Detecting Sepsis Using Sepsis-Related Organ Failure Assessment (SOFA) and an Electronic Sepsis Prompt in Intensive Care Unit Adult Patients

By
© 2018
Teresa Rincon
PhD, University of Kansas, 2018
BSN, California State University at Sacramento, 2006
ADN, Sacramento City College, 1996

Submitted to the graduate degree program in Nursing and the
the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements
for the degree of Doctor of Philosophy

_____
Chair: Janet Pierce, Ph.D., APRN, FAAN

_____
Member: E. LaVerne Manos, DNP, RN-BC

_____
Member: Kelly A. Bosak, Ph.D., APRN, BC

_____
Member: Qiuhua Shen, Ph.D., APRN, RN

_____
Member: Devin C. Koestler, Ph.D.

Date Defended: 17 July 2018

The dissertation committee for Teresa Rincon certifies that this is the approved version of the following dissertation:

Detecting Sepsis Using Sepsis-Related Organ Failure Assessment (SOFA) and an Electronic Sepsis Prompt in Intensive Care Unit Adult Patients

_____

Chair: Janet Pierce, Ph.D., APRN, FAAN

Date Approved: 23 July 2018

Abstract

Sepsis is an elusive and costly syndrome that is one of the leading causes of death globally. Annually, there are approximately 19 million cases of sepsis that result in more than 5 million deaths. The Agency for Healthcare Research and Quality (AHRQ) ranked sepsis as the most expensive condition ($23.7 billion) for patients treated in hospitals in the United States (U.S.). Nurses are critical in the early identification of sepsis and implementation of therapeutic interventions known as the “sepsis bundle”.

Previously, sepsis was described as a systemic, pro-inflammatory response to an infection. Sepsis was defined as two or more systemic inflammatory response syndrome (SIRS) criteria with a suspected infection, severe sepsis was defined as sepsis with organ failure and septic shock was defined as severe sepsis with shock. For several decades SIRS criteria with organ failure criteria have been used to develop measurement systems for detection of sepsis. A recent study comparing SIRS criteria to the sepsis-related organ failure assessment (SOFA) score demonstrated that SOFA had greater prognostic accuracy of mortality in patients with an infection than SIRS. This led to sepsis definition changes in 2016. The term “severe sepsis” was dropped and sepsis was defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection leading to tissue injury and organ failure.

Many clinicians were concerned that this new definition might lead to late detection of sepsis. What was unknown was how well SIRS with organ failure criteria compared with SOFA in detection of sepsis. Many clinicians in the U.S. working in a TeleICU had been using SIRS with organ failure criteria to support early identification of sepsis. Using human factors science concepts, their practice was studied and an electronic

sepsis alert (sepsis prompt) was developed. Thus, the overall objective of this dissertation was to conduct a retrospective study using a large U.S. data repository to determine if an electronic prompt, that uses SIRS and organ failure (OF) criteria, can detect sepsis. Another objective of this study was to determine the prognostic accuracy of the SOFA score and the sepsis prompt in discriminating in-hospital mortality among patients with sepsis in the intensive care unit.

Among 2,020,489 patients admitted to ICUs associated with a TeleICU from January 1, 2010, to December 31, 2015, at 459 hospitals throughout the U.S., we identified 912,509 (45%) eligible patients at 183 hospitals. We compared the performance of the SOFA score and sepsis prompt criteria in detecting sepsis. Of those in the primary cohort, a secondary cohort was derived based on presence of sepsis resulting 186,870 (20.5%) patients.

To assess performances of the SOFA score and the sepsis prompt (a Fuzzy Logic SIRS and OF algorithm) to detect sepsis, we calculated diagnostic performance of an increase in the SOFA score of 2 or more and criteria met for the Fuzzy Logic SIRS and OF algorithm. For predictive validity, training of baseline risk models was performed on training sets with prediction and performance analytics completed on test sets for each cohort for the outcomes of mortality and sepsis. Results were expressed as the fold change in outcome over deciles of baseline risk of death or risk of sepsis, area under the receiver operating characteristic curve (AUROC), and sensitivity, specificity, and negative and positive predictive values.

In the primary cohort (912,509) there were 86,219 (9.4%) who did not survive their hospital stay and 186,870 (20.5%) with suspected sepsis of whom 34,617 (18.5%) did

not survive hospitalization. The Fuzzy Logic SIRS/OF (crude AUROC 0.67, 99% CI: 0.66-0.67 and adjusted AUROC 0.77, 99% CI: 0.77-0.77) outperformed SOFA (crude AUROC 0.61, 99% CI: 0.61-0.61 and adjusted AUROC 0.74, 99% CI: 0.74-0.74) in discrimination of sepsis in both crude and adjusted AUROC (in-between differences AUROC 0.06; z-value 49.06 and AUROC 0.03; z-value 36.22, respectively). In the primary cohort, Fuzzy Logic SIRS/OF (crude AUROC 0.67, 99% CI: 0.67-0.68 and adjusted AUROC 0.78, 99% CI: 0.77-0.78) outperformed SOFA (crude AUROC 0.64, 99% CI: 0.64-0.64 and adjusted AUROC 0.76, 99% CI: 0.76-0.76) in prognostic accuracy of mortality in both crude and adjusted AUROC (in-between differences AUROC 0.03; z-value 24.68 and AUROC 0.02; z-value 14.74, respectively). In the secondary cohort, Fuzzy Logic SIRS/OF (crude AUROC 0.57, 99% CI: 0.57-0.58 and adjusted AUROC 0.69, 99% CI: 0.68-0.70) outperformed SOFA (crude AUROC 0.56, 99% CI: 0.56-0.56 and adjusted AUROC 0.68, 99% CI: 0.67-0.68) in prognostic accuracy of mortality in both crude and adjusted AUROC (in-between differences AUROC 0.01; z-value 6.86 and AUROC 0.01; z-value 7.53, respectively).

The results of this study demonstrated that among adult ICU patients, the predictive validity for sepsis and in-hospital mortality of a complex algorithm based on Fuzzy Logic applied to expanded SIRS criteria with organ failure criteria was better than SOFA for detection of sepsis and for prognostic accuracy of mortality. The findings of this study support the use of a computer-enhanced algorithm that includes a combination of expanded SIRS with organ failure criteria as a tool to assist nurses and healthcare providers in early identification of sepsis.

Acknowledgments

To my parents, Bud and Ann, who have blessed me with unconditional love, words of wisdom, and constant prayers, all of which have helped to sustain me through not only this journey, but through all of life's important seasons. You have showed us that finding our purpose (our calling) starts with a commitment to serving God and others. To my husband, Chris, you never stopped believing in me, even when I doubted myself. I am thankful for the love, support, and perseverance that you have shown during this long and arduous journey. To my children, Vincent, Christopher, Annette and Natalie, you will always be my joy. I hope that I have inspired you to chase your dreams, seek your talents, and to honor your calling. To Dianah, Denise, Lynda, and Christine, the long girl talks, laughter, and your enduring friendship, will forever be a sweet retreat for me. To Dennis, through your personal struggle I learned to be a better patient advocate. To Monica, thank you for reminding me of my calling and the difference it makes.

To my mentors, Dr. Ruth Kleinpell and Dr. Tom Ahrens, thank you for encouraging me to pursue my doctorate and engage in research. To Dr. Janet Pierce, I have been truly blessed to have you as my advisor. Your advice, passion for nursing and scientific inquiry, amazing attention to detail, and supervision through this journey will never be forgotten. To my dissertation committee (Dr. Manos, Dr. Koestler, Dr. Shen, and Dr. Bosak), thank you for your insights and guidance. To all the nurses of whom I speak of in this dissertation, thank you for your steadfast commitment to saving lives and for allowing me to study and write about your practice. Lastly, I would like to thank Philips Healthcare and the research team at MIT for their partnership in this research and acknowledge that the contents of this dissertation may not reflect their opinions.

Table of Contents

List of Abbreviations

- Acquired Immunodeficiency syndrome (AIDS)
- Activated partial thromboplastin time (aPTT)
- Acute Physiology Age Chronic Health Evaluation (APACHE)
- Adjusted Odds Ratio (AOR)
- Admission, discharge, transfer (ADT)
- Adult Patient Database (APD)
- Agency for Healthcare Research and Quality (AHRQ)
- American Association of Critical Care Nurses (ACCN)
- American College of Chest Physicians (CHEST)
- American Thoracic Society (ATS)
- Area Under the Receiver Operating Characteristics (AUROC)
- Australia and New Zealand Intensive Care Society (ANZICS)
- Body Mass Index (BMI)
- Clinical decision support system (CDSS)
- Compensatory Anti-Inflammatory Response Syndrome (CARS)
- Confidence intervals (CI)
- Centers for Medicare & Medicaid Services (CMS)
- Computerized Physician Order Entry (CPOE)
- eICU® Research Institute (eRI)
- Emergency department (ED)
- Electronic health records (EHR)

- European Society of Intensive Care Medicine (ESICM)
- Evidence-based knowledge management (EBKM)
- Evidence-based practice (EBP)
- Fraction of inspired oxygen (FiO_2)
- Health Insurance Portability and Accountability Act (HIPAA)
- Human immunodeficiency virus (HIV)
- Intensive care unit (ICU)
- Interferon gamma (INF-γ)
- Interleukin (IL)
- Information services (IS)
- Intelligence, surveillance and reconnaissance (ISR)
- Institutional review board (IRB)
- Knowledge management (KM)
- Mean arterial pressure (MAP)
- Mixed Antagonist Response Syndrome (MARS)
- Multiple organ dysfunction syndrome (MODS)
- Multiple organ failure (MOF)
- National Institute of Standards and Technology (NIST)
- Organ Failure (OF)
- Partial pressure of carbon-dioxide in arterial blood ($PaCO_2$)
- Partial pressure of oxygen in arterial blood (PaO_2)
- Persistent inflammation, immunosuppression, and catabolism syndrome (PICS)

- Plan, Do, Study, Act (PDSA)
- Platelet-activating factor (PAF)
- Prothrombin time / international normalized rate (PT INR)
- Quick Sepsis-Related Organ Failure Assessment (qSOFA)
- Receiver operator characteristics (ROC)
- Sepsis-Related Organ Failure Assessment (SOFA)
- Society of Critical Care Medicine (SCCM)
- Standard deviation (SD)
- Standard error (SE)
- Surgical Infection Society (SIS)
- Surviving Sepsis Campaign (SSC)
- Systemic inflammatory response syndrome (SIRS)
- Systolic blood pressure (SBP)
- Sutter health rapid electronic discrete data (SHREDD)
- Telemedicine or telehealth intensive care unit (TeleICU)
- Transforming growth factor-beta (TGF-β)
- Tumor necrosis factor (TNF)
- Variance inflation factor (VIF)
- White blood cell (WBC)

List of Figures

List of Tables

Chapter 1.

General Introduction

Sepsis is a widespread, time-sensitive, and deadly syndrome with approximately 19 million cases leading to 5 million deaths world-wide annually.[1,2] The Agency for Healthcare Research and Quality ranked sepsis as the most expensive condition for Medicare patients treated in hospitals in the United States (U.S.).[3] Although previous epidemiology studies on severe sepsis and septic shock have reported mortality rates ranging from 25% to 70%,[1,2,4-6] others have demonstrated that early identification and targeted, timely therapies can lead to improvements in mortality.[7] Current therapies for sepsis, severe sepsis, and septic shock are largely targeted at controlling symptoms versus curative treatments.

Major predictors of risk of developing infections and sepsis are age, immunosuppression, and other comorbid chronic conditions such as cancer, diabetes, and human immunodeficiency virus (HIV) disease.[8] Regardless of where the infection occurs, the host's own immune responses lead to pro-inflammatory, anti-inflammatory, and coagulopathic cascades of the sepsis continuum that can have devastating consequences.[9]

Clinicians have struggled with how to identify and care for patients with sepsis. Sepsis, severe sepsis, and septic shock were defined in a consensus statement from the American College of Chest Physicians (CHEST) and the Society of Critical Care Medicine (SCCM) in 1992 as:1) sepsis as two or more systemic inflammatory response syndrome (SIRS) criteria with an infection; 2) severe sepsis as sepsis with organ failure; and 3) septic shock as defined as severe sepsis with hypotension that is not resolved with adequate fluid resuscitation (Sepsis-1).[10] By 2001, in an international consensus paper, the definitions had broadened to include a more comprehensive list of criteria

(Sepsis-2).[11]

A recent retrospective study (2015) of over 1 million patients identified with severe sepsis, from the Australia and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD), demonstrated one patient in eight with severe sepsis would be missed if detection criteria relied on the presence of two or more of the SIRS criteria defined by Bone et al. in 1992.[10,12] Several factors led to questions regarding the usefulness of SIRS criteria to detect severe sepsis: 1) the human body is able to suppress pro-inflammation using anti-inflammation signaling and pathways; 2) some patients are unable to initiate a SIRS response (elderly and immunosuppressed); and 3) some medications can conceal SIRS, particularly drugs that affect heart rate, respiratory rate, or elevation in body temperature.

In 2016, the third international sepsis definition defined sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to an infection that leads to tissue injury and organ failure (Sepsis-3).[13] The new definition determined that having a sepsis-related organ failure assessment (SOFA) score or a new modified score known as the quick SOFA (qSOFA) of two or more with a suspected infection, had higher discrimination of sepsis than having two or more SIRS. Concerns that earlier stages of sepsis, when the syndrome is actually at its most treatable, might be identified too late have been raised.[14,15]

Statement of the Problem

Predicting at-risk populations and identifying severe sepsis and septic shock earlier in its progression are essential in reducing mortality and preventing complications.[16] Unfortunately, clinicians and scientists question which criterion to use to detect severe

sepsis. The presence of two or more SIRS criteria is used frequently to determine if a patient has sepsis and severe sepsis.[10,17,18] Additional research is needed to validate if this definition is definitive enough to detect severe sepsis in adult ICU patients. The **primary objective** of this dissertation was to conduct a retrospective study using a large data repository to determine if an electronic prompt can detect sepsis and to determine the prognostic accuracy of the SOFA score and the sepsis prompt in discriminating in-hospital mortality among patients with sepsis in the intensive care unit (ICU).

Chapter 1 is an overview of the dissertation including the aims, research questions, hypothesis, definitions, background and significance, operational framework, and assumptions. Chapter 2 is a published article that relates to expert critical care nurses working in a TeleICU who developed and implemented a sepsis-screening tool and process. Chapter 3 is a published article that evaluates the usability of an electronic sepsis prompt that was designed based on the TeleICU nurse process and tool.[19] Chapter 4 describes the results of a retrospective study that was conducted to assess the discriminatory capacities of the electronic sepsis prompt to detect sepsis and for prognostic accuracy of mortality compared to a SOFA score of two or more in intensive care unit (ICU) patients during the first 24 hours of ICU admission. Chapter 5 is the summation of this dissertation. Below are the proposed aims, research questions, and hypothesis for this study.

Research Aims, Questions and Hypotheses

Aim 1: To determine if an electronic sepsis prompt that uses systemic inflammatory response syndrome and organ failure criteria identifies sepsis in the electronic health

record (EHR) for adult intensive care unit (ICU) patients.

Research question 1: Using the electronic intensive care unit (eICU) Research Institute (eRI) data repository, how accurately does the electronic sepsis prompt detect sepsis in adult ICU patients within the first 24 hours of admission to the ICU?

Aim 2: To determine the effect of an increase in sepsis-related organ failure assessment (SOFA) score of 2 or more points and the presence of an electronic sepsis prompt within the first 24 hours of ICU admission in discriminating in-hospital mortality among adult ICU patients with sepsis.

Research hypothesis 2a: Using the eICU Research Institute (eRI) data repository, adult ICU patients with sepsis who have an increase in SOFA score of 2 or more in the first 24 hours of their ICU stay will have higher in-hospital mortality rates than sepsis patients with a SOFA score less than 2.

Research hypothesis 2b: Using the eICU Research Institute (eRI) data repository, adult ICU patients with sepsis who have presence of an electronic sepsis prompt in the first 24 hours of their ICU stay will have higher in-hospital mortality rates than sepsis patients without presence of a sepsis prompt.

Research Question 2a: What are the differences in the in-hospital mortality rates in adult ICU patients with sepsis using an increase in the SOFA score of 2 or more versus the electronic sepsis prompt?

Definition of Terms

Acute Physiology Age Chronic Health Evaluation (APACHE)

Conceptual definition: Is a severity-adjusted methodology that predicts outcomes for critically ill adult patients.[20] The APACHE algorithm is built into the eCareManager

system. Each ICU patient in the eCareManager system received a severity of illness score if all required data elements for the algorithm are present. A previous study using this same data set demonstrated that approximately 80% of patients have an APACHE IVa score of ≥ 1.[21]

Operational definition: APACHE IVa ≥ 1 scores for each patient in the data repository were used to determine the severity of illness and risk of mortality in this study population. An APACHE IVa score of at least 1 must be present.

Body Mass Index (BMI)

Conceptual definition: BMI is calculated by dividing a person's weight in kilograms by height in meters squared.[22] BMI is used to screen for weight categories that may contribute to the morbidity and mortality of a patient.

Operational definition: The BMI were used to describe the population of interest. BMI is calculated for each patient and available in the data set.

Broad-spectrum antibiotics

Conceptual definition: Administration of broad-spectrum antibiotics is critical to decreasing mortality in severely septic patients.[23] The SSC recommends broad-spectrum bacterial coverage for gram-positive and gram-negative organisms with administration timing less than three hours of identification of severe sepsis.[18] The study that led to the third international sepsis definition used two concurrent events: 1) antibiotics must be ordered within 72 hours of first body fluid culture, and 2) culture must be within 24 hours of first antibiotic dose, to define infection.[24]

Operational definition: Medications ordered by licensed care providers were interfaced into eCareManager from pharmacy operating systems and include date and time when

ordered. We did not include antibiotic as a variable of interest because actual administration times were not present in the dataset nor were microbiology laboratory data related to body fluid cultures.

Comorbid conditions

Conceptual definition: Comorbid conditions also termed comorbidity, are additional conditions existing during the clinical course of a patient who is being treated for another condition; comorbidity is associated with increased death, complications, and costs in healthcare.[25]

Operational definition: For this study, a comorbid condition was defined as a chronic condition present on admission to the ICU. Comorbid conditions were captured as discrete data elements in the admission note of eCareManager in the chronic health section of the history and physical. The following comorbid conditions were consistently documented for APACHE data collection in all TeleICUs and were used in this study: acquired Immunodeficiency syndrome (AIDS), liver failure and/or cirrhosis, diabetes mellitus, patients on dialysis, various respiratory and cardiac comorbid conditions, immune suppression in the last 6 months (radiation therapy, chemotherapy, daily use of non-cytotoxic immunosuppressive drugs or high dose steroid use), leukemia/myeloma, non-Hodgkin's lymphoma, and solid tumor with metastasis.

Compensatory Anti-Inflammatory Response Syndrome (CARS)

Conceptual definition: Immunosuppression due to the activation of anti-inflammatory mediators in an effort to achieve homeostasis by suppressing systemic inflammatory response syndrome (SIRS).[26]

Operational definition: To compensate for pro-inflammatory cytokine activation in SIRS,

anti-inflammatory mediators such as interleukin (IL) 10, IL-13, IL-4, soluble tumor necrosis factor receptors (TNFR) I and II, and transforming growth factor-beta (TGF-β) are activated. This consecutively leads to monocyte deactivation, defective phagocytosis, distorted antigen presentation, and diminished production of inflammatory cytokines (immunosuppression).[9,27]

eICU® Research Institute (eRI)

Conceptual definition: The eICU Research Institute supports critical care research and analysis using an extensive ICU-centric longitudinal data set. These data are collected and aggregated across the entire eICU Program customer base.[28] Business associate agreements among the participating programs guide data use and sharing. Privacert, Inc. (Pittsburgh, Pennsylvania) has certified it as Health Insurance Portability and Accountability Act (HIPAA) compliant under safe harbor standards.[21] Philips representatives have reported to this researcher that the data repository is growing at a rate of more than 400,000 ICU patient stays per year and currently contains data for over 2.5 million patients.

Operational definition: The data for this study were derived from patients in the eRI data repository who were admitted to an ICU during the study period (January 1, 2010 through December 31, 2015). Data were transferred from Philips Healthcare to the Massachusetts Institute of Technology (MIT) in Cambridge, Massachusetts. The researcher was granted access a publicly available subset of eRI known as the eICU Collaborative Research Database.[29] The subset was used to review the content and structure of the data tables and to test code that was written in the R statistical programming language (https://www.r-project.org).[30] The researcher traveled to the MIT

campus on a regular basis to analyze all patient level data needed for this study.

First 24 hours of ICU Stay:

Conceptual definition: Most patients who were treated in the ICU for severe sepsis meet the definition within the first 24 hours of the ICU stay. This method has been used successfully in a recent severe sepsis epidemiology study using secondary analysis of a large database in Australia and New Zealand.[12]

Operational definition: ICU admission dates and times were present in the eRI data repository and were used to determine the first 24 hours of the ICU stay for each patient.

Hospital characteristics

Conceptual definition: Describing hospital characteristics is a common approach used in studies. It assists the reader to determine how generalizable the results are to other hospitals.

Operational definition**:** The eRI data repository contains basic hospital characteristic information.[21] The following characteristics were stratified by number of licensed beds, community size, hospital size < 100 beds, 100-249 beds, 250-500 beds, > 500 beds, and hospital type (teaching, non-teaching, and the geographic regions: Midwest, South, Northeast, West, Unknown).

Hospital discharge location

Conceptual definition: Hospital discharge location is considered a reportable outcome measure[31] and was analyzed for the following locations: discharge to home, discharge to other acute care hospital, discharge to skilled nursing facility, and discharge to rehabilitation or chronic care facility.

Operational definition: Hospital discharge location was interfaced from admission, discharge, and transfer (ADT) systems into eCareManager.

Hospital length of stay (LOS)

Conceptual definition: Hospital LOS is commonly described in hospital reported data. [31] It is calculated using hospital admission and discharge dates and times.

Operational definition: Hospital admission and discharge dates and times were interfaced from ADT systems into eCareManager. Predicted and actual hospital LOS averages as well as standardized LOS ratios (actual hospital days divided by predicted hospital days) were reported.

Hospital Mortality

Conceptual definition: The death of a person as their discharge disposition from the hospital.

Operational definition: Hospital mortality was interfaced from the ADT systems into eCareManager as “expired” or discharged (“alive”) and were used for analyzing mortality rates as well as in predictive modeling statistical methods. Predicted and actual hospital mortality total numbers and percentages as well as standardized mortality ratios (actual deaths divided by predicted deaths) were reported.

Hypotension

Conceptual definition: Low blood pressure in a person that causes symptoms related to lack of perfusion such as dizziness, confusion, weakness, fatigue, and fainting.[32] According to severe sepsis consensus definitions a systolic blood pressure (SBP) < 90 mm Hg, a mean arterial pressure (MAP) < 65 mm Hg or a SBP reduction of < 40 mm Hg from baseline are considered hypotension.[10,18] Ventricular dysfunction along with

hypovolemia (caused by venodilation, increases sensible loss and vascular leak) leads to hypotension and hypoperfusion in severely septic patients.[33]

Operational definition: For this study, hypotension was defined as SBP < 90 mm Hg, MAP < 65 mm Hg or SBP reduction of < 40 mm Hg from baseline or on medications to support the blood pressure (vasopressors). Vital sign data and medications ordered by licensed care providers were interfaced or entered directly into eCareManager from vital sign monitoring systems, electronic health record (EHR) nursing flow sheets, and pharmacy operating systems.

Hypoperfusion

Conceptual definition: A condition of acute peripheral circulatory failure due to derangement of circulatory control or loss of circulating fluid. Hypoperfusion abnormalities have been described in the literature as lactic acidosis, alterations in mental status and oliguria.[10,18]

Operational definition: For this study, the following parameters were considered hypoperfusion: a lactate > 2 mmol/L interfaced from laboratory systems into eCareManager; urine output < 35 ml/hr for three hours (excludes chronic renal failure patients) interfaced from nursing flow sheet or documented directly into eCareManager; or documentation of alterations in mental status documented diagnosis in the Active Diagnosis/Problem List or the care plan sections of eCareManager.

Infection

Conceptual definition: Infection occurs when a pathogen invades and begins to multiply within a host.[34] Manifestations of local (e.g., cellulitis, abscess, purulent sputum or discharge, unexplained localized pain) or systemic (fever or malaise) infections as well

as recent abdominal or gastrointestinal surgeries/procedures or aspiration or documented diagnosis of and/or therapies for infection.[35] These therapeutic interventions include antimicrobial therapy (excluding prophylactic therapies) and microbiology diagnostic tests (cultures and sensitivities). The definition of severe sepsis is dependent on the presence of an infection and an organ failure.[10]

Operational definition: Diagnostic groups used to define documented "infection" derived from the APACHE admission diagnosis (updated in either the admission notes or the care plan sections) or active diagnoses selected from the problem list (known as Active Diagnosis/Problem List) in the eCareManager system. The eCareManager system uses the International Classification of Diseases, 10th ed. A comprehensive list of diagnoses can be found in Chapter 4, Table 6. Terms were mapped to equivalent concepts in the eRI data repository. Active infection was defined as:

1. Non-operative group: endocarditis, pneumonia (parasitic, bacterial, or viral), gastrointestinal infections (perforation, cholangitis, abscess/cyst, peritonitis), neurologic infections, renal infection/abscess, viral myositis, septic arthritis, septic thrombophlebitis, cellulitis and localized soft tissue infections, systemic/other infections, sepsis, severe sepsis, or septic shock.
2. Post-operative group: respiratory infection, gastrointestinal tract perforation or rupture, cholecystitis or cholangitis, appendicitis, fistula or abscess surgery, peritonitis, cranial infection/abscess, cellulitis and localized soft tissue infections.

Intensive Care Unit (ICU) Admission Source

Conceptual definition: ICU admission source has been linked to outcomes in patients with sepsis[36] and was analyzed for the following locations: direct admit; floor;

emergency department; operating room, procedural area, or post-anesthesia care unit; step-down/intermediate care unit; and other.

Operational definition: Hospital discharge locations were interfaced from admission, discharge, and transfer (ADT) systems into eCareManager.

Mixed Antagonist Response Syndrome (MARS):

Conceptual definition: The presence of SIRS in a patient with CARS.[26]

Operational Definition: An acute alteration in baseline of more than one of the following: 1) temperature > 38°C or < 36°C; 2) heart rate > 90 beats/minute; 3) tachypnea (respiratory rate > 20 breaths/minute) or hyperventilation ($PaCO_2$ < 32 mmHg); 4) white blood cell (WBC) > 12,000 or < 4,000 cu mm or 10% immature neutrophils (bands)[10] with activation of anti-inflammatory mediators in an effort to achieve homeostasis.[37]

Multiple organ dysfunction syndrome (MODS) also termed multiple organ failure (MOF):

Conceptual definition: The presence of more than one organ dysfunction or failure in the acutely ill whereby homeostasis cannot be maintained without therapeutic intervention.[9,10] Severe sepsis remains a chief cause of MODS and prolonged ICU stays in critically ill patients.[38]

Operational definition: Patients in the eRI data repository was stratified by none, one, two, three, and more than three organ failures.

Organ failure/dysfunction (acute)

Conceptual definition: Marik describes tissue hypoperfusion and hypoxia as dominate factors in organ failure in severe sepsis. He explains that in severe sepsis systemic vasodilatation, hypovolemia, altered microvascular flow, intravascular coagulation, and

myocardial depression are the precursors to tissue hypoperfusion and hypoxia.[33] The definition of severe sepsis is dependent on the presence of an infection and an acute organ failure.

Operational definition: Patients in the eRI data repository with an active infection and an acute organ failure met the definition of sepsis. A complete list of ICD 10 codes and diagnoses can be found in Chapter 1 Table 6. Patients with one or more of the following diagnoses documented in the Active Diagnoses/Problem Lists of eCareManager: acute lung injury, acute renal failure, acute glomerulonephritis, renal shutdown (unspecified), hemodialysis (except in chronic renal failure), acute hepatic failure or necrosis, hepatic encephalopathy (except in chronic hepatic failure), hepatitis (septic or unspecified), disseminated intravascular coagulation (DIC), purpura fulminans, coagulopathy, thrombocytopenia (primary, secondary or unspecified), acidosis (metabolic or lactic), acute respiratory failure, acute respiratory distress syndrome (ARDS), acute respiratory insufficiency, respiratory arrest, ventilator management, hypotension (postural, arterial, constitutional, transient, or specific type not elsewhere classified), shock (cardiogenic, circulatory or septic), sepsis with single organ dysfunction, sepsis with multi-organ dysfunction syndrome, transient organic psychosis, anoxic brain injury, acute encephalopathy, coma, and altered consciousness (unspecified).[5]

Sepsis prompt:

Conceptual definition: An electronic alert for detection of severe sepsis that uses a deterministic algorithm based on data from biomedical devices, laboratory systems, and other clinical information systems.[39,40]

Operational definition: The sepsis prompt algorithm used signs of inflammation criteria

plus one or more acute organ failure criteria. Abnormal values that triggered the sepsis prompt are listed below. It should be noted that combinations of two or more abnormal or near abnormal values coupled with organ failure criteria can cause the prompt to fire.

Signs of Inflammation Criteria:

1. Temperature > 38°C or < 36°C: Data obtained from eCareManager nursing flow sheet (or interfaced from vital signs monitoring system when available) and only includes values within most recent 12 hours.
2. White Blood Cell (WBC) > 12,000 or < 4,000 cu mm or 10% immature neutrophils (bands) interfaced from laboratory operating system and only includes values within most recent 24 hours.
3. Tachypnea: Respiratory rate > 20 breaths/minute or hyperventilation: $PaCO_2$ < 32 mm Hg: Data were derived from eCareManager respiratory flow sheet, nursing flow sheet and interfaced from vital signs monitoring system; only includes values within most recent two hours.
4. Tachycardia: Heart rate > 90 beats/minute: Data obtained from eCareManager nursing flow sheet and interfaced from vital signs monitoring system; only includes values within most recent two hours.
5. Altered or decreased mental status data were derived from the eCareManager Care Plan or Active Diagnoses/Problem Lists; only active selections are used.
6. Hyperglycemia as defined by glucose value > 140 mg/dl in the absence of diabetes and glucose ≥ 350 mg/dl in the presence of diabetes interfaced from laboratory operating system and only includes values within most recent six hours.
7. Lactate ≥ 2 mmol/L interfaced from laboratory operating system and only includes

values within most recent 24 hours and excludes first six hours post cardiac surgery.

8. Coagulopathy: International normalized ratio (INR) >1.5 interfaced from laboratory operating systems and only includes values within most recent 24 hours; exclude if patient on warfarin.
9. *Organ Failure Criteria:*

a. Cardiovascular (hypotension): SBP < 90 mm Hg or mean arterial pressure (MAP) < 65 mm Hg or on vasopressors
b. Respiratory (hypoxemia): PaO_2 < 70 mm Hg on room air or PaO_2/FiO_2 < 200 in the absence of pneumonia as infection source or acute lung injury with PaO_2/FiO_2 < 200 when intubated where PaO_2 is partial pressure of oxygen in arterial blood and FiO_2 is fraction of inspired oxygen
c. Renal: increase in creatinine by 0.4 mg/dL from baseline or urine output < 35 ml/hr for three hours (excludes chronic renal failure patients).
d. Metabolic acidosis: a base deficit ≥ 5.0 mEq/L or a potential of Hydrogen (pH) < 7.30 except with partial pressure of arterial carbon dioxide ($PaCO_2$) > 50.
e. Liver: bilirubin > 4 mg/dl (34.2 mmol/L) or combinations of elevated liver function studies: aspartate aminotransferase (AST) > 80 IU/dL, alanine aminotransferase (ALT) > 80 IU/dL, and albumin levels < 3.5 g/dL interfaced from laboratory operating system and only includes values within most recent 24 hours and excludes chronic liver failure.
f. Hematology (any two): platelet counts <100,000 μL and/or INR > 1.5 (excludes patients on warfarin) or aPTT > 60 (excludes patients on heparin) interfaced from

laboratory operating system and only includes values within most recent 24 hours.

Sepsis and Severe Sepsis

Conceptual Definition: A whole-body inflammation caused by an infection. Sepsis is a syndrome that has been characterized by a systemic response to an infection that often causes fever, increased heart rate, increased breathing rate, and confusion.[10,12] Large epidemiology studies have defined severe sepsis as infection and organ failure using International Classification of Diseases (ICD-9) codes.[4-6] The consensus definitions of sepsis have changed over the years:

Sepsis 1 refers to the Bone et al. (1992) consensus sepsis definition that included ≥ 2 SIRS criteria with suspected or confirmed infection. [10]

Sepsis 2 refers to the Levy et al. (2001) consensus sepsis definition that included ≥ 2 SIRS expanded criteria with suspected or confirmed infection. [11]

Sepsis 3 refers to the Singer et al. (2016) consensus sepsis definition: a life-threatening organ dysfunction caused by a dysregulated host response to infection that leads to tissue injury and organ failure. [13]

Both sepsis 1 and 2 included a definition of severe sepsis**:** ≥ 2 SIRS criteria with suspected or confirmed infection and organ failure. The Sepsis 3 definition eliminated the term “severe sepsis” and now uses the term “sepsis” to it.

Operational Definition: For the purpose of this study, a patient who was in the eRI data repository that had a documented infection and an acute organ failure in the first 24 hours of their ICU stay was determined to have a diagnosis of severe sepsis.

Sepsis-induced hypotension

Conceptual definition: Severe sepsis with hypotension in the absence of other causes.[10]

Hypotension is a principal feature in septic shock with improving blood pressure as a therapeutic goal.[18]

Operational Definition: For this study, sepsis induced hypotension was a systolic blood pressure (SBP) < 90 mm Hg, mean arterial blood pressure (MAP) < 65 mm Hg, or a reduction of SBP ≥ 40 mm Hg from baseline in the absence of other causes.[10,18]

Septic shock*:*

Conceptual definition: Persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg and a serum lactate level > 2 mmol/L (18 mg/dL) despite adequate volume resuscitation. Septic shock is characterized by underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality (hospital mortality > 40%).

Operational Definition: Patients in the ICU that have hypotension or abnormal perfusion indicators such as lactic acidosis (lactate > 2 mmol/L); oliguria (urine output < 0.5 ml/kg/hour for 2 hours), decreased capillary fill or mottling, or acute alteration in mental status despite administration of fluids. These patients require a fluid resuscitation bolus of 30 mL/kg of a crystalloid solution for hypotension or they have a lactate value of > 2 mmol/L.

Sepsis-Related Organ Failure Assessment

Conceptual Definition: Organ failure leads to worse outcome in sepsis. The sepsis-related organ failure assessment (SOFA) score is used to numerically quantify the number and severity of acute organ dysfunction. The new consensus definition (Sepsis 3) recommends the use of SOFA to screen for sepsis in ICU patients.

Operational definition: Patients in the eRI data repository with an acute alteration in

baseline whose SOFA score is 2 or more indicated a positive identification of sepsis according to the Sepsis 3 definition. Baseline SOFA scores were assigned for three chronic health conditions: 1) patients with chronic respiratory impairment were assigned 2 points; 2) patients with chronic hepatic failure were assigned 4 points; and 3) patients with chronic renal organ failure (defined as being on dialysis upon admission to the ICU) were assigned 4 points.[41] Baseline SOFA points were subtracted from the total SOFA score with a net score of 2 or more considered a positive SOFA score.

Systemic Inflammatory Response Syndrome (SIRS):

Conceptual definition: A pro-inflammatory response to an insult (e.g., fever, tachycardia, tachypnea, and leukocytosis).[42] The Sepsis-1 definition included 4 SIRS criteria (listed in the operational definition)[10] and the Sepsis-2 expanded SIRS criteria[11] can be found in Table 4 of this chapter.

Operational Definition: An acute alteration in baseline of more than one of the following: 1) temperature > 38°C or < 36°C; 2) heart rate > 90 beats/minute; 3) tachypnea (respiratory rate > 20 breaths/minute) or hyperventilation ($PaCO_2$ < 32 mm Hg); 4) white blood cell (WBC) > 12,000 or < 4,000 cu mm or 10% immature neutrophils (bands).[10]

Telemedicine or Telehealth Intensive Care Unit (TeleICU)

Conceptual definition: According to the American Telemedicine Association TeleICU Guidelines Workgroup, TeleICU is the application of critical care using a network of audio-visual communication and computer systems. The authors describe TeleICU teams as comprised of clinical experts (intensivists, advanced practice providers, and critical care nurses) whose knowledge and expertise is leveraged across a diverse spectrum of critically ill patients in a variety of clinical and geographically dispersed

settings.[43]

Operational Definition: eICU® is a trade name that refers to TeleICUs that use a common vendor (Philips) as their Telehealth platform. eICUs from around the U.S. participate in the eRI.

Vasopressors

Conceptual definition: Vasopressors are potent medications that increase vascular constriction and are required to sustain life and maintain perfusion in the face of life-threatening hypotension.[18] Adequate fluid resuscitation should be attempted but should not delay the use of vasopressors in patients with septic shock.[18]

Operational definition: Vasopressor infusions start and stop times are interfaced from pharmacy operating systems into the medication section of eCareManager or interfaced or documented directly into the nursing flow sheet in eCareManager. Vasopressor use was stratified by none, one, two, three, and more than three and were used to determine cardiovascular organ failure for SOFA scoring and the sepsis prompt.

Background and Significance

Sepsis is characterized by an infection and as early as 1985 Goris et al. hypothesized that in septic patients there is a massive activation of inflammatory mediators whereby systemic damage to vascular endothelia cause increased permeability and impaired oxygen availability to the mitochondria despite adequate arterial oxygen transport.[44] The continuum of this syndrome has been categorized as sepsis, severe sepsis, and septic shock which are the maladaptive immune response of the host to an infectious process which can lead to multiple organ failure (MOF).[45]

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-

3) were released in 2016 and describe sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to an infection that leads to tissue injury and organ failure.[13] This new definition encourages the use of a SOFA score of two or more to be used to determine the presence of sepsis in intensive care unit patients with an infection. Given that the SOFA score relies on organ failure criteria (Table 1) and diminishes reliance on SIRS criteria leading to concerns that earlier stages of sepsis might be identified too late.[14,15]

Table 1. Sepsis-related Organ Failure Assessment (SOFA) Score Variables and Scoring Cut-offs

	SOFA score			
Variables	**1**	**2**	**3**	**4**
Respiratory				
PaO_2 FIO_2 (mm Hg)	< 400	< 300	< 220	< 100
Coagulation				
Platelets $\times 10^3/mm^3$	< 150	< 100	< 50	< 20
Liver				
Bilirubin (mg/dL)	1.2 - 1.9	2.0 - 5.9	6.0 - 11.9	> 12.0
Cardiovascular				
Hypotension	Mean arterial pressure < 70 mmHg		Any vasopressor medication	
Central Nervous System				
Glasgow Coma Score	13 - 14	10 - 12	6 - 9	< 6
Renal				
Creatinine (mg/dL) or urine output, ml/dl	1.2 - 1.9	2.0 - 3.4	3.5 - 4.9 or < 500	> 5.0 or < 200

PaO_2, partial pressure of oxygen in arterial blood; FiO_2, fraction of inspired oxygen; mm Hg, millimeters of mercury; ml/dL, millimeters per deciliter; mg/dL, milligrams per deciliter; Vasopressor medication: Dopamine, dobutamine, epinephrine, norepinephrine; [a] Adapted from Singer et al.[10]

The literature describes an anti-inflammatory response host-pathogen immune profile known as the compensatory anti-inflammatory response syndrome (CARS) as well as a mismatched host-pathogen immune profile known as a mixed antagonistic

response syndrome (MARS).[26,27] These host-pathogen immune responses can lead to abnormal coagulation pathways, microcirculatory dysfunction, immunosuppression, and finally organ injury, cell death, and death of the individual if uncorrected.[26,27]

In sepsis, the immune response to a microbial attack begins with macrophages using pattern recognition receptors to identify invaders and trigger intracellular signaling. Peptidoglycan and lipopolysaccharide proteins bind to toll-like receptors on the surface of immune cells activating intracellular signal-transduction pathways. This then activates the SIRS or pro-inflammatory cytokines: interleukin-1 (IL-1), IL-2, IL-6, IL-8, interferon gamma (INF-γ), and platelet-activating factor (PAF). The inflammatory response is thought to cause widespread tissue injury as certain lymphocytes, dendritic cells, and epithelial cells rapidly undergo apoptosis.[27] Indirectly, caspase-3 proteolytic enzymes, thought to be the major trigger for apoptosis, are activated by extrinsic and intrinsic pathways.[46]

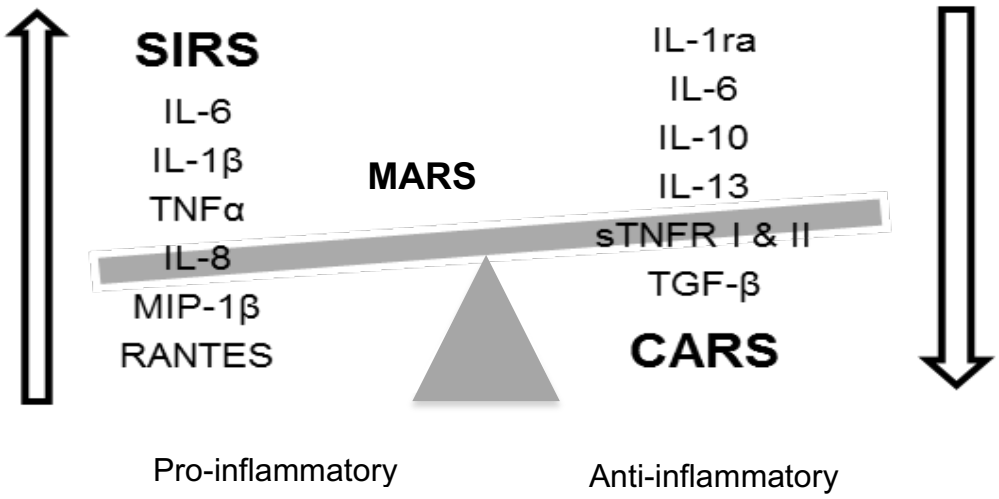
During apoptosis cells shrink and form small in-capsulated membranes that quickly undergo phagocytosis by other nearby cells such as macrophages.[47] Other disease states associated with apoptosis are neurodegenerative disorders, acute lung injury, and various autoimmune and chronic inflammatory disease states.[46] Reducing apoptosis may play an important role by lessening the immunosuppressive cascade known as the compensatory anti-inflammatory response syndrome (CARS).[26]

In CARS anti-inflammatory mediators such as interleukin 10 (IL-10) and transforming growth factor-beta (TGF-β) are activated. As anti-inflammatory mechanisms begin to accelerate, the immune system becomes depressed (immunoparesis or immunoparalysis) leading to monocyte deactivation and defective phagocytosis,

distorted antigen presentation, and diminished production of inflammatory cytokines.[27] T-regulatory cells and myeloid-derived suppressor cells (a heterogeneous population of immature myeloid cells) also become involved as the adaptive immune system attempts to downregulate the innate pro-inflammatory state. [48]

The immune system attempts to reach homeostasis (adaptive immune response) by using anti-inflammatory cytokines (CARS) to reduce synthesis of pro-inflammatory cytokines (SIRS), which in turn can lead to a third syndrome known as mixed antagonist response syndrome (MARS) (Figure 1).[9,26,27,37] In ICU patients, the severely compromised immune system can become "exhausted" leading to death or a prolonged state also known as persistent inflammation, immunosuppression, and catabolism syndrome (PICS).[9] In more recent years, fewer patients reportedly display SIRS criteria and more develop PICS which in turn leads to prolonged ICU stays and MODS.[9,38]

Figure 1. Pro-Inflammatory, Anti-inflammatory, and Mixed Antagonist Adaptive Immune Responses



SIRS, systemic inflammatory response syndrome; MARS, mixed antagonist response syndrome; CARS, compensatory anti-inflammatory response syndrome; IL, interleukin; IL-1ra, interleukin-1 receptor antigen; TNF, tumor necrosis factor; sTNFR, soluble TNF receptor; MIP-1β, macrophage inflammatory protein, and RANTES, regulated on activation of normal T-cell expressed and secreted; TGF, transforming growth factor

A PubMed search conducted on May 30, 2015, for the last 10 years revealed over 20,000 articles that met the initial search criteria of “sepsis screening.[49] The purpose of this review was to examine what criteria were consistently being used to screen for sepsis and severe sepsis in adult populations within hospital and pre-hospital settings.

