2017-04-12

# Recent Trends in Sepsis Mortality, Associations between Initial Source of Sepsis and Hospital Mortality, and Predictors of Sepsis Readmission in Sepsis Survivors

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# RECENT TRENDS IN SEPSIS MORTALITY, ASSOCIATIONS BETWEEN INITIAL SOURCE OF SEPSIS AND HOSPITAL MORTALITY, AND PREDICTORS OF SEPSIS READMISSION IN SEPSIS SURVIVORS

A Dissertation Presented

by

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Submitted to the Faculty of the
University of Massachusetts Graduate School of Biomedical Sciences, Worcester
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

APRIL 12, 2017

CLINICAL AND POPULATION HEALTH RESEARCH

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Clinical and Population Health Research
April 12, 2017

## DEDICATION

This dissertation is dedicated to my friends, family, and those friends who might as well be family

## ACKNOWLEDGEMENTS

This work could not have been completed without the support and guidance of many people, to whom I would like to express my gratitude.

To my thesis mentor, Roger Luckmann, MD, MPH, for his unwavering support of me throughout the process. I am also indebted to my dissertation committee of Gyorgy Frendl, MD, PhD; Kate Lapane, PhD; Craig Lilly, MD; and Sharina Person, PhD. I am additionally indebted to Stavroula Chrysanthopoulou, PhD; and Stephen Heard, MD, both members of my thesis research and advisory committee. The combined academic, epidemiologic, and clinical knowledge of this group is truly breathtaking and it is only through their support and patience that I have reached this point in my academic journey.

An additional special thanks goes to the eICU team. In particular, Teresa Rincon RN, Linda Doherty and Gurudev Lotun for their ongoing administrative support and contagious energy.

This dissertation could not have been completed without the support of the University HealthSystem Consortium, and in particular Samuel Hohmann, PhD or without the support of Amy Pakyz, PharmD and Jon DeShazo, PhD and their tremendous aid in understanding the Cerner HealthFacts® database. Further thanks go to the hundreds of unnamed and unrecognized people who help to make sure resources like the UHC and HealthFacts datasets continue to exist – I shudder to think of the state of research and healthcare if resources such as these were no longer available.

I have also benefitted tremendously from the support of the faculty, staff, and students of the Clinical and Population Health Research Program/Department of

Quantitative Health Sciences. In particular, I am grateful to Christine Ulbricht, PhD and Jacob Hunnicutt, soon to be PhD, for their willingness to read the entirety of this dissertation and their readiness to listen to me vent.

I am also grateful for my learning communities support, especially Sarah McGee MD, Michael Ennis MD, Phillip Fournier MD, and David Hatem MD. They have formed the backbone of the learning communities and the mentorship will be paid forward.

I am tremendously indebted to Phillip Fournier, MD; John Haran, MD; and Vincent Kan, MD for their generosity in letting me peek into their clinical worlds. The lessons I have learned defy summary in words, and the patience and experiences that they offered me opportunity to partake in will not be forgotten.

Last but definitely not least, I am beyond grateful to my friends and family. In particular, Allen Evans, whose admonishment that “It is a mistake to think you’re not good enough” has stayed with me. To my Olympia Fencing Center and Richmond Fencing Club families -- thank you for taking me in. Without you all to share my joys and my tears, I would not be here. To my harem, whose dauntless support and laser-sharp wits I would never want to be on the outside of. To Michael Williams, thank you for challenging me to be better, yet being there for me unconditionally.

## ABSTRACT

**Background**: Sepsis, a leading cause of US deaths, is associated with high mortality, although advances in early recognition and treatment have increased survivorship. Many aspects of sepsis pathophysiology and epidemiology have not been fully elucidated; the heterogeneous nature of infections that lead to sepsis has made fully characterizing the underlying epidemiology challenging.

**Methods**: The University HealthSystem Consortium (UHC) from 2011-2014 and the Cerner HealthFacts® database from 2008-2014 were used. We examined associations between infection source and in-hospital mortality in the UHC dataset, stratified by age and presenting sepsis stage. We examined recent temporal trends in present-on-admission (POA) sepsis diagnoses and mortality and predictors of 30-day sepsis readmissions following sepsis hospitalizations using the HealthFacts® dataset.

**Results**: Patients with sepsis due to genitourinary or skin, soft tissue, or bone sources had lower mortality than patients with sepsis due to respiratory sources regardless of age or presenting sepsis stage. Overall diagnoses of sepsis increased from 2008-2014; however, POA diagnoses and case fatality rates decreased. Factors that predicted re-hospitalization for sepsis included discharge to hospice, admission from or discharge to a skilled nursing facility, and abdominal infection.

**Conclusion**: Further investigation will reveal more detail to explain the impact of infection source on in-hospital sepsis mortality for all age groups and sepsis stages. Decreasing mortality rates for all POA sepsis stages and all age groups suggest current approaches to sepsis management are having broad impact. Sepsis survivors are at

significant risk for re-hospitalization; further studies are needed to understand the post discharge risks and needs of survivors.

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## LIST OF ABBREVIATIONS

AHR – Adjusted Hazard Rate Ratio

AOR – Adjusted Odds Ratio

APACHE – Acute Physiology and Chronic Health Evaluation

CI –Confidence Interval

CMS – Centers for Medicare and Medicaid Services

CNS – Central Nervous System

ED – Emergency Department

EHR – Electronic Health Record

GI - Gastrointestinal

GU – Genitourinary

HIPAA – Health Insurance Portability and Accountability Act

HR – Crude Hazard Rate Ratio

ICD-9CM – International Classification of Diseases, 9$^{th}$ Revision, Clinical Modification

ICU – Intensive Care Unit

OR – Odds Ratio

POA – Present-on-admission

qSOFA – Quick Sequential/Sepsis-related Organ Failure Assessment

SIRS – Systemic Inflammatory Response Syndrome

SNF – Skilled Nursing Facility

SOFA – Sequential/Sepsis-related Organ Failure Assessment

SSTB – Skin, Soft Tissue, and Bone

UHC – University HealthSystem Consortium

UHC CDBRM - University Healthsystem Consortium Clinical Database/Resource Manager

US – United States

## PREFACE

Chapter II of this dissertation is under preparation as:

Motzkus CA, Lilly CM, Chrysanthopoulou SA, Hohmann S, Heard SO, Lapane KL Luckmann RL. Mortality Rates Differ among Patients with Sepsis Present on Admission by Infection Source

Chapter III of this dissertation is under preparation as:

Motzkus CA, Lilly CM, Chrysanthopoulou SA, Pakyz AL, Heard SO, Lapane KL Luckmann RL. Recent Trends is Sepsis Diagnosis and Mortality

Chapter IV of this dissertation is under preparation as:

Motzkus CA, Lilly CM, Chrysanthopoulou SA, Pakyz AL, Heard SO, Lapane KL Luckmann RL. Predictors of Subsequent Sepsis Readmission after a Sepsis Hospitalization

# CHAPTER I

# INTRODUCTION

## Sepsis

Sepsis is a pathophysiologic over-response and resulting immune dysregulation to an infection. The 2014 guidelines typically subdivide sepsis into three stages of increasing clinical severity: sepsis, severe sepsis, and septic shock. Over a million Americans are affected each year, and estimates of deaths due to sepsis range from 10-60% of those affected.[1] Sepsis is the leading cause of death in hospitals; however, recent polls indicate that only half of adults know what sepsis is.[2] Among patients receiving care in the intensive care unit (ICU), sepsis is the leading non-cardiac cause of death.[3–5] In addition to the significant impact on human life, sepsis costs the US healthcare system an estimated 14.6 billion dollars in 2008, making it one of the most expensive diseases to treat.[6]

Consensus clinical definitions for sepsis, severe sepsis, and septic shock have been updated repeatedly to define more relevant clinical groups.[7–9] According to the 2003 consensus definition, sepsis is the presence of an infection along with 2 or more of these physiological markers of the systemic inflammatory response syndrome (SIRS): Temperature >38.3 degrees Celsius or <36 degrees Celsius, heart rate >90 beats per minute, respiratory rate >20 breaths per minute, white blood cell count >12,000 $microL^{-1}$ or <4,000 $microL^{-1}$ or greater than 10% immature white blood cell forms (bandemia). Severe sepsis is defined as the presence of sepsis with sepsis-induced tissue or organ dysfunction. Septic shock is defined as fluid-unresponsive sepsis-induced hypotension, and is a form of distributive shock often associated with elevated serum lactate >4 mg/dl, a marker of tissue hypoperfusion.[8] The 2016 update of the clinical definition of sepsis,

and its reliance on the Sequential/Sepsis-related Organ Failure Assessment Score (SOFA) in the ICU and quick SOFA (qSOFA)in other hospital and pre-hospital settings[10,11], are subject to ongoing debate in the emergency and critical care medicine communities as to the new definition's validity and usefulness.[12,13] In this new paradigm, severe sepsis has been rebranded as sepsis and the SIRS criteria have been discarded. Although the ICD-9CM and ICD-10 code definitions have not yet been changed to reflect the new criteria, these shifts in definition will likely complicate research using data collected after the release of the new definitions. The new sepsis definitions, when applied to study populations will engender a group of research findings that are not comparable to prior studies. These changes may create difficulties placing study findings in context and better understanding how to identify, treat, and plan for long-term care of patients facing sepsis in the hospital and living with its aftermath. Research conducted with data collected prior to the 2016 changes widely uses the standard definitions of sepsis from the 2003 consensus definitions.

Controversy surrounding sepsis is not limited to how this disease should be defined. Treatment of patients with sepsis, and in particular the multi-step standardized protocols of care for patients with sepsis has undergone many trials and failed attempts at identifying gold standards of treatment.[14–17] While early empiric antibiotics and fluid resuscitation with circulatory support have emerged as the mainstays of treatment, recent meta-analyses have put the specific recommendations of a popular protocol (Early Goal-Directed Therapy) into doubt in favor of less stringent protocols relying on clinician gestalt.[18,19] The list of failed adjunctive therapies for sepsis is too long to enumerate in

this dissertation.[20] Regardless of specific therapies used, the importance of prompt intervention is difficult to overstate as mortality has been reported to increase 8% for every hour delay of initial treatment inviting comparisons to the concept of a "golden hour" for treatment as has been widely accepted by those providing trauma care.[21,22]

Infections of many different types can lead to sepsis. Clinical comorbidities and other patient characteristics that create susceptibility to infection often lead to an increased chance of progression to sepsis as well. In particular, the very young, very old, asplenic, burn, and immunosuppressed (whether through iatrogenic or natural means) patients are at particularly high risk of developing infections and subsequent sepsis, although sepsis can affect any patient, even those in prior good health.[23] Though the underlying infection leading to sepsis cannot always be identified, the most common source of sepsis is a respiratory infection, usually pneumonia, followed by genitourinary sources, with other common sources of sepsis including intra-abdominal infection, skin, soft tissue, or bone infection, and central nervous system infections also contributing to the population of patients with sepsis.[24] Sepsis can be conceptualized as the interaction of pathogen factors, e.g. virulence characteristics of the causative microbe, and host factors, i.e. race, sex, and comorbidity status. Features of individual organ systems, such as the relative anatomic protection of the genitourinary system and the tendency of antibiotics to concentrate in the genitourinary system, may also differentially impact the body's response to infectious insults.[25]

Infection source may have an important link to mortality through several mechanisms: 1) direct infection-caused organ damage at the site and related organ

dysfunction (ex. Pneumonia-related hypoxemia), which could in turn be affected by preexisting disease and/or reduced organ reserve related to aging, 2) virulence of the pathogens more frequently isolated from that site (ex. Antibiotic-resistant pathogens),[26] 3) capacity of the organ or anatomic space (ex. abdominal cavity) to contain infection, and 4) the capacity of the patient with or without treatment to adapt to the organ failure (ex. Immunosuppression), which in turn is related to the role of the organ in supporting life. It is also possible that anatomic sources differ in their susceptibility to sepsis induced damage related to the release of products of the disordered immune response or the sepsis stage at which infection is typically recognized at the affected source organ,[27–30] or be related to organ dysfunction or immune impairment which predisposed to the infection.[31,32] Nevertheless, the current literature is mixed on whether infection source is associated with mortality. Some reports confirm an association while others do not, suggesting that infection source may not drive mortality once the pathophysiologic disarray of sepsis has taken hold.[33]

With the aging of the US population, the need to understand the unique disease patterns and manifestations of illness in the elderly is becoming ever more pressing. Older adults may not display the classic symptoms and signs of infections such as fever and increased white blood cell count, delaying the recognition and subsequent treatment in this group of patients.[34] Further, older adults have higher comorbidity burdens and less physiologic reserve than younger patients, making them more susceptible to poor outcomes from critical illness.[35,36] Additionally, even if older adults survive their initial hospitalization, they are at increased risk of readmission and long-term poor outcomes

regardless of the initial cause of hospitalization.[37] Given these concerns, it is especially important to understand the epidemiology of sepsis among older adults so that diagnosis and treatment can be appropriately tailored and for better prediction of long-term functional outcomes.

Sepsis research is taking place in many settings and many forms ranging from basic laboratory studies to quality improvement projects to large scale clinical trials. Administrative data provides many benefits that contribute to its utility for understanding the epidemiology of sepsis. Administrative datasets are typically large, allowing for a bird's eye view of a patient's interaction with the healthcare system, and depending on the exact data elements included, can provide insight into identification, treatment, and management of patients with sepsis. Given that different administrative datasets collect information about different groups of people, conduct of multiple observational studies is beneficial for replication of findings and understanding the nature of associations that may change based on the population studied.[38,39]

One distinction made to understand sepsis is the distinction between healthcare facility acquired sepsis and community acquired sepsis. Patients developing healthcare associated infections and subsequent sepsis are more likely to experience negative outcomes owing in part to the more virulent nature of nosocomial pathogens and the already weakened host due to the hospital stay.[40,41] Community-acquired sepsis can be approximated using the present-on-admission (POA) flag in administrative datasets which was widely implemented following the requirement for its mandate by the Centers for Medicare and Medicaid Services (CMS) on October 1, 2008.[42,43] POA sepsis cases

represent a distinct challenge to the healthcare system because they require acute healthcare providers in pre-hospital, emergency, and other care delivery settings to rapidly identify patients with sepsis and to initiate treatment. The CDC has also instituted a campaign encouraging patients to self-advocate if they suspect sepsis. These POA sepsis cases represent multiple opportunities for early intervention to reduce poor outcomes. Elucidating the epidemiology of POA sepsis may contribute to improvements in sepsis recognition, management, and treatment in the emergency department and during the initial hours following hospital admission regardless of care setting.

## Specific Aims

This dissertation explores underlying epidemiologic patterns related to sepsis mortality and readmissions. This work was undertaken to: 1) clarify risk factors for in-hospital mortality from sepsis with regards to the initial infection source, 2) understand broader temporal trends of diagnosis and sepsis fatalities, and 3) understand the nature of patients hospitalized with sepsis more than once in a 30-day period.

***Aim 1***. *Examine relative rates of sepsis mortality for hospitalized patients by initial infection source*:

- Examine differences in relative mortality from sepsis by initial infection source
- Evaluate differences in relative mortality from sepsis by infection source stratified by age subgroups
- Evaluate differences in relative mortality from sepsis by infection source stratified by presenting stage of sepsis

*Hypothesis: Patients presenting with sepsis due to genitourinary sources will have lower mortality rates than patients presenting with respiratory sources of infection.*

***Aim 2***. *Measure trends in overall and stage-specific in-hospital mortality rates from sepsis over time*:

- Characterize patterns and rates of diagnosis of sepsis
- Examine trends of case fatality rates from sepsis stratified by age subgroups

- Examine trends of case fatality rates from sepsis stratified by presenting stage of sepsis

***Hypothesis****: Case fatality rates will decrease over time while diagnosis rates increase.*

*Aim 3. Evaluate predictors of subsequent re-hospitalization for sepsis within 30 days of discharge for an intial hospitalization for sepsis*:

- Characterize patients who are re-hospitalized with sepsis within 30 days of an initial discharge from a hospitalization for sepsis
- Characterize associations between features of the index hospitalization and the risk for readmission with sepsis

***Hypothesis****: Patients with increased comorbidity burden will have a higher risk of readmission with sepsis.*

## Data Sources

Aim 1 involved analysis of data from the University HealthSystem Consortium (UHC). The UHC is an alliance of academic medical centers in the US dedicated to improving quality of care and cost effectiveness, originally formed in 1991.[44] As of 2015, UHC was acquired by Vizient, although UHC has maintained their own name and network.[45] Nearly all of the academic medical centers in the US participate in the UHC and data collected includes information from hospitalizations, patient demographics, pharmacy records, diagnoses, and procedures. Previous research has validated that UHC

achieves high-levels of concordance with patient level individual data from electronic medical records.[46]

Cerner HealthFacts® is a database maintained by the Cerner Corporation (Kansas City, MO) with the stated goal of "transforming healthcare by eliminating error, variance and waste for healthcare providers and consumers around the world."[47] More than 84 million patient encounters, 151 million pharmacy orders, and 1.3 billion lab results are included in the nearly decade long maintenance of the HealthFacts® database; the validity of the HealthFacts database is comparable to other national databases and is considered generalizable to the healthcare seeking population of the US.[47,48]

**Significance**

The work undertaken in this dissertation has significance for clinical providers, health services researchers, and policy makers. Understanding the role infection source plays with mortality from sepsis could lead to opportunities to refine treatment protocols for patients presenting with sepsis by the initial insulting infection source. Further, understanding the role of initial insulting infection source may allow for risk adjustment tools, such as the commonly used APACHE acuity score, to be calibrated more accurately when taking these findings into account.[49] Description of the temporal trends of POA sepsis diagnoses and case fatality rates, especially when viewed in the larger context of all sepsis diagnoses and mortality, has important implications for understanding the nature of CMS-mandated coding changes and their implementation and their impact on care. Ongoing study of temporal trends of mortality from sepsis allows clinicians and policymakers the opportunity to perpend the aspects of treatment protocols

and recognition programs that may be having the greatest impact on care for patients with sepsis. With ongoing scrutiny of costs of care, and the identification of any readmission and sepsis itself as a driver of cost, the potential to profoundly influence cost at the overlap of sepsis hospitalizations and readmissions is high. With reimbursement penalties on the horizon, understanding predictors of readmission is important to hospital systems and allow them to appropriately target post-discharge services to those patients at highest risk of readmission. Supporting patients with post-discharge care also provides benefit to individual patients as additional support after an unanticipated hospitalization may help mitigate some of the long term effects of sepsis that lead to poorer quality of life. Overall, this dissertation aims to make a significant contribution to understanding the underlying epidemiology of sepsis.

# CHAPTER II

# MORTALITY RATES DIFFER AMONG PATIENTS WITH SEPSIS PRESENT ON ADMISSION BY INFECTION SOURCE

## Abstract

**Objective**: The relevance and impact of the initial infection source leading to sepsis has been disputed in the literature. This study aims to clarify the role initial infection source may have as related to in-hospital mortality for patients with sepsis.

**Methods**: We conducted a retrospective cohort study using the University Healthsystem Consortium data from 2011-2014. We identified patients with present-on-admission sepsis diagnoses using ICD9-CM codes 038, 785.52, 995.1, 995.2 in any position. Patients were identified to have respiratory, abdominal, genitourinary, skin, soft tissue, or bone infections, or central nervous system infections present at the time of their admission to the hospital using ICD9-CM data. Cox proportional hazards models were used to estimate hazard rate ratios between infection source and hospital mortality with patients with respiratory infections serving as the referent group. Adjusted hazard rate ratios were calculated adjusted for age, sex, Charlson-Deyo comorbidity index, emergency department admission, and presenting stage of sepsis. Hazard rate ratios were also calculated for stratified analyses by age group and presenting stage of sepsis.

**Results**: We identified 100,446 patients with sepsis with overall mortality of 18.0%. Patients with an initial source of sepsis due to a genitourinary infection experienced hospital mortality at a rate 48% lower than patients with sepsis due to a respiratory infection (95% CI 0.50-0.55) after adjustment for age, sex, Charlson-Deyo comorbidity index, emergency admission, and presenting stage of sepsis. Patients with sepsis from an initial source of sepsis due to a skin, soft tissue, or bone infection experienced hospital mortality at a rate 47% lower than patients with sepsis due to a respiratory infection after

adjustment for age, sex, Charlson-Deyo comorbidity index, emergency admission, and presenting stage of sepsis. These relationships persisted in the stratified analyses by age and presenting stage of sepsis.

**Conclusion**: This study found a consistent association between genitourinary and skin, soft tissue, or bone infections and lesser rates of mortality among patients presenting with sepsis. This study adds evidence to the role initial infection source plays in outcomes from sepsis after controlling for other important risk factors for mortality from sepsis.

## Introduction

Sepsis, the immune system's dysregulated response to an infection, continues to have high mortality rates despite ongoing campaigns promoting recognition and treatment protocols, and places a high cost burden on the healthcare system.[3,50,51] Infections leading to sepsis may start in different organ systems including the lungs, genitourinary system, abdomen, or skin and soft tissues. Sepsis mortality may be affected by initial source of infection; however, this hypothesis is disputed as others believe that the systemic immune response to sepsis leads to mortality independent of the infection source.[52,53] A recent systematic review was unable to form conclusive statements on the role of infection source in sepsis mortality due to persistent issues with misclassification of infection source, disease heterogeneity, and detailed reporting.[33]

Older patients are disproportionately affected by incidence of sepsis and mortality from sepsis.[34] Research studying older adults' immune response to sepsis has revealed differences when compared to younger patients in both human and animal research.[54,55] Older adults may have more susceptibility to infection, and may be less likely to have their infections recognized promptly as older patients often do not mount stereotypical responses to infection such as fever.[56] Comorbidities more common among the elderly, such as chronic obstructive pulmonary disease and chronic kidney disease, likely contribute to both infection susceptibility and sepsis susceptibility, and acute management of sepsis may be complicated by these underlying medical conditions.[57]

The objective of this study is to evaluate the role of infection source in mortality from sepsis. We hypothesized that mortality differences by infection source would be less apparent as patient age increased. We also hypothesized that mortality differences by infection source would be minimal among patients presenting with higher acuity sepsis disease, e.g. septic shock, at the time of their admission. This study is important as increasing pressure is placed on hospitals to evaluate care for patients with sepsis, and understanding differences in rates of mortality of sepsis stemming from variable infection sources may generate hypotheses for future work developing risk profiles for patients with sepsis.

## Methods

### *Study Design and Setting*

We conducted a retrospective cohort study using data extracted from the University Healthsystem Consortium Clinical Database/Resource Manager (UHC CDBRM) from the first quarter of 2011 through the final quarter of 2014. The UHC CDBRM was established in 1984 and is composed of 114 academic medical centers and 320 affiliated hospitals representing 95% of the academic medical centers in the United States and has been validated in prior studies of patients with infectious diseases and sepsis.[58–60]

### *Eligibility Criteria*

To be considered for the study, patients must have had a hospital stay during the study period, be aged 18 years or older at admission, with a diagnosis of sepsis, severe sepsis or septic shock at the time of the hospital admission. Diagnoses of sepsis and

septic shock were determined using ICD-9CM codes (038, 785.52, 995.1, 995.2) in any position. Timing of diagnosis of cases was determined using UHC's present-on-admission (POA) indicator, which has been validated in other infectious diseases.[61] Patients with sepsis, severe sepsis, or septic shock who had multiple infection codes indicated as POA or no infection code fitting one of the predetermined infection categories were excluded from the final analytic sample. Patients with lengths of stay longer than 30 days were excluded from the final analytic sample as these patients likely experienced events during their hospital course that resulted in poorer outcomes disproportionate to most of the patients included in the UHC database.

***Exposure: Infection Classification***

The conceptual exposure of this study was the initial infection source that led to the development of sepsis. ICD-9CM codes (Supplementary Table 2.1) noted as POA were used to classfy patients into one of five groups: Respiratory, Abdominal, Genitourinary (GU), Skin, soft tissue, and bone (SSTB), and Central nervous system (CNS). Respiratory infections were considered the referent group consistent with prior literature[53] as these infections generally make up the preponderance of infections that progress to sepsis, severe sepsis, or septic shock.

***Outcome: Time to Hospital Mortality***

The primary outcome measure was time to in-hospital mortality. Mortality was determined by the use of the patient's discharge status as recorded in the UHC CDBRM, and time to hospital mortality was calculated as time of admission with POA sepsis subtracted from time of hospital discharge.

### *Potential Confounders*

Comorbidities, age, sex, emergency admission status, year and quarter of hospital admission, and presenting stage of sepsis were considered as possible confounders. Race and ethnicity designations at the time of hospital admission are known to be underestimated and subject to considerable misclassification, therefore we did not categorize patients into race or ethnicity categories for this study. Hospital, ICU length of stay, and organ dysfunction were reported but not considered as possible confounders given that these variables may be part of the causal pathway between initial infection source and hospital mortality. Comorbidities were considered using the Charlson-Deyo comorbidity index using ICD-9CM codes from the admission for sepsis.[62,63] Age for initial modeling was categorized as 18-54, 55-64, 65-74, 75-84, and 85+ years; the final three age categories are consistent with US census categories for the young old, middle old, and oldest old. Known differences in outcomes from sepsis according to a patient's sex have been previously observed, with women experiencing disproportionate mortality.[64,65] Patients with sepsis who are admitted through the emergency department have been shown to have improved outcomes compared to those patients directly admitted to hospital wards.[66,67] Diagnosis patterns and outcomes for patients with sepsis have changed over time.[68–71] As such, year and quarter of hospital admission were considered as potential confounders to account for temporal trends. Presenting stage of sepsis was considered as a surrogate for illness severity. If multiple codes for POA sepsis, severe sepsis, or septic shock existed, patients were categorized according to the highest acuity diagnosis present.

### *Statistical Analyses*

We summarized patient characteristics by source of infection. Proportions were reported for categorical variables, and data were summarized by means and standard deviations, or medians and interquartile ranges for normally and non-normally distributed continuous variables respectively. Cox proportional hazards models estimated hazard rate ratios between infection source and time to in-hospital mortality, adjusted for age, sex, Charlson-Deyo comorbidity index, emergency department admission, and presenting stage of sepsis. Other covariates were tested for inclusion using a 10% change of estimate threshold and evaluated for collinearity by inspection of standard errors and subsequently ruled out. Robust sandwich covariance matrix estimates were used to account for clustering by hospital. We reported crude hazard rate ratios (HR), adjusted hazard rate ratios (AHR), and 95% confidence intervals (CI).

### *Stratified Analyses*

We hypothesized that older patients may have unique responses to specific infection sources leading to sepsis. We therefore conducted an additional set of stratified analyses dividing the population into the young and middle aged (18-64 years old), the young old (65 years-74 years), the middle old (75 years – 84 years), and the oldest old (85 years+). Cox proportional hazards models estimated hazard rate ratios within these subgroups. Within each strata, patients with respiratory infections remained the referent group consistent with the primary analysis.

Others have hypothesized that the initial source of infection does not affect outcomes once the physiologic disarray from septic shock has taken effect. Therefore, we pre-specified stratified analyses by presenting stage of sepsis to evaluate whether there were differences in outcomes among patients who presented with different initial infections at any level of acuity.

Finally, we conducted an analysis limiting follow-up time to 48 hours. The purpse of this analysis was to: 1) clarify associations among a subgroup of patients whose death was almost certainly due to their disease present at the time of admission, 2) determine if associations were similar among patients experiencing mortality early, and 3) understand if there is a group of patients with such severe disease at the time of presentation that no intervention was likely to change the disease progression.

