; **Cancer** = any tumor, metastasis, lymphoma, or leukemia; **Diuretic** = loop, thiazide-like, or potassium sparing.

BMI = Body mass index; **CVA/TIA** = Cerebrovascular accident / transient ischemic attack; OSA = Obstructive sleep apnea; IPFS = Inpatient physiological failure score; **COPD** = Chronic obstructive pulmonary disease; **ACE/ARB** = Angiotensin-Converting Enzyme/Angiotensin II Receptor.

Chi-square tests were performed for categorical variables; Wilcoxon Rank Sum tests were performed for continuous variables.

Appendix C – Global Trigger Tool worksheet

	Cares Module Triggers	+	Event Description and Harm Category (E-I)
C1	Transfusion or use of blood products		
C2	Code/arrest/rapid response team		
C3	Acute dialysis		
C4	Positive blood culture		
C5	X-ray or Doppler studies for emboli or DVT		
C6	Decrease of greater than 25% in hemoglobin or hematocrit		
C7	Patient fall		
C8	Pressure ulcers		
C9	Readmission within 30 days		
C10	Restraint use		
C11	Healthcare-associated infection		
C12	In-hospital stroke		
C13	Transfer to higher level of care		
C14	Any procedure complication		
C15	Other		
	Surgical Module Triggers		
S1	Return to surgery		
S2	Change in procedure		
S3	Admission to intensive care post-op		
S4	Intubation/reintubation/BiPap in Post Anesthesia Care Unit (PACU)		
S5	X-ray intra-op or in PACU		
S6	Intra-op or post-op death		
S7	Mechanical ventilation greater than 24 hours post-op		
S8	Intra-op epinephrine, norepinephrine, naloxone, or romazicon		
S9	Post-op troponin level greater than 1.5 ng/ml		
S10	Injury, repair, or removal of organ		
S11	Any operative complication		

	Medication Module Triggers	+	Event Description and Harm Category (E-I)
M1	*Clostridium difficile* positive stool		
M2	Partial thromboplastin time greater than 100 seconds		
M3	International Normalized Ratio (INR) greater than 6		
M4	Glucose less than 50 mg/dl		
M5	Rising BUN or serum creatinine greater than 2 times baseline		
M6	Vitamin K administration		
M7	Benadryl (Diphenhydramine) use		
M8	Romazicon (Flumazenil) use		
M9	Naloxone (Narcan) use		
M10	Anti-emetic use		
M11	Over-sedation/hypotension		
M12	Abrupt medication stop		
M13	Other		
	Intensive Care Module Triggers		
I1	Pneumonia onset		
I2	Readmission to intensive care		
I3	In-unit procedure		
I4	Intubation/reintubation		
	Perinatal Module Triggers		
P1	Terbutaline use		
P2	3rd- or 4th-degree lacerations		
P3	Platelet count less than 50,000		
P4	Estimated blood loss > 500 ml (vaginal) or > 1,000 ml (C-section)		
P5	Specialty consult		
P6	Oxytocic agents		
P7	Instrumented delivery		
P8	General anesthesia		
	Emergency Department Module Triggers		
E1	Readmission to ED within 48 hours		
E2	Time in ED greater than 6 hours		

Not utilized for this study

Not utilized for this study

Figure C.1 – The Global Trigger Tool worksheet and the list of triggers used in this study.

Appendix D – Categories and types of adverse events

Table D.1 – Incidence and types of adverse events found under the category "infection".

Adverse event category	% of all adverse events
Infection	18.9%

Type of infection	Incidence (%)
Bacteremia (line or catheter associated)	13.2
Catheter associated UTI	62.3
Cellulitis or local catheter site infection	3.8
Clostridium Difficile	2.8
Health-care associated pneumonia	14.2
Ventilator associated pneumonia	1.9
Procedure site infection	0.9
Other	0.9

Table D.2 – Incidence and types of adverse events found under the category "medication".

Adverse event category	% of all adverse events
Medication	**43.9%**

Type of medication	Incidence(%)
Fall	8.3
Decubiti	1.4
Device failure or malfunction	36.6
Pulmonary embolus	1.4
Plan of care	0.7
Readmission Premature discharge (25.5%) Medication change (48.4%) Other (26.1%)	33.1
Respiratory failure	5.5
Triage	4.8
Other	8.2

Table D.3 – Incidence and types of adverse events found under the category "patient care".

Adverse event category	% of all adverse events
Patient Care	**26.3%**

Type of patient care event	Incidence(%)
Acute kidney injury	22.1
Arrhythmia	1.6
Allergy	8.0
Rash (95%) Anaphylaxis (5%)	
Bradycardia	3.2
Coagulopathy	15.7
Epistaxis (7.7%) GI bleed (33.3%) Hematoma (non procedural) (18.0%) Hematuria (18.0%) Hemoptysis (10.3%) Intracranial hemorrhage (12.7%)	
Digoxin toxicity	1.2
Hypoglycemia	8.0
Hypotension	20.1
Medication error	2.0
Wrong dose (60%) Wrong patient (20%) Wrong medication (20%)	
Mental status changes	8.4
Delirium/hallucinations (68.2%) Lethargy or somnolence (31.2%)	
Respiratory Failure	4.8
Electrolyte abnormalities	0.4
Other	4.5

Table D.4 – Incidence and types of adverse events found under the category "procedure".

Adverse event category	% of all adverse events
Procedure	**10.9%**

Type of procedure	Incidence (%)
Bleeding at puncture site	11.3
Hematoma	38.7
Pseudoaneurysm	4.8
Wrong site	1.6
Pneumothorax	4.8
Other	38.8