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Improved Methods of Sepsis Case Identification and the Effects of Treatment with Low Dose Steroids: A Dissertation

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IMPROVED METHODS OF SEPSIS CASE IDENTIFICATION AND THE EFFECTS OF TREATMENT WITH LOW DOSE STEROIDS

A Dissertation Presented

By

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DEDICATION

To my beloved husband, Hangsheng,

who always supports me in my determination to find and to realize my potential

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ABSTRACT

Sepsis is the leading cause of death among critically ill patients and the 10th most common cause of death overall in the United States. The mortality rates increase with severity of the disease, ranging from 15% for sepsis to 60% for septic shock. Patient with sepsis can present varied clinical symptoms depending on the personal predisposition, causal microorganism, organ system involved, and disease severity. To facilitate sepsis diagnosis, the first sepsis consensus definitions was published in 1991 and then updated in 2001. Early recognition of a sepsis patient followed with timely and appropriate treatment and management strategies have been shown to significantly reduce sepsis-related mortality, and allows care to be provided at lower costs. Despite the rapid progress in the knowledge of pathophysiological mechanisms of sepsis and its treatment in the last two decades, identifying patient with sepsis and therapeutic approaches to sepsis and its complications remains challenging to critical care clinicians. Hence, the objectives of this thesis were to 1) evaluate the test characteristics of the two sepsis consensus definitions and delineate the differences in patient profile among patients meeting or not meeting sepsis definitions; 2) determine the relationship between the changes in several physiological parameters before sepsis onset and sepsis, and to determine whether these parameters could be used to identify sepsis in critically ill adults; 3) evaluate the effect of corticosteroids therapy on patient mortality.

Data used in this thesis were prospectively collected from an electronic medical record system for all the adult patients admitted into the seven critical care units (ICUs) in a tertiary medical center. Besides analyzing data at the ICU stay level, we investigated

patient information in various time frames, including 24-hour, 12-hour, and 6-hour time windows.

In the first study of this thesis, the 1991 sepsis definition was found to have a high sensitivity of 94.6%, but a low specificity of 61.0%. The 2001 sepsis definition had a slightly increased sensitivity but a decreased specificity, which was 96.9% and 58.3%, respectively. The areas under the ROC curve for the two consensus definitions were similar, but less than optimal. The sensitivity and area under the ROC curve of both definitions were lower at the 24-hour time window level than those of the unit stay level, though the specificity increased slightly. At the time window level, the 1991 definitions performed slightly better than the 2001 definition.

In the second study, minimum systolic blood pressure performed the best, followed by maximum respiratory rate in discriminating sepsis patients from SIRS patients. Maximum heart rate and maximum respiratory rate can differentiate sepsis patients from non-SIRS patients fairly well. The area under ROC of the combination of five physiological parameters was 0.74 and 0.90 for comparing sepsis to non-infectious SIRS patients and comparing sepsis to non-SIRS patients, respectively. Parameters typically performed better in 24-hour windows compared to 6-hour or 12-hour windows.

In the third study, significantly increased hospital mortality and ICU mortality were observed in the group treated with low-dose corticosteroids than the control group based on the propensity score matched comparisons, and multivariate logistic regression analyses after adjustment for propensity score alone, covariates, or propensity score (in deciles) and covariates.

This thesis advances the existing knowledge by systemically evaluating the test characteristics for the 1991 and 2001 sepsis consensus definitions, delineating physiological signs and symptoms of deterioration in the preceding 24 hours prior to sepsis onset, assessing the prediction performances of single or combined physiological parameters, and examining the use of corticosteroids treatment and survival among septic shock patients. In addition, this thesis sets an innovative example on how to use data from electronic medical records as these surveillance systems are becoming increasingly popular. The results of these studies suggest that a more parsimonious set of definitional criteria for sepsis diagnosis are needed to improve sepsis case identification. In addition, continuously monitored physiological parameters could help to identify patients who show signs of deterioration prior to developing sepsis. Last but not least, caution should be used when considering a recommendation on the use of low dose corticosteroids in clinical practice guidelines for the management of sepsis.

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Chapter I Introduction

1.1 Background and Significance

Definition of sepsis

The systemic inflammatory response syndrome (SIRS) is a generalized physiological response to a wide variety of pro-inflammatory disease states, including infection, trauma, burns, and pancreatitis, which is characterized by pathological changes in body temperature, tachycardia, tachypnea, and abnormalities in total and differential white blood cell count. Sepsis is defined as SIRS with an infectious etiology and can be further categorized as severe sepsis, when infection and the host response result in organ dysfunction (e.g., acute renal failure), or as septic shock, when sepsis is complicated by acute circulatory failure characterized by persistent arterial hypotension despite adequate volume resuscitation.[1, 2]

Epidemiology of sepsis in US

Sepsis is the leading cause of death among critically ill patients in non-coronary intensive care units (ICUs) and the 10th most common overall cause of death in the United States.[3] There is increasing evidence that the incidence of sepsis has been increasing over time in the American population, from 164,000 cases (83 per 100,000 population) in 1979 to nearly 660,000 (240 per 100,000 population) in 2000.[3, 4] Sepsis is

often lethal, and its mortality rates range from 15% for sepsis to 60% for septic shock in the early 2000s.[5-7] Certain vulnerable sub-populations, such as persons 65 years or older, neonates and infants, immunocompromised individuals, and critically ill patients, are at increased risk for developing severe sepsis.[8] In fact, the number of deaths attributable to severe sepsis and myocardial infarction are approximately the same. Caring for patients with sepsis costs as much as $50,000 per patient, resulting in an economic burden of nearly $17 billion annually in the US, on an annual basis.[9]

Evolvement of sepsis definition

Prior to 1991, the physiological derangements characteristic of sepsis were referred to by a variety of terms that were often used interchangeably, including "sepsis", "septicemia", "septic syndrome", "bacteremia", "infection", and "septic shock." The lack of a consensus case definition complicated the evaluation of studies by clinicians and researchers.[10, 11] In 1991, the American College of Chest Physicians and the Society of Critical Medicine convened a conference that published consensus definitions of sepsis, severe sepsis, and septic shock. Sepsis was defined as the combination of infection and a systemic inflammatory response. Severe sepsis was defined as sepsis complicated by organ dysfunction. Septic shock in adults was defined as "acute circulatory failure characterized by persistent arterial hypotension" (systolic arterial pressure < 90 mmHg, mean arterial blood pressure <60, or > 40 mmHg reduction from baseline in systolic blood pressure), despite adequate volume resuscitation, and unexplained by other causes.[1] A new syndrome termed SIRS was introduced to define when this systemic response was

present. Patients meeting any 2 of the following criteria were defined as having SIRS: body temperature ≥38°C or <36°C, heart rate >90/min, respiration >20/min or PaCO2 <32 mmHg, and white blood cell count >12.0 x 10^9/L or <4.0 x 10^9/L. The utility and biological implications of a systemic inflammatory response to infection were soon evident and the term SIRS evolved from an epidemiological construct to a term used by bedside clinicians.[12-15]

Experience with the 1991 case definitions led to concerns for its validity, including its characteristics of being overly sensitive but not specific.[16, 17] An international conference was convened in 2001 to reappraise, enhance, and improve upon the 1991 definition. The expanded definition of sepsis still required that documented or suspected infection be present, but it expanded the SIRS criteria to a list of 7 general, 5 inflammatory, 3 hemodynamic, 7 organ dysfunction, or 2 tissue perfusion criteria, some of which also had to be present.[2] Although there is good reason to believe that the expanded definition would more efficiently identify sepsis in its early stages, the degree to which the expansion by the 2001 case definition has caused more non infected individuals to meet the definition is unknown. In addition, the impact of these alterations on the case definition and on the test characteristics has not been well studied to date.

Importance of the early diagnosis of sepsis

Early recognition and treatment for sepsis with appropriate antimicrobial agents[18, 19] and management strategies[20] has been shown to significantly reduce sepsis-related mortality. The identification of the responsible pathogen provides guidance on narrower

spectrum antimicrobial therapy and is thought to reduce the emergence of antibiotic-resistance microorganisms.[21] The effective and early treatment of serious infections prevents progression to organ dysfunction or even septic shock, and allows care to be provided at lower cost.[19]

Difficulty in making the early diagnosis of sepsis

Identifying patients with early sepsis can be difficult since non-infectious conditions, such as trauma and pancreatitis, can also cause the definitional criteria for SIRS to be met.[22] The mechanistic explanation for this overlap is that sepsis and non-infectious inflammatory disorders share common pathways that lead to the activation of cytokines, such as tumor necrosis factor alpha, that can cause the signs and symptoms of systemic inflammatory response used in the case definitions. Determining whether an infection is present can also be problematic, especially early in the evolution of sepsis before hypotension and organ failure are present. Indeed, identifying pathogens in patients with sepsis has been problematic and bacterial identification rates reported as low as 30% are not uncommon.[12] Bacterial growth also depends on the site of infection and could be altered by prior antimicrobial therapy.[23] Even when pathogens are identified, the time required to isolate and report them often greatly exceeds the time window when sepsis is present and not yet complicated by hypotension or organ dysfunction.[20] Knowing how to best identify patients with early sepsis is critical for achieving better outcomes for patients with sepsis.

Treatment of severe sepsis and septic shock

Severe sepsis and septic shock represent a more severe stage along the continuum of systemic inflammatory response to infection. Mediated with multiple inflammatory pathways and pro-inflammatory mediators including cytokines, patients at this stage usually fail to maintain homeostasis and develop abnormalities in circulation, which include increased vascular permeability, decreased intravascular volume, vasodilatation and depression of myocardial function, and imbalance among oxygen demand, oxygen extraction and oxygen delivery. Correspondingly, the therapeutic approach to severe sepsis and septic shock consists of initial volume and fluid resuscitation often combined with vasopressors and inotropic therapy, initiation of appropriate antimicrobial therapy, infection source identification and control, steroid therapy for patients who poorly respond to vasopressor therapy, and recombinant human activated protein C (rhAPC) for patients with high risk of death.[24] Blood product usage is part of treatment as clinically indicated (red blood cell transfusions when the hemoglobin value is less than 7.0 g/dl; transfusion of platelets when the platelet count less than 5000/mm^3 or the patient is at high risk of bleeding or requires an operative procedure). Supportive therapies (mechanical ventilation of sepsis-induced acute lung injury (ALI), or acute respiratory distress syndrome (ARDS); sedation, analgesia, and neuromuscular blockade, glucose control, renal replacement therapy, bicarbonate therapy, deep venous thrombosis prophylaxis therapy, and stress ulcer prophylaxis are also part of the approach to patients with sepsis.[22, 25, 26]

Importantly, early goal-directed resuscitation during the first 6 hours after the recognition of hypoperfusion in septic patients, referred to as the "golden hours", has demonstrated significant reductions in the 28-day mortality rate. Starting with fluid resuscitation subsequently combined with appropriate vasopressors, transfusion of red blood cells, and inotropic agents, patients are able to achieve the goals of central venous pressure (CVP) (8 – 12 mmHg), mean arterial pressure (MAP) (not less than 65 mmHg), urine output (greater than 0.5 mL·kg·hr), and central venous oxygen saturation (greater than 70%; or mixed venous oxygen saturation more than 65%). A few mechanisms contribute to the survival benefit of early goal directed therapy: reversal of circulatory abnormalities and tissue hypoxia, preventing cardiovascular collapse, and attenuating tissue hypoxia related endothelial cell activation and loss of barrier function, activation of the coagulation system, increased vascular permeability and reduced vascular tone.[20]

Critical illness-related corticosteroid insufficiency (CIRCI) in septic shock

Activation of the hypothalamic-pituitary-adrenal (HPA) axis is an important adaptive process in critical illness for restoring and maintaining cellular and organ homeostasis. This activation leads to increased secretion of cortisol from the adrenal cortex, which is under the influence of adreno-corticotrophic hormone (ACTH) from the pituitary, and corticotropin-releasing hormone from the hypothalamus. During an acute illness, including severe infection, trauma, burns, and surgery, the production of cortisol can be increased by as much as six-fold, depending on the severity of the disease. Cortisol exerts protective physiologic effects through modulating metabolism (increasing

blood glucose concentration), cardiovascular function (maintaining microvascular perfusion, and increasing sensitivity of vascular muscle to endogenous or exogenous vasopressors agents), and the immune system (reducing transcription of proinflammatory factors, such as cytokine, chemokine, and eicosanoids, down-regulating immune cells' number and their function).[27, 28]

Increasing evidence has shown that the adaptive HPA axis function is often impaired during critical illnesses including septic shock .[29] The dysfunction could happen at any level of HPA axis function and contribute to either structural damage, or in most cases, reversible dysfunction of the HPA axis. The prevalence of CIRCI in severe sepsis and septic shock patients has been reported to be as high as 60% (by metyrapone testing) in ICUs.[30, 31] The mechanism of HPA axis dysfunction is incompletely understood, but is thought to be related to insufficient cortisol production from adrenal or systemic inflammation-associated glucocorticoid resistance. As a result, the degree of HPA axis activation and severity of illness affects the function of metabolic, cardiovascular systems and immune response to severe infection in severe sepsis and septic shock.[32, 33]

Steroid therapy in septic shock

Whether moderate-dose hydrocortisone improves mortality in septic shock patients is still controversial.[32, 34, 35] Although there have been randomized controlled trials [34, 36-40] conducted to evaluate the survival benefits associated with the administration of steroid therapy to septic shock patients, differences in study's sample size, inclusion criteria, and characteristics of steroid administration (for example, starting

time, dosage, and treatment duration) have considerably limited our ability to derive meaningful comparisons across studies.

The contradictory results of the 2 better powered trials, namely the study by Annane et al. [34] and European multicenter study (CORTICUS) [36], have triggered debates with regard to the benefits of steroid use in septic shock patients. While the French multi-center trial demonstrated significant 28-day mortality reduction among a subset of septic shock patients with abnormal HPA function who received corticosteroid therapy compared to those without corticosteroid therapy, the CORTICUS study did not illustrate improved survival among septic shock patients who received hydrocortisone regardless of HPA function. Several factors could possibly contribute to the observed differences between these two studies: 1) The patients' characteristics were different. The patients enrolled in the French study were sicker than those in the CORTICUS study, with the 28-day mortality in the comparison groups being 61%, 31.5%, respectively. In addition, all of the patients enrolled in the French study were mechanically ventilated before enrollment, while 88.2% (440 among 499 patients) received ventilatory support at the time of baseline enrollment in the CORTICUS study. 2) The treatments differed. The patients in the steroid therapy arm in the French study received both hydrocortisone and fludrocortisone for 7 days, whereas those in CORTICUS study received only hydrocortisone for a total of 11 days. 3) The enrollment time of the two studies also differed. Participants in the study by Annane et al. were enrolled within 8 hours after septic shock onset and within 72 hours for CORTICUS study. Recent meta-analyses of randomized trials reported heterogeneous effects of corticosteroids therapy on mortality,

which can vary across patient characteristics, underlying risk, treatment dose and duration.

1.2 Specific aims

This dissertation analyzed the data from an adult intense care units (ICUs) electronic surveillance system to achieve the specific aims listed below:

Aim 1: To assess the test characteristics (sensitivity and specificity) of the 1991 and 2001 consensus case definitions of sepsis in a population of patients admitted to adult intensive care units using adjudicated sepsis cases as the reference standard;

Aim 2: To determine the best method for identifying sepsis cases by defining the algorithms that optimize diagnostic performance for scoring elements of the sepsis case definition. These variables include heart rate, respiratory rate, blood pressure and body temperature that are continuously monitored and recorded into an electronic monitoring system;

Aim 3: To examine the association between administration of steroid therapy and mortality at hospital and ICU discharge among septic shock patients; and to access its survival benefit, if it exists, being associated with certain patient characteristics

1.3 Study Significance

Sepsis is a treatable disease with an unfortunately high mortality rate. On the one hand, there is increasing evidence that early diagnosis followed by appropriate treatment with antimicrobials and other supportive management is beneficial. The difficulty of early diagnosis was recognized decades ago and it remains challenging today. Part of this is due to overlap in the clinical criteria that define SIRS and sepsis. Though the consensus definitions of sepsis are widely adopted in clinical practice, their test characteristics, as well as the changes given by the expanded 2001 consensus definition, haven't been well studied. Rigorous evaluations of sepsis consensus definitions are needed by calculating their test characteristics including sensitivity, specificity, and area under the receiver operating characteristic (ROC) curve. In addition, a systematic comparisons of the 1991 and 2001 definitions are well justified to allow the consistent description and evaluation of patients with sepsis, streamline the interpretations of clinical trials and therapeutic interventions, and provide an evidence based approach for determining if the 2001 conference achieved its aims of improving the utility of these definitions for case identification.

Despite a large number of investigations using these definitions, the test characteristics of the available diagnostic parameters have not been well validated, and none are widely clinically applied. These observations support the need to identify the best routinely available parameters for distinguishing patients with sepsis, particularly before the onset of organ dysfunction and hypotension. Moreover, current widely used electronic monitoring systems enables us to continuously monitor patient's physiological

parameters, including heart rate, respiratory rate, blood pressure and body temperature, and values of these parameters were readily available for systematic analysis. It is likely that a model including these more completely collected parameters will have increased predictive power to detect septic patients from those with systemic inflammatory responses that are not due to infection. Furthermore, this model will also have implications for clinicians in terms of timely evaluation and diagnoses of septic patients.

While substantial progress has been made in our understanding of the effects of steroid therapy in septic shock patients, significant controversy remains surrounding the issue of whether administration of corticosteroids leads to survival benefits. The clinical significance of the third aim is to provide evidence about whether, in a clinical setting not constrained by clinical trial entry criteria, septic shock patients receiving steroid would have improved survival outcome. Moreover, it also enables us to investigate whether certain patient characteristics are associated with the effects of the low-dose corticosteroid treatment; whereas its survival benefit, if it exists, would differ across patient subgroups.

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Chapter II Sepsis Definition Evaluation

Aim 1

An Evaluation of the Diagnostic Accuracy of the 1991 ACCP/SCCM and the 2001 SCCM/ESICM/ACCP/ATS/SIS Sepsis Definition

Abstract

Background

The 1991 and 2001 sepsis case definitions are widely adopted in clinical practice. Limited research has been conducted comparing their test characteristics. In addition, the impact of these alterations for the 2001 case definitions and on the test characteristics has not yet been well studied.

Objectives

To assess the test characteristics of 1991 consensus definition, and 2001 consensus definition, respectively, compared to sepsis case adjudication by three senior intensive care clinicians.

Study Design

Patient demographic, physiological and laboratory data were collect from patients admitted into ICUs in a tertiary medical center. Sensitivity, specificity, and the area under the ROC curve for the two consensus definitions were calculated and compared by comparing the number of patients who met or did not meet consensus definitions versus the number of patients who were diagnosed with sepsis or not by adjudication. Logistic regressions were performed to identify significant independent factors associated with sepsis diagnosis. The analysis was conducted at the ICU unit stay level as well as at the 24-hour time window level. Fever, high white blood cell count or immature white blood cell, low GCS score, edema, positive fluid, high cardiac index, low PaO_2/FiO_2 ratio, and high levels of creatinine and lactate were significantly related to sepsis of both definitions and adjudication.

Results

Overall inter-rate reliability among the adjudicators was good (Kappa was 0.68). The 1991 sepsis definition had a high sensitivity of 94.6%, but a low specificity of 61.0%. The 2001 sepsis definition had slightly increased sensitivity but decreased specificity, which were 96.9% and 58.3%, respectively. The area under the ROC curve was not statistically different (0.78 and 0.78, respectively). The sensitivity and area under the ROC curve of both definitions were lower at the 24-hour time window level than that of the unit stay level, though the specificity increased slightly. At the time window level, the 1991 definitions performed slightly better than the 2001 definition.

Conclusions

Both the 1991 and the 2001 sepsis definition have a high sensitivity but low specificity; the 2001 definition has slightly increased sensitivity and decreased specificity. The diagnostic performances of the two definitions range from modest to good compared to the adjudication results. A more parsimonious set of definitional criteria for sepsis diagnosis is likely to improve current sepsis case identification.

2.1 Introduction

Sepsis has been recognized since antiquity [1] and is currently the leading cause of death among critically ill adults and the 10th most common cause of death in the United States. [2, 3] The incidence of sepsis increased from 164,000 cases (82.7 cases per 100,000 population) identified in 1979 to nearly 660,000 (240.4 cases per 100,000 population) in 2000. [4] Certain vulnerable sub-populations, such as people older than 65, neonates and infants, immuno-compromised individuals, and critically ill patients, are reported to be at a 1.8 to 65 fold increased risk of developing sepsis. [5-8] Despite advances in the care of septic patients, the mortality rates for sepsis in United States have remained high and range from 15% for uncomplicated sepsis to 60% for septic shock. [9, 10]

Prior to 1991, the physiological derangements characteristics of sepsis were referred to by a variety of terms that were often used interchangeably, including "sepsis", "septicemia", "septic syndrome", "bacteremia", "infection", and "septic shock." The lack of a consensus case definition complicated the evaluation of studies and confused communication among clinicians and researchers. In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened a conference in an attempt to provide a framework of standardized definitions of sepsis. The proposed consensus definitions of this conference included sepsis, severe sepsis, septic shock, and a newly introduced terminology of "systemic inflammatory response syndrome (SIRS)". SIRS represents a systemic inflammatory response independent of the etiology, and was considered to be present when a patient meets any two of the following

criteria: body temperature ≥38°C or <36°C, heart rate >90/min, respiration >20/min or PaCO2 <32 mmHg, and white blood cell (WBC) count >12.0 x 10^9/L or <4.0 x 10^9/L, or >10% immature (band) forms. Sepsis was defined as a systemic inflammatory response caused by infection. Severe sepsis was defined as sepsis complicated by organ dysfunction, hypotension or hypoperfusion, and septic shock as a subset of severe sepsis with "sepsis induced hypotension" (systolic arterial pressure < 90 mmHg, or > 40 mmHg reduction from baseline in systolic blood pressure) with perfusion abnormalities, despite adequate volume resuscitation. [11]

The utility and biological implications of a systemic inflammatory response to infection were soon evident and the term SIRS evolved from an epidemiological construct to a term used as a screening tool to enroll participants in clinical trials in the years that followed. [12] The wide adoption of these definitions allowed assessment of the test characteristics. However, experience with the 1991 case definitions in clinical practice as well as in large sepsis clinical trials led to concerns for its validity. SIRS criteria alone appeared to be overly sensitive and yet not specific as most patients in Intensive Care Units (ICUs) and many patients in general wards were reported to meet SIRS criteria at some time point during their hospital stay, [9, 13-15] despite many of these patients were without clinical evidence of infection.

An international conference was convened in 2001 to reappraise, enhance, and improve upon the 1991 definition. The expanded definition of sepsis still requires that a documented or suspected infection be present, but it expanded the SIRS criteria to a list of 7 general, 5 inflammatory, 3 hemodynamic, 7 organ dysfunction, or 2 tissue perfusion

criteria, some of which had to also be present. [16] Although there is good reason to believe that the expanded definition more comprehensively captures systemic responses to infection and could more efficiently identify sepsis in its early stages, the impact of these alterations of the case definition on the test characteristics have not yet been well studied.