Exclusion criteria for the literature search included no biomarker or device screening processes, no manuscripts over 10 years old and no abstracts. Search criteria used in PubMed included: “sepsis,” “severe sepsis,” and/or “septic shock.” These were combined with one or more of the following terms: “early identification,” “detection,” “screening,” “tool,” or “alert.” The reviewer focused on the following inclusion criteria:

1. Some form of sepsis screening criteria must have been used and described in such a way that the reader can ascertain what SIRS and organ failure criteria were used.
2. Only screening processes designed for adult populations.

With the filtering, the search was reduced to 36 manuscripts with 20 key articles that described both manual and health information system alerts that have been implemented for screening for sepsis and severe sepsis in the hospital and pre-hospital settings (Table 2).

Table 2. Diagnostic Criteria for Severe Sepsis Screening

Author	Year	Alert or Manual	Setting	Used SIRS*	Δ SIRS	More than SIRS*	Organ/Perfusion criteria**				
							LAC ARF	BP	RESP	LOC	
Alsolamy[50]	2014	Alert	ED	Y	N	N	Y	Y	Y	N	N
Amland[51]	2014	Alert	HOSP	Y	Y	Y	Y	Y	N	N	Y
Buck[52]	2014	Alert	HOSP	Y	N	Y	Y	Y	Y	Y	Y
Campbell[53]	2008	Manual	ICU	Y	N	Y	Y	Y	Y	Y	Y
Croft[54]	2014	Both	ICU	Y	Y	Y	N	Y	N	Y	N
Giuliano[55]	2011	Alert	ICU	Y	N	Y	N	Y	N	N	N
Gyang[56]	2015	Manual	ICU	Y	N	N	Y	Y	Y	N	Y
Harrison[57]	2015	Alert	ICU	Y	Y	N	Y	Y	N	N	N
Hooper[58]	2012	Alert	ICU	Y	Y	N	N	N	N	N	N
McKinley[59]	2011	Both	ICU	Y	N	N	Y	Y	Y	Y	Y
Moore[60]	2009	Manual	ICU	Y	Y	N	Y	Y	N	N	Y
Nelson[61]	2011	Alert	ED	Y	N	Y	Y	Y	Y	Y	Y
Nguyen[62]	2014	Alert	ED	Y	N	N	Y	Y	N	N	N
Patocka[63]	2014	Manual	ED	N	Y	Y	N	Y	N	Y	N
Rincon[64]	2011	Manual	ICU	Y	N	Y	Y	Y	Y	Y	Y
Sawyer[65]	2011	Alert	WARD	Y	Y	Y	N	Y	Y	N	N
Singer[66]	2014	Manual	ED	N	N	Y	Y	N	N	Y	N
Tsoukalas[67]	2015	Alert	ICU	N	Y	Y	N	Y	N	N	N
Wallgren[68]	2014	Manual	ED	N	N	Y	N	Y	Y	Y	N
Westphal[69]	2011	Manual	HOSP	Y	N	Y	Y	Y	Y	Y	Y

ED, emergency department,; ICU, intensive care unit: HOSP, throughout the hospital; WARD, general adult floor (non-ICU); *SIRS criteria defined: Temperature (TEMP) > 38°C or < 36°C; heart rate (HR) > 90 beats/minute; respiratory rate (RR) > 20 breaths/min; white blood cell (WBC) >12,000 or < 4,000 cu mm and >10% bands[10] Δ = changed or altered

**Where organ failure criteria related to the following included: LAC, lactate; BP, blood pressure; RESP, respiratory system; LOC, level of consciousness/mental status alterations; ARF, acute renal failure (urine output and/or creatinine criteria)

Although most (79%) of the articles used four SIRS criteria in their screening tools, only 32% adhered to ≥ two SIRS criteria. The most common addition was changes in mental status or elevated glucose levels in the absence of diabetes. The Surviving Sepsis Campaign endorses these criteria.[18] White blood cells were most commonly not used in screening and some screening tools or processes did not include heart rate parameters. For example, although Amland and Hahn-Cover defined severe sepsis as

clinical evidence of SIRS with evidence of organ system dysfunction, they altered the Bone et al. SIRS criteria. These alterations included a SIRS threshold when ≥ **three** of the following **five** criteria were satisfied: 1) temperature > 38.3°C or < 36°C; 2) heart rate > 95 beats/min; 3) respiratory rate > 22 breaths/min; 4) WBC count > 12 000 cells/mm^3 or < 4000 cells/mm^3, or > 10% immature (band) forms; or 5) glucose 141 to < 200 mg/dL. The threshold for severe SIRS was satisfied when ≥ **two** of the **five** SIRS criteria were present and ≥ **one** of **four** organ dysfunction criteria were present: 1) systolic blood pressure < 90 mm Hg and/or mean arterial pressure < 65 mm Hg; 2) serum lactate > 2.0 mmol/L; 3) total bilirubin ≥ 2.0 mg/dL and < 10.0 mg/dL; or 4) serum creatinine increase by 0.5 mg/dL from baseline.[51]

Some sepsis screening processes were based on weighting of the four SIRS criteria along with a selection of other parameters described in the 2001 international consensus paper, primarily mental status and systolic blood pressure (Table 3).[54,60] Several of the sepsis alerts describe some component of weighting within an algorithmic alert in order to balance sensitivity and specificity.[50,57,67] No consistent pattern or use of criteria for severe sepsis screening was identified.

Table 3. Diagnostic Criteria from the International Sepsis-2 Consensus Definition

Diagnostic Criteria for Sepsis
Core temperature > 38.3°C or < 36°C
Heart rate > 90 beats/min or > 2 SD above the normal value
Tachypnea
Altered mental status
Significant edema or positive fluid balance (> 20 mL/kg over 24 hours)
Hyperglycemia (plasma glucose > 120 mg/dL or 7.7 mmol/L) in the absence of diabetes
Leukocytosis (WBC count > 12,000 µL-1)
Leukopenia (WBC count < 4000 µL-1)
Normal WBC count with > 10% immature forms
Plasma C-reactive protein > 2 SD above the normal value
Plasma procalcitonin > 2 SD above the normal value
Arterial hypotension (SBP < 90 mm Hg, MAP < 70, or an SBP decrease < 40 mm Hg in adults or > 2 SD below normal for age)
SvO_2 < 70%
Arterial hypoxemia (PaO_2/FiO_2 < 300)
Acute oliguria (urine output < 0.5 mL/kg/hr or 45 mmol/L for at least 2 hours)
Creatinine increase < 0.5 mg/dL
Coagulation abnormalities (PT INR > 1.5 or aPTT > 60 secs)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000 µL)
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 mmol/L)
Hyperlactatemia (> 1 mmol/L)
Decreased capillary refill or mottling

WBC, white blood cell; SD, standard deviation; SBP, systolic blood pressure; MAP, mean arterial pressure; SvO_2, mixed venous oxygen saturation; PaO_2, partial pressure of oxygen in arterial blood; FiO_2, fraction of inspired oxygen; hr, hour; PT INR, prothrombin time / international normalized rate; aPTT, activated partial thromboplastin time. *Adapted from Levy MM, Fink MP, Marshall JC, et al: SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med.2001;31(4),1250-1256.*

The first telehealth intensive care unit (TeleICU) on the west coast of the U.S. was implemented in 2003.[64] TeleICU teams provide augmented care delivery through monitoring and assessment of critically ill patients using telecommunications, health information systems, and hardware tools.[70,71] TeleICU teams are generally staffed with experienced critical care nurses, intensivist physicians, critical care trained advanced practice providers and other disciplines that allow expert knowledge to be disseminated

to geographically dispersed and clinically diverse hospitals.[43]

By 2004, nurses in the west coast TeleICU started screening patients remotely for severe sepsis for multiple ICUs across one geographical area known as the Sacramento-Sierra region.[64] Table 4 displays the criteria used by the TeleICU nurses. The west coast TeleICU nurses performed an important role in translating knowledge into evidence (knowledge translators), collected data related to the severe sepsis screening criteria (knowledge acquisition), and later these data were used to develop and refine a sepsis alert known as the sepsis prompt (knowledge creation).[19] These concepts will be discussed in greater detail in chapters 2 and 3. There will be an in-depth evaluation of the usability of the sepsis prompt using the conceptual framework of human factors science.

Table 4. Sepsis Screening Criteria Used by the TeleICU Nurse

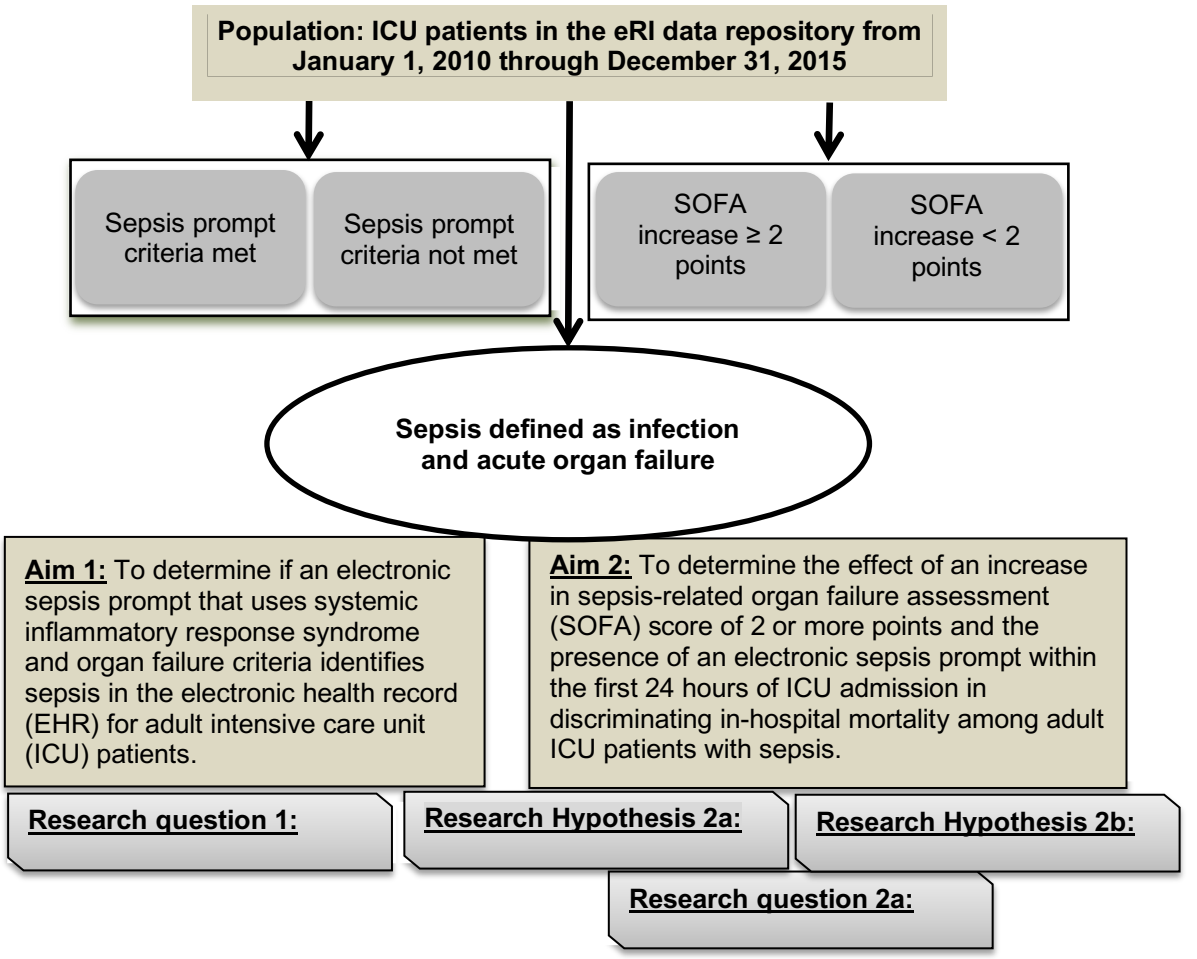
SIRS Criteria	**Organ Dysfunction Criteria**
Hyperthermia > 38.3°C or hypothermia < 36°C	SBP < 90 mm Hg or MAP < 65 mm Hg or decrease > 40 mm Hg from baseline
Tachycardia > 90 bpm	Creatinine > 2.0 mg/dl (176.8 mmol/L) or urine output < 0.5 ml/kg/hr for 2 hours
WBC > 12,000 µL or < 4,000 µL or > 10% bands	Bilirubin > 2 mg/dl (34.2 mmol/L)
Tachypnea > 20 bpm	Platelet count < 100,000 µL
Additional Criteria	Lactate > 2 mmol/L (18.0 mg/dl)
Hyperglycemia (> 120 mg/dl) in the absence of diabetes	Coagulopathy (INR > 1.5 or aPTT > 60 secs)
Acute altered mental status	Acute lung injury with PaO_2/FiO_2 < 250 in the absence of pneumonia as infection source
	Acute lung injury with PaO_2/FiO_2 < 200 in the presence of pneumonia as infection source

WBC, white blood cell; SD, standard deviation; SBP, systolic blood pressure; MAP, mean arterial pressure; PT INR, prothrombin time / international normalized rate; aPTT, activated partial thromboplastin time PaO_2, partial pressure of oxygen in arterial blood; FiO_2, fraction of inspired oxygen; hr, hour

Operational conceptual framework

The eRI data repository provides physiologic, mortality, and demographic variables for a large population of critically ill patients located in multiple ICUs across the U.S. For this retrospective study the demographic, mortality, and physiological data were available on over 2 million patient encounters during the period of January 1, 2010 to December 31, 2015. After inclusion/exclusion criteria were applied the number of eligible patients was reduced to 912,509 (primary cohort). The researcher then applied the definition of sepsis (formerly known as severe sepsis) to this group of subjects (186,870). Chapter 4 Table 6 describes the diagnoses used to define sepsis. An operational conceptual framework was created to provide theoretical structure for the study (Figure 2).

Figure 2. Operational Conceptual Framework



Research question 1: Using the electronic intensive care unit (eICU) Research Institute (eRI) data repository, how accurately does the electronic sepsis prompt detect sepsis in adult ICU patients within the first 24 hours of admission to the ICU**?** **Research hypothesis 2a**: Using the eICU Research Institute (eRI) data repository, adult ICU patients with sepsis who have an increase in SOFA score of 2 or more in the first 24 hours of their ICU stay will have higher in-hospital mortality rates than sepsis patients with a SOFA score less than 2. **Research hypothesis 2b:** Using the eICU Research Institute (eRI) data repository, adult ICU patients with sepsis who have presence of an electronic sepsis prompt in the first 24 hours of their ICU stay will have higher in-hospital mortality rates than sepsis patients without presence of a sepsis prompt. **Research Question 2a**: What are the differences in the in-hospital mortality rates in adult ICU patients with sepsis using an increase in the SOFA score of 2 or more versus the electronic sepsis prompt?

eRI, eICU Research Institute; EHR, electronic health record; SOFA, sepsis-related organ failure assessment; APACHE, acute physiology age, chronic health, evaluation; ICU, intensive care unit;

For Aim #1 the researcher determined if a sepsis prompt that used expanded SIRS criteria (Fuzzy Logic applied) with organ failure (OF) criteria identified sepsis. For Aim

#2 the researcher determined the effect for a SOFA score ≥ 2 and for when the sepsis prompt criteria were met for prognostic accuracy of mortality. A binary classification process was used to label each patient record as having sepsis or no sepsis present within the first 24 hours of ICU admission. Chapter 4 and Chapter 5 includes additional information and discussion related to the aims of this study.

Assumptions

This study was based on the following assumptions:

1. The consensus definition of severe sepsis (sepsis 2) requiring two or more SIRS criteria and organ failure criteria will detect sepsis more often than SOFA score of two or more. However, there will be some ICU patients that went undetected for sepsis.
2. The consensus definition of severe sepsis (sepsis 3) requiring a SOFA score of two or more will have greater prognostic accuracy of mortality than a sepsis prompt using SIRS criteria and organ failure.
3. These study findings are generalizable to other ICU patients because of the large database that will be used. The data are obtained from over 2.5 million ICU patients that stayed in more than 400 ICUs in approximately 300 hospitals. This will include at least 40 states in the U.S.
4. The physiological variables (e.g. blood pressures, heart rate, and temperature) in this study are measurable. Data obtained from highly sophisticated electronic operating systems that are interfaced with ICU patient electronic records, which include laboratory values, medication orders, and vital sign measurements. Mortality variables in this study are measurable through hospital discharge dispositions that

are interfaced directly from each patient's hospital ADT health information system.

5. Chronic health and demographic variables are measurable in this study through interfaced data from ADT health information systems.
6. Interfaced data from the source reduces issues associated with alterations in the methods of collecting data that can vary from one person to the next (administration variation).[72]

Limitations

1. The patients with symptoms that meet the SIRS criteria and organ failure were examined for the first 24 hours of the ICU stay only. This limits the use of data related to symptoms meeting SIRS criteria before or after that time and may miss patients who demonstrate organ failure on day two.
2. Multiple imputation for missingness was impractical due to the complexity and size of the data set. Missingness was minimized by excluding hospitals where no evidence of interfaces or documentation for laboratory, vital sign, medication, and diagnosis related data existed (convenience sample).
3. The accuracy of specific diagnostic coding of infection and organ failure were not independently monitored, that could lead to systematic bias. Other severe sepsis epidemiology studies have relied on clinical modification diagnostic code data.[4-6]

Conclusion

Early identification of sepsis and severe sepsis is a resource intensive process that requires expert knowledge of immunologic responses to infectious diseases. There are no tests or biomarkers to aid in prognostic and diagnostic efforts. Using experts (knowledge translators) and designing sophisticated, deterministic algorithms built into

health information systems (alerts) are needed to support these efforts. This study determined the discriminatory capacity of SIRS with organ dysfunction criteria used by an electronic sepsis prompt versus using a SOFA score of two or more to in detecting sepsis in adult ICU patients.

References

1. Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *Am J Respir Crit Care.* 2016;193(3):259-272.

2. Rhee C, Dantes R, Epstein L, et al. Incidence and trends of sepsis in us hospitals using clinical vs claims data, 2009-2014. *JAMA.* 2017;318(13):1241-1249.

3. Torio CM, Moore BJ. *Statistical Brief #204. Healthcare Cost and Utilization Project (HCUP).* Rockville, MD: Agency for Healthcare Research and Quality (AHRQ);2016.

4. Angus D, Linde-Zwirble W, Lidicker J, Clermont G, Carcillo J, Pinsky M. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29(7):1303-1310.

5. Martin G, Mannino D, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med.* 2003;348(16):1546-1554.

6. Dombrovskiy V, Martin A, Sunderram J, Paz H. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med.* 2007;35(5):1244-1250.

7. Levy M, Dellinger R, Townsend S, et al. The surviving sepsis campaign: Results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med.* 2010;38(2):367-374.

8. Han J, Cribbs S, Martin G. Sepsis, Severe Sepsis, and Septic Shock. In: Hall J, Schmidt G, Kress J, eds. *Principles of Critical Care*. 4th ed. New York, NY: McGraw-Hill; 2015.

9. Gentile L, Cuenca A, Efron P, et al. Persistent inflammation and immunosuppression: A common syndrome and new horizon for surgical intensive care. *J Trauma Acute Care Surg.* 2012;72(6):1491-1501.

10. Bone R, Balk R, Cerra F, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM consensus conference committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest.* 1992;101(6):1644-1655.

11. Levy M, Fink M, Marshall J, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med.* 2003;31(4):1250-1256.

12. Kaukonen K-M, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med.* 2015;372(17):1629-1638.

13. Singer M, Deutschman C, Seymour C, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):801-810.

14. Simpson SQ. New Sepsis Criteria: A Change We Should Not Make. *Chest.* 2016;149(5):1117-1118.

15. Genga KR, Russell JA. Update of Sepsis in the Intensive Care Unit. *J Innate Immun.* 2017;9(5):441-455.

16. Mouncey P, Osborn T, Power G, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med.* 2015;372(14):1301-1311.

17. Sprung CL, Sakr Y, Vincent J-L, et al. An evaluation of systemic inflammatory response syndrome signs in the sepsis occurrence in acutely ill patients (SOAP) study. *Intensive Care Med.* 2006;32(3):421-427.

18. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med.* 2013;39(2):165-228.

19. Rincon T. Integration of evidence-based knowledge management in microsystems: a Tele-ICU experience. *Crit Care Nurs Q.* 2012;35(4):335-340.

20. Zimmerman J, Kramer A, McNair D, Malila F. Acute physiology and chronic health evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med.* 2006;34(5):1297-1310.

21. Lilly C, Zuckerman I, Badawi O, Riker R. Benchmark data from more than 240,000 adults that reflect the current practice of critical care in the United States. *Chest.* 2011;140(5):1232-1242.

22. National Center for Chronic Disease Prevention and Health Promotion. Body Mass Index (BMI). *Division of Nutrition, Physical Activity, and Obesity* 2015; http://www.cdc.gov/healthyweight/assessing/bmi/. Accessed June 28, 2015.

23. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med.* 2014:1-7.

24. Seymour C, Liu V, Iwashyna T, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):762-774.

25. Valderas J, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. *An Fam Med.* 2009;7(4):357-363.

26. Bone R, Grodzin C, Balk R. Sepsis: a new hypothesis for pathogenesis of the disease process. *Chest.* 1997;112(1):235-243.

27. Myrianthefs P, Karabatsos E, Baltopoulos G. Sepsis and Immunoparalysis. In: Hall J, Schmidt G, JP. K, eds. *Principles of Critical Care*. 4th ed. New York, NY: McGraw-Hill; 2015.

28. Philips Healthcare. eICU Research Institute: Big data that's changing the face of critical care. *eRI* 2018; https://www.usa.philips.com/healthcare/solutions/enterprise-telehealth/eri. Accessed March 7, 2018.

29. The MIT Lab for Computational Physiology eICU Collaborative Research Database. 2016; http://eicu-crd.mit.edu/. Accessed March 7, 2018.

30. R Core Team. R: A language and environment for statistical computing. 2016; https://www.R-project.org/.

31. CMS.gov. Outcome Measures. *Hospital Quality Initiative* 2014; http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/OutcomeMeasures.html. Accessed July 5, 2015.

32. Bakris G. Heart and Blood Vessel Disorders: Low Blood Pressure. *Merck Manual Home Edition*. Kenilworth, NJ: Merck & Co., Inc.; 2014.

33. Marik P. The Management of Sepsis In: Irwin R, Rippe J, eds. *Irwin & Rippe's Intensive Care Medicine*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.

34. National Institutes of Health (NIH). Understanding Emerging and Re-emerging Infectious Diseases. *Biological Sciences Curriculum Study*. Bethesda, MD: National Institutes of Health (US); 2008.

35. Tunkel A. Manifestations of infection. *Biology of Infectious Disease*. Kenilworth, NJ: Merck & Co., Inc.; 2012.

36. Motzkus CA, Chrysanthopoulou SA, Luckmann R, Rincon TA, Lapane KL, Lilly CM. ICU Admission Source as a Predictor of Mortality for Patients With Sepsis. *J Intensive Care Med.* 2017:885066617701904.

37. Bone R. Sir Issac Newton, sepsis, SIRS, and CARS. *Crit Care Med.* 1996;24(7):1125-1128.

38. Hotchkiss R, Opal S. Immunotherapy for sepsis: a new appraoch against an ancient foe. *N Engl J Med.* 2010;363(1):87-89.

39. Blum J, Kruger G, Sanders K, Gutierrez J, Rosenberg A. Specificity improvement for network distributed physiologic alarms based on a simple deterministic reactive intelligent agent in the critical care environment. *J Clin Monit Comput.* 2009;23(1):21-30.

40. Phansalkar S, Edworthy J, Hellier E, et al. A review of human factors principles for the design and implementation of medication safety alerts in clinical information systems. *J Am Med Inform Assoc* 2010;17(5):493-501.

41. Raith EP, Udy AA, Bailey M, et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. *JAMA.* 2017;317(3):290-300.

42. Russell J. Management of sepsis. *N Engl J Med* 2006;355(16):1699-1713.

43. ATA TeleICU Practice Guidelines Work Group. Guidelines for TeleICU Operations. *ATA Standards & Guidelines.* 2014;2014(June 21). http://www.americantelemed.org/resources/standards/ata-standards-guidelines#.U7gm1hbZf1p.

44. Goris R, te Boekhorst T, Nuytinck J, Gimbrère J. Multiple-organ failure. Generalized autodestructive inflammation? *Arch Surg.* 1985;120(10):1109-1115.

45. Hotchkiss R, Karl I. The pathophysiology and treatment of sepsis. *N Engl J Med.* 2003;348(2):138-150.

46. Perl M, Chung C, Ayala A. Apoptosis. *Crit Care Med.* 2005;33(12):S526-S529.

47. Mescher A. Chapter 3. The Cell Nucleus: Apoptosis. In: Junqueira L, Carneiro J, eds. *Junqueira's Basic Histology: Text & Atlas* 12th ed. New York. Chicago. San Francisco. London.: The McGraw-Hill Companies; 2010.

48. Cuenca A, Delano M, Kelly-Scumpia K, et al. A paradoxical role for myeloid-derived suppressor cells in sepsis and trauma. *Mol Med.* 2011;17(3-4):281-292.

49. PubMed Health Internet. Sepsis screening. 2015; http://www.ncbi.nlm.nih.gov/pubmedhealth/. Accessed May 30, 2015.

50. Alsolamy S, Al Salamah M, Al Thagafi M, et al. Diagnostic accuracy of a screening electronic alert tool for severe sepsis and septic shock in the emergency department. *BMC Med Inform Decis Mak* 2014;14(105):1-6.

51. Amland R, Hahn-Cover K. Clinical decision support for early recognition of sepsis. *AM J Med Qual.* 2014:1-8.

52. Buck K. Developing an early sepsis alert program. *J Nurs Care Qual.* 2014;29(2):124–132.

53. Campbell J. The effect of nurse champions on compliance with keystone intensive care unit sepsis-screening protocol. *Crit Care Nurs Q.* 2008;31(3):251-269.

54. Croft C, Moore F, Efron P, et al. Computer versus paper system for recognition and management of sepsis in surgical intensive care. *J Trauma Acute Care Surg.* 2014;76(2):311-318.

55. Giuliano K, Lecardo M, Staul L. Impact of protocol watch on compliance with the surviving sepsis campaign. *Am J Crit Care.* 2011;20(4):313-321.

56. Gyang E, Shieh L, Forsey L, Maggio P. A nurse-driven screening tool for early identification of sepsis in an intermediate care unit setting. *J Hosp Med.* 2015;10(2):97-103.

57. Harrison A, Thongprayoon C, Kashyap R, et al. Developing the surveillance algorithm for detection of failure to recognize and treat severe sepsis. *Mayo Clin Proc.* 2015;90(2):639-644.

58. Hooper M, Weavind L, Wheeler A, et al. Randomized trial of automated, electronic monitoring to facilitate early detection of sepsis in the intensive care unit. *Crit Care Med.* 2012;40(7):2096-2101.

59. McKinley BA, Moore LJ, Sucher JF, et al. Computer protocol facilitates evidence-based care of sepsis in the surgical intensive care unit. *J Trauma.* 2011;70(5):1153-1167.

60. Moore L, Jones S, Kreiner L, et al. Validation of a screening tool for the early identification of sepsis. *J Trauma.* 2009;66(6):1539–1547.

61. Nelson J, Smith B, Jared J, Younger J. Prospective trial of real-time electronic surveillance to expedite early care of severe sepsis. *Ann Emerg Med.* 2011;57(5):500-504.

62. Nguyen S, Mwakalindile E, Booth J, et al. Automated electronic medical record sepsis detection in the emergency department. *PeerJ.* 2014;2(e343).

63. Patocka C, Turner J, Xue X, Segal E. Evaluation of an emergency department triage screening tool for suspected severe sepsis and septic shock. *J Healthc Qual.* 2013;36(1):52-61.

64. Rincon T, Bourke G, Seiver A. Standardizing sepsis screening and management via a Tele-ICU program improves patient care. *Telemed J E Health.* 2011:1-5.

65. Sawyer A, Deal E, Labelle A, et al. Implementation of a real-time computerized sepsis alert in nonintensive care unit patients. *Crit Care Med.* 2011;39(3):469-473.

66. Singer A, Taylor M, Domingo A, et al. Diagnostic characteristics of a clinical screening tool combination with measuring a bedside lactate level in emergency department patients with suspected sepsis. *Acad Emerg Med.* 2014;21(8):853-857.

67. Tsoukalas A, Albertson T, Tagkopoulos I. From data to optimal decision making: A data-driven, probabilistic machine learning approach to decision support for patients with sepsis. *JMIR Med Inform.* 2015;3(1):1-15.

68. Wallgren U, Castren M, Svensson A, Kurland L. Identification of adult septic patients in the prehospital setting: a comparison of two screening tools and clinical judgment. *Eur J Emerg Med.* 2014;21(4):260-265.

69. Westphal G, Koenig Á, Caldeira Filho M, et al. Reduced mortality after the implementation of a protocol for the early detection of severe sepsis. *J Crit Care.* 2011;26(1):76-81.

70. Lilly C, Thomas E. Tele-ICU: Experience to date. *J Intensive Care Med.* 2010;25(1):16-22.

71. Goran SF. A second set of eyes: An introduction to Tele-ICU. *Crit Care Nurse.* 2010;30(4):46-55.

72. Polit D, Beck C. *Nursing Research: Generalizing and Assessing Evidence for Nursing Practice.* 9th ed. Philadelphia, PA: Lippincott, Williams, & Wilkins 2011.

Chapter 2.

Integration of Evidence-Based Knowledge Management in Microsystems: A TeleICU Experience

This chapter has previously been published in whole. It is reprinted here with adaptation and additional content with permission.

Rincon, T.A. Integration of Evidence-Based Knowledge Management in Microsystems: A TeleICU Experience. Crit Care Nurs Q. 2012;35(4): 335-340.

Abstract

Experts assert that timely, safe, effective, and patient-centered care cannot be achieved within the existing framework of care systems. The systems used in healthcare are based on unrealistic expectations on human cognition and vigilance. This is highlighted by the lack of dependence on computerized systems that can provide relevant and usable knowledge to clinicians when they need it. Knowledge-based care and evidence-based clinical decision-making needs to replace the unscientific care that is being delivered in healthcare. Evidence-based knowledge management with an information technology structure is needed to support sound clinical decision-making and to influence organizational adoption of evidence-based practice in healthcare.

Sepsis remains a significant cause of mortality and morbidity, despite medical advances and evidence-based recommendations for treatment of severe sepsis. It is a complex syndrome that has been shown to be difficult to define, diagnose, and treat. Thus, supporting bedside teams with real-time knowledge and expertise to target early identification of severe sepsis and compliance to evidence-based practice bundles is important to improve patient outcomes. This chapter includes a discussion related to the use of a centralized, remote team of expert nurses that use an open-source software application to advance clinical decision-making and execution of the severe sepsis bundle.

Introduction

More than a decade ago, the Institute of Medicine (IOM) released a report highlighting the number of errors that harm and kill patients every year in the U.S.[1] Since then, data reflect that errors causing harm continue to occur in hospitals and that

patients are suffering devastating consequences due to ineffective safety interventions and monitoring systems.[2] This chapter focuses on key principles of evidence-based knowledge management (EBKM) to assess the effectiveness of an open source software application solution and to analyze the significance of integration of EBKM at the level where patient care occurs. This topic will be addressed in four sections: 1) decision-making and errors that harm patients, 2) integration of knowledge management into clinical practice, 3) description of the tools used to target a sepsis in a large health system, and 4) successful integration of EBKM using a Telehealth intensive care unit (TeleICU) team.

Decision-Making and Errors That Harm Patients

Multiple decisions that impact patient care in positive and sometimes negative ways are made by nurses every day.[3] Studies of nurses reveal troubling discoveries regarding nurse decision-making such as difficulty articulating the rationale for practice patterns as well as high error rates that lead to patient harm.[4-6] Inadequate knowledge and lack of experience have been cited as major contributors of mistakes that harm patients.[1,7] For example, in a computer-simulation study of tachyarrhythmia case studies, incorrect treatments were chosen by nurses 87% of the time with deadly consequences.[8] Other studies indicate that novice nurses are more likely to miss important cues needed to prevent mistakes and that nurses in general do not consider current evidence when making patient care decisions.[9,10] According to the American Association of Critical Care Nurses (AACN), optimizing care delivery in order to reduce complications and life-threatening situations is an important element of nursing practice.[11]

Also concerned about mistakes, the IOM proposed six dimensions to improve healthcare performance by delivering care that is timely, safe, effective, and patient-centered.[1] Berwick explained that care providers protect and honor unscientific variations in care due to unchallenged hierarchal cultures, an unwillingness to change local routines, and lack of information systems that put knowledge at the point of use. He asserted that the IOM framework stresses the need for healthcare change in a four level model: 1) the patient/family experience (Level A), 2) the functioning of small units of care providers or microsystems (Level B), 3) the performance of the organization that supports these microsystems (Level C), and 4) the environment of policy, payment, professional growth, and other factors (Level D).[12]

Care teams or microsystems need to be involved in building the structure of process improvement plans, i.e., the ways in which care can be delivered.[13] Evidence that can be readily shared at the microsystem level, teamwork aimed at improving care coordination, and better tools to measure performance and outcomes were important to reengineering care systems.[12] However, knowledge can be complex to understand and even more difficult to disseminate. Translating evidence into usable, relevant, and accessible knowledge is an important concept to achieving better, safer care.

Integration of Knowledge Management into Clinical Practice

Knowledge Management (KM) is defined as a process that incorporates acquisition, sharing, translation and application of knowledge.[14,15] Knowledge translation focuses on closing the gap between knowledge and practice in order to improve outcomes and clinician effectiveness.[16] Evidence-based practice (EBP) is defined as the use of current best evidence in clinical decision-making.[17] Evidence-Based Knowledge Management

(EBKM) incorporates EBP and KM concepts to expand, cultivate and use the right knowledge at the right time among the right individuals; this in turn influences organizational knowledge and advances organizational performance.[18] Knowledge governance concerns the treatment of patients at the microsystem level; What is the level of information and decision-making for the patient? Are the services up-to-date and well supervised? Is everything being done to prevent mistakes and errors?[18]

Clinical decision support systems (CDSS) can assist clinicians at the microsystem level in sorting data, prioritizing care and adapting evidence-based practice but they are difficult to develop.[19,20] Linking of Electronic Health Records (EHRs) with CDSS to support evidence-based practice and decision-making has been shown to improve clinician efficiency and decision-making.[15,21]

Yellowlees et al. described that some clinical software systems are inflexible and not interoperable; but open source applications have source codes that are available for anyone to review, change, and distribute, creating a flexible, user friendly, intuitive, and interoperable platform. The authors explained that non-proprietary, open source applications can be developed and refined rapidly, and do not require high level information technology support and are not cost prohibitive.[22] The downside is that clinicians at the bedside in the acute care setting may not have the tools or time to effectively and efficiently adapt to computerized systems.[20]

Description of the Tools and Targets in a Large Health System

The first Telehealth Intensive Care Unit (TeleICU) emerged on the healthcare landscape in 2000.[23] TeleICUs are staffed with healthcare professionals providing care to critically ill patients remotely using software applications and technological tools to

assess, monitor and treat critically ill patients.[24,25] TeleICUs leverage experienced critical care nurses and specialist physicians across diverse health systems.[24] TeleICUs are a tool that can be used to support quality improvement measures across diverse populations and geographical landscapes.

Rincon et al. describe a process and an electronic smart form developed by nurses in a TeleICU to support early identification and treatment of sepsis for critically ill patients in nine hospitals and 161 critical care beds across Northern California. The authors describe how TeleICU nurses worked with Information Services staff to develop an effective solution to screen, prompt treatment, and track and retrieve data for reporting. This resulted in a custom built, open source document sharing application (smart form) known as the Sutter Health Rapid Electronic Discrete Data (SHREDD). The smart form was used to target severe sepsis early identification and treatment while at the same time collect data on compliance to the Surviving Sepsis Campaign (SSC) bundle.[26]

In most settings, nurses are using downloadable paper forms from the SSC for screening and data collection. This was not a practical solution for a high acuity, high volume environment like the TeleICU. The paper forms did not allow for rapid sorting and locating of relevant information. They required close proximity of care providers, a scan to email or fax solution, or verbal recitation of data for information sharing. In order for analysis and tracking of information to occur, data then need to be manually entered into a database or spreadsheet. This set of steps is common and widespread throughout healthcare.

The SHREDD tool was a flexible, user friendly, intuitive, and interoperable platform

that promoted information sharing. The platform was interoperable allowing for ease of data transfer into spreadsheet type aggregation for reporting. Later a business intelligence solution was integrated into the design that supported better reporting options. This further reduced the resource intensity for data reporting.

Successful Integration of EBKM Using a TeleICU Team

The SHREDD collected the clinical information into discrete data fields supporting easy sharing among the team and rapid data reporting. Several factors led to rapid development and adoption: the small number of expert nurses that needed to be trained, a culture of nurse empowerment, and collaboration between end users and the Information Services team during the development and execution of the tool.[27] The SHREDD and the TeleICU nurse process accomplished integration of EBKM in the following ways:

1. New knowledge acquisition: The discrete data collected on severe sepsis screening criteria were used to develop decision-support logic for an electronic computerized sepsis screening alert known as the sepsis prompt. The sepsis prompt was integrated into the TeleICU software system.[28] This electronic decision support tool further enhanced nurse efficiency and increased the frequency of screening patients in the ICU for sepsis.
2. The SHREDD tool allowed for the capture of discrete data elements in near real-time that led to research utilization and research activity for incidence of severe sepsis and compliance to the SSC bundle in a large health system.[26,29,30] Retrospective data collection was a time-consuming resource intensive process that has been judged as unreliable and complicated by time and resource factors in the acute care

setting.[31,32] Prospective data collection by experienced critical care nurses was achieved using the TeleICU structure and the SHREDD tool.

3. A social network of knowledge brokers was leveraged virtually across multiple hospitals, resulting in knowledge transfer. Knowledge brokers were experts who help to link research to knowledge users to improve the value and use of evidence-based practices.[33,34] The average years of nursing experience in the TeleICU was 15 years and greater than 90% of the physicians were Intensivists (board certified in critical care). With supply-and-demand issues for both nurses and intensivists, using a platform such as a TeleICU to support knowledge brokering is important to delivering safe patient care in the acute care setting.
4. According to the principles of knowledge governance, interactions between individual knowledge and group knowledge directly impact organizational performance and outcomes.[35] The TeleICU process and SHREDD integrated individual and group knowledge at the microsystem level in real-time. This not only provided the platform to enhance organizational insight, but it also created a venue where clinicians could question local habits and work towards dismantling hierarchical cultures that suppressed knowledge translation**.** The TeleICU structure allowed for real-time observation of treatment patterns at the microsystem level, concurrent evaluation, and prompting of evidence-based decision-making, as well as organizational insight into whether up-to-date services were being delivered across a large health system.