### *Ethical Considerations*

This research was approved by the University of Massachusetts Institutional Review Board; the informed consent requirement was waived.

## Results

From 2011-2014, there were 330,304 adult inpatient encounters in the UHC database with a diagnosis of sepsis, severe sepsis, or septic shock. Of these encounters, 237,045 had a sepsis diagnosis present on admission to the hospital, representing 189,636 unique patients. We excluded 15,414 patients with lengths of stay greater than 30 days. We excluded 73,776 patients with multiple infections present-on-admission or with sepsis diagnoses without a POA infection recorded or an infection not fitting into one of

the five exposure categories resulting in an analytic sample of 100,446 patients. (Figure 2.1)

Among all patients with sepsis included in this study, 34.0% were identified as having a respiratory infection, 16.9% were identified as having an abdominal infection, 36.4% were identified as having a GU infection, 11.9% as having a SSTB infection, and 0.9% were identified as having a CNS infection. Patients presenting with respiratory or GU infections were more often older than age 85 than in cases of other infections. The majority of patients presenting with CNS infections were younger than patients presenting with other types of infections, with most (68%) being under age 65. Women generally accounted for less than half of the patients presenting with any infection, with the exception of GU infections. Patients presenting with a CNS infection had longer ICU lengths of stay than patients presenting with other infections; however their median hospital length of stay was not generally different from patients presenting with other infections. (Table 2.1)

Overall hospital mortality in this study was 16.1%. Compared to patients with respiratory infections, our referent group, patients with GU or SSTB infections had approximately half the risk of death while in the hospital after adjustment for age, sex, ED admission, Charlson-Deyo comorbidity status, and presenting stage of sepsis. (GU: AHR: 0.52 95%CI 0.50-0.55 $p<0.0001$; SSTB: AHR: 0.53 95%CI: 0.49-0.57 $p<0.0001$) Patients with abdominal or CNS infections had approximately the same rate of death compared to patients with respiratory infections after adjustment for age, sex, ED

admission, Charlson-Deyo comorbidity status, and presenting stage of sepsis (Abdominal: AHR: 0.99 95%CI 0.95-1.03 p=0.4751; CNS: AHR: 1.10 95%CI 0.94-1.27 p=0.2388). (Figure 2.2,Table 2.2)

***Results Stratified by Age Group***

When stratified by age group, most characteristics were evenly distributed. Almost 90% of the oldest old were admitted through the emergency department. Regardless of age group, patients had a moderate level of comorbidity burden. Length of stay was generally similar amongst age groups, although both ICU and hospital length of stay were somewhat shorter among the oldest old patients, possibly due to early death among this age group. (Supplementary Table 2.2)

An increase in mortality was observed among age subgroups with 14.3% observed mortality in the young and middle aged, 17.3% mortality in the young old, 17.8% mortality in the middle old, and 25.7% mortality in the oldest old. (Figure 2.2) Among the group of patients under age 65, patients who initially presented to the hospital with a GU or SSTB infection had lower rates of mortality compared to patients who initially presented to the hospital with a respiratory infection. (GU: AHR: 0.49 95%CI 0.45-0.53 p<0.0001; SSTB: AHR: 0.48 95%CI: 0.44-0.52 p<0.0001) Among the group of patients under age 65, those presenting with CNS infections had higher rates of mortality relative to patients under 65 initially presenting with a CNS infection (AHR: 1.29 95%CI 1.07-1.55 p=0.0072). Patients under age 65 who presented with an abdominal infection had comparable rates of mortality compared to patients who presented with a respiratory

infection. (AHR: 1.01 95%CI 0.95-1.07 p=0.7064) (Figure 2.5A, Supplementary Table 2.3) Among patients 65-74, those presenting with GU or SSTB infections continued to have lower rates of mortality compared to those patients age 65-74 presenting with respiratory infections. (GU: AHR: 0.51 95%CI 0.47-0.55 p<0.0001; SSTB: AHR:0.53 95%CI: 0.47-0.59 p<0.0001) Among those aged 65-74, patients presenting with abdominal infections also had lower rates of mortality compared to patients aged 65-74 presenting with respiratory infections (AHR: 0.81 95%CI 0.73-0.89 p<0.0001). For patients aged 65-74, those presenting with CNS infections did not have notably different rates of mortality compared to those presenting with respiratory infections. (AHR: 0.85, 95%CI 0.61-1.19 p=0.3426) (Figure 2.5B, Supplementary Table 2.4) For patients aged 75-84, these overall relationships of lower mortality rates for those presenting with GU, SSTB, and abdominal infections compared to those presenting with respiratory infections remained consistent. For patients aged 75-84, those presenting with CNS infections did not have mortality rates differing from those presenting with respiratory infections. (AHR: 0.87 95% CI 0.60-1.26 p=0.4602) (Figure 2.5C, Supplementary Table 2.5) Among the oldest old, those presenting with GU, SSTB, or abdominal infections had lower rates of mortality compared to those presenting with respiratory infections, although this relationship was less pronounced among this age group for those presenting with SSTB infections. (AHR: 0.74, 95%CI 0.62-0.87, p=0.0004) (Figure 2.5D, Supplementary Table 2.6)

***Results Stratified by Presenting Stage of Sepsis***

An expected increase in mortality was observed as the severity of the presenting stage of sepsis increased, with 5.3% mortality in those presenting with sepsis, 12.8% mortality in those presenting with severe sepsis, and 26.3% mortality among those presenting with septic shock. (Figure 2.3) For those patients presenting with sepsis and a GU or SSTB infection, lower rates of mortality were observed compared to those presenting with sepsis and a respiratory infection. (GU: AHR: 0.41 95%CI 0.36-0.45 p<0.0001; SSTB: AHR: 0.30 95% CI: 0.25-0.36 p<0.0001) Among those patients presenting with sepsis and an abdominal infection, there were also relatively lower rates of mortality compared to those presenting with sepsis and a respiratory infection. (AHR: 0.80 95% CI 0.70-0.91 p=0.0007) For those patients presenting with sepsis and a CNS infection, rates of mortality were not significantly different than for those patients presenting with sepsis and a respiratory infection. (AHR: 1.26 95%CI 0.89-1.79 p=0.1932) (Figure 2.6A, Supplementary Table 2.7) Among patients presenting with severe sepsis and a GU or SSTB infection, rates of mortality continued to be lower than for those patients presenting with severe sepsis and a respiratory infection. (GU: AHR: 0.48 95% CI 0.44-0.53 p<0.0001; SSTB: AHR: 0.41 95% CI: 0.35-0.47 p<0.0001) For those patients presenting with severe sepsis and a CNS infection, there were also lower rates of mortality compared to those patients presenting with severe sepsis and a respiratory infection (AHR: 0.74 95% CI 0.54-1.00, p=0.0493); however, this estimate is less stable as relatively few patients present with severe sepsis and a CNS infection. Among those patients presenting with severe sepsis and an abdominal infection, there were not statistically significant differences in time to mortality compared to those

patients presenting with severe sepsis and a respiratory infection. (AHR: 1.03 95% CI 0.93-1.15 p=0.5414) (Figure 2.6B, Supplementary Table 2.8) Among patients presenting with septic shock, those with either a GU or SSTB infection had lower rates of mortality than those presenting with septic shock and a respiratory infection (GU: AHR: 0.57 95% CI 0.54-0.61 p<0.0001; SSTB: AHR: 0.63 95% CI 0.58-0.68 p<0.0001) Among patients presenting with septic shock and an abdominal or CNS infection, there were not statistically significant differences in rates of mortality when compared to those presenting with septic shock and a respiratory infection. (Abdominal: AHR: 1.00 95% CI 0.96-1.05 p=0.9554; CNS: AHR: 1.18 95%CI 0.98-1.42 p=0.790) (Figure 2.6C, Supplementary Table 2.9)

### *Outcomes Limited to 48 Hours*

Overall hospital mortality at 48 hours was 5.3%. When limited to 48 hours of follow-up time, patients presenting with SSTB infections had lower rates of 48-hour mortality compared to patients presenting with respiratory infections (AHR: 0.61 95%CI 0.54-0.68 p<0.0001). Notably, patients presenting with CNS infections had a higher rate of mortality compared to patients presenting with respiratory infections when limited to 48 hours of follow-up time (AHR: 1.28 95% CI 1.00-1.65 p=0.0506). (Table 2.3)

## Discussion

This study found an association between the initial presenting source of infection and rates of in-hospital mortality from sepsis. Initial presentation of patients with sepsis due to a GU or SSTB infection was associated with a lower rate of in-hospital mortality

when compared to patients initially presenting with sepsis due to respiratory infections among hospitalized patients, and within subgroups of hospitalized patients. For patients presenting with sepsis due to an abdominal infection, there were not appreciable differences in the rate of in-hospital mortality across all hospitalized patients included in the study when compared to those patients presenting with sepsis due to a respiratory infection.

This study found greater mortality among patients presenting with more severe forms of sepsis spectrum disease, regardless of the presenting type of infection. There was also greater mortality with increased age regardless of the presenting type of infection, consistent with existing literature that older patients have a lessened ability to withstand the physiologic onslaught of infection and immune disarray from sepsis.[34] However, while observed mortality was greater with both advancing age and severity of presenting illness, there remained a strong, consistent association of presentation with GU or SSTB infection and rates of in-hospital mortality when compared to patients presenting with respiratory infection consistently observed within age and presenting stage of sepsis strata; however, despite these somewhat encouraging findings, there remain opportunities for improvement of care.

Our study's findings are consistent with other research in this area. Our previous systematic review found support for lower in-hospital mortality among patients with GU or SSTB infections.[33] Other studies have also found decreased mortality risk among patients presenting with GU infections, although these studies have been limited to

patients with severe sepsis or septic shock or to the ICU setting.[53,72] This study did not find evidence to support previous studies' assertions that abdominal infections portend worse outcomes for patients with sepsis.[53] Possible explanations for this finding may be due to the groupings of abdominal infections which represent considerable heterogeneity of infections and pathogens or demographics of different patients with abdominal infections. Another possible explanation is that patients with more severe illness, regardless of the source of sepsis, may present with such profound immune dysregulation that the underlying cause is less important than the rectification of the manifestations of disease. At least one other study has also shown a lack of difference in mortality based on initial infection source, positing that the primary driver of mortality is related to the organ dysfunction and the efficacy of resuscitation in septic shock.[52]

The consistent association between GU infections and lower in-hospital mortality suggest that there may be unique characteristics of this patient group that has important implications for future research design as well as clinical care. Potential explanations for this mortality benefit may include the amenability of these infections to source control interventions, the relatively protected anatomic site due to the barrier functions of the GU system, and a tendency for antibiotics to concentrate within the GU system.[25,73] The association with lesser mortality compared to patients with respiratory infections suggest that protocols emphasizing prompt identification, rapid source control, and appropriate antimicrobial use have been successful.[74] Nevertheless, it remains possible that absolute mortality could still be improved with identification of at-risk patients in the community setting and curative management for GU infections prior to progression to sepsis and

prevent other serious consequences of severe infection and sepsis such as lasting end-organ damage.[75]

This study also found a consistent association between SSTB infections and lower in-hospital mortality compared to patients with respiratory infections, a finding which was somewhat attenuated in the oldest old. This finding may be due to increased breakdown in the skin in older adults and increased seriousness of skin infections in this group due to additional comorbidities or particular conditions such as pressure ulcers.[76,77] We speculate that there may also be a delay in diagnosis due to skin and soft tissue infections that are not readily visible and may not be rapidly recognized, particularly in these oldest patients who are more likely to have limited mobility.[78] This relative increased mortality also suggests that the oldest old patients may have a decreased ability to heal relatively superficial wounds resulting in increased likelihood of progressive infection.[34,79] These findings suggest that efforts to monitor skin breakdown in the elderly, particularly in high risk settings such as skilled nursing facilities are warranted and may have mortality benefits in addition to improving quality of life when pressure ulcers and other painful skin infections are identified early.[78,80] These findings potentially offer opportunities for care improvement and cost efficiency.

This study has important limitations. First, despite extensive cross-checking of lists it is possible that misclassification of the exposure occurred due to infections not being properly recorded or due to sepsis not being due to the infection recorded at admission. While we attempted to ensure that sepsis was due to the presenting infection

by requiring that both a sepsis code and an infection code were present on admission, this may have been imperfect and some cases of sepsis may have been due to other causes of infection rather than those recorded at admission. Conversely, patients admitted with an infection may have developed sepsis after their admission but not had their sepsis documented, and this sepsis would have not been detected in our study. We lacked true cause of death data; however, we attempted to limit the effects of other possible hospital sequelae by limiting the analysis to those with lengths of stay less than 30 days, and performing an additional subgroup analysis limiting the follow-up of the population to 48 hours. It is assumed that these early deaths are likely due to the continuation of the sepsis process at admission. Finally, this study includes only academic medical centers and their affiliated hospitals, limiting generalizability to other settings. Despite these limitations, the association between certain infections and mortality is strong and indicates that anatomic source of infection should be considered in other studies of sepsis, and offer an opportunity for tailoring of care.

This study adds to the existing literature on the role of initial infection source as it relates to sepsis mortality. Where randomized clinical trials are ethically and logistically impossible, observational studies are needed to further our understanding of the epidemiology of sepsis spectrum disease and the role of the initial infection source. This study suggests that risk stratification of patients is possible and perhaps necessary based on the initial infection source. Such approaches may have increasing relevance as sepsis comes under increasing scrutiny by those interested in hospital payments, as well as having important clinical implications.

Table 2.1: Baseline Demographics and Clinical Characteristics of Patients with Sepsis Present-on-Admission by Infection Source

| Characteristic | | Respiratory Infection (n=34,117) | Abdominal Infection (n=16,982) | Genitourinary Infection (n=36,524) | Skin, Soft Tissue, and Bone Infection (n=11,937) | CNS Infection (n=886) |
|---|---|---|---|---|---|---|
| | | Percentage | | | | |
| **Age (Years)** | **18-54** | 27.6 | 32.8 | 22.4 | 38.5 | 43.5 |
| | **55-64** | 22.2 | 27.0 | 18.0 | 25.2 | 24.5 |
| | **65-74** | 22.3 | 21.0 | 20.9 | 18.6 | 18.1 |
| | **75-84** | 16.9 | 12.9 | 21.9 | 11.6 | 11.0 |
| | **85+** | 11.0 | 6.3 | 16.8 | 6.1 | 3.1 |
| **Women** | | 41.8 | 43.1 | 56.5 | 38.1 | 42.4 |
| **Length of Stay (Days)** | | Median (Interquartile Range) | | | | |
| | **Total** | 7.0 (4.0-13.0) | 8.0 (4.0-14.0) | 6.0 (4.0-9.0) | 9.0 (5.0-15.0) | 9.0 (5.0-15.0) |
| | **ICU** | 2.0 (0.0-6.0) | 2.0 (0.0-6.0) | 0.0 (0.0-3.0) | 1.0 (0.0-4.0) | 3.0 (1.0-7.0) |
| **Emergency Department Admission** | | 74.2 | 66.1 | 82.2 | 75.4 | 66.9 |
| **Severity Indices & Clinical Comorbidities** | | | | | | |
| | **Charlson-Deyo Comorbidity Score** | | | | | |
| | **0** | 16.8 | 13.1 | 18.2 | 16.8 | 26.6 |
| | **1-3** | 51.0 | 34.0 | 53.4 | 48.2 | 52.9 |
| | **4+** | 32.3 | 52.9 | 28.4 | 35.0 | 20.4 |
| **Year of Hospital Admission** | **2011** | 17.8 | 18.6 | 18.6 | 16.7 | 20.2 |
| | **2012** | 21.4 | 22.3 | 21.9 | 21.3 | 20.9 |
| | **2013** | 27.0 | 25.9 | 25.7 | 26.8 | 27.5 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **2014** | 33.8 | 33.3 | 33.8 | 35.2 | 31.4 |
| **Quarter of Hospital Admission** | **First** | 28.5 | 23.9 | 23.1 | 22.6 | 24.6 |
| | **Second** | 24.0 | 23.8 | 24.1 | 24.8 | 25.5 |
| | **Third** | 20.5 | 24.9 | 25.3 | 25.1 | 23.1 |
| | **Fourth** | 27.0 | 27.4 | 27.5 | 27.5 | 26.8 |
| **Presenting Stage of Sepsis** | **Sepsis** | 27.7 | 25.3 | 38.3 | 39.8 | 35.8 |
| | **Severe Sepsis** | 25.0 | 20.8 | 26.5 | 24.6 | 30.4 |
| | **Septic Shock** | 47.3 | 54.0 | 35.3 | 35.6 | 33.9 |
| **Organ Dysfunction** | | | | | | |
| | **Cardiovascular** | 54.2 | 60.3 | 43.6 | 42.4 | 37.5 |
| | **Hematologic** | 18.9 | 31.2 | 18.1 | 17.3 | 21.4 |
| | **Hepatic** | 5.1 | 9.5 | 2.8 | 2.7 | 3.6 |
| | **Neurologic** | 15.4 | 10.4 | 18.7 | 11.1 | 34.4 |
| | **Renal** | 52.4 | 56.7 | 65.3 | 53.8 | 34.9 |
| | **Respiratory** | 54.5 | 24.2 | 17.7 | 17.1 | 38.4 |

Table 2.2: Effect Estimates of Hospital Mortality by Infection Source for Patients with Sepsis, Severe Sepsis, or Septic Shock

| | Number of Deaths | Person-days | Mortality Rate per 1,000 person-days | Mortality (%) | Crude Hazard Rate Ratio (95% Confidence Interval, p-value) | Adjusted Hazard Rate Ratio* (95% Confidence Interval, p-value) |
|---|---|---|---|---|---|---|
| **Respiratory Infection (n=34,117)** | 7,254 | 312,212 | 9.2 | 21.3 | **Referent** | |
| **Abdominal Infection (n=16,982)** | 4,175 | 169,786 | 10.0 | 24.6 | 1.06 (1.01-1.11, p=0.0082) | 0.99 (0.95-1.03, p=0.4751) |
| **Genitourinary Infection (n=36,524)** | 3,299 | 276,355 | 7.6 | 9.0 | 0.51 (0.48-0.54, p<0.0001) | 0.52 (0.50-0.55, p<0.0001) |
| **Skin, Soft Tissue, and Bone Infection (n=11,937)** | 1,259 | 125,273 | 10.5 | 10.6 | 0.44 (0.41-0.47, p<0.0001) | 0.53 (0.49-0.57, p<0.0001) |
| **CNS Infection (n=886)** | 175 | 9,792 | 11.1 | 19.8 | 0.79 (0.68-0.91, p=0.0016) | 1.10 (0.94-1.27, p=0.2388) |

* Adjusted for age, sex, Charlson-Deyo Comorbidity Index, emergency admission, and presenting stage of sepsis

Table 2.3: Effect Estimates of Hospital Mortality by Infection Source for Patients with Sepsis Limited to 48 Hours of Follow-up Time

| | Number of Deaths | Person-days | Mortality Rate (per 1,000 person-days) | Mortality (%) | Crude Hazard Rate Ratio (95% Confidence Interval, p-value) | Adjusted Hazard Rate Ratio* (95% Confidence Interval, p-value) |
|---|---|---|---|---|---|---|
| **Respiratory Infection (n=34,117)** | 2,398 | 65,624 | 1.9 | 7.0 | **Referent** | |
| **Abdominal Infection (n=16,982)** | 1,369 | 32,620 | 1.9 | 8.1 | 1.15 (1.06-1.24, p=0.0005) | 1.09 (1.02-1.17, p=0.0144) |
| **Genitourinary Infection (n=36,524)** | 1,118 | 71,371 | 2.0 | 3.1 | 0.43 (0.40-0.47, p<0.0001) | 0.48 (0.45-0.52, p<0.0001) |
| **Skin, Soft Tissue, and Bone Infection (n=11,937)** | 397 | 23,403 | 2.0 | 3.3 | 0.47 (0.41-0.53, p<0.0001) | 0.61 (0.54-0.68, p<0.0001) |
| **CNS Infection (n=886)** | 56 | 1,715 | 1.9 | 6.3 | 0.90 (0.68-1.18, p=0.4248) | 1.28 (1.00-1.65, p=0.0506) |

* Adjusted for age, sex, Charlson-Deyo Comorbidity Index, emergency admission, and presenting stage of sepsis

Figure 2.1 Selection of Participants

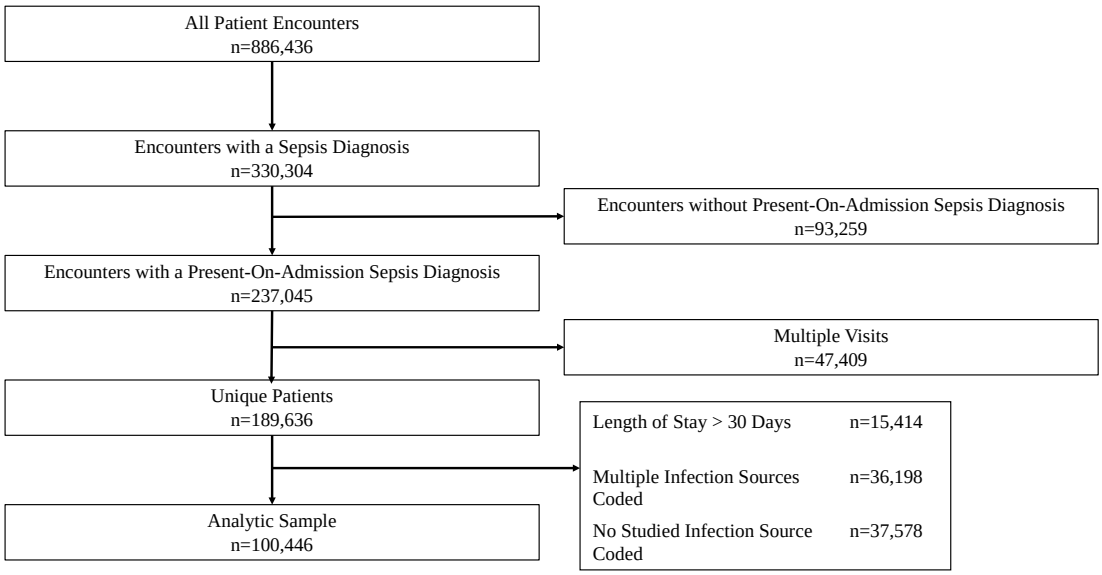


Figure 2.2 Percent Mortality by Initial Infection Source by Age Strata: <65, 65-74, 75-84, 85+

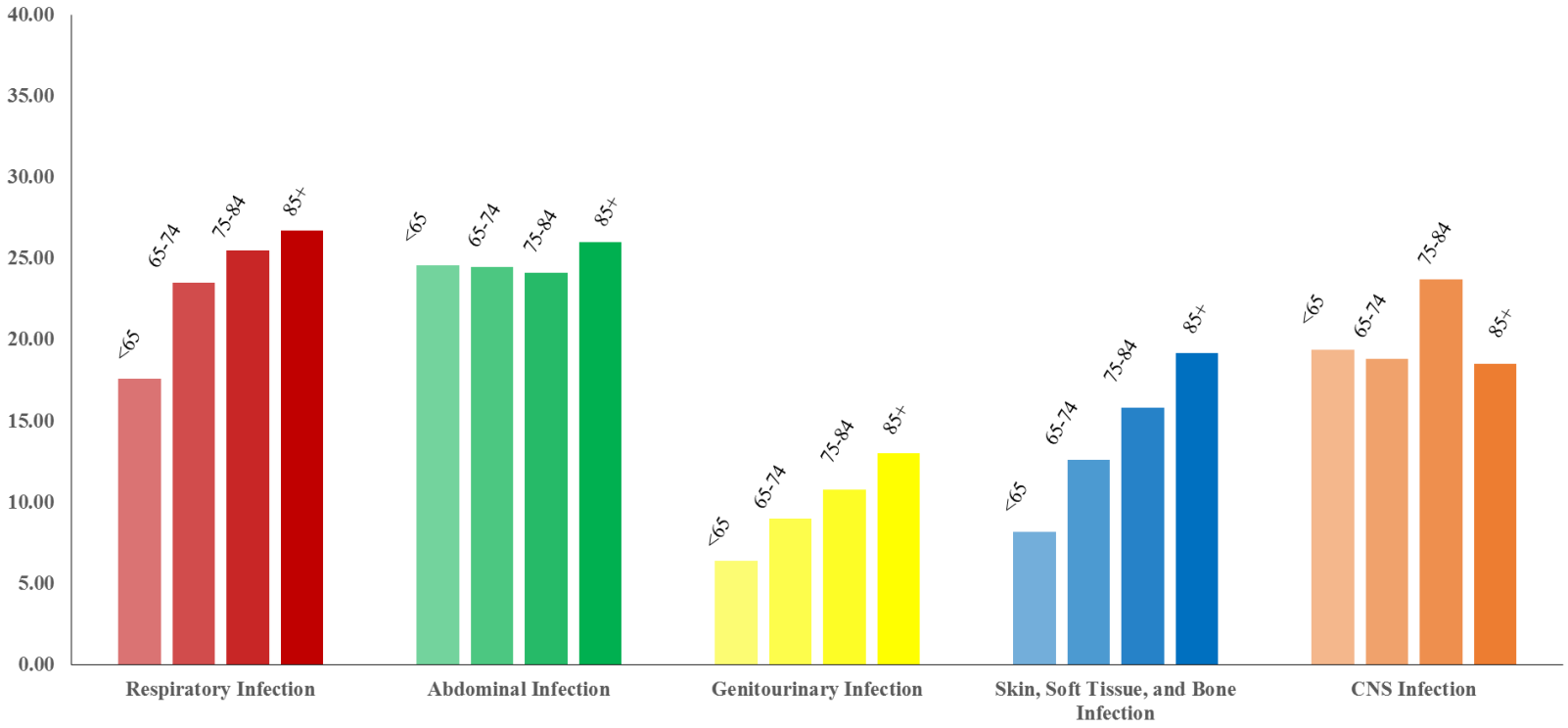


Figure 2.3 Percent Mortality by Initial Infection Source by Presenting Stage of Sepsis: Sepsis, Severe Sepsis, Septic Shock