Though the consensus definitions of sepsis have been widely adopted in clinical practice, limited research has been conducted comparing their test characteristics. In addition, systematic comparison of the 1991 and 2001 definitions are well justified to allow the consistent description and evaluation of patients with sepsis, and allow more informative comparison of sepsis clinical trials and therapeutic interventions that used the alterative definitions. Therefore, the aim of this study is to assess the test characteristics (i.e. sensitivity, specificity, and the area under the ROC curve) of 1991 consensus definition, and 2001 consensus definition, respectively, compared to sepsis case adjudication by three senior intensive care clinicians.

2.2 Methods

Study Design

This is an observational study conducted in seven intensive care units (ICUs) of an academic medical center, including three medical, two surgical, one cardiac, and one mixed unit for trauma, burns, neurosurgical and strokes. The seven ICUs serve as the major source of intensive care in the greater Worcester, Massachusetts area. Patients admitted into the units originated from various sources, including the emergency department, general wards, operating rooms, and other hospitals or health care centers in

or adjacent to central Massachusetts. The medical center started employing an electronic medical record system in June 2006 and finished implementing the system in all seven ICUs before May, 2007. All consecutive ICU admissions to the ICUs from October 2007 to December 2008 were included in this study as the study target population. This study was part of the "Identifying Patients with Sepsis" project conducted in our ICUs and data were collected from existing data base without patient identifiers under a waiver of informed consent from our Human Subjects Committee.

Data collection

Patient demographic characteristics were acquired from the electronic medical records, including age, gender, race, marital status, height, weight, and admission source. Race was classified as white, black and other; marital status was categorized as married, single, or widowed. Admission source was classified as emergency department (ED), general wards, operating room, and other. Admission diagnosis was recorded at the time of ICU admission and classified by major body systems, which included cardiovascular, gastrointestinal, respiratory, genitourinary, neurology, and other system. Acute Physiology and Chronic Health Evaluation (APACHE) IV score, and one of its components, Acute Physiological Score (APS) (Cerner, Kansas City, MO) were calculated from data collected by the electronic medical record and used as the measures of patient acute severity. In addition, clinical outcomes such as hospital length of stay, ICU length of stay, hospital mortality, and unit mortality were also collected for the comparison between sepsis and non-sepsis patients.

Physiological parameters included heart rate, respiratory rate, systolic blood pressure, mean blood pressure, temperature, urine output, edema, positive fluid balance, cardiac index, capillary refill or mottling, ileus, and Glasgow Coma Score. A patient's physiological status was assessed and updated every 30 to 60 minutes during the initial 24 to 48 hours of ICU stay and was updated every 2 to 4 hours when a patient was deemed stable or was ready for ICU discharge. Laboratory test results and their corresponding test time were also collected for WBC count, band, platelet, aPTT, INR, glucose, creatinine, total bilirubin, lactate, c reactive protein (CRP), PaO2, FiO2, PaO2/FiO2 ratio, PaCO2, SvO_2, and microbiology tests (specimen type, site of acquisition, test time, sites with positive culture, organism type) from the electronic medical record system.

Adjudication of sepsis cases

All the sepsis cases were adjudicated by three senior intensive care physicians by medical records review. The algorithm of case adjudication is illustrated in Figure 2.1. A patient with sepsis had to meet the SIRS criteria and have a confirmed diagnosis of infection. Patient was classified as having severe sepsis if the patient met organ dysfunction criteria.[17] When the patient had hypotension despite adequate volume resuscitation, the case was diagnosed as having septic shock. The time when sepsis was present was also determined. For subjects that developed sepsis before or at the time of ICU admission, the disease onset time was taken as the time of ICU admission.

A random sample of 1,000 patients, about 7.1% of all patients during the study period, was selected for sepsis adjudication. Each physician first completed the same training set which was consisted of 40 patients randomly selected from the 1,000 patients. A consensus meeting was then convened to resolve the differences and standardized the adjudication approach among physicians. A final sample of 960 patients were adjudicated, among whom 60 patients were reviewed by all three physicians. These 60 patients were used to estimate the agreement between physicians based on the Kappa statistic. The Interpretation of Kappa value was: 0 as poor; 0 to 0.2 as slight; 0.2 to 0.4 as fair; 0.4 to 0.6 as moderate; 0.6 to 0.8 as substantial; and 0.8 to 1.0 as almost perfect agreement [18].

Analysis Unit

The main analysis was conducted at the ICU unit stay level: a patient was classified as having sepsis if she/he was adjudicated as sepsis or met the sepsis definition any time during the ICU stay. Furthermore, analysis was performed at the 24-hour time window level because sepsis might not be present during the whole ICU stay. Within each of 24-hour time window, sepsis determined using the criteria of the 1991 or 2001 definitions was compared to presence of sepsis by adjudication. In addition, sensitivity analysis was conducted assuming sepsis was present for 2 and 5 days after its diagnosis to check the robustness of the results. The reason is that sepsis usually requires a standard

course of antimicrobial treatment based on the infected site and organism type, and during the treatment course, patients were considered to continuously have sepsis.

Statistical Analysis

Patient baseline demographic variables, admission diagnosis, and disease severity were summarized by calculating means for continuous variables and frequencies for categorical variables. The highest values or lowest values of each variable, as indicated by consensus definitions during the ICU stay or within each time window was used to determine whether a patient met specific criteria of consensus definitions. We then tabulated and compared the number of patients who met or did not meet consensus definitions versus the number of patients who were diagnosed with sepsis or not by adjudication. Using the adjudicated outcome as the reference standard, sensitivity, specificity, and the area under the ROC curve were calculated compared for the two consensus definitions. It is likely that many patients were diagnosed as having sepsis at the time of ICU admission, and these patients might be different, in patient characteristics, underlying diseases, acuity, infectious pathogen, from those who developed sepsis during their ICU stay. Therefore, a subgroup analysis was conducted for those patients with a diagnosis of sepsis at the time of ICU admission. Finally, logistic regressions were performed at the 24-hour window level to identify significant independent factors associated with sepsis diagnosis, where robust standard errors were used to account for the dependence between observations within the same patient (regression analyses using generalized estimating equations did not converge, which

might be due to the fact that 89% of adjudicated cases had a sepsis diagnosis at the time of ICU admission so that only one time window was available for these cases).

2.3 Results

Patient Characteristics

The final analytical sample consisted of 960 patients, among them, 353 (36.8%) were adjudicated as sepsis (n=83), severe sepsis (n=150), or septic shock (n=120). As illustrated in Table 2.1, no significant differences were present between sepsis patients and non-sepsis patients with regard to age, gender, race, marital status, and body mass index. However, sepsis patients had higher acuity, as measured by APS score (63.6 vs. 45.3, $p<0.01$) and APACHE IV score (77.0 vs. 57.1). About one quarter of sepsis patients were transferred from wards, compared to 12.7% of non-sepsis patients. Sepsis patients were less likely to be admitted from an operating room than non-sepsis patients (11.1% vs. 24.2%). A larger proportion of sepsis patients had an admission diagnosis of cardiovascular or respiratory disease. Without exception, sepsis patients had worse clinical outcomes for all measures, longer hospital (15.5 vs. 9.2) and ICU length of stay (7.8 vs. 3.6), and higher hospital (26.1% vs. 10.2%) and ICU mortality (17.9% vs. 6.9%).

As shown in Table 2.2, we compared three groups of sepsis patients determined by adjudication (353 patients), the 1991 sepsis definition (571 patients), and 2001 sepsis definition (595 patients), respectively. Despite the large differences in the number of sepsis patients identified using these 3 methods, the patient characteristics were very similar. No statistically significant different characteristics were found between

adjudicated sepsis cases and those determined by the 1991 definition, or between the cases determined by the two definitions. Nevertheless, adjudicated sepsis patients seemed to be sicker than those identified by the 2001 definition, as indicated in the mean APS score (63.6 vs. 59.5, $p<0.05$) and APACHE score (77.0 vs. 72.6, $p<0.05$). Furthermore, ICU length of stay was significantly longer among adjudicated sepsis cases than that of the sepsis patients determined by the 2001 definition (7.8 vs. 6.7, $p<0.05$).

Sepsis Adjudication

Each of three senior physicians, who specialized in intensive care, adjudicated one third of ICU cases. There were 60 cases adjudicated by all three physicians, and the inter-rater reliability between physicians was evaluated using Kappa statistic. When patients were classified as sepsis or non-sepsis, the Kappa statistics for any two of the three physicians were 0.66, 0.73, and 0.64, respectively. The overall Kappa statistic was 0.68. When patients were classified as non-sepsis, sepsis, severe sepsis, and septic shock, the Kappa statistics decreased. For pair-wise comparisons, the Kappa statistic ranged from 0.55 to 0.66, whereas the overall Kappa statistic was 0.61.

Test Characteristics of the 1991 and 2001 Definitions

As shown in Table 2.3, compared to the adjudication results at the unit stay level, i.e., whether a patient ever had sepsis during the ICU stay, both definitions had a high sensitivity (94.6% and 96.9%, respectively) but a low specificity (61.0% and 58.3%%, respectively). The area under the ROC curve was not statistically different (0.78 and

0.78, respectively). The sensitivity of both definitions (77.7% and 81.1%%, respectively) was much lower at the time window level than that of the unit stay level, though the specificity increased slightly. The area under the ROC curve was also lower at the time window level, and the 1991 definitions performed slightly better than the 2001 definition (0.72 vs. 0.70, $p<0.01$). When it was assumed that sepsis diagnosis was present for at least 2 and 5 days, the sensitivity increased but the specificity decreased, and the area under the ROC curve was lower compared to those of the unit stay level and the time window level. In these cases, the 1991 definition's area under the ROC curve was slightly larger than that of the 2001 definition. The majority of sepsis patients (89.0%) in this study had an admission diagnosis of sepsis. Subgroup analysis of these patients found similar test characteristics of the two sepsis definitions compared to those observed in the main analysis (Appendix Table 2.1).

Significant Biophysical Parameters for the Prediction of Sepsis

The majority of the definition criteria were significantly associated with sepsis by definition or adjudication based on bivariate analyses (see details in Appendix Table 2.2). Table 2.4 presents the biophysical parameters that were significant predictors of sepsis based on regression analysis. The dependent variables of three regressions were adjudicated outcome, sepsis as defined by the 1991 definition, and sepsis as defined by the 2001 definition. There were ten biophysical parameters that appeared to be significant predictors in all regressions, including fever (temperature >38°C), white blood cell count $>12.0 \times 10^9$/L or $<4.0 \times 10^9$/L, band (immature white blood cell >10%), GCS (Glasgow

coma score <15), edema, positive fluid balance (>20 ml/kg in 24 hours), cardiac index >3.5 L/min/M, PaO_2/FiO_2 <300, creatinine >0.5 ml/dL, and lactate >1 mmol/L. Hypothermia, respiratory rate, $PaCO_2$, and heart rate were significant in the regressions using the 1991 and 2001 definitions, but not in the regression based on the adjudication outcome. Abnormal SvO_2 appeared in only two cases and perfectly predicted non-sepsis cases, which was also the case for Ileus (absent bowel sounds) in 88 adjudicated non-sepsis cases.

2.4 Discussion

Sepsis is a complex disease and the underlying pathobiological mechanisms have not been completely delineated. Accurate and reliable definitions of sepsis are fundamental for early disease identification, which thus allows timely therapeutic intervention, and improved interpretation and application of knowledge from clinical studies. This study was conducted to examine the test characteristics of the 1991 and the 2001 sepsis consensus definitions. We found that, compared to adjudicated sepsis, both the 1991 and 2001 definitions had relatively high sensitivity and low specificity. The criteria used for the two definitions include signs and symptoms that a patient could present with during the course of infection-induced systemic inflammatory response. However, they are not specific to sepsis, and many other conditions could also manifest these signs and symptoms. For example, tachycardia and tachypnea may be present in heart failure, anemia, respiratory failure, and hypovolemia. Increased white blood cell count is not rare in conditions like trauma, pancreatitis, hemorrhage, myocardial

infarction, and pulmonary edema. Furthermore, both the 1991 and 2001 sepsis definitions had suboptimal differentiation performance, as measured by AUCs, which could be due to the overlap of these signs and syndromes with other diseases.

Expanding the sepsis definition by including a detailed list of possible manifestations of sepsis, the 2001 consensus definitions more inclusively reflect the spectrum of clinical responses to infection. Compared to the 1991 definition, the 2001 sepsis definition had a slightly increased sensitivity and decreased specificity. This was expected since the added criteria in 2001 sepsis definition, like the other criteria in the 1991 sepsis definition, are not specific for sepsis; whereas, other conditions could also present with these signs and symptoms. When looking across entire ICU stay, the area under the ROC curve of the 2001 sepsis definition was not significantly different from that of the 1991 sepsis definition which suggests that using the 2001 definition does not improve the discriminatory power compared to the 1991 definition. In deed, at a 24-hour time window level, we found decreased diagnostic performance of the 2001 definitions than that of the 1991 definition. Moreover, the extended list of possible signs of systemic responses in the 2001 definition is complicated and less parsimonious.

When taking into account the time of sepsis diagnosis by evaluating more clinically relevant time windows, the differences between adjudicated sepsis and the two definitions were larger, as reflected by a decreased sensitivity and area under the ROC curve. Since both of the current definitions do not specify a time frame, it is not clear within what time frame a patient meeting the defined criteria can be diagnosed with sepsis. This makes it difficult to design a retrospective study where a time window has to

be defined in an arbitrary way. For the purpose of this study, it was defined as a 24-hour window since routine laboratory testing is reviewed on a daily basis. In addition, as all the adjudication was conducted retrospectively by reviewing patient progress notes, it was challenging to precisely identify the exact time when a patient developed sepsis. On the other hand, as every input into the electronic medical record system has a corresponding recording time, our analytic algorithm determined the onset time of sepsis as the time when a patient had both a diagnosis of infection and met any two of the SIRS criteria. When the diagnoses using the 1991 and 2001 definitions based on electronic data were compared to the manually adjudicated diagnoses at the time window level rather than the unit stay level, the area under the ROC curve declined, especially that of the 2001 definition. Since the test characteristics varied depending on the time frame within which diagnostic criteria are evaluated, it may be useful for clinicians if a guideline is provided in the sepsis definition regarding the time frame within which the defined criteria should be met in order to diagnose a patient as having sepsis.

From our regression analyses, we identified the predictors of sepsis diagnosis. Given the complexity of using the extended list of diagnostic criteria as defined in the 2001 definition, one possible solution is to shorten the list based on a more parsimonious set of criteria as identified by regressions analyses. We found that significant predictors of the 2001 definition, including fever, white blood cell count, the presence of early myeloid forms (bands), GCS, edema, positive fluid balance, cardiac index, PaO_2/FiO_2, creatinine, and lactate, whereas in the 1991 definition, 2 of the 4 SIRS criteria (respiratory rate and heart rate) were not among the set of predictors that were significant

in all regressions. As these were significant predictors of sepsis, it is likely that using them will improve specificity for sepsis diagnosis with a minimal decrease in sensitivity. A further approach would be to create a weighting system that assigns different weights (e.g., based on the magnitude and precision of estimated coefficients) for various criteria because some criteria may contribute more than others as indicated by their odds ratios. For instance, having white blood cell with >10% in early myeloid forms (band) was associated with 6-fold increased risk of developing sepsis, and patients with abnormal lactate were nearly 7 times more likely to have sepsis than those with a normal lactate level. Additional research using larger dataset is warranted to further validate the new set of criteria and generate a weighting system empirically.

Strengths of our study include careful and rigorous data collection in an electronic medical record system; the independent adjudication of sepsis based on medical records by the three adjudicators; clearly defined time windows that reflect bedside clinical practice and a thorough exploration of our data. This study has several important limitations. First, only patients admitted to an adult ICU were included in this study. As a result, the findings might not be generalizable to other settings such as emergency rooms or general wards or ICUs caring for less severely ill patients. Second, the agreement among adjudicators was substantial rather than perfect despite adjudicating practice cases and the consensus meetings before the final adjudication. Lastly, there were 960 patients included in the study. A larger sample size would be expected to generate more robust results.

2.5 Conclusions

Despite extensive efforts, sepsis diagnosis remains difficult as some other diseases states have similar clinical presentations and many share the same pathophysiological processes. Our findings suggest that both the 1991 and the 2001 sepsis definition have a high sensitivity but low specificity. By expanding the SIRS criteria, the 2001 definition has slightly increased sensitivity and decreased specificity. The diagnostic performances of the two definitions range from modest to good compared to the adjudication results. A more parsimonious set of definitional criteria for sepsis diagnosis, identified and validated in future studies, is likely to improve the efficiency and reliability of current criteria for sepsis case identification.

Table 2.1 Patient Characteristics

Characteristics	Sepsis Patients (n=353)	Non-Sepsis Patients (n=607)	P Value
Age, mean ± SD	64.82±16.62	63.28±17.00	0.17
Female Gender, n (%)	158(44.76)	261(43.00)	0.60
Race n (%)			
White	302(85.55)	541(89.13)	0.10
Black	11(3.12)	15(2.47)	0.55
Other	40(11.33)	51(8.40)	0.14
Married Status n (%)	158(44.76)	305(50.25)	0.10
BMI, mean ± SD	28.01±7.76	28.41±7.68	0.44
APS Score, mean ± SD	63.61±26.55	45.31±23.66	<0.01
APACHE Score, mean ± SD	76.95±28.24	57.13±25.70	<0.01
Admission Source, n (%)			
Emergency Room	199(56.37)	356(58.65)	0.49
Ward	88(24.93)	77(12.69)	<0.01
Operation Room	39(11.05)	147(24.22)	<0.01
Other Hospital	27(7.65)	24(3.95)	0.01
Operative Diagnosis, n (%)	40(11.33)	141(23.23)	<0.01
Admission Diagnosis, n (%)			
Cardiovascular	98(27.76)	247(40.69)	<0.01
Gastrointestinal	56(15.86)	81(13.34)	0.28
Respiratory	100(28.33)	57(9.39)	<0.01
Genitourinary	12(3.40)	10(1.65)	0.08
Neurology	51(14.45)	115(18.95)	0.08
Other	36(10.20)	97(15.98)	0.01
Clinical Outcomes			
Hospital Length of Stay, mean ± SD	15.46±15.38	9.16±8.73	<0.01
ICU Length of Stay, mean ± SD	7.76±8.51	3.64±3.94	<0.01
Hospital Mortality	92(26.06)	62(10.21)	<0.01
Unit Mortality	63(17.85)	42(6.92)	<0.01

Table 2.2 Characteristics of Sepsis Patients Determined Using Various Methods

Characteristics	Adjudicated Sepsis	1991 Definition	2001 Definition
No. of Sepsis Cases (%)	353 (36.77)	571 (59.48)	595 (61.98)
Age, mean ± SD	64.82±16.62	64.06±17.20	64.25±17.15
Female Gender, n (%)	158(44.76)	263(46.06)	274(46.05)
Race n (%)			
White	302(85.55)	497(87.04)	518(87.06)
Black	11(3.12)	19(3.33)	19(3.19)
Other	40(11.33)	55(9.63)	58(9.75)
Married Status n (%)	158(44.76)	245(42.91)	259(43.53)
BMI, mean ± SD	28.00±7.77	28.08±7.68	28.14±7.73
APS Score, mean ± SD	63.61±26.55	60.22±26.78	59.48±26.72*
APACHE Score, mean ± SD	76.95±28.24	73.25±28.40	72.57±28.31*
Admission Source, n (%)			
Emergency Room	199(56.37)	322(56.39)	341(57.31)
Ward	88(24.93)	134(23.47)	134(22.52)
Operation Room	39(11.05)	76(13.31)	80(13.45)
Other Hospital	27(7.65)	39(6.83)	40(6.72)
Operative Diagnosis, n (%)	40(11.33)	77(13.49)	80(13.45)
Admission Diagnosis, n (%)			
Cardiovascular	98(27.76)	159(27.85)	165(27.73)
Gastrointestinal	56(15.86)	86(15.06)	89(14.96)
Respiratory	100(28.33)	135(23.64)	140(23.53)
Genitourinary	12(3.40)	15(2.63)	15(2.52)
Neurology	51(14.45)	102(17.86)	112(18.82)
Other	36(10.20)	74(12.96)	74(12.44)
Clinical Outcomes			
Hospital Length of Stay, mean ± SD	15.46±15.38	14.11±13.81	13.93±13.66
ICU Length of Stay, mean ± SD	7.76±8.51	6.80±7.54	6.70±7.43*
Hospital Mortality	92(26.06)	127(22.24)	128(21.51)
Unit Mortality	63(17.85)	88(15.41)	88(14.79)

* Comparison between adjudicated sepsis and those defined by the 2001 definition, $p<0.05$; ** $p<0.01$. All the comparisons between adjudicated sepsis and those defined by the 1991 definition were not statistically significant at the 5% level, as well as those between patients by two definitions.

Table 2.3 Test Characteristics of 1991 and 2001 Sepsis Definition‡

Characteristics	1991 Definition			2001 Definition		
	Sensitivity	Specificity	Area Under ROC	Sensitivity	Specificity	Area Under ROC
Unit Stay Level	94.6%	61.0%	0.778	96.9%	58.3%	0.776
Time Window Level	77.7%	66.0%	0.719	81.1%	58.8%	0.699**
Time Window Level: assume sepsis diagnosis valid for 2 days	87.2%	43.7%	0.655	90.1%	38.0%	0.640**
Time Window Level: assume sepsis diagnosis valid for 5 days	90.8%	38.9%	0.648	93.2%	35.8%	0.645*

‡Adjudication outcome: 353 sepsis cases (37%), 607 of non-sepsis cases.

* Comparing area under ROC curve between two definitions: $p<0.05$; ** $p<0.01$.

Table 2.4 Predictive Capability of Diagnostic Criteria in Sepsis Diagnosis (Regression Analysis)†

Biophysical Parameters	Adjudicated Outcome (Odds Ratio, 95% CI)	1991 Definition (Odds Ratio, 95% CI)	2001 Definition (Odds Ratio, 95% CI)
Fever	1.56 (1.19, 2.05)	1.91 (1.70, 2.15)	1.63 (1.44, 1.85)
Hypothermia	0.80 (0.51, 1.26)	1.40 (1.15, 1.71)	0.82 (0.69, 0.98)
Respiratory Rate	1.04 (0.72, 1.50)	3.26 (2.82, 3.77)	1.22 (1.09, 1.37)
PaCO2	1.02 (0.72, 1.44)	0.75 (0.62, 0.90)	0.64 (0.54, 0.75)
WBC	1.50 (1.16, 1.95)	2.04 (1.86, 2.25)	1.30 (1.19, 1.42)
Band	6.08 (4.50, 8.21)	3.76 (2.96, 4.77)	2.67 (2.14, 3.35)
Heart Rate	1.01 (0.75, 1.35)	3.25 (2.92, 3.62)	1.27 (1.16, 1.39)
GCS	1.40 (1.07, 1.85)	1.48 (1.34, 1.64)	1.58 (1.44, 1.73)
Edema	0.44 (0.34, 0.57)	-	1.29 (1.17, 1.41)
Fluid	2.27 (1.11, 4.64)	-	2.15 (1.83, 2.52)
Glucose	2.12 (1.64, 2.74)	-	1.00 (0.91, 1.09)
CRP	2.59 (0.74, 9.10)	-	1.09 (0.48, 2.48)
Systolic Blood Pressure	1.25 (0.93, 1.69)	-	1.14 (1.03, 1.27)
Mean Blood Pressure	0.86 (0.62, 1.20)	1.19 (1.07, 1.32)	1.07 (0.97, 1.19)
Cardiac Index	0.22 (0.08, 0.61)	-	0.22 (0.15, 0.32)
PaCO2 & FiO2	1.55 (1.15, 2.09)	1.38 (1.24, 1.54)	1.30 (1.18, 1.45)
Urine Output	0.98 (0.72, 1.34)	0.80 (0.71, 0.90)	0.78 (0.70, 0.87)
Creatinine	1.43 (1.10, 1.86)	1.19 (1.08, 1.31)	1.19 (1.09, 1.30)
PTINR	1.27 (0.86, 1.87)	-	0.97 (0.82, 1.15)
aPPT	0.68 (0.43, 1.07)	-	1.10 (0.93, 1.30)
Ileus‡	-	-	1.01 (0.62, 1.65)
Platelet	0.74 (0.53, 1.05)	1.10 (0.95, 1.28)	1.13 (0.98, 1.31)
Total Bilirubin	2.31 (1.25, 4.27)	1.27 (0.91, 1.79)	1.30 (0.94, 1.80)
Vasopressor	1.28 (0.89, 1.83)	0.73 (0.61, 0.88)	-
Lactate	6.68 (4.94, 9.05)	-	1.74 (1.45, 2.09)
Capillary	0.71 (0.52, 0.98)	-	1.01 (0.91, 1.13)

† Abnormal SvO2 predicted non-sepsis perfectly in 2 cases and thus was excluded from the regressions.