Conclusion

A limitation of this approach was resistance to the use of a technological

infrastructure to support cares processes and measure quality of care. Initially the tool was developed for the bedside clinicians as a checklist and piloted in the TeleICU. Unfortunately, clinicians at the microsystem level are task and information saturated, leaving little time to view tools built into computerized systems. The TeleICU nurses continue to screen patients for severe sepsis and collect data related to sepsis bundle compliance.

The strengths of this approach were that expert nurses in the TeleICU could use information technology tools to accomplish important principles of knowledge governance and EBKM. They could assess patients at the time of the patient encounter, and influence repetitive, continual, and routine diffusion of evidence-based practices at multiple hospitals in a large healthcare system.[33-35] Data collection through the SHREDD also allowed near-real time auditing and feedback. This is an important knowledge translation method that is felt to motivate quality improvement at the microsystem level.[36] Concurrent data collection also allowed for organizational insight into how care was being delivered to patients at the microsystem level.

Leveraging knowledge brokers across multiple hospitals can have a significant influence upon knowledge dissemination and can exert organizational pressure on hierarchical barriers that impede the execution of EBP. Utilization of open-source software applications can be used to support nurse decision making, disseminate pertinent knowledge, and sustain a focus on evidence-based practice through real-time information sharing and rapid data analysis and reporting. More research on the use of open source software tools and platforms for knowledge brokering within the acute care setting is needed.

References

1. Institute of Medicine. *To Err is Human: Building a Safer Health System.* Washington DC: National Academy of Sciences;2000.

2. Landrigan CP, Parry GJ, Bones CB, Hackbarth AD, Goldmann DA, Sharek PJ. Temporal trends in rates of patient harm resulting from medical care. *N Engl J Med.* 2010;363(22):2124-2134.

3. Thompson C, Dowding D. Clinical awareness and prevention of error in clinical decision-making. *Nurs Times.* 2004;100(23):40-43.

4. Henneman EA, Gawlinski A, Rothschild JM, Landrigan CP, Bates DW. Serious errors in intensive care: The critical care safety study: The incidence and nature of adverse events and serious medical errors in intensive care. *Crit Care Med.* 2006;34(2):579-580.

5. Henneman EA. Unreported errors in the intensive care unit: a case study of the way we work. *Crit Care Nurse.* 2007;27(5):27.

6. Meurier CE. Understanding the nature of errors in nursing: using a model to analyse critical incident reports of errors which had resulted in an adverse or potentially adverse event. *J Adv Nurs.* 2000;32(1):202-207.

7. Reason J. *Human Error.* New York, NY: Cambridge University Press; 1990.

8. Henry SB. Clinical decision making of critical care nurses managing computer-simulated tachydysrhythmias. *Heart & Lung.* 1991;20(5 part 1):469-477.

9. Ebright P. Themes surrounding novice nurse near-miss and adverse-event situations. *J Nurs Adm.* 2004;34(11):531-538.

10. Bosch M, Faber MJ, Cruijsberg J, et al. Effectiveness of patient care teams and the role of clinical expertise and coordination: A literature review. *Med Care Res and Rev* 2009;66:5S-35S.

11. AACN. AACN Scope and Standards for Acute and Critical Care Nursing Practice 2008; http://www.aacn.org/WD/Practice/Docs/130300-Standards_for_Acute_and_Critical_Care_Nursing.pdf. Accessed June 10, 2010.

12. Berwick DM. A user's manual for the IOM's 'Quality Chasm' report. *Health Aff.* 2002;21(3):80-90.

13. Curtis JR, Cook DJ, Wall RJ, et al. Intensive care unit quality improvement: A "how-to" guide for the interdisciplinary team. *Crit Care Med.* 2006;34(1):211-218.

14. Wickramasinghe N. Practising what we preach: are knowledge management systems in practice really knowledge management systems? *Bus Process Manage J.* 2003;9(3):295-316.

15. Bali RK, Dwivedi AN, eds. *Healthcare Knowledge Management: Issues, Advances and Successes.* New York, NY: Springer Science Business Media, LLC; 2007.

16. Scott S, Albrecht L, O'Leary K, et al. A Protocol for a systematic review of knowledge translation strategies in the allied health professions. *Implement Sci* 2011;6(58):1-19.

17. Goode CJ. Evidence-Based Practice. In: Oman KS., Krugman ME., Fink RM., eds. *Nursing Research Secrets*. Philadelphia, Pennsylvania: Hanley & Belfus, Inc; 2003.

18. Corrao S, Arcoraci V, Arnone S, et al. Evidence-Based Knowledge Management: an approach to effectively promote good health-care decision-making in the Information Era. *Interm Emerg Med.* 2009;4:99-106.

19. George EL, Henneman EA, Tasota FJ. Nursing implications for the prevention of adverse drug events in the intensive care unit. *Crit Care Med.* 2010;38(6):S136-144.

20. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. *BMJ.* 2005(March):2-8.

21. Straus S, Haynes RB. Managing evidence-based knowledge: the need for relaible, relevant and readable resources. *Can Med Assoc J.* 2009;180(9):942-945.

22. Yellowlees PM, Marks SL, Hogarth M, Turner S. Standards-based, open-source electronic health record systems: a desireable future for the U.S. health industry. *Telemed J E Health.* 2008;14(3):284-288.

23. Goran SF. A second set of eyes: An introduction to Tele-ICU. *Crit Care Nurse.* 2010;30(4):46-55.

24. Lilly C, Thomas E. Tele-ICU: Experience to date. *J Intensive Care Med.* 2010;25(1):16-22.

25. Lilly C, Cody S, Zhao H, et al. Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. *JAMA.* 2011;305(21):E1-9.

26. Rincon T, Bourke G, Ikeda D. Centralized, remote care improves sepsis identification, bundle compliance and outcomes. *Chest.* 2007;132(4):557b-558b.

27. Rincon T, Bourke G, Seiver A. Standardizing sepsis screening and management via a Tele-ICU program improves patient care. *Telemed J E Health.* 2011:1-5.

28. Badawi O, Fromm R, Rincon T, et al. Using annotated electronic patient data to develop a predictive model for identifying severe sepsis 463. *Crit Care Med.* 2009;37(12):A224.

29. Rincon T, Bourke G, Ikeda D, Seiver A. Screening for severe sepsis: an incidence analysis 923. *Crit Care Med.* 2007;35(12):A257.

30. Rincon T, Farrell W, Daly M, Seiver A. Increased documentation of ICD-9-CM codes 995.92 and 785.52 with template-oriented monitoring and screening by a Tele-ICU A4. *Crit Care Med.* 2009;37(12).

31. DeVon H, Ryan C, Zerwic J. Is the medical record an accurate reflection of patients' symptoms during acute myocardial infarction? *West J Nurs Res.* 2004;26(5):547-560.

32. Cruz C, Meshberg E, Shofer F, McCusker C. Interrater reliability and accuracy of clinicians and trained research assistance performing prospective data collection in emergency department patient with potential acute coronary syndrome. *Ann Emerg Med.* 2009;54(1):1-7.

33. Rivard LM, Russell DJ, Roxborough L, Ketelaar M, Bartlett DJ, Rosenbaum P. Promoting the use of measurement tools in practice: a mixed-methods study of the activities and experiences of physical therapist knowledge brokers. *Phys Ther* 2010;90(11):1580-1590.

34. Glegg S. Knowledge brokering as an intervention in paediatric rehabilitation practice. *Int J Ther Rehabil.* 2010;17(4):203-211.

35. French B, Thomas LH, Baker P, Burton CR, Pennington L, Roddam H. What can managment theories offer evidence-based practice? A comparative analysis of measurement tools for organisational context. *Implement Sci.* 2009;4(28):1-15.

36. Needham D. Patient safety, quality of care, and knowledge translation in the intensive care unit. *Respir Care.* 2010;55(7):922-928.

Chapter 3.

Design Implications of a Sepsis Alert Used by TeleICU Nurses:

A Human Factors Evaluation

This chapter has previously been published in whole. It is reprinted here with adaptation and additional content with permission.

Rincon T.A., Manos E.L., Pierce J.D. Telehealth Intensive Care Unit Nurse Surveillance of Sepsis. Comput Inform Nurs. 2017;35(9):459-464.

Abstract

Severe sepsis is a difficult to define and diagnose syndrome that requires time-sensitive therapies to prevent mortality and morbidity. A review of the literature reveals attempts by clinicians and scientists to design severe sepsis early warning systems and alerts within biometric and other clinical information systems. Alerts are alarm notification systems built within software applications to support clinical decision-making. Alarm fatigue, a major technology hazard that may directly affect how clinical information is responded to, communicated, translated. During information exchange in critical care, complex information is communicated among providers, patients, computers, and biometric devices. For critical care nurses, this communication requires high-level cognitive processing, filtering, and situational awareness. There is concern that the addition of alerts may lead to further information and sensory overload (alert fatigue). It is proposed that the science of human factors engineering uses empirical methods to examine the cognitive, behavioral, and physical interactions of human beings with systems and can be used to influence the design and implementation of electronic alerts.

Introduction

A serious concern in nursing is alarm fatigue in the hospital setting. Responding to bedside physiologic alarms requires visual, spatial, and manual demands along with sense making of multiple competing stimuli. Unfortunately, alarm systems can overwhelm clinicians with data or distract them from more clinically significant information, which can lead to user dissatisfaction and desensitization or alarm fatigue.[1,2] Electronic alerts use predictive modeling procedures to develop deterministic

algorithms based on data from biomedical devices, laboratory systems, and other clinical information systems to support decision-making in complex environments. Incorporating human factors principles in alert design offers the potential to minimize alert fatigue and improve acceptance and use of alerts.[3]

The science of human factors uses empirical methods to examine the cognitive, behavioral, and physical interactions of human beings. It does this by means of devices, procedures, products, computer information systems, and equipment in all aspects of the setting in which people work.[4] Human factors science has been used in critical care environments to evaluate nurse performance when completing tasks.[4-7] However, these principles are not consistently employed to evaluate the interaction (sensory stimuli, cognitive functions and physical tasks) of nurses with alarms and alerts.

The usability of an alert is determined by three factors: 1) impact on user efficiency, 2) accuracy-learnability-memorability, and 3) user satisfaction with overall design.[8] Adding clinical alerts into electronic health information systems can increase the usability of a system but also intensify signal desensitization. An iterative process is required because it is relatively impossible for a user interface to sufficiently meet usability criteria with the first design.[9]

Understanding the needs and limitations of the end user is the foundation of a successful interaction with any system. The idea that each care provider must “know all” and “do all” makes it difficult to develop usable clinical decision support tools such as alerts. Other professions such as air traffic control and intelligence, surveillance and reconnaissance (ISR) teams support operations in complex environments. Teams within these logistic centers are composed of highly trained individuals using

telecommunication and high-tech hardware and software applications to monitor for and mitigate adverse outcomes.[10]

An expert team of critical care nurses working in a Telehealth intensive care unit (TeleICU) provided surveillance using high-tech audio-video and clinical decision support alerting tools to support effective and efficient screening for severe sepsis.[11] They also used knowledge translation, a process that closes the gap between evidence-based research and its use in critical care environments through synthesis, dissemination, and diffusion methods.[12] The purpose of this article is to describe how human factors principles were used during the design phase of the sepsis alert system. Also included will be a discussion of possible opportunities to improve the usability of a sepsis alert known as the sepsis prompt being used by TeleICU nurses throughout the United States (U.S.).

Human Factors Science

Human factors engineering is a science that explores the interactions of humans with a system in order to enhance performance, improve safety, and increase user satisfaction.[8] Success, from a human factors standpoint, is to reduce the negative impacts of a system's design (dissatisfaction, stress, errors, costs, and delays) while influencing positive impacts such as optimizing individual performance, improving efficiency, and safety.[13] Employing a human factors approach to examine errors and failures that occur in critical care can lead providers towards more accurate diagnoses and better care processes.[14]

During sensory and information processing stages:

1. Multiple tasks can interfere with other sensory and information processing

activities.

2. A single visual modality does not compete with a single auditory modality, but multiple visual (or multiple auditory) stimuli will compete with each other for the same resources within the brain.
3. When tasks compete for the same resources, the user must task switch because the brain cannot process both tasks at the same time. This is often referred to a multi-tasking.[15]

For example, operating a vehicle requires visual, spatial, and manual demands so when adding another task such as manual dialing of a phone number or texting, competition for the same resources in the brain will occur. This leads to task switching.

According to Wickens et al., cognitive task analysis is used in human factors to understand the human-system interactions such as complex decision-making and reasoning, knowledge translation, and large and complex rule structures that all occur during sensory processing. The authors explain that bottom-up processing occurs when lower levels of sensory processing move upwards to the higher centers of the brain for cognitive processing. Manipulation of perceived information is also part of processing and is influenced by both sensory and cognitive aspects. Working memory is a temporary, top-down processing activity that uses knowledge stored in long-term memory and requires a wide variety of mental activities such as comprehension, visualization, decision-making, and problem solving.[8]

Critical care nurses work in complex, highly interruptive environments that require use of both bottom-up and top-down processing. Depending on the level of expertise, most intensive care unit (ICU) nurses can accelerate the filtering and sense making

needed to respond to the multiple stimuli in an ICU. Unfortunately, the amount of task switching needed to accomplish this level of response leads to fatigue, and eventually a desensitization of alarms (alarm fatigue) occurs.

Human factors science focuses on the design of software and its interactions with the humans that are using it. Factors such as fatigue, mental workload, anxiety, stress, cognitive, and perceptual abilities, as well as display and control principles influence the human-computer interaction.[8] User-centered design, or usability engineering, involves an early focus on the user, empirical evaluation, iterative design methods, and a design that directly involves the end users.[8]

Rationale for Clinical Alerting Tools

For over 20 years, concerns with excessive alarms in the ICU have been discussed in the literature.[3,16-21] Recent studies in ICUs indicate that biomedical devices can produce as many as one critical alert every 92 seconds with less than 15% being clinically relevant.[17,18] The volume of clinically insignificant biomedical alarms contributes to caregivers becoming overwhelmed, distracted and desensitized, making alarm hazards number one in a top ten list of health technology hazards for the last four years.[22]

Alarm notification systems that are built within software applications are known as alerts and have been used to support clinical decision-making.[23] Algorithms using multiple parameters, trends over time, and filtered signal quality data from biomedical devices, laboratory systems, and other clinical information systems are the foundation of these alerts.[18,21,23] Ways to reduce alarm fatigue have been described as adjusting alarms to meet the needs of each individual patient, teaching nurses how to respond to

alarms, enhancing alarm audibility, using other technology to reduce false alarms, and developing more sophisticated alarm notification systems.[21] The idea that a group of highly trained and experienced critical care nurses to monitor alerts and alarms while conducting high-level surveillance and intelligence gathering to mitigate the misses associated with alarm fatigue is a concept that needs further exploration.

Business Needs and Purpose of a Sepsis Alert

Sepsis is a time-sensitive syndrome that is characterized by an infection (suspected or confirmed) plus systemic inflammatory response syndrome (SIRS). Severe sepsis is associated with acute organ dysfunction with hypotension despite adequate fluid resuscitation.[24] The Surviving Sepsis Campaign (SSC) has promoted severe sepsis screening and provides a paper tool that uses SIRS and organ dysfunction criteria to assist clinicians in early identification.[25]

Although the pro-inflammatory process that is characterized by SIRS is most commonly described in severe sepsis, both an anti-inflammatory response host-pathogen immune profile and a mismatched host-pathogen immune profile have been described.[26,27] In brief, a combination of leaking and clotting in the vascular beds occurs due to a hyper-inflammatory response to the infectious process which leads to impaired oxygen and nutrient availability and consumption of cells.[24] Cells and tissue begin to die leading to tissue death, organ dysfunction, and possibly death.[24,28,29]

Worldwide, one in four persons with severe sepsis will die. In the U.S. from 1993 to 2003, there was a significant increase in mortality for patients with sepsis as the number of deaths nearly doubled.[30,31] Epidemiology studies have reported increased incidence of sepsis cases in the U.S. with costs associated with sepsis care in hospitals as high

$24.3 billion annually.[31-33]

The SSC and the National Quality Forum are working toward a common goal to make severe sepsis a national quality initiative aimed at improving care, cost, and survivability.[30,34,35] Although data suggest that early recognition can lead to more timely treatment of severe sepsis, care providers continue to struggle with implementing effective and efficient screening processes.[36,37] The SSC provides a paper screening tool to assist nurses and other care providers with identifying severe sepsis, [25,38] but manual processes are resource intensive and difficult to sustain.

Manual screening processes report that nurses are screening patients on admission and once per shift.[39,40] More frequent screening of high-risk populations may be needed given the rapid onset and progression of severe sepsis. Sepsis experts support the use of computer-enhanced screening tools such as early warning systems and alerts to assist nurses with early recognition of severe sepsis.[38,41]

Simplifying and standardizing the screening approach can lead to less confusion, improve efficiency, and decreased errors associated with missed screening.[41] Also, as screening for severe sepsis becomes more standardized and embedded into clinical information systems, nurses should have more time to care for individual patient needs.[14] Ensuring that an alert is placed so that the end user sees it, identifies the severity of the situation appropriately, and understands its meaning can assist in mitigating misses.[3,14]

Using Human Factors Science to Evaluate the Sepsis Prompt

An alert known as the sepsis prompt was developed to support early recognition of severe sepsis in critically ill patients and has been deployed at TeleICUs throughout the

U.S.[42] The American Telemedicine Association describes TeleICU as an application of critical care using audio-visual communication and computer systems to support bedside teams in earlier identification and evidence-based treatment of patients.[43] According to the Network for Excellence in Health Innovation, by 2012 there were 54 civilian and government TeleICU centers in the U.S. covering thousands of adult ICU beds, from rural to regional hospitals to large academic medical centers.[44]

Despite widespread use of the sepsis prompt, a description of how the alert was designed has not been described in the literature. Design implications should be considered when developing a sepsis alert. Questions that should be considered include the following: Whom on the care team should respond to the alert? How often will the alarm fire? What is the mechanism of firing (visual versus auditory alerts)? How and where will visual alerts be displayed? What type of sound will an auditory alert make? How will a particular alert be distinguishable from other alerts? How many alerts are too many?

Although electronic health record vendors claim that clinical alerts can be developed within their products, expertise in human factors science appears to be lacking. Clinical alerts need to be not only intuitive (learnable, understandable, recognizable, and actionable) but also clinically relevant and manageable.[45] Human factors engineering is a systematic, iterative process that, when appropriately coordinated and incorporated into a system's design, can improve the human-computer interaction.

Sensory Processing (placement, visibility, and distinctiveness)

The placement, visibility, and distinctiveness of an alert are important in terms of the user's ability to differentiate them from other stimuli. Visual alerts need to be located in

the operator's visual field, be placed in order of importance, and make clear what situation is being indicated.[8,45] The sepsis prompt was placed in the Message Center (Figure 3) which is located on the census screen in the center of the electronic page. This screen is next to each individual patient's name as well as on the screen that opens when a user initially accesses the electronic health record for an individual patient.

Figure 3. Message Center with Sepsis Prompt

Image used with permission from Philips Healthcare (Appendix A)

The Message Center is where other related clinical alerts are found. Wickens et al. describe the importance of placing related alerts in close mental proximity with each other reduces information access costs.[8] The brightness, background contrast, and lettering characteristics were all considered during design of the visual properties of the sepsis prompt. To identify the severity of the alert (hazard matching), the color red was used and the word "SEPSIS" was placed within the icon. Signal words improve learnability and avoid confusability with other Message Center visual alerts.

Cognitive Processing

Wickens et al. provide a comprehensive description of cognitive processing and mental modeling. The authors explain that signals are perceived and interpreted according to user expectations based on knowledge and experience. They describe

how limitations of human cognition, situational awareness, problem solving, and organization and retention of information in long-term memory all affects responses to stimuli. Explanations of how situational awareness in adaptive decision-making is influenced by the ability of an expert to identify the system state, assess, and define the overall task, and then develop an appropriate plan support the need to develop alerts based in mental modeling.[8]

The screening methodology for the sepsis prompt was designed after the mental modeling of expert nurses trained to screen large populations of critically patients for severe sepsis from two TeleICUs in Northern California. TeleICU nurses keep the health information system open at all times. Unlike the nurses who are providing hands-on care, these nurses use the TeleICU system to conduct their routine assessments and continuously survey patients using the open system. This increases the likelihood of successful alert management and mitigates misses that have been associated with other systems.

Two questions related to suspected infectious process and organ dysfunction were included in the design: 1) Do you suspect the patient is infected? 2) Do you suspect the organ dysfunction is a response to the infection? This was considered an important element of clinical decision-making that would be difficult to automate. The sepsis prompt scanned each patient's relevant data in the clinical information system every two hours and automatically fired when criteria were met. This procedure increased opportunities for proactive responses and decreased the manual tasks that relied on recall.

The criteria for organ failure include cardiovascular (hypotension or on

vasopressors), respiratory (hypoxemia), renal (low urine output or creatinine increases), metabolic acidosis (pH), liver (bilirubin), hematology (hematocrit), altered mental status (clinical documentation), and perfusion (lactate) parameters (Table 5). When the prompt fires, the end user can view additional information related to why the prompt fired. The organ dysfunction criteria within the details are expandable, with abnormal values highlighted in red and normal ranges visible, but the criteria found within the "signs of inflammation" section within the details do not have these features. This increases the need for nurses to use recall or to navigate away from the prompt in search of more information.

Table 5. Sepsis Prompt Screening Criteria

Signs of Inflammation	Data Collected From	Comments
Temperature	Nursing flow sheet or interfaced vital signs	Only values within 12 hours
WBC Counts and Bands	Laboratory	Only values within 24 hours
Respiratory Rate	Respiratory and nursing flow sheets or interfaced vital signs	Only values within 2 hours
Heart Rate	Nursing flow sheet or interfaced vital signs	Only values within 2 hours
Systolic Blood Pressure	Interfaced vital signs	Only values within 2 hours
Mental Status	Care plan or active diagnoses/problem lists	Only active selections
Serum Glucose	Interfaced from laboratory	Only values within 6 hours
Lactate	Interfaced from laboratory	Only values within 24 hours*
PT INR	Interfaced from Laboratory	Excluded if patient on warfarin

WBC, white blood cell; ABG, arterial blood gases; PT INR, prothrombin time international normalized rate; * (excludes first 6 hours post cardiac surgery)

Since an individual's long-term memory is inclined to forget certain things in order to

remember other things, Wickens et al. suggest using visual cues that keep the user focused on the task are important to successful alert management and end user efficiency. The authors describe that instinctive and automatic tendencies (habits) exemplify how long-term memory works too well and triggers responses that may no longer be appropriate. They explain that predictive aiding seeks to promote proactive versus reactive responses. It replaces memory with visual information displays.[8]

Information related to what abnormal parameters caused the sepsis prompt to fire should be displayed in ways that are more meaningful. In this way information access costs can be minimized, focused attention enhanced, distractions lessened, and users will be able to use parallel cognitive processing.[8] In analyzing the sepsis prompt's design, users are able to visualize multiple sources of information related to the task of sepsis screening. However, enhancements related to displaying what abnormal parameters caused the prompt to fire are needed. For example, signs of inflammation criteria such as temperature, white blood cell count, respiratory rate, heart rate, blood pressure, mental status, blood sugar, lactate, and blood clotting abnormalities, are available for viewing but are not highlighted for ease of interpretation.

Sensitivity Thresholds

Some diseases are considered time-sensitive and have catastrophic outcomes when not caught and treated early. Sensitivity thresholds for identifying diseases such as an evolving myocardial infarction or acute ischemic stroke are set very low and care teams are taught to respond quickly to even vague and sometimes atypical symptomology to avoid misses. Since severe sepsis is a time-sensitive syndrome that is difficult to diagnose, the development of a sepsis alert requires an understanding of how and why

users might respond to it.

Heeger introduced signal detection theory (Figure 4) and criterion response (Figure 5) which involves a specific language and graphic representation for analyzing decision-making. It provides a framework for evaluating whether a response to a signal was good, referred to as hits and correct rejections in the theory, as well as bad responses referred to as false alarms and misses. To measure the discrimination or sensitivity of an alert (how well the signal leads the user to the correct response), the author suggests the following:

1. Assess whether a signal was or was not present
2. Determine whether a response was or was not present
3. Decide if a correct response (hit or correct rejection of noise) to a signal was or was not present (Figure 4).[46,47]

Figure 4. Signal Detection Theory

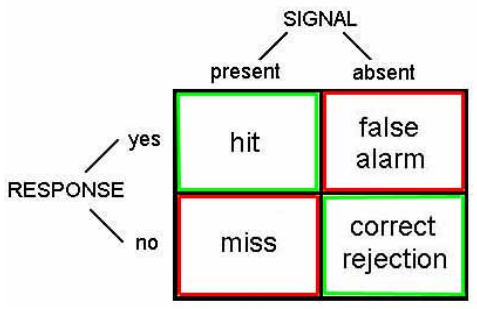
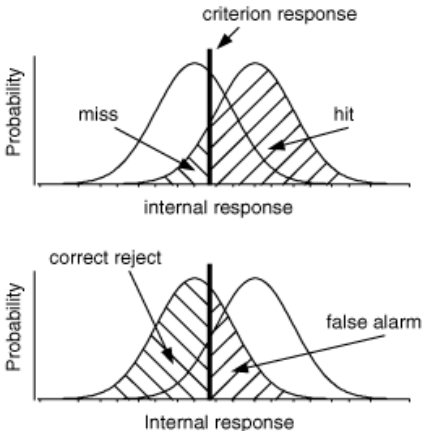


Figure 5. Criterion Response



Images used with permission from D. Heeger (Appendix B)

Heeger also describes that both the distinctiveness of a signal (placement, visibility, and hazard matching) as well as the criterion allowed (low versus high) could affect

discrimination. There are various reasons a low criterion for a signal may be set so that "yes" is chosen more often, leading to more chances for hits with a tolerance for false alarms (Figure 5 top). The author explains that if the responder chooses a high criterion, than "no" will be chosen more frequently, which can lead to more misses (Figure 5 bottom).[46,47]

In fuzzy signal detection theory, a variable can assume a continuous range of values in order to represent the threat or danger that a disorder might be present.[8] Fuzzy logic imitates the sense-making (reasoning) of care providers in order to develop computer-based algorithms based on degree of correctness versus "absolutely true" or "absolutely false" decision trees.[48] Fuzzy logic has been used in diverse algorithms for glycemic control with the artificial pancreas, medical decision-making algorithms to control mechanical ventilation in respiratory distress syndrome, and diagnostic algorithms for implantable cardioverter defibrillators.[49-51] For the development of the sepsis prompt, fuzzy logic was applied to expanded SIRS criteria. Within the Fuzzy Logic SIRS algorithm most variables contributed to the score within a range of partial point values to a value of one based on how far they deviate from normal.

After several testing attempts, the sepsis prompt was set to screen all patients registered in the TeleICU system every two hours. Certain suppression criteria, such as not counting a high creatinine value for a chronic renal failure patient or a high glucose value for a known diabetic patient, and suppression of lactate for first 6 hours post cardiac surgery, were added to decrease the frequency of false alerts. There were three different dismissal options ranging from 2 to 72 hours. After these changes occurred, the TeleICU nurses reported that the sepsis prompt saved them time and improved

overall efficiency when compared to their manual process.

Sensitivity and Specificity of the Sepsis Prompt

Data from a retrospective cohort of consecutive ICU patients (admitted to multiple hospitals in a large health system between May 2008 and August 2008) were analyzed to determine the sensitivity and specificity of the sepsis prompt. During this study nurses used the SSC screening criteria to support manual screening of over 6,000 ICU patients from 22 hospitals, with 874 cases of severe sepsis identified (15%).[42] Nurses working in the TeleICU screened all patients upon admission and at least every 72 hours (patients with suspected or known infections were to be screened every 12 hours).

The TeleICU nurses were trained to assess for suspected or confirmed infection using the following criteria:

1. Manifestations of local infection such as cellulitis, presences of an abscess, purulent sputum or discharge, and unexplained localized pain.
2. Systemic manifestations such as fever, malaise or change in level of consciousness.
3. Highly suspect surgeries/procedures especially those involving the gastrointestinal system.
4. Documented diagnosis of or therapies for infection in the health record such as but not limited to antimicrobial therapy (excluding prophylactic therapies) and orders for cultures and sensitivities.

If an ICU patient was suspected or confirmed to have an infection and met two or more SIRS criteria and organ failure, then the TeleICU nurse would report this as a positive severe sepsis screen. The nurse would immediately notify a physician (usually

the TeleICU intensivist) who would then medically diagnose the patient with severe sepsis.

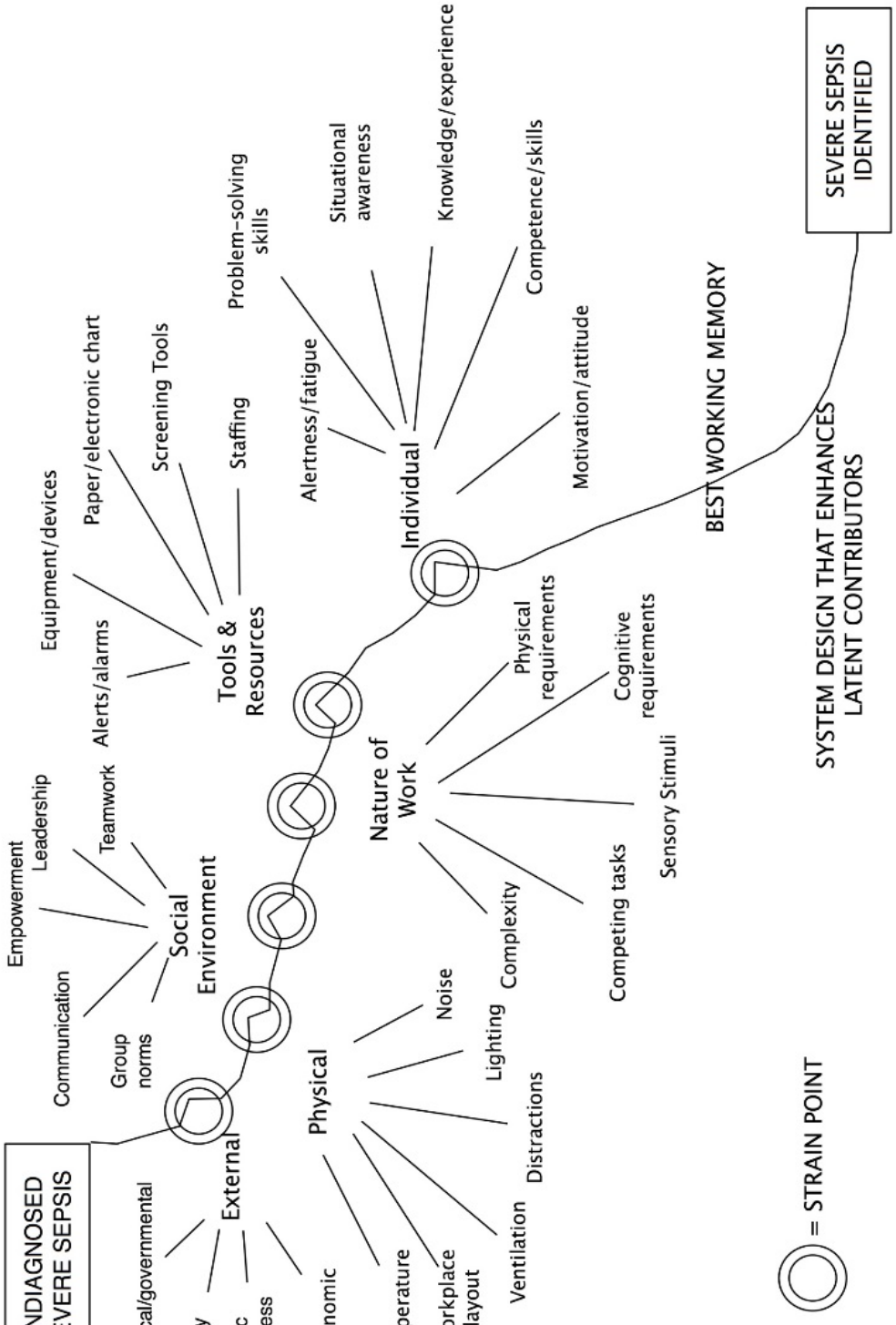
Patients were randomized 1:1 into training and test sets for cross validation after 10 systemic inflammatory response syndrome (SIRS) criteria were electronically captured from the clinical information system at 30-minute intervals. The receiver operator characteristics (ROC) in logistic regression and a machine learning algorithm were used to predict the discrimination characteristics of the model. Authors reported that a sensitivity of 0.90 and a specificity of 0.80 were achieved.[42] In other words, the prompt could correctly identifying every patient who had severe sepsis 90% of the time with 80% of healthy people being correctly identified as not having the condition.

Discussion

A group of expert TeleICU nurses managed the sepsis prompt for early identification of severe sepsis. Assigning one group of nurses to respond to the alerts enhanced *social environment* aspects such as empowerment, opened communication, and collaboration pathways with bedside teams, and was supported by leadership. The *physical environment* of the TeleICU was found to have fewer distractions and be more conducive to alert monitoring than the bedside environment. Enhancing *tools and resources* with an alert that screened patients every two hours increased the opportunities for proactive screening while decreasing the manual tasks of screening.

Factors that influence patient care processes and system interactions and have been described in HF conceptual frameworks.[52,53] Creating an alert that was usable and relevant to the practice of TeleICU nurses mitigated strain points or system factors that can influence sepsis screening (Figure 6).

Figure 6. Severe Sepsis Identification Strain Points



The *nature of work* related to of detection of severe sepsis requires high-level cognitive requirements. Using highly trained and experienced critical care nurses enhanced the nature of the work. Using nurses working in a controlled environment mitigated task switching. The characteristics of TeleICU nurses (high levels of situational awareness, problem solving, motivation, knowledge, experience, and competence related to screening for severe sepsis) allowed designers to use a cognitive task analysis approach during design and evaluation. This led to enhanced usability of the sepsis prompt over the manual screening process.

The TeleICU nurses were already using (and in fact had assisted in the development of) a severe sepsis detection process. This may have been predisposed them to response bias; and as such they were willing to accommodate more false alarms than nurses who are not familiar with either severe sepsis screening. In contrast, nurses who have not adopted a severe sepsis screening process may not place the same level of value on this alert and find it a nuisance. More research in this area is needed.

The prompt was both distinctive and learnable by the TeleICU nurses and the design supported focused attention and minimized distraction. Moving the sepsis prompt closer to other infectious disease information such as antimicrobial therapies, invasive lines and tubes, temperature, and white blood cell counts could be considered for future design. The addition of red font for organ dysfunction parameters allowed the nurses to visualize quickly the criteria that caused the prompt to fire. Using the same red font in the signs of inflammation section should be considered.

Expanding the use of fuzzy logic in the design of the prompt may lead to less false alerts. For example, fuzzy logic could answer the question related to new infectious

process or suspicion of infection by incorporating additional data elements that are generally present in the TeleICU system. Refining the algorithm further by excluding specific populations of patients that could have SIRS from a non-infectious source, such as new trauma admissions and post-operative cardiac surgery patients could improve the specificity of the alert. Additional research to determine its performance in identification of severe sepsis as well as its association with in-hospital outcomes and timeliness of therapeutic interventions is needed.

Conclusion

Screening patients for severe sepsis is a resource intensive process that requires high-level cognitive processing. Expert nurses working in a controlled environment with a specific role to observe and respond to a sepsis alert provide an effective and efficient approach to managing a complex sepsis screening process. The sepsis prompt allowed nurses to transition from a manual process to more automated screening process for a high-risk population of patients. Human factors concepts were used to evaluate a sepsis alert design and were used to enhance the usability and mitigate the strain points that impact early identification of severe sepsis.

References

1. ECRI Institute. Pioneering applied scientific research in healthcare. *About ECRI* 2014; https://www.ecri.org/About/Pages/default.aspx. Accessed July 12, 2014.

2. Association for the Advancement of Medical Instrumentation. Clinical alarms. 2011. http://www.aami.org/htsi/alarms/pdfs/2011_Alarms_Summit_publication.pdf. Accessed December 3, 2014.

3. Sendelbach S, Funk M. Alarm fatigue: A patient safety concern. *Adv Crit Care.* 2013;24(4):378-386.

4. Henriksen K, Dayton E, Keyes M, Carayon P, Hughes R. Understanding Adverse Events: A Human Factors Framework. In: Hughes R, ed. *Patient Safety and Quality: An Evidence-Based Handbook for Nurses*. Rockville, MD: Agency for Healthcare Research and Quality; 2008:67.

5. Russ A, Fairbanks R, Karsh B, Militello L, Saleem J, Wears R. The science of human factors: seperating fact from fiction. *BMJ Qual Saf.* 2013;22(11):802-808.

6. Wakefield M. The Quality Chasm Series: Implications for Nursing. In: Hughes R, ed. *Patient Safety and Quality: An Evidence-Based Handbook for Nurses*. Rockville, MD: Agency for Healthcare Research and Quality; 2008.

7. Carayon P, Gurses A. A human factors engineering conceptual framework of nursing workload and patient safety in intensive care units. *Intensive Crit Care Nurs.* 2005;21(5):284-301.

8. Wickens C, Lee J, Liu Y, Becker S. *An Introduction to Human Factors Engineering.* 2nd ed. Upper Saddle River, New Jersey Pearson Education, Inc., ; 2004.

9. Nielsen J. Iterative user interface design. *IEEE Computer.* 1993;26(11):32-41.

10. NATO. Joint intelligence, surveillance and reconnaissance. *North Altlantic Treaty Organization* 2015; http://www.nato.int/cps/en/natolive/topics_111830.htm. Accessed May 25, 2015.

11. Rincon T. Integration of Evidence-Based Knowledge Management in Microsystems: A Tele-ICU Experience. *Crit Care Nurs Q.* 2012;35(4):335-340.

12. Black M, Schorr C, Levy M. Knowledge translation and the multifaceted interventions in the intensive care unit. *Crit Care Med.* 2012;40(4):1324-1328.

13. Carayon P, Alvarado C, Hundt A. Work System Design in Health Care. In: Carayon P, ed. *Handbook of Human Factors and Economics in Health Care and Patient Safety*. Boca Raton, FL: Taylor & Francis Group, LLC; 2012:65-80.

14. Harder K, Marc D. Human factors issues in the intensive care unit. *Adv Crit Care.* 2013;14(4):405-414.

15. Wickens C. Multiple resources and performance prediction. *Theor Issues in Ergon Sci.* 2002;3(2):159-177.

16. Drew B, Califf R, Funk M, et al. Practice standards for electrocardiographic monitoring in hospital settings: an American Heart Association scientific statement from the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young: endorsed by the International Society of Computerized Electrocardiology and the American Association of Critical-Care Nurses. *Circulation.* 2004;110(17):2721-2746.

17. Creighton Graham K, Cvach M. Monitor alarm fatigue: standardizing use of physiological monitors and decreasing nuisance alarms. *Am J Crit Care.* 2010;19(1):28-34.

18. Siebig S, Kuhls S, Imhoff M, Gather U, Imerich J, Wrede C. Intensive care unit alarms—How many do we need? *Crit Care Med.* 2010;38(2):451-456.

19. Lawless S. Crying wolf: false alarms in a pediatric intensive care unit. *Crit Care Med.* 1994;22(6):981-985.

20. Chambrin M-C, Ravaus P, Calvelo-Aros D, Jaborska A, Chopin C, Boniface B. Multicentric study of monitoring alarms in the adult intensive care unit (ICU) a descriptive analysis. *Intensive Care Med.* 1999;25(12):1360-1366.

21. Cvach M. Monitor alarm fatigue: An integrative review. *Biomed Instrum Technol.* 2012;46(4):268-277.

22. ECRI Institute. ECRI Institute announces top 10 health technology hazards for 2015. *News Release* 2015; https://www.ecri.org/press/Pages/ECRI-Institute-Announces-Top-10-Health-Technology-Hazards-for-2015.aspx. Accessed May 1, 2015.

23. Blum J, Kruger G, Sanders K, Gutierrez J, Rosenberg A. Specificity improvement for network distributed physiologic alarms based on a simple deterministic reactive intelligent agent in the critical care environment. *J Clin Monit Comput.* 2009;23(1):21-30.

24. Russell J. Management of sepsis. *N Engl J Med* 2006;355(16):1699-1713.

25. Surviving Sepsis Campaign. Protocols and checklists. *Surviving Sepsis Campaign Resources* 2014; http://www.survivingsepsis.org/Resources/Pages/Protocols-and-Checklists.aspx. Accessed June 7, 2014.

26. Myrianthefs P, Karabatsos E, Baltopoulos G. Sepsis and Immunoparalysis. In: Hall J, Schmidt G, JP. K, eds. *Principles of Critical Care*. 4th ed. New York, NY: McGraw-Hill; 2015.

27. Bone R, Grodzin C, Balk R. Sepsis: a new hypothesis for pathogenesis of the disease process. *Chest.* 1997;112(1):235-243.

28. Ely E, Goyette R. Sepsis with Acute Organ Dysfunction. In: Hall J, Schmidt G, Wood L, eds. *Principles of Critical Care*. 3rd ed. New York, NY: The McGraw-Hill Companies; 2005.

29. Hotchkiss RS, Tinsley KW, Swanson PE, Karl IE. Endothelial cell apoptosis in sepsis. *Crit Care Med.* 2002;30(5):S225-S228.

30. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med.* 2013;39(2):165-228.

31. Dombrovskiy V, Martin A, Sunderram J, Paz H. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med.* 2007;35(5):1244-1250.

32. Angus D, Linde-Zwirble W, Lidicker J, Clermont G, Carcillo J, Pinsky M. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29(7):1303-1310.

33. Lagu T, Rothberg M, Steingrub J, Lindenauer P. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. *Crit Care Med.* 2012;40(3):754-761.

34. National Quality Forum. Statement from NQF on review of sepsis measure. 2014; http://www.qualityforum.org/News_And_Resources/Press_Releases/2014/Statement_from_NQF_on_Review_of_Sepsis_Measure.aspx. Accessed July 3, 2014.

35. National Quality Forum. Severe sepsis and septic shock: Management bundle (composite measure 0500). 2013; http://www.qualityforum.org. Accessed July 3, 2014.

36. Levy M, Dellinger R, Townsend S, et al. The surviving sepsis campaign: Results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med.* 2010;38(2):367-374.

37. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med.* 2014:1-7.

38. Rivers E, Ahrens T. Improving outcomes for severe sepsis and septic shock: tools for early identification of at-risk patients and treatment protocol implementation. *Crit Care Clin.* 2008;23:S1-S47.

39. Rincon T, Bourke G, Seiver A. Standardizing sepsis screening and management via a Tele-ICU program improves patient care. *Telemed J E Health.* 2011:1-5.

40. Moore L, Jones S, Kreiner L, et al. Validation of a screening tool for the early identification of sepsis. *J Trauma.* 2009;66(6):1539–1547.

41. Aitken LM, Williams G, Harvey M, et al. Nursing considerations to complement the Surviving Sepsis Campaign guidelines. *Crit Care Med.* 2011;39(7):1800-1818.

42. Badawi O, Fromm R, Rincon T, et al. Using annotated electronic patient data to develop a predictive model for identifying severe sepsis 463. *Crit Care Med.* 2009;37(12):A224.

43. ATA TeleICU Practice Guidelines Work Group. Guidelines for TeleICU Operations. *ATA Standards & Guidelines.* 2014;2014(June 21). http://www.americantelemed.org/resources/standards/ata-standards-guidelines#.U7gm1hbZf1p.

44. NEHI. Emerging best practices for Tele-ICU care nationally. *NEHI Issue Brief* 2013; http://www.nehi.net/writable/publication_files/file/nehi_issue_brief_final_emerging_best_practices_for_teleicu_1_.pdf. Accessed November 11, 2014.

45. Phansalkar S, Edworthy J, Hellier E, et al. A review of human factors principles for the design and implementation of medication safety alerts in clinical information systems. *J Am Med Inform Assoc* 2010;17(5):493-501.

46. Heeger D. Signal Detection Theory. 2007. http://www.cns.nyu.edu/~david/handouts/sdt/sdt.html. Accessed May 20, 2015.

47. Heeger D. Signal Detection Theory Handout. 1998. http://www-psych.stanford.edu/~lera/psych115s/notes/signal/. Accessed March 25, 2015.

48. Cintula P, Fermüller CG, Noguera C. Fuzzy Logic. *The Stanford Encyclopedia of Philosophy* 2017; Fall 2017:https://plato.stanford.edu/archives/fall2017/entries/logic-fuzzy/. Accessed March 31, 2018.

49. Nimri R, Phillip M. Artificial pancrease: fuzzy logic and control of glycemia. *Curr Opin Endocrinol Diabetes Obes.* 2014;21(4):251-256.

50. Nguyen B, Bernstein D, Bates J. Controlling mechanical ventilation in acute respiratory distress syndrome with fuzzy logic. *J Crit Care.* 2014;29(4):551-556.

51. Bardossy A, Blinowska A, Kuzmicz W, et al. Fuzzy logic-based diagnostic algorithm for implantable cardioverter defibrillators. *Artif Intell Med.* 2014;60(2):113-121.

52. Carayon P, Wood KE. Patient Safety: The Role of Human Factors and Systems Engineering. *Studies in health technology and informatics.* 2010;153:23-46.

53. Carayon P, Hundt AS, Karsh BT, et al. Work system design for patient safety: the SEIPS model. *Qual Saf Health Care.* 2006;15(Suppl 1):i50-i58.

Chapter 4.

Prognostic Accuracy of the SOFA score and a Sepsis Prompt in Discriminating Mortality and Sepsis among Patients in Intensive Care

Introduction

Each year there are over 19 million cases of sepsis globally that result in more than 5 million deaths.[1] Long term cognitive dysfunction [2] and increased mortality[3] rates following sepsis have been reported. In the United States (U.S.), sepsis kills more individuals annually than breast cancer, prostate cancer, and acquired immunodeficiency syndrome (AIDS) combined.[4] Sepsis is costly with estimates of more than $20 billion a year spent on sepsis care in the U.S.[5,6] Early identification has been recognized as a major challenge to executing targeted sepsis therapies and nurses have been described as playing a significant role in sepsis recognition.[7,8]

Sepsis has recently been defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection that leads to tissue injury and organ failure.[9] This new definition is based on the sepsis-related organ failure assessment (SOFA) score and a new modified score known as qSOFA, has not been uniformly accepted in the clinical community. Concerns that earlier stages of sepsis, when the syndrome is actually at its most treatable, might be identified too late have been raised.[10,11] This is important to nursing because nurses have historically used a combination of SIRS or expanded SIRS and organ failure criteria to screen patients for sepsis. A comprehensive list of sepsis screen tools and processes that use these criteria are included in Table 2 of Chapter 1 of this dissertation.[12-31]

Based on Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), Raith et al. conducted a retrospective cohort study of the prognostic accuracy of SOFA, qSOFA, and SIRS for mortality using adult intensive care unit (ICU) admissions in 182 hospitals in the Australia and New Zealand Intensive Care Society

(ANZICS) Adult Patient Database for years 2010-2015.[32] The results of both studies concluded that SOFA outperformed SIRS and qSOFA in prognostic accuracy for mortality for ICU patients.[32,33] What has not been reported is the discriminatory capacity of SIRS and organ failure versus SOFA scoring for detection of sepsis. The overall objective of this dissertation was to conduct a retrospective study using a large U.S. data repository to determine if an electronic prompt, that uses SIRS and organ failure criteria, can detect sepsis. Another objective of this study was to determine the prognostic accuracy of the SOFA score and the sepsis prompt in discriminating in-hospital mortality among patients with sepsis in the intensive care unit. Below are the specific aims, research questions, and hypothesis for this study.

Research Aims, Questions and Hypotheses

Aim 1: To determine if an electronic sepsis prompt that uses systemic inflammatory response syndrome and organ failure criteria identifies sepsis in the electronic health record (EHR) for adult intensive care unit (ICU) patients.

Research question 1: Using the electronic intensive care unit (eICU) Research Institute (eRI) data repository, how accurately does the electronic sepsis prompt detect sepsis in adult ICU patients within the first 24 hours of admission to the ICU?

Aim 2: To determine the effect of an increase in sepsis-related organ failure assessment (SOFA) score of 2 or more points and the presence of an electronic sepsis prompt within the first 24 hours of ICU admission in discriminating in-hospital mortality among adult ICU patients with sepsis.

Research hypothesis 2a: Using the eICU Research Institute (eRI) data repository, adult ICU patients with sepsis who have an increase in SOFA score of 2 or more in the first

24 hours of their ICU stay will have higher in-hospital mortality rates than sepsis patients with a SOFA score less than 2.

Research hypothesis 2b: Using the eICU Research Institute (eRI) data repository, adult ICU patients with sepsis who have presence of an electronic sepsis prompt in the first 24 hours of their ICU stay will have higher in-hospital mortality rates than sepsis patients without presence of a sepsis prompt.

Research Question 2a: What are the differences in the in-hospital mortality rates in adult ICU patients with sepsis using an increase in the SOFA score of 2 or more versus the electronic sepsis prompt?

Methods

The University of Kansas Institutional Review Board (IRB) reviewed the methodology and determined that this study did not require Human Subjects approval at KUMC (Appendix C and Appendix D). The eRI database has been independently analyzed and has been certified as meeting safe harbor standards by Privacert, Inc. (Pittsburgh, Pennsylvania).[34] All data were de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule.[35] The eRI publications committee approved of use of the complete dataset (Appendix E). The Massachusetts Institute of Technology (MIT) in Cambridge, Massachusetts approved use of the subset (Appendix F).

Study Design, Setting, and Population

A retrospective cohort study was performed using existing data in a large critical care clinical database of hospitals in the U.S., known as the Philips eICU Research Institute (eRI). All patients admitted to intensive care units (ICU) from January 1, 2010

through December 31, 2015 were screened for inclusion. Patient records within the eRI were gathered primarily through HL7 interfaces from laboratory operating systems, vital sign monitoring systems, pharmaceutical operating systems, admission-discharge-transfer (ADT) systems, and various clinical documentation systems known as electronic health records (EHR) as well as direct entry into the Telehealth intensive care unit (TeleICU) health information system (HIS).

This dataset contains billions of variables (laboratory, medication orders, and vital sign measurements) related to care of ICU patients. Most of the Tele-ICUs in the U.S. contribute data to the eRI database. The Philips eCareManager system is the electronic health information system used by care providers working in the Tele-ICUs. Many ICU care providers used eCareManager as their primary documentation system. However, most hospitals now use electronic health record (EHR) solutions that are better suited to support documentation and storing of patient health information across the care continuum. The data within the eRI database were extracted from the clinical information in the eCareManager system.

A publicly available subset of eRI known as the eICU Collaborative Research Database[36] was used to complete a comprehensive review of the content and structure of the data tables and to test code that was written in the R statistical programming language (https://www.r-project.org).[37] Both datasets contain enormous quantities of digital data collected through routine monitoring of ICU patients. The complete dataset and the subset were made available through the work of Philips Healthcare and collaborators at MIT's Laboratory for Computational Physiology.[36,38]

The data collection time period was the first 24 hours of the ICU stay. This time

period was chosen for several reasons: 1) the consensus definition of sepsis does not specify within what time frame to include or ignore increases in SOFA scoring criteria;[9] 2) several recently published retrospective studies using a large critical care dataset have used this timeframe;[32,39] and 3) other studies have demonstrated that a high proportion of patients present to the ICU with sepsis.[11]

Inclusion/Exclusion Criteria

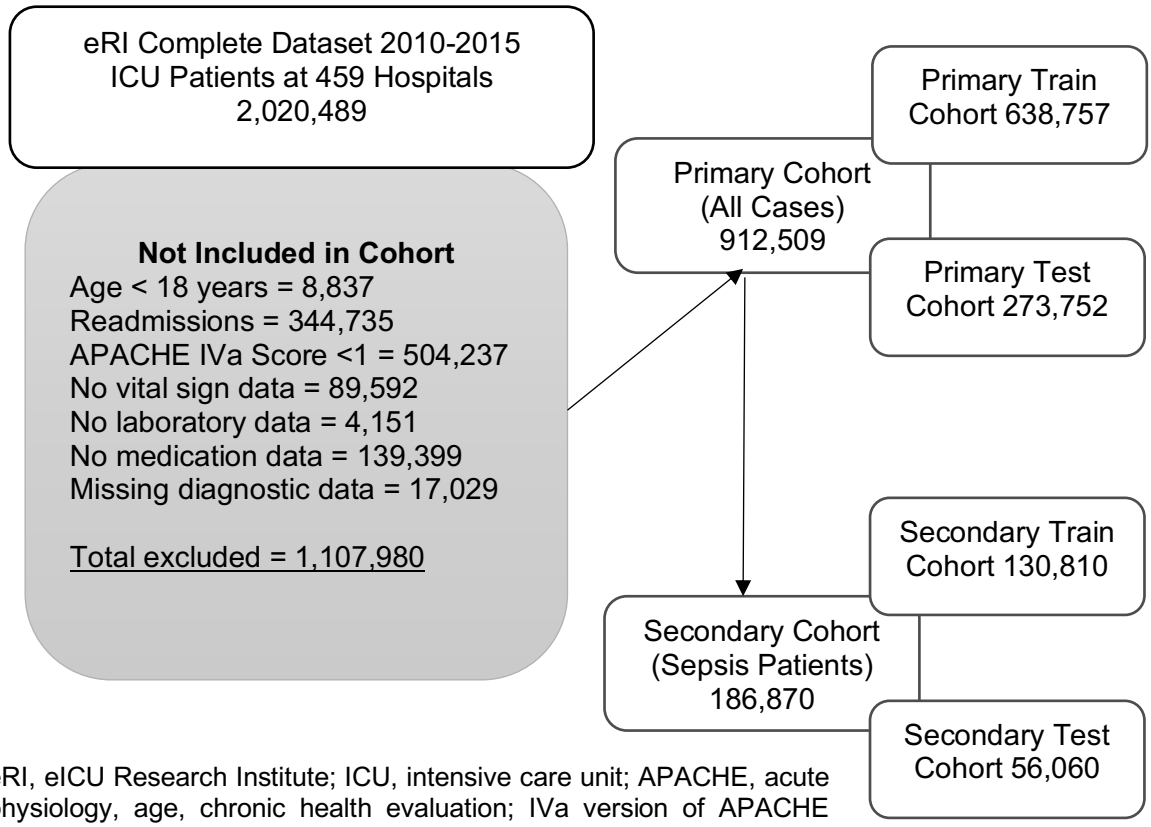
Records for ICU patients admitted between January 1, 2010 and December 31, 2015 were included in the complete data extract from the eRI database. Patients less than 18 years of age and ICU readmissions during the same hospitalization were excluded. Non-ICU level patients are sometimes boarded in ICUs. To control for this, patients with an APACHE (acute physiology, age, chronic health evaluation) IVa score of less than one were excluded. APACHE acuity scoring is considered the gold standard for risk adjustment models for adult critically ill patients.[40,41]

Primary and Secondary Cohorts for Study Aims

The eligible patients for both of the aims of this study and the sequential order in which exclusion criteria were applied for the cohorts are described in Figure 7. The overall objective of this study was to determine if an electronic prompt that uses SIRS and organ failure criteria, could detect sepsis. To test **Aim 1**, all eligible patients (sepsis and non-sepsis) were included, whereas to test **Aim 2**, only patients with sepsis were included. Patients without any evidence of the following variables were excluded: laboratory, vital sign, medication, and diagnosis related data. The mortality and sepsis models were trained on a randomly selected subset of 70% of the cohort and tested on the remaining 30%. The secondary cohort required excluding patients without sepsis.

This further reduced the cohort to only cases with sepsis. The discriminatory capacities of an increase in SOFA score by 2 or more points and meeting the sepsis prompt criteria for in-hospital mortality was completed using both the primary and secondary cohorts.

Figure 7. Eligible Population and Explanation of Cohorts



eRI, eICU Research Institute; ICU, intensive care unit; APACHE, acute physiology, age, chronic health evaluation; IVa version of APACHE algorithm

The designs and findings from several previous studies using the complete dataset were used to identify inclusion and exclusion criteria that would best support decision-making related to missingness and generalizability.[34,42-44] To reduce introduction of missingness, hospitals where no evidence of interfaces or documentation for laboratory, vital sign, medication, and diagnosis related data existed, were excluded (convenience

sample). This form of missingness is likely a limitation of information technology resources. Due to the complexity and size of the data set, multiple imputation versus complete case analysis with sensitivity analysis were not conducted.[45]

A limitation of complete case analysis is loss of power, reduced generalizability and potential bias due to unknown missing data mechanisms. However, due to the large number of patients and hospitals within the complete study dataset, this was not a limitation. Secondly, patients that show no activity in vital sign, laboratory, medication, and diagnosis tables are not missing data at random; they are likely missing because of a lack of interface between hospital information systems and the eCareManager system. For these reasons, a decision was made in advance to exclude hospitals with no activity in the tables associated with interfaced data.

Defining Mortality and Sepsis Outcomes

After selection for inclusion, records underwent a binary classification process to label them as sepsis or non-sepsis. Using Angus et al.[46] and Martin et al.[47] criteria, sepsis was defined as having either a severe sepsis or a septic shock diagnosis, or an infection diagnosis with an acute organ failure diagnosis (Table 6) recorded in the health record during a 24-hour period after the admission to the ICU. In-hospital mortality was defined as alive or deceased at hospital discharge. Hospitals that contributed to the eRI dataset participated in collection of APACHE data variables. The APACHE diagnosis was used for accurate classification of a patient's primary diagnosis.[48] The 448 unique APACHE diagnoses were categorized into groups using the ANZICS Adult Patient Database Data Dictionary for Software Programmers.[49]

Table 6. ICD-10 Codes Used to Define Sepsis

International Classification of Diseases 10th (ICD-10) revision codes and descriptions

Infection: *AIDS, HIV positive*: B20, Z21, R75; *Bacterial diseases:* A00-01, A03, A30-A31, A39, A42-A43, A48, A69, A75, A77-A79, B47, B95, B96, M60; *Bacterial zoonoses infections:* A02, A20-A28, A35; *Fungal infections:* B37-B44, B48; *Genito-urinary tract infections:* N15.1, N34, N39.0, N41, N70-N77; *Gastrointestinal infections: abscesses (appendicitis, cholecystitis, colitis, diverticulitis, gastroenteritis, hepatitis, peritonitis, perforation):* A04, A08, A09, B15-17, B19, K22.3, K35-K37, K57.01, K61, K63.0, K63.1, K65, K68, K75.0, K75.1, K81.0, K81.2, K82.2; *Infection related to device or procedure:* K68.11, T81.4XX, T80.212A, T84.5, T84.6, T84.7; *Intracranial/intraspinal infections:* A39, G06, G08; *Meningitis, myelitis, encephalitis, and encephalomyelitis:* G00-G04, G06, G08; *Pericarditis, endocarditis, myocarditis, thrombophlebitis:* I30-I33, I38-I41, I80; *Pneumonia, all forms:* J12-J18; *Sepsis, septicemia, bacteremia:* R65, A40, A41, R78.81; *Skin, bone, joint infections:* A46, A66, A67, L03, L04, L08, L88, L89, M00, M01, M72.6, M86; *Sexually transmitted diseases:* A50-A54; *Tuberculosis: all forms:* A15, A17-A19; *Upper/lower respiratory infections (sinusitis, pharyngitis, tonsillitis, laryngitis, tracheitis, bronchitis):* A37, A38, J01-J06, J20-J22, J44.0, J44.1, J47.0, J47.1, J85, J86, J98.5; *Viral infections:* B25, B27, B33, B97, J11
Organ Failure: *Altered mental status, obtundation, stupor, coma, delirium, encephalopathy, anoxic brain damage:* F05, G93.1, G93.40, R40, R41; *Heart Failure:* I50.2; *Hematologic: DIC, TTP, thrombocytopenia:* D65, D69.59, D96.6; *Hepatic failure:* K72, K76; *Renal failure:* N17; *Respiratory failure:* J21, J80, J81, J96 (excluding J96.1, J96.12), R09.02, R09.1, R09; *Shock states (without trauma), hypotension:* E86, I95.89, I95.9, R57, T81
Sepsis: *Septic shock:* R65.21; *Severe sepsis:* R65.20; *Toxic shock syndrome:* A48.32;

ICD 10, International Classification of Diseases 10th revisions; AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; OF, organ failure; DIC, disseminated intravascular coagulation; TTP, thrombotic thrombocytopenic purpura

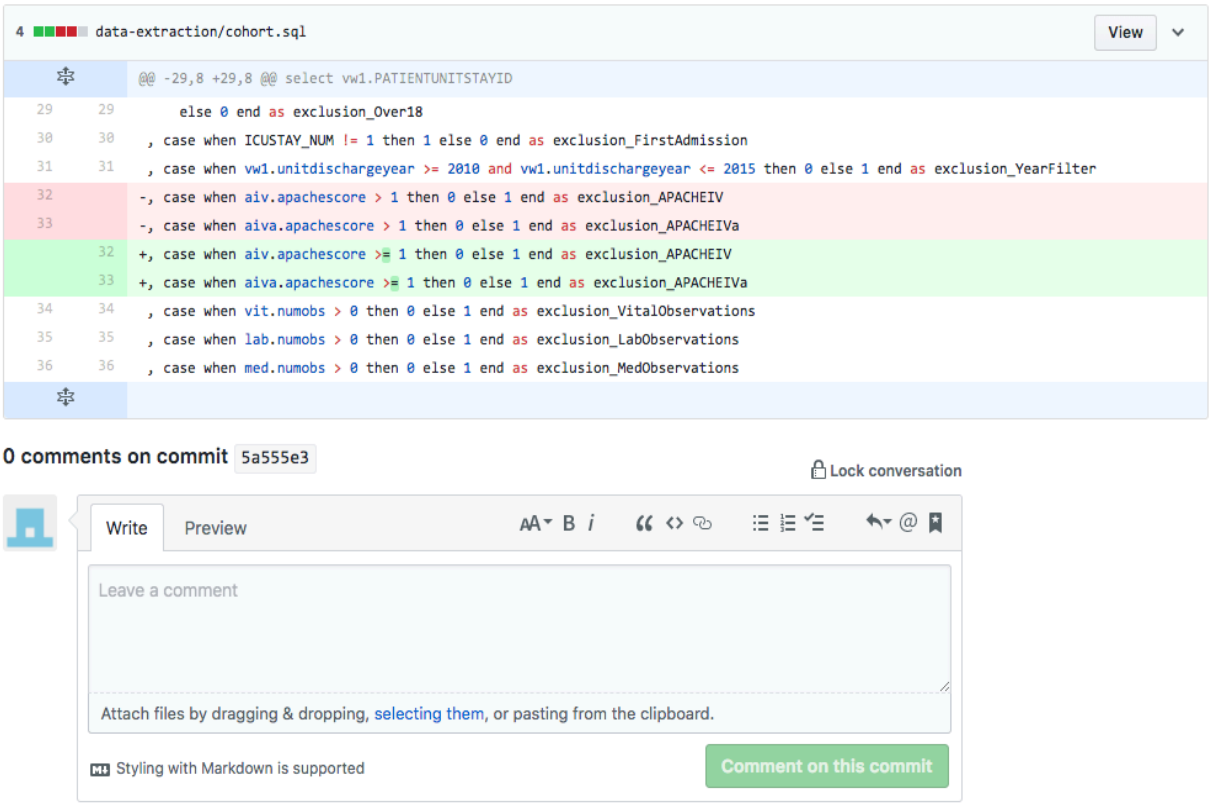
Data Extraction and Management

The researcher collaborated with the MIT Laboratory for Computational Physiology research team to extract both the subset and the comprehensive datasets from the eRI complete dataset. Members of the MIT research team were granted access to both the eICU-CRD and the eRI datasets to extract the dataset from various tables using Postgres Structured Query Language (SQL). The researcher determined which variables would be extracted and provided the data definitions for each variable. The SQL code was then published on a GitHub repository where access was granted to the researcher and the MIT research team members assigned to the study. In the same manner as the Medical Information Mart for Intensive Care (MIMIC) Code Repository, all code used in this study will be made available to the research community upon

publication in a peer reviewed journal.[50]

To ensure that independent and dependent variables were present and that the code and variable definitions were consistent, members of the MIT research team and the researcher were able to review in code as well as participate in conversations using comment boxes on a collaborative code hosting platform known as GitHub (Figure 8).[51] Github is designed to facilitate code sharing and information exchange.

Figure 8. Example of Data Extraction Code and Communication on GitHub



Assessment of Clinical Criteria for Baseline Models

Baseline models were developed to support risk-adjusted analysis for both sepsis and mortality. These models were constructed using all available information at the time of ICU admission and variables were consistent with baseline model variables used by

studies conducted by Raith et al. 2017 and Seymour et al. 2016.[32,33] Age, gender, body mass index (BMI), ethnicity, ICU admission source, physician specialty (critical care versus non-critical care), hospital size, hospital discharge year, and comorbid conditions (dialysis, aids, hepatic failure, diabetes, immunosuppression, leukemia, lymphoma, metastatic cancer, and selected cardiovascular and respiratory conditions), and use of thrombolytic therapy prior to ICU admission use were included in baseline models (adjusted analysis). Models were trained on a randomly selected subset of 70% of the primary and secondary cohorts and tested on the remaining 30%.

Complete patient information existed for most variables, however, chronic comorbidities were treated as 'documented evidence', and so patients with an unknown status were coded as 'No'. For all other variables with missing information (admission source, gender, diabetic status, ethnicity, height/weight, and hospital), an additional category for 'Other/Unknown' was created. Variables associated with each measurement system were managed in a similar manner. Organ failure/dysfunction variables were treated as 'documented evidence' so patients with an unknown status were coded as 'No'. Both validated and invalidated vital sign data (temperature, heart rate, blood pressure, respiratory rate) were available and were included in a hierarchical manner: 1) nurse charted value (validated); 2) invalidated data value (vital sign integrated data); 3) APACHE value (documented worst value according to APACHE IV logic).[48]

Determining Clinical Criteria for the SOFA Score

Data cutoff for organ failure variables for the SOFA scoring (Chapter 1, Table 1) were determined using recent studies.[9,32,39] Baseline SOFA scores were assigned for

three chronic health conditions using the same methodology as the Raith et al 2017.[32] This included patients with chronic respiratory impairment that received 2 baseline points, and those with chronic hepatic failure or chronic renal failure (defined as being on dialysis upon admission to the ICU) that received 4 baseline points. Baseline SOFA points were subtracted from the total SOFA score. A net score of 2 or more was considered a positive SOFA score.

Determining Clinical Criteria for the Sepsis Prompt

The sepsis alert uses a computer-based proprietary algorithm based on Fuzzy Logic applied to selected expanded SIRS criteria[52] and organ failure criteria.[53] Fuzzy Logic imitates the sense-making (reasoning) within computer-based algorithms based on degree of correctness versus more simplistic methods that use “absolutely true” or “absolutely false” decision trees.[54] Fuzzy Logic has been used in multiple other clinical settings such as glycemic control with the artificial pancreas[55], medical decision-making algorithms to control mechanical ventilation in respiratory distress syndrome[56], improving classification of cancer and biomarker mining,[57] and diagnostic algorithms for implantable cardioverter defibrillators.[58]

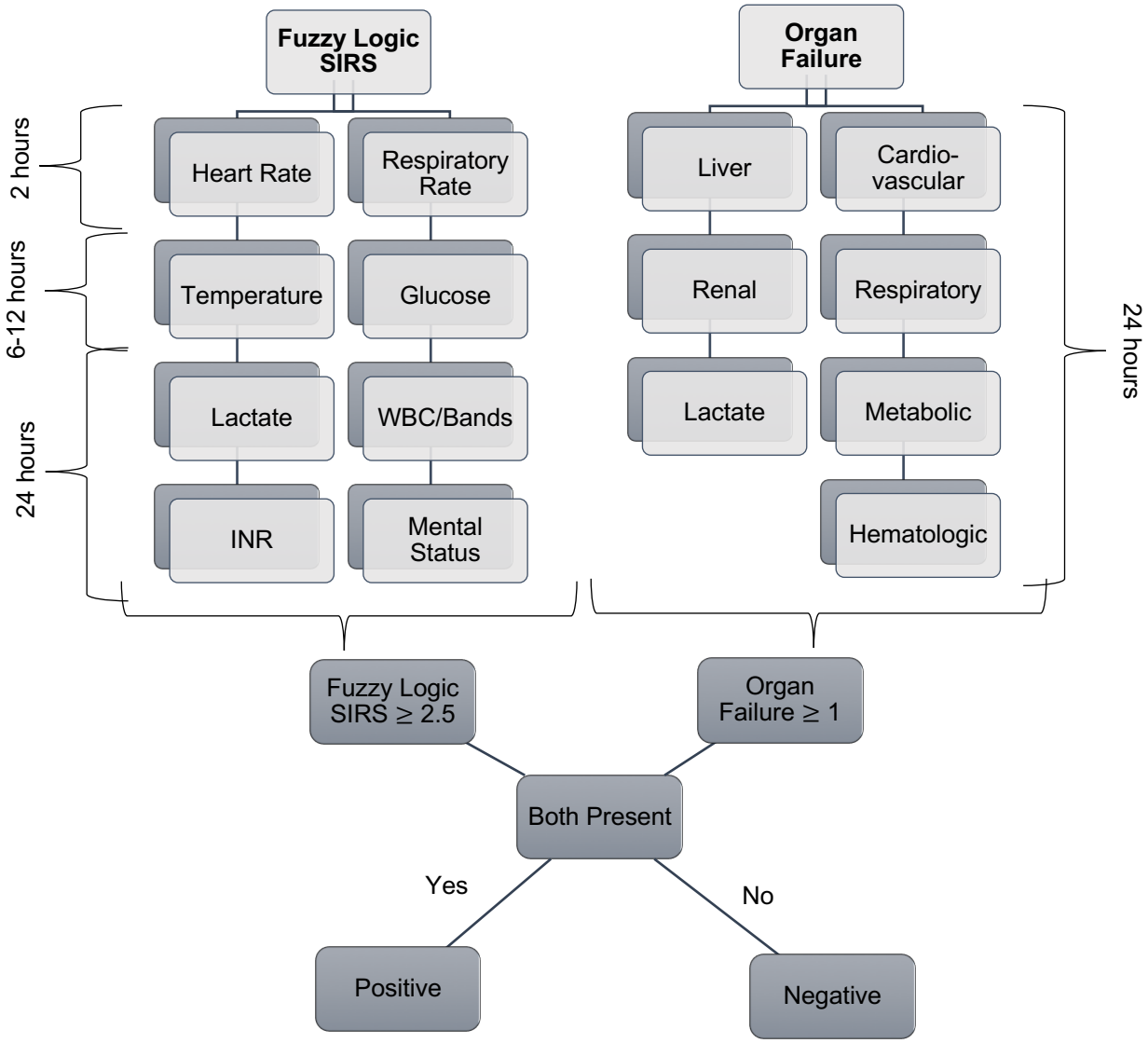
The sepsis alert was originally released in early 2007 with a software version upgrade. By June of 2007 the sepsis prompt was removed from the version upgrade but was remained running on a handful of sites through 2009. There were various upgrades of the software between the years of 2009-2012. Earlier versions had trigger offsets of 30 minutes while in later versions the offset was expanded to 2 hours. There were five different variables in the dataset related to the sepsis prompt but there was little documentation regarding which one of the five, or which combination of the five

variables, denoted a positive alert.

While the sepsis prompt algorithm was not codified, during the initial design of the prompt the inputs and outputs had been documented and it was known that the structure was additive. The relationship of the input to the output was not known. The MIT Computational Research Laboratory was able to decipher the rules related to the inputs and outputs by applying linear regression until a perfect fit was achieved. This determined the rules to apply related to the Fuzzy Logic SIRS and Organ Failure (OF) algorithms including which variables to include and how much weight each variable contributed.

Within the Fuzzy Logic SIRS algorithm, mental status and lactate were the only variables with dichotomous values (0 or 1), all other variables contributed to the score with a range of partial point values to a value of one based on how far they deviate from normal. The Organ Failure (OF) variables were values (0 or 1). If the Fuzzy Logic expanded SIRS algorithm did not meet the threshold of 2.5, international normalized ratio (INR) and lactate were used towards the score. Variables only contribute to the score once. Temperatures ≥ 46° Celsius (C) and ≤ 33°C were considered artifact and were coded as zero. INR and activated partial thromboplastin time (aPTT) values were ignored if warfarin and heparin medications were listed as active. Both Fuzzy Logic SIRS and OF scores of ≥ 2.5 or ≥ 1, respectively, had to be present for a positive score. Variables were reviewed from 2 hours to 24 hours. The sepsis prompt (Fuzzy Logic SIRS/OF) is a proprietary algorithm that is built with the TeleICU eCareManager System. The list of inputs in the Fuzzy Logic SIRS and OF corresponded with the list of inputs from the vendor for the sepsis prompt (Figure 9).

Figure 9. Fuzzy Logic Systemic Inflammatory Response Syndrome (SIRS) and Organ Failure Criteria



The Fuzzy Logic organ failure (OF) criteria were: 1) liver variables (any one): bilirubin greater than 4 milligrams per deciliter (mg/dL), alanine aminotransferase (ALT) greater than 80 IU/dL, aspartate aminotransferase (AST) greater than 80 IU/dL, serum albumin less than 3.5 grams per deciliter (gm/dL) or INR greater than 1.5; 2) cardiovascular variables (any one): systolic blood pressure (SBP) < 90 millimeters of

mercury (mm Hg) or mean arterial pressure (MAP) < 65 mm Hg or vasopressor medications; 3) renal variables (any one): urine output (UO) < 35 milliliters per hour (ml/hr) for 3 hr or increase in creatinine by 0.4 mg/dL from baseline; 4) respiratory variable (any one): arterial partial pressure of oxygen (PaO_2) less than 70 mm Hg on room air or ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2/FiO_2) < 200 when intubated; 5) metabolic variables (any one): potential of hydrogen (pH) < 7.30 (except with partial pressure of arterial carbon dioxide ($PaCO_2$) > 50 or a base deficit ≥ to 5.0 milliequivalents per liter (mEq/L); 6) hematologic variables (any two): platelets < 100,000 per microliter (microL), or INR > 1.5, or aPTT > 60 sec.

Statistical Analysis

All analyses were preformed using the R statistical program (https://www.r-project.org).[37] Descriptive statistics were used to discover and assess missingness of data. Discrimination tests are useful for measuring the performance of prognostic algorithms and measuring systems.[59] Power for discrimination for sepsis and in-hospital mortality was determined using area under the receiver operator curve (AUROC) for each measurement system. Delong's test[60] was used to compare the difference between AUROCs for each measurement system individually (unadjusted analysis) and in conjunction with baseline risk models (adjusted analysis). The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated for each measurement system.

Given that both of the outcomes were binary, logistic regression was used for the baseline models to understand the associations between baseline risk factors and the outcomes of sepsis and mortality. Variables used in the models were similar with

previous sepsis studies (Raith et al. and Seymour et al.). The primary and secondary cohorts were partitioned into training and test sets to provide a better estimate of the error rate in unseen data. The odds ratios were completed on the training sets and the discrimination tests (AUROC, sensitivity, specificity, PPV, and NPV) were analyzed on the test sets. AUROC describe the ability of the model or measurement system to correctly classify patients with versus without the condition or outcome. Analysis of AUROCs were used to determine discrimination of sepsis and prognostic accuracy of mortality in this study.

Results

Cohorts and Encounter Characteristics

Data pertaining to ICU admissions in 459 hospitals across the U.S. were recorded in the eRI Database for the period of 2010-2015. Following inclusion/exclusion criteria, the final cohort of 912,509 patients from 183 hospitals were identified for the primary aim. Training of the models were completed on the randomly selected subset of 70% of the primary cohort (638,757) with prediction and performance tested on the test cohort of 30% (273,752). For the secondary aim, the final cohort of patients with sepsis was 186,870 and the randomly selected training cohort consisted of 130,810 (70%) with a test cohort of 56,060 (30%). The training and testing cohorts were consistent in their clinical characteristics with respective to their associated complete cohorts. These consistencies along with differences between the primary and secondary cohort are explained below.

Characteristics of Primary Cohort

Patients in the primary cohort (912,509) were randomly selected for the training

cohort (638,757; 70%), and the test cohort (273,752; 30%). Patient and hospital demographic level data with or without sepsis and survivors versus non-survivor are described in Table 7 and Table 8, respectively. Sepsis was present in 20.5%, 20.4%, and 20.5% respectively, of the populations in each of the primary cohorts with expired patients comprising 9.4% in each cohort (Table 7). Each comorbid condition was compared to patients without the condition. For example, in the primary cohort (All) there were 22,883 (3.2% of all non-sepsis patients) and 7,751 (4.1% of all sepsis patients) who were receiving renal dialysis prior to ICU admission (Table 7). Dialysis patients in each group were compared to non-dialysis patients to determine if differences were statistically significant.

