Long-Term Mortality, Healthcare Use, and Costs Associated with Sepsis: A Population-Based Retrospective Cohort Study

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PREFACE

Contributions of the student

Kelly Farrah is the main author of the content found in this thesis. Kednapa Thavorn and Lauralyn McIntyre developed the initial concept, wrote the original grant application and secured funding for the project (The Ottawa Hospital Academic Medical Organization Innovation Fund grant number: 2017-24). Kelly Farrah, Kednapa Thavorn, Lauralyn McIntyre, and Doug Coyle collaborated to develop the final study designs and contributed to interpretation of the data. Kelly Farrah, Kednapa Thavorn and Robert Talarico contributed to the acquisition of data. Kelly Farrah carried out analysis of the data and drafted the manuscripts. All authors listed reviewed the manuscripts for important intellectual content and approved the versions presented in this thesis.

Ethics and Confidentiality

This study used information collected under section 45 of Ontario's Personal Health Information Protection Act and, as such, did not require review by a Research Ethics Board. To ensure the privacy and confidentiality of patient's information, all data within the ICES datasets was de-identified after linkage using a patient-specific encrypted identifier. Data was accessed only through ICES uOttawa. Only study personnel had access to the study data. As per ICES procedures, cells with less than six observations were suppressed to limit potential breaches of confidentiality.

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Thesis Advisory Committee

Dr. Kednapa Thavorn, Role: Co-supervisor. Dr. Thavorn was my primary co-supervisor and advised on all aspects of the thesis project. As an ICES scientist she supervised access to data and data analysis.

Dr. Lauralyn McIntyre, Role: Co-supervisor. As a critical care physician with expertise in sepsis, Dr. McIntyre provided advice and guidance regarding the clinical care of sepsis patients and the natural history of the condition.

Dr. Doug Coyle, Role: Thesis advisory committee member. As a health economist, Dr. Coyle provided advice and guidance on matters relating to determining health services utilization and health system cost.

THESIS ABSTRACT

The mortality and cost burden of sepsis in-hospital is high, however, there is limited information on long-term outcomes for sepsis patients post-discharge. This thesis examines the long-term mortality and healthcare costs associated with sepsis. A population-based retrospective cohort study was conducted using Ontario health administrative data. Cases, including sepsis patients with organ dysfunction (severe), and without (non-severe) were identified using a validated algorithm. Sepsis cases and non-sepsis hospital controls were matched 1:1 based on propensity score, age, sex, admission type, and admission date. Regression methods were used to adjust for remaining confounders. The thesis presents data on long-term mortality and rehospitalizations in sepsis patients compared to matched controls. The thesis also examines hospital length of stay and long-term incremental healthcare costs of sepsis. Overall the thesis indicates that the mortality and cost burden of severe sepsis exceeds those of matched controls at 1-year and up to 5-years following index hospitalization.

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Contents

ABBREVIATIONS

ACCP	American College of Chest Physicians
ADG	Johns Hopkins' Aggregated Diagnosis Groups
CHF	Congestive heart failure
CI	Confidence interval
CIHI	Canadian Institute for Health Information
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
ED	Emergency department
ICES	Institute for Clinical Evaluative Sciences
ICU	Intensive care unit
ICD	International Statistical Classification of Diseases and Related Health Problems
IQR	Interquartile range
HR	Hazard ratio
LTC	Long-term care
LOS	Length of stay
OHIP	Ontario Health Insurance Plan
OR	Odds ratio
Q1	First quarter
Q3	Third quarter
SCCM	Society of Critical Care Medicine
Sepsis-3	Third International Consensus Definitions for Sepsis and Septic Shock
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
Std diff	Standardized difference.
ON	Ontario
US	United States

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Chapter 1: Introduction

According to the most recent Sepsis-3 definitions, sepsis is a "dysregulated host response to an infection" that results in "life-threatening organ dysfunction".[1] It is a major cause of mortality worldwide[2] and is also one of the most costly conditions to treat in-hospital.[3] While the short-term mortality and healthcare costs for sepsis patients are known to be high, there is limited information on the long-term mortality and incremental healthcare costs associated with sepsis in Canada. The aim of this thesis project was to examine the long-term mortality and healthcare costs in sepsis patients compared to hospitalized non-sepsis patients in an Ontario-wide cohort.

1.1 Notes on Thesis Organization

This thesis is article-based, structured around two discrete manuscripts prepared for journal publication. The first chapter provides an introductory literature review describing the definition of sepsis, its epidemiology, a summary of previous research on sepsis-associated mortality and healthcare costs, as well as an overview of the issues surrounding identifying sepsis in health administrative data. The second chapter consists of an article describing results on the long-term mortality and hospital readmissions associated with sepsis. The third chapter consists of an article presenting results on the long-term incremental healthcare costs and hospital length of stay associated with sepsis. The fourth chapter discusses the results of both articles, putting them into context of the current evidence base, presenting conclusions and suggesting directions for future research. The appendices provide additional methodological details and data from the sensitivity analyses.

1.2 Definition of Sepsis

Sepsis is a complex syndrome with variable signs and symptoms and no diagnostic gold standard.[4] As such, it is challenging to define and diagnose.[4] Over the past 30 years, the definition of sepsis has

evolved based on new knowledge of the pathophysiology and treatment of the condition.[5] In 1991, the first consensus clinical definitions of sepsis were developed at a conference convened by the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM).[6] These broad definitions were intended to standardize the terminology for sepsis, since previous usage of terms such as "septicemia", "bacteremia", and "septic shock" was inconsistent, which made interpretation of individual trials and comparison between studies difficult.[6] The ACCP/SCCM consensus definitions are provided in Table 1. They used the term "systemic inflammatory response syndrome" (SIRS) to distinguish the inflammatory process that can occur regardless of whether or not an infection is present. The syndrome of sepsis was defined in a continuum with SIRS as a base. Briefly, sepsis was demarcated by the presence of both infection and a systemic inflammatory response. Severe sepsis was characterized as sepsis, complicated with organ dysfunction. Septic shock was defined as severe sepsis, with hypotension despite adequate fluid resuscitation.[6]

Table 1. ACCP/SCCM 1991 Consensus Definitions of Sepsis

SIRS	"The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions: • Temperature >38°C or <36°C • Heart rate >90 beats/min • Respiratory rate >20 breaths/min or $PaCO_2$ <32 torr (<4.3 kPa) • White blood cell count >12,000 cells/mm^3, <4,000 cells/mm^3, or 10% immature (band forms)"
Sepsis	"The systemic response to infection. This systemic response is manifested by two or more of the above SIRS conditions."
Severe Sepsis	"Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status."
Septic Shock	"Severe sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured."

Source: ACCP/SCCM 1991[6]

Ten years later, the ACCP/SCCM definitions were revisited in a second consensus conference attended by a group of experts from North American and European critical care societies.[7] The resulting 2001 definitions (Sepsis-2) modified the 1991 definitions slightly by broadening the signs and symptoms listed in the definition, but they did not fundamentally change the previous definitions due to a lack of evidence, in particular, the lack of established biomarkers.[7]

Almost 15 years later, the definition of sepsis was again re-thought in an international consensus conference convened by the SCCM and European Society of Intensive Medicine and led by a task force of 19 experts.[1] The resulting definitions were called the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) and were published in 2016. This time, the definition of sepsis changed significantly: The Sepsis-3 definitions moved away from previous dependence on the SIRS criteria, given its limited sensitivity and specificity. The task force concluded that the idea of sepsis as a continuum was misleading, and that the phrase "severe sepsis" was redundant. As such, "severe sepsis" was eliminated as a category. Sepsis, by this definition, is severe and always includes organ dysfunction. According to the Sepsis-3 definition, sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[1] Septic shock is defined as "a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone."[1] The Sepsis-3 definitions also include specific clinical criteria to help operationalize the recognition and diagnosis of sepsis and septic shock, which are presented in Table 2. Organ dysfunction is clinically operationalized as a change of two or more points in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) Score.[1] The Sepsis-3 criteria highlight the increased mortality risk with these states: the criteria are associated with an excess in-hospital mortality rate of more than 10% for sepsis and more than 40% for septic shock.[1]

Table 2. Sepsis-3 Clinical Criteria for Sepsis and Septic Shock

Term	Definition	Clinical Criteria
Sepsis	"Life-threatening organ dysfunction caused by a dysregulated host response to infection."	"Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection."
Septic Shock	"A subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality."	"…sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation."

Source: Singer et al. 2016.[1]

The variation in definitions of terminology used to describe sepsis, particularly the change to Sepsis-3, can make it challenging to compare study results over the years, or to study patterns in the condition over a period of years.

1.2.1 A Note on the Use of Sepsis Terminology in this Thesis

In this thesis, I use a Sepsis-2 case definition of sepsis that was modified for use within health administrative data.[8] This case definition is the only algorithm that has been validated in Canada. Further, the accrual period of this study falls, for the most part, within a period before the Sepsis-3 definitions were published, thus the diagnosis and administrative coding of sepsis in hospitals during this period reflect Sepsis-2 definitions. In the present research, I define sepsis as follows:

Sepsis: The systemic response to infection, including patients with and without organ dysfunction (severe sepsis and non-severe sepsis, as defined below).

Severe Sepsis: Sepsis patients with documented presence of acute organ dysfunction in at least one system, including septic shock.

Non-severe sepsis: The presence of infection without organ dysfunction.

As the presence of two or more SIRS criteria could not be definitely ascertained for sepsis cases in the health administrative databases used in this study, non-severe sepsis cases identified in these datasets may have included patients with infection without SIRS.

When reporting results from other research, I will use the terminology used by the authors themselves to describe their work, specifying the definition used where possible. Much of this research was published before the Sepsis-3 definitions were established, and therefore, reflects previous characterisations of sepsis. In particular, the administrative database coding used in Canadian hospitals to describe diagnoses in hospitals -- ICD-10-CA (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada) -- was last updated in 2009,[9] and therefore, reflects the conceptualization of sepsis outlined in the pre-2016 definitions.

1.3 Epidemiology of Sepsis

Looking at data within the past two decades, studies in many countries have described an increasing incidence of sepsis, including the United States,[10] New Zealand,[11] Spain,[12,13] Germany,[14,15] France,[16] Brazil,[17] and Taiwan.[18,19] A 2018 literature review based on data from the past three decades concluded that the rise in sepsis incidence is ongoing.[20]

There is debate over the true causes behind the trend of rising incidence of sepsis. It is possible that increases in incidence represent a real epidemiological shift in the condition,[21] especially considering the aging population in many high-income countries.[22] On the other hand, there is some evidence that the rise in incidence may be inflated due to changes in administrative data coding practices and/or improved awareness, recognition, and documentation of sepsis among physicians.[23–26] For example, the introduction of the United States Centers of Medicare and Medicaid Services guidance on coding led to an apparent increase in sepsis incidence, in effect, capturing a greater number of less severely ill patients.[27]

A 2016 systematic overview of sepsis incidence meta-analyzed 27 studies from 7 high-income countries and estimated the incidence rate of hospitalized sepsis cases of any severity to be 288 per 100,000 person-years, and the incidence rate for severe sepsis (including septic shock) cases as 148 per 100,000 person-years.[28] However, individual estimates of severe sepsis incidence vary widely from study to study, depending on the definition used, study design, data source, time period, ages included, and region.[29]

The nationwide incidence rate of sepsis in Canada is currently unknown. The most recent national statistics on hospitalizations for sepsis in Canada (excluding Quebec) were detailed in a 2009 report by the Canadian Institute for Health Information (CIHI).[5] Over 30,000 Canadians were hospitalized with sepsis in 2008-09, with sepsis leading to 10.9% of all in-hospital deaths.[5] In 2008-09, the population-based hospitalization rate for sepsis of any severity was 103.2 per 100,000, which did not represent a significant increase from 2004-05. For severe sepsis (including septic shock) the hospitalization rate and was 39.7 per 100,000 in 2008-09, a 17.8% increase from 2004-05 rates.[5] As these estimates were based on administrative data, and previous research has found that sepsis is "highly undercoded",[8] they likely underestimate the true incidence of sepsis in Canada. In a validation study, a revised sepsis algorithm by Jolley et al. improved the sensitivity of the sepsis definition by 25.5% compared to the original CIHI 2009 ICD-10-CA case-coded algorithm.[8]

1.3.1 Baseline Risk Factors for Sepsis

There are several patient characteristics that can increase an adult's susceptibility to developing sepsis. Advanced age,[30–37] co-morbidities,[30,35,37–41] male sex,[10,22,30,31,33,42] physical inactivity,[43] lower socioeconomic status,[30,44] residence in a long-term care facility,[36] tobacco smoking,[30,34,45] vitamin D deficiency,[46,47] limited access to medical care,[48] and genetic traits[49–51] have all been associated with a higher risk of sepsis, to varying degrees. There is also evidence of differences in the occurrence of sepsis

depending on race[30,33,52–54] although these disparities may be mediated by other risk factors such as co-morbid conditions.[40,54] Additionally, there is evidence of a seasonal variability in the incidence of sepsis.[31,55] Studies have also assessed risk factors related to specific types of sepsis, including post-traumatic sepsis,[33,37,56,57] post-surgical[58] and other forms of nosocomial sepsis,[45,59,60] as well as maternal sepsis.[61,62]

1.4 Sepsis-Associated Mortality

While there is evidence that case fatality of sepsis has decreased,[28] the mortality burden of sepsis remains high. In Canada, sepsis accounted for 10.9% of all deaths occurring in hospitals in 2009.[5] Globally, it is estimated that sepsis causes or contributes to up to 5.3 million deaths per year.[15] Most previous research has focused on short term outcomes, typically in-hospital mortality or 28-day mortality. A 2016 meta-analysis of 14 studies estimated that the crude hospital case-fatality rate for sepsis of any type was 21%.[28] Looking at severe sepsis only, the meta-analytic estimate from 18 studies was 28%.[28] In Canada, the 2008-2009 crude in-hospital mortality was 30.5% for all sepsis patients, 45.2% for severe sepsis patients only, and 20.9% for uncomplicated sepsis (without organ dysfunction).[5]

As more people are surviving sepsis,[20] it is increasingly important to look at long-term outcomes, in particular mortality, in sepsis patients rather than simply in-hospital or 30-day outcomes. Additionally, previous studies have not typically examined sepsis-attributable mortality; more commonly, previous research examined overall mortality and did not use control groups. A 2016 systematic review identified 43 studies reporting on one-year mortality in patients with sepsis. Considering only the studies that used non-sepsis controls, associations between sepsis and risk post-acute mortality were inconsistent.[63] Hazards ratios were higher in studies which used general population or community controls compared to studies using hospitalized controls.[63] Compared to the general population, studies reported critically ill sepsis patients to have a two to five times higher risk of mortality post-discharge.[63] Compared to

hospitalized controls, sepsis was independently associated with an increased risk of long-term mortality in four studies.[64–67] However, as the severity of illness in the control group increased, this association no longer remained.[63]

In the past three years since the 2016 systematic review was published, two retrospective cohort studies with non-sepsis control groups have examined long-term mortality in sepsis patients compared to non-sepsis patients. Prescott et al. 2016 studied attributable late mortality (31 days to two years) in severe sepsis patients over 65 years of age.[68] Patients with severe sepsis were compared to three propensity-matched groups of non-sepsis patients: 1) non-hospitalized controls; 2) patients hospitalized with non-sepsis infection; and 3) patients hospitalized with acute sterile inflammatory conditions (non-infectious in origin). Compared to the two control groups of hospitalized patients, mortality remained higher for severe sepsis patients for at least 6 months to a year.[68] Thompson et al. 2018[69] analyzed a subset of critically ill patients from a larger trial, comparing ICU patients with sepsis (1991 consensus definitions) to a propensity-matched cohort of ICU patients without sepsis. They reported no difference in survival between sepsis cases and non-sepsis controls over 2 years follow-up.[69]

The physiological reasons why sepsis would increase mortality in the long-term are unclear, and it is inconclusive whether the sepsis itself is the actual cause behind apparent increases in individual studies. As sepsis survivors can be debilitated for extended periods of time, it is possible that this decreased function could raise their risk of developing further illnesses. There is data to suggest that sepsis survivors experience prolonged immunosuppression, which may also increase their risks of further morbidity and mortality.[70] The organ dysfunction resulting from severe sepsis, is another potential mechanism of increased morbidity and mortality risk in sepsis survivors.

1.5 Sepsis-Associated Health System Costs

There is consensus in the literature that sepsis is an expensive condition to treat in hospitals, incurring extremely large costs to healthcare systems worldwide. Septicemia ranked first on the Agency for Healthcare Research and Quality's (AHRQ) list of most expensive conditions in hospitalized patients, costing US hospitals an estimated $24 billion a year in 2013.[3] Similarly, annual costs for severe sepsis are high in Germany, with direct costs estimated at $4.962 billion nationally in 2011.[71] In England, Wales and Northern Ireland the costs of septic shock alone was estimated to be £293.2 million per year in 2012.[72] Previous literature has focused primarily on hospital costs resulting from sepsis. A 2017 systematic review by Arefian et al. identified 37 studies on hospital costs of sepsis.[73] Based on the included studies, the authors calculated that the median of the mean hospital cost of sepsis per patient was $32,421 (IQR $20,745-$40,835) (2014 US dollars).[73] There was wide variation in the estimates of cost per hospitalization between studies, with median cost per stay ranging from $5,051 to $64,788. The main driver of costs for sepsis patients tends to be length of stay, particularly ICU length of stay.[74–76]

Sepsis survivors may experience sepsis-associated morbidity that increases health resource utilization, yet only a small number of past studies have looked at long-term costs post-discharge. Braun et al. conducted a retrospective analysis of US claims data for severe sepsis patients from 1995-1998, reporting that at one-year follow-up total inpatient and outpatient costs per case were $48,996.[77] A large proportion of these costs were likely a result of rehospitalizations. According to Chang et al. rehospitalizations are "common and costly".[78] They reported that 20.4% of sepsis patients are readmitted to a hospital within 30 days of discharge, most commonly with a diagnosis of septicemia (29.2%).[78] A later study in 2018 estimated the mean cost per hospital readmission for sepsis patients ranged from $14,312 for survivors of sepsis without organ dysfunction to $18,587 for septic shock survivors.[79] A cost-analysis in Alberta, which looked at post-discharge costs in sepsis survivors over 3

years, found that the majority (88%) of costs were accrued via hospital readmissions in the first year after discharge.[80]

In the past five years, two previous studies have examined incremental long-term costs in sepsis patients compared to non-sepsis controls.[69,81] Prescott et al.[81] conducted an observational cohort study using 1988-2005 data from the US Health and Retirement Study linked with Medicare claims. At 1-year follow-up, patients with severe sepsis had higher healthcare resource use post-sepsis compared to before sepsis and also had higher resource use compared to non-sepsis hospitalized matched controls.[81] Thompson et al.[69] conducted a propensity score matched analysis in a subset of Australian ICU patients with and without sepsis who were part of a larger randomized controlled trial. They found that after 2-year follow-up, healthcare resource use, including cost of ICU and hospital treatment, was higher in sepsis cases compared to critically ill non-sepsis controls.[69]

Systematic reviews of studies on the costs of sepsis and economic evaluations of treatments for sepsis have found that studies in this area tend to be of relatively low quality,[73,82] with many studies inadequately reporting their costing methodology.[83] Additionally, few studies have examined the incremental costs in sepsis patients compared to other hospitalized patients or population controls. Further, there is a lack of recent information on the health care system costs of sepsis in a Canadian context.

1.6 Identification of Sepsis in Administrative Databases

Although many studies of sepsis outcomes in the past 20 years have made use of national or regional health administrative datasets to identify large samples of patients, there is no “gold standard” method for case definition of sepsis using these sources and there is ongoing debate about the accuracy of sepsis coding, particularly for determining incidence rates of sepsis. Some have called for a harmonized case definition to improve comparability between studies.[84] Estimates of sepsis incidence and mortality

can vary widely depending on the coding algorithm used to identify sepsis cases. For example, in Wilhelms et al.'s analysis of a national Swedish discharge dataset, three different coding strategies based on ICD-10 codes for sepsis resulted in "three almost separate cohorts of patients with severe sepsis."[85]

In 2015 Jolley et al. published a systematic review of sepsis case definitions used in administrative health databases.[84] The 12 included studies included 38 different case definitions. These definitions contained more than 130 unique ICD codes. Across the definitions there was a wide range in positive predictive value (5.6%-100%), sensitivity (5.9%-82.3%) and negative predictive value (62.1% to 99.7%).[84]

The earliest, and subsequently most commonly used, coding algorithm for severe sepsis is the Angus implementation.[22] Published in 2001, it set a precedent for sepsis case definition.[22] The algorithm is based on ICD-9 (International Classification of Diseases, Ninth Revision) codes, defining severe sepsis using a combination of codes for underlying infection in addition to codes representing organ dysfunction. The case definition used in CIHI's 2009 report on sepsis[5] is based on the Angus implementation, but translated into ICD-10. The Martin implementation has also been used in various administrative database studies of sepsis.[10] Similar to the Angus approach, it is based on ICD-9 and uses codes for septicemia or disseminated infection in combination with codes for acute organ dysfunction.[10] In one validation study the Angus approach had much higher sensitivity compared to the Martin approach (50.3% vs 16.8% respectively).[86] Another approach, is to use only explicit codes for sepsis, which may be a more specific, but less sensitive method. Ford et al., for example, compared all three different approaches to develop a severe sepsis mortality prediction model.[87]

Only two previous studies validated ICD-10 case definitions for sepsis in a Canadian population. Both used data from the province of Alberta,[8,88] and one was limited to postoperative sepsis only.[88] The study by Quan et al. created ICD-10 case definitions based on the Agency for Healthcare Research and Quality

patient safety indictors, which include post-operative sepsis. The number of patients in the sample with post-operative sepsis was small: only 41 patients, and the positive predictive value of the ICD-10 code definition used was very low: 9.8%.[88]

Jolley et al. developed and validated an "optimized" version of the ICD-10 code algorithm for sepsis and severe sepsis previously used in the 2009 CIHI report.[8] The revised algorithm included an additional seven ICD-10 codes to define sepsis. Jolley et al. used two validation cohorts, one with 1001 ICU patients (604 with sepsis), while the other was a smaller random sample of non-ICU records. Both cohorts were drawn from patients admitted to one of three hospitals in the Calgary region, from 2009-2012.[8]

Regardless of the algorithm used for case identification, there is evidence that sepsis is under-coded in administrative health data that uses ICD-9 and ICD-10,[84,89] which would negatively affect the sensitivity of any case definition based on these codes. Because of this issue, Jolley et al. concluded that administrative data alone is probably insufficient to study incidence of sepsis accurately.[84] However, based on the results of their systematic review, they stated that coding algorithms would be acceptable for studying risk factors or outcomes of sepsis, although they may only represent a subset of the true cases.[84] Finally, ICD-9 and ICD-10 case definitions do not reflect the updated definition of sepsis as outlined in the 2016 Sepsis-3 definition.

1.7 Knowledge Gaps

The last national picture of sepsis hospitalizations in Canada was conducted in 2009.[5] Further, data from the studies of costs in Canadian sepsis patients are almost 20 years old.[74,80] Although recent studies from the US[68,81] and Australia[69] have examined long-term mortality and healthcare resource use in sepsis patients, Canadian data is lacking and results could vary given differences in health systems, payment mechanisms, and patient demographics. Having accurate and current data on sepsis on a provincial level would provide policy-makers with a picture of the epidemiology and health system costs of sepsis in

Canada that could inform decision making. Current information on the healthcare costs and trajectory of health outcomes in sepsis patients is necessary in order to accurately model the costs and benefits in economic evaluations of interventions aimed at sepsis patients. The results of these economic models can help decision-makers determine which interventions provide the best value for money. Additionally, while it is known that sepsis presents a high mortality burden in the short-term, studies on the long-term attributable outcomes are lacking. Many studies did not include a non-sepsis control group, and in those that did, results have been inconsistent.[63] At a 2018 colloquium on sepsis survivorship data on sepsis survivors beyond one-year follow-up was highlighted as a important gap in current research.[2] As more people are surviving episodes of sepsis,[20] it is important to accurately determine the long-term health trajectory of sepsis patients. This study aims to fill the above knowledge gaps by examining long-term mortality, healthcare costs, and health resource utilization in sepsis patients compared to non-sepsis hospital controls in an Ontario cohort. We hypothesize that sepsis patients will have a higher relative rate of long-term mortality, higher health system costs and healthcare resource use compared to non-sepsis controls.

1.8 Objectives

The objectives of this thesis are:

1. To estimate attributable all-cause mortality in sepsis (Sepsis-2) patients compared to non-sepsis hospitalized patients up to 5 years from index admission.
2. To estimate the attributable rehospitalizations of sepsis (Sepsis-2) patients compared to non-sepsis hospitalized patients up to 5 years from index admission.
3. To estimate the incremental health system costs of sepsis (Sepsis-2) patients compared to non-sepsis patients 1 year from index admission.

4. To estimate the incremental hospital and ICU length of sepsis (Sepsis-2) patients compared to non-sepsis hospitalized patients during index hospital admission.

Chapter 2: Long-term Mortality and Rehospitalizations Associated with Sepsis: A Population-Based Retrospective Cohort Study

The following is an unpublished manuscript formatted for journal submission (not yet submitted, planned submission date: January 2020)

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2.1 Abstract

Importance: The long-term health outcomes attributable to sepsis are unclear.

Objectives: To determine the attributable all-cause mortality and hospital readmissions in sepsis patients compared to hospitalized non-sepsis controls up to 5-years after index admission.

Design: We conducted a population-based, retrospective cohort study using health administrative data housed at ICES. We identified a cohort of adults (≥18) hospitalized between April 1, 2012 and March 31, 2016, with follow-up to March 31, 2017.

Setting: Hospitals in Ontario, Canada.

Participants: A validated Canadian algorithm was used to identify sepsis cases with all remaining hospitalized patients serving as potential controls. Cases and controls were matched 1:1 on propensity score, age, sex, admission type, and admission date.

Exposure: Hospitalization with a diagnostic code for sepsis according to Sepsis-2 definitions. Patients with non-severe sepsis (without organ dysfunction) and severe sepsis (including septic shock) were considered as subgroups.

Main Outcome(s) and Measure(s): All-cause mortality and hospital readmission up to 5-years from index admission date were determined using survival analyses and controlling for remaining confounders.

Results: Out of 1,869,635 eligible patients hospitalized during the four-year accrual period, 270,669 (14.5%) had a diagnosis of sepsis, including 91,987 (4.9%) with severe sepsis. Of all cases identified, 196,922 were successfully matched: 64,204 had severe sepsis and 132,718 had non-severe sepsis. Severe sepsis patients had higher mortality rates up to 5 years after index admission compared to matched controls (hazard ratio [HR] 1.66, 95% confidence interval [CI]: 1.63-1.68). Comparing only cases and controls who survived index hospitalization, severe sepsis patients had higher relative mortality (HR: 1.35, 95% CI: 1.32-1.38) and rehospitalization rates (HR: 1.53, 95% CI: 1.50-1.55) over 5 years post-discharge. On average, non-severe sepsis survivors had higher rehospitalization rates (HR: 1.41, 95% CI: 1.40-1.43) and long-term post-discharge mortality rates (HR: 1.32, 95% CI:1.30-1.33) compared to hospital controls. Relative mortality rates were highest among severe sepsis patients <65 years-old compared to older age groups.

Conclusions and Relevance: Severe sepsis was associated with a higher risk of death and rehospitalization up to 5 years after index hospitalization. These results highlight the need for effective post-discharge follow-up care for sepsis survivors.

2.2 INTRODUCTION

While some previous studies have reported an increased risk of long-term mortality in sepsis patients,[64–67] it remains inconclusive whether this apparent increase can be attributed to sepsis, or if it is caused by confounders such as pre-existing co-morbidities.[90] As such, a 2016 systematic review on sepsis and long-term mortality called for high-quality studies using control groups that adequately account for confounding factors.[63] The review's authors noted significant heterogeneity between the 43 included studies reporting 1-year mortality.[63] Further, only a minority of these studies used non-sepsis control groups. Among the controlled studies, the associations between sepsis and post-discharge mortality were inconsistent, and risk varied depending on the health status of controls: as the severity of illness in the control group increased, the association between sepsis and long-term mortality diminished.[63]

This pattern was reflected in two studies published subsequent to the 2016 review.[68,69] Thompson et al. 2018,[69] compared intensive care unit (ICU) patients with sepsis to a propensity-matched cohort of ICU patients without sepsis. They reported no significant difference in survival between cases and controls over 2 years.[69] Prescott et al.[68] examined attributable late mortality (31-days to 2-years) in sepsis patients ≥65 years compared to three different propensity-matched non-sepsis control groups. They concluded that over 20% of sepsis survivors had a late death which could not be attributed to their pre-sepsis health status.[68]

A complicating factor in interpreting results from previous studies is the varying levels of sepsis severity and types; for instance, some studies dealt specifically with pneumonia, others with severe sepsis, or bacteremia. Another complication is the changing definition of sepsis. The 2016 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3),[1] redefined sepsis as an abnormal immune response to infection that results in "life-threatening organ dysfunction,"[1] eliminating the "severe sepsis" label used in previous definitions.[7] For the present research, we use the previous Sepsis-2

definitions, since Sepsis-2 definitions were used for recording sepsis in hospital admission records during this study's accrual period and the validated algorithm for identifying cases was based on these definitions.

The primary objective of this study was to estimate mortality attributable to sepsis up to 5 years after index admission date by comparing patients with sepsis to matched non-sepsis hospitalized controls. Secondary objectives were to evaluate the relative hospital readmission rate and post-discharge mortality for up to 5 years in sepsis patients and matched controls who survived index hospitalization.

2.3 METHODS

Study Design and Data Sources

We conducted a population-based, retrospective propensity score matched cohort study using health administrative data housed at ICES, a non-profit research institute housing health-related datasets from the Canadian province of Ontario. Individual-level data was linked across ICES databases through unique patient identifiers. Table 6 in the data supplement (page 33) describes the databases used. For confidentiality, study data is not publicly available; however, access may be granted under certain conditions (ices.on.ca/DAS).

Identification of Cohort for Matching

All adult patients (≥18) admitted to an Ontario hospital between April 1, 2012 and March 31, 2016 were identified using the Canadian Institute for Health Information's (CIHI) Discharge Abstract Database (DAD). Exclusion criteria are detailed in the data supplement (Table 7). Sepsis cases were flagged using a validated International Classification of Diseases-10 (ICD-10) definition (Table 8, data supplement).[8] Exposure was stratified according to sepsis type: non-severe sepsis and severe sepsis (including septic

shock). Patients were classified as having non-severe sepsis if they had a code indicating an infection or sepsis, but no code for organ dysfunction. Cases were classified as having severe sepsis if, in addition to having a code for sepsis, they had at least one organ dysfunction code. Patients were classified as potential controls if they had no sepsis codes from the above definition recorded during the study period. If a patient had more than one hospitalization during the accrual period, only the first visit was eligible for inclusion.

Propensity Score Matching

To account for potential confounding factors, we matched sepsis patients with hospitalized non-sepsis patients. Matching variables included: age (+/- 1 year), sex, admission date (+/- 30 days), admission type (urgent or elective), and logit of the propensity score[91] (caliper width 0.25 standard deviations). Matching variables and variables in the propensity score model were selected based on previous literature and expert opinion of a critical care physician (LM) (see supplement, Table 9). We used a greedy matching algorithm to pair cases 1:1 with controls without replacement. A standardized difference of ≤0.10 was considered to indicate good balance between cases and controls for a given variable.[92]

Censoring

Patients were followed from index admission date until they died, became ineligible for OHIP, or reached the study end date (March 31, 2017), whichever came first.

Outcomes

All-cause mortality from index admission was determined using the Registered Persons Database. Time to first hospital readmission post-discharge was determined from CIHI's DAD. For rehospitalization and

post-discharge mortality, we reconducted the propensity score matching, including only patients who survived the index hospitalization.

Analysis

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). Statistical significance was assessed at the two-sided 5% significance level.

We described survival time using Kaplan-Meier curves, and time to rehospitalization using cumulative incidence function curves.

We used Cox proportional hazards regression to assess attributable mortality. The robust sandwich variance estimator was used to account for the correlation between matched cases and controls. For time to first hospital readmission, we used a cause-specific Cox regression hazard model with robust sandwich variance estimators, taking into account the competing risk of death.

In the above analyses, we adjusted for baseline variables with >0.10 standardized difference after matching, and index admission hospital type (teaching, community ≥100 beds, or community <100 beds). The proportional hazards assumption was assessed using log(-log(S(t)) plots and a model-based method with time-varying covariates.

We conducted a subgroup analysis by three age groups, repeating the analyses for: patients aged <65 years, 65-84 years, and ≥85 years.

We conducted a sensitivity analysis using an alternate case definition of sepsis: the ICD-10 case definition from the 2009 CIHI sepsis report.[5]

We also conducted an analysis comparing outcomes for between patients with severe and non-severe sepsis, in which severe sepsis patients were matched with non-severe sepsis controls and analyses performed as above.

2.4 RESULTS

Out of 1,869,635 patients hospitalized during the four-year accrual period who met the inclusion criteria, 270,669 (14.5%) had a diagnosis of sepsis according to the Jolley et al. algorithm, including 91,987 (4.9%) who had diagnostic codes for severe sepsis (see Figure 1 for patient selection flow diagram). The final cohort consisted of 196,922 matched pairs, with 27% of cases unmatched. Compared to matched cases, unmatched cases had higher healthcare resource use and comorbidities (see Table 10, supplement). Of the matched cases, 64,204 (33%) had severe and 132,718 (67%) had non-severe sepsis (no organ dysfunction) over the four-year accrual period.

Table 3 presents characteristics for cases and controls pre-and post-matching. Before matching, there were some stark differences between cases and the pool of controls: cases were much older on average (73 versus 53 years), were more likely to be receiving homecare (46% versus 10%), and to have higher morbidity burden (average Johns Hopkins Aggregated Diagnosis Groups® [ADG] Score[93] 29.5 versus 11.7). After matching, the variables were well balanced overall, although a few remained over the 0.10 standardized difference threshold (between 0.11-0.19). For severe sepsis patients, propensity score variables with residual imbalances included: rural residence, number of emergency department visits in the past year, and mean ADG Score. For non-severe sepsis, these included: homecare use, hospitalization, number of physician visits in the past year, and previous diagnosis of COPD. There were a small number of missing observations for hospital type and rural residence (<0.01%). These observations were excluded from the models. The median follow-up time for the whole cohort was 762 days (2.1 years) (see Table 4). Characteristics for the analysis of hospital survivors are presented in the data supplement (Table 11).

Table 4 presents descriptive data on mortality, rehospitalization, and follow-up time. Table 5 summarizes attributable mortality and rehospitalizations. Analysis of sepsis cases with and without

organ dysfunction are presented separately as results from these two groups differed for some outcomes.

Long-Term Mortality Rates from Index Admission

Sepsis cases had higher death rates compared to controls during follow-up, for severe sepsis: 54.8% vs. 36.2%; for non-severe sepsis: 40.1% vs. 31.7% (Table 4). Kaplan-Meier survival curves for the two case groups versus their respective controls are shown in Figure 2. Over the 5-years of follow-up, severe sepsis patients had a higher relative mortality rate compared to matched controls (HR: 1.66, 95% CI: 1.63-1.68). For non-severe sepsis cases, plots of log(-log(S(t)) indicated non-proportional hazards: their relative mortality rate was lower than controls at 30-days (HR:0.75, 95% CI: 0.73-0.77) and higher than controls in later periods (e.g. from 1-6 months HR:1.16, 95% CI: 1.13-1.19). Estimates for alternate time points are provided in Table 12 (data supplement). Considering the entire follow-up period, relative mortality for non-severe sepsis patient versus controls was HR: 1.18, 95% CI: 1.17-1.20. However, this hazard ratio and those for non-severe patients in Table 5 should be understood only as a population average for the entire interval given the non-proportional hazards.[94]

Long-Term Post-Discharge Mortality in Hospital Survivor Cohort

Comparing only cases and controls who survived index hospitalization, the relative mortality rates up to 5-years post-discharge were HR: 1.35 (95% CI: 1.32-1.38) for severe sepsis and HR: 1.32 (95% CI: 1.30-1.33) for non-severe sepsis (Table 5). However, there was some evidence of non-proportional hazards for both severe and non-severe sepsis cohorts. For non-severe sepsis patients versus matched controls, there was no statistically significant difference in mortality in the first 30-days post-discharge (HR: 0.97, 95% CI: 0.93-1.01). For both case groups, the hazard ratios increased over time (see data supplement Table 13). The data supplement Figure 6 shows Kaplan Meier curves of post-discharge survival.

Time to Rehospitalization in Hospital Survivor Cohort

Crude rehospitalization rates in matched cases and controls who survived to discharge were, for severe sepsis: 62.2% vs. 48.4%; for non-severe sepsis: 60.1% vs. 47.1% (Table 4). Sepsis patients had higher relative rates of hospital readmission up to 5-years after initial discharge: for severe cases (HR: 1.53, 95% CI: 1.50-1.55) and non-severe sepsis (HR: 1.41, 95% CI: 1.40-1.43) (Table 5). See data supplement Figure 8 for cumulative incidence functions.

Age Subgroup Analysis

Mortality differences between cases and controls were more pronounced in the younger age group (<65 years) and attenuated in the elderly (≥85 years) (Table 5). Younger severe sepsis cases had the highest relative mortality rates, compared to their respective matched controls: HR 2.49, 95% CI: 2.37-2.62. Relative hospital readmission rates between cases and controls were similar across age groups.

Sensitivity Analysis – CIHI Definition

Compared to the Jolley et al. definition, the CIHI sepsis algorithm identified far fewer cases (48,319 versus 270,669). Estimates of 5-year relative mortality rates for severe sepsis were higher using the CIHI definitions versus the primary analysis (HR 2.10 versus 1.66). In contrast to the primary results, non-severe sepsis patients had higher relative mortality rates compared to controls over the entire follow-up period (see data supplement Figure 9). Estimates of post-discharge mortality and rehospitalization rates were similar to the primary analysis (Table 5).

Severe Sepsis Cases versus Non-Severe Sepsis Controls

Compared to matched non-severe sepsis controls, patients with severe sepsis had higher relative mortality rates for up to 2 years post-discharge (HR: 1.15, 95% CI: 1.13-1.18) (see data supplement Figure 10, Table 16). Rehospitalization rates were slightly higher for severe sepsis patients at 1-year versus non-severe sepsis controls (HR: 1.09, 95% CI: 1.07-1.10).

2.5 DISCUSSION

Our study found that, compared to other hospitalized patients, severe sepsis patients had higher relative mortality rates of up to 5-years after index admission. In patients who survived initial hospitalization, severe sepsis cases had 53% higher rehospitalisation rates and 35% higher relative mortality rate up to 5-years post-discharge compared to their non-sepsis controls.

Attributable effects for patients with non-severe sepsis were more complex. These cases had lower 30-day relative mortality compared to controls, but higher long-term mortality rates up to 5-years. In hospital survivors, non-severe patients had significantly higher mortality from 30-days up to 5-years post-discharge. They also had 41% higher readmission rates compared to controls for up to 5-years. Lower short-term mortality among non-severe sepsis versus controls may be because non-severe sepsis patients had no organ dysfunction by definition, while the controls might have an organ dysfunction that was not related to sepsis.

In both case groups, relative mortality rates tended to attenuate with age. Sepsis patients <65 years had the highest attributable mortality rates. As cases were matched with controls on age, these higher relative rates in younger age groups likely reflect general population trends of higher mortality risk with age (whether case or control, elderly patients have a higher risk of death). On average, cases identified in this study were older in comparison with previous studies on sepsis (e.g. mean 73 years versus 63 years in the Thompson et al[69]).

Interestingly, post-discharge hazard ratios increased over time, and after 6-months were similar in severe sepsis and non-severe sepsis compared to their respective control groups. The similarity in estimates between the two subgroups makes it difficult to make causal inferences about sepsis and long-term mortality. There were large differences in pre-index health status between all sepsis patients and hospital controls, making it challenging to fully eliminate confounding factors between matched

cases and controls. However, in a sensitivity analysis comparing severe sepsis patients versus non-severe sepsis controls, severe sepsis patients had higher post-discharge mortality for up to 2-years, providing evidence that severe sepsis increases long-term mortality risk.

Results from previous research on long-term sepsis mortality have been inconsistent. A 2016 systematic review on post-discharge sepsis mortality identified 13 previous studies that used hospital controls.[64–67,81,95–102] Of these studies, sepsis was associated with an increased risk of post-discharge mortality in four.[64–67] Generally, as the severity of illness in the comparison group increased, this association waned. Our control group was broader than some previous studies examining similar outcomes, it included any hospitalized patient over 18-years old without a diagnostic code for sepsis, which may explain some differences in findings. For example, Prescott et al.'s 2018 study was limited to adults 65 or older and found that mortality rates in sepsis survivors remained higher for 6-months to 2- years post-discharge, depending on the control group used.[68] Thomson et al.'s study, which found that sepsis cases had no significant mortality difference at two-years compared to matched controls, was restricted ICU patients.[69]

Our study also differed in the coding definition used to identify sepsis patients. To our knowledge this study is the first to use the Canadian validated algorithm[8] to study attributable outcomes. The Jolley et al. definition showed higher sensitivity compared to CIHI's 2009 algorithm in a validation study.[8] Others have noted challenges in sepsis case identification using health administrative data: sensitivity is generally low and different coding definitions can result in wide variation in estimates of incidence and outcomes.[84] The Jolley et al. algorithm identified a greater number of patient compared to the CIHI definitions: 3 times the number of severe sepsis cases and 8 times the number of non-severe cases. Given that estimates of short-term mortality were higher using the CIHI definition, the additional cases identified by Jolley seem to have a lower severity of illness.

Strengths and Limitations

A strength of this study is our access to population-based data for over 13 million Ontarians. Additionally, we were able to link many province-wide health administrative and demographic databases. Our use of propensity-score matching with hospital controls allowed us to control for imbalances in important baseline characteristics between cases and controls, including ADG Score, which has been correlated with 1-year mortality in a general Ontario population.[93]

Given the differences between cases and controls before matching, there was large number of unmatched cases after 1:1 propensity score matching. Further, as patients entered the study at different times, follow-up time varied between participants, although the study all participants followed for a minimum of 1-year or until death.

As this study was reliant upon previously collected health administrative data, we did not have access to data on some potential confounding variables. For example, ICES databases had limited information on the clinical characteristics of patients, such as laboratory values and physiologic measurements, which could have led to unmeasured confounding. Further, previous studies have found that the coding of sepsis in administrative databases can be inconsistent,[84,103] and may vary over time and across different institutions. This limitation was mitigated, in part, by making use of a previously validated algorithm to identify cases.[8] As the ICD-10 codes and the case definition used in this study were based on previous definitions of sepsis, it was not possible for us to identify sepsis according to the clinical criteria specified in the Sepsis-3 definitions.

Additionally, though the case definition was validated in a Canadian population, its performance is not perfect. The validation study of the coding algorithm in an ICU population found that, for any sepsis its

was sensitivity 71.9% and specificity was 85.4%, while for severe sepsis, sensitivity was 65.1% and specificity was 88.2%.[8] In a smaller sample of non-ICU patients the sensitivity and specificity for any sepsis was 60% and 94.7%, respectively. For non-ICU severe sepsis, sensitivity and specificity were 25% and 99.5%, respectively.[8] Given imperfect validity some misclassification bias is expected. We expect that this bias would be non-differential and would bias the estimates towards the null.

Conclusions

In this analysis we found that severe sepsis is associated with higher long-term mortality compared to non-sepsis hospital controls, even considering only the post-discharge period in hospital survivors. Sepsis was also associated with greater rehospitalization rates for up to 5 years post-discharge compared to hospitalized controls. Relative mortality rates varied by age group, with younger sepsis patients (<65 years) having the largest attributable differences compared to matched controls. Results indicate the need for careful follow-up of severe sepsis survivors after hospital discharge.

2.6 Tables and Figures for Chapter 2

Table 3. Baseline Characteristics of Sepsis Cases and Non-Sepsis Hospital Controls, Before and After Matching

	BEFORE MATCHING			AFTER MATCHING					
	Control Pool N=1,598,966	**All Cases** N= 270,669	**Std. Diff.**	**Matched Hospital Controls** N= 132,718	**Non-Severe Sepsis** N= 132,718 *Unmatched= 45,964 (26%)*	**Std. Diff**	**Matched Hospital Controls** N=64,204	**Severe Sepsis (or Shock)** N=64,204 *Unmatched= 27,783 (30%)*	**Std. Diff.**
Age, mean (SD)	53 (20)	73 (16)	**1.12**	73 (16)	73 (16)	**0.00**	74 (15)	74 (15)	**0.00**
<65, n (%)	1067238 (67)	67245 (25)	**0.93**	34815 (26)	34681 (26)	**0.00**	14847 (23)	14826 (23)	**0.00**
65-84, n (%)	432504 (27)	128736 (47)	**0.43**	61557 (46)	61070 (46)	**0.01**	31602 (49)	31414 (49)	**0.01**
≥ 85, n (%)	99224 (6)	74688 (28)	**0.60**	36346 (27)	36967 (28)	**0.01**	17755 (28)	17964 (28)	**0.01**
Female, n (%)	1012110 (63)	149296 (55)	**0.17**	77655 (59)	77655 (59)	**0.00**	33091 (52)	33091 (52)	**0.00**
Rural, n (%)	209042 (13)	34790 (13)	**0.01**	17412 (13)	19711 (15)	**0.05**	7958 (12)	5644 (9)	**0.12**
Income quintile*, n (%)									
1 (lowest)	318043 (20)	62370 (23)	**0.08**	29635 (22)	29435 (22)	**0.00**	15551 (24)	14633 (23)	**0.03**
2	319126 (20)	56982 (21)	**0.03**	27767 (21)	27418 (21)	**0.01**	13747 (21)	13755 (21)	**0.00**
3	319241 (20)	52993 (20)	**0.01**	25994 (20)	26200 (20)	**0.00**	12592 (20)	12540 (19)	**0.00**
4	333067 (21)	51069 (19)	**0.05**	25423 (19)	25629 (19)	**0.00**	11713 (18)	12155 (19)	**0.02**
5 (highest)	301890 (19)	45682 (17)	**0.05**	23241 (17)	23253 (17)	**0.00**	10186 (16)	10822 (17)	**0.03**
missing	7599 (0.5)	1573 (0.6)	**0.01**	658 (0.5)	783 (0.6)	**0.01**	415 (0.7)	299 (0.5)	**0.02**
Marginalization†, n (%)									
1 (lowest)	299829 (19)	36172 (13)	**0.15**	18337 (14)	18712 (14)	**0.01**	8072 (13)	8252 (13)	**0.01**
2	360347 (23)	48027 (18)	**0.12**	24076 (18)	24301 (18)	**0.00**	10947 (17)	11323 (18)	**0.02**
3	350612 (22)	57883 (21)	**0.01**	28659 (22)	28842 (22)	**0.00**	13691 (21)	13576 (21)	**0.00**
4	293876 (18)	55249 (20)	**0.05**	26885 (20)	26844 (20)	**0.00**	13368 (21)	13089 (20)	**0.01**
5 (highest)	281107 (18)	70529 (26)	**0.21**	33598 (25)	32633 (25)	**0.02**	17407 (27)	17482 (27)	**0.00**
missing	13195 (0.8)	2809 (1)	**0.02**	1163 (1)	1386 (1)	**0.02**	719 (1)	482 (1)	**0.04**
Prior cancer, n (%)	158015 (10)	46167 (17)	**0.21**	16181 (12)	19302 (14)	**0.07**	8432 (13)	9417 (15)	**0.04**
Prior CHF, n (%)	103562 (6)	80437 (30)	**0.63**	28230 (21)	29725 (22)	**0.03**	17175 (27)	19710 (31)	**0.09**
Prior CKD, n (%)	8213 (0.5)	8955 (3)	**0.21**	2323 (2)	1277 (1)	**0.07**	1646 (3)	2852 (4)	**0.10**
Prior COPD, n (%)	216224 (14)	105392 (39)	**0.60**	39944 (30)	47909 (36)	**0.13**	24813 (39)	22868 (36)	**0.06**
Prior diabetes, n (%)	304691 (19)	107551 (40)	**0.47**	45115 (34)	46154 (35)	**0.02**	25642 (40)	26851 (42)	**0.04**
LTC resident, n (%)	9445 (0.6)	15738 (6)	**0.36**	8254 (6)	11185 (8)	**0.08**	5021 (8)	5045 (8)	**0.00**
ADG score,[93] mean (SD)	11.7 (18.8)	29.5 (13.4)	**1.09**	27 (14)	26 (13)	**0.05**	31 (13)	34 (19)	**0.19**
Healthcare use, past year									
Hospitalization, n (%)	39442 (2.5)	93692 (34.6)	**0.91**	10506 (8)	15836 (12)	**0.13**	5384 (8)	7162 (11)	**0.09**

	BEFORE MATCHING			AFTER MATCHING					
	Control Pool **N=1,598,966**	**All Cases** **N= 270,669**	**Std. Diff.**	**Matched Hospital Controls** **N= 132,718**	**Non-Severe Sepsis** **N= 132,718** *Unmatched= 45,964 (26%)*	**Std. Diff**	**Matched Hospital Controls** **N=64,204**	**Severe Sepsis (or Shock)** **N=64,204** *Unmatched= 27,783 (30%)*	**Std. Diff.**
Homecare user, n (%)	166558 (10)	125251 (46)	**0.87**	39595 (30)	47523 (36)	**0.13**	24030 (37)	23054 (36)	**0.03**
ED visits									
Mean (SD)	0.9 (1.8)	1.4 (2.7)	**0.22**	1.1 (2.5)	1.2 (2.1)	**0.02**	1.3 (2.8)	1.0 (1.7)	**0.12**
Median (Q1-Q3)	0 (0-1)	1 (0-2)	**0.29**	0 (0-1)	1 (0-2)	**0.06**	1 (0-2)	0 (0-1)	**0.12**
Physician visits									
Mean (SD)	16.5 (13.0)	25.4 (23.2)	**0.48**	17.5 (15.8)	19.3 (18.1)	**0.11**	19.0 (16.7)	20.0 (19.6)	**0.06**
Median (Q1-Q3)	14 (8-22)	19 (10-33)	**0.37**	14 (7-22)	15 (8-24)	**0.09**	15 (8-24)	15 (8-25)	**0.01**
Index Admission									
Urgent admission, n (%)	821012 (51)	259107 (96)	**1.16**	127285 (96)	127285 (96)	**0.00**	61601 (96)	61601 (96)	**0.00**
Admission Date, n (%)									
Apr 2012 – Mar 2013	474080 (30)	68848 (25)	**0.09**	42449 (32)	42579 (32)	**0.00**	18941 (30)	18979 (30)	**0.00**
Apr 2013 – Mar 2014	416610 (26)	68471 (25)	**0.02**	31691 (24)	31546 (24)	**0.00**	14857 (23)	14819 (23)	**0.00**
Apr 2014 – Mar 2015	370348 (23)	68911 (25)	**0.05**	30723 (23)	30865 (23)	**0.00**	15347 (24)	15431 (24)	**0.00**
Apr 2015 – Mar 2016	337928 (21)	64439 (24)	**0.06**	27855 (21)	27728 (21)	**0.00**	15059 (23)	14975 (23)	**0.00**
Hospital Type‡, n (%)									
Teaching	527824 (33)	75888 (28)	**0.11**	38771 (29)	34458 (26)	**0.07**	18785 (29)	19010 (30)	**0.01**
Community ≥ 100 beds	839121 (52)	141260 (52)	**0.01**	69862 (53)	66658 (50)	**0.05**	33938 (53)	37478 (58)	**0.11**
Community < 100 beds	231990 (15)	53512 (20)	**0.14**	24081 (18)	31596 (24)	**0.14**	11480 (18)	7716 (12)	**0.16**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = congestive heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; ON= Ontario; Q1 = first quarter; Q3 = third quarter; SD = standard deviation; Std Diff = standardized difference.

*Neighbourhood level income

†Ontario Marginalization Index[104]

‡Variable not used for hard matching or in propensity score.

Table 4. Descriptive Characteristics of Long-Term Outcomes of Sepsis Cases and Matched Non-Sepsis Controls

		Matched Controls N =132,718	Non-Severe Sepsis N = 132,718	Matched Controls N = 64,204	Severe Sepsis (including Shock) N= 64,204
		N (%)	N (%)	N (%)	N (%)
Mortality, up to 5 years (from index date)	All ages	42061 (31.69)	53185 (40.07)	23244 (36.20)	35182 (54.80)
	<65	3642 (10.50)	5993 (17.28)	2273 (15.33)	5344 (36.04)
	65-84	18136 (29.70)	24448 (40.03)	10703 (34.07)	16861 (53.67)
	≥ 85	20283 (54.87)	22744 (61.53)	10268 (57.16)	12977 (72.24)
Days follow-up					
Mean (SD)	All ages	862 (560)	812 (547)	790 (558)	609 (560)
Median (Q1-Q3)	All ages	851 (420-1344)	783 (379-1262)	755 (349-1246)	505 (42-1047)
Hospital Survivor Cohort*		**N= 124,244**	**N= 124,244**	**N= 48,852**	**N= 48,852**
Mortality, up to 5 years (from discharge date)	All ages	33036 (26.59)	44725 (36.00)	14460 (29.60)	19823 (40.58)
	<65	2849 (8.36)	5330 (15.63)	1342 (11.22)	2497 (20.87)
	65-84	14393 (25.07)	20842 (36.30)	6571 (27.45)	9334 (39.00)
	≥ 85	15792 (48.24)	18551 (56.67)	6543 (50.53)	7988 (61.68)
Hospital readmission (up to 5-years from Index discharge date)	All ages	58494 (47.08)	74619 (60.06)	23634 (48.38)	30394 (62.22)
	<65	13422 (39.37)	17324 (50.81)	5179 (43.30)	6784 (56.71)
	65-84	28638 (49.88)	36639 (63.82)	12156 (50.79)	15642 (65.35)
	≥ 85	16433 (50.20)	20656 (63.10)	6296 (48.62)	7968 (61.52)
Days follow-up,†					
Mean (SD)	All ages	920 (526)	856 (524)	862 (524)	773 (520)
Median (Q1-Q3)	All ages	911 (501-1376)	823 (437-1289)	829 (448-1297)	722 (368-1182)

SD = standard deviation; Q1 = first quarter; Q3 = third quarter.

*Data is from a re-matched analysis of cases and controls who survived index hospitalization.

†From day of discharge from index hospitalization to day of censoring.

Note: For age subgroups, cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of cases.

Table 5. Relative Mortality and Rehospitalization Rates for Sepsis Cases and Matched Non-Sepsis Controls, by Sepsis Type and Age Group

Outcome		Non-Severe Sepsis (no organ dysfunction) vs. Matched Controls		Severe sepsis (including septic shock) vs. Matched Controls	
Mortality Rate		**Crude HR (95% CI)**	**Adjusted* HR (95% CI)**	**Crude HR (95% CI)**	**Adjusted* HR (95% CI)**
Mortality (up to 5 years from index admission date)	All ages	1.30 (1.29-1.32)	1.18 (1.17-1.20)	1.79 (1.77-1.82)	1.66 (1.63-1.68)
	<65	1.70 (1.63-1.77)	1.33 (1.27-1.39)	2.75 (2.62-2.88)	2.49 (2.37-2.62)
	65-84	1.40 (1.38-1.43)	1.27 (1.25-1.30)	1.87 (1.83-1.92)	1.76 (1.72-1.80)
	≥ 85	1.14 (1.12-1.16)	1.10 (1.08-1.12)	1.52 (1.48-1.55)	1.45 (1.41-1.49)
	CIHI Def.‡	1.36 (1.32-1.40)	1.38 (1.33-1.43)	2.11 (2.05-2.16)	2.10 (2.05-2.16)
Post-Discharge† (up to 5 years from discharge date) Hospital survivors	All ages	1.43 (1.41-1.45)	1.32 (1.30-1.33)	1.48 (1.46-1.51)	1.35 (1.32-1.38)
	<65	1.95 (1.87-2.04)	1.54 (1.47-1.61)	1.99 (1.86-2.12)	1.79 (1.67-1.91)
	65-84	1.54 (1.51-1.57)	1.41 (1.38-1.44)	1.54 (1.49-1.59)	1.41 (1.36-1.45)
	≥ 85	1.24 (1.21-1.26)	1.23 (1.20-1.25)	1.36 (1.31-1.40)	1.29 (1.25-1.33)
	CIHI Def.‡	1.23 (1.19-1.28)	1.26 (1.21-1.32)	1.29 (1.24-1.35)	1.27 (1.21-1.33)
Time to Hospital Readmission†‖					
(up to 5-years from discharge date) Hospital survivors	All ages	1.48 (1.47-1.50)	1.41 (1.40-1.43)	1.57 (1.55-1.60)	1.53 (1.50-1.55)
	<65	1.45 (1.42-1.48)	1.35 (1.32-1.39)	1.55 (1.50-1.61)	1.48 (1.43-1.54)
	65-84	1.52 (1.50-1.54)	1.45 (1.42-1.47)	1.59 (1.56-1.63)	1.54 (1.50-1.57)
	≥ 85	1.47 (1.44-1.50)	1.45 (1.42-1.48)	1.59 (1.54-1.65)	1.56 (1.51-1.61)
	CIHI Def.‡	1.49 (1.47-1.50)	1.48 (1.46-1.50)	1.55 (1.53-1.58)	1.53 (1.50-1.55)

CI = confidence interval; HR = hazard ratio

*Adjusted for hospital type, and propensity score variables with standardized difference > 0.10.

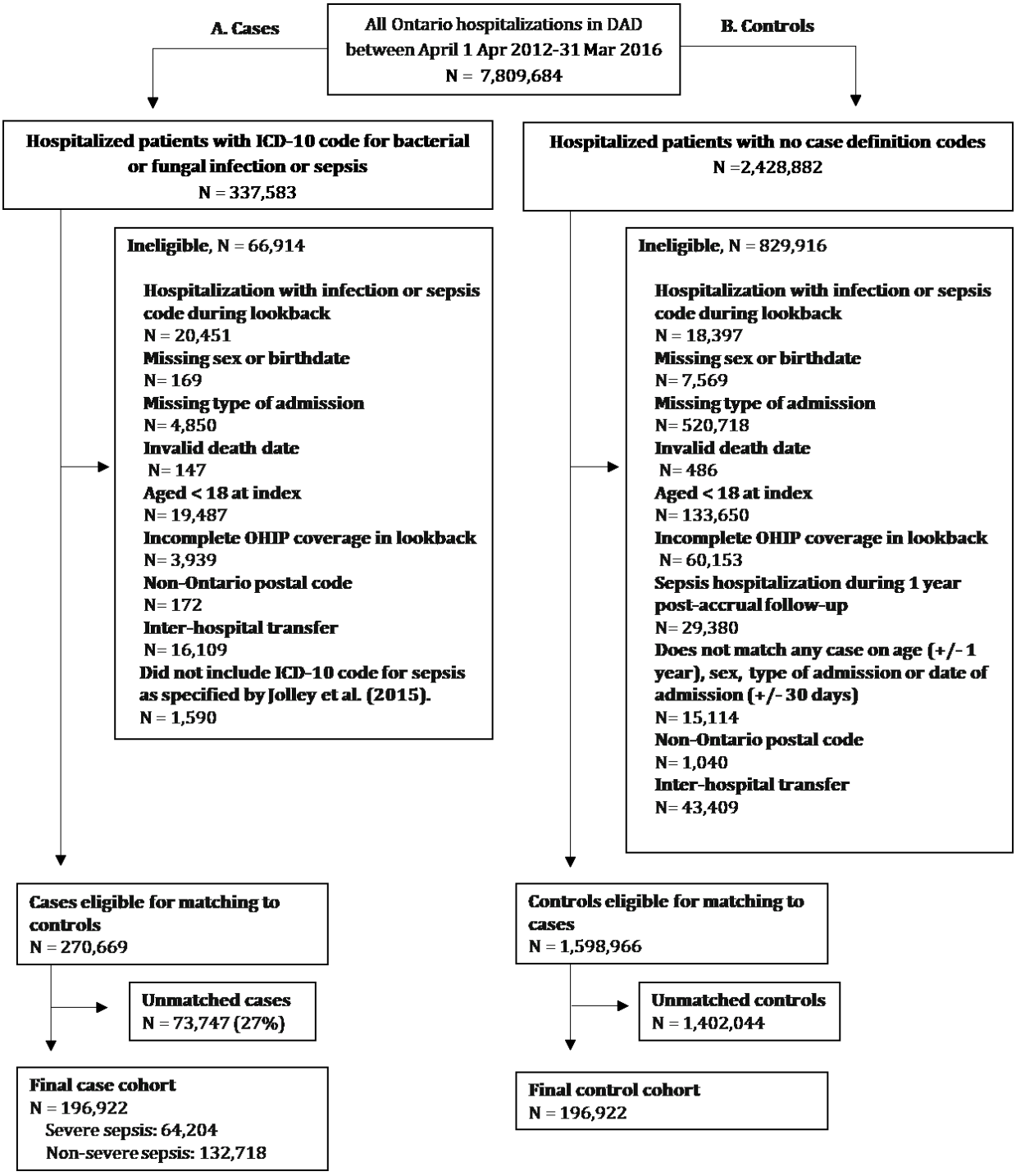
†Data is from a re-matched analysis of cases and controls who survived index hospitalization.

‡Data is from a sensitivity analysis using CIHI's 2009 administrative data case definition for sepsis (for non-severe sepsis N = 16464 matched pairs; for severe sepsis N = 19850 matched pairs). Results shown for all ages.

‖ Readmission after index admission discharge date to an acute care hospital in Ontario.

Note: For age subgroups, cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of cases.

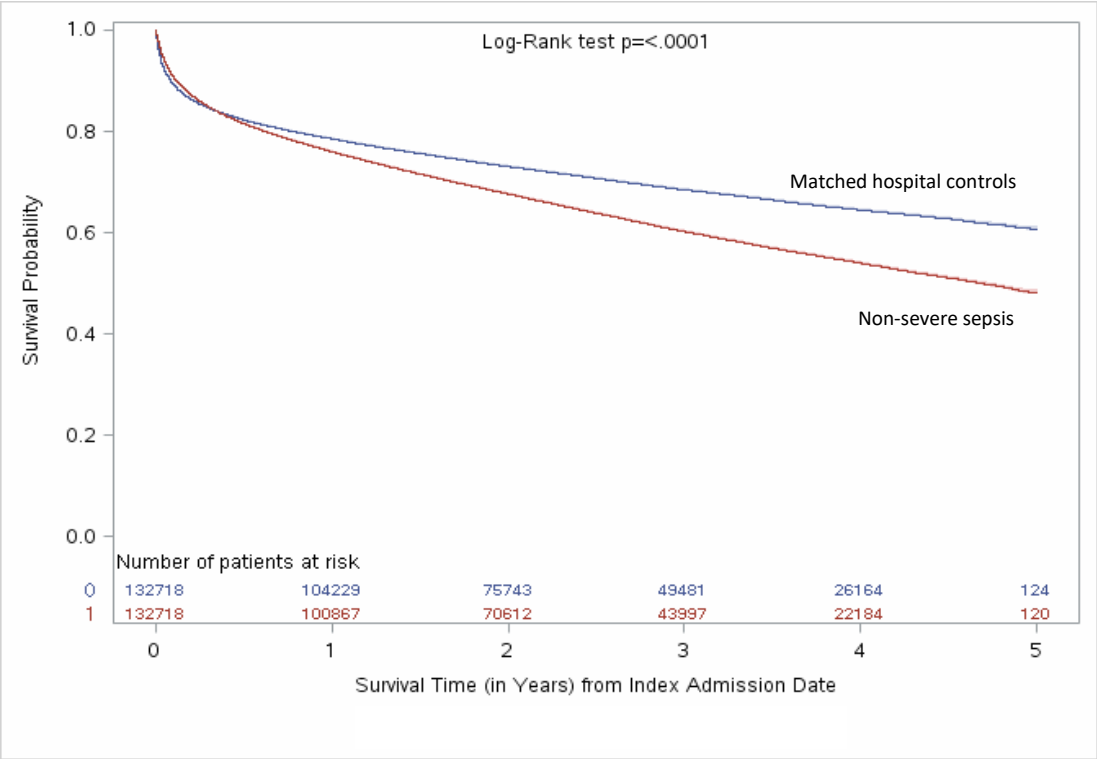
Figure 1. Cohort Creation Flow Chart



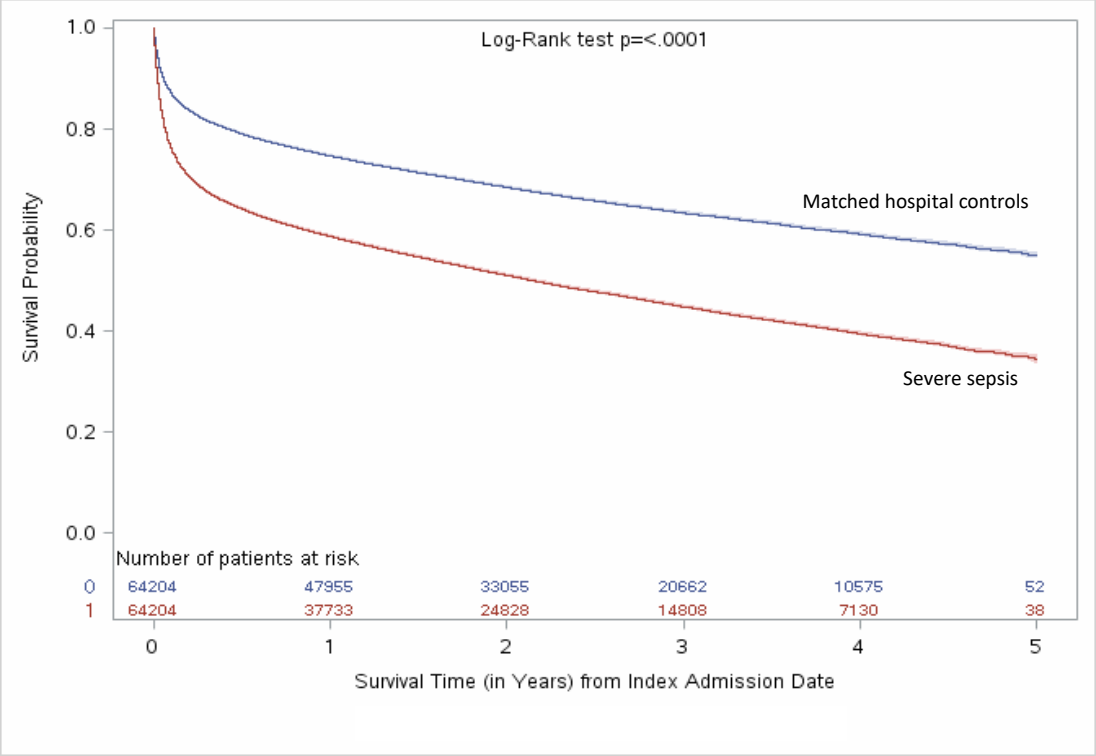
Note: Exclusions were applied sequentially in order presented.

Figure 2. Kaplan Meier Survival Curves: Sepsis Cases versus Matched Non-Sepsis Controls

a) Non-Severe Sepsis Cases versus Matched Hospital Controls



b) Severe Sepsis Cases versus Matched Hospital Controls



2.6.1 Data Supplement Chapter 2

Table 6. Description of Data Sources (ICES-Housed Administrative Databases) Used in Analysis

Database	Description	Use
Health Services		
DAD	Discharge Abstract Database	Exposure (sepsis), secondary outcome ascertainment (readmission), covariate (previous hospitalization, hospital admission characteristic)
CCRS	Continuing Care Reporting System	Covariate: residence in long term care
HCD	Home Care Database	Covariate: use of homecare services
NACRS	National Ambulatory Care Reporting System	Covariate: number of ED visits
Care Providers		
IPDB	ICES Physician Database	Covariate: number of physician visits
Coding & Geography		
PCCF	Postal Code Conversion File	Covariate: residence location
Facilities		
INST	Ontario health care institutions	Covariate: hospital type
ICES-Derived Cohorts		
ODD	Ontario Diabetes Dataset	Covariate: Diabetes prior to index
CHF	Congestive Heart Failure	Covariate: CHF prior to index
COPD	Chronic Obstructive Pulmonary Disease	Covariate: COPD prior to index
Population and Demographics		
CENSUS	Ontario Census Area Profiles	Neighborhood level socioeconomic status
RPDB	Registered Persons Database	Outcome: mortality; covariate: age, sex
Other		
ACG	Johns–Hopkins Adjusted Clinical Group	Covariate: ADG Score[93]
ONMARG	Ontario Marginalization Index	Covariate: Marginalization quintile
OCR	Ontario Cancer Registry	Covariate: Cancer prior to index

Data linkage, privacy and confidentiality: All databases listed above are housed at ICES, an independent, non-profit organisation funded by Ontario's Ministry of Health and Long-Term Care (MOHLTC). Datasets were linked at ICES using a unique encrypted identifier to maintain patient privacy and confidentiality. Data was accessed on site at ICES uOttawa. Only study personnel had access to the study data. As per ICES procedures, cells with less than six observations were suppressed to limit potential breaches of confidentiality.

Data cleaning: Data cleaning and preparation was conducted for all datasets. Patients with missing information on date of birth, sex, or type of admission were excluded (< 2% of cases). Patients with non-Ontario postal costs were excluded (0.05% of cases). Patients with invalid death dates were excluded (<0.05% of cases). For patients with missing information on residence location, Ontario Marginalization Index[104] or neighbourhood income, a category for "missing" was created before propensity score modeling was done. Patients with missing values after propensity score matching was done were excluded from the analysis if there were a small number of values (<1% of total participants).

Table 7. Cohort Exclusion Criteria

Cases	Controls
Hospitalization with diagnostic code for sepsis in 2-year period prior to index admission date.	Hospitalization with diagnostic code for sepsis in 2-year period prior to index admission date.
Missing information on sex or birthdate.	Missing information on sex or birthdate.
Missing information on type of admission.	Missing information on type of admission.
Invalid death date.	Invalid death date.
Age <18 years old at index admission date.	Age <18 years old at index admission date.
Incomplete Ontario Health Insurance Plan (OHIP) coverage in 2-year period prior to index admission date	Incomplete Ontario Health Insurance Plan (OHIP) coverage in 2-year period prior to index admission date
Non-Ontario postal code.	Non-Ontario postal code.
Interhospital transfer during index admission.	Interhospital transfer during index admission.
	Hospitalization with a diagnostic code for sepsis during 1-year post-accrual follow-up period.
	Do not match any potential cases on hard matching variables, age (+/- 1 year), sex, type of admission, and date of admission (+/- 30 days).

Table 8. ICD-10-CA Codes Used to Define Sepsis Cases

a) Codes Used to Define Cases

PRIMARY ANALYSIS: JOLLEY ET AL ALGORITHM[17]	
Sepsis	**Severe Sepsis (Including Septic Shock)**
A03.9, A02.1, A20.7, A21.7, A22.7, A23.9, A24.1, A26.7, A28.0, A28.2, A32.7, A39.2, A39.3, A39.4, A40, A40.0, A40.1, A40.2, A40.3, A40.8, A40.9, A41, A41.0, A41.1, A41.2, A41.3, A41.4, A41.5, A41.50, A41.51, A41.52, A41.58, A41.8, A41.80, A41.88, A41.9, A42.7, B00.7, B37.7, P36.0, P36.1, P36.2, P36.3, P36.4, P36.5, P36.8, P36.9, P35.2, P37.2, P37.5, **A04.7, B95.48, B95.6, B96.2, J18.9, J44.0, N39.0**	**R57.2 septic shock** OR Sepsis code, plus a code for organ disfunction in any one of six systems, including: *Respiratory:* J96.0, J96.9, J80, R09.2 *Cardiovascular:* R57.0, R57.1, R57.8, R57.9, I95.1, I95.8, I95.9 *Renal:* N17.0, N17.1, N17.2, N17.8, N17.9 *Hepatic:* K72.0, K72.9, K76.3 *Neurologic:* F05.0, F05.9, G93.1, G93.4, G93.80 *Hematologic:* D69.5, D69.6, D65 *Intervention codes (CCI):* 1.GZ.31.CA-ND, 1.GZ.31.CR-ND, 1.GZ.31.GP-ND
SENSITIVITY ANALYSIS: CIHI 2009 DEFINITION[5]	
Sepsis	**Severe Sepsis (Including Septic Shock)**
A03.9, A02.1, A20.7, A21.7, A22.7, A23.9, A24.1, A26.7, A28.0, A28.2, A32.7, A39.2, A39.3, A39.4, A40, A40.0, A40.1, A40.2, A40.3, A40.8, A40.9, A41, A41.0, A41.1, A41.2, A41.3, A41.4, A41.5, A41.50, A41.51, A41.52, A41.58, A41.8, A41.80, A41.88, A41.9, A42.7, B00.7, B37.7, P36.0, P36.1, P36.2, P36.3, P36.4, P36.5, P36.8, P36.9, P35.2, P37.2, P37.5	Sepsis code, plus a code for organ disfunction in any one of six systems, including: *Respiratory:* J96.0, J96.9, J80, R09.2 *Cardiovascular:* R57.0, R57.1, R57.2, R57.8, R57.9, I95.1, I95.8, I95.9 *Renal:* N17.0, N17.1, N17.2, N17.8, N17.9 *Hepatic:* K72.0, K72.9, K76.3 *Neurologic:* F05.0, F05.9, G93.1, G93.4, G93.80 *Hematologic:* D69.5, D69.6, D65 *Intervention codes (CCI):* 1.GZ.31.CA-ND, 1.GZ.31.CR-ND, 1.GZ.31.GP-ND

CIHI = Canadian Institute for Health Information; ICD = International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada
All codes identified as diagnosis type: 'M, 1, 2, W, X, or Y'.
Bolded codes = unique to Jolley sepsis algorithm

b) Description of Codes Used to Define Cases

Code	Description[9]	Jolley et al.[8]	CIHI 2009[5]
Sepsis: One or more of the following codes on Index Admission Record			
A03.9	Shigellosis, unspecified	✓	✓
A02.1	Salmonella sepsis	✓	✓
A20.7	Septicaemic plague	✓	✓
A21.7	Generalized tularaemia	✓	✓
A22.7	Anthrax sepsis	✓	✓

A23.9	Brucellosis, unspecified	✓	✓
A24.1	Acute and fulminating melioidosis	✓	✓
A26.7	Erysipelothrix sepsis	✓	✓
A28.0	Pasteurellosis	✓	✓
A28.2	Extraintestinal yersiniosis	✓	✓
A32.7	Listerial sepsis	✓	✓
A39.2	Acute meningococcaemia	✓	✓
A39.3	Chronic meningococcaemia	✓	✓
A39.4	Meningococcaemia, unspecified	✓	✓
A40	Streptococcal sepsis	✓	✓
A40.0	Sepsis due to streptococcus, group A	✓	✓
A40.1	Sepsis due to streptococcus, group B	✓	✓
A40.2	Sepsis due to streptococcus, group D	✓	✓
A40.3	Sepsis due to Streptococcus pneumoniae	✓	✓
A04.7	Enterocolitis due to Clostridium difficile	✓	
A40.8	Other streptococcal sepsis	✓	✓
A40.9	Streptococcal sepsis, unspecified	✓	✓
A41	Other sepsis	✓	✓
A41.0	Sepsis due to Staphylococcus aureus	✓	✓
A41.1	Sepsis due to other specified staphylococcus	✓	✓
A41.2	Sepsis due to unspecified staphylococcus	✓	✓
A41.3	Sepsis due to Haemophilus influenzae	✓	✓
A41.4	Sepsis due to anaerobes	✓	✓
A41.5	Sepsis due to other Gram-negative organisms	✓	✓
A41.50	Sepsis due to Escherichia coli [E.coli]	✓	✓
A41.51	Sepsis due to Pseudomonas	✓	✓
A41.52	Sepsis due to Serratia	✓	✓
A41.58	Sepsis due to other gram-negative organisms Includes: Gram-negative sepsis NOS	✓	✓
A41.8	Other specified sepsis	✓	✓
A41.80	Sepsis due to enterococcus Excludes: due to Streptococcus D (A40.2)	✓	✓
A41.88	Other specified sepsis	✓	✓
A41.9	Sepsis, unspecified Includes: Septicaemia	✓	✓
A42.7	Actinomycotic sepsis	✓	✓
B00.7	Disseminated herpesviral disease Includes: Herpesviral sepsis	✓	✓
B37.7	Candidal sepsis	✓	✓
B95.48	Other streptococcus as the cause of diseases classified to other chapters	✓	
B95.6	Staphylococcus aureus as the cause of diseases classified to other chapters	✓	
B96.2	Escherichia coli [E. coli] as the cause of diseases classified to other chapters	✓	
J18.9	Pneumonia, unspecified	✓	

J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection	✓	
N39.0	Urinary tract infection, site not specified	✓	
P36.0	Sepsis of newborn due to streptococcus, group B	✓	✓
P36.1	Sepsis of newborn due to other and unspecified streptococci	✓	✓
P36.2	Sepsis of newborn due to Staphylococcus aureus	✓	✓
P36.3	Sepsis of newborn due to other and unspecified staphylococci	✓	✓
P36.4	Sepsis of newborn due to Escherichia coli	✓	✓
P36.5	Sepsis of newborn due to anaerobes	✓	✓
P36.8	Other bacterial sepsis of newborn	✓	✓
P36.9	Bacterial sepsis of newborn, unspecified	✓	✓
P35.2	Congenital herpesviral [herpes simplex] infection	✓	✓
P37.2	Neonatal (disseminated) listeriosis	✓	✓
P37.5	Neonatal candidiasis	✓	✓
Septic Shock			
R57.2	Septic shock	✓	✓
Organ Disfunction (used in severe sepsis definition)			
Respiratory			
J96.0	Acute respiratory failure	✓	✓
J96.9	Respiratory failure, unspecified	✓	✓
J80	Adult respiratory distress syndrome	✓	✓
R09.2	Respiratory arrest	✓	✓
Cardiovascular			
R57.0	Cardiogenic shock	✓	✓
R57.1	Hypovolaemic shock	✓	✓
R57.2	Septic shock	✓	✓
R57.8	Other shock	✓	✓
R57.9	Shock, unspecified	✓	✓
I95.1	Orthostatic hypotension	✓	✓
I95.8	Other hypotension	✓	✓
I95.9	Hypotension, unspecified	✓	✓
Renal			
N17.0	Acute renal failure with tubular necrosis	✓	✓
N17.1	Acute renal failure with acute cortical necrosis	✓	✓
N17.2	Acute renal failure with medullary necrosis	✓	✓
N17.8	Other acute renal failure	✓	✓
N17.9	Acute renal failure, unspecified	✓	✓
Hepatic			
K72.0	Acute and subacute hepatic failure	✓	✓
K72.9	Hepatic failure, unspecified	✓	✓
K76.3	Infarction of liver	✓	✓
Neurologic			
F05.0	Delirium not superimposed on dementia, so described	✓	✓
F05.9	Other delirium	✓	✓

G93.1	Anoxic brain damage, not elsewhere classified	✓	✓
G93.4	Encephalopathy, unspecified	✓	✓
G93.80	Metabolic encephalopathy	✓	✓
Hematologic			
D69.5	Secondary thrombocytopenia	✓	✓
D69.6	Thrombocytopenia, unspecified	✓	✓
D65	Disseminated intravascular coagulation [defibrination syndrome]	✓	✓
Mechanical Ventilation Procedure Codes[105]			
1.GZ.31.CA-ND	Ventilation, respiratory system NEC, invasive per orifice approach by endotracheal intubation, positive pressure (e.g. CPAP, BIPAP)	✓	✓
1.GZ.31.CR-ND	Ventilation, respiratory system NEC, invasive per orifice with incision approach for intubation through tracheostomy, positive pressure (e.g. CPAP, BIPAP)	✓	✓
1.GZ.31.GP-ND	Ventilation, respiratory system NEC, Invasive percutaneous Transluminal approach (e.g. transtracheal jet) through needle, positive pressure (e.g. CPAP, BIPAP)	✓	✓

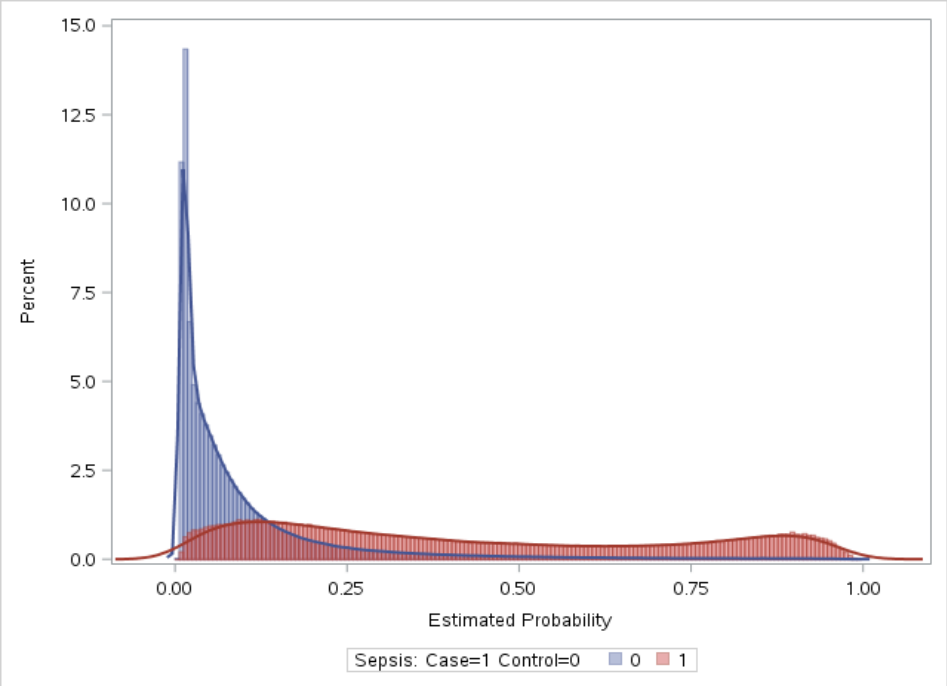
Table 9. Variables Used for Hard Matching and in Propensity Score Model

Variable name	Definition	Scale	Unit & Valid range/levels	Matching Type
Age	Patient's age at time of index hospitalization	Continuous	18–120 Years	Hard Matching +/ 1 year
Sex	Patient's biological gender	Dichotomous	Male or female	Hard Matching
Type of admission	Whether index admission was elective or urgent	Dichotomous	Elective vs urgent	Hard Matching
Date of Admission	Index hospital admission date	Date	April 1, 2012-March 31, 2016	Hard matching +/- 30 days
Long term care status	Type of setting a patient lives in prior to index hospitalization	Dichotomous	Long-term care vs community setting	Propensity score variable
Residence location	Whether patient lives in a rural or urban area	Dichotomous	Rural vs urban	
Ontario's marginalization index[104]	Level of marginalization of patient's neighbourhood based on four factors: dependency, deprivation, ethnic concentration, and instability	Ordinal	Quintile: 1-5 (1 =lowest marginalization, 5 = highest marginalization)	
Neighbourhood Income	Income quintile attributed to patient on the basis of census data and postal code	Ordinal	Quintile: 1-5 1 = lowest income, 5 = highest income	
ADG Score[93]	Weighted score of 32 Johns Hopkins Aggregated Diagnosis Groups® (ADGs) (2 years prior to index admission)	Continuous	−37 to 76	
Cancer	Inclusion in Ontario Cancer Registry of cancer cases prior to index admission in past 5 years	Dichotomous	Cancer (Yes or No)	
Diabetes	Inclusion in Ontario Diabetes Dataset prior to index admission	Dichotomous	Diabetes (Yes or No)	
Chronic Obstructive Pulmonary Disease (COPD)	Inclusion in COPD ICES-derived cohort prior to index admission	Dichotomous	COPD (Yes or No)	

Congestive Heart Failure (CHF)	Inclusion in CHF ICES-derived cohort prior to index admission	Dichotomous	CHF (Yes or No)	
Chronic Kidney Disease	Codes for chronic kidney disease or dialysis used by Ontario Renal Reporting System in 12 months prior to index admission	Dichotomous	Chronic kidney disease (Yes or No)	
Hospitalisation in past year	Hospital admission in the 12 months prior to index admission	Dichotomous	Hospitalization (Yes or No)	
ER visit in past year	Number of visits made to the emergency room by a patient in the 12 months prior to index admission	Continuous	Count: 0 to 365	
Physician visits in past year	Number of visits a patient made to physicians in the 12 months prior to index admission	Continuous	Count: 0 to 365	
Homecare use in past year	Use of homecare services in the 12 months prior to index admission	Dichotomous	Homecare (Yes or No)	

Figure 3. Plot of Propensity Scores for Sepsis Cases and Non-Sepsis Controls Before and After Matching (Primary Analysis)

a) Pre-Match



b) Post-Match

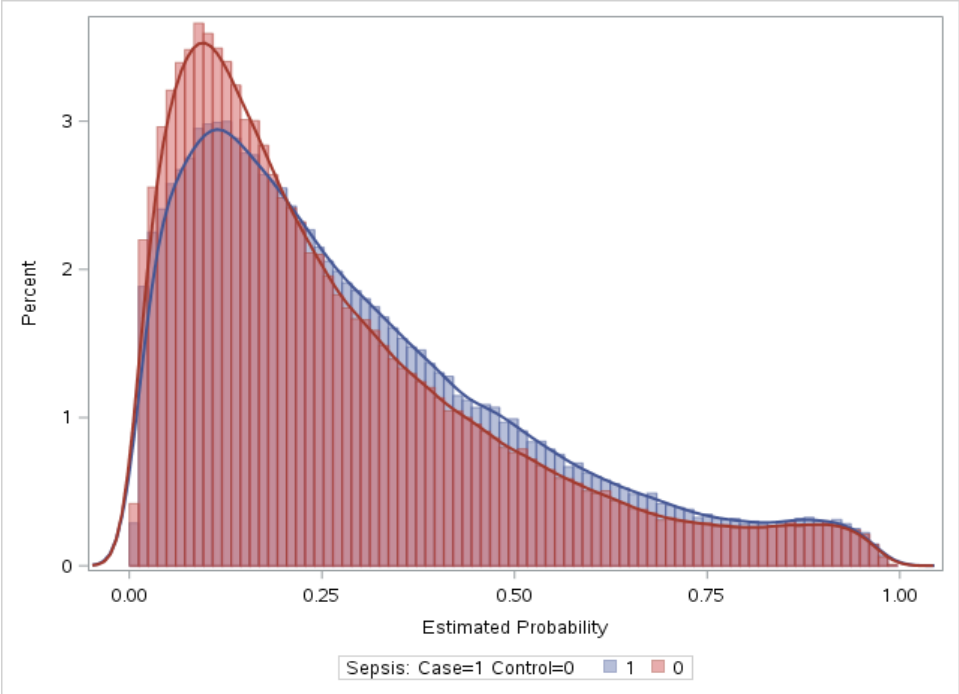


Table 10. Characteristics of Matched and Unmatched Sepsis Cases, Primary Analysis

	Non-Severe Sepsis (Infection alone)			Severe Sepsis or Septic Shock		
	Unmatched cases N= 45,964	**Matched cases N= 132,718**	**Std. Diff.**	**Unmatched cases N= 27,783**	**Matched cases N= 64,204**	**Std. Diff**
Age, mean (SD)	73.4 (16.0)	72.9 (16.5)	**0.03**	74.0 (14.3)	74.2 (14.9)	**0.01**
<65, n (%)	11313 (25)	34681 (26)	**0.03**	6425 (23)	14826 (23)	**0.00**
65-84, n (%)	22094 (48)	61070 (46)	**0.04**	14158 (51)	31414 (49)	**0.04**
≥ 85, n (%)	12557 (27)	36967 (28)	**0.01**	7200 (26)	17964 (28)	**0.05**
Female, n (%)	25008 (54)	77655 (59)	**0.08**	13542 (49)	33091 (52)	**0.06**
Rural, n (%)	6930 (15)	19711 (15)	**0.01**	2505 (9)	5644 (9)	**0.01**
Income quintile*, n (%)						
1 (lowest)	11405 (25)	29435 (22)	**0.06**	6897 (25)	14633 (23)	**0.05**
2	9727 (21)	27418 (21)	**0.01**	6082 (22)	13755 (21)	**0.01**
3	8893 (19)	26200 (20)	**0.01**	5360 (19)	12540 (19)	**0.01**
4	8350 (18)	25629 (19)	**0.03**	4935 (18)	12155 (19)	**0.03**
5 (highest)	7275 (16)	23253 (17)	**0.05**	4332 (15)	10822 (17)	**0.03**
missing	314 (1)	783 (1)	**0.01**	177 (1)	299 (1)	**0.02**
Marginalization Index†, n (%)						
1 (lowest)	5811 (13)	18712 (14)	**0.04**	3397 (12)	8252 (13)	**0.02**
2	7847 (17)	24301 (18)	**0.03**	4556 (16)	11323 (18)	**0.03**
3	9708 (21)	28842 (22)	**0.01**	5757 (21)	13576 (21)	**0.01**
4	9626 (21)	26844 (20)	**0.02**	5690 (21)	13089 (20)	**0.00**
5 (highest)	12329 (27)	32633(25)	**0.05**	8085 (29)	17482 (27)	**0.04**
missing	643 (1)	1386 (1)	**0.03**	298 (1)	482 (1)	**0.03**
Prior cancer, n (%)	11218 (24)	19302 (15)	**0.25**	6230 (22)	9417 (15)	**0.20**
Prior CHF, n (%)	17560 (38)	29725 (22)	**0.35**	13442 (48)	19710 (31)	**0.37**
Prior CKD, n (%)	1937 (4)	1277 (1)	**0.21**	2889 (10)	2852 (4)	**0.23**
Prior COPD, n (%)	21665 (47)	47909 (36)	**0.23**	12950 (47)	22868 (36)	**0.22**
Prior diabetes, n (%)	20116 (44)	46154 (35)	**0.18**	14430 (52)	26851 (42)	**0.20**
LTC resident, n (%)	5166 (11)	11185 (8)	**0.09**	3155 (11)	5045 (8)	**0.12**
ADG score,[93] mean (SD)	30.7 (13.0)	26.5 (13.2)	**0.32**	32.8 (12.9)	33.5 (12.8)	**0.06**
Healthcare use, past year						
Homecare user, n (%)	34245 (75)	47523 (36)	**0.84**	20429 (74)	23054 (36)	**0.82**
Hospitalization, n (%)	44648 (97)	15836 (12)	**3.31**	26046 (94)	7162 (11)	**2.94**
ED visits						
Mean (SD)	2.3 (4.3)	1.2 (2.1)	**0.32**	1.9 (3.3)	1.0 (1.7)	**0.34**
Median (Q1-Q3)	1 (0-3)	1 (0-2)	**0.47**	1 (0-2)	0 (0-1)	**0.46**

	Non-Severe Sepsis (Infection alone)			Severe Sepsis or Septic Shock		
	Unmatched cases N= 45,964	**Matched cases N= 132,718**	**Std. Diff.**	**Unmatched cases N= 27,783**	**Matched cases N= 64,204**	**Std. Diff**
Physician visits						
Mean (SD)	40.8 (26.2)	19.3 (18.1)	**0.96**	41.6 (27.1)	20.0 (19.6)	**0.91**
Median (Q1-Q3)	34 (22-53)	15 (8-24)	**1.23**	35 (22-54)	15 (8-25)	**1.19**
Index Admission						
Urgent admission, n (%)	43908 (96)	127285 (96)	**0.02**	26313 (95)	61601 (96)	**0.06**
Admission Date, n (%)						
Apr 2012 – Mar 2013	4770 (10)	42579 (32)	**0.55**	2520 (9)	18979 (30)	**0.54**
Apr 2013 – Mar 2014	14094 (31)	31546 (24)	**0.16**	8012 (29)	14819 (23)	**0.13**
Apr 2014 – Mar 2015	14032 (31)	30865 (23)	**0.16**	8583 (31)	15431 (24)	**0.15**
Apr 2015 – Mar 2016	13068 (28)	27728 (21)	**0.18**	8668 (31)	14975 (23)	**0.18**
Hospital Type‡, n (%)						
Teaching	13269 (29)	34458 (26)	**0.07**	9151 (33)	19010 (30)	**0.07**
Community ≥ 100 beds	21703 (47)	66658 (50)	**0.06**	15421 (55)	37478 (58)	**0.06**
Community < 100 beds	10989 (24)	31596 (24)	**0.00**	3211 (12)	7716 (12)	**0.01**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = congestive heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; ON= Ontario; Q1 = first quarter; Q3 = third quarter; SD = standard deviation; Std Diff = standardized difference.