‡ Presence of ileus predicted non-sepsis perfectly in 88 adjudicated cases.

Appendix Table 2.1 Test Characteristics of 1991 and 2001 Sepsis Definition among Patients with a Diagnosis of Sepsis at Admission‡

Characteristics	1991 Definition			2001 Definition		
	Sensitivity	Specificity	Area Under ROC	Sensitivity	Specificity	Area Under ROC
Unit Stay Level	94.9%	60.2%	0.775	97.5%	57.7%	0.776
Time Window Level	83.8%	66.7%	0.752	87.9%	59.5%	0.737**
Time Window Level: assume sepsis diagnosis valid for 2 days	89.1%	44.0%	0.665	92.4%	38.5%	0.655**
Time Window Level: assume sepsis diagnosis valid for 5 days	92.0%	39.3%	0.656	94.8%	36.8%	0.658

‡Adjudication outcome: 314 sepsis cases (35%), 575 of non-sepsis cases.

* Comparing area under ROC curve between two definitions: $p<0.05$; ** $p<0.01$.

Appendix Table 2.2 Predictive Capability of Diagnostic Criteria in Sepsis Diagnosis (Bivariate Analysis)†

Biophysical Parameters	Adjudicated Outcome (Odds Ratio, 95% CI)	1991 Definition (Odds Ratio, 95% CI)	2001 Definition (Odds Ratio, 95% CI)
Fever (>38°C)	2.21 (1.79, 2.73)	2.92 (2.65, 3.22)	-
Fever (>38.3°C)	2.45 (1.95, 3.07)	-	2.38 (2.13, 2.67)
Hypothermia	2.13 (1.57, 2.89)	1.23 (1.05, 1.45)	0.96 (0.82, 1.12)
Respiratory Rate	1.70 (1.24, 2.33)	4.31 (3.74, 4.97)	1.67 (1.50, 1.86)
PaCO2	4.17 (3.28, 5.29)	1.65 (1.43, 1.90)	1.30 (1.13, 1.50)
WBC	3.33 (2.68, 4.14)	2.68 (2.47, 2.92)	1.73 (1.60, 1.87)
Band	17.44 (13.87, 21.93)	5.14 (4.21, 6.28)	4.07 (3.32, 4.98)
Heart Rate	1.82 (1.42, 2.33)	4.23 (3.81, 4.70)	1.69 (1.55, 1.84)
GCS	1.54 (1.23, 1.93)	2.06 (1.88, 2.25)	2.04 (1.87, 2.21)
Edema	0.58 (0.48, 0.71)	-	1.66 (1.53, 1.80)
Fluid	5.55 (2.79, 11.06)	-	2.96 (2.54, 3.45)
Glucose	4.01 (3.22, 4.99)	-	1.32 (1.22, 1.44)
CRP	4.37 (1.74, 11.00)	-	1.34 (0.69, 2.61)
Systolic Blood Pressure	2.72 (2.22, 3.33)	-	1.45 (1.33, 1.58)
Mean Blood Pressure	1.76 (1.36, 2.27)	1.42 (1.30, 1.56)	1.36 (1.25, 1.49)
SvO2┼	0.00 (0.00, 48.34)	-	0.00 (0.00, 2.58)
Cardiac Index	0.46 (0.16, 1.38)	-	0.36 (0.25, 0.52)
PaCO2 & FiO2	3.56 (2.89, 4.39)	2.15 (1.98, 2.34)	1.91 (1.76, 2.08)
Urine Output	1.38 (1.09, 1.74)	0.75 (0.68, 0.83)	0.76 (0.69, 0.84)
Creatinine	2.84 (2.30, 3.50)	1.59 (1.47, 1.73)	1.56 (1.44, 1.69)
PTINR	3.05 (2.34, 3.97)	-	1.31 (1.13, 1.52)
aPPT	1.36 (0.95, 1.95)	-	1.15 (0.98, 1.34)
Ileus╪	0.00 (0.00, 1.09)	-	1.12 (0.74, 1.70)
Platelet	1.90 (1.47, 2.47)	1.36 (1.20, 1.54)	1.41 (1.25, 1.59)
Total Bilirubin	4.13 (2.73, 6.27)	1.80 (1.36, 2.38)	1.96 (1.48, 2.60)
Vasopressor	5.53 (4.38, 6.99)	1.35 (1.16, 1.57)	-
Lactate	20.61 (16.59, 25.60)	-	2.78 (2.38, 3.24)
Capillary	1.12 (0.87, 1.43)	-	1.35 (1.22, 1.48)

┼ Abnormal SvO2 predicted non-sepsis perfectly in 2 cases.

╪ Presence of ileus predicted non-sepsis perfectly in 88 adjudicated cases.

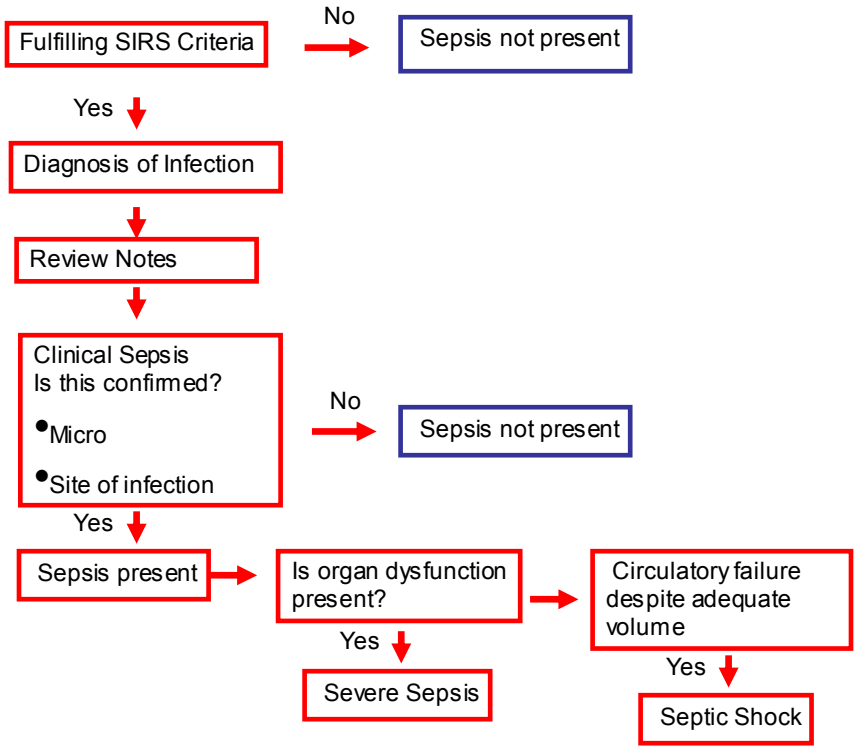

Figure 2.1 Sepsis Adjudication Flow Chart

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Chapter III Early Prediction of Sepsis

Aim 2

Early Prediction of Sepsis in Critically Ill Patients -- Use of continuously monitored physiological parameters

Abstract

Background

Early recognition and treatment for sepsis remain challenging in clinical practice. The physiological criteria for SIRS and sepsis have been widely adopted by clinicians since their introduction, and are widely available in ICUs. However, it is currently unknown how to best utilize these sources of information for early recognition of sepsis cases.

Objectives

To determine changes in several physiological parameters before the onset of sepsis and their relationship with sepsis onset, and to determine whether these parameters could be used to identify sepsis in critically ill adults

Study Design

Patient physiological data were collected from an electronic medical record system implemented in all the ICUs in a tertiary medical center. The patient population was randomly divided into a "derivation set" and a "validation set". The physiological parameters within 24 hours, 12 hours, or 6 hours before sepsis onset were compared among sepsis, non-infectious SIRS and non-SIRS groups. The predictive performances were assessed for various measurements of each parameter, shock index, and the measurement of "trending" (the relationship of time and the changes in physiological parameters). The best (maximum value of area under the ROC curve) measurement of each physiological parameter was selected into regression models for predicting sepsis onset.

Results

Parameters typically performed better in 24-hour windows compared to 6-hour or 12-hour windows. Minimum systolic blood pressure performed the best, followed by maximum respiratory rate in discriminating sepsis patients from SIRS patients. Maximum heart rate and maximum respiratory rate can differentiate sepsis patients from non-SIRS patients fairly well. The area under ROC of the combination of five parameters reached 0.76 for comparing sepsis to SIRS in the training set and 0.74 in the validation set. When comparing sepsis to non-SIRS, the area under the curve reached 0.94 in the training set and 0.90 in the validation set. Compared to the combinations, the

combination of the parameters' trending and the shock index did poorly in differentiating sepsis from either SIRS or non-SIRS patients.

Conclusions

Continuously monitored physiological parameters could help to identify patients who show signs of deterioration in the preceding 24 hours prior to developing sepsis.

3.1 Introduction

Sepsis is defined as a systemic inflammatory response syndrome (SIRS) with an infectious etiology that can progress into severe sepsis, when infection and the host response result in organ dysfunction, or septic shock, when sepsis is complicated by acute circulatory failure characterized by persistent arterial hypotension despite adequate volume resuscitation[1, 2]. Sepsis is the leading cause of death among critically ill patients and the 10th most common cause of death overall in the United States [3].

Early recognition and treatment for sepsis with appropriate antimicrobial agents [4, 5] and management strategies [6] have been shown to significantly reduce sepsis-related mortality. However, accurately diagnosing of sepsis before patients deteriorate and develop organ dysfunction is an important goal that is often difficult to achieve in practice. The clinical symptoms of systemic inflammation are neither specific nor uniform since non-infectious conditions, such as trauma, thermal injury, seizures, toxidromes, and pancreatitis, can also cause the SIRS criteria to be present [7]. Determining whether an infection is present can also be problematic because the bacterial identification rates for patients with sepsis has been reported as low as 30%[8]. In addition, bacterial growth also depends on the site of the infection, the ability to collect and process appropriate specimens, and previous antimicrobial treatment. The time required to isolate and report them can exceed the time window when sepsis is present without hypotension or organ dysfunction [6]. Multiple biomarkers, including procalcitonin, c-reactive protein (CRP), and interleukin- (IL) 6, have been proposed to facilitate a

physician's ability to identify patients with sepsis; however, there is currently no universally accepted single biomarker or biomarker combinations for sepsis [9]. Of the many candidate biomarkers investigated, plasma procalcitonin concentration has been investigated most comprehensively. Nevertheless, robust systematic reviews revealed procalcitonin had sub-optimal performance of discriminating sepsis from SIRS [10, 11].

The physiological criteria for SIRS and sepsis have been widely adopted by clinicians since their introduction. In addition, these criteria and hemodynamic parameters, which primarily focus on blood pressure, have been advocated as practice parameters for the hemodynamic management of septic patients [6, 12, 13]. With the proliferation of constant surveillance monitoring of patients by means of the electronic medical record systems in intensive care units, the usefulness of the commonly, continuously available physiological parameters and their role in early recognition of sepsis cases are particularly appealing.

However, it is currently unknown how to best utilize these sources of information to identify patients with sepsis. One possible strategy would be to monitor changes in vital signs over time and measure their association with systemic inflammation response to infection. By analyzing the changing patterns of patients' physiologic parameters, this strategy could have the potential of identifying pre-symptomatic patients with an increased risk for developing sepsis, facilitating physicians to initiate early and appropriate therapeutic intervention. In fact, a study of the perceptions and practices of critical care clinicians and nurses with regard to continuously monitoring common physiological parameters reported that the majority of intensivists and critical care nurses

considered it important to continuously monitor hemodynamic parameters and routinely used these parameters for identifying signs of deterioration in patients with sepsis [14]. Moreover, studies of critically ill infants have demonstrated that continuous heart rate characteristics monitoring aids the early diagnosis of neonatal sepsis [15-18].

Prior studies have attempted to use discrete physiological parameters, values that were recorded at the time of ICU admission, or the most abnormal value within the first 24 hours of the ICU stay, to identify patient with sepsis [19-21]. However, few studies have assessed the clinical usefulness of continuously monitored physiological parameters for adult patients with sepsis. Therefore, we conducted this study to determine changes in several physiological parameters before the onset of sepsis and their relationship with sepsis onset, and to determine whether these parameters could be used to identify sepsis in critically ill adults. The aims of our study were accomplished using the following stepwise approach. First, we evaluated the characteristics of each physiological parameter by measuring changes in these parameters during a time window of 24 hours, 12 hours, or 6 hours before sepsis diagnosis. Then, we compared the predictive performance of various measures of each parameter to identify candidate measures of these parameters. Third, various combinations of these physiological parameters' candidate measures were constructed and their diagnostic accuracy for predicting sepsis onset was evaluated within the following 6, 12, or 24 hours, respectively. The specific physiological parameters chosen for this study included body temperature, heart rate, respiratory rate and blood pressure. They were termed "physiomakers", as opposed to "biomarkers" which generally denote laboratory measurements. They were selected based on the definition

criteria [1, 2] and the recommendations from the guidelines of practice parameters for hemodynamic support [12, 13]. They are also widely and readily available to critical care providers, are among the "triggers" of suspension, and are frequently referred to when making a diagnosis of sepsis.

3.2 Methods

Study Design

This is an observational study conducted in seven intensive care units (ICUs), which includes three medical, two surgical, one cardiac, and one mixed unit for trauma, burn, neurosurgical and stroke, in a single academic tertiary care medical center. The seven ICUs serve as the primary sources of intensive care in the greater Worcester, Massachusetts area. Patients admitted into the units originate from various sources, including the emergency department, general wards, operating rooms, and other hospitals or health care centers in or adjacent to central Massachusetts. The medical center began employing an electronic medical record system in June, 2006 and finished implementing the system in all seven ICUs by May, 2007. All consecutive ICU admissions to the ICUs from October, 2007 to December, 2009 were included in this study. Since this study was part of the "Identifying Patients with Sepsis" project conducted in our ICUs, and data were collected from existing databases without patient identifiers, our hospital Institutional Review Board approved the study and waived the requirement of informed consent.

Patient Population

All consecutive adult patients admitted to any of the seven ICUs from October 2007 to December 2008 were enrolled in this study. The patients were screened and categorized into three groups:

Group 1: Sepsis group. Patients who had a recorded diagnosis of sepsis, severe sepsis, or septic shock in their electronic medical records during an ICU stay. To distinguish the different stages of sepsis, we defined sepsis as a less severe stage without organ dysfunction or septic shock. Severe sepsis was defined as sepsis complicated by organ dysfunction without fluid refractory hypotension. Septic shock was considered present when sepsis was complicated by circulatory failure despite fluid resuscitation [1, 2]. Patients with an admission diagnosis of sepsis were excluded from this analysis since no data, including the physiological parameters prior to ICU admission, were available in the electronic medical record system.

Group: 2 SIRS only group. Patients in this group met SIRS criteria but were never diagnosed with sepsis during their ICU stay. SIRS was defined as having two or more of the following conditions present: (1) temperature greater than 38 °C or less than 36 °C; (2) heart rate greater than 90 beats per minute; (3) respiratory rate greater than 20 breaths per minute or partial pressure of carbon dioxide (PaCO2) less than 32mmHg; (4) white blood cell count greater than 12,000 cells per cubic millimeter or less than 4,000 cells per cubic millimeter or immature myeloid (band) forms greater than 10% [1].

Group 3: non-SIRS group. The patients in this group were not diagnosed with sepsis nor met the SIRS criteria during their ICU stay.

The predictive performances of physiomarkers to distinguish sepsis patients from patients in the SIRS group and from the non-SIRS group were separately evaluated using group 2 and group 3, respectively. The primary outcome was the diagnosis of sepsis, while the presence of severe sepsis or septic shock was considered to be the secondary outcome.

Sepsis onset time was defined as the earliest time of sepsis diagnosis and was applied to all sepsis cases regardless of whether they progressed from sepsis to severe sepsis or septic shock within their ICU stay. For patients whose earliest sepsis diagnoses were severe sepsis or septic shock, the disease onset time was considered to be the time of the first diagnosis of severe sepsis or septic shock. The SIRS onset time was defined as the time when a patient met any two or more than two of the SIRS criteria.

Patients age less than 18 years, those with ICU length of stay less than 6 hours, or those without recorded values for any of the physiomarkers were excluded. Patients with an admission diagnosis of sepsis, severe sepsis, or septic shock were also excluded as the physiological measures we used to predict sepsis onset were not available for these patients.

Data collection

Patient demographic information, physiological values, lab tests, diagnoses, multidisciplinary care plans, care givers' notes including nursing assessment and critical care flow sheet records, care provider orders, and corresponding treatments, were recorded into the electronic medical record system by health care providers and were

collected for the entire unit stay. Patient demographic characteristics included age, gender, race, marital status, height, weight, body mass index, admission source, and admission diagnosis. Race was classified as white, black or other; admission source was classified as emergency department (ED), floor, operating room (OR), or other; admission diagnosis was categorized by organ system as well as by an operative and non-operative diagnosis. Acute Physiology and Chronic Health Evaluation (APACHE) IV score, and one of its components, Acute Physiological Score (APS), (Cerner, Kansas City, MO) were calculated from data collected by the electronic medical record. Microsoft SQL server 2000 was used to extract patient information from the data server.

We obtained values and corresponding time of assessment for continuously monitored physiomarkers, including heart rate, respiratory rate, blood pressure, and temperature. In the electronic system, a patient's physiological status and vital signs were measured, validated, and updated every 30 to 60 minutes during the initial 24 to 48 hours of their ICU stay and every 2 to 4 hours when a patient became relatively stable or was ready for ICU discharge.

Because we were interested in predicting the onset of sepsis, we only analyzed values recorded prior to sepsis onset. We compared the physiological parameters within 24 hours, 12 hours, or 6 hours before sepsis onset among the different groups. For the SIRS only group, values recorded within 24 hours, 12 hours, and 6 hours after SIRS onset were used. Since patients in the non-SIRS group had no disease "onset time", we used the values recorded within 24 hours, 12 hours, and 6 hours after ICU admission. Furthermore, as non-SIRS patients might have more abnormal physiomarkers during the

time close to ICU admission, we also used the values recorded between 24th hour and 30th hour after ICU admission, to assess the robustness of the results.

Data validation

Since the investigated physiomarkers were automatically recorded into the electronic system, with the exception of temperature being manually entered, a validation algorithm was set up to detect and correct parameters with extreme or non-physiological values. First, a senior intensive care physician was consulted to generate a reference list of possible value ranges for each physiomarker based on his expertise (heart rate: 20 ~ 360 beats per minute; temperature between 30 ~ 42 °C, respiratory rate: 3 ~ 55 breaths per minute; systolic blood pressure: 40 ~ 300 mmHg; and diastolic blood pressure: 20 ~ 150 mmHg). Second, we checked the distribution of each physiomarker and compared the values lower than the 1st percentile or higher than the 99th percentile to the reference value ranges. We then identified patients with physiomarker values outside the reference range and reviewed their entire nursing care flowsheet. We made corrections to the problematic values: 1) if the values recorded right before and after the problematic values were all within the reference range, we replaced the problematic value by the mean of the two values recorded before and after; 2) if the temperature was inappropriately recorded in the Fahrenheit scale, we converted it to the Celsius scale; 3) problematic noninvasive blood pressures were compared to invasive blood pressure for patients with an arterial catheter. If the invasive blood pressure values were within the reference range, the problematic noninvasive blood pressure values were excluded from the analysis.

Statistical Analysis

Patient's baseline demographic variables, admission diagnosis, and disease severity were summarized by calculating means and medians for continuous variables and frequencies for categorical variables. Differences between sepsis and SIRS patients or between sepsis and the non-SIRS patients were determined using t test, Wilcoxon rank sum test, chi square test or Fisher exact test, as appropriate. We first plotted the values of the physiomarkers for all three groups of patients along the time axis for the 24 hours before sepsis onset. The purpose was to visually explore any correlation between clinical parameters' value changes and sepsis onset. The patient population was randomly divided into two subsets, two thirds in a "training set" in which the physiomarkers and prediction models are obtained, and the remaining one third in a "validation set" where the diagnostic performance of the parameter(s) and the model are evaluated. In this way, we could evaluate the parameter(s) or model fairly to avoid overfitting.

We evaluated the independent predictive ability of each physiomarker measurement (original value, mean, median, standard deviation, the division of standard deviation by mean, interquartile range, and range), trending, as well as the shock index [22] (heart rate/systolic blood pressure), with sepsis onset, within the next 24 hours by performing a bivariate analysis. "Trending" was defined as the relationship of time and the changes in physiomarkers for each patient. To determine the trending for each patient, we fitted a Lowess curve for the values recorded within the 24 hours period using time as the independent variable and the physiomarker as the dependent variable. Estimated slope

coefficients were then generated and considered as the measurement of "trending". Receiver operating characteristic (ROC) curves were constructed and the areas under the receiver operating characteristic curve (AUC) were calculated for the different measurements of each physiomarker. Their corresponding optimal cut-off points were determined by maximizing the Youden's Index [23]. We applied these optimal cut-off points to the validation set and assessed their predictive performance by calculating the sensitivities and specificities. Candidates selected on the basis of the highest AUC values among the measurements of the investigated physiomarkers were the maximum values of temperature, respiratory rate, and heart rate, the minimum values of systolic and diastolic blood pressure, and shock index, which were all significantly associated with sepsis onset ($p< 0.1$). The measure of trending by estimated slope coefficient was also selected to be a candidate for multivariate regression analysis.

A series of multivariate logistic regression models were constructed in the training set including different combinations of the candidate variables. Correlation among predictors was examined by using Spearman's correlation test. The "best" model was chosen based on the combination of characteristics of having one of the highest values of AUC and being a parsimonious model. Based on the model parameter estimates from the training set, we predicted the diagnosis of sepsis using the validation set. Prediction and discrimination performances of the models were determined by AUC.

The same process was carried out for subgroup analyses of patients with severe sepsis or septic shock. It was also applied to the parameters recorded within 24 hours, 12 hours, or 6 hours before acute sepsis onset. A p value of 0.05 or less using 2-tailed tests

was considered as significant in the multivariate regression models. Statistical analysis was performed using Stata, version 10.0 (StataCorp LP, College Station, TX, USA).