Table 7. Comparison of Patient and Hospital Level Demographic, Comorbid Conditions, Measurement Systems, Illness Severity, Outcome, and Diagnostic Data among Critical Ill Patients in eRI Database in the Primary Cohorts for Sepsis Outcome

Primary Cohort for Sepsis Outcome

	ALL		TRAIN		TEST	
Level	**Non-Sepsis**	**Sepsis**	**Non-Sepsis**	**Sepsis**	**Non-Sepsis**	**Sepsis**
No.	725639	186870	508143	130614	217496	56256
Age, mean (SD)	62.2 (17.3)	65.7 (16.2)	62.2 (17.3)	65.7 (16.2)	62.2 (17.3)	65.7 (16.3)
Male, No. (%)	395985 (54.6)	94548 (50.6)	277322 (54.6)	66309 (50.8)	118663 (54.6)	28239 (50.2)
Ethnicity, No. (%)						
Caucasian	553821(76.3)	141546 (75.7)	387776 (76.3)	98903 (75.7)	166045 (76.3)	42643 (75.8)
African American	84902 (11.7)	20390 (10.9)	59296 (11.7)	14267 (10.9)	25606 (11.8)	6123 (10.9)
Hispanic	30536 (4.2)	10857 (5.8)	21511 (4.2)	7597 (5.8)	9025 (4.1)	3260 (5.8)
Asian	9221 (1.3)	2474 (1.3)	6436 (1.3)	1726 (1.3)	2785 (1.3)	748 (1.3)
Native American	5248 (0.7)	1517 (0.8)	3690 (0.7)	1063 (0.8)	1558 (0.7)	454 (0.8)
Other	41911 (5.8)	10086 (5.4)	29434 (5.8)	7058 (5.4)	12477 (5.7)	3028 (5.4)
Body Mass Index, No. (%)						
0-18.5	31764 (4.4)	12245 (6.6)	22018 (4.3)	8543 (6.5)	9746 (4.5)	3702 (6.6)
18.5-25	202170 (27.9)	55468 (29.7)	142000 (27.9)	38763 (29.7)	60170 (27.7)	16705 (29.7)
25-35	338933 (46.7)	77589 (41.5)	237064 (46.7)	54246 (41.5)	101869 (46.8)	23343 (41.5)
> 35	125888 (17.3)	36166 (19.4)	88250 (17.4)	25347 (19.4)	37638 (17.3)	10819 (19.2)
Other	26884 (3.7)	5402 (2.9)	18811 (3.7)	3715 (2.8)	8073 (3.7)	1687 (3.0)
ICU Admission Source (%)						
Floor	107913 (14.9)	46723 (25.0)	75484 (14.9)	32718 (25.0)	32429 (14.9)	14005 (24.9)
OR/Proc	166553 (23.0)	9890 (5.3)	116616 (22.9)	6896 (5.3)	49937 (23.0)	2994 (5.3)
Direct Admit	80562 (11.1)	17476 (9.4)	56281 (11.1)	12286 (9.4)	24281 (11.2)	5190 (9.2)
ED	351730 (48.5)	104745 (56.1)	246638 (48.5)	73163 (56.0)	105092 (48.3)	31582 (56.1)
Other	5693 (0.8)	2070 (1.1)	3971 (0.8)	1432 (1.1)	1722 (0.8)	638 (1.1)
SDU	13188 (1.8)	5966 (3.2)	9153 (1.8)	4119 (3.2)	4035 (1.9)	1847 (3.3)
Physician Specialty No %						
Crit. Care	194821 (26.8)	72415 (38.8)	136403 (26.8)	50538 (38.7)	58418 (26.9)	21877 (38.9)
Other	530818 (73.2)	114455 (61.2)	371740 (73.2)	80076 (61.3)	159078 (73.1)	34379 (61.1)
Hospital Discharge Year No. (%)						
2010	88588 (12.2)	22942 (12.3)	62141 (12.2)	16041 (12.3)	26447 (12.2)	6901 (12.3)
2011	95007 (13.1)	27029 (14.5)	66311 (13.0)	18911 (14.5)	28696 (13.2)	8118 (14.4)
2012	119084 (16.4)	30085 (16.1)	83377 (16.4)	20982 (16.1)	35707 (16.4)	9103 (16.2)
2013	133576 (18.4)	33722 (18.0)	93463 (18.4)	23573 (18.0)	40113 (18.4)	10149 (18.0)
2014	142947 (19.7)	35240 (18.9)	99984 (19.7)	24652 (18.9)	42963 (19.8)	10588 (18.8)
2015-2016	146437 (20.2)	37852 (20.3)	102867 (20.2)	26455 (20.3)	43570 (20.0)	11397 (20.3)
Teaching Hospital No. (%)						
Unknown	30704 (4.2)	7211 (3.9)	21505 (4.2)	4989 (3.8)	9199 (4.2)	2222 (3.9)
No	476998 (65.7)	121044 (64.8)	333954 (65.7)	84817 (64.9)	143044 (65.8)	36227 (64.4)
Yes	217937 (30.0)	58615 (31.4)	152684 (30.0)	40808 (31.2)	65253 (30.0)	17807 (31.7)
Hospital Size No. (%)						
Unknown	58989 (8.1)	13689 (7.3)	41273 (8.1)	9525 (7.3)	17716 (8.1)	4164 (7.4)
<100	26993 (3.7)	9779 (5.2)	18836 (3.7)	6858 (5.3)	8157 (3.8)	2921 (5.2)
100-249	163833 (22.6)	43284 (23.2)	114834 (22.6)	30264 (23.2)	48999 (22.5)	13020 (23.1)
250-500	131717 (18.2)	35396 (18.9)	92109 (18.1)	24798 (19.0)	39608 (18.2)	10598 (18.8)
>500	344107 (47.4)	84722 (45.3)	241091 (47.4)	59169 (45.3)	103016 (47.4)	25553 (45.4)
US Region No. (%)						
Midwest	313401 (43.2)	69674 (37.3)	219455 (43.2)	48714 (37.3)	93946 (43.2)	20960 (37.3)
Northeast	46163 (6.4)	27360 (14.6)	32453 (6.4)	19065 (14.6)	13710 (6.3)	8295 (14.7)
South	229437 (31.6)	54550 (29.2)	160617 (31.6)	38089 (29.2)	68820 (31.6)	16461 (29.3)

West	90846 (12.5)	25937 (13.9)	63645 (12.5)	18269 (14.0)	27201 (12.5)	7668 (13.6)
Unknown	45792 (6.3)	9349 (5.0)	31973 (6.3)	6477 (5.0)	13819 (6.4)	2872 (5.1)
Comorbid Conditions No. (%)						
Dialysis	22883 (3.2)	7751 (4.1)	15933 (3.1)	5443 (4.2)	6950 (3.2)	2308 (4.1)
AIDS	418 (0.1)	472 (0.3)	313 (0.1)	314 (0.2)	105 (0.0)	158 (0.3)
Hepatic Failure	14231 (2.0)	4834 (2.6)	9980 (2.0)	3404 (2.6)	4251 (2.0)	1430 (2.5)
Diabetes	159066 (21.9)*	40750 (21.8)*	111538 (22.0)*	28446 (21.8)*	47528 (21.9)*	12304 (21.9)*
Immunosuppression	13906 (1.9)	7475 (4.0)	9757 (1.9)	5258 (4.0)	4149 (1.9)	2217 (3.9)
Leukemia	4157 (0.6)	2427 (1.3)	2967 (0.6)	1679 (1.3)	1190 (0.5)	748 (1.3)
Lymphoma	2413 (0.3)	1201 (0.6)	1727 (0.3)	857 (0.7)	686 (0.3)	344 (0.6)
Metastatic CA	12984 (1.8)	4523 (2.4)	9040 (1.8)	3161 (2.4)	3944 (1.8)	1362 (2.4)
Respiratory	156269 (21.5)	63588 (34.0)	109598 (21.6)	44515 (34.1)	46671 (21.5)	19073 (33.9)
Cardiovascular	161435 (22.2)	45771 (24.5)	113251 (22.3)	32064 (24.5)	48184 (22.2)	13707 (24.4)
Admitted with Myocardial Infarction with/without Thrombolytics						
With	16351 (2.3)	384 (0.2)	11479 (2.3)	288 (0.2)	4872 (2.2)	96 (0.2)
Without	709288 (97.7)	186486 (99.8)	496664 (97.7)	130326 (99.8)	212624 (97.8)	56160 (99.8)
SOFA Positive No. (%)						
	467451 (64.4)	160765 (86.0)	327426 (64.4)	112309 (86.0)	140025 (64.4)	48456 (86.1)
Fuzzy Logic Positive No. (%)						
	350438 (48.3)	152070 (81.4)	245500 (48.3)	106186 (81.3)	104938 (48.2)	45884 (81.6)
APACHE IVa (mean (SD))						
	52.0 (24.0)	69.5 (28.0)	52.0 (24.0)	69.5 (28.0)	51.9 (23.9)	69.5 (28.1)
Hospital Mortality No. (%)						
Survived	674037 (92.9)	152253 (81.5)	471957 (92.9)	106446 (81.5)	202080 (92.9)	45807 (81.4)
Expired	51602 (7.1)	34617 (18.5)	36186 (7.1)	24168 (18.5)	15416 (7.1)	10449 (18.6)
ICU Mortality No. (%)						
Survived	689161 (95.0)	161938 (86.7)	482543 (95.0)	113179 (86.7)	206618 (95.0)	48759 (86.7)
Expired	36436 (5.0)	24921 (13.3)	25573 (5.0)	17429 (13.3)	10863 (5.0)	7492(13.3)
Hospital LOS (mean (SD))						
	7.0 (8.7)	10.3 (12.2)	7.0 (8.4)	10.3 (11.4)	7.1 (9.34)	10.4 (13.9)
ICU LOS (mean (SD))						
	2.8 (3.8)	4.2 (5.1)	2.8 (3.7)	4.2 (5.1)	2.8 (3.78)	4.2 (5.20)
APACHE Group No. (%)						
Cardiovascular	275329 (37.9)	20019 (10.7)	193044 (38.0)	13941 (10.7)	82285 (37.8)	6078 (10.8)
GI	83127 (11.5)	11546 (6.2)	58099 (11.4)	8030 (6.1)	25028 (11.5)	3516 (6.2)
Gynecological	2293 (0.3)	117 (0.1)	1611 (0.3)	84 (0.1)	682 (0.3)	33 (0.1)
Hematologic	5761 (0.8)	1058 (0.6)	3982 (0.8)	751 (0.6)	1779 (0.8)	307 (0.5)
Metabolic	68815 (9.5)	6050 (3.2)	48203 (9.5)	4201 (3.2)	20612 (9.5)	1849 (3.3)
MusculoSkel/Skin	9185 (1.3)	2270 (1.2)	6406 (1.3)	1591 (1.2)	2779 (1.3)	679 (1.2)
Neuro	113662 (15.7)	9248 (4.9)	79614 (15.7)	6459 (4.9)	34048 (15.7)	2789 (5.0)
Renal/GU	17170 (2.4)	4955 (2.7)	12081 (2.4)	3468 (2.7)	5089 (2.3)	1487 (2.6)
Respiratory	89707 (12.4)	46348 (24.8)	62754 (12.3)	32443 (24.8)	26953 (12.4)	13905 (24.7)
Sepsis	14033 (1.9)	83565 (44.7)	9783 (1.9)	58478 (44.8)	4250 (2.0)	25087 (44.6)
Trauma	39475 (5.4)	1020 (0.5)	27664 (5.4)	706 (0.5)	11811 (5.4)	314 (0.6)
Undefined	7082 (1.0)	674 (0.4)	4902 (1.0)	462 (0.4)	2180 (1.0)	212 (0.4)

eRI, eICU Research Institute; No., number; SD, standard deviation; OR, operating room; ED, emergency department, SDU, step-down unit; US, United States; AIDS, acquired immune deficiency syndrome; CA, cancer; SOFA, sepsis-related organ failure assessment; APACHE, acute physiology age, chronic health, evaluation; ICU, intensive care unit; LOS, length of stay; GI, gastrointestinal; MusculoSkel, musculoskeletal; GU, genitourinary; All p-values were significant at the < 0.001 with the exception of values denoted with *. Each comorbid condition was compared to patients without the condition.

The mean age was 62.2 years of age with a standard deviation (SD) of 17.3 for patients without sepsis versus and 66.5 (SD 14.9 - 15) years for patients with sepsis. The mean age for survivors versus expired patients was 62.2 (SD 17.2) and 69.5 - 69.6 years (SD 14.9-15.0), respectively, in all three of the primary cohorts. Mortality (Table 8) was 9.4%, 9.4% and 9.5% respectively, in each of the primary cohorts. Within ethnic groups, Caucasians comprised 76% of all sepsis cases and 76.6-76.9% of all expired patients in each cohort, followed by African Americans (sepsis 10.9% and expired patients 10.5-10.7%), Hispanics (sepsis 5.8% and expired patients (4.6-4.7%), patients in the other/unknown category (5.4% and 5.6–5.9%) respectively), Asians (1.3% and 1.4% respectively), and Native Americans (0.8% and 0.7–0.8% respectively).

More patients admitted to the ICUs had a BMI between 25-35 (416,522; 46.2%); this was consistent in the training cohort (45.6%) and in the test cohort (45.7%). The following results were consistent in each of the primary cohorts: 50% of the ICU admissions came from the emergency department (ED) with 29% admitted to a specialty service designated as critical care, 47% were at hospitals with more than 500 beds, 30% were located in teaching hospitals, and 42% were located in the Midwest region of the U.S. More patients were discharge from ICUs when compared with the subsequent year. The growth in the number of eRI consortium hospitals as well as increased demand for ICU level of care may have contributed to these increases.

The following comorbid conditions were present: 24.1% with chronic respiratory issues, 22.7% with cardiovascular conditions, 21.9% with diabetes, 3.4% on dialysis, 2.3% immunosuppression, 2.1% hepatic failure, 1.9% metastatic cancer, or < 1% (leukemia, lymphoma, and AIDS) in expired patients 90.4 (SD 31.6–31.8) versus 51.9

(SD 22.2) for survivors and 69.5 (SD 28.0-28.1) for patients with sepsis versus those without sepsis 51.9-52.0 (SD 23.9-24.0). Average APACHE scores for survivors versus expired patients were consistent across the primary cohorts 51.9 (SD 22.2) and 90.4 (SD 31.6-31.8) respectively. Average APACHE scores for non-sepsis versus sepsis were consistent across the primary cohorts 51.9-52.0 (SD 24.0) and 69.5 (SD 28.0) respectively. Hospital LOS differences for survivors (7.7 days; SD 8.8-10.6) versus expired patients (8.0 days; SD 10.3-12.3) were smaller than the ICU LOS differences between survivors (2.9 days; SD 3.8-3.9) versus expired patients (4.5 days; SD 5.8-5.9). Hospital and ICU length of stay (LOS) was higher in patients with sepsis (10.3-10.4 days; SD 11.4-13.9) and (4.2 days; SD 5.1-5.2), respectively versus non-sepsis in each of the primary cohorts (7.0-7.1 days SD 8.4-9.3) and (2.8 days; SD 3.7-3.8) respectively (Table 7 and Table 8).

Table 8. Comparison of Patient and Hospital Level Demographic, Comorbid Conditions, Measurement Systems, Illness Severity, Outcome, and Diagnostic Data among Critical Ill Patients in eRI Database in the Primary Cohorts for Mortality Outcome

Primary Cohort for Mortality Outcome

	ALL		TRAIN		TEST	
Level	**Survived**	**Expired**	**Survived**	**Expired**	**Survived**	**Expired**
No.	826290	86219	578403	60354	247887	25865
Age, mean (SD)	62.3 (17.2)	69.5 (15.0)	62.3 (17.2)	69.5 (15.0)	62.2 (17.2)	69.6 (14.9)
Male, No. (%)	444766 (53.8)	45767 (53.1)	311478 (53.9)	32153 (53.3)	133288 (53.8)	13614 (52.6)
Ethnicity, No. (%)						
Caucasian	629231 (76.2)	66136 (76.7)	440442 (76.1)	46237 (76.6)	188789 (76.2)	19899 (76.9)
African American	96168 (11.6)	9124 (10.6)	67218 (11.6)	6345 (10.5)	28950 (11.7)	2779 (10.7)
Hispanic	37359 (4.5)	4034 (4.7)	26262 (4.5)	2846 (4.7)	11097 (4.5)	1188 (4.6)
Asian	10468 (1.3)	1227 (1.4)	7297 (1.3)	865 (1.4)	3171 (1.3)	362 (1.4)
Native American	6085 (0.7)	680 (0.8)	4251 (0.7)	502 (0.8)	1834 (0.7)	178 (0.7)
Other	46979 (5.7)	5018 (5.8)	32933 (5.7)	3559 (5.9)	14046 (5.7)	1459 (5.6)
Body Mass Index, No. (%)						
0-18.5	37672 (4.6)	6337 (7.3)	26136 (4.5)	4425 (7.3)	11536 (4.7)	1912 (7.4)
18.5-25	230063 (27.8)	27575 (32.0)	161487 (27.9)	19276 (31.9)	68576 (27.7)	8299 (32.1)
25-35	381728 (46.2)	34794 (40.4)	266965 (46.2)	24345 (40.3)	114763 (46.3)	10449 (40.4)
> 35	148643 (18.0)	13411 (15.6)	104144 (18.0)	9453 (15.7)	44499 (18.0)	3958 (15.3)
Other	28184 (3.4)	4102 (4.8)	19671 (3.4)	2855 (4.7)	8513 (3.4)	1247 (4.8)
ICU Admission Source (%)						
Floor	131068 (15.9)	23568 (27.3)	91755 (15.9)	16447 (27.3)	39313 (15.9)	7121 (27.5)
OR/Procedural	169828 (20.6)	6615 (7.7)	118866 (20.6)	4646 (7.7)	50962 (20.6)	1969 (7.6)
Direct Admit	87805 (10.6)	10233 (11.9)	61389 (10.6)	7178 (11.9)	26416 (10.7)	3055 (11.8)
ED	415282 (50.3)	41193 (47.8)	290878 (50.3)	28923 (47.9)	124404 (50.2)	12270 (47.4)
Other	6616 (0.8)	1147 (1.3)	4621 (0.8)	782 (1.3)	1995 (0.8)	365 (1.4)
SDU	15691 (1.9)	3463 (4.0)	10894 (1.9)	2378 (3.9)	4797 (1.9)	1085 (4.2)
Physician Specialty No %						
Critical Care	235008 (28.4)	32228 (37.4)	164468 (28.4)	22473 (37.2)	70540 (28.5)	9755 (37.7)
Other	591282 (71.6)	53991 (62.6)	413935 (71.6)	37881 (62.8)	177347 (71.5)	16110 (62.3)
Hospital Discharge Year No. (%)						
2010	100104 (12.1)	11426 (13.3)	70122 (12.1)	8060 (13.4)	29982 (12.1)	3366 (13.0)
2011	109790 (13.3)	12246 (14.2)	76656 (13.3)	8566 (14.2)	33134 (13.4)	3680 (14.2)
2012	134912 (16.3)	14257 (16.5)	94361 (16.3)	9998 (16.6)	40551 (16.4)	4259 (16.5)
2013	151717 (18.4)	15581 (18.1)	106208 (18.4)	10828 (17.9)	45509 (18.4)	4753 (18.4)
2014	162398 (19.7)	15789 (18.3)	113555 (19.6)	11081 (18.4)	48843 (19.7)	4708 (18.2)
2015-2016	167369 (20.3)	16920 (19.6)	117501 (20.3)	11821 (19.6)	49868 (20.1)	5099 (19.7)
Teaching Hospital No. (%)						
Unknown	34473 (4.2)	3442 (4.0)	24103 (4.2)	2391 (4.0)	10370 (4.2)	1051 (4.1)
No	543349 (65.8)	54693 (63.4)	380455 (65.8)	38316 (63.5)	162894 (65.7)	16377 (63.3)
Yes	248468 (30.1)	28084 (32.6)	173845 (30.1)	19647 (32.6)	74623 (30.1)	8437 (32.6)
Hospital Size No. (%)						
Unknown	66107 (8.0)	6571 (7.6)	46212 (8.0)	4586 (7.6)	19895 (8.0)	1985 (7.7)
<100	34747 (4.2)	2025 (2.3)	24283 (4.2)	1411 (2.3)	10464 (4.2)	614 (2.4)
100-249	190062 (23.0)	17055 (19.8)	133114 (23.0)	11984 (19.9)	56948 (23.0)	5071 (19.6)
250-500	151081 (18.3)	16032 (18.6)	105734 (18.3)	11173 (18.5)	45347 (18.3)	4859 (18.8)
>500	384293 (46.5)	44536 (51.7)	269060 (46.5)	31200 (51.7)	115233 (46.5)	13336 (51.6)
US Region No. (%)						
Midwest	352325 (42.6)	30750 (35.7)	246590 (42.6)	21579 (35.8)	105735 (42.7)	9171 (35.5)
Northeast	63922 (7.7)	9601 (11.1)	44879 (7.8)	6639 (11.0)	19043 (7.7)	2962 (11.5)
South	256647 (31.1)	27340 (31.7)	179575 (31.0)	19131 (31.7)	77072 (31.1)	8209 (31.7)

West	102962 (12.5)	13821 (16.0)	72176 (12.5)	9738 (16.1)	30786 (12.4)	4083 (15.8)
Unknown	50434 (6.1)	4707 (5.5)	35183 (6.1)	3267 (5.4)	15251 (6.2)	1440 (5.6)
Comorbid Conditions No. (%)						
Dialysis	26798 (3.2)	3836 (4.4)	18717 (3.2)	2659 (4.4)	8081 (3.3)	1177 (4.6)
AIDS	766 (0.1)	124 (0.1)	536 (0.1)	91 (0.2)	230 (0.1)*	33 (0.1)*
Hepatic Failure	15833 (1.9)	3232 (3.7)	11109 (1.9)	2275 (3.8)	4724 (1.9)	957 (3.7)
Diabetes	183788 (22.2)	16028 (18.6)	128765 (22.3)	11219 (18.6)	55023 (22.2)*	4809 (18.6)*
Immunosuppression	17783 (2.2)	3598 (4.2)	12487 (2.2)	2528 (4.2)	5296 (2.1)	1070 (4.1)
Leukemia	5313 (0.6)	1271 (1.5)	3759 (0.6)	887 (1.5)	1554 (0.6)	384 (1.5)
Lymphoma	3042 (0.4)	572 (0.7)	2179 (0.4)	405 (0.7)	863 (0.3)	167 (0.6)
Metastatic CA	14269 (1.7)	3238 (3.8)	9917 (1.7)	2284 (3.8)	4352 (1.8)	954 (3.7)
Respiratory	195414 (23.6)	24443 (28.3)	136974 (23.7)	17139 (28.4)	58440 (23.6)	7304 (28.2)
Cardiovascular	183305 (22.2)	23901 (27.7)	128526 (22.2)	16789 (27.8)	54779 (22.1)	7112 (27.5)
Admitted with Myocardial Infarction with/without Thrombolytics						
With	15352 (1.9)	1383 (1.6)	10788 (1.9)	979 (1.6)	4564 (1.8)*	404 (1.6)*
Without	810938 (98.1)	84836 (98.4)	567615 (98.1)	59375 (98.4)	243323 (98.2)*	25461 (98.4)*
SOFA Positive No. (%)						
	546746 (66.2)	81470 (94.5)	382666 (66.2)	57069 (94.6)	164080 (66.2)	24401 (94.3)
Fuzzy Logic Positive No. (%)						
	427824 (51.8)	74684 (86.6)	299375 (51.8)	52311 (86.7)	128449 (51.8)	22373 (86.5)
APACHE IVa (mean (SD))						
	51.9 (22.2)	90.4 (31.8)	51.9 (22.2)	90.4 (31.8)	51.9 (22.2)	90.4 (31.6)
ICU Mortality No. (%)						
Survived	826246 (100.0)	24853 (28.8)	578376 (100.0)	17346 (28.7)	247870 (100.0)	7507 (29.0)
Expired	NA	61357 (71.2)	NA	43002 (71.2)	NA	18355 (71.0)
Hospital LOS (mean (SD))						
	7.7 (9.4)	8.0 (11.8)	7.7 (8.8)	8.0 (12.4)	7.7 (10.6)*	8.0 (10.3)*
ICU LOS (mean (SD))						
	2.9 (3.9)	4.5 (5.84)	2.9 (3.8)	4.5 (5.8)	2.9 (3.9)	4.5 (5.9)
Sepsis No. (%)						
Non-Sepsis	674037 (81.6)	51602 (59.8)	471957 (81.6)	36186 (60.0)	202080 (81.5)	15416 (59.6)
Sepsis	152253 (18.4)	34617 (40.2)	106446 (18.4)	24168 (40.0)	45807 (18.5)	10449 (40.4)
APACHE Group No. (%)						
Cardiovascular	270546 (32.7)	24802 (28.8)	189581 (32.8)	17404 (28.8)	80965 (32.7)	7398 (28.6)
GI	87106 (10.5)	7567 (8.8)	60841 (10.5)	5288 (8.8)	26265 (10.6)	2279 (8.8)
Gynecological	2381 (0.3)	29 (0.0)	1675 (0.3)	20 (0.0)	706 (0.3)	9 (0.0)
Hematologic	6220 (0.8)	599 (0.7)	4305 (0.7)	428 (0.7)	1915 (0.8)	171 (0.7)
Metabolic	73481 (8.9)	1384 (1.6)	51452 (8.9)	952 (1.6)	22029 (8.9)	432 (1.7)
MusculoSkel/Skin	10969 (1.3)	486 (0.6)	7637 (1.3)	360 (0.6)	3332 (1.3)	126 (0.5)
Neurologic	111809 (13.5)	11101 (12.9)	78309 (13.5)	7764 (12.9)	33500 (13.5)	3337 (12.9)
Renal/GU	20549 (2.5)	1576 (1.8)	14448 (2.5)	1101 (1.8)	6101 (2.5)	475 (1.8)
Respiratory	118873 (14.4)	17182 (19.9)	83157 (14.4)	12040 (19.9)	35716 (14.4)	5142 (19.9)
Sepsis	79999 (9.7)	17599 (20.4)	55966 (9.7)	12295 (20.4)	24033 (9.7)	5304 (20.5)
Trauma	37405 (4.5)	3090 (3.6)	26209 (4.5)	2161 (3.6)	11196 (4.5)	929 (3.6)
Undefined	6952 (0.8)	804 (0.9)	4823 (0.8)	541 (0.9)	2129 (0.9)	263 (1.0)

eRI, eICU Research Institute; No., number; SD, standard deviation; OR, operating room; ED, emergency department, SDU, step-down unit; US, United States; AIDS, acquired immune deficiency syndrome; CA, cancer; SOFA, sepsis-related organ failure assessment; APACHE, acute physiology age, chronic health, evaluation; ICU, intensive care unit; LOS, length of stay; GI, gastrointestinal; MusculoSkel, musculoskeletal; GU, genitourinary; All p-values were significant at the < 0.001 with the exception of values denoted with *. Each comorbid condition was compared to patients without the condition.

A positive SOFA score was present in 69% of the patients in each cohort, 94-95% of expired patients and 86% of sepsis patients. Fuzzy Logic SIRS/OF criteria were met in 55% of patients with 87% of expired patients and 81-82% of sepsis patients meeting criteria. Thirty-two percent had an APACHE diagnosis from the cardiovascular group followed by 15% with respiratory diagnoses, 13.5% with neurological disorders, 11% with sepsis, and 10% with gastrointestinal diagnoses. Of patients with sepsis, 45% had an APACHE sepsis diagnosis followed by respiratory (25%) and cardiovascular (11%) diagnoses. Any patient with an ICU admission source of operating room or procedural area could not have a sepsis diagnosis due to APACHE rules.[48]

Characteristics of the Secondary Cohort

Patients with sepsis (186,870) were in the secondary cohort and were randomly split into the training cohort (130,810; 70%), and the test cohort (56,060; 30%) and experienced a mortality rate of 18.5% in each cohort. Patient and hospital demographic level data and the comorbid conditions, the measurement systems of interest in this study, severity of illness scores, outcomes (mortality, sepsis, length of stay in days) and APACHE admission diagnostic data for mortality are described in Table 9 respectively. The mean ages were higher for patients in the secondary cohort (sepsis only cases) with survivors' ages being 64.7-64.8 years (SD 16.3-16.4) and expired patients 70.0-70.1 (SD 14.5-14.6). Just as with the primary cohort, Caucasians represented the highest number of ethnic groups (75.8%) followed by African Americans, Hispanic, Asian, Native American, and all other groups.

Table 9. Comparison of Patient and Hospital Level Demographic, Comorbid Conditions, Measurement Systems, Illness Severity, Outcome, and Diagnostic Data among Critical Ill Patients in eRI Database in the Secondary Cohorts for Mortality Outcome

Secondary Cohort for Mortality Outcome

	ALL		TRAIN		TEST	
Level	**Survived**	**Expired**	**Survived**	**Expired**	**Survived**	**Expired**
No.	152253	34617	106578	24232	45675	10385
Age, mean (SD)	64.7 (16.4)	70.0 (14.6)	64.7 (16.4)	70.0 (14.6)	64.81 (16.30)	70.07 (14.53)
Male, No. (%)	76719 (50.4)	17829 (51.5)	53769 (50.5)*	12424 (51.3)*	22950 (50.2)*	5405 (52.0)*
Ethnicity, No. (%)						
Caucasian	115132 (75.6)	26414 (76.3)	80530 (75.6)	18535 (76.5)	34602 (75.8)	7879 (75.9)*
African American	16920 (11.1)	3470 (10.0)	11914 (11.2)	2416 (10.0)	5006 (11.0)	1054 (10.1)
Hispanic	8765 (5.8)	2092 (6.0)	6137 (5.8)	1450 (6.0)	2628 (5.8)	642 (6.2)
Asian	1976 (1.3)	498 (1.4)	1392 (1.3)	329 (1.4)	584 (1.3)	169 (1.6)
Native American	1209 (0.8)	308 (0.9)	836 (0.8)	222 (0.9)	373 (0.8)	86 (0.8)
Other	8251 (5.4)	1835 (5.3)	5769 (5.4)	1280 (5.3)	2482 (5.4)	555 (5.3)
Body Mass Index, No. (%)						
0-18.5	9272 (6.1)	2973 (8.6)	6508 (6.1)	2047 (8.4)	2764 (6.1)	926 (8.9)
18.5-25	44152 (29.0)	11316 (32.7)	31003 (29.1)	7903 (32.6)	13149 (28.8)	3413 (32.9)
25-35	64045 (42.1)	13544 (39.1)	44797 (42.0)	9471 (39.1)	19248 (42.1)	4073 (39.2)
> 35	30721 (20.2)	5445 (15.7)	21405 (20.1)	3873 (16.0)	9316 (20.4)	1572 (15.1)
Other	4063 (2.7)	1339 (3.9)	2865 (2.7)	938 (3.9)	1198 (2.6)	401 (3.9)
ICU Admission Source (%)						
Floor	35751 (23.5)	10972 (31.7)	25010 (23.5)	7793 (32.2)	10741 (23.5)	3179 (30.6)
OR/Procedural	8538 (5.6)	1352 (3.9)	5954 (5.6)	945 (3.9)	2584 (5.7)	407 (3.9)
Direct Admit	13854 (9.1)	3622 (10.5)	9666 (9.1)	2532 (10.4)	4188 (9.2)	1090 (10.5)
ED	88208 (57.9)	16537 (47.8)	61768 (58.0)	11468 (47.3)	26440 (57.9)	5069 (48.8)
Other	1577 (1.0)	493 (1.4)	1134 (1.1)	351 (1.4)	443 (1.0)	142 (1.4)
SDU	4325 (2.8)	1641 (4.7)	3046 (2.9)	1143 (4.7)	1279 (2.8)	498 (4.8)
Physician Specialty No %						
Critical Care	58220 (38.2)	14195 (41.0)	40870 (38.3)	9925 (41.0)	17350 (38.0)	4270 (41.1)
Other	94033 (61.8)	20422 (59.0)	65708 (61.7)	14307 (59.0)	28325 (62.0)	6115 (58.9)
Hospital Discharge Year No. (%)						
2010	18203 (12.0)	4739 (13.7)	12720 (11.9)	3348 (13.8)	5483 (12.0)	1391 (13.4)
2011	21714 (14.3)	5315 (15.4)	15194 (14.3)	3643 (15.0)	6520 (14.3)	1672 (16.1)
2012	24356 (16.0)	5729 (16.5)	17078 (16.0)	3927 (16.2)	7278 (15.9)	1802 (17.4)
2013	27646 (18.2)	6076 (17.6)	19352 (18.2)	4319 (17.8)	8294 (18.2)	1757 (16.9)
2014	29207 (19.2)	6033 (17.4)	20506 (19.2)	4226 (17.4)	8701 (19.0)	1807 (17.4)
2015	30737 (20.2)	6697 (19.3)	21463 (20.1)	4747 (19.6)	9274 (20.3)	1950 (18.8)
2016	390 (0.3)	28 (0.1)	265 (0.2)	22 (0.1)	125 (0.3)	6 (0.1)
Teaching Hospital No. (%)						
Unknown	5757 (3.8)	1454 (4.2)	4025 (3.8)	1045 (4.3)	1732 (3.8)*	409 (3.9)*
No	99123 (65.1)	21921 (63.3)	69311 (65.0)	15301 (63.1)	29812 (65.3)*	6620 (63.7)*
Yes	47373 (31.1)	11242 (32.5)	33242 (31.2)	7886 (32.5)	14131 (30.9)*	3356 (32.3)*
Hospital Size No. (%)						
Unknown	11209 (7.4)	2480 (7.2)	7798 (7.3)	1739 (7.2)	3411 (7.5)	741 (7.1)
<100	8704 (5.7)	1075 (3.1)	6179 (5.8)	733 (3.0)	2525 (5.5)	342 (3.3)
100-249	36233 (23.8)	7051 (20.4)	25287 (23.7)	4952 (20.4)	10946 (24.0)	2099 (20.2)
250-500	28670 (18.8)	6726 (19.4)	19941 (18.7)	4694 (19.4)	8729 (19.1)	2032 (19.6)
>500	67437 (44.3)	17285 (49.9)	47373 (44.4)	12114 (50.0)	20064 (43.9)	5171 (49.8)
US Region No. (%)						
Midwest	58909 (38.7)	10765 (31.1)	41136 (38.6)	7589 (31.3)	17773 (38.9)	3176 (30.6)
Northeast	22034 (14.5)	5326 (15.4)	15585 (14.6)	3714 (15.3)	6449 (14.1)	1612 (15.5)

South	43920 (28.8)	10630 (30.7)	30697 (28.8)	7385 (30.5)	13223 (29.0)	3245 (31.2)
West	19805 (13.0)	6132 (17.7)	13877 (13.0)	4294 (17.7)	5928 (13.0)	1838 (17.7)
Unknown	7585 (5.0)	1764 (5.1)	5283 (5.0)	1250 (5.2)	2302 (5.0)	514 (4.9)
Comorbid Conditions No. (%)						
Dialysis	6173 (4.1)	1578 (4.6)	4312 (4.0)	1116 (4.6)	1861 (4.1)*	462 (4.4)*
AIDS	378 (0.2)*	94 (0.3)*	281 (0.3)*	72 (0.3)*	97 (0.2)*	22 (0.2)*
Hepatic Failure	3399 (2.2)	1435 (4.1)	2367 (2.2)	984 (4.1)	1032 (2.3)	451 (4.3)
Diabetes	34597 (22.7)	6153 (17.8)	24139 (22.6)	4317 (17.8)	10458 (22.9)	1836 (17.7)
Immunosuppression	5699 (3.7)	1776 (5.1)	4022 (3.8)	1230 (5.1)	1677 (3.7)	546 (5.3)
Leukemia	1769 (1.2)	658 (1.9)	1270 (1.2)	449 (1.9)	499 (1.1)	209 (2.0)
Lymphoma	903 (0.6)	298 (0.9)	642 (0.6)	210 (0.9)	261 (0.6)*	88 (0.8)*
Metastatic CA	3165 (2.1)	1358 (3.9)	2243 (2.1)	948 (3.9)	922 (2.0)	410 (3.9)
Respiratory	52520 (34.5)	11068 (32.0)	36905 (34.6)	7875 (32.5)	15615 (34.2)	3193 (30.7)
Cardiovascular	36119 (23.7)	9652 (27.9)	25331 (23.8)	6729 (27.8)	10788 (23.6)	2923 (28.1)
Admitted with Myocardial Infarction with/without Thrombolytics						
With	248 (0.2)	136 (0.4)	183 (0.2)	96 (0.4)	65 (0.1)	40 (0.4)
Without	152005 (99.8)	34481 (99.6)	106395 (99.8)	24136 (99.6)	45610 (99.9)	10345 (99.6)
SOFA Positive No. (%)						
	127524 (83.8)	33241 (96.0)	89152 (83.6)	23255 (96.0)	38372 (84.0)	9986 (96.2)
Fuzzy Logic Positive No. (%)						
	119892 (78.7)	32178 (93.0)	83895 (78.7)	22467 (92.7)	35997 (78.8)	9711 (93.5)
APACHE IVa (mean (SD))						
	63.9 (23.9)	93.8 (31.7)	63.9 (23.9)	93.6 (31.7)	64.04 (23.83)	94.40 (31.79)
ICU Mortality No. (%)						
Survived	152246 (100.0)	9692 (28.0)	106574 (100.0)	6737 (27.8)	45672 (100.0)	2955 (28.5)
Expired	NA	24921 (72.0)	NA	17491 (72.2)	NA	7430 (71.5)
Hospital LOS (mean (SD))						
	10.6 (12.1)	9.0 (12.7)	10.6 (12.0)	9.0 (12.7)	10.68 (12.43)	8.92 (12.76)
ICU LOS (mean (SD))						
	4.07 (4.87)	4.76 (6.14)	4.0 (4.9)	4.7 (6.0)	4.10 (4.96)	4.83 (6.55)
APACHE Group No. (%)						
Cardiovascular	14818 (9.7)	5201 (15.0)	10368 (9.7)	3676 (15.2)	4450 (9.7)	1525 (14.7)
GI	9293 (6.1)	2253 (6.5)	6525 (6.1)	1593 (6.6)	2768 (6.1)	660 (6.4)
Gynecological	114 (0.1)	3 (0.0)	75 (0.1)	1 (0.0)	39 (0.1)	2 (0.0)
Hematologic	879 (0.6)	179 (0.5)	633 (0.6)	124 (0.5)	246 (0.5)	55 (0.5)
Metabolic	5645 (3.7)	405 (1.2)	3949 (3.7)	264 (1.1)	1696 (3.7)	141 (1.4)
MusculoSkel/Skin	2075 (1.4)	195 (0.6)	1404 (1.3)	150 (0.6)	671 (1.5)	45 (0.4)
Neurologic	7803 (5.1)	1445 (4.2)	5418 (5.1)	1033 (4.3)	2385 (5.2)	412 (4.0)
Renal/GU	4411 (2.9)	544 (1.6)	3083 (2.9)	384 (1.6)	1328 (2.9)	160 (1.5)
Respiratory	38058 (25.0)	8290 (23.9)	26711 (25.1)	5801 (23.9)	11347 (24.8)	2489 (24.0)
Sepsis	67853 (44.6)	15712 (45.4)	47490 (44.6)	10926 (45.1)	20363 (44.6)	4786 (46.1)
Trauma	837 (0.5)	183 (0.5)	588 (0.6)	126 (0.5)	249 (0.5)	57 (0.5)
Undefined	467 (0.3)	207 (0.6)	334 (0.3)	154 (0.6)	133 (0.3)	53 (0.5)

eRI, eICU Research Institute; No., number; SD, standard deviation; ED, emergency department, SDU, step-down unit; US, United States; AIDS, acquired immune deficiency syndrome; CA, cancer; SOFA, sepsis-related organ failure assessment; APACHE, acute physiology age, chronic health, evaluation; ICU, intensive care unit; LOS, length of stay; GI, gastrointestinal; MusculoSkel, musculoskeletal; GU, genitourinary; All p-values were significant at the < 0.001 with the exception of values denoted with *. Each comorbid condition was compared to patients without the condition.

BMIs of 25 to 35 had the most number of patients (41.5%) when compared to other BMI ranges. The ED as the source of ICU admission occurred more often (56%) than

other sources of admission. More patients were managed by critical care designated specialty services (39%) in the secondary cohort when compared to the primary cohort (29%). Other differences in the secondary cohort from the primary cohort was admission to teaching hospitals 31% versus 30% respectively, admission to hospitals > 500 beds 45% versus 47%, and 37% from the Midwest versus 42%.

The following comorbid conditions were present in the secondary cohort and differed from the primary cohort: 34.0% with chronic respiratory issues (versus 24.1%), 24.5% with cardiovascular conditions (versus 22.7%), 4.1% on dialysis (versus 3.4%), 4.0% immunosuppression (versus 2.3%), and 2.5% hepatic failure (versus 2.1%), 2.4% metastatic cancer (1.9%), 1.1% leukemia (versus < 1%), 0.6% lymphoma (versus 0.4%), 0.2% patients were admitted to the ICU with a MI and received thrombolytic therapy prior to ICU admission (versus 1.8%) and 0.3% AIDS (versus 0.1%). SOFA score of 2 or more was present in 86% of the patients in each cohort and Fuzzy Logic SIRS/OF criteria were met in 81% in the secondary cohorts. As expected, the average APACHE scores were higher in the secondary cohort than in the primary cohort: expired patients 93.6-94.4 (SD 31.7-31.8) versus 63.9-64.0 (SD 23.8-23.9) for survivors.

Hospital LOS for survivors in the secondary cohort were longer (10.6-10.7 days; SD 12.1-12.4) than for expired patients (8.8-9.0 days; SD 12.7-12.8). This differed from hospital LOS in the primary cohort (survivors 7.7 days; SD 8.8-10.6 versus expired patients 8.0 days; SD 10.3-12.3). Mortality was 18.5% in the secondary cohort versus 9.4% the primary cohort as were the average APACHE scores this indicated a higher risk of mortality and of longer LOS. ICU LOS for survivors (4.1 days; SD 4.8-5.0) was less than for expired patients (4.7-4.8 days; SD 6.0-6.5). Sepsis APACHE diagnoses

were present in 44.7% of the secondary cohort, followed by respiratory diagnoses (24.8%), cardiovascular (10.7%), gastrointestinal diagnoses (6.2%), and all other diagnoses were used in less than 5% of the secondary cohort.

Frequency of Missing Data among Clinical and Laboratory Values in the Primary Cohort

For vital sign data, temperature had the highest number of missing values with 17,387 (< 2%) followed by SBP missing 184 values (< 1%) missing values; missing values were coded as normal. There were no missing heart rate, MAP, or respiratory values; this is likely because these values are required for APACHE scoring. Participating sites collect data for APACHE IVa scoring which requires a Glasgow Coma Scale (GCS); 9,882 (1%) had missing GCS and were coded as normal (score of 15). Although urine output was missing in almost half of the records, after inclusion/exclusion criteria were applied all of cases that had evidence of laboratory values being present allowing creatinine values to be used primarily for SOFA scoring. Missing laboratory values in the cohort include: creatinine 88,585 (10%); bilirubin 534,627 (59%); lactate 697,840 (76%); PaO_2 566,288 (62%); $PaCO_2$ 566,412 (62%) platelets 121,367 (13%); INR 547,794 (60%); aPTT 645,624 (71%); white blood cell (WBC) 117,929 (13%); Bands 836,281 (92%); pH 576,985 (63%); base deficit 853,461 (94%); AST 528,607 (58%); ALT 533,653 (58%); and albumin 548,672 (60%).

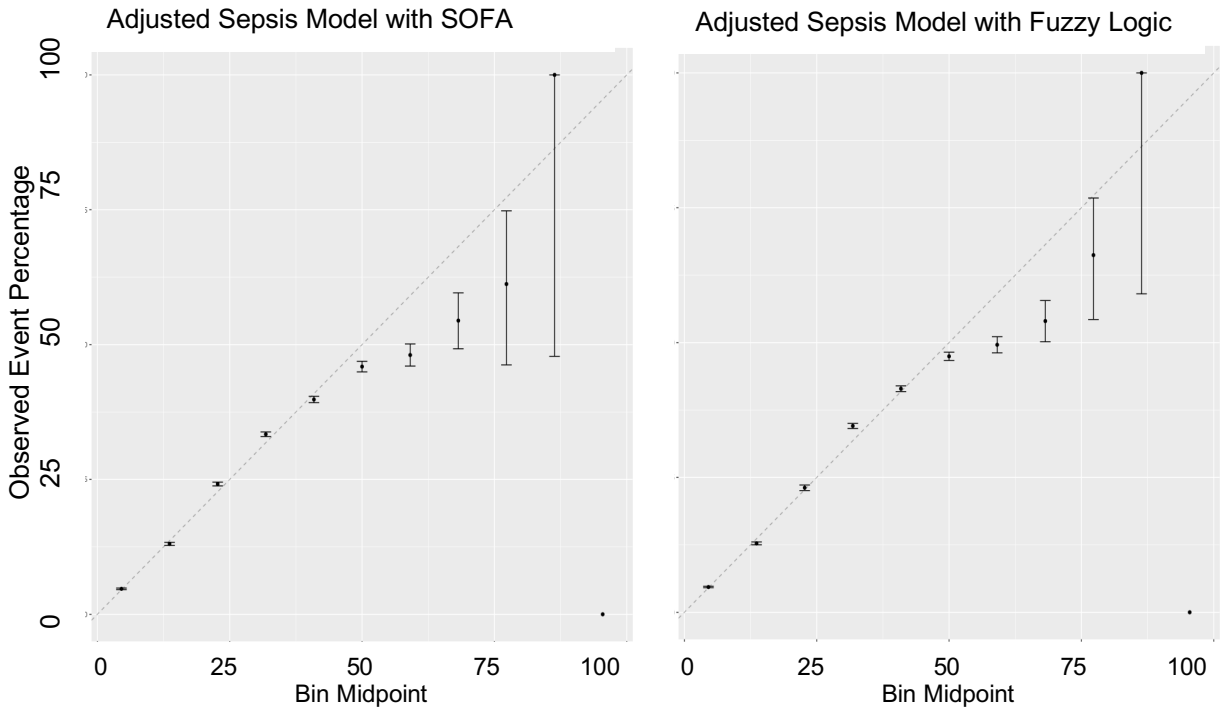
Patient and hospital level demographic information was missing at varying levels. There were 40,393 patients classified as other/unknown for ethnicity, 53 patients were missing information related to gender while another 170 were classified as other or unknown and 53 patients were missing ICU discharge disposition. There were 32,286 patients without BMI calculations due to missing heights and/or weights. There were

37,915 hospitals classified as unknown for teaching status and 55,141 were missing hospital region information.

Calibration of the Models

The calibration for the sepsis model is found in Figure 10, compare differences in actual versus predicted rates of sepsis, measuring the agreement between the observed outcome to the predicted probablities.[61] The adjusted measurement systems (SOFA and Fuzzy Logic SIRS/OF) demonstrated accurate prediction of the sepsis until around the midpoint when the observed points began to drift below the 45 degree line. This indicated an under estimation of the probability of the outcomes at higher proportions for the outcomes of sepsis.