*Neighbourhood level income

†Ontario Marginalization Index[104]

‡Variable not used for hard matching or in propensity score.

Table 11. Hospital Survivor Cohort: Characteristics of Sepsis Cases and Non-Sepsis Controls, Before and After Matching

	BEFORE MATCHING			AFTER MATCHING					
	Control Pool N=1,560,911	**All Cases** N= 233,785	**Std. Diff.**	**Matched Hospital Controls** N=124,244	**Non-Severe Sepsis (no organ dysfunction)** N= 124,244 *Unmatched= 41,179 (25%)*	**Std. Diff**	**Matched Hospital Controls** N=62,077	**Severe Sepsis (including shock)** N=62,077 *Unmatched = 19,510 (24%)*	**Std. Diff.**
Age, mean (SD)	52.5 (20.1)	72.8 (16.1)	**1.11**	72.2 (16.6)	72.3 (16.7)	**0.00**	73.5 (15.2)	73.5 (15.2)	**0.00**
<65, n (%)	1058560 (68)	61222 (26)	**0.92**	34220 (28)	34096 (27)	**0.00**	11959 (25)	11964 (24)	**0.00**
65-84, n (%)	414960 (26)	111065 (48)	**0.44**	57754 (46)	57415 (46)	**0.01**	24051 (49)	23935 (49)	**0.00**
≥ 85, n (%)	87391 (6)	61498 (26)	**0.59**	32270 (26)	32733 (26)	**0.01**	12842 (26)	12953 (27)	**0.01**
Female, n (%)	994245 (64)	131428 (56)	**0.15**	73059 (59)	73059 (59)	**0.00**	25832 (53)	25832 (53)	**0.00**
Rural, n (%)	202368 (13)	30270 (13)	**0.00**	16246 (13)	18196 (15)	**0.05**	6095 (12)	4289 (9)	**0.12**
Income quintile*, n (%)									
1 (lowest)	309387 (20)	53823 (23)	**0.08**	27928 (22)	27539 (22)	**0.01**	11730 (24)	11019 (22)	**0.03**
2	311034 (20)	48946 (21)	**0.03**	25903 (21)	25675 (21)	**0.01**	10241 (21)	10354 (21)	**0.01**
3	311752 (20)	45829 (20)	**0.01**	24181 (19)	24525 (20)	**0.00**	9483 (19)	9691 (20)	**0.01**
4	325948 (21)	44231 (19)	**0.05**	23683 (19)	23979 (19)	**0.00**	9036 (19)	9257 (19)	**0.01**
5 (highest)	295465 (19)	39598 (17)	**0.05**	21897 (18)	21808 (18)	**0.02**	8045 (16)	8297 (17)	**0.01**
missing	7325 (0.5)	1358 (0.6)	**0.02**	652 (1)	718 (1)	**0.01**	317 (1)	234 (1)	**0.02**
Marginalization†, n (%)									
1 (lowest)	294656 (19)	31625 (14)	**0.15**	17140 (14)	17608 (14)	**0.01**	6265 (13)	6447 (13)	**0.01**
2	353499 (23)	41795 (18)	**0.12**	22605 (18)	22851 (18)	**0.00**	8351 (17)	8678 (18)	**0.02**
3	342244 (22)	50060 (21)	**0.01**	26966 (22)	27126 (22)	**0.01**	10602 (22)	10328 (21)	**0.01**
4	285982 (18)	47468 (20)	**0.05**	25002 (20)	25066 (20)	**0.01**	10158 (21)	9888 (20)	**0.01**
5 (highest)	271818 (17)	60366 (26)	**0.21**	31339 (25)	30312 (24)	**0.00**	12923 (26)	13137 (27)	**0.01**
missing	12712 (0.8)	2471 (1.0)	**0.03**	1192 (1)	1281 (1)	**0.01**	553 (1)	374 (1)	**0.04**
Prior cancer, n (%)	148157 (9)	36650 (16)	**0.19**	13631 (11)	17220 (14)	**0.09**	5550 (11)	6256 (13)	**0.04**
Prior CHF, n (%)	93755 (6)	65690 (28)	**0.61**	25634 (21)	26752 (22)	**0.02**	12370 (25)	14141 (29)	**0.08**
Prior CKD, n (%)	7109 (0.5)	6091 (3)	**0.18**	1802 (1)	1261 (1)	**0.04**	1020 (2)	1609 (3)	**0.07**
Prior COPD, n (%)	204149 (13)	89810 (38)	**0.61**	37591 (30)	44313 (36)	**0.12**	18711 (38)	16909 (35)	**0.08**
Prior diabetes, n (%)	292228 (19)	92391 (40)	**0.47**	42501 (34)	43130 (35)	**0.01**	19329 (40)	20736 (42)	**0.06**
Residence in LTC, n (%)	16180 (1)	19862 (9)	**0.36**	7428 (6)	9504 (8)	**0.07**	3666 (8)	3583 (7)	**0.01**
ADG Score,[93] mean (SD)	11.2 (18.7)	28.8 (13.4)	**1.09**	26.7 (14.0)	26.0 (13.1)	**0.05**	30.0 (12.9)	32.8 (12.9)	**0.22**

	BEFORE MATCHING			AFTER MATCHING					
	Control Pool	**All Cases**	**Std. Diff.**	**Matched Hospital Controls**	**Non-Severe Sepsis (no organ dysfunction)**	**Std. Diff**	**Matched Hospital Controls**	**Severe Sepsis (including shock)**	**Std. Diff.**
	N=1,560,911	**N= 233,785**		**N=124,244**	**N= 124,244** *Unmatched= 41,179 (25%)*		**N=62,077**	**N=62,077** *Unmatched = 19,510 (24%)*	
Healthcare use, past year									
Hospitalization, n (%)	37281 (2)	78313 (34)	**0.89**	9733 (8)	14872 (12)	**0.14**	3813 (8)	5270 (11)	**0.10**
Homecare user, n (%)	151483 (10)	103770 (44)	**0.85**	35960 (29)	42739 (34)	**0.12**	17405 (36)	16573 (34)	**0.04**
ED visits									
Mean (SD)	0.9 (1.8)	1.4 (2.8)	**0.22**	1.1 (2.6)	1.2 (2.1)	**0.01**	1.3 (2.9)	1.0 (1.7)	**0.12**
Median (Q1-Q3)	0 (0-1)	1 (0-2)	**0.30**	0 (0-1)	1 (0-2)	**0.05**	1 (0-2)	0 (0-1)	**0.12**
Physician visits									
Mean (SD)	16.4 (12.8)	24.7 (22.5)	**0.46**	17.2 (15.5)	19.2 (17.9)	**0.12**	18.3 (15.9)	19.6 (19.1)	**0.07**
Median (Q1-Q3)	14 (8-22)	18 (10-32)	**0.35**	13 (7-22)	14 (8-24)	**0.09**	14 (8-23)	15 (8-25)	**0.02**
Index Admission									
Urgent admission, n (%)	784684 (50)	223495 (96)	**1.19**	118947 (96)	118947 (96)	**0.00**	46733 (96)	46733 (96)	**0.00**
Admission Date, n (%)									
Apr 2012 – Mar 2013	461239 (30)	59061 (25)	**0.10**	39356 (32)	39450 (32)	**0.00**	13961 (29)	13954 (29)	**0.00**
Apr 2013 – Mar 2014	407025 (26)	59171 (25)	**0.02**	29721 (24)	29547 (24)	**0.00**	11308 (23)	11333 (23)	**0.00**
Apr 2014 – Mar 2015	361907 (23)	59531 (25)	**0.05**	28806 (23)	29007 (23)	**0.00**	11772 (24)	11836 (24)	**0.00**
Apr 2015 – Mar 2016	330740 (21)	56022 (24)	**0.07**	26361 (21)	26240 (21)	**0.00**	11811 (24)	11729 (24)	**0.00**
Hospital Type‡, n (%)									
Teaching	51640 (33)	65363 (28)	**0.11**	36086 (29)	32485 (26)	**0.06**	14245 (29)	14571 (30)	**0.01**
Community ≥ 100 beds	821077 (53)	121181 (52)	**0.02**	65720 (53)	62485 (50)	**0.05**	25817(53)	28208 (58)	**0.10**
Community < 100 beds	223664 (14)	47232 (20)	**0.16**	22436 (18)	29268 (24)	**0.14**	8788 (18)	6073 (12)	**0.16**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = congestive heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; ON= Ontario; Q1 = first quarter; Q3 = third quarter; SD = standard deviation; Std Diff = standardized difference.

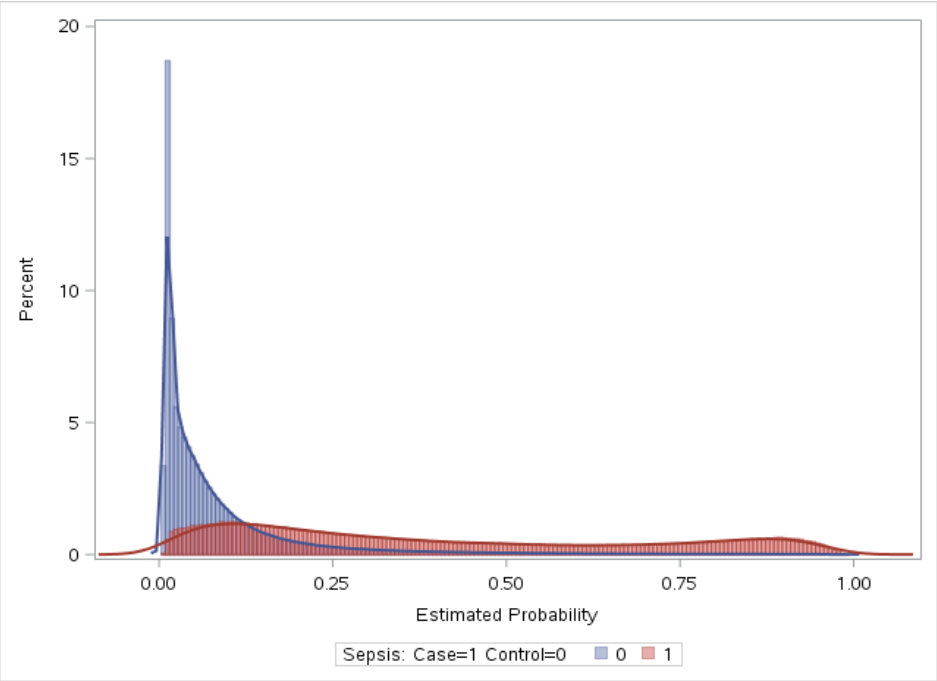
*Neighbourhood level income

†Ontario Marginalization Index[104]

‡Variable not used for hard matching or in propensity score.

Figure 4. Hospital Survivor Cohort: Plot of Propensity Scores for Sepsis Cases and Non-Sepsis Controls Before and After Matching

a) Pre-Match



b) Post-Match

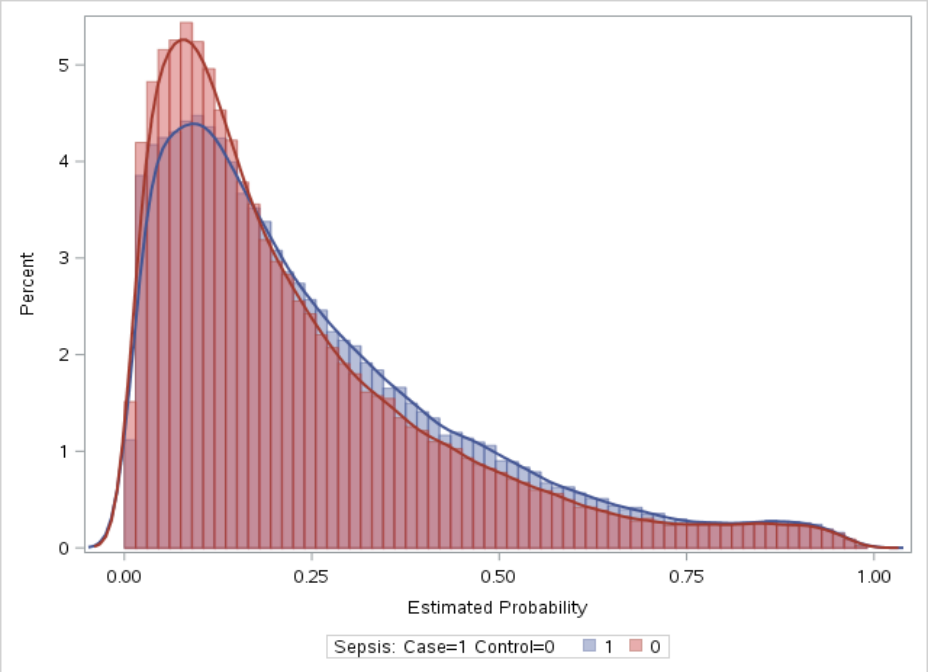
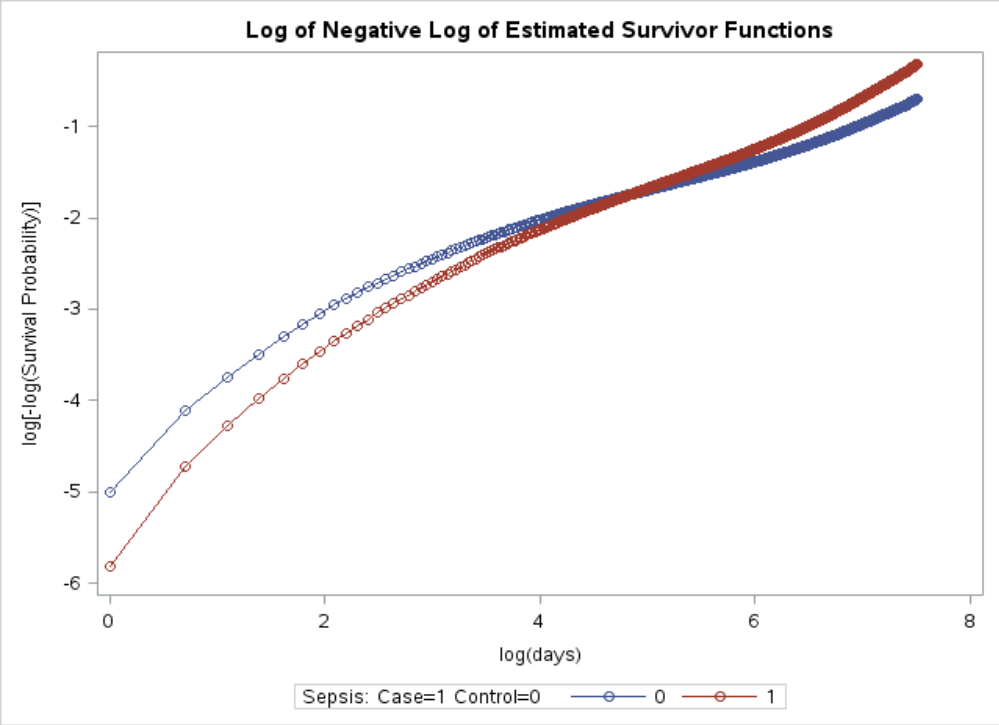


Figure 5. Proportional Hazard Test. Plot of Log(-Log)Survival, 5-Year Mortality (Primary Analysis)

a) Non-Severe Sepsis Cases versus Matched Non-Sepsis Hospital Controls



b) Severe Sepsis Cases versus Matched Non-Sepsis Hospital Controls

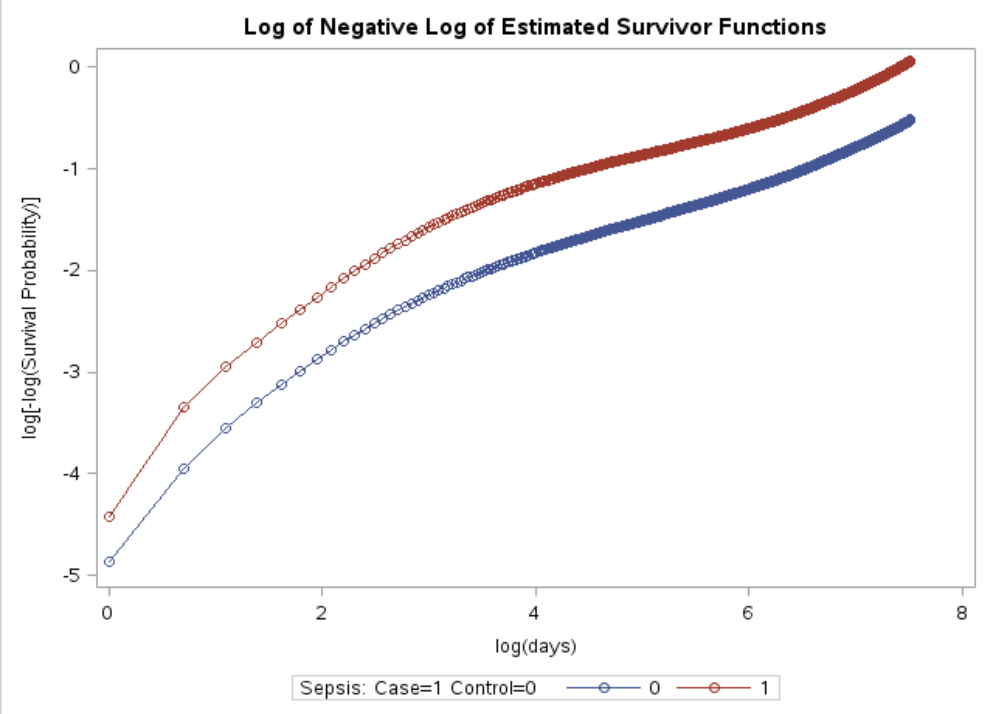
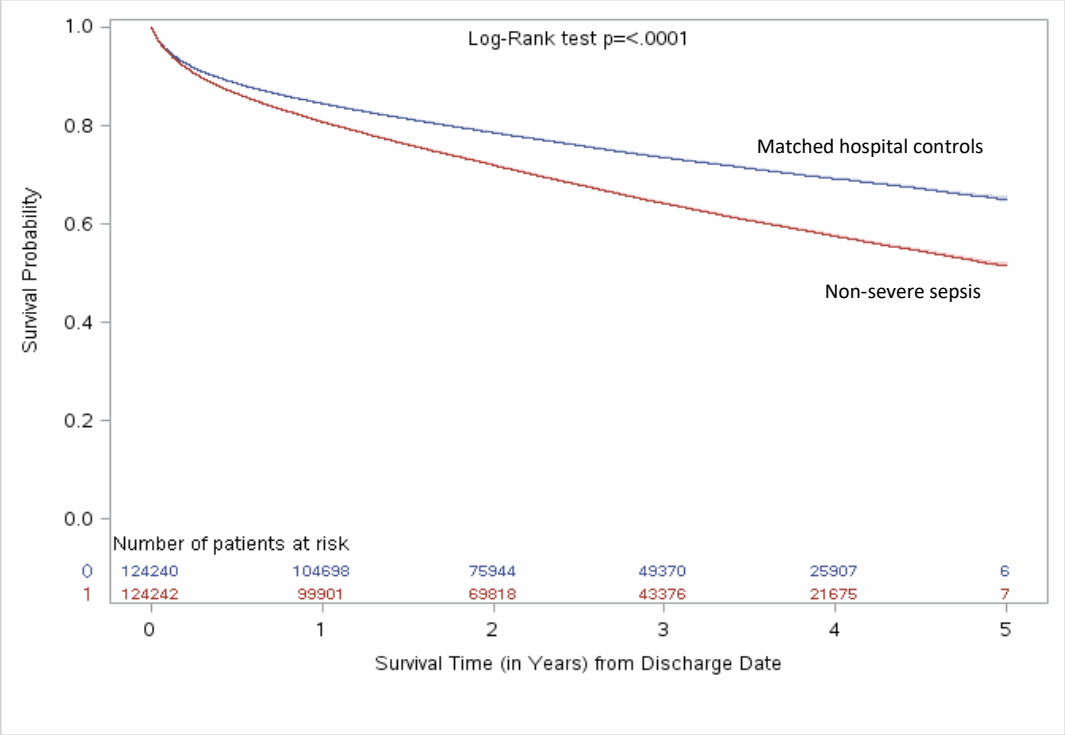


Figure 6. Hospital Survivor Cohort: Kaplan Meir Survival Curves – Post-Discharge Survival

a) Non-Severe Sepsis Cases versus Matched Non-Sepsis Hospital Controls



b) Severe Sepsis versus Matched Non-Sepsis Hospital Controls

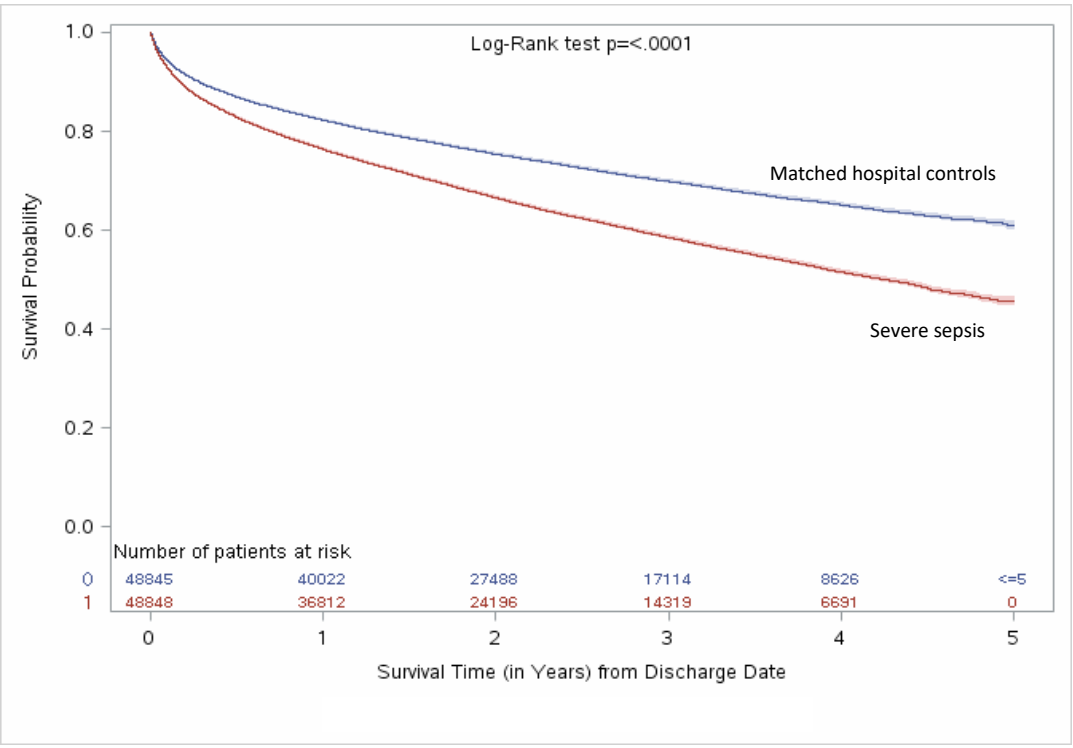
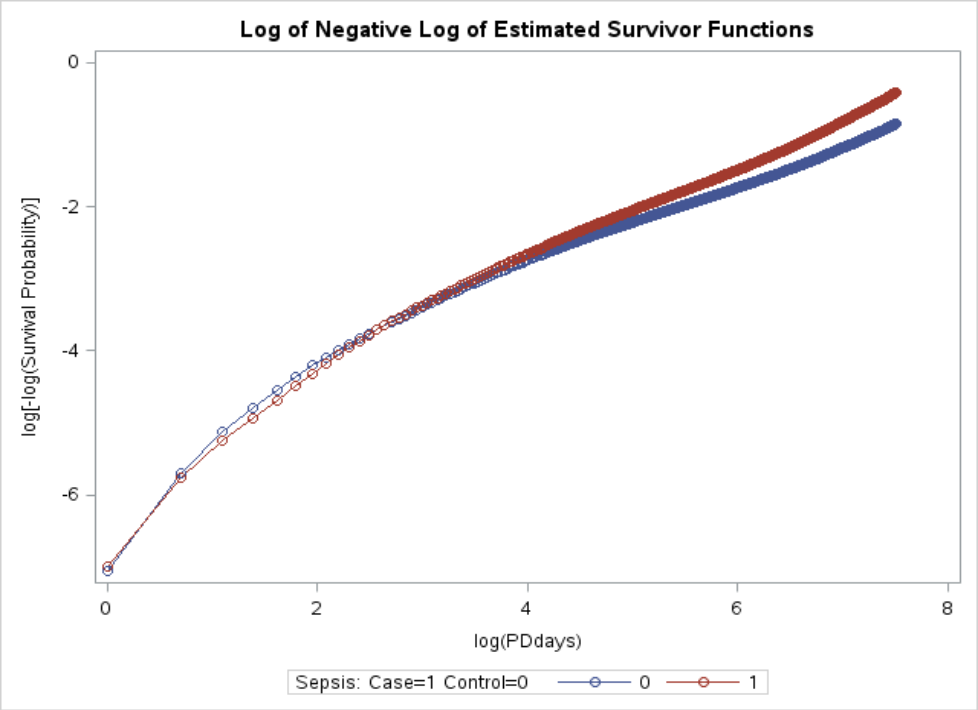


Figure 7. Hospital Survivor Cohort. Proportional Hazard Test. Plot of Log(-Log)Survival, Post-Discharge Mortality

a) Non-Severe Sepsis Cases versus Matched Non-Sepsis Hospital Controls



b) Severe Sepsis Cases versus Matched Non-Sepsis Hospital Controls

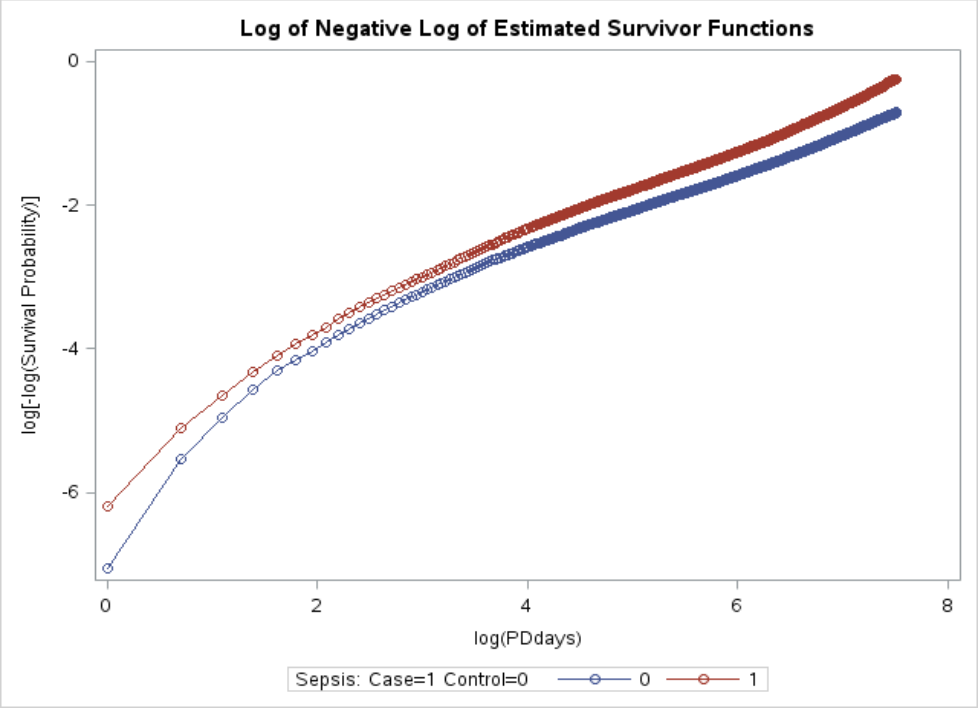
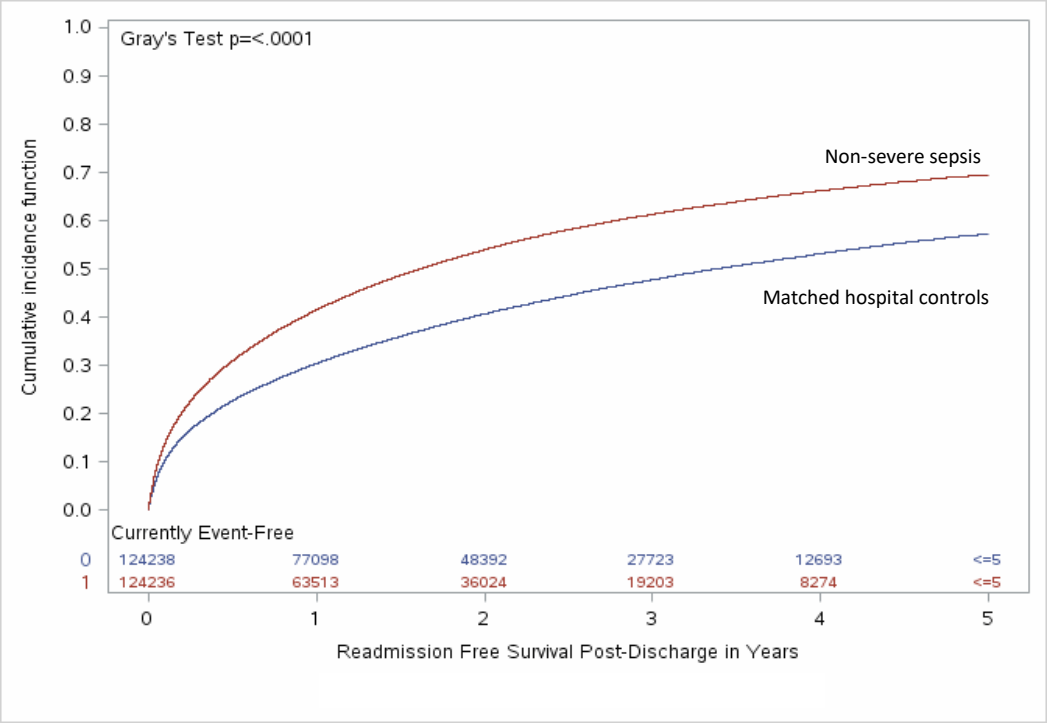


Figure 8. Hospital Survivor Cohort: Cumulative Incidence Function – Time to Hospital Readmission

a) Non-Severe Sepsis versus Matched Non-Sepsis Hospital Controls



b) Severe Sepsis versus Matched Non-Sepsis Hospital Controls

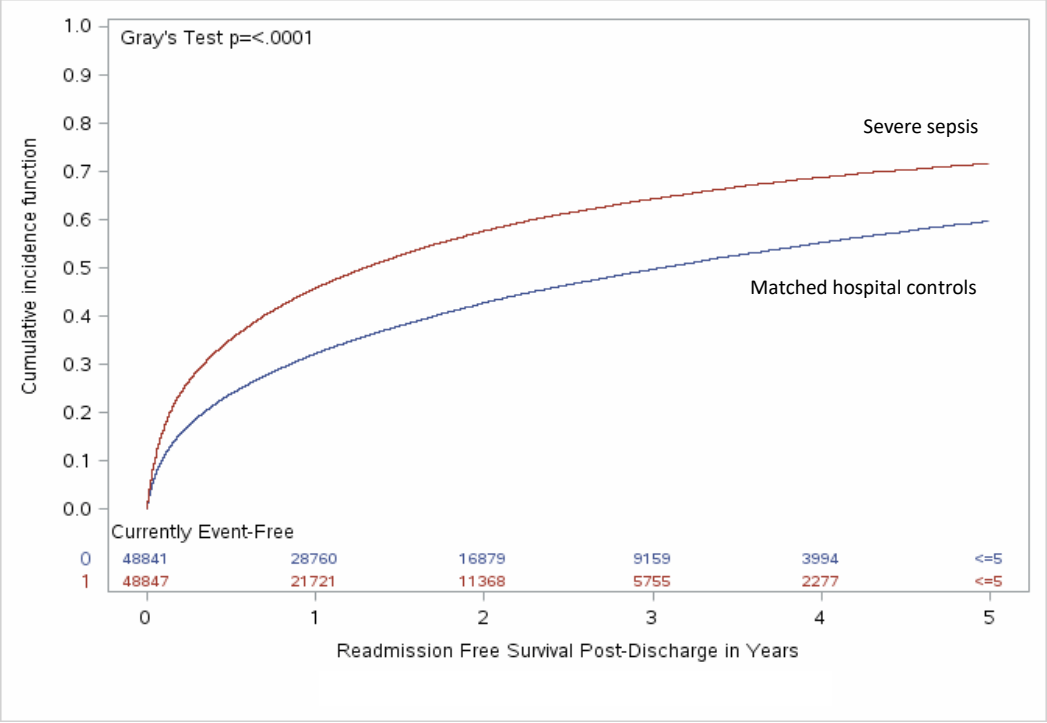


Table 12. Alternate Time Horizons: Mortality in Sepsis Cases versus Non-Sepsis Matched Controls at Different Time Periods During Follow-up

	Non-Severe Sepsis (No Organ Dysfunction) versus Controls						Severe Sepsis versus Controls					
Time Period*	N at Risk†		Mortality (%)		HR_{crude} (95% CI)	HR_{adj}‡ (95% CI)	N at Risk		Mortality (%)		HR_{crude} (95% CI)	HR_{adj}‡ (95% CI)
	Case	Control	Case	Control			Case	Control	Case	Control		
0-30 day	132718	132718	8.2	9.9	0.82 (0.80-0.85)	0.75 (0.73-0.77)	64204	64204	22.3	12.0	1.96 (1.91-2.02)	1.83 (1.78-1.89)
30-183 day	121713	119543	11.1	8.7	1.29 (1.26-1.33)	1.16 (1.13-1.19)	49881	56475	17.4	10.2	1.79 (1.73-1.85)	1.64 (1.59-1.70)
6–12 month	108209	109182	6.8	4.6	1.51 (1.46-1.57)	1.36 (1.31-1.41)	41210	50728	8.5	5.5	1.57 (1.50-1.65)	1.46 (1.38-1.53)
Year 2	100831	104202	9.8	6.2	1.61 (1.56-1.66)	1.45 (1.41-1.50)	37716	47945	11.5	7.3	1.61 (1.54-1.69)	1.48 (1.41-1.55)
Year 3	70542	75666	9.3	5.4	1.79 (1.72-1.86)	1.63 (1.57-1.70)	24784	33015	10.3	6.2	1.68 (1.59-1.78)	1.53 (1.44-1.62)
Year 4	43926	49410	8.2	4.6	1.84 (1.74-1.94)	1.70 (1.61-1.79)	14785	20622	9.2	5.1	1.87 (1.72-2.02)	1.70 (1.57-1.84)
Year 5	22136	26098	5.5	2.9	1.95 (1.78-2.14)	1.80 (1.64-1.97)	7113	10550	6.2	3.6	1.79 (1.56-2.05)	1.66 (1.44-1.90)

Adj. = adjusted; CI = confidence interval; HR = hazard ratio.

*From index admission date.

†At beginning of time period.

‡Adjusted for hospital type and propensity score variables > 0.1 standardized difference.

Table 13. Hospital Survivor Cohort: Alternate Time Horizons, Mortality in Sepsis Cases versus Non-Sepsis Matched Controls (Post-Discharge Follow-Up)

	Non-Severe Sepsis (No Organ Dysfunction) versus Controls						Severe Sepsis versus Controls					
Time Period* (Post-Discharge)	N at Risk†		Mortality (%)		HR_{crude} (95% CI)	HR_{adj}‡ (95% CI)	N at Risk		Mortality in Time Period (%)		HR_{crude} (95% CI)	HR_{adj}‡ (95% CI)
	Case	Control	Case	Control			Case	Control	Case	Control		
0-30 day	124236	124238	4.6	4.4	1.05 (1.01-1.09)	0.97 (0.93-1.01)	48847	48841	6.4	5.1	1.26 (1.19-1.32)	1.14 (1.08-1.20)
30-183 day	118575	118829	9.4	7.4	1.28 (1.25-1.32)	1.16 (1.13-1.19)	45719	46334	11.5	8.4	1.40 (1.34-1.46)	1.28 (1.23-1.34)
6–12 month	107406	110012	6.6	4.6	1.46 (1.41-1.51)	1.33 (1.28-1.38)	40425	42440	7.8	5.4	1.47 (1.39-1.55)	1.36 (1.29-1.43)
Year 2	99774	104576	9.8	6.3	1.58 (1.53-1.63)	1.45 (1.41-1.50)	36734	39976	11.3	7.3	1.57 (1.49-1.64)	1.42 (1.36-1.50)
Year 3	69703	75840	9.2	5.5	1.71 (1.65-1.78)	1.60 (1.54-1.66_	24149	27449	10.1	6.1	1.69 (1.59-1.80)	1.52 (1.42-1.62)
Year 4	43298	49278	8.1	4.6	1.81 (1.72-1.91)	1.70 (1.61-1.79)	14282	17079	9.2	5.3	1.80 (1.65-1.96)	1.63 (1.49-1.78)
Year 5	25836	21616	5.3	3.0	1.82 (1.66-2.00)	1.70 (1.55-1.86)	6669	8602	5.8	3.2	1.92 (1.65-2.25)	1.69 (1.44-1.98)

Adj. = adjusted; CI = confidence interval; HR = hazard ratio.

*From index admission date.

†At beginning of time period.

‡Adjusted for hospital type and propensity score variables > 0.1 standardized difference.

Table 14. Descriptive Characteristics of In-Hospital and 1-Year Mortality and Rehospitalization by Age and Sepsis Type

		Matched Controls N =132,718	Non-Severe Sepsis N = 132,718	Matched Controls N = 64,204	Severe Sepsis (including shock) N= 64,204
		N (%)	N (%)	N (%)	N (%)
In-hospital death	All ages	10103 (7.61)	8512 (6.41)	5941 (9.25)	15270 (23.78)
	<65	789 (2.28)	720 (2.08)	531 (3.58)	2837 (19.14)
	65-84	4386 (7.18)	3667 (6.00)	2739 (8.72)	7476 (23.80)
	≥ 85	4928 (13.33)	4125 (11.16)	2671 (14.87)	4957 (27.59)
1-year mortality	All ages	28489 (21.47)	31851 (24.00)	16249 (25.31)	26471 (41.23)
	<65	2462 (7.10)	3644 (10.51)	1551 (10.46)	4170 (28.13)
	65-84	12319 (20.17)	14301 (23.42)	7456 (23.73)	12592 (40.08)
	≥ 85	13708 (37.08)	13906 (37.62)	7242 (40.31)	9709 (54.05)
Hospital Survivor Cohort		**N= 124,244**	**N= 124,244**	**N= 48,852**	**N= 48,852**
30-day readmission	All ages	11243 (9.05)	15060 (12.12)	4571 (9.36)	7045 (14.42)
(from discharge date)	<65	2740 (8.04)	3782 (11.09)	1073 (8.97)	1628 (13.61)
	65-84	5445 (9.48)	7309 (12.73)	2324 (9.71)	3568 (14.91)
	≥ 85	3058 (9.34)	3969 (12.13)	1173 (9.06)	1849 (14.28)
1-year readmission	All ages	37711 (30.35)	51532 (41.48)	15738 (32.22)	22314 (45.68)
(from discharge date)	<65	8523 (25.00)	11901 (34.91)	3431 (28.68)	4945 (41.34)
	65-84	18366 (31.99)	25170 (43.84)	8015 (33.49)	11403 (47.64)
	≥ 85	10822 (33.06)	14461 (44.18)	4290 (33.13)	5966 (46.07)
1-year mortality	All ages	19236 (15.48)	23867 (19.21)	8655 (17.72)	11518 (23.59)
(from discharge date)	<65	1715 (5.03)	3021 (8.86)	783 (6.55)	1382 (11.55)
	65-84	8429 (14.68)	10903 (18.99)	3925 (16.40)	5281 (22.06)
	≥ 85	9092 (27.78)	9943 (30.38)	3947 (30.48)	4855 (37.49)

Note: For age subgroups, cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of case.

Table 15. Attributable In-Hospital and 1-Year Mortality and Rehospitalization, by Sepsis Type and Age Group

Outcome		Non-Severe Sepsis (No Organ Dysfunction) vs. Matched Controls		Severe Sepsis (Including Septic Shock) vs. Matched Controls	
		Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
In-hospital mortality	All ages	0.82 (0.80-0.85)	0.87 (0.84-0.89)	3.16 (3.05-3.27)	3.09 (2.99-3.20)
	<65	0.91 (0.82-1.01)	0.81 (0.70-0.93)	6.84 (6.15-7.60)	6.29 (5.63-7.02)
	65-84	0.82 (0.78-0.86)	0.86 (0.82-0.91)	3.34 (3.18-3.51)	3.27 (3.11-3.44)
	≥ 85	0.81 (0.78-0.85)	0.84 (0.80-0.88)	2.20 (2.09-2.33)	2.23 (2.11-2.36)
		Crude HR (95% CI)	**Adjusted HR (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
1-Year mortality rate	All ages	1.11 (1.10-1.13)	1.01 (0.99-1.02)	1.84 (1.80-1.87)	1.71 (1.67-1.74)
	<65	1.50 (1.43-1.57)	1.10 (1.04-1.15)	3.04 (2.87-3.21)	2.73 (2.58-2.90)
	65-84	1.16 (1.13-1.19)	1.04 (1.02-1.07)	1.91 (1.85-1.96)	1.80 (1.75-1.85)
	≥ 85	0.99 (0.97-1.01)	0.96 (0.94-0.98)	1.50 (1.46-1.55)	1.44 (1.39-1.48)
Hospital Survivors					
1-year post-discharge mortality	All ages	1.25 (1.23-1.27)	1.14 (1.12-1.16)	1.35 (1.31-1.38)	1.23 (1.20-1.27)
	<65	1.79 (1.69-1.90)	1.29 (1.21-1.37)	1.75 (1.60-1.91)	1.56 (1.42-1.71)
	65-84	1.30 (1.27-1.34)	1.18 (1.15-1.21)	1.36 (1.30-1.41)	1.24 (1.19-1.29)
	≥ 85	1.09 (1.06-1.12)	1.08 (1.05-1.11)	1.27 (1.22-1.32)	1.21 (1.16-1.26)
		Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
30-day readmission, hospital survivors	All ages	1.39 (1.35-1.43)	1.36 (1.33-1.40)	1.64 (1.57-1.71)	1.65 (1.58-1.72)
	<65	1.43 (1.36-1.51)	1.34 (1.27-1.42)	1.60 (1.47-1.73)	1.56 (1.43-1.70)
	65-84	1.40 (1.34-1.45)	1.37 (1.31-1.42)	1.64 (1.55-1.73)	1.59 (1.50-1.69)
	≥ 85	1.34 (1.28-1.41)	1.33 (1.27-1.40)	1.68 (1.55-1.81)	1.70 (1.57-1.84)
		Crude HR (95% CI)	**Adjusted HR (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
1-year readmission, hospital survivors	All ages	1.48 (1.47-1.50)	1.41 (1.40-1.43)	1.57 (1.55-1.60)	1.53 (1.50-1.55)
	<65	1.50 (1.46-1.54)	1.36 (1.33-1.40)	1.60 (1.53-1.67)	1.52 (1.46-1.59)
	65-84	1.49 (1.46-1.52)	1.41 (1.38-1.44)	1.62 (1.57-1.66)	1.56 (1.51-1.60)
	≥ 85	1.44 (1.40-1.47)	1.41 (1.38-1.45)	1.60 (1.54-1.67)	1.57 (1.51-1.63)

CI = confidence interval; HR = hazard ratio.

*Adjusted for hospital type, and propensity score variables with standardized difference > 0.10.

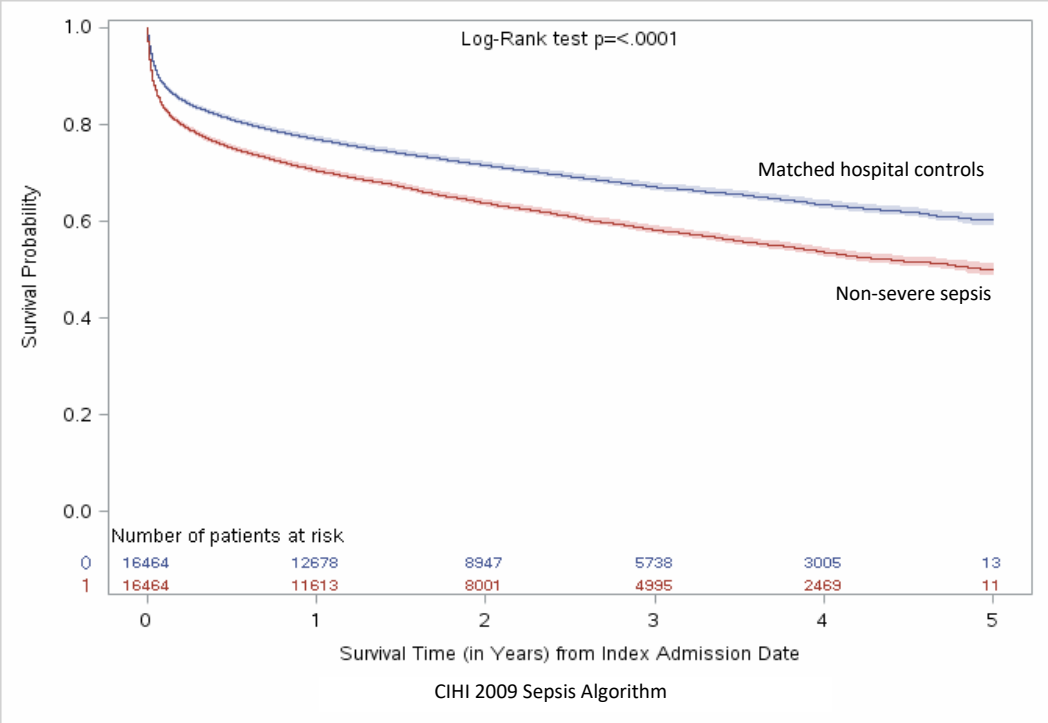
†Data is from a re-matched analysis of cases and controls who survived index hospitalization.

|| Readmission after index admission discharge date to an acute care hospital in Ontario.

Note: For age subgroups, cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of cases.

Figure 9. CIHI Cohort: Long-Term Survival, Sepsis Cases versus Matched Non-Sepsis Controls, Kaplan Meier Survival Curves

a) Non-Severe Sepsis (CIHI 2009 Definition) versus Matched Non-Sepsis Hospital Controls



b) Severe Sepsis (CIHI 2009 Definition) versus Matched Non-Sepsis Hospital Controls

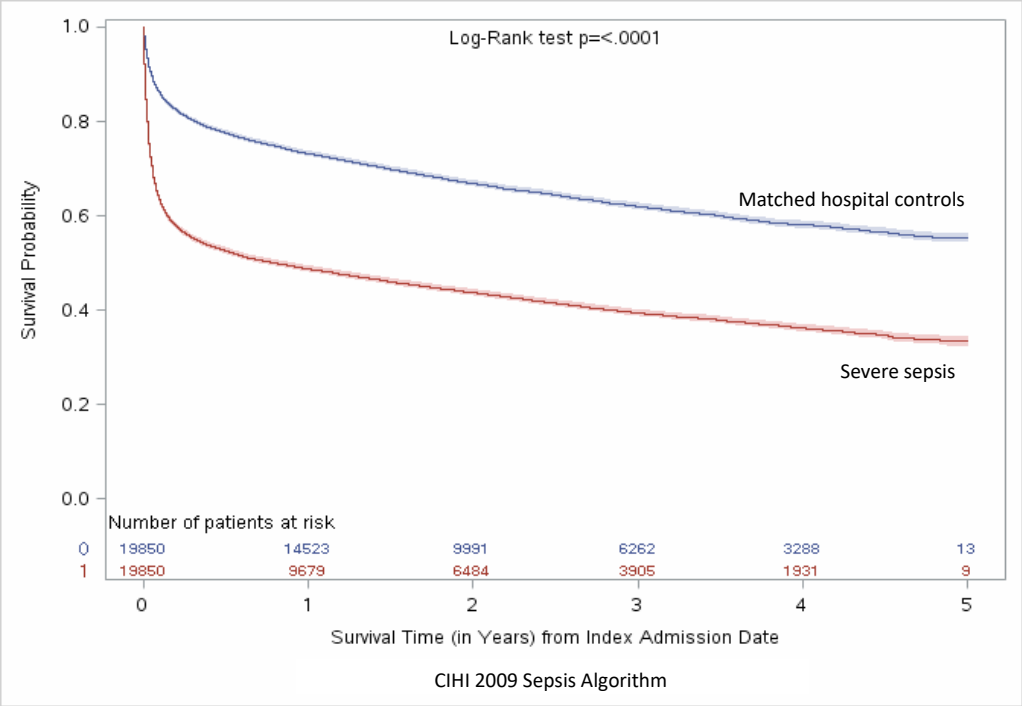
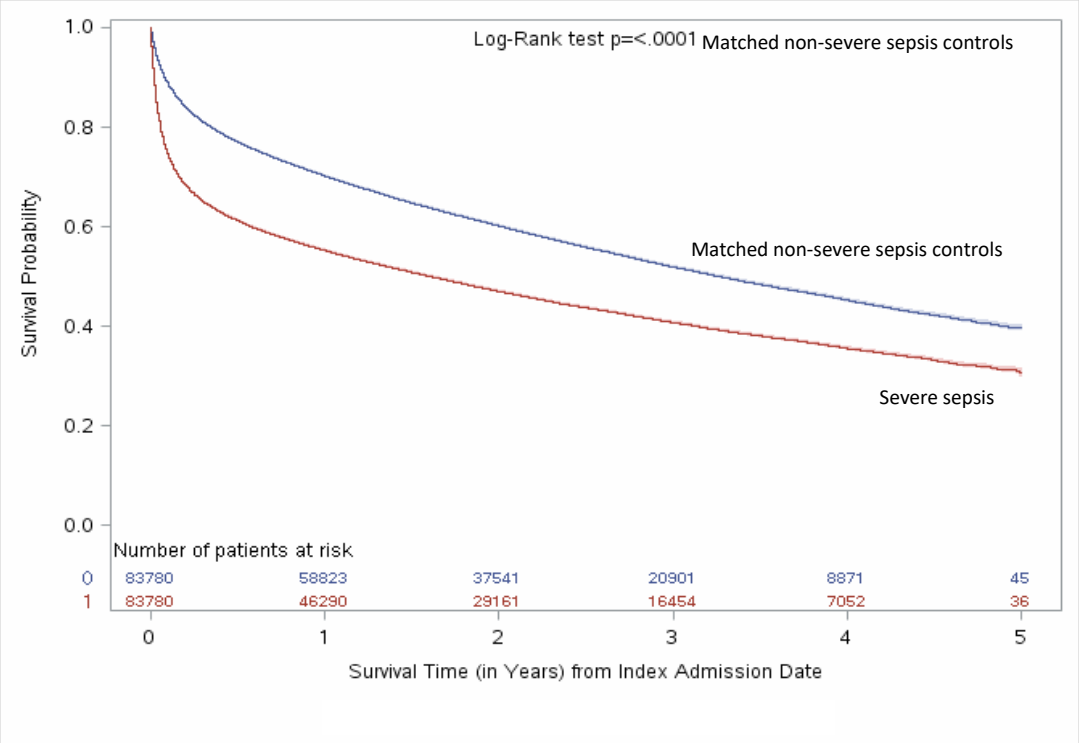


Figure 10. Severe Sepsis versus Non-Severe Sepsis Matched Controls: Kaplan—Meier Survival Curves

a) Mortality from Index Admission Date



b) Post-Discharge Mortality (Hospital Survivor Cohort)

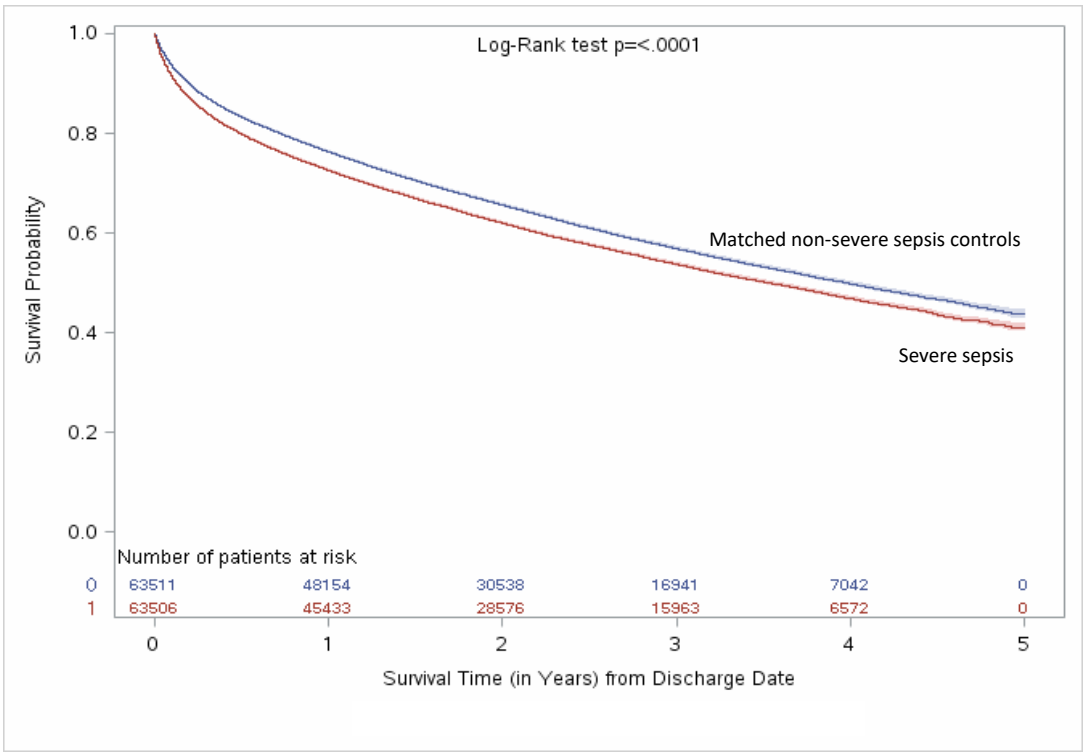


Table 16. Severe Sepsis Cases versus Matched Non-Severe Sepsis Matched Controls: Mortality at Different Time Horizons

a) From Index Hospital Admission Date

Time Period*	N at Risk†		Mortality (%)		HR_{crude} (95% CI)	HR_{adj}‡ (95% CI)
	Severe	Non-severe	Severe	Non-severe		
0-30 day	83780	83780	23.74	10.12	2.56 (2.49-2.62)	2.57 (2.50-2.63)
30-183 day	63885	75294	19.74	14.33	1.43 (1.40-1.47)	1.43 (1.39-1.46)
6–12 month	51271	64502	9.77	8.86	1.11 (1.07-1.15)	1.11 (1.07-1.16)
Year 2	46264	58785	13.00	12.46	1.05 (1.01-1.09)	1.07 (1.03-1.11)
Year 3	29111	37496	11.00	11.30	0.97 (0.93-1.01)	0.98 (0.93-1.02)
Year 4	16429	20858	9.53	9.56	0.99 (0.93-1.06)	1.00 (0.93-1.07)
Year 5	7035	8846	6.34	6.34	1.00 (0.88-1.13)	1.01 (0.89-1.14)
Overall	83780	83780	48742 (58.18)	39109 (46.68)	1.49 (1.48-1.51)	1.50 (1.48-1.52)

CI = confidence interval; HR = hazard ratio.

*From date of index hospitalization admission.

†At beginning of time period.

‡Adjusted for hospital type (all propensity score variables were <0.1).

b) Hospital Survivor Cohort (From Hospital Discharge Date)

Post-Discharge Time Period*	N at Risk†		Mortality n (%)		HR_{crude} (95% CI)	HR_{adj}‡ (95% CI)
	Severe	Non-severe	Severe	Non-severe		
0-30 day	63506	63511	7.58	5.58	1.38 (1.32-1.44)	1.38 (1.33-1.45)
30-183 day	58688	59964	13.66	11.87	1.16 (1.13-1.20)	1.16 (1.13-1.20)
6–12 month	59964	58688	9.07	8.33	1.10 (1.05-1.14)	1.10 (1.05-1.14)
Year 2	50643	52836	12.70	12.16	1.05 (1.01-1.09)	1.05 (1.01-1.09)
Year 3	29351	30982	11.07	11.02	1.00 (0.95-1.05)	1.01 (0.96-1.06)
Year 4	15916	16894	9.49	9.16	1.03 (0.96-1.11)	1.04 (0.97-1.12)
Year 5	6552	7014	5.97	5.90	1.04 (0.91-1.19)	1.04 (0.91-1.20)
Overall	63506	63511	44.43	41.28	1.12 (1.11-1.14)	1.13 (1.11-1.15)

CI = confidence interval; HR = hazard ratio.

*From discharge date of index hospitalization.

†At beginning of time period.

‡Adjusted for hospital type (all propensity score variables were <0.1).

Chapter 3: Long-Term Healthcare Costs and Health Services Utilization Associated with Sepsis: A Population-Based Retrospective Cohort Study

3.1 Link to previous manuscript

The previous chapter addressed the first and second objectives of this thesis, examining long-term attributable mortality and hospital readmission in patients with sepsis (with and without organ dysfunction) defined using the Sepsis-2 definition (modified for administrative data) compared to matched non-sepsis hospital controls. The following manuscript builds on this work by examining long-term healthcare costs and hospital length of stay in this same cohort. Given the high short-term costs documented in sepsis patients and the lack of information on costs in a Canadian context, it is imperative to look at economic outcomes in addition to clinical ones in sepsis patients compared to non-sepsis controls. This second manuscript addresses the third and fourth objectives of this thesis, assessing incremental health system costs in the first year after index admission date and also annually up to 5 years after index admission, as well as incremental length of stay (total and ICU) during index hospital admission, in sepsis patients (with and without organ dysfunction) compared to matched hospitalized controls.

3.2 Manuscript

The following is an unpublished manuscript formatted for journal submission (submitted to CMAJ in December 2019)

Authors: Kelly Farrah, Lauralyn McIntyre, Robert Talarico, Christopher J. Doig, Monica Taljaard, Murray Krahn, Alan J. Forster, Doug Coyle, Kednapa Thavorn

3.3 Abstract

Objective: To determine the incremental 1-year healthcare costs and hospital length of stay in sepsis patients compared to non-sepsis hospital controls.

Methods: We conducted a population-based retrospective cohort study to determine the 1-year incremental healthcare costs and hospital length of stay in adults (≥18 years) with sepsis patients compared to matched hospital controls using provincial health administrative data. We used a validated Canadian ICD-10 algorithm to identify sepsis cases (modified Sepsis-2) and non-sepsis controls hospitalized in Ontario between April 1, 2012 and March 31, 2016, with follow-up to March 31, 2017. Cases and controls were matched 1:1 on propensity score, age, sex, type of admission, and admission date. Generalized linear models were used to adjust for any remaining confounders. We also examined incremental annual healthcare costs in years 2-5 for those who had follow-up in these periods. Costs were adjusted for inflation to 2018 Canadian dollars.

Results: In total, 196,922 of 270,669 sepsis cases were successfully matched with controls. Of these, 64,204 cases had severe sepsis (infection plus organ dysfunction) and 132,718 cases had non-severe sepsis (no organ dysfunction). Mean incremental cost 1-year after index admission in sepsis cases compared to controls were: $29,238 (95% confidence interval [CI]: $28,568-$29,913) for severe sepsis patients; and $9,475 (95% CI: $9,150-$9,727) for non-severe sepsis. Incremental index admission hospital costs for sepsis patients compared to controls were $23,530 ($22,974-$24,019) for severe

sepsis and $1,966 ($1,889-$2,128) for non-severe cases. Sepsis patients spent longer in hospital during index hospitalization: an additional 12.52 days (12.26-12.98) for severe, and 3.77 days (3.57-3.87) for non-severe cases on average. Healthcare costs for both case groups remained higher compared to matched hospital controls for up to five years after index admission. One-year Incremental costs were highest among sepsis patients under 65-years compared to older age groups ($47,104, 95% CI: $45,059-$48,422).

Conclusions: Severe sepsis is associated with significant healthcare costs, primarily surrounding index hospitalization, but also up to 5 years after index admission. We estimate that the annual 1-year incremental costs to the Ontario health system total approximately $672.4 million for severe sepsis patients; and $423.2 million for patients with non-severe sepsis.

3.4 INTRODUCTION

Sepsis has a major burden worldwide in terms of mortality, morbidity, and healthcare resource use. Not only is it one of the primary causes of mortality in hospitalized patients, it is also one of the most expensive medical conditions to treat in-hospital.[106] Septicemia (infection in the bloodstream) ranked first on the Agency for Healthcare Research and Quality's list of most expensive conditions, costing hospitals in the United States an estimated $24 billion a year in 2013.[3]

According to the most recent Sepsis-3 definitions, sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[1] It can worsen to septic shock, in which "underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality".[1]

Previous cost analyses on sepsis have focused primarily on hospital costs; however there is growing interest in post-discharge costs, given that sepsis may increase risk of long-term morbidity and mortality in hospital survivors.[107] Physical and mental sequalae in sepsis survivors are sometimes referred to as "post-sepsis syndrome."[108]

In the past five years, two previous studies, one conducted in the US,[81] the other in Australia,[69] have examined attributable long-term costs in sepsis patients. Prescott et al. conducted an observational cohort study in patients over 65 years old using 1988-2005 data from the United States Health and Retirement Study linked with Medicare claims.[81] At 1-year follow-up, patients with severe sepsis had higher healthcare resource use post-sepsis compared to before sepsis and also had higher resource use compared to non-sepsis hospitalized matched controls.[81] In 2018, Thompson et al. published a propensity score matched study analyzing a subset of Australian intensive care unit (ICU) patients who were part of a larger randomized controlled trial.[69] They found that after 2-year follow-up, healthcare

resource use, including cost of ICU and hospital treatment, was higher in sepsis cases compared to critically ill non-sepsis controls.[69]

There is a lack of recent information on the health system costs of sepsis in a Canadian context. Data from two previous Canadian studies on the costs of sepsis in Alberta[80] and Quebec,[74] are now almost 20 years old. These studies are also limited in that neither used a non-sepsis control group, making it unclear whether their estimates of long-term resource use and costs were attributable to sepsis or to unrelated diagnoses.

Comparison of previous literature on healthcare costs of sepsis is further complicated by changes in the clinical definition of sepsis, which was redefined in the 2016 Sepsis-3 definitions. Previously, the Sepsis-2 definitions described the syndrome of sepsis as a continuum using three categories: sepsis (infection with systemic inflammatory response), severe sepsis (sepsis complicated by organ dysfunction), and septic shock (severe sepsis worsened by "persistent arterial hypotension unexplained by other causes").[7] In this article we use Sepsis-2 definitions (modified for health administrative data[8]), as these definitions are employed by the validated algorithm used to identify cases in health administrative data in Canada. We define "non-severe" sepsis as sepsis cases in which there is no documented organ dysfunction.

The primary objective of this study was to determine 1-year incremental healthcare costs of sepsis patients compared to hospitalized non-sepsis controls, considering two case groups: sepsis cases with organ dysfunction (severe sepsis, including septic shock) and without organ dysfunction (non-severe sepsis). Secondary objectives were to determine total hospital length of stay and ICU length of stay during index hospitalization, as well as to assess annual incremental healthcare costs between case and control groups in years 2-5 after index admission date.

3.5 METHODS

A complete description of cohort development has been described elsewhere [see Chapter 2]. Briefly, we conducted a population-based retrospective matched cohort study using Ontario provincial health administrative data housed at ICES. Ontario is Canada's largest province, with a population of over 13 million, and it operates a publicly funded health care system. Cases and controls were drawn from a pool of patients (≥18 years) admitted to a hospital in Ontario between April 1, 2012 and March 31, 2016, which were identified using Canadian Institute for Health Information's (CIHI) Discharge Abstract Database. Patients were followed up to March 31, 2017. A 2-year lookback period was used to identify patients' health status prior to index admission.

Diagnosis of sepsis during index admission was defined using validated and optimized International Classification of Diseases-10, Canada Revision (ICD-10-CA) coded case definition.[8] Exposure was stratified into two groups according to level of severity: 1) non-severe sepsis (i.e. presence of one of the codes indicating sepsis, but no documented organ dysfunction); and 2) severe sepsis or septic shock (i.e. one of the previous codes indicating sepsis, as well as a code reflecting the presence of organ dysfunction or explicit code for septic shock). Eligible controls did not have any code indicating presence of an infection during index admission or subsequent follow-up. See Table 8 for full list of codes included in the algorithm.

All eligible cases were matched to controls on a 1:1 basis using age (+/- 1 year), sex, date of admission (+/- 30 days), type of admission (urgent or elective), and logit of the propensity score (caliper width 0.25 standard deviations). The propensity score was estimated using a logistic regression that included baseline variables thought to be associated with both the development of sepsis and healthcare costs based on a consultation with a clinical expert (LM) and a literature review, including measures of socioeconomic status, residence location (rural versus urban), residence in a long-term care facility,

prior co-morbidities (previous cancer, diabetes, congestive heart failure, chronic kidney disease, or chronic obstructive pulmonary disease [COPD]), and medical history prior to index admission (including the Johns Hopkins Aggregated Diagnostic Groups® (ADG) Score,[93] previous hospital admission in the past year, use of homecare services in the past year, number of emergency department visits in the past year, and physician visits in the past year).

Direct health system costs during the index admission and post-hospital discharge were traced up to 5 years after index admission date. Individual-level healthcare costs were computed from the public payer's perspective using an ICES macro[109] designed to capture individual subject's encounters with the healthcare system and attach unit costs to services used during those encounters. Costs over the follow-up period were standardized to their equivalent Canadian dollar value in 2018 to adjust for inflation using health sector-specific consumer price indices.

Cost categories included are: hospitalization costs (including inpatient hospitalizations, same day surgery, inpatient mental health admissions, and outpatient hospital visits), emergency department visits, inpatient rehabilitation, complex continuing care, long-term care, Ontario Health Insurance Plan (OHIP) costs (including primary and specialist physician visits, non-physician services, and laboratory services), homecare use, and prescription drug use (for subjects eligible for the Ontario Drug Benefit program).

The following cost categories were excluded: co-payments, costs to informal caregivers, private insurance, overhead and capital expenditures, community-level services (such as day outreach programs). See Table 17 for further information on cost components and costing methods by resource category.

We described total and subdivided health system costs using mean, standard deviation, median, and interquartile range. To determine incremental 1-year healthcare costs between sepsis cases and

controls, we used generalized linear models with a log link function and a gamma distribution, adjusting for paired nature of the data using an exchangeable covariant structure. This model was selected as all patients had costs greater than zero with a highly right skewed distribution. Generalized linear models have been found to perform well with cost data, particularly when using gamma distribution.[110]

We determined incremental lengths of stay using generalized estimating equations with negative binomial link functions and log distribution, adjusting for paired data using an exchangeable covariant structure.

For the analysis of incremental healthcare costs in years 2-5 we analyzed each year separately, and for each year only included patients who were still under follow-up at the beginning of the year under analysis. Since patients in years 2-5 may have had 0 healthcare costs, we used a two-part model[111] consisting of a logistic model to calculate the probability of costs being positive, followed by a generalized linear model, as above for 1-year costs, to determine the difference in adjusted mean costs between cases and controls.

For all models, we included variables that were over 0.10 standardized difference after matching, as well as hospital type during index admission (teaching hospital, community hospital with ≥100 beds, community hospital with <100 beds). We used 1,000 bootstrap replicates with replacement on the full sample size to determine 95% confidence intervals (CIs) for the difference in means.

As a scenario analysis, we repeated the above methodology for healthcare costs at 1-year considering only cases and controls who survived the index hospitalization.

As healthcare costs of sepsis have been found to vary by age group,[22,77,112,113] we conducted a subgroup analysis by age, repeating the analysis for patients <65, between 65-84 years, and those ≥85 years old.

We conducted a sensitivity analysis using an alternate case definition of sepsis: the ICD-10 codes used in the 2009 CIHI sepsis report.[5]

3.6 RESULTS

Of 270,669 cases identified by the Jolley et al. algorithm during the four-year accrual period, 196,922 (72.7%) were successfully matched with a control. Of these, 64,204 (32.6%) had severe sepsis (including septic shock) and 132,718 (67.4%) had non-severe sepsis. Analysis of cases with severe and non-severe sepsis are presented separately as results from these two groups were heterogenous. The characteristics of patients before and after matching have been previously described (see Chapter 2). A plot of standardized differences pre-and post-matching is provided in Figure 11. Before matching cases were more likely to be older, have an urgent versus elective admission, be receiving homecare, and have more co-morbidities. After matching, most variables were balanced, while a few variables remained over the 0.10 threshold (0.11-0.19). These included homecare use, prior hospitalization and number of physician visits in the past year, and COPD for non-severe sepsis, and, for severe cases, rural residence, ADG score,[93] and number of emergency department visits in past year. These variables were included as covariates in the regression models. Observations with missing values were excluded from the models, as the number of missing values was very small (<0.01%). The mean follow-up time was 2.1 years (median: 2.0 years, minimum: 1 day, maximum: 5 years). Characteristics of the hospital survivor cohort are presented in the data supplement (section 3.9.1: Figure 12, Tables 22-23).

For those who had follow-up in years 2-5, almost all (>98%) had >0 healthcare costs.

Use of Healthcare Services at 1-Year

Crude differences in the use of healthcare services between sepsis cases and non-sepsis controls are presented in Table 18. At 1-year, a smaller proportion of severe sepsis patients were users of laboratory and non-physician services and provincially funded prescriptions compared to matched controls, but

had higher proportions of usage of complex continuing care, rehabilitation, homecare, and long-term care compared to controls. Compared to matched controls, a larger proportion of cases with non-severe sepsis were users of homecare services, long term care homes, prescription drugs funded by the province, and emergency departments at 1-year from index admission date. The crude differences for all other categories were small (<3%).

Index Hospitalization Costs

Crude healthcare costs for sepsis and non-sepsis cohorts are provided in Tables 19 and 20. The crude cost of index hospitalization costs averaged $37,953 (median: $18,139) for severe sepsis patients versus $12,888 (median: $8,488) for matched controls. The crude index hospitalization costs for patients with non-severe sepsis averaged $13,985 (median: $8,949) compared to $12,001 (median: $7,983) for matched controls. Adjusted incremental costs of sepsis patients versus matched controls are shown in Table 21. After adjustment, severe sepsis patients cost, on average, an additional $23,530 (95% CI: $22,974-$24,019) during index hospitalization, and non-severe patients cost an additional $1,966 (95% CI: $1,889-$2,128) compared to their respective matched controls.

One-Year Healthcare Costs

One-year from index hospitalization date, total mean healthcare costs for patients with severe sepsis totalled $66,781 (median: $43,033) versus $35,372 (median: $22,285) for controls (Table 19). In patients with non-severe sepsis the mean 1-year healthcare costs were $42,481 (median: $27,272) versus $32,087 (median: $19,521) for matched controls. Plots of distribution of crude 1-year costs for cases and controls are provided in the data supplement (section 3.9.1: Figure 13). The adjusted 1-year incremental costs were $29,238 (95% CI: $28,568-$29,913) for severe sepsis cases and $9,475 (95% CI: $9,150-$9,727) for non-severe sepsis and compared to their respective matched controls (Table 21). For both

case groups acute hospitalizations (including index hospitalization and rehospitalizations) was the cost component with the largest crude differential between cases and controls at 1-year.