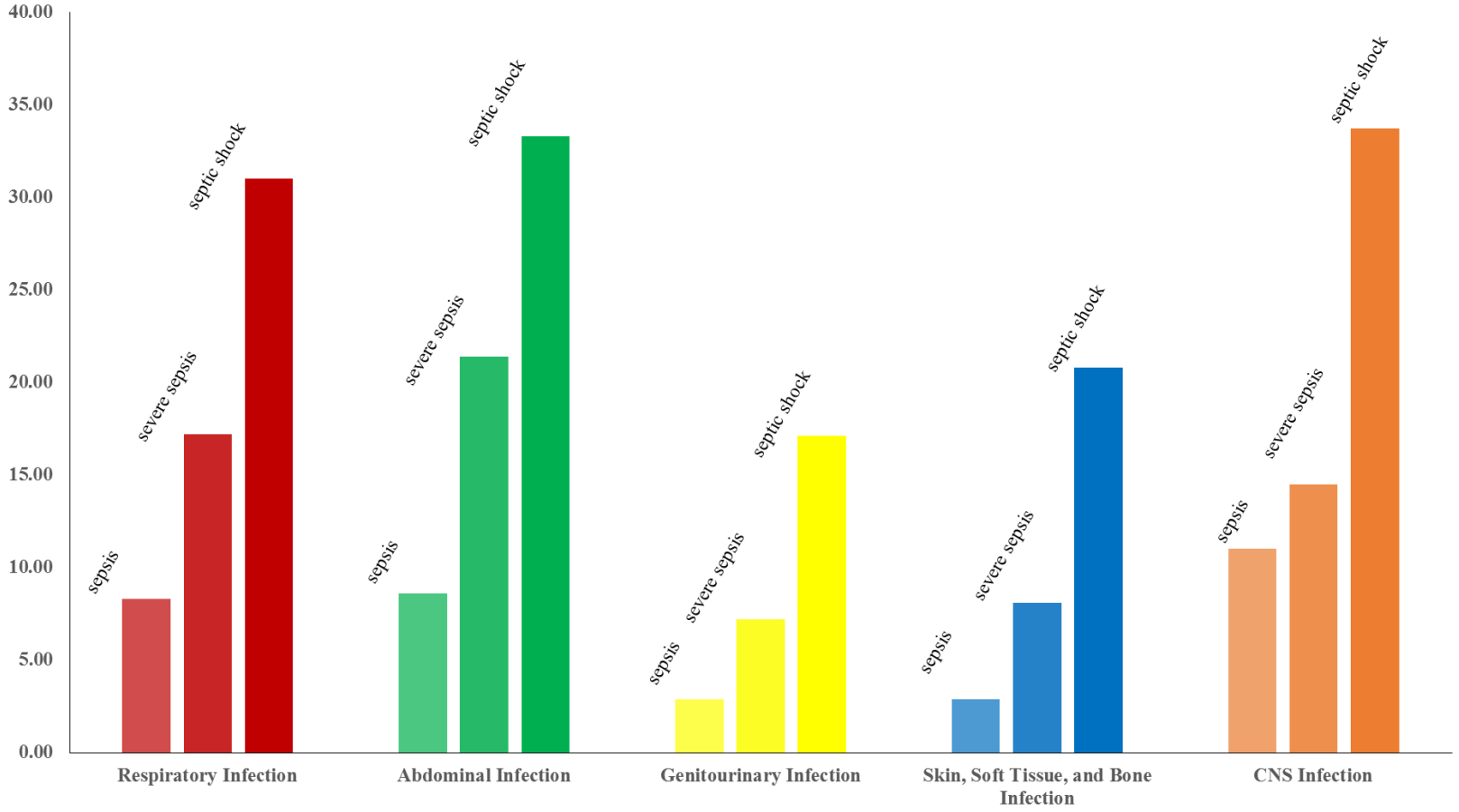


Figure 2.4 Kaplan-Meier Survival Curves of In-hospital Mortality by Initial Infection Source

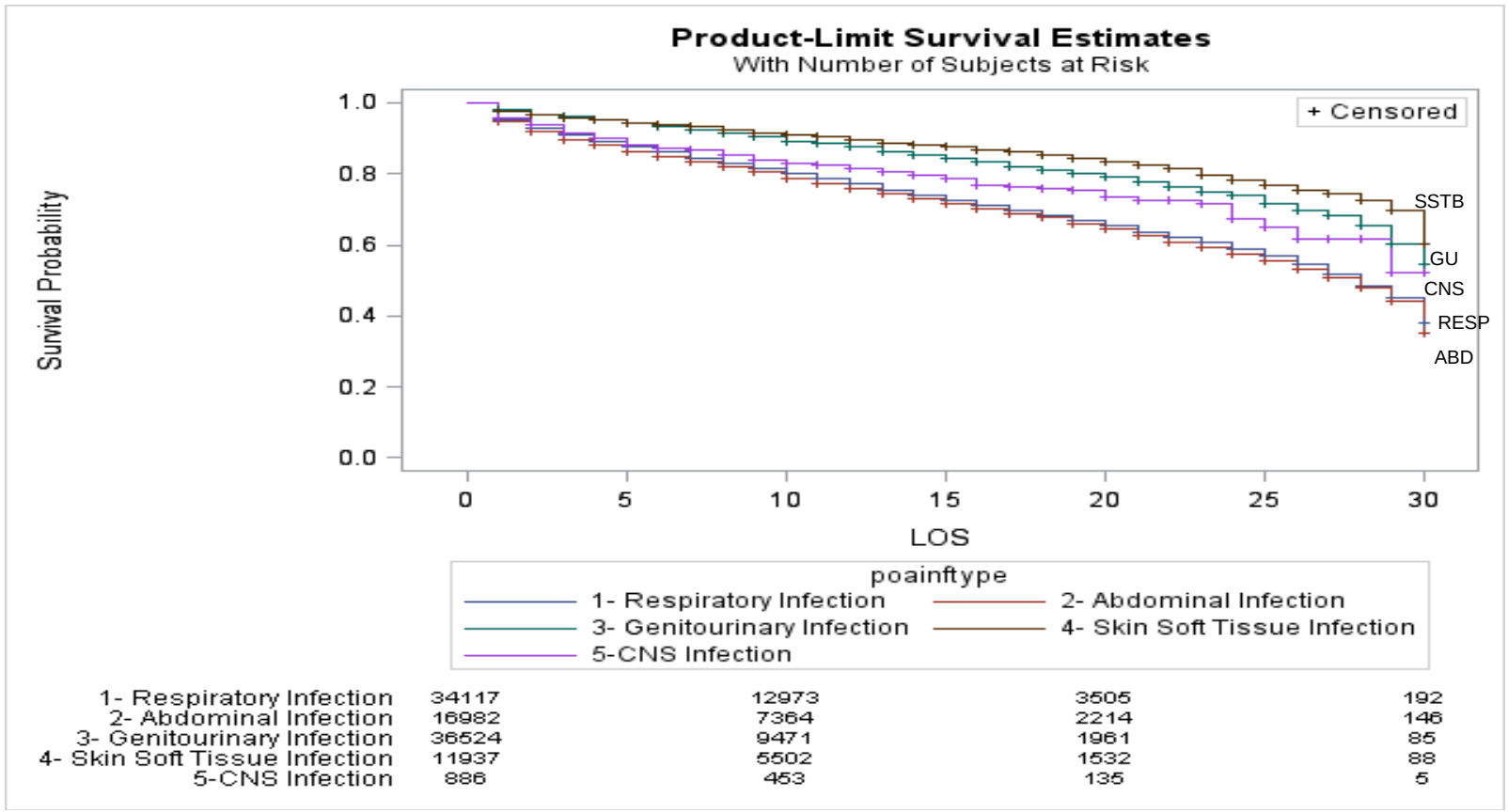


Figure 2.5a Effect Estimates of Time to Hospital Mortality for Patients under Age 65 Adjusted for Sex, Charlson-Deyo Comorbidity Index, Emergency Admission, and Presenting Stage of Sepsis

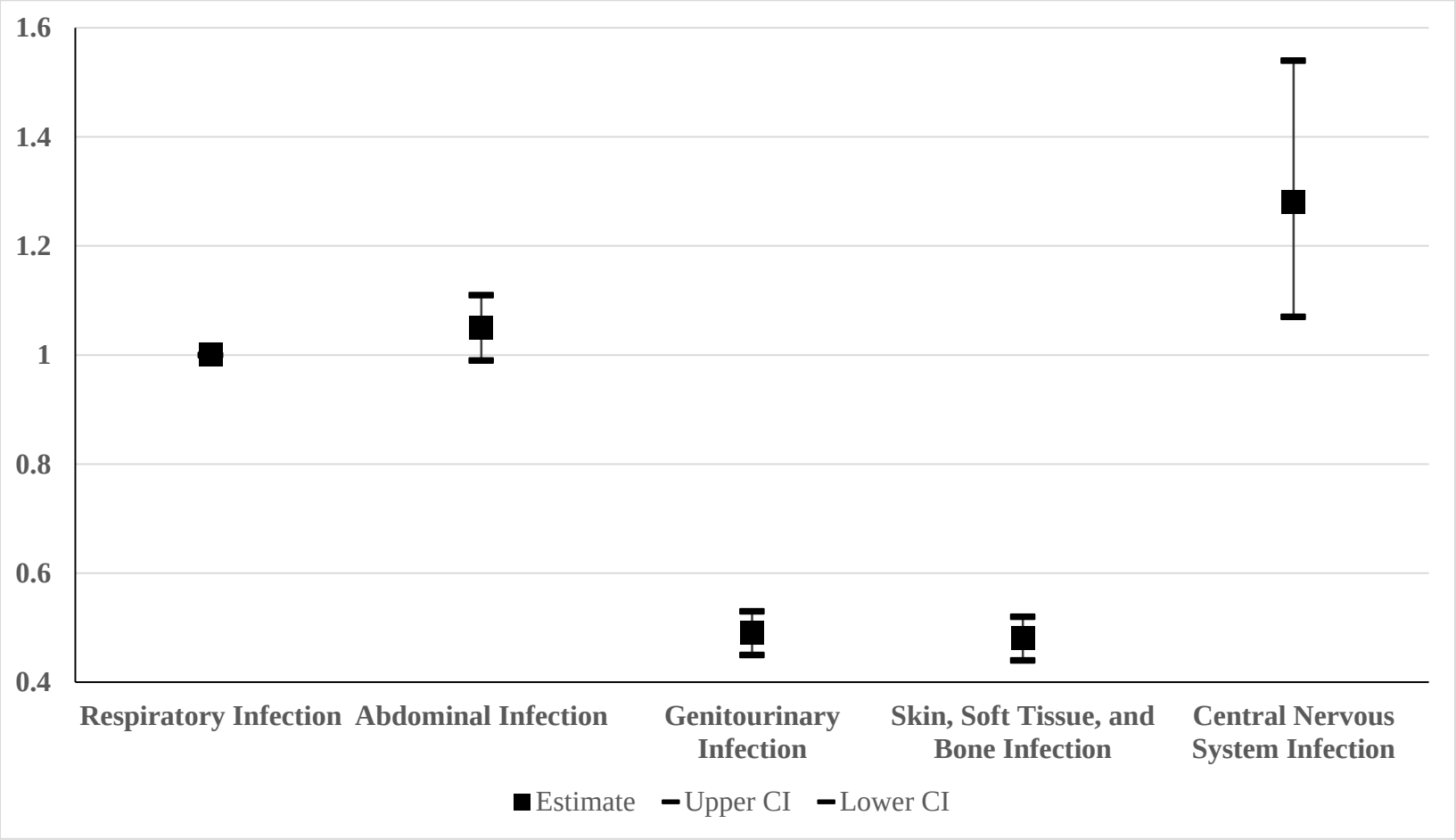


Figure 2.5b Effect Estimates of Time to Hospital Mortality for Patients Age 65-74 Adjusted for Sex, Charlson-Deyo Comorbidity Index, Emergency Admission, and Presenting Stage of Sepsis

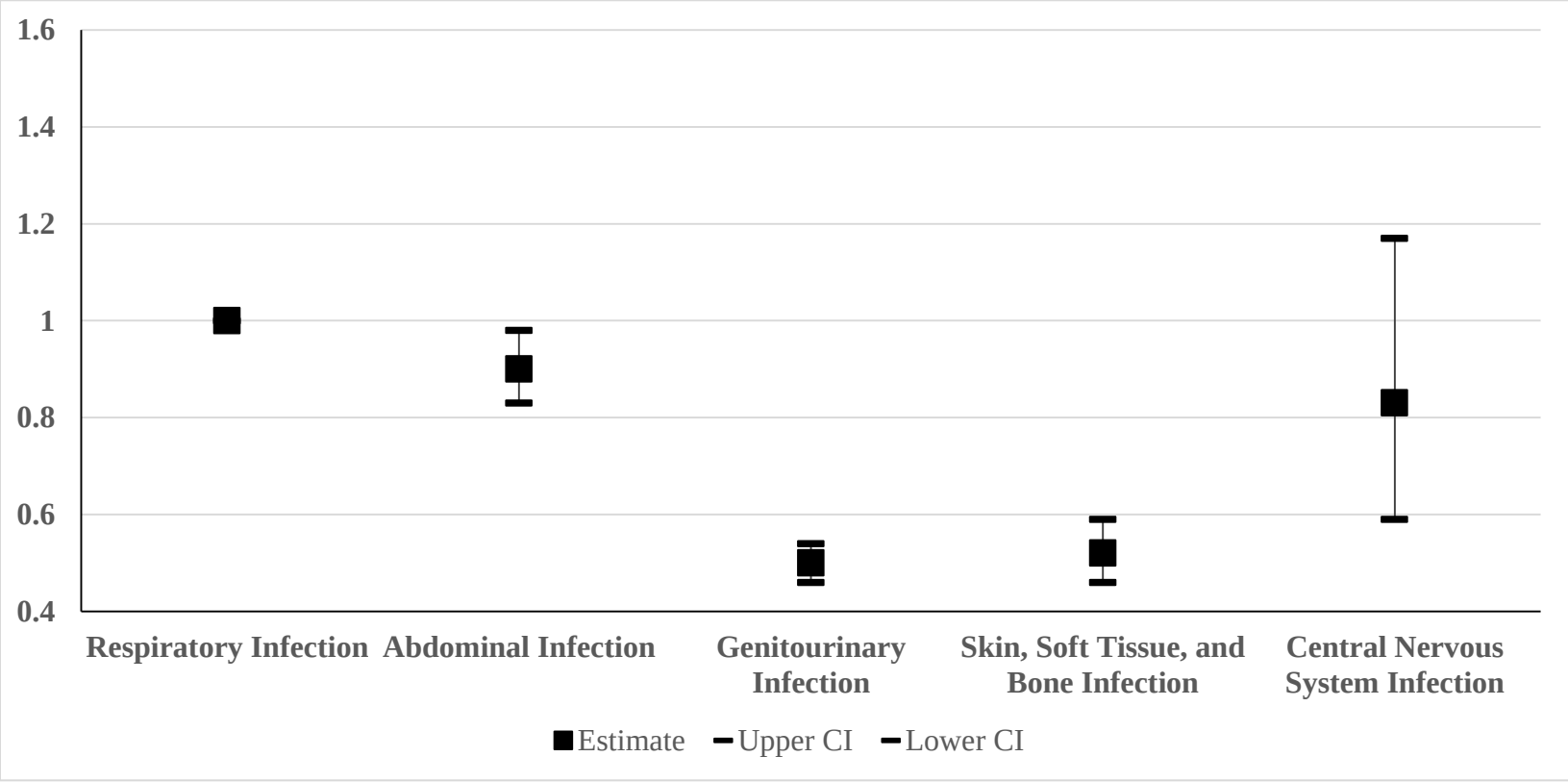


Figure 2.5c Effect Estimates of Time to Hospital Mortality for Patients Age 75-84 Adjusted for Sex, Charlson-Deyo Comorbidity Index, Emergency Admission, and Presenting Stage of Sepsis

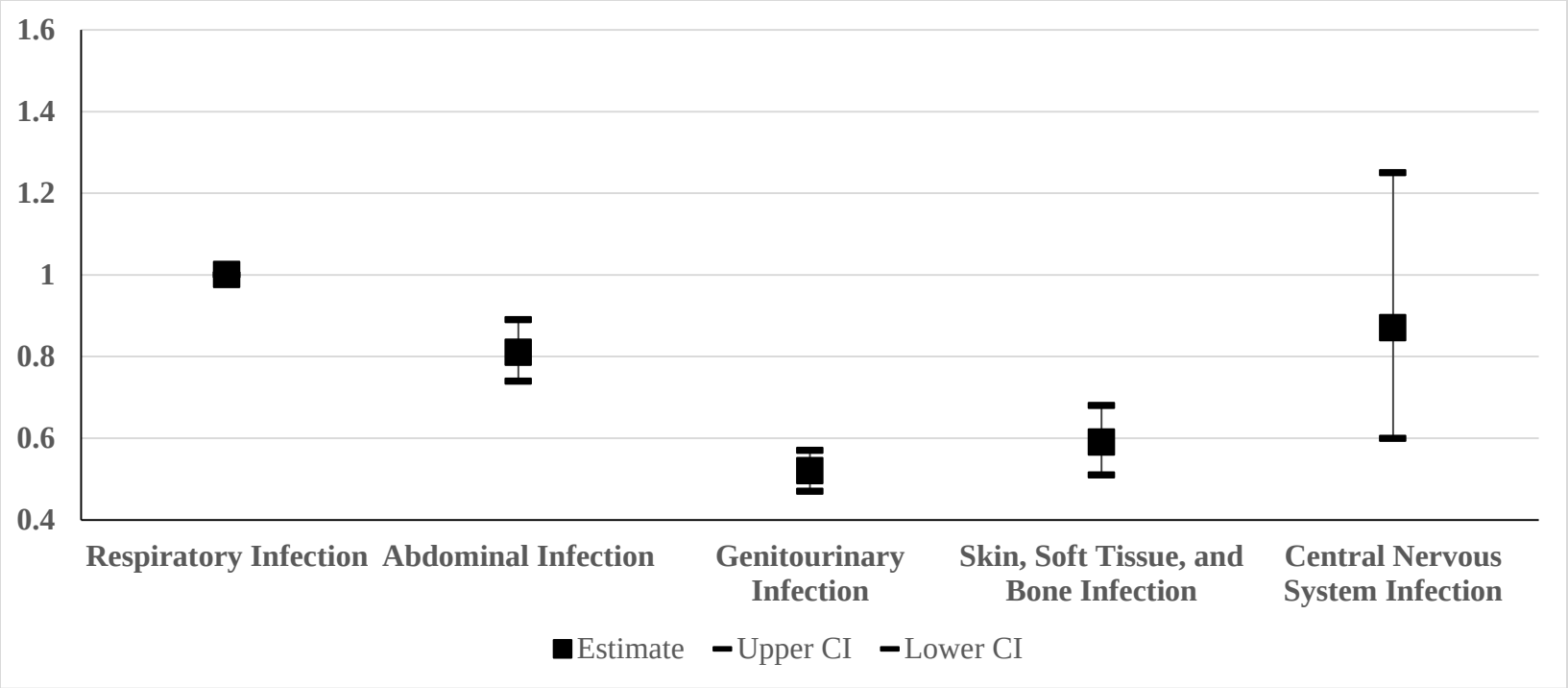


Figure 2.5d Effect Estimates of Time to Hospital Mortality for Patients Age 85+ Adjusted for Sex, Charlson-Deyo Comorbidity Index, Emergency Admission, and Presenting Stage of Sepsis

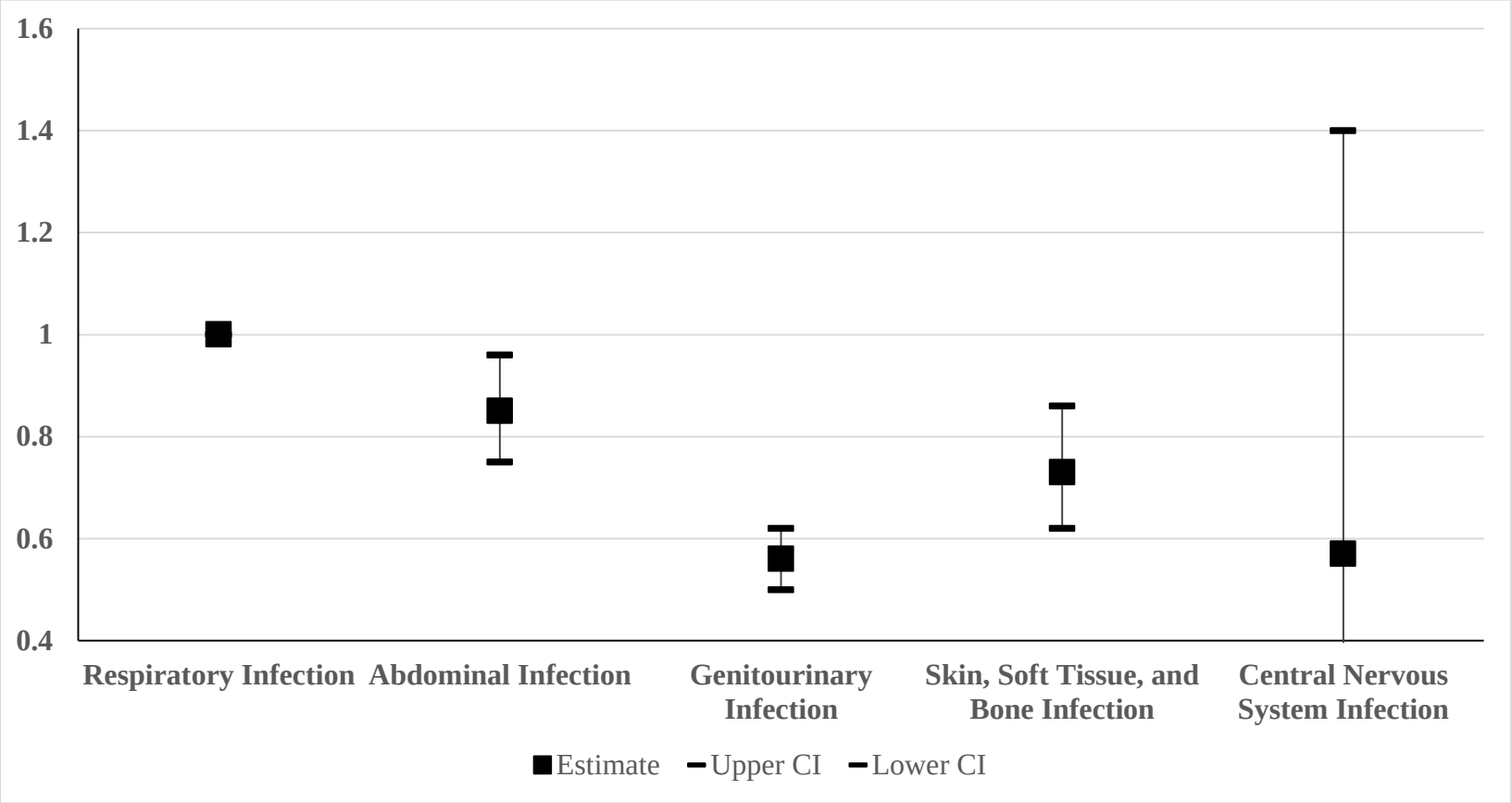


Figure 2.6a Effect Estimates of Time to Hospital Mortality for Patients Presenting with Sepsis Adjusted for Sex, Charlson-Deyo Comorbidity Index, Emergency Admission, and Age

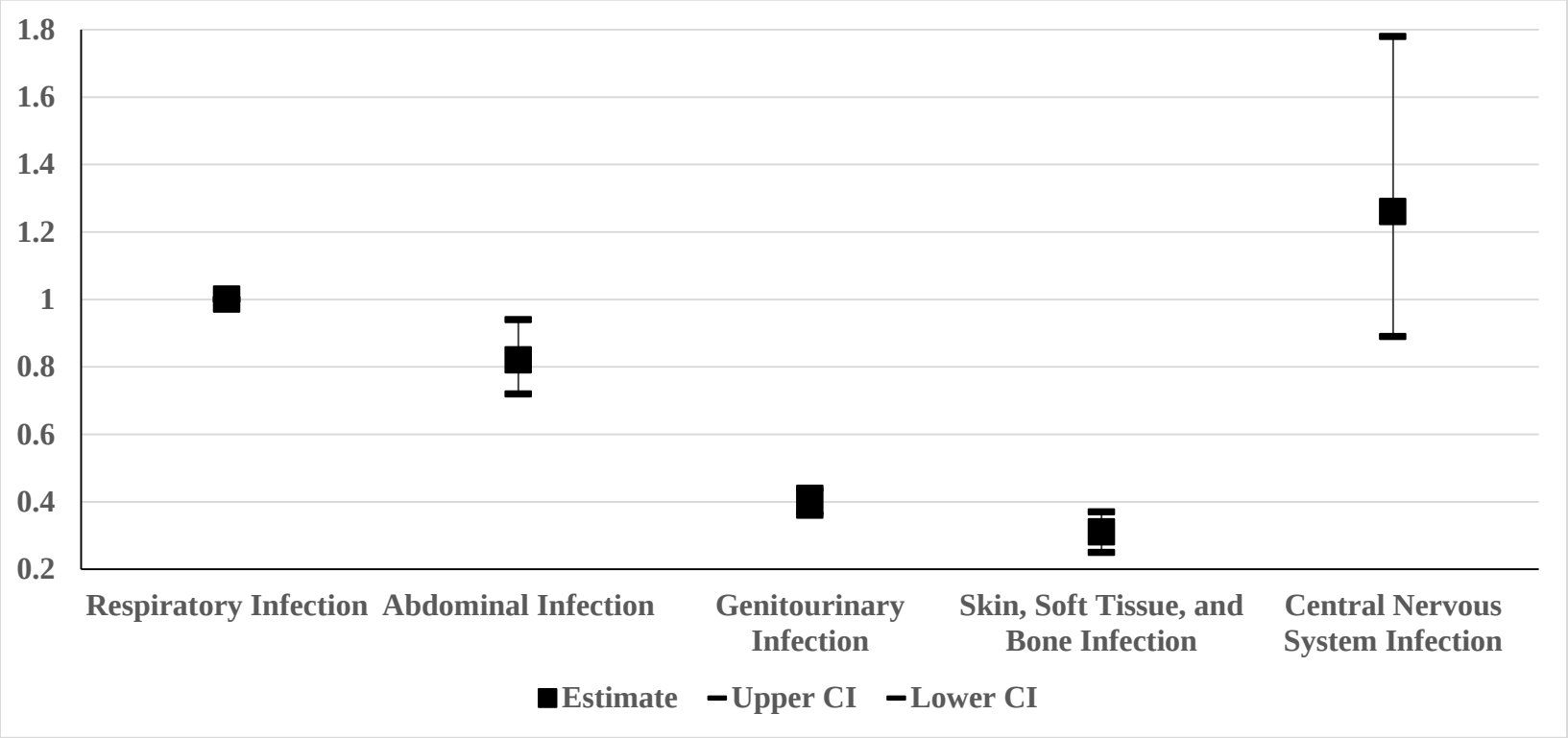


Figure 2.6b Effect Estimates of Time to Hospital Mortality for Patients Presenting with Severe Sepsis Adjusted for Sex, Charlson-Deyo Comorbidity Index, Emergency Admission, and Age