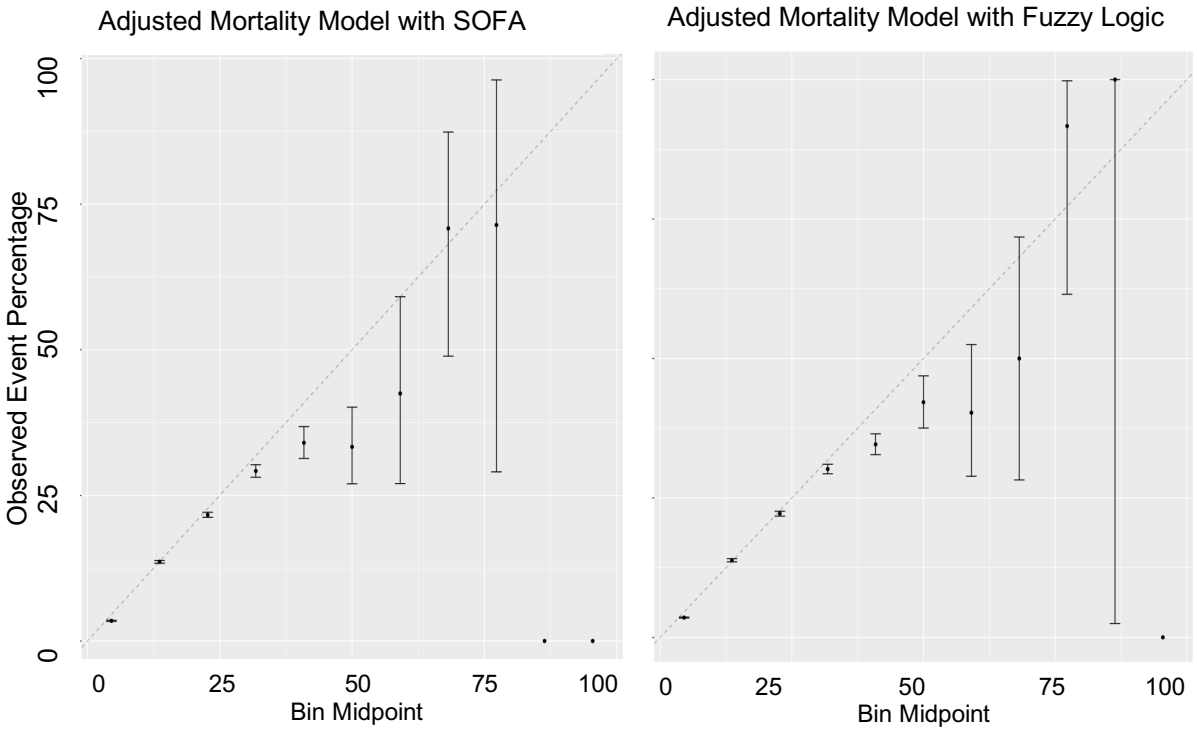
Figure 10. Calibration of Sepsis Model with SOFA and Fuzzy Logic



SOFA, sepsis-related organ failure assessment; Fuzzy Logic refers to the algorithm for the sepsis prompt that included expanded systemic inflammatory response syndrome criteria and organ failure criteria. Calibration completed on the test sets.

The calibration for the mortality model compare differences in actual versus predicted rates of mortality, measuring the agreement between the observed outcome to the predicted probablities.[61] The adjusted measurement systems (SOFA and Fuzzy Logic SIRS/OF) demonstrated better accuracy of sepsis when compared to mortality. The observed points began to drift below the 45 degree line before the midpoint (Figure 11). This indicated an under estimation of the probability of the outcomes of mortality.

Figure 11. Calibration of Mortality Model with SOFA and Fuzzy Logic



SOFA, sepsis-related organ failure assessment; Fuzzy Logic refers to the algorithm for the sepsis prompt that included expanded systemic inflammatory response syndrome criteria and organ failure criteria. Calibration completed on the test sets.

Odds Ratios and Confidence Intervals for SOFA Score and Fuzzy Logic SIRS/OF Criteria Met for Patients in the Primary Cohort for Sepsis

Adjusted Odds Ratios (AOR) for sepsis and Confidence Intervals (CI) were estimated on the training cohort and prediction and performance analyses were

completed on the testing cohort. A positive SOFA score (Table 10) was associated with a significant increase in odds of sepsis (AOR 3.21, 99% CI: 3.15-3.26). Fuzzy Logic SIRS/OF was associated with a significant increase in odds of sepsis (AOR 4.46, 99% CI: 4.39-4.53). Statistical significance was considered a p-value <0.001. Older patients with positive measurement scores had significantly higher odds of sepsis when compared to patients under 25 years of age with odds increasing with each had Fuzzy Logic SIRS/OF criteria met and for patients with a positive SOFA score in each age group.

Table 10. Adjusted Odds Ratio (AOR) and 99% Confidence Intervals (CI) for Positive SOFA Scores and Fuzzy Logic SIRS/OF Criteria for Sepsis for the Primary Cohort

Primary Cohort Training Set: Sepsis		**SOFA**			**Fuzzy Logic**		
Total Observations	**638,757**	**AOR**	**CI**	**p**	**AOR**	**CI**	**p**
Measurement System		3.21	3.15 – 3.26	<.001	4.46	4.39 – 4.53	<.001
Ages vs.18 to < 25	25 - < 35	1.15	1.09 – 1.21	<.001	1.22	1.16 – 1.29	<.001
	35 - < 45	1.32	1.25 – 1.38	<.001	1.46	1.39 – 1.54	<.001
	45 - < 55	1.51	1.44 – 1.58	<.001	1.71	1.64 – 1.80	<.001
	55 - < 65	1.76	1.68 – 1.84	<.001	2.04	1.95 – 2.13	<.001
	65 - < 75	1.79	1.71 – 1.87	<.001	2.11	2.01 – 2.20	<.001
	75 - < 85	1.85	1.77 – 1.94	<.001	2.28	2.17 – 2.38	<.001
	85+	2.03	1.93 – 2.12	<.001	2.60	2.48 – 2.73	<.001
Gender vs. Male	Female	1.10	1.09 – 1.11	<.001	1.04	1.02 – 1.05	<.001
Ethnicity vs. Caucasian	African American	0.90	0.88 – 0.91	<.001	0.97	0.95 – 0.99	0.009
	Hispanic	1.49	1.44 – 1.53	<.001	1.49	1.45 – 1.54	<.001
	Asian	1.05	0.99 – 1.11	0.108	1.12	1.05 – 1.18	<.001
	Native American	1.27	1.18 – 1.36	<.001	1.31	1.21 – 1.41	<.001
	Other	1.06	1.03 – 1.09	<.001	1.05	1.02 – 1.08	0.002
BMI Ranges vs. <18.5	18.5 - < 25	0.78	0.76 – 0.81	<.001	0.80	0.78 – 0.83	<.001
	25 - < 35	0.73	0.71 – 0.75	<.001	0.75	0.73 – 0.77	<.001
	35+	0.87	0.84 – 0.90	<.001	0.89	0.86 – 0.92	<.001
	Unknown	0.57	0.55 – 0.60	<.001	0.63	0.60 – 0.66	<.001
ICU Admission Source versus Floor/Ward	OR/Procedural	0.14	0.14 – 0.15	<.001	0.14	0.13 – 0.14	<.001
	Direct Admit	0.56	0.55 – 0.58	<.001	0.63	0.62 – 0.65	<.001
	ED	0.77	0.75 – 0.78	<.001	0.76	0.74 – 0.77	<.001
	Other	0.83	0.77 – 0.88	<.001	0.90	0.84 – 0.96	0.001
	SDU	1.01	0.97 – 1.05	0.697	1.06	1.01 – 1.10	0.009
Hospital Teaching Status vs. Unknown	No	0.82	0.78 – 0.86	<.001	0.79	0.75 – 0.83	<.001
	Yes	0.84	0.80 – 0.89	<.001	0.81	0.77 – 0.85	<.001
Hospital Size (No. of Beds) vs. Unknown	< 100	1.87	1.79 – 1.96	<.001	1.86	1.78 – 1.95	<.001
	100-249	1.36	1.31 – 1.41	<.001	1.36	1.31 – 1.42	<.001
	250-500	1.29	1.25 – 1.34	<.001	1.30	1.25 – 1.35	<.001
	> 500	1.12	1.08 – 1.16	<.001	1.11	1.08 – 1.16	<.001
Specialty Service Critical Care	No	0.58	0.57 – 0.58	<.001	0.61	0.60 – 0.61	<.001
Hospital Discharge Year vs. 2010	2011	1.10	1.08 – 1.13	<.001	1.10	1.07 – 1.13	<.001
	2012	0.97	0.94 – 0.99	0.006	0.96	0.94 – 0.99	0.002
	2013	0.98	0.96 – 1.00	0.079	0.96	0.94 – 0.99	0.002
	2014	0.95	0.92 – 0.97	<.001	0.94	0.92 – 0.97	<.001
	2015-2016	0.98	0.96 – 1.01	0.19	0.98	0.96 – 1.00	0.105
With vs Without Comorbid Conditions	Dialysis	1.37	1.33 – 1.42	<.001	1.31	1.27 – 1.36	<.001
	AIDS	3.72	3.14 – 4.41	<.001	3.79	3.18 – 4.51	<.001
	Hepatic failure	1.00	0.96 – 1.05	0.862	0.97	0.93 – 1.01	0.168
	Diabetes	0.92	0.90 – 0.93	<.001	1.05	1.03 – 1.06	<.001

	Immuno-suppression	1.77	1.71 – 1.85	<.001	1.69	1.63 – 1.76	<.001
	Leukemia	1.50	1.41 – 1.60	<.001	1.49	1.39 – 1.59	<.001
	Lymphoma	1.46	1.34 – 1.60	<.001	1.41	1.29 – 1.55	<.001
	Metastatic CA	1.08	1.03 – 1.13	0.002	1.02	0.97 – 1.07	0.414
	Respiratory	1.68	1.65 – 1.70	<.001	1.48	1.46 – 1.50	<.001
	Cardiovascular	0.89	0.87 – 0.90	<.001	0.93	0.91 – 0.94	<.001
AMI With vs. Without Thrombolytics	Thrombolytics	0.12	0.11 – 0.14	<.001	0.12	0.11 – 0.14	<.001

AOR, Adjusted Odd Ratio; eRI, eICU Research Institute; SIRS, systemic inflammatory response syndrome; OF, organ failure; SOFA, sepsis-related organ failure assessment; AOR, adjusted odds ratio; CI, confidence interval; vs., versus; OR/Procedural, operating room/procedural area; ED, emergency department, SDU, step-down unit; US, United States; ICU, intensive care unit; LOS, length of stay AIDS, acquired immune deficiency syndrome; CA, cancer; AMI, acute myocardial infarction.

Higher odds of sepsis were seen in patients who met criteria for Fuzzy Logic SIRS/OF versus patients with a positive SOFA score. In older age groups, there was no overlap in CIs between the measurement systems. For example, starting at the 35 to 45 years group, patients who met criteria for Fuzzy Logic SIRS/OF had higher odds of sepsis (AOR 1.46, 99% CI: 1.39-1.49; p-value < 0.001) versus patients in the same age group with a positive SOFA score (AOR 1.32, 99% CI: 1.25-1.38, p-value < 0.001). Odds of sepsis were higher in every age group for patients who met criteria for Fuzzy Logic SIRS/OF versus patients with positive SOFA scores. Patients aged 85+ years had the highest odds of sepsis (AOR 2.60, 99% CI: 2.48-2.73, p-value < 0.001) for positive Fuzzy Logic SIRS/OF and (AOR 2.03, 99% CI: 1.93-2.01, p-value < 0.001) positive SOFA score. Patients with Fuzzy Logic SIRS/OF criteria and positive SOFA scores had significant increases in odds of sepsis in females when compared to males (Fuzzy Logic SIRS/OF AOR 1.04, 99% CI: 1.02-1.05 versus SOFA AOR 1.10, 99% CI: 1.09-1.11).

Among those patients who met criteria for Fuzzy Logic SIRS/OF, odds of sepsis increased significantly for non-Caucasians with the exception of African American and

ethnicity unknown that were not significantly different (AOR 0.97, 99% CI: 0.97-0.99 p-value 0.009 and AOR 1.05, 99% CI: 1.05-1.08 p-value 0.002). Among patients with a positive SOFA score, odds of sepsis increased for Native Americans and those patients categorized as unknown (AOR 1.34, 99% CI: 1.22-1.48, p-value < 0.001 and AOR 1.19, 99% CI: 1.15-1.24, p-value < 0.001, respectively) while other ethnic groups were not significantly different (Table 10). For patients who met criteria for Fuzzy Logic SIRS/OF or with positive SOFA scores, there was a significant increase in odds of sepsis for low weight patients (BMI of < 18.5) when compared with other BMI range groups (Table 10).

Patients with an ICU admission source of step-down unit (SDU), when compared to admissions from the floor, had higher odds of sepsis when Fuzzy Logic SIRS/OF criteria were met (AOR 1.06 99% CI: 1.01-1.10, p-value < 0.001) and when SOFA scores were positive (AOR 1.01; 99% CI: 0.97-1.05, p-value < 0.001). All other sources of admissions had a lower risk of odds of sepsis than patients admitted from the floor. Odds of sepsis were significantly lower in all other years when compared to patients discharged in 2010 except for 2011 for SOFA (AOR 1.10, 99% CI: 1.08-1.13) and Fuzzy Logic SIRS/OF (AOR 1.10, 99% CI: 1.07-1.13).

Patients with diabetes versus patients without diabetes who a positive SOFA score were at lower risk of sepsis (AOR 0.92; 99% CI 0.90-0.93, p-value < 0.001) whereas patients with diabetes who met criteria for Fuzzy Logic SIRS/OF the odds of sepsis increased (AOR 1.05; 99% CI 1.03-1.06, p-value < 0.001). Lower odds of sepsis were observed in patients who met measurement system thresholds and had a cardiovascular comorbid condition, as did patients admitted with an acute myocardial infarction (AMI) who received thrombolytic therapy prior to ICU admission (Table 10).

Patients who met the thresholds for SOFA and Fuzzy Logic SIRS/OF had significant increases in odds of sepsis with the presence of all other comorbid conditions except for metastatic cancer (AOR 1.08; 99% CI 1.03-1.13, p-value < 0.002 and AOR 1.02; 99% CI 0.97-1.07, p-value < 0.414, respectively).

Odds Ratios and Confidence Intervals for SOFA Score and Fuzzy Logic SIRS/OF Criteria Met for Patients in the Primary Cohort for Mortality

Adjusted Odds Ratios (AOR) for mortality and Confidence Intervals (CI) were estimated on the training cohort (Table 11) and prediction and performance analyses were completed on testing cohort. Having a positive SOFA score (≥ 2) increased the odds of death versus a negative score (AOR 7.54, 99% CI: 7.28-7.82). This was also true for patients who met criteria for Fuzzy logic versus those that did not (AOR 5.81, 99% CI: 5.67-5.95, p-value < 0.001). Older patients' positive measurement scores had statistically significant increase in odds of death when compared to patients under 25 years of age (Table 11). For example, patients aged 65 years to 75 years who met criteria for Fuzzy Logic SIRS/OF (AOR 3.66, 99% CI: 3.38-3.97, p-value < 0.001) versus patients in the same age group with a positive SOFA score (AOR 3.1, 99% CI: 2.86-3.36, p-value < 0.001). Patients who met thresholds within each measurement system had significant lower odds of death in females (Fuzzy Logic SIRS/OF AOR 0.92, 99% CI: 0.90-0.93 versus SOFA AOR 0.98, 99% CI: 0.96-1.00).

Table 11. Adjusted Odds Ratio (AOR) and 99% Confidence Intervals (CI) for Positive SOFA Scores and Fuzzy Logic SIRS/OF Criteria for Mortality for the Primary Cohort

Primary Cohort Training Set: Mortality		**SOFA**			**Fuzzy Logic**		
Total Observations	**638,757**	**AOR**	**CI**	**p**	**AOR**	**CI**	**p**
Measurement System		7.54	7.28 – 7.82	<.001	5.81	5.67 – 5.95	<.001
Ages vs.18 to < 25	25 - < 35	1.24	1.13 – 1.37	<.001	1.30	1.18 – 1.43	<.001
	35 - < 45	1.49	1.36 – 1.63	<.001	1.61	1.48 – 1.76	<.001
	45 - < 55	1.99	1.84 – 2.17	<.001	2.23	2.05 – 2.42	<.001
	55 - < 65	2.50	2.31 – 2.72	<.001	2.87	2.65 – 3.12	<.001
	65 - < 75	3.10	2.86 – 3.36	<.001	3.66	3.38 – 3.97	<.001
	75 - < 85	3.93	3.63 – 4.27	<.001	4.93	4.55 – 5.35	<.001
	85+	4.77	4.40 – 5.19	<.001	6.34	5.84 – 6.89	<.001
Gender vs. Male	Female	0.98	0.96 – 1.00	0.035	0.92	0.90 – 0.93	<.001
Ethnicity vs. Caucasian	African American	0.97	0.94 – 1.00	0.024	1.07	1.03 – 1.10	<.001
	Hispanic	1.05	1.01 – 1.09	0.027	1.04	1.00 – 1.09	0.052
	Asian	1.10	1.02 – 1.18	0.013	1.18	1.10 – 1.28	<.001
	Native American	1.34	1.22 – 1.48	<.001	1.40	1.27 – 1.54	<.001
	Other	1.19	1.15 – 1.24	<.001	1.18	1.14 – 1.23	<.001
BMI Ranges vs. <18.5	18.5 - < 25	0.73	0.70 – 0.76	<.001	0.75	0.72 – 0.77	<.001
	25 - < 35	0.62	0.60 – 0.64	<.001	0.63	0.61 – 0.66	<.001
	35+	0.68	0.65 – 0.71	<.001	0.69	0.66 – 0.72	<.001
	UNK	1.03	0.98 – 1.09	0.253	1.14	1.08 – 1.20	<.001
ICU Admission Source versus Floor/Ward	OR/Procedural	0.23	0.23 – 0.24	<.001	0.23	0.22 – 0.24	<.001
	Direct Admit	0.73	0.71 – 0.76	<.001	0.83	0.81 – 0.86	<.001
	ED	0.65	0.64 – 0.67	<.001	0.64	0.63 – 0.66	<.001
	Other	0.92	0.85 – 0.99	0.037	1.01	0.93 – 1.10	0.819
	SDU	1.16	1.10 – 1.22	<.001	1.23	1.17 – 1.29	<.001
Hospital Teaching Status vs. Unknown	No	0.96	0.90 – 1.03	0.246	0.93	0.87 – 0.99	0.024
	Yes	0.86	0.80 – 0.92	<.001	0.82	0.77 – 0.88	<.001
Hospital Size (No. of Beds) vs. Unknown	< 100	0.61	0.57 – 0.66	<.001	0.58	0.54 – 0.63	<.001
	100-249	0.97	0.92 – 1.02	0.212	0.97	0.92 – 1.02	0.171
	250-500	1.07	1.02 – 1.13	0.008	1.07	1.02 – 1.13	0.009
	> 500	1.24	1.18 – 1.30	<.001	1.25	1.19 – 1.31	<.001
Specialty Service	No	0.74	0.72 – 0.75	<.001	0.78	0.76 – 0.79	<.001
Critical Care Hospital Discharge Year vs. 2010	2011	0.97	0.93 – 1.00	0.045	0.96	0.93 – 0.99	0.02
	2012	0.94	0.91 – 0.97	<.001	0.93	0.90 – 0.97	<.001
	2013	0.91	0.88 – 0.94	<.001	0.89	0.87 – 0.92	<.001
	2014	0.87	0.85 – 0.90	<.001	0.87	0.84 – 0.89	<.001
	2015-2016	0.88	0.86 – 0.91	<.001	0.88	0.85 – 0.91	<.001
With vs Without Comorbid Conditions	Dialysis	1.52	1.45 – 1.59	<.001	1.40	1.34 – 1.47	<.001
	AIDS	1.61	1.27 – 2.02	<.001	1.59	1.25 – 2.01	<.001
	Hepatic failure	1.75	1.66 – 1.83	<.001	1.78	1.69 – 1.86	<.001
	Diabetes	0.73	0.72 – 0.75	<.001	0.87	0.85 – 0.89	<.001

	Immuno-suppression	1.41	1.34 – 1.48	<.001	1.34	1.28 – 1.41	<.001
	Leukemia	1.48	1.37 – 1.60	<.001	1.49	1.37 – 1.61	<.001
	Lymphoma	1.28	1.14 – 1.43	<.001	1.25	1.11 – 1.40	<.001
	Metastatic CA	1.98	1.88 – 2.09	<.001	1.90	1.80 – 2.00	<.001
	Respiratory	1.12	1.10 – 1.14	<.001	0.97	0.95 – 0.99	0.007
	Cardiovascular	1.06	1.04 – 1.08	<.001	1.12	1.10 – 1.14	<.001
AMI With vs. Without Thrombolytics	Thrombolytics	1.28	1.19 – 1.37	<.001	1.21	1.13 – 1.30	<.001

AOR, Adjusted Odd Ratio; eRI, eICU Research Institute; SIRS, systemic inflammatory response syndrome; OF, organ failure; SOFA, sepsis-related organ failure assessment; AOR, adjusted odds ratio; CI, confidence interval; vs., versus; OR/Procedural, operating room/procedural area; ED, emergency department, SDU, step-down unit; US, United States; ICU, intensive care unit; LOS, length of stay AIDS, acquired immune deficiency syndrome; CA, cancer; AMI, acute myocardial infarction.

Among those patients who met criteria for Fuzzy Logic SIRS/OF, odds of death increased for non-Caucasians with the exception of Hispanics that were not significantly different (AOR 1.04, 99% CI: 1.00-1.09 p-value 0.05). Among patients with a positive SOFA score, odds of death significantly increased for Native Americans and those patients categorized as unknown (AOR 1.34, 99% CI: 1.22-1.48 and AOR 1.19, 99% CI: 1.15-1.24, respectively) while other ethnic groups differences were not significantly different. Patients who met criteria for Fuzzy Logic SIRS/OF or had a positive SOFA scores, a BMI of < 18.5 were associated with significant increased odds of death when compared with other BMI range groups except for SOFA differences in the unknown group (AOR 1.03, 99% CI: 0.98-1.09).

Patients with an ICU admission source of step-down unit (SDU), when compared to admissions from the floor, had increased odds of death when Fuzzy Logic SIRS/OF criteria were met (AOR 1.23; 99% CI: 1.17-1.29, p-value < 0.001) and when SOFA scores were positive (AOR 1.16; 99% CI: 1.10-1.22, p-value < 0.001). All other sources of admissions had significant lower odds of death than patients admitted from the floor

(Table 11). Adjusted odds of death were significantly lower odds of death in all other years when compared to patients discharged in 2010 (Table 11). Patients with comorbid conditions who met measurement systems thresholds versus those who did not, had significant increases in odds of death in all conditions except diabetic patients (SOFA AOR 0.73, 99% CI: 0.72-0.75, p-value < 0.001 and Fuzzy Logic SIRS/OF AOR 0.87, 99% CI: 0.85-0.89, p-value < 0.001).

Odds Ratios and Confidence Intervals for SOFA Score and Fuzzy Logic SIRS/OF Criteria Met for Patients in the Secondary Cohort for Mortality

Adjusted Odds Ratios (AOR) for mortality and confidence intervals (CI) were estimated on the secondary training cohort (Table 12) and prediction and performance analyses were completed on secondary testing cohort. Having a positive SOFA score was associated with a significant increase in odds of death (AOR 4.13, 99% CI: 3.86–4.42, p-value < 0.001) versus a negative score. For patients with Fuzzy Logic SIRS/OF criteria met versus not met, the odds of death were lower when compared to SOFA (AOR 3.51, 99% CI: 3.33-3.69, p-value < 0.001).

Table 12. Adjusted Odds Ratio (AOR) and 99% Confidence Intervals (CI) for Positive SOFA Scores and Fuzzy Logic SIRS/OF Criteria for Mortality for the Secondary Cohort

Secondary Cohort Training Set: Mortality		**SOFA**			**Fuzzy Logic**		
Total Observations	**130,810**	**AOR**	**CI**	**p**	**AOR**	**CI**	**p**
Measurement System		4.13	3.86 – 4.42	<.001	3.51	3.33 – 3.69	<.001
Ages vs.18 to < 25	25 - < 35	1.34	1.12 – 1.61	0.001	1.36	1.14 – 1.63	<.001
	35 - < 45	1.64	1.39 – 1.94	<.001	1.72	1.46 – 2.04	<.001
	45 - < 55	1.97	1.69 – 2.31	<.001	2.11	1.81 – 2.47	<.001
	55 - < 65	2.54	2.18 – 2.97	<.001	2.73	2.35 – 3.19	<.001
	65 - < 75	3.10	2.67 – 3.62	<.001	3.39	2.92 – 3.96	<.001
	75 - < 85	3.88	3.34 – 4.53	<.001	4.39	3.78 – 5.13	<.001
	85+	4.47	3.84 – 5.24	<.001	5.19	4.45 – 6.08	<.001
Gender vs. Male	Female	1.00	0.97 – 1.03	0.976	0.97	0.94 – 1.00	0.029
Ethnicity vs. Caucasian	African American	0.94	0.89 – 0.99	0.013	0.99	0.95 – 1.04	0.823
	Hispanic	1.03	0.96 – 1.09	0.407	1.04	0.98 – 1.11	0.227
	Asian	0.99	0.87 – 1.12	0.827	0.99	0.87 – 1.12	0.873
	Native American	1.39	1.18 – 1.62	<.001	1.40	1.19 – 1.63	<.001
	Other	1.04	0.98 – 1.11	0.200	1.04	0.98 – 1.11	0.215
BMI Ranges vs. <18.5	18.5 - < 25	0.76	0.72 – 0.80	<.001	0.76	0.72 – 0.81	<.001
	25 - < 35	0.65	0.61 – 0.69	<.001	0.66	0.62 – 0.69	<.001
	35+	0.65	0.61 – 0.69	<.001	0.66	0.62 – 0.71	<.001
	UNK	1.00	0.91 – 1.10	0.975	1.07	0.97 – 1.17	0.159
ICU Admission Source versus Floor/Ward	OR/Procedural	0.53	0.50 – 0.58	<.001	0.53	0.49 – 0.57	<.001
	Direct Admit	0.85	0.80 – 0.89	<.001	0.89	0.85 – 0.94	<.001
	ED	0.61	0.59 – 0.63	<.001	0.58	0.56 – 0.60	<.001
	Other	0.98	0.86 – 1.11	0.721	1.02	0.89 – 1.15	0.813
	SDU	1.18	1.09 – 1.27	<.001	1.24	1.15 – 1.33	<.001
Hospital Teaching Status vs. Unknown	No	0.76	0.68 – 0.85	<.001	0.74	0.66 – 0.83	<.001
	Yes	0.67	0.60 – 0.75	<.001	0.65	0.58 – 0.73	<.001
Hospital Size (No. of Beds) vs. Unknown	< 100	0.67	0.60 – 0.76	<.001	0.67	0.60 – 0.75	<.001
	100-249	1.10	1.01 – 1.21	0.037	1.11	1.01 – 1.21	0.029
	250-500	1.24	1.13 – 1.35	<.001	1.26	1.15 – 1.38	<.001
	> 500	1.41	1.29 – 1.54	<.001	1.43	1.31 – 1.56	<.001
Specialty Service Critical Care	No	0.90	0.87 – 0.93	<.001	0.90	0.87 – 0.93	<.001
Hospital Discharge Year vs. 2010	2011	0.93	0.88 – 0.98	0.005	0.93	0.88 – 0.98	0.006
	2012	0.89	0.84 – 0.94	<.001	0.89	0.84 – 0.94	<.001
	2013	0.88	0.84 – 0.93	<.001	0.88	0.83 – 0.92	<.001
	2014	0.82	0.77 – 0.86	<.001	0.81	0.77 – 0.85	<.001
	2015-2016	0.87	0.82 – 0.91	<.001	0.87	0.82 – 0.91	<.001
With vs Without Comorbid Conditions	Dialysis	0.31	0.19 – 0.47	<.001	0.32	0.20 – 0.49	<.001
	AIDS	1.30	1.21 – 1.40	<.001	1.26	1.17 – 1.35	<.001
	Hepatic failure	2.00	1.84 – 2.16	<.001	2.07	1.91 – 2.24	<.001
	Diabetes	0.70	0.68 – 0.73	<.001	0.78	0.75 – 0.81	<.001
	Immuno-suppression	1.16	1.08 – 1.25	<.001	1.15	1.07 – 1.24	<.001
	Leukemia	1.32	1.18 – 1.48	<.001	1.35	1.20 – 1.51	<.001

	Lymphoma	1.23	1.04 – 1.45	0.012	1.23	1.04 – 1.44	0.014
	Metastatic CA	1.83	1.68 – 1.99	<.001	1.82	1.67 – 1.98	<.001
	Respiratory	0.95	0.92 – 0.98	<.001	0.88	0.85 – 0.91	<.001
	Cardiovascular	1.12	1.08 – 1.16	<.001	1.16	1.12 – 1.20	<.001
AMI With vs. Without Thrombolytics	Thrombolytics	2.64	2.04 – 3.40	<.001	2.64	2.04 – 3.41	<.001

AOR, Adjusted Odd Ratio; eRI, eICU Research Institute; SIRS, systemic inflammatory response syndrome; OF, organ failure; SOFA, sepsis-related organ failure assessment; AOR, adjusted odds ratio; CI, confidence interval; vs., versus; OR/Procedural, operating room/procedural area; ED, emergency department, SDU, step-down unit; US, United States; ICU, intensive care unit; LOS, length of stay AIDS, acquired immune deficiency syndrome; CA, cancer; AMI, acute myocardial infarction.

As with the primary cohort, older patients in the secondary cohort with positive measurement scores had a significant increase in odds of death when compared to patients under 25 years of age (Table 12). These increases were higher for patients who met criteria versus those who did not for Fuzzy Logic SIRS/OF compared with patients with positive versus negative SOFA scores (Table 12). Gender differences were not significantly different from males (Fuzzy Logic SIRS/OF AOR 0.97, 99% CI: 0.94-1.00, p-value 0.03 versus SOFA AOR 1.00, 99% CI: 0.97-0.03, p-value 0.98).

Among those patients who met criteria for Fuzzy Logic SIRS/OF, odds of death increased for Native Americans (AOR 1.40, 99% CI: 1.19-1.63, p-value < 0.001) and among patients with a positive SOFA score, odds of death significantly increased for Native Americans (AOR 1.39, 99% CI: 1.18-1.62, p-value < 0.001). Other ethnic groups' differences were not significantly different from Caucasians. Patients with lower BMI (< 18.5) who met criteria for Fuzzy Logic SIRS/OF or had a positive SOFA scores had statistically significant increased odds of death when compared with other BMI range groups except the unknown group (SOFA AOR 1.00, 99% CI: 0.91-1.10, p-value 0.20 and Fuzzy Logic SIRS/OF AOR 1.07, 99% CI: 0.97-1.17, p-value 0.16).

ICU admission source of step-down unit (SDU), when compared to admissions from

the floor, had increased odds of death when Fuzzy Logic SIRS/OF criteria were met (AOR 1.24; 99% CI: 1.15-1.33, p-value < 0.001) and when SOFA scores were positive (AOR 1.18; 99% CI: 1.09-1.27, p-value < 0.001). All other sources of admissions had significant lower odds of death than patients admitted from the floor (Table 12) except for the "other" group (SOFA AOR 0.98; 99% CI: 0.86-1.11, p-value < 0.721 and Fuzzy Logic SIRS/OF AOR 1.02, 99% CI: 0.89-1.15, p-value 0.813). Odds of death were significantly lower odds of death in all years when compared to patients discharged in 2010 (Table 12) except for 2011 (SOFA AOR 0.93; 99% CI: 0.88-0.98, p-value < 0.005 and Fuzzy Logic SIRS/OF AOR 0.93, 99% CI: 0.88-0.98, p-value 0.006).

Patients with renal, liver, cardiovascular, immunosuppression, metastatic cancer comorbid conditions had significant increases in odds of death in both SOFA and Fuzzy Logic SIRS/OF. For patients with/without lymphoma a significant difference was not detected. Diabetic patients in the secondary cohort had lower odds of death (similar to findings in the primary cohort) when the threshold for a measurement system was met versus when it was not met (SOFA AOR 0.70, 99% CI: 0.68-0.73, p-value < 0.001 and Fuzzy Logic SIRS/OF AOR 0.73, 99% CI: 0.75-0.81, p-value < 0.001). Patients with respiratory co-morbid conditions had lower odds of death with positive SOFA (AOR 0.95, 99% CI: 0.92-0.98, p-value < 0.001) and when Fuzzy Logic SIRS/OF criteria were met (AOR 0.88, 99% CI: 0.85-0.91, p-value < 0.001). Sepsis patients who had received thrombolytic therapy for AMI prior to ICU admission had significant increase in odds of death versus sepsis patients admitted with AMI who had not received thrombolytic therapy (SOFA AOR 2.64, 99% CI: 2.04-3.40, p-value < 0.001 and Fuzzy Logic SIRS/OF AOR 2.64, 99% CI: 2.04-3.41, p-value < 0.001) (Table 12).

Discrimination of SOFA Score and Fuzzy Logic SIRS/OF Criteria Met

Prediction and performance analyses (discrimination) were completed on the primary test cohort (273,752 adult ICU patients) and the secondary test cohort (56,060 adult ICU patients with sepsis). Sensitivity and specificity analyses were used to evaluate the ability of each measurement system to correctly identify patients with/without death or sepsis, while the positive predictive value (PPV) and negative predictive values (NPV) were used to determine the prevalence of death or sepsis within the cohort.[59] The sensitivity, specificity, NPV, and PPV for Fuzzy Logic SIRS/OF and SOFA are found in Table 13.

Table 13. Sensitivity, Specificity, NPV, and PPV for Each Measurement System

Predictor	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Primary Aim Cohort: Sepsis				
SOFA ≥ 2 score	86.1%	35.6%	90.9%	25.7%
Fuzzy Logic criteria met	81.6%	51.8%	91.6%	30.4%
Primary Aim Cohort: Mortality				
SOFA ≥ 2 score	94.3%	33.8%	98.3%	12.9%
Fuzzy Logic criteria met	86.5%	48.2%	97.2%	14.8%
Secondary Aim Cohort: Mortality				
SOFA ≥ 2 score	96.2%	16.0%	94.8%	20.7%
Fuzzy Logic criteria met	93.5%	21.2%	93.5%	21.2%

NPV; negative predictive value; PPV, positive predictive value; SOFA, sepsis-related organ failure assessment

In the primary cohort, SOFA had higher sensitivity for both sepsis and mortality (86.1% and 94.3%, respectively) when compared to Fuzzy Logic SIRS/OF (81.6% and 86.5%, respectively. Whereas, Fuzzy Logic SIRS/OF exhibited higher specificity in both sepsis and mortality (51.8% and 48.2%, respectively) than SOFA (35.6% and 33.8%, respectively). In the secondary cohort, SOFA had higher sensitivity for mortality (96.2%) when compared to Fuzzy Logic SIRS/OF (93.5%) while Fuzzy Logic SIRS/OF had higher specificity (21.2%) than SOFA (16%).

When Fuzzy Logic SIRS/OF criteria were not met in the primary cohort there was a high probability that sepsis was not present (NPV 91.6%) and even higher probability that the patient survived (NPV 97.2%). SOFA exhibited similar NPV (90.9% for sepsis and 98.3% for mortality). On the other hand, when Fuzzy Logic SIRS/OF criteria were met there was a marginal probability that sepsis was present (PPV 30.4%) and a low probability that the patient died (PPV 14.8%) in the primary cohort. SOFA exhibited similar findings for sepsis (PPV 25.7%) and for mortality (PPV 12.9%). In the secondary cohort NPV was higher for SOFA (94.8%) than for Fuzzy Logic SIRS/OF (93.5%) while PPV was higher for Fuzzy Logic SIRS/OF (PPV 21.2%) than for SOFA (PPV 20.7%). Specificity, sensitivity, PPV, NPV are useful analyses to determine how well each measurement system correctly identified the condition when it was present. Receiver operator characteristic curves are a plot of false positives against true positives for all cut-off values.

Fuzzy Logic SIRS/OF (AUROC 0.67, 99% CI: 0.66-0.67) outperformed SOFA (AUROC 0.61, 99% CI: 0.61-0.61) in discrimination of sepsis with between group difference AUROC 0.06 (z-value 49.06). Likewise, when considered along with baseline risk prediction of sepsis (adjusted analysis), Fuzzy Logic SIRS/OF demonstrated greater discriminatory capacity for sepsis (AUROC 0.77, 99% CI: 0.77-0.77) than SOFA (AUROC 0.74, 99% CI: 0.74-0.74) with between-group difference AUROC 0.03 (z-value of 36.22). All between differences were significant at p-value <0.0001. AUROCs (crude and adjusted) and in-between differences are found in Table 14.

Table 14. Discrimination of SOFA vs Fuzzy Logic SIRS/OF and Study Outcomes

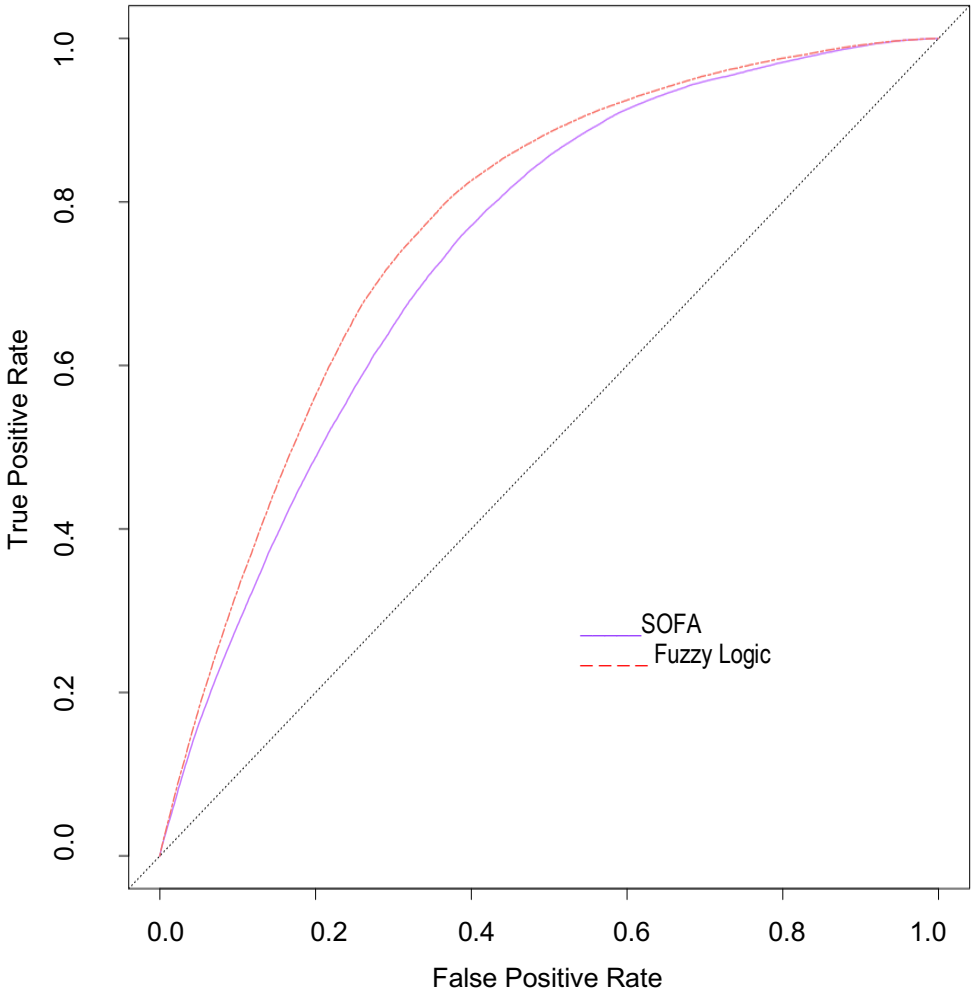
	SOFA	Fuzzy Logic
Primary Cohort Sepsis		
Crude AUROC	0.609	0.667
(99% CI)	(0.607-0.611)	(0.664-0.669)
Adjusted AUROC	0.740	0.771
(99% CI)	(0.737-0.743)	(0.768-0.773)
Primary Cohort Mortality		
Crude AUROC	0.641	0.673
(99% CI)	(0.639-0.643)	(0.670-0.676)
Adjusted AUROC	0.759	0.777
(99% CI)	(0.756-0.763)	(0.773-0.780)
Secondary Cohort Mortality		
Crude AUROC	0.561	0.573
(99% CI)	(0.558-0.564)	(0.570-0.578)
Adjusted AUROC	0.676	0.689
(99% CI)	(0.669-0.683)	(0.682-0.696)

In-Between Difference	**Primary Cohort Sepsis**	**Primary Cohort Mortality**	**Secondary Cohort Mortality**
Crude AUROC	0.058	0.032	0.012
Z-Value	49.06	24.679	6.863
P value	<0.0001	<0.0001	<0.0001
Adjusted AUROC	0.031	0.018	0.013
Z-Value	36.22	14.737	7.533
P value	<0.0001	<0.0001	<0.0001

SIRS, systemic inflammatory response syndrome; OF, organ failure; SOFA, sepsis-related organ failure assessment; CI, confidence intervals, AUROC, area under the receiver operator curve; Mort, mortality; Z-Value calculated using Delong's test to compare differences between AUROC[60]

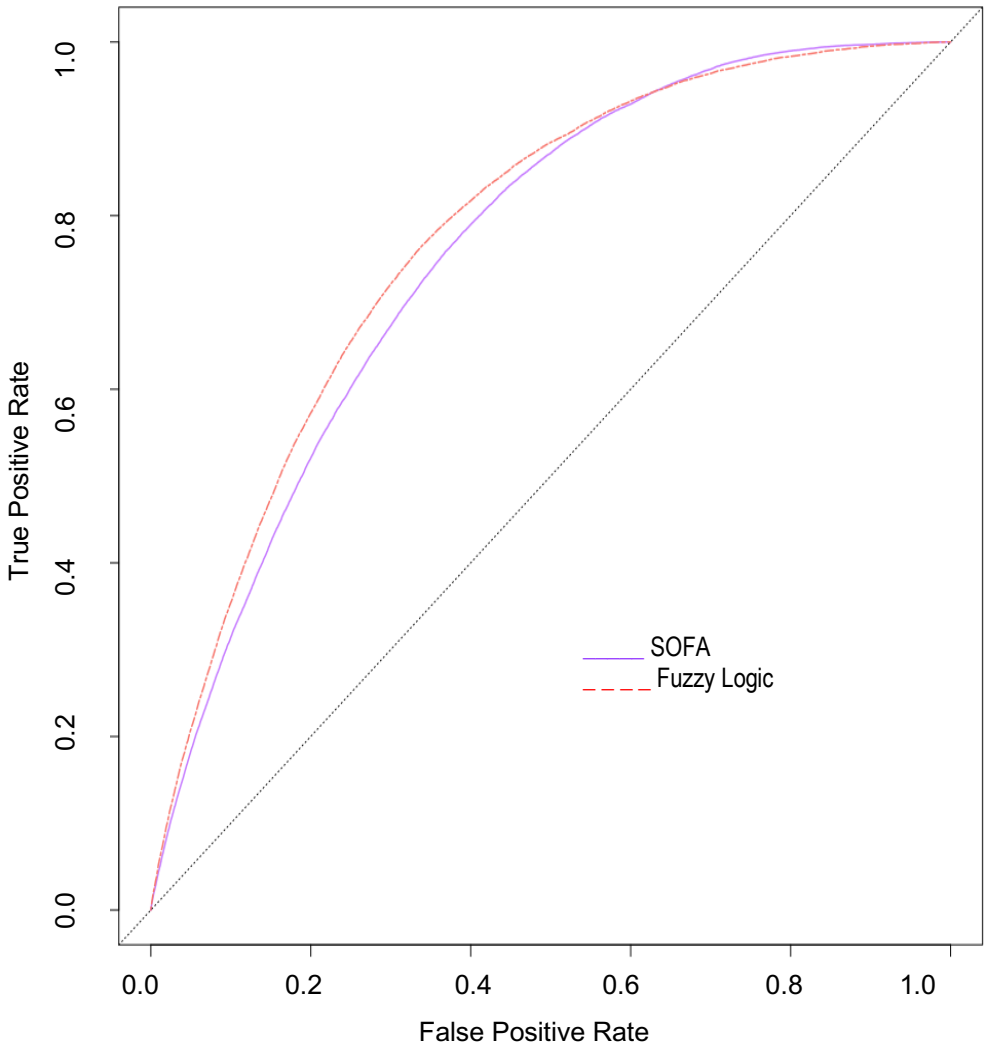
Crude Fuzzy Logic SIRS/OF (AUROC 0.67, 99% CI: 0.67-0.68) outperformed SOFA (AUROC 0.64, 99% CI: 0.64-0.64) for mortality. Fuzzy Logic SIRS/OF demonstrated better discrimination in the adjusted model (AUROC 0.78, 99% CI: 0.77-0.78) than SOFA (AUROC 0.76, 99% CI: 0.76-0.76) for mortality. Adjusted AUROCs for sepsis and for mortality are found in Figures 12, 13, and 14.