3.3 Results

Patient Characteristics

After excluding 274 patients for whom values of physiological parameters were not available, the final analytic sample consisted of 14,466 ICU patients who were admitted at a single tertiary care medical center between October, 2007 and December, 2009, included 1,917 sepsis patients, 10,370 SIRS only patients, and 2,179 non-SIRS patients. The mean age of the study subjects was between 62 to 65 years, and it varied across the three groups with the sepsis group significantly older than the other two groups. About 40% of the study subjects were female, and nearly 90% were white. Compared to the other two groups of patients, sepsis patients were less likely to be married at the time of ICU admission. In accordance with sepsis definition, sepsis patients had significantly higher acuity scores than SIRS or non-SIRS patients. Sepsis patients were more likely to have been transferred from other patient wards and less likely to have been transferred from an operating room. Sepsis patients more often had an admitting diagnosis of a gastrointestinal or respiratory disease (Table 3.1).

Clinical Outcomes

Patients developing sepsis during their ICU stay stayed an average of 16.0 days in the hospital and 8.3 days in the ICU, which were significantly longer than those of SIRS

only (11.4 and 4.6 days respectively) or non-SIRS patients (5.6 and 1.6 days respectively). 34.3% of patients with sepsis died during their hospitalization and 26.9% of them died during their ICU stay; on the other hand, 8.9% and 12.5% of patients with SIRS died in an ICU or in the hospital, respectively. 96.9% of non-SIRS patients survived the hospital stay.

Individual Parameter Time Patterns

The changes in individual parameters over time in three different time windows are depicted as Lowess curves (Figure 3.1 – 3.3). Compared to SIRS or non-SIRS patients, sepsis patients exhibited declining diastolic and systolic blood pressures which were much lower than those of the other two patient groups. Trends in heart rate, respiratory rate, and body temperature for sepsis patients either slightly increased or decreased over time, but they were constantly above those of SIRS or non-SIRS patients.

Individual Parameter Performance on Discriminating Sepsis from SIRS

Overall, no individual parameter alone performed well in discriminating sepsis patients from SIRS patients, with the highest area under ROC curve being less than 0.75. Tables 3.2, 3.3, and 3.4 show the performance of individual parameters during 6-hour, 12-hour, and 24-hour time windows prior to disease onset, respectively. Based on the validation set, minimum values of the two blood pressure parameters had a higher area under the ROC (ranging from 0.66 to 0.72) than that of median, maximum, inter-quartile range, mean, or standard deviation. It was the same case across all three time windows.

Heart rate did not show a consistent pattern across three time windows, with median, inter-quartile range, and maximum performing best in each of the time windows. The maximum value of temperature always performed better than other measures, with the area under the ROC curve varying from 0.58 to 0.63. In two of the three time windows, the maximum value of respiratory rate demonstrated a better performance than the other measures. Finally, among the five routinely collected physiological parameters, diastolic blood pressure, systolic blood pressure, heart rate, temperature, and respiratory rate, systolic blood pressure performed best in discriminating sepsis patients from SIRS patients. This finding was consistent in all three time windows.

Test Characteristics of Individual Parameters for Discriminating Sepsis from SIRS

Individual parameters had sub-optimal predictive ability for differentiating sepsis from SIRS in the validation set. The sensitivity and specificity of these parameters were less than 60% and 80%, respectively (Tables 3.2 – 3.4). The best measurement among the investigated physiological parameters was minimum systolic blood pressure (optimal cutoff point 86), yielding a sensitivity of 56% and a specificity of 78% in a 24-hour window, followed by maximum respiratory rate (optimal cutoff point 26) in a 24-hour window, with the sensitivity and specificity being 51% and 74%. In general, test characteristics were better in the 24-hour time window than the other time frames.

Individual Parameter Performance for Discriminating Sepsis from non-SIRS

As expected, individual parameters performed much better in comparing sepsis to non-SIRS than comparing sepsis to SIRS patients. As shown in Tables 3.5 – 3.7, heart rate had the largest area under the ROC curve among all individual parameters, varying between 0.87 and 0.89. Both the mean or maximum values of heart rate performed well in differentiating sepsis from non-SIRS patients. Mean diastolic blood pressure and minimum systolic blood pressure could more accurately classify sepsis patients than other measures such as median or maximum, but both parameters were no better than heart rate or respiratory rate. The area under the ROC curve of maximum temperature ranged from 0.71 to 0.80, and that of mean or maximum respiratory rate from 0.80 to 0.84.

Test Characteristics of Individual Parameters for Discriminating Sepsis from Non-SIRS

Maximum heart rate with a cutoff point of 90 can accurately classify sepsis from non-SIRS and achieved a sensitivity of 80% and a specificity of 89% in a 24-hour window (Table 3.7). Maximum respiratory rate could also differentiate sepsis patients from non-SIRS patients fairly well, and its sensitivity and specificity were 73% and 85% in a 24-hour window. In contrast, the two blood pressure measures and temperature had relatively lower sensitivity and specificity in all three time windows. Parameters typically performed better in 24-hour windows compared to 6-hour or 12-hour windows.

Performance of Combined Parameters

The combination of all five parameters performed better than the individual parameters (Table 3.8 – 3.10); the longer the time window, the better the performance. In a 24-hour window, the area under ROC of the combination of five parameters reached 0.76 for comparing sepsis to SIRS in the training set (Figure 3.4), and 0.74 in the validation set (Table 3.10). When comparing sepsis to non-SIRS, the area under the curve reached 0.94 (Figure 3.5) in the training set and 0.90 in the validation set (Table 3.10). Since diastolic blood pressure is less clinically relevant to sepsis diagnosis, we also tested removing it from the combination of the five parameters and found the area under ROC only slightly changed.

Compared to other combinations, the combination of the parameter slopes of change over time did poorly in differentiating sepsis from either SIRS or non-SIRS patients, as did the standardized mean (mean divided by standard deviation). The area under ROC curve was in a range of 0.50 and 0.66 for both combinations of parameters. Interestingly, the shock index, measured as the ratio of systolic blood pressure over heart rate, also did poorly in differentiating sepsis from SIRS patients. However, the shock index had an increased area under ROC curve (0.80 – 0.85) when comparing sepsis to non-SIRS cases.

Test Characteristics of Combined Parameters

Based on the optimal cutoff point for each parameter, a patient was classified as having sepsis if at least one minimum measure of two blood pressure parameters was

abnormal and at least one maximum measure of the other three parameters was abnormal (Tables 3.8 – 3.10). In distinguishing sepsis from SIRS, the sensitivity was between 28% and 49%, and the specificity between 77% and 89%. For sepsis and non-SIRS patients, both the sensitivity and specificity were higher than those separating sepsis from SIRS, and the best combination showed a sensitivity of only 62% and a specificity of 77%. Other more restrictive criteria such as at least one abnormal minimum measure of two blood pressure parameters and at least two abnormal maximum measurements of the other three parameters resulted in much lower sensitivities but higher specificities (data not shown).

Sensitivity Analyses

About 52% of the sepsis patients had severe sepsis or septic shock. The subgroup analysis among these patients showed that the predictive performance of physiological parameters for distinguishing severe sepsis or septic shock from the other conditions, including SIRS only or non-SIRS patients, was similar to that of identifying sepsis patient (including sepsis, severe sepsis, and septic shock). The sensitivity and specificity were slightly improved and yet the area under ROC curve was not significantly different from the latter (data not shown). In addition, compared to the results using the data within 6 hours after ICU admission for the non-SIRS patients, those based on the data from between the 24th and 30th hour after admission did not change the main findings. The sensitivity and specificity of heart rate and temperature slightly increased; whereas, those of blood pressure parameters and respiratory rate declined (Appendix Table 3.1). The

performances of most comprehensive measures (except standardized mean) based on the 24th-30th hour data for non-SIRS patients also slightly decreased compared to those in the main analysis (Appendix Table 3.2).

3.4 Discussion

Although included in the definition of sepsis, and widely adopted by clinicians and routinely monitored in ICUs, physiological parameters, including heart rate, respiratory rate, blood pressure, and temperature, have generally been reported to have inferior diagnostic performance in identifying sepsis patients from SIRS or non-SIRS patients. In a study which evaluated the parameters included in SIRS criteria among patients with suspected infection in an emergency department, it was concluded that the SIRS criteria had little usefulness and correlated poorly with infection [21]. In another study which analyzed the project IMPACT data set, collected from 94 hospitals and more than 120 ICUs, the investigator reported that a model with heart rate, mean arterial pressure, temperature, and respiratory rate yielded a sensitivity of 59.4%, and a specificity of 67.7% [19]. Bossink et al. also reported very low specificity of the SIRS definition [20]. Attempting to find a parameter that could facilitate clinicians making sepsis diagnosis, especially early diagnosis, most contemporary work focuses on more expensive laboratory test including c-reactive protein, procalcitonin, and gene-expression profiling.[24, 25]

Realizing that previous studies only included a limited number of values for the studied parameters, this study systematically collected all the values for the continuously

monitored physiological parameters from an electronic medical record system, and evaluated various parameter measurements, trends of parameters, and derived predictors including the shock index. We demonstrated that sepsis patients tended to be more physiologically disarranged as having higher heart rates, lower blood pressure, higher temperatures and higher respiratory rates, compared to SIRS or non-SIRS patients. More importantly, continuously monitored physiological parameters measured 24 hours before disease onset have improved performance for identifying sepsis from SIRS patients and excellent predictive accuracy for distinguishing sepsis from non-SIRS critically ill adult patients. For a single parameter, minimum systolic blood pressure and maximum heart rate recorded within 24 hours of the disease onset performed the best for identifying sepsis from SIRS or non-SIRS patients, with an area under the ROC curve 0.69 and 0.89, respectively; at the optimal cutoffs of 86 mmHg and 90 beats pre minutes, they had a sensitivity of 56% and 80%, and a specificity of 78% and 89%, respectively. The combination of these physiological parameters (the two minimum blood pressure parameters and the other three maximum parameters) achieved area under ROC curve of 0.74 and 0.90 in differentiating sepsis from SIRS and non-SIRS patients, respectively, which were comparable to the published values of area under ROC curve reported for procalcitonin [10, 11].

To our knowledge, this is the first study on the usefulness of continuously monitored physiological parameters that are readily available in ICUs. This study has several innovative features in distinguishing sepsis from SIRS only or non-SIRS patients:

First, we applied a longer period of continuously monitored physiological parameters to establish measurements that demonstrated improved predictive performance for these parameters. After collecting all the recorded values, we measured the characteristics and changes over time for each parameter by calculating the maximum, minimum, variance (standard deviation), inter-quartile range and trend over time (slope of fitted linear line). Candidate measures were chosen based on the highest values of area under ROC curve. Shock index has been reported to be an indicator of left ventricular function during critical illnesses. In the patient population of our ICUs, shock index was shown to be no better than other measures in predicting onset of sepsis. This may be due to the fact that early in the disease course, septic patients have normal left ventricular function; whereas, impaired left ventricular function can develops as sepsis advances. Moreover, other diseases, including hemorrhage and trauma, can also lead to suppressed left ventricular function [22].

Secondly, we were able to use values of physiological parameters that were recorded before sepsis was diagnosed. Along with the purpose of predicting sepsis onset among critically ill patients rather than comparing the differences in these parameters between sepsis and SIRS or non-SIRS, we demonstrated that patients experienced subtle physiological deteriorations before symptoms became clinically apparent and before a diagnosis of sepsis was made. In fact, being able to recognize these subtle changes by using the most sensitive measures of these physiological parameters would assist in identification of sepsis in its early stage. It would also allow interventions and treatment to be administrated in a more timely manner for these patients. Additionally, analyzing

values recorded before sepsis onset also ensured that the relationship between physiological symptoms and sepsis was not confounded by treatment or other interventions for sepsis.

Thirdly, we explored alternative time windows of 6-hour, 12-hour and 24-hour to determine the earliest time for predicting sepsis by comparing the parameter's predictive performance. A challenge in clinical practice and research is that current definitions of sepsis do not provide corresponding time frame references for concurrence of the definitional criteria, especially in a longitudinal direction. For example, "a reduction in systolic blood pressure $\geq$ 40 mmHg from baseline" gives no information of a time perspective within which systolic blood pressure should be monitored and compared to its baseline value, and variance could exist within several hours, half a day, or even one day. Our approach of selecting the optimal time window provides clinicians and researchers a tangible, well defined observational time frame when they are reviewing or analyzing physiological parameters longitudinally. In our patient population, the 24-hour time window was the optimal one, which suggests that sub-acute physiological changes in sepsis patients could happen up to 24-hours before the syndromes became clinically apparent and sepsis was diagnosed.

The strengths of our study were that it was the first study to evaluate the usefulness of continuously monitored physiological parameters and their role for sepsis recognition and early diagnosis. Although laboratory tests and culture tests provide valuable information in confirming sepsis diagnosis, it is the deterioration in the commonly available monitored physiological changes that usually draws a clinician's

attention and leads to subsequent diagnostic examination. Our study also demonstrated that among the investigated parameters, minimum systolic blood pressure and maximum heart rate had the highest diagnostic accuracy. Moreover, we were aware of the issue of overfitting and addressed it by randomly splitting the study population into a derivation set and a validation set.

It was counterintuitive that estimated slope coefficients, the measurement of "trending", did not yield better performance compared to other combined measures, although sepsis patients did show a declining trend in diastolic and systolic blood pressure before disease onset. However, compared to SIRS or non-SIRS patients, blood pressure measures among sepsis patients were consistently lower, while heart rate, respiratory rate, and body temperature of sepsis patients were constantly higher. These findings serve as a caution against the over interpretation of trends for these physiological parameters.

Previous studies reported inconsistent performance of diagnostic tests which was partially due to mixed control populations. Critically ill patients with SIRS syndrome have an increased risk of developing sepsis compared to those not meeting SIRS criteria [8]. To address this concern, we examined the physiological parameters by comparing the changes between sepsis and non-infected SIRS and between sepsis and non-SIRS patients, respectively. As expected, the diagnostic performance was better for the latter.

Several limitations in our study merit consideration. First, our patients were from a single health care system, so the results of this study may not be generalizable. Secondly, although the combinations of the physiological parameters had good predictive

power, it was not sufficient to accurately predict who would develop sepsis within next 24 hours. Instead, clinicians should integrate these physiological signs with other patient characteristics, underlying disease severity, and comorbidities, and initiate other diagnostic tests to determine if sepsis is present. Nonetheless, the physiological parameters we presented in this study could help clinicians recognize sepsis patients earlier before they progress into a more severe stage. Third, we focused on patients who developed sepsis during their ICU stay, so our results may not be applicable to patients in other settings or who are recognized as having sepsis at the time of ICU admission.

3.5 Conclusions

The signs and symptoms of sepsis are highly variable and dynamic. Continuously monitored physiological parameters could help to identify patients who show signs of deterioration in the preceding 24 hours prior to being diagnosed as having sepsis. Our findings confirm prior studies that physiological parameters do not appear to be sepsis specific and had limited power of identifying patients with sepsis from non-infectious SIRS patients. However, the physiological parameters had excellent performances for distinguishing sepsis patient from non-SIRS patients in ICUs.

Table 3.1 Patient Characteristics

Characteristics	Sepsis Patients (n=1,917)	SIRS Patients (n=10,370)	Non-SIRS Patients (n=2,179)
Age, mean ± SD	64.55±16.28	62.44±17.44**	63.12±16.36*
Female Gender, n (%)	837(43.66)	4,415(42.57)	841(38.60)**
Race n (%)			
White	1,683(87.79)	9,266(89.35)*	1,924(88.30)
Black	68(3.55)	290(2.80)	69(3.17)
Other	166(8.66)	814(7.85)	186(8.54)
Married Status n (%)	835(43.56)	4,866(46.92)*	1,178(54.06)**
BMI, mean ± SD	28.84±8.30	28.84±29.93	28.32±8.45
APS Score, mean ± SD	72.64±30.02	48.19±23.97**	32.27±14.90**
APACHE Score, mean ± SD	86.07±31.55	59.76±26.04**	43.73±18.36**
Admission Source, n (%)			
Emergency Room	1,096(57.17)	5,486(52.90)**	1,389(63.74)**
Ward	391(20.40)	1,693(16.33)**	227(10.42)**
Operation Room	157(8.19)	2,189(21.11)**	369(16.93)**
Other Hospital	273(14.24)	919(8.86)**	132(6.06)**
Operative Diagnosis, n (%)	132(6.89)	2,000(19.29)**	304(13.95)**
Admission Diagnosis, n (%)			
Cardiovascular	791(41.26)	3,298(31.80)**	882(40.48)
Gastrointestinal	282(14.71)	1,242(11.98)**	171(7.85)**
Respiratory	393(20.50)	1,708(16.47)**	106(4.86)**
Genitourinary	91(4.75)	218(2.10)**	28(1.28)**
Neurology	72(3.76)	1,762(16.99)**	601(27.58)**
Other	288(15.02)	2,142(20.66)**	391(17.94)*
Clinical Outcomes			
Hospital Length of Stay, mean ± SD	16.07±18.50	11.40±13.37**	5.57±6.96**
ICU Length of Stay, mean ± SD	8.28±10.44	4.64±7.70**	1.56±1.20**
Hospital Mortality	657(34.27)	1,297(12.51)**	67(3.07)**
Unit Mortality	515(26.86)	924(8.91)**	33(1.51)**

* $p<0.05$ compared to sepsis patients; ** $p<0.01$ compared to sepsis patients.

Table 3.2 Individual Parameter Performance Comparing Sepsis to SIRS in a 6-hour Window

Parameter		Area Under ROC Using Training Set	Area Under ROC Using Validation Set	Optimal Cutoff Point	Sensitivity in Training Set	Specificity in Training Set	Sensitivity in Validation Set	Specificity in Validation Set
Diastolic Blood Pressure (Sepsis n=475; SIRS n=6,276)	Minimum	**0.6369**	**0.6660**	**45**	**43.0%**	**72.3%**	**45.4%**	**71.3%**
	Median	0.6373	0.6484	53	42.7%	72.9%	44.2%	71.7%
	Maximum	0.6109	0.6218	63	46.1%	70.8%	46.2%	70.4%
	Inter Quarter Range	0.5252	0.4964	9	32.8%	60.2%	37.8%	59.6%
	Mean	0.6419	0.6601	53	42.5%	74.2%	44.6%	72.7%
	Standard Deviation	0.5482	0.4793	8	31.4%	56.0%	37.8%	55.6%
Systolic Blood Pressure (Sepsis n=465; SIRS n=6,278)	Minimum	**0.6744**	**0.7210**	**94**	**44.5%**	**75.4%**	**56.0%**	**75.3%**
	Median	0.6612	0.6892	107	46.7%	74.0%	54.1%	73.7%
	Maximum	0.6244	0.6299	120	45.6%	72.8%	46.7%	71.8%
	Inter Quarter Range	0.5325	0.5167	15	34.2%	66.3%	30.9%	67.6%
	Mean	0.6655	0.6929	107	46.7%	74.9%	52.1%	74.7%
	Standard Deviation	0.4975	0.4308	12	33.8%	61.5%	32.8%	62.9%
Heart Rate (Sepsis n=462; SIRS n=6,294)	Minimum	0.5439	0.5395	78	35.1%	60.0%	36.3%	61.2%
	Median	**0.5687**	**0.5533**	**94**	**45.5%**	**68.5%**	**41.6%**	**66.2%**
	Maximum	0.5511	0.5393	101	45.2%	67.5%	45.4%	64.9%
	Inter Quarter Range	0.5311	0.5040	7	35.9%	64.3%	36.3%	62.0%
	Mean	0.5623	0.5505	95	44.4%	68.4%	42.4%	66.5%
	Standard Deviation	0.5176	0.4981	6	32.7%	57.2%	30.2%	56.0%
Temperature (Sepsis n=433; SIRS n=5,870)	Minimum	0.5859	0.5784	37	52.4%	61.3%	49.0%	61.6%
	Median	0.5902	0.5803	37	61.7%	50.3%	58.6%	50.6%
	Maximum	**0.5853**	**0.5827**	**38**	**22.6%**	**86.0%**	**25.1%**	**86.1%**
	Inter Quarter Range	0.5209	0.5146	0	52.2%	52.7%	50.2%	52.8%
	Mean	0.5892	0.5822	37	61.7%	49.9%	59.4%	50.3%
	Standard Deviation	0.4968	0.4747	5	43.4%	53.0%	42.6%	53.0%
Respiratory Rate (Sepsis n=488; SIRS n=6,124)	Minimum	0.5902	0.5629	16	29.7%	59.6%	32.3%	61.1%
	Median	**0.6133**	**0.5956**	**21**	**45.3%**	**74.3%**	**41.9%**	**73.1%**
	Maximum	0.5912	0.5895	23	50.6%	66.9%	51.1%	66.5%
	Inter Quarter Range	0.4901	0.5004	3	34.0%	66.8%	31.9%	69.1%
	Mean	0.6079	0.5935	21	46.7%	72.6%	42.8%	71.8%
	Standard Deviation	0.4780	0.4404	3	29.3%	67.3%	29.3%	65.4%

Table 3.3 Individual Parameter Performance Comparing Sepsis to SIRS in a 12-hour Window

Parameter		Area Under ROC Using Training Set	Area Under ROC Using Validation Set	Optimal Cutoff Point	Sensitivity in Training Set	Specificity in Training Set	Sensitivity in Validation Set	Specificity in Validation Set
Diastolic Blood Pressure (Sepsis n=357; SIRS n=5,764)	Minimum	**0.6261**	**0.6307**	**42**	**42.3%**	**71.8%**	**41.3%**	**71.7%**
	Median	0.6399	0.6027	53	42.3%	73.1%	35.3%	72.2%
	Maximum	0.6178	0.5676	67	45.1%	70.5%	38.9%	70.9%
	Inter Quarter Range	0.5133	0.4995	10	34.7%	60.4%	36.5%	62.4%
	Mean	0.6493	0.6093	53	43.1%	74.5%	36.5%	73.7%
	Standard Deviation	0.5753	0.4885	9	30.3%	54.0%	35.9%	56.1%
Systolic Blood Pressure (Sepsis n=350; SIRS n=5,772)	Minimum	**0.6655**	**0.6742**	**90**	**45.1%**	**74.4%**	**48.3%**	**75.9%**
	Median	0.6507	0.6535	107	46.6%	73.1%	47.1%	74.5%
	Maximum	0.6035	0.5753	126	46.6%	70.1%	39.1%	71.4%
	Inter Quarter Range	0.5239	0.5328	16	35.4%	63.9%	35.1%	64.7%
	Mean	0.6555	0.6548	107	45.4%	74.1%	44.8%	75.1%
	Standard Deviation	0.5086	0.4460	13	36.0%	57.9%	39.7%	57.3%
Heart Rate (Sepsis n=363; SIRS n=5,765)	Minimum	0.5472	0.5221	75	32.8%	60.0%	37.3%	61.0%
	Median	0.5630	0.5465	94	43.3%	67.5%	42.2%	67.3%
	Maximum	**0.5519**	**0.5639**	**105**	**45.7%**	**67.0%**	**43.5%**	**66.7%**
	Inter Quarter Range	0.5160	0.5536	9	32.8%	66.9%	39.1%	67.0%
	Mean	0.5610	0.5507	95	43.0%	68.3%	42.2%	68.5%
	Standard Deviation	0.5411	0.4524	7	33.9%	54.7%	39.8%	56.5%
Temperature (Sepsis n=324; SIRS n=5,639)	Minimum	0.5782	0.5779	37	40.7%	71.3%	38.0%	74.9%
	Median	0.6134	0.5843	37	62.7%	52.3%	57.1%	53.8%
	Maximum	**0.6280**	**0.6033**	**38**	**31.8%**	**83.9%**	**23.4%**	**84.5%**
	Inter Quarter Range	0.5881	0.5584	1	13.3%	88.5%	13.6%	87.1%
	Mean	0.6151	0.5902	38	19.4%	91.5%	16.3%	92.8%
	Standard Deviation	0.4931	0.4410	1	6.5%	77.4%	12.5%	75.1%
Respiratory Rate (Sepsis n=358; SIRS n=5,666)	Minimum	0.5650	0.5549	15	31.3%	59.2%	33.5%	60.9%
	Median	0.6242	0.6148	21	42.2%	75.2%	50.0%	73.8%
	Maximum	**0.6053**	**0.6400**	**25**	**42.5%**	**73.4%**	**50.6%**	**72.9%**
	Inter Quarter Range	0.5110	0.5325	3	38.3%	64.4%	42.7%	64.8%
	Mean	0.6160	0.6131	21	42.2%	72.9%	53.1%	71.5%
	Standard Deviation	0.5027	0.5279	3	36.6%	63.0%	42.1%	64.4%