One-Year Healthcare Costs in Hospital Survivor Cohort

Compared to those who died in-hospital, hospital survivors had lower average costs during index hospitalization ($35,957 versus $44,349 for severe; $13,612 versus $19,433 for non-severe patients), while average total 1-year costs were higher. Crude hospital costs by survival status are presented in supplemental data (section 3.9.1: Table 24). The incremental mean 1-year healthcare costs in sepsis hospital survivors versus matched non-sepsis controls who survived index hospitalization were $34,405 (95% CI: $33,631-$35,220) in severe sepsis and $9,630 (95% CI: $9,263-$9,824) in non-severe cases (Table 21).

Length of Stay During Index Admission

Crude and adjusted length of stay index hospital stay (including days in ICU and total length of hospital stay) for sepsis and non-sepsis cohorts are provided in Tables 18 and 21, respectively. The average hospital length of stay for severe sepsis patients was 20.84 days (median: 11) versus 8.04 days (median: 4) for matched controls. For non-severe sepsis length of stay averaged 11.1 days (median: 6) versus 7.4 (median: 4) for matched controls. Crude length of stay by hospital survival status is presented in supplemental data (section 3.9.1: Table 24). After adjustment, severe cases stayed an additional 12.52 days (95% CI: 12.26-12.98); and non-severe cases stayed an additional 3.77 days (95% CI: 3.57-3.87) during index admission compared to matched controls. Severe sepsis resulted in an estimated additional 4.68 days (95% CI: 4.50-4.83) in ICU, while patients with non-severe sepsis had fewer ICU days, -0.22 (95% CI: -0.23, -0.18) on average versus matched controls.

Healthcare Costs in Years 2-5

Table 20 presents crude healthcare costs for years 2-5. Crude mean annual healthcare costs for all patient groups were substantially lower in years 2-5 compared to year 1. Costs remained higher in sepsis patients compared to controls throughout follow-up, but the adjusted difference in costs trended downward from year 2-5: $13,390-$10,640 for severe cases; $9,078-$7,847 for non-severe cases (Table 21).

Age Subgroup Analysis

One-year crude and adjusted incremental costs by age subgroup in sepsis patients and non-sepsis matched controls are presented in Tables 19 and 21. Adjusted incremental mean index hospitalization costs and total 1-year healthcare costs were higher for patients in the youngest age group (<65) and lowest in the oldest age group (≥ 85), across all comparisons, with the exception of hospital costs for non-severe cases versus controls. Severe sepsis patients <65 had the highest index hospitalization costs (mean: $52,455; median: $24,535), as well as the highest total 1-year healthcare costs (mean: $82,180; median: $47,773).

Sensitivity Analysis

An analysis using the 2009 CIHI ICD-10 case definition[5] produced similar results, although the estimates of hospital costs during index admission and 1-year total mean incremental healthcare costs for sepsis patients were somewhat higher using the CIHI definition compared to the primary analysis (see Table 21).

3.7 DISCUSSION

In this study we found that patients with sepsis incur high costs to the Ontario healthcare system compared to non-sepsis hospital controls. Compared to matched controls, severe sepsis patients incurred an average additional healthcare cost of $29,238 (95% CI: $28,568-$29,913) in the year after index admission date. One-year incremental costs for non-severe sepsis compared to matched controls were smaller, on average, at $9,475 ($9,150-$9,727). Generally, incremental 1-year healthcare costs were higher for cases in the youngest age group (<65) and lower for cases in the oldest age group (≥ 85).

Hospital costs made up the largest component of incremental 1-year costs for both groups. Index hospitalization costs were particularly high for severe sepsis cases: $37,953 (median: $18,139), and incremental hospital costs rose as age group decreased, averaging $52,455 (median: $24,535) for cases under 65 years.

Analysis of annual costs in subsequent years provides evidence that costs for cases remain elevated compared to controls for up to 5 years after index admission date, although the difference is much smaller than in year 1.

Our results are consistent with Prescott et al.'s 2018 study which found sepsis patients had higher resource use compared to non-sepsis hospitalized matched controls at one-year,[81] as well as Thompson et al.'s study which found that healthcare resource use was higher for sepsis patients after 2-year follow-up compared to critically ill non-sepsis controls.[69]

The smaller incremental cost in non-severe cases at 1-year found in this analysis is unsurprising and is consistent with previous literature which has found an association between the severity of the septic episodes and hospital costs. For example, in their 2017 systematic review, Arefian et al. found that studies that restricted to severe sepsis or septic shock reported higher hospital costs compared to studies including sepsis without organ dysfunction.[73]

Higher hospital costs in sepsis patients may be driven by longer lengths of stay in hospital, which previous studies have found to be a key contributor to in-hospital costs for sepsis, particularly ICU length of stay.[74–76] Here we found that, on average, severe sepsis patients spent an additional 12.52 days total in-hospital, and 4.68 days in ICU, while non-severe sepsis patients spent an additional 3.77 hospital days during index admission, but less time in ICU (-0.22 days) compared to non-sepsis controls.

Previous research has also found that healthcare costs of sepsis vary significantly in different age groups, with elderly severe sepsis patients having lower hospital costs compared to younger cases.[22,77,112,113] We similarly found lower costs in elderly patients, and higher costs for cases <65 years. There are several possible reasons why younger patients with severe sepsis might have higher long-term costs: 1) younger patients were more likely to be admitted to the ICU during hospital admissions and had longer lengths of stay in hospital and in ICU; 2) younger patients are more likely to live longer, in general, compared to older patients, and therefore may simply have more time to accrue healthcare costs compared to patients ≥85 year old; 3) sicker patients may be more likely to survive their illness if they are younger.

Consistent with previous research,[73,77,114–116] we found that sepsis patients who died in-hospital incurred higher costs during index hospitalization compared to sepsis patients who survived to discharge. However, sepsis patients who survived index hospitalization had higher incremental costs over 1-year of follow-up compared to matched controls, unsurprisingly given the additional potential time to accrue healthcare costs. Higher healthcare costs and associated healthcare resource use in sepsis survivors could result from increased frailty and sustained immunosuppression post-discharge.[70]

Limitations

This study has several limitations. There is currently no gold standard to identify patients with sepsis in administrative health databases, and the challenges associated with identifying sepsis cases have been previously noted.[84] Given that the sensitivity and precision of the ICD-10 coded definition used to

identify cases is not perfect, some misclassification bias is expected. It is anticipated that this bias would be non-differential and would therefore bias the estimates towards the null. Additionally, Sepsis-2 definitions were used as opposed to the more recent Sepsis-3 definitions, since the validated ICD-10 case definition used the former sepsis definition. A further limitation is that we did not have access to a temporal breakdown of hospital cost; for example, how much was spent on ICU or in the first day of hospitalization, which restricts the granularity of understanding of how hospital costs accrue. Additionally, this analysis only takes into account certain types of healthcare costs. For example, it does not cover drug costs that patients paid out of pocket or costs covered by private insurance or productivity losses.[117] Further, after 1-year patients had varying follow-up time, due to the staggered accrual period. Finally, there was a large proportion of unmatched cases due to the differences in characteristics between the pool of cases and controls.

CONCLUSION

Severe sepsis is associated with significant healthcare costs in the first year after index hospitalization compared to matched hospitalized controls. Differences in one-year costs for non-severe cases compared to controls were less pronounced. Considering the entire four years of hospitalizations (including unmatched cases) during the study's accrual period, we estimate that the total sum of the one-year incremental cost sepsis in Ontario is $672.4 million for severe sepsis patients; and $423.2 million for patients with non-severe sepsis.

The total cost estimate should be cautiously interpreted as it is sensitive to the annual incidence of sepsis hospitalizations. The true incidence of sepsis in Ontario is unknown. There was a large difference between number of sepsis cases identified Jolley et al. algorithm and the CIHI 2009 algorithm (91,987 versus 27,105 severe sepsis; and 178,682 versus 21,214 non-severe sepsis cases, respectively). In the sensitivity analysis using the CIHI 2009 case definition of sepsis, the estimate of total cost is $207.0

million dollars annually for severe sepsis patients and $41.7 million annually for patients with non-severe sepsis. However, the Jolley et al. algorithm has demonstrated higher sensitivity compared to the 2009 CIHI definition (71.9% vs. 46.4% for all sepsis cases) in a validation study.[8]

The results of this study indicate the high health resource burden of sepsis in Ontario. Future research should aim to identify healthcare interventions that can reduce length of initial hospital stay, particularly ICU length of stay, for sepsis patients or prevent rehospitalizations for sepsis survivors, potentially resulting in significant savings to the healthcare system.

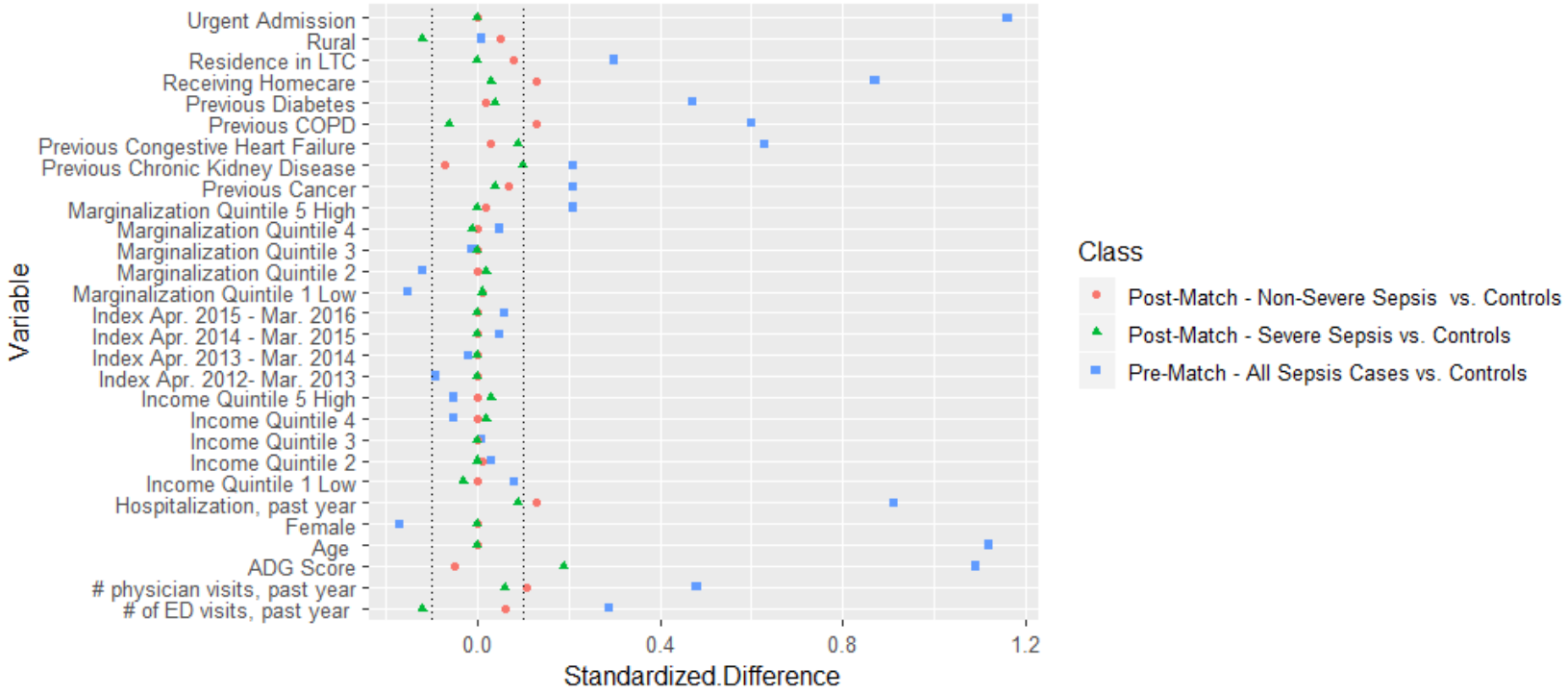
3.8 Tables and Figures for Chapter 3

Table 17. Cost Components and Costing Methods

Cost Component	Consumer Price Index	Costing Methods
• Inpatient hospitalizations	Health care	Resource intensity weight x cost per weighted case
• Emergency department visits • Dialysis visits • Oncology clinic visits	Health Care	Resource intensity weight x cost per weighted case
• Rehabilitation admissions	Health Care	Rehabilitation patient group x Rehabilitation cost weight
• Complex continuing care admissions • Long-term care	Health Care	Complex continuing care= Case mix index x Cost per weighted day Long term care (LTC)= Length of stay (based on LTC flags) x cost per day from Ontario Ministry of Health and Long-Term Care
• Home care services	Health Care Services	Standard cost per service
• Mental health admissions	Health Care	(Days of stay x case mix index) x cost per weighted day
• Outpatient physician visits • Laboratory services • Non-physician services	Health Care Services	Outpatient visits =Fee-for-service claims and "shadow-billed" claims Laboratory services = technical + professional fees
• Capitation costs	Health Care Services	Base rate x age-sex multiplier + applicable premiums.
• Medication use	Medicinal and Pharma Products	Total payments

Source: Kuwornu P, Wodchis W, Calzavar A. A methodological guide on using the GETCOST macro for costing studies. Toronto (ON): ICES; 2017 Feb.

Figure 11. Standardized Difference of Baseline Characteristics in Sepsis Cases versus Non-Sepsis Controls Before and After Matching



ADG = Johns Hopkins' Aggregated Diagnosis Groups; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care.

Table 18. Healthcare Resource Utilization and Outcomes at 1-Year, Sepsis Cases versus Matched Non-Sepsis Controls, by Sepsis Type

	Non-Severe Sepsis (no organ dysfunction) N=132,718	Matched Hospital Controls N=132,718	Crude % Difference	Severe Sepsis (including septic shock) N=64,204	Matched Hospital Controls N=64,204	Crude % Difference
	N (%)	N (%)		N (%)	N (%)	
Resource Utilization (number of patients with > 0 costs for cost category)						
Emergency visits	115003 (86.66)	110215 (83.05)	3.61	53636 (83.54)	53708 (83.66)	-0.12
Complex continuing care	10317 (7.77)	7593 (5.72)	2.05	6143 (9.57)	4001 (6.23)	3.34
Long-term care	21410 (16.13)	14876 (11.21)	4.92	9295 (14.48)	8697 (13.55)	0.93
LTC at Index	*11185 (8.43)*	*8254 (6.22)*	*2.21*	*5045 (7.86)*	*5021 (7.82)*	*0.04*
Rehabilitation	9688 (7.30)	9284 (7.00)	0.30	6728 (10.48)	4531 (7.06)	3.42
Homecare	64363 (48.50)	52408 (39.49)	9.01	30240 (47.10)	27388 (42.66)	4.44
Homecare at Index	*47523 (35.81)*	*39595 (29.83)*	*5.98*	*23054 (35.91)*	*24030 (37.43)*	*-1.52*
Prescriptions*	110842 (83.52)	105204 (79.27)	4.25	46476 (72.39)	52603 (81.93)	-9.54
Physician services	132694 (100)	132689 (100)	0.00	64191 (100)	64183 (100)	0.00
Other OHIP services†	102754 (77.43)	101101 (76.18)	1.25	40740 (63.46)	48232 (75.13)	-11.67
Acute Hospitalizations	132718 (100)	132718 (100)	0.00	64204 (100)	64204 (100)	0.00
Index Hospitalization Outcome	**N (%)**	**N (%)**		**N (%)**	**N (%)**	
In-hospital death	8512 (6.41)	10103 (7.61)	-1.20	15270 (23.78)	5941 (9.25)	14.53
ICU admission	13429 (10.12)	19582 (14.75)	-4.63	28489 (44.37)	10360 (16.14)	28.23
Total Hospital LOS (days)						
Mean (SD)	11.11 (22.26)	7.38 (15.87)	3.73	20.84 (36.15)	8.04 (15.76)	12.80
Median (Q1-Q3)	6 (3-11)	4 (2-8)	2	11 (5-23)	4 (2-9)	7
ICU LOS (days)						
Mean (SD)	0.50 (1.96)	0.72 (4.06)	-0.22	5.57 (16.31)	0.83 (3.17)	4.75
Median (Q1-Q3)	0 (0-0)	0 (0-0)	0	0 (0-6)	0 (0-0)	0

ICU = intensive care unit; LTC = long-term care; LOS = length of stay; OHIP = Ontario Health Insurance Plan; Q1 = first quarter; Q3 = third quarter; SD = standard deviation.

*Includes prescription drug claims covered by the Ontario Drug Benefit program.

†Includes laboratory services, and non-physician services covered by the Ontario Health Insurance Plan.

Table 19. Crude Mean Total and Subdivided 1-Year Healthcare Costs, Sepsis Cases vs Matched Non-Sepsis Controls, by Sepsis Type (C$2018)

	Non-Severe (no organ dysfunction) N=132,718	Matched Controls N=132,718	Crude Difference (95% CI)	Severe Sepsis (including septic shock) N=64,204	Matched Controls N=64,204	Crude Difference (95% CI)
	Mean (SD)	**Mean (SD)**		**Mean (SD)**	**Mean (SD)**	
Emergency visits	1162 (1134)	961 (1026)	201 (193-209)	1073 (1047)	1004 (1115)	69 (5, 81)
Complex cont. care	2745 (15759)	1739 (11919)	1006 (900-1104)	3831 (19672)	1864 (12262)	1967 (1792, 2141)
Long-term care	4115 (12121)	2715 (9926)	1401 (1322-1483)	3253 (10706)	3298 (10914)	-45 (-162, 72)
Rehabilitation	1687 (7282)	1511 (6440)	176 (124-230)	2499 (9343)	1541 (6570)	958 (869, 1044)
Homecare	2788 (7277)	1785 (5258)	1004 (957-1048)	2669 (7092)	2055 (5690)	614 (544, 683)
Prescription drugs*	2492 (5784)	1911 (4777)	581 (543-622)	2077 (5031)	2148 (5677)	-71 (-132, -13)
Physician services	4710 (4275)	4414 (3848)	296 (266-326)	7222 (7600)	4651 (4031)	2571 (2509, 2633)
Other OHIP services†	273 (412)	242 (369)	31 (28-34)	240 (393)	246 (366)	-6 (-10, -2)
Hospitalizations	22509 (29477)	16811 (22951)	5698 (5495-5897)	43912 (63320)	18565 (25145)	25347 (24839, 25836)
Index hospitalization	13986 (17525)	12001 (15477)	1985 (1859-2115)	37953 (66300)	12888 (16829)	25065 (24554-25575)
Age group‡ <65	12233 (16989)	10153 (15034)	2080 (1846-2321)	52455 (85291)	11819 (19777)	40636 (39159-42117)
65-84	14397 (18194)	12548 (16296)	1849 (1653-2043)	39065 (67535)	13306 (17010)	25759 (25080-26448)
≥ 85	14949 (16760)	12829 (14313)	2120 (1890-2333)	24039 (36905)	13039 (13496)	11000 (10456-11580)
Total 1-Year Cost	42481 (44151)	32087 (34940)	10394 (10098-10693)	66781 (78492)	35372 (37384)	31409 (30721-32039)
Age group‡						
<65 years	35421 (46783)	24521 (33697)	10899 (10317-11527)	82180 (99754)	30259 (38975)	51921 (50111-53788)
65-84 years	44481 (44991)	33473 (35776)	11008 (10555-11452)	68473 (78226)	36390 (38221)	32083 (31123-33001)
≥ 85 years	45800 (39201)	36896 (33516)	8903 (8392-9403)	51112 (51579)	37811 (34023)	13301 (12381-14128)
Survival Status 1-year						
Survivors	41827 (43971)	31483 (34915)	10344 (10014-10710)	75279 (82498)	35634 (37687)	39645 (38634-40436)
Decedents	44550 (44652)	34297 (34943)	10253 (9621-10908)	54666 (70656)	34597 (36467)	20069 (19018-21055)
	Median (IQR)	**Median (IQR)**		**Median (IQR)**	**Median (IQR)**	
Index hospitalization	8949 (8840)	7983 (8157)	966 (917-1025)	18139 (28092)	8488 (8726)	9651 (9492-9797)
Total 1-Year Cost	27272 (44063)	19521 (30302)	7751 (7535-8003)	43033 (62038)	22285 (34243)	20748 (20206-21203)

CI = confidence interval; cont. = continuing; IQR = interquartile range; OHIP =Ontario Health Insurance Plan; SD = standard deviation.

*Includes prescription drug claims covered by the Ontario Drug Benefit program.

†Includes laboratory services and non-physician services covered by the Ontario Health Insurance Plan.

‡Cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of cases.

Table 20. Cohort Size, Number of Deaths, and Crude Mean Total 1-5 Year Healthcare Costs, Sepsis Cases versus Matched Non-Sepsis Controls, by Sepsis Type (C$2018)*

	Non-severe (no organ dysfunction)	Matched Controls	Total Cohort Size	Severe Sepsis (including septic shock)	Matched Controls	Total Cohort Size
Cohort Size	**N**	**N**	**N**	**N**	**N**	**N**
Year 1	132718	132718	265436	64201	64201	128402
Year 2	100822	104194	205016	37710	47936	85646
Year 3	70466	75602	146068	24758	32972	57730
Year 4	43843	49338	93181	14758	20586	35344
Year 5	22083	26036	48119	7080	10523	17603
Deaths	**N (%)**	**N (%)**	**% Difference**	**N (%)**	**N (%)**	**% Difference**
Year 1	31850 (24.00)	28488 (21.47)	2.53	26470 (41.23)	16247 (25.31)	15.92
Year 2	9889 (9.81)	6480 (6.22)	3.59	4344 (11.52)	3498 (7.30)	4.22
Year 3	6582 (9.34)	4045 (5.35)	3.99	2539 (10.26)	2049 (6.21)	4.05
Year 4	3589 (8.19)	2251 (4.56)	3.63	1362 (9.23)	1044 (5.07)	4.16
Year 5	1215 (5.50)	755 (2.90)	2.60	440 (6.21)	381 (3.62)	2.59
Costs	**Mean (SD)**	**Mean (SD)**	**Crude Difference (95% CI)**	**Mean (SD)**	**Mean (SD)**	**Crude Difference (95% CI)**
Pre-Index†	15425 (26027)	11374 (20796)	4051 (3908-4199)	15879 (28606)	13432 (22448)	2447 (2199-2704)
Year 1	42481 (44151)	32087 (34940)	10394 (10098-10693)	66781 (78492)	35372 (37384)	31409 (30721-32039)
Year 2	24541 (35910)	16110 (27142)	8431 (8167-8680)	31396 (49143)	18980 (29607)	12416 (11817-12934)
Year 3	23904 (35203)	15485 (27026)	8419 (8118-8706)	29411 (44844)	18396 (29243)	11014 (10418-11616)
Year 4	23263 (35732)	15307 (26505)	7956 (7560-8367)	28267 (42921)	18035 (29038)	10232 (9500-10999)
Year 5	23023 (36469)	15695 (26914)	7327 (6755-7875)	28205 (43788)	17920 (29739)	10285 (9149-11499)

CI = confidence interval; OHIP =Ontario Health Insurance Plan; SD = standard deviation

*Only includes patients who had follow-up at the start of the year of analysis.

†Covering 12 months before index admission date. This 12-month period began 30 days before index admission and ended 13 months prior to admission in order to exclude costs related to reason for index hospital admission.

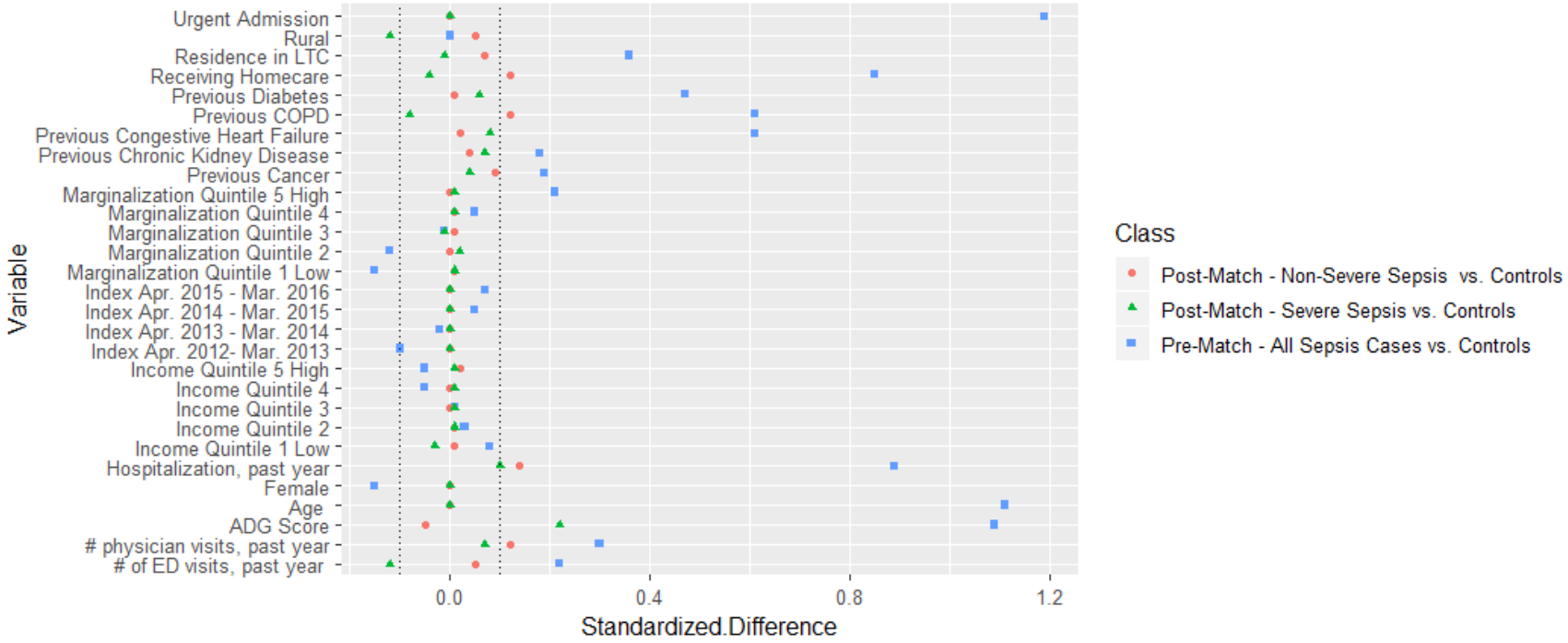
Table 21. Adjusted* Outcomes for Sepsis Cases and Matched Non-Sepsis Controls, by Sepsis Type and Age Group

Outcome		Non-Severe Sepsis (no organ dysfunction) vs. Matched Hospital Controls	Severe Sepsis (including septic shock) vs. Matched Hospital Controls
		Adjusted Mean Difference (95% CI)	Adjusted Mean Difference (95% CI)
Hospital LOS	All ages	3.77 (3.57-3.87)	12.52 (12.26-12.98)
	<65	3.53 (3.13-3.59)	15.01 (14.24-15.55)
	65-84	3.97 (3.67-4.14)	12.54 (12.06-13.09)
	≥ 85	3.80 (3.57-4.12)	9.46 (8.94-10.33)
	CIHI Def.†	4.08 (3.60-4.47)	14.20 (13.44-14.73)
ICU LOS	All ages	-0.22 (-0.23, -0.18)	4.68 (4.50-4.83)
	<65	-0.18 (-0.24, -.009)	7.68 (7.32-8.06)
	65-84	-0.26 (-0.27, -0.22)	4.70 (4.42-4.91)
	≥ 85	-0.18 (-0.19, -0.13)	1.48 (1.28-1.61)
	CIHI Def.†	0.05 (0.02-0.12)	6.47 (6.43-6.99)
Hospital Costs	All ages	1966 (1889-2128)	23530 (22974-24019)
	<65	2082 (1846-2346)	35051 (33811-36424)
	65-84	1881 (1757-2140)	23678 (22845-24359)
	≥ 85	2066 (1855-2284)	10559 (10011-11242)
	CIHI Def.†	3124 (2720-3507)	31299 (30428-32670)
1-Year Costs (from index admission date)	All ages	9475 (9150-9727)	29238 (28568-29913)
	<65	10680 (9681-11134)	47104 (45059-48422)
	65-84	10303 (10154-11031)	29254 (28434-30303)
	≥ 85	8647 (8140-9136)	12604 (11633-13431)
	CIHI Def.†	7870 (6873-8777)	30542 (28822-31529)
Hospital Survivors‡			
1-Year Costs (from index admission date)	All ages	9630 (9263-9824)	34405 (33631-35220)
	<65	10908 (10179-11575)	51937 (49437-53185)
	65-84	10309 (10110-10988)	34969 (33140-35402)
	≥ 85	9409 (8625-9927)	17870 (16741-18928)
	CIHI Def.†	12070 (10630-12716)	47825 (44779-48788)
Year 2-5 Costs§			
Year 2	All ages	9078 (8795-9373)	13390 (12788-13999)
Year 3	All ages	8984 (8639-9346)	11824 (11113-12493)
Year 4	All ages	8405 (7981-8879)	10848 (9971-11689)
Year 5	All ages	7847 (6992-8214)	10640 (9334-11667)

*Adjusted for hospital type, and propensity score variables with standardized difference > 0.10. For non-severe sepsis: homecare use in previous year, hospitalizations in previous year, previous chronic obstructive pulmonary disease, number of physician visits in past year; for severe sepsis: rural residence, Johns Hopkins' Aggregated Diagnosis Group (ADG) Score,[93] and number of emergency department visits in previous year.
†Data is from a sensitivity analysis using CIHI's administrative data case definition (non-severe sepsis N = 16464 matched pairs; for severe sepsis N = 19850 matched pairs).
‡Data is from an analysis of cases and controls who survived index hospitalization (for non-severe-sepsis N = 124244 matched pairs; for severe sepsis N = 48852 matched pairs. Using the CIHI case definition: non-severe N = 13862 matched pairs; for severe sepsis N = 12068 matched pairs; CIHI case definition).
§Data includes only cases and controls who had follow-up at the beginning of the year under analysis.
Note: For age subgroups, cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of case.

3.8.1 Data Supplement for Chapter 3

Figure 12. *Hospital Survivor Cohort* Standardized Difference of Baseline Characteristics in Sepsis Cases versus Non-Sepsis Controls Before and After Matching



ADG = Johns Hopkins' Aggregated Diagnosis Groups; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care.

Table 22. *Hospital Survivor Cohort Healthcare Resource Utilization and Outcomes 1-Year After Index Admission, Sepsis Cases versus Matched Non-Sepsis Controls**

	Infection (no organ dysfunction) N= 124,242	Matched Hospital Controls N=124,242	Crude % Difference	Sepsis (including septic shock) N= 48,852	Matched Hospital Controls N= 48,852	Crude % Difference
	N (%)	**N (%)**		**N (%)**	**N (%)**	
Resource Utilization						
Emergency visits	108822 (87.59)	103976 (83.69)	3.90	42790 (87.60)	41502 (84.97)	2.63
Complex cont. care	10274 (8.27)	7622 (6.13)	2.14	5996 (12.27)	3310 (6.78)	5.49
Long-term care	20024 (16.12)	14692 (11.83)	4.29	8137 (16.66)	6825 (13.97)	2.69
Rehabilitation	9613 (7.74)	9367 (7.54)	0.20	6656 (13.63)	3784 (7.75)	5.88
Homecare	63226 (50.89)	52362 (42.15)	8.74	28938 (59.24)	22220 (45.49)	13.75
Prescriptions†	108713 (87.50)	105094 (84.59)	2.91	43613 (89.28)	43017 (88.07)	1.21
Physician services	100	100	0.00	100	100	0.00
Other OHIP services‡	102366 (82.39)	102165 (82.23)	0.16	40211 (82.32)	40333 (82.57)	-0.25
Acute Hospitalizations	124242 (100)	124242 (100)	0.00	48852 (100)	48852 (100)	0.00
Index Hospitalization Outcome	**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Discharge home, no support	60722 (48.87)	72504 (58.36)	-9.49	16414 (33.60)	26385 (54.01)	-20.41
ICU admission	12166 (9.79)	16464 (13.25)	-3.46	19054 (39.00)	6981 (14.29)	24.71
Total Hospital LOS (days)						
Mean (SD)	10.69 (21.23)	7.09 (14.34)	3.60	21.25 (35.31)	7.80 (16.52)	13.45
Median (Q1-Q3)	6 (3-11)	4 (2-8)	2	11 (6-23)	4 (2-8)	7
ICU LOS (days)						
Mean (IQR)	0.49 (1.93)	0.60 (2.21)	-0.11	4.80 (13.46)	0.68 (2.40)	4.12
Median (Q1-Q3)	0 (0-0)	0 (0-0)	0	0 (0-5)	0 (0-5)	0

ICU = intensive care unit; LTC = long-term care; LOS = length of stay; OHIP = Ontario Health Insurance Plan; Q1 = first quarter; Q3 = third quarter; SD = standard deviation.

*Data is from a scenario analysis of cases and controls who survived index hospitalization.

†Includes prescription drug claims covered by the Ontario Drug Benefit program.

‡Includes laboratory services and non-physician services covered by the Ontario Health Insurance Plan.

Table 23. Hospital Survivor Analysis*: Crude Mean Total and Subdivided 1-Year Healthcare Costs, Cases versus Matched Non-Sepsis Controls, by Sepsis Type

	Non-Severe (no organ dysfunction) N=124,242	Matched Hospital Controls N=124,242	Crude Difference (95% CI)	Severe Sepsis (including septic shock) N=48,852	Matched Hospital Controls N=48,852	Crude Difference (95% CI)
	Mean (SD)	**Mean (SD)**		**Mean (SD)**	**Mean (SD)**	
Emergency visits	1207 (1148)	998 (1045)	209 (202-218)	1242 (1134)	1043 (1110)	199 (184-212)
Complex cont. care	2928 (16236)	1876 (12386)	1052 (938-1168)	5002 (22353)	2067 (13097)	2934 (2705-3173)
Long-term care	4362 (12428)	3093 (10560)	1269 (1181-1352)	4225 (12019)	3725 (11596)	499 (365-640)
Rehabilitation	1791 (7473)	1626 (6663)	165 (108-220)	3275 (10586)	1674 (6803)	1601 (1495-1713)
Homecare	2974 (7475)	1969 (5528)	1005 (952-1051)	3497 (7900)	2249 (5938)	1248 (1165-1334)
Prescription drugs†	2657 (5918)	2081 (4263)	576 (535-615)	2715 (5613)	2322 (4708)	393 (329-459)
Physician services	4903 (4331)	4592 (4312)	311 (275-344)	7900 (7653)	4791 (4121)	3109 (3033-3182)
Other OHIP services‡	292 (420)	263 (376)	29 (26-32)	314 (423)	272 (379)	42 (38-47)
Acute Hospitalizations	22928 (29698)	16938 (22257)	5990 (5778-6201)	45584 (60367)	18497 (24797)	27087 (26544-27642)
Index hospitalization	13584 (16251)	11468 (13353)	2116 (2004-2236)	35906 (58854)	12260 (15257)	23646 (23056-24170)
Age group§ <65	11999 (16101)	9825 (13690)	2174 (1953-2384)	50518 (76593)	10927 (15132)	39591 (38319-40972)
65-84	13902 (16576)	11885 (13608)	2017 (1855-2195)	35477 (57673)	12630 (15667)	22847 (22116-23564)
≥ 85	14675 (15702)	12448 (12358)	2227 (2001-2502)	23201 (33775)	12808 (14518)	10393 (9760-11023)
Total 1-Year Cost	44043 (44672)	33438 (34996)	10605 (10327-10920)	73753 (77303)	36641 (37595)	37112 (36359-37862)
Age group§ <65	35715 (46856)	24606 (33460)	11109 (10502-11686)	87498 (99076)	29169 (37363)	58328 (56599-60322)
65-84	45943 (45532)	34777 (35453)	11166 (10733-11630)	74117 (75410)	37726 (38667)	36391 (35360-37417)
≥ 85	49385 (39299)	40289 (33860)	9096 (8494-9798)	60387 (51095)	41538 (34652)	18849 (17773-19943)
	Median (IQR)	**Median (IQR)**		**Median (IQR)**	**Median (IQR)**	
Index hospitalization	8853 (8424)	7883 (7816)	970 (918-1024)	17750 (25452)	8335 (8323)	9451 (9250-9603)
Total 1-Year Cost	28967 (45382)	20780 (32077)	8178 (7936-8464)	51054 (64533)	23479 (35535)	27575 (26910-28192)

CI = confidence interval; IQR = interquartile range; OHIP =Ontario Health Insurance Plan; SD = standard deviation.

*Data is from a scenario analysis of cases and controls who survived index hospitalization.

†Includes prescription drug claims covered by the Ontario Drug Benefit program.

‡Includes outpatient physician visits, laboratory services, and non-physician services covered by the Ontario Health Insurance Plan.

§Cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of cases.

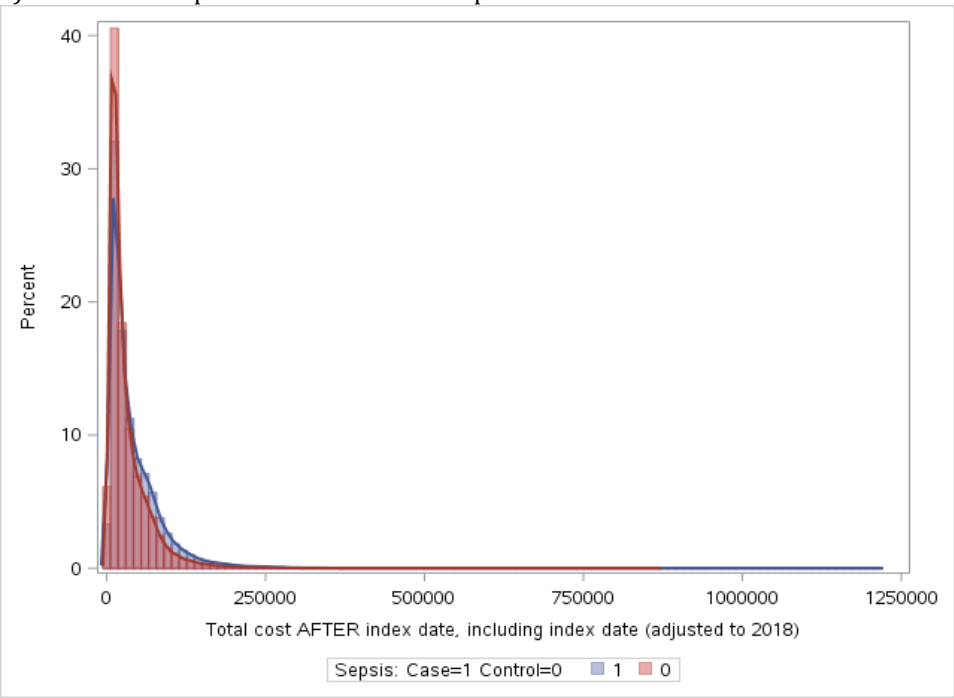
Table 24. Index Hospitalization Costs and Length of Stay by Hospital Survival Status, Sepsis Cases versus Matched Non-Sepsis Controls (Primary Analysis)

	Non-Severe Sepsis (no organ dysfunction)	Matched Hospital Controls	Crude % Difference	Severe Sepsis (including septic shock)	Matched Hospital Controls	Crude % Difference
Hospital Survivors						
	N=124,206	**N= 122,615**		**N=48,934**	**N=58,263**	
Index hospitalization cost						
Mean (SD)	13612 (16407)	11493 (13867)	2119	35957 (59162)	12291 (14859)	23666
Median (IQR)	8862 (8439)	7872 (5310)	990	17732 (25450)	8357 (8282)	9375
Total Hospital LOS (days)						
Mean (SD)	10.73 (21.48)	7.07 (15.57)	3.66	21.26 (35.52)	7.73 (14.89)	13.53
Median (Q1-Q3)	6 (3-11)	4 (2-8)	2	11 (6-23)	4 (2-8)	7
ICU LOS (days)						
Mean (IQR)	0.49 (1.93)	0.62 (3.85)	-0.13	4.81 (13.72)	0.70 (2.69)	4.11
Median (Q1-Q3)	0 (0-0)	0 (0-0)	0	0 (0-5)	0 (0-0)	0
Hospital Decedents						
	N=8,512	**N= 10,103**		**N=15,270**	**N= 5,941**	
Index hospitalization cost						
Mean (SD)	19433 (28793)	18164 (27782)	1269	44349 (84927)	18741 (29284)	25608
Median (IQR)	11392 (17214)	10241 (15434)	1151	20194 (37820)	10717 (15999)	9477
Total Hospital LOS (days)						
Mean (SD)	16.59 (31.00)	11.05 (18.80)	5.54	19.47 (38.07)	11.07 (22.37)	8.40
Median (Q1-Q3)	8 (3-19)	5 (2-13)	3	9 (3-21)	6 (2-13)	3
ICU LOS (days)						
Mean (IQR)	0.71 (2.32)	1.94 (5.86)	-1.24	8.01 (22.53)	2.04 (6.02)	5.97
Median (Q1-Q3)	0 (0-0)	0 (0-2)	0	2 (0-8)	0 (0-2)	2

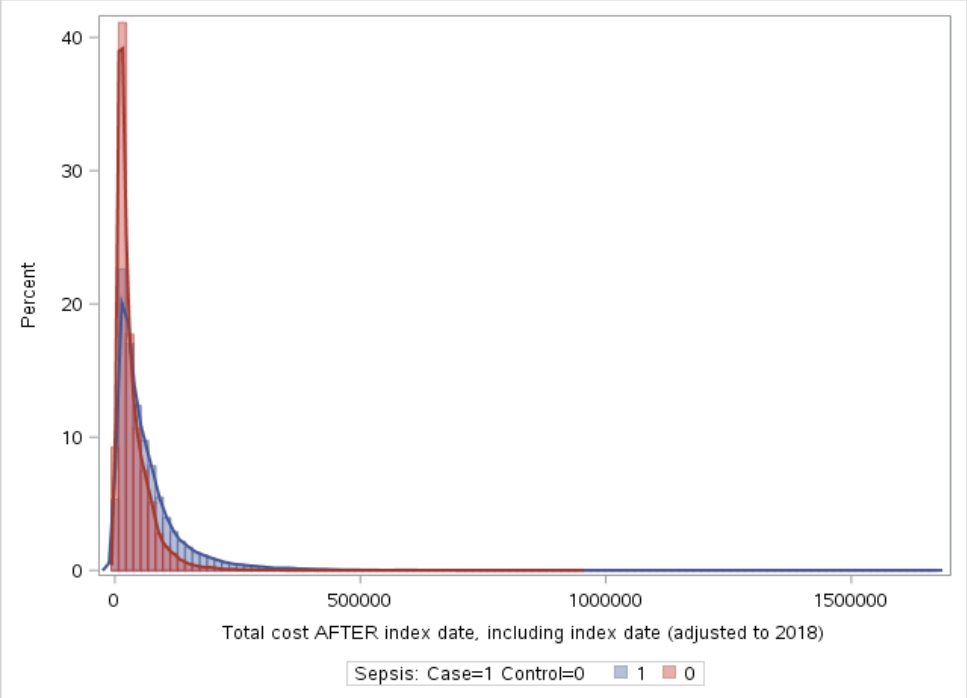
ICU = intensive care unit; LOS = length of stay; Q1 = first quarter; Q3 = third quarter; SD = standard deviation.

Figure 13. Plot of Total 1-Year Healthcare Costs Per Person (Primary Analysis) in Sepsis Cases versus Matched Non-Sepsis Controls (C$2018)

a) Non-Severe Sepsis versus Matched Hospital Controls



b) Severe Sepsis versus Matched Hospital Controls



Chapter 4: Discussion & Conclusions

4.1 Summary of Findings

A summary of results from the primary analysis, subgroup analyses, and sensitivity analyses is provided in Appendix A.

The two manuscripts above provide evidence of the increased risk of long-term mortality and higher healthcare costs following severe sepsis. Patients who are hospitalized for severe sepsis experience higher mortality rates, more frequent rehospitalizations, longer lengths of stay in hospital and ICU, as well as higher healthcare costs compared to hospitalized patients without sepsis. These higher mortality and rehospitalization risks and incremental costs persist for at least a year and up to five years after index admission date.

The subgroup analysis of patients aged <65, 65-84 and ≥ 85 years found that differences in mortality and costs between cases and controls were larger among younger patients, and smaller in the elderly. Further data on the age subgroup analysis can be found in Appendix B and Appendix C.

Differences between sepsis cases and non-sepsis matched controls were less pronounced in the analysis of patients who are hospitalized with non-severe sepsis (infection without organ dysfunction). Although these patients did not experience higher mortality compared to controls during index hospitalization, their long-term mortality rates (30 days post-discharge to up to 5-years post-discharge) were significantly higher than matched non-sepsis hospital controls, and they incurred higher costs both during index hospitalization and in subsequent years. Findings for non-severe patients differed somewhat depending on the definition of sepsis used. In the sensitivity analysis using the CIHI 2009 sepsis algorithm[5] non-severe patients had higher relative mortality compared to controls over the entire follow-up period (Appendix D). Non-severe cases identified using the Jolley et al.[8] definition may have

had a lower severity of illness during index hospital admission. An additional analysis in which non-severe sepsis patients (as defined by Jolley et al. algorithm[8]) were matched only with controls who had no documented organ dysfunction codes, found that non-severe cases had slightly higher odds of hospital mortality compared to this control group (see Appendix E).

During the post-discharge period severe and non-severe sepsis patients had similar differences in mortality and hospital readmission rates in the later years of follow-up, compared to their respective controls. Relative mortality rates for all sepsis survivors increased over time in the months and years post-discharge compared to matched controls.

While sepsis cases had a higher relative risk of mortality over post-discharge follow-up compared to controls, the proportion of deaths in matched non-sepsis hospital controls during the full length of follow-up was also high: 26.59% and 29.60% for controls matched with non-severe and severe sepsis survivors respectively. This finding could be explained by older age (average ~73 years) and poor baseline health status of the control group, since people who develop sepsis tend to be older and sicker than the general population, these pre-sepsis baseline characteristics are reflected in propensity score matched non-sepsis controls after 1:1 matching.

In the sensitivity analysis comparing patients with severe sepsis to matched controls with non-severe sepsis, severe sepsis patients had higher mortality for up to two years post discharge, higher rates of hospital readmission at 1-year, and significantly higher healthcare costs for up to four years after index admission. These results suggest that organ dysfunction is a potential mechanism for higher mortality and rehospitalization for severe sepsis patients. Additional details on this sensitivity analysis are provided in Appendix F.

This study cannot determine a causal relationship between sepsis and excess long-term mortality and hospital readmission. Further research is required determine whether the higher risks of long-term

mortality and rehospitalization seen in this cohort is due to some aspect(s) of previous health status or patient characteristics not measured in the current study or whether it is due to sequelae resulting from infectious episode itself, for instance, sustained immunosuppression post-discharge. There is, however, a growing body of evidence that sepsis is associated with the development of health complications in survivors that may persist for months or years after hospital discharge including: new long-term cognitive[118] and physical limitations,[119] psychological challenges, such as depression,[119,120] cardiovascular complications,[121–123] decreased quality of life in survivors, and, in some studies, decreased survival.[64–67] These negative outcomes in sepsis survivors are sometimes referred to as "post-sepsis syndrome".[124]

The sequalae encompassed in post-sepsis syndrome could potentially lead to higher rehospitalization rates for sepsis patients, which were observed in the present study. These results are also consistent with previous research reporting high 30,[119,125–128] 90[128,129], and 180[119,127] day readmission rates for patients hospitalized for sepsis. Research examining hospital readmission diagnoses have reported that subsequent infection or sepsis is one of the most common reasons for rehospitalization after sepsis.[125,126,130] While the underlying causes of the higher odds of rehospitalizations in sepsis patients are unknown, several factors have been associated with higher readmission rates in sepsis patients, including: patient sociodemographic factors,[127] prior comorbidities, discharge to a healthcare facility, and index hospital characteristics (such as longer length of stay and use of parental nutrition, as well as type of hospital on index admission).[119]

The present research provides a much-needed picture of the frequency and outcomes of sepsis in a Canadian context. The last national examination of sepsis hospitalizations in Canada was conducted in 2009 by CIHI[5] and data on costs of sepsis in Canada are almost two decades old. In this study we found that sepsis is a frequent diagnosis in Ontario hospitals. Considering the four-year accrual period, over 22,996 people per year (4.9%) were hospitalized with diagnostic code indicating severe sepsis, while 44,670 per year (9.6%) had a code non-severe sepsis in the province of Ontario alone. Given the high

morbidity, mortality, and cost burden and the large number of people affected by these conditions, policy interventions focusing on these groups could potentially have a significant impact.

4.2 Policy Implications

Lessening the morbidity and mortality burden in sepsis (Sepsis-3) survivors has been recognized as a key area of research internationally.[131] As part of a 2017 resolution highlighting sepsis as a global health priority, the World Health Organization urged member states to improve to access to appropriate healthcare for sepsis (Sepsis-3) survivors.[131] In 2018, the International Sepsis Forum held a colloquium on sepsis survivorship in which participating experts identified data on survivors beyond one year as one of the most important gaps in research.[2] The present analysis contributes to this research agenda by providing estimates of mortality and costs up to 5-years from index admission date. The higher mortality and healthcare cost burden found in this study warrant further investigation to determine which patients might be at highest risk for poor long-term outcomes, to what extent the higher mortality and resource burden could potentially be reduced through modifiable factors, and which healthcare interventions (during index hospitalization and post-discharge) may be effective and preventing morbidity and mortality in sepsis patients.

Given the high costs observed in this study for sepsis survivors, years after discharge, healthcare interventions that target sepsis survivors could not only improve clinical outcomes for these patients, but could potentially result in long-term cost saving for healthcare systems. In particular, interventions that either prevent development of sepsis, shorten lengths of stay in hospital or ICU, or reduce hospital readmissions post-sepsis could result in financial savings, as hospital costs represented the highest category of sub-divided healthcare costs for these patients. The greatest savings may be seen in

interventions directed at younger sepsis patients (<65 years), as this subgroup had the largest difference in healthcare costs compared to non-sepsis controls.

Currently, there insufficient evidence to make specific recommendations about which policies or interventions could have a positive impact on long-term outcomes in sepsis patients. More evidence is needed in order to determine to what extent the higher mortality, readmissions, and costs seen in sepsis cases are preventable, and if so, which interventions would be effective in reducing risk. Currently, there is some evidence that a large number of hospital readmissions in sepsis survivors are "potentially preventable."[130] Looking at diagnosis codes for 90-day hospital readmissions, Prescott et al. found that 42% of readmission in severe sepsis survivors (≥50 years old) were for conditions that are potentially preventable or treatable in ambulatory care.[130] Subsequent infection was the most common primary readmission diagnosis after hospitalization for severe sepsis. Some have suggested that recurrent infection may be a mediator of the higher mortality risk seen in sepsis survivors.[68] Potential interventions that could reduce risk of rehospitalizations include: patient education at discharge (e.g. to promote routine hygiene precautions), providing support for new functional limitations or disabilities, limiting use of broad-spectrum antibiotic exposure where possible, and probiotic supplements or fecal microbiota transplantation to restore microbiome in higher risk patients.[132] In one previous study, a nurse-driven protocolized assessment was found to reduce acute readmissions in sepsis patients discharged to an inpatient rehabilitation facility, compared to standard of care (36% to 25% in 8 weeks).[133] Post-discharge processes found effective at preventing hospital readmission for other conditions could also be applied to sepsis survivors, for example: medication reconciliation and symptom tracking or early follow-up with a primary care physician.[119]

Considering in-hospital management of sepsis, there is evidence that early recognition and treatment of sepsis can improve patient outcomes and lower healthcare costs in-hospital.[134] Ongoing education and awareness for patients, caregivers and clinical staff could aid with early recognition of sepsis signs and

symptoms. Additionally, new developments in diagnostic point-of-care technologies may help more rapidly identify pathogens in patients with suspected sepsis.[135] Blood cultures typically take 24-72 hours to inform targeted antibiotic therapy from the time the blood culture bottle is flagged positive.[136] This delay in microbial identification can result in a window of time in which a patient's antibiotic treatment may be inadequate or overly broad. Earlier targeted therapy may improve patient outcomes and reduce hospital length of stay in sepsis patients. These types of technologies may be particularly useful in rural and remote environments, where there are additional barriers to early diagnosis and treatment of sepsis.[134]

Aside from clinical interventions, making improvements in the coding of sepsis within health administrative databases would assist researchers in accurately estimating the incidence of sepsis and its outcomes. The coding of sepsis within administrative databases is known to be suboptimal, with a tendency to be under-coded when using ICD-9 and ICD-10 case definitions.[84] Combinations of multiple different codes are typically used to capture sepsis diagnoses. For example, the algorithm used in this study contains over 50 ICD-10 codes to identify sepsis cases and a further 30 classification codes to identify organ dysfunction for severe sepsis cases.[8] As there is currently no "gold standard" to identify sepsis cases within health administrative data, different studies use different algorithms, which hinders comparison between studies. With the introduction of ICD-11, there is an opportunity to update and simplify coding of sepsis in Canadian health data. Sepsis coding could be revised to reflect the new Sepsis-3 definitions of sepsis.[1] A single code for "sepsis", and a code for "septic shock", both based on the specific clinical criteria outlined in Sepsis-3 could facilitate the identification of cases for research.

4.3 Methodological Strengths

The use of province-wide health administrative data over a five-year period allowed a large sample size of population-level data and the ability to perform a complete case analysis. It also allowed the ability to

link databases which provided access to information on patient's baseline health and demographic characteristics before hospital admission. We observed large imbalances in many characteristics between cases and controls before matching. Through propensity score and hard matching, we were able to achieve good balance in these characteristics, matching on baseline health, socioeconomic, and demographic characteristics associated with sepsis and mortality. This process allowed us to control for important confounding factors. The few variables that were >0.10 standardized difference after matching were added as variables in the regression models, and we also took matching into account in the analysis by using conditional regression methods and robust sandwich variance estimators.

An additional strength of this analysis is that it examines a survivor only cohort in addition to following patients from index admission date. Shankar-Hari et al. have noted the benefit of looking at survivor only cohort to get a more accurate estimate of long-term outcomes of sepsis patients since it eliminates the "competing risk of hospital mortality on long-term mortality."[137] In-hospital mortality data from the acute illness phase can mask trends in long-term mortality. A survivor cohort examining post-discharge outcomes eliminates this source of bias. According to Ranzani et al. using hospital discharge as the starting point for long-term mortality "will include patients with the minimal requirements to sustain an adequate condition in a non-monitored environment but will add a survivors' bias."[138] We have addressed potential limitations in the selection of starting date for follow-up by considering mortality both from admission date for the entire cohort and mortality from discharge date in the survivor cohort.

Results of this study were reported in accordance with the RECORD Checklist,[139] a guideline for reporting results of studies using routinely collected data (see Appendix H).

4.4 Methodological Limitations

As with all studies using health administrative data to analyze sepsis outcomes, this study is limited by the lack of gold standard for defining sepsis within these datasets. In particular, previous case definitions

have been found to lack sensitivity.[84] It is a strength that the study used an ICD-10 case definition (Jolley et al.) previously validated in a Canadian population,[8] which was found to have higher sensitivity compared to the CIHI algorithm used for the 2009 sepsis, while maintaining acceptable specificity.[8] However, the sensitivity and precision of this algorithm, like all such sepsis case definitions, is imperfect. As such, we expect that some non-differential misclassification bias has occurred, which could have biased the estimates towards the null. Further, both the Jolley et al. and the CIHI sepsis algorithms include few codes specific to viral infections. As viral infections can also result in sepsis, this lack of viral codes could have resulted in some sepsis cases being misclassified as controls. However, general sepsis codes (such as A41.9 "Sepsis, unspecified") and broad infections codes (such as J18.9 "Pneumonia Unspecified") could have also captured sepsis resulting from viral infections.

There also exists some ambiguity as to the timing of the sepsis diagnosis, since the admission records in CIHI's DAD do not include specific dates of diagnoses associated with ICD-10 codes. Although we can identify hospital records in which a diagnostic code was recorded, we cannot tell exactly when the sepsis episode first occurred, which may have led to some imprecision on the estimates of survival time. Further, because of this temporality issue, we cannot distinguish between community acquired sepsis and hospital acquired sepsis within the health administrative datasets used in this analysis. Hospital acquired sepsis is less common than community-acquired sepsis. It is associated with hospital safety and tends to have worse outcomes compared to community acquired sepsis.[140] According to CIHI, Ontario's rate of in-hospital sepsis in 2017-2018 was 4.3 per 1,000 hospitalizations.[141] This represents a minority of total sepsis cases. Using CIHI's ICD-10 case definition,[140] in-hospital sepsis occurred in 2.7% (7,192/270,669) of the total sepsis cases identified during the four-year accrual period of the present analysis.

A similar timing issue occurs with regard to the diagnosis of organ dysfunction. We can tell that acute organ dysfunction was present during the encounter, but not whether it occurred subsequent to the

infection. If a patient's organ dysfunction occurred prior to the infection, patients may have been misclassified as having severe sepsis, when in fact the organ dysfunction was not a result of the infection itself.

A large proportion of sepsis cases (27%) were unmatched, which could limit the generalizability of the results, particularly given that unmatched sepsis cases tended to be have higher levels of morbidity and healthcare usage prior to the sepsis episode. To examine this issue, an analysis was done in which all eligible cases and controls were included without matching, and outcomes were analysed using regression models including all variables from the propensity score model. Results were similar to the primary analysis, however, estimates of attributable mortality, hospital readmission, and incremental 1-year healthcare costs were higher compared to estimates from the primary analysis (Appendix G).

As per the study design, controls had no hospitalizations with a diagnosis of sepsis recorded during the entire accrual period and post-accrual follow-up time. For cases only the first sepsis hospitalization was considered for entry into the cohort. It is possible that this feature of the study design may have led to the control group being generally healthier. A more sophisticated analysis would have allowed controls to become cases later on during follow-up, and would have tracked rehospitalizations with a sepsis diagnosis in cases. However, this type of analysis was beyond the scope of this thesis.

Additionally, we did not separately analyze septic shock patients as a subgroup, because of a lack of information on the validity of ICD-10 coding for this type of sepsis. It is possible that given the severity of this condition, that long-term outcomes for this patient group may be different than those of patients with severe sepsis without shock.

For the age subgroup analysis, we performed exploratory analyses for three different age groups: seniors (65-84 years old), the oldest old (>84 years old), and younger adults (<65 years old). The latter age group contains a wide range of ages, and there may be differences in outcomes between younger

and older adults within this subgroup of sepsis patients (e.g. those 18-34 years old versus 35-64 years old). In the present analysis, we found that the subgroup of sepsis patents <65 years old had the largest difference in mortality and healthcare costs compared to their age-matched controls. It is possible that the trend of higher attributable long-term mortality and healthcare costs in younger subgroups would continue if we split the adult group in to smaller groupings.

Results of this study, especially regarding healthcare costs, may not be generalizable to jurisdictions that have different healthcare systems compared to the province of Ontario, in particular those in lower-or-middle income countries or regions do not have public single-payer systems. Further, as we excluded any patient who had an inter-hospital transfer on index admission, the results of the cost analysis did not take into account any costs that resulted from transporting patients from one hospital to another. This exclusion may limit the generalizability of the results to rural or remote areas where transfers may be more common. Of all patients hospitalized during the accrual period, 4.8% of cases and 1.8% of controls were excluded for having an inter-hospital transfer. Given that inter-hospital transfers incur additional expenses during hospitalization, we expect that excluding transfers may have underestimated incremental costs in sepsis patients compared to non-sepsis controls.

The ICES macro used to determine costs employs a gross costing methodology to calculate hospital costs multiplying resource intensity weight by cost per weighted case.[109] This method is limited in that it does not allow for analysis of variations in costs between hospitals. However, it is a standard and commonly used methodology in Canada and provides an average of hospital costs across different institutions.

4.4.1 Potential Sources of Confounding

There are other limitations resulting from the use of health administrative data. Although we used propensity score matching on the most relevant variables available to reduce potential confounding, there is still the potential for unmeasured confounders—variables not available through administrative

data—to have influenced the analysis. In particular, we did not have access to some patient characteristics that may be potential confounders, such as comorbidities not recorded in the administrative data sets, general measures of health, such as frailty, clinical characteristics (such as SOFA score and lactate levels), or other potential risk factors such as smoking, obesity, or physical inactivity.

The algorithm used to define sepsis was not based solely on the "most responsible diagnosis" (Type M) but also included any pre-admit co-morbidities and post-admit comorbidities (Type 1 and Type 2) and service transfer codes (W, X, Y) recorded during a hospital admission. We did not analyze information on the most responsible diagnosis in cases and controls during index hospitalization, which could potentially be a source of residual confounding, as patients admitted with more severe conditions may have worse outcomes compared to those with milder conditions. We also did not have information on reasons for hospital readmission or cause of death.

Further, we only had access to neighbourhood level data on socioeconomic status, which could have led to residual confounding. We were unable to determine whether patients had been prescribed antibiotics or vasopressor during their hospital stay, which some other studies have used as an additional flag to confirm diagnosis of sepsis.

Because of the stark differences between sepsis cases and non-sepsis controls before index hospital admission, it was challenging to find appropriate matches of cases and controls, and consequently many cases went unmatched (27%). As mentioned above, these unmatched cases tended to have higher morbidity levels and healthcare resource use prior to index admission. Of the cases that were matched, there were still some variables >0.10 standardized difference between cases and controls after 1:1 matching. This limitation was mitigated in part by adding these remaining unbalanced variables to regression models.

The increase in hazard ratios in later time periods of follow-up may be due to the effect of confounding, especially as the hazard ratios for post-discharge mortality and readmission were similar between severe and non-severe sepsis cases and their respective controls. It is also possible that this increase in hazard ratios was due to a survival bias introduced by examining a cohort of hospital survivors only.

The similarity in long-term post-discharge mortality between severe and non-severe sepsis patients compared to their respective controls was unexpected given that severe sepsis patients had high short-term mortality, while non-severe sepsis patients did not. The additional analysis of severe sepsis cases versus non-sepsis controls, provides some further evidence to support an effect of severe sepsis on post-discharge mortality, as severe cases had higher mortality rates for up to 2 years compared to non-severe cases and higher readmission rates for 1-year post-discharge. The severe versus non-severe sepsis comparison also had fewer unmatched cases (9%), and all the propensity score variables were balanced (<0.1 standardized difference) (Appendix F).

Some studies use an instrumental variables methodology to adjust for potential unmeasured confounding factors. This approach was not used in the present analysis, because there was no clear variable that would have served as an appropriate instrumental variable. Previous research has found that instrumental variables are "less useful when strong confounding exists, because strong instruments cannot be found and assumptions will be easily violated."[142]

4.5 Areas for Future Research

Data from the present study will be used to develop an economic model to predict the lifetime healthcare resource use, mortality, and morbidity of sepsis patients post-discharge. The model will take the form of a Markov model which describe how patients transition through a series of mutually-exclusive health states starting from index admission (hospitalization, long-term care, community, or death etc.). Populating this model will also require the collection of more nuanced information on

healthcare resource utilization, such as days spent in hospital, long-term care, and the community post-discharge. Once developed, this economic model could be employed to determine the cost-effectiveness of interventions aimed at improving the health of sepsis patients. Policy makers could then use this information to select drugs, devices, or policy interventions that provide the best quality of life for sepsis patients for the amount of money spent.

Future research should also seek additional validation on the Jolley et al.[8] definition of sepsis. This study is the first one we are aware of that uses the Jolley et al. case definition to study outcomes in sepsis patients. This algorithm was validated in an Alberta population, and should, ideally be validated in an Ontario population before it is used in other studies in the province. The true incidence of sepsis in Canada is unknown, but it may vary from province to province, which could have an impact on the specificity of the case definition. Further, the validation study only had a very small sample of non-ICU patients, yet it identified many non-ICU patients in the present study. The validation study also did not specifically validate codes for a subset of patients with septic shock, and relative mortality rates may differ in this subgroup of sepsis patients. To address these limitations, a subsequent validation study is needed, preferably a chart review of ICU and non-ICU patients in Ontario hospitals, considering septic shock patients as a separate subgroup. Such a study should also consider how well the case definition identifies patients according to Sepsis-3 definitions. The number of cases identified was vastly different depending on whether the CIHI 2009 or Jolley et al. case definitions was used. An additional validation study would help determine which case definition is more suitable for research on sepsis incidence and outcomes. Given the lack of standardization in the identification of sepsis in administrative databases, future research should compare whether different algorithms result in different results in estimates of attributable mortality and incremental healthcare costs related to sepsis.

The wide variety of different case definitions previously employed in sepsis research using health administrative data hinders comparison between studies.[84] Although the Sepsis-3 definitions have

established a definition of sepsis with corresponding clinical parameters, it would be challenging to use these revised definitions to identify sepsis patients in hospital administrative records due to the lack of clinical parameters such as patients' SOFA scores. The upcoming 11th revisions to the ICD medical classification system should ideally incorporate the revised sepsis definitions to facilitate the identification of sepsis cases in administrative data.

Health administrative data could also be linked between provinces in order to have a fuller picture of sepsis in a Canadian context. Data from CIHI's DAD could be linked with datasets from individual hospitals, such as The Ottawa Hospital, to provide additional information on patients' clinical characteristics. Linking data from electronic health records across different hospitals with other health administrative data would provide more granular data, such as use of diagnostic tests, use of antibiotics or vasopressors, SOFA score, and types of organ supports provided in intensive care units. Having this information would enable researchers to more precisely characterize patients, their clinical trajectory, and their outcomes. Such research could also examine reasons for rehospitalisation in sepsis patients compared to controls. This information would help us understand the higher rate of readmissions in sepsis cases, to determine to what extent they may be preventable, and which interventions may be useful in preventing or reducing rehospitalizations for sepsis survivors.

The present research cannot determine a causal relationship between severe sepsis and long-term mortality, particularly given the potential unmeasured confounding factors on patients clinical and social-demographic characteristics, which may represent non-modifiable risk factors. More research is needed to understand the clinical context of why severe sepsis patients might experience higher mortality after hospital discharge and to what extent the higher mortality may be preventable through healthcare interventions. What are the biological mechanisms behind the apparent increases in long-term mortality in sepsis patients? Understanding why sepsis patients might experience higher relative mortality rates compared to other hospitalized patients would help health systems and healthcare

providers to determine how to best provide follow-up care to sepsis survivors. Future research should examine whether there are patient characteristics or other factors that put sepsis survivors at a higher risk. Health administrative data could be used to develop a risk model that could predict the risk of mortality and hospital readmission in sepsis patients post-discharge, potentially allowing clinicians to identity and offer targeted interventions to patients at the highest levels of risk.

Given the evidence of higher risk of long-term mortality, healthcare costs, and healthcare resources utilization in sepsis patients, investment in research on this patient population is needed in order to determine the extent to which the burden of sepsis is preventable, what patient, treatment and hospital-related characteristics put sepsis survivors at higher risk of poor long-term outcomes, and which interventions are effective at improving patients outcomes and reducing healthcare costs for sepsis patients post-discharge.

5.0 References

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APPENDIX A: Summary of Adjusted Outcomes from Primary, Subgroup and Sensitivity Analyses

Table A1: Severe Sepsis versus Matched Controls, Summary of Outcomes from Primary, Subgroup, and Sensitivity Analysis

Outcome	Primary	Age <65 Years*	Age 65-84 Years*	Age <84 years*	CIHI 2009†	Multivariate‡	Severe vs. Non§
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Hospital Mortality	3.09 (2.99-3.20)	6.29 (5.63-7.02)	3.27 (3.11-3.44)	2.23 (2.11-2.36)	6.86 (6.39-7.37)	4.21 (4.12-4.30)	6.87 (6.66-7.10)
ICU Admission	4.28 (4.15-4.41)	7.91 (7.38-8.48)	4.05 (3.88-4.22)	2.34 (2.20-2.50)	9.98 (9.31-10.69)	4.14 (4.07-4.22)	4.00 (3.87-4.13)
30-day readmission‖	1.65 (1.58-1.72)	1.56 (1.43-1.70)	1.59 (1.50-1.69)	1.70 (1.57-1.84)	1.61 (1.49-1.75)	1.68 (1.64-1.73)	1.15 (1.12-1.19)
	Mean (95% CI¶)	**Mean (95% CI¶)**	**Mean (95% CI¶)**	**Mean (95% CI¶)**	**Mean (95% CI¶)**	**Mean (95% CI¶)**	**Mean (95% CI¶)**
Hospital LOS	12.5 (12.3-13.0)	15.0 (14.2-15.6)	12.54 (12.1-13.1)	9.5 (8.9-10.3)	14.2 (13.4-14.7)	12.0 (11.8-12.1)	8.02 (7.78-8.38)
ICU LOS	4.7 (4.5-4.8)	7.7 (7.3-8.1)	4.7 (4.4-4.9)	1.5 (1.3-1.6)	6.47 (6.43-6.99)	2.5 (2.4-2.7)	4.50 (4.44-4.68)
Index hospital costs 2018 CAD	23530 (22974-24019)	35051 (33811-36424)	23678 (22845-24359)	10559 (10011-11242)	31299 (30428-32670)	23116 (22851-23218)	18886 (18488-19318)
1-year costs 2018 CAD	29238 (28568-29913)	47104 (45059-48422)	29254 (28434-30303)	12604 (11633-13431)	30542 (28822-31529)	36502 (35846-36608)	15706 (14714-15856)
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Mortality Rate							
1-year from index	1.71 (1.67-1.74)	2.73 (2.58-2.90)	1.80 (1.75-1.85)	1.44 (1.39-1.48)	2.39 (2.31-2.46)	2.11 (2.08-2.14)	1.77 (1.74-1.80)
5-year from index	1.66 (1.63-1.68)	2.49 (2.37-2.62)	1.76 (1.72-1.80)	1.45 (1.41-1.49)	2.10 (2.05-2.16)	2.01 (1.99-2.04)	1.50 (1.49-1.52)
Post-discharge 1-year	1.23 (1.20-1.27)	1.56 (1.42-1.71)	1.24 (1.19-1.29)	1.21 (1.16-1.26)	1.19 (1.12-1.26)	1.51 (1.48-1.54)	1.18 (1.16-1.21)
Post-discharge 5-year	1.35 (1.32-1.38)	1.79 (1.67-1.91)	1.41 (1.36-1.45)	1.29 (1.25-1.33)	1.27 (1.21-1.33)	1.63 (1.61-1.66)	1.13 (1.11-1.15)
Readmission‖							
1-year	1.56 (1.53-1.60)	1.52 (1.46-1.59)	1.56 (1.51-1.60)	1.57 (1.51-1.63)	1.55 (1.52-1.58)	1.58 (1.56-1.60)	1.09 (1.07-1.10)
5-year	1.53 (1.50-1.55)	1.48 (1.43-1.54)	1.54 (1.50-1.57)	1.56 (1.51-1.61)	1.53 (1.50-1.55)	1.74 (1.72-1.76)	1.06 (1.05-1.08)

CI = confident interval; CIHI = Canadian Institute for Health Information; HR = hazard ration; ICU = intensive care unit; LOS = length of stay; OR = odds ratio.

Adjusted for hospital type, and propensity score variables with standardized difference > 0.10. Except for the multivariate analysis, which was adjusted for age, sex and all variables in the propensity score model for the primary analysis.

* For age subgroup analyses, cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of cases.

†Data is from a sensitivity analysis using CIHI's administrative data case definition (N = 19850 matched pairs. For hospital survivor cohort: N = 12068 matched pairs).

‡ Data is from a sensitivity analysis including all eligible cases and controls [Jolley et al. algorithm] (N = 91982 cases, 1598935 controls). For this analysis patients were not matched each propensity score variable, as well as age and sex were added regression models as covariates.

§ Data is from a sensitivity analysis comparing severe sepsis patients with non-severe sepsis controls (N =63511 matched pairs).

‖ Readmission after index admission discharge date to an acute care hospital in Ontario.

¶ Confidence intervals calculated based on 1,000 bootstrap replicates on full sample size, with the exception of the multivariate analysis in which confidence intervals were calculated on a 10% sample.

Table A2: Non-Severe Sepsis versus Matched Controls, Summary of Outcomes from Primary, Subgroup, and Sensitivity Analysis

Outcome	Primary	Age <65 Years	Age 65-84 Years	Age <84 years	CIHI 2009	Multivariate	No Organ Dys.
	OR 95% CI	**OR 95% CI**	**OR 95% CI**	**OR 95% CI**	**OR 95% CI**	**OR 95% CI**	**OR 95% CI**
Hospital Mortality	0.87 (0.84-0.89)	0.81 (0.70-0.93)	0.86 (0.82-0.91)	0.84 (0.80-0.88)	2.12 (1.95-2.31)	0.98 (0.95-1.00)	1.17 (1.13-1.21)
ICU Admission	0.71 (0.69-0.73)	0.85 (0.81-0.89)	0.68 (0.65-0.70)	0.62 (0.59-0.66)	1.17 (1.10-1.25)	0.72 (0.70-0.73)	0.88 (0.86-0.91)
30-day readmission	1.36 (1.33-1.40)	1.34 (1.27-1.42)	1.37 (1.31-1.42)	1.33 (1.27-1.40)	1.39 (1.28-1.50)	1.54 (1.52-1.57)	1.37 (1.34-1.41
	Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**
Hospital LOS	3.77 (3.57-3.87)	3.53 (3.13-3.59)	3.97 (3.67-4.14)	3.80 (3.57-4.12)	4.08 (3.60-4.47)	4.11 (4.02-4.16)	4.38 (4.19-4.49)
ICU LOS	-0.22 (-0.23, -0.18)	-0.18 (-0.2, -0.0)	-0.26 (-0.27, -0.22)	-0.18 (-0.19, -0.13)	0.05 (0.02-0.12)	0.03 (0.02-0.04)	0.08 (0.06-0.09)
Index hospital costs 2018 CAD	1966 (1889-2128)	2082 (1846-2346)	1881 (1757-2140)	2066 (1855-2284)	3124 (2720-3507)	2342 (2272-2429)	3514 (3397-3616)
1-year costs 2018 CAD	9475 (9150-9727)	10680 (9681-11134)	10303 (10154-11031)	8647 (8140-9136)	7870 (6873-8777)	16120 (15933-16319)	11618 (11052-11614)
	HR 95% CI	**HR 95% CI**	**HR 95% CI**	**HR 95% CI**	**HR 95% CI**	**HR 95% CI**	**HR 95% CI**
Mortality Rate							
1-year from index	1.01 (0.99-1.02)	1.10 (1.04-1.15)	1.04 (1.02-1.07)	0.96 (0.94-0.98)	1.35 (1.29-1.41)	1.26 (1.24-1.27)	1.20 (1.18-1.22)
5-year from index	1.18 (1.17-1.20)	1.33 (1.27-1.39)	1.27 (1.25-1.30)	1.10 (1.08-1.12)	1.38 (1.33-1.43)	1.46 (1.44-1.47)	1.35 (1.33-1.36)
Post-discharge 1-year	1.14 (1.12-1.16)	1.29 (1.21-1.37)	1.18 (1.15-1.21)	1.08 (1.05-1.11)	1.12 (1.05-1.18)	1.43 (1.40-1.45)	1.19 (1.17-1.21)
Post-discharge 5-year	1.32 (1.30-1.33)	1.54 (1.47-1.61)	1.41 (1.38-1.44)	1.23 (1.20-1.25)	1.26 (1.21-1.32)	1.63 (1.61-1.65)	1.38 (1.36-1.40)
Readmission							
1-year	1.40 (1.38-1.41)	1.36 (1.33-1.40)	1.41 (1.38-1.44)	1.41 (1.38-1.45)	1.46 (1.44-1.48)	1.57 (1.56-1.59)	1.42 (1.40-1.44)
5-year	1.41 (1.40-1.43)	1.35 (1.32-1.39)	1.45 (1.42-1.47)	1.45 (1.42-1.48)	1.48 (1.46-1.50)	1.64 (1.63-1.65)	1.44 (1.43-1.46)

CI = confident interval; CIHI = Canadian Institute for Health Information; HR = hazard ration; ICU = intensive care unit; LOS = length of stay; OR = odds ratio.

Adjusted for hospital type, and propensity score variables with standardized difference > 0.10. Except for the multivariate analysis, which was adjusted for age, sex and all variables in the propensity score model for the primary analysis.

* For age subgroup analyses, cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of cases.

†Data is from a sensitivity analysis using CIHI's administrative data case definition N = 16464 matched pairs. For hospital survivor cohort N = 13862 matched pairs.

‡ Data is from a sensitivity analysis including all eligible cases and controls [Jolley et al. algorithm] (N = 178673 non-severe sepsis cases, 1598935 non-sepsis controls). For this analysis patients were not matched each propensity score variable, as well as age and sex were added regression models as covariates.

§ Data is from a sensitivity analysis comparing non-severe sepsis patients with controls who had no documented organ dysfunction on index hospital admission (N =63511 matched pairs).

‖ Readmission after index admission discharge date to an acute care hospital in Ontario.

¶ Confidence intervals calculated based on 1,000 bootstrap replicates on full sample size, with the exception of the multivariate analysis in which confidence intervals were calculated on a 10% sample

APPENDIX B. Additional Data for Age Subgroup Analysis

This appendix provides additional information not presented above for the subgroup analysis of three age groups: patients <65 years, between 65-84 years, and over 84 years. All analyses described in the primary analysis were repeated for each age subgroup. For each age group, cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of cases.

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Table B1: Ages <65 Years: Post-Matching Baseline Characteristics of Cases and Controls

	AFTER MATCHING					
	Matched Controls **N= 34,681**	**Non-Severe Sepsis (no organ dysfunction)** **N= 34,681** *Unmatched =24.6%*	**Std. Diff**	**Matched Controls** **N= 14,826**	**Severe Sepsis (including shock)** **N= 14,826** *Unmatched =30.2%*	**Std. Diff.**
Age						
Mean (SD)	50.1 (11.9)	50.1 (11.9)	**0.00**	52.5 (10.6)	52.4 (10.6)	**0.01**
Median (Q1-Q3)	53 (43-60)	53 (43-60)	**0.00**	55 (48-61)	55 (48-60)	**0.01**
Female, n (%)	19351 (55.8)	19351 (55.8)	**0.00**	7003 (47.2)	7003 (47.2)	**0.00**
Rural, n (%)	4484 (12.9)	4983 (14.4)	**0.04**	1827 (12.3)	1470 (9.9)	**0.08**
Income quintile, n (%)						
1 (lowest)	8597 (24.8)	8628 (24.9)	**0.00**	4255 (28.7)	4042 (27.3)	**0.03**
2	7082 (20.4)	7314 (21.1)	**0.02**	3274 (22.1)	3243 (21.9)	**0.01**
3	6626 (19.1)	6721 (19.4)	**0.01**	2799 (18.9)	2743 (18.5)	**0.01**
4	6550 (18.9)	6387 (18.4)	**0.01**	2454 (16.6)	2559 (17.3)	**0.02**
5 (highest)	5597 (16.1)	5382 (15.5)	**0.02**	1908 (12.9)	2153 (14.5)	**0.05**
missing	229 (0.7)	249 (0.7)	**0.01**	136 (0.9)	86 (0.6)	**0.04**
ON Marginalization Index, n (%)						
1 (lowest)	6227 (18.0)	5925 (17.1)	**0.02**	2181 (14.7)	2279 (15.4)	**0.02**
2	7190 (20.7)	7251 (20.9)	**0.00**	2793 (18.8)	2854 (19.2)	**0.01**
3	7656 (22.1)	7771 (22.4)	**0.01**	3238(21.8)	3285 (22.2)	**0.01**
4	6676 (19.3)	6696 (19.3)	**0.00**	3087 (20.8)	2970 (20.0)	**0.02**
5 (highest)	6494 (18.7)	6492 (18.7)	**0.00**	3230 (21.8)	3286 (22.2)	**0.01**
missing	438 (1.3)	546 (1.6)	**0.03**	297 (2.0)	152 (1.0)	**0.08**
Prior cancer, n (%)	3034 (8.8)	4686 (13.5)	**0.15**	1583 (10.7)	2064 (13.9)	**0.10**
Prior CHF, n (%)	2381 (6.9)	2364 (6.8)	**0.00**	1740 (11.7)	2033 (13.7)	**0.06**
Prior CKD, n (%)	776 (2.2)	441 (1.3)	**0.07**	601 (4.1)	1150 (7.8)	**0.16**
Prior COPD, n (%)	6994 (20.2)	8568 (24.7)	**0.11**	4733 (31.9)	3970 (26.8)	**0.11**
Prior diabetes, n (%)	8527 (24.6)	9065 (26.1)	**0.04**	4994 (33.7)	5052 (34.1)	**0.01**
Residence in LTC, n (%)	295 (0.9)	628 (1.8)	**0.08**	222 (1.5)	243 (1.6)	**0.01**
ADG score, mean (SD)	20.1 (15.2)	20.5 (13.5)	**0.03**	26.6 (13.8)	29.8 (13.4)	**0.24**
Healthcare use, past year						
Hospitalization, n (%)	3184 (9.2)	4428 (12.8)	**0.11**	1580 (10.7)	1914 (12.9)	**0.07**
Receiving homecare, n (%)	4972 (14.3)	6970 (20.1)	**0.15**	3297 (22.2)	3191 (21.5)	**0.02**

	AFTER MATCHING					
	Matched Controls **N= 34,681**	**Non-Severe Sepsis (no organ dysfunction)** **N= 34,681** *Unmatched =24.6%*	**Std. Diff**	**Matched Controls** **N= 14,826**	**Severe Sepsis (including shock)** **N= 14,826** *Unmatched =30.2%*	**Std. Diff.**
ED visits						
Mean (SD)	1.5 (3.8)	1.5 (2.8)	**0.01**	1.8 (4.7)	1.2 (2.2)	**0.18**
Median (Q1-Q3)	1 (0-2)	1 (0-2)	**0.08**	1 (0-2)	0 (0-2)	**0.21**
Physician visits						
Mean (SD)	16.3 (17.5)	19.1 (21.2)	**0.15**	19.1 (19.5)	20.3 (23.5)	**0.06**
Median (Q1-Q3)	11 (5-21)	13 (6-24)	**0.13**	13 (6-25)	13 (6-26)	**0.03**
Index Admission						
Urgent admission, n (%)	32640 (94.1)	32640 (94.1)	**0.00**	14079 (95.0)	14079 (95.0)	**0.00**
Index Admission Date, n (%)						
Apr 2012 – Mar 2013	11179 (32.2)	11170 (32.2)	**0.00**	4632 (31.2)	4631 (31.2)	**0.00**
Apr 2013 – Mar 2014	8216 (23.7)	8216 (23.7)	**0.00**	3434 (23.2)	3446 (23.2)	**0.00**
Apr 2014 – Mar 2015	7702 (22.2)	7715 (22.2)	**0.00**	3341 (22.5)	3323 (22.4)	**0.00**
Apr 2015 – Mar 2016	7584 (21.9)	7580 (21.9)	**0.00**	3419 (23.1)	3426 (23.1)	**0.00**
Hospital Type*, n (%)						
Teaching	11566 (33.3)	10429 (30.1)	**0.07**	5018 (33.8)	5362 (36.2)	**0.05**
Community ≥ 100 beds	17738 (51.2)	16827 (48.5)	**0.05**	7589 (51.2)	7986 (53.9)	**0.05**
Community < 100 beds	5376 (15.5)	7422 (21.4)	**0.15**	2218 (15.0)	1478 (10.0)	**0.15**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = Congestive heart failure; CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; ON= Ontario; SD = standard deviation; Std Diff = standardized difference.
*Variable not used for hard matching and was not included in propensity score model.