Figure 12. AUROC Adjusted Sepsis Prediction for the Primary Cohort Test Sets



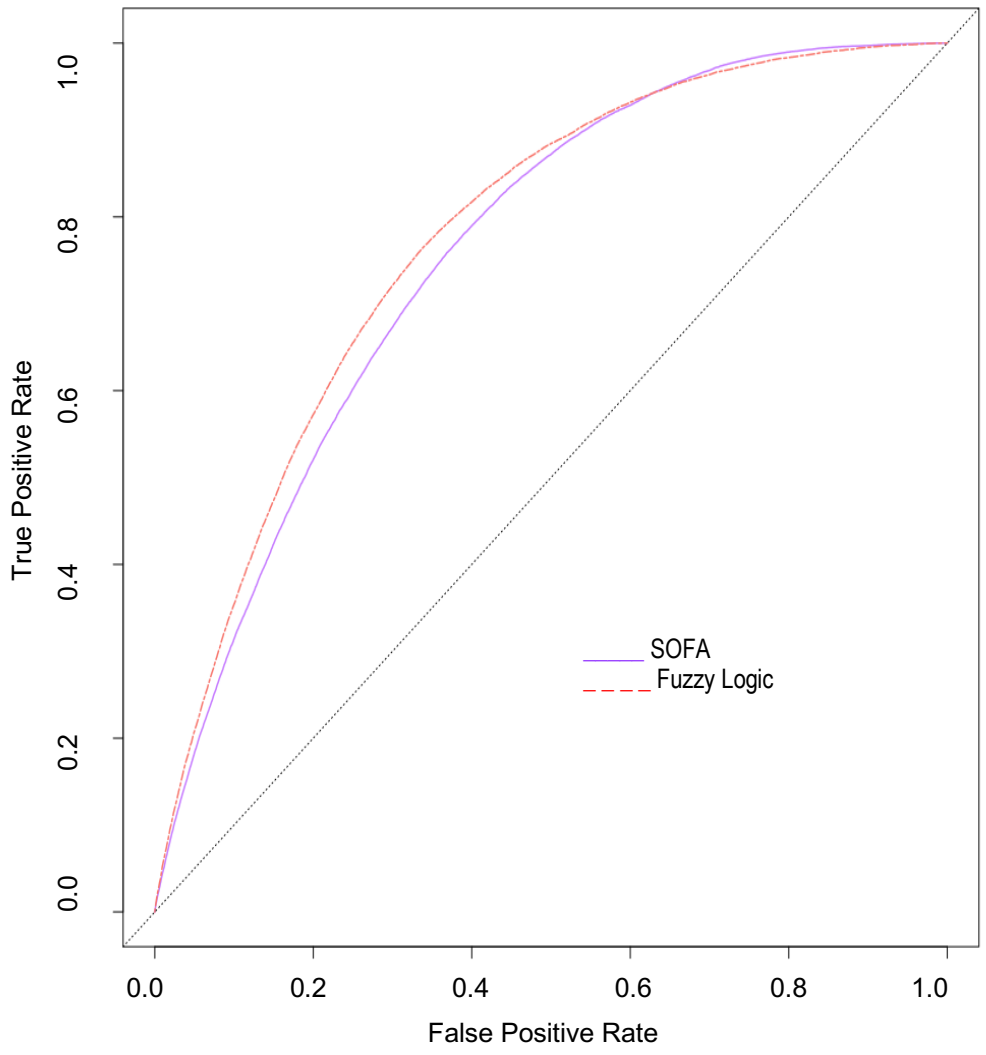
AUROC, Area Under the Receiver Operator Characteristic Curves (AUROC); SOFA, sepsis-related organ failure assessment; Fuzzy Logic, an algorithm applied to expanded systemic inflammatory response syndrome criteria and organ failure criteria

Figure 13. AUROC Adjusted Mortality Prediction for the Primary Cohort Test Sets



AUROC, Area Under the Receiver Operator Characteristic Curves (AUROC); SOFA, sepsis-related organ failure assessment; Fuzzy Logic, an algorithm applied to expanded systemic inflammatory response syndrome criteria and organ failure criteria

Figure 14. AUROC Adjusted Mortality Prediction for the Secondary Cohort Test Sets



AUROC, Area Under the Receiver Operator Characteristic Curves (AUROC); SOFA, sepsis-related organ failure assessment; Fuzzy Logic, an algorithm applied to expanded systemic inflammatory response syndrome criteria and organ failure criteria

Discrimination of mortality in the secondary test cohort, demonstrated similar trends with Fuzzy Logic SIRS/OF (AUROC 0.57, 99% CI: 0.57-0.58) outperforming SOFA (AUROC 0.56, 99% CI: 0.56-0.56) with between-group difference AUROC 0.01 (z-value 6.86, p-value < 0.0001). When considered along with baseline risk prediction of mortality (adjusted analysis), Fuzzy Logic SIRS/OF demonstrated better discrimination

(AUROC 0.69, 99% CI: 0.68-0.70) than SOFA (AUROC 0.68, 99% CI: 0.67-0.68). The between group difference was 0.01 (z-value 7.53, p-value < 0.0001).

Patients in the primary cohort who met thresholds within each measurement system had a greater incremental increase across all deciles of baseline risk for sepsis (Table 15). For patients with Fuzzy Logic SIRS/OF crtieria met and with SOFA score of 2 or more, greater incremental percent increases across all deciles of baseline risk for mortality were also demonstrated (Table 16).

Table 15. Percentage of Change over Deciles of Risk for Sepsis for Primary Cohort Training Sets

Decile of Risk	No.	SOFA Score				Fuzzy Logic Criteria			
		< 2 Points		≥ 2 Points		Not Met		Met	
Sepsis Present		yes	no	yes	no	yes	no	yes	no
1	29214	445	12149	1386	15234	395	13638	1436	13745
		3.66%		9.10%		2.90%		10.45%	
2	30053	533	10095	2133	17292	542	13638	2124	14013
		5.28%		12.34%		4.05%		15.16%	
3	30904	742	9963	2804	17395	719	13338	2827	14020
		7.45%		16.12%		5.39%		20.16%	
4	31856	741	9901	3742	17472	899	13377	3584	13996
		7.48%		21.42%		6.72%		25.61%	
5	32675	854	9577	4444	17800	1054	13568	4244	13809
		8.92%		24.97%		7.77%		30.73%	
6	33528	866	8554	5271	18837	1130	12865	5007	14526
		10.12%		27.98%		8.78%		34.47%	
7	34212	922	7782	5931	19577	1324	12301	5529	15058
		11.85%		30.30%		10.76%		36.72%	
8	34889	916	6785	6598	20590	1351	11311	6163	16064
		13.50%		32.04%		11.94%		38.37%	
9	35677	898	5856	7404	21519	1397	10409	6905	16966
		15.33%		34.41%		13.42%		40.70%	
10	37000	883	4609	8743	22765	1561	8749	8065	18625
		19.16%		38.41%		17.84%		43.30%	

SOFA, sepsis-related organ failure assessment; Fuzzy Logic, an algorithm applied to expanded systemic inflammatory response syndrome and organ failure criteria

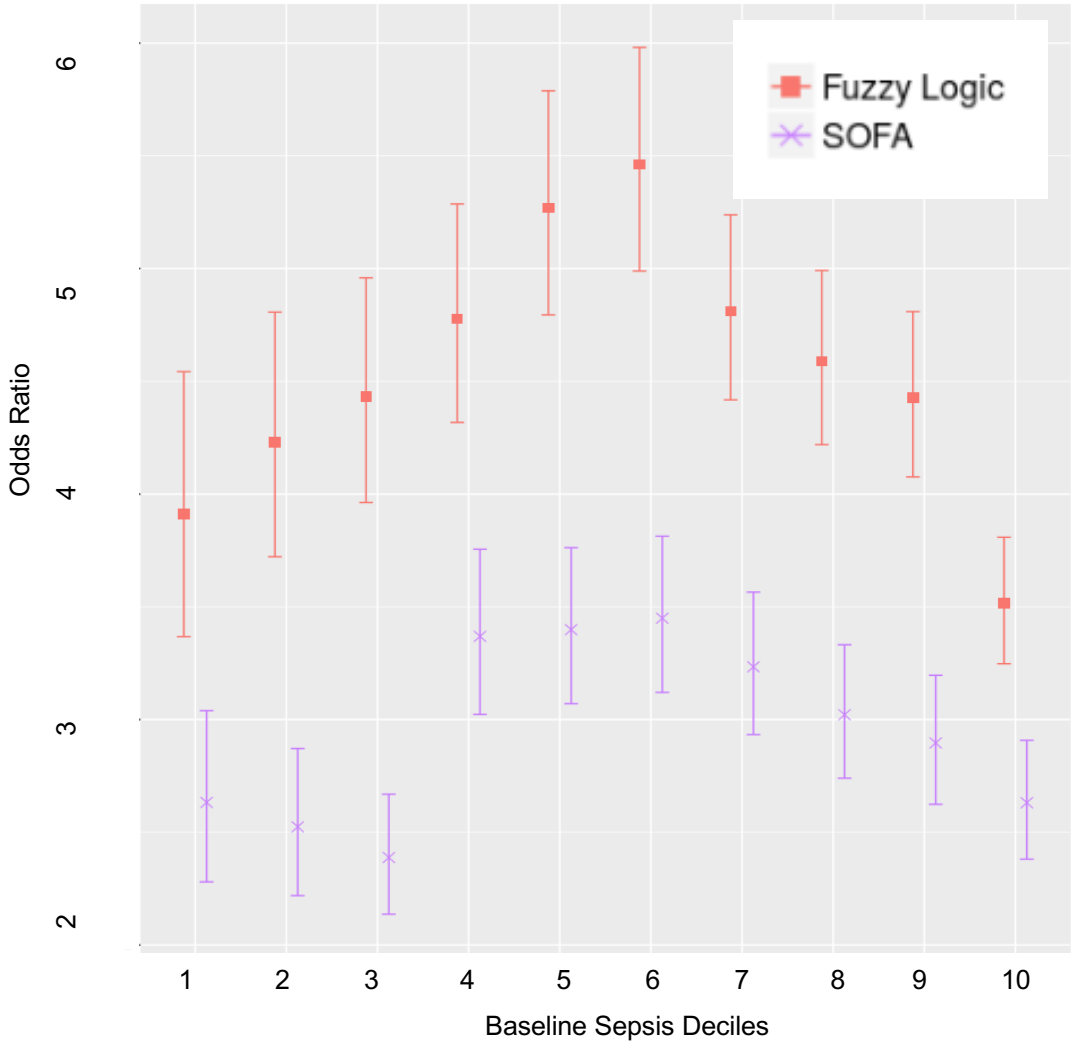
Table 16. Percentage of Change over Deciles of Risk for Mortality for Primary Cohort Training Sets

Decile of Risk	No.	SOFA Score				Fuzzy Logic Criteria			
		< 2 Points		≥ 2 Points		Not Met		Met	
Expired		yes	no	yes	no	yes	no	yes	no
1	27912	21	12149	508	15234	51	13638	478	13745
		0.17%		3.33%		0.37%		3.48%	
2	28255	31	10095	837	17292	91	13374	777	14013
		0.31%		4.84%		0.68%		5.54%	
3	28491	48	9963	1085	17395	129	13338	1004	14020
		0.48%		6.24%		0.97%		7.16%	
4	28945	66	9901	1506	17472	199	13377	1373	13996
		0.67%		8.62%		1.49%		9.81%	
5	29238	119	9577	1742	17800	272	13568	1589	13809
		1.24%		9.79%		2.00%		11.51%	
6	29835	156	8554	2288	18837	351	12865	2093	14526
		1.82%		12.15%		2.73%		14.41%	
7	30247	158	7782	2730	19577	408	12301	2480	15058
		2.03%		13.94%		3.32%		16.47%	
8	31092	227	6785	3490	20590	541	11311	3176	16064
		3.35%		16.95%		4.78%		19.77%	
9	31872	254	5856	4243	21519	617	10409	3880	16966
		4.34%		19.72%		5.93%		22.87%	
10	33730	384	4609	5972	22765	833	8749	5523	18625
		8.33%		26.23%		9.52%		29.65%	

SOFA, sepsis-related organ failure assessment; Fuzzy Logic, an algorithm applied to expanded systemic inflammatory response syndrome and organ failure criteria

Visually, Fuzzy Logic ORs were higher than SOFA and there was no overlap in confidence intervals (CI 99%) between them across all deciles in the primary cohort for sepsis (Figure 15). This indicates superior discrimination of sepsis by Fuzzy Logic over SOFA. The bell-shaped apperance of Fuzzy Logic indicated escalating odds of sepsis until about the 6th decile when the odds ratios begin to decline. In deciles 1-3 SOFA appears to have decending odds of sepsis with increased odds in deciles 4-6 after which the odds of sepsis diminish.

Figure 15. Odds Ratio Change over Deciles of Risk for Sepsis for Primary Cohort Training Sets

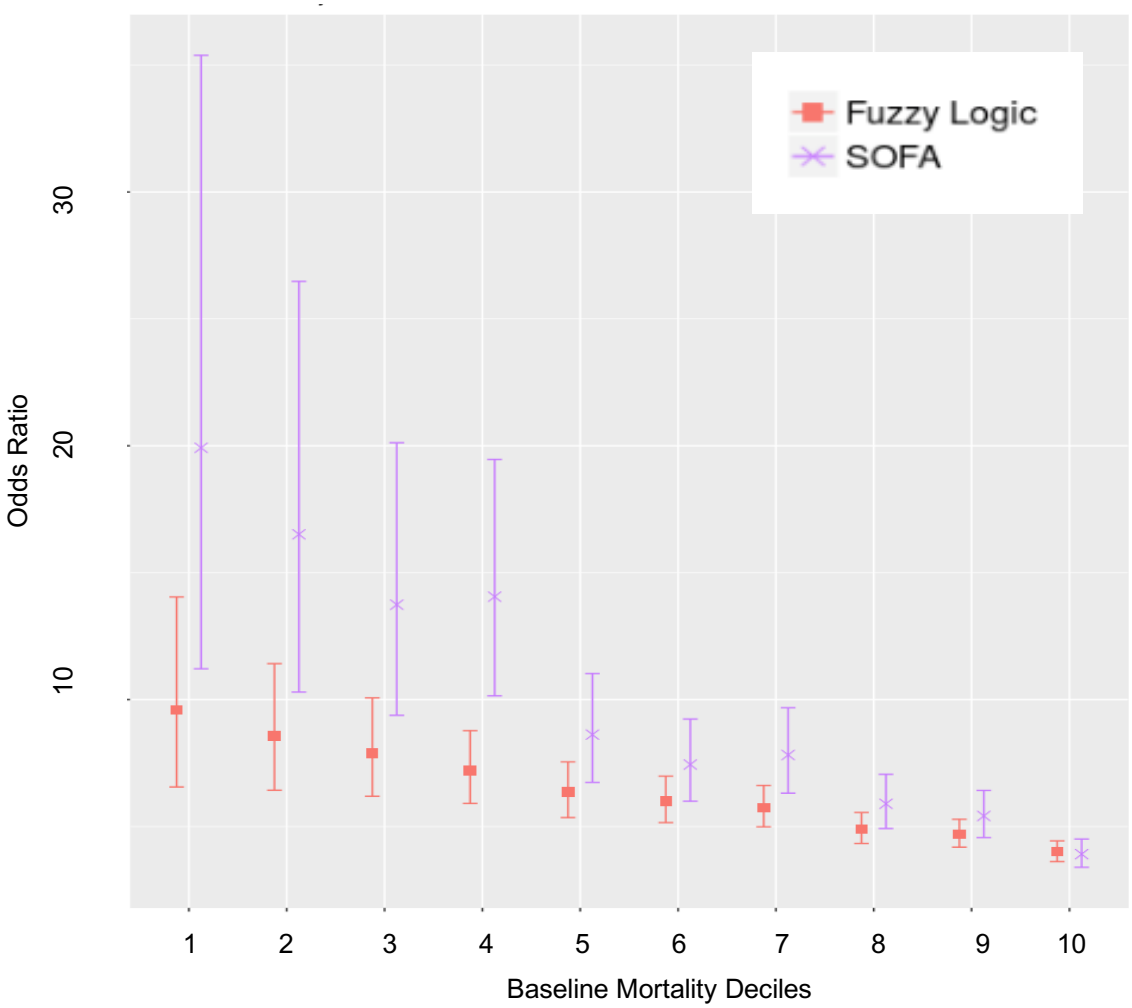


SOFA, sepsis-related organ failure assessment; Fuzzy Logic, an algorithm applied to expanded systemic inflammatory response syndrome and organ failure criteria

The OR changes across deciles of mortality risk (Figure 16) demonstrate the odds of death actual decrease with each increasing decile. SOFA ORs were higher than Fuzzy Logic SIRS/OF and the CIs for SOFA are quite wide in quartiles 1-4 and by quartile 5 the CIs begin to shrink and come down to almost meet Fuzzy Logic SIRS/OF. The ORs

for both measurement systems decrease like stair steps after the first decile (lowest risk) to the 10th decile (highest risk) and there is overlap in every decile except decile 4.

Figure 16. Odds Ratio Change over Deciles of Risk for Mortality for Primary Cohort Training Sets



SOFA, sepsis-related organ failure assessment; Fuzzy Logic, an algorithm applied to expanded systemic inflammatory response syndrome and organ failure criteria

For patients with Fuzzy Logic SIRS/OF crtieria met and with SOFA score of 2 or more in the secondary cohort, greater incremental percent increases across all deciles of baseline risk for mortality were demonstrated (Table 17). Visually, Fuzzy Logic ORs and CIs overlap with the SOFA ORs and CIs across all deciles indicating lack of

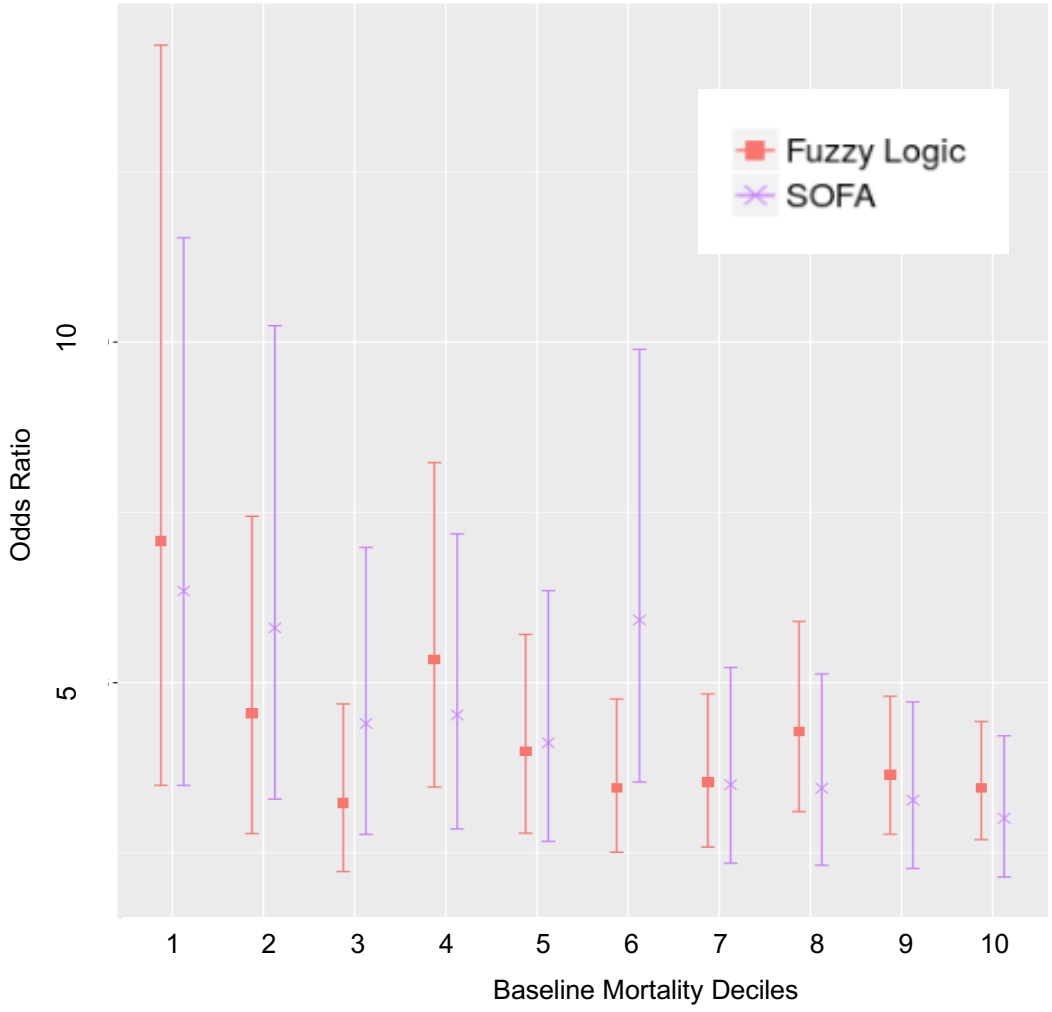
difference among the measurement systems (Figure 17). The ORs for both SOFA and Fuzzy Logic appear to have significant variablity and without a clear pattern across the 10 deciles. This differs from the pattern visualized over deciles of risk for mortality in the primary cohort (Figure 16). This may be explained by the difference in the number of patients between the cohorts.

Table 17. Percentage Change over Deciles of Risk for Mortality for Secondary Cohort Training Sets

		SOFA Score				Fuzzy Logic Criteria			
Decile of Risk	**No.**	**< 2 Points**		**≥ 2 Points**		**Not Met**		**Met**	
Expired		yes	no	yes	no	yes	no	yes	no
1	5981	20	1401	354	4206	14	1144	360	4463
		1.43%		8.42%		1.22%		8.07%	
2	6156	22	1024	519	4591	30	1100	511	4515
		2.15%		11.30%		2.73%		11.32%	
3	6311	34	929	670	4678	55	1109	649	4498
		3.66%		14.32%		4.96%		14.43%	
4	6391	34	843	760	4754	39	1078	755	4519
		4.03%		15.99%		3.62%		16.71%	
5	6523	39	762	880	4842	59	1066	860	4538
		5.12%		18.17%		5.53%		18.95%	
6	6648	27	656	1005	4960	76	1064	956	4552
		4.12%		20.26%		7.14%		21.00%	
7	6784	47	607	1135	4995	80	983	1102	4619
		7.74%		22.72%		8.14%		23.86%	
8	6958	48	524	1310	5076	75	924	1283	4676
		9.16%		25.81%		8.12%		27.44%	
9	7200	58	500	1535	5107	108	950	1485	4657
		11.60%		30.06%		11.37%		31.89%	
10	7493	70	456	1818	5149	138	934	1750	4671
		15.35%		35.31%		14.78%		37.47%	

SOFA, sepsis-related organ failure assessment; Fuzzy Logic, an algorithm applied to expanded systemic inflammatory response syndrome and organ failure criteria

Figure 17. Odds Ratio Change Over Deciles of Risk for Mortality for Secondary Cohort Training Sets



SOFA, sepsis-related organ failure assessment; Fuzzy Logic, an algorithm applied to expanded systemic inflammatory response syndrome criteria and organ failure criteria

Sensitivity Analysis

To assess robustness, a number of sensitivity analyses were performed and included: 1) sepsis versus non-sepsis patients, 2) mortality for patients with and without sepsis (primary cohort) and mortality for patients with sepsis (secondary cohort), and 3)

using adjusted model (baseline risk) versus unadjusted analyses. In each, case Fuzzy Logic SIRS/OF demonstrated better discrimination when compared to SOFA.

Discussion

The discriminatory capacity of binary measures for the SOFA score (2 or more) and Fuzzy Logic SIRS/OF (criteria met) were assessed in a large ICU population of patients between 2010 and 2015. The expanded SIRS using Fuzzy Logic and with OF criteria demonstrated superior prognostic accuracy for sepsis detection when compared to the SOFA score among ICU patients in U.S. hospitals. Although SOFA scores may be a useful predictor of mortality, Fuzzy Logic SIRS/OF also demonstrated strong discrimination for mortality. This study demonstrated that the use of expanded SIRS criteria with OF might be useful in identifying critically ill patients with sepsis with equal or greater prognostic accuracy than SOFA scores of 2 or more.

In large retrospective studies using adult ICU cohorts, Raith et al.[32] and Seymour et al.[33] reported that SOFA demonstrated superior discrimination when compared to SIRS and qSOFA. Seymour et al. also reported that SOFA was not significantly different from the more complex Logistic Organ Dysfunction System (LODS); a scoring system that uses WBC counts, serum urea levels, and prothrombin times along with variables consistent with SOFA scoring. The results of the Seymour et al. study led to changes in the definitions of sepsis and recommendations advocating for the use of SOFA scores of 2 or more in the ICU setting for prognostication of sepsis and dissuaded clinicians from using traditional methods of using a combination of SIRS with organ failure criteria.

As mentioned previously in this chapter, some experts in the fields of critical care and sepsis have raised concerns that reliance on organ failure measurement systems

might identify sepsis too late.[10,11] Comparing SIRS criteria to a scoring systems that included organ failure criteria (LODS, SOFA, qSOFA) was not consistent with real-world experiences reported in the literature where a combination of SIRS and organ failure criteria have been used for sepsis detection.[12-31]

For this study, the researcher tested an algorithm that used selected expanded SIRS criteria with Fuzzy Logic applied, along with organ failure criteria and compared its performance to the SOFA score of 2 or more. This allowed the researcher to compare sepsis detection criteria that were being used within the clinical setting by nursing against SOFA scores of 2 or more. Secondly, by using diagnostic data to determine the presence of sepsis (Table 6) allowed the researcher to analyze the discriminatory capacity of these measurement systems for detection of sepsis versus analyzing the prognostic accuracy of mortality for patients with infection as done in previous studies. Third, the discriminatory capacity of each measurement system for mortality among sepsis patients was also analyzed. This allowed the researcher to determine the prognostic accuracy for mortality of these measurement systems in a cohort of ICU sepsis patients. The results of this study demonstrated that the use of SIRS criteria along with organ failure criteria within a clinical decision support (CDS) algorithm could effectively be used to detect sepsis and to prognosticate mortality in adult patients within the first 24 hours of ICU admission.

Historically, simplified scoring systems were necessary because of ease of interpretability and lack of available real-time physiological and patient characteristic data that could be used to develop advanced algorithmic alerts in the EHR. However, with the recent integration of electronic health information systems, performance of

scoring systems should be considered alongside simplicity and interpretability. Computerized alerting systems can synthesize thousands of data points using complex algorithms and notify nurses in real- or near real-time that their patients may meet sepsis criteria.[62]

Health care organizations have been required to integrate CDS since the advent of the "meaningful use" EHR incentive program.[63] Most organizations have developed CDS for computerized physician order entry (CPOE) yet there is still a high incidence of reports of sepsis CDS in the literature.[1,64] In ICU's, simplistic scoring systems are easy to interpret and can be used without a computer. However, if nurses' use computerized algorithmic decision support systems they can enhance discrimination and timing of identification of sepsis.[13,19,24,65]

This study's cohort represented adult patients located in coronary care, surgical, trauma, neuroscience, and medical intensive care units in over 180 hospitals across the United States (U.S.). The patients represented in this study are broadly distributed regarding hospital and community size, U.S. regions, presence or absence of teaching programs, and models of ICU staffing. Patients within varying age groups, gender differences, ethnic backgrounds, and comorbid conditions were represented in this study. This broad representation supports generalizability of these results.

Of interest, in patients with diabetes who met criteria for Fuzzy Logic SIRS/OF had higher odds of sepsis (primary cohort) and lower odds of mortality (both primary and secondary cohorts) while patients with diabetes with a positive SOFA score had both lower odds of sepsis and lower odds of mortality. Type II diabetes, like sepsis, has been described as a disease with altered immunity with dysregulated immune pathways

(protracted inflammation and immune suppression).[66] This may contribute to higher odds of sepsis as seen in this study. Diabetic patients in both the primary and secondary cohorts had lower odds of death when the threshold for a measurement system was met versus when it was not met. A meta-analysis by Siegelaar et al. 2011 found that diabetes was not associated with increased mortality risk for ICU patients except for cardiac surgery patients, supporting this finding.[67] On the other hand, according to Koh et al. 2012, epidemiological studies have produced conflicting results regarding diabetic patients with infections and/or sepsis and risk of mortality.[68]

In this study, sepsis patients who had received thrombolytic therapy for AMI prior to ICU admission had significant increase in odds of death versus sepsis patients admitted with AMI who had not received thrombolytic therapy. Inflammation and coagulation are common, co-occurring abnormalities in septic patients and are likely activated by multiple mediators.[69] It has been postulated that the sepsis inflammatory cascade and/or profound perfusion abnormalities in septic shock may predispose a patient to AMI.[70,71] Coagulopathy in acute sepsis (CAS) has been described as a disorder whereby the coagulation cascade becomes diffusely activated, leading to consumption of multiple clotting factors and disseminated intravascular coagulation (DIC).[69] The goal of thrombolytic therapies is to disrupt the coagulation cascade. This disruption along with the coagulation disturbances occurring in acute sepsis may predispose patients to greater risk. More research in this area is needed.

The ORs for Fuzzy Logic SIRS/OF were higher than SOFA across all deciles of risk for sepsis (Figure 15) and OR CIs did not overlap indicating significant differences. There were overlap of OR CIs demonstrating that Fuzzy Logic SIRS/OF and SOFA

were not statistically significantly different across deciles of risk for mortality in both the primary and secondary cohorts (Figure 16 and Figure 17). In the primary cohort (Figure 16), the smaller confidence intervals in the higher mortality risk deciles were likely due to larger numbers of higher risk patients in these deciles. ORs were useful in explaining the association of the models when conditioned with Fuzzy Logic SIRS/OF and SOFA but were not useful to measure discrimination (prognostic accuracy).

Fuzzy Logic SIRS/OF AUROCs were significantly different demonstrating superior discriminatory capacity for sepsis than SOFA (Table 14). Fuzzy Logic SIRS/OF AUROCs were significantly different demonstrating better prognostic accuracy of mortality than SOFA in both the primary and secondary cohorts (Table 14). The AUROC findings of this study demonstrate that using a combination of SIRS criteria, with Fuzzy Logic applied, along with organ failure criteria (algorithm for an electronic sepsis prompt) had superior discrimination for identifying adult ICU patients with sepsis when compared to SOFA (**Aim 1**). These findings also revealed the discriminatory capacity for in-hospital mortality of an increase in SOFA score of 2 or more points versus the presence of an electronic sepsis prompt within the first 24 hours of ICU admission in among adult ICU patients with sepsis (**Aim 2**).

Limitations

There are several limitations of this study. First, the data are entered prospectively into the database and this investigation was retrospective. Confounding variables are a threat in any observational data due to the effects of exposure on a particular outcome being associated with additional factors.[72] In randomization, cofounders are more equally distributed between groups. Although this researcher has used research

transparency through code sharing along with careful selection of inclusion/exclusion criteria and a deep understanding of the dataset used in this study to mitigate this limitation, this bias cannot be eliminated. Second, the dataset does not include information related to mortality post hospital discharge, consequently in-hospital mortality was chosen for this endpoint.

Third, sepsis is a difficult condition to define without clear delineation of onset. Thus, the decision to use diagnostic data to define sepsis in this cohort was used. Fourth, demographic, comorbid conditions and diagnostic data within the model was dependent on accurate documentation. There was no way to measure the accuracy of these data variables within the dataset. Fifth, the complexity and size of the data set was impractical to do multiple imputation for missingness and to apply analytics related to when a threshold of a measurement system was met.

Sixth, after applying the inclusion/exclusion criteria for year, age, APACHE score, and readmission, the exclusions related to the use of complete case analysis reduced the primary cohort to 45.2% of the complete cohort that introduces uncertainty regarding generalizability. Seventh, we did not exclude patients with limitations of care or comfort care status, and this could have skewed the outcome of mortality. Eighth, the sepsis alert is a proprietary algorithm with limited publicly available documentation on how it was coded. The MIT team was able to work with the researcher and vendor to interpret the rules related to the inputs and outputs. This allowed the researcher to normalize the behavior over time and use a consistent approach for analyzing measurement systems.

Conclusions

For patients with sepsis, early detection has been shown to be crucial for improving

outcome and survival. However, sepsis can be difficult to diagnose quickly and often patients become critically ill and often die. The results of this study demonstrate that among ICU patients, the predictive validity for sepsis and in-hospital mortality of a complex algorithm based on Fuzzy Logic applied to expanded SIRS criteria with organ failure criteria was better than SOFA for detection of sepsis. The findings of this study also suggest that using a complex algorithm was also a better method than SOFA for prognostic accuracy of mortality.

Early identification of sepsis has been cited as one of the biggest obstacles to timely therapeutic interventions aimed at saving lives and reducing complications.[73] For example, delays in administration of broad-spectrum antibiotics in sepsis and septic shock that have been linked with increased mortality.[74-77] The findings of this study support the use of computer-enhanced algorithms that include a combination of expanded SIRS with organ failure criteria as a tool to assist nurses in early identification of sepsis.

References

1. Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *Am J Respir Crit Care.* 2016;193(3):259-272.

2. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis. *JAMA.* 2010;304(16):1787-1794.

3. Davis JS, He V, Anstey NM, Condon JR. Long term outcomes following hospital admission for sepsis using relative survival analysis: a prospective cohort study of 1,092 patients with 5 year follow up. *PLoS One.* 2014;9(12):e112224.

4. National Institute of General Medical Sciences. Sepsis fact sheet. 2014; http://www.nigms.nih.gov/Education/Pages/factsheet_sepsis.aspx. Accessed June 26, 2015.

5. Lagu T, Rothberg M, Steingrub J, Lindenauer P. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. *Crit Care Med.* 2012;40(3):754-761.

6. Torio CM, Moore BJ. *Statistical Brief #204. Healthcare Cost and Utilization Project (HCUP).* Rockville, MD: Agency for Healthcare Research and Quality (AHRQ);2016.

7. Kleinpell R. Promoting early identification of sepsis in hospitalized patients with nurse-led protocols. *Crit Care.* 2017;21(1):10.

8. Aitken LM, Williams G, Harvey M, et al. Nursing considerations to complement the Surviving Sepsis Campaign guidelines. *Crit Care Med.* 2011;39(7):1800-1818.

9. Singer M, Deutschman C, Seymour C, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):801-810.

10. Simpson SQ. New Sepsis Criteria: A Change We Should Not Make. *Chest.* 2016;149(5):1117-1118.

11. Genga KR, Russell JA. Update of Sepsis in the Intensive Care Unit. *J Innate Immun.* 2017;9(5):441-455.

12. Alsolamy S, Al Salamah M, Al Thagafi M, et al. Diagnostic accuracy of a screening electronic alert tool for severe sepsis and septic shock in the emergency department. *BMC Med Inform Decis Mak* 2014;14(105):1-6.

13. Amland R, Hahn-Cover K. Clinical decision support for early recognition of sepsis. *AM J Med Qual.* 2014:1-8.

14. Buck K. Developing an early sepsis alert program. *J Nurs Care Qual.* 2014;29(2):124–132.

15. Campbell J. The effect of nurse champions on compliance with keystone intensive care unit sepsis-screening protocol. *Crit Care Nurs Q.* 2008;31(3):251-269.

16. Croft C, Moore F, Efron P, et al. Computer versus paper system for recognition and management of sepsis in surgical intensive care. *J Trauma Acute Care Surg.* 2014;76(2):311-318.

17. Giuliano KK. *Physiologic monitoring for critically ill patients: Testing a predictive model for the early identification of sepsis*, Boston College; 2005.

18. Gyang E, Shieh L, Forsey L, Maggio P. A nurse-driven screening tool for early identification of sepsis in an intermediate care unit setting. *J Hosp Med.* 2015;10(2):97-103.

19. Harrison A, Thongprayoon C, Kashyap R, et al. Developing the surveillance algorithm for detection of failure to recognize and treat severe sepsis. *Mayo Clin Proc.* 2015;90(2):639-644.

20. Hooper M, Weavind L, Wheeler A, et al. Randomized trial of automated, electronic monitoring to facilitate early detection of sepsis in the intensive care unit. *Crit Care Med.* 2012;40(7):2096-2101.

21. McKinley BA, Moore LJ, Sucher JF, et al. Computer protocol facilitates evidence-based care of sepsis in the surgical intensive care unit. *J Trauma.* 2011;70(5):1153-1167.

22. Moore L, Jones S, Kreiner L, et al. Validation of a screening tool for the early identification of sepsis. *J Trauma.* 2009;66(6):1539–1547.

23. Nelson J, Smith B, Jared J, Younger J. Prospective trial of real-time electronic surveillance to expedite early care of severe sepsis. *Ann Emerg Med.* 2011;57(5):500-504.

24. Nguyen S, Mwakalindile E, Booth J, et al. Automated electronic medical record sepsis detection in the emergency department. *PeerJ.* 2014;2(e343).

25. Patocka C, Turner J, Xue X, Segal E. Evaluation of an emergency department triage screening tool for suspected severe sepsis and septic shock. *J Healthc Qual.* 2013;36(1):52-61.

26. Rincon T, Bourke G, Seiver A. Standardizing sepsis screening and management via a Tele-ICU program improves patient care. *Telemed J E Health.* 2011:1-5.

27. Sawyer A, Deal E, Labelle A, et al. Implementation of a real-time computerized sepsis alert in nonintensive care unit patients. *Crit Care Med.* 2011;39(3):469-473.

28. Singer A, Taylor M, Domingo A, et al. Diagnostic characteristics of a clinical screening tool combination with measuring a bedside lactate level in emergency department patients with suspected sepsis. *Acad Emerg Med.* 2014;21(8):853-857.

29. Tsoukalas A, Albertson T, Tagkopoulos I. From data to optimal decision making: A data-driven, probabilistic machine learning approach to decision support for patients with sepsis. *JMIR Med Inform.* 2015;3(1):1-15.

30. Wallgren U, Castren M, Svensson A, Kurland L. Identification of adult septic patients in the prehospital setting: a comparison of two screening tools and clinical judgment. *Eur J Emerg Med.* 2014;21(4):260-265.