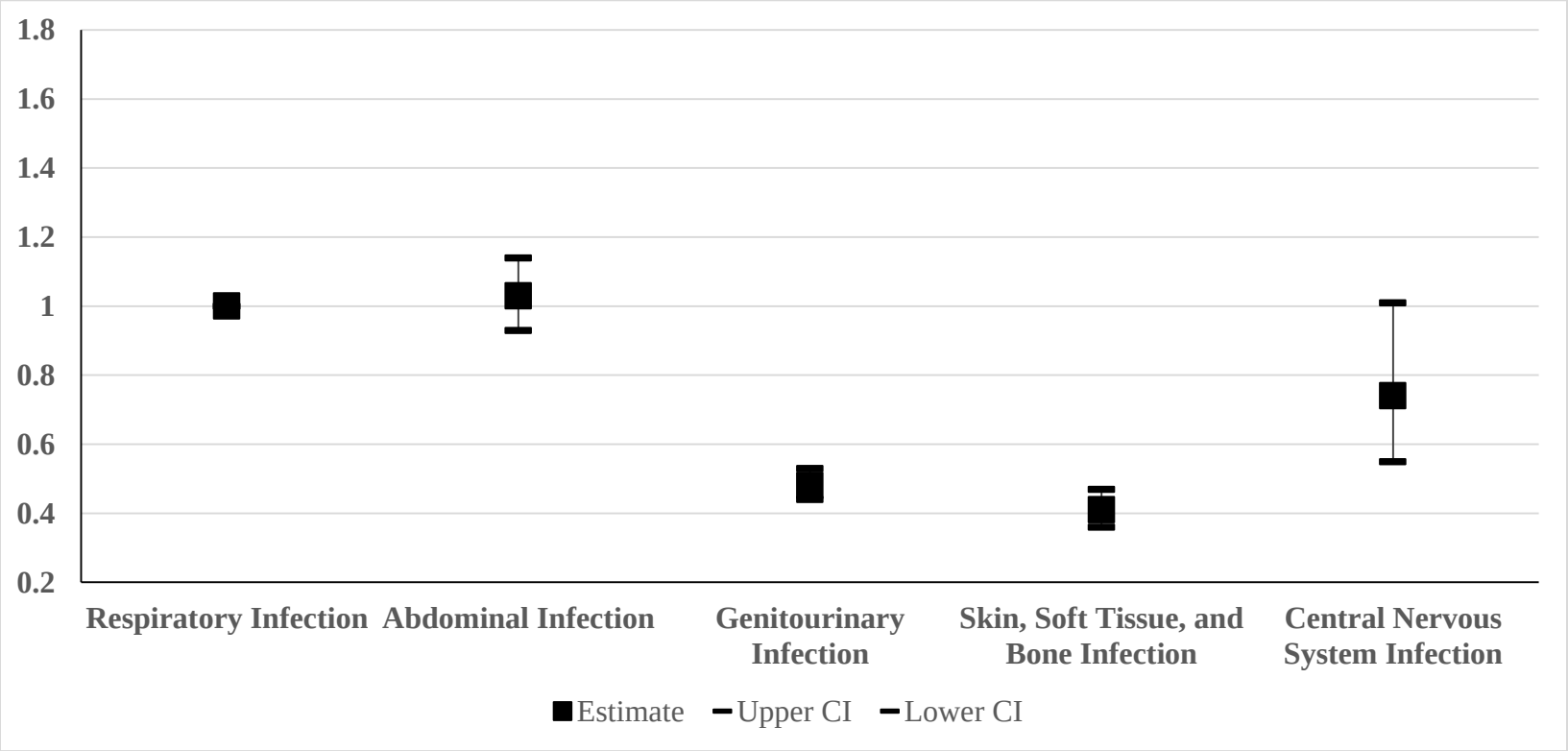
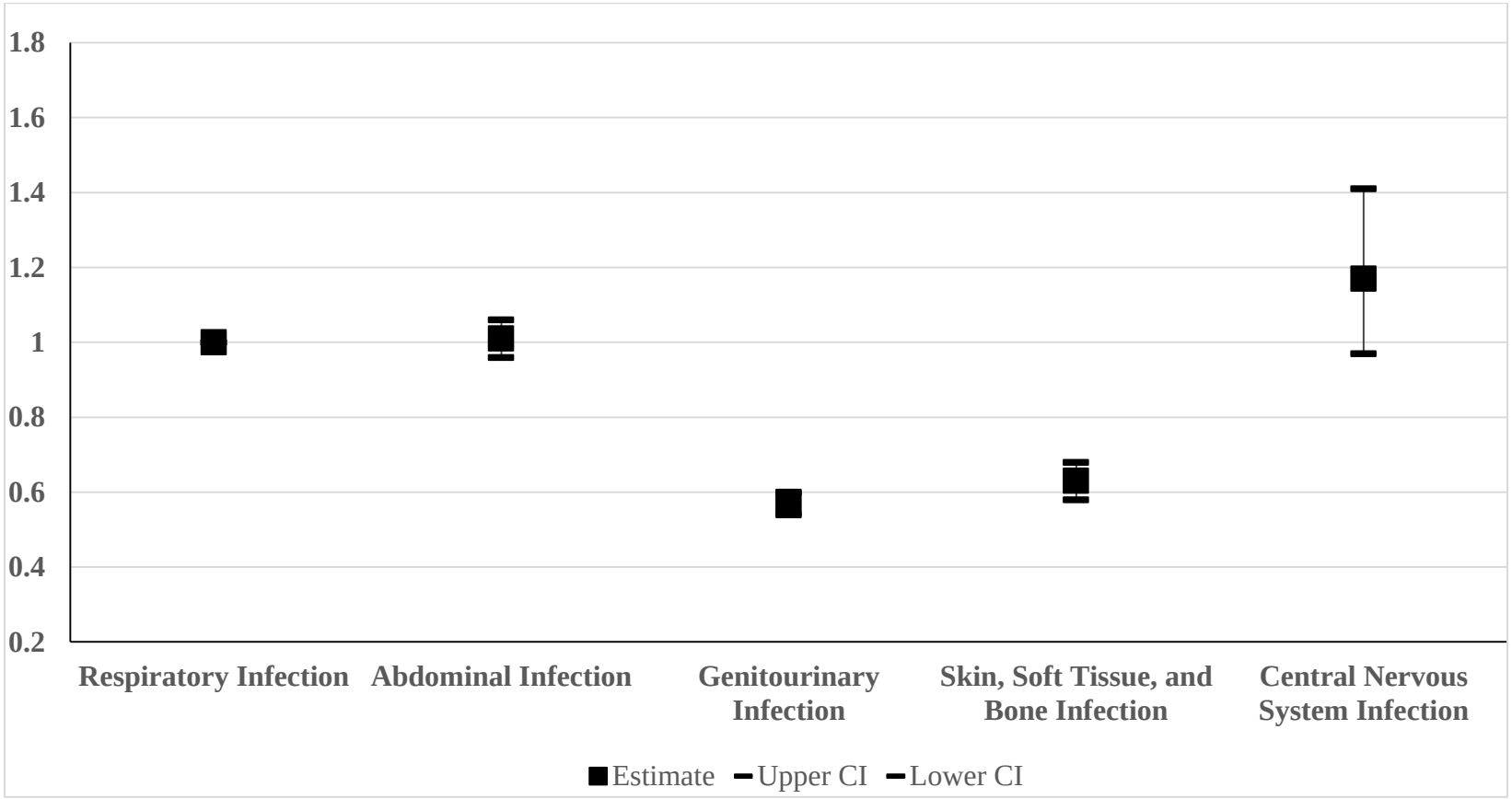


Figure 2.6c Effect Estimates of Time to Hospital Mortality for Patients Presenting with Septic Shock Adjusted for Sex, Charlson-Deyo Comorbidity Index, Emergency Admission, and Age



Supplementary Table 2.1: ICD-9 CM Codes Used to Identify Sepsis, Infection Source, and Organ Dysfunction Categories

| | ICD-9CM Codes |
|---|---|
| **Sepsis** | 995.91, 038 |
| **Severe Sepsis** | 995.92 |
| **Septic Shock** | 785.5 |
| **Respiratory Infections** | 010, 011, 012, 013, 014, 015, 016, 017, 018, 032, 033, 034, 461, 462, 463, 464, 465, 480, 481, 482, 483, 484, 485, 486, 491.21 |
| **Abdominal Infections** | 001, 002, 003, 004, 005, 008, 0845, 009, 540, 541, 542, 543.9, 562.01, 563.203, 562.11, 562.13, 566, 567, 569.5, 569.61, 569.71, 569.83, 572, 575 |
| **Genitourinary Infections** | 590, 595, 597, 598, 599, 601, 604, 614, 615, 616 |
| **Skin, Soft Tissue, and Bone Infections** | 451, 680, 681, 682, 683, 686, 711, 728.86, 730, 785.4 |
| **Central Nervous System Infections** | 036, 090, 320, 322, 324, 325 |
| **Cardiovascular Failure** | 375, 376.6, 458, 785.5 |
| **Hematologic Failure** | 286.6, 286.9, 287.4, 287.5 |
| **Hepatic Failure** | 570, 573.4 |
| **Neurologic Failure** | 293, 348.1, 348.3 |
| **Renal Failure** | 584 |
| **Respiratory Failure** | 335, 518.8, 786.03, 799.1, 967 |

Supplementary Table 2.2: Baseline Demographics and Clinical Characteristics of Patients with Sepsis Present-On-Admission by Infection Source and Age Category

| Characteristic | | Respiratory Infection | Abdominal Infection | Genitourinary Infection | Skin, Soft Tissue, and Bone Infection | CNS Infection |
|---|---|---|---|---|---|---|
| **Age (Years)** | | Percentage | | | | |
| **Women** | **<65** | 41.2 | 40.9 | 60.9 | 36.1 | 40.9 |
| | **65-74** | 40.0 | 42.2 | 50.6 | 37.3 | 43.1 |
| | **75-84** | 41.6 | 47.1 | 51.9 | 41.7 | 46.4 |
| | **85+** | 48.9 | 59.5 | 59.4 | 55.0 | 59.3 |
| **Length of Stay (Days)** | | Median (Interquartile Range) | | | | |
| **Total** | **<65** | 8.0 (4.0-14.0) | 8.0 (4.0-15.0) | 6.0 (3.0-10.0) | 9.0 (5.0-15.0) | 9.0 (5.0-15.0) |
| | **65-74** | 8.0 (4.0-13.0) | 8.0 (4.0-14.0) | 6.0 (4.0-10.0) | 9.0 (5.0-15.0) | 11.0 (5.5-16.0) |
| | **75-84** | 7.0 (4.0-12.0) | 8.0 (4.0-14.0) | 6.0 (4.0-10.0) | 8.0 (5.0-14.0) | 9.0 (5.0-15.0) |
| | **85+** | 6.0 (3.0-10.0) | 7.0 (4.0-12.0) | 6.0 (4.0-9.0) | 7.0 (4.0-11.0) | 10.0 (6.0-13.0) |
| **ICU** | **<65** | 3.0 (0.0-7.0) | 2.0 (0.0-6.0) | 1.0 (0.0-3.0) | 1.0 (0.0-4.0) | 3.0 (1.0-8.0) |
| | **65-74** | 2.0 (0.0-7.0) | 2.0 (0.0-6.0) | 1.0 (0.0-3.0) | 1.0 (0.0-4.0) | 4.0 (1.0-8.0) |
| | **75-84** | 2.0 (0.0-6.0) | 2.0 (0.0-6.0) | 0.0 (0.0-3.0) | 1.0 (0.0-4.0) | 3.0 (1.0-7.0) |
| | **85+** | 1.0 (0.0-3.0) | 1.0 (0.0-4.0) | 0.0 (0.0-2.0) | 0.0 (0.0-2.0) | 2.0 (0.0-4.0) |
| **Emergency Department Admission** | **<65** | 70.8 | 63.5 | 79.3 | 75.0 | 66.8 |
| | **65-74** | 72.2 | 64.7 | 79.6 | 73.3 | 63.1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **75-84** | 77.7 | 72.3 | 83.7 | 75.2 | 67.0 |
| | **85+** | 88.2 | 83.0 | 90.6 | 85.0 | 92.6 |
| Charlson-Deyo Comorbidity Score | | | | | | |
| 0 | **<65** | 22.3 | 14.1 | 25.0 | 20.6 | 30.2 |
| | **65-74** | 11.5 | 10.5 | 14.4 | 10.3 | 16.9 |
| | **75-84** | 10.1 | 12.1 | 12.7 | 9.4 | 20.6 |
| | **85+** | 12.7 | 14.7 | 13.7 | 11.7 | 25.9 |
| 1-3 | **<65** | 49.1 | 27.8 | 50.8 | 48.1 | 51.2 |
| | **65-74** | 50.0 | 37.2 | 52.3 | 45.8 | 58.8 |
| | **75-84** | 53.0 | 46.4 | 54.4 | 47.9 | 51.6 |
| | **85+** | 58.2 | 56.6 | 59.6 | 57.3 | 63.0 |
| 4+ | **<65** | 28.6 | 58.1 | 24.2 | 31.4 | 18.6 |
| | **65-74** | 38.6 | 52.3 | 33.4 | 44.0 | 24.4 |
| | **75-84** | 37.0 | 41.6 | 32.8 | 42.7 | 27.8 |
| | **85+** | 29.1 | 28.6 | 26.7 | 31.0 | 11.1 |
| **Year of Hospital Admission** | | | | | | |
| 2011 | **<65** | 18.5 | 18.5 | 18.3 | 16.6 | 19.9 |
| | **65-74** | 16.7 | 18.1 | 18.0 | 17.4 | 21.9 |
| | **75-84** | 17.7 | 19.6 | 19.1 | 17.6 | 21.7 |
| | **85+** | 17.2 | 19.3 | 19.2 | 14.5 | 11.1 |
| 2012 | **<65** | 21.5 | 23.0 | 22.1 | 21.2 | 21.4 |
| | **65-74** | 20.9 | 20.5 | 20.7 | 20.4 | 16.9 |
| | **75-84** | 21.5 | 21.8 | 22.1 | 22.7 | 18.6 |
| | **85+** | 21.8 | 22.4 | 22.9 | 21.6 | 40.7 |
| 2013 | **<65** | 26.5 | 25.6 | 25.3 | 26.8 | 27.6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **65-74** | 27.9 | 26.4 | 26.0 | 26.1 | 25.0 |
| | **75-84** | 26.7 | 26.3 | 26.0 | 26.4 | 34.0 |
| | **85+** | 27.7 | 25.7 | 25.6 | 29.3 | 18.5 |
| 2014 | **<65** | 33.4 | 32.9 | 34.3 | 35.4 | 31.1 |
| | **65-74** | 34.5 | 35.0 | 35.3 | 36.1 | 36.3 |
| | **75-84** | 34.1 | 32.4 | 32.9 | 33.3 | 25.8 |
| | **85+** | 33.4 | 32.7 | 32.3 | 34.6 | 29.6 |
| **Quarter of Hospital Admission** | | | | | | |
| **First** | **<65** | 28.8 | 23.7 | 22.6 | 22.8 | 25.9 |
| | **65-74** | 27.8 | 24.4 | 22.8 | 21.8 | 16.9 |
| | **75-84** | 28.0 | 23.2 | 22.9 | 22.2 | 25.8 |
| | **85+** | 29.6 | 25.8 | 25.2 | 23.8 | 37.0 |
| **Second** | **<65** | 24.1 | 23.9 | 24.8 | 24.9 | 25.6 |
| | **65-74** | 24.3 | 22.9 | 23.5 | 24.3 | 25.6 |
| | **75-84** | 23.7 | 25.1 | 24.1 | 25.2 | 24.7 |
| | **85+** | 23.2 | 23.6 | 23.0 | 25.3 | 25.9 |
| **Third** | **<65** | 20.6 | 25.2 | 25.5 | 25.3 | 22.6 |
| | **65-74** | 20.8 | 24.7 | 26.1 | 25.1 | 27.5 |
| | **75-84** | 21.0 | 24.8 | 25.2 | 24.5 | 21.7 |
| | **85+** | 18.7 | 23.2 | 23.8 | 24.5 | 14.8 |
| **Fourth** | **<65** | 26.6 | 27.3 | 27.1 | 27.0 | 25.9 |
| | **65-74** | 27.2 | 28.1 | 27.5 | 28.8 | 30.0 |
| | **75-84** | 27.3 | 26.9 | 27.8 | 28.2 | 27.8 |
| | **85+** | 28.5 | 27.3 | 28.0 | 26.3 | 22.2 |
| **Presenting Stage of Sepsis** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Sepsis** | **<65** | 28.0 | 26.1 | 38.4 | 41.0 | 36.5 |
| | **65-74** | 26.0 | 23.7 | 36.9 | 37.7 | 33.1 |
| | **75-84** | 27.8 | 23.5 | 38.5 | 36.8 | 38.1 |
| | **85+** | 29.6 | 26.5 | 39.5 | 39.7 | 25.9 |
| **Severe Sepsis** | **<65** | 24.1 | 19.5 | 25.0 | 24.2 | 29.4 |
| | **65-74** | 24.7 | 21.0 | 26.7 | 24.2 | 33.1 |
| | **75-84** | 25.5 | 23.2 | 27.4 | 25.1 | 28.9 |
| | **85+** | 29.0 | 26.8 | 28.5 | 29.3 | 40.7 |
| **Septic Shock** | **<65** | 47.9 | 54.4 | 36.6 | 34.8 | 34.1 |
| | **65-74** | 49.4 | 55.3 | 36.4 | 38.1 | 33.8 |
| | **75-84** | 46.7 | 53.3 | 34.1 | 38.2 | 33.0 |
| | **85+** | 41.3 | 46.7 | 32.0 | 31.0 | 33.3 |
| **Organ Dysfunction** | | | | | | |
| Cardiovascular | **<65** | 54.8 | 61.0 | 45.8 | 41.4 | 37.9 |
| | **65-74** | 56.1 | 61.5 | 44.1 | 45.1 | 36.9 |
| | **75-84** | 53.1 | 59.5 | 41.6 | 44.8 | 36.1 |
| | **85+** | 49.3 | 51.7 | 40.6 | 39.7 | 37.0 |
| Hematologic | **<65** | 21.0 | 36.4 | 20.3 | 17.1 | 24.9 |
| | **65-74** | 18.5 | 27.9 | 18.3 | 18.3 | 12.5 |
| | **75-84** | 16.8 | 21.2 | 16.4 | 16.5 | 17.5 |
| | **85+** | 13.4 | 13.7 | 14.5 | 16.5 | 11.1 |
| Hepatic | **<65** | 6.1 | 12.6 | 3.4 | 2.6 | 5.0 |
| | **65-74** | 4.8 | 7.8 | 3.1 | 2.1 | 1.3 |
| | **75-84** | 4.1 | 4.9 | 2.4 | 3.0 | 1.0 |
| | **85+** | 3.1 | 3.1 | 2.1 | 0.8 | 0 |
| Neurologic | **<65** | 13.5 | 9.4 | 12.4 | 8.6 | 31.7 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | **65-74** | 15.5 | 10.4 | 19.0 | 14.8 | 41.3 |
| | **75-84** | 17.3 | 12.8 | 23.5 | 15.8 | 37.1 |
| | **85+** | 21.0 | 15.6 | 27.0 | 17.8 | 44.4 |
| Renal | **<65** | 49.2 | 55.9 | 62.5 | 53.1 | 32.9 |
| | **65-74** | 53.1 | 58.1 | 67.0 | 56.6 | 32.5 |
| | **75-84** | 57.4 | 58.7 | 66.7 | 55.4 | 33.0 |
| | **85+** | 59.8 | 63.3 | 67.3 | 58.4 | 70.4 |
| Respiratory | **<65** | 54.9 | 25.2 | 17.0 | 16.4 | 39.2 |
| | **65-74** | 56.3 | 24.6 | 19.2 | 19.3 | 41.9 |
| | **75-84** | 53.9 | 21.5 | 17.5 | 18.1 | 29.9 |
| | **85+** | 49.6 | 19.0 | 17.4 | 15.0 | 29.6 |

Supplementary Table 2.3: Effect Estimates of Hospital Mortality by Infection Source for Patients under Age 65

| | Number of Deaths | Person-days | Mortality Rate per 1,000 person-days | Mortality (%) | Crude Hazard Rate Ratio (95% Confidence Interval, p-value) | Adjusted Hazard Rate Ratio* (95% Confidence Interval, p-value) |
|---|---|---|---|---|---|---|
| **Respiratory Infection (n=16,987)** | 2,994 | 163,151 | 9.6 | 17.6 | **Referent** | |
| **Abdominal Infection (n=10,160)** | 2,495 | 103,440 | 10.2 | 24.6 | 1.31 (1.23-1.40, p<0.0001) | 1.01 (0.95-1.07, p=0.7064) |
| **Genitourinary Infection (n=14,755)** | 942 | 111,699 | 7.6 | 6.4 | 0.45 (0.41-0.49, p<0.0001) | 0.49 (0.45-0.53, p<0.0001) |
| **Skin, Soft Tissue, and Bone Infection (n=7,603)** | 622 | 81,627 | 10.7 | 8.2 | 0.42 (0.39-0.46, p<0.0001) | 0.48 (0.44-0.52, p<0.0001) |
| **CNS Infection (n=602)** | 117 | 6,635 | 11.0 | 19.4 | 0.98 (0.82-1.17, p=0.8010) | 1.29 (1.07-1.55, p=0.0072) |

* Adjusted for sex, Charlson-Deyo Comorbidity Index, emergency admission, and presenting stage of sepsis

Supplementary Table 2.4: Effect Estimates of Hospital Mortality by Infection Source for Patients Age 65-74

| | Number of Deaths | Person-days | Mortality Rate (per 1,000 person-days) | Mortality (%) | Crude Hazard Rate Ratio (95% Confidence Interval, p-value) | Adjusted Hazard Rate Ratio* (95% Confidence Interval, p-value) |
|---|---|---|---|---|---|---|
| **Respiratory Infection (n=7,607)** | 1,791 | 71,644 | 9.4 | 23.5 | **Referent** | |
| **Abdominal Infection (n=3,561)** | 874 | 36,094 | 10.1 | 24.5 | 0.97(0.90-1.04, p=0.3965) | 0.89 (0.82-0.97, p=0.0063) |
| **Genitourinary Infection (n=7,631)** | 689 | 59,860 | 7.8 | 9.0 | 0.46 (0.42-0.50, p<0.0001) | 0.51 (0.47-0.55, p<0.0001) |
| **Skin, Soft Tissue, and Bone Infection (n=2,223)** | 279 | 23,805 | 10.7 | 12.6 | 0.47 (0.42-0.53, p<0.0001) | 0.53 (0.47-0.59, p<0.0001) |
| **CNS Infection (n=160)** | 30 | 1,837 | 11.5 | 18.8 | 0.67 (0.47-0.95, p=0.0255) | 0.85 (0.61-1.19, p=0.3426) |

* Adjusted for sex, Charlson-Deyo Comorbidity Index, emergency admission, and presenting stage of sepsis

Supplementary Table 2.5: Effect Estimates of Hospital Mortality by Infection Source for Patients Age 75-84

| | Number of Deaths | Person-days | Mortality Rate (per 1,000 person-days) | Mortality (%) | Crude Hazard Rate Ratio (95% Confidence Interval, p-value) | Adjusted Hazard Rate Ratio* (95% Confidence Interval, p-value) |
|---|---|---|---|---|---|---|
| **Respiratory Infection (n=5,775)** | 1,470 | 49,822 | 8.6 | 25.5 | **Referent** | |
| **Abdominal Infection (n=2,189)** | 527 | 21,156 | 9.7 | 24.1 | 0.84 (0.77-0.92, p=0.0003) | 0.81 (0.73-0.89, p<0.0001) |
| **Genitourinary Infection (n=7,990)** | 866 | 61,410 | 7.7 | 10.8 | 0.47 (0.43-0.52, p<0.0001) | 0.53 (0.48-0.58, p<0.0001) |
| **Skin, Soft Tissue, and Bone Infection (n=1,385)** | 219 | 13,688 | 9.9 | 15.8 | 0.55 (0.47-0.63, p<0.0001) | 0.59 (0.51-0.68, p<0.0001) |
| **CNS Infection (n=97)** | 23 | 1,051 | 10.8 | 23.7 | 0.75 (0.52-1.08, p=0.1249) | 0.87 (0.60-1.26, p=0.4602) |

* Adjusted for sex, Charlson-Deyo Comorbidity Index, emergency admission, and presenting stage of sepsis

Supplementary Table 2.6: Effect Estimates of Hospital Mortality by Infection Source for Patients Age 85+

| | Number of Deaths | Person-days | Mortality Rate (per 1,000 person-days) | Mortality (%) | Crude Hazard Rate Ratio (95% Confidence Interval, p-value) | Adjusted Hazard Rate Ratio* (95% Confidence Interval, p-value) |
|---|---|---|---|---|---|---|
| **Respiratory Infection (n=3,748)** | 999 | 27,595 | 7.4 | 26.7% | **Referent** | |
| **Abdominal Infection (n=1,072)** | 279 | 9,096 | 8.5 | 26.0% | 0.87 (0.77-0.99, p=0.0305) | 0.85 (0.75-0.96, p=0.0095) |
| **Genitourinary Infection (n=6,148)** | 802 | 43,386 | 7.1 | 13.0% | 0.51 (0.46-0.57, p<0.0001) | 0.56 (0.51-0.62, p<0.0001) |
| **Skin, Soft Tissue, and Bone Infection (n=726)** | 139 | 6,153 | 8.5 | 19.2% | 0.64 (0.54-0.76, p<0.0001) | 0.74 (0.62-0.87, p=0.0004) |
| **CNS Infection (n=27)** | 5 | 269 | 10.0 | 18.5% | 0.55 (0.22-1.35, p=0.1896) | 0.57 (0.23-1.42, p=0.2291) |

* Adjusted for sex, Charlson-Deyo Comorbidity Index, emergency admission, and presenting stage of sepsis

Supplementary Table 2.7: Effect Estimates of Hospital Mortality by Infection Source for Patients Presenting with Sepsis

| | Number of Deaths | Person-days | Mortality Rate (per 1,000 person-days) | Mortality (%) | Crude Hazard Rate Ratio (95% Confidence Interval, p-value) | Adjusted Hazard Rate Ratio* (95% Confidence Interval, p-value) |
|---|---|---|---|---|---|---|
| **Respiratory Infection (n=9,453)** | 788 | 75,539 | 8.0 | 8.3% | **Referent** | |
| **Abdominal Infection (n=4,290)** | 368 | 40,321 | 9.4 | 8.6% | 0.85 (0.75-0.96, p=0.0069) | 0.80 (0.70-0.91 p=0.0007) |
| **Genitourinary Infection (n=13,974)** | 406 | 91,539 | 6.6 | 2.9 | 0.45 (0.40-0.50, p<0.0001) | 0.41 (0.36-0.45, p<0.0001) |
| **Skin, Soft Tissue, and Bone Infection (n=4,753)** | 139 | 46,436 | 9.8 | 2.9% | 0.28 (0.23-0.34, p<0.0001) | 0.30 (0.25-0.36, p<0.0001) |
| **CNS Infection (n=317)** | 35 | 3,488 | 11.0 | 11.0% | 0.95 (0.68-1.32, p=0.7434) | 1.26 (0.89-1.79, p=0.1932) |

* Adjusted for age, sex, Charlson-Deyo Comorbidity Index, and emergency admission

Supplementary Table 2.8: Effect Estimates of Hospital Mortality by Infection Source for Patients Presenting with Severe Sepsis

| | Number of Deaths | Person-days | Mortality Rate (per 1,000 person-days) | Mortality (%) | Crude Hazard Rate Ratio (95% Confidence Interval, p-value) | Adjusted Hazard Rate Ratio* (95% Confidence Interval, p-value) |
|---|---|---|---|---|---|---|
| **Respiratory Infection (n=8,530)** | 1,469 | 78,453 | 9.2 | 17.2% | **Referent** | |
| **Abdominal Infection (n=3,527)** | 753 | 36,307 | 10.3 | 21.4% | 1.09(0.98-1.21, p=0.1160) | 1.03 (0.93-1.15, p=0.5414) |
| **Genitourinary Infection (n=9,675)** | 694 | 72,311 | 7.5 | 7.2% | 0.53 (0.48-0.58, p<0.0001) | 0.48 (0.44-0.53, p<0.0001) |
| **Skin, Soft Tissue, and Bone Infection (n=2,940)** | 237 | 31,416 | 10.7 | 8.1% | 0.40 (0.35-0.46, p<0.0001) | 0.41 (0.35-0.47, p<0.0001) |
| **CNS Infection (n=269)** | 39 | 3,216 | 12.0 | 14.5% | 0.63 (0.47-0.84, p=0.0019) | 0.74 (0.54-1.00, p=0.0493) |

* Adjusted for age, sex, Charlson-Deyo Comorbidity Index, and emergency admission

Supplementary Table 2.9: Effect Estimates of Hospital Mortality by Infection Source for Patients Presenting with Septic Shock

| | Number of Deaths | Person-days | Mortality Rate (per 1,000 person-days) | Mortality (%) | Crude Hazard Rate Ratio (95% Confidence Interval, p-value) | Adjusted Hazard Rate Ratio* (95% Confidence Interval, p-value) |
|---|---|---|---|---|---|---|
| **Respiratory Infection (n=16,134)** | 4,997 | 158,220 | 9.8 | 31.0% | **Referent** | |
| **Abdominal Infection (n=9,165)** | 3,054 | 93,158 | 10.2 | 33.3% | 1.04 (0.99-1.09, p=0.1149) | 1.00 (0.96-1.05, p=0.9554) |
| **Genitourinary Infection (n=12,875)** | 2,199 | 112,505 | 8.7 | 17.1% | 0.60 (0.57-0.64, p<0.0001) | 0.57 (0.54-0.61, p<0.0001) |
| **Skin, Soft Tissue, and Bone Infection (n=4,244)** | 883 | 47,421 | 11.2 | 20.8% | 0.60 (0.55-0.66, p<0.0001) | 0.63 (0.58-0.68, p<0.0001) |
| **CNS Infection (n=300)** | 101 | 3,088 | 10.3 | 33.7% | 1.05 (0.88-1.26, p=0.5810) | 1.18 (0.98-1.42, p=0.0790) |

* Adjusted for age, sex, Charlson-Deyo Comorbidity Index, and emergency admission

# CHAPTER III

# RECENT TRENDS IN SEPSIS DIAGNOSIS AND MORTALITY

## Abstract

**Objective**: To highlight recent trends in the reporting of diagnoses and case fatality rates of present-on-admission sepsis hospitalizations

**Method**: We conducted a retrospective cohort study using Cerner HealthFacts® data from October 1, 2008 through June 30, 2014. ICD-9CM diagnoses and present-on-admission (POA) notation was used to identify hospitalizations with sepsis, severe sepsis, or septic shock and trends in diagnosis and case fatality rates were evaluated.