Table B2: Ages 65-84 Years: Post-Matching Baseline Characteristics of Cases and Controls

	AFTER MATCHING					
	Matched Controls	**Non-Severe Sepsis (no organ dysfunction)**	**Std. Diff**	**Matched Controls**	**Severe Sepsis (including shock)**	**Std. Diff.**
	N= 61,070	**N= 61,070** *Unmatched =26.6%*		**N= 31,414**	**N= 31,414** *Unmatched =31.1%*	
Age						
Mean (SD)	75.8 (5.7)	75.8 (5.7)	**0.01**	75.7 (5.7)	75.8 (5.7)	**0.01**
Median (Q1-Q3)	76 (71-81)	77 (71-81)	**0.01**	76 (71-81)	76 (71-81)	**0.01**
Female, n (%)	33396 (54.7)	33396 (54.7)	**0.00**	15214 (48.4)	15214 (48.4)	**0.00**
Rural, n (%)	8602 (14.1)	9747 (16.0)	**0.05**	4159 (13.2)	2948 (9.4)	**0.12**
Income quintile, n (%)						
1 (lowest)	13222 (21.7)	13216 (21.6)	**0.00**	7385 (23.5)	6888 (21.9)	**0.04**
2	12939 (21.2)	12697 (20.8)	**0.01**	6674 (21.3)	6845 (21.8)	**0.01**
3	12054 (19.7)	11979 (19.6)	**0.00**	6274 (20.0)	6230 (19.8)	**0.00**
4	11792 (19.3)	11943 (19.6)	**0.01**	5811 (18.5)	6030 (19.2)	**0.02**
5 (highest)	10817 (17.7)	10916 (17.9)	**0.00**	5097 (16.2)	5290 (16.8)	**0.02**
missing	246 (0.4)	319 (0.5)	**0.02**	173 (0.5)	131 (0.4)	**0.02**
ON Marginalization Index, n (%)						
1 (lowest)	8527 (14.0)	8856 (14.5)	**0.02**	4153 (13.2)	4248 (13.5)	**0.01**
2	11269 (18.4)	11272 (18.5)	**0.00**	5582 (17.8)	5781 (18.4)	**0.02**
3	13465 (22.1)	13543 (22.2)	**0.00**	6791 (21.6)	6708 (21.3)	**0.01**
4	12302 (20.1)	12212 (20.0)	**0.00**	6488 (20.7)	6338 (20.2)	**0.01**
5 (highest)	15051 (24.6)	14633 (24.0)	**0.02**	8134 (25.9)	8125 (25.9)	**0.00**
missing	456 (0.8)	554 (0.9)	**0.02**	266 (0.8)	214 (0.7)	**0.02**
Prior cancer, n (%)	9184 (15.0)	10862 (17.8)	**0.07**	4943 (15.7)	5552 (17.7)	**0.05**
Prior CHF, n (%)	13553 (22.2)	14287 (23.4)	**0.03**	8689 (27.7)	10106 (32.2)	**0.10**
Prior CKD, n (%)	1314 (2.2)	680 (1.1)	**0.08**	852 (2.7)	1459 (4.6)	**0.05**
Prior COPD, n (%)	21052 (34.5)	25666 (42.0)	**0.16**	13352 (42.5)	12586 (40.1)	**0.05**
Prior diabetes, n (%)	24861 (40.7)	25198 (41.3)	**0.01**	14311 (45.6)	15170 (48.3)	
Residence in LTC, n (%)	2914 (4.8)	4372 (7.2)	**0.10**	1873 (6.0)	1957 (6.2)	**0.01**
ADG score, mean (SD)	28.8 (12.7)	27.9 (12.2)	**0.07**	31.7 (12.4)	34.2 (12.4)	**0.20**
Healthcare use, past year						
Hospitalization, n (%)	5157 (8.4)	7933 (13.0)	**0.15**	2834 (9.0)	3780 (12.0)	**0.10**
Receiving homecare, n (%)	17442 (28.6)	21377 (35.0)	**0.14**	11227 (35.7)	10692 (34.0)	**0.04**

	AFTER MATCHING					
	Matched Controls **N= 61,070**	**Non-Severe Sepsis (no organ dysfunction)** **N= 61,070** *Unmatched =26.6%*	**Std. Diff**	**Matched Controls** **N= 31,414**	**Severe Sepsis (including shock)** **N= 31,414** *Unmatched =31.1%*	**Std. Diff.**
ED visits						
Mean (SD)	1.0 (2.0)	1.1 (1.9)	**0.03**	1.1 (2.0)	0.9 (1.5)	**0.12**
Median (Q1-Q3)	0 (0-1)	0 (0-2)	**0.06**	1 (0-2)	0 (0-1)	**0.11**
Physician visits						
Mean (SD)	18.8 (15.9)	20.6 (18.0)	**0.11**	20.0 (16.7)	21.0 (19.4)	**0.06**
Median (Q1-Q3)	15 (8-24)	16 (9-26)	**0.10**	16 (9-25)	16 (9-27)	**0.02**
Index Admission						
Urgent admission, n (%)	58209 (95.3)	58209 (95.3)	**0.00**	29768 (94.8)	29768 (94.8)	**0.00**
Index Admission Date, n (%)						
Apr 2012 – Mar 2013	19772 (32.4)	19848 (32.5)	**0.00**	9420 (30.0)	9453 (30.1)	**0.00**
Apr 2013 – Mar 2014	14398 (23.6)	14326 (23.5)	**0.00**	7155 (22.8)	7106 (22.6)	**0.00**
Apr 2014 – Mar 2015	14150 (23.2)	14211 (23.3)	**0.00**	7478 (23.8)	7539 (24.0)	**0.00**
Apr 2015 – Mar 2016	12750 (20.9)	12685 (20.8)	**0.00**	7361 (23.4)	7316 (23.3)	**0.00**
Hospital Type*, n (%)						
Teaching	17580 (28.8)	15463 (25.3)	**0.08**	9026 (28.7)	8920 (28.4)	**0.01**
Community ≥ 100 beds	31999 (52.4)	30400 (49.8)	**0.05**	16489 (52.5)	18517 (58.9)	**0.13**
Community < 100 beds	11488 (18.8)	15204 (24.9)	**0.15**	5899 (18.8)	3977 (12.7)	**0.17**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = Congestive heart failure; CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; ON= Ontario; SD = standard deviation; Std Diff = standardized difference.
*Variable not used for hard matching and was not included in propensity score model.

Table B3: Ages ≥ 85 Years: Post-Matching Baseline Characteristics of Cases and Controls

	AFTER MATCHING					
	Matched Controls	**Non-Severe Sepsis (no organ dysfunction)**	**Std. Diff**	**Matched Controls**	**Severe Sepsis (including shock)**	**Std. Diff.**
	N= 36,967	**N= 36,967** *Unmatched =25.4%*		**N= 17,964**	**N= 17,964** *Unmatched =28.6%*	
Age						
Mean (SD)	89.5 (3.7)	89.6 (3.6)	**0.03**	89.5 (3.7)	89.5 (3.6)	**0.03**
Median (IQR)	89 (87-92)	89 (87-92)	**0.03**	89 (87-92)	89 (87-92)	**0.03**
Female, n (%)	24908 (67.4)	24908 (67.4)	**0.00**	10874 (60.5)	10874 (60.5)	**0.00**
Rural, n (%)	4326 (11.7)	4981 (13.5)	**0.05**	1972 (11.0)	1226 (6.8)	**0.15**
Income quintile, n (%)						
1 (lowest)	7816 (21.1)	7591 (20.5)	**0.01**	3911 (21.8)	3703 (20.6)	**0.03**
2	7746 (21.0)	7407 (20.0)	**0.02**	3799 (21.1)	3667 (20.4)	**0.02**
3	7314 (19.8)	7500 (20.3)	**0.01**	3519 (19.6)	3567 (19.9)	**0.01**
4	7081 (19.2)	7299 (19.7)	**0.01**	3448 (19.2)	3566 (19.8)	**0.02**
5 (highest)	6827 (18.5)	6955 (18.8)	**0.01**	3181 (17.7)	3379 (18.8)	**0.03**
missing	183 (0.5)	215 (0.6)	**0.01**	106 (0.6)	82 (0.5)	**0.02**
ON Marginalization Index, n (%)						
1 (lowest)	3583 (9.7)	3931 (10.6)	**0.03**	1738 (9.7)	1725 (9.6)	**0.00**
2	5617 (15.2)	5778 (15.6)	**0.01**	2572 (14.3)	2688 (15.0)	**0.02**
3	7538 (20.4)	7528 (20.4)	**0.00**	3662 (20.4)	3583 (19.9)	**0.01**
4	7907 (21.4)	7936 (21.5)	**0.00**	3793 (21.1)	3781 (21.1)	**0.00**
5 (highest)	12053 (32.6)	11508 (31.1)	**0.03**	6043 (33.6)	6071 (33.8)	**0.00**
missing	269 (0.7)	286 (0.8)	**0.01**	156 (0.9)	116 (0.6)	**0.03**
Prior cancer, n (%)	3963 (10.7)	3754 (10.2)	**0.02**	1906 (10.6)	1801 (10.0)	**0.02**
Prior CHF, n (%)	12296 (33.3)	13074 (35.4)	**0.04**	6746 (37.5)	7571 (42.1)	**0.09**
Prior CKD, n (%)	233 (0.6)	156 (0.4)	**0.03**	193 (1.1)	243 (1.3)	**0.03**
Prior COPD, n (%)	11898 (32.2)	13675 (37.0)	**0.10**	6728 (37.4)	6312 (35.1)	**0.05**
Prior diabetes, n (%)	11727 (31.7)	11891 (32.2)	**0.01**	6337 (35.3)	6629 (36.9)	**0.03**
Residence in LTC, n (%)	5045 (13.7)	6185 (16.7)	**0.09**	2926 (16.3)	2845 (15.8)	**0.01**
ADG score, mean (SD)	31.2 (12.7)	29.9 (12.5)	**0.10**	33.5 (12.3)	35.4 (12.5)	**0.15**
Healthcare use, past year						
Hospitalization, n (%)	2165 (5.9)	3475 (9.4)	**0.13**	970 (5.4)	1468 (8.2)	**0.11**
Receiving homecare, n (%)	17181 (46.5)	19176 (51.9)	**0.11**	9506 (52.9)	9171 (51.0)	**0.04**

	AFTER MATCHING					
	Matched Controls **N= 36,967**	**Non-Severe Sepsis (no organ dysfunction)** **N= 36,967** *Unmatched =25.4%*	**Std. Diff**	**Matched Controls** **N= 17,964**	**Severe Sepsis (including shock)** **N= 17,964** *Unmatched =28.6%*	**Std. Diff.**
ED visits						
Mean (SD)	0.9 (1.5)	1.0 (1.5)	**0.03**	1.0 (1.7)	0.9 (1.4)	**0.06**
Median (IQR)	0 (0-1)	0 (0-1)	**0.03**	0 (0-1)	0 (0-1)	**0.06**
Physician visits						
Mean (SD)	16.4 (13.6)	17.3 (14.6)	**0.06**	17.1 (13.0)	17.8 (15.8)	**0.05**
Median (IQR)	14 (8-21)	14 (8-22)	**0.05**	14 (8-21)	14 (8-22)	**0.02**
Index Admission						
Urgent admission, n (%)	36436 (98.6)	36436 (98.6)	**0.00**	17754 (98.8)	17754 (98.8)	**0.00**
Index Admission Date, n (%)						
Apr 2012 – Mar 2013	11498 (31.1)	11561 (31.3)	**0.00**	4889 (27.2)	4895 (27.2)	**0.00**
Apr 2013 – Mar 2014	9077 (24.6)	9004 (24.4)	**0.00**	4268 (23.8)	4267 (23.8)	**0.00**
Apr 2014 – Mar 2015	8871 (24.0)	8939 (24.2)	**0.00**	4528 (25.2)	4569 (25.4)	**0.00**
Apr 2015 – Mar 2016	7521 (20.3)	7463 (20.2)	**0.00**	4279 (23.8)	4233 (23.6)	**0.00**
Hospital Type*, n (%)						
Teaching	9625 (26.0)	8566 (23.2)	**0.07**	4741 (26.4)	4728 (26.3)	**0.00**
Community ≥ 100 beds	20125 (54.4)	19431 (52.6)	**0.04**	9860 (54.9)	10975 (61.1)	**0.13**
Community < 100 beds	7217 (19.5)	8970 (24.3)	**0.11**	3363 (18.7)	2261 (12.6)	**0.17**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = Congestive heart failure; CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; ON= Ontario; SD = standard deviation; Std Diff = standardized difference.
*Variable not used for hard matching and was not included in propensity score model.

Table B4: Length of Stay and Hospital Costs on Index Admission by Age Group and Sepsis Status

	Age Group	Non-Severe (no organ dysfunction)	Matched Controls	Severe Sepsis (including shock)	Matched Controls
Total Hospital LOS					
Mean (SD)	<65	7.83 (16.07)	4.74 (10.73)	22.47 (39.72)	5.77 (14.15)
	65-84	11.48 (24.30)	7.57 (17.20)	21.26 (36.97)	8.18 (15.82)
	≥85	13.56 (23.33)	9.52 (17.21)	18.74 (31.18)	9.67 (16.67)
Median (Q1-Q3)	<65	4 (2-8)	3 (1-5)	11 (5-25)	3 (2-6)
	65-84	6 (3-11)	4 (2-8)	11 (5-23)	4 (2-9)
	≥85	7 (4-15)	5 (3-10)	10 (5-21)	6 (3-11)
ICU LOS					
Mean (SD)	<65	0.63 (2.30)	0.81 (6.61)	9.44 (20.94)	1.03 (3.70)
	65-84	0.54 (1.99)	0.81 (2.88)	5.78 (16.53)	0.92 (3.40)
	≥85	0.32 (1.48)	0.48 (2.07)	2.02 (9.29)	0.51 (2.06)
Median (Q1-Q3)	<65	0 (0-0)	0 (0-0)	4 (0-11)	0 (0-0)
	65-84	0 (0-0)	0 (0-0)	0 (0-6)	0 (0-0)
	≥85	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Hospital Costs					
Mean (SD)	<65	12233 (16989)	10153 (15034)	52455 (85291)	11819 (19777)
	65-84	14397 (18194)	12548 (16296)	39065 (67535)	13306 (17010)
	≥85	14949 (16760)	12829 (14313)	24040 (36905)	13040 (13496)
Median (Q1-Q3)	<65	7565 (6809)	6652 (5769)	24535 (49036)	7241 (6880)
	65-84	9162 (8963)	8351 (8429)	18797 (40351)	8729 (8949)
	≥85	10162 (10104)	9085 (9685)	15099 (14687)	9209 (9637)

ICU = intensive care unit; Q =quartile; LOS = length of stay; SD = standard deviation
Note: cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of cases.

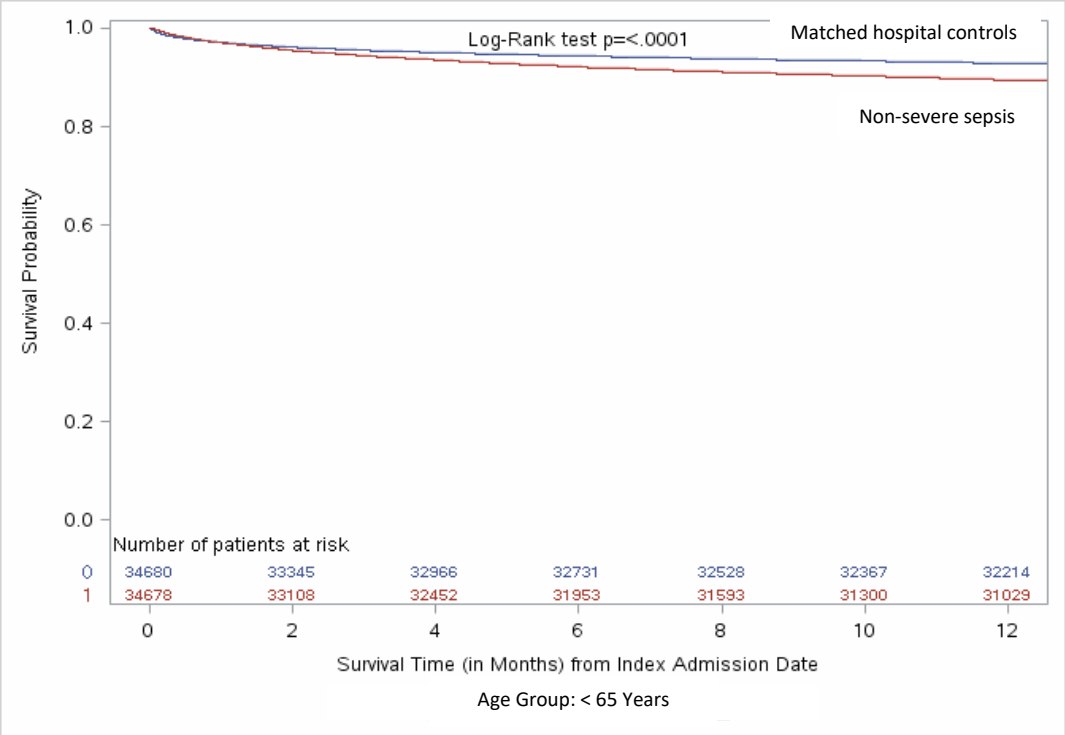
Table B5: Crude Annual Health Care Costs by Age Group and Sepsis Status (C$2018)

	Year	Non-Severe (no organ dysfunction)	Matched Controls	Severe Sepsis (including shock)	Matched Controls
<65 Years					
Mean (SD)	Year 0*	12538 (28415)	8024 (19907)	14097 (33442)	10878 (22815)
	Year 1	35421 (46783)	24521 (33697)	82180 (99754)	30259 (38975)
	Year 2	17296 (38345)	9808 (24214)	27801 (56303)	13205 (29142)
	Year 3	16433 (36386)	9238 (24321)	25769 (52074)	13164 (28454)
	Year 4	16606 (37474)	9246 (23456)	25363 (50137)	13110 (28315)
	Year 5	17100 (38786)	9927 (24841)	25912 (49673)	13185 (30426)
Median (Q1-Q3)	Year 0*	3076 (9527)	2069 (5702)	3665 (11276)	3187 (8847)
	Year 1	17779 (31612)	13119 (18054)	47774 (83171)	16506 (25491)
	Year 2	4050 (14022)	2325 (7086)	6653 (24249)	3566 (10389)
	Year 3	3599 (12766)	2188 (6445)	5926 (21989)	3432 (10539)
	Year 4	3461 (12563)	2209 (6615)	5549 (21466)	3432 (10695)
	Year 5	3681 (13130)	2349 (6990)	6001 (23579)	3680 (10515)
65-84 Years					
Mean (SD)	Year 0*	15813 (26140)	11740 (21366)	15851 (28294)	13512 (22796)
	Year 1	44481 (44991)	33473 (35775)	68473 (78226)	36390 (38221)
	Year 2	25864 (35592)	16740 (27764)	31664 (48454)	19144 (29569)
	Year 3	25681 (35210)	16261 (27756)	30234 (43648)	18596 (29722)
	Year 4	25244 (34950)	16335 (26857)	28795 (39578)	18644 (29519)
	Year 5	25296 (35756)	16776 (26535)	28924 (41165)	18989 (29352)
Median (Q1-Q3)	Year 0*	6203 (13193)	4684 (8272)	6350 (12605)	5517 (10034)
	Year 1	29158 (44517)	20899 (29947)	44874 (63244)	22966 (33977)
	Year 2	11276 (33117)	6066 (15134)	13609 (39019)	7334 (19392)
	Year 3	10910 (33673)	5816 (14545)	12672 (39779)	7015 (18114)
	Year 4	10731 (32870)	5800 (14733)	12858 (37259)	6968 (18548)
	Year 5	10684 (34306)	6076 (15974)	12133 (39324)	7084 (19582)
≥85 Years					
Mean (SD)	Year 0*	17491 (23096)	13910 (20238)	17401 (24432)	15401 (21295)
	Year 1	45800 (39201)	36896 (33516)	51112 (51579)	37811 (34023)
	Year 2	31613 (31124)	23520 (27617)	35448 (39539)	25766 (28779)
	Year 3	31800 (30742)	23677 (26993)	33205 (33301)	25692 (27533)
	Year 4	31681 (31458)	24321 (28152)	32986 (34624)	25619 (27109)
	Year 5	31231 (29499)	25947 (29186)	32405 (32940)	25834 (27261)
Median (Q1-Q3)	Year 0*	7203 (18953)	5477 (11882)	7157 (17440)	6345 (14454)
	Year 1	35302 (46968)	26364 (38444)	37149 (50690)	27191 (39750)
	Year 2	23155 (43375)	12124 (34356)	26602 (44081)	14867 (38570)
	Year 3	24238 (43440)	12629 (36138)	25650 (43862)	15340 (40589)
	Year 4	24380 (43963)	13190 (37538)	24790 (43712)	15565 (40271)
	Year 5	24408 (43520)	14997 (40576)	24161 (44063)	15803 (39751)

*12-month period covering 13 months-1-month period prior to index admission date.
Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
Note: cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of cases.

Figure B1: Kaplan Meier Plots: 1-Year Survival <65 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, <65 Years



b) Severe sepsis versus Matched Hospital Controls, <65 Years

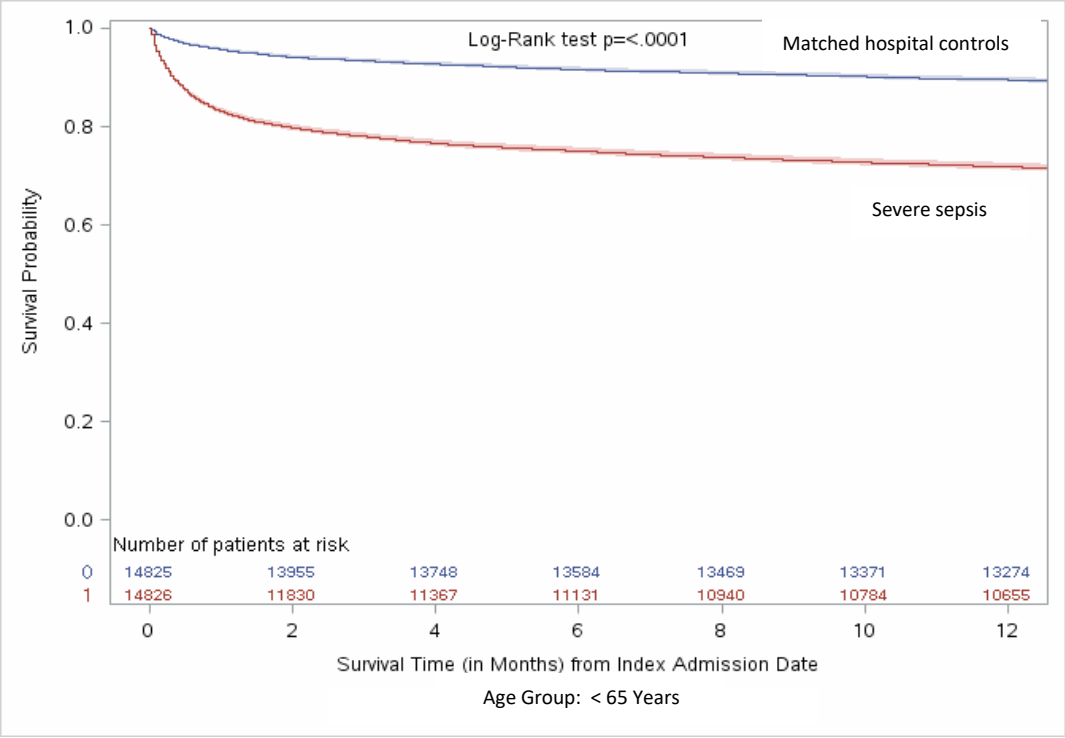
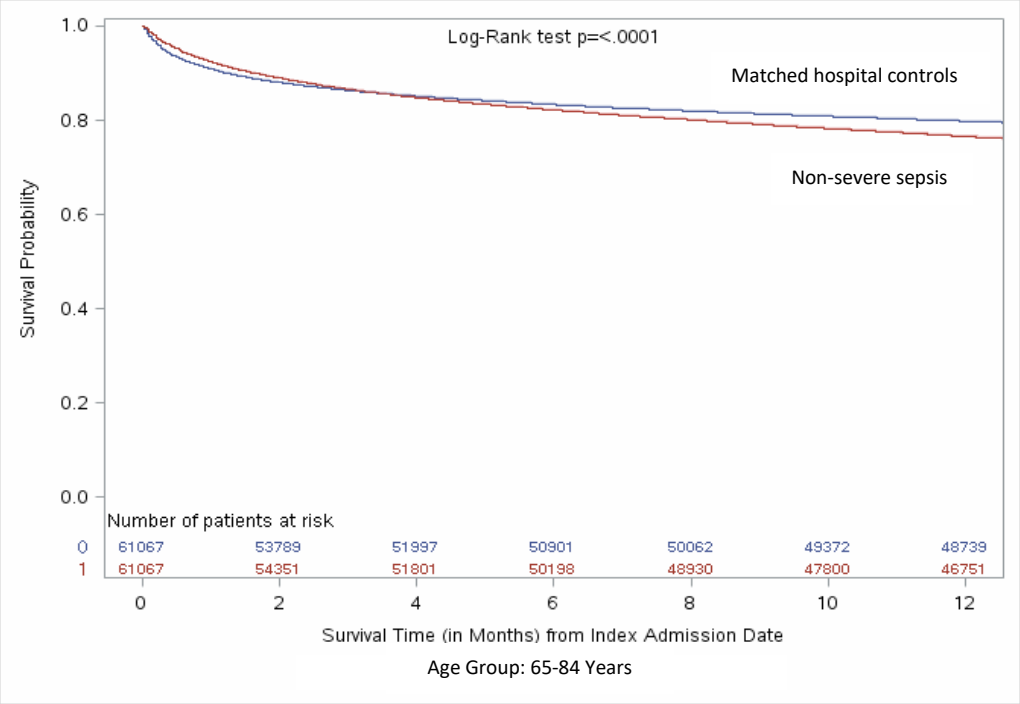


Figure B2: Kaplan Meier Plots: 1-Year Survival 65-84 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, 65-84 Years



b) Severe sepsis versus Matched Hospital Controls, 65-84 Years

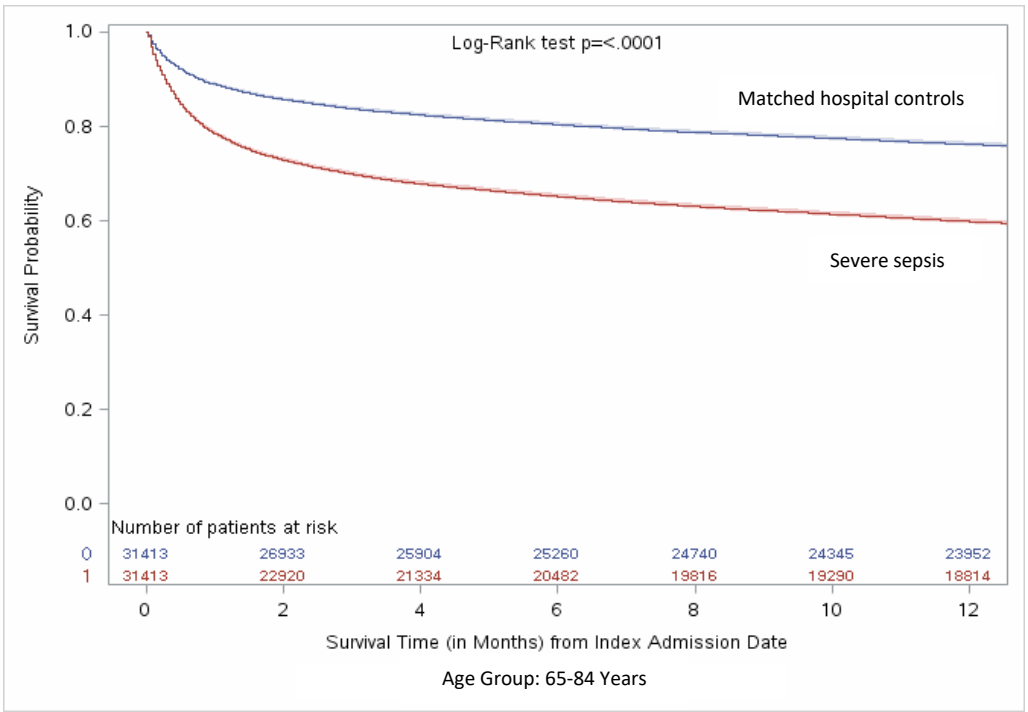
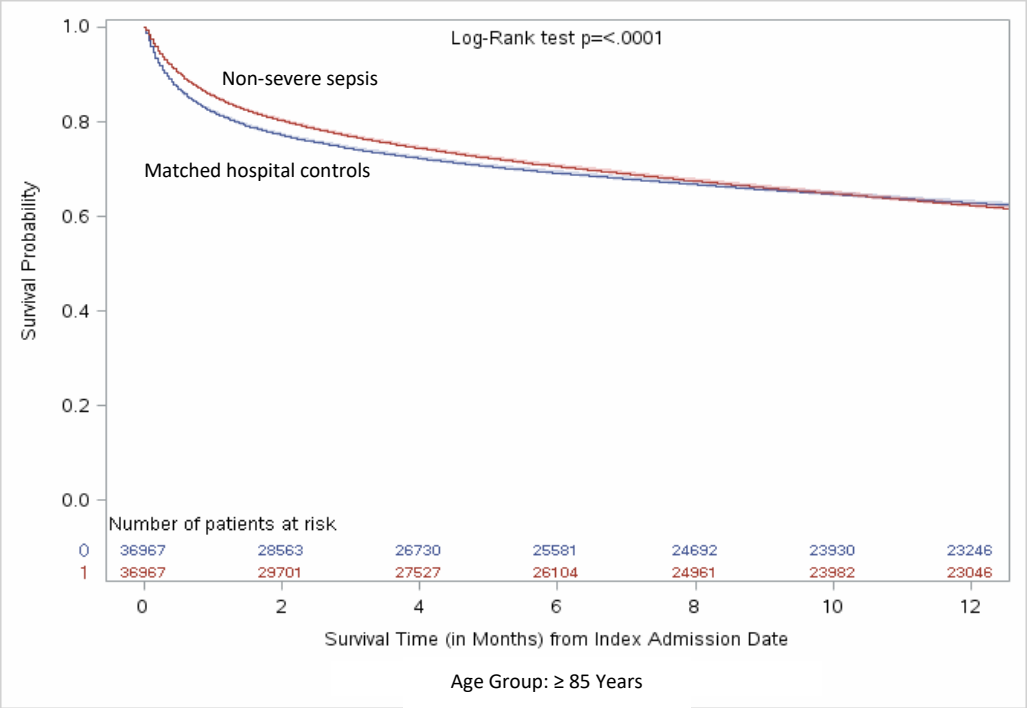


Figure B3: Kaplan Meier Plots: 1-Year Survival, ≥ 85 Years

a) Non-Severe versus Matched Hospital Controls, ≥85 Years



b) Severe Sepsis versus Matched Hospital Controls, ≥85 Years

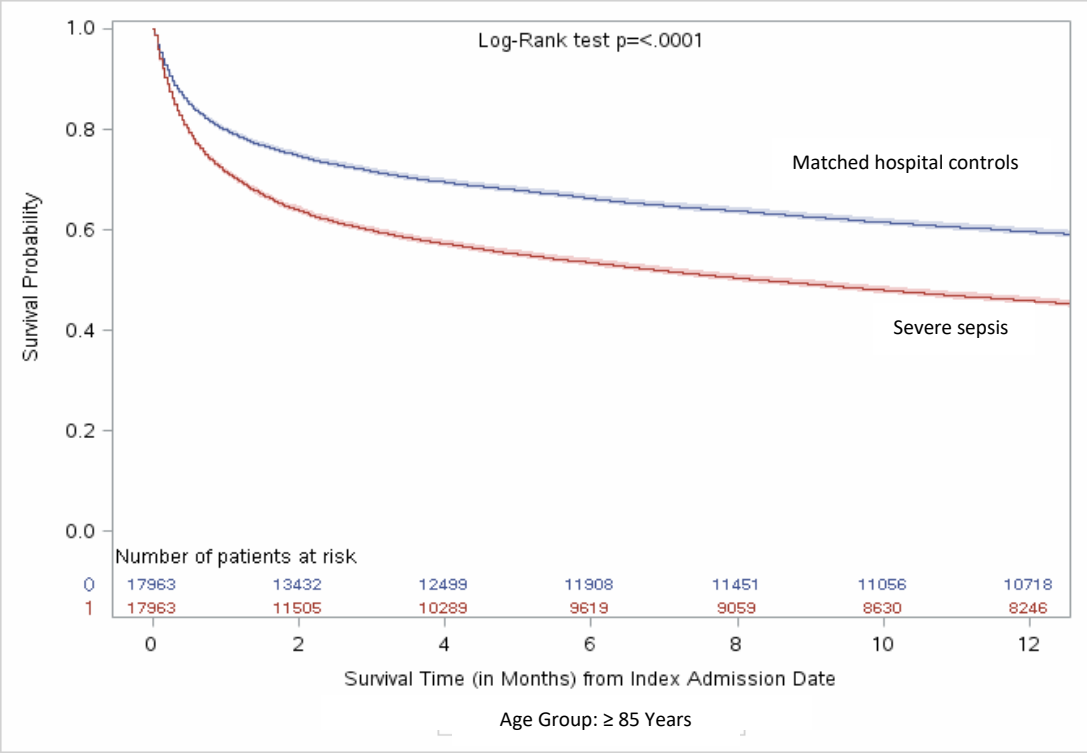
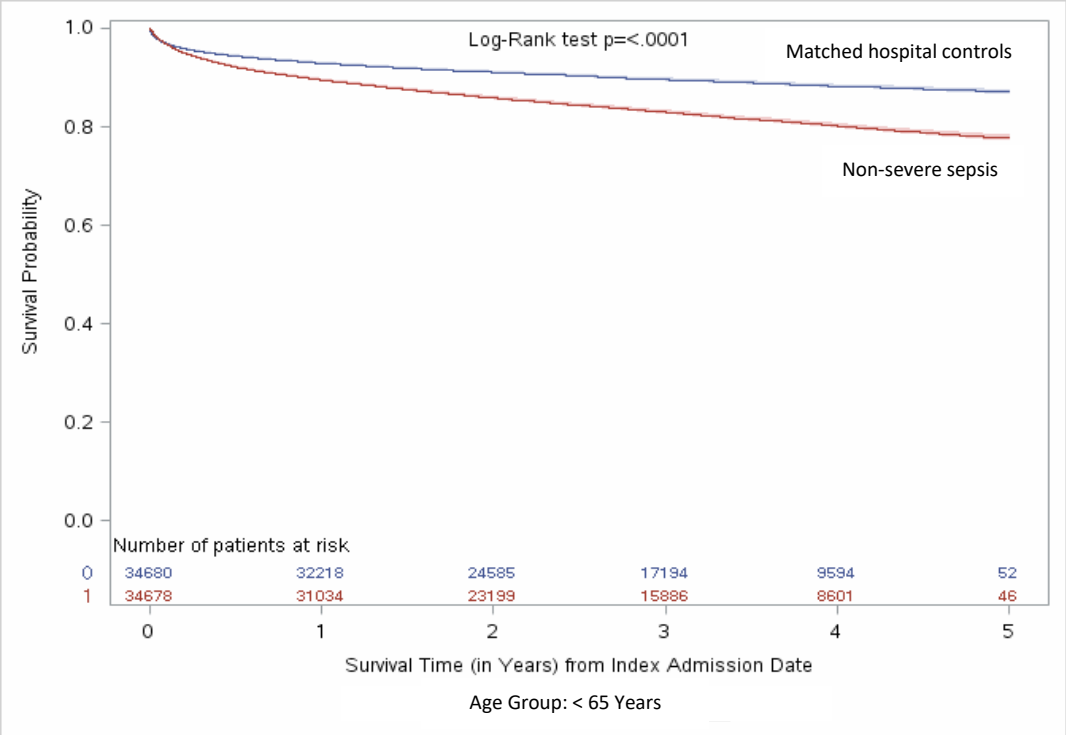


Figure B4: Kaplan Meier Plots: Survival, 5-Year Time Horizon, <65 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, <65 Years



b) Severe Sepsis versus Matched Hospital Controls, <65 Years

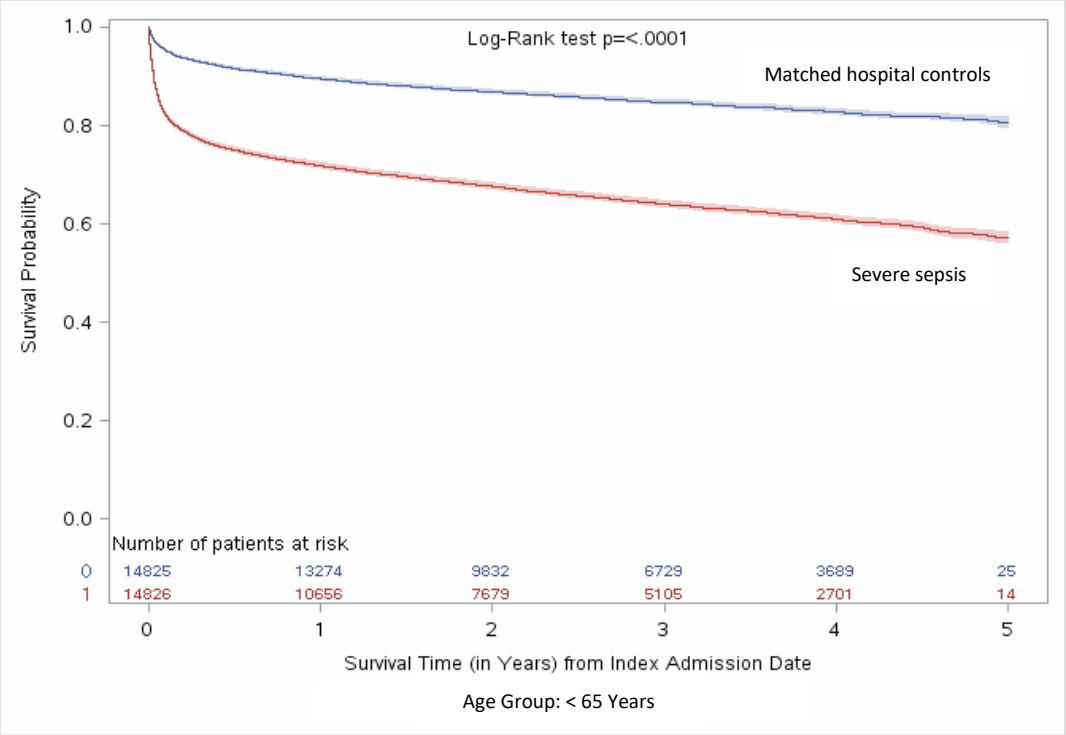
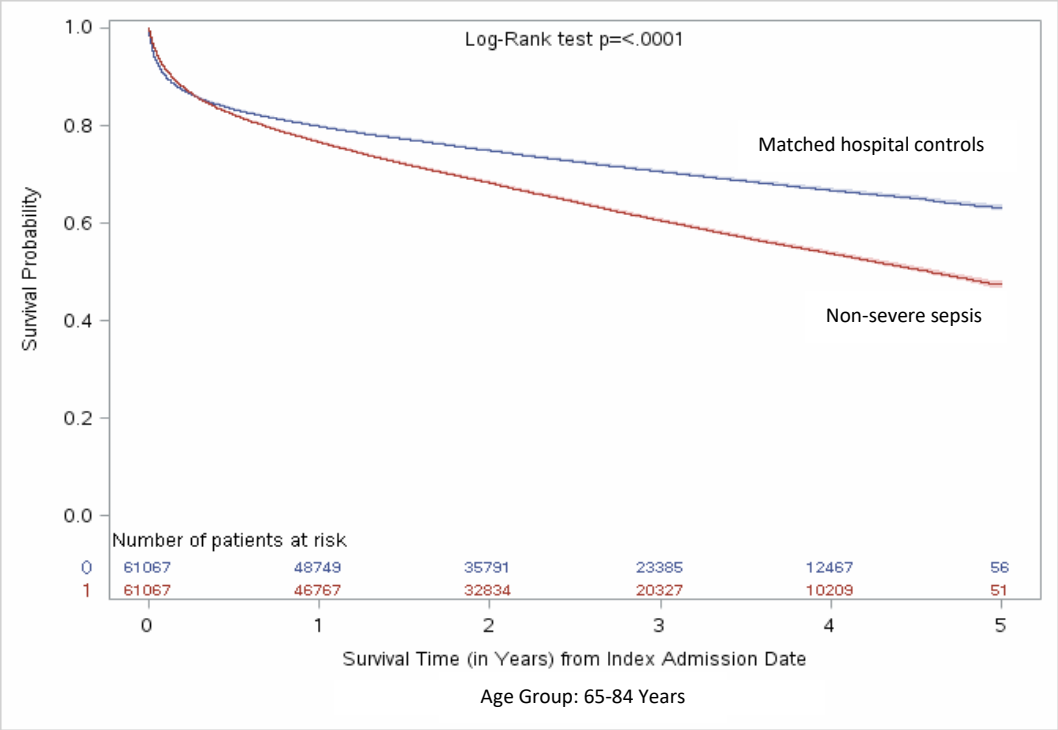


Figure B5: Kaplan Meier Plots: Survival, 5-Year Time Horizon, 65-84 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, 65-84 Years



b) Severe Sepsis versus Matched Hospital Controls, 65-84 Years

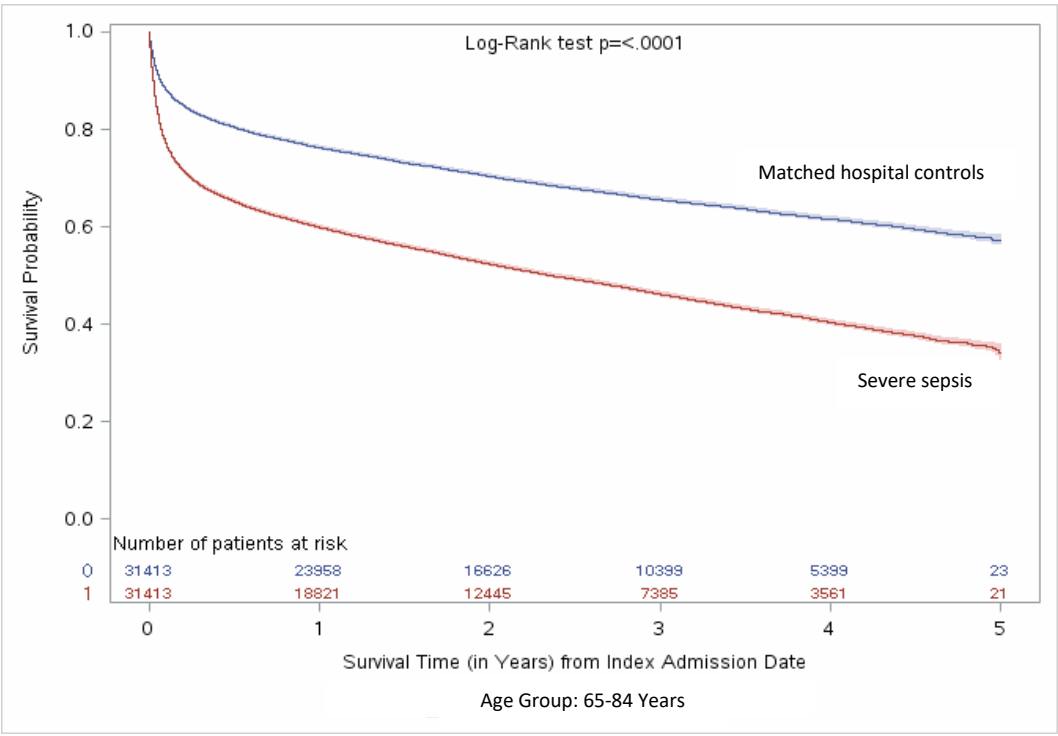
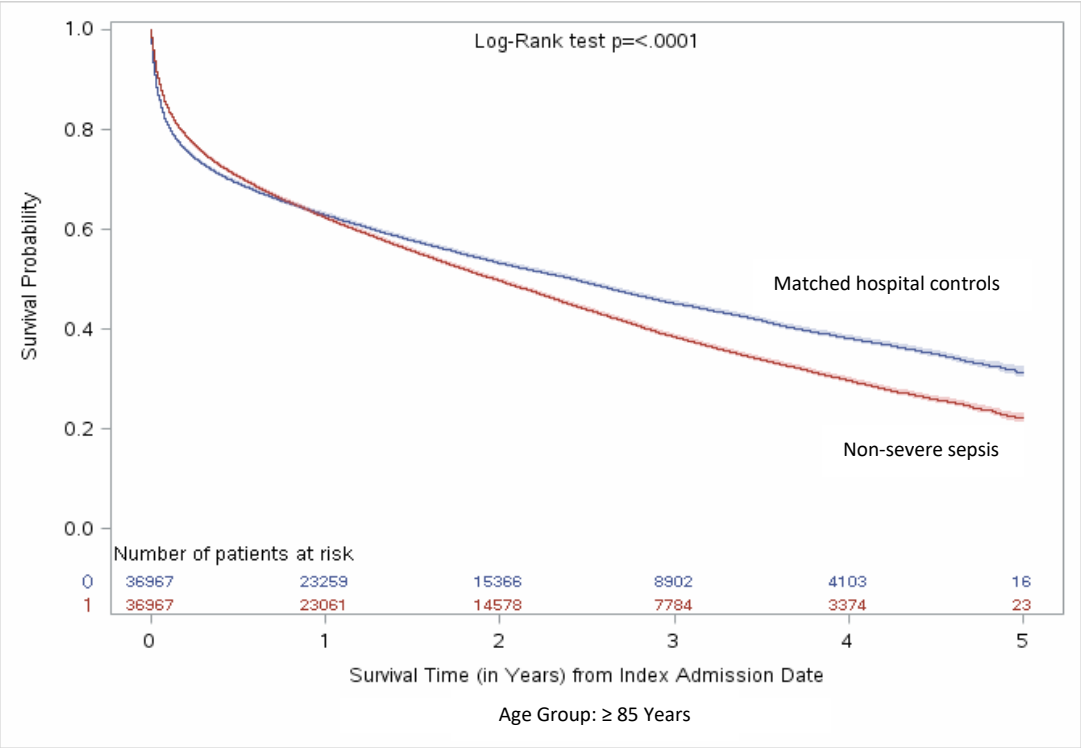


Figure B6: Kaplan Meier Plots: Survival, 5-Year Time Horizon, ≥85 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, ≥ 85 Years



b) Severe Sepsis versus Matched Hospital Controls, ≥ 85 Years

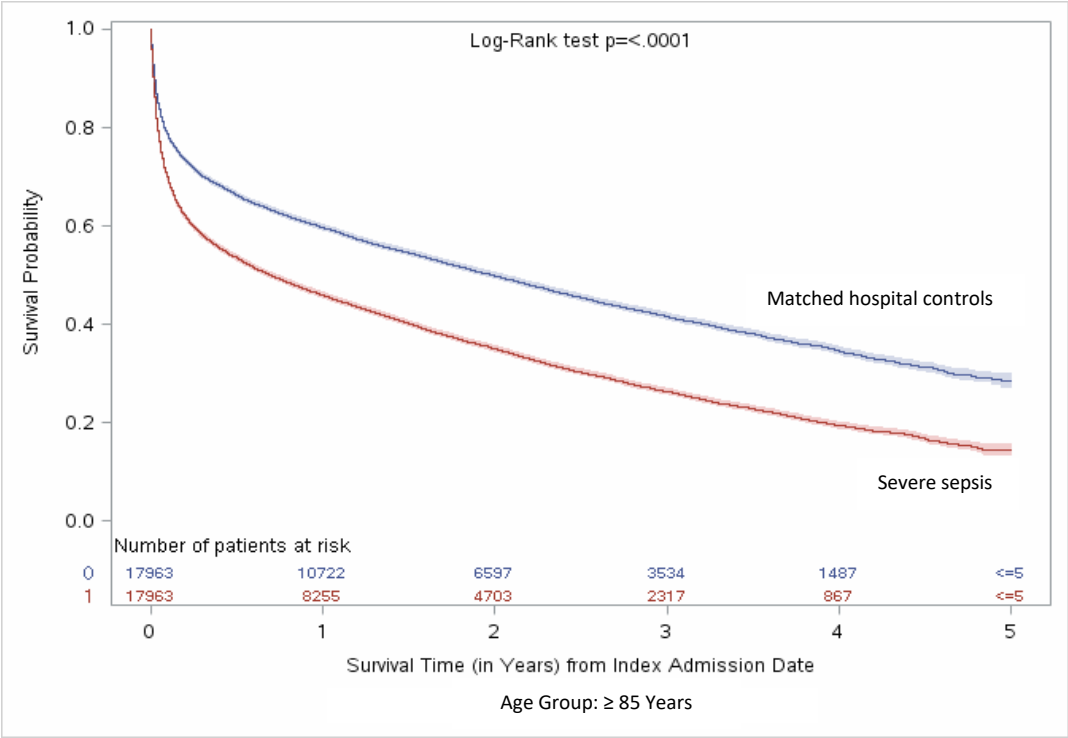
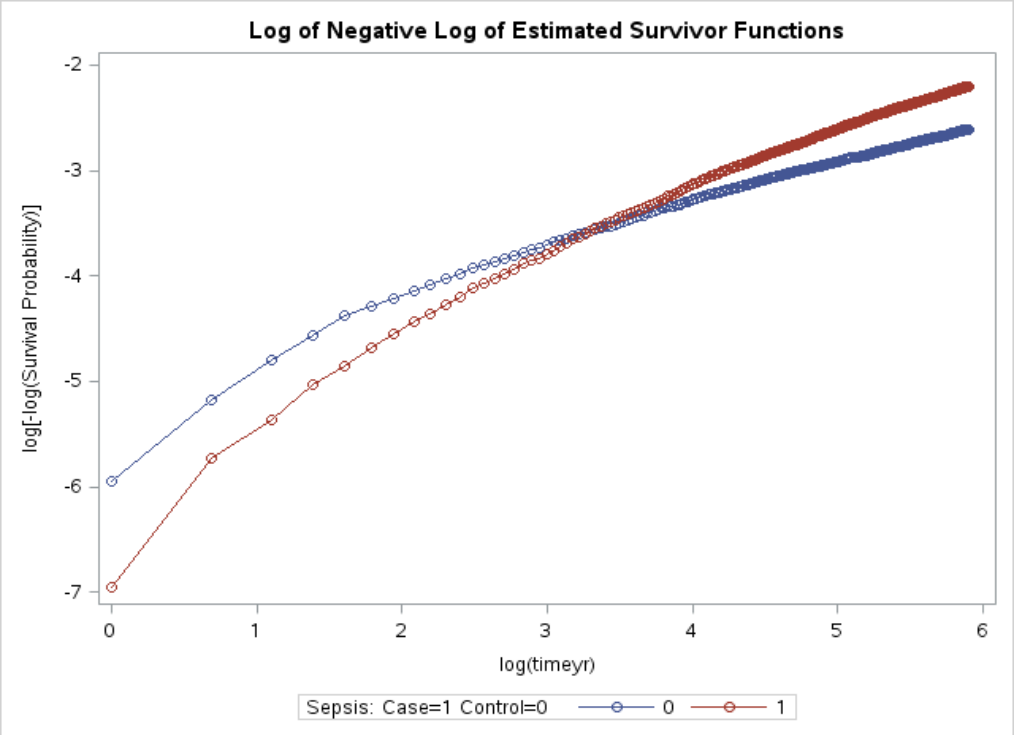


Figure B7: Testing for Proportional Hazards Assumption, log(-log(Survival)), 1-Year Survival Age Group: <65 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, <65 Years



b) Severe Sepsis versus Matched Hospital Controls, <65 Years

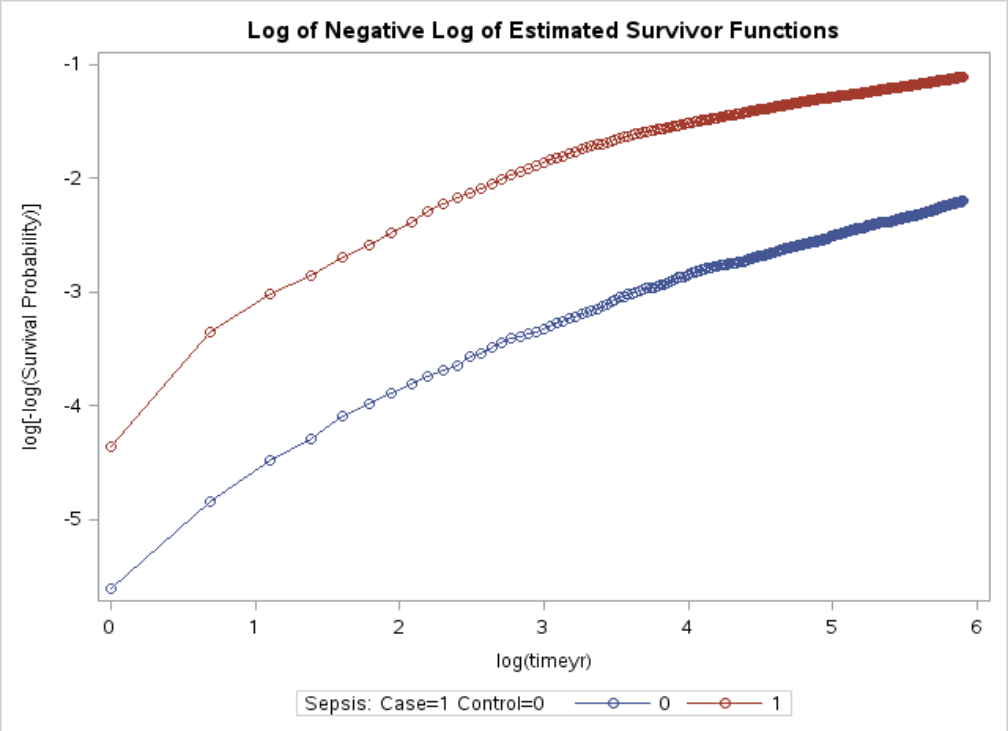
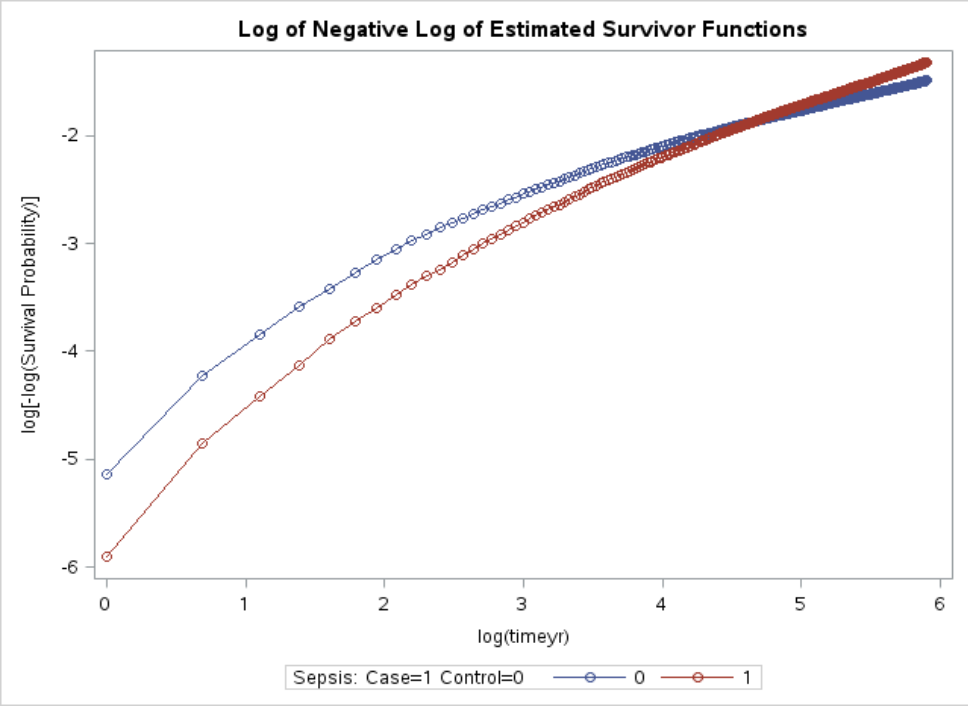


Figure B8: Testing for Proportional Hazards Assumption, log(-log(Survival)), 1-Year Survival, Age Group: 65-84 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, 65-84 Years



b) Severe Sepsis versus Matched Hospital Controls, 65-84 Years

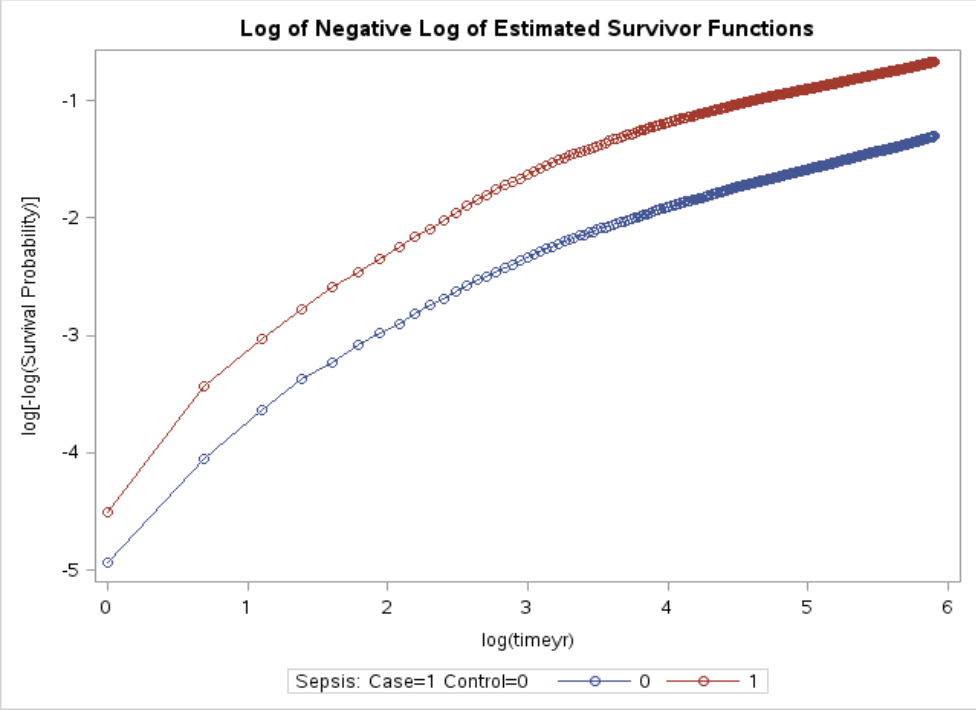
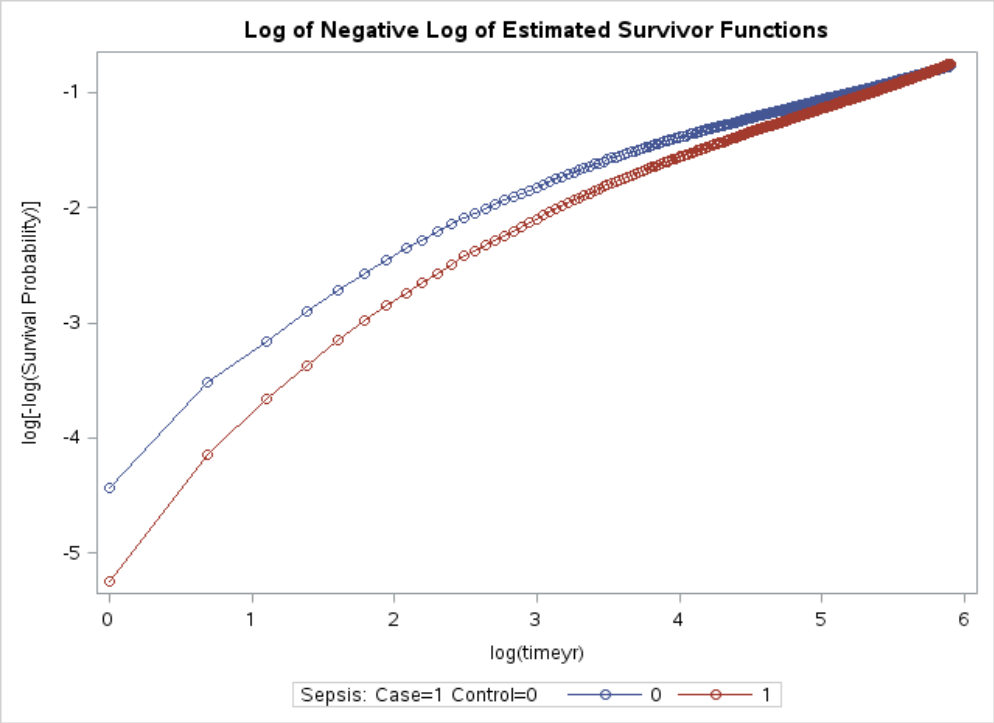


Figure B9: Testing for Proportional Hazards Assumption, log(-log(Survival)), 1-Year Survival, Age Group: ≥84 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, ≥84 Years



b) Severe Sepsis versus Matched Hospital Controls, ≥85 Years

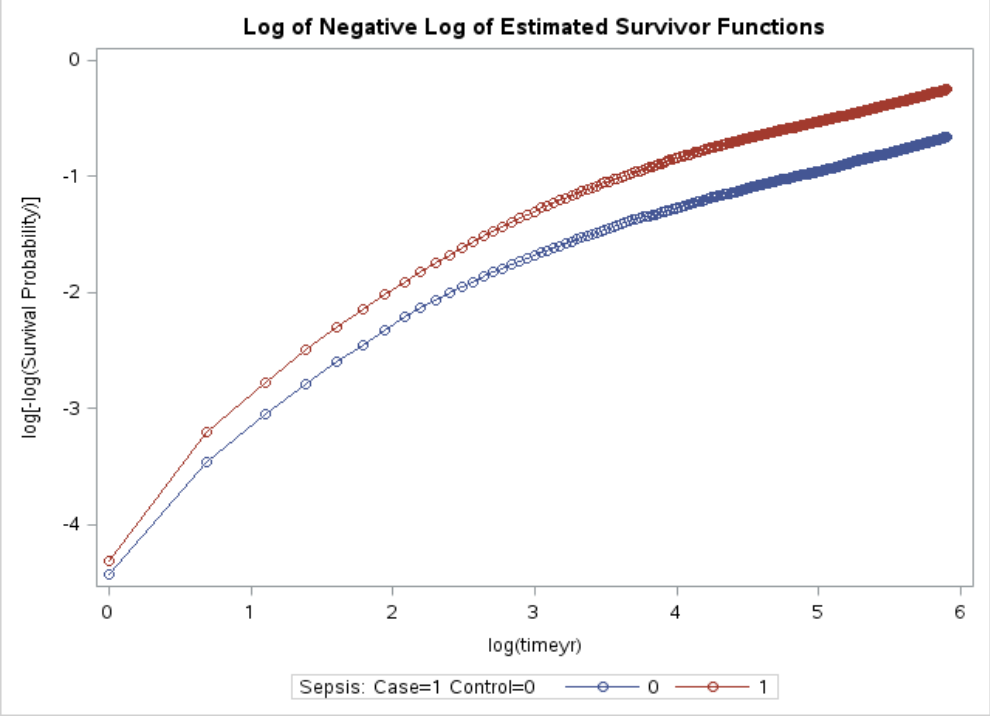
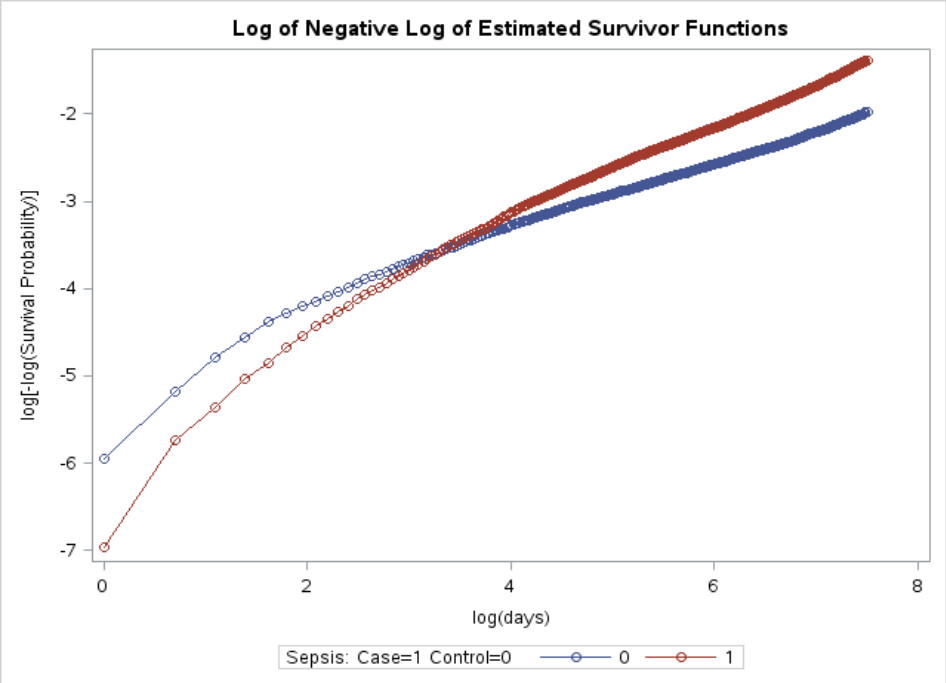


Figure B10: Testing for Proportional Hazards Assumption, log(-log(Survival)), Survival Full-Follow-up Time. Age Group: <65 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, <65 Years



b) Severe Sepsis versus Matched Hospital Controls, <65 Years

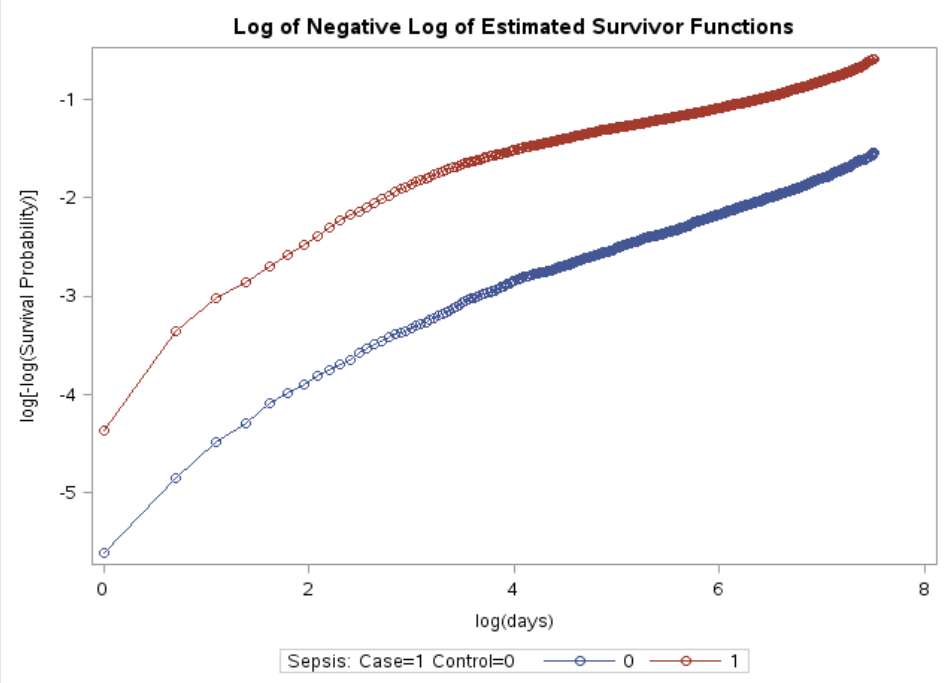
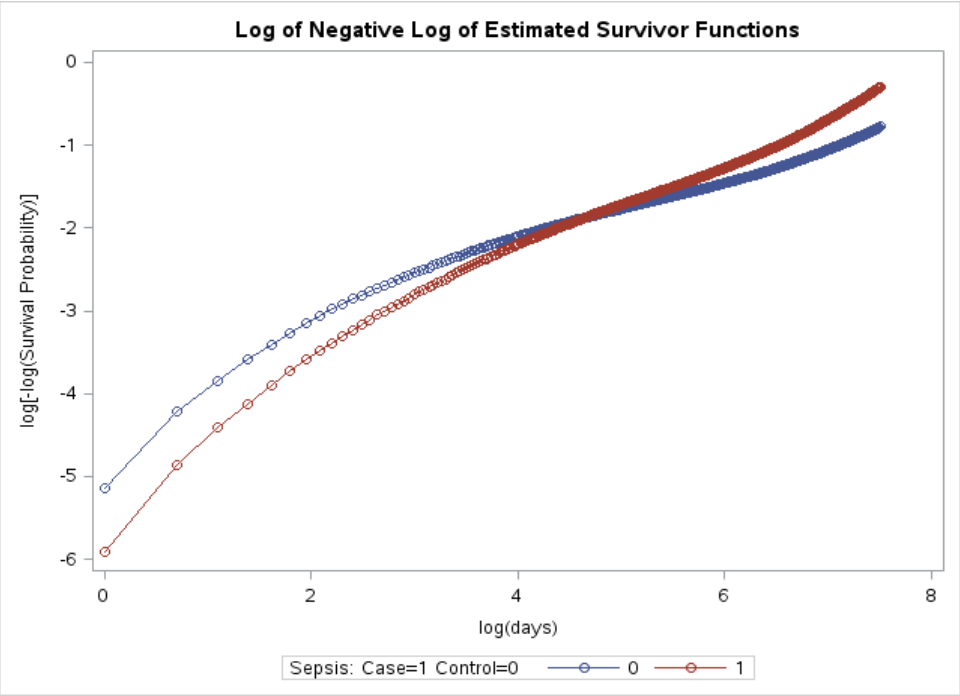


Figure B11: Testing for Proportional Hazards Assumption, log(-log(Survival)), Survival Full-Follow-up Time, Age Group: 65-84 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, 65-84 Years



b) Severe Sepsis versus Matched Hospital Controls, 65-84 Years

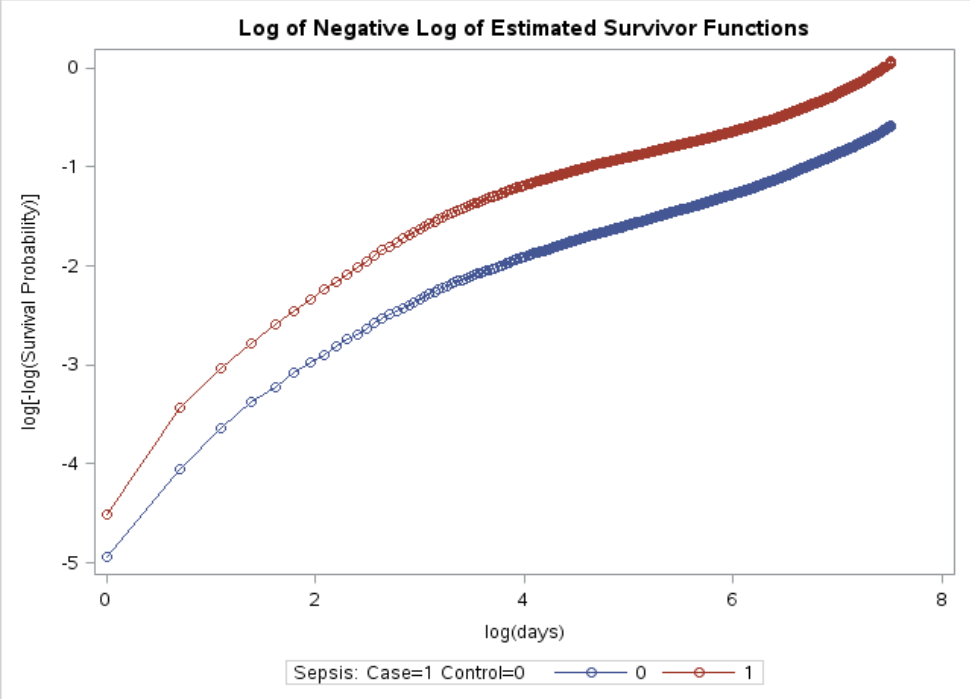
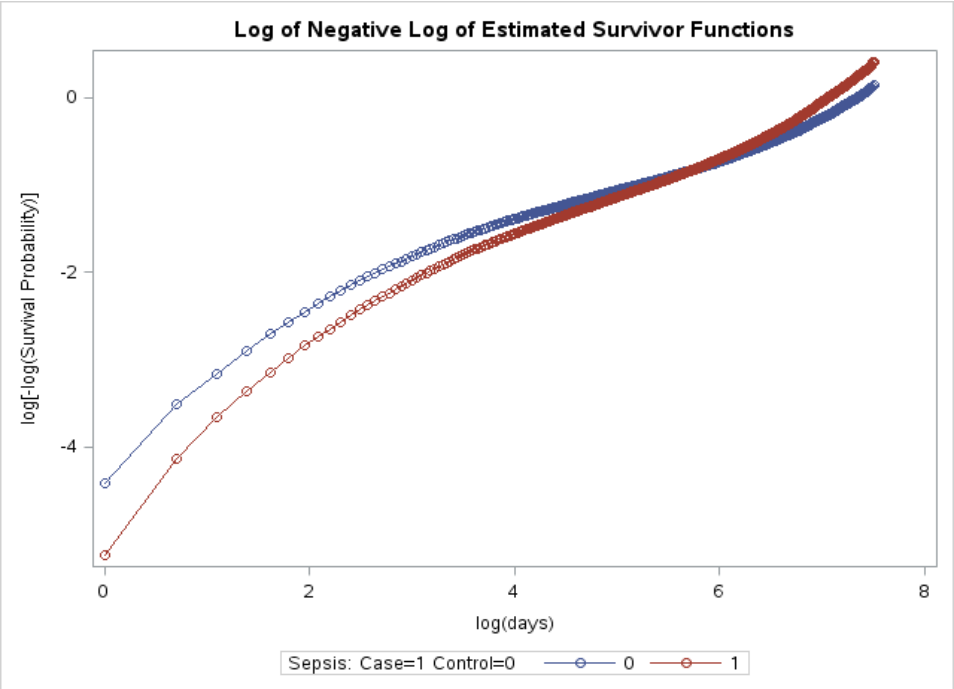
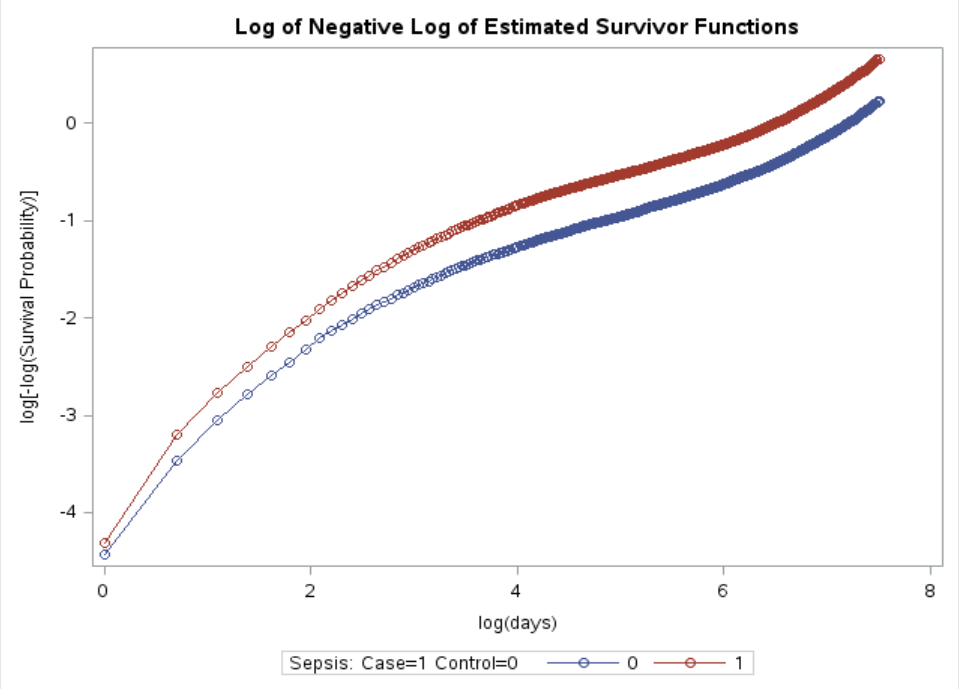


Figure B12: Testing for Proportional Hazards Assumption, log(-log(Survival)), Survival Full-Follow-up Time, Age Group: ≥85 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, ≥85 Years



b) Severe Sepsis versus Matched Hospital Controls, ≥85 Years



APPENDIX C. Additional Data for Hospital Survivor Cohort Matching: Age Subgroup Analysis

This appendix provides additional information not presented above for the age subgroup analysis of the hospital survivor cohort. As in the above subgroup analysis, there were three age groups: patients <65 years, between 65-84 years, and over 84 years. All analyses described in the primary analysis were repeated for each age subgroup of patients who survived index hospitalization. For each age group, cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of cases.

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Table C1: Hospital Survivor Cohort: Ages <65 Years, Post-Matching Baseline Characteristics of Cases and Controls

	AFTER MATCHING					
	Matched Controls **N= 34,095**	**Non-Severe Sepsis (no organ dysfunction)** **N= 34,095** *Unmatched =23.5%*	**Std. Diff**	**Matched Controls** **N= 11,962**	**Severe Sepsis (including shock)** **N= 11,962** *Unmatched =28.1%*	**Std. Diff.**
Age						
Mean (SD)	50.00 (11.98)	49.98 (11.97)	**0.00**	52.10 (10.94)	52.05 (10.93)	**0.00**
Median (Q1-Q3)	53 (43-60)	53 (43-60)	**0.00**	55 (47-60)	55 (47-60)	**0.01**
Female, n (%)	19072 (55.94)	19072 (55.94)	**0.00**	5797 (48.46)	5797 (48.46)	**0.00**
Rural, n (%)	4458 (13.08)	4876 (14.30)	**0.04**	1493 (12.48)	1184 (9.90)	**0.08**
Income quintile, n (%)						
1 (lowest)	8532 (25.02)	8464 (24.82)	**0.00**	3417 (28.57)	3262 (27.27)	**0.03**
2	7082 (20.77)	7181 (21.06)	**0.01**	2549 (21.31)	2637 (22.04)	**0.02**
3	6544 (19.19)	6592 (19.33)	**0.00**	2195 (18.35)	2222 (18.58)	**0.01**
4	6242 (18.31)	6317 (18.53)	**0.01**	2065 (17.26)	2033 (17.00)	**0.01**
5 (highest)	5452 (15.99)	5294 (15.53)	**0.01**	1623 (13.57)	1734 (14.50)	**0.03**
missing	243 (0.71)	247 (0.72)	**0.00**	113 (0.94)	74 (0.62)	**0.04**
ON Marginalization Index, n (%)						
1 (lowest)	5986 (17.56)	5836(17.12)	**0.01**	1790 (14.96)	1851 (15.47)	**0.01**
2	6968 (20.44)	7147 (20.96)	**0.01**	2258 (18.88)	2315 (19.35)	**0.01**
3	7628 (22.37)	7651 (22.44)	**0.00**	2711 (22.66)	2614 (21.85)	**0.02**
4	6565 (19.26)	6563 (19.25)	**0.00**	2531 (21.16)	2384 (19.93)	**0.03**
5 (highest)	6434 (18.87)	6359 (18.65)	**0.01**	2449 (20.47)	2669 (22.31)	**0.04**
missing	514 (1.51)	539 (1.58)	**0.01**	223 (1.86)	129 (1.08)	**0.07**
Prior cancer, n (%)	2711 (7.95)	4403 (12.91)	**0.16**	1112 (9.30)	1338 (11.19)	**0.06**
Prior CHF, n (%)	2435 (7.14)	2300 (6.75)	**0.02**	1366 (11.42)	1585 (13.25)	**0.06**
Prior CKD, n (%)	612 (1.79)	466 (1.37)	**0.03**	350 (2.93)	701 (5.86)	**0.14**
Prior COPD, n (%)	6986 (20.49)	8343 (24.47)	**0.10**	3792 (31.70)	3176 (26.55)	**0.11**
Prior diabetes, n (%)	8455 (24.80)	8908 (26.13)	**0.03**	3909 (32.68)	4145 (34.65)	**0.04**
Residence in LTC, n (%)	279 (0.82)	584 (1.71)	**0.08**	155 (1.30)	179 (1.50)	**0.02**
ADG score, mean (SD)	19.94 (15.19)	20.24 (13.47)	**0.02**	25.44 (13.71)	28.99 (12.43)	**0.26**
Healthcare use, past year						
Hospitalization, n (%)	3073 (9.01)	4424 (12.98)	**0.13**	1165 (9.74)	1453 (12.15)	**0.08**
Receiving homecare, n (%)	4993 (14.64)	6639 (19.47)	**0.13**	2470 (20.65)	2315 (19.35)	**0.03**

	AFTER MATCHING					
	Matched Controls **N= 34,095**	**Non-Severe Sepsis (no organ dysfunction)** **N= 34,095** *Unmatched =23.5%*	**Std. Diff**	**Matched Controls** **N= 11,962**	**Severe Sepsis (including shock)** **N= 11,962** *Unmatched =28.1%*	**Std. Diff.**
ED visits						
Mean (SD)	1.51 (3.83)	1.49 (2.76)	**0.01**	1.78 (4.67)	1.15 (2.25)	**0.17**
Median (Q1-Q3)	1 (0-1)	1 (0-2)	**0.07**	1 (0-2)	0 (0-2)	**0.21**
Physician visits						
Mean (SD)	16.15 (17.19)	19.00 (21.03)	**0.15**	17.70 (17.80)	19.57 (22.53)	**0.09**
Median (Q1-Q3)	11 (5-21)	13 (6-24)	**0.12**	13 (6-23)	13 (5-25)	**0.00**
Index Admission						
Urgent admission, n (%)	32059 (94.03)	32059 (94.03)	**0.00**	11322 (94.65)	11322 (94.65)	**0.00**
Index Admission Date, n (%)						
Apr 2012 – Mar 2013	10900 (31.97)	10877 (31.90)	**0.00**	3672 (30.70)	3663 (30.62)	**0.00**
Apr 2013 – Mar 2014	8070 (23.67)	8103 (23.77)	**0.00**	2804 (23.44)	2810 (23.49)	**0.00**
Apr 2014 – Mar 2015	7631 (22.38)	7632 (22.38)	**0.00**	2691 (22.50)	2697 (22.55)	**0.00**
Apr 2015 – Mar 2016	7494 (21.98")	7483 (21.95)	**0.00**	2795 (23.37)	2792 (23.34)	**0.00**
Hospital Type*, n (%)						
Teaching	11226 (32.93)	10271 (30.13)	**0.06**	3948(33.01)	4318 (36.10)	**0.07**
Community ≥ 100 beds	17585 (51.58)	16548 (48.54)	**0.06**	6085 (50.87)	6414 (53.62)	**0.06**
Community < 100 beds	5283 (15.50)	7273 (21.33)	**0.15**	1928 (16.12)	1230 (10.28)	**0.17**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = Congestive heart failure; CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; ON= Ontario; SD = standard deviation; Std Diff = standardized difference.
*Variable not included in propensity score model.
Missing values: rural: 6; Hospital type: 5.