Table 3.4 Individual Parameter Performance Comparing Sepsis to SIRS in a 24-hour Window

Parameter		Area Under ROC Using Training Set	Area Under ROC Using Validation Set	Optimal Cutoff Point	Sensitivity in Training Set	Specificity in Training Set	Sensitivity in Validation Set	Specificity in Validation Set
Diastolic Blood Pressure (Sepsis n=213; SIRS n=4,942)	Minimum	**0.6384**	**0.6440**	**40**	**42.2%**	**72.3%**	**50.9%**	**73.9%**
	Median	0.6184	0.6257	53	38.8%	73.0%	47.4%	73.7%
	Maximum	0.5520	0.5608	71	44.6%	67.3%	42.1%	66.9%
	Inter Quarter Range	0.5223	0.5269	11	25.6%	60.9%	28.1%	62.5%
	Mean	0.6276	0.6310	53	41.3%	75.0%	42.1%	74.5%
	Standard Deviation	0.5583	0.5232	10	25.6%	56.8%	28.1%	57.9%
Systolic Blood Pressure (Sepsis n=217; SIRS n=4,938)	Minimum	**0.6907**	**0.6934**	**86**	**49.6%**	**77.7%**	**55.6%**	**77.8%**
	Median	0.6341	0.6351	107	49.6%	74.7%	49.2%	73.1%
	Maximum	0.5565	0.5426	131	42.6%	68.0%	34.9%	66.7%
	Inter Quarter Range	0.5285	0.5210	18	34.8%	65.3%	44.4%	66.7%
	Mean	0.6410	0.6376	107	48.7%	76.2%	41.3%	74.1%
	Standard Deviation	0.5028	0.4550	14	36.5%	57.0%	50.8%	58.3%
Heart Rate (Sepsis n=220; SIRS n=4,942)	Minimum	0.4902	0.5249	74	37.0%	60.0%	33.3%	59.3%
	Median	0.5579	0.5179	96	45.0%	70.0%	35.9%	70.4%
	Maximum	0.5969	0.5754	110	48.0%	71.3%	47.4%	70.4%
	Inter Quarter Range	**0.5406**	**0.5977**	**10**	**44.0%**	**65.7%**	**37.2%**	**67.3%**
	Mean	0.5534	0.5210	97	44.0%	69.5%	34.6%	70.1%
	Standard Deviation	0.5150	0.4989	8	37.0%	57.5%	43.6%	60.2%
Temperature (Sepsis n=220; SIRS n=4,835)	Minimum	0.5861	0.5119	37	24.6%	78.2%	40.7%	77.2%
	Median	0.6515	0.5846	37	67.2%	52.4%	70.4%	53.3%
	Maximum	**0.6916**	**0.6315**	**38**	**39.3%**	**81.9%**	**46.3%**	**82.8%**
	Inter Quarter Range	0.5781	0.5656	1	16.4%	86.9%	14.8%	87.6%
	Mean	0.6592	0.5888	38	14.8%	92.2%	29.6%	92.1%
	Standard Deviation	0.5322	0.4717	1	7.4%	80.0%	3.7%	79.7%
Respiratory Rate (Sepsis n=208; SIRS n=4,873)	Minimum	0.4929	0.5207	14	36.6%	68.3%	30.3%	68.3%
	Median	0.6121	0.6324	21	46.4%	74.2%	47.0%	74.3%
	Maximum	**0.6529**	**0.6706**	**26**	**51.8%**	**73.7%**	**51.5%**	**74.3%**
	Inter Quarter Range	0.5473	0.5702	3	47.3%	61.1%	42.4%	61.5%
	Mean	0.6078	0.6230	21	48.2%	71.5%	47.0%	71.8%
	Standard Deviation	0.5584	0.5532	3	45.5%	60.1%	39.4%	60.7%

Table 3. 5 Individual Parameter Performance Comparing Sepsis to Non-SIRS in a 6-hour Window

Parameter		Area Under ROC Using Training Set	Area Under ROC Using Validation Set	Optimal Cutoff Point	Sensitivity in Training Set	Specificity in Training Set	Sensitivity in Validation Set	Specificity in Validation Set
Diastolic Blood Pressure (Sepsis n=475; non-SIRS n=1,381)	Minimum	0.6944	0.6351	45	46.7%	76.4%	38.6%	71.3%
	Median	0.6912	0.6553	53	46.9%	77.9%	36.7%	77.5%
	Maximum	0.6703	0.6315	64	49.9%	74.6%	44.8%	75.0%
	Inter Quarter Range	0.5636	0.5717	9	34.6%	56.0%	34.4%	57.2%
	Mean	**0.7029**	**0.6565**	**54**	**51.6%**	**77.3%**	**42.9%**	**76.6%**
	Standard Deviation	0.5384	0.5446	8	32.9%	62.8%	34.8%	61.9%
Systolic Blood Pressure (Sepsis n=465; non-SIRS n=1,381)	Minimum	**0.7384**	**0.7121**	**95**	**53.6%**	**79.7%**	**48.7%**	**79.9%**
	Median	0.7207	0.6993	107	51.2%	79.8%	49.4%	79.5%
	Maximum	0.6765	0.6564	122	50.1%	75.6%	49.8%	74.9%
	Inter Quarter Range	0.5116	0.5251	15	33.8%	64.1%	31.7%	64.8%
	Mean	0.7262	0.7053	108	51.2%	78.5%	53.7%	77.8%
	Standard Deviation	0.5198	0.5138	11	41.7%	62.9%	38.6%	64.8%
Heart Rate (Sepsis n=465; non-SIRS n=1,381)	Minimum	0.8272	0.8483	69	19.6%	34.0%	18.2%	31.1%
	Median	0.8428	0.8645	82	66.7%	87.8%	67.2%	89.7%
	Maximum	0.8493	0.8645	88	67.5%	87.8%	71.8%	88.3%
	Inter Quarter Range	0.5534	0.5510	6	42.4%	63.3%	43.2%	64.6%
	Mean	**0.8463**	**0.8688**	**82**	**67.3%**	**87.9%**	**69.1%**	**89.2%**
	Standard Deviation	0.5818	0.5891	5	43.0%	69.6%	44.8%	70.3%
Temperature (Sepsis n=455; non-SIRS n=1,210)	Minimum	0.6876	0.6885	37	43.7%	88.8%	40.2%	92.5%
	Median	0.7015	0.7088	38	26.8%	98.1%	24.9%	99.2%
	Maximum	**0.7023**	**0.7141**	**37**	**48.6%**	**85.0%**	**52.4%**	**87.8%**
	Inter Quarter Range	0.5418	0.5351	0	52.5%	54.9%	49.3%	55.7%
	Mean	0.7022	0.7080	37	70.1%	56.9%	69.9%	59.2%
	Standard Deviation	0.5489	0.4772	1	43.5%	50.8%	46.3%	48.7%
Respiratory Rate (Sepsis n=463; non-SIRS n=1,368)	Minimum	0.7670	0.7517	15	25.3%	39.4%	24.4%	39.9%
	Median	0.7935	0.7992	18	64.4%	82.5%	65.8%	84.5%
	Maximum	0.7937	0.8008	21	63.9%	86.2%	64.2%	88.0%
	Inter Quarter Range	0.5144	0.5132	2	44.9%	58.0%	46.1%	60.8%
	Mean	**0.8013**	**0.8017**	**18**	**68.9%**	**80.2%**	**67.3%**	**81.6%**
	Standard Deviation	0.5710	0.5722	2	51.6%	65.2%	51.2%	64.1%

Table 3.6 Individual Parameter Performance Comparing Sepsis to non-SIRS in a 12-hour Window

Parameter		Area Under ROC Using Training Set	Area Under ROC Using Validation Set	Optimal Cutoff Point	Sensitivity in Training Set	Specificity in Training Set	Sensitivity in Validation Set	Specificity in Validation Set
Diastolic Blood Pressure (Sepsis n=350; non-SIRS n=1,327)	Minimum	0.6545	0.5951	43	46.6%	73.3%	40.8%	68.3%
	Median	0.6626	0.6200	54	46.0%	75.7%	40.8%	72.6%
	Maximum	0.6362	0.6137	68	43.7%	73.4%	48.9%	73.8%
	Inter Quarter Range	0.5478	0.5530	10	34.3%	57.7%	37.4%	58.3%
	Mean	**0.6705**	**0.6293**	**54**	**47.4%**	**75.5%**	**43.1%**	**72.9%**
	Standard Deviation	0.5465	0.5551	9	31.7%	64.2%	32.8%	61.5%
Systolic Blood Pressure (Sepsis n=350; non-SIRS n=1,327)	Minimum	**0.7145**	**0.6715**	**91**	**50.9%**	**79.2%**	**45.4%**	**77.4%**
	Median	0.7021	0.6497	108	52.0%	77.2%	39.1%	79.1%
	Maximum	0.6339	0.6001	128	52.3%	71.9%	39.1%	73.6%
	Inter Quarter Range	0.4937	0.4825	16	35.4%	62.8%	35.1%	61.0%
	Mean	0.7026	0.6552	108	50.6%	78.0%	39.1%	81.2%
	Standard Deviation	0.5128	0.5428	12	37.7%	64.9%	44.8%	62.9%
Heart Rate (Sepsis n=343; non-SIRS n=1,335)	Minimum	0.8467	0.8333	67	18.1%	30.0%	21.0%	29.9%
	Median	0.8604	0.8631	81	69.1%	89.5%	69.1%	90.5%
	Maximum	0.8645	0.8667	89	72.6%	87.9%	73.5%	87.6%
	Inter Quarter Range	0.5616	0.5744	8	42.6%	70.9%	39.8%	71.7%
	Mean	**0.8660**	**0.8667**	**81**	**70.6%**	**88.8%**	**69.1%**	**90.0%**
	Standard Deviation	0.5996	0.6060	6	46.1%	71.0%	42.0%	71.3%
Temperature (Sepsis n=350; non-SIRS n=1,298)	Minimum	0.6514	0.6865	37	33.1%	93.9%	34.8%	93.6%
	Median	0.7006	0.7352	38	28.9%	97.7%	33.5%	97.1%
	Maximum	**0.7373**	**0.7659**	**38**	**28.3%**	**99.4%**	**25.3%**	**99.6%**
	Inter Quarter Range	0.5927	0.5821	1	14.0%	93.5%	12.0%	93.9%
	Mean	0.7098	0.7476	38	35.1%	96.5%	33.5%	97.0%
	Standard Deviation	0.5746	0.5161	1	9.4%	87.8%	7.0%	87.2%
Respiratory Rate (Sepsis n=336; non-SIRS n=1,334)	Minimum	0.7427	0.6919	14	22.3%	45.6%	29.0%	45.3%
	Median	0.8250	0.7728	18	67.3%	85.5%	63.4%	83.6%
	Maximum	**0.8273**	**0.8005**	**22**	**66.1%**	**88.3%**	**62.9%**	**85.4%**
	Inter Quarter Range	0.5513	0.5350	3	39.6%	76.3%	39.8%	77.2%
	Mean	0.8317	0.7709	19	64.6%	89.5%	56.5%	88.0%
	Standard Deviation	0.6299	0.6439	2	61.6%	57.9%	63.4%	59.2%

Table 3.7 Individual Parameter Performance Comparing Sepsis to Non-SIRS in a 24-hour Window

Parameter		Area Under ROC Using Training Set	Area Under ROC Using Validation Set	Optimal Cutoff Point	Sensitivity in Training Set	Specificity in Training Set	Sensitivity in Validation Set	Specificity in Validation Set
Diastolic Blood Pressure (Sepsis n=222; non-SIRS n=902)	Minimum	0.5826	0.5954	39	36.0%	70.2%	40.5%	70.0%
	Median	0.6341	0.6361	54	43.7%	73.8%	39.7%	74.6%
	Maximum	0.6247	0.6242	74	47.8%	72.5%	50.0%	73.3%
	Inter Quarter Range	0.5706	0.6212	11	30.2%	60.2%	26.2%	58.3%
	Mean	**0.6379**	**0.6429**	**55**	**47.8%**	**74.0%**	**43.7%**	**72.4%**
	Standard Deviation	0.5808	0.5806	9	37.8%	52.3%	38.9%	46.6%
Systolic Blood Pressure (Sepsis n=222; non-SIRS n=902)	Minimum	**0.6729**	**0.6978**	**88**	**49.1%**	**75.4%**	**51.6%**	**76.4%**
	Median	0.6629	0.6612	110	52.3%	74.2%	49.2%	72.9%
	Maximum	0.5850	0.6162	135	46.4%	69.2%	44.4%	68.7%
	Inter Quarter Range	0.4855	0.4619	18	37.4%	63.2%	32.5%	68.7%
	Mean	0.6639	0.6678	109	49.6%	75.5%	50.0%	75.1%
	Standard Deviation	0.5111	0.5009	14	37.8%	65.2%	38.1%	65.8%
Heart Rate (Sepsis n=222; non-SIRS n=902)	Minimum	0.8455	0.8220	63	16.7%	32.7%	19.1%	36.4%
	Median	0.8758	0.8627	79	72.5%	90.1%	73.0%	88.7%
	Maximum	**0.8786**	**0.8943**	**90**	**78.8%**	**90.2%**	**80.2%**	**88.5%**
	Inter Quarter Range	0.5799	0.6370	9	41.4%	71.5%	53.2%	73.7%
	Mean	0.8804	0.8713	79	75.7%	89.4%	74.6%	87.6%
	Standard Deviation	0.6250	0.6679	7	46.0%	75.2%	51.6%	75.5%
Temperature (Sepsis n=220; non-SIRS n=894)	Minimum	0.6534	0.6908	37	42.7%	85.6%	51.3%	89.3%
	Median	0.7328	0.7907	37	51.4%	88.4%	63.3%	91.0%
	Maximum	**0.7719**	**0.8005**	**38**	**62.3%**	**79.0%**	**70.1%**	**83.6%**
	Inter Quarter Range	0.5776	0.6189	1	10.0%	96.2%	16.2%	95.0%
	Mean	0.7403	0.7941	38	38.2%	96.8%	45.3%	98.9%
	Standard Deviation	0.6167	0.6501	1	4.6%	98.9%	6.8%	99.1%
Respiratory Rate (Sepsis n=228; non-SIRS n=893)	Minimum	0.6857	0.6236	13	28.1%	51.4%	39.2%	51.5%
	Median	0.7937	0.7839	18	66.2%	82.4%	65.8%	81.0%
	Maximum	**0.8120**	**0.8387**	**23**	**70.2%**	**85.6%**	**73.3%**	**84.5%**
	Inter Quarter Range	0.5584	0.5880	3	48.7%	70.3%	52.5%	68.8%
	Mean	0.7969	0.7944	19	65.8%	87.4%	60.8%	85.6%
	Standard Deviation	0.6696	0.6991	3	44.7%	88.1%	49.2%	86.9%

Table 3.8 Performance of Combined Parameters in a 6-hour Window

Parameter	Measure	Area Under ROC Compared to SIRS*		Area Under ROC Compared to Non-SIRS**	
		Training Set	Validation Set	Training Set	Validation Set
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Minimum Minimum Maximum Maximum Maximum	0.7096	0.6906	0.9062	0.9260
Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Minimum Maximum Maximum Maximum	0.7079	0.7139	0.8985	0.9221
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Slope of Parameter Change Over Time	0.5928	0.6152	0.6313	0.6630
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Mean/Standard Deviation	0.5816	0.5464	0.5972	0.5280
Systolic Blood Pressure Heart Rate	Systolic Blood Pressure/Heart Rate	0.6462	0.6199	0.8487	0.8501
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Minimum*** Minimum*** Maximum*** Maximum*** Maximum***	Training Set: Sensitivity=26.4% Specificity=89.2%	Validation Set: Sensitivity=28.3% Specificity=89.1%	Training Set: Sensitivity=40.4% Specificity=92.2%	Validation Set: Sensitivity=42.0% Specificity=93.0%

*There are 451 sepsis cases and 5791 SIRS cases in the training set, 226 sepsis cases and 2879 SIRS cases in the validation set.
**There are 451 sepsis cases and 1204 other cases in the training set, 226 sepsis cases and 625 other cases in the validation set.
*** Based on the optimal cutoff points, at least one abnormal blood pressure measure and at least one other abnormal measure.

Table 3. 9 Performance of Combined Parameters in a 12-hour Window

Parameter	Measure	Area Under ROC Compared to SIRS*		Area Under ROC Compared to Non-SIRS**	
		Training Set	Validation Set	Training Set	Validation Set
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Minimum Minimum Maximum Maximum Maximum	0.7012	0.7094	0.9150	0.9286
Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Minimum Maximum Maximum Maximum	0.7003	0.7068	0.9114	0.9177
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Slope of Parameter Change Over Time	0.5999	0.5678	0.6181	0.6425
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Mean/Standard Deviation	0.6153	0.5007	0.5807	0.5190
Systolic Blood Pressure Heart Rate	Systolic Blood Pressure/Heart Rate	0.6284	0.6051	0.8465	0.8331
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Minimum*** Minimum*** Maximum*** Maximum*** Maximum***	Training Set: Sensitivity=38.7% Specificity=81.7%	Validation Set: Sensitivity=35.2% Specificity=82.7%	Training Set: Sensitivity=53.5% Sensitivity=88.0%	Validation Set: Sensitivity=43.2% Sensitivity=86.0%

*There are 344 sepsis cases and 5,505 SIRS cases in the training set, 162 sepsis cases and 2,792 SIRS cases in the validation set.
**There are 344 sepsis cases and 1299 other cases in the training set, 162 sepsis cases and 680 other cases in the validation set.
***Based on the optimal cutoff points, at least one abnormal blood pressure measure and at least one other abnormal measure

Table 3.10 Performance of Combined Parameters in a 24-hour Window

Parameter	Measure	Area Under ROC Compared to SIRS*		Area Under ROC Compared to Non-SIRS**	
		Training Set	Validation Set	Training Set	Validation Set
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Minimum Minimum Maximum Maximum Maximum	0.7560	0.7442	0.9383	0.8992
Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Minimum Maximum Maximum Maximum	0.7555	0.7436	0.9342	0.8971
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Slope of Parameter Change Over Time	0.6005	0.6078	0.5635	0.6495
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Mean/Standard Deviation	0.5938	0.5159	0.6585	0.5882
Systolic Blood Pressure Heart Rate	Systolic Blood Pressure/Heart Rate	0.6119	0.6005	0.8344	0.8089
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Minimum*** Minimum*** Maximum*** Maximum*** Maximum***	Training Set: Sensitivity=48.2% Specificity=77.8%	Validation Set: Sensitivity=48.6% Specificity=77.4%	Training Set: Sensitivity=59.6% Sensitivity=77.5%	Validation Set: Sensitivity=62.4% Sensitivity=77.3%

*There are 228 sepsis cases and 4,738 SIRS cases in the training set, 109 sepsis cases and 2,385 SIRS cases in the validation set.
**There are 228 sepsis cases and 883 other cases in the training set, 109 sepsis cases and 463 other cases in the validation set.
***Based on the optimal cutoff points, at least one abnormal blood pressure measure and at least one other abnormal measure.

Appendix Table 3.1 Individual Parameter Performance Comparing Sepsis to Non-SIRS in a 6-hour Window (24th-30th hour data for non-SIRS)

Parameter		Area Under ROC Using Training Set	Area Under ROC Using Validation Set	Optimal Cutoff Point	Sensitivity in Training Set	Specificity in Training Set	Sensitivity in Validation Set	Specificity in Validation Set
Diastolic Blood Pressure (Sepsis n=481; non-SIRS n=690)	Minimum	**0.6281**	**0.6482**	**44**	**40.3%**	**73.3%**	**42.8%**	**73.1%**
	Median	0.6282	0.6266	53	43.9%	72.3%	42.0%	70.8%
	Maximum	0.5965	0.5896	63	46.8%	71.3%	44.9%	66.6%
	Inter Quarter Range	0.5580	0.5225	10	32.0%	60.9%	27.6%	64.9%
	Mean	0.6328	0.6314	53	45.3%	72.9%	43.6%	70.0%
	Standard Deviation	0.5458	0.4985	8	33.7%	60.4%	33.3%	64.0%
Systolic Blood Pressure (Sepsis n=481; non-SIRS n=690)	Minimum	**0.7051**	**0.7327**	**95**	**50.5%**	**78.1%**	**54.3%**	**78.2%**
	Median	0.6841	0.6924	107	51.1%	77.0%	45.7%	78.5%
	Maximum	0.6054	0.6275	120	46.0%	69.9%	46.1%	72.2%
	Inter Quarter Range	0.5187	0.5119	14	36.8%	64.2%	37.5%	61.8%
	Mean	0.6784	0.6964	107	48.9%	76.8%	48.2%	81.0%
	Standard Deviation	0.5517	0.5425	11	40.8%	66.7%	40.3%	66.0%
Heart Rate (Sepsis n=481; non-SIRS n=690)	Minimum	0.8550	0.8458	68	18.1%	31.9%	14.4%	32.3%
	Median	0.8758	0.8698	79	71.7%	89.6%	74.1%	86.7%
	Maximum	0.8857	0.8716	86	71.5%	89.6%	71.6%	89.0%
	Inter Quarter Range	0.5926	0.5596	6	44.1%	68.1%	39.9%	70.0%
	Mean	**0.8794**	**0.8738**	**79**	**71.7%**	**89.3%**	**74.5%**	**85.3%**
	Standard Deviation	0.6029	0.5939	5	44.1%	70.4%	42.8%	73.9%
Temperature (Sepsis n=464; non-SIRS n=601)	Minimum	0.6591	0.6518	37	46.6%	87.5%	38.6%	92.0%
	Median	0.6876	0.6855	38	27.2%	98.3%	23.2%	99.4%
	Maximum	**0.7038**	**0.7125**	**37**	**60.6%**	**76.7%**	**55.9%**	**81.8%**
	Inter Quarter Range	0.5925	0.6363	0	50.0%	66.6%	54.6%	68.7%
	Mean	0.6878	0.6851	38	27.2%	98.3%	26.4%	98.4%
	Standard Deviation	0.5855	0.4001	1	46.3%	38.8%	40.5%	36.7%
Respiratory Rate (Sepsis n=470; non-SIRS n=688)	Minimum	0.7123	0.7213	15	25.7%	50.2%	23.5%	53.7%
	Median	0.7545	0.7412	19	61.1%	82.6%	59.1%	81.2%
	Maximum	0.7700	0.7339	21	65.7%	81.7%	60.7%	76.8%
	Inter Quarter Range	0.5328	0.4590	2	47.9%	59.0%	40.5%	56.6%
	Mean	**0.7584**	**0.7492**	**19**	**62.3%**	**81.3%**	**60.3%**	**78.3%**
	Standard Deviation	0.5837	0.5111	2	54.7%	63.5%	45.3%	60.7%

Appendix Table 3. 2 Performance of Combined Parameters in a 6-hour Window (24th-30th hour data for non-SIRS)

Parameter	Measure	Area Under ROC Compared to SIRS*		Area Under ROC Compared to Non-SIRS**	
		Training Set	Validation Set	Training Set	Validation Set
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Minimum Minimum Maximum Maximum Maximum	0.7096	0.6906	0.9163	0.9206
Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Minimum Maximum Maximum Maximum	0.7079	0.7139	0.9133	0.9185
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Slope of Parameter Change Over Time	0.5928	0.6152	0.5632	0.5636
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Mean/Standard Deviation	0.5816	0.5464	0.6160	0.5895
Systolic Blood Pressure Heart Rate	Systolic Blood Pressure/Heart Rate	0.6462	0.6199	0.8653	0.8486
Diastolic Blood Pressure Systolic Blood Pressure Heart Rate Temperature Respiratory Rate	Minimum*** Minimum*** Maximum*** Maximum*** Maximum***	Training Set: Sensitivity=26.4% Specificity=89.2%	Validation Set: Sensitivity=28.3% Specificity=89.1%	Training Set: Sensitivity=40.4% Specificity=91.7%	Validation Set: Sensitivity= 42.0% Specificity= 95.0%

*There are 451 sepsis cases and 5791 SIRS cases in the training set, 226 sepsis cases and 2879 SIRS cases in the validation set.
**There are 451 sepsis cases and 601 other cases in the training set, 226 sepsis cases and 301 other cases in the validation set.
*** Based on the optimal cutoff points, at least one abnormal blood pressure measure and at least one other abnormal measure.