**Results**: At the end of the study period, there was a rate of reported diagnosis for sepsis, severe sepsis, or septic shock of 624 per 100,000 hospitalizations and a case fatality rate of 10.8%. From the fiscal year beginning October 1, 2008 through June 30, 2014, there was a statistically significant decline in the reporting of POA sepsis diagnoses (β-estimate = -104.5, p=0.0051). There was also a statistically significant decrease in case fatality rate over the study period (β-estimate = -1.77, p=0.0014).

**Conclusions**: This study found decreasing trends of POA sepsis in the context of increases of overall sepsis diagnosis. A decrease in case fatality rate was also observed, possibly representing better care for patients with sepsis or an inflation of denominator due to the residual effects of increased numbers of diagnoses, a dispute ongoing in the literature.

## Introduction

Recent investigations into trends of incidence and mortality from sepsis have been limited to academic medical centers[81], while other investigations of trends in incidence and mortality are now outdated or did not consider the full spectrum of disease comprising sepsis, severe sepsis, and septic shock.[4,5,69,82–84] Increased attention to sepsis due to educational campaigns[74] and Centers for Disease Control programs[23] emphasizing patient advocacy directed at asking patients to raise concerns of sepsis and clinician awareness have led to a focus on improving recognition and treatment which may affect the trends observed among reporting of diagnosis and case fatality rates. Yet, there remains disagreement and questions about sepsis diagnosis and fatality rates, and variations world-wide.[85] Additionally, prior work has suggested that the oldest old, who make up an increasing proportion of healthcare utilization, may be driving trends upward among patients with sepsis, although there may be different patterns of sepsis identification and recognition due to physiologic changes leading to different disease presentation in this population, rendering evolving disease more difficult to recognize for clinicians.[34]

In addition to changes in recognition and treatment of sepsis, systematic changes in coding practices and variable definitions of severe sepsis in administrative data have led to discrepancies in estimates of sepsis incidence and mortality.[86] Further, the implementation of the present-on admission (POA) indicator, resulting in payment penalties to hospitals for preventable conditions that were not coded as POA, has led to increased attention to sepsis due to community acquired infections.[43] Hospitalizations

with sepsis coded as POA reflect presumably community acquired instances of sepsis and present an opportunity for further educational efforts targeted to healthcare consumers and practitioners to reduce the burden of disease in the community setting and to focus on early identification and swift treatment to intervene before disease progression to organ dysfunction with the accompanying higher mortality.

This paper seeks to understand recent trends in POA sepsis incidence and mortality and provide an update to the existing understanding of trends in this disease process. This paper additionally seeks to analyze subgroups of patients by age and presenting stage of sepsis to determine whether there are differences in trends occurring among the oldest, most vulnerable groups of patients affected by sepsis.

## Methods

### Study Design and Setting

The HealthFacts® database is maintained by Cerner Corporation (Kansas City, MO), one of the largest electronic health record (EHR) vendors in the US. Data is contributed by both community and academic hospitals and checked for quality, as well as deidentified and made HIPAA compliant. Over 500 hospitals contribute data annually, representing 133 million hospital encounters and 84 million unique patients through the timespan covered by the database.[48] HealthFacts contains information about a person's hospital encounter, including diagnoses, demographics, and vital status at discharge. The POA indicator was implemented for all hospital systems nationwide starting on October 1, 2007. HealthFacts is updated regularly, and at the time of this manuscript, contains data through June 30, 2014.

**Eligibility Criteria**

To be considered for the study, patients must have had a hospital discharge date during the study period (10/1/2008-6/30/2014), be aged 18 years or older at admission, and have a diagnosis of sepsis, severe sepsis or septic shock coded as present at the time of hospital admission. Diagnoses of sepsis, severe sepsis, and septic shock were determined using ICD-9CM codes. (Supplementary Table 3.1) Timing of diagnosis of cases was determined using the POA indicator. This method of determining POA status has been validated in other infectious processes[61] and found to be valid and reliable. Only encounters from hospitals contributing data to all years in the study period were considered eligible, so as to account for potential differences in coding practices at different institutions and differences in the case mix of the population at different contributing institutions.

**Age Strata**

Encounters were classified according to age group at the time of admission. Age categories were: 18-34, 35-64, 65-74, 75-84, and 85+, with the last three categories reflecting the census categorizations of the young old, middle old, and oldest old.

**Statistical Analyses**

We categorized diagnoses by presenting stage of sepsis and presented changes of incidence rates over the years of the study. If multiple ICD-9CM codes were present, priority was given to the most severe stage of sepsis coded as POA i.e. if codes for both septic shock and severe sepsis were coded as POA, the patient's encounter would have

been classified as presenting with septic shock. Linear regression models were used to test for linear trends over time. SAS 9.4 (SAS Institute, Cary, NC) was used for all analysis. All rates were calculated to be expressed as per 100,000 hospitalizations. Case fatality rates were calculated as the number of deaths divided by the number of sepsis diagnoses in a given year; linear regression models were again used to test for trends over time.

An additional sensitivity analysis was performed to investigate trends for sepsis that was not indicated as POA to assess this study's comparability with other studies investigating trends of sepsis diagnosed and documented at any point within the hospital stay.

This research was reviewed by the University of Massachusetts Institutional Review Board and determined to not be human subjects research.

## Results

68 hospitals contributed data continuously over each year in the study. Over the study period, there were 5,090,729 hospitalizations. (Figure 3.1) Of these hospitalizations, 45,581 had a sepsis, severe sepsis, or septic shock diagnosis noted as POA. Patients comprising the 18-34 year old age group comprised a relative minority (5-9%) of all patients admitted to the hospital with sepsis, severe sepsis, or septic shock. The majority of hospitalizations presenting with sepsis, severe sepsis, or septic shock were among patients aged 35-64 years old, with hospitalizations of patients aged 65-74 or 75-84 comprising roughly two-fifths of hospitalizations for sepsis, severe sepsis, or septic

shock in any given year. The oldest-old patients (aged 85+) comprised 11-17% of patients with hospitalizations for sepsis, severe sepsis, or septic shock. Almost two-thirds of hospitalizations presented with sepsis, although this does not exclude the possibility that these hospitalizations later progressed to severe sepsis or septic shock after admission to the hospital. Approximately one-fifth of hospitalizations presented with severe sepsis, and approximately 15% presented with septic shock at the time of their hospitalization. (Table 3.1)

After an initial increase during the first year of the study, decreases in POA diagnosis rates over all subsequent years for all presenting stages of sepsis, sepsis, severe sepsis, and septic shock were observed. (Figure 3.2) Linear trends were statistically significant for all presenting stages of sepsis. (Table 3.2) We noted trends for aggregated incidence of hospitalization for a sepsis related diagnosis were similar across age categories. We also noted a striking difference and direct relationship in age and the incidence of sepsis related hospitalizations. (Figure 3.3) While the overall trends in diagnoses were the same, there were differences among the age categories. The lowest rates of diagnosis of sepsis over the course of the study were among those aged 18-34 with rates moving from 269.2 diagnoses per 100,000 hospitalizations to 202.2 diagnoses per 100,000 hospitalizations at study end. These lowest rates of diagnosis in the 18-34 age group also held for severe sepsis (84.0 diagnoses/100,000 hospitalizations for 2008 to 60.8 diagnoses/100,000 hospitalizations for 2013) and septic shock (50.6 diagnoses/100,000 hospitalizations for 2008 to 26.9 diagnoses/100,000 hospitalizations for 2013). For any given year of the study, rates of diagnosis of sepsis, severe sepsis, or

septic shock were similar among patients aged 65-74, 75-84, and 85+. Patients aged 35-64 had comparable rates of diagnosis of sepsis or severe sepsis to those in older age categories, but septic shock diagnoses occurred at rates lower than those in older age categories. (Figure 3.3a-c, Supplementary Table 3.2)

Overall, absolute case fatality rates decreased by 10.7% for hospitalizations presenting with sepsis, 16.6% for severe sepsis, and 19.7% for septic shock. Case fatality rates were lowest for patients presenting with sepsis, higher for patients presenting with severe sepsis, and higher still for patients presenting with septic shock. (Figure 3.4) In general, the highest case fatality rates were observed in hospitalizations for those 85+, but this difference was most apparent in hospitalizations for patients presenting with sepsis compared to other age groups in those presenting with sepsis. (Figure 3.5) It is worth noting that a significant decline in case fatality rates was observed for even the oldest old patients for any presenting stage of sepsis. (Supplementary Table 3.2)

All sepsis diagnoses, e.g. those that were not limited to those present at the time of admission, showed an overall increase, with nearly a 10-fold increase from fiscal year 2008 to fiscal year 2014. (Supplementary Figure 3.1) There was little variability in the total number of overall hospitalizations during this same time period, indicating that the denominators for calculating diagnosis rates were similar across years of the study. (Supplementary Figure 3.2)

## Discussion

Overall, this study found a significant downward trend of presumably community-acquired diagnosis of sepsis, severe sepsis, and septic shock, using the POA indicator. This trend was consistent among all age subgroups. We also found a consistent downward trend of sepsis-related case fatality rates, even among the oldest old patients and most severely ill patients included in the study.

The findings of this study add to and support the current literature. There has been a documented downward trend in mortality from sepsis regardless of methods of evaluating trends.[4,70] The crude rate of reported sepsis diagnoses was higher in this study compared to other studies, although the case fatality rates were comparable, likely due to the inclusion of the full spectrum of sepsis diagnoses available. Like other studies[5,87,88], we did observe a continuing upward trend of all reported sepsis diagnoses; however, we found a decrease in reported diagnoses of POA sepsis. Our sensitivity analyses documented a trend of increasing diagnoses of all forms of sepsis consistent with prior studies. A number of potential explanations exist for these findings. Increased recognition, furthered by the efforts of educational outreaches such as the Surviving Sepsis Campaign and other organizations, could have led to increased reporting of diagnoses. Indeed, the Surviving Sepsis campaign released a major communication in 2008, temporally associating itself with the requirement of POA coding of diagnoses observed in this study.[89] Differences in coding within administrative databases can also lead to discrepancies of reported trends.[90] There is also the possibility of increased incidence of the underlying infections that progress to sepsis, although other

investigations have concluded that this is an unlikely explanation.[68] Further, this study focuses on a unique subset of all reported sepsis diagnoses, those diagnoses specifically designated as POA, and extends the years under study which raises the possibility of trends continuing to change while the practice of POA coding and documentation continues to stabilize as it is implemented and standardized.

The advent of POA coding has led to increased focus on both the accuracy of coding and the impact systematic changes of coding practice have on large scale trends across disease processes.[42,91] However, the consistency of the trends observed from our study leads to further speculation about non-systematic factors that may also influence trends. Changes of incidence of reporting of sepsis diagnoses are likely related to changes of recognition among clinical providers in part due to the myriad of quality improvement and other projects dedicated to rapid recognition of the patient with new or evolving infection and organ dysfunction.[22] In addition, there is further investigation warranted into the study of clinician patterns of documentation to standardize what appears in the electronic medical record and to determine patterns of clinician behavior.

Our study found decreases of sepsis related case fatality regardless of presenting stage of sepsis. Concerns of false deflations of sepsis-related mortality due to higher rates of reported diagnoses for sepsis appear not to play a major role in this study as we found both that rates of reported sepsis diagnoses were decreasing for our study and that percent from baseline changes were similar among sepsis, severe sepsis, and septic shock. Higher case fatality rates in older adults are possibly explained by differences in immune

function, presenting signs and symptoms of sepsis that may be more difficult to recognize, and weakened barrier functions.[34] However, case fatality rates decreased among all age groups, suggesting that additional factors, such as improving evidence based treatments for sepsis, are having the intended effect.[17] This combination of findings, with both decreases in POA diagnosis rates and case fatality rates, suggests that there is measurable improvement in the management and care of patients with sepsis.

This study has a number of limitations. First, by only including POA cases of sepsis, the findings of this study do not apply to cases of sepsis acquired within the hospital, although a small proportion of included hospitalizations may represent transfer of patients between care institutions who could represent healthcare acquired infections. Findings for POA cases of sepsis may represent potential opportunities for caregivers outside of inpatient settings to identify and begin management of patients with sepsis, thereby contributing to lower acuity at the time of hospital presentation and improved outcomes. Defining cases by ICD-9CM diagnoses means we may have missed instances of sepsis, particularly of severe sepsis. However, using this definition allows us to understand better what is being documented as a result of the POA implementation and offers a very specific rather than sensitive definition. We were unable to adjust for a number of other factors, such as severity of illness and comorbidities, that likely affect a patient's course of illness and outcomes from sepsis. We were also unable to account for physican and other healthcare provider characteristics that may affect diagnosis and management, as volume of sepsis cases and clinical biases have been shown to play a role in identification and early recognition of patients with sepsis.[92,93] Selection bias may

affect these results, as only hospitals who contributed data for all years of the study were included, and system level variables may affect decisions of which EHR system is used therefore affecting systematic documentation practices. Finally, the findings of this study may not be generalizable to hospital systems not using the Cerner EHR system.

This study adds to the existing body of evidence for epidemiologic trends of sepsis and extends the field by expanding to include hospitalizations through the midpoint of 2014. This study also leverages a large clinical database, and uses that to extend our study through the full spectrum of sepsis progression. While this study supports improvements in the treatment of patients with sepsis as evidenced by the decrease in case fatality rates, much work remains to be done to improve the recognition and care of patients with sepsis. With the recent move in the United States to ICD-10 coding, as well as the implementation of new sepsis definitions, care guidelines, and reimbursement metrics,[9,11,13] there remains a role for investigation into epidemiologic trends of diagnosis and mortality of sepsis and leveraging the power of large clinical datasets containing clinically relevant indicators.

Table 3.1: Baseline Characteristics by Fiscal Year

| | 2008 (n=9,777) | 2009 (n=11,033) | 2010 (n=8,146) | 2011 (n=7,126) | 2012 (n=4,767) | 2013 (n=3,536) |
|---|---|---|---|---|---|---|
| **Age Group in Years** | | | | | | |
| **18-34** | 5.8% | 5.9% | 6.1% | 5.2% | 6.7% | 8.3% |
| **35-64** | 40.5% | 42.8% | 39.6% | 38.7% | 37.6% | 40.1% |
| **65-74** | 19.4% | 18.7% | 19.5% | 19.5% | 22.0% | 22.3% |
| **75-84** | 20.4% | 20.0% | 19.8% | 19.7% | 19.0% | 16.9% |
| **85+** | 14.0% | 12.6% | 16.0% | 16.9% | 14.7% | 12.5% |
| **Presenting Stage of Sepsis** | | | | | | |
| **Sepsis** | 61.0% | 59.2% | 58.9% | 59.4% | 60.1% | 59.8% |
| **Severe Sepsis** | 24.0% | 25.6% | 25.5% | 25.6% | 25.8% | 26.8% |
| **Septic Shock** | 17.1% | 11.5% | 15.6% | 15.0% | 14.1% | 13.4% |

Table 3.2: Beta-estimates for Linear Regressions of Trends over Time

| | Diagnosis Rates | | Case Fatality Rates | |
|---|---|---|---|---|
| **Presenting Stage** | Beta-estimate (95% Confidence interval) | p-value for trend | Beta-estimate (95% Confidence Interval) | p-value for trend |
| **Sepsis** | -104.52 (-156.71 to -52.34) | 0.0051 | -1.77 (-2.49 - -1.05) | 0.0014 |
| **Severe Sepsis** | -40.13 (-67.03 to -13.23) | 0.0143 | -2.97 (-3.86 - -2.07) | 0.0004 |
| **Septic Shock** | -28.06 (-42.08 to -14.03) | 0.0051 | -3.25 (-4.28 - -2.23) | 0.0004 |