Table C2: Hospital Survivor Cohort, Ages 65-84 Years: Post-Matching Baseline Characteristics of Cases and Controls

	AFTER MATCHING					
	Matched Controls	**Non-Severe Sepsis (no organ dysfunction)**	**Std. Diff**	**Matched Controls**	**Severe Sepsis (including shock)**	**Std. Diff.**
	N= 57,412	**N= 57,414** *Unmatched =25.7%*		**N= 23,934**	**N= 23,935** *Unmatched =29.2%*	
Age						
Mean (SD)	75.68 (5.76)	75.75 (5.72)	**0.01**	75.65 (5.75)	75.68 (5.71)	**0.00**
Median (Q1-Q3)	76 (71-81)	76 (71-81)	**0.01**	76 (71-81)	76 (71-81)	**0.00**
Female, n (%)	31602 (55.04)	31602 (55.04)	**0.00**	11942 (49.90)	11942 (49.90)	**0.00**
Rural, n (%)	7913 (13.78)	8997 (15.67)	**0.05**	3224 (13.47)	2224 (9.29)	**0.13**
Income quintile, n (%)						
1 (lowest)	12541 (21.84)	12419 (21.63)	**0.01**	5478 (22.89)	5136 (21.46)	**0.03**
2	12059 (21.00)	11944 (20.80)	**0.00**	5068 (21.17)	5127 (21.42)	**0.01**
3	11222 (19.55)	11284 (19.65)	**0.00**	4715 (19.70)	4809 (20.09)	**0.01**
4	11066 (19.27)	11184 (19.48)	**0.01**	4499 (18.80)	4650 (19.43)	**0.02**
5 (highest)	10267 (17.88)	10288 (17.92)	**0.00**	4043 (16.89)	4105 (17.15)	**0.01**
Missing	257 (0.45)	295 (0.51)	**0.01**	131 (0.55)	108 (0.45)	**0.01**
ON Marginalization Index, n (%)						
1 (lowest)	7918 (13.79)	8323 (14.50)	**0.02**	3229 (13.49)	3303 (13.80)	**0.01**
2	10651 (18.55)	10597 (18.46)	**0.00**	4221 (17.64)	4443 (18.56)	**0.02**
3	12591 (21.93)	12755 (22.22)	**0.01**	5241 (21.90)	5135 (21.45)	**0.01**
4	11531 (20.08)	11467 (19.97)	**0.00**	4921 (20.56)	4805 (20.08)	**0.01**
5 (highest)	14295 (24.90)	13769 (23.98)	**0.02**	6104 (25.50)	6080 (25.40)	**0.00**
Missing	426 (0.74)	503 (0.88)	**0.01**	218 (0.91)	169 (0.71)	**0.02**
Prior cancer, n (%)	7783 (13.56)	9648 (16.80)	**0.09**	3240 (13.54)	3694 (15.43)	**0.05**
Prior CHF, n (%)	12611 (21.97)	13211 (23.01)	**0.03**	6274 (26.21)	7419 (31.00)	**0.11**
Prior CKD, n (%)	1007 (1.75)	660 (1.15)	**0.05**	565 (2.36)	795 (3.32)	**0.06**
Prior COPD, n (%)	20192 (35.17)	23993 (41.79)	**0.14**	10093 (42.17)	9319 (38.93)	**0.07**
Prior diabetes, n (%)	23648 (41.19)	23712 (41.30)	**0.00**	10908 (45.58)	11748 (49.08)	**0.07**
Residence in LTC, n (%)	2689 (4.68)	3785 (6.59)	**0.08**	1442 (6.02)	1423 (5.95)	**0.00**
ADG score, mean (SD)	28.39 (12.61)	27.52 (12.25)	**0.07**	30.95 (12.28)	33.64 (12.37)	**0.22**
Healthcare use, past year						
Hospitalization, n (%)	4754 (8.28)	7364 (12.83)	**0.15**	1990 (8.31)	2780 (11.61)	**0.11**
Receiving homecare, n (%)	15977 (27.83)	19402 (33.79)	**0.13**	8235 (34.41)	7763 (32.43)	**0.04**

	AFTER MATCHING					
	Matched Controls **N= 57,412**	**Non-Severe Sepsis (no organ dysfunction)** **N= 57,414** *Unmatched =25.7%*	**Std. Diff**	**Matched Controls** **N= 23,934**	**Severe Sepsis (including shock)** **N= 23,935** *Unmatched =29.2%*	**Std. Diff.**
ED visits						
Mean (SD)	1.03 (1.98)	1.08 (1.83)	**0.03**	1.14 (2.13)	0.93 (1.61)	**0.12**
Median (Q1-Q3)	0 (0-1)	0 (0-1)	**0.05**	1 (0-2)	0 (0-1)	**0.11**
Physician visits						
Mean (SD)	18.35 (15.36)	20.40 (17.67)	**0.12**	19.53 (16.06)	20.62 (18.80)	**0.06**
Median (Q1-Q3)	15 (8-23)	16 (9-26)	**0.11**	16 (9-25)	16 (9-26)	**0.02**
Index Admission						
Urgent admission, n (%)	54634 (95.16)	54634 (95.16)	**0.00**	22615 (94.49)	22615 (94.49)	**0.00**
Index Admission Date, n (%)						
Apr 2012 – Mar 2013	18379 (32.01)	18462 (32.16)	**0.00**	6940 (29.00)	6947 (29.02)	**0.00**
Apr 2013 – Mar 2014	13622 (23.73)	13480 (23.48)	**0.01**	5405 (22.58)	5422 (22.65)	**0.00**
Apr 2014 – Mar 2015	13319 (23.20)	13439 (23.41)	**0.00**	5775 (24.13)	5802 (24.24)	**0.00**
Apr 2015 – Mar 2016	12092 (21.06)	12033 (20.96)	**0.00**	5814 (24.29)	5764 (24.08)	**0.00**
Hospital Type*, n (%)						**0.00**
Teaching	16429 (28.62)	14566 (25.37)	**0.07**	6955 (29.06)	6796 (28.39)	**0.01**
Community ≥ 100 beds	30211 (52.62)	28686 (49.97)	**0.05**	12525 (52.33)	13993 (58.46)	**0.12**
Community < 100 beds	10772 (18.76)	14159 (24.66)	**0.14**	4453 (18.61)	3146 (13.14)	**0.15**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = Congestive heart failure; CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; ON= Ontario; SD = standard deviation; Std Diff = standardized difference.
*Variable not included in propensity score model.
Missing values: rural 7; hospital type: <6

Table C3: Hospital Survivor Cohort, Ages ≥ 85 Years: Post-Matching Baseline Characteristics of Cases and Controls

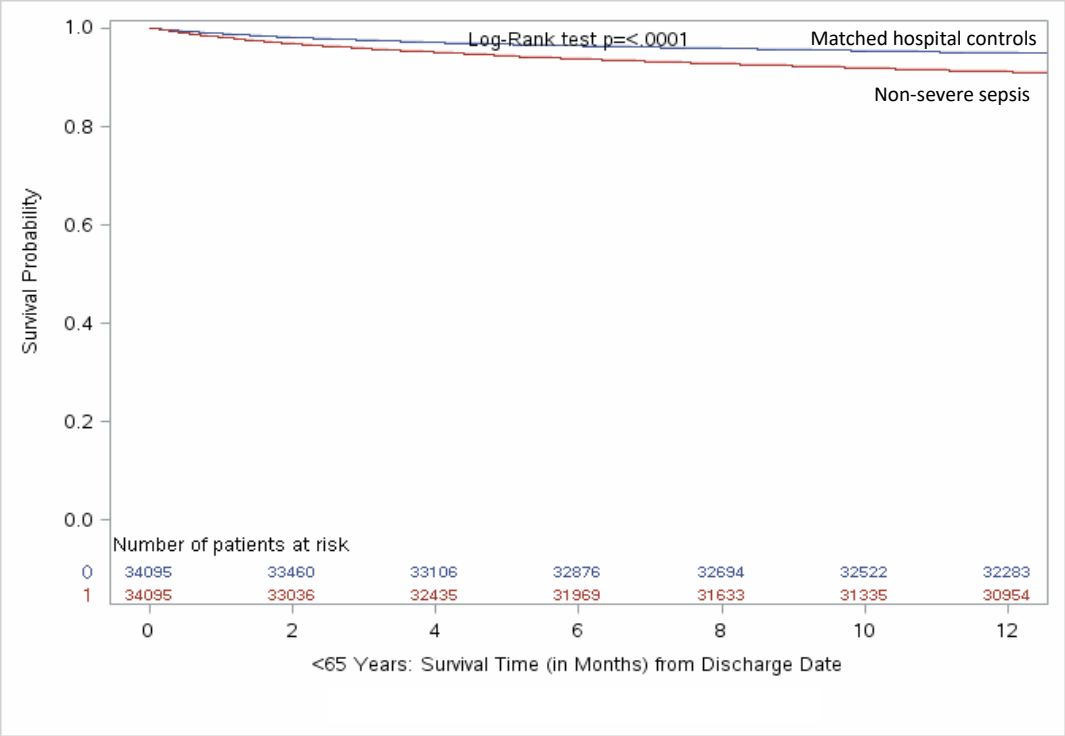
	AFTER MATCHING					
	Matched Controls	**Non-Severe Sepsis (no organ dysfunction)**	**Std. Diff**	**Matched Controls**	**Severe Sepsis (including shock)**	**Std. Diff.**
	N= 32,733	**N= 32,733** *Unmatched =24.9%*		**N=12,949**	**N= 12,949** *Unmatched =27.7%*	
Age						
Mean (SD)	89.37 (3.65)	89.47 (3.56)	**0.03**	89.35 (2.60)	89.43 (5.52)	**0.02**
Median (Q1-Q3)	89 (86-92)	89 (87-92)	**0.03**	89 (87-92)	89 (87-92)	**0.02**
Female, n (%)	22382 (68.38)	22382 (68.38)	**0.00**	8090 (62.48)	8090 (62.48)	**0.00**
Rural, n (%)	3874 (11.84)	4323 (13.21)	**0.04**	1377 (10.63)	880 (6.79)	**0.14**
Income quintile, n (%)						
1 (lowest)	6854 (20.94)	6656 (20.33)	**0.01**	2834 (21.89)	2621 (20.24)	**0.04**
2	6762 (20.66)	6549 (20.01)	**0.02**	2622 (20.25)	2589 (19.99)	**0.01**
3	6414 (19.59)	6648 (20.31)	**0.02**	2573 (19.87)	2660 (20.54)	**0.02**
4	6373 (19.47)	6478 (19.79)	**0.01**	2469 (19.07)	2572 (19.86)	**0.02**
5 (highest)	6178 (18.87)	6226 (19.02)	**0.00**	2378 (18.36)	2457 (18.97)	**0.02**
missing	152 (0.46)	176 (0.54)	**0.01**	73 (0.56)	52 (0.40)	**0.02**
ON Marginalization Index, n (%)						
1 (lowest)	3236 (9.89)	3449 (10.54)	**0.02**	1244 (9.61)	1292 (9.98)	**0.01**
2	4986 (15.23)	5107 (15.60)	**0.01**	1872 (14.46)	1920 (14.83)	**0.01**
3	6745 (20.61)	6719 (20.53)	**0.00**	2648 (20.45)	2578 (19.91)	**0.01**
4	6906 (21.10)	7036 (21.50)	**0.01**	2705 (20.89)	2699 (20.84)	**0.00**
5 (highest)	10608 (32.41)	10183 (31.11)	**0.03**	4368 (33.73)	4387 (33.87)	**0.00**
missing	252 (0.77)	239 (0.73)	**0.00**	112 (0.86)	75 (0.58)	**0.03**
Prior cancer, n (%)	3136 (9.58)	3168 (9.68)	**0.00**	1198 (9.25)	1223 (9.44)	**0.01**
Prior CHF, n (%)	10588 (32.35)	11240 (34.34)	**0.04**	4727 (36.50)	5135 (39.65)	**0.06**
Prior CKD, n (%)	183 (0.56)	135 (0.41)	**0.02**	105 (0.81)	113 (0.87)	**0.01**
Prior COPD, n (%)	10412 (31.81)	11977 (36.59)	**0.10**	4823 (37.25)	4412 (34.07)	**0.07**
Prior diabetes, n (%)	10396 (31.76)	10509 (32.11)	**0.01**	4512 (34.84)	4842 (37.39)	**0.05**
Residence in LTC, n (%)	4460 (13.63)	5134 (15.68)	**0.06**	2067 (15.96)	1981 (15.30)	**0.02**
ADG score, mean (SD)	30.62 (12.57)	29.40 (12.38)	**0.10**	32.65 (12.32)	34.93 (12.61)	**0.18**
Healthcare use, past year						
Hospitalization, n (%)	1904 (5.82)	3083 (9.42)	**0.14**	658 (5.08)	1037 (8.01)	**0.12**
Receiving homecare, n (%)	14987 (45.79)	16697 (51.01)	**0.10**	6697 (51.72)	6492 (50.13)	**0.03**

	AFTER MATCHING					
	Matched Controls **N= 32,733**	**Non-Severe Sepsis (no organ dysfunction)** **N= 32,733** *Unmatched =24.9%*	**Std. Diff**	**Matched Controls** **N=12,949**	**Severe Sepsis (including shock)** **N= 12,949** *Unmatched =27.7%*	**Std. Diff.**
ED visits						
Mean (SD)	0.94 (1.54)	0.96 (1.54)	**0.02**	0.97 (1.65)	0.89 (1.40)	**0.05**
Median (Q1-Q3)	0 (0-1)	0 (0-1)	**0.02**	0 (0-1)	0 (0-1)	**0.05**
Physician visits						
Mean (SD)	16.38 (13.48)	17. (14.3)	**0.06**	16.73 (13.25)	17.61 (15.55)	**0.06**
Median (Q1-Q3)	13 (8-21)	14 (8-22)	**0.04**	14 (8-21)	14 (8-22)	**0.02**
Index Admission						
Urgent admission, n (%)	32250 (98.52)	32250 (98.52)	**0.00**	12789 (98.76)	12789 (98.76)	**0.00**
Index Admission Date, n (%)						
Apr 2012 – Mar 2013	10075 (30.78)	10110 (30.89)	**0.00**	3349 (25.86)	3344 (25.82)	**0.00**
Apr 2013 – Mar 2014	8028 (24.53)	7963 (24.33)	**0.00**	3098 (23.92)	3101 (23.94)	**0.00**
Apr 2014 – Mar 2015	7856 (24.00)	7936 (24.24)	**0.01**	3300 (25.48)	3333 (25.74)	**0.01**
Apr 2015 – Mar 2016	6774 (20.69)	6724 (20.54)	**0.00**	3202 (24.73)	3173 (24.50)	**0.01**
Hospital Type*, n (%)						
Teaching	8430 (25.75)	7648 (23.36)	**0.06**	3341 (25.80)	3456 (26.69)	**0.02**
Community ≥ 100 beds	17922 (54.75)	17249 (52.70)	**0.04**	7204 (55.63)	7798 (60.21)	**0.09**
Community < 100 beds	6380 (19.49)	7836 (23.94)	**0.11**	2404 (18.57)	1697 (13.10)	**0.15**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = Congestive heart failure; CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; ON= Ontario; SD = standard deviation; Std Diff = standardized difference.
*Variable not included in propensity score model.

Figure C1: Kaplan Meier Plots: Post-Discharge Survival, 1-Year, Ages <65 Years

a) Non-Severe versus Matched Hospital Controls, <65 Years



b) Severe Sepsis versus Matched Hospital Controls, <65 Years

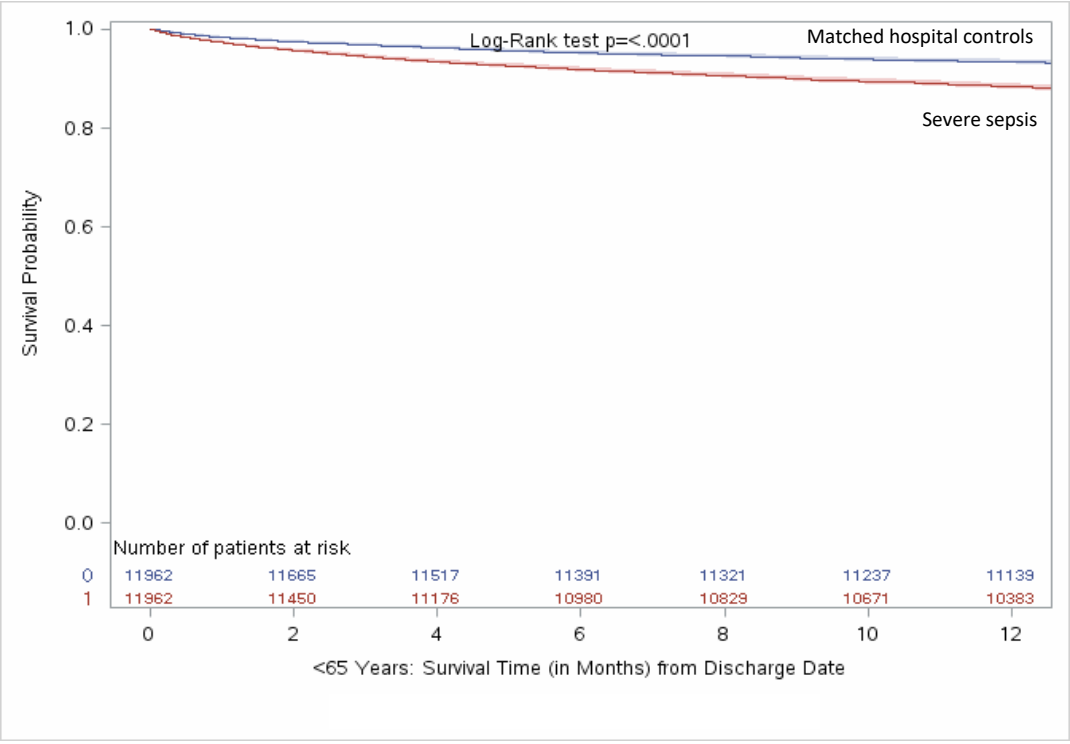
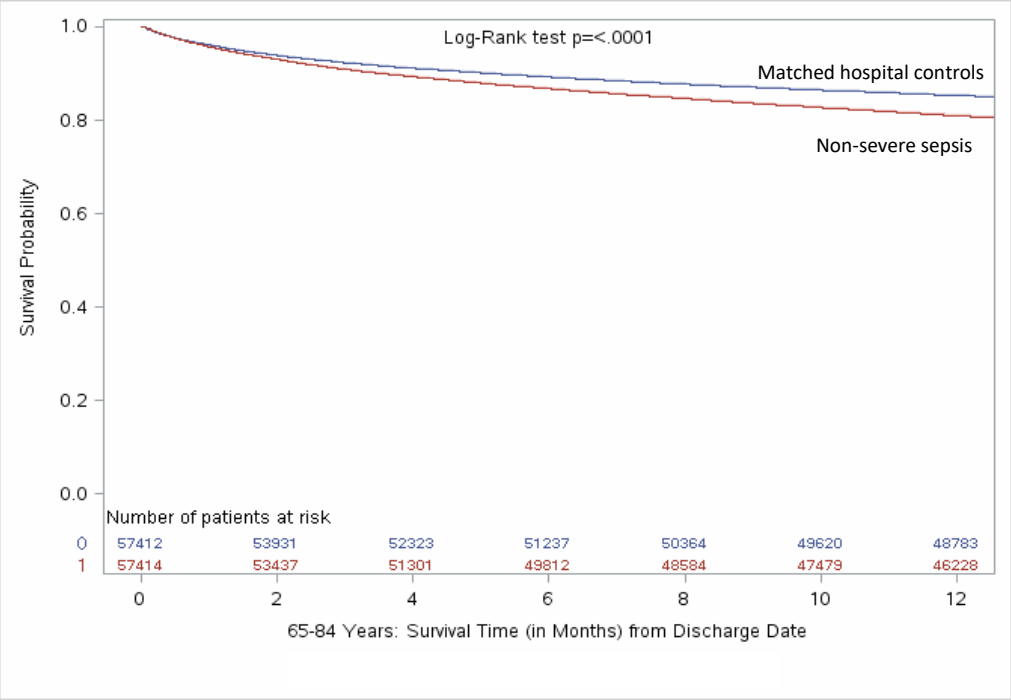


Figure C2: Kaplan Meier Plots: Post-Discharge Survival, 1-Year, Ages 65-84 Years

a) Non-Severe versus Matched Hospital Controls, 65-84 Years



b) Severe Sepsis versus Matched Hospital Controls, 65-84 Years

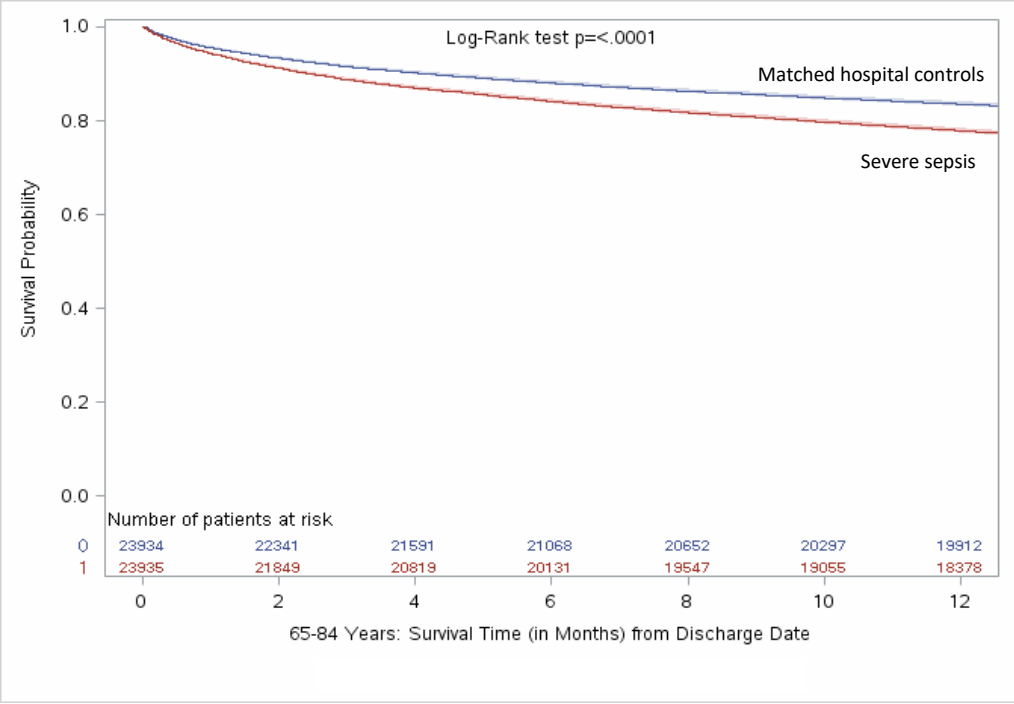
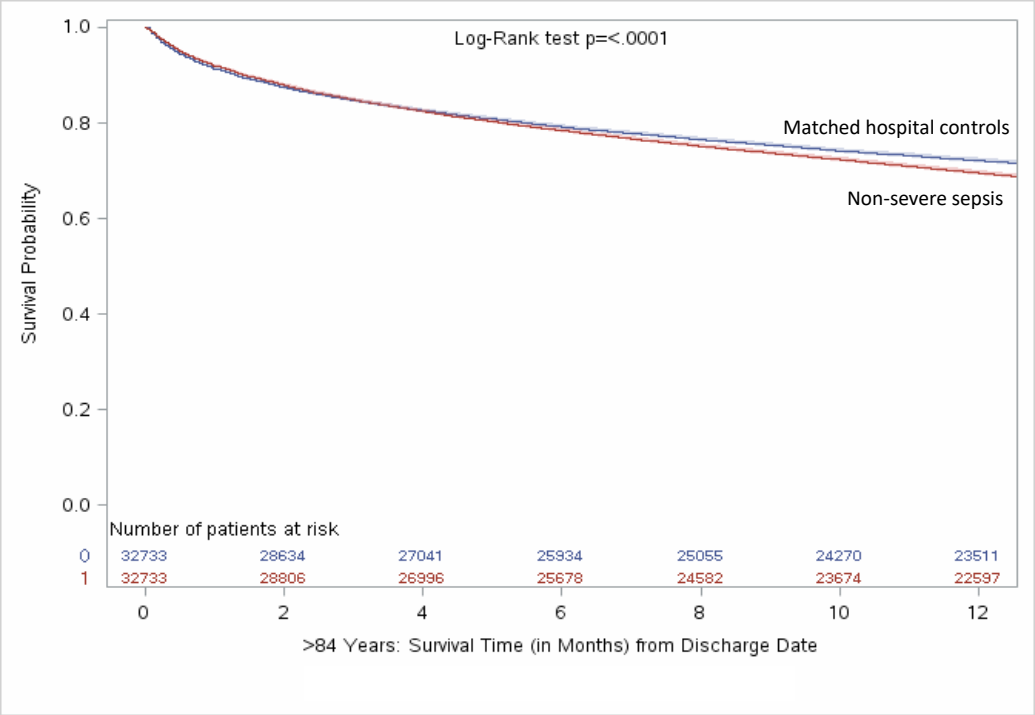


Figure C3: Kaplan Meier Plots: Post-Discharge Survival, 1-Year, Ages ≥85 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, ≥85 Years



b) Severe Sepsis versus Matched Hospital Controls, ≥85 Years

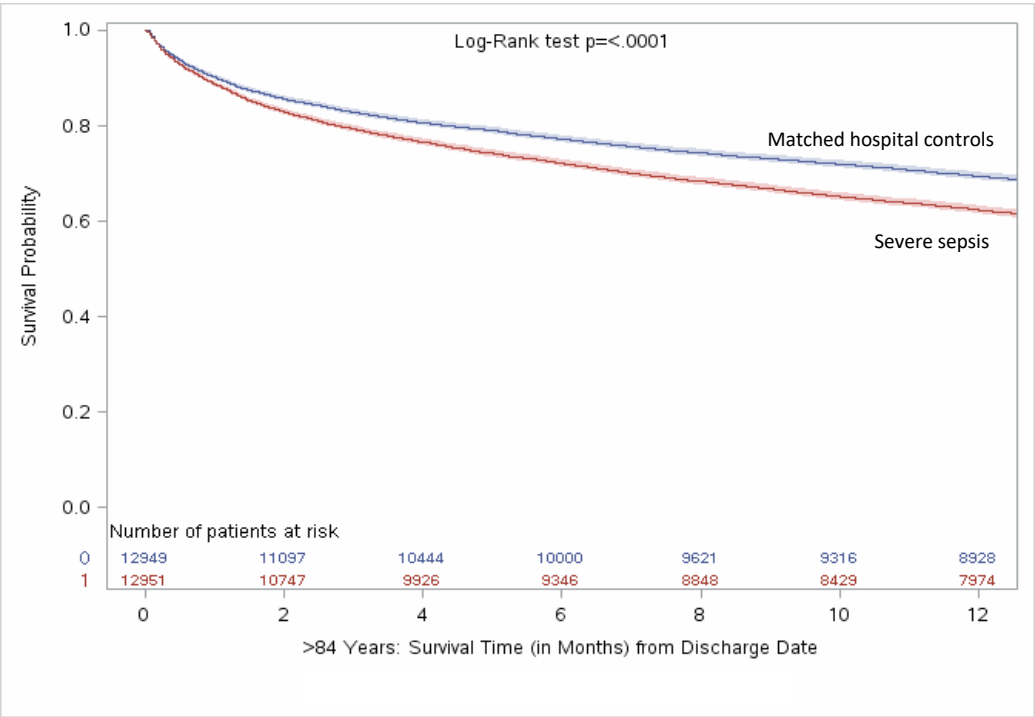
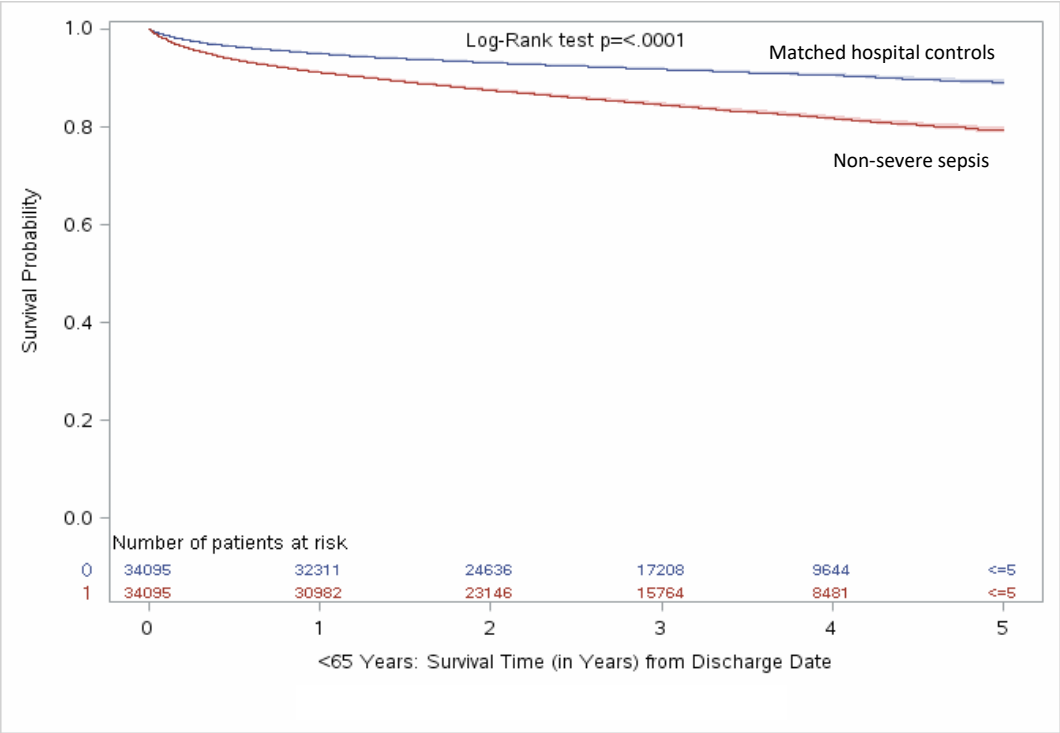


Figure C4: Kaplan Meier Plots: Post-Discharge Survival, 5-Year, Ages <65 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, <65 Years



b) Severe Sepsis versus Matched Hospital Controls, <65 Years

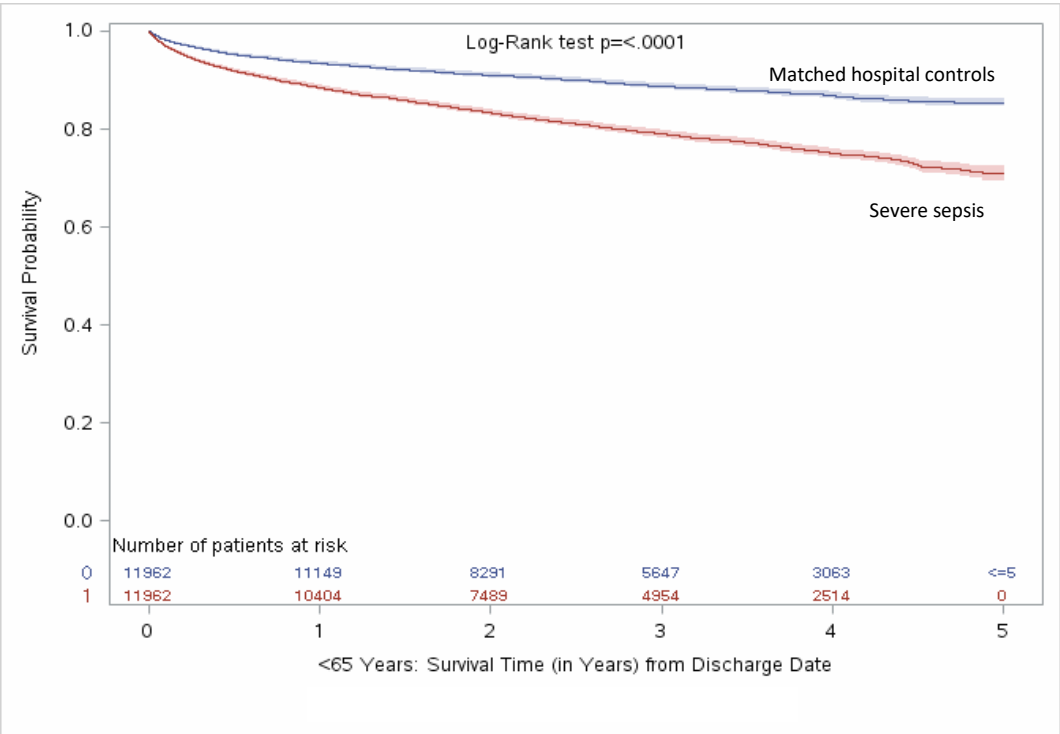
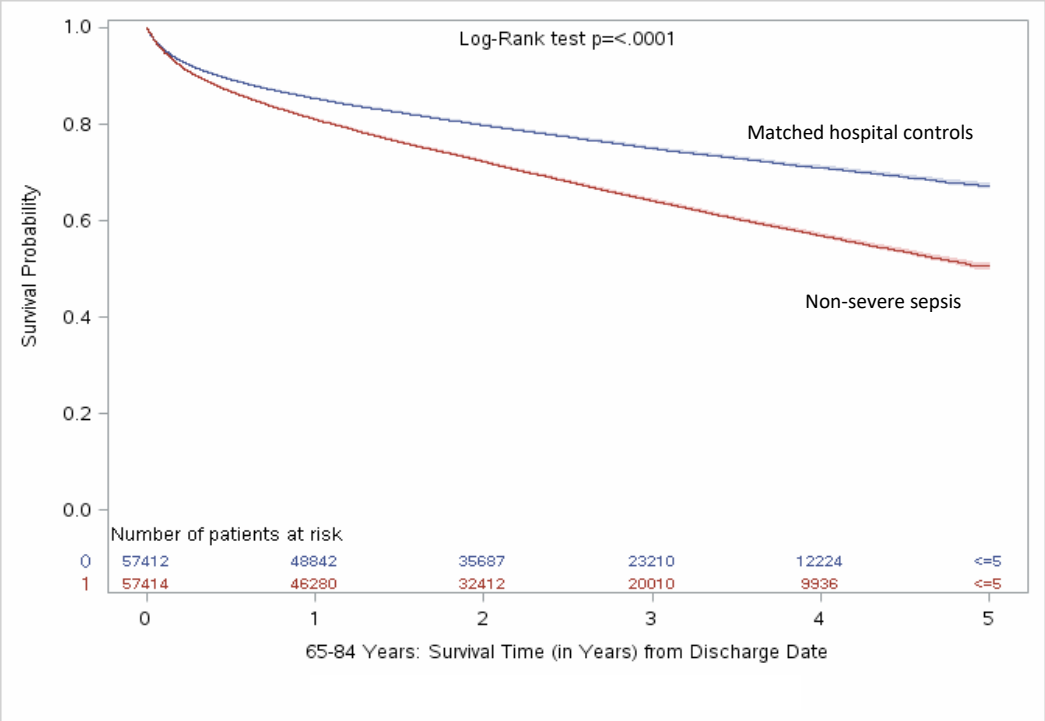


Figure C5: Kaplan Meier Plots: Post-Discharge Survival, 5-Year, Ages 65-84 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, 65-84 Years



b) Severe Sepsis versus Matched Hospital Controls, 65-84 Years

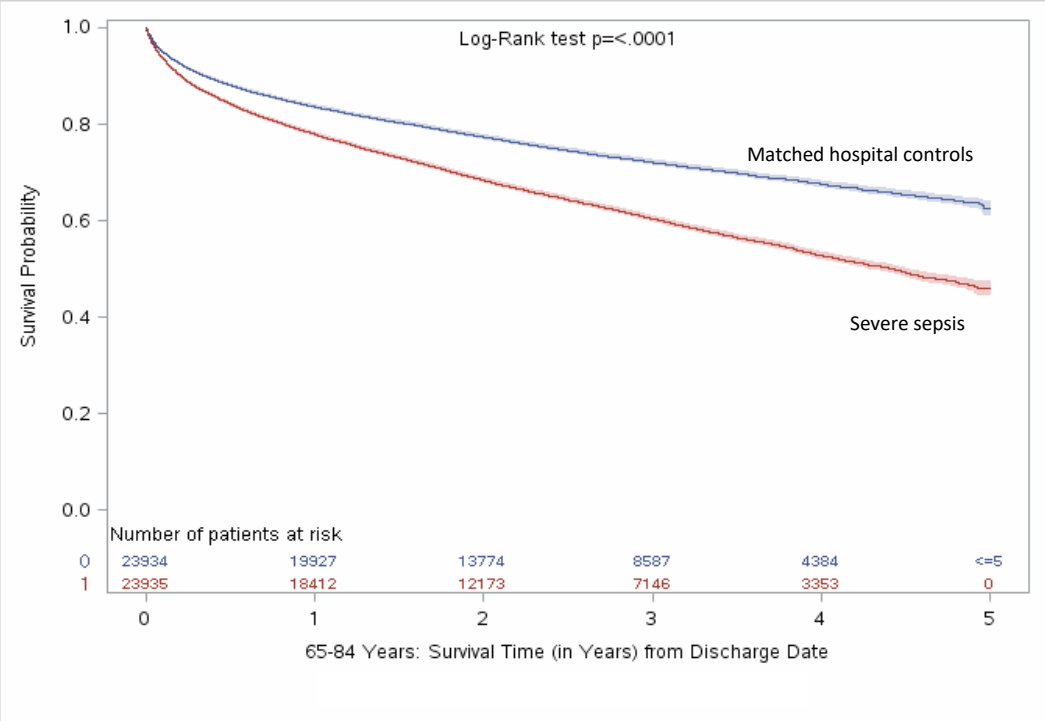
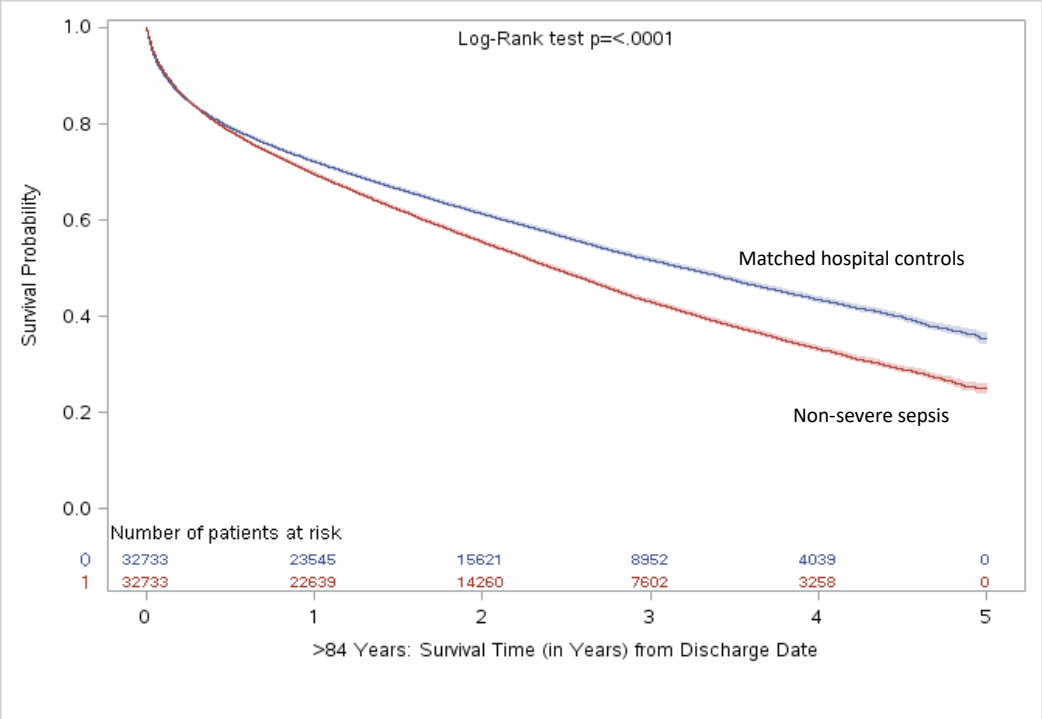


Figure C6: Kaplan Meier Plots: Post-Discharge Survival, 5-Year, Ages ≥85 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, ≥85 Years



b) Severe Sepsis versus Matched Hospital Controls, ≥85 Years

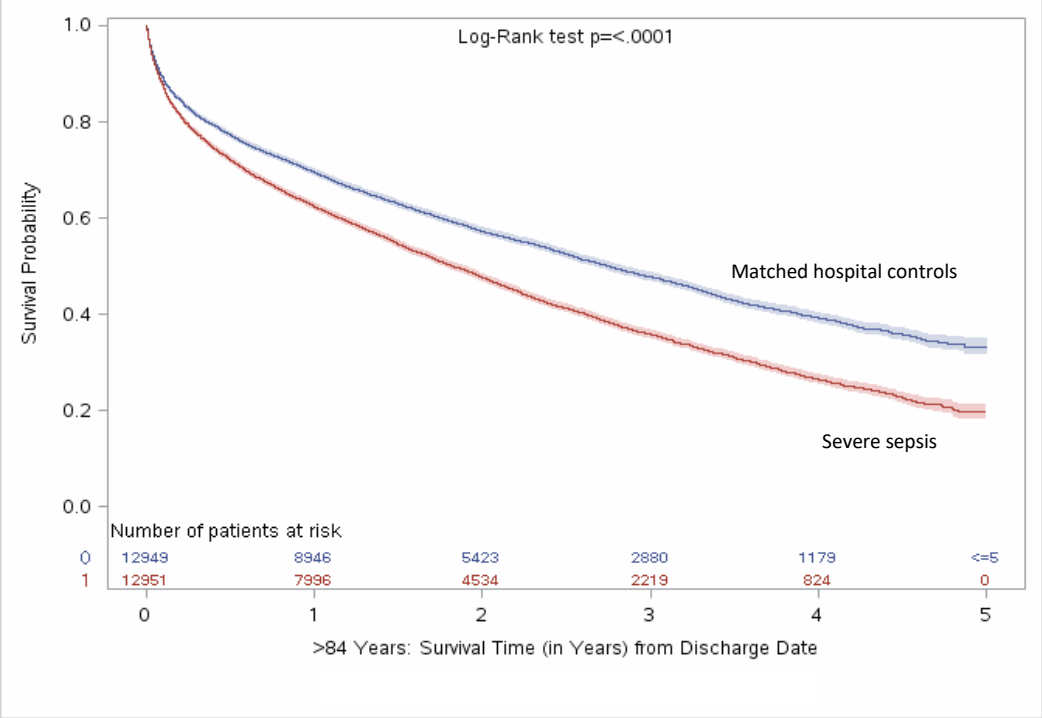
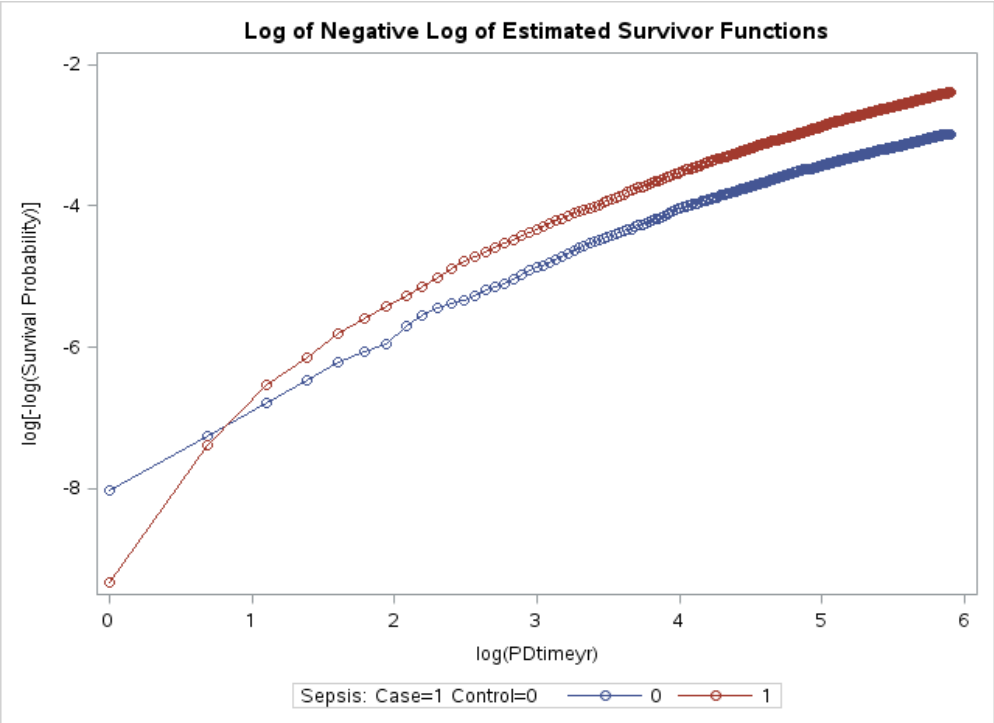


Figure C7: Testing for Proportional Hazards Assumption, log(-log(Survival)), 1-Year Survival, Ages <65 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, <65 Years



b) Severe Sepsis versus Matched Hospital Controls, <65 Years

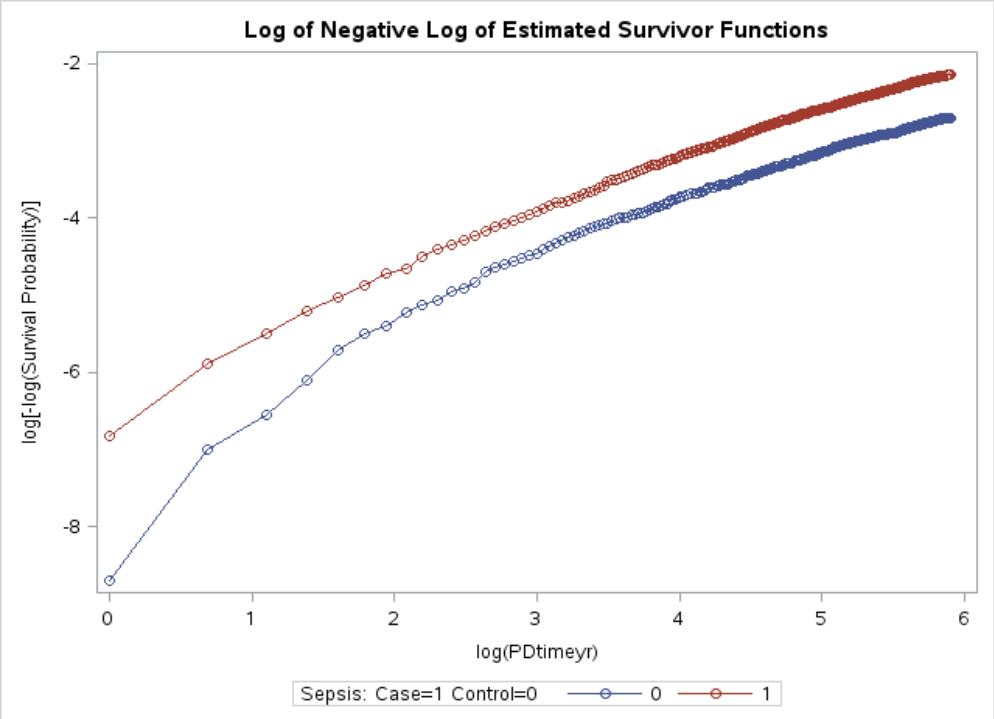
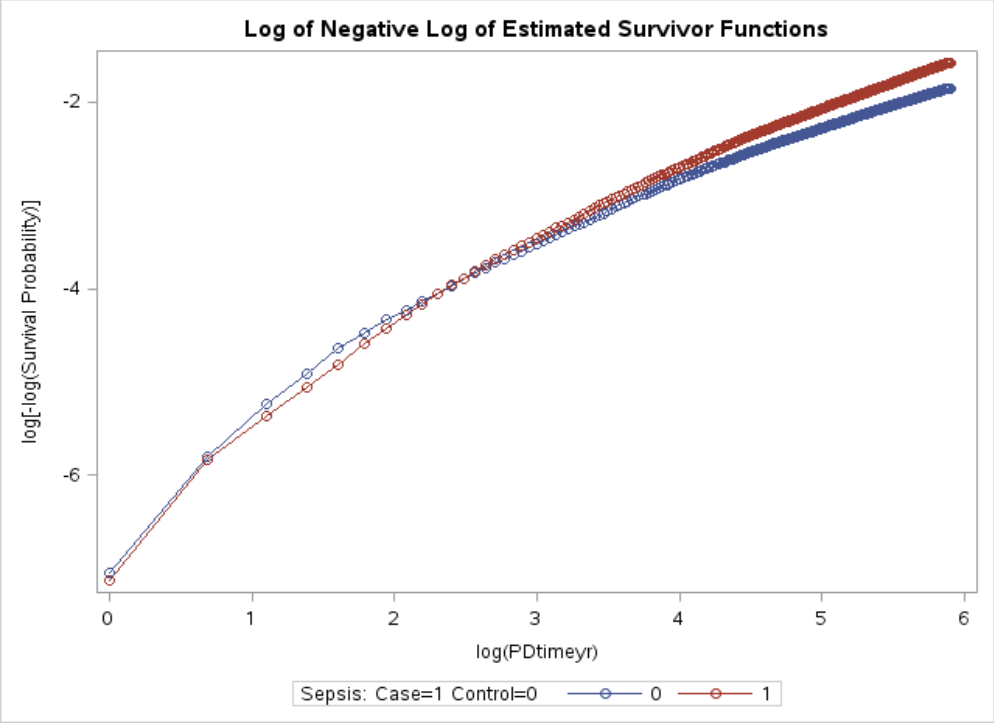


Figure C8: Testing for Proportional Hazards Assumption, log(-log(Survival)), 1-Year Survival, Ages 65-84 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, 65-84 Years



b) Severe Sepsis versus Matched Hospital Controls, 65-84 Years

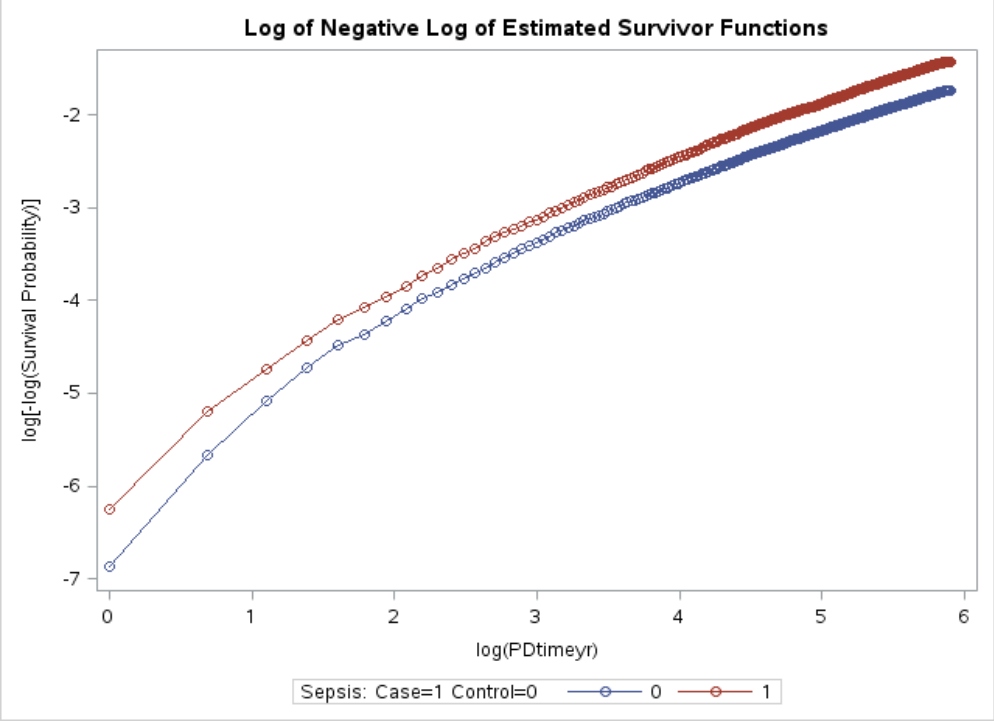
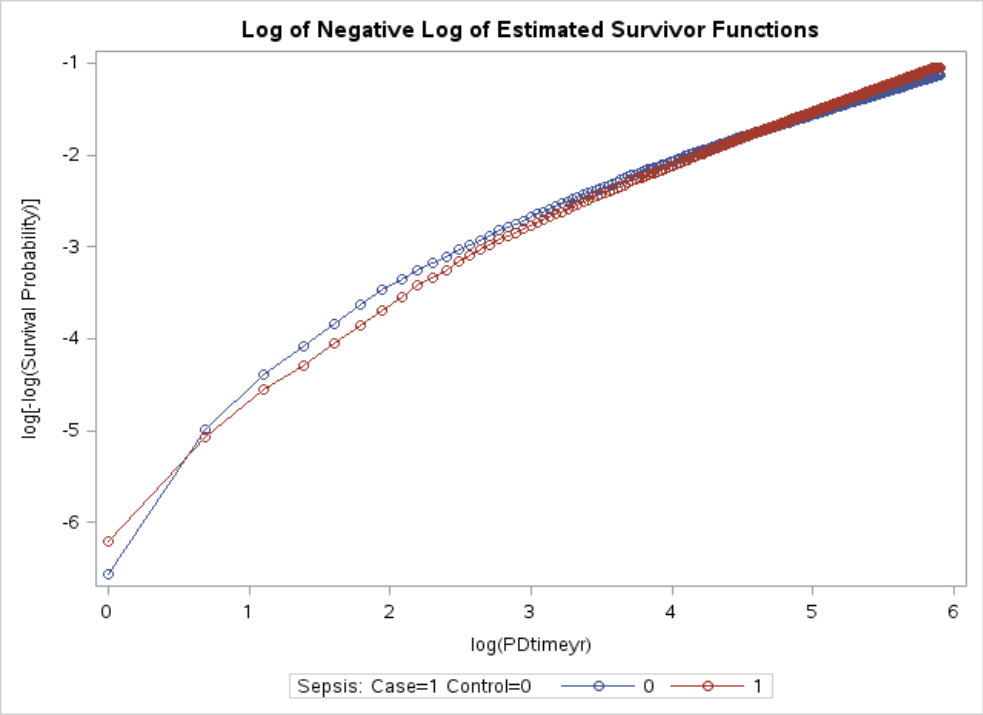


Figure C9: Testing for Proportional Hazards Assumption, log(-log(Survival)), 1-Year Survival, Ages ≥85 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, ≥85 Years



b) Severe Sepsis versus Matched Hospital Controls, ≥85 Years

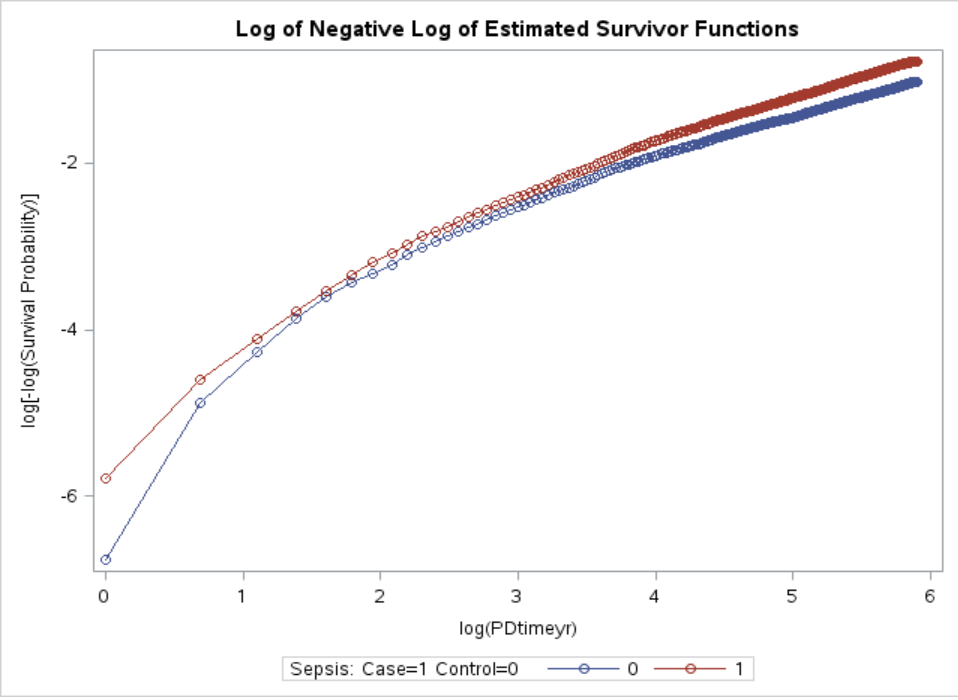
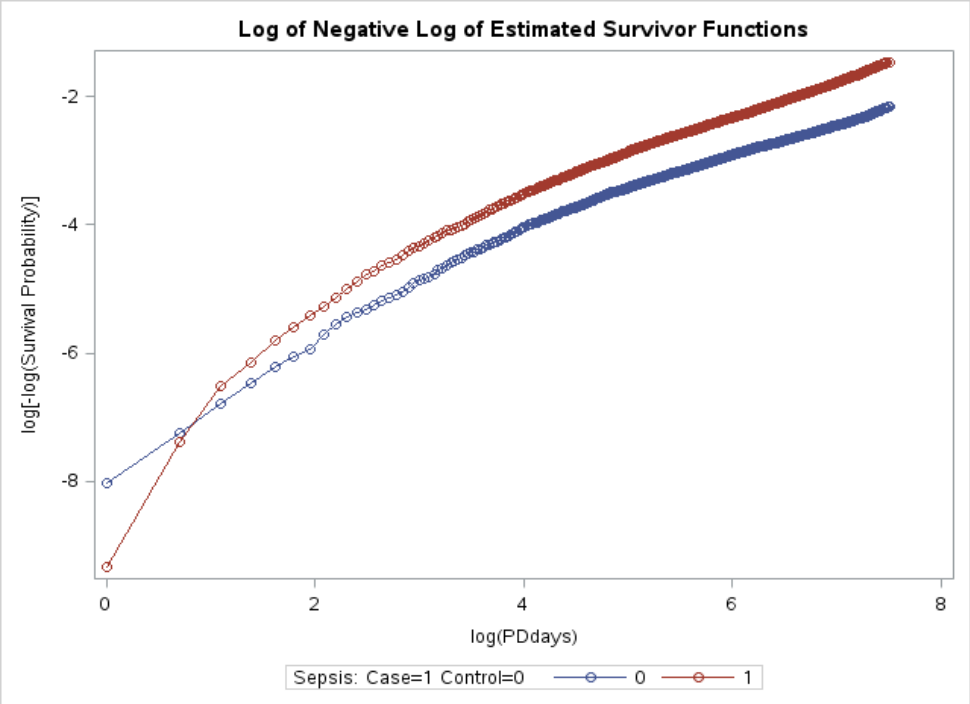


Figure C10: Testing for Proportional Hazards Assumption, log(-log(Survival)), 5-Year Survival, Ages <65 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, <65 Years



b) Severe Sepsis versus Matched Hospital Controls, <65 Years

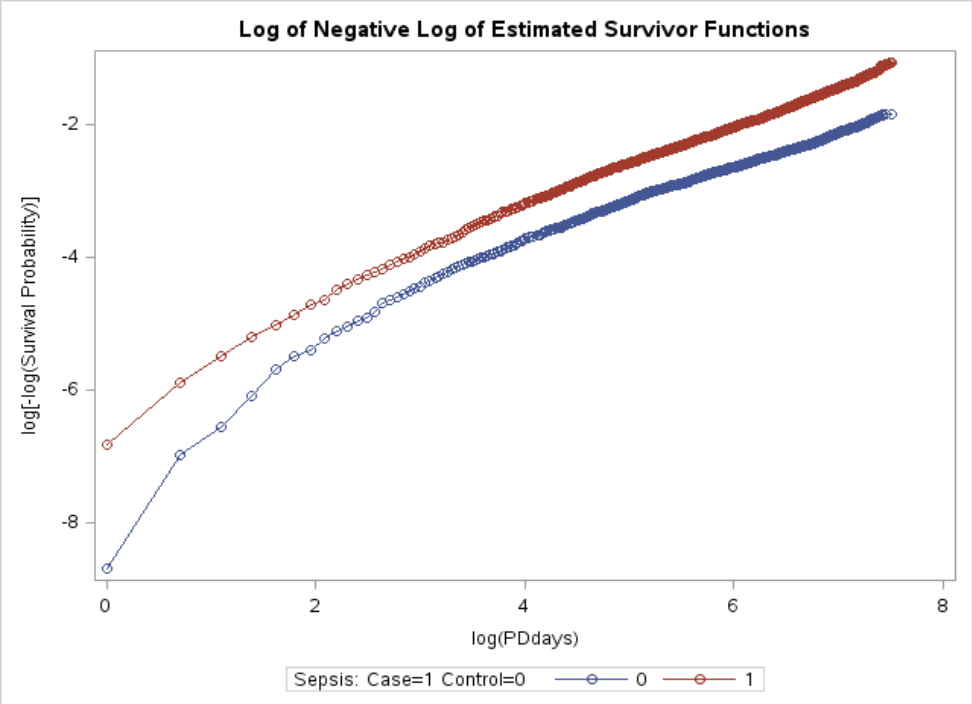
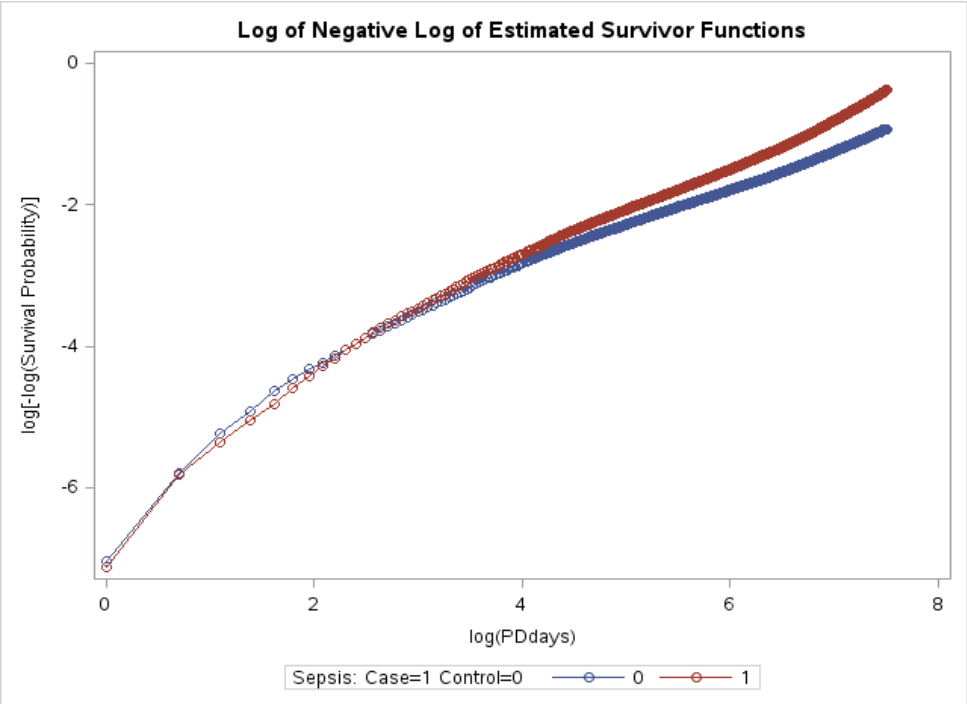


Figure C11: Testing for Proportional Hazards Assumption, log(-log(Survival)), 5-Year Survival, Ages 65-84 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, 65-84 Years



b) Severe Sepsis versus Matched Hospital Controls, 65-84 Years

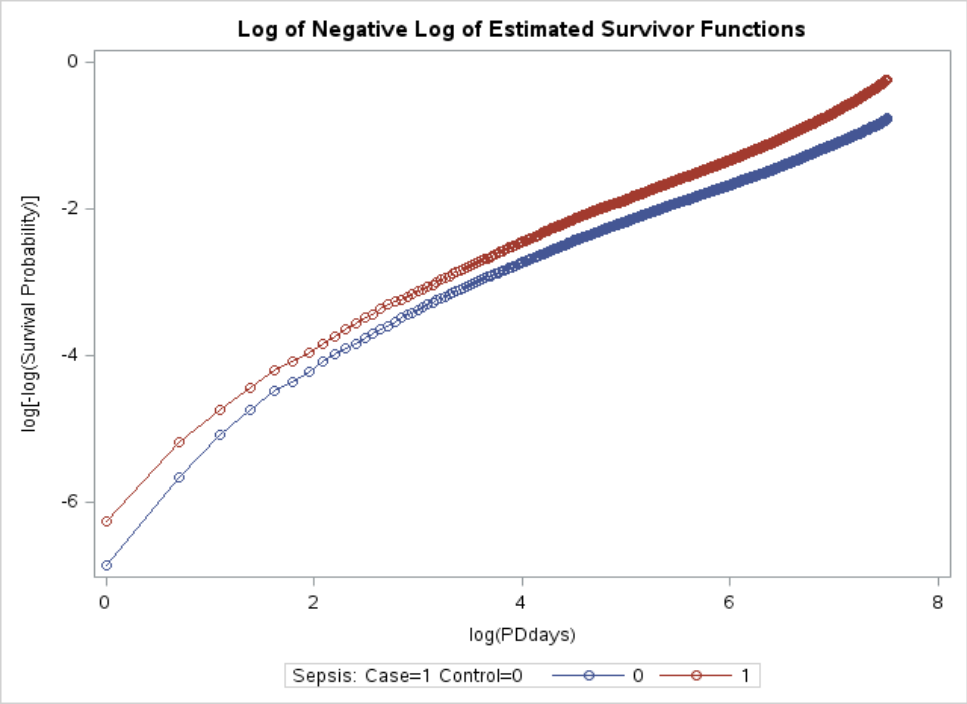
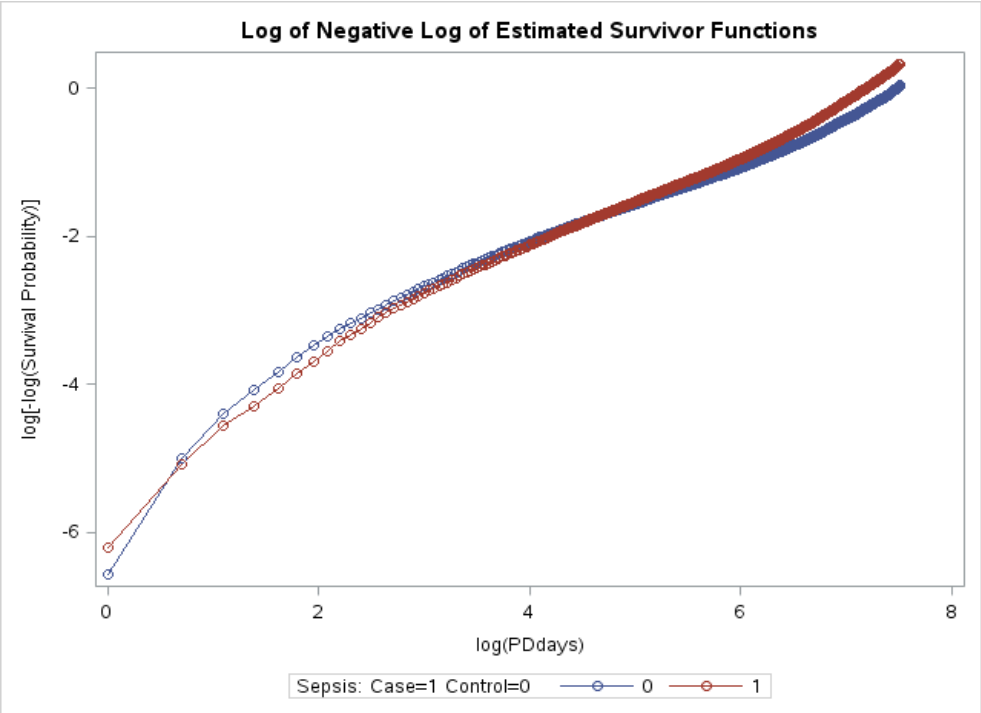


Figure C12: Testing for Proportional Hazards Assumption, log(-log(Survival)), 5-Year Survival, Ages ≥85 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, ≥85 Years



b) Severe Sepsis versus Matched Hospital Controls, ≥85 Years

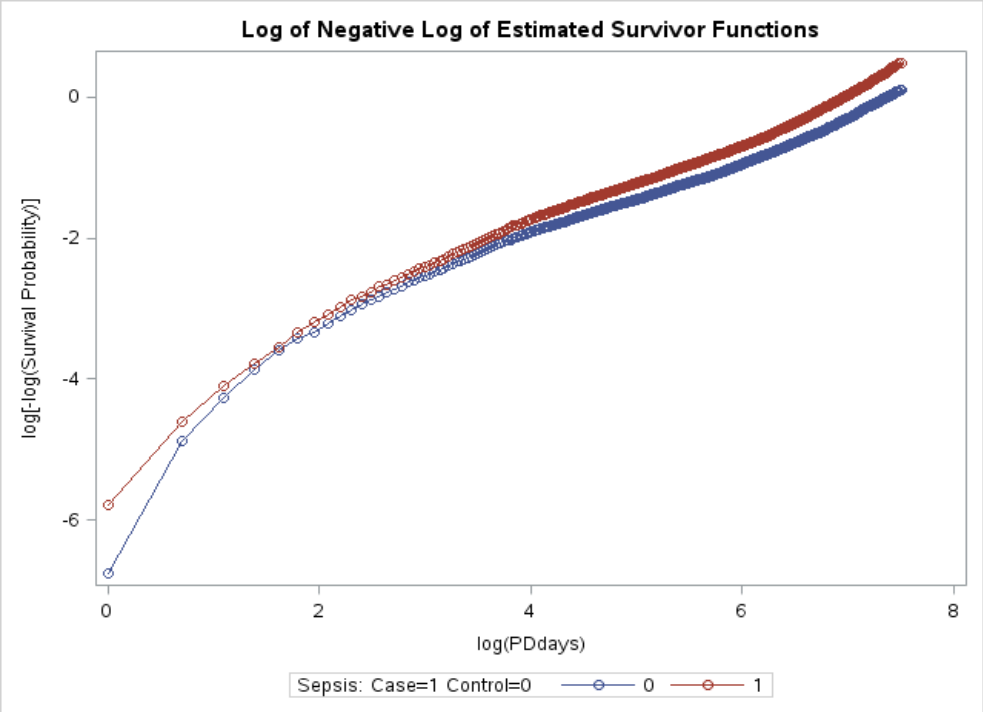
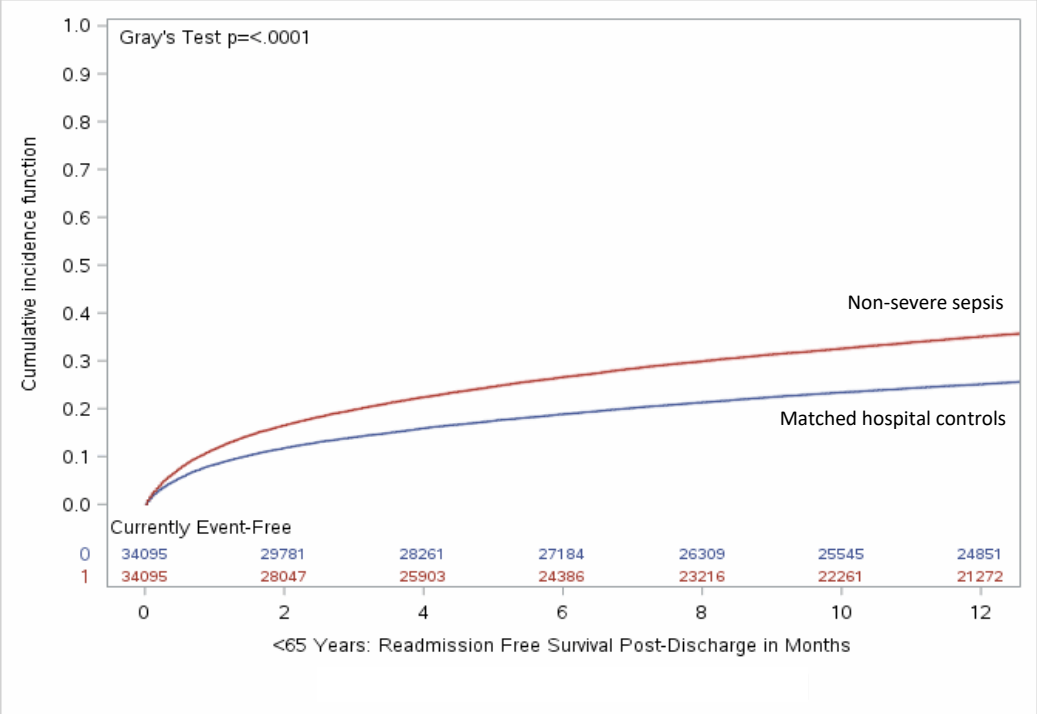


Figure C13: Time to Hospital Readmission, 1-Year. Hospital Survivor Cohort, Ages <65 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, <65Years



b) Severe Sepsis versus Matched Hospital Controls, <65 Years

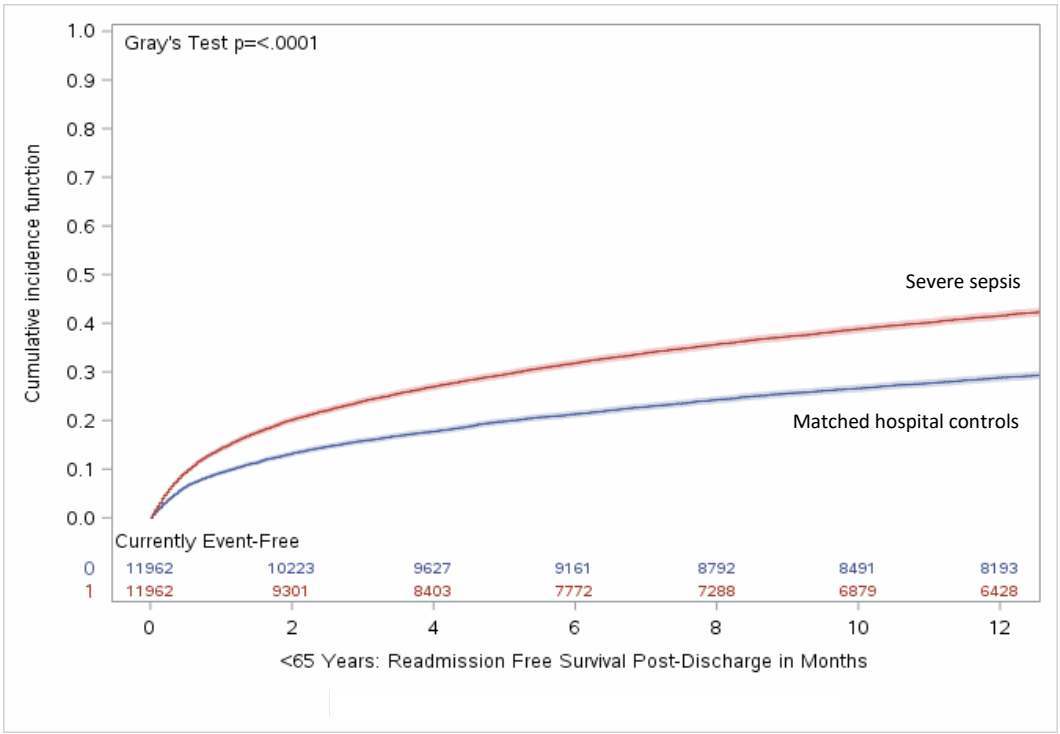
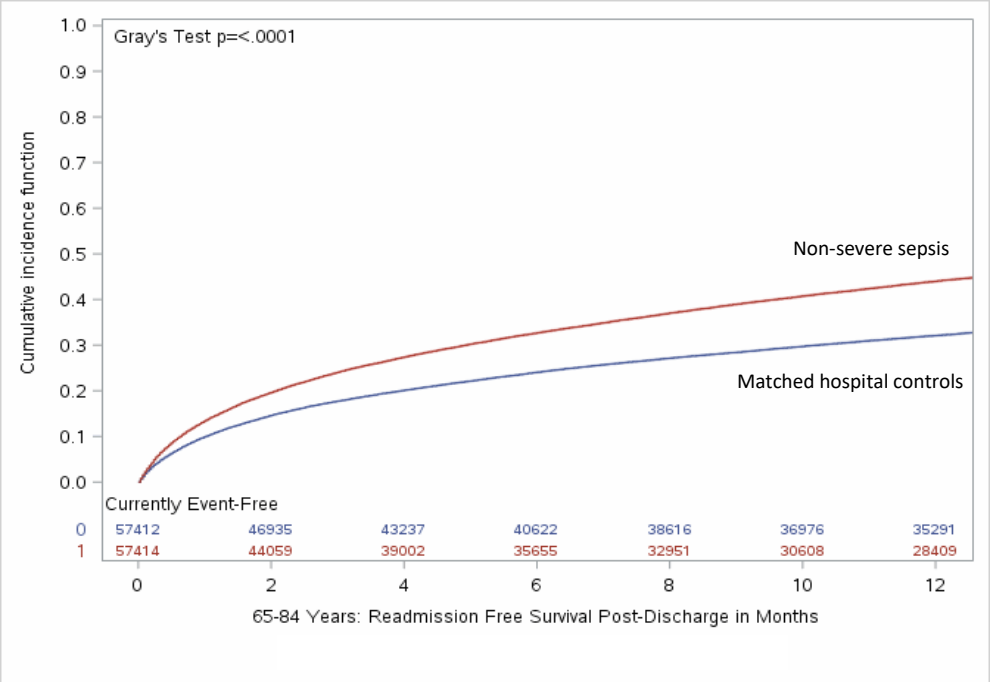