Figure 3.1 Individual Measure Time Patterns in a 6-hour Window

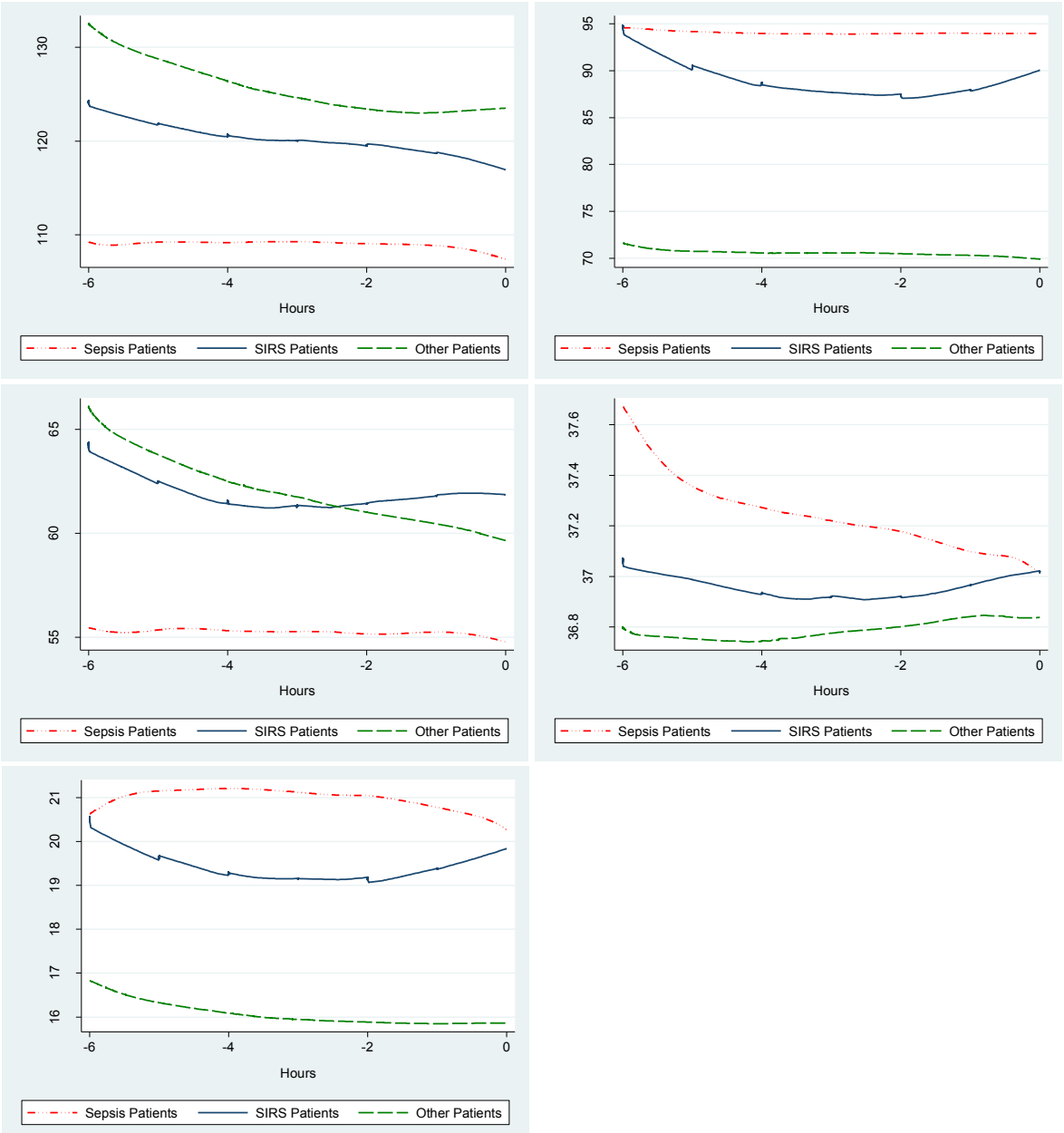


Figure 3.2 Individual Measure Time Patterns in a 12-hour Window

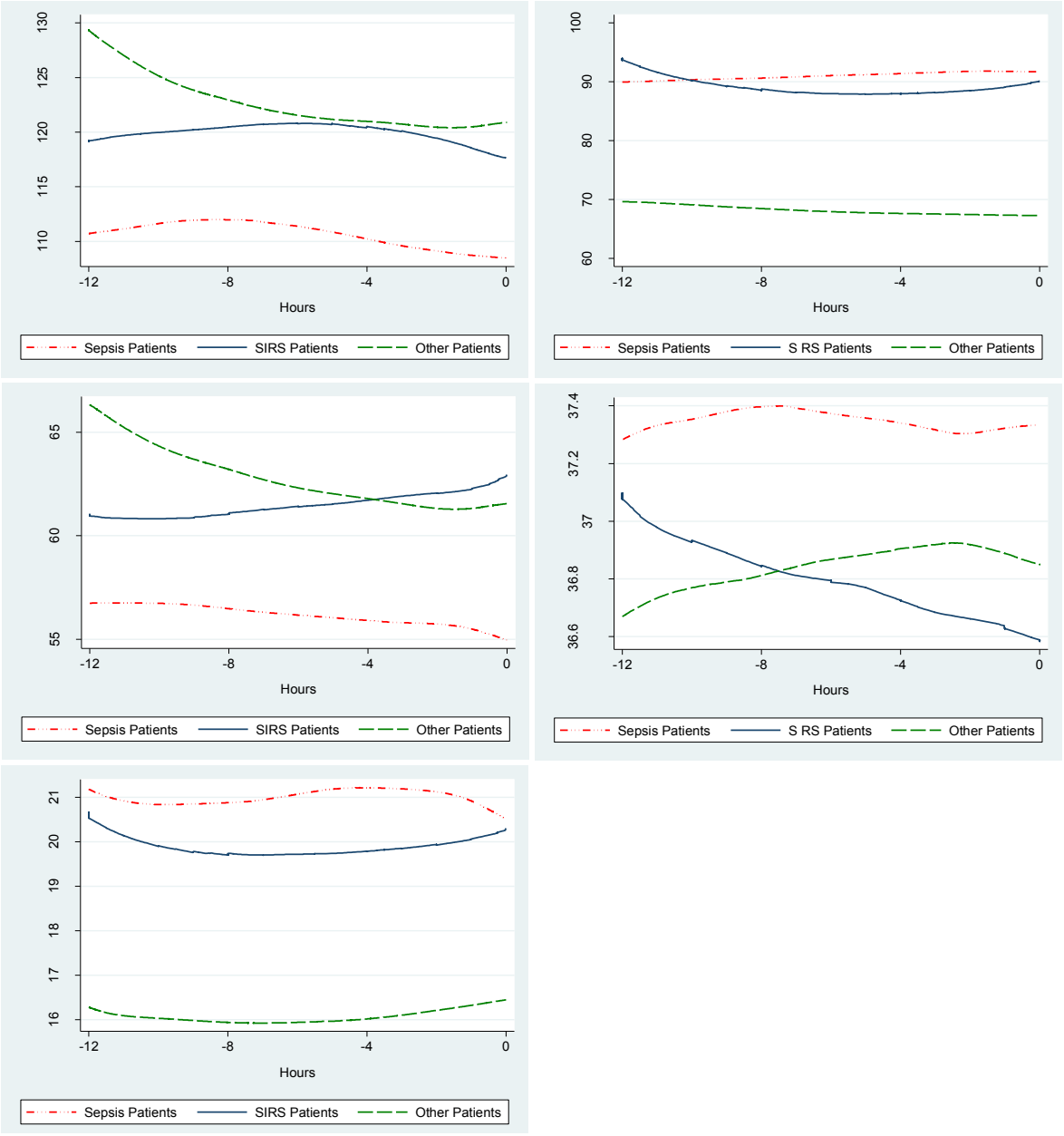


Figure 3.3 Individual Measure Time Patterns in a 24-hour Window

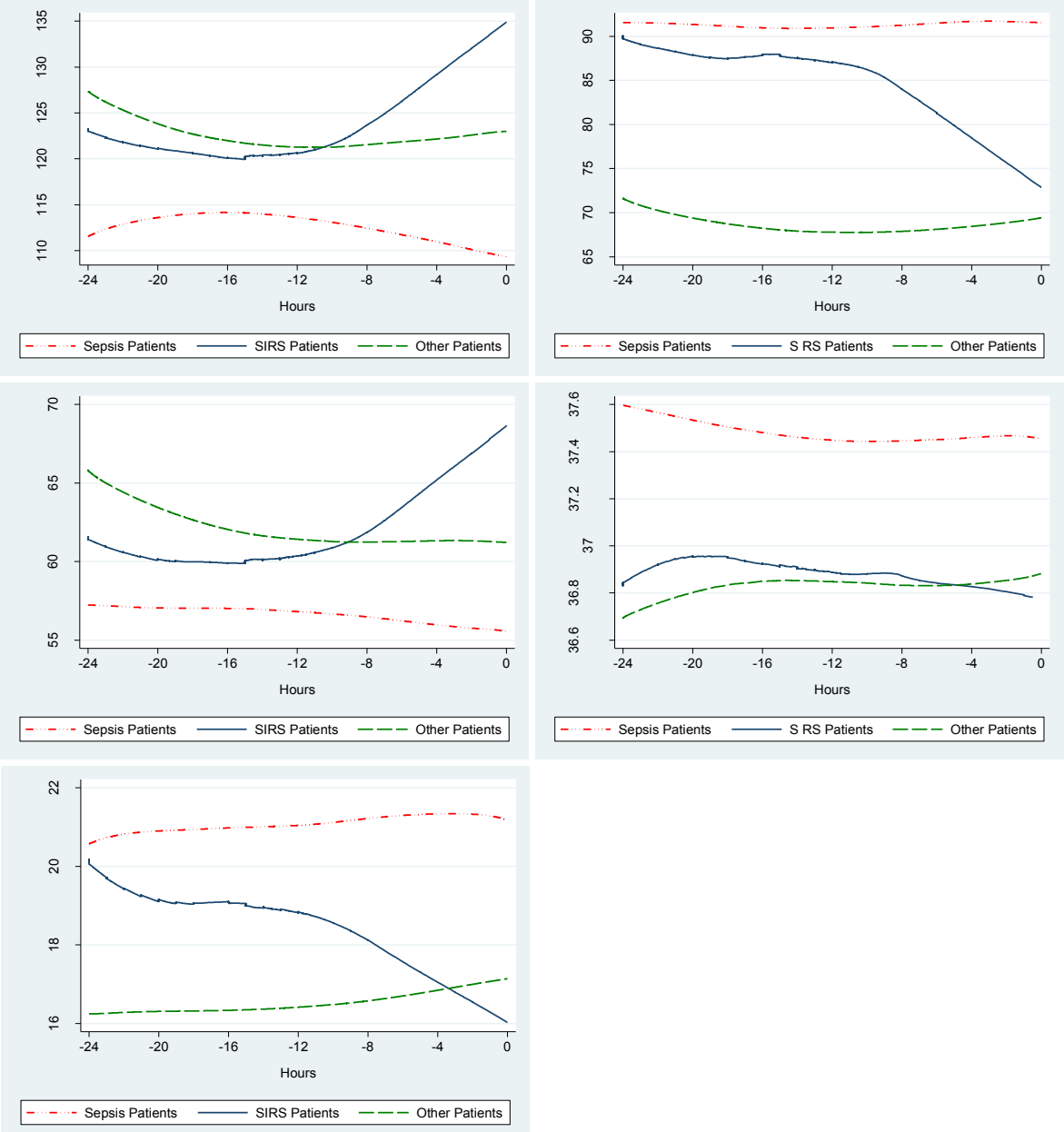


Figure 3.4 ROC Curve Based on the Model Using All Five Continuous Measures, Compared to SIRS Patients

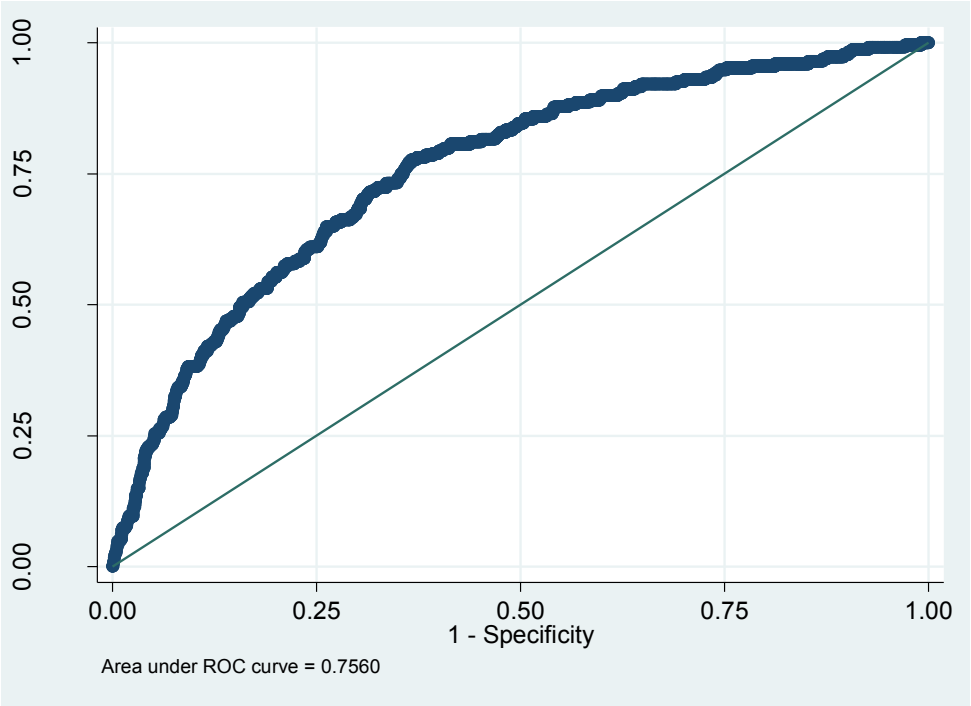
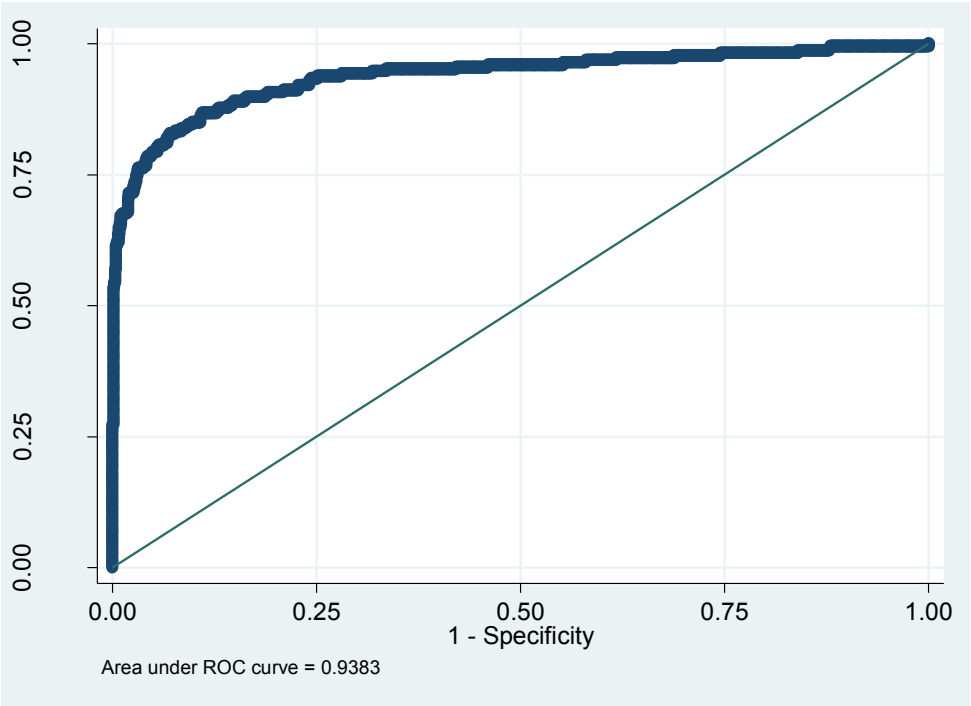


Figure 3.5 ROC Curve Based on the Model Using All Five Continuous Measures, Compared to Other Non-SIRS Patients



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Chapter IV Corticosteroid Treatment among Septic Shock Patients

Aim 3:

The Effectiveness of Corticosteroid Treatment on Septic Shock Patient Outcomes in Intensive Care Units

Abstract

Background

Septic shock is a deadly disease with an unfortunately high mortality. The effect of prolonged moderate-dose corticosteroid replacement therapy on mortality in septic shock patients remains controversial.

Objectives

To provide insight into the effects of low dose corticosteroids treatment as applied in clinical practice, we conducted this study by examining the use of corticosteroids treatment as well as its association with mortality in a large cohort of septic shock patients.

Study Design

Data were collected from 841 consecutive septic shock adult patients admitted into seven ICUs between October 2007 and December 2009. We calculated a propensity

score for each patient to adjust for treatment selection bias. Differences in hospital and ICU mortality were evaluated using the McNemar test between propensity score matched pairs. The association of corticosteroid therapy with hospital mortality and ICU mortality were also determined using multivariate logistic regression after adjustment for propensity score alone, covariates, or propensity score (in deciles) and covariates.

Results

Of the 841 septic shock patients, 698 (83 %) had septic shock at ICU admission or shock onset within the initial 24 hours after unit admission, and a total of 34% of (290 out of 841) patients received corticosteroid therapy. Propensity scores of 279 patients receiving low-dose corticosteroids were successfully matched with 279 patients without low-dose corticosteroids treatment.). For matched pairs, significantly increased hospital mortality and ICU mortality were observed in the group treated with low-dose corticosteroids than the control group, OR was 1.44 (95% CI: 1.01, 2.08) and 1.57 (95% CI: 1.07, 2.32), respectively. Multivariate logistic regression after adjustment for propensity score alone, covariates, or propensity score (in deciles) and covariates generated similar results. Subgroup analyses showed a consistent, non-significant trend that patients receiving corticosteroids were associated with a higher mortality by divided patients by acuity, septic shock onset time, and treated with vasopressors, etomidate, or low-dose corticosteroid treatment initiated within 8, 24, or 72 hours or later after shock onset.

Conclusions

No survival benefits were identified in septic shock patients receiving low-dose corticosteroids. The results hold for all of the investigated subgroups across levels of disease severity, early or late onset during ICU stay, the timing of corticosteroids administration, and treatment with vasopressors or etomidate.

4.1 Introduction

Septic shock is the most common cause of death in Intensive Care Units (ICUs), with a mortality rate ranging from 30% to 60% [1-3]. Patients with septic shock fail to maintain hemodynamic homeostasis and develop abnormalities in circulation, which include increased vascular permeability, decreased intravascular volume, vasodilatation and myocardial depression, and imbalances of oxygen demand, extraction and delivery. It is thought that an intact adrenal cortex and adequate production of cortisol contributes to host ability to survive sepsis[4]. Additionally, increasing evidence has shown that critically ill patients develop adrenal insufficiency, referred to as critical illness-related corticosteroid insufficiency (CIRCI), with a prevalence of up to 60% in patients with septic shock[5].

Since the introduction of corticosteroids as an adjunctive therapy in severe sepsis and septic shock a half century ago, its therapeutic role, in terms of efficacy and safety, has been debated. Although it is widely recognized that a short course of high dose corticosteroids is ineffective [6-9], whether prolonged moderate-dose corticosteroid replacement therapy improves mortality in septic shock patients remains controversial. The discrepant results of the two recent, landmark trials, the French multicenter study and European multicenter trial (CORTICUS) [10, 11], have fueled debates with regard to the benefits of low dose corticosteroid use in septic shock patients. The French multi-center trial demonstrated that low dose corticosteroid significantly reduced mortality among patients with CIRCI and refractory septic shock despite fluid challenge and vasopressor

treatment. These results had subsequently been incorporated into the Surviving Sepsis Campaign (SSC) Guidelines of 2004, which recommended low dose corticosteroids for septic shock patients who require vasopressor therapy to maintain adequate blood pressure despite adequate fluid resuscitation [12]. However, the CORTICUS study did not find improved survival among septic shock patients who received low-dose hydrocortisone treatment, despite their adrenal status. The most recent SSC guidelines recommended low-dose corticosteroids only for adult patients who responded poorly to fluid resuscitation and vasopressor therapy [13]. Recent meta-analyses of randomized trials reported heterogeneous effects of corticosteroids therapy on mortality [14-17], which included patient characteristics, underlying risk, treatment dose and duration.

While randomized controlled trials have generated conflicting results, appropriately designed observational studies can provide insight into the effects of low dose corticosteroids treatment as applied in clinical practice. We conducted a retrospective study of prospectively collected data by examining the use of corticosteroids treatment as well as its association with mortality in a large cohort of septic shock patients admitted to ICUs of our tertiary hospital. The main objective of this study was to examine the effectiveness of corticosteroids treatment on hospital mortality in all septic shock patients. We also aimed to evaluate the association of this therapy with ICU mortality, as well as treatment efficacies within different patient subgroups.

4.2 Methods

Data Source

This study collected data from the electronic medical records system of an academic medical center, which included seven ICUs: three medical, two surgical, one cardiac, and one mix unit for trauma, burn, neurosurgical and stroke. Patient information, including physiological values, lab tests, diagnoses, care plans and notes, and corresponding treatment, was recorded into this system during their entire unit stay by health care providers. Microsoft SQL was used to extract patient information from the data server. An advantage of this electronic system, compared to paper based medical chart extraction, is that, at a lower labor cost, it provides more detailed information about each patient.