Figure 3.1 Population Selection

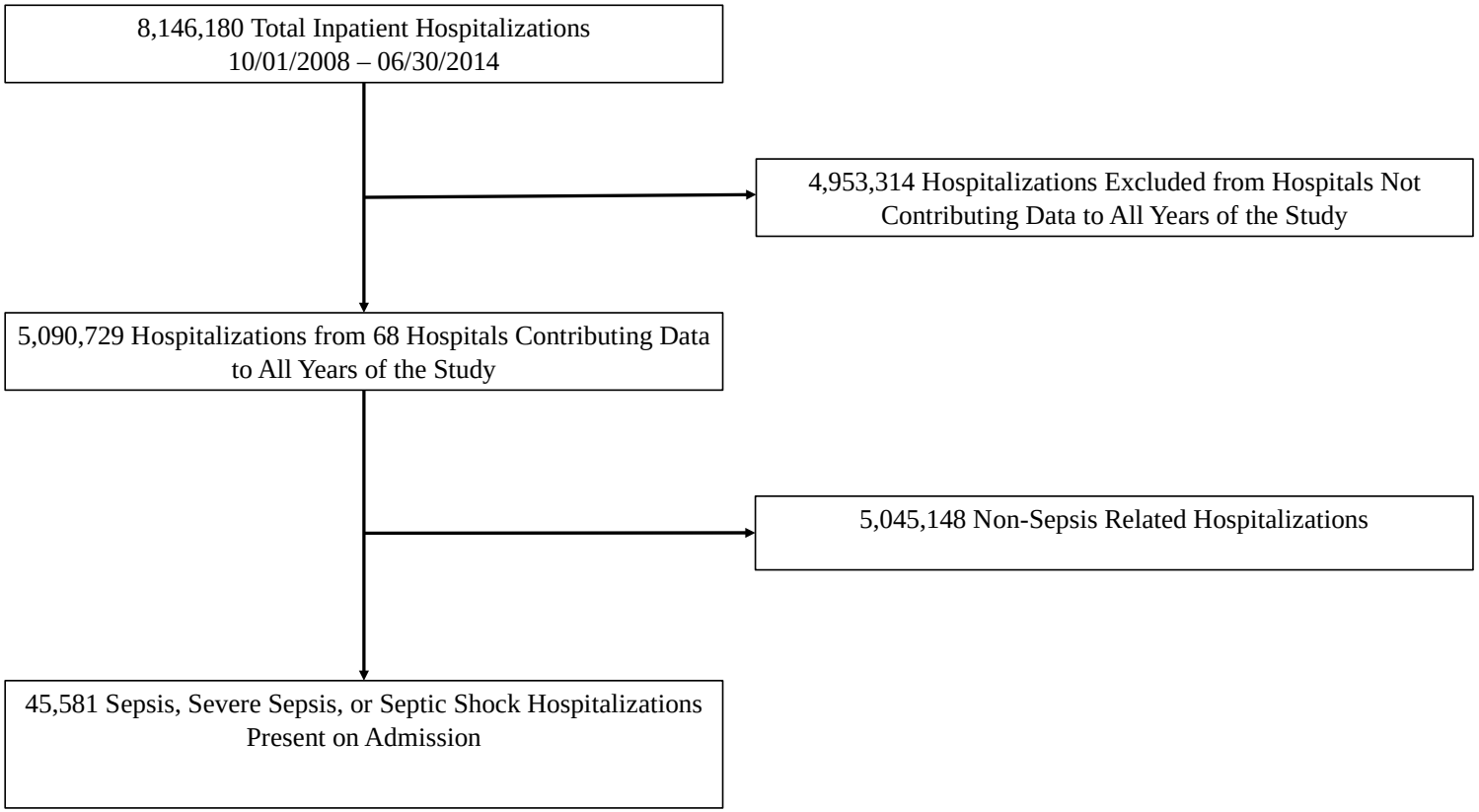


Figure 3.2: Sepsis Diagnoses per 100,000 Hospitalizations

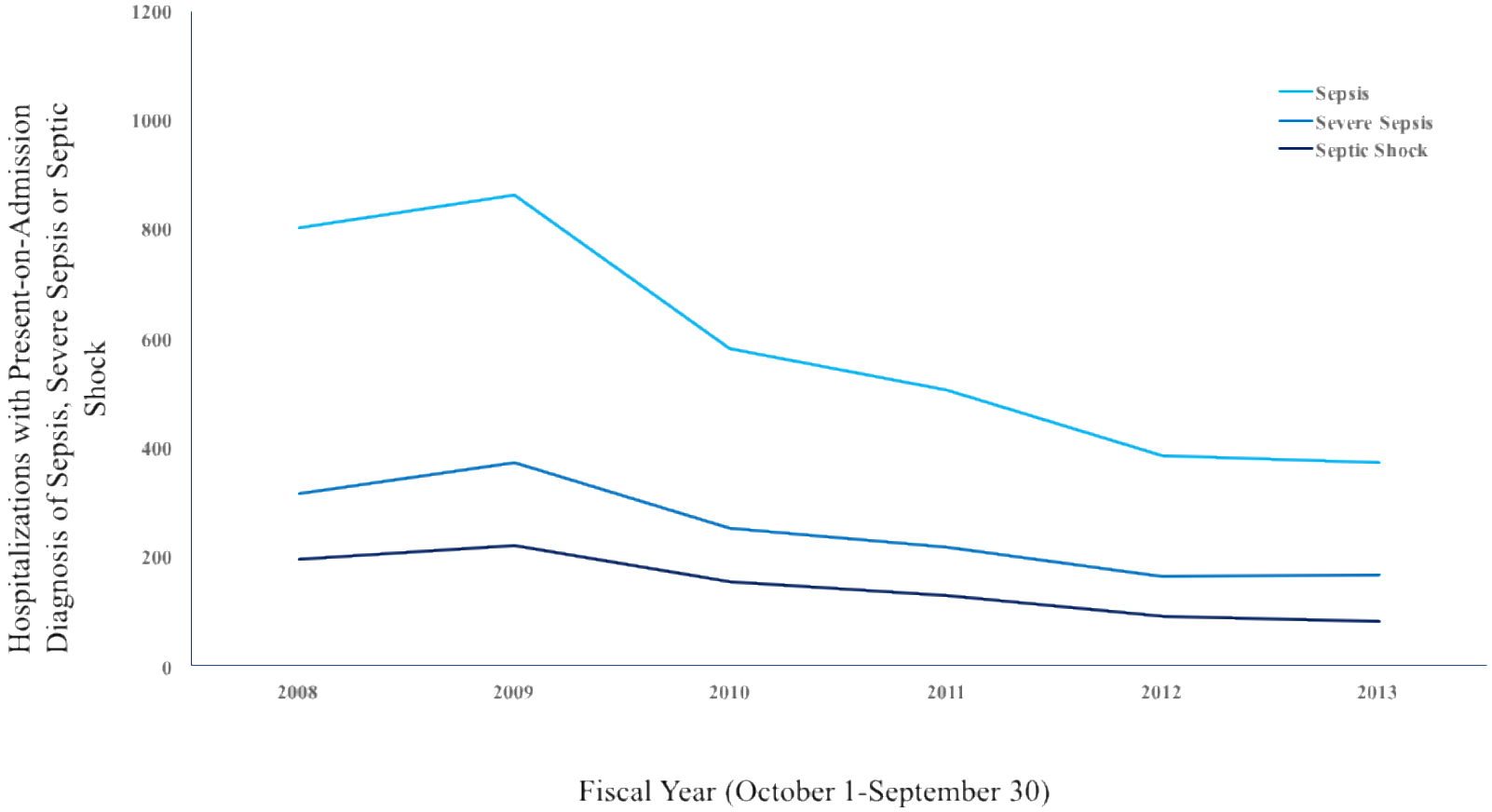


Figure 3.3a: Sepsis Diagnoses by Age Group per 100,000 Hospitalizations

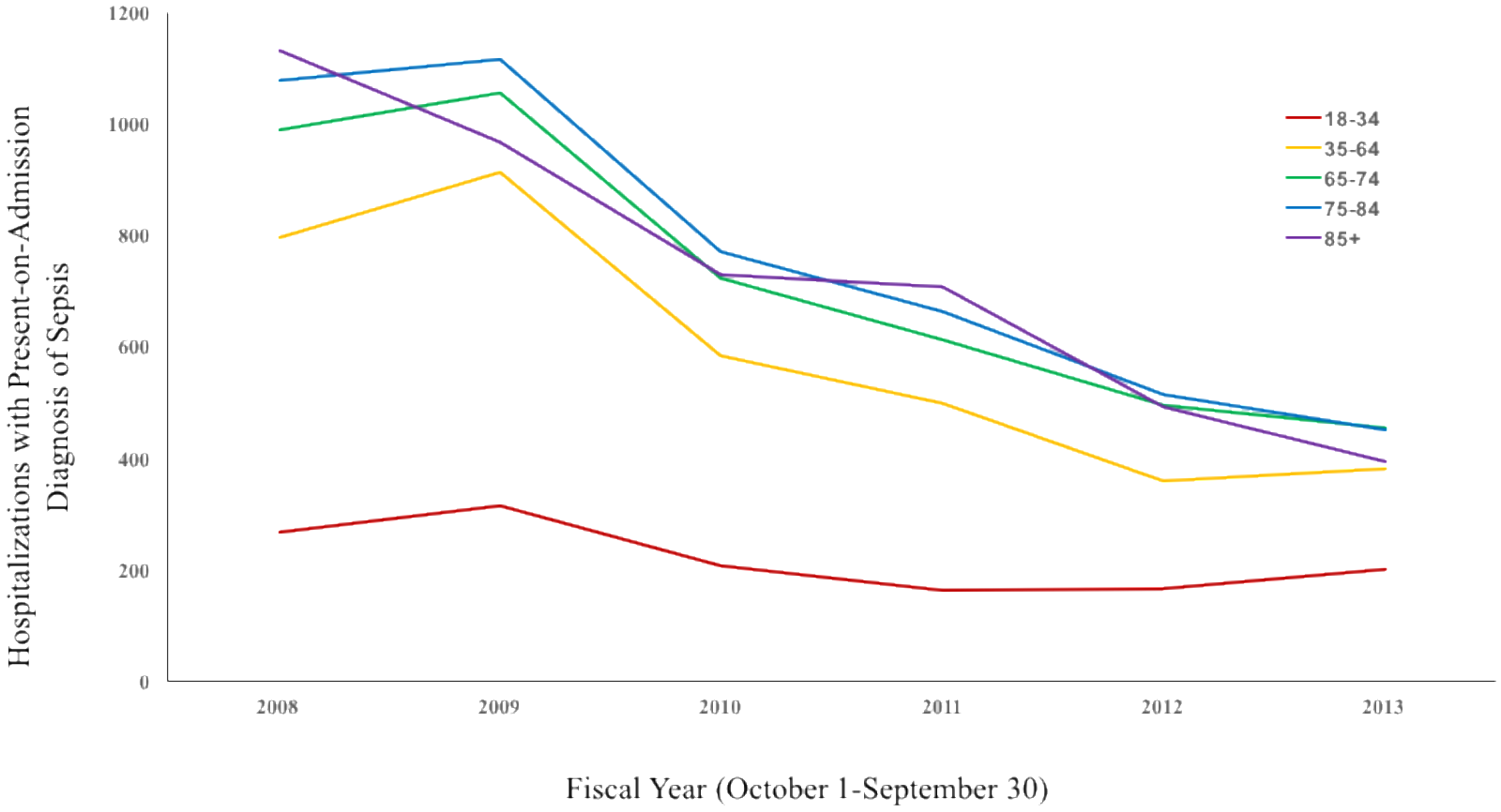


Figure 3.3b: Severe Sepsis Diagnoses by Age Group per 100,000 Hospitalizations

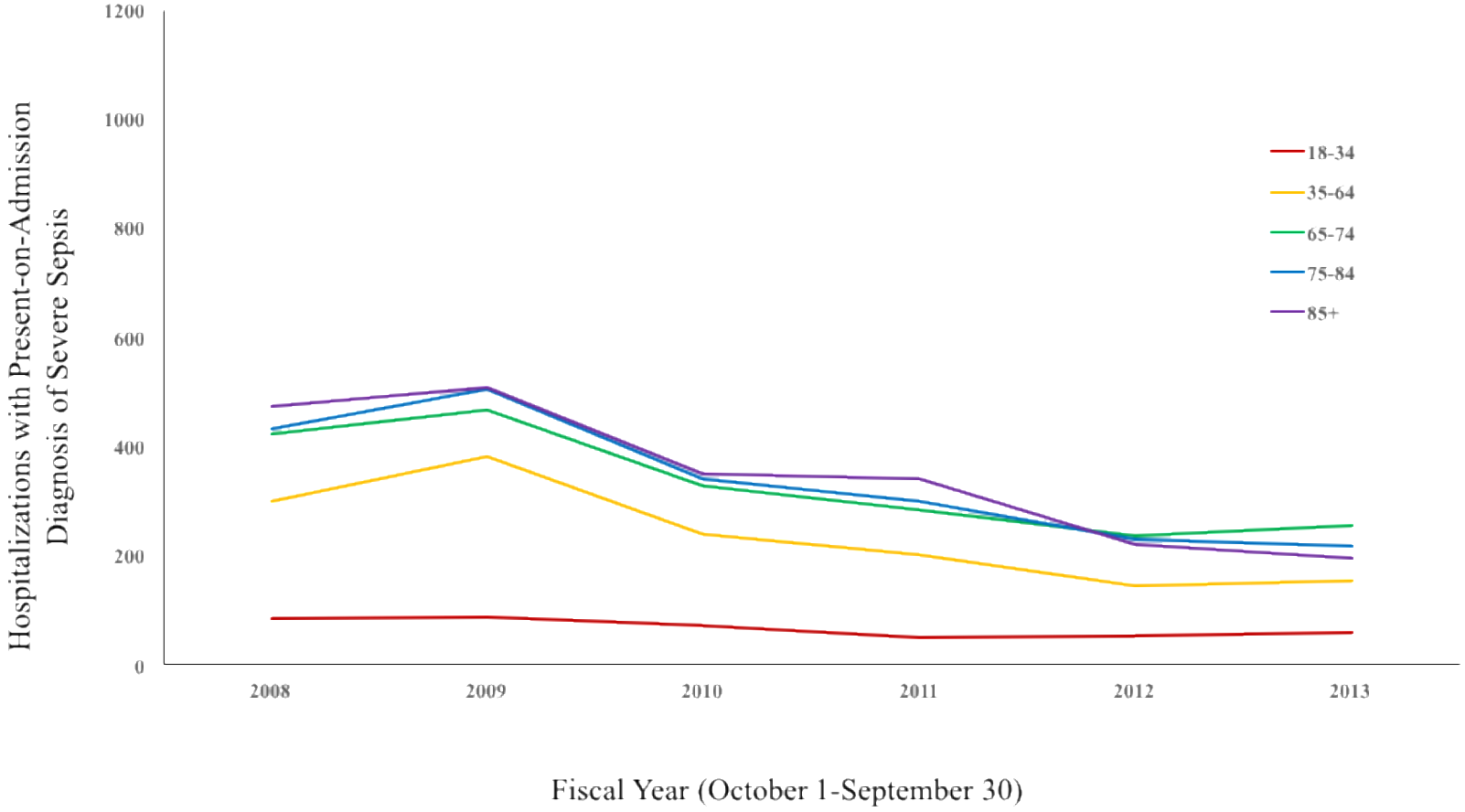


Figure 3.3c: Septic Shock Diagnoses by Age Group per 100,000 Hospitalizations

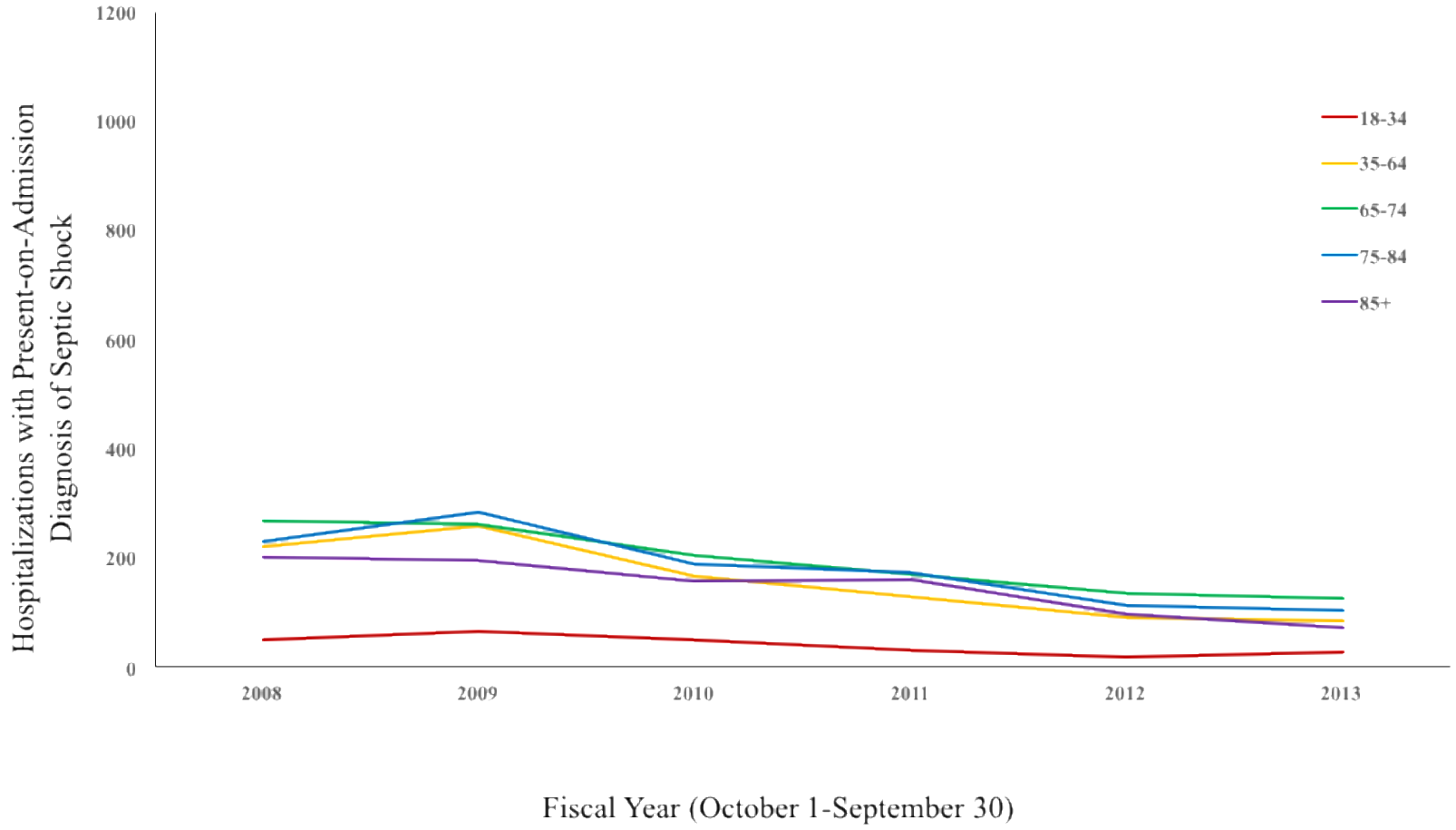


Figure 3.4: Case Fatality Rates for Patients with Sepsis, Severe Sepsis, or Septic Shock

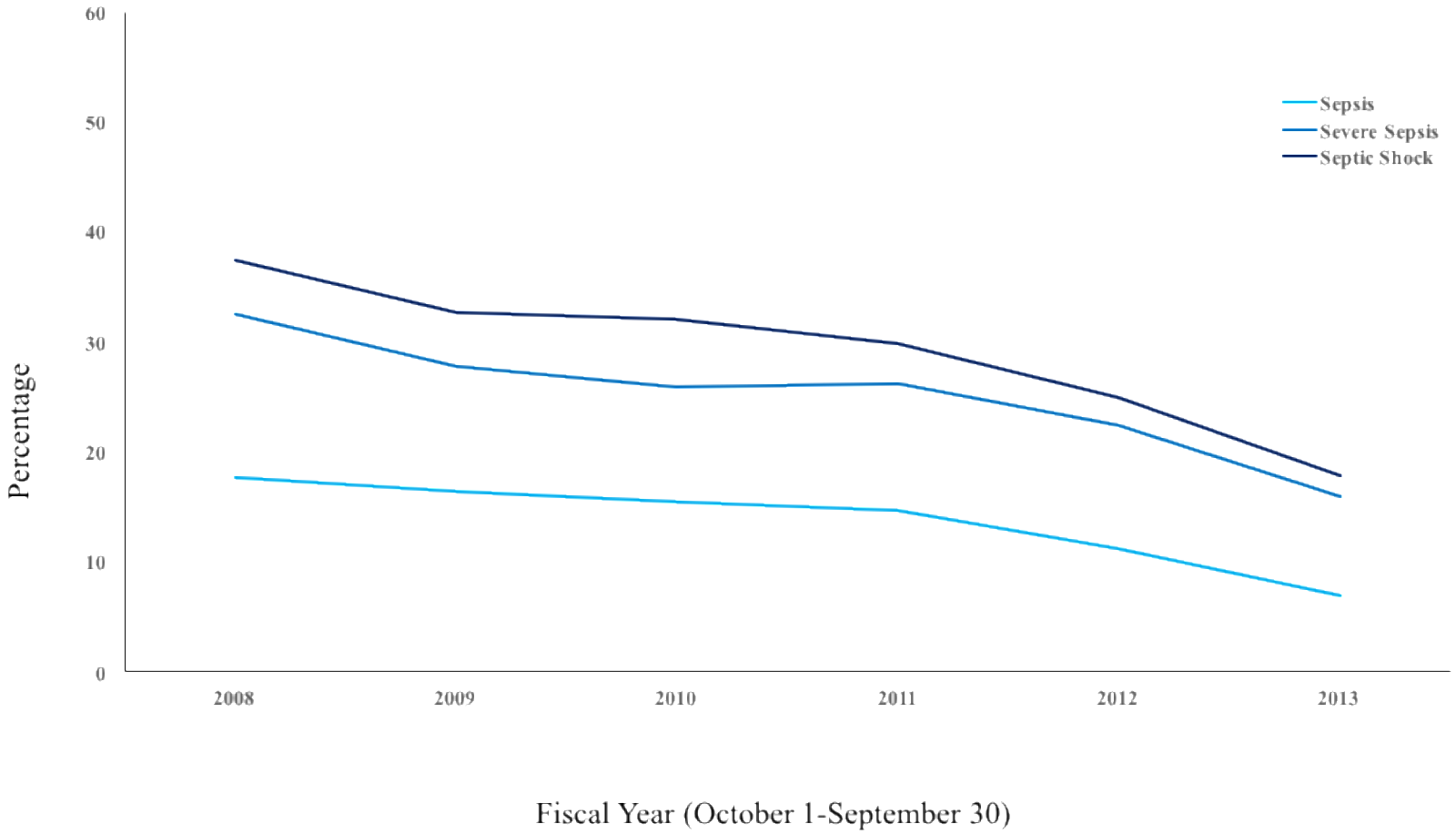


Figure 3.5a: Case Fatality Rates for Patients with Sepsis by Age Group

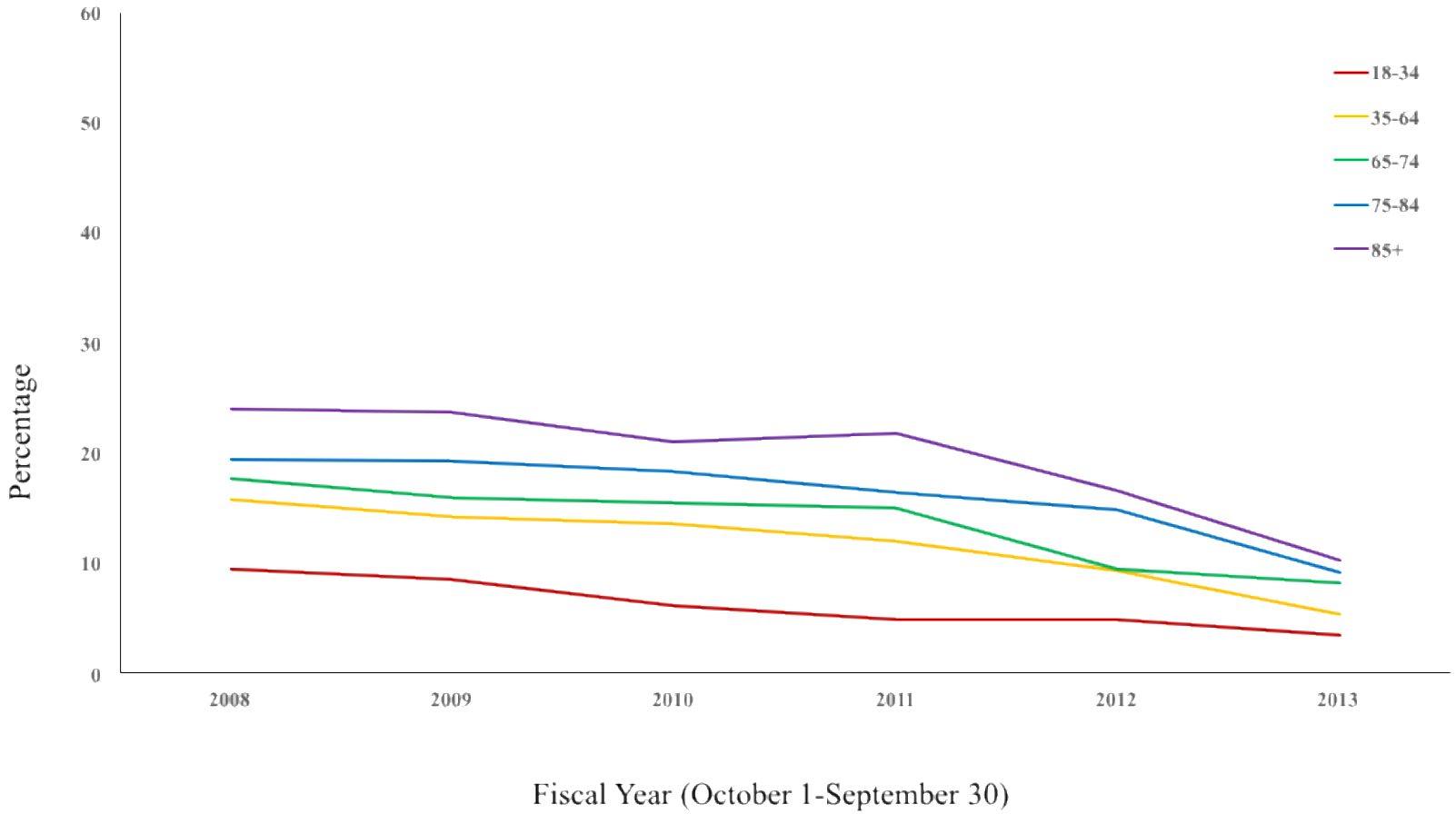


Figure 3.5b: Case Fatality Rates for Patients with Severe Sepsis by Age Group

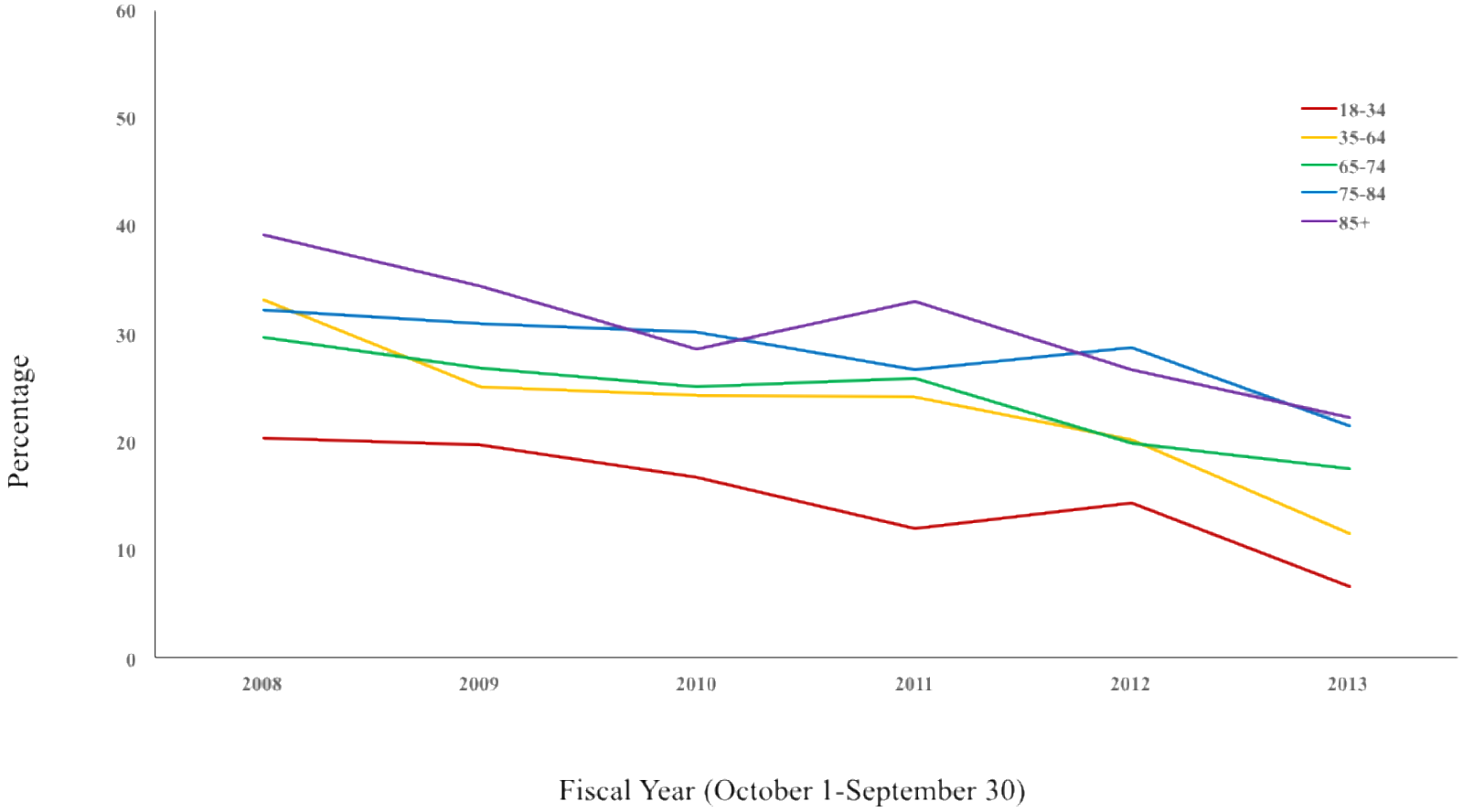
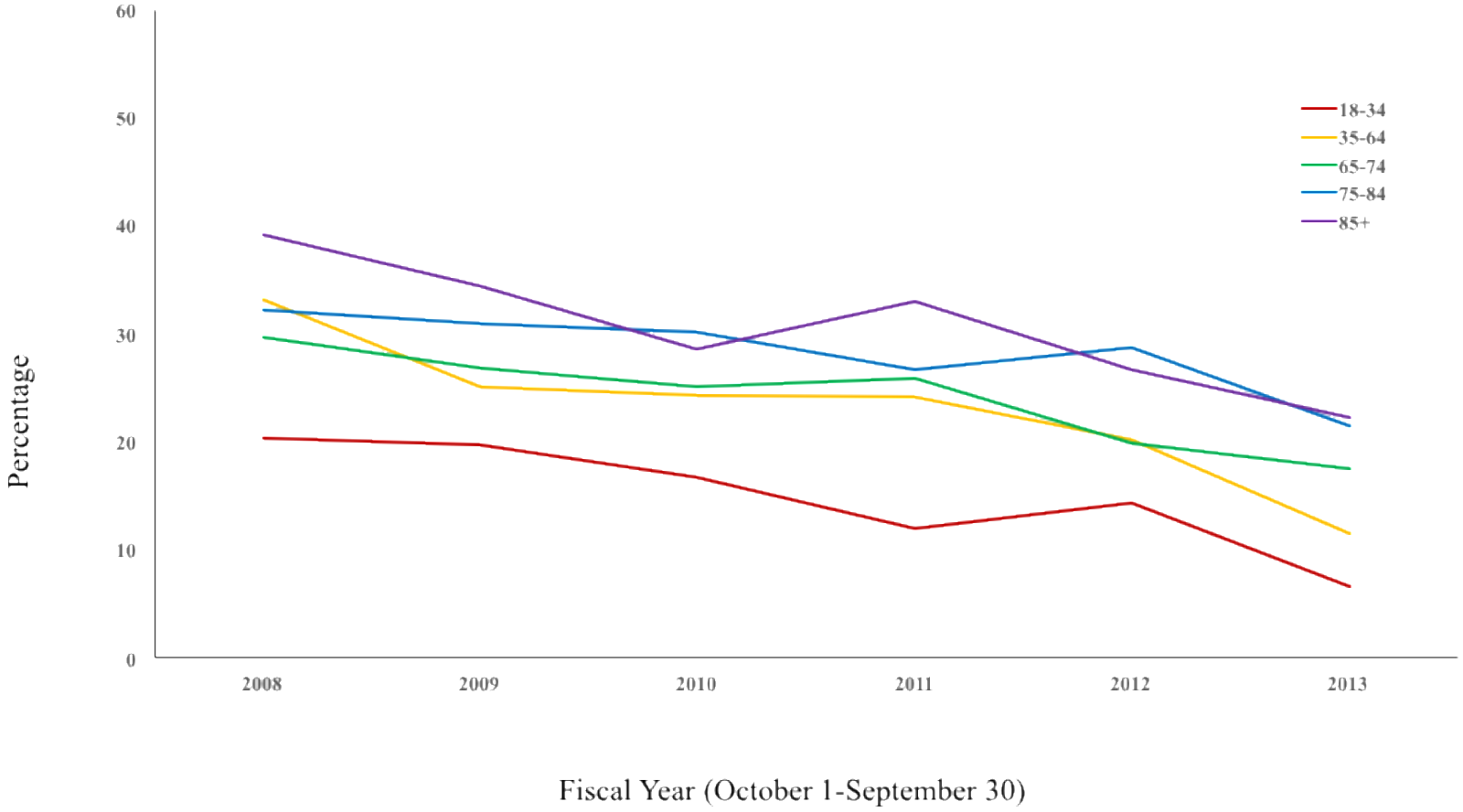


Figure 3.5c: Case Fatality Rates for Patients with Septic Shock by Age Group



Supplementary Table 3.1: ICD-9CM Diagnosis Codes for Sepsis, Severe Sepsis, and Septic Shock

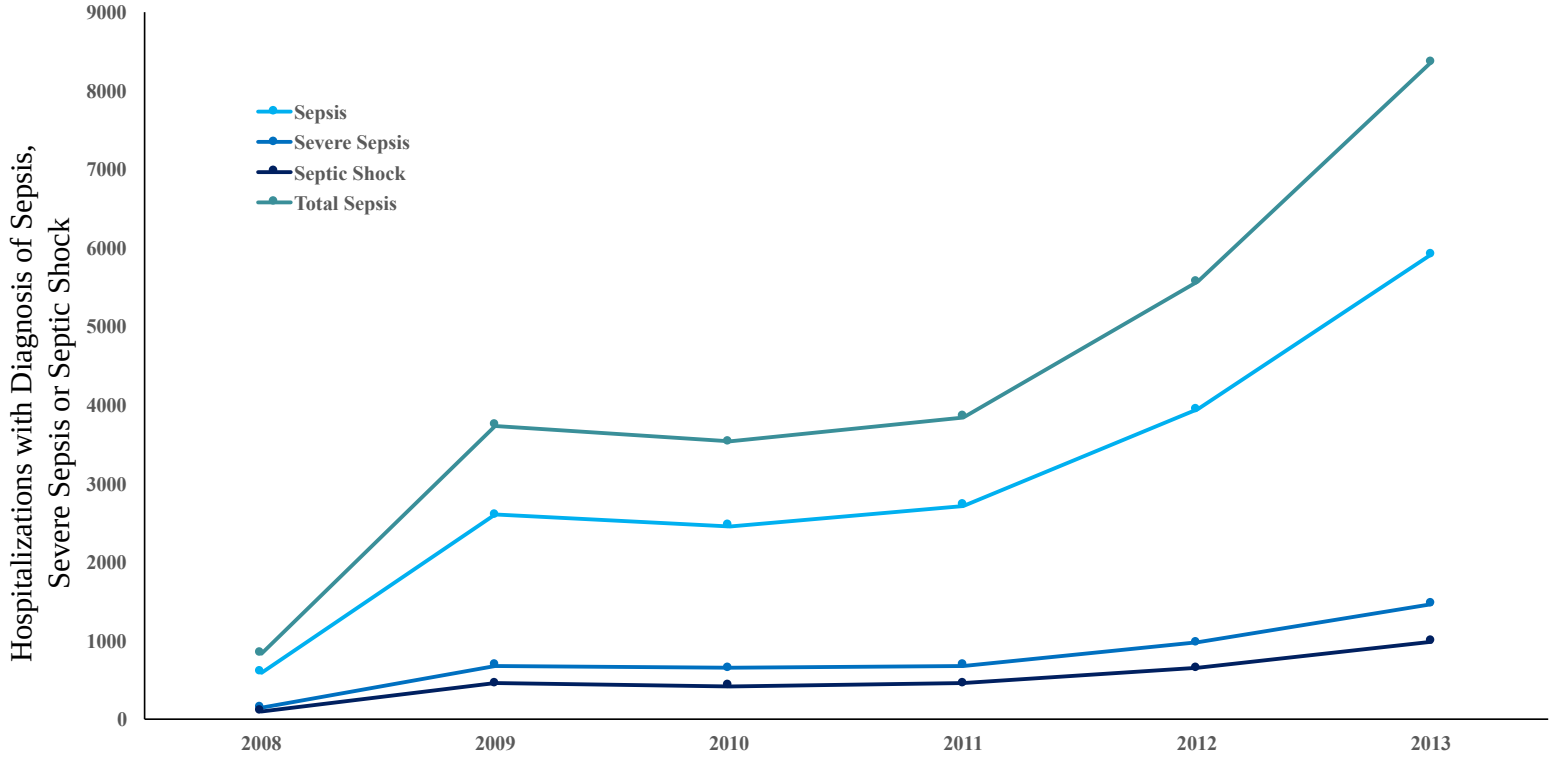
| | ICD-9CM Codes |
|---|---|
| **Sepsis** | 995.91, 038 |
| **Severe Sepsis** | 995.92 |
| **Septic Shock** | 785.5 |