Figure C14: Time to Hospital Readmission, 1-Year. Hospital Survivor Cohort. Ages 65-84 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, 65-84 Years



b) Severe Sepsis versus Matched Hospital Controls, 65-84 Years

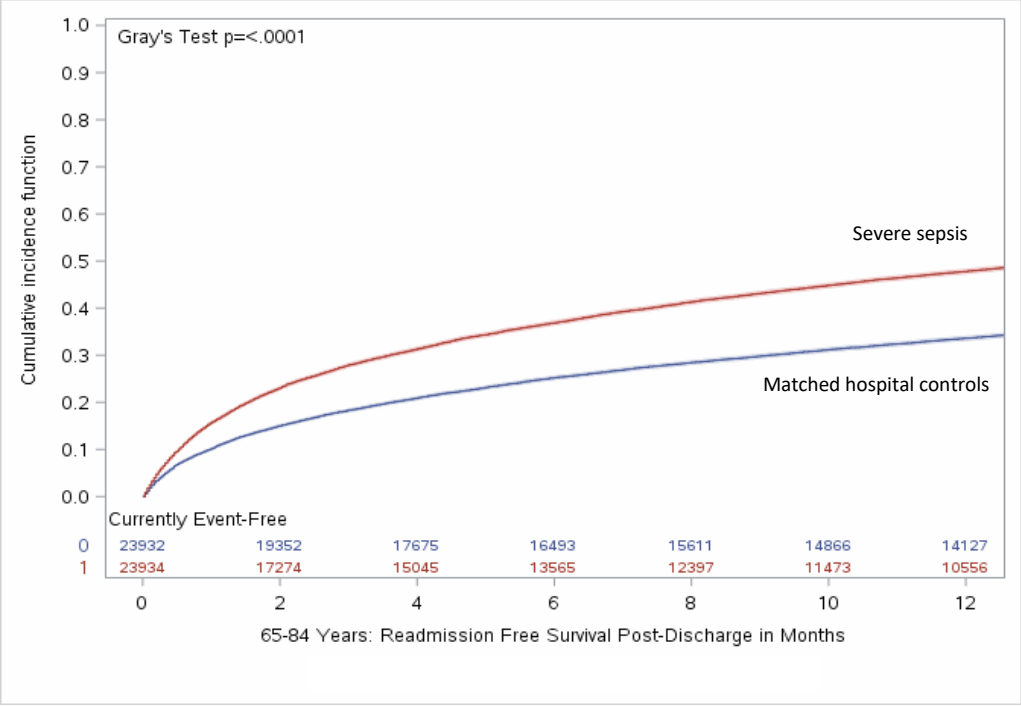
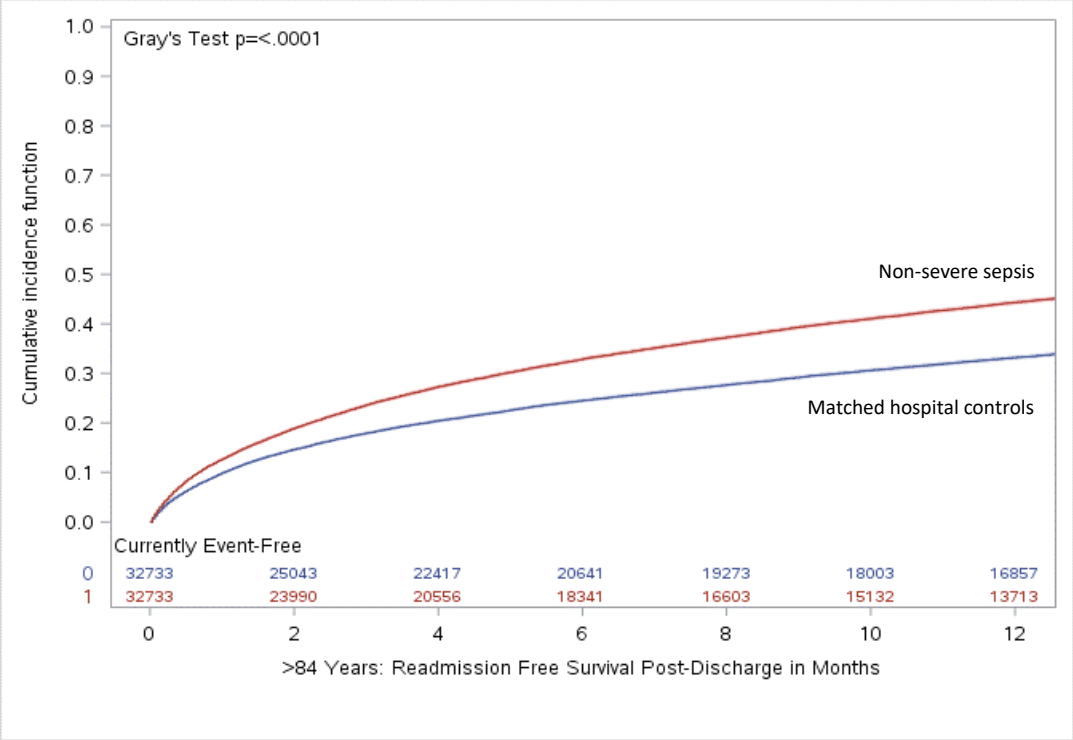


Figure C15: Time to Hospital Readmission, 1-Year. Hospital Survivor Cohort, Ages ≥85 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, ≥85 Years



b) Severe Sepsis versus Matched Hospital Controls, ≥85 Years

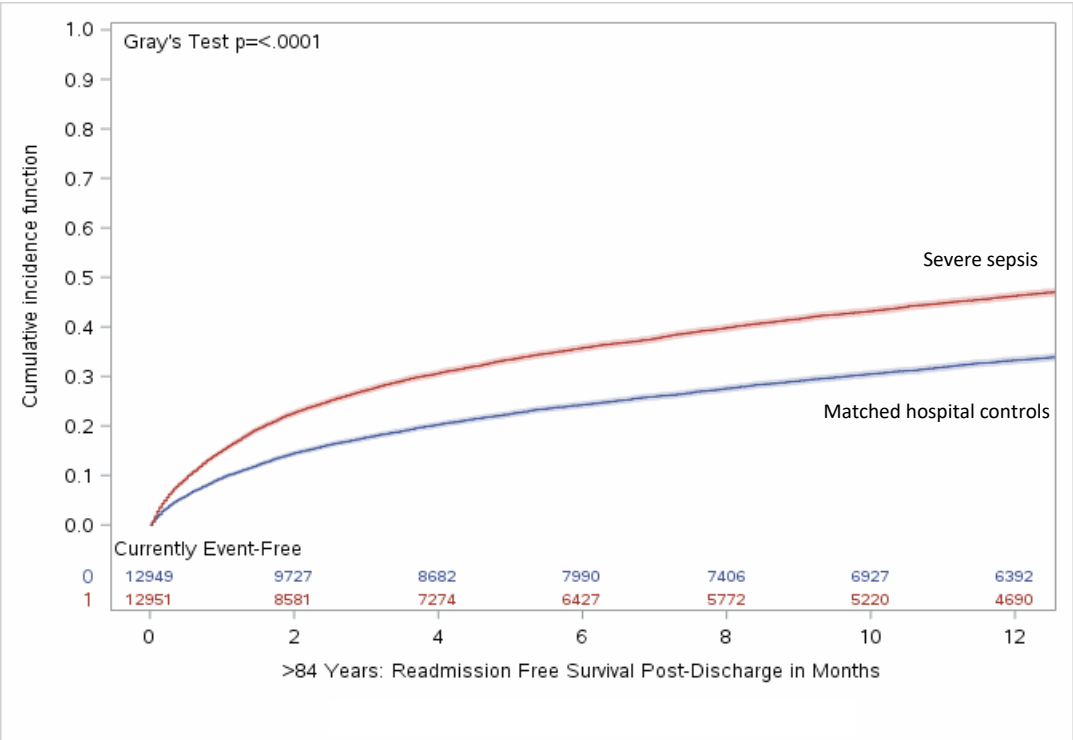
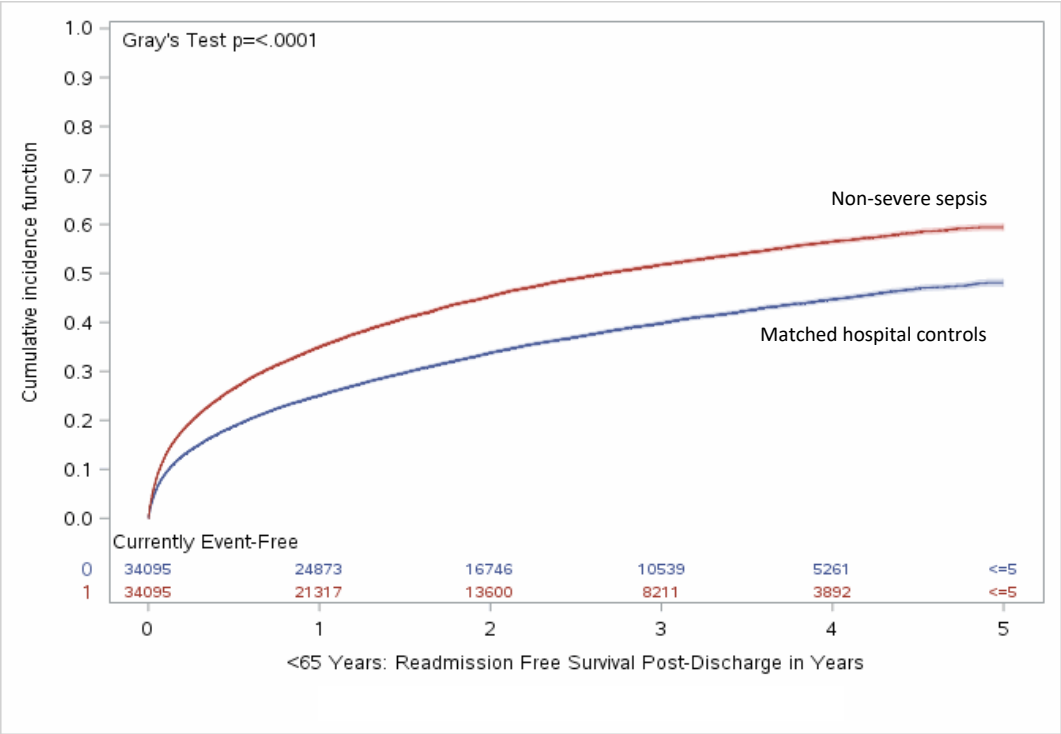


Figure C16: Time to Hospital Readmission, 5-Year. Hospital Survivor Cohort. Ages <65 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, <65 Years



b) Severe Sepsis versus Matched Hospital Controls, <65 Years

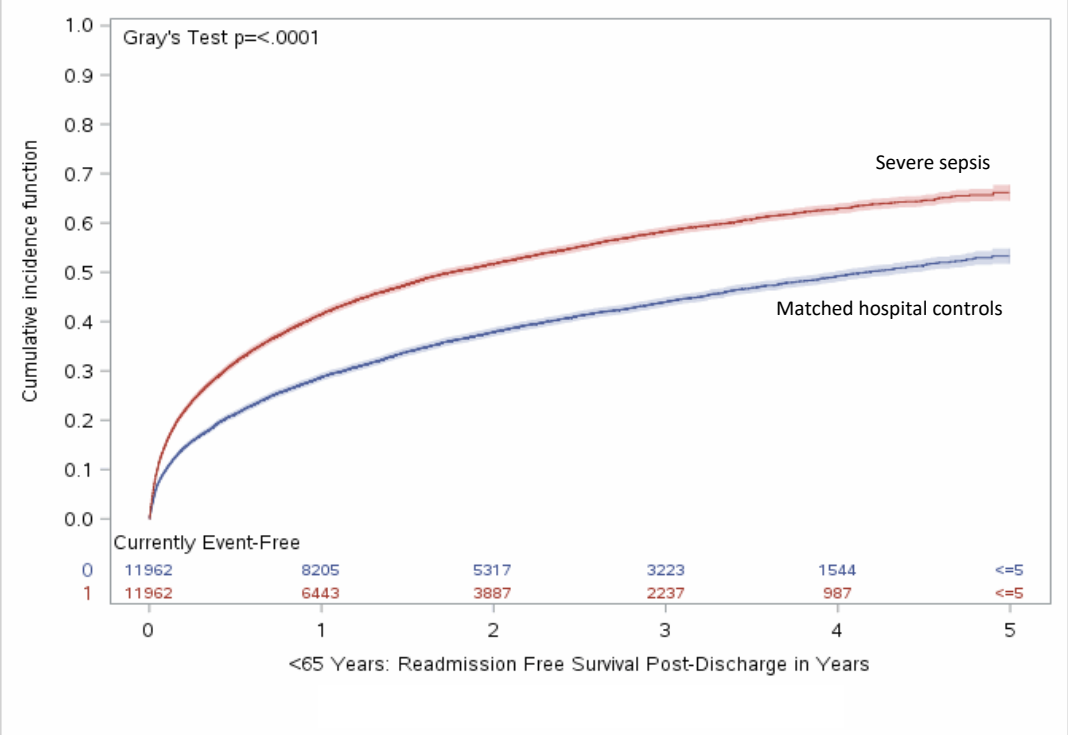
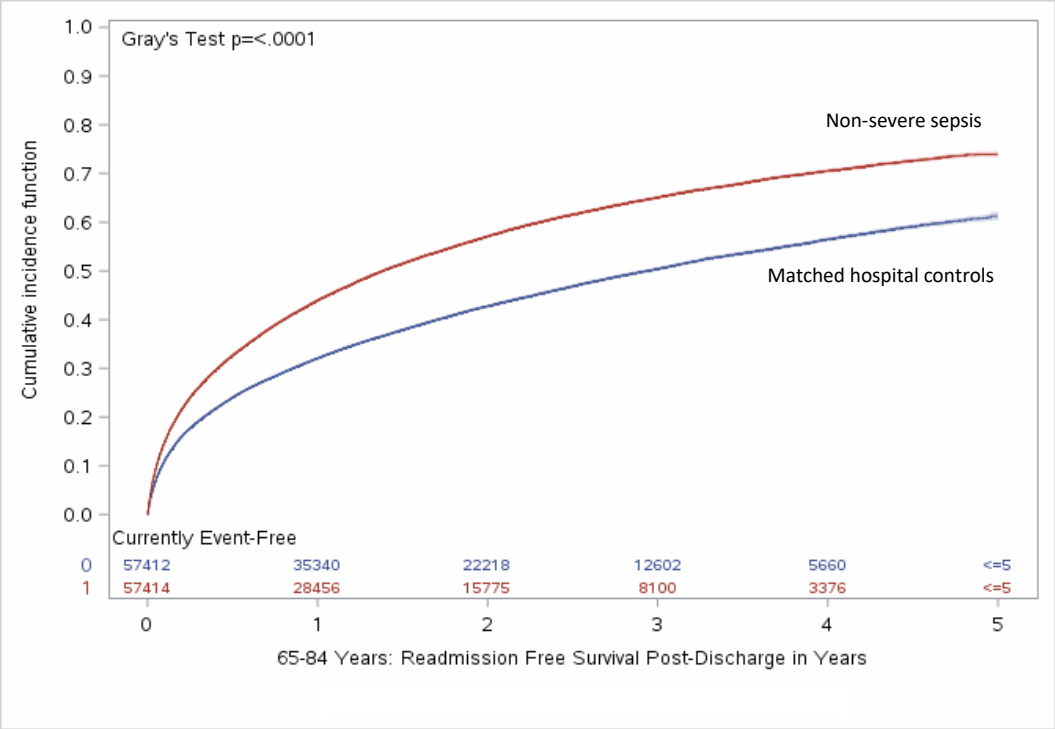


Figure C17: Time to Hospital Readmission, 5-Year. Hospital Survivor Cohort. Ages 65-84 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, 65-84 Years



b) Severe Sepsis versus Matched Hospital Controls, 65-84 Years

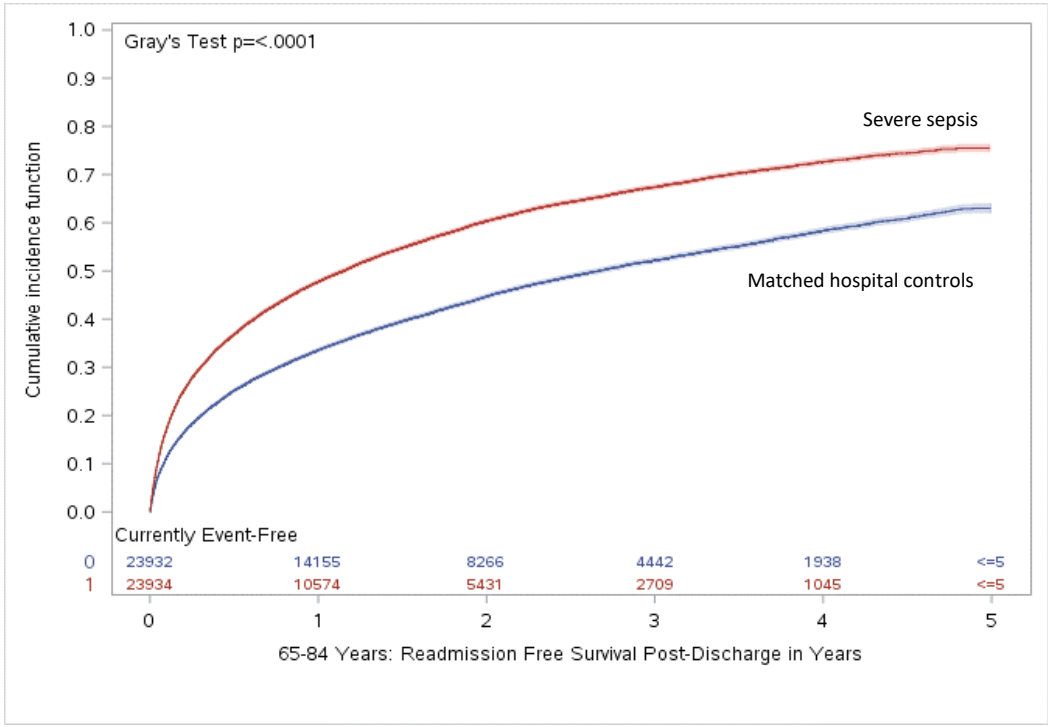
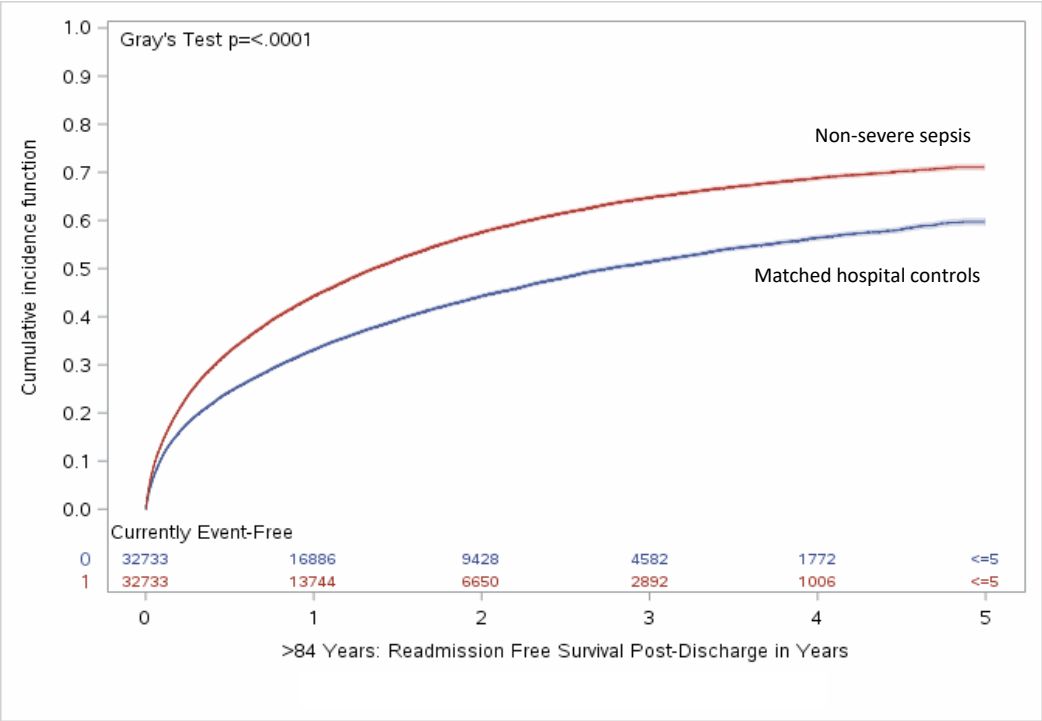
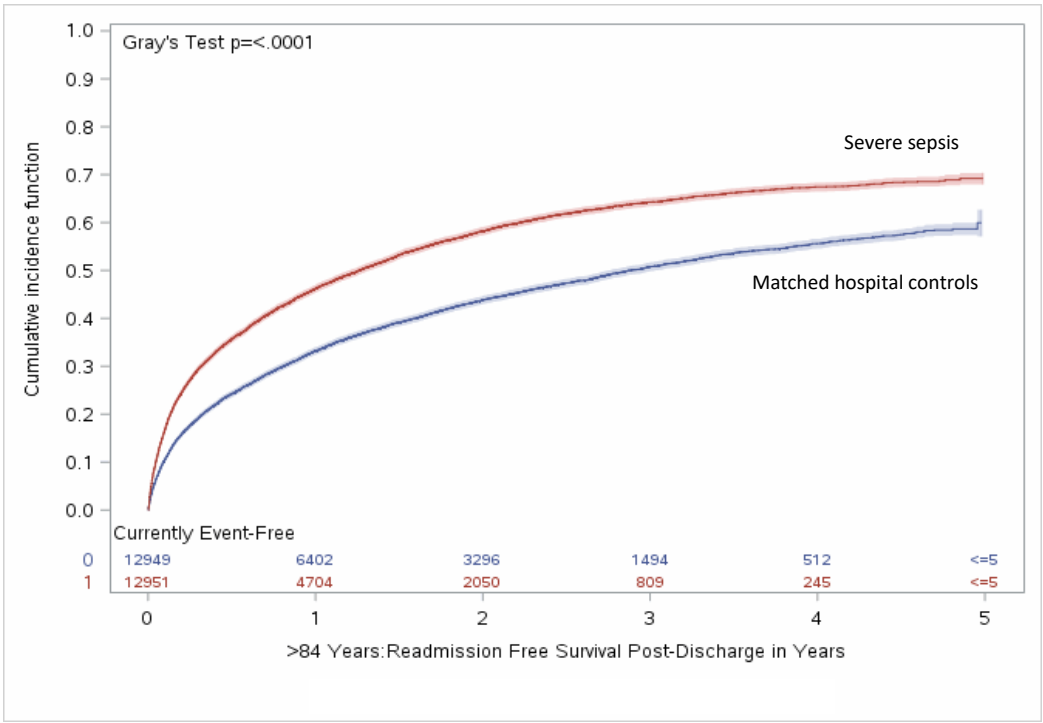


Figure C18: Time to Hospital Readmission, 5-Year. Hospital Survivor Cohort. Ages ≥85 Years

a) Non-Severe Sepsis versus Matched Hospital Controls, ≥ 85 Years



b) Severe Sepsis versus Matched Hospital Controls, ≥ 85 Years



APPENDIX D. Additional Data for Sensitivity Analysis Using CIHI 2009 Sepsis Definition

This section provides data not included above on the sensitivity analysis in which sepsis is defined using the health administrative definition used by the CIHI 2009 report on sepsis.[5] All analyses described in the primary analysis were repeated with the sepsis cases identified by this alternate sepsis definition. The CIHI 2009 definition includes seven fewer codes compared to the Jolley et al. algorithm. The differences between the two case definitions for sepsis are highlighted in Table 8 above.

List of Tables in Appendix D

List of Figures in Appendix D

Table D1: CIHI Definition. Baseline Characteristics of Cases and Controls, Before and After Matching

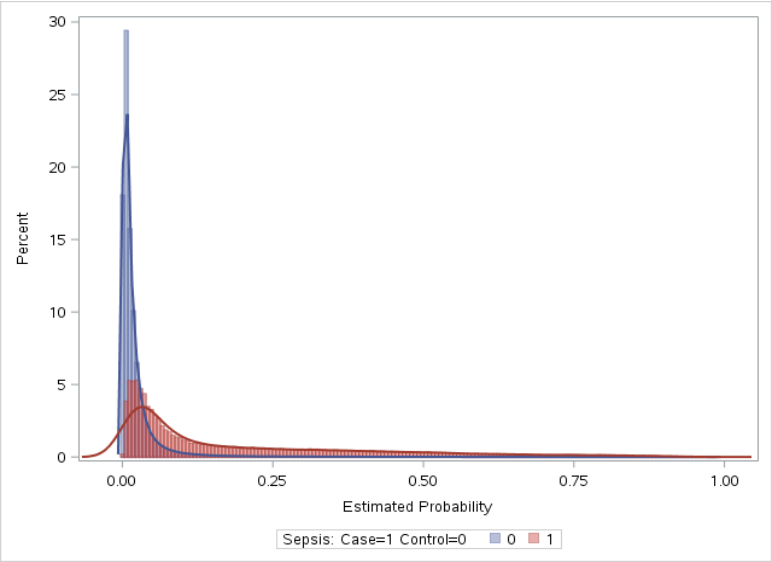
	BEFORE MATCHING			AFTER MATCHING					
	Control Pool	**All Cases**	**Std. Diff.**	**Matched Controls**	**Non-Severe (no organ failure)**	**Std. Diff**	**Matched Controls**	**Severe Sepsis (or shock)**	**Std. Diff.**
	N=1,598,966	**N= 48,319**		**N= 16,464**	**N= 16,464** *Unmatched =22.4%*		**N=19,850**	**N=19,850** *Unmatched =26.8%*	
Age, mean (SD)	53.03 (20.3)	70.01 (16.2)	**0.92**	69.4 (17.3)	69.4 (17.3)	**0.00**	70.9 (15.3)	70.9 (15.3)	**0.00**
<65	1067238 (67)	15911 (33)	**0.72**	5649 (34.3)	5653 (34.3)	**0.00**	6168 (31.1)	6191 (31.2)	**0.00**
65-84	432504 (27)	22753 (47)	**0.42**	7294 (44.3)	7335 (44.6)	**0.01**	9659 (48.7)	9661 (48.7)	**0.00**
≥ 85	99224 (6)	9655 (20)	**0.42**	3521 (21.4)	3476 (21.1)	**0.01**	4023 (20.3)	3998 (20.1)	**0.00**
Female	1012110 (63)	22056 (46)	**0.36**	7797 (47.4)	7797 (47.4)	**0.00**	9122 (46.0)	9122 (46.0)	**0.00**
Rural	209042 (13)	5399 (11)	**0.06**	1757 (10.7)	2487 (15.1)	**0.13**	1915 (9.7)	1733 (8.7)	**0.03**
Income quintile									
1 (lowest)	318043 (20)	11166 (23)	**0.08**	3955 (24.0)	3507 (21.3)	**0.07**	5113 (25.8)	4590 (23.1)	**0.06**
2	319126 (20)	10137 (21)	**0.03**	3471 (21.1)	3349 (20.3)	**0.02**	4238 (21.3)	4208 (21.2)	**0.00**
3	319241 (20)	9440 (20)	**0.01**	3222 (19.6)	3311 (20.1)	**0.01**	3822 (19.3)	3841 (19.3)	**0.00**
4	333067 (21)	9124 (19)	**0.05**	3101 (18.8)	3206 (19.5)	**0.02**	3494 (17.6)	3788 (19.1)	**0.04**
5 (highest)	301890 (19)	8174 (17)	**0.05**	2613 (15.9)	2988 (18.1)	**0.06**	3065 (15.4)	3328 (16.8)	**0.04**
missing	7599 (0.5)	278 (0.6)	**0.01**	102 (0.6)	103 (0.6)	**0.00**	118 (0.6)	95 (0.5)	**0.02**
ON Marginalization Index									
1 (lowest)	299829 (19)	6576 (14)	**0.14**	2173 (13.2)	2432 (14.8)	**0.05**	2568 (12.9)	2629 (13.2)	**0.01**
2	360347 (23)	8902 (18)	**0.10**	3043 (18.5)	3145 (19.1)	**0.02**	3596 (18.1)	3594 (18.1)	**0.00**
3	350612 (22)	10578 (22)	**0.00**	3645 (22.1)	3687 (22.4)	**0.01**	4319 (21.8)	4299 (21.7)	**0.00**
4	293876 (18)	9760 (20)	**0.05**	3292 (20.0)	3283 (19.9)	**0.00**	4046 (20.4)	4008 (20.2)	**0.00**
5 (highest)	281107 (18)	11951 (25)	**0.18**	4111 (25.0)	3700 (22.5)	**0.06**	5077 (25.6)	5163 (26.0)	**0.01**
missing	13195 (0.8)	552 (1.1)	**0.03**	200 (1.2)	217 (1.3)	**0.01**	244 (1.2)	157 (0.8)	**0.04**
Prior cancer	158015 (10)	9709 (20)	**0.29**	2176 (13.2)	2871 (17.4)	**0.12**	3191 (16.1)	3346 (16.9)	**0.02**
Prior CHF	103562 (6)	13019 (27)	**0.57**	3783 (23.0)	3134 (19.0)	**0.10**	5136 (25.9)	5366 (27.0)	**0.03**
Prior CKD	8213 (0.5)	3725 (7.7)	**0.37**	1351 (8.2)	259 (1.6)	**0.31**	2041 (10.3)	1251 (6.3)	**0.14**
Prior COPD	216224 (14)	14993 (31)	**0.43**	4634 (28.2)	4395 (26.7)	**0.03**	6408 (32.3)	6274 (31.6)	**0.01**
Prior diabetes	304691 (19)	20889 (43)	**0.54**	6716 (40.8)	6248 (38.0)	**0.06**	9578 (48.3)	8196 (41.3)	**0.14**
Residence in LTC	19064 (1.2)	4816 (10)	**0.39**	1400 (8.5)	1757 (10.7)	**0.07**	2055 (10.4)	1683 (8.5)	**0.06**
ADG score, mean (SD)	11.66 (18.8)	31.72 (13.48)	**1.23**	29.7 (14.2)	28.1 (13.4)	**0.11**	33.0 (13.0)	34.1 (13.3)	**0.09**
Healthcare use, past year									
Hospitalization, n (%)	39442 (2.5)	18054 (37)	**0.85**	1750 (10.6)	3257 (19.8)	**0.26**	2167 (10.9)	3539 (17.8)	**0.20**
Homecare use, n (%)	166558 (10)	22057 (46)	**0.85**	5364 (32.6)	6231 (37.9)	**0.11**	7604 (38.3)	6889 (34.7)	**0.07**

	BEFORE MATCHING			AFTER MATCHING					
	Control Pool	**All Cases**	**Std. Diff.**	**Matched Controls**	**Non-Severe (no organ failure)**	**Std. Diff**	**Matched Controls**	**Severe Sepsis (or shock)**	**Std. Diff.**
	N=1,598,966	**N= 48,319**		**N= 16,464**	**N= 16,464** *Unmatched =22.4%*		**N=19,850**	**N=19,850** *Unmatched =26.8%*	
ED visits									
Mean (SD)	0.9 (1.8)	1.4 (2.8)	**0.23**	1.3 (2.9)	1.3 (2.4)	**0.01**	1.4 (4.1)	1.0 (1.8)	**0.12**
Median (Q1-Q3)	0 (0-1)	1 (0-2)	**0.30**	1 (0-2)	1 (0-2)	**0.04**	1 (0-2)	0 (0-1)	**0.14**
Physician visits									
Mean (SD)	16.45 (12.96)	28.01 (26.28)	**0.56**	20.5 (19.6)	22.3 (21.6)	**0.09**	22.7 (20.8)	21.4 (21.3)	**0.06**
Median (Q1-Q3)	14 (7-22)	20 (10-37)	**0.42**	15 (8-26)	16 (9-28)	**0.08**	16 (9-28)	16 (8-27)	**0.09**
Index Admission									
Urgent admission, n (%)	821012 (51)	46966 (97)	**1.23**	16154 (98.1)	16154 (98.1)	**0.00**	19304 (97.3)	19304 (97.3)	**0.00**
Index Admission Date									
Apr 2012 – Mar 2013	474080 (30)	11239 (23)	**0.15**	5007 (30.4)	4976 (30.2)	**0.00**	5910 (29.8)	5886 (29.6)	**0.00**
Apr 2013 – Mar 2014	416610 (26)	11866 (25)	**0.03**	3844 (23.4)	3888 (23.6)	**0.01**	4492 (22.6)	4518 (22.8)	**0.00**
Apr 2014 – Mar 2015	370348 (23)	12578 (26)	**0.07**	3858 (23.4)	3853 (23.4)	**0.00**	4770 (24.0)	4757 (24.0)	**0.00**
Apr 2015 – Mar 2016	337928 (21)	12636 (26)	**0.12**	3755 (22.8)	3747 (22.8)	**0.00**	4678 (23.6)	4689 (23.6)	**0.00**
Hospital Type*									
Teaching	527824 (33)	12907 (27)	**0.14**	5087 (30.9)	3794 (23.0)	**0.18**	6146 (31.0)	5352 (27.0)	**0.09**
Community ≥ 100 beds	839121 (52)	27459 (57)	**0.09**	8776 (53.3)	8682 (52.7)	**0.01**	10640 (53.6)	12247 (61.7)	**0.16**
Community < 100 beds	231990 (15)	7953 (16)	**0.05**	2601 (15.8)	3988 (24.2)	**0.21**	3064 (15.4)	2251 (11.3)	**0.12**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = Congestive heart failure; CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; ON= Ontario; SD = standard deviation; Std Diff = standardized difference.
*Variable not included in propensity score model.
Number of missing values: rural = 38; hospital type = 31.

Figure D1: CIHI Definition. Plot of Propensity Scores for Cases and Controls Before and After Matching

a) Pre-Match



b) Post-Match

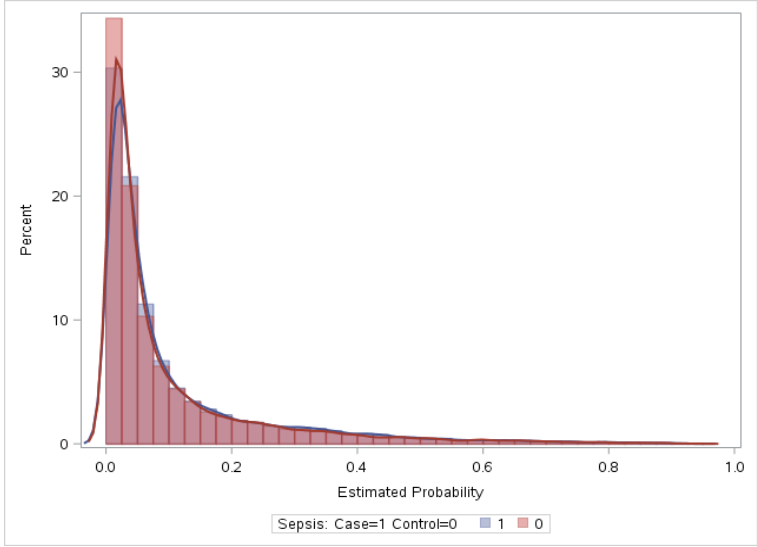


Table D2: CIHI Definition. Hospital Survivor Cohort. Baseline Characteristics of Cases and Controls, Before and After Matching

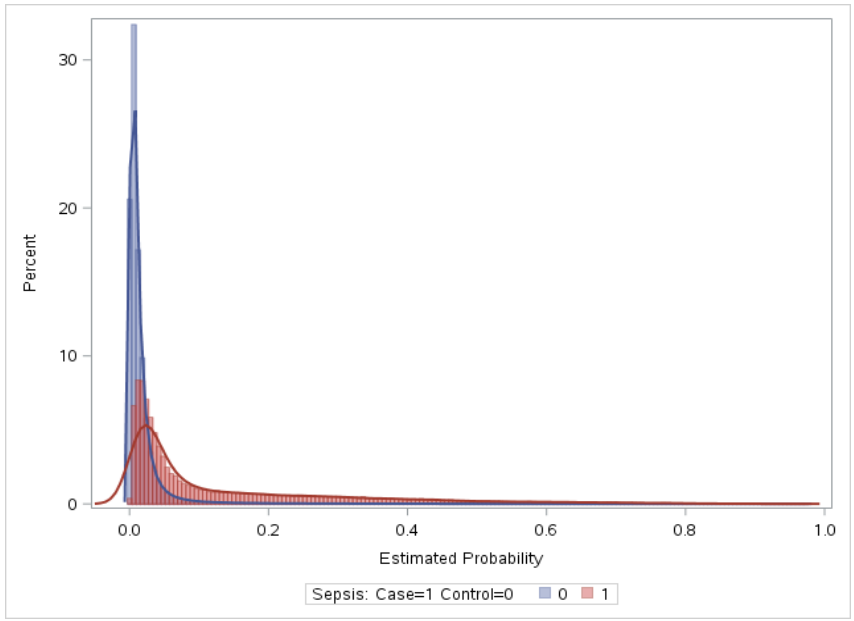
	BEFORE MATCHING			AFTER MATCHING					
	Control Pool **N=1,560,571**	**All Cases** **N= 33,850**	**Std. Diff.**	**Matched Controls** **N= 13,862**	**Non-Severe Sepsis (no organ dysfunction)** **N= 13,862** *Unmatched = 22.7%*	**Std. Diff**	**Matched Controls** **N=12,068**	**Severe Sepsis (including shock)** **N= 12,068** *Unmatched =24.6%*	**Std. Diff**
Age, mean (SD)	52.5 (20.1)	67.9 (16.7)	**0.83**	67.7 (17.3)	67.7 (17.3)	**0.00**	68.8 (15.8)	68.7 (15.8)	**0.00**
<65	1058495 (68)	12715 (38)	**0.64**	5270 (38.0)	5269 (38.0)	**0.00**	4314 (35.7)	4353 (36.1)	**0.01**
65-84	414805 (26)	15556 (46)	**0.41**	6153 (44.4)	6176 (44.6)	**0.00**	5778 (47.9)	5753 (47.7)	**0.00**
≥ 85	87271 (6)	5579 (16)	**0.35**	2439 (17.6)	2417 (17.4)	**0.00**	1976 (16.4)	1962 (16.2)	**0.00**
Female	994064 (64)	15388 (45)	**0.37**	6466 (46.7)	6466 (46.7)	**0.00**	5573 (46.2)	5573 (46.2)	**0.00**
Rural	202314 (13)	4005 (12)	**0.03**	1520 (11.0)	2049 (14.8)	**0.11**	1227 (10.2)	1077 (8.9)	**0.04**
Income quintile									
1 (lowest)	309326 (20)	7765 (23)	**0.08**	3464 (25.0)	2948 (21.3)	**0.09**	3163 (26.2)	2772 (23.0)	**0.08**
2	310975 (20)	7002 (21)	**0.02**	2851 (20.6)	2824 (20.4)	**0.00**	2522 (20.9)	2513 (20.8)	**0.00**
3	311690 (20)	6667 (20)	**0.01**	2684 (19.4)	2758 (19.9)	**0.01**	2269 (18.8)	2381 (19.7)	**0.02**
4	325867 (21)	6402 (19)	**0.05**	2527 (18.2)	2726 (19,7)	**0.04**	2172 (18.0)	2302 (19.1)	**0.03**
5 (highest)	295393 (19)	5807 (17)	**0.05**	2225 (16.0)	2523 (18.2)	**0.06**	1852 (15.3)	2034 (16.9)	**0.04**
missing	7320 (0.5)	207 (0.6)	**0.02**	111 (0.8)	83 (0.6)	**0.02**	90 (0.8)	66 (0.5)	**0.02**
ON Marginalization Index									
1 (lowest)	294599 (19)	4805 (14)	**0.13**	2026 (14.6)	2107 (15.2)	**0.02**	1579 (13.1)	1661 (13.8)	**0.02**
2	353433 (23)	6453 (19)	**0.09**	2568 (18.5)	2698 (19.5)	**0.02**	2236 (18.5)	2273 (18.8)	**0.01**
3	342170 (22)	7539 (22)	**0.01**	3056 (22.1)	3148 (22.7)	**0.02**	2676 (22.2)	2663 (22.1)	**0.00**
4	285918 (18)	6655 (20)	**0.03**	2705 (19.5)	2762 (19.9)	**0.01**	2466 (20.4)	2353 (19.5)	**0.02**
5 (highest)	271744 (17)	7970 (24)	**0.15**	3306 (23.8)	2964 (21.4)	**0.06**	2917 (24.2)	3014 (25.0)	**0.02**
missing	12707 (0.8)	428 (1.3)	**0.04**	201 (1.5)	183 (1.3)	**0.01**	194 (1.6)	104 (0.9)	**0.07**
Prior cancer	148036 (9)	6141 (18)	**0.25**	1704 (12.3)	2219 (16.0)	**0.11**	1690 (14.0)	1709 (14.2)	**0.00**
Prior CHF	93665 (6)	7820 (23)	**0.50**	2774 (20.0)	2355 (17.0)	**0.08**	2702 (22.4)	2934 (24.3)	**0.05**
Prior CKD	7103 (0.5)	1862 (6)	**0.30**	886 (6.4)	227 (1.6)	**0.24**	958 (7.9)	637 (5.3)	**0.11**
Prior COPD	204028 (13)	9776 (29)	**0.40**	3812 (27.5)	3576 (25.8)	**0.04**	3642 (30.2)	3545 (29.4)	**0.02**
Prior diabetes	292120 (19)	14486 (43)	**0.54**	5746 (41.5)	5214 (37.6)	**0.08**	5991 (49.6)	5025 (41.6)	**0.16**
Residence in LTC	16180 (1)	2970 (9)	**0.36**	1024 (7.4)	1186 (8.6)	**0.04**	1121 (9.3)	926 (7.7)	**0.06**
ADG score, mean (SD)	11.2 (18.7)	30.4 (13.6)	**1.18**	28.8 (14.4)	27.3 (13.4)	**0.11**	31.7 (13.3)	33.2 (13.4)	**0.11**
Healthcare use, past year									
Hospitalization, n (%)	37281 (2)	11903 (35)	**0.92**	1399 (10.1)	2371 (17.1)	**0.21**	1129 (9.4)	1807 (15.0)	**0.17**

	BEFORE MATCHING			AFTER MATCHING					
	Control Pool **N=1,560,571**	**All Cases** **N= 33,850**	**Std. Diff.**	**Matched Controls** **N= 13,862**	**Non-Severe Sepsis (no organ dysfunction)** **N= 13,862** *Unmatched = 22.7%*	**Std. Diff**	**Matched Controls** **N=12,068**	**Severe Sepsis (including shock)** **N= 12,068** *Unmatched =24.6%*	**Std. Diff**
Homecare use, n (%)	151483 (10)	14187 (42)	**0.79**	4090 (29.5)	4677 (33.7)	**0.09**	4341 (36.0)	3618 (30.0)	**0.13**
ED visits									
Mean (SD)	0.9 (1.8)	1.4 (2.9)	**0.23**	1.3 (2.5)	1.3 (2.4)	**0.02**	1.5 (4.4)	1.0 (1.9)	**0.15**
Median (Q1-Q3)	0 (0-1)	1 (0-2)	**0.30**	1 (0-2)	1 (0-2)	**0.01**	1 (0-2)	0 (0-1)	**0.19**
Physician visits									
Mean (SD)	16.4 (12.8)	26.7 (25.2)	**0.52**	20.1 (19.2)	21.3 (20.6)	**0.06**	21.8 (19.7)	20.3 (20.1)	**0.08**
Median (Q1-Q3)	14 (8-22)	19 (10-35)	**0.37**	15 (8-25)	15 (8-27)	**0.05**	16 (9-27)	15 (8-26)	**0.11**
Index Admission									
Urgent admission, n (%)	784354 (50)	32959 (97)	**1.27**	13591 (98.1)	13591 (98.1)	**0.00**	11762 (97.5)	11762 (97.5)	**0.00**
Index Admission Date									
Apr 2012 – Mar 2013	461123 (30)	7742 (23)	**0.15**	4157 (30.0)	4141 (29.9)	**0.00**	3388 (28.1)	3390 (28.1)	**0.00**
Apr 2013 – Mar 2014	406940 (26)	8368 (25)	**0.03**	3250 (23.4)	3270 (23.6)	**0.00**	2805 (23.2)	2781 (23.0)	**0.00**
Apr 2014 – Mar 2015	361844 (23)	8743 (26)	**0.06**	3228 (23.3)	3227 (23.3)	**0.00**	2892 (24.0)	2915 (24.2)	**0.00**
Apr 2015 – Mar 2016	330664 (21)	8997 (26)	**0.13**	3227 (23.3)	3224 (23.2)	**0.00**	2983 (24.7)	2982 (24.7)	**0.00**
Hospital Type*									
Teaching	516081 (33)	8746 (26)	**0.16**	4326 (31.2)	3160 (22.8)	**0.19**	3696 (30.6)	3154 (26.1)	**0.10**
Community ≥ 100 beds	820886 (53)	19017 (56)	**0.07**	7333 (52.9)	7416 (53.5)	**0.01**	6418 (53.2)	7419 (61.5)	**0.17**
Community < 100 beds	223574 (14)	6087 (18)	**0.10**	2203 (15.9)	3286 (23.7)	**0.20**	1954 (16.2)	1495 (12.4)	**0.11**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = Congestive heart failure; CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; ON= Ontario; SD = standard deviation; Std Diff = standardized difference.
*Variable not included in propensity score model.

Figure D2: CIHI Definition. Hospital Survivors. Plot of Propensity Scores for Cases and Controls Before and After Matching

a) Pre-Match



b) Post-Match

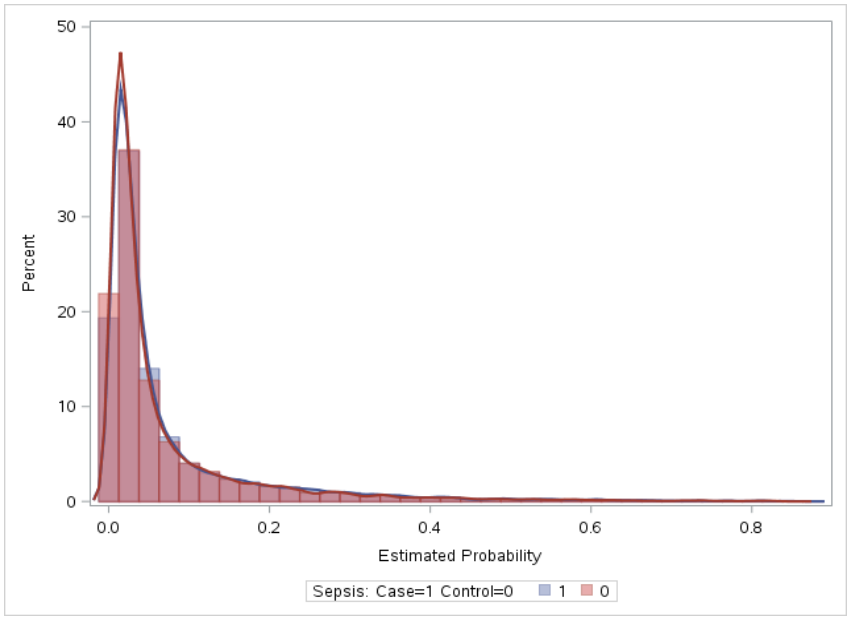
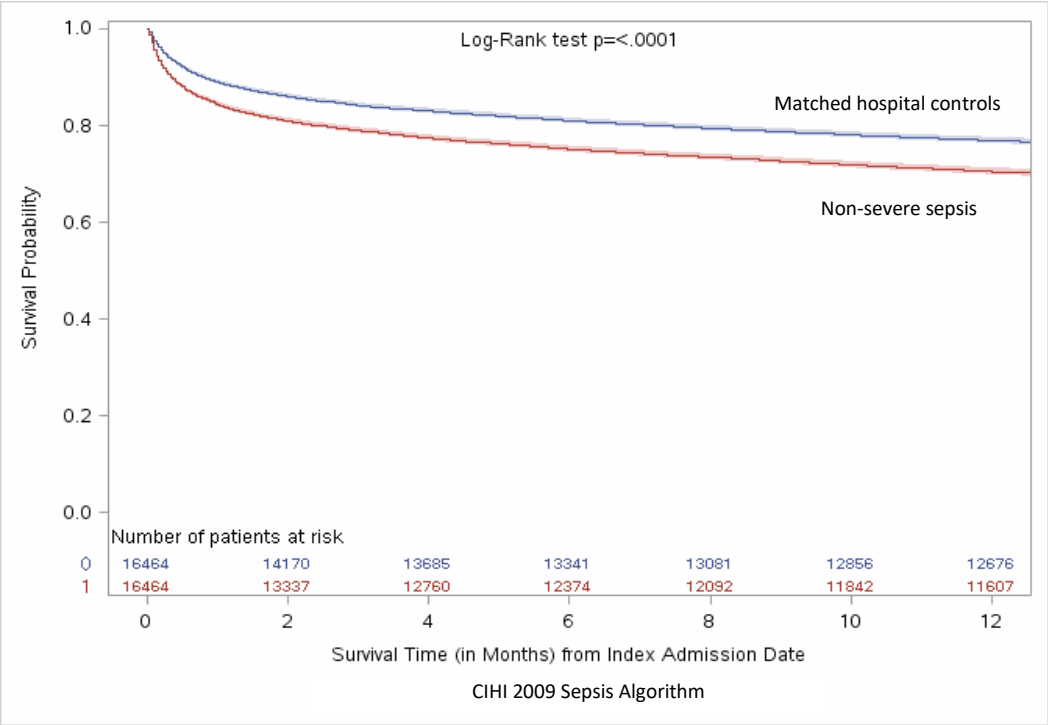


Figure D3: CIHI Definition, 1-Year Survival Kaplan Meier Plots

a) Non-Severe Sepsis versus Matched Hospital Controls



b) Severe Sepsis versus Matched Hospital Controls

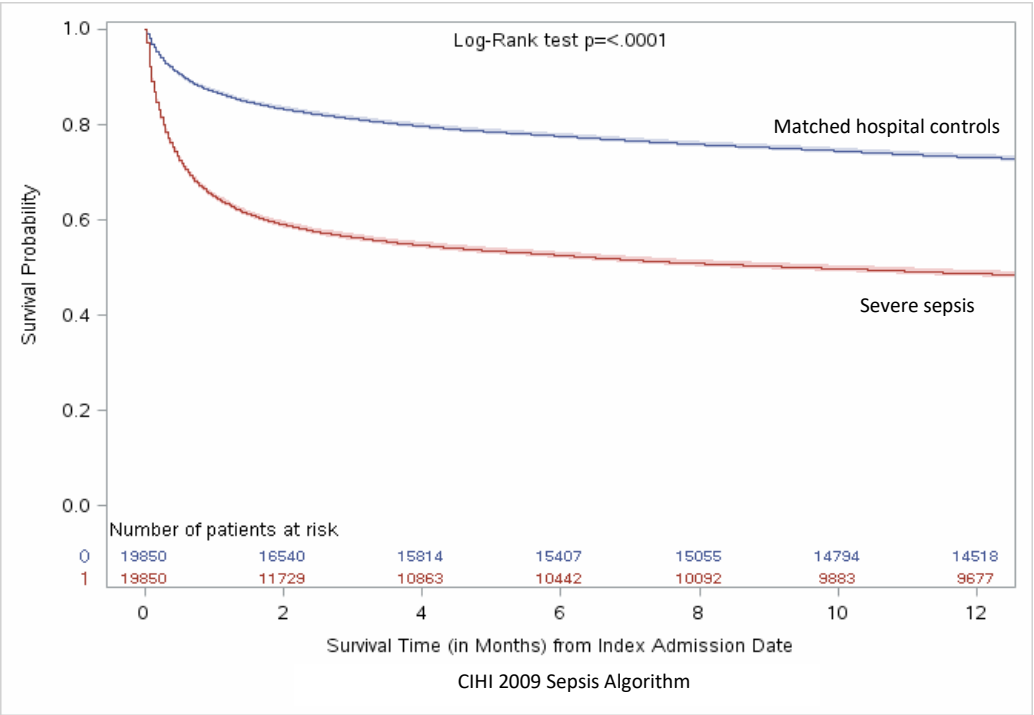
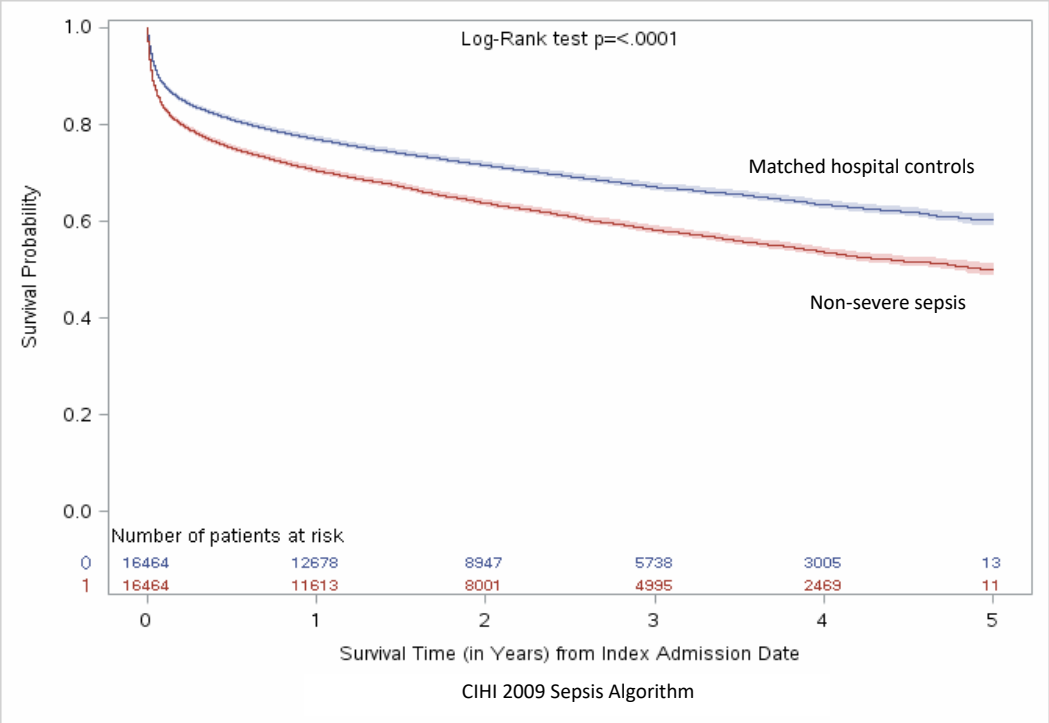


Figure D4: CIHI Definition, 5-Year Survival Kaplan Meier Plots

a) Non-Severe Sepsis versus Matched Hospital Controls



b) Severe Sepsis versus Matched Hospital Controls

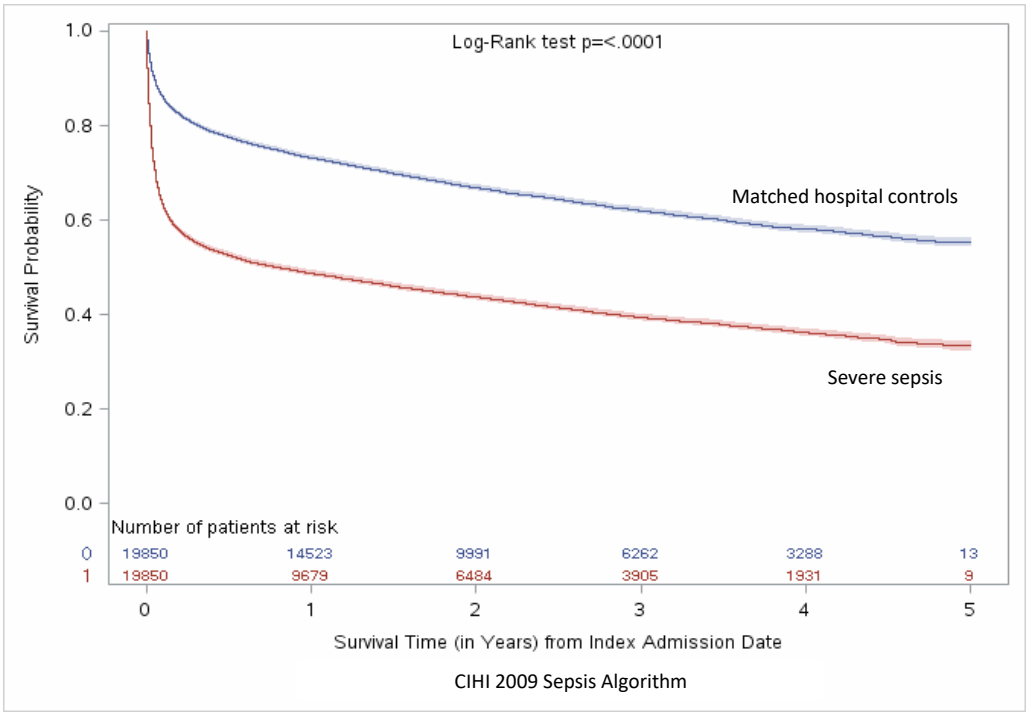
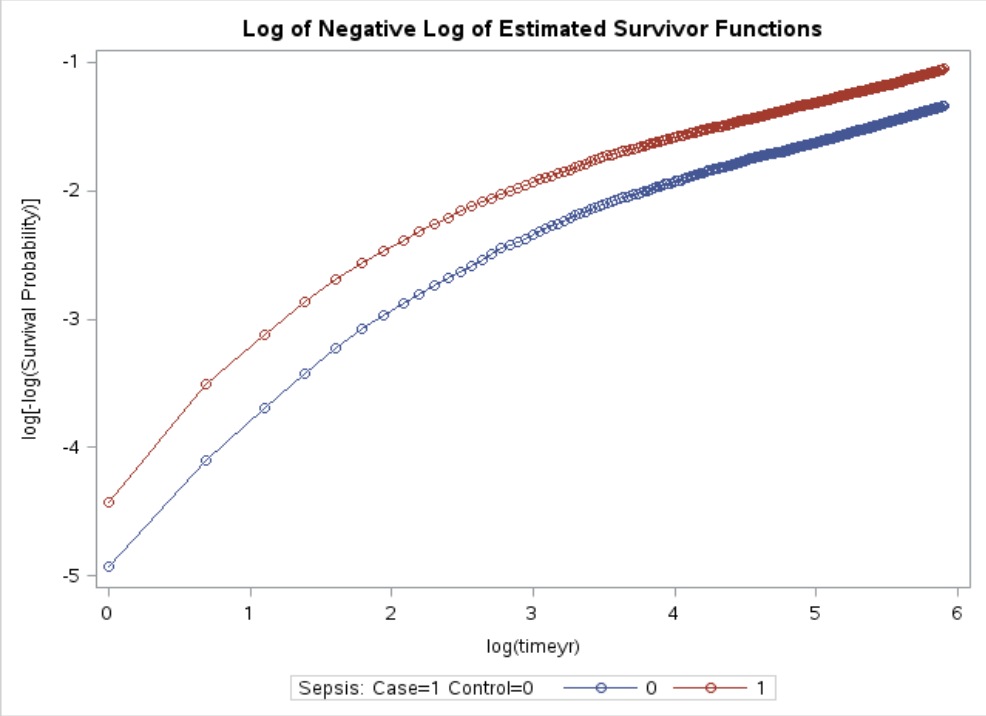


Figure D5: CIHI Cohort, Proportional Hazards Test, log(-log)survival, 1-Year Survival

a) Non-Severe Sepsis versus Matched Hospital Controls



b) Severe Sepsis versus Matched Hospital Controls

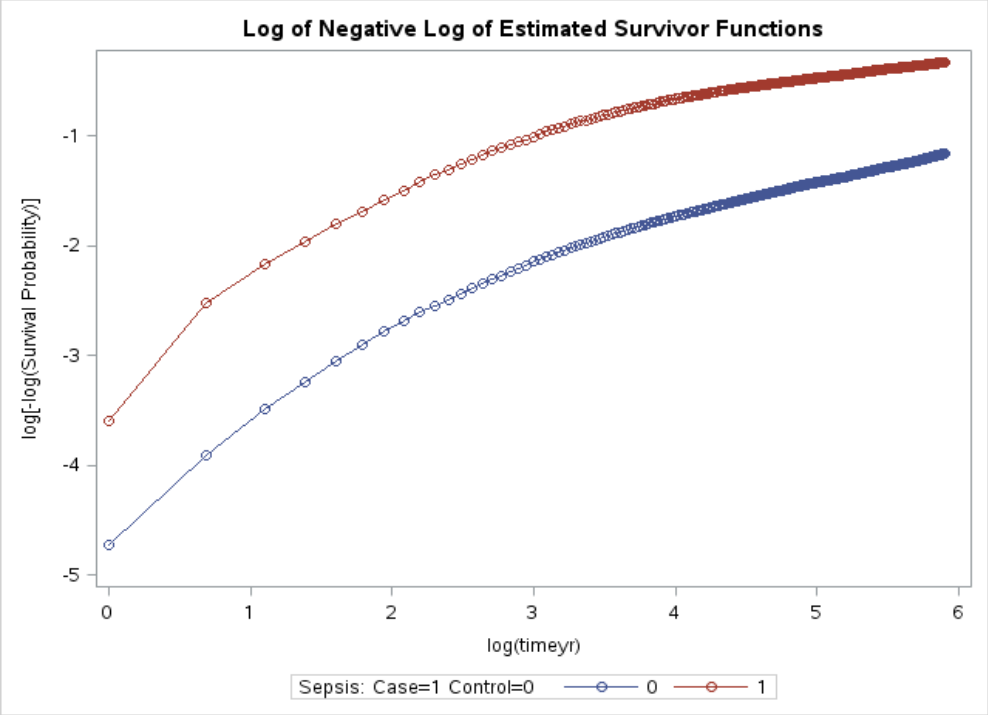
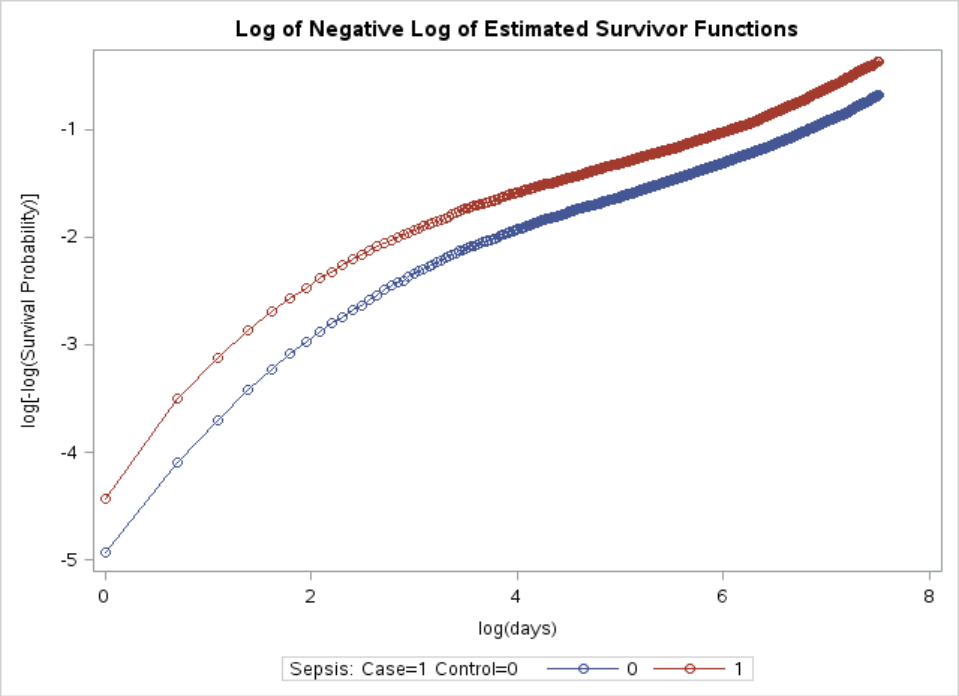


Figure D6: CIHI Cohort, Proportional Hazards Test, 5-Year Survival log(-log)survival

a) Non-Severe Sepsis versus Matched Hospital Controls



b) Severe Sepsis versus Matched Hospital Controls

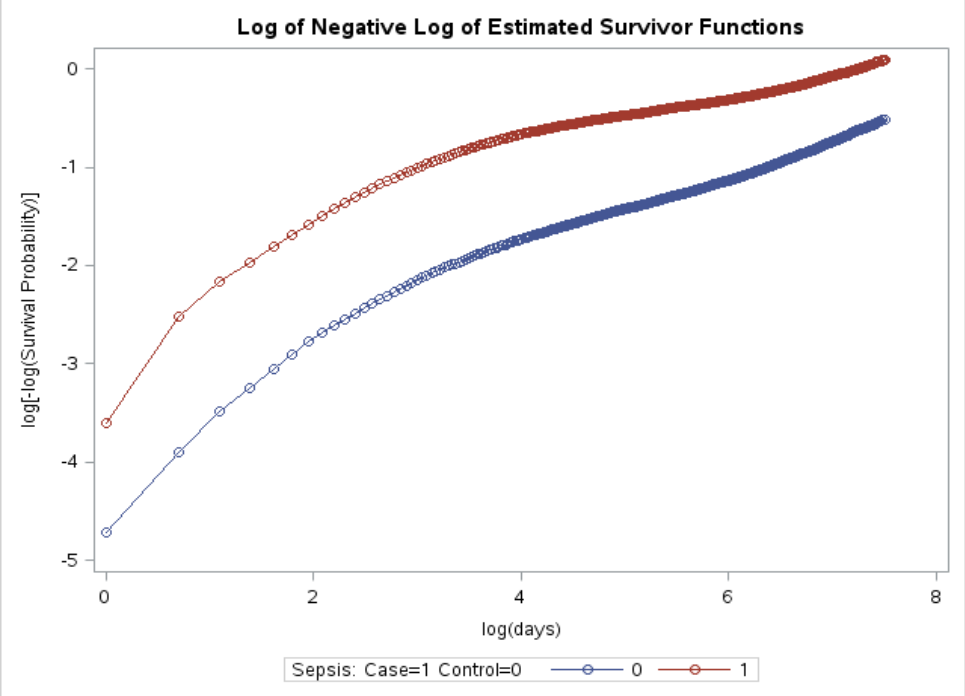
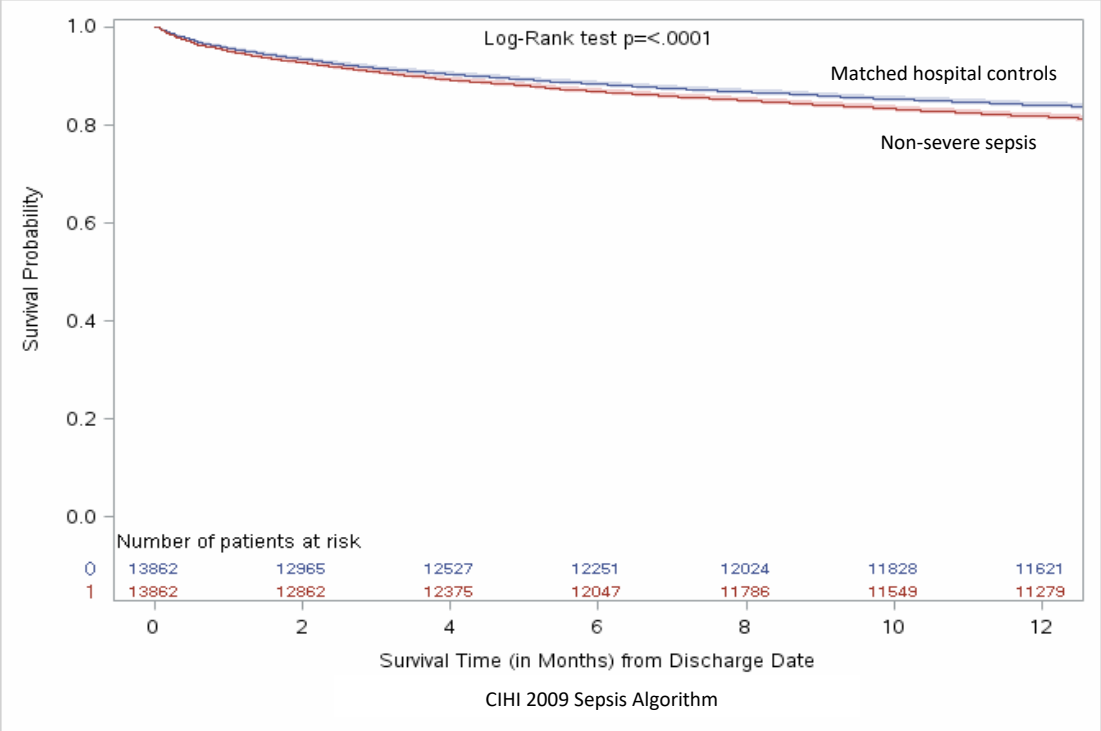


Figure D7: CIHI Definition, Hospital Survivors Post-Discharge 1-Year Survival Kaplan Meier Plots

a) Non-Severe Sepsis versus Matched Hospital Controls



b) Severe Sepsis versus Matched Hospital Controls

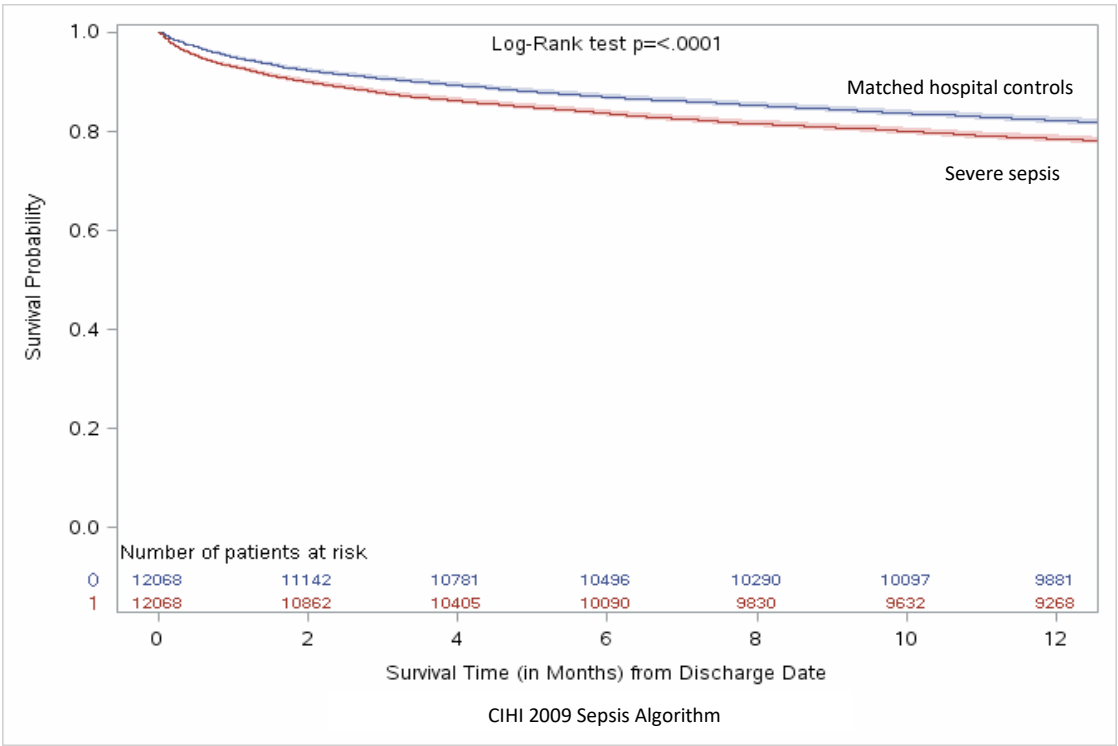
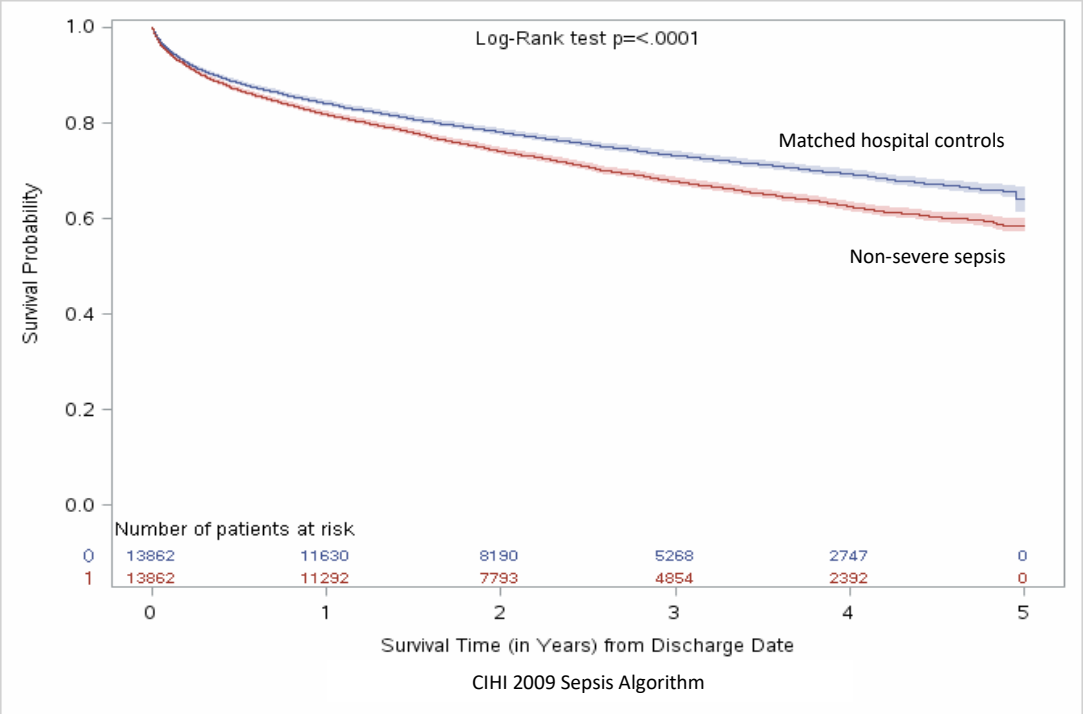


Figure D8: CIHI Definition, Hospital Survivors Post-Discharge 5-Year Survival Kaplan Meier Plots

a) Non-Severe Sepsis Survivors versus Matched Hospital Controls



b) Severe Sepsis Survivors versus Matched Hospital Controls

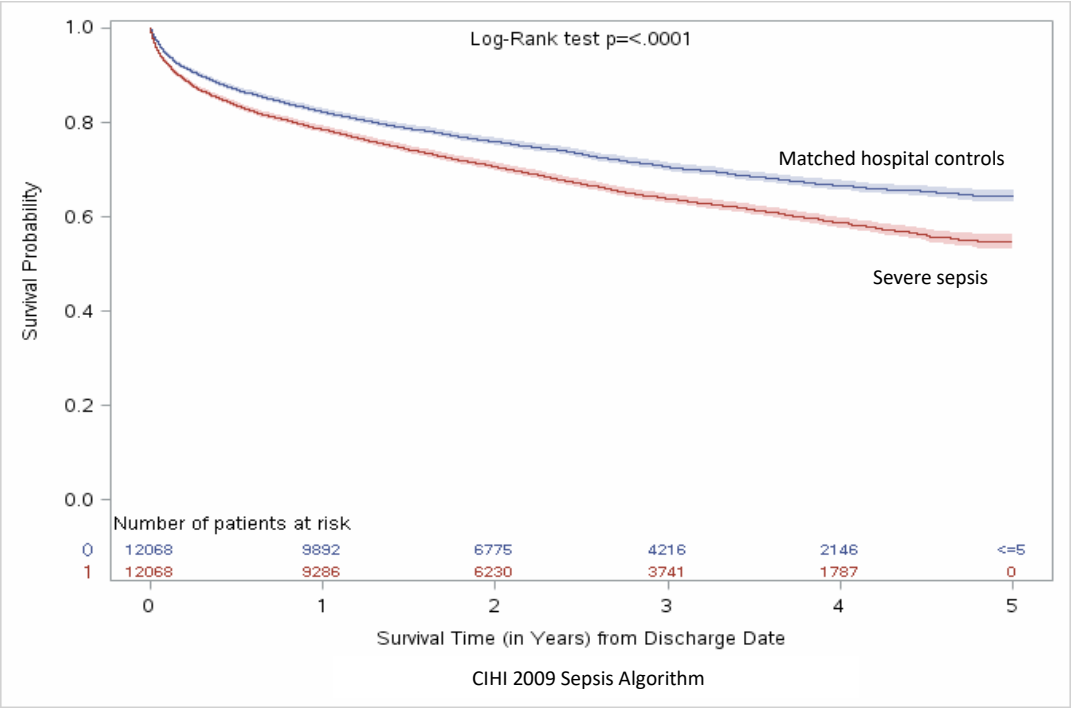
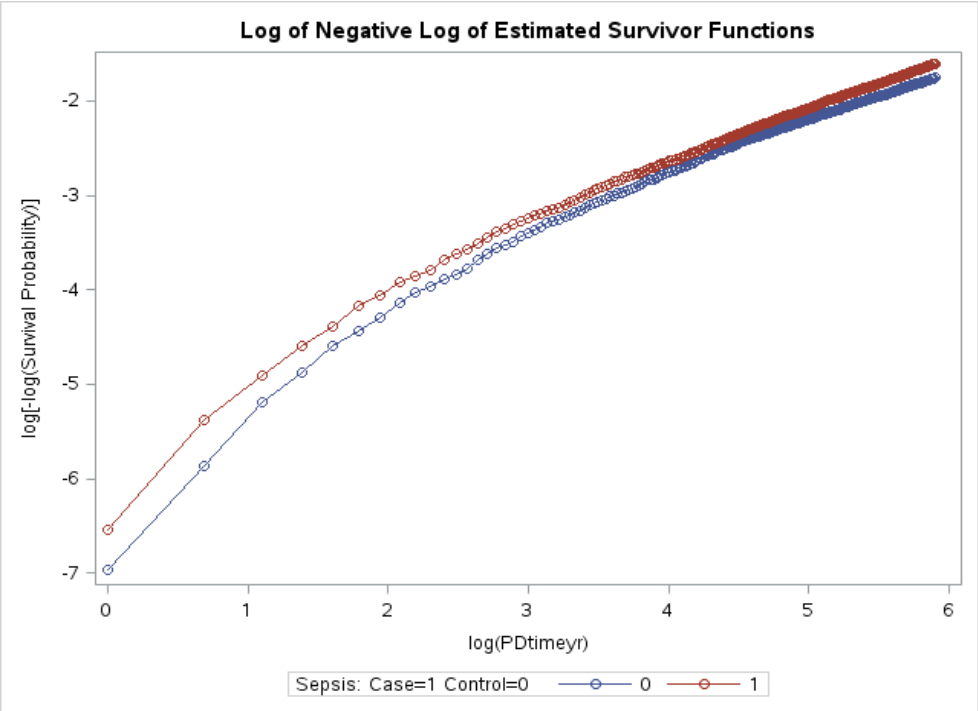


Figure D9: CIHI Cohort, Proportional Hazards Test, log(-log)survival, 1-Year Post-Discharge Survival

a) Non-Severe Sepsis versus Matched Hospital Controls



b) Severe Sepsis versus Matched Hospital Controls

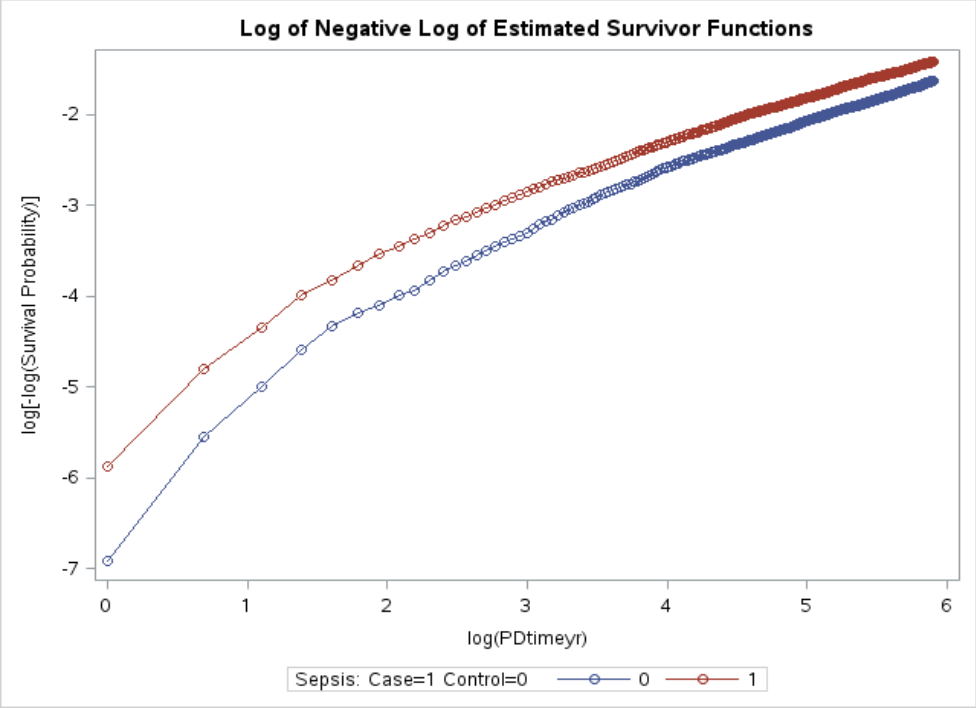
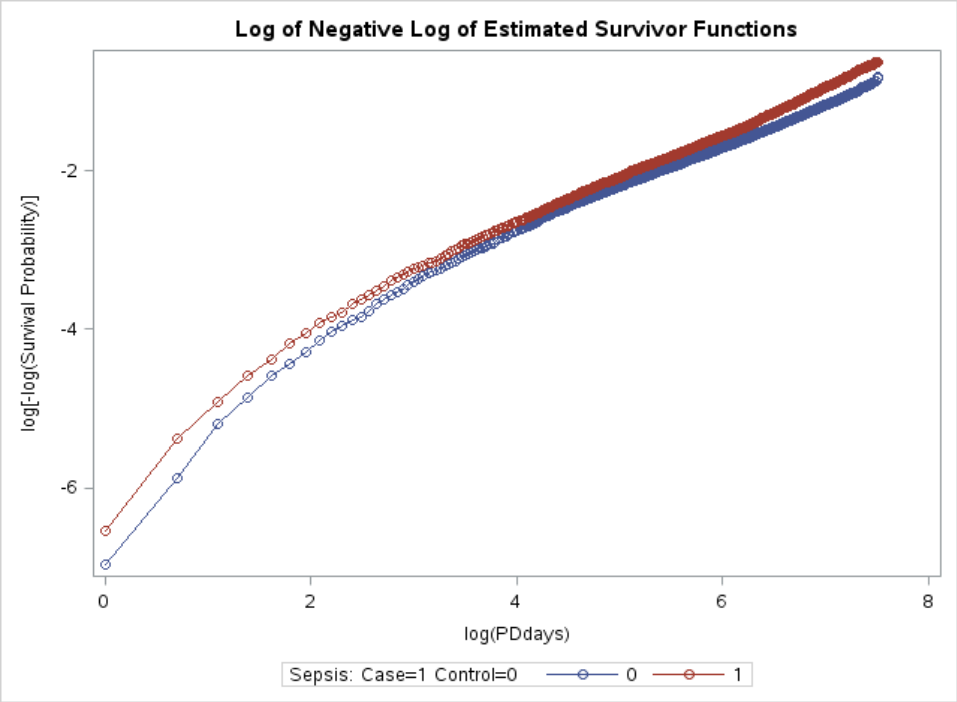