Study Design and Population

This was a retrospective observational cohort study. All consecutive adult patients admitted into seven ICUs between October 2007 and December 2009 were analyzed if they were diagnosed with septic shock at anytime during their ICU stay. Patients with underlying diseases requiring long-term corticosteroid treatment were excluded.

This study was part of the "Identifying Patients with Sepsis" project conducted in our ICUs and data were collected from existing data without patient identifiers. Our Human Subjects Committee approved the study and waived the requirement of informed consent.

Data Collection

Septic Shock and Shock Onset Time

Septic shock in this study was defined as a patient for whom a septic shock diagnosis was recorded at any time during an ICU stay. The administration time of the first dose vasopressor was defined as the septic shock onset time because clinicians usually checked patient status and prescribed appropriate vasopressor based on their best judgment before they entered notes and prescription orders into the electronic system at the work station in the ICU. For patients with care limitations such as “do not resuscitate (DNR)”, “comfort measures only”, and “no vasopressors/inotropes”, their earliest septic shock diagnosis time was considered as the shock onset time. Thus we considered as baseline values all the covariates recorded at the time of shock onset or the ones closest to shock onset time, since they were more likely to reflect patient status at or right before their condition started deteriorating.

Steroid Treatment

Steroid treatment was defined as the intravenous administration of hydrocortisone in conjunction with a diagnosis of septic shock. The start time of the first dose of hydrocortisone was considered as the start time of steroid treatment. We did not collect the treatment duration or the total dosage given to patients since some patients were discharged from ICU before steroid treatment termination, and the treatment information was not available after unit discharge.

Patient Outcomes

The primary patient outcome was pre-specified as hospital mortality; secondary outcomes included ICU mortality. We decided a priori not to measure the association between steroid treatment and time to vasopressor therapy withdrawal because some patients were discharged from the units before vasopressor withdrawal.

Covariates

Patient demographic characteristics, including age, gender, race, marital status, height, weight, and admission source were used as covariates. Race was classified as white, black and other; marital status was categorized as married, single, or widowed. Admission source was classified as emergency department (ED), floor, operating room (OR), and other.

Physiological parameters included heart rate, respiratory rate, blood pressure, temperature, urine output, ventilation status and Glasgow Coma Score. A patient's physiological status was assessed and updated every 30 to 60 minutes during the initial 24 to 48 hours of ICU stay and is updated every 2 to 4 hours for stable patients. We obtained test results and corresponding test time for laboratory tests including WBC count, band, platelet, hemoglobin, hematocrit, PT, PTT, INR, glucose, creatinine, albumin, anion gap, ALT, AST, blood urea nitrogen, bilirubin, lactate, c-reactive protein (CRP), sodium, potassium, cortisol, PaO2, FiO2, PaO2/FiO2 ratio, PaCO2, pH, base excess, and microbiology tests (specimen, sites of acquisition, test time, sites with positive culture, organism type). Acute Physiology And Chronic Health Evaluation

(APACHE) IV score, and one of its components, Acute Physiological Score (APS) were calculated using a commercially available program (Cerner, Kansas City, MO).

Comorbid diseases were identified by searching patients' admission diagnoses, diagnoses made after the time of ICU admission, and physicians' daily care notes. Fourteen disease categories associated with patient outcome or physician's decisions about steroid treatment were pre-specified by consulting a senior intensivist: hypertension, coronary artery disease, congestive heart failure, neurological disease, chronic obstructive pulmonary disease, other pulmonary disorder, localized cancer, metastatic cancer, diabetes, cirrhosis, other liver disorder, chronic renal failure, AIDS, and immunosuppression. In addition, we identified patients who had received chemotherapy within the last 6 months, underwent organ transplant, or had received corticosteroids within the last 4 months.

DNR status and other care limitation

A patient was classified as DNR present if he/she was designated "Comfort measures only" or "Do not resuscitate (DNR)" in the electronic record. Other care limitation consisted of "No CPR", "No cardioversion", "No blood draws", "No intubation", "No blood products", and "No vasopressors or inotropes".

Procedure and Treatment

We identified patients who received an arterial catheter, central venous catheter, mechanical ventilation, etomidate, a fluid bolus, antimicrobial therapy, vasopressor,

and/or recombinant human activated protein C (rhAPC) during their ICU stay. The start time of each procedure/treatment was categorized as before shock onset, at or within 6 hours of shock onset, or 6 hours after shock onset.

Propensity Score Match

To adjust for such treatment selection bias, we calculated a propensity score for each patient to indicate his/her probability of receiving corticosteroid therapy. By consulting a senior critical care specialist, we pre-specified a list of variables that could affect the decision to use corticosteroid therapy. These included age, gender, race, unit admission source, ICU admission diagnosis, DNR status, Glasgow Coma Score, weight, temperature, blood pressure, respiratory rate, heart rate, PaO2/FiO2 ratio, PacO2, pH, WBC, hematocrit, sodium, potassium, creatinine, bilirubin, albumin, urine output, lactate, culture test, cancer, AIDS, cirrhosis, immunosuppression, chemotherapy within the past six months, corticotropin stimulation test, central venous catheters, arterial catheters, fluid bolus administration, vasopressor prescription, rhAPC, mechanical ventilation, etomidate, and antimicrobial therapy. We used the test values that were recorded closest to septic shock onset time because clinicians were most likely to refer to them in the context of making a treatment decision regarding the use of corticosteroids. Multivariate logistic regression with corticosteroid treatment as the outcome was used to determine the probability of receiving corticosteroids for each patient. The adequacy of the propensity score in adjusting for the effect of included covariates was evaluated by determining whether covariates were balanced between patients with or without corticosteroid

therapy. Patients without corticosteroids therapy were then matched to patients with corticosteroids therapy using nearest neighbor one-to-one match algorithm without replacement. We also imposed a caliper of 0.10 on the maximum propensity score distance between two patients within the same matched pair to ensure the balance between the two groups. Sensitivity analysis was performed to determine if there was unmeasured hidden bias that was not accounted for in the propensity regression.

Analyses

Summary statistics were calculated using mean and medians for continuous variables and frequencies for categorical variables. Differences between groups with and without corticosteroid therapy were determined using t test, Wilcoxon rank sum test, chi square test or Fisher exact test, as appropriate. Differences in hospital and ICU mortality were evaluated using the McNemar test. The association of corticosteroid therapy with hospital mortality and ICU mortality were determined using multivariate logistic regression after adjustment for propensity score alone, covariates, or propensity score (in deciles) and covariates.

4.3 Results

Patient Characteristics

There were 13,199 patient ICU admissions between October 2007 and December 2009. Of these patients, 919 had a diagnosis of septic shock during their ICU stay. Seventy-six patients with an inaccurate unit admission registration were excluded from analysis. We also excluded those with inflammatory bowel disease, Addison's disease, adrenalectomy, myasthenia gravis, or emphysema, to remove the possible confounder that these patients might benefit from adrenal replacement therapy independent of any indication of septic shock treatment. In addition, their propensity of receiving corticosteroids was equal to 1, which made it impossible to find matching patients in the untreated group who also had these chronic conditions.

Of the 841 septic shock patients, 698 (83 %) had septic shock at ICU admission or shock onset within the initial 24 hours after unit admission; an additional 143 (17 %) were diagnosed with septic shock later during their ICU stay; the average shock onset time for this group was 121 hours (SD: 195) after ICU admission. A total of 34% of (290 out of 841) patients received corticosteroid therapy, and 77% (649 out of 841) received vasopressors. Of the patients receiving vasopressors, 38% (245 out of 649) received low-dose corticosteroids; whereas, 16% (45 out of 290) receiving low-dose corticosteroids never received vasopressors. The baseline characteristics of these patients are shown in Table 4.1. Patients treated with low-dose corticosteroids were more likely to be female, younger (mean age 62.2 versus 65.7 years), and have a higher body mass index (BMI). There were fewer treated patients having DNR or other care limitations orders at

baseline. All the patients in this study were severely ill, but the APACHE IV scores and APS scores were significantly higher in the low-dose corticosteroids group compared to the group without low-dose corticosteroid treatment. The physiological values and lab tests results were comparable, except for lactate and heart rate which were more abnormal in patients treated with low-dose corticosteroids. There was a non-significant trend toward the low-dose corticosteroids group receiving more aggressive management at baseline such as central venous catheterization, arterial catheterization, etomidate administration, and mechanical ventilation. Additionally, patients receiving low dose corticosteroids were more likely to receive other treatments (vasopressors and rhAPC) for septic shock.

Unadjusted outcomes for hospital and ICU mortality and length of stay are summarized in Table 4.2. Patients treated with low-dose corticosteroids had significantly higher unadjusted hospital and ICU mortality than patients not treated with low-dose corticosteroids. Moreover, patients receiving corticosteroids stayed longer both in the ICU and in the hospital compared to those not receiving corticosteroids.

Propensity Matched Analysis

The area under the receiver operating characteristics curve (ROC) was 0.72 for the multivariate logistic regression of low-dose corticosteroids treatment among all patients, implying good differentiation between patients treated with and those not treated with low-dose corticosteroids. Propensity scores for the two treatment groups largely overlapped, and 279 patients receiving low-dose corticosteroids (propensity score mean,

0.42; range, 0.05 – 0.85) were successfully matched with 279 patients without low-dose corticosteroids treatment (propensity score mean, 0.39; range, 0.05 – 0.86). Patient base line characteristics were much more similar and balanced (no significant differences were present for any of the covariates) between the exposure group and matched control group, as shown in Table 4.3 and Figure 4.1. Similar propensity regression models were carried out for the prospectively defined subgroups and the ROCs ranged from 0.72 to 0.83. For each subgroup analysis, the same one to one propensity matching strategy was conducted before comparing outcomes between the low-dose corticosteroid group and control group. The number of successfully matched pairs for each subgroup analysis is presented in Appendix Table 4.1.

Relationship of Low-Dose Corticosteroids Therapy with Mortality

The unadjusted possibility of dying in the hospital conditional on treatment exposure was significantly higher in the low-dose corticosteroid group than the group not treated with low-dose corticosteroids (OR, 1.67; 95% CI: 1.26, 2.23; P <0.01). For matched pairs, a significantly increased hospital mortality was observed in the exposure group (52% vs. 43%; OR, 1.44; 95% CI: 1.01, 2.08; P =0.04) (Table 4.4).

Similarly, ICU mortality was consistently higher in the group treated with low-dose corticosteroids than the control group in both the unadjusted (OR, 1.88; 95% CI: 1.40, 2.51; P<0.01) and matched group comparisons (OR, 1.57; 95% CI: 1.07, 2.32; P =0.01).

Subgroup analyses were conducted by patient severity based on APACHE score, among patients with septic shock onset within 24 hours after ICU admission, and among patients treated with vasopressors, etomidate, or low-dose corticosteroid treatment initiated within 8, 24, or 72 hours or later after shock onset. For hospital mortality, most subgroup analyses showed a non-significant trend that patients receiving corticosteroids were associated with a higher mortality (Appendix Table 4.1). Among patients with higher acuity, whose APACHE score was above the median, regression analyses controlling for other covariates showed a significantly higher mortality for patients receiving than those not receiving low-dose corticosteroid treatment for septic shock (OR, 1.72; 95% CI: 1.05, 2.81; P =0.03). For patients treated with corticosteroids after 8 hours of shock onset, regression analyses demonstrated that treated patients were 44% more likely to die in the hospital than those in the control group. However, the propensity score match did not detect significant differences in hospital mortality for all the subgroup analyses. The patterns were similar for ICU mortality when comparing the treatment to control group patients.

Finally, our statistical power analysis indicated that with a sample size of 841 where 34.5% were treated patients, we had 80% power to detect an absolute difference of 17 percentage points in hospital mortality between two groups, or a corresponding odds ratio of 1.445, based on a 2 sided test and a statistical significance level of 0.05.

4.4 Discussion

The Surviving Sepsis Campaign (SSC) 2008 guidelines recommend low-dose corticosteroids for patients who respond poorly to fluid resuscitation and vasopressor treatment in spite of the uncertain treatment effects on patient survival. Moreover, it has been reported that low-dose corticosteroids have been widely adopted in clinical practice globally [18]. This study, to our knowledge, is the largest study in the US that specifically evaluated the relationship of low-dose corticosteroids with mortality in ICU patients with septic shock in a clinical setting. We found that about one third of our ICU patients with septic shock received low-dose corticosteroids, and they had higher hospital mortality than those who not treated with corticosteroids.

Being aware that this was an observational study and patients were not randomly assigned to treatment group, we followed these steps to account for potentially confounding variables when we assessed the association of low-dose corticosteroids with patient mortality. First, we used propensity score analysis to balance the probability of being treated with low-dose corticosteroids. We identified an extensive list of variables that related to the decision to prescribe low-dose corticosteroids and calculated propensity scores to account for these variables. Two hundred seventy-nine pairs of patients were then matched on propensity of the treatment with corticosteroids, and their baseline characteristics were evenly distributed between patients treated with and not treated with low-dose corticosteroids. Comparing the two groups of patients demonstrated significantly higher hospital and ICU mortality for patients in the corticosteroid treatment group than the comparison group. Second, the effectiveness of

low-dose corticosteroids on patient mortality was evaluated by a series of multivariate logistic regression analyses using the entire patient population (n=841) and multiple subgroups. Effect estimates from these models consistently pointed to increased risk of death for the group of patients treated with low-dose corticosteroids, although these estimates modestly differed in their magnitude. In addition, the propensity score method generated more conservative effect estimates of treatment, which were found to be closer to the null effect (OR=1). Thirdly, subgroup analyses were conducted for important patient characteristics including disease severity, vasopressor treatment, early or late septic shock onset during the course of ICU stay, low-dose corticosteroid treatment initiated within 8, 24, or 72 hours or later after shock onset, and treatment with etomidate. Results from these subgroup analyses failed to identify beneficial effects of treatment with low dose corticosteroids.

We found there was no survival benefit, but increased harm associated with low-dose corticosteroids treatment. These results are consistent with previous studies which found no benefits or even higher mortality with low-dose corticosteroid treatment [11, 16, 18-20]. Our results distinct from the findings of randomized controlled trial by Annane et al. and those of two recent meta-analyses of randomized controlled trials [10, 14, 15]. A possible explanation for these divergent findings is that the effects of corticosteroids depend on the patient's underlying risk: a true positive effect, if it exists, could be obscured by lumping heterogeneous groups of patients together. However, we conducted a series of subgroup analyses and failed to identify any subgroup that benefited from the low-dose corticosteroid treatment. Moreover, the patient population in our study differed from

those in randomized controlled trials. Indeed, 15% of the patients in our study were not treated with a vasoconstrictor and would have been excluded from trails of septic shock. In addition, increased mortality for patients treated with low dose corticosteroids without or before fluid bolus and vasopressors treatment might partially explain why harm was detected in clinical practice that was not noted in the clinical trials. Another possible explanation for the findings of our study is that low-dose corticosteroids therapy may serve as an indicator that patients treated with low-dose corticosteroids are also the ones receiving more aggressive, invasive care in our ICUs. It is possible that these more aggressive treatments may cause harm themselves or offset any benefits from corticosteroid therapy. A fourth explanation is that we still do not thoroughly understand the mechanisms for low-dose corticosteroids therapy. Although increased cortisol is believed to exert protective physiologic effects through modulating metabolism, maintaining microvascular perfusion, increasing sensitivity of vascular muscle to endogenous or exogenous vasopressors agents, and modulating the immune system function [21-23] , it has also been reported that treatment with low-dose corticosteroids induces hyperglycemia, which in itself is a risk factor for mortality in the ICU. Additionally, the study by Ho, et al. found that plasma nitric oxide (NO) levels were not decreased by hydrocortisone administration [24].

The strength of this study is that it included a substantial number of patients in a clinical practice setting. In addition, we were able to accurately measure patients' baseline characteristics; especially for those who had septic shock onset later during their ICU stay. Their "baseline" characteristics at ICU admission may not reflect actual

baseline characteristics at shock onset. A rigorous analytical strategy was applied to this study including using propensity score to adjust for treatment selection bias. Our study was limited by its observational design, for which we could not exclude the possibility that our findings were confounded by unmeasured factors. Another limitation was that we only included patients from a single healthcare system, which may not be representative of healthcare systems in other geographic areas. Finally, there was a consistent trend in all the subgroup analyses that associated low dose corticosteroid treatment with a higher mortality; as suggested by our power analysis, however, we might have lacked adequate power to detect the differences in mortality between the corticosteroid treatment group and the comparison group due to smaller sample sizes used in the subgroup analyses.

4.5 Conclusions

In conclusion, this study did not identify survival benefits in septic shock patients receiving low-dose corticosteroids. The results hold for all of the investigated subgroups across levels of disease severity, early or late onset during ICU stay, the timing of corticosteroids administration, and treatment with vasopressors or etomidate. These findings suggest that caution should be used when considering a recommendation for the use of low dose corticosteroids in clinical practice guidelines for the management of sepsis.

Table 4.1 Patient Characteristics before Propensity Score Match

Characteristics	Treated Patients (n=290)	Control Patients (n=551)	Bias (%)	P Value
Age, mean ± SD	62.20±15.89	65.74±16.37	-21.95	<0.01
Female Gender, n (%)	147 (50.69)	235 (42.65)	16.17	0.03
Race, n (%)				
White	260 (89.66)	479 (86.93)	8.48	0.25
Black	7 (2.41)	22 (3.99)	-8.98	0.23
Other	23 (7.93)	50 (9.07)	-4.1	0.58
Married Status, n (%)	122 (42.07)	251 (45.55)	-7.03	0.33
BMI, mean ± SD	29.09±8.46	28.29±7.71	9.95	0.16
APS Score, mean ± SD	84.25±30.93	75.30±27.05	30.81	<0.01
APACHE Score, mean ± SD	97.56±31.36	89.09±28.64	28.23	<0.01
DNR status, n (%)	15 (5.17)	48 (8.71)	-13.96	0.06
Admission Source, n (%)				
Emergency Room	161 (55.52)	326 (59.17)	-7.38	0.31
Ward	55 (18.97)	111 (20.15)	-2.97	0.68
Operation Room	28 (9.66)	41 (7.44)	7.93	0.27
Other Hospital	46 (15.86)	73 (13.25)	7.42	0.30
Operative Diagnosis, n (%)	25 (8.62)	33 (5.99)	10.13	0.15
Admission Diagnosis, n (%)				
Cardiovascular	129 (44.48)	247 (44.83)	-0.69	0.92
Gastrointestinal	43 (14.83)	71 (12.89)	5.62	0.43
Respiratory	66 (22.76)	108 (19.60)	7.73	0.28
Genitourinary	8 (2.76)	31 (5.63)	-14.34	0.06
Neurology	7 (2.41)	23 (4.17)	-9.88	0.19
Other	37 (12.76)	71 (12.89)	-0.38	0.96
Comorbidities, n (%)				
Hypertension	137 (47.24)	285 (51.72)	-8.98	0.22
Coronary Artery Disease	53 (18.28)	125 (22.69)	-10.94	0.14
Chronic Heart Failure	40 (13.79)	96 (17.42)	-10.01	0.17
Neurological Disease	161 (55.52)	291 (52.81)	5.43	0.45
Chronic Pulmonary Disease	91 (31.38)	165 (29.95)	3.11	0.67
Cancer	71 (24.48)	102 (18.51)	14.57	0.04
Diabetes	80 (27.59)	177 (32.12)	-9.93	0.17
Liver Disease	44 (15.17)	88 (15.97)	-2.2	0.76
Chronic Renal Failure	21 (7.24)	56 (10.16)	-10.38	0.16
GCS score, mean ± SD	11.69±4.10	11.86±4.12	-4.11	0.57
Temperature, mean ± SD	37.12±1.26	37.13±1.06	-0.66	0.93
Temperature less than 36 °C, n (%)	33 (11.38)	49 (8.89)	8.25	0.25
Heart Rate, mean ± SD	99.07±23.42	95.43±20.56	16.48	0.02

Respiratory Rate, mean ± SD	21.98±6.94	21.29±6.00	10.68	0.13
Diastolic Blood Pressure, mean ± SD	53.97±14.55	51.55±15.79	15.94	0.03
Systolic Blood Pressure, mean ± SD	101.64±24.19	100.95±22.03	2.97	0.68
Urine Output (ml) in 24 Hours, mean ± SD	1,625.09±1,755.75	2,041.94±4,486.25	-12.24	0.13
WBC Count, mean ± SD	14.52±11.70	15.20±13.06	-5.47	0.46
Band, mean ± SD	17.24±15.93	16.67±15.07	3.66	0.61
Creatinine, mean ± SD	2.07±1.61	2.23±2.06	-8.47	0.26
Glucose, mean ± SD	134.46±73.70	145.70±118.03	-11.42	0.14
HCT, mean ± SD	30.87±6.36	31.24±6.40	-5.88	0.42
Lactate, mean ± SD	3.77±3.97	2.69±2.70	31.73	<0.01
paCO2, mean ± SD	41.52±13.06	41.50±12.66	0.21	0.98
FiO2, mean ± SD	66.39±25.50	61.67±25.65	18.48	0.01
PH, mean ± SD	7.29±0.13	7.31±0.12	-18.6	0.01
Potassium, mean ± SD	4.26±0.84	4.29±0.86	-3.67	0.61
Sodium, mean ± SD	138.10±5.30	138.67±5.74	-10.34	0.16
Total Bilirubin, mean ± SD	2.33±4.43	2.09±4.40	5.52	0.45
Platelet, mean ± SD	176.74±107.00	200.03±117.73	-20.7	0.01
BUN, mean ± SD	34.68±24.03	39.44±31.16	-17.13	0.02
AnionGap, mean ± SD	9.67±5.36	9.21±4.38	9.22	0.19
Albumin, mean ± SD	2.76±0.89	2.81±0.86	-5.01	0.49
Cortisol, mean ± SD	21.16±17.81	22.76±18.77	-8.72	0.23
CRP, mean ± SD	9.61±18.20	10.78±21.24	-5.93	0.42
Direct Bilirubin, mean ± SD	0.58±1.70	0.52±1.64	3.8	0.60
ALT, mean ± SD	106.13±340.18	108.95±473.09	-0.68	0.93
AST, mean ± SD	217.59±1,021.47	188.45±842.77	3.11	0.66
Treatment at or before shock onset, n (%)				
Central venous catheter	182 (62.76)	317 (57.53)	10.69	0.14
Arterial catheter	66 (22.76)	107 (19.42)	8.19	0.25
Mechanical ventilation	113 (38.97)	183 (33.21)	12	0.10
Vasopressor	245 (84.48)	404 (73.32)	27.62	<0.01
Etomidate	84 (28.97)	124 (22.50)	14.82	0.04
Antimicrobial	279 (96.21)	520 (94.37)	8.66	0.25
rhAPC	16 (5.52)	3 (0.54)	29.32	<0.01

Table 4.2 Unadjusted outcomes

Outcome	Treated Patients (n=290)	Control Patients (n=551)	P Value
Hospital Mortality, n (%)	150 (51.72%)	215 (39.02%)	<0.01
ICU mortality, n (%)	134 (46.21%)	173 (31.40%)	<0.01
Hospital Length of Stay, mean ± SD	18.11±18.54	14.58±15.00	<0.01
ICU Length of Stay, mean ± SD	12.04±14.33	8.04±9.69	<0.01