Supplementary Table 3.2: Beta-Estimates from Linear Regression of Trends over Time for Age Subgroups

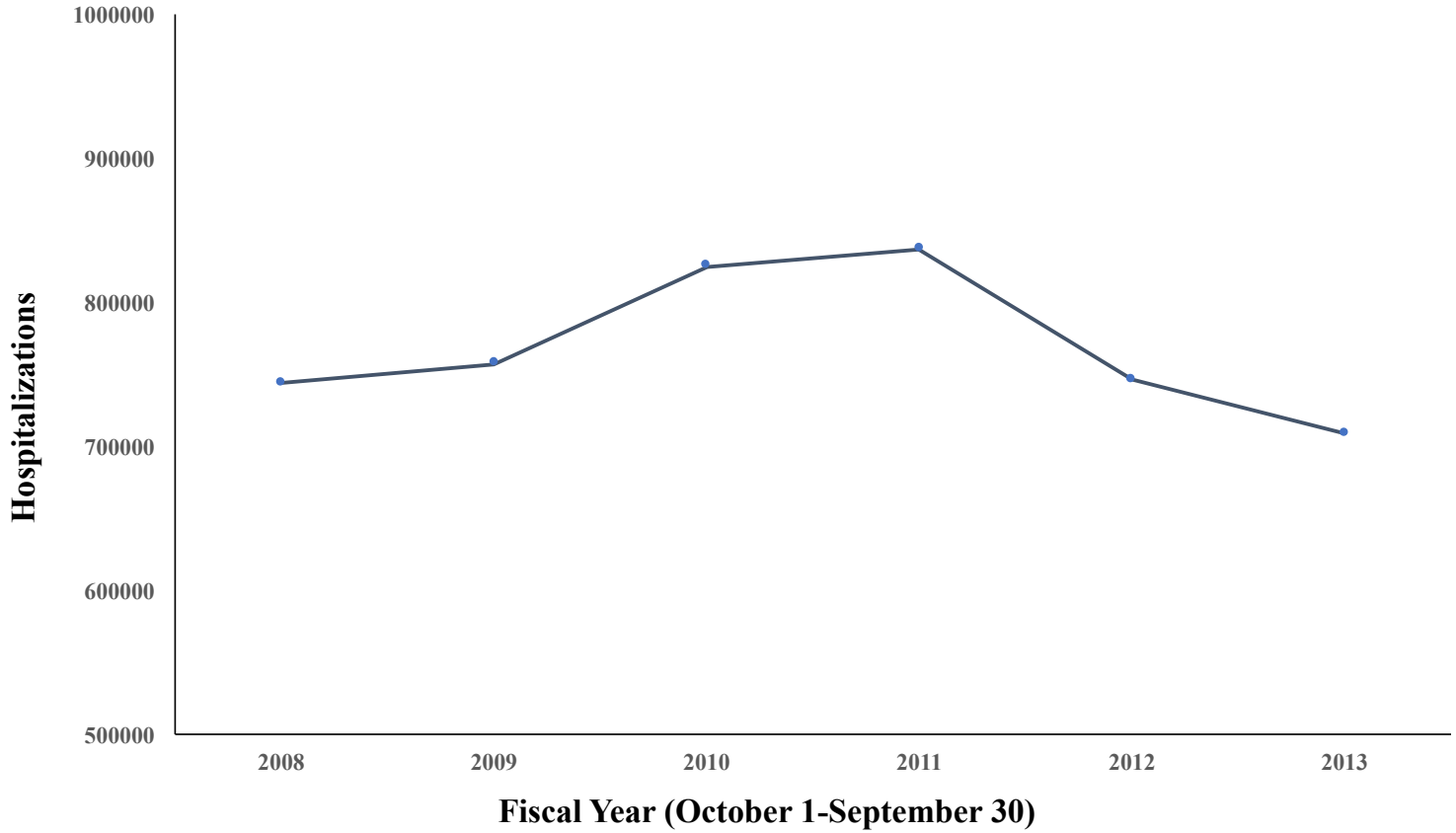
| | Diagnosis Rates | | Case Fatality Rates | |
|---|---|---|---|---|
| **Presenting Stage** | Beta-estimate (95% Confidence interval) | p-value for trend | Beta-estimate (95% Confidence Interval) | p-value for trend |
| **Sepsis** | | | | |
| **18-34** | -23.70 (-54.05 to 6.64) | 0.0960 | -1.51 (-2.06 to -0.97) | 0.0008 |
| **35-64** | -108.73 (-178.38 to -39.08) | 0.0123 | -1.55 (-2.32 to -0.77) | 0.0037 |
| **65-74** | -127.64 (-188.14 to -67.14) | 0.0042 | -1.43 (-2.40 to -0.46) | 0.0128 |
| **75-84** | -143.95 (-199.64 to -88.26) | 0.0020 | -2.43 (-3.52 to -1.33) | 0.0024 |
| **85+** | -146.63 (-180.57 to -112.68) | 0.0003 | -2.36 (-3.49 to -1.23) | 0.0002 |
| **Severe Sepsis** | | | | |
| **18-34** | -7.03 (-14.03 to -0.03) | 0.0493 | -3.35 (-4.85 to -1.85) | 0.0023 |
| **35-64** | -42.33 (-75.48 to -9.18) | 0.0239 | -3.19 (-4.55 to -1.83) | 0.0018 |
| **65-74** | -44.98 (-75.32 to -14.63) | 0.0147 | -2.25 (-2.95 to -1.54) | 0.0004 |
| **75-84** | -55.50 (-89.37 to -21.63) | 0.0104 | -3.34 (-5.75 to -0.93) | 0.0161 |
| **85+** | -64.87 (-94.19 to -35.56) | 0.0036 | -3.71 (-5.36 to -2.06) | 0.0022 |

| | | | | |
|---|---|---|---|---|
| **Septic Shock** | | | | |
| **18-34** | -7.83 (-14.81 to -0.84) | 0.0359 | -3.81 (-6.21 to -1.42) | 0.0094 |
| **35-64** | -34.75 (54.28 to -15.19) | 0.0079 | -1.83 (-3.77 to -0.11) | 0.0602 |
| **65-74** | -31.97 (-41.41 to -22.54) | 0.0007 | -4.63 (-5.65 to -3.60) | <0.0001 |
| **75-84** | -33.45 (-55.54 to -11.36) | 0.0136 | -4.71 (-7.61 to -1.82) | 0.0086 |
| **85+** | -26.65 (-37.01 to -16.28) | 0.0020 | -5.82 (-7.31 to -4.33) | 0.0002 |

Supplementary Figure 3.1: All (POA and non-POA Inclusive) Sepsis Diagnoses per 100,000 Hospitalizations by Fiscal Year



Supplementary Figure 3.2: Number of Inpatient Encounters per Fiscal Year



# CHAPTER IV

# PREDICTORS OF SUBSEQUENT SEPSIS READMISSION AFTER A SEPSIS HOSPITALIZATION

## Abstract

**Objective**: To identify predictors of subsequent readmissions for sepsis after an index hospitalization for sepsis

**Method**: Using the Cerner HealthFacts® Database, we identified 57,530 hospitalizations for sepsis, severe sepsis, and septic shock using a combination of ICD-9CM codes (038, 785.52, 995.1, 995.92) and present-on-admission flags for adult inpatients after October 1, 2008. Predictors of re-hospitalization (yes/no) were identified from a logistic regression model. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) were reported

**Results**: Of 50,089 patients who survived an index hospitalization with sepsis, 18.6% were readmitted within 30 days for all causes, and 1,380 were re-hospitalized for sepsis, severe sepsis, or septic shock within 30 days of their initial discharge. Increased risk of re-hospitalization for sepsis compared to patients not readmitted during the same time frame was found for patients who were initially admitted with sepsis due to abdominal infections (AOR: 1.22 95% CI: 1.05-1.43), patients discharged to hospice (AOR: 2.98 95% CI: 2.41-3.68), patients initially admitted from a skilled nursing facility (AOR: 1.58 95% CI: 1.28-1.95), and patients initially discharged to a skilled nursing facility (AOR:1.95 95% CI: 1.65-2.31). 22.3% of patients readmitted with sepsis expired during their subsequent hospitalization for sepsis.

**Conclusions**: Patients readmitted within 30 days of a hospitalization for the same underlying cause, sepsis, reflect potential opportunities for improvements in patient care but also reflect the continued need for improved understanding of the long-term

implications of surviving sepsis. Given increasing national pressure to reduce readmissions after sepsis healthcare encounters, understanding factors that may be amenable to modification is important. We found increased risk for sepsis readmissions among patients initially discharged to hospice, suggesting that there may be additional efforts needed to care for these complex patients in their preferred setting.

## Introduction

Hospital readmissions, especially those in the immediate time period following an initial hospitalization, have become a focus of national interest as they may represent initial quality of care as well as continuity of post-discharge care and potential opportunities for preventative efforts to reduce readmissions.[94] The Centers for Medicare and Medicaid Services (CMS) have developed penalties for 30-day readmissions following an initial hospitalization for pneumonia, acute myocardial infarction, and stroke, all disease processes with clearly defined best practices for acute and post-acute care.[95–97] CMS has indicated its movement towards targeting sepsis for a readmission reduction program with publication of the SEP-1 metrics[98], but as of yet has not targeted reimbursement penalties to readmissions for sepsis.

Sepsis has traditionally been treated as an acute event, with patients surviving to discharge thought of as cured. However, current research is increasingly showing long term effects from sepsis ranging from decreased quality of life to immune effects resulting from the initial immunologic disarray.[37] Case fatality rates have been steadily declining with corresponding reports of increases in diagnoses, resulting in an increased number of people who are at risk for subsequent readmission.[4] Further, the aging of the US population has led to an increase in the number of people who are at higher risk for both an initial hospitalization for sepsis and at increased risk for all causes of readmission.[99]

Current research on readmissions of people initially surviving a sepsis hospitalization has consistently emphasized the high percentage of patients readmitted for

any cause and the high cost of these readmissions.[100] These studies use a wide variety of techniques, time windows for readmissions, and definitions of sepsis resulting in readmission estimates ranging from 19-32%.[101] A high percentage of these readmissions have been attributed to infectious causes in other studies[102,103]; however, little remains known about the frequency of repeat readmissions for sepsis among sepsis survivors. Increased attention to this population could illuminate potential areas for interventions to reduce readmission and to improve post-acute care, in addition to providing useful information about the ongoing immune effects of sepsis.

This study aims to identify predictors of 30-day readmissions for sepsis, severe sepsis, or septic shock among patients surviving an initial hospitalization for sepsis, severe sepsis, or septic shock.

## Methods

*Study Design and Setting*

We conducted a retrospective cohort study using data extracted from the Cerner HealthFacts® Database. The HealthFacts® database is comprised of de-identified patient level information including information on their encounters and diagnoses. Over 500 healthcare facilities use the Cerner system, representing 133 million inpatient and outpatient encounters from 84 million patients over two decades. Cerner corporation (Kansas City, MO) maintains the HealthFacts® database.[48]

*Eligibility Criteria*

To be considered for the study, patients must have had a hospital stay during the study period, October 1,2008 through June 30 2014, be aged 18 years or older at admission, and have a diagnosis of sepsis, severe sepsis or septic shock at the time of the hospital admission. Diagnoses of sepsis, severe sepsis, and septic shock were determined using ICD-9CM codes (038, 785.52, 995.1, 995.92) from any coded field; however, the diagnosis must have been flagged as present-on-admission (POA) in the HealthFacts® Database. Finally, patients must have survived their initial hospitalization to be considered eligible for a subsequent readmission.

*Index Hospitalizations*

Index hospitalizations were considered as the first hospitalization during the study period, and in concordance with the Agency for HealthCare Research and Quality definition of index hospitalizations, did not require a period free of hospitalizations prior to the index event.[104]

*Outcome: 30-Day Hospital Readmission*

The primary outcome measure for this study was hospital readmission within 30 days of the index discharge date due to sepsis, severe sepsis, or septic shock as identified by the previously listed ICD-9 CM codes and marked as POA. Patients who had multiple encounters represented within the database but that had a discharge date and subsequent admission date separated by less than 24 hours were considered to be part of the same hospitalization.

*Potential Predictors of Hospital Readmission*

Comorbidities, presenting stage of sepsis, age, sex, race, marital status, organ dysfunction during the index hospitalization, initial source of admission, discharge location from the index hospitalization, length of stay of index hospitalization, weekend admission, and source of index infection were considered potential predictors of 30-day readmission. Comorbidities were identified in accordance with those comorbidities considered in the Charlson-Deyo Comorbidity index.[63,105] Presenting stage of sepsis was identified as the most highly acute form of sepsis at time of admission, e.g. if a patient had codes for both septic shock and severe sepsis noted as POA, the patient would be classified as having presented with septic shock. Age was divided into categories from 18-35, 35-64, 65-74, 75-84, and 85+ with the latter three categories corresponding to the census categories for the young old, old old, and oldest old.[106] Sex has been explored in the literature as a predictor of both sepsis outcomes and hospital readmissions.[65] Although race data are notoriously misclassified in hospital and claims data, nevertheless racial disparities in sepsis outcomes and readmissions have been documented and warrant further investigation.[107,108] Marital status has been shown to be an important proxy for social support and to impact likelihood of readmissions.[109] Organ dysfunction during the initial hospitalization indicates more severe illness.[110] Patients admitted from skilled nursing facilities (SNF) are likely to have different pathogen mixes and be more prone to repeat admission, and patients who are discharged to a SNF after a hospitalization are more likely to experience a readmission.[103] Length of stay during the initial hospitalization has been established as a predictor of both sepsis hospitalizations and

readmissions.[103] Admission through the emergency department has been associated with improved hospital outcomes for patients with sepsis[66,111], and admission on weekends compared to weekdays has been associated with poorer outcomes.[112] Initial source of infection is associated with differences in sepsis hospitalization outcomes, and certain infections may be prone to repeat hospitalization.[33] Patients with infections identified at the start of their hospital admission using ICD-9CM codes (Supplementary Table 4.1) and the POA flag were classified into one of the following infection groups: respiratory, gastrointestinal (GI), genitourinary (GU), skin, soft tissue, and bone (SSTB), and central nervous system (CNS).

*Statistical Analyses*

We summarized patient characteristics by readmission status. Proportions were reported for categorical variables, and data were summarized by means and standard deviations, or medians and interquartile ranges for normally and non-normally distributed continuous variables respectively. Unadjusted logistic regression models were used to examine the association between each potential predictor of readmission and 30-day readmission for sepsis, severe sepsis, or septic shock. A complete, adjusted logistic regression was then fit to the data to examine all potential predictors of 30-day readmission for sepsis, severe sepsis, or septic shock. Crude and adjusted odds ratios (ORs, AORs), 95% confidence intervals (95% CI), and two-sided p-values are reported. SAS 9.4 was used for all analyses.

*Ethical Considerations*

This research was deemed not human subjects research by the University of Massachusetts Institutional Review Board; the informed consent requirement was waived.

## Results

During the study period, there were 8,146,180 adult inpatient encounters. Of these encounters, 57,530 patients were admitted with a diagnosis of sepsis, severe sepsis, or septic shock. Almost 13% of these patients expired before hospital discharge, leaving 50,089 sepsis survivors. Of these survivors, 40,770 were not readmitted to the same healthcare system within 30 days, while 9,319 patients were readmitted within 30 days for any cause. Of these readmitted patients, 1,380 were admitted with a diagnosis of sepsis, severe sepsis, or septic shock. (Figure 4.1)

A majority of the patients included in this study were over the age of 65 among both the group of survivors who were readmitted within 30 days of their initial discharge and those who were not. Approximately three-quarters of the patients included were identified as white, and one-third of patients were married. One quarter of patients were admitted on a Saturday or Sunday. Patients who were readmitted with sepsis within 30 days of their initial discharge had a median length of index hospital stay of 8 days (interquartile range 4-13 days) while patients who survived an index hospitalization of sepsis and were not re-hospitalized within 30 days had a median length of stay of 7 days during their index admission (interquartile range 4-11 days). (Table 4.1)

Among the patients readmitted within 30 days with sepsis, severe sepsis, or septic shock, the median length of stay was 6 days (interquartile range 3-11 days). The majority of patients (59.1%) who were readmitted within 30 days initially presented with sepsis rather than severe sepsis or septic shock. Nearly one quarter (22.3%) of patients readmitted within 30 days died during this subsequent hospitalization, and one quarter were discharged to a SNF while 7.8% were discharged to hospice. (Table 4.2)

The mix of infections present at the time of initial admission was relatively even between groups, with approximately 30% of patients having a respiratory infection, 40% of patients having a GU infection, 12-13% having SSTB infections, and less than 1% having CNS infections. Among patients who were readmitted within 30 days just over 15% had a GI infection during the index admission while 11.8% of those patients not readmitted within 30 days had a GI infection. Among those who had an initial hospitalization with a respiratory infection, 51.9% also had a respiratory infection at the time of readmission, while 12.5% had a GI infection, 31.9% had a GU infection, 9.1% had a SSTB infection and 0.3% had a CNS infection. Some patients had multiple infections at the time of readmission, therefore percentages do not sum to 100 percent. Among patients who were readmitted within 30 days with sepsis who initially had a GI infection, 46.6% were readmitted with a GI infection while 24.6% were readmitted with a respiratory infection, 29.6% were readmitted with a GU infection, 11.4% were readmitted with a SSTB infection and 0.8% were readmitted with a CNS infection. For patients who had an index admission with a GU infection, 64.7% were also readmitted with a GU infection. 25.6% of patients initially admitted with a GI infection were later readmitted

with a respiratory infection, while 14.0% were readmitted with a GI infection, 9.6% were readmitted with a SSTB infection and 0.3% were readmitted with a CNS infection. Of the patients who were initially admitted with a SSTB infection, 44.1% had a SSTB infection at the time of readmission while 18.5% had a respiratory infection, 12.7% had a GI infection, 31.0% had a GU infection and 0.7% had a CNS infection. (Figure 4.2) Of note, on closer examination of the breakdown of GI infections, 8.6% of patients readmitted within 30 days with sepsis, severe sepsis, or septic shock had an initial diagnosis of *Clostridium diffiicle* with 11.2% of patients having a diagnosis of *Clostridium difficile* on readmission at 30 days.

Unadjusted analyses revealed associations between increased age, number of comorbidities, index hospitalization length of stay of greater than or equal to 7 days, initial abdominal infection, discharge to SNF or discharge to hospice, and admission from a SNF and increased risk of readmission to the same hospital system within 30 days with sepsis, severe sepsis, or septic shock. Additionally, unadjusted analyses revealed associations between admission with severe sepsis or septic shock rather than sepsis, or organ failure on the index hospitalization excluding cardiovascular failure and readmission to the same hospital system with sepsis, severe sepsis, or septic shock within 30 days. (Table 4.3)

Adjusted models revealed associations between 1-3 Charlson-Deyo comorbidities, 4+ Charlson-Deyo comorbidities, initial abdominal source of infection, discharge to a SNF or hospice, hematologic failure during the index hospitalization, and admission from

a SNF with an increased risk of re-hospitalization with sepsis, severe sepsis, or septic shock within 30 days. These associations persisted with adjustment for other demographic characteristics and hospitalization characteristics. (Table 4.3)

## Discussion

This study investigates potential predictors of readmission with sepsis, severe sepsis, or septic shock within 30 days of discharge from a hospitalization for sepsis, severe sepsis, or septic shock. Among patients who survived to discharge from an initial hospitalization, 2.8% of patients were readmitted within 30 days with a sepsis diagnosis. This study found that initial discharge to hospice or to a SNF, initial admission from a SNF, initial abdominal infection, and a Charlson-Deyo comorbidity index score greater than 1 were associated with an increased risk of readmission with a sepsis spectrum diagnosis within 30 days after an initial survived hospitalization for a sepsis spectrum diagnosis. In addition, we investigated the mix of infections present on re-admission to the hospital, and found that in many cases at the re-hospitalization, infections were present in the same organ system as at the start of the initial hospitalization.

Recent attention to the readmission of patients with sepsis for any cause has illustrated the high prevalence and cost of these readmissions.[59,113,114] Our study's all-cause readmission risk of 22% is consistent with other studies of readmissions of patients initially hospitalized for sepsis. Additionally, other studies have found high rates of readmissions due to infections, accounting for nearly half of readmissions after sepsis depending on the time period evaluated[100,103], but have not directly investigated the

nature of patients who have been re-hospitalized with sepsis and the predictors of these readmissions. Our study expands the current literature by investigating predictors of readmissions for those patients who are readmitted with the same condition as their initial hospitalization.

Our study observed that patients who were initially discharged to hospice were almost three times as likely to be readmitted with a sepsis diagnosis within 30 days compared to patients who were discharged home. On the surface, this finding may appear to be counterintuitive as the goals of hospice care are generally palliative and patients and their families often expressly voice a desire to avoid additional hospital stays.[115,116] However, the phenomenon of re-hospitalization after transfer to hospice care has been documented as part of a concern that hospice benefits may seek to avoid paying for costly hospitalizations; those patients who elected to receive hospice care due to an infectious diagnosis were more than twice as likely than patients who elected hospice care due to a diagnosis of cancer to be rehospitalized.[117] Our study adds weight to the concern that the rapid expansion of hospice benefits has created a need for additional support of caregivers, both paid and familial, to further understand how best to manage the comfort of their patient or loved one. Additional support in the form of more detailed instructions on how to manage common symptoms of escalating infection that cause patient discomfort such as shortness of breath, rapid heart rate, and altered mental status, could lead to an improvement of care for patients in concordance with their wishes and peace of mind for caregivers who may elect hospitalization out of the concern and fear of watching distressing symptomatic manifestations of acute illness. Additionally, patients

and their families may have found relief and reassurance in therapies administered at the hospital and determining what those therapies were and if they can be administered in a hospice setting may alleviate readmission burden among these patients.

This study found an association between admission to the hospital from a SNF and readmission to the hospital within 30 days with a repeat diagnosis of sepsis compared to patients who were admitted from other settings. We also observed an association between patients who were discharged to a SNF and readmission to the hospital within 30 days with a subsequent diagnosis of sepsis. The "revolving door" pattern of SNF stays and rehospitalizations has been well documented previously.[118] Many possibilities exist for these associations, including that patients who are cared for in SNFs generally have poorer health and greater numbers of comorbidities. However, there may still be additional opportunities to improve care for patients in SNFs to alleviate the burden of readmissions and break the cycle of frequent hospitalizations through improved post-discharge care.

The primary focus of this study was the risk of readmission with sepsis after an index hospitalization for sepsis. Although the inciting infection for sepsis may not always be known despite efforts to collect blood cultures prior to antibiotic administration, nevertheless the initial source of infection for many patients may provide valuable insight into the disease process and possible sequelae the patient may experience as a result. In our study, patients who initially presented to the hospital with sepsis likely due to a GI infection were more likely to be readmitted with a subsequent diagnosis of sepsis, and

nearly half of these readmissions were also for a GI source of infection. Some GI infections, such as *C.difficile*, are known to have high rates of recurrence[119] and our study did find that 70% of patients readmitted for sepsis with a GI infection had a diagnosis of *C. difficile*. Among patients who were readmitted after an initial hospitalization for sepsis and a GU infection, nearly two-thirds of these patients also had a diagnosis of a GU infection during the readmission. These findings suggest that some patients with certain infection types may be at particularly high risk for repeated infections. Efforts to identify these patients could prevent the progression of infection to sepsis if appropriate interventions, such as removal of indwelling catheters, may be implemented and found to be beneficial to preventing additional hospitalizations.

This study has a number of limitations. First, the use of ICD-9 CM codes to explicitly define patients with sepsis, severe sepsis, or septic shock results in a specific rather than a sensitive definition of sepsis. This definition provides the advantage that very few false positive cases are likely to have been included in this study; however, there may be limited inferences able to be made to patients with sepsis defined according to other strategies. Nearly all studies of readmissions suffer from an inability to identify patients who were readmitted to hospital systems outside of the location of the initial index hospitalization and this study is no exception. Similarly, we were unable to account for patients who died outside of the hospital and future investigations would benefit from strategies accounting for competing risks. An important future direction of research is to include long-term follow-up of patients discharged after a hospitalization for sepsis to better understand the trajectory of these patients, and how it relates to their health

trajectory prior to their hospitalization. There may be misclassification of the predictors considered in this study and there are elements of care such as time to administration of appropriate antibiotics and other unmeasured characteristics of patients with sepsis that we were unable to account for. Nonetheless, we believe that this study offers valuable insights into the nature of patients who are repeatedly hospitalized for sepsis and provides potential new directions for future investigations.

This study leveraged a national EHR database to investigate readmissions for patients who had an additional episode of sepsis within 30 days of discharge for an initial hospitalization with sepsis. Given that sepsis exacts a high cost in terms of mortality, morbidity, and quality of life for patients and high financial costs for healthcare systems, understanding correlates of additional episodes of sepsis may generate further insights to strengthen care of individual patients and improvements to the healthcare delivery system to tackle this heterogeneous, multi-faceted problem.