Figure D10: CIHI Cohort, Proportional Hazards Test, log(-log)survival, 5-Year Post-Discharge Survival

a) Non-Severe Sepsis versus Matched Hospital Controls



b) Sever Sepsis versus Matched Hospital Controls

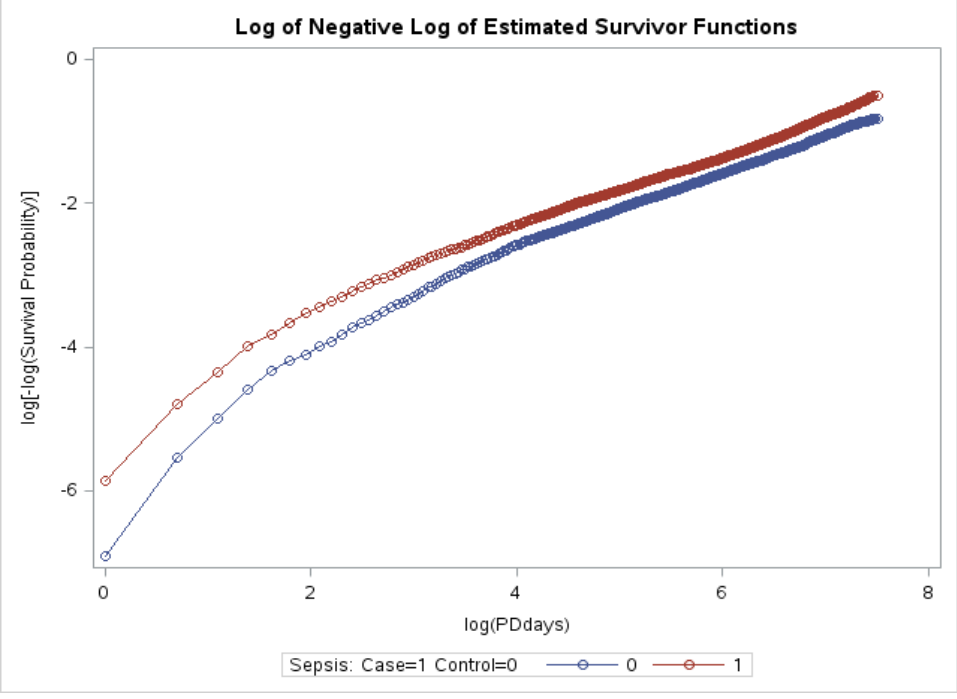
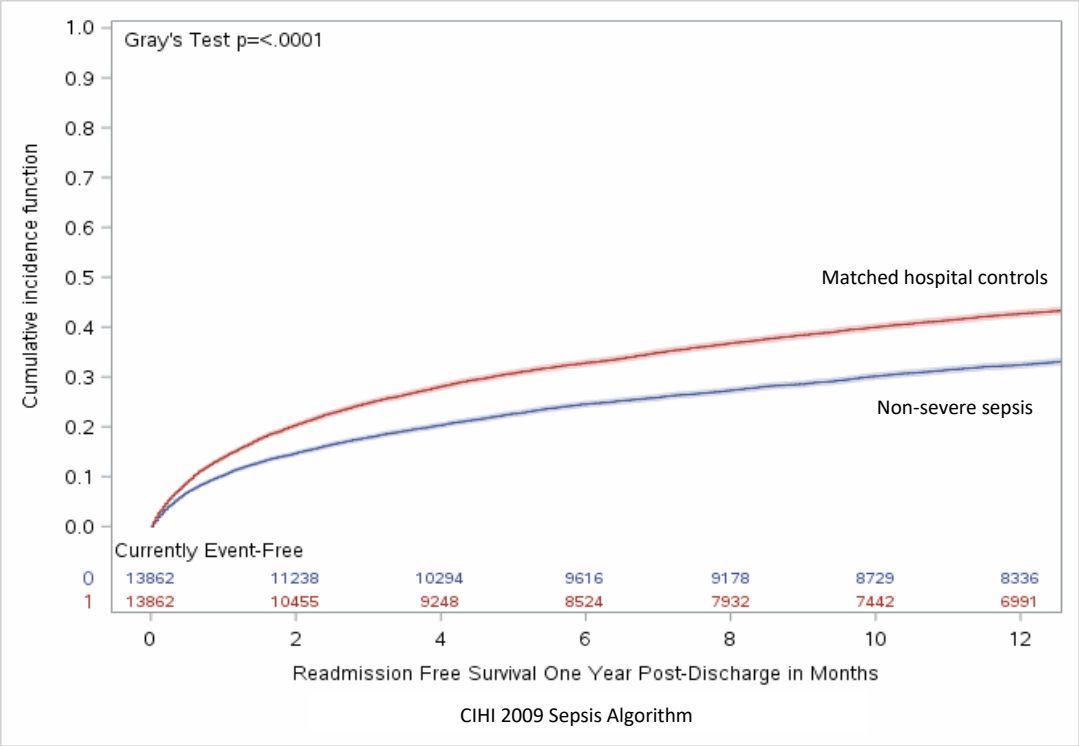


Figure D11: CIHI Cohort: Time to Hospital Readmission, 1-Year Post-Discharge

a) Non-Severe Sepsis versus Matched Hospital Controls



b) Severe sepsis versus Matched Hospital Controls

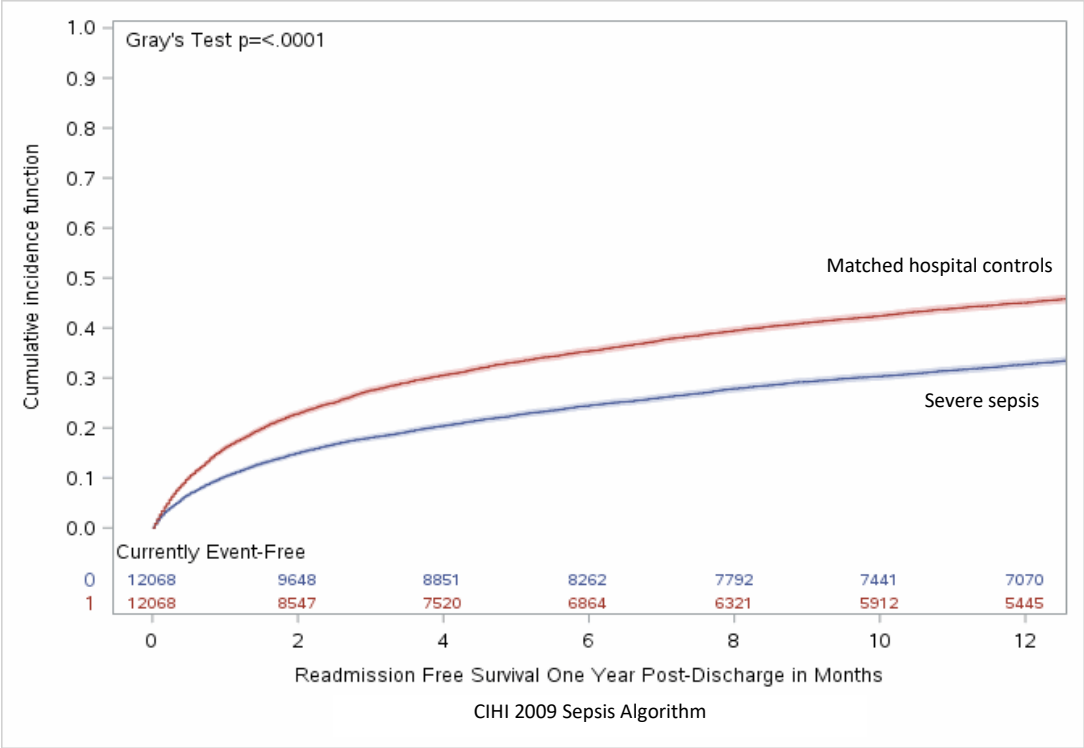
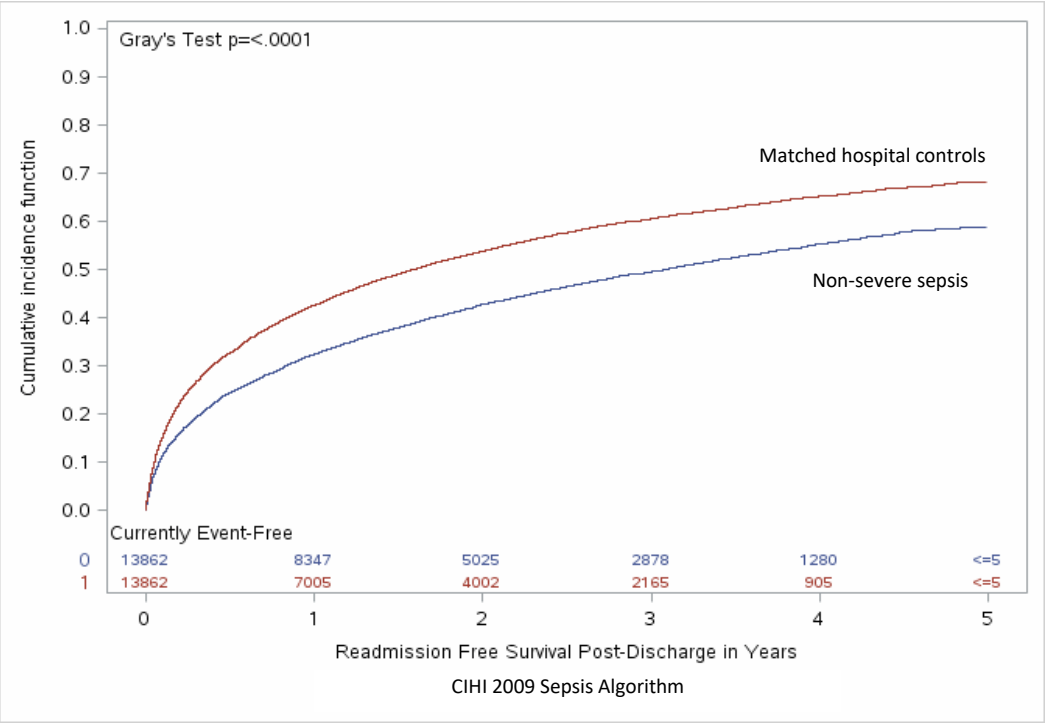


Figure D12: CIHI Cohort: Time to Hospital Readmission, 5-Year Post-Discharge

a) Non-Severe Sepsis versus Matched Hospital Controls



b) Severe Sepsis versus Matched Hospital Controls

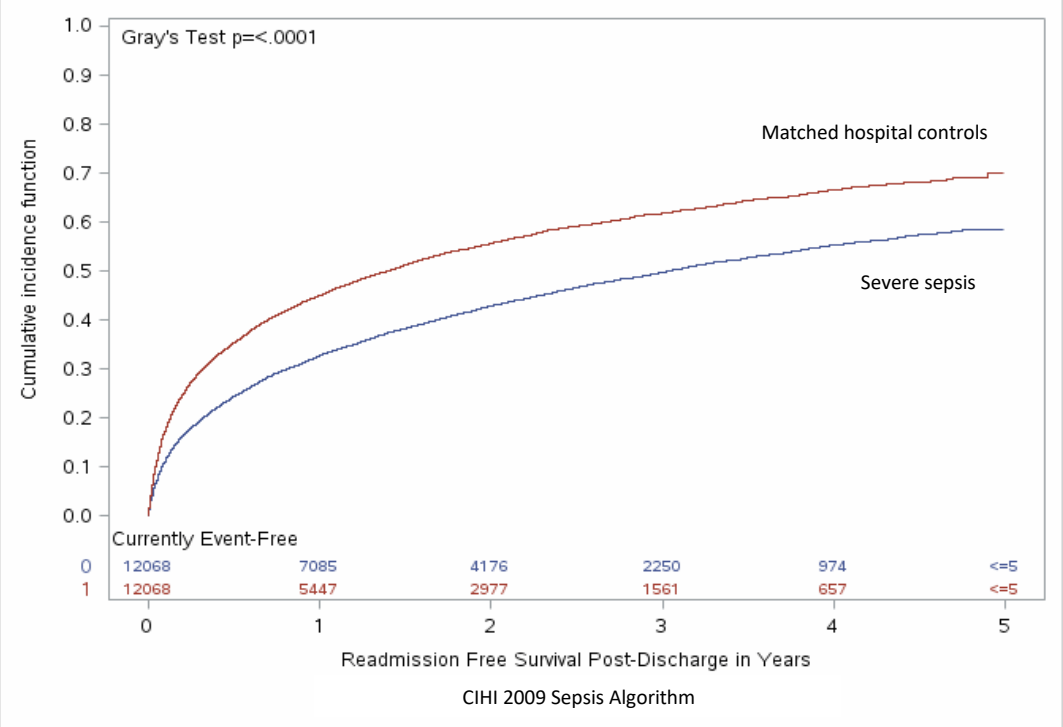


Table D3: CIHI: Mortality in Cases versus Controls at Different Time Periods During Follow-up

	Non-Severe Sepsis versus Controls						Severe Sepsis versus Controls					
Time Period*	**N at Risk†**		**Mortality (%)**		**OR_{crude} (95% CI)**	**OR_{adj}‡ (95% CI)**	**N at Risk**		**Mortality (%)**		**OR_{crude} (95% CI)**	**OR_{adj}‡ (95% CI)**
	Case	**Control**	**Case**	**Control**			**Case**	**Control**	**Case**	**Control**		
Hospital	16464	16464	13.9	8.6	1.82 (1.69-1.96)	2.12 (1.95-2.31)	19850	19850	38.6	10.2	6.13 (5.75-6.53)	6.86 (6.39-7.37)
	Case	**Control**	**Case**	**Control**	**HR_{crude}**	**HR_{adj}‡**	**Case**	**Control**	**Case**	**Control**	**HR_{crude}**	**HR_{adj}‡**
0-30 day	16464	16464	15.6	11.1	1.45 (1.38-1.54)	1.51 (1.43-1.61)	19850	19850	34.9	13.0	3.10 (2.96-3.23)	3.06 (2.93-3.20)
30-183 day	13896	14640	8.9	11.0	1.25 (1.16-1.34)	1.19 (1.10-1.28)	12917	17259	19.2	10.8	1.89 (1.78-2.00)	1.88 (1.77-1.99)
6–12 month	12370	13337	6.2	5.0	1.25 (1.13-1.38)	1.20 (1.08-1.34)	10432	15397	7.3	5.7	1.28 (1.16-1.41)	1.28 (1.16-1.42)
Year 2	11607	12675	8.5	6.2	1.37 (1.25-1.50)	1.40 (1.27-1.54)	9676	14516	9.0	7.5	1.21 (1.11-1.32)	1.23 (1.13-1.35)
Year 3	7992	8941	7.3	5.3	1.40 (1.24-1.57)	1.44 (1.27-1.63)	6477	9977	8.3	6.1	1.39 (1.24-1.56)	1.40 (1.25-1.57)
Year 4	4987	5732	6.1	4.2	1.49 (1.26-1.76)	1.53 (1.29-1.81)	3901	6245	6.2	4.9	1.28 (1.08-1.51)	1.29 (1.09-1.52)
Year 5	2463	2999	3.5	2.6	1.36 (1.01-1.85)	1.38 (1.02-1.89)	1928	3283	4.1	2.7	1.60 (1.18-2.17)	1.62 (1.19-2.21)
Overall	16464	16464	41.4	32.6	1.36 (1.32-1.40)	1.38 (1.33-1.43)	19850	19850	60.0	37.4	2.11 (2.05-2.16)	2.10 (2.05-2.16)

Adj. = adjusted; CI = confidence interval; HR = hazard ratio; OR = odds ratio.

*From index admission date.

†At beginning of time period.

‡Adjusted for hospital type and propensity score variables >0.10 standardized difference

Table D4: CIHI Hospital Survivor Cohort: Mortality and Hazard Rates in Cases versus Controls (Post-Discharge Follow-Up)

	Non-Severe Sepsis versus Controls						Severe Sepsis versus Controls					
Time Post-Discharge*	**N at Risk†**		**Mortality (%)**		**HR_{crude} (95% CI)**	**HR_{adj}‡ (95% CI)**	**N at Risk**		**Mortality (%)**		**HR_{crude} (95% CI)**	**HR_{adj}‡ (95% CI)**
	Case	**Control**	**Case**	**Control**			**Case**	**Control**	**Case**	**Control**		
0-30 day	13862	13862	4.9	4.3	1.15 (1.03-1.28)	1.18 (1.05-1.32)	12068	12068	6.9	4.9	1.42 (1.28-1.57)	1.35 (1.21-1.50)
30-183 day	13185	13271	8.7	7.7	1.13 (1.04-1.23)	1.09 (1.00-1.19)	11233	11471	10.1	8.6	1.20 (1.10-1.30)	1.18 (1.08-1.28)
6–12 month	12042	12248	5.8	4.8	1.22 (1.10-1.36)	1.23 (1.10-1.38)	10087	10489	6.1	5.4	1.14 (1.02-1.28)	1.14 (1.01-1.28)
Year 2	11279	11621	8.4	6.4	1.31 (1.19-1.44)	1.38 (1.25-1.52)	9268	9881	8.8	6.7	1.31 (1.18-1.45)	1.29 (1.16-1.44)
Year 3	7785	8181	7.2	5.3	1.38 (1.22-1.56)	1.48 (1.30-1.68)	6220	6761	8.2	5.8	1.42 (1.25-1.62)	1.37 (1.20-1.56)
Year 4	4846	5258	6.0	4.1	1.49 (1.25-1.77)	1.54 (1.29-1.84)	3732	4206	6.0	4.3	1.43 (1.17-1.74)	1.33 (1.09-1.63)
Year 5	2388	2739	3.4	3.1	1.10 (0.81-1.49)	1.11 (0.81-1.52)	1783	2144	3.8	2.0	2.04 (1.39-2.99)	1.89 (1.25-2.77)
Overall	13862	13862	31.7	26.6	1.23 (1.19-1.28)	1.26 (1.21-1.32)	12068	12068	34.8	28.4	1.29 (1.24-1.35)	1.27 (1.21-1.33)

Adj. = adjusted; CI = confidence interval; HR = hazard ratio.

*From discharge date of index hospitalization.

†At beginning of time period.

‡ Adjusted for hospital type and propensity score variables >0.10 standardized difference (for non-severe comparison: rural residence, hospitalization in previous year, cancer prior to admission, ADG score, chronic kidney disease prior to admission; for severe comparison: homecare use in previous year, hospitalization in previous year, chronic kidney disease prior to admission, ADG score, number of ED visits in previous year.

Table D5: CIHI Hospital Survivor Cohort: Rehospitalizations in Cases versus Controls (Post-Discharge Follow-Up)

Time Post-Discharge	**Rehospitalization N (%)**		**OR_{crude} (95% CI)**	**OR_{adj*} (95% CI)**	**Rehospitalization N (%)**		**OR_{crude} (95% CI)**	**OR_{adj*} (95% CI)**
	Case	**Control**			**Case**	**Control**		
30 Days	1833 (13.2)	1368 (9.9)	1.39 (1.29-1.50)	1.39 (1.28-1.50)	1834 (15.2)	1186 (9.8)	1.64 (1.52-1.77)	1.61 (1.49-1.75)
Time Post-Discharge	**Rehospitalization N (%)**		**HR_{crude} (95% CI)**	**HR_{adj*} (95% CI)**	**Rehospitalization N (%)**		**HR_{crude} (95% CI)**	**HR_{adj*} (95% CI)**
	Case	**Control**			**Case**	**Control**		
1 Year	5899 (42.6)	4479 (32.3)	1.48 (1.46-1.50)	1.46 (1.44-1.48)	5422 (44.9)	3932 (32.6)	1.59 (1.56-1.62)	1.55 (1.52-1.58)
Up to 5 year	8201 (59.2)	6753 (48.7)	1.49 (1.47-1.50)	1.48 (1.47-1.50)	7234 (59.9)	5815 (48.2)	1.55 (1.53-1.58)	1.53 (1.50-1.55)

Adj. = adjusted; CI = confidence interval; HR = hazard ratio; OR = odds ratio.

*Adjusted for hospital type and propensity score variables >0.10 standardized difference (for non-severe comparison: rural residence, hospitalization in previous year, cancer prior to admission, ADG score, chronic kidney disease prior to admission; for severe comparison: homecare use in previous year, hospitalization in previous year, chronic kidney disease prior to admission, ADG score, number of ED visits in previous year.

Table D6: CIHI Definition. Healthcare Resource Utilization and Outcomes 1-Year After Index Admission, Cases vs Matched Controls

	Non-Severe (no organ dysfunction) N= 16,462	Matched Controls N= 16,462	Crude % Difference	Severe Sepsis (or septic shock) N=19,850	Matched Controls N=19,850	Crude % Difference
	N (%)	**N (%)**		**N (%)**	**N (%)**	
Resource Utilization (number of patients with > 0 costs for cost category)						
Emergency visits	14225 (86.40)	13840 (84.06)	2.34	16287 (82.05)	16541 (83.33)	-1.28
Complex continuing care	1108 (6.73)	864 (5.25)	1.48	1602 (8.07)	1170 (5.89)	2.18
Long-term care	2285 (13.88)	1987 (12.07)	1.81	2167 (10.92)	2833 (14.27)	-3.35
LTC at index						
Rehabilitation	914 (5.55)	955 (5.80)	-0.25	1760 (8.87)	1176 (5.92)	2.95
Homecare	8239 (50.04)	6109 (37.11)	12.93	7942 (40.01)	8036 (40.48)	-0.47
Homecare at index						
Prescriptions*	12635 (76.74)	12670 (76.96)	-0.22	11687 (58.88)	15818 (79.69)	-20.81
Physician services	100	100	0.00	100	100	0.00
Other OHIP services†	11599 (70.45)	12136 (73.71)	-3.26	10070 (50.73)	14528 (73.19)	-22.46
Acute Hospitalizations	100	100	0.00	100	100	0.00
Index Hospitalization Outcome	**N (%)**	**N (%)**		**N (%)**	**N (%)**	
In-hospital death	2295 (13.94)	1408 (8.55)	5.39	7663 (38.60)	2033 (10.24)	28.26
ICU admission	2896 (17.59)	2830 (17.19)	0.40	12569 (63.32)	3637 (18.32)	45.00
Total Hospital LOS (days)						
Mean (SD)	11.13 (20.04)	7.65 (17.54)	3.48	22.41 (40.55)	8.29 (16.38)	14.12
Median (Q1-Q3)	6 (3-12)	4 (2-8)	2	11 (5-25)	4 (2-9)	7
ICU LOS (days)						
Mean (SD)	0.84 (2.43)	0.93 (3.25)	-0.08	8.22 (20.03)	1.07 (4.15)	7.15
Median (Q1-Q3)	0 (0-0)	0 (0-0)	0	3 (0-9)	0 (0-0)	3

ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; LTC = long-term care; OHIP = Ontario Health Insurance Plan; SD = standard deviation.

*Includes prescription drug claims covered by the Ontario Drug Benefit program.

†Includes laboratory services, and non-physician services covered by the Ontario Health Insurance Plan.

‡Discharge disposition after index admission.

Table D7: CIHI Definition. Crude Mean Total and Subdivided 1-Year Healthcare Costs, Cases vs Matched Controls, by Sepsis Type (C$2018)

	Non-Severe (no organ dysfunction) N= 16,464	Matched Controls N= 16,464	Crude Difference (95% CI)	Severe Sepsis (or septic shock) N= 19,850	Matched Controls N= 19,850	Crude Difference (95% CI)
	Mean (SD)	**Mean (SD)**		**Mean (SD)**	**Mean (SD)**	
Emergency visits	1121 (1137)	1007 (1137)	1134 (91-137)	973 (960)	1028 (1349)	-55 (-79, -33)
Complex cont. care	2554 (16283)	1778 (13247)	776 (452-1090)	3386 (19213)	1717 (11909)	1670 (1375-1989)
Long-term care	3147 (11191)	2935 (10532)	212 (-5, 444)	2000 (8795)	3562 (11519)	-1562 (-1751, -1375)
Rehabilitation	1276 (6491)	1312 (62034)	-37 (-171, 105)	2001 (8016)	1343 (6461)	657 (512-793)
Homecare	2692 (6993)	1810 (5641)	882 (750-1014)	2137 (6570)	1944 (5377)	193 (80-302)
Prescription drugs*	2440 (6149)	2170 (9489)	271 (74-435)	1752 (5323)	2279 (4636)	-527 (-626, -422)
Physician services	5032 (5488)	5028 (4629)	4 (-102, 106)	7909 (12277)	5323 (5034)	2586 (2419-2799)
Other OHIP services†	233 (372)	234 (366)	-1 (-9, 7)	177 (334)	246 (380)	-69 (-77, -63)
Acute Hospitalizations	24928 (34689)	21189 (31555)	3740 (3078-4480)	51319 (75761)	23376 (32884)	27943 (26758-29076)
Index hospitalization						
Mean (SD)	15488 (18638)	13255 (20562)	2233 (1801-2668)	48106 (83242)	14303 (20196)	33803 (32624-34976)
Median (IQR)	10278 (9050)	8220 (8766)	2058 (1911-2209)	21958 (40482)	8733 (9635)	13225 (12829-13603)
Total 1-Year Cost						
Mean (SD)	43424 (49418)	37464 (44099)	5960 (5007-6957)	71654 (91834)	40819 (44473)	30835 (29415-32222)
Median (IQR)	26201 (43598)	21286 (36848)	4915 (4302-5663)	41399 (71361)	24859 (41518)	16540 (15558-17573)

CI = confidence interval; IQR = interquartile range; OHIP = Ontario Health Insurance Plan; SD = standard deviation.
*Includes prescription drug claims covered by the Ontario Drug Benefit program.
†Includes laboratory services and non-physician services covered by the Ontario Health Insurance Plan.

Table D8: Crude Mean Total 2-5 Year Healthcare Costs, Cases vs. Controls, by Sepsis Type (C$2018)*

	Non-Severe (no organ dysfunction)	Matched Controls	Cohort Size	Severe Sepsis (including septic shock)	Matched Controls	Cohort Size
Cohort Size	**N**	**N**	**N**	**N**	**N**	**N**
Year 1	16464	16464	32928	19848	19848	39696
Year 2	11607	12671	24278	9675	14515	24190
Year 3	7986	8933	16919	6476	9965	16441
Year 4	4978	5728	10706	3894	6237	10131
Year 5	2454	2990	5444	1920	3276	5196
Deaths	**N (%)**	**N (%)**	**% Difference**	**N (%)**	**N (%)**	**% Difference**
Year 1	4851 (29.46)	3785 (22.99)	6.47	10170 (51.24)	5325 (26.83)	24.41
Year 2	982 (8.46)	786 (6.20)	2.26	869 (8.98)	1091 (7.52)	1.46
Year 3	585 (7.33)	475 (5.32)	2.01	540 (8.34)	605 (6.07)	2.27
Year 4	304 (6.11)	241 (4.21)	1.90	242 (6.21)	306 (4.91)	1.30
Year 5	84 (3.42)	78 (2.61)	0.81	78 (4.06)	88 (2.69)	1.37
Costs	**Mean (SD)**	**Mean (SD)**	**Crude Difference (95% CI)**	**Mean (SD)**	**Mean (SD)**	**Crude Difference (95% CI)**
Pre-Index†	20281 (32612)	16029 (28256)	4252 (3704-4819)	18243 (32938)	18659 (29903)	-416 (-985.261, 120)
Year 1	43424 (49418)	37464 (44099)	5960 (5007-6957)	71654 (91834)	40819 (44473)	30835 (29415-32222)
Year 2	23858 (38716)	20239 (35314)	3619 (2729-4515)	30359 (54297)	23773 (37204)	6586 (5394-7793)
Year 3	23363 (39607)	19039 (34847)	4323 (3171-5480)	27749 (48905)	22536 (36378)	5212 (3827-6648)
Year 4	22525 (38881)	18388 (34229)	4137 (2769-5536)	25584 (43062)	21855 (36818)	3729 (2216-5301)
Year 5	23133 (39124)	16882 (30483)	6250 (4452-8080)	25929 (45201)	19298 (33292)	6631 (4409-9143)
Costs	**Median (IQR)**	**Median (IQR)**	**Crude Difference (95% CI)**	**Median (IQR)**	**Median (IQR)**	**Crude Difference (95% CI)**
Pre-Index†	6773 (24037)	5116 (13479)	1657 (1455-1853)	6291 (17990)	6570 (17480)	-279 (-468, -60)
Year 1	26201 (43598)	21286 (36848)	4915 (4302-5663)	41399 (71361)	24859 (41518)	16540 (15558-17573)
Year 2	8053 (28348)	6030 (20011)	2023 (1679-2434)	9930 (34941)	8131 (27650)	1799 (1286-2605)
Year 3	6924 (26809)	5558 (18045)	1366 (994-1797)	8370 (31478)	7450 (24555)	920 (435-1547)
Year 4	6657 (25629)	5418 (16487)	1239 (649-1807)	8157 (28642)	7113 (22641)	1044 (341-1677)
Year 5	6691 (26529)	5280 (15236)	1411 (722-2034)	8272 (28914)	6406 (18747)	1866 (832-2670)

CI = confidence interval; IQR = interquartile range; SD = standard deviation

*Only includes patients who had follow-up at the start of the year of analysis.

†12 month period prior to admission (running from 13 months – 1 month before index admission date).

Table D9: Adjusted* Attributable Costs for Cases and Matched Controls, by Sepsis Type and Age Group

Outcome	Non-Severe Sepsis (no organ dysfunction) vs. Matched Controls	Severe Sepsis (including septic shock) vs. Matched Controls
	Adjusted Mean (95% CI)†	Adjusted Mean (95% CI)†
Index Admission		
Hospital LOS	4.08 (3.60-4.47)	14.21 (13.44-14.73)
ICU LOS	0.05 (0.02-0.12)	6.47 (6.43-6.99)
Hospital Costs	3124 (2720-3507)	31299 (30428-32670)
Long-Term Costs		
1-Year Costs		
Full Cohort	7870 (6873-8777)	30542 (28822-31529)
Hospital Survivors‡	9109 (8053-10143)	47825 (44779-48788)
Year 2-5 Costs§		
Year 2	4192 (3047-5163)	6461 (5459-7958)
Year 3	4517 (3174-5838)	4897 (3979-6741)
Year 4	3442 (2256-5334)	3275 (2153-5426)
Year 5	6000 (3792-8040)	5392 (4481-9451)

*Adjusted for hospital type, and propensity score variables with standardized difference > 0.10. For non-severe sepsis: homecare use in the year before index admission, hospitalization in year before index admission, cancer prior to index admission, rural residence, and John Hopkins Adjusted Diagnostic Group Score; for severe sepsis: diabetes prior to index admission, number of emergency department visits in the year before index admission, and hospitalization in year before index admission.

†Calculated using 1,000 bootstrap replicates on full sample size, with replacement.

‡Data is from an analysis of cases and controls who survived index hospitalization (for non-severe sepsis N = 13,862 matched pairs; for severe sepsis N=12,068 matched pairs).

§Data includes only cases and controls who had follow-up at the beginning of the year under analysis.

Table D10: CIHI Definition. Survivor Cohort. Healthcare Resource Utilization and Outcomes 1-Year After Index Admission, Sepsis Cases vs Matched Controls

	Non-Severe (no organ dysfunction) N= 13,862	Matched Controls N=13,862	Crude % Difference	Severe Sepsis (or septic shock) N=12,068	Matched Controls N= 12,068	Crude % Difference
	N (%)	N (%)		N (%)	N (%)	
Resource Utilization (number of patients with > 0 costs for cost category)						
Emergency visits	12257 (88.42)	11757 (84.81)	3.61	10698 (88.65)	10310 (85.43)	3.22
Complex continuing care	1032 (7.44)	798 (5.76)	1.68	1530 (12.68)	770 (6.38)	6.30
Long-term care	1788 (12.90)	1596 (11.51)	1.39	1562 (12.94)	1641 (13.60)	-0.66
LTC at index	*1186 (8.56)*	*1024 (7.39)*	*1.17*	*926 (7.67)*	*1121 (9.29)*	*-1.62*
Rehabilitation	866 (6.25)	912 (6.58)	-0.33	1727 (14.31)	789 (6.54)	7.77
Homecare	7675 (55.37)	5510 (39.75)	15.62	5226 (43.30)	7230 (59.91)	16.61
Homecare at index	*4677 (33.74)*	*4090 (29.51)*	*4.23*	*3618 (29.98)*	*4341 (35.97)*	*-5.99*
Prescriptions*	11845 (85.45)	11288 (81.43)	4.02	10356 (85.81)	10249 (84.93)	0.88
Physician services	100	100	0.00	100	100	0.00
Other OHIP services†	11268 (81.29)	11209 (80.86)	0.43	9700 (80.38)	9807 (81.26)	-0.88
Acute Hospitalizations	100	100	0.00	100	100	0.00

LTC = long-term care; OHIP = Ontario Health Insurance Plan.

*Includes prescription drug claims covered by the Ontario Drug Benefit program.

†Includes laboratory services, and non-physician services covered by the Ontario Health Insurance Plan.

Table D11: CIHI Definition. Hospital Survivor Cohort. Crude Mean Total and Subdivided 1-Year Healthcare Costs, Cases vs Matched Controls, by Sepsis Type (C$2018)

	Non-severe (no organ dysfunction) N=13,862	Matched Controls N=13,862	Crude Difference (95% CI)	Severe sepsis (including septic shock) N=12,068	Matched Controls N=12,068	Crude Difference (95% CI)
	Mean (SD)	**Mean (SD)**		**Mean (SD)**	**Mean (SD)**	
Emergency visits	1213 (1175)	1068 (12567)	144 (115-175)	1234 (1081)	1085 (1389)	149 (120-182)
Complex cont. care	2812 (16979)	1844 (12394)	968 (625-1331)	5503 (24183)	1896 (12806)	3607 (3117-4094)
Long-term care	3676 (12052)	3166 (10913)	511 (265-755)	3261 (11075)	3771 (11896)	-509 (-769, -239)
Rehabilitation	1466 (7000)	1496 (6765)	-30 (-191, -124)	3302 (10086)	1457 (6411)	1845 (1640-2064)
Homecare	3088 (7398)	1830 (5058)	1258 (1110-1401)	3504 (8202)	2169 (5983)	1335 (1160-1519)
Prescription drugs*	2822 (6560)	2275(5119)	547 (414-681)	2832 (6562)	2578 (5224)	255 (119-408)
Physician services	5501 (5650)	5235 (5446)	266 (138-384)	9463 (9143)	5431 (5047)	4032 (3859-4225)
Other OHIP services†	272 (390)	256 (372)	16 (7-24)	285 (385)	259 (365)	25 (16-34)
Acute Hospitalizations	26345 (35638)	20919 (29252)	5426 (4733-6115)	58511 (73393)	22789 (32733)	35722 (34255-37188)
Index hospitalization	15122 (16423)	12207 (15616)	2915 (2758-3948)	49094 (73316)	12959 (16103)	36135 (34894-37573)
Total 1-Year Cost	47195 (50416)	38089 (41807)	9106 (8051-10121)	87897 (91853)	41435 (44957)	46461 (44583-48411)

CI = confidence interval; OHIP =Ontario Health Insurance Plan; SD = standard deviation

*Includes prescription drug claims covered by the Ontario Drug Benefit program.

†Includes laboratory services and non-physician services covered by the Ontario Health Insurance Plan.

APPENDIX E: Additional Data for Sensitivity Analysis of Non-Severe Cases versus Controls without Organ Dysfunction

In the primary analysis, by definition, non-severe sepsis patients had no codes for acute organ dysfunction recorded on index hospital admission. Controls in the primary analysis could have had an organ function unrelated to sepsis. In this sensitivity analysis non-severe sepsis cases are compared only with controls who had none of the codes for acute organ dysfunction recorded during index admission. All analyses from the primary analysis were repeated, exclude anyone who had one or more of the codes for organ dysfunction included in the Jolley et al. sepsis definition during their index hospital admission.

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Table E1: Baseline Characteristics of Cases and Controls, Before and After Matching (Controls without Organ Dysfunction)

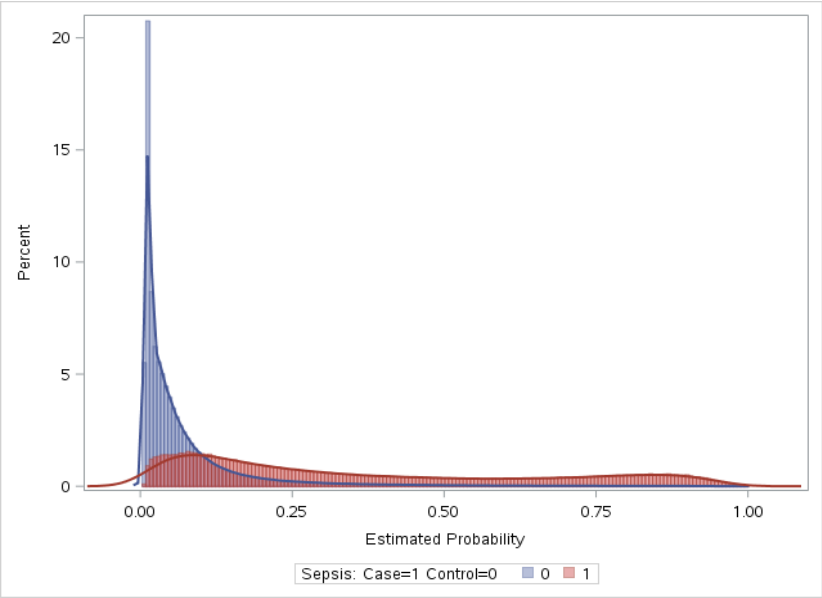
	BEFORE MATCHING			AFTER MATCHING		
	Control Pool (no organ dysfunction) N=1,497,941	**Non-Severe Sepsis Cases N= 178,682**	**Std. Diff.**	**Matched Controls (no organ dysfunction) N= 133,961**	**Non-Severe Sepsis (no organ dysfunction) N= 133,961** *Unmatched* = 25%	**Std. Diff**
Age, mean (SD)	52.07 (20.17)	73.05 (16.39)	**1.14**	72.9 (16.5)	72.9 (16.5)	**0.00**
<65, n (%)	1028170 (69)	45994 (26)	**0.95**	35077 (26.18)	34981 (26.11)	**0.00**
65-84 n (%)	386060 (26)	83164 (46)	**0.44**	61982 (46.27)	61665 (46.03)	**0.00**
≥ 85 n (%)	83711 (5)	49524 (28)	**0.62**	36902 (27.55)	37315 (27.86)	**0.01**
Female n (%)	972002 (65)	102663 (57)	**0.15**	78427 (58.54)	78427 (58.54)	**0.00**
Rural n (%)	197998 (13)	26641 (15)	**0.05**	19053 (14.22)	19758 (14.75)	**0.01**
Income quintile n (%)						
1 (lowest)	295999 (20)	40840 (23)	**0.08**	30435 (22.72)	29703 (22.17)	**0.01**
2	297921 (20)	37145 (21)	**0.02**	28001 (20.90)	27690 (20.67)	**0.01**
3	299401 (20)	35093 (20)	**0.01**	26192 (19.55)	26516 (19.79)	**0.01**
4	313548 (21)	33979 (19)	**0.05**	25455 (19.00)	25831 (19.28)	**0.01**
5 (highest)	284003 (19)	30528 (17)	**0.05**	23100 (17.24)	23431 (17.49)	**0.01**
missing	7069 (0.5)	1097 (0.6)	**0.02**	778 (0.58)	790 (0.59)	**0.00**
Marginalization Index, n (%)						
1 (lowest)	284150 (19)	24523 (14)	**0.14**	17985 (13.43)	18875 (14.09)	**0.02**
2	340593 (23)	32148 (18)	**0.12**	24061 (17.96)	24540 (18.32)	**0.01**
3	328565 (22)	38550 (22)	**0.01**	28935 (21.60)	29154 (21.76)	**0.00**
4	274184 (18)	36470 (20)	**0.05**	27461 (20.50)	27109 (20.24)	**0.01**
5 (highest)	257981 (17)	44962 (25)	**0.20**	34122 (25.47)	32884 (24.55)	**0.02**
missing	12468 (0.8)	2029 (1.1)	**0.03**	1397 (1.04)	1399 (1.04)	**0.00**
Prior cancer, n (%)	146050 (10)	30520 (17)	**0.22**	16515 (12.33)	19684 (14.69)	**0.07**
Prior CHF, n (%)	82497 (6)	47285 (26)	**0.60**	28601 (21.35)	30058 (22.44)	**0.03**
Prior CKD, n (%)	5294 (0.4)	3214 (1.8)	**0.14**	1463 (1.09)	1523 (1.14)	**0.00**
Prior COPD, n (%)	191302 (13)	69574 (39)	**0.63**	44376 (33.13)	48077 (35.89)	**0.06**
Prior diabetes, n (%)	267884 (18)	66270 (37)	**0.44**	45926 (34.28)	46711 (34.87)	**0.01**
Residence in LTC, n (%)	16018 (1.1)	16351 (9.2)	**0.37**	9722 (7.26)	11018 (8.22)	**0.04**
ADG score, mean (SD), n (%)	10.4 (18.5)	27.6 (13.3)	**1.06**	27.0 (13.8)	26.5 (13.2)	**0.04**
Healthcare use, past year						
Hospitalization, n (%)	36076 (2.4)	60484 (33.9)	**0.89**	11471 (8.56)	17242 (12.87)	**0.14**

Homecare use, n (%)	146699 (9.8)	81768 (45.8)	**0.88**	43872 (32.75)	48028 (35.85)	**0.07**
ED visits						
Mean (SD)	0.9 (1.8)	1.4 (2.9)	**0.24**	1.2 (2.8)	1.2 (2.1)	**0.02**
Median (Q1-Q3)	0 (0-1)	1 (0-2)	**0.32**	1 (0-2)	1 (0-2)	**0.01**
Physician visits						
Mean (SD)	16.4 (12.8)	24.8 (22.6)	**0.46**	17.8 (15.9)	19.5 (18.3)	**0.10**
Median (Q1-Q3)	14 (8-22)	18 (10-32)	**0.35**	14 (8-23)	15 (8-23)	**0.07**
Index Admission						
Urgent admission, n (%)	741022 (49)	171193 (96)	**1.22**	128481 (95.9)	128481 (95.9)	**0.00**
Index Admission Date, n (%)						
Apr 2012 – Mar 2013	446480 (30)	47349 (27)	**0.07**	43303 (32.33)	43336 (32.35)	**0.00**
Apr 2013 – Mar 2014	391614 (26)	45640 (26)	**0.01**	31814 (23.75)	31759 (23.71)	**0.00**
Apr 2014 – Mar 2015	345794 (23)	44897 (25)	**0.05**	30835 (23.02)	31010 (23.15)	**0.00**
Apr 2015 – Mar 2016	314053 (21)	40796 (23)	**0.05**	28009 (20.91)	27856 (20.79)	**0.00**
Hospital Type*, n (%)						
Teaching	485995 (32)	47727 (27)	**0.13**	37730 (28.17)	34901 (26.05)	**0.05**
Community ≥ 100 beds	788966 (53)	88361 (49)	**0.06**	69658 (52.00)	67247(50.20)	**0.04**
Community < 100 beds	222951 (15)	42585 (24)	**0.23**	26568 (19.83)	31807 (23.74)	**0.09**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = Congestive heart failure; CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; SD = standard deviation; Std Diff = standardized difference.
*Variable not included in propensity score model.
Missing values: rural: 31, hospital type: 38.

Figure E1: Plot of Propensity Scores for Cases and Controls Before and After Matching, Controls without Organ Dysfunction

a) Pre-Match



b) Post-Match

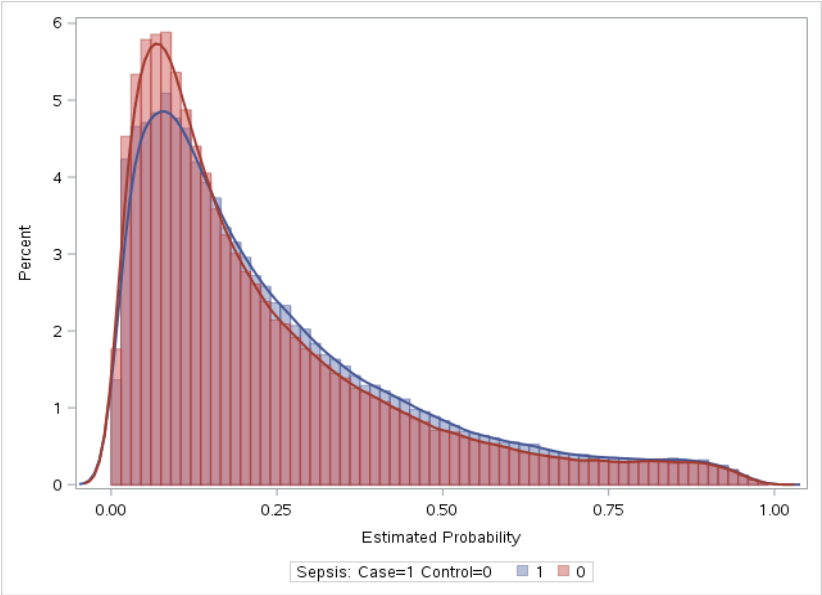


Table E2: Hospital Survivors. No Organ Dysfunction. Baseline Characteristics of Cases and Controls, Before and After Matching

	BEFORE MATCHING			AFTER MATCHING		
	Control Pool (no organ dysfunction) N=1,476,463	**Non-Severe Sepsis (no organ dysfunction) N= 165,254**	**Std. Diff.**	**Matched Controls N= 125,153**	**Non-Severe Sepsis N= 125,153** *Unmatched* **= 24.3%**	**Std. Diff**
Age, mean (SD)	51.72 (20.02)	72.43 (16.55)	**1.13**	72.3 (16.6)	72.3 (16.6)	**0.00**
<65, n (%)	1023780 (69)	44577 (27)	**0.94**	34364 (27.5)	34281 (27.4)	**0.00**
65-84, n (%)	376578 (26)	77171 (47)	**0.45**	58201 (46.5)	57858 (46.2)	**0.01**
≥ 85, n (%)	76105 (5)	43506 (26)	**0.61**	32588 (26.0)	33014 (26.4)	**0.01**
Female, n (%)	961134 (65)	95664 (58)	**0.15**	73658 (58.9)	73658 (58.9)	**0.00**
Rural , n (%)	193143 (13)	24170 (15)	**0.04**	17706 (14.2)	18162 (14.5)	**0.01**
Income quintile, n (%)						
1 (lowest)	291282 (20)	37837 (23)	**0.08**	28769 (23.0)	27756 (22.2)	**0.02**
2	293386 (20)	34302 (21)	**0.02**	26017 (20.8)	25842 (20.7)	**0.00**
3	295176 (20)	32399 (20)	**0.01**	24423 (19.5)	24670 (19.7)	**0.00**
4	309445 (21)	31431 (19)	**0.05**	23674 (18.9)	24193 (19.3)	**0.01**
5 (highest)	280274 (19)	28288 (17)	**0.05**	21545 (17.2)	21970 (17.5)	**0.01**
missing	6900 (1)	997 (1)	**0.02**	725 (0.6)	722 (0.6)	**0.00**
Marginalization Index, n (%)						
1 (lowest)	281187 (19)	22800 (14)	**0.14**	16981 (13.6)	17731 (14.2)	**0.02**
2	336657 (23)	29882 (18)	**0.12**	22364 (17.9)	23037 (18.4)	**0.01**
3	323807 (22)	35722 (22)	**0.01**	27255 (21.8)	27350 (21.9)	**0.00**
4	269730 (18)	33604 (20)	**0.05**	25357 (20.3)	25218 (20.1)	**0.00**
5 (highest)	252967 (17)	41386 (25)	**0.19**	31854 (25.4)	30535 (24.4)	**0.02**
missing	12115 (1)	1860 (1)	**0.03**	1342 (1.1)	1282 (1.0)	**0.00**
Prior cancer, n (%)	139306 (9)	26501 (16)	**0.20**	13873 (11.1)	17450 (13.9)	**0.09**
Prior CHF, n (%)	77621 (5)	42277 (26)	**0.59**	25913 (20.7)	27063 (21.6)	**0.02**
Prior CKD, n (%)	5062 (0.3)	2925 (1.8)	**0.14**	1345 (1.1)	1379 (1.1)	**0.00**
Prior COPD, n (%)	184456 (12)	63756 (39)	**0.63**	40933 (32.7)	44446 (35.5)	**0.06**
Prior diabetes, n (%)	261293 (18)	61257 (37)	**0.45**	42812 (34.2)	43572 (34.8)	**0.01**
Residence in LTC, n (%)	14040 (1)	14004 (8)	**0.36**	8562 (6.8)	9369 (7.5)	**0.03**
ADG score, mean (SD)	10.1 (18.4)	27.1 (13.3)	**1.06**	26.5 (13.8)	26.0 (13.1)	**0.04**
Healthcare use, past year						
Hospitalization, n (%)	34706 (2)	54737 (33)	**0.88**	10359 (8.3)	15922 (12.7)	**0.15**

Homecare use, n (%)	136947 (9)	73005 (44)	**0.86**	39024 (31.2)	43012 (34.4)	**0.07**
ED visits						
Mean (SD)	0.9 (1.8)	1.4 (2.9)	**0.24**	1.2 (2.8)	1.1 (2.0)	**0.03**
Median (Q1-Q3)	0 (0-1)	1 (0-2)	**0.32**	0 (0-2)	1 (0-2)	**0.01**
Physician visits						
Mean (SD)	16.4 (12.6)	24.4 (22.1)	**0.44**	17.5 (15.6)	19.3 (18.1)	**0.11**
Median (Q1-Q3)	14 (8-22)	18 (10-32)	**0.33**	14 (7-22)	15 (8-24)	**0.08**
Index Admission						
Urgent Admission, n (%)	720506 (49)	158118 (96)	**1.23**	119817 (95.7)	119817 (95.7)	**0.00**
Index Admission Date, n (%)						
Apr 2012 – Mar 2013	438827 (30)	43448 (26)	**0.08**	39912 (31.9)	39976 (31.9)	**0.00**
Apr 2013 – Mar 2014	386231 (26)	42175 (26)	**0.01**	29826 (23.8)	29739 (23.8)	**0.00**
Apr 2014 – Mar 2015	341179 (23)	41573 (25)	**0.05**	28982 (23.2)	29106 (23.3)	**0.00**
Apr 2015 – Mar 2016	310226 (21)	38058 (23)	**0.05**	26433 (21.1)	26332 (21.0)	**0.00**
Hospital Type*, n (%)						
Teaching	480645 (32)	44459 (27)	**0.12**	35633 (28.5)	32775 (26.2)	**0.05**
Community ≥ 100 beds	779557 (53)	82047 (50)	**0.03**	65187 (52.1)	63065 (50.4)	**0.03**
Community < 100 beds	216233 (15)	38739 (23)	**0.23**	24331 (19.4)	29307 (23.4)	**0.10**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = Congestive heart failure; CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; Q = quartile; SD = standard deviation; Std Diff = standardized difference.
*Variable not included in propensity score model.
Missing values: Rural 26, hospital type: 37.

Table E3: No Organ Dysfunction Matching. Descriptive Characteristics of Index Hospital Admission and Long-Term Outcomes

	Matched Controls (no organ dysfunction) N =133,961	Non-Severe Sepsis (no organ dysfunction) N = 133,961
Total Hospital LOS (days)		
Mean (SD)	6.84 (15.23)	11.09 (22.05)
Median (Q1-Q3)	4 (2-7)	6 (3-11)
ICU LOS (days)		
Mean (IQR)	0.43 (1.48)	0.50 (1.97)
Median (Q1-Q3)	0 (0-0)	0 (0-0)
	N (%)	**N (%)**
ICU admission	14982 (11.18)	13549 (10.11)
In-hospital death	7401 (5.52)	8557 (6.39)
1-year mortality	26582 (19.84)	32146 (24.00)
Mortality (up to 5 years)	41282 (30.82)	53759 (40.13)
Days Follow-up		
Mean (SD)	878 (551)	813 (547)
Median (IQR)	867 (913)	784 (885)
Hospital Survivor Matching	**N=125,153**	**N= 125,153**
1-year post-discharge mortality	19207 (15.35)	24008 (19.18)
Up to 5-year post-discharge mortality	33366 (26.66)	45036 (35.99)
30-day hospital readmission	11284 (9.02)	15173 (12.12)
1-year hospital readmission	38205 (30.53)	51998 (41.55)
Up to 5-year hospital readmission	59045 (47.18)	75311 (60.18)

ICU = intensive care unit; IQR = interquartile range; LOS = length of stay (in days); SD = standard deviation.
†Data is from a re-matched analysis of cases and controls who survived index hospitalization.
Note: cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of cases.

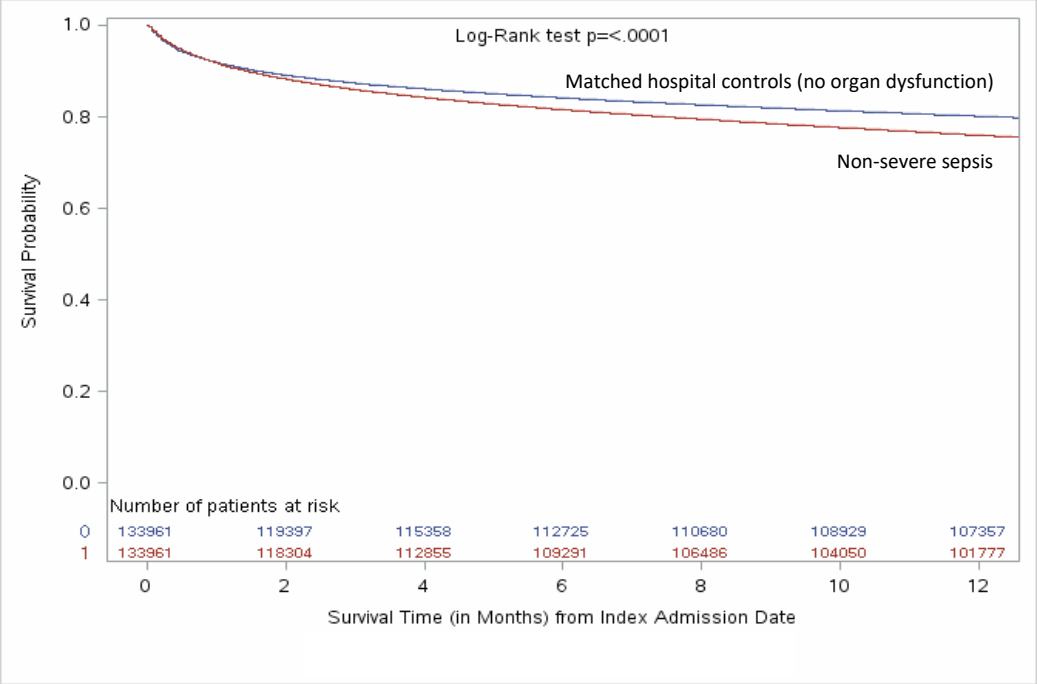
Table E4. Crude and Adjusted Outcomes for Cases and Matched Controls, by Sepsis Type and Age Group (No Organ Dysfunction Matching)

Outcome	Non-Severe Sepsis (no organ dysfunction) vs. Matched Controls (no organ dysfunction)	
	Crude Mean (95% CI)	**Adjusted* Mean (95% CI)**
Hospital LOS (days)	4.25 (4.11-4.39)	4.38 (4.19-4.49)
ICU LOS (days)	0.06 (0.06-0.09)	0.08
	Crude OR (95% CI)	**Adjusted* OR (95% CI)**
ICU Admission	0.89 (0.87-0.92)	0.88 (0.86-0.91)
Hospital Death	1.18 (1.14-1.22)	1.17 (1.13-1.21)
Mortality Rate	**Crude HR (95% CI)**	**Adjusted* HR (95% CI)**
1-Year	1.23 (1.21-1.25)	1.20 (1.18-1.22)
Up to-5 Years	1.37 (1.35-1.39)	1.35 (1.33-1.36)
Hospital Survivors		
1-Year Mortality (from discharge)	1.26 (1.24-1.29)	1.19 (1.17-1.21)
Up to 5 years (from discharge)	1.43 (1.41-1.45)	1.38 (1.36-1.40)
1-year readmission‡	1.47 (1.45-1.49)	1.42 (1.40-1.44)
Up to 5 years readmission‡	1.48 (1.47-1.50)	1.44 (1.43-1.46)

CI = confidence interval; HR = hazard ratio; ICU = intensive care unit; LOS = length of stay; OR = odds ratio.
*Adjusted for hospital type, and propensity score variables with standardized difference > 0.10 (hospitalization in the year before index admission date, number of physician visits in the year before index admission date).
†Data is from a re-matched analysis of cases and controls who survived index hospitalization.
‡Readmission after index admission discharge date to an acute care hospital in Ontario.

Figure E3: No Organ Dysfunction Matching, 1-Year Survival, Kaplan Meier Plots

a) 1-Year



b) 5-Year

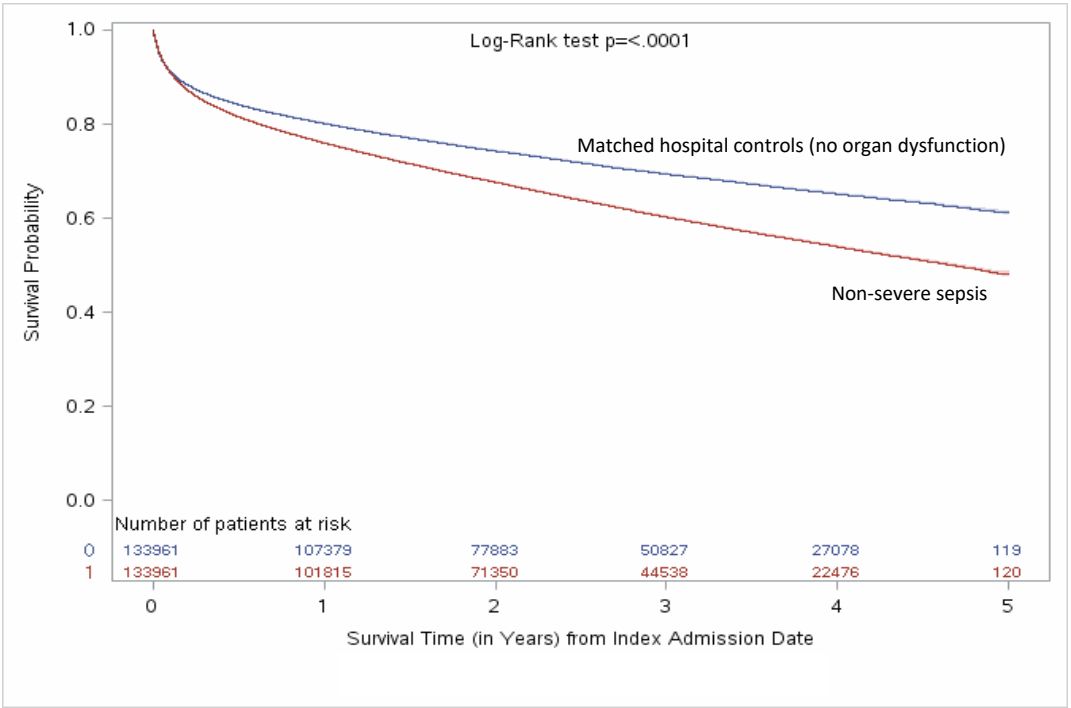
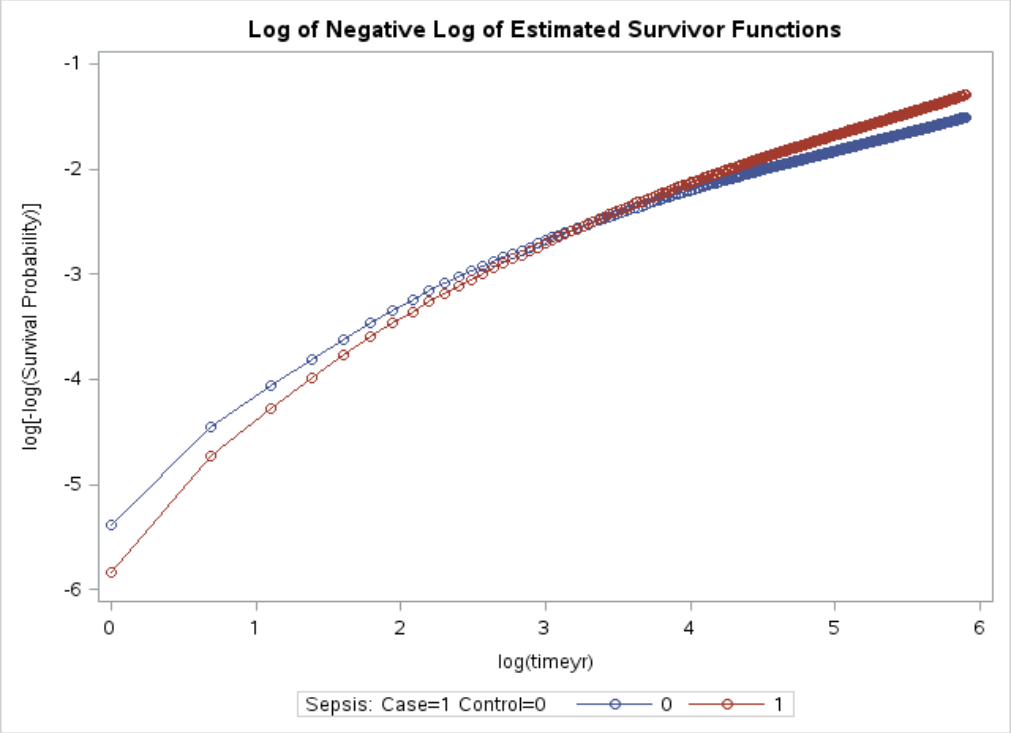


Figure E4: No Organ Dysfunction Matching, Test of Proportional Hazards

a) 1-Year Survival



b) 5-Year Survival

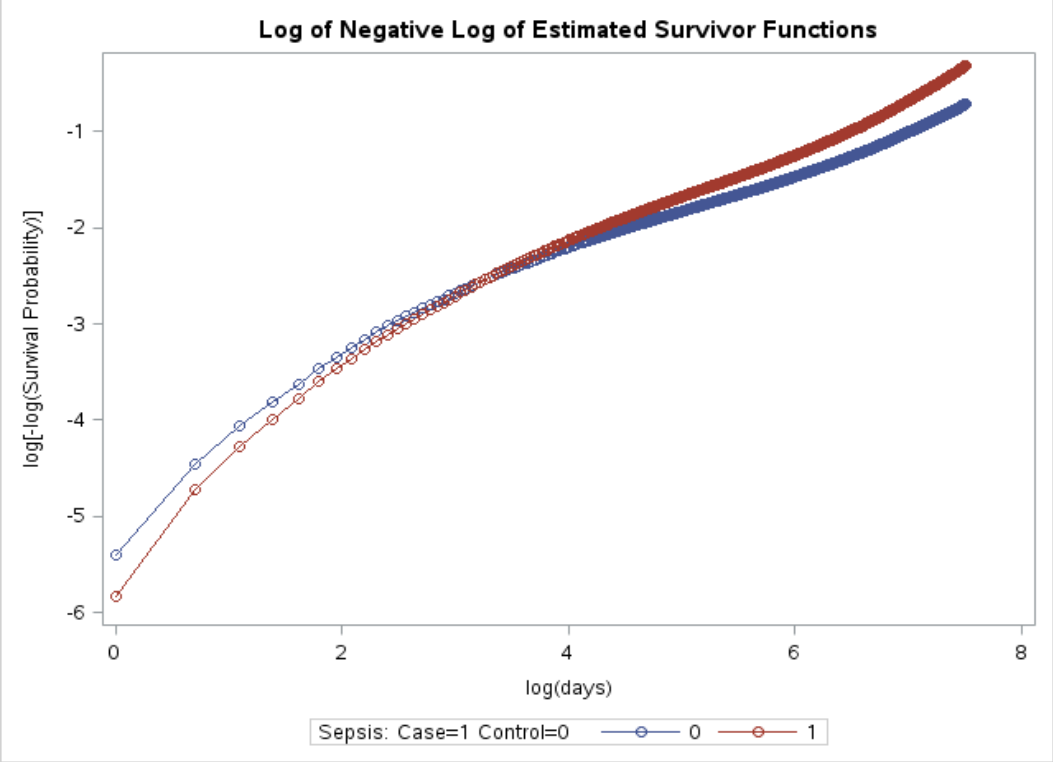
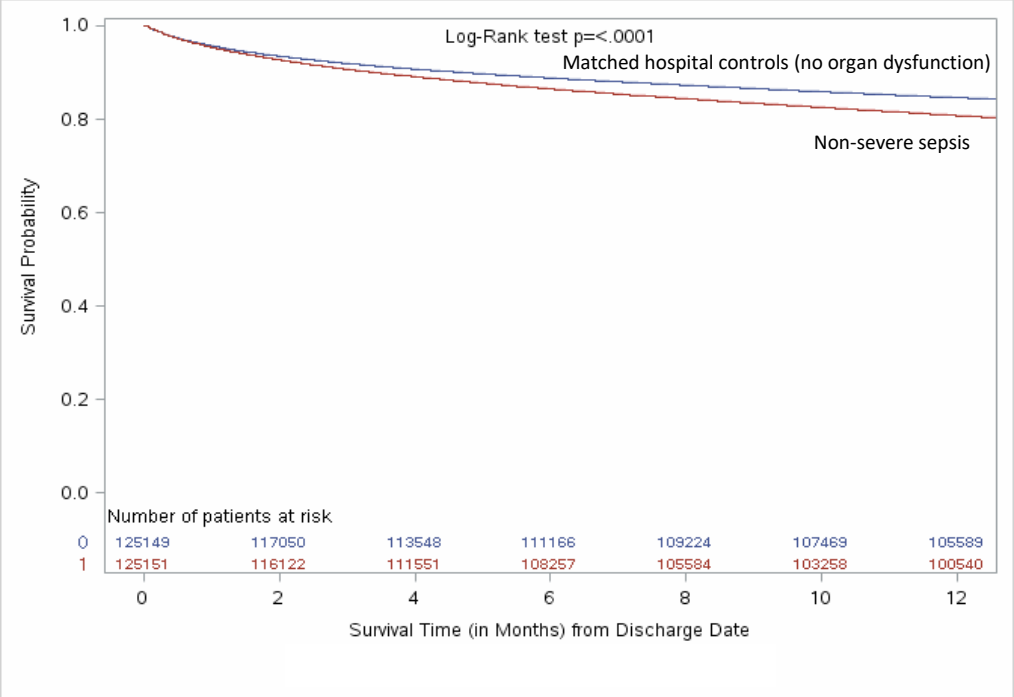


Figure E5: No Organ Dysfunction Matching, Survivor Cohort, Post-Discharge Survival, Kaplan Meier Plots

a) 1-Year



b) 5-Year

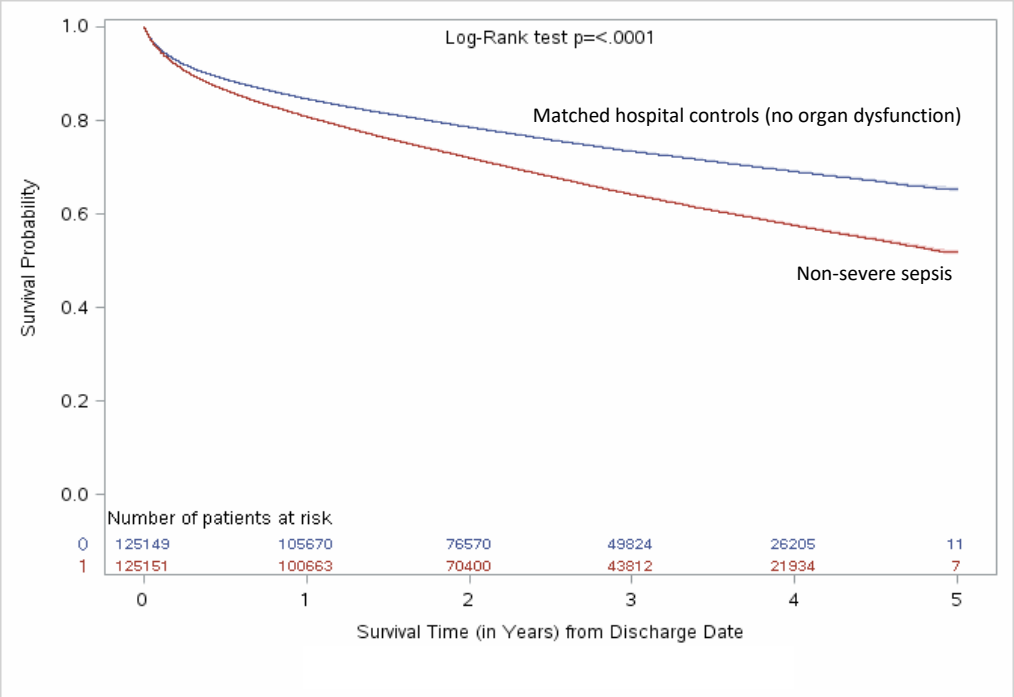
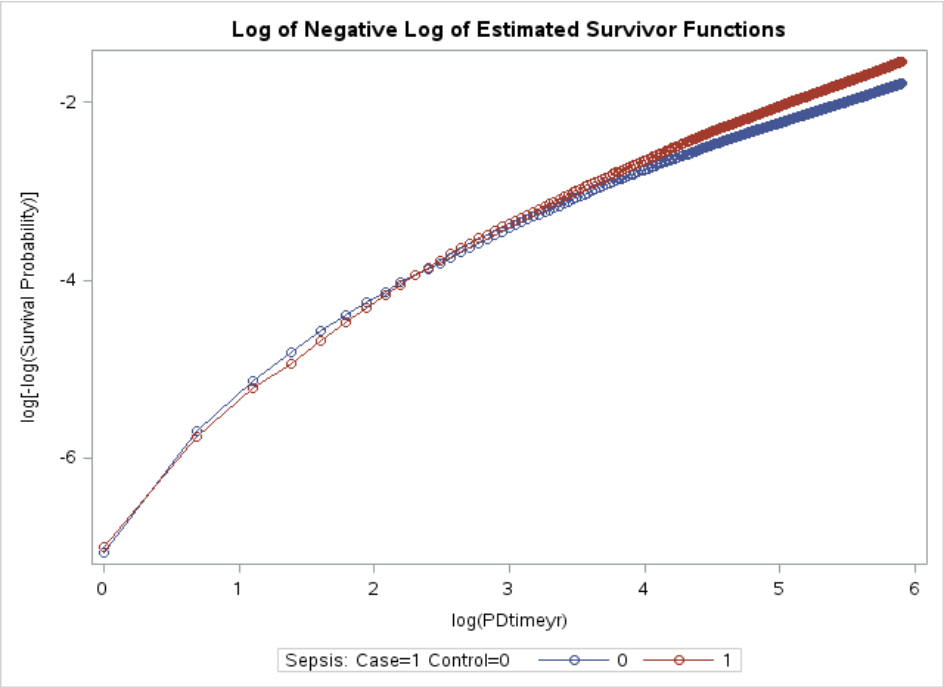


Figure E6: No Organ Dysfunction Matching, Survivor Cohort, Post-Discharge Survival, Test of Proportional Hazards

a) 1-Year



b) 5-Year

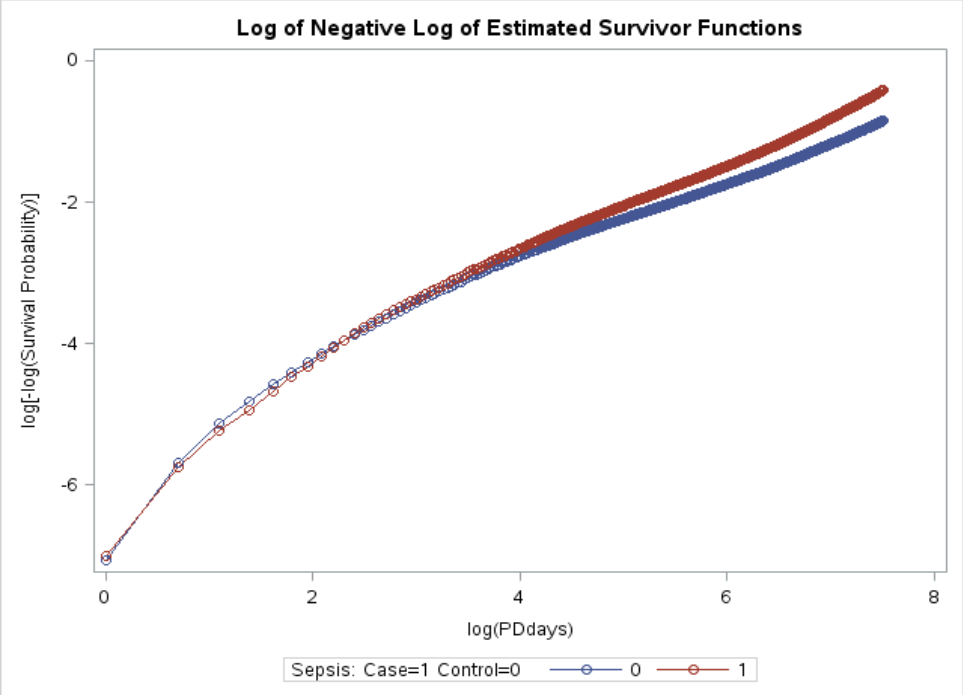
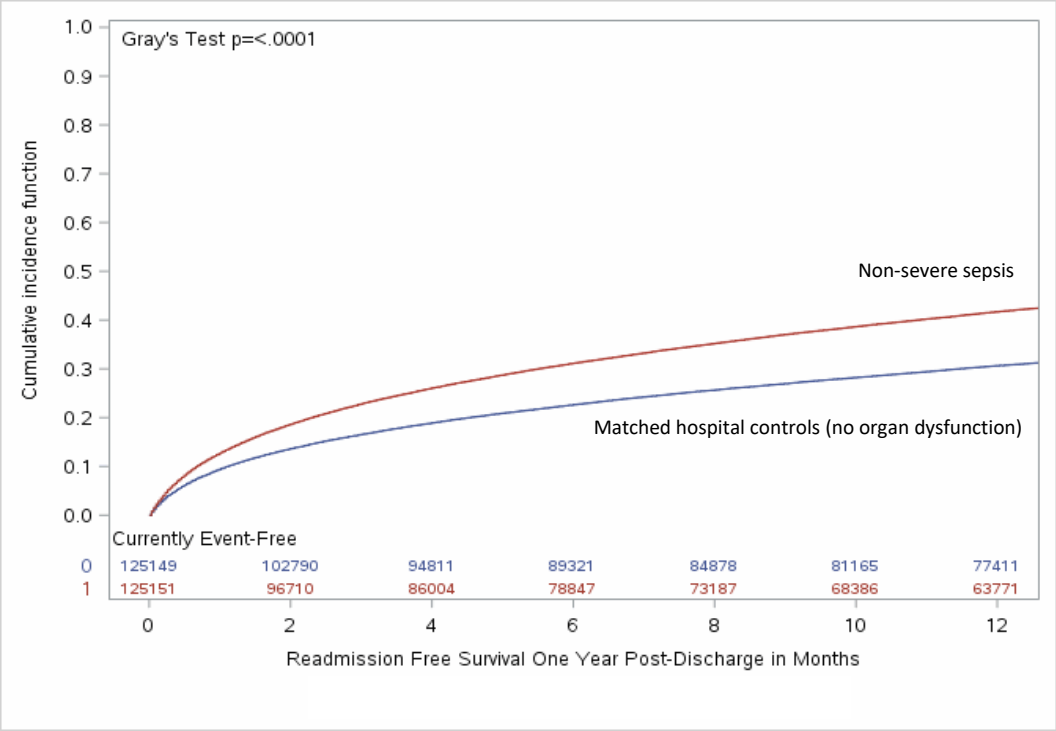


Figure E7: No Organ Dysfunction Matching, Survivor Cohort, Readmission, CIF Plots

a) 1-Year



b) 5-Year

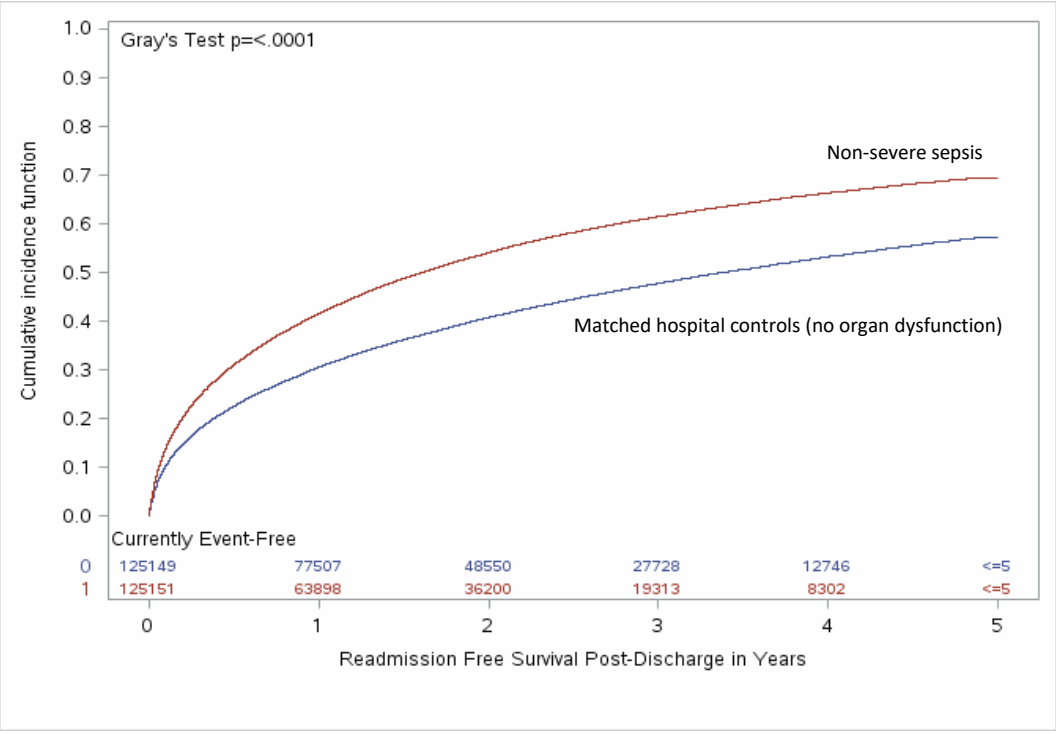


Table E5: No Organ Dysfunction Matching. Healthcare Resource Utilization and Outcomes 1-Year After Index Admission, Cases vs Matched Controls

	Non-Severe Sepsis (no organ dysfunction) N= 133,961	Matched Controls (no organ dysfunction) N= 133,961	Crude % Difference
	N (%)	N (%)	
Resource Utilization (number of patients with > 0 costs for cost category)			
Emergency visits	116111 (86.68)	111696 (83.39)	3.29
Complex continuing care	10518 (7.85)	7593 (5.67)	2.18
Long-term care	21351 (15.94)	16840 (12.57)	3.37
LTC at Index	*11018 (8.22)*	*9722 (7.26)*	*0.96*
Rehabilitation	9804 (7.32)	9419 (7.03)	0.29
Homecare	65101 (48.60)	54151 (40.43)	8.17
Homecare at Index	*48028 (35.85)*	*43872 (32.75)*	*3.10*
Prescriptions*	111885 (83.53)	108802 (81.23)	2.30
Physician services	133933 (100)	133923 (100)	0.00
Other OHIP services†	103664 (77.39)	104202 (77.79)	-0.40
Acute Hospitalizations	133961 (100)	133961 (100)	0.00

LTC = long-term care; OHIP = Ontario Health Insurance Plan

*Includes prescription drug claims covered by the Ontario Drug Benefit program.

†Includes laboratory services, and non-physician services covered by the Ontario Health Insurance Plan.

‡Discharge disposition after index admission.

Table E6: No Organ Dysfunction Matching. Crude Mean Total and Subdivided 1-Year Healthcare Costs, Cases vs Matched Controls, by Sepsis Type (C$2018)

	Non-Severe Sepsis (no organ dysfunction) N= 133,961	Matched Controls (no organ dysfunction) N= 133,961	Crude Difference (95% CI)
	Mean (SD)	**Mean (SD)**	
Emergency visits	1164 (1122)	983 (1050)	181 (173-189)
Complex cont. care	2774 (15849)	1699 (11578)	1075 (966-1182)
Long-term care	4068 (12050)	3185 (10790)	883 (803-958)
Rehabilitation	1688 (7266)	1515 (6433)	173 (122-230)
Homecare	2790 (7270)	1874 (5375)	917 (867-962)
Prescription drugs*	2490 (5772)	1986 (4254)	504 (467-545)
Physician services	4734 (4300)	4262 (3911)	472 (441-501)
Other OHIP services†	273 (413)	247 (369)	26 (23-29)
Acute Hospitalizations	22666 (29594)	15615 (20279)	7050 (6864-7225)
Index hospitalization			
Mean (SD)	13990 (17383)	10494 (11341)	3496 (3394-3617)
Median (IQR)	8965 (8877)	7554 (7233)	1411 (1365-1459)
Total 1-Year Cost			
Mean (SD)	42648 (44335)	31366 (32876)	11282 (10988-11557)
Median (IQR)	27365 (44174)	19307 (29923)	8058 (7830-8289)

CI = confidence interval; IQR = interquartile range; OHIP =Ontario Health Insurance Plan; SD = standard deviation
*Includes prescription drug claims covered by the Ontario Drug Benefit program.
†Includes laboratory services and non-physician services covered by the Ontario Health Insurance Plan.