Table 4.3 Patient Characteristics after Propensity Score Match

Characteristics	Treated Patients (n=279)	Control Patients (n=279)	Bias (%)	P Value
Age, mean ± SD	62.43±15.84	63.14±16.54	-4.42	0.60
Female Gender, n (%)	140 (50.18)	141 (50.54)	-0.72	0.93
Race, n (%)				
White	250 (89.61)	247 (88.53)	3.45	0.68
Black	7 (2.51)	7 (2.51)	0	1.00
Other	22 (7.89)	25 (8.96)	-3.87	0.65
Married Status, n (%)	118 (42.29)	115 (41.22)	2.18	0.80
BMI, mean ± SD	28.93±8.26	28.92±8.51	0.06	0.99
APS Score, mean ± SD	83.22±30.46	80.91±28.20	7.85	0.35
APACHE Score, mean ± SD	96.67±31.08	94.27±29.67	7.9	0.35
DNR status, n (%)	15 (5.38)	16 (5.73)	-1.56	0.85
Admission Source, n (%)				
Emergency Room	157 (56.27)	149 (53.41)	5.76	0.50
Ward	53 (19.00)	59 (21.15)	-5.37	0.53
Operation Room	26 (9.32)	23 (8.24)	3.8	0.65
Other Hospital	43 (15.41)	48 (17.20)	-4.85	0.57
Operative Diagnosis, n (%)	23 (8.24)	15 (5.38)	11.4	0.18
Admission Diagnosis, n (%)				
Cardiovascular	126 (45.16)	121 (43.37)	3.61	0.67
Gastrointestinal	42 (15.05)	41 (14.70)	1.01	0.91
Respiratory	59 (21.15)	58 (20.79)	0.88	0.92
Genitourinary	8 (2.87)	11 (3.94)	-5.93	0.48
Neurology	7 (2.51)	8 (2.87)	-2.22	0.79
Other	37 (13.26)	40 (14.34)	-3.12	0.71
Comorbidities, n (%)				
Hypertension	132 (47.31)	132 (47.31)	0	1.00
Coronary Artery Disease	51 (18.28)	54 (19.35)	-2.75	0.75
Chronic Heart Failure	40 (14.34)	39 (13.98)	1.03	0.90
Neurological Disease	155 (55.56)	162 (58.06)	-5.07	0.55
Chronic Pulmonary Disease	87 (31.18)	86 (30.82)	0.77	0.93
Cancer	69 (24.73)	61 (21.86)	6.79	0.42
Diabetes	77 (27.60)	79 (28.32)	-1.6	0.85
Liver Disease	43 (15.41)	43 (15.41)	0	1.00
Chronic Renal Failure	21 (7.53)	26 (9.32)	-6.46	0.45
GCS score, mean ± SD	11.75±4.08	11.40±4.49	8.1	0.34
Temperature, mean ± SD	37.10±1.25	37.14±1.12	-3.89	0.65
Temperature less than 36 °C, n (%)	32 (11.47)	32 (11.47)	0	1.00
Heart Rate, mean ± SD	98.35±22.90	98.45±20.15	-0.48	0.95
Respiratory Rate, mean ± SD	21.86±6.97	21.56±6.28	4.54	0.59

Diastolic Blood Pressure, mean ± SD	53.49±14.33	53.74±18.02	-1.52	0.86
Systolic Blood Pressure, mean ± SD	100.99±23.96	101.04±23.58	-0.2	0.98
Urine Output (ml) in 24 Hours, mean ± SD	1,667.23±1,773.44	1,686.91±1,979.75	-1.05	0.90
WBC Count, mean ± SD	14.74±11.78	14.74±9.86	-0.06	0.99
Band, mean ± SD	17.18±15.86	17.67±15.79	-3.11	0.71
Creatinine, mean ± SD	2.07±1.62	2.08±1.75	-0.6	0.94
Glucose, mean ± SD	134.97±74.88	132.41±63.64	3.68	0.66
HCT, mean ± SD	30.85±6.37	31.04±6.41	-2.91	0.73
Lactate, mean ± SD	3.69±3.86	3.19±3.20	14.18	0.09
paCO2, mean ± SD	41.35±12.99	41.90±13.08	-4.21	0.62
FiO2, mean ± SD	65.37±25.32	63.68±25.18	6.7	0.43
PH, mean ± SD	7.29±0.13	7.30±0.14	-4.66	0.58
Potassium, mean ± SD	4.26±0.85	4.28±0.88	-1.83	0.83
Sodium, mean ± SD	138.06±5.37	138.32±5.56	-4.66	0.58
Total Bilirubin, mean ± SD	2.36±4.50	2.70±5.99	-6.38	0.45
Platelet, mean ± SD	177.57±106.80	186.23±110.48	-7.97	0.35
BUN, mean ± SD	34.75±24.14	35.15±24.66	-1.63	0.85
AnionGap, mean ± SD	9.63±5.39	9.38±4.44	5.01	0.55
Albumin, mean ± SD	2.75±0.90	2.76±0.87	-1.58	0.85
Cortisol, mean ± SD	21.30±18.11	22.79±18.71	-8.12	0.34
CRP, mean ± SD	9.68±18.55	9.27±14.69	2.46	0.77
Direct Bilirubin, mean ± SD	0.59±1.73	0.73±2.20	-7.41	0.38
ALT, mean ± SD	108.91±346.46	152.25±629.71	-8.53	0.31
AST, mean ± SD	221.01±1,040.83	263.31±1,046.69	-4.05	0.63
Treatment at or before shock onset, n (%)				
Central venous catheter	174 (62.37)	178 (63.80)	-2.97	0.73
Arterial catheter	61 (21.86)	59 (21.15)	1.74	0.84
Mechanical ventilation	108 (38.71)	100 (35.84)	5.93	0.48
Vasopressor	235 (84.23)	234 (83.87)	0.98	0.91
Etomidate	77 (27.60)	72 (25.81)	4.05	0.63
Antimicrobial	268 (96.06)	263 (94.27)	8.36	0.32
rhAPC	7 (2.51)	2 (0.72)	14.26	0.09

Table 4.4 Hospital Mortality by Hydrocortisone Use

Hospital Mortality	N	Odds Ratio	95% CI		P-value
			Low	High	
Unadjusted Difference	841	1.67	1.26	2.23	<0.01
Propensity Score Matched	558	1.44	1.01	2.08	0.04
Adjusted Difference Controlling for Other Covariates	841	1.58	1.10	2.26	0.01
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	841	1.51	1.04	2.20	0.03

Table 4.5 ICU Mortality by Hydrocortisone Use

ICU Mortality	N	Odds Ratio	95% CI		P-value
			Low	High	
Unadjusted Difference	841	1.88	1.40	2.51	<0.01
Propensity Score Matched	558	1.57	1.08	2.32	0.01
Adjusted Difference Controlling for Other Covariates	841	1.65	1.14	2.38	0.01
Adjusted Difference Controlling for Other Covariates and the Docile of Propensity Score	841	1.56	1.06	2.28	0.02

Appendix Table 4.1 Hospital Mortality by Hydrocortisone Use – Subgroup Analysis

Hospital Mortality	N	Odds Ratio	95% CI		P-value
			Low	High	
Subgroup Analysis - 50% more severe patients					
Unadjusted Difference	468	1.51	1.03	2.20	0.04
Propensity Score Matched	310	1.32	0.81	2.18	0.24
Adjusted Difference Controlling for Other Covariates	468	1.72	1.05	2.81	0.03
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	468	1.40	0.82	2.41	0.22
Subgroup Analysis - 50% less severe patients					
Unadjusted Difference	361	1.71	1.05	2.79	0.03
Propensity Score Matched	196	1.11	0.57	2.17	0.75
Adjusted Difference Controlling for Other Covariates	361	1.38	0.77	2.49	0.28
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	361	1.04	0.54	2.02	0.91
Subgroup Analysis - septic shock onset within 24hr after ICU admission					
Unadjusted Difference	698	1.63	1.19	2.24	<0.01
Propensity Score Matched	448	1.33	0.89	2.01	0.14
Adjusted Difference Controlling for Other Covariates	698	1.43	0.96	2.13	0.08
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	698	1.42	0.93	2.17	0.11
Subgroup Analysis - treated with vasopressor					
Unadjusted Difference	650	1.64	1.22	2.20	<0.01
Propensity Score Matched	464	1.22	0.83	1.82	0.29
Adjusted Difference Controlling for Other Covariates	650	1.43	0.97	2.12	0.07
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	650	1.42	0.94	2.13	0.09
Subgroup Analysis - treated with etomidate					
Unadjusted Difference	208	1.29	0.74	2.25	0.37
Propensity Score Matched	110	1.14	0.52	2.53	0.72
Adjusted Difference Controlling for Other Covariates	207	1.53	0.69	3.38	0.29
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	207	1.39	0.55	3.56	0.49
Subgroup Analysis - corticosteroids use within 8 hours after shock onset					
Unadjusted Difference	713	1.52	1.07	2.16	0.19
Propensity Score Matched	300	1.24	0.74	2.09	0.39
Adjusted Difference Controlling for Other Covariates	713	1.17	0.74	1.85	0.51
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	713	1.07	0.65	1.75	0.80
Subgroup Analysis - corticosteroids use after 8 hours after shock onset					
Unadjusted Difference	679	1.89	1.28	2.78	<0.01

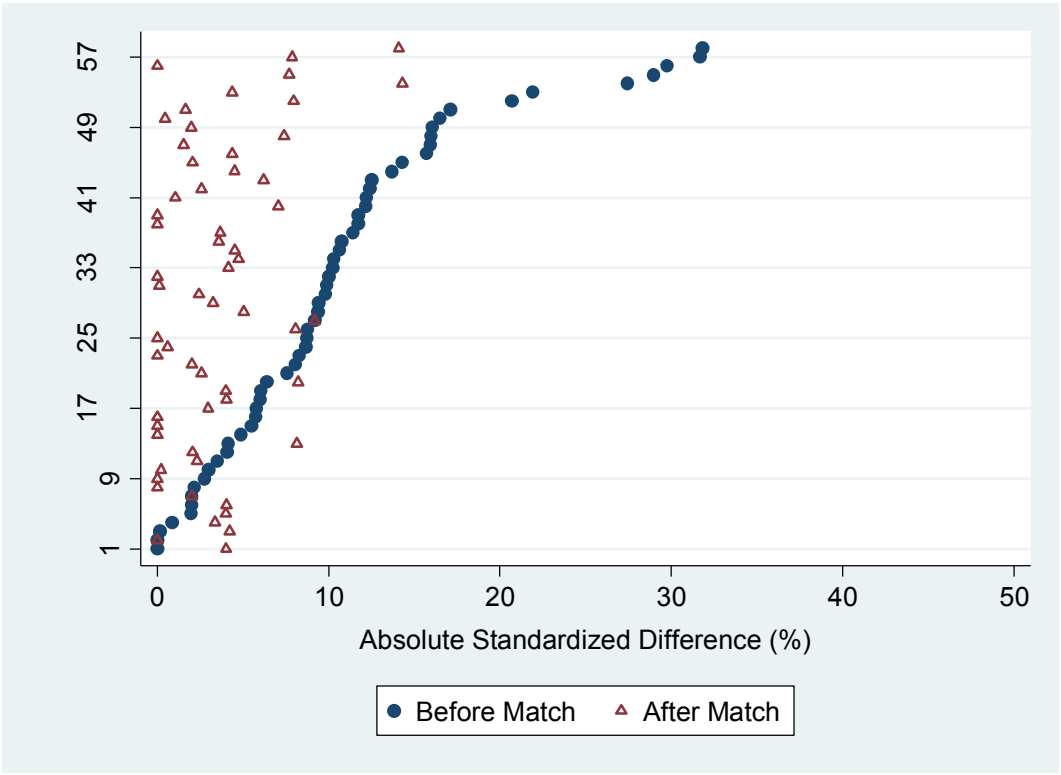
Propensity Score Matched	250	1.44	0.86	2.45	0.14
Adjusted Difference Controlling for Other Covariates	679	2.30	1.42	3.71	<0.01
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	679	2.21	1.36	3.59	<0.01
Subgroup Analysis - corticosteroids use within 24 hours after shock onset					
Unadjusted Difference	721	1.93	1.37	2.74	<0.01
Propensity Score Matched	306	1.16	0.70	1.92	0.55
Adjusted Difference Controlling for Other Covariates	721	1.41	0.89	2.23	0.14
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	721	1.34	0.83	2.17	0.24
Subgroup Analysis - corticosteroids use after 24 hours after shock onset					
Unadjusted Difference	671	1.37	0.92	2.03	0.12
Propensity Score Matched	234	1.63	0.89	3.06	0.09
Adjusted Difference Controlling for Other Covariates	671	1.76	1.09	2.83	0.02
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	671	1.74	1.06	2.86	0.03
Subgroup Analysis - corticosteroids use within 72 hours after shock onset					
Unadjusted Difference	798	1.65	1.22	2.24	<0.01
Propensity Score Matched	466	1.02	0.69	1.50	0.93
Adjusted Difference Controlling for Other Covariates	798	1.33	0.90	1.97	0.15
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	798	1.31	0.87	1.95	0.20
Subgroup Analysis - corticosteroids use after 72 hours after shock onset					
Unadjusted Difference	594	1.80	0.96	3.35	0.07
Propensity Score Matched	84	2.33	0.84	7.41	0.07
Adjusted Difference Controlling for Other Covariates	594	2.98	1.43	6.20	<0.01
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	594	2.56	1.19	5.48	0.02

Appendix Table 4.2 ICU Mortality by Hydrocortisone Use – Subgroup Analysis

ICU Mortality	N	Odds Ratio	95% CI		P-value
			Low	High	
Subgroup Analysis - 50% more severe patients					
Unadjusted Difference	468	1.63	1.12	2.38	0.01
Propensity Score Matched	310	1.28	0.79	2.10	0.29
Adjusted Difference Controlling for Other Covariates	468	1.56	0.96	2.55	0.08
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	468	1.51	0.88	2.58	0.13
Subgroup Analysis - 50% less severe patients					
Unadjusted Difference	361	2.03	1.21	3.40	0.01
Propensity Score Matched	196	1.29	0.66	2.60	0.42
Adjusted Difference Controlling for Other Covariates	355	1.49	0.78	2.85	0.23
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	355	1.26	0.60	2.65	0.54
Subgroup Analysis - septic shock onset within 24hr after ICU admission					
Unadjusted Difference	698	1.75	1.26	2.42	<0.01
Propensity Score Matched	448	1.24	0.83	1.89	0.27
Adjusted Difference Controlling for Other Covariates	698	1.31	0.86	1.99	0.20
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	698	1.27	0.82	1.98	0.29
Subgroup Analysis - treated with vasopressor					
Unadjusted Difference	650	1.81	1.31	2.49	<0.01
Propensity Score Matched	464	1.33	0.90	1.98	0.13
Adjusted Difference Controlling for Other Covariates	650	1.54	1.03	2.30	0.04
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	650	1.55	1.02	2.36	0.04
Subgroup Analysis - treated with etomidate					
Unadjusted Difference	208	1.48	0.85	2.59	0.17
Propensity Score Matched	110	1.13	0.53	2.44	0.72
Adjusted Difference Controlling for Other Covariates	207	1.53	0.71	3.33	0.28
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	207	1.75	0.71	4.33	0.23
Subgroup Analysis - corticosteroids use within 8 hours after shock onset					
Unadjusted Difference	713	1.75	1.22	2.50	0.02
Propensity Score Matched	300	1.30	0.79	2.17	0.28
Adjusted Difference Controlling for Other Covariates	713	1.23	0.77	1.95	0.39
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	713	1.07	0.64	1.78	0.79
Subgroup Analysis - corticosteroids use after 8 hours after shock onset					
Unadjusted Difference	679	2.05	1.39	3.03	<0.01
Propensity Score Matched	250	1.52	0.87	2.70	0.11
Adjusted Difference Controlling for Other Covariates	679	2.41	1.48	3.94	<0.01
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	679	2.47	1.49	4.08	<0.01

Subgroup Analysis - corticosteroids use within 24 hours after shock onset					
Unadjusted Difference	721	2.29	1.61	3.25	<0.01
Propensity Score Matched	306	1.13	0.68	1.87	0.63
Adjusted Difference Controlling for Other Covariates	721	1.55	0.97	2.47	0.07
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	721	1.45	0.89	2.37	0.14
Subgroup Analysis - corticosteroids use after 24 hours after shock onset					
Unadjusted Difference	671	1.41	0.94	2.12	0.10
Propensity Score Matched	234	1.72	0.93	3.27	0.06
Adjusted Difference Controlling for Other Covariates	671	1.81	1.11	2.96	0.02
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	671	1.83	1.09	3.07	0.02
Subgroup Analysis - corticosteroids use within 72 hours after shock onset					
Unadjusted Difference	798	1.90	1.40	2.59	<0.01
Propensity Score Matched	466	1.16	0.78	1.73	0.44
Adjusted Difference Controlling for Other Covariates	798	1.46	0.98	2.17	0.06
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	798	1.38	0.91	2.08	0.13
Subgroup Analysis - corticosteroids use after 72 hours after shock onset					
Unadjusted Difference	594	1.73	0.92	3.24	0.09
Propensity Score Matched	84	2.40	0.79	8.70	0.09
Adjusted Difference Controlling for Other Covariates	594	3.11	1.44	6.73	<0.01
Adjusted Difference Controlling for Other Covariates and the Deciles of Propensity Score	594	2.51	1.13	5.54	0.02

Figure 4.1 Patient Characteristics before and after propensity match



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Chapter V General Discussions and Final Conclusions

Despite the rapid progress in the knowledge of pathophysiological mechanisms of sepsis and its treatment in the last two decades, sepsis remains as the one of the most challenging diseases to critical care clinicians. This dissertation seeks to improve our understanding of the diagnostic accuracies of sepsis definitions, promote early recognition of sepsis, and advance our knowledge of the treatment effects of low-dose steroids. Using the data from the seven ICUs in an academic tertiary care medical center, I systematically evaluated the test characteristics of the 1991 and 2001 sepsis definitions; explored the algorithms for continuously monitored physiological parameters to maximize their diagnostic performance in identifying sepsis patients; and examined the effectiveness of corticosteroids treatment on mortality in septic shock patients.

Test characteristics of the 1991 and 2001 consensus sepsis definitions in adult critically ill patients using adjudicated sepsis cases as the reference standard

Although the 1991 and 2001 consensus definitions [1, 2] of sepsis have been widely adopted in clinical practice since their publication, their test characteristics, as well as the changes given by the expanded 2001 consensus definition, have not been well studied. The research objective of this study was to assess their test characteristics (i.e. sensitivity, specificity, and the area under the ROC curve) of the 1991 and 2001 consensus definition, respectively, compared to sepsis case adjudication by three senior intensive

care clinicians. I demonstrated that, compared to adjudicated sepsis, both the 1991 and 2001 definitions had relatively high sensitivity, low specificity, and suboptimal area under the ROC curve. Indeed, the criteria in the two definitions include signs and symptoms that a patient could present during the course of infection-induced systemic inflammatory response. However, they are not specific to sepsis, and many other conditions could also have these signs and symptoms.

Adding more criteria to the definition list, the 2001 sepsis definition has a detailed list of possible manifestations in sepsis. Compared to the 1991 definition, the 2001 sepsis definition had a slightly increased sensitivity, decreased specificity and decreased area under the ROC curve. In addition, when taking into account sepsis diagnosis time, the differences between adjudicated sepsis and the two definitions became larger. This pointed to the dilemma in clinical practice that, on one hand, the signs and symptoms of sepsis patients are dynamic; whereas on the other hand, neither of the two definitions provided a time reference within which the defined criteria should be met in order to diagnose a patient as having sepsis. From our regression analyses, I also identified the predictors of sepsis that could improve the specificity of sepsis diagnosis.

Using continuously monitored physiological parameters to predict the onset of Sepsis in Critically Ill Patients

Early recognition and treatment for sepsis have been shown to significantly reduce sepsis-related mortality.[3, 4] However, accurately diagnosing of sepsis, especially before patients deteriorate and develop organ dysfunction, is an important goal but often

difficult to achieve in practice.[5] Previous studies have reported that physiological parameters, like heart rate, respiratory rate, body temperature, and blood pressure, had inferior diagnostic performance in identifying sepsis patients from the SIRS or non-SIRS patients.[6, 7] However, no studies have assessed the clinical usefulness of continuously monitored physiological parameters for adult patient with sepsis. The goal of this study was to determine, first, the changes of the continuously monitored physiological parameters, before the onset of sepsis and their relationships with sepsis onset; and second, to determine whether these parameters could be used to identify sepsis in critically ill adults. I demonstrated that, as early as 24 hours before sepsis diagnosis, septic patients tended to be more physiologically disarranged by having higher heart rates, lower blood pressure, higher temperatures and higher respiratory rates, compared to SIRS or non-SIRS patients. More importantly, continuously monitored physiological parameters measured 24 hours before disease onset have improved performance in identifying sepsis from SIRS patients and excellent predictive accuracy in distinguishing sepsis from non-SIRS critically ill adult patients. The combination of these physiological parameters (the minimum blood pressure parameters and the maximum values of heart rate, respiratory rate and body temperature) achieved area under ROC curve of 0.74 and 0.90 in differentiating sepsis from SIRS and non-SIRS, respectively, which were comparable to that of procalcitonin published in the literature so far.[8, 9]

The Effectiveness of Corticosteroid Treatment on Septic Shock Patient Outcomes in Intensive Care Units

Since the introduction of corticosteroids as an adjunctive therapy in severe sepsis and septic shock a half century ago, its therapeutic role, in terms of efficacy and safety, has been debated. Landmark randomized controlled trials have generated conflicting results with regard to the mortality benefit of low-dose corticosteroid treatment.[10, 11] Recent meta-analyses of randomized trials reported heterogeneous effects of corticosteroids therapy on mortality,[12-14] which was influenced by patient characteristics, underlying mortality risk, treatment dose and duration. The purpose of this study was to examine the effectiveness of corticosteroids treatment on mortality in all septic shock patients admitted to the ICUs of an academic medical center. Since this is an observational study, the corticosteroids treatment decision was confounded by the patient factors which were also related to their outcomes. To adjust for such treatment selection bias, I calculated a propensity score for each patient to indicate his/her probability of receiving corticosteroid therapy. I found that about one third of our ICU patients with septic shock received low-dose corticosteroids, and they had higher hospital mortality than the ones who received no corticosteroids treatment. I also conducted a series of subgroup analyses and failed to identify any subgroup that benefit from the low-dose corticosteroid treatment across levels of disease severity, early or late onset during ICU stay, corticosteroids administration time, or treatment with vasopressors or etomidate.

Final Conclusions

The three studies in this dissertation contribute to the existing literature regarding the test characteristics of sepsis definitions, sepsis prediction, and corticosteroids treatment effects among septic shock patients. The findings that both the 1991 and 2001 sepsis definitions have suboptimal diagnostic accuracy emphasize the needs for more specific criteria. Continuously monitored physiological parameters serve as good candidates to predict sepsis acute onset among critically ill patients. The promising results of the predicting algorithms could be used, as early as 24 hours before sepsis onset, to identify sepsis. Moreover, the findings that no survival benefit, or even a slightly increased harm, was associated with low-dose corticosteroids treatment in our medical center calls for great caution regarding the usage of corticosteroids treatment among septic shock patients. Last but not least, these studies utilized innovative analytic approaches, for example, the data validation rules and the time windows, and offered new ideas for future exploration of data collected by electronic medical record systems.

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