31. Westphal G, Koenig Á, Caldeira Filho M, et al. Reduced mortality after the implementation of a protocol for the early detection of severe sepsis. *J Crit Care.* 2011;26(1):76-81.

32. Raith EP, Udy AA, Bailey M, et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. *JAMA.* 2017;317(3):290-300.

33. Seymour C, Liu V, Iwashyna T, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):762-774.

34. Lilly C, Zuckerman I, Badawi O, Riker R. Benchmark data from more than 240,000 adults that reflect the current practice of critical care in the United States. *Chest.* 2011;140(5):1232-1242.

35. U.S. Department of Health & Human Services. Guidance regarding methods for de-identification of protected health information in accordance with the health insurance portability and accountability act (HIPAA) privacy rule. *Health Information Privacy* 2010; http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/De-identification/guidance.html#dates. Accessed June 28, 2015.

36. The MIT Lab for Computational Physiology eICU Collaborative Research Database. 2016; http://eicu-crd.mit.edu/. Accessed March 7, 2018.

37. R Core Team. R: A language and environment for statistical computing. 2016; https://www.R-project.org/.

38. Goldberger AL, Amaral LAN, Glass L, et al. PhysioBank, PhysioToolkit, and PhysioNet. *Components of a New Research Resource for Complex Physiologic Signals.* 2000;101(23):e215-e220.

39. Kaukonen K-M, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med.* 2015;372(17):1629-1638.

40. Zimmerman J, Kramer A, McNair D, Malila F. Acute physiology and chronic health evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med.* 2006;34(5):1297-1310.

41. Keegan M, Gajic O, Afessa B. Comparison of APACHE III, APACHE IV, SAPS 3, and MPM III and Influence of Resuscitation Status on Model Performance. *Chest.* 2012;142(4):851-858.

42. McPhee LC, Badawi O, Fraser GL, et al. Single-Dose Etomidate Is Not Associated With Increased Mortality in ICU Patients With Sepsis: Analysis of a Large Electronic ICU Database*. *Crit Care Med.* 2013;41(3):774-783.

43. Badawi O, Waite MD, Fuhrman SA, Zuckerman IH. Association between intensive care unit–acquired dysglycemia and in-hospital mortality*. *Crit Care Med.* 2012;40(12):3180-3188.

44. Waite MD, Fuhrman SA, Badawi O, Zuckerman IH, Franey CS. Intensive care unit-acquired hypernatremia is an independent predictor of increased mortality and length of stay. *J Crit Care.* 2013;28(4):405-412.

45. Dong Y, Peng CY. Principled missing data methods for researchers. *SpringerPlus.* 2013;2(1):222.

46. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med.* 2001;29(7):1303-1310.

47. Martin G, Mannino D, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med.* 2003;348(16):1546-1554.

48. Manganaro L, Stark M. APACHE® Foundations User Guide Cerner Corporation; 2010. Accessed February 16, 2013.

49. Pilcher D, Litton E, Millar J, Huckson S, Gian S. APD Data Dictionary for Software Programmers. In: Committee ACM, ed. *ANZICS Core - Adult Patient*

Database Carlton South VIC ANZICS Centre for Outcome and Resource Evaluation; 2017.

50. Johnson AE, Stone DJ, Celi LA, Pollard TJ. The MIMIC Code Repository: enabling reproducibility in critical care research. *J Am Med Inform Assoc.* 2018;25(1):32-39.

51. GitHub. Hello World. *GitHub Guides* 2016; https://guides.github.com/activities/hello-world/#what. Accessed August 5, 2017.

52. Levy M, Fink M, Marshall J, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med.* 2003;31(4):1250-1256.

53. Rincon TA, Manos EL, Pierce JD. Telehealth Intensive Care Unit Nurse Surveillance of Sepsis. *CIN: Computers, Informatics, Nursing.* 2017;35(9):459-464.

54. Cintula P, Fermüller CG, Noguera C. Fuzzy Logic. *The Stanford Encyclopedia of Philosophy* 2017; Fall 2017:https://plato.stanford.edu/archives/fall2017/entries/logic-fuzzy/. Accessed March 31, 2018.

55. Nimri R, Phillip M. Artificial pancrease: fuzzy logic and control of glycemia. *Curr Opin Endocrinol Diabetes Obes.* 2014;21(4):251-256.

56. Nguyen B, Bernstein D, Bates J. Controlling mechanical ventilation in acute respiratory distress syndrome with fuzzy logic. *J Crit Care.* 2014;29(4):551-556.

57. Moteghaed NY, Maghooli K, Garshasbi M. Improving Classification of Cancer and Mining Biomarkers from Gene Expression Profiles Using Hybrid Optimization Algorithms and Fuzzy Support Vector Machine. *J Med Signals Sens.* 2018;8(1):1-11.

58. Bardossy A, Blinowska A, Kuzmicz W, et al. Fuzzy logic-based diagnostic algorithm for implantable cardioverter defibrillators. *Artif Intell Med.* 2014;60(2):113-121.

59. Lalkhen AG, McCluskey A. Clinical tests: sensitivity and specificity. *Continuing Education in Anaesthesia Critical Care & Pain.* 2008;8(6):221-223.

60. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics.* 1988;44(3):837-845.

61. Jiang X, Osl M, Kim J, Ohno-Machado L. Calibrating predictive model estimates to support personalized medicine. *J Am Med Inform Assoc.* 2012;19(2):263-274.

62. Makam AN, Nguyen OK, Auerbach AD. Diagnostic accuracy and effectiveness of automated electronic sepsis alert systems: A systematic review. *J Hosp Med.* 2015;10(6):396-402.

63. Campbell R. The Five Rights of Clinical Decision Support: CDS Tools Helpful for Meeting Meaningful Use. 2018; http://library.ahima.org/doc?oid=300027#.Wt6I2NPwZTZ. Accessed April 22, 2018.

64. Liu V, Escobar GJ, Greene JD, et al. Hospital deaths in patients with sepsis from 2 independent cohorts. *JAMA.* 2014;312(1):90-92.

65. Nemati S, Holder A, Razmi F, Stanley MD, Clifford GD, Buchman TG. An Interpretable Machine Learning Model for Accurate Prediction of Sepsis in the ICU. *Crit Care Med.* 2018;46(4):547-553.

66. Frydrych LM, Fattahi F, He K, Ward PA, Delano MJ. Diabetes and Sepsis: Risk, Recurrence, and Ruination. *Front Endocrino.* 2017;8:271.

67. Siegelaar SE, Hickmann M, Hoekstra JBL, Holleman F, DeVries JH. The effect of diabetes on mortality in critically ill patients: a systematic review and meta-analysis. *Crit Care.* 2011;15(5):R205-R205.

68. Koh GCKW, Peacock SJ, van der Poll T, Wiersinga WJ. The impact of diabetes on the pathogenesis of sepsis. *Eur J Clin Microbiol Infect Dis* 2012;31(4):379-388.

69. Simmons J, Pittet J-F. The Coagulopathy of Acute Sepsis. *Curr Opin Anaesthesiol.* 2015;28(2):227-236.

70. Shah M, Patnaik S, Maludum O, et al. Mortality in sepsis: Comparison of outcomes between patients with demand ischemia, acute myocardial infarction and neither demand ischemia nor acute myocardial infarction. *Clinical cardiology.* 2018.

71. Smilowitz NR, Gupta N, Guo Y, Bangalore S. Comparison of Outcomes of Patients With Sepsis With Versus Without Acute Myocardial Infarction and Comparison of Invasive Versus Noninvasive Management of the Patients With Infarction. *The American journal of cardiology.* 2016;117(7):1065-1071.

72. MIT Critical Data. Secondary Analysis of Electronic Health Records. Cambridge, MA: Massachusett's Institute of Technology; 2016.

73. Vincent J-L. The Clinical Challenge of Sepsis Identification and Monitoring. *PLoS Medicine.* 2016;13(5):e1002022.

74. Liu VX, Fielding-Singh V, Greene JD, et al. The Timing of Early Antibiotics and Hospital Mortality in Sepsis. *Am J Respir Crit Care Med.* 2017;196(7):856-863.

75. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med.* 2013;39(2):165-228.

76. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med.* 2014:1-7.

77. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006;34(6):1589-1596.

Chapter 5.

Summary of Chapters, Discussion, Implications, and Conclusion

The primary objective of this dissertation was to conduct a retrospective study using a large data repository to determine if an electronic prompt can detect sepsis and to determine the prognostic accuracy of the SOFA score and the sepsis prompt in discriminating in-hospital mortality among patients with sepsis in the intensive care unit (ICU). The primary aims of this study were: **Aim 1** To determine if an electronic sepsis prompt that uses systemic inflammatory response syndrome and organ failure criteria identifies sepsis in the electronic health record (EHR) for adult intensive care unit (ICU) patients; and **Aim 2** To determine the effect of an increase in sepsis-related organ failure assessment (SOFA) score of 2 or more points and the presence of an electronic sepsis prompt within the first 24 hours of ICU admission in discriminating in-hospital mortality among adult ICU patients with sepsis. This chapter includes a summary of each chapter with an overall discussion of the results from the study (Chapter 4), implications for practice, recommendation for future research, and conclusion.

Summary of Chapters

The first chapter of this dissertation describes the challenges of early identification of sepsis, the changes in how sepsis has been defined over the years, the incidence and pathophysiology of sepsis, and the complications that patients suffer related to sepsis. Chapter 1 also describes the operational conceptual framework that was used for the theoretical structure for study design, the assumptions, the potential limitations, and the importance of determining what system of measure might be more useful in identifying sepsis. In this chapter, the examination of performance for Systemic Inflammatory Response Syndrome (SIRS) with organ failure (OF) criteria versus sepsis-related organ failure scores (SOFA) for identification of sepsis in adult ICU patients with known or

suspected infection was discussed.

There have been many publications in literature describing diagnostic criteria used for early identification of sepsis. For this study, the researcher focused on 20 publications that are listed in chapter 1 (Table 2). Most of these publications described using the four original SIRS criteria (80%) as described by Bone et al. in 1992[1], but only 30% actually adhered to two or more SIRS criteria as a positive threshold. Some included only 3 SIRS criteria while others included 5 or more SIRS using an additional criteria from the expanded SIRS list published by Levy et al. in 2003.[2] Other studies combined SIRS or expanded SIRS with organ dysfunction criteria. Others added weights to criteria within the algorithmic alerts.

Chapter 1 also described how nurses working in a remote location were able to develop and execute a sepsis screening process for over 400 intensive care unit (ICU) beds located at more than 20 hospitals in Northern California. This “remote location”, known as a telehealth ICU (TeleICU), was the first on the West Coast and the second in the nation. This system included data collection workflow information that was supported by telecommunication technologies, health information systems, and a locally developed data collection and information sharing platform.[3]

Chapter 2 is a published article, describing how TeleICU nurses supported bedside teams in early identification and treatment of sepsis using a knowledge management approach.[4] This chapter focused on key concepts of evidence-based knowledge management (EBKM) and assessed the effectiveness of an open source software application solution and analyzed the significance of the integration of EBKM at the time when care is being delivered. Four specific areas were highlighted: 1) the significance of

decision-making and errors that harm patients, 2) the integration of knowledge management into clinical practice and workflows, 3) a description of the tools used to target sepsis in a large health system, and 4) successful integration of EBKM using nurses working in a TeleICU as knowledge translators.[4]

In the literature, there are three major contributing factors to errors by nurses that were identified: 1) Lack of knowledge and experience, inability to articulate the rationale for practice patterns, 2) not considering current evidence during decision-making, and 3) frequent interruptions.[5-7] How unchallenged hierarchal cultures lead to protecting and honoring unscientific variations and use of outdated protocols in care are highlighted in chapter 2.[8] This unwillingness to change local routines coupled with lack of information systems that provide the right information at the right time to someone with the evidence-based knowledge leads to a perpetual cycle of mistakes.

Also in chapter 2, there is a review of knowledge management (KM) that incorporates acquisition, sharing, translation, and application of knowledge.[9,10] Knowledge translation closes the gap between knowledge and practice[11] and provides a gateway for evidence-based decision-making to occur.[12] The use of TeleICU nurses as sepsis experts expanded and cultivated KM by providing the right knowledge at the right time by the right individuals with the right tools. This allowed these experts to assess patients at the correct time while influencing repetitive, continual, and routine diffusion of evidence-based practices at multiple hospitals in a large healthcare system. The data collection tools they developed and used allowed near-real time auditing and feedback that provided the health system insight into how care was being delivered to patients and where improvement in care delivery was needed.

Chapter 3 is a published article describing the assessment of design of the sepsis prompt created for and used by TeleICU nurses using a human factors evaluation approach.[13] The science of human factors engineering studies the interaction of users with systems with a goal of reducing end-user dissatisfaction, enhancing performance, and improving safety of a design.[14,15] Alerts are notifications built within health information software applications to assist with clinical decision-making. There have been many reports of clinicians and scientists to designing sepsis early warning systems, but what had not been well described in the literature was the usability of these alerting systems. Usability assessment is a technique within human factors science to determine how well the user interacts with the system. Success is determined by reducing negative design impacts (dissatisfaction, mistakes, costs, inefficiencies, level of stress to end user) while improving positive impacts (error avoidance, improved efficiency, enhanced individual performance, and reduction in unsafe practices).[14,15]

Also discussed in Chapter 3 is the use of cognitive task analysis to evaluate the task-switching, complex decision-making, reasoning, and knowledge translation that occur during sensory and information processing stages.[16] Using a scientific approach to evaluate the usability of a system allows designers to overcome design flaws that interfere with important sensory and information processing activities, reduce competition for these resources, and reduce task-switching (often referred to as multi-tasking).[16] Clinical alert design needs to ensure that applicable information is provided to an individual who understands its meaning, using the most suitable channel with appropriate hazard matching at the right time in the workflow. If this can be achieved,

the severity of the situation along in conjunction with EBKM can mitigate alert fatigue (desensitization) and improve clinical decision-making at the point when care is being delivered.

Figure 6 in Chapter 3 describes potential strain points or factors associated with patient care processes like assessing patients for sepsis. These strains include: 1) external forces that dictate policy and public awareness of sepsis; 2) social components that impact the ability to embrace change and let go of old ways; 3) physical components that can cause distractions or diminish performance; 4) tools and resources that enhance productivity, 5) individual competency, alertness, knowledge, and motivation; and 6) the intricacy of the nature of the work, all influence how early and how well clinicians identify this complex and elusive syndrome.[17,18]

The TeleICU nurses were motivated and experienced critical care nurses, who because of their advanced knowledge, were set aside to provide surveillance using high-tech audio-video and clinical decision support tools. Using an iterative process, designers used cognitive task analysis to gain deeper insight into the manual sepsis screening process developed and used by these nurses. The designers also evaluated the human-system exchanges of the nurses with the sepsis prompt and made alterations to its design based on user-centered interpretations. The fuzzy logic computing algorithm along with suppression techniques were used to improve the discriminatory capacity of the sepsis prompt. The combination of these interventions mitigated various latent contributors (strains) that negatively impact early identification of sepsis.

Chapter 4 is the major study of this dissertation in a manuscript format. The primary

objective of this dissertation was to conduct a retrospective study using a large data repository to determine if an electronic prompt can detect sepsis and to determine the prognostic accuracy of the SOFA score and the sepsis prompt in discriminating in-hospital mortality among patients with sepsis in the intensive care unit. The Fuzzy Logic with expanded SIRS and OF criteria algorithm and the SOFA score logic were both applied to the dataset. Each case was then analyzed to determine if Fuzzy Logic SIRS/OF criteria were met or if a SOFA score of 2 or more was present in the first 24 hours of ICU admission.

In order **to determine if an electronic sepsis prompt that uses systemic inflammatory response syndrome and organ failure criteria identifies sepsis in the electronic health record (EHR) for adult intensive care unit (ICU) patients** (**Aim 1**), all cases underwent a binary classification process using diagnostic codes to determine the presence of sepsis (Chapter 4, Table 6). Fuzzy Logic area under the operating receiver curves (AUROCs) for sepsis were higher (in both crude and adjusted analyses) than for positive SOFA scores and differences were statistically significant (Chapter 4, Table 14).

The findings in this study indicated that the Fuzzy Logic SIRS/OF criteria used by the electronic sepsis prompt demonstrated greater discriminatory capacity over SOFA scores of two or more in detecting sepsis among ICU patients in U.S. hospitals. These findings answered **Research question 1: Using the electronic intensive care unit (eICU) Research Institute (eRI) data repository, how accurately does the electronic sepsis prompt detect sepsis in adult ICU patients within the first 24 hours of admission to the ICU?**

To determine the effect of an increase in sepsis-related organ failure assessment (SOFA) score of 2 or more points and the presence of an electronic sepsis prompt within the first 24 hours of ICU admission in discriminating in-hospital mortality among adult ICU patients with sepsis (Aim 2), analyses for mortality were completed on all cases (primary cohort) and on a secondary cohort of only patients with sepsis. The adjusted odds ratio (AOR) findings of this study (Chapter 4, Table 12) demonstrated that sepsis patients with a SOFA score of 2 or more, versus patients with a SOFA score less than 2, had higher odds of mortality among ICU patients in U.S. hospitals in the secondary cohort (AOR 4.13, 99% CI: 3.86-4.42, p-value <0.001).

This finding addresses **Research hypothesis 2a: Using the eICU Research Institute (eRI) data repository, adult ICU patients with sepsis who have an increase in SOFA score of 2 or more in the first 24 hours of their ICU stay will have higher in-hospital mortality rates than sepsis patients with a SOFA score less than 2.**

The adjusted odds ratio (AOR) findings of this study (Chapter 4, Table 12) demonstrated that sepsis patients who met Fuzzy Logic SIRS/OF criteria, versus those that did not met criteria, had higher odds of mortality among ICU patients in U.S. hospitals in the secondary cohort (AOR 3.51, 99% CI: 3.33-3.69, p-value < 0.001).

This finding addresses **Research hypothesis 2b: Using the eICU Research Institute (eRI) data repository, adult ICU patients with sepsis who have presence of an electronic sepsis prompt in the first 24 hours of their ICU stay will have higher in-hospital mortality rates than sepsis patients without presence of a**

sepsis prompt.

The findings of this study demonstrated that the Fuzzy Logic SIRS/OF criteria used by the electronic sepsis prompt demonstrated better discriminatory capacity than SOFA scores of two or more in prognostic accuracy of mortality among ICU patients in U.S. hospitals in both the primary and secondary cohorts. AUROCs for mortality for Fuzzy Logic SIRS/OF criteria were higher (in both crude and adjusted analyses) than for positive SOFA scores and differences were statistically significant in both cohorts (Chapter 4, Table 14). These findings answered **Research question 2a: What are the differences in the in-hospital mortality rates in adult ICU patients with sepsis using an increase in the SOFA score of 2 or more versus the electronic sepsis prompt?**

It is important to note that the sensitivity of SOFA was higher (86.1%) versus Fuzzy Logic SIRS/OF (81.6%) and the specificity was higher with FL SIRS/OF (51.8%) versus SOFA (35.6%) for sepsis (Chapter 4, Table 13). The positive predictive value (PPV 30.4%), the probability that patients who met FL SIRS/OF criteria had sepsis, and the negative predictive value (NPV 91.6%), the probability that patients who did not meet Fuzzy Logic SIRS/OF criteria did not have sepsis, were higher than for SOFA score of 2 or more (PPV 25.7%, NPV 90.9%). This trend of higher sensitivity and lower specificity with SOFA was consistent when analyzing the outcome of mortality (Chapter 4, Table 13).

Most clinical tests and measurement systems fall short of correctly identifying all patients with a disease while also correctly identifying patients without the disease.[19] To interpret the results of this study, the investigator initially decided that having more false

positives (the patient does not have sepsis but the measurement system is positive) versus false negatives (the patient has sepsis but the measurement system is negative) was better as it would mitigate missing patients with sepsis.[19] This decision included considering accuracy of true positives (the patient has sepsis and the measurement system is positive) versus the true negatives (the patient does not have sepsis and the measurement system is negative).

Alternatively, a perfect measurement system would never miss and would not alarm when there was no real clinical indication. In practice, nurses have become desensitized to clinical warning systems primarily due to clinical alarms and alerts being designed with high sensitivity at the expense of specificity.[20] The Joint Commission continues to identify alarm management as an important patient safety goal for hospitals with a focus of making improvements to ensure that alarms on medical equipment are heard and responded to on time.[21] The National Institute of Standards and Technology (NIST) and Agency for Healthcare Research and Quality (AHRQ) have both identified that the use of clinical warning systems built into electronic health records have led to desensitization of clinical alerts (alert fatigue) that consecutively may result in patient injury.[22-24] Thus it is important to consider a balance between sensitivity and specificity when interpreting these results.

The receiver operator characteristic curves illustrate the false positives against true positives for all cut-off values with a perfect test equal to 1.0.[19] The unadjusted AUROC for SOFA score of 2 or more was accurate approximately 60% of the time versus meeting criteria for FL SIRS/OF, which was marginally better (accurate 67% of the time). Once baseline risk adjustments were made, both of the measurement systems

had improved with SOFA increasing accuracy to 74% and FL SIRS/OD increasing to 77%. Thus, the researcher determined that the Fuzzy Logic SIRS/OF algorithm was more specific, sensitive than that of the SOFA. However, that both measurement systems have opportunities for improvement.

Discussion

Sepsis remains an elusive syndrome to delineate, identify, and diagnose, despite multiple attempts by experts throughout the last three decades to define it.[1,2,25] New definitions related to sepsis have created concern in the clinical community and confusion related to sepsis identification methods.[26] Historically, simplistic sepsis screening methods have been preferred due to ease of interpretability but as described in this dissertation, the impact to efficiency, educational burden, and concerns regarding timeliness of assessments (frequency of screening) are real concerns in nursing. However, with the recent integration of electronic health information systems, computerized warning systems (alerts) can use complex algorithms to synthesize thousands of data points to notify nurses in real- or near real-time that their patients may be septic.[27]

To ensure that an alert is usable, the five rights of clinical decision support (CDS) should be considered: 1) right information, 2) right person, 3) right format, 4) right channel, and 5) right time.[28] Chapter 2 of this dissertation focused on the “right person” within the conceptual framework of EBKM. The use of experts in the role of knowledge translators conducting surveillance was further discussed in chapter 3. Using human factors science techniques (cognitive task analysis, user-centered design, and usability) led to the development of the electronic sepsis prompt. The researcher assessed and

described the sensory and cognitive processing that occurred when expert nurses responded to the electronic sepsis prompt.

Working with sepsis expert nurses (user-centered design) influenced decisions regarding when and how often the alert should fire (right time). The second international definition of sepsis along with the cognitive task analysis of the sepsis expert nurse process determined the sepsis prompt criteria. The findings of the study (Chapter 4) demonstrated that the decisions regarding what criteria to include (expanded SIRS and OF) within a Fuzzy Logic algorithm outperform the more simplistic method of a SOFA score of 2 or more among adult ICU patients in the U.S in prognostic accuracy of mortality and sepsis detection.

Implications for Practice

The information from this dissertation has important nursing implications related to improving early recognition of sepsis and quality of care. Although bedside nurses provide continuous interaction when caring for patients who are critically ill and injured, there are barriers (strain points) associated with patient care processes like assessing patients for sepsis that may hinder early detection. Awareness and knowledge of sepsis, use of outdated protocols, distractions, individual competency, alertness, and motivation all influence how early and how well nurses identify sepsis.

Standardized knowledge related to sepsis detection and anticipating therapeutic interventions has been described as important to early detection of sepsis and is a resource intensive process.[29-31] Using specially trained sepsis responders has been reported in the literature as an effective way to save lives and decrease complications in septic patients.[30,32] Others have demonstrated that the use of complex sepsis alerts

built within EHRs along with designated sepsis response teams may be a more sustainable approach to reducing mortality, morbidity, and cost.[30,31,33] A human factors science approach focused on expert nurse surveillance behaviors along with advanced statistical modelling can be used to improve the performance and acceptance of sepsis alerts. This in turn has implications for timely identification of sepsis and subsequent improvement in mortality, complications, and ultimately cost of care.

Recommendations for Future Research

Additional research on discriminatory accuracy and the usability of electronic alerts designed to support early sepsis detection is needed. Simplistic measurement tools may be useful in some circumstances but with the advent of the EHR, research in expert clinician surveillance behaviors coupled with the use of machine learning and artificial intelligence can lead to greater accuracy in sepsis detection. Human factors science can be used to evaluate human-system interactions and ensure that the right person receives relevant, timely, and appropriate information at the right time using the right median.

Human factors science can also guide the creation of environments and tools that reduce other strain points that impede early identification of complex and difficult to identify diseases and syndromes like sepsis. Studies that focus on what role and what level of expertise is needed for effective early detection of sepsis is important to mitigating errors of omission and misses. Research is needed to better understand the surveillance behaviors that ICU and TeleICU nurses use when interacting with complex algorithmic alerts and clinical decision support tools in the care of critically ill and injured patients.

Conclusion

The incidence of septic shock has steadily increased during the past several decades.[34] Early identification of sepsis by nurses and the healthcare team is essential to initiate early treatment and reduce in-hospital mortality in patients with sepsis.[31,35,36] Surveillance activities and tools that enhance timely and effective detection of sepsis and support clinical decision-making by nurses can lead to further reductions in mortality and morbidity. Nurses have historically used a combination of SIRS and organ failure criteria to screen for sepsis however, more recent definitions emphasize the use of SOFA. The findings of this study suggest that SOFA scoring may have limited utility for detecting sepsis the ICU patients and more complex computer enhanced algorithms that use SIRS criteria with OF may detect sepsis more effectively.

References

1. Bone R, Balk R, Cerra F, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM consensus conference committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest.* 1992;101(6):1644-1655.

2. Levy M, Fink M, Marshall J, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med.* 2003;31(4):1250-1256.

3. Rincon T, Bourke G, Seiver A. Standardizing sepsis screening and management via a Tele-ICU program improves patient care. *Telemed J E Health.* 2011:1-5.

4. Rincon T. Integration of evidence-based knowledge management in microsystems: a Tele-ICU experience. *Crit Care Nurs Q.* 2012;35(4):335-340.

5. Landrigan CP, Parry GJ, Bones CB, Hackbarth AD, Goldmann DA, Sharek PJ. Temporal trends in rates of patient harm resulting from medical care. *N Engl J Med.* 2010;363(22):2124-2134.

6. Henneman E, Gawlinski A, Blank F, Henneman P, Jordan D, McKenzie J. Strategies used by critical care nurses to identify, interrupt, and correct medical errors. *Am J Crit Care.* 2010;19(6):500-509.

7. George EL, Henneman EA, Tasota FJ. Nursing implications for the prevention of adverse drug events in the intensive care unit. *Crit Care Med.* 2010;38(6):S136-144.

8. Berwick DM. A user's manual for the IOM's 'Quality Chasm' report. *Health Aff.* 2002;21(3):80-90.

9. Wickramasinghe N. Practising what we preach: are knowledge management systems in practice really knowledge management systems? *Bus Process Manage J.* 2003;9(3):295-316.

10. Bali RK, Dwivedi AN, eds. *Healthcare Knowledge Management: Issues, Advances and Successes.* New York, NY: Springer Science Business Media, LLC; 2007.

11. Scott S, Albrecht L, O'Leary K, et al. A Protocol for a systematic review of knowledge translation strategies in the allied health professions. *Implement Sci* 2011;6(58):1-19.

12. Goode CJ. Evidence-Based Practice. In: Oman KS., Krugman ME., Fink RM., eds. *Nursing Research Secrets*. Philadelphia, Pennsylvania: Hanley & Belfus, Inc; 2003.

13. Rincon TA, Manos EL, Pierce JD. Telehealth intensive care unit nurse surveillance of sepsis. *Comput Inform Nurs.* 2017;35(9):459-464.

14. Carayon P, Alvarado C, Hundt A. Work System Design in Health Care. In: Carayon P, ed. *Handbook of Human Factors and Economics in Health Care and Patient Safety*. Boca Raton, FL: Taylor & Francis Group, LLC; 2012:65-80.

15. Carayon P, Xie A, Kianfar S. Human Factors and Ergonomics. *Making Health Care Safer II: An Updated Critical Analysis of the Evidence for Patient Safety Practices*. Rockville, MD: Agency for Healthcare Research and Quality 2013:325-350.

16. Wickens C. Multiple resources and performance prediction. *Theor Issues in Ergon Sci.* 2002;3(2):159-177.

17. Carayon P, Gurses A. A human factors engineering conceptual framework of nursing workload and patient safety in intensive care units. *Intensive Crit Care Nurs.* 2005;21(5):284-301.

18. Carayon P, Wood KE. Patient Safety: The Role of Human Factors and Systems Engineering. *Studies in health technology and informatics.* Vol 1532010:23-46.

19. Lalkhen AG, McCluskey A. Clinical tests: sensitivity and specificity. *Continuing Education in Anaesthesia Critical Care & Pain.* 2008;8(6):221-223.

20. Sendelbach S, Funk M. Alarm fatigue: A patient safety concern. *Adv Crit Care.* 2013;24(4):378-386.

21. The Joint Commission. Hospital: 2018 National Patient Safety Goals. 2018; https://www.jointcommission.org/hap_2017_npsgs/. Accessed June 17, 2018.

22. Schumacher RM, Lowry SZ. *NIST Guide to the Processes Approach for Improving the Usability of Electronic Health Records.* Washington DC2010.

23. Patient Safety Network. Alert Fatigue: Patient Safety Primer. 2017; https://psnet.ahrq.gov/primers/primer/28/alert-fatigue. Accessed June 17, 2018.

24. Lowry SZ, Quinn MT, Ramaiah M, et al. A Human Factors Guide to Enhance EHR Usability of Critical User Interactions when Supporting Pediatric Patient Care; NISTIR 7865. Washington DC: National Institute of Standards and Technology, U.S. Department of Commerce; 2012.

25. Singer M, Deutschman C, Seymour C, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):801-810.

26. Simpson SQ. New Sepsis Criteria: A Change We Should Not Make. *Chest.* 2016;149(5):1117-1118.

27. Makam AN, Nguyen OK, Auerbach AD. Diagnostic accuracy and effectiveness of automated electronic sepsis alert systems: A systematic review. *J Hosp Med.* 2015;10(6):396-402.

28. Campbell R. The Five Rights of Clinical Decision Support: CDS Tools Helpful for Meeting Meaningful Use. 2018; http://library.ahima.org/doc?oid=300027#.Wt6I2NPwZTZ. Accessed April 22, 2018.

29. Bentley J, Henderson S, Thakore S, Donald M, Wang W. Seeking Sepsis in the Emergency Department- Identifying Barriers to Delivery of the Sepsis 6. *BMJ quality improvement reports.* 2016;5(1).

30. Guirgis FW, Jones L, Esma R, et al. Managing sepsis: Electronic recognition, rapid response teams, and standardized care save lives. *J Crit Care.* 2017;40:296-302.

31. Jones SL, Ashton CM, Kiehne L, et al. Reductions in Sepsis Mortality and Costs After Design and Implementation of a Nurse-Based Early Recognition and Response Program. *Jt Comm J Qual Saf* 2015;41(11):AP1-AP3.

32. Rivers E, Ahrens T. Improving outcomes for severe sepsis and septic shock: tools for early identification of at-risk patients and treatment protocol implementation. *Crit Care Clin.* 2008;23:S1-S47.

33. Grek A, Booth S, Festic E, et al. Sepsis and Shock Response Team: Impact of a Multidisciplinary Approach to Implementing Surviving Sepsis Campaign Guidelines and Surviving the Process. *Am J Med Qual.* 2017;32(5):500-507.

34. Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *Am J Respir Crit Care.* 2016;193(3):259-272.

35. Levy M, Dellinger R, Townsend S, et al. The surviving sepsis campaign: Results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med.* 2010;38(2):367-374.

36. Torsvik M, Gustad LT, Mehl A, et al. Early identification of sepsis in hospital inpatients by ward nurses increases 30-day survival. *Crit Care.* 2016;20(1):244.

Appendix

Appendix A. Permission to Use Sepsis Prompt Image from Philips Healthcare

DATE: July 19, 2018
TO: Philips Healthcare
RE: eCareManager Sepsis Prompt Screen Shots

Dear PERMISSIONS EDITOR:

Permission is requested on a non-exclusive basis to use this material in the dissertation entitled "Detecting Sepsis Using Sepsis-Related Organ Failure Assessment (SOFA) and an Electronic Sepsis Prompt in Intensive Care Unit Adult Patients" by Ms. Teresa Rincon. Permission is also requested to include the material in CD-ROM or other electronic format in English and in foreign translations with distribution rights throughout the world.

Permission is for screen shots, and approval is requested to offset and, if necessary, to redraw or modify the illustration or figure.

Full credit to the original sources will be given.

The signed permission approval should be sent directly to my attention at the address indicated below.

Sincerely,

PLEASE RETURN TO:
Teresa.rincon@umassmemorial.org
281 Lincoln Street
Worcester, MA 01605

PERMISSION IS GRANTED TO USE THE MATERIAL REQUESTED

Signed: 

Date: July 19, 2018

Appendix B. Permission to Use Images from Dr. David Heeger Ph.D.

Re: Request to use an image

David Heeger [david.heeger@nyu.edu]
Sent: Monday, May 25, 2015 9:41 AM
To: Teresa Rincon
Cc: David Heeger [david.heeger@nyu.edu]

Dear Teresa,

Yes, you have my permission to use those figures in your dissertation.

Sincerely,

David Heeger
Professor of Psychology and Neural Science
New York University

Center for Neural Science
4 Washington Place, room 809
New York, NY 10003

phone: 212-998-7868
email: david.heeger@nyu.edu
web: http://www.cns.nyu.edu/~david

On May 22, 2015, at 5:31 PM, Teresa Rincon wrote:

> Dear Dr. Heeger,
>
> I am a student at the University of Kansas School of Nursing in the Doctor of Philosophy program with a minor in Applied Healthcare Informatics. My area of interest is to examine the performance of a sepsis alert for systemic inflammatory response syndrome (SIRS) positive versus SIRS negative severe sepsis. The third chapter of my dissertation is an evaluation of the sepsis alert using human factors principles. I am incorporating Signal Detection Theory in this chapter. I would like permission to use some content and images from your handouts I found on-line: http://www-psych.stanford.edu/~lera/psych115s/notes/signal/ and on http://www.cns.nyu.edu/%7edavid/handouts/sdt-advanced.pdf.
>
> I am requesting your permission to use two images in a manuscript entitled **Design Implications of a Sepsis Alert: A Human Factors Evaluation.** I plan to submit this manuscript to the following journal: Intensive and Critical Care Nurse and I plan to use this publication as a chapter in my dissertation manuscript. Please see attached document.
>
> Kind Regards,
> Teresa A Rincon RN, BSN, CCRN-E, FCCM

Appendix C. University of Kansas School Human Research Determination Letter: Not Human Subjects Research

The University of Kansas Medical Center

Human Research Protection Program

October 1, 2015

Project Title: Detection of Severe Sepsis in Adult Intensive Care Unit Patients Using a Large Database
Investigators: Janet Pierce, PhD, PRN, eCRN, FAAN
Teresa Rincon RN, BSN, CCRN-E, FCCM
Department: School of Nursing
Determination: Not human subjects research

Dear Investigator:

Thank you for your submission. This letter certifies that the above referenced project has been evaluated by the KUMC Human Research Protection Program (HRPP).

This study will use data from Philips eICU Research Institute to determine whether the systemic inflammatory response syndrome criteria and an electronic prompt can detect severe sepsis in patients in adult intensive care units. The data have been independently certified as meeting HIPAA safe harbor standards. The data were collected for reporting purposes, and they are being provided to you by an outside source so that you are not able to ascertain individual identities. Therefore, your analysis does not involve human subjects and does not require IRB review.

Please note that if you revise your activities to interact directly with human subjects, or to obtain identifiable data about individuals, you should contact our office immediately. If this were to occur, the HRPP would re-evaluate your project's regulatory status. Please feel free to contact our office with any questions.

Very truly yours,

Kyle Stephens, MA, CIP
Assistant Director, Human Research Protection Program

Mail-Stop 1032, 3901 Rainbow Blvd., Kansas City, KS 66160
Phone: (913) 588-0942 Fax: (913) 588-5771 kblackwe@kumc.edu

Appendix D. Email Confirmation from University of Kansas School of Medicine Human Research Regarding Changes to Study Aims and Adding Year 2015

RE: Attached Image

Christopher Griffith
Sent: Friday, March 11, 2016 3:47 PM
To: Teresa Rincon
Cc: Janet Pierce

Hi Teresa,

IRB staff would only need to review this if you were adding research procedures. For the types of changes you are suggesting, no further review is required. The initial determination letter still applies.

Best regards,

Chris

Christopher Griffith, J.D., CIP
IRB Coordinator
Human Research Protection Program
University of Kansas Medical Center
(913) 588-1240 | humansubjects@kumc.edu
(913) 588-1379 | cgriffith@kumc.edu
4330 Shawnee Mission Parkway, Suite 350, Fairway, KS 66205
MS# 1032, 3901 Rainbow Blvd, Kansas City, KS 66160
IRB Website | eCompliance

From: Teresa Rincon
Sent: Friday, March 11, 2016 12:34 PM
To: Christopher Griffith
Cc: Janet Pierce
Subject: FW: Attached Image

Dear Chris,

I am a candidate in the PhD program and the School of Nursing. Based on the new international consensus definitions for sepsis and septic shock I needed to make some chnages to my dissertation study. The IRB determined that this was a QI project and "not human subjects" research. My changes include adding de-identified subjects from one additional year (adding 2015), adding the new definitions, and expanding the research aims to include the new definitions. I am attaching the IRB letter and a draft document that contains those changes for your review.

I appreciate your feedback on this matter.
Kind Regards,
Teresa Rincon
cell# 774-261-0560

PS I left you a voicemail message as well. My conference call at 2 pm CST was just cancelled so I am available anytime between now and 3 pm CST or after or after 4 pm. We can also set up a time next week to discuss as needed.

Appendix E. Approval to Use the eICU Research Institute (eRI) Complete Dataset

Teresa Rincon RN, BSN, CCRN-E, FCCM
eICU Ops Director
UMassMemorial Medical Center
Office: 508-793-6311
Email: Teresa.Rincon@umassmemorial.org

Re: ***Detection of Severe Sepsis in Adult Intensive Care Unit Patients Using a Large Database***

Dear Teresa Rincon:

On behalf of the eICU Research Institute and Philips Healthcare, I would like to confirm your study proposal, "Detection of severe sepsis in adult intensive care unit patients using a large database" was approved for research during the October 2015 eICU Research Institute meeting. You have been granted access, along with our academic research partners at MIT, to use the eICU Research Institute database to support this study. The data may only be used to support this specific study and all manuscripts must be reviewed by the eICU Research Institute Publications Committee prior to submission for peer review.

Congratulations and please let me know if you have any further questions.

Sincerely,

Omar Badawi, PharmD, MPH, FCCM
Director, Clinical Analytics & Reporting
Philips eICU Program
Patient Care Analytics

217 E. Redwood Street, Suite 1900, Baltimore, MD 21202
Work: 410-843-4531, Fax: 410-276-1970
Email: omar.badawi@philips.com

PHILIPS

Appendix F. Data Use Agreement for eICU Collaborative Research Dataset (Subset of eRI)

PhysioNet DUA for tarincon1@gmail.com-- approved
1 message

DoNotReply@physionet.org <DoNotReply@physionet.org> Tue, May 15, 2018 at 4:21 PM
To: tarincon1@gmail.com

Thank you for your interest in the PhysioNet Clinical Databases (MIMIC-II, MIMIC-III, eICU Collaborative Research Database).

Your request for access to PhysioNet restricted databases has been approved. Your access should be activated shortly.

For access, log in to PhysioNetWorks and click on the relevant link on your PhysioNetWorks home page.

Information about building databases from downloaded data files is available on the databases' respective PhysioNetWorks pages.

You may also log in to the MIMIC QueryBuilder (http://mimic.physionet.org/gettingstarted/querybuilder/) using your PhysioNetWorks username and password.

Appendix G. Copyright Clearance for Chapter 2

Copyright Clearance Center RightsLink®

Home | Account Info | Help

Wolters Kluwer

Title: Integration of Evidence-Based Knowledge Management in Microsystems: A Tele-ICU Experience
Author: Teresa Rincon
Publication: Critical Care Nursing Quarterly
Publisher: Wolters Kluwer Health, Inc.
Date: Oct 1, 2012
Copyright © 2012, © 2012 Lippincott Williams

Logged in as:
Teresa Rincon
Account #:
3001312340
LOGOUT

License Not Required

This request is granted gratis and no formal license is required from Wolters Kluwer. Please note that modifications are not permitted. Please use the following citation format: author(s), title of article, title of journal, volume number, issue number, inclusive pages and website URL to the journal page.

BACK | CLOSE WINDOW

Appendix F Copyright Clearance for Chapter 3

Copyright Clearance Center RightsLink®

Home | Account Info | Help

Wolters Kluwer

Title: Telehealth Intensive Care Unit Nurse Surveillance of Sepsis

Author: Teresa Rincon, E. Manos, and Janet Pierce

Publication: CIN: Computers, Informatics, Nursing

Publisher: Wolters Kluwer Health, Inc.

Date: Sep 1, 2017

Copyright © 2017, Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Logged in as:
Teresa Rincon
LOGOUT

License Not Required

This request is granted gratis and no formal license is required from Wolters Kluwer. Please note that modifications are not permitted. Please use the following citation format: author(s), title of article, title of journal, volume number, issue number, inclusive pages and website URL to the journal page.

BACK | CLOSE WINDOW