Table E7: No Organ Dysfunction Matching Crude Mean Total 1-5 Year Healthcare Costs, Cases vs. Controls (C$2018)

	Non-Severe Sepsis (no organ dysfunction)	Matched Controls (no organ dysfunction)	Cohort Size
Cohort Size*	**N**	**N**	**N**
Year 1	133961	133961	267922
Year 2	101766	107342	209108
Year 3	71203	77722	148925
Year 4	44385	50675	95060
Year 5	22374	26940	49314
Deaths	**N (%)**	**N (%)**	**% Difference**
Year 1	32143 (24.00)	26574 (19.84)	4.16
Year 2	9997 (9.82)	7022 (6.54)	3.28
Year 3	6653 (9.34)	4405 (5.67)	3.67
Year 4	3662 (8.25)	2398 (4.73)	3.52
Year 5	1238 (5.53)	835 (3.10)	2.43
Costs	**Mean (SD)**	**Mean (SD)**	**Crude Difference (95% CI)**
Pre-Index	15626 (26402)	11994 (20840)	3632 (3484-3802)
Year 1	42648 (44335)	31366 (32876)	11282 (10988-11557)
Year 2	24645 (36086)	16364 (26656)	8282 (8028-8540)
Year 3	23992 (35419)	15794 (26383)	8198 (7866-8495)
Year 4	23403 (36134)	15668 (26705)	7736 (7328-8123)
Year 5	23198 (36731)	15900 (27373)	7298 (6700-7861)

CI = confidence interval; OHIP =Ontario Health Insurance Plan; SD = standard deviation
*Only includes patients who had follow-up at the start of the year of analysis.

Table E8: Adjusted* Incremental Costs for Cases and Matched Controls (2018 CAD)

Outcome	Non-Severe Sepsis vs. Matched Controls (no organ dysfunction)
	Adjusted Mean Difference (95% CI)
Hospital Costs	3514 (3397-3616)
1-Year Costs	11618 (11052-11614)
Hospital Survivors†	10796 (10376-10925)
Year 2-5 Costs‡	
Year 2	8233 (7970-8510)
Year 3	8140 (7826-8443)
Year 4	7643 (7220-8078)
Year 5	7205 (6656-7754)

*Adjusted for hospital type, and propensity score variables with standardized difference > 0.10 (hospitalization in the year before index admission date).

†Data is from an analysis of cases and controls who survived index hospitalization (N = 125,153 matched pairs).

‡Data includes only cases and controls who had follow-up at the beginning of the year under analysis. Those with 0 costs were excluded.

Table E9: No Organ Dysfunction Matching. Hospital Survivor Cohort. Healthcare Resource Utilization and Outcomes 1-Year After Index Admission, Cases vs Matched Controls

	Infection (no organ dysfunction) N=125,151	Matched Controls (no organ dysfunction) N=125,149	Crude % Difference
	N (%)	N (%)	
Resource Utilization (number of patients with > 0 costs for cost category)			
Emergency visits	109612 (87.58)	104931 (83.84)	3.74
Complex continuing care	10394 (8.31)	7417 (5.93)	2.38
Long-term care	19977 (15.96)	16026 (12.81)	3.15
LTC at Index	*9369 (7.49)*	*8562 (6.84)*	*0.65*
Rehabilitation	9731 (7.78)	9068 (7.25)	0.53
Homecare	63818 (50.99)	52491 (41.94)	9.05
Homecare at Index	*43012 (34.37)*	*39024 (31.18)*	*3.19*
Prescriptions*	109544 (87.53)	106155 (84.82)	2.71
Physician services	100	100	0.00
Other OHIP services†	103102 (82.38)	102906 (82.23)	0.15
Acute Hospitalizations	100	100	0.00

*Includes prescription drug claims covered by the Ontario Drug Benefit program.
†Includes laboratory services, and non-physician services covered by the Ontario Health Insurance Plan.
‡Discharge disposition after index admission.

Table E10: No Organ Dysfunction Matching. Hospital Survivor Cohort. Crude Mean Total and Subdivided 1-Year Healthcare Costs, Cases vs Matched Controls, by Sepsis Type (C$2018)

	Non-Severe Sepsis (no organ dysfunction) N=125,151	Matched Controls (no organ dysfunction) N=125,149	Crude Difference (95% CI)
	Mean (SD)	**Mean (SD)**	
Emergency visits	1208 (1140)	1012 (1088)	196 (188-204)
Complex cont. care	2945 (16336)	1796 (11906)	1149 (1036-1260)
Long-term care	4309 (12353)	3449 (11177)	860 (774-945)
Rehabilitation	1802 (7503)	1562 (6519)	240 (187-293)
Homecare	2983 (7493)	1968 (5453)	1015 (966-1067)
Prescription drugs*	2655 (5913)	2102 (4181)	553 (514-592)
Physician services	4915 (4329)	4398 (3517)	517 (488-549)
Other OHIP services†	292 (420)	262 (377)	29 (27-3)
Acute Hospitalizations	22989 (29720)	15772 (20327)	7217 (7028-7427)
Index hospitalization			
Mean (SD)	13605 (16276)	10284 (10629)	3321 (3213-3426)
Median (IQR)	8867 (8445)	7503 (6926)	1364 (1318-1415)
Total 1-Year Cost			
Mean (SD)	44098 (44740)	32321 (33037)	11777 (11496-12082)
Median (IQR)	28985 (45372)	20095 (30928)	8890 (8644-9142)

CI = confidence interval; OHIP =Ontario Health Insurance Plan; SD = standard deviation

*Includes prescription drug claims covered by the Ontario Drug Benefit program.

†Includes laboratory services and non-physician services covered by the Ontario Health Insurance Plan.

APPENDIX F: Additional Data for Sensitivity Analysis of Severe Sepsis cases Versus Controls with Non-Severe Sepsis

This appendix provides additional data not included above on the sensitivity analysis in which patients with severe sepsis were compared to patients with non-severe sepsis. In this analysis severe sepsis cases were matched with non-sepsis controls, following the same processes as the primary analysis. All analyses were repeated as above comparing attributable outcomes between sepsis patients with and without organ dysfunction.

List of Tables in Appendix F

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Table F1: Baseline Characteristics of Cases and Controls, Before and After Matching (Severe versus non-severe sepsis)

	BEFORE MATCHING			AFTER MATCHING		
	Non-Severe Sepsis (controls) N= 178,682	**Severe Sepsis Cases N= 91,987**	**Std. Diff.**	**Matched Non-Severe Controls N= 83,780**	**Severe Sepsis Cases N= 83,780** *Unmatched* = 8.9%	**Std. Diff**
Age, mean (SD)	73.05 (16.39)	74.17 (14.71)	**0.07**	74.99 (14.18)	74.98 (14.18)	**0.00**
<65, n (%)	45994 (25.74)	21251 (23.10)	**0.06**	17638 (21.05)	17678 (21.10)	**0.00**
65-84, n (%)	83164 (46.54)	45572 (49.54)	**0.06**	42117 (50.27)	42061 (50.20)	**0.00**
≥ 85, n (%)	49524 (27.72)	25164 (27.36)	**0.01**	24025 (28.68)	24041 (28.70)	**0.00**
Female, n (%)	102663 (57.46)	46633 (50.70)	**0.14**	43315 (51.70)	43315 (51.70)	**0.00**
Rural, n (%)	26641 (14.91)	8149 (8.86)	**0.19**	8007 (9.56)	7623 (9.10)	**0.02**
Income quintile, n (%)						
1 (lowest)	40840 (22.86)	21530 (23.41)	**0.01**	19628 (23.43)	19422 (23.18)	**0.01**
2	37145 (20.79)	19837 (21.57)	**0.02**	17938 (21.41)	17946 (21.42)	**0.00**
3	35093 (19.64)	17900 (19.46)	**0.00**	16296 (19.45)	16331 (19.49)	**0.00**
4	33979 (19.02)	17090 (18.58)	**0.01**	15572 (18.59)	15706 (18.75)	**0.00**
5 (highest)	30528 (17.09)	15154 (16.47)	**0.02**	13904 (16.60)	13944 (16.64)	**0.00**
missing	1097 (0.61)	476 (0.52)	**0.01**	442 (0.53)	431 (0.51)	**0.00**
ON Marginalization Index, n (%)						
1 (lowest)	24523 (13.72)	11649 (12.66)	**0.03**	10813 (12.91)	10551 (12.59)	**0.01**
2	32148 (17.99)	15879 (17.26)	**0.02**	14656 (17.49)	14443 (17.24)	**0.01**
3	38550 (21.57)	19333 (21.02)	**0.01**	17560 (20.96)	17599 (21.01)	**0.00**
4	36470 (20.41)	18779 (20.41)	**0.00**	17058 (20.36)	17158 (20.48)	**0.00**
5 (highest)	44962 (25.16)	25567 (27.79)	**0.06**	22984 (27.43)	23316 (27.83)	**0.01**
Missing	2029 (1.14)	780 (0.85)	**0.03**	709 (0.85)	713 (0.85)	**0.00**
Prior cancer, n (%)	30520 (17.08)	15647 (17.01)	**0.00**	15001 (17.91)	14201 (16.95)	**0.03**
Prior CHF, n (%)	47285 (26.46)	33152 (36.04)	**0.21**	28197 (33.66)	29405 (35.10)	**0.03**
Prior CKD, n (%)	3214 (1.80)	5741 (6.24)	**0.23**	2278 (2.72)	2525 (3.01)	**0.02**
Prior COPD, n (%)	69574 (38.94)	35818 (38.94)	**0.00**	33750 (40.28)	33153 (39.57)	**0.01**
Prior diabetes, n (%)	66270 (37.09)	41281 (44.88)	**0.16**	36503 (43.57)	36557 (43.63)	**0.00**
Residence in LTC, n (%)	16351 (9.15)	8200 (8.91)	**0.01**	7527 (8.98)	7932 (9.47)	**0.02**
ADG score, mean (SD)	27.57 (13.28)	33.31 (12.85)	**0.44**	32.09 (12.55)	32.53 (12.42)	**0.04**
Healthcare use, past year						
Hospitalization, n (%)	60484 (33.85)	33208 (36.10)	**0.05**	30880 (36.86)	29852 (35.63)	**0.03**
Homecare use, n (%)	81768 (45.76)	43483 (47.27)	**0.03**	40147 (47.92)	40295 (48.10)	**0.00**

ED visits						
Mean (SD)	1.44 (2.88)	1.23 (2.35)	**0.08**	1.28 (1.95)	1.23 (2.04)	**0.02**
Median (Q1-Q3)	1 (0-2)	1 (0-2)	**0.09**	1 (0-2)	1 (0-2)	**0.05**
Physician visits						
Mean (SD)	24.83 (22.55)	26.50 (24.27)	**0.07**	26.25 (22.84)	25.91 (23.63)	**0.01**
Median (Q1-Q3)	18 (10-32)	19 (10-35)	**0.06**	20 (11-34)	19 (10-34)	**0.04**
Index Admission						
Urgent admission, n (%)	171193 (95.81)	87914 (95.57)	**0.01**	81553 (97.34)	81553 (97.34)	**0.00**
Index Admission Date, n (%)						
Apr 2012 – Mar 2013	47349 (26.50)	21499 (23.37)	**0.07**	19744 (23.57)	19692 (23.50)	**0.00**
Apr 2013 – Mar 2014	45640 (25.54)	22831 (24.82)	**0.02**	20727 (24.74)	20757 (24.78)	**0.00**
Apr 2014 – Mar 2015	44897 (25.13)	24014 (26.11)	**0.02**	21957 (26.21)	21977 (26.23)	**0.00**
Apr 2015 – Mar 2016	40796 (22.83)	23643 (25.70)	**0.07**	21352 (25.49)	21354 (25.49)	**0.00**
Hospital Type*, n (%)						
Teaching	47727 (26.71)	28161 (30.61)	**0.09**	23043 (27.51)	24801 (29.60)	**0.05**
Community ≥ 100 beds	88361 (49.45)	52899 (57.51)	**0.16**	43879 (52.38)	48592 (58.00)	**0.11**
Community < 100 beds	42585 (23.83)	10927 (11.88)	**0.32**	16854 (20.12)	10387 (12.40)	**0.21**

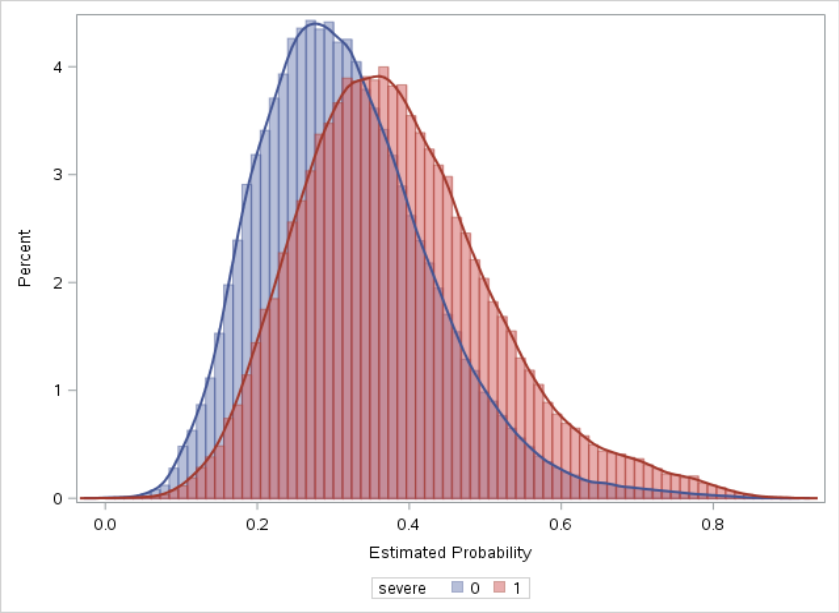
ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = Congestive heart failure; CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; ON= Ontario; Q= quartile SD = standard deviation; Std Diff = standardized difference.

*Variable not included in propensity score model.

Missing values: rural =13, hospital type= 9.

Figure F1: Plot of Propensity Scores for Severe Sepsis versus Non-Severe Controls, Before and After Matching

a) Pre-Match



b) Post-Match

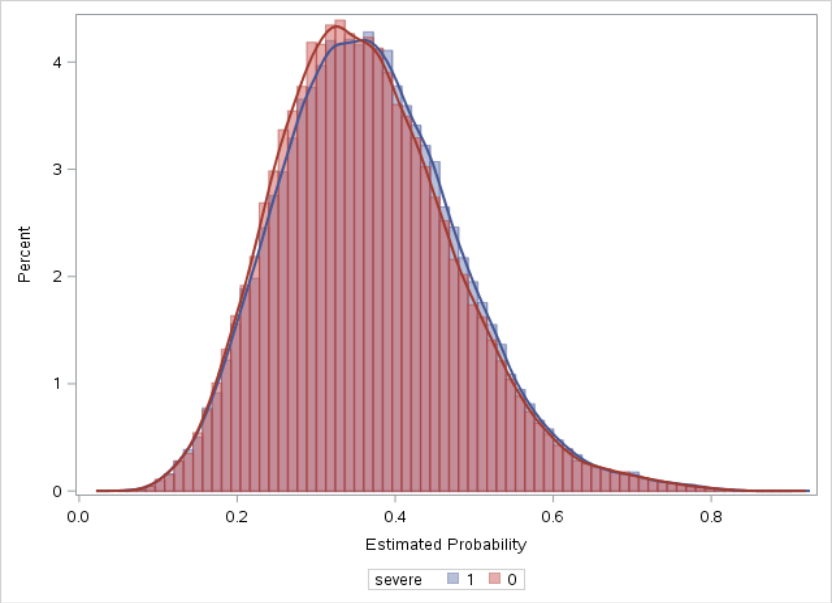


Table F2: Hospital Survivors: Baseline Characteristics of Cases and Controls, Before and After Matching (Severe versus non-severe sepsis)

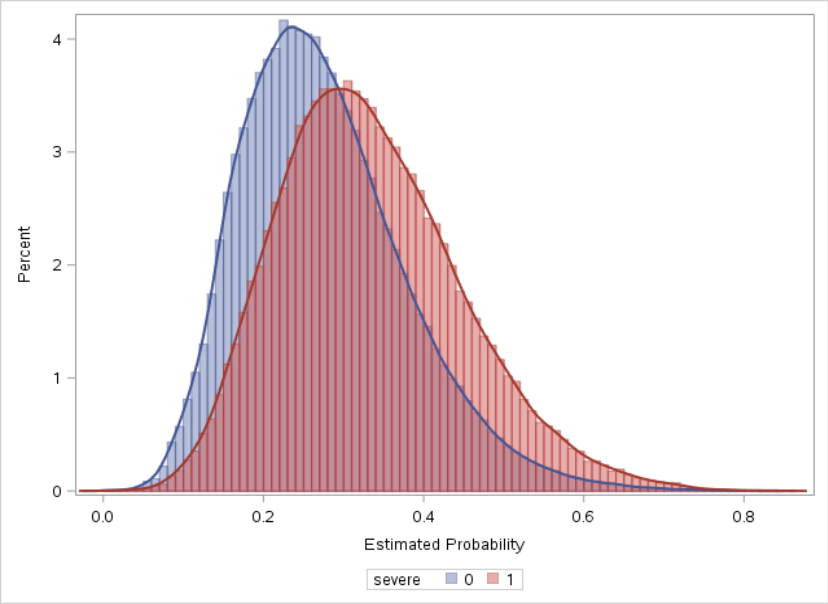
	BEFORE MATCHING			AFTER MATCHING		
	Non-Severe Sepsis (controls) N=165,423	**Severe Sepsis Cases N= 68,362**	**Std. Diff.**	**Matched Non-Severe Controls N= 63,511**	**Severe Sepsis Cases N= 63,511** *Unmatched* = 9.3%	**Std. Diff**
Age, mean (SD)	72.44 (16.55)	73.57 (15.04)	**0.07**	74.29 (14.47)	74.28 (14.47)	**0.00**
<65, n (%)	44587 (26.95)	16635 (24.33)	**0.06**	14255 (22.44)	14326 (22.56)	**0.00**
65-84, n (%)	77245 (46.70)	33820 (49.47)	**0.06**	32031 (50.43)	31991 (50.37)	**0.00**
≥ 85, n (%)	43591 (26.35)	17907 (26.19)	**0.00**	17225 (27.12)	17194 (27.07)	**0.00**
Female, n (%)	95759 (57.89)	35669 (52.18)	**0.11**	33610 (52.92)	33610 (52.92)	**0.00**
Rural, n (%)	24191 (14.62)	6079 (8.89)	**0.18**	6045 (9.52)	5766 (9.08)	**0.02**
Income quintile, n (%)						
1 (lowest)	37872 (22.89)	15951 (23.33)	**0.01**	14646 (23.06)	14693 (23.13)	**0.00**
2	34339 (20.76)	14607 (21.37)	**0.01**	13552 (21.34)	13527 (21.30)	**0.00**
3	32430 (19.60)	13399 (19.60)	**0.00**	12386 (19.50)	12450 (19.60)	**0.00**
4	31463 (19.02)	12768 (18.68)	**0.01**	12020 (18.93)	11928 (18.78)	**0.00**
5 (highest)	28320 (17.12)	11278 (16.50)	**0.02**	10568 (16.64)	10570 (16.64)	**0.00**
Missing	999 (0.60)	359 (0.53)	**0.01**	339 (0.53)	343 (0.54)	**0.00**
ON Marginalization Index n (%)						
1 (lowest)	22815 (13.79)	8810 (12.89)	**0.03**	8333 (13.12)	8159 (12.85)	**0.01**
2	29912 (18.08)	11883 (17.38)	**0.02**	11175 (17.60)	10991 (17.31)	**0.01**
3	35759 (21.62)	14301 (20.92)	**0.02**	13262 (20.88)	13284 (20.92)	**0.00**
4	33643 (20.34)	13825 (20.22)	**0.00**	12820 (20.19)	12904 (20.32)	**0.00**
5 (highest)	41431 (25.05)	18935 (27.70)	**0.06**	17333 (27.29)	17605 (27.72)	**0.00**
missing	1863 (1.13)	608 (0.89)	**0.02**	588 (0.93)	568 (0.89)	**0.01**
Prior cancer, n (%)	26558 (16.05)	10092 (14.76)	**0.04**	9804 (15.44)	9358 (14.73)	**0.00**
Prior CHF, n (%)	42344 (25.60)	23346 (34.15)	**0.19**	20557 (32.37)	21367 (33.64)	**0.03**
Prior CKD, n (%)	2928 (1.77)	3163 (4.63)	**0.16**	1794 (2.82)	1840 (2.90)	**0.00**
Prior COPD, n (%)	63831 (38.59)	25979 (38.00)	**0.01**	24990 (39.35)	24585 (38.71)	**0.01**
Prior diabetes, n (%)	61321 (37.07)	31070 (45.45)	**0.17**	28091 (44.23)	28301 (44.56)	**0.01**
Residence in LTC, n (%)	14004 (8.47)	5858 (8.57)	**0.00**	5366 (8.45)	5692 (8.96)	**0.02**
ADG score, mean (SD)	27.15 (13.27)	32.79 (12.92)	**0.43**	31.83 (12.63)	32.17 (12.49)	**0.03**
Healthcare use, past year						
Hospitalization, n (%)	54737 (33.09)	23576 (34.49)	**0.03**	22361 (35.21)	21679 (34.13)	**0.02**

Homecare use, n (%)	73005 (44.13)	30765 (45.00)	**0.02**	28794 (45.34)	29062 (45.76)	**0.01**
ED visits						
Mean (SD)	1.44 (2.92)	1.25 (2.44)	**0.07**	1.27 (1.96)	1.23 (2.07)	**0.02**
Median (Q1-Q3)	1 (0-2)	1 (0-2)	**0.09**	1 (0-2)	1 (0-2)	**0.05**
Physician visits						
Mean (SD)	24.36 (22.10)	25.51 (23.33)	**0.05**	25.40 (22.24)	25.13 (22.94)	**0.01**
Median (Q1-Q3)	18 (10-32)	19 (10-33)	**0.05**	19 (11-33)	19 (10-33)	**0.03**
Index Admission						
Urgent admission, n (%)	158285 (95.69)	65210 (95.39)	**0.01**	61797 (97.30)	61797 (97.30)	**0.00**
Index Admission Date, n (%)						
Apr 2012 – Mar 2013	43492 (26.29)	15569 (22.77)	**0.08**	14552 (22.91)	14491 (22.82)	**0.00**
Apr 2013 – Mar 2014	42215 (25.52)	16956 (24.80)	**0.02**	15769 (24.83)	15786 (24.86)	**0.00**
Apr 2014 – Mar 2015	41622 (25.16)	17909 (26.20)	**0.02**	16658 (26.23)	16682 (26.27)	**0.00**
Apr 2015 – Mar 2016	38094 (23.03)	17928 (26.23)	**0.07**	16532 (26.03)	16552 (26.06)	**0.00**
Hospital Type*, n (%)						
Teaching	44492 (26.90)	20871 (30.53)	**0.08**	17669 (27.82)	18857 (29.69)	**0.04**
Community ≥ 100 beds	82145 (49.66)	39036 (57.10)	**0.15**	33220 (52.31)	36550 (57.55)	**0.11**
Community < 100 beds	38777 (23.44)	8455 (12.37)	**0.29**	12620 (19.87)	8104 (12.76)	**0.19**

ADG = Johns Hopkins' Aggregated Diagnosis Groups; CHF = Congestive heart failure; CKD = Chronic kidney disease; COPD = chronic obstructive pulmonary disease; ED= emergency department; LTC = long-term care; ON= Ontario; SD = standard deviation; Std Diff = standardized difference.
*Variable not included in propensity score model.
Missing values: rural 10, hospital type 9

Figure F2: Hospital Survivors: Plot of Propensity Scores for Severe Sepsis versus Non-Severe Controls, Before and After Matching

a) Pre-Match



b) Post-Match

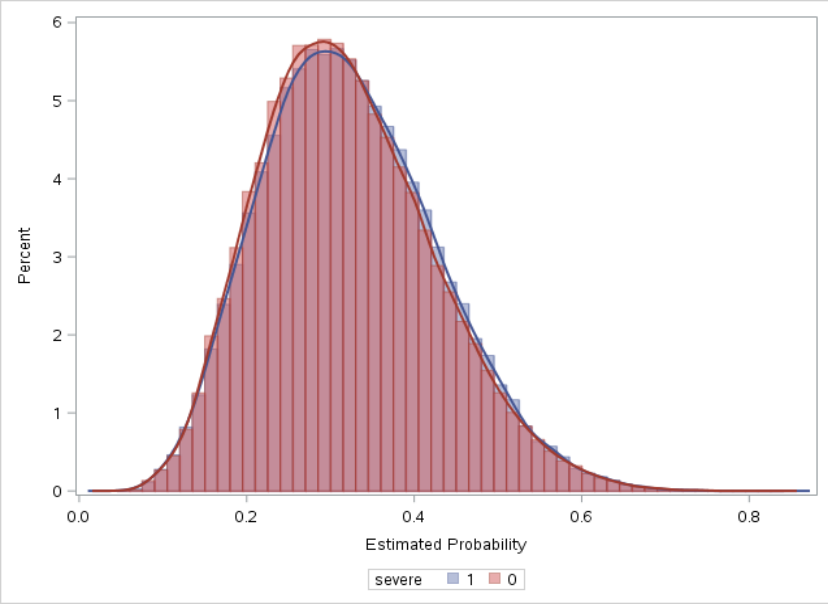
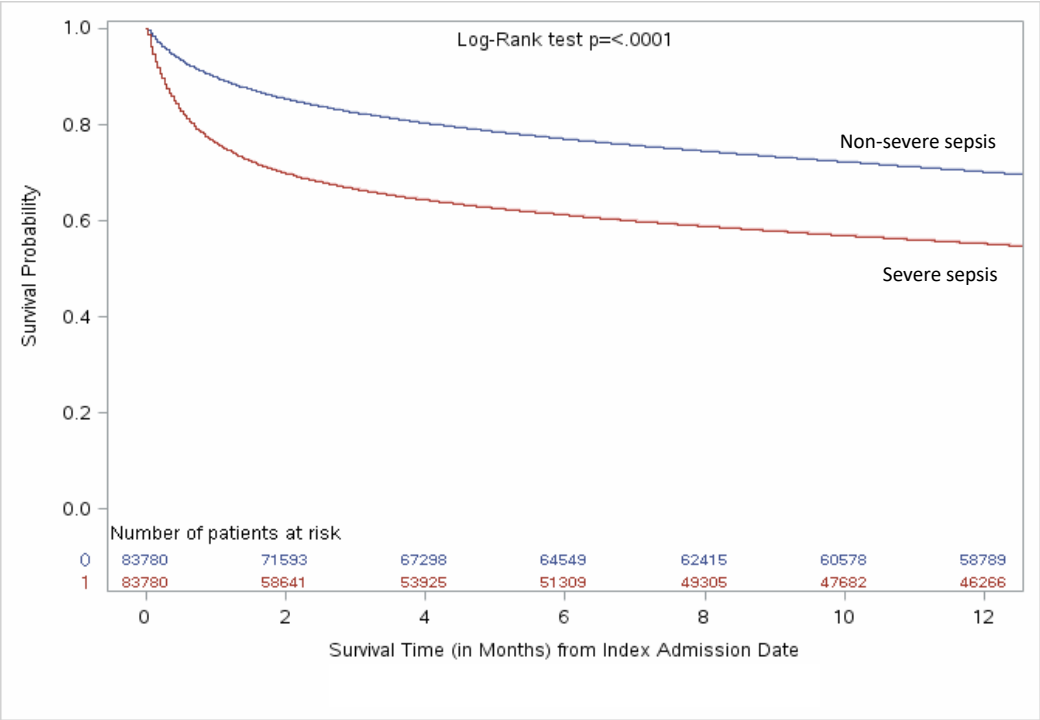


Figure F3: Severe Sepsis versus Non-Severe Controls, Mortality Kaplan Meier Plots

a) 1-Year



b) 5 – Years

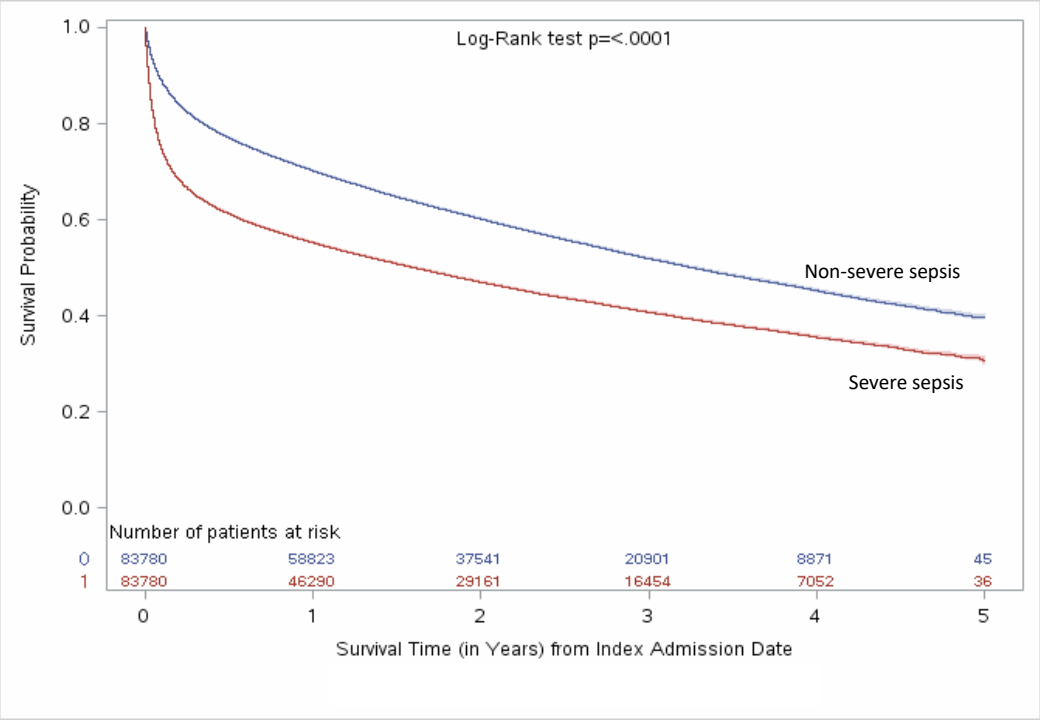
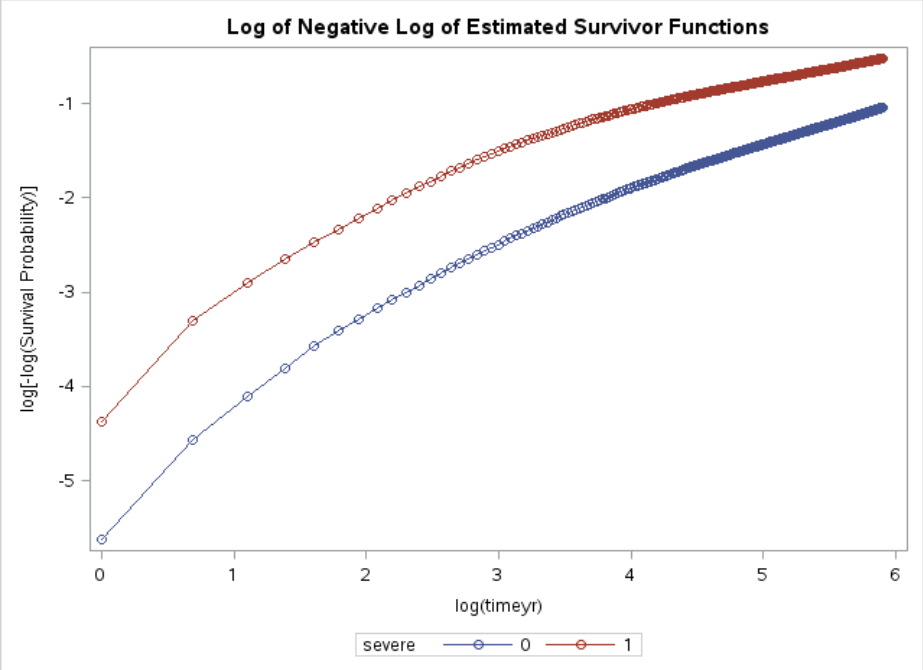


Figure F4: Severe Sepsis versus Non-Severe Controls Matching, Test of Proportional Hazards.

a) 1-Year Mortality



b) 5-Year Mortality

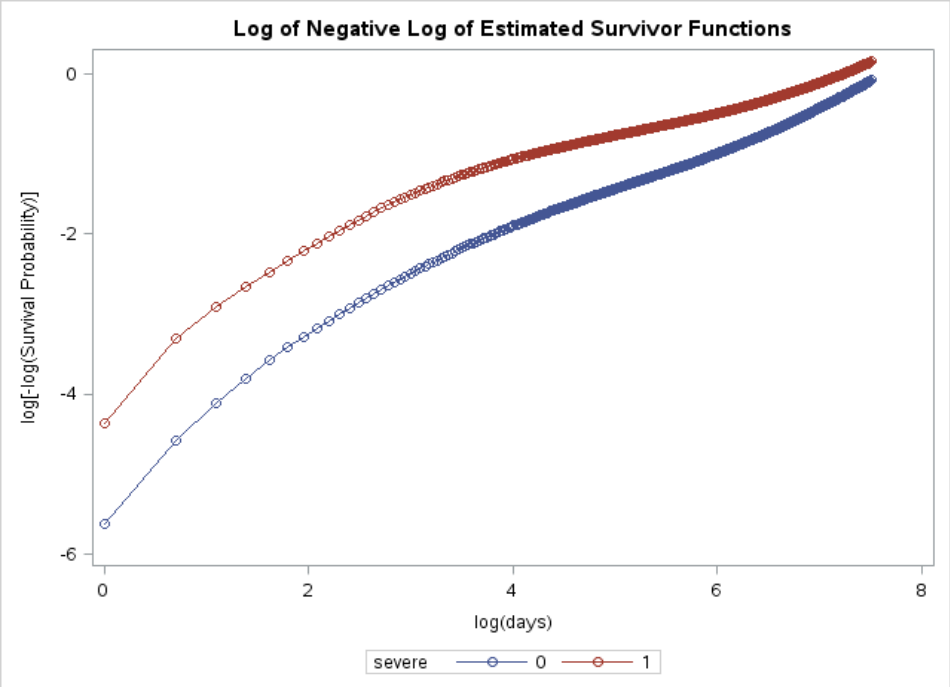
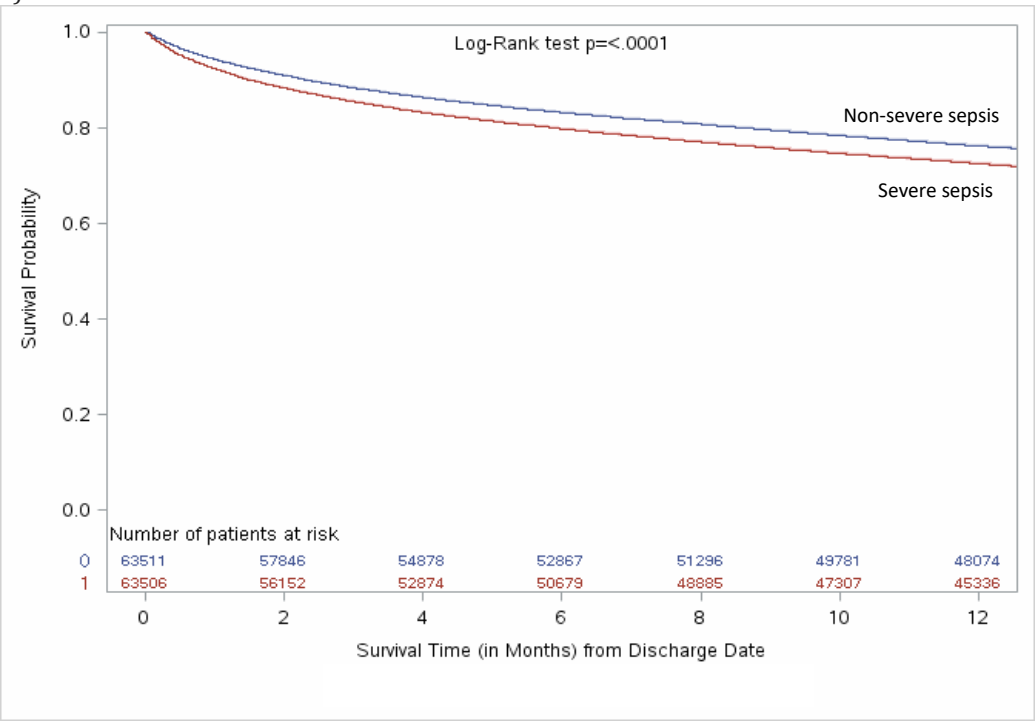


Figure F5: Severe Sepsis versus Non-Severe Controls, Survivor Cohort, 1-Year Post-Discharge Mortality Kaplan Meier Plots

a) 1-Year



b) 5-Year

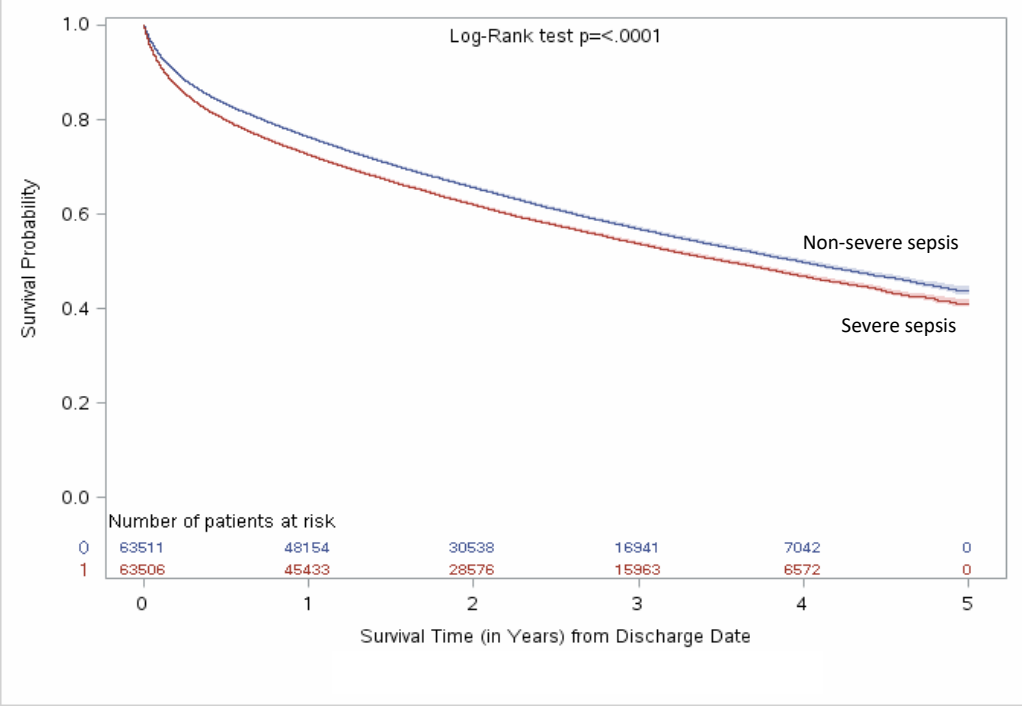
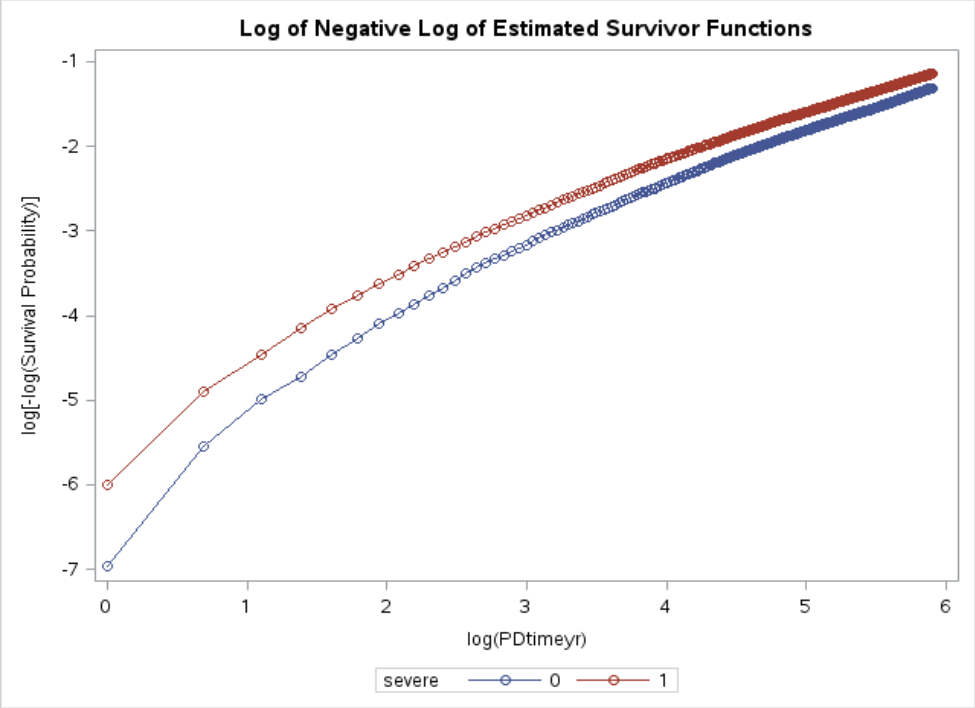


Figure F6: Survivor Cohort: Severe Sepsis versus Non-Severe Controls Matching, Test of Proportional Hazards.

a) 1 Year Post-Discharge Mortality



b) 5-Year Post-Discharge Mortality

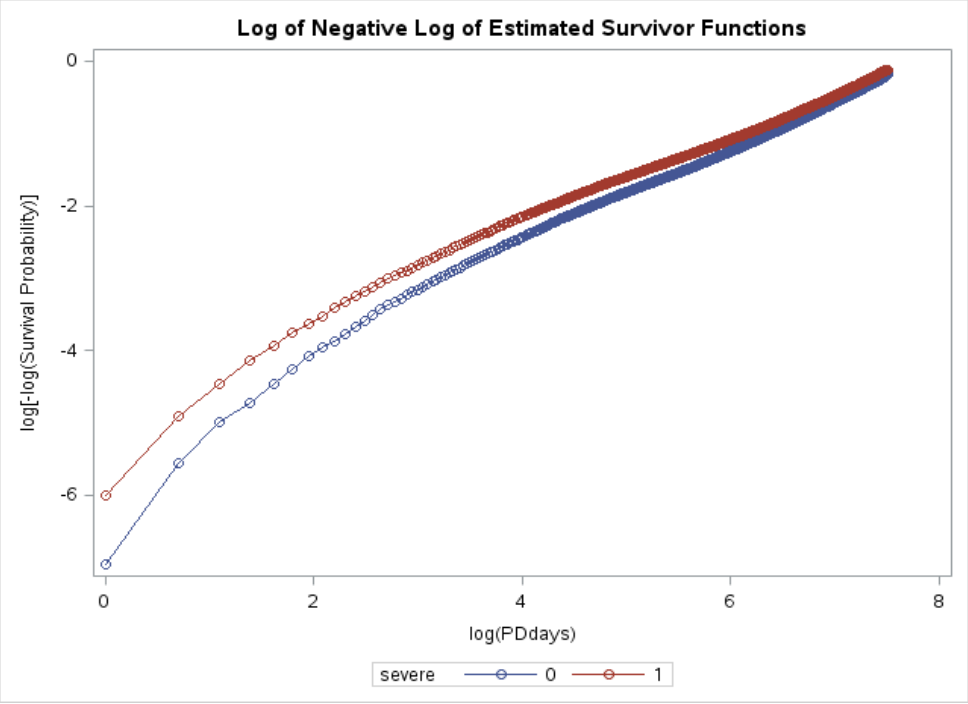
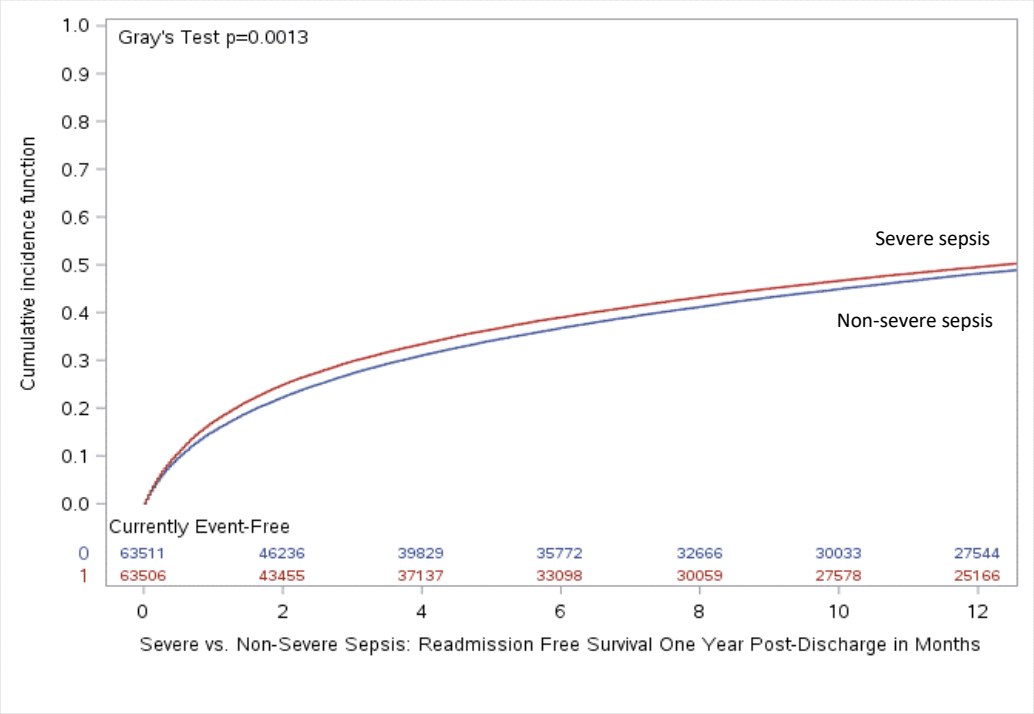


Figure F7: Survivor Cohort: Severe Sepsis versus Non-Severe Controls Matching

a) 1-Year Readmission, CIF Plots



b) 5-Year Readmission, CIF Plots

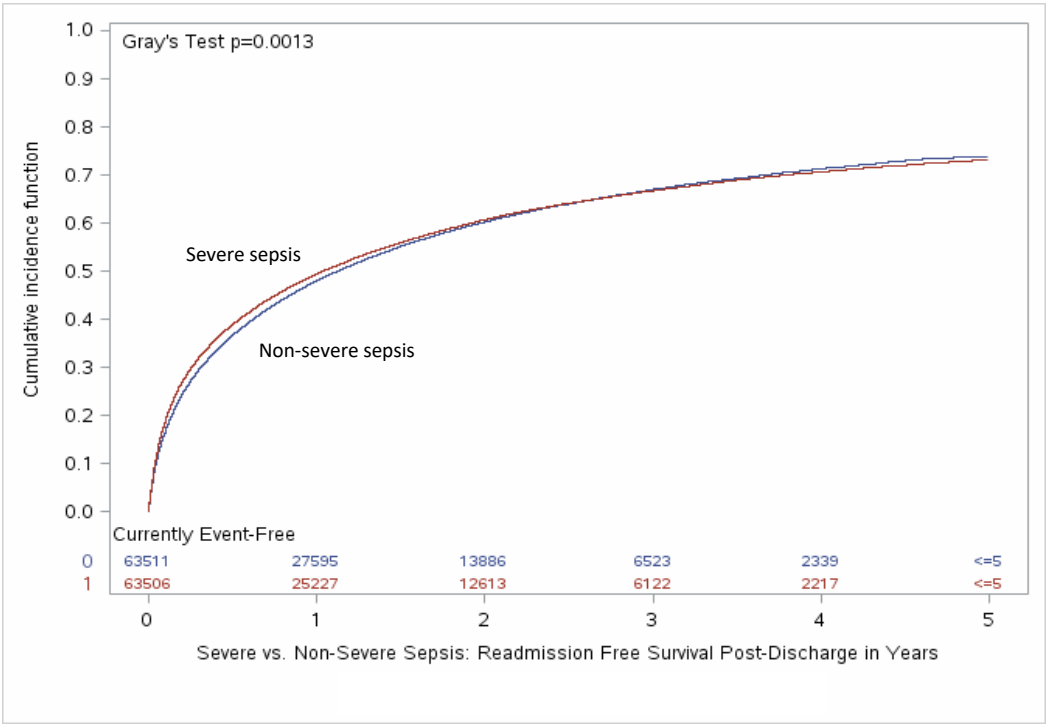


Table F3: Severe versus Non-Severe Sepsis. Descriptive Characteristics of Index Hospital Admission and Long-Term Outcomes

	Matched non-Severe Controls N =83,780	Severe Sepsis N = 83,780
	N (%)	N (%)
ICU admission	9034 (10.78)	35173 (41.98)
In-hospital death	6636 (7.92)	20823 (24.85)
1-year mortality	24957 (29.79)	37490 (44.75)
Mortality up to 5 years	39109 (46.68)	48742 (58.18)
Follow-up time		
Mean (SD)	700 (518)	556 (536)
Median (IQR)	645 (862)	444 (916)
Hospital LOS		
Mean (SD)	12.20 (23.55)	20.58 (35.55)
Median (Q1-Q3)	6 (3-13)	11 (5-23)
ICU LOS		
Mean (SD)	0.54 (2.03)	5.02 (15.43)
Median (Q1-Q3)	0 (0-0)	0 (0-5)
Hospital Survivor Matching	**N=63511**	**N= 63506**
1-year post-discharge mortality	15037 (23.68)	17395 (27.39)
5-year post-discharge mortality	26219 (41.28)	28215 (44.43)
30-day readmissions	9215 (14.51)	10382 (16.35)
1-yr readmissions	30476 (47.99)	31323 (49.32)
Up to 5-year readmissions	40957 (64.49)	40895 (64.40)
Follow-up time		
Mean (SD)	749 (498)	711 (506)
Median (IQR)	702 (754)	653 (804)

ICU = intensive care unit; IQR = interquartile range; LOS = length of stay (in days); SD = standard deviation.
†Data is from a re-matched analysis of cases and controls who survived index hospitalization.
Note: For age groups, cases were grouped by age with their corresponding matched controls. Controls could be +/- one year the age of cases.

Table F4. Severe versus Non-Severe Sepsis: Attributable Mortality, Readmission, Length of Stay – Cases and Matched Controls

Outcome	Severe Sepsis vs. Non-Severe Matched Controls	
	Crude Mean (95% CI)	**Adjusted Mean (95% CI)**
Hospital LOS	8.38 (8.08-8.67)	8.02 (7.78-8.38)
ICU LOS	4.48 (4.37-4.59)	4.50 (4.44-4.68)
Hospital Cost	20460 (20012-20894)	18886 (18488-19318)
Hospital Cost (survivors)	19078 (18628-19532)	17563 (17231-18073)
	Crude OR (95% CI)	**Adjusted OR (95% CI)**
ICU Admission	6.58 (6.39-6.79)	6.87 (6.66-7.10)
Hospital Death	3.95 (3.82-4.07)	4.00 (3.87-4.13)
Mortality Rate	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
1-Year	1.76 (1.73-1.79)	1.77 (1.74-1.80)
Up to-5 Years	1.49 (1.48-1.51)	1.50 (1.49-1.52)
Hospital Survivors		
1-Year Mortality (from discharge)	1.18 (1.16-1.21)	1.18 (1.16-1.21)
Up to 5 years (from discharge)	1.12 (1.11-1.14)	1.13 (1.11-1.15)
1-year readmission	1.09 (1.07 -1.10)	1.09 (1.07-1.10)
Up to 5 years readmission	1.06 (1.05-1.08)	1.06 (1.05-1.08)

*Adjusted for hospital type (no propensity score variables with standardized difference > 0.10)
CI = confidence interval; HR = hazard ratio; ICU = intensive care unit; LOS = length of stay (in days); OR = odds ratio.
†Data is from a re-matched analysis of cases and controls who survived index hospitalization.
|| Readmission after index admission discharge date to an acute care hospital in Ontario.

Table F5: Mortality in Cases versus Controls at Different Time Periods During Follow-up

	Severe Sepsis versus Non-Severe Sepsis Controls					
Time Period	**N at Risk†**		**Mortality (%)**		**HR_{crude} (95% CI)**	**HR_{adj}‡ (95% CI)**
	Case	**Control**	**Case**	**Control**		
0-30 day	83780	83780	23.74	10.12	2.56 (2.49-2.62)	2.57 (2.50-2.63)
30-183 day	63885	75294	19.74	14.33	1.43 (1.40-1.47)	1.43 (1.39-1.46)
6–12 month	51271	64502	9.77	8.86	1.11 (1.07-1.15)	1.11 (1.07-1.16)
Year 2	46264	58785	13.00	12.46	1.05 (1.01-1.09)	1.07 (1.03-1.11)
Year 3	29111	37496	11.00	11.30	0.97 (0.93-1.01)	0.98 (0.93-1.02)
Year 4	16429	20858	9.53	9.56	0.99 (0.93-1.06)	1.00 (0.93-1.07)
Year 5	7035	8846	6.34	6.34	1.00 (0.88-1.13)	1.01 (0.89-1.14)
Overall	83780	83780	58.18	46.68	1.49 (1.48-1.51)	1.50 (1.48-1.52)

Table F6: Healthcare Resource Utilization and Outcomes 1-Year After Index Admission, Severe versus Non-Severe Sepsis

	Severe Sepsis or Septic Shock N= 83,780	**Matched Non-Severe Controls N=83,780**	**Crude % Difference**
	N (%)	**N (%)**	
Resource Utilization			
Emergency visits	70356 (83.98)	73226 (87.40)	-3.42
Complex cont. care	8520 (10.17)	7776 (9.28)	0.89
Long-term care	13425 (16.02)	14528 (17.34)	-1.32
LTC at Index	*7932 (9.47)*	*7527 (8.98)*	*0.49*
Rehabilitation	8559 (10.22)	6763 (8.07)	2.15
Homecare	41202 (49.18)	45534 (54.35)	-5.17
Homecare at Index	*40295 (48.10)*	*40147 (47.92)*	*0.18*
Prescriptions*	61116 (72.95)	72171 (86.14)	-13.19
Physician services	100	100	0.00
Other OHIP services	51764 (61.79)	63437 (75.72)	-13.93
Acute Hospitalizations	100	100	0.00
Index Hospital Outcome	**N (%)**	**N (%)**	
Hospital Mortality	20823 (24.85)	6636 (7.92)	16.93
ICU admission	35173 (41.98)	9034 (10.78)	31.2
Total Hospital LOS (days)			
Mean (SD)	20.58 (35.55)	12.20 (23.55)	8.38
Median (Q1-Q3)	11 (5-23)	6 (3-13)	5
ICU LOS (days)			
Mean (IQR)	5.02 (15.43)	0.54 (2.03)	4.48
Median (Q1-Q3)	0 (0-5)	0 (0-0)	0

*Includes prescription drug claims covered by the Ontario Drug Benefit program.

†Includes laboratory services and non-physician services covered by the Ontario Health Insurance Plan.

Table F7: Severe Sepsis Cases vs. Non-Severe Sepsis Crude Mean Total and Subdivided 1-Year Healthcare Costs

	Severe Sepsis or Septic Shock N= 83,780	Matched Non-Severe Sepsis Controls N=83,780	Crude Difference (95% CI)
	Mean (SD)	**Mean (SD)**	
Emergency visits	1125 (1137)	1268 (1261)	-144 (-156, -132)
Complex cont. care	3904 (19762)	3333 (17580)	571 (399, 744)
Long-term care	3509 (11107)	4313 (12314)	-804 (-907, -693)
Rehabilitation	2319 (8846)	1823 (7547)	496 (415, 575)
Homecare	2876 (7342)	3320 (7813)	-445 (-511, -377)
Prescription drugs†	2186 (5132)	2839 (5817)	-653 (-703, -596)
Physician services	6999 (8313)	5285 (4734)	1714 (1658, 1778)
Other OHIP services‡	231 (379)	267 (3901)	-36 (-40, -33)
Acute Hospitalizations	42533 (59816)	26337 (33306)	16196 (15714-16625)
Index hospitalization			
Mean (SD)	35431 (60655)	14971 (19026)	20460 (20012-20894)
Median (IQR)	17579 (25328)	9657 (9498)	7922 (7785-8068)
Total 1-Year Cost			
Mean (SD)	65682 (75040)	48786 (48520)	16896 (16290-17485)
Median (IQR)	43401 (61469)	33142 (48951)	10259 (9735-10720)

CI = confidence interval; OHIP =Ontario Health Insurance Plan; SD = standard deviation

*Data is from a scenario analysis of cases and controls who survived index hospitalization.

†Includes prescription drug claims covered by the Ontario Drug Benefit program.

‡Includes outpatient physician visits, laboratory services, and non-physician services covered by the Ontario Health Insurance Plan.

Table F8: Severe Sepsis versus Non-Severe Controls. Mean Total Healthcare Costs Years 1-5, (C$2018)

	Severe Sepsis or septic shock	Matched Non-Severe Controls	Total	
Cohort Size	**N**	**N**	**N**	
Year 1	83780	83780	167560	
Year 2	46255	58785	105040	
Year 3	29084	37447	66531	
Year 4	16398	20820	37218	
Year 5	7000	8820	15820	
Year	**Median (IQR)**	**Median (IQR)**	**Crude Difference (95% CI)**	
Pre-Index	9832 (26923)	10382 (27723)	-550 (-748, -341)	
Year 1	43401 (61469)	33142 (48951)	10259 (9735, 10720)	
Year 2	15993 (42969)	14902 (40843)	1091 (677, 1508)	
Year 3	14021 (42518)	13873 (40484)	148 (-439, 687)	
Year 4	12402 (39649)	12455 (38397)	-53 (-697, 621)	
Year 5	11029 (38024)	11242 (36961)	-213 (-1070, 523)	
Year	**Mean (SD)**	**Mean (SD)**	**Crude Difference (95% CI)**	**Adjusted Difference (95% CI)**
Pre-Index	22839 (33518)	23626 (33706)	-788 (-1095, -483)	n/a
Year 1	65682 (75040)	48786 (48520)	16896 (16290, 17485)	15706 (14714, 15856)
Year 2	33824 (49731)	30662 (41251)	3162 (2597, 3707)	3174 (2640, 3687)
Year 3	31619 (45611)	29952 (41655)	1666 (994, 2310)	1703 (1019, 2403)
Year 4	29923 (43883)	28393 (41105)	1530 (667, 2366)	1550 (723, 2418)
Year 5	28509 (43047)	27342 (39950)	1167 (-146, 2439)	1261 (-61, 2505)

APPENDIX G: Sensitivity Analysis: Multivariate Regression Analysis (No Matching)

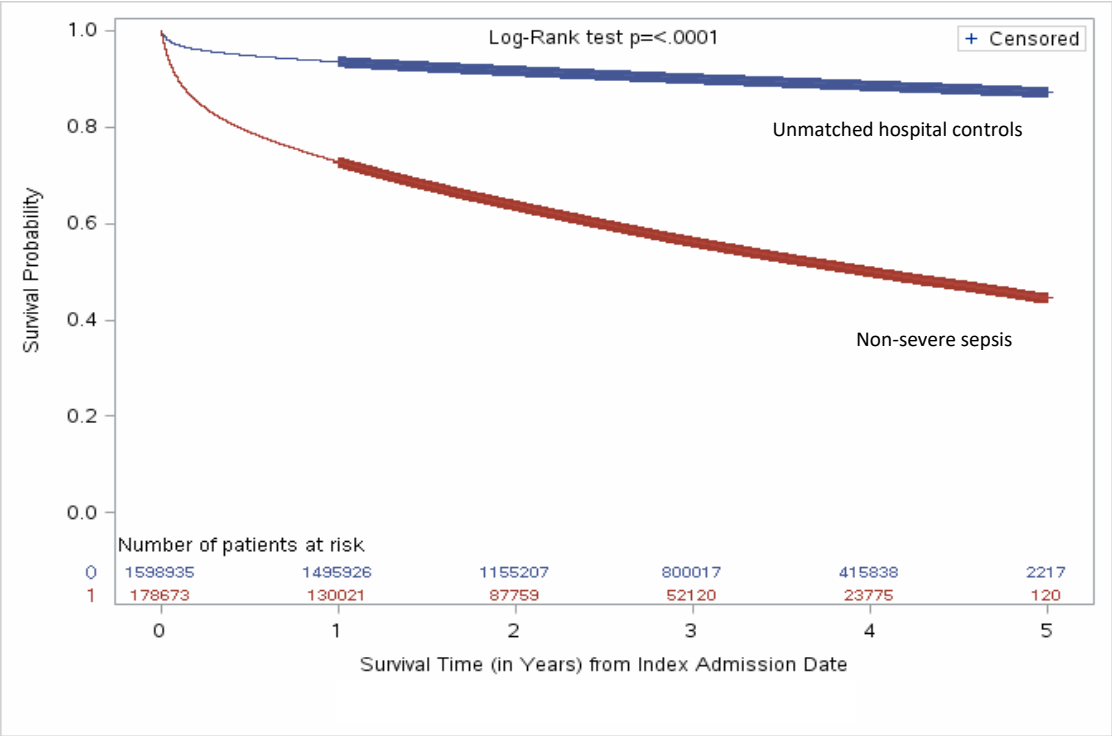
In this sensitivity analysis, all eligible cases and controls were included, without any matching. Regression models were run as above (without features designed to account for matching). All variables used to develop the propensity score, as well as age and sex, were included as covariates in the regression models.

Tables in Appendix G

Figures in Appendix G

Figure G1: Unmatched Cohort of Cases and Controls, Survival Kaplan Meier Plots

a) Non-Severe Sepsis versus Non-Sepsis Hospital Controls



b) Severe Sepsis versus Non-Sepsis Hospital Controls

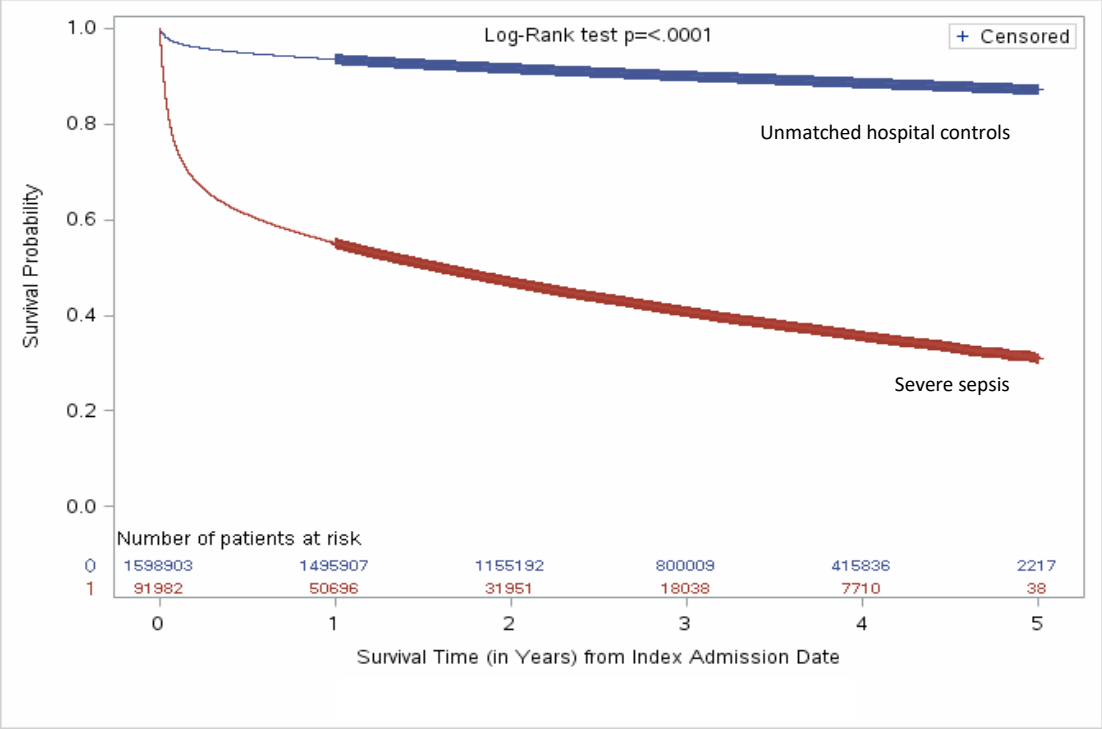
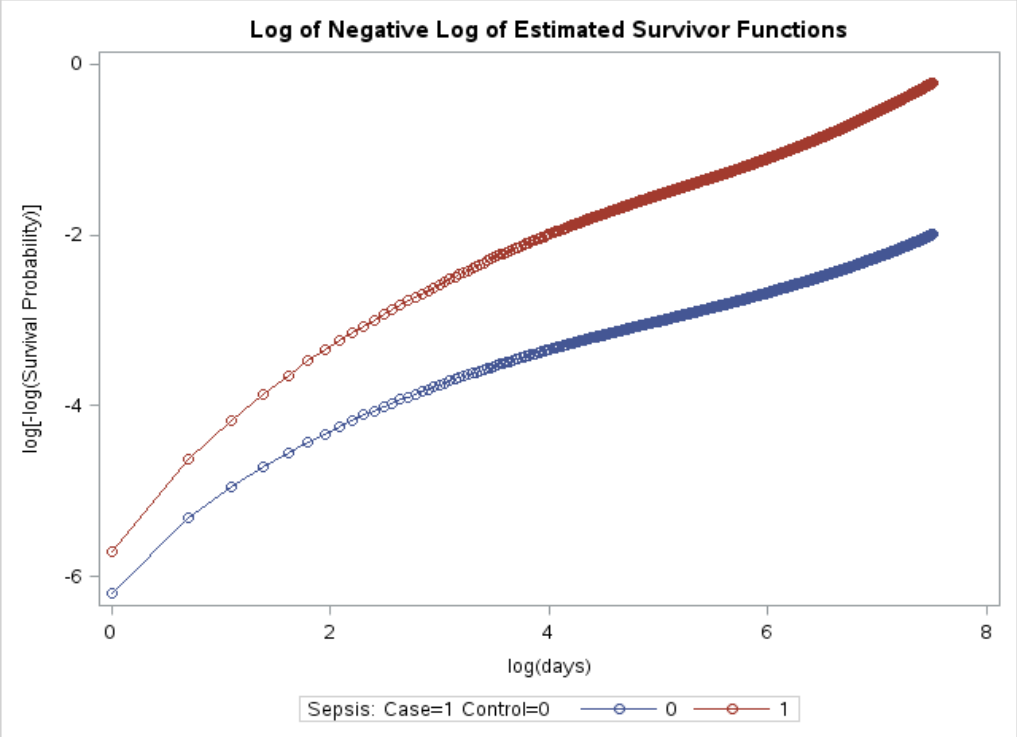


Figure G2: Unmatched Cohort of Cases and Controls, Test of Proportional Hazards

a) Non-Severe Sepsis Cases versus Non-Sepsis Hospital Controls



b) Severe Sepsis Cases versus Non-Sepsis Hospital Controls

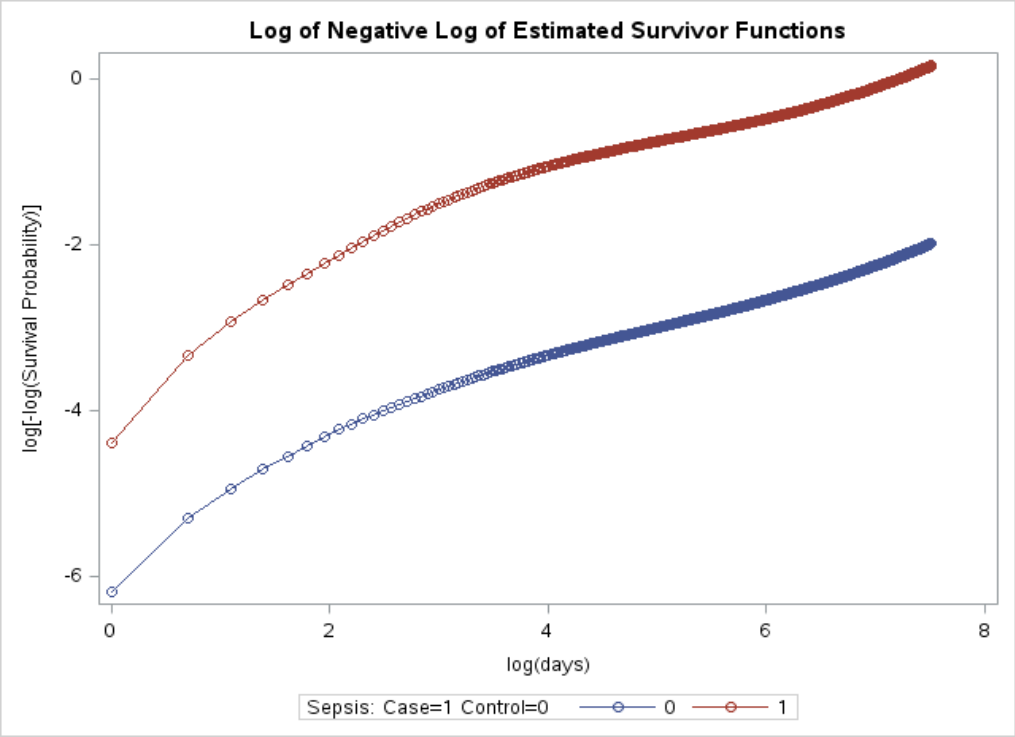
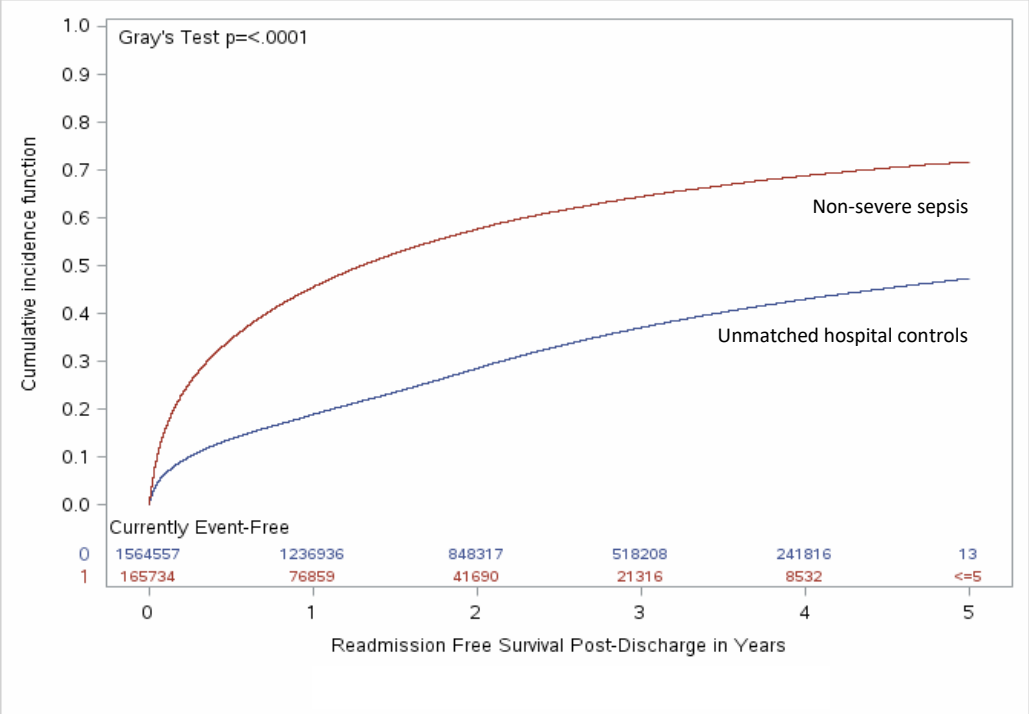


Figure G3: Unmatched Cohort of Cases and Controls. Time to Hospital Readmission, CIF Plots

a) Non-Severe Sepsis Cases versus Non-Sepsis Hospital Controls



b) Severe Sepsis Cases versus Non-Sepsis Hospital Controls

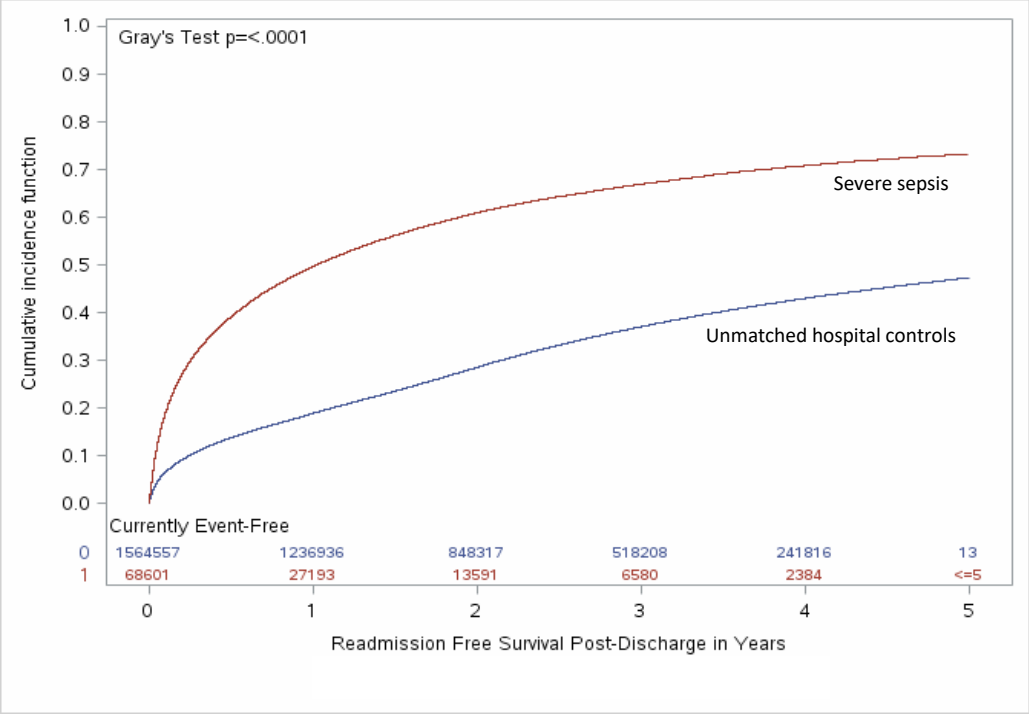


Table G1: All Eligible Cases and Controls (Unmatched). Descriptive Characteristics of Index Hospital Admission and Long-Term Outcomes

	Non-sepsis Hospital Controls N =1,598,935	Non-Severe Sepsis N = 178,673	Severe Sepsis N = 91,982
	N (%)	N (%)	N (%)
ICU admission	166733 (10.43)	18243 (10.21)	40765 (44.32)
In-hospital death	34338 (2.15)	12928 (7.24)	23376 (25.41)
1-year mortality	102996 (6.44)	48652 (27.23)	41286 (44.88)
Mortality up to 5 years	160923 (10.06)	77417 (43.33)	53474 (58.14)
Follow-up time			
Mean (SD)	1062 (483)	754 (535)	555 (536)
Median (IQR)	1095 (791)	716 (890)	441 (915)
Hospital LOS			
Mean (SD)	4.12 (9.09)	11.53 (23.11)	21.52 (36.89)
Median (Q1-Q3)	2 (1-4)	6 (3-12)	11 (5-24)
ICU LOS			
Mean (SD)	0.44 (2.40)	0.51 (2.01)	5.66 (17.19)
Median (Q1-Q3)	0 (0-0)	0 (0-0)	0 (0-6)
Hospital Cost			
Mean (SD)	9290 (11501)	14364 (18295)	38520 (66977)
Median (IQR)	6555 (6112)	9184 (9056)	18397 (28522)
Post-discharge mortality (up to 5 years)	126578/1564597 (8.09)	64,489/165745 (38.91)	30098/68606 (43.87)
30-day readmissions	91299 (5.71)	22971 (12.86)	11310 (12.30)
1-yr readmissions	295372 (18.47)	75407 (42.20)	34023 (36.99)
Up to 5-year readmissions	571020 (35.71)	104009 (58.21)	44289 (48.15)

ICU = intensive care unit; IQR = interquartile range; LOS = length of stay (in days); SD = standard deviation.

Table G2. Multivariate Analysis (All Cases and Controls, Unmatched): Attributable Mortality, Readmission, Length of Stay

Outcome	Non-Severe Sepsis vs. Hospital Controls		Severe Sepsis vs. Hospital Controls	
	Crude Mean (95% CI)	**Adjusted* Mean (95% CI†)**	**Crude Mean (95% CI)**	**Adjusted* Mean (95% CI†)**
Hospital LOS	7.41 (7.34-7.48)	4.11 (4.02-4.16)	17.41 (17.20-17.55)	11.97 (11.78-12.09)
ICU LOS	0.08 (0.07-0.09)	0.03 (0.02-0.04)	5.23 (5.12-5.31)	2.52 (2.42-2.70)
Hospital Cost	5076 (5019-5147)	2342 (2272-2429)	29227 (28711-29386)	23116 (22851-23218)
1-Year Cost	25944 (25712-26082)	16120 (15933-16319)	49553 (48856-49749_	36502 (35846-36608)
	Crude OR (95% CI)	**Adjusted* OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted* OR (95% CI)**
ICU Admission	0.98 (0.96-0.99)	0.72 (0.70-0.73)	6.84 (6.74-6.93)	4.14 (4.07-4.22)
Hospital Death	3.55 (3.48-3.63)	0.98 (0.95-1.00)	15.53 (15.25-15.81)	4.21 (4.12-4.30)
Mortality Rate	**Crude HR (95% CI)**	**Adjusted* HR (95% CI)**	**Crude HR (95% CI)**	**Adjusted* HR (95% CI)**
1-Year	4.69 (4.64-4.74)	1.26 (1.24-1.27)	9.02 (8.92-9.13)	2.11 (2.08-2.14)
Up to-5 Years	5.35 (5.31-5.40)	1.46 (1.44-1.47)	8.73 (8.64-8.81)	2.01 (1.99-2.04)
Hospital Survivors				
1-Year Mortality (from discharge)	5.40 (5.33-5.47)	1.43 (1.40-1.45)	6.79 (6.68-6.90)	1.51 (1.48-1.54)
Up to 5 years (from discharge)	6.00 (5.94-6.06)	1.63 (1.61-1.65)	7.29 (7.20-7.38)	1.63 (1.61-1.66)
1-year readmission‖	3.03 (3.01-3.05)	1.57 (1.56-1.59)	3.55 (3.51-3.59)	1.58 (1.56-1.60)
Up to 5 years readmission‖	2.70 (2.68-2.72)	1.64 (1.63-1.65)	3.16 (3.13-3.19)	1.74 (1.72-1.76)

CI = confidence interval; HR = hazard ratio; ICU = intensive care unit; LOS = length of stay (in days); OR = odds ratio.

*Adjusted for hospital type and all variables used in propensity score model.

†95% CIs are from a 10% random sample.

‖Readmission after index admission discharge date to an acute care hospital in Ontario.

APPENDIX H: RECORD Statement (Reporting Guideline for Observational Studies using Routinely Collected Health Data).

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	a) Title (Population-based retrospective cohort study) b) Abstract	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1 Abstract "health administrative data housed at ICES" (many databases used so did not list all here). 1.2 Abstract (Ontario, April 1 2012-March 31, 2017). 1.3 N/A all databases housed at ICES.
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction: paragraph 1.		

Objectives	3	State specific objectives, including any prespecified hypotheses	Last paragraph of introduction.		
Methods					
Study Design	4	Present key elements of study design early in the paper	1st sentence of Methods section		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	1st & 2nd sentences of Methods section.		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching	a) 2nd paragraph of methods section b) Matched criteria described in detail in Table 9	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1; 2nd paragraph of methods section (Jolley et al algorithm). Full codes used provided in Table 8. 6.2 Validation study referenced in 2nd paragraph of methods section. 6.3 All databases used were housed and linked through ICES identifiers.

		criteria and the number of controls per case			
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1. List of codes to define exposure provided in Table 8. No specific codes used for other variables.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	See 2.3 under Outcomes See Table 8 for exposure codes See Table 9 for covariates. See Table 17 for cost components		
Bias	9	Describe any efforts to address potential sources of bias	See 2.3 Propensity score matching		
Study size	10	Explain how the study size was arrived at	See 2.3 Identification of Cohort…		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	See 2.3 Propensity score matching and Table 9 for description of covariates		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions	a) See 2.3 Propensity Score Matching, Analysis b) See 2.3 Analysis c) See Note beneath Table 6, and Section 2.4		

		(c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	d) See Propensity Score Matching e) See 2.3 Analysis		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	See notes under Table 6
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	See 2.3 1st Study design and data sources
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the	See Figure 1, flow diagram	RECORD 13.1: Describe in detail the selection of the persons included in	See Figure 1 flow diagram

		study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	See Table 3		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	See Table 4		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence	See Table 5		

		interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	See 2.3 Analysis		
Discussion					
Key results	18	Summarise key results with reference to study objectives	See 2.5, 3.7, 4.1		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	See 2.5 Strengths and limitations 3.7 Limitations 4.4 Limitations & 4.4.1 Confounding	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	See 2.5 Strengths and limitations 3.7 Limitations 4.4 Limitations & 4.4.1 Confounding
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	See 2.5 Discussion, 3.7 Discussion, 4.2 Policy Implications		

Generalisability	21	Discuss the generalisability (external validity) of the study results	See. 4.4 Limitations		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	See Preface, funding and data sources		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	See 2.3 Study design and data source

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLoS Med. 2015 Oct 6;12(10):e1001885.