Table 4.1: Demographic and Clinical Characteristics of Patients' Index Hospitalization for Sepsis by Readmission Status

| | | Sepsis Survivors without a 30-day Readmission (n=40,770) | Sepsis Survivors Readmitted within 30 days (n=1,380) |
|---|---|---|---|
| | ***Demographic Characteristics*** | | |
| | | *Percentage* | |
| **Age (years)** | 18-34 | 7.3 | 3.6 |
| | 35-64 | 39.7 | 38.6 |
| | 65-74 | 20.0 | 22.6 |
| | 75-84 | 19.5 | 19.8 |
| | 85+ | 13.5 | 15.4 |
| **Women** | | 51.4 | 48.5 |
| **Race** | | | |
| | White | 74.9 | 74.3 |
| | Black | 18.2 | 20.3 |
| | Other or Unknown | 6.9 | 5.4 |
| **Married** | | 36.8 | 37.0 |
| **Charlson-Deyo Comorbidity Index** | | | |
| | 0 | 18.6 | 10.1 |
| | 1-3 | 53.3 | 53.0 |
| | 4+ | 28.1 | 36.8 |
| | ***Hospitalization Characteristics*** | | |
| **Weekend Admission** | | 25.7 | 24.1 |
| **Length of Stay in Days (Median, IQR)** | | 7.0 (4.0-11.0) | 8.0 (4.0-13.0) |
| **Initial Infection Source** | | | |
| | **Respiratory** | 27.5 | 29.2 |
| | **Abdominal** | 11.8 | 15.3 |
| | **Genitourinary** | 39.2 | 39.1 |
| | **Skin, Soft Tissue, and Bone Infection** | 13.7 | 12.4 |
| | **Central Nervous System** | 0.8 | 0.7 |
| **Organ Failures** | | | |
| | **Cardiovascular** | 12.8 | 13.2 |
| | **Hematologic** | 13.4 | 17.8 |
| | **Hepatic** | 1.8 | 2.6 |
| | **Neurologic** | 10.8 | 14.4 |
| | **Renal** | 35.9 | 41.8 |
| | **Respiratory** | 24.1 | 27.2 |
| **Admission Source** | | | |
| | **Emergency Department** | 31.2 | 28.8 |
| | **Transfer from a Skilled Nursing** | 5.1 | 9.6 |

| | | |
|---|---|---|
| **Facility (SNF)** | | |
| **Physician or Clinic Referral** | 47.2 | 42.8 |
| **Other** | 16.5 | 18.8 |
| **Discharge Location** | | |
| **Home** | 38.4 | 23.1 |
| **SNF** | 23.2 | 31.4 |
| **Hospice** | 5.1 | 11.2 |
| **Other** | 33.3 | 34.3 |
| **Presenting Stage of Sepsis** | | |
| **Sepsis** | 65.5 | 58.6 |
| **Severe Sepsis** | 16.4 | 18.2 |
| **Septic Shock** | 18.1 | 23.3 |

Table 4.2: Characteristics of the Subsequent Hospitalization for Patients Re-hospitalizaed with Sepsis

| Characteristic | Sepsis Survivors Readmitted within 30 days (n=1,380) |
|---|---|
| **Length of Stay in Days (Median, IQR)** | 6.0 (3.0-11.0) |
| *Percentage* | |
| **Admission Source** | |
| **Emergency Department** | 19.1 |
| **Transfer from a SNF** | 11.3 |
| **Physician or Clinic Referral** | 40.7 |
| **Other** | 28.8 |
| **Discharge Location** | |
| **Home** | 19.0 |
| **SNF** | 23.6 |
| **Hospice** | 7.8 |
| **Other** | 27.3 |
| **Deaths** | 22.3 |
| **Presenting Stage of Sepsis** | |
| **Sepsis** | 59.1 |
| **Severe Sepsis** | 18.6 |
| **Septic Shock** | 22.3 |

Table 4.3: Effect Estimates for Predictors of 30-day Re-hospitalization with Sepsis

| | | Odds Ratio (95% CI) | Adjusted Odds Ratio (95% CI) |
|---|---|---|---|
| | ***Demographic Characteristics*** | | |
| **Age (years)** | 18-34 | Ref | Ref |
| | 35-64 | 1.96 (1.47-2.63, p<0.0001) | 1.44 (1.07-1.95, p=0.0161) |
| | 65-74 | 2.28 (1.69-3.09, p<0.001) | 1.44 (1.06-1.97, p=0.0216) |
| | 75-84 | 2.05 (1.51-2.78, p<0.0001) | 1.20 (0.87-1.65, p=0.2667) |
| | 85+ | 2.31 (1.70-3.16, p<0.0001) | 1.28 (0.92-1.78, p=01441) |
| **Women** | | 0.89 (0.80-0.99, p=0.0319) | 0.91 (0.82-1.02, p=0.0965) |
| **Race** | | | |
| | White | Ref | Ref |
| | Black | 1.12 (0.98-1.29, p=0.0917) | 1.09 (0.95-1.26, p=0.2225) |
| | Other or Unknown | 0.80 (0.63-1.01, p=0.0622) | 0.85 (0.67-1.07, p=0.1673) |
| **Married** | | 1.01 (0.90-1.13, p=0.8645) | 1.06 (0.94-1.19, p=0.3710) |
| **Charlson-Deyo Comorbidity Index** | | | |
| | **0** | Ref | Ref |
| | **1-3** | 1.82(1.52-2.19, p<0.0001) | 1.57 (1.30-1.89, p<0.0001) |
| | **4+** | 2.40 (1.98-2.89, p<0.0001) | 1.83 (1.50-2.22, p<0.0001) |
| | ***Hospitalization Characteristics*** | | |
| **Weekend Admission** | | 0.92 (0.81-1.04, p=0.1912) | 0.92 (0.81-1.04, p=0.1906) |
| **Length of Stay ≥ 7 Days** | | 1.33 (1.20-1.49, p<0.0001) | 1.03 (0.91-1.16, p=0.6305) |
| **Initial Infection Source** | | | |
| | **Respiratory** | 1.09 (0.97-1.22, p=0.1697) | 1.07 (0.94-1.21, p=0.2984) |
| | **Abdominal** | 1.35 (1.16-1.57, p<0.0001) | 1.22 (1.05-1.43, p=0.0117) |
| | **Genitourinary** | 0.99 (0.89-1.11, p=0.9195) | 0.98 (0.87-1.10, p=0.6935) |
| **Skin, Soft Tissue, and Bone Infection** | | 0.90 (0.76-1.05, p=0.1810) | 0.89 (0.75-1.05, p=0.1652) |

| | | |
|---|---|---|
| **Central Nervous System** | 0.94 (0.50-1.77, p=0.8456) | 0.94 (0.50-1.77, p=0.8448) |
| **Discharge Location** | | |
| **Home** | Ref | Ref |
| **SNF** | 2.25 (1.94-2.61, p<0.0001) | 1.95 (1.65-2.31, p<0.0001) |
| **Hospice** | 3.64 (2.99-4.43, p<0.0001) | 2.98 (2.41-3.68, p<0.0001) |
| **Other** | 1.71 (1.48-1.98, p<0.0001) | 1.56 (1.34-1.81, p<0.0001) |
| **Presenting Stage of Sepsis** | | |
| **Sepsis** | Ref | Ref |
| **Severe Sepsis** | 1.24 (1.08-1.44, p=0.0032) | 1.07 (0.91-1.25, p=0.4124) |
| **Septic Shock** | 1.44 (1.26-1.64, p<0.0001) | 1.17 (1.01-1.36, p=0.0357) |
| **Organ Failures-Index Hospitalization** | | |
| **Cardiovascular** | 1.04 (0.89-1.22, p=0.6401) | 0.92 (0.79-1.08, p=0.3236) |
| **Hematologic** | 1.40 (1.22-1.61, p<0.0001) | 1.24 (1.07-1.43, p=0.0040) |
| **Hepatic** | 1.45 (1.03-2.03, p=0.0320) | 1.04 (0.73-1.48, p=0.8198) |
| **Neurologic** | 1.38 (1.18-1.61, p<0.0001) | 1.09 (0.93-1.28, p=0.2960) |
| **Renal** | 1.28 (1.15-1.43, p<0.0001) | 1.03 (0.92-1.17, p=0.5964) |
| **Respiratory** | 1.18 (1.04-1.33, p=0.0088) | 0.90 (0.79-1.04, p=0.1402) |
| **Index Admission Source** | | |
| **Emergency Department** | Ref | ref |
| **Transfer from a Skilled Nursing Facility (SNF)** | 2.04 (1.67-2.50, p<0.0001) | 1.58 (1.28-1.95, p<0.001) |
| **Physician or Clinic Referral** | 0.99 (0.87-1.12, p=0.8184) | 1.01 (0.88-1.15, p=0.9331) |
| **Other** | 1.24 (1.06-1.45, p=0.0089) | 1.10 (0.94-1.31, p=0.2096) |

Figure 4.1: Population Selection

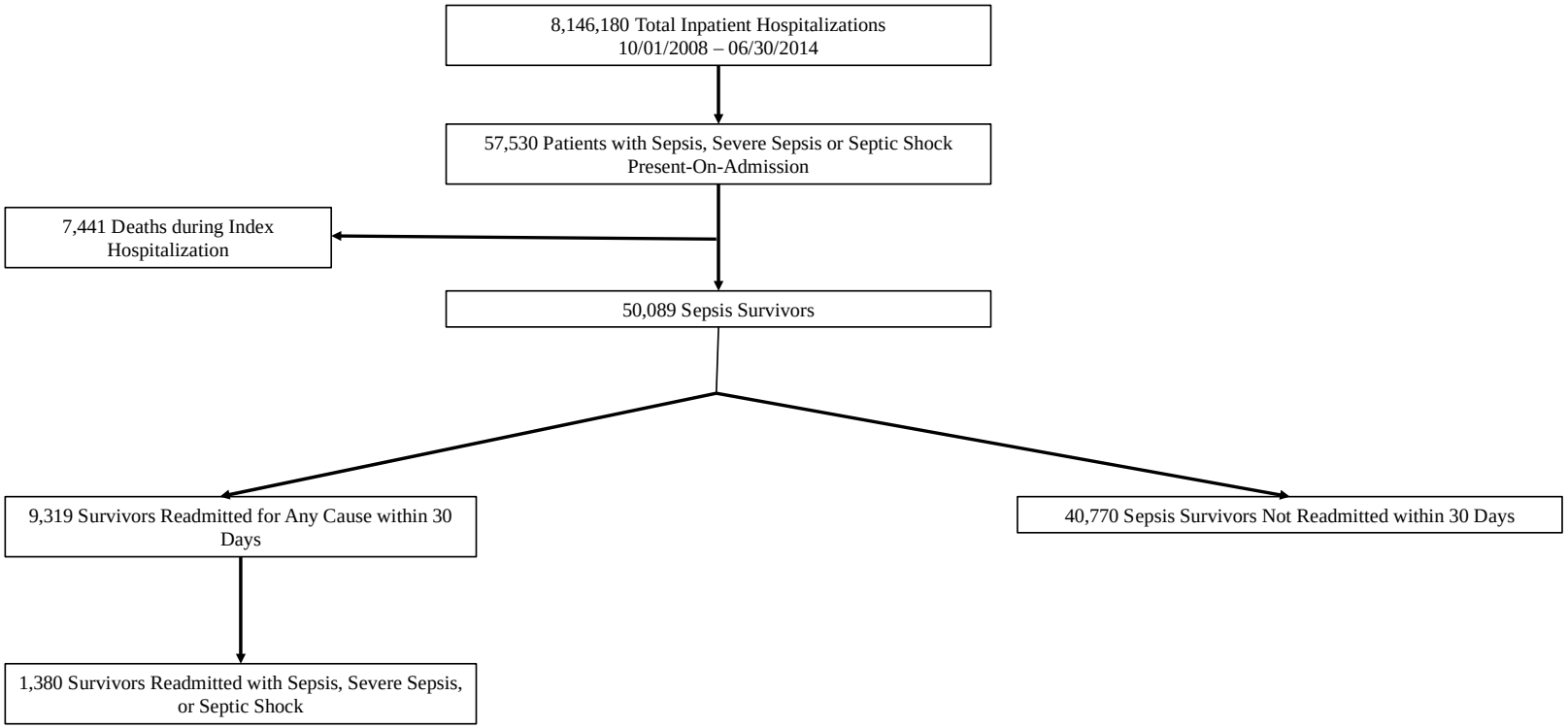
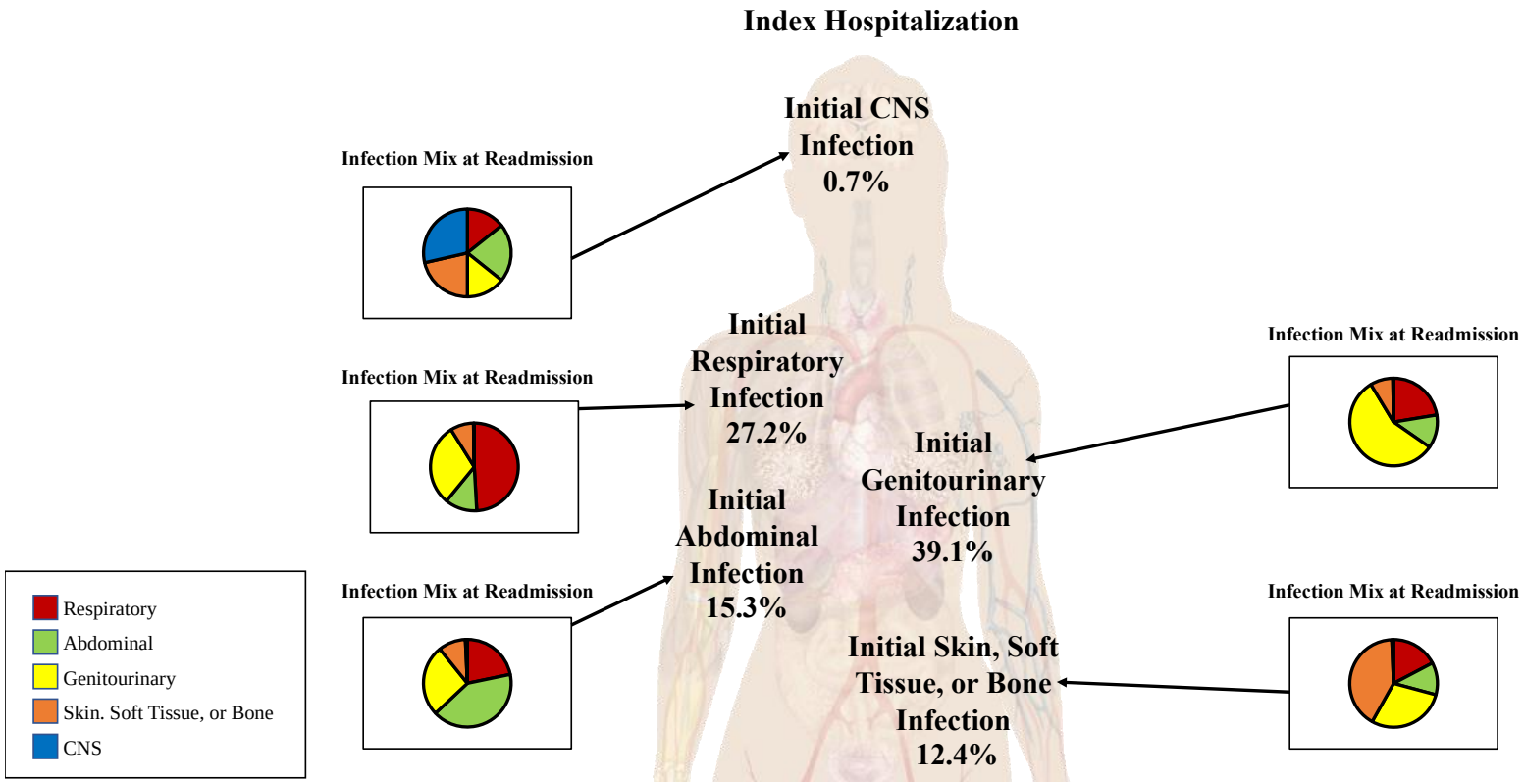


Figure 4.2: Initial Infection Source and Subsequent Infection Source at 30-day Re-hospitalization for Sepsis, Severe Sepsis, or Septic Shock




*Human illustration by Mikael Häggström (All used images are in public domain) [CC0], via Wikimedia Commons, Numbers presented superimposed on image are from this study

Supplementary Table 4.1: ICD9-CM Codes for Sepsis Identification, Infection Source and Organ Dysfunction Classification

| | ICD-9CM Codes |
|---|---|
| **Sepsis** | 995.91, 038 |
| **Severe Sepsis** | 995.92 |
| **Septic Shock** | 785.5 |
| **Respiratory Infections** | 010, 011, 012, 013, 014, 015, 016, 017, 018, 032, 033, 034, 461, 462, 463, 464, 465, 480, 481, 482, 483, 484, 485, 486, 491.21 |
| **Abdominal Infections** | 001, 002, 003, 004, 005, 008, 0845, 009, 540, 541, 542, 543.9, 562.01, 563.203, 562.11, 562.13, 566, 567, 569.5, 569.61, 569.71, 569.83, 572, 575 |
| **Genitourinary Infections** | 590, 595, 597, 598, 599, 601, 604, 614, 615, 616 |
| **Skin, Soft Tissue, and Bone Infections** | 451, 680, 681, 682, 683, 686, 711, 728.86, 730, 785.4 |
| **Central Nervous System Infections** | 036, 090, 320, 322, 324, 325 |
| **Cardiovascular Failure** | 375, 376.6, 458, 785.5 |
| **Hematologic Failure** | 286.6, 286.9, 287.4, 287.5 |
| **Hepatic Failure** | 570, 573.4 |
| **Neurologic Failure** | 293, 348.1, 348.3 |
| **Renal Failure** | 584 |
| **Respiratory Failure** | 335, 518.8, 786.03, 799.1, 967 |

# CHAPTER V

# DISCUSSION AND CONCLUSIONS

*Overall Purpose*

The overall purpose of this dissertation was to better understand: 1) the underlying epidemiology of POA sepsis and the role of the initial infection source as related to in-hospital mortality from sepsis; 2) recent trends in POA sepsis diagnosis and case fatality rates, in the context of the overall trends of increasing sepsis diagnoses and falling sepsis mortality; and 3) predictors of 30-day subsequent readmission with sepsis for patients who were initially hospitalized with sepsis.

*Role of Infection Source across Chapters II and IV*

Prior research has investigated the role of initial infection source as it relates to hospital mortality with inconclusive or contradictory findings.[33,52,53] Prior studies examining in-hospital mortality and initial infection source used many different means of identifying infections and creating exposure categories, and this heterogeneity has contributed to different conclusions being reached.[33,52,53,120] This dissertation evaluated the role of the initial infection source and its relationship with both in-hospital mortality and 30-day readmissions due to sepsis. Through careful curation of ICD9-CM codes related to infections, categories that were determined to be of broad clinical relevance were created. For both Chapters II and IV, microbiology data was not included in the assessment of these categories. We did not pursue the inclusion of microbiological data as this information is often not readily available at the time of the patient's presentation and we hoped for these studies to provide epidemiologic information that might be of use to the initial evaluating clinician.

In Chapter II, we presented findings that indicate patients presenting with initial GU or SSTB infections experienced lower rates of time to in-hospital mortality when compared to patients presenting with respiratory infections. In Chapter IV, we evaluated predictors of 30-day readmissions with sepsis, and did not find that initial GU or SSTB infections were associated with either an increased or decreased risk of re-hospitalization with a subsequent sepsis diagnosis. Given that patients with GU or SSTB infections are more likely to survive their initial hospital stay, it might be expected that more of these patients would be represented among those patients with sepsis re-hospitalizations within 30 days. The observation that these patients are not overrepresented among patients who are readmitted with sepsis suggests a number of potential explanations. Patients with initial GU or SSTB infections may have had their underlying infections definitively cured, and had factors that predisposed them to the initial infection sufficiently modified, through means such as operative source control and removal of blockages, that they did not experience recurrence. Alternatively, it is possible that these patients after experiencing an infection that progressed to sepsis, were able to identify infections prior to progression to sepsis and sought treatment earlier. It is also possible, though somewhat unlikely that patients with GU or SSTB infections were more likely to die outside of a hospital setting, therefore precluding their inclusion by a readmissions study, but would also prevent their death from being captured by a study of hospital mortality. The work presented in this dissertation indicates a pressing need to further understand the long term outcomes of patients affected by sepsis.

While other studies have reported increased rates of hospital mortality for patients presenting with sepsis due to a GI infection[79,121], our findings from Chapter II do not support that conclusion; however, we did find that patients with an initial sepsis hospitalization due to a GI infection source were more likely to experience rehospitalization for sepsis within 30 days than those patients presenting with other types of infections. We have postulated a number of potential explanations for this finding, including that certain GI infections such as those caused by *C. difficile* are more likely to recur than other types of infections. It is also possible that patients with GI infections may delay to seek care due to misattribution of symptoms and therefore their infections may progress to sepsis before care is sought. Care for intra-abdominal infections may also have substantially improved in the years following the initial studies examining the associations between infection source and hospital mortality. Indeed, care protocols have been changing for disease processes that were once thought to be settled, such as the growing movement towards interval appendectomy for patients with complicated, perforated appendicitis, but it is unclear what effect changes of individual infection management has had thus far on outcomes for patients with sepsis.

*Role of Age among Patients with Sepsis across Chapters II, III, and IV*

Chapters II-IV each examined the role of age among patients with sepsis, albeit in different manners. Prior clinical and basic science work has provided evidence for differences of immune function among older adults[56], and older adults often have broader representation of comorbidities associated with aging including cardiovascular and pulmonary diseases, in addition to general structural changes such as the weakening of

barrier structures like the complex network of proteins of the skin.[122] Older patients have less physiologic reserve than younger patients and may also have different goals of care for critical illness than younger, previously healthy patients.[123] Sepsis is known to disproportionately affect older adults[54], as reflected in Chapter III of this dissertation; however the improvement in case fatality rates seen regardless of age suggests that campaigns emphasizing sepsis recognition have had beneficial effects across broad groups of patients. Age was also a consideration when evaluating predictors for 30 day readmissions due to sepsis, and there is some evidence that a survivor effect may take place, i.e. those patients who survive to the oldest ages have generally better health status than their peers who may have met death earlier.[124–127] Further, as shown in Chapter II of this dissertation, relative mortality of initial infection source did not markedly change within age strata. Taken together, these findings suggest that the fundamental dysfunction of sepsis may not markedly vary with age, but that there may be many factors that play a role at the complex intersection of aging and sepsis pathophysiology.

*Role of Presenting Stage of Sepsis across Chapters II, III and IV*

We considered the role of presenting stage of sepsis across Chapters II-IV of this dissertation. There is an undeniable need for early intervention for patients with sepsis to prevent catastrophic outcomes, with documented increases of mortality of 8% for every hour that care is delayed.[22,128] While there may always be patients whose underlying infection progresses so rapidly as to lead to these patients presenting when they are already critically ill, early identification of patients at risk of sepsis must remain a priority as to maximize the possibility of positive results, whether through definitive curative care

or through earlier initiation of conversations surrounding the patient's goals of care, particularly for those near the end of life, where death is not necessarily a negative outcome.[129,130] Patients presenting for care who have already progressed to severe sepsis or septic shock have unequivocally higher rates of mortality. Current changes circulated for definitions of sepsis essentially eliminate the category of sepsis as a stage, due to the difficulties of potentially overidentifying patients with sepsis due to the lack of specificity present in the SIRS criteria.[9] However, adoption of this definition, while potentially useful in some contexts for identifying "true" cases of sepsis may also have repercussions for patient care which will be difficult to ameliorate.

*Implications of Considering Present-on-Admission Diagnoses of Sepsis Only*

Limiting our analyses to POA cases of sepsis intimates that these cases of sepsis are primarily community-acquired, which has a number of potential implications. Community- acquired sepsis presents opportunities for primary prevention taking the form of identifying, treating, and managing patients who develop infection prior to progression to sepsis. Educating all patients, but particularly those patients with comorbid conditions such as diabetes and immunosuppressive conditions that predispose them to infections with strategies to prevent infection may relieve some of the burden of sepsis among these patients. Understanding the epidemiology of POA cases of sepsis is also relevant as patient education efforts to increase awareness of sepsis are undertaken. These campaigns, such as the one by the Centers for Disease Control and Prevention encouraging patients to ask "Do you think this might be sepsis?", cannot be understood without the context of the underlying epidemiology. Evaluating POA cases of sepsis also

has relevance to hospital systems and payers as CMS considers reimbursement penalties to hospitals for sepsis quality metrics such as SEP-1.[131] With the changing environment of healthcare and reimbursement, the issues surrounding sepsis reimbursement require a thorough understanding of where outcomes may be most impacted. This includes understanding how sources of sepsis impact mortality differentially, and raising the possibility that other factors should be considered with potential reimbursement metrics, particularly since definitive treatment for sepsis has not yet moved past the guidelines of antibiotics, fluid resuscitation, and support for organ dysfunction despite sensational news reporting of potential "cures".[19,132]

*Overall Limitations of this Dissertation*

While this dissertation addresses several questions about the underlying epidemiology of sepsis, there are a number of questions raised by this work and limitations of its design and scope. First, this dissertation relies on ICD-9CM coded definitions of sepsis, severe sepsis, and septic shock. This definition ensures that the cases detected are specific for sepsis, but means that a number of cases of sepsis were likely excluded from this analysis.[133] These cases may have had sepsis, but not been identified in the clinical documentation as such. Further research should be conducted using alternate definitions of sepsis to examine whether associations are consistent. This dissertation work focused on POA cases of sepsis, therefore the conclusions may not be generalizable to those cases of sepsis acquired in the hospital. Administrative data has a number of inherent limitations,[134] and conclusions drawn from these data sources cannot replace data collected through experimental designs. However, given ethical implications

and temporal limitations, administrative data provides valuable insight into patterns of healthcare use and associations generating hypotheses that can be tested in future work.

*Clinical Implications of this Dissertation*

Sepsis is a disease process which has been known about for centuries, and yet there remains many questions about sepsis epidemiology, treatment, identification, and follow-up care.[135] Further work is needed to understand this heterogeneous, complex disease process, and how best to care for patients with sepsis who encounter an often-fragmented healthcare system. Care providers need additional support and evidence to aid in identifying these patients, initiating the best possible care for a given individual, and planning for the long-term effects of sepsis and the need for patient supports. Healthcare systems need to enable communication interdisciplinarily and interprofessionally to create comprehensive plans for caring for all patients, therefore improving care for patients with sepsis. These findings add granularity to research on sepsis, and provide support for future innovations of care for patients with sepsis including more tailored approaches to treatment.

*Future Research Implications of this Dissertation*

This dissertation generates new hypotheses even as it potentially contributes to the understanding of the underlying epidemiology of sepsis. Questions raised by Chapter II include whether initial infection source, independent of microbiology, maintains an association with in-hospital mortality when further subdivisions are applied to exposure categories e.g. what is the differential impact of uncomplicated cystitis vs pyelonephritis if both infections progress to sepsis? When controlling for underlying dysfunction in an

organ, pathogen species, and other factors, do differences in the infection source play an independent role in mortality from sepsis? Chapter III raises the question of whether documentation and reporting changes advocated by CMS have sufficiently stabilized to use these trends as estimates for future clinical planning. Chapter III also raises the question of precisely which elements of improved sepsis care are driving the decline in mortality from sepsis. Chapter IV raises questions including what can be done to support patients after they are discharged from the hospital, as well as which infections may need more intense follow-up care for survivors of sepsis. Understanding how best to provide non-curative care to patients in a way that is sensitive to their needs for those who have elected hospice is a pressing concern with the increase in hospice providers and services available. Future qualititative work may be necessary to understand the wishes and needs of patients and their caregivers who are discharged to hospice with an infectious diagnosis. Across all chapters, there remains a need to better understand long-term outcomes of patients with sepsis and to improve long-term models of care.

*Final Summary*

Overall, our studies describe a number of characteristics of patients with POA sepsis. The findings that patients with GU or SSTB infections had lower rates of in-hospital mortality than patients with respiratory infections contributes to the literature in this domain. Further, we extended the knowledge of recent trends in sepsis diagnoses and mortality and how these trends are observed for POA cases of sepsis. Finally, we identified a particularly vulnerable group of patients and identified predictors of re-hospitalization that warrant future study.

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