2023

Comparison of Sepsis-2 and Sepsis-3 definition in pediatric population

BOSTON UNIVERSITY

ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

COMPARISON OF SEPSIS-2 AND SEPSIS-3 DEFINITION IN PEDIATRIC POPULATION

by

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B.A., University of California, Berkeley, 2019

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2023

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ACKNOWLEDGMENTS

I would like to thank Dr. Koichi Yuki, Dr. Jean Spencer, Amanda Baier and Dr. Izabela Leahy for giving me the opportunity to perform this research as well as helping me throughout the writing process.

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ABSTRACT

Background: Sepsis is a severe disease that is associated with significant morbidity and mortality in both adult and pediatric patients. In 2016, the definition of sepsis was reevaluated in adult population and characterized as a state of organ dysfunction in response to an infection. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) standardized the use of the Sequential Organ Failure Assessment (SOFA) for diagnosing adult septic cases. Unfortunately, the consensus conference did not address pediatric sepsis. The SOFA specific to pediatric population was not available then. Following the Sepsis-3 definition, several SOFA tools were proposed for pediatric use (pSOFA). One of the pSOFA was validated in a cohort.

Objective: The focus of this study was to validate the new definition of sepsis in pediatric patients by using a newly developed pSOFA tool. In addition, the study attempted to identify risk factors associated with mortality and sepsis in children.

Methods: This study examined a total of 806 critically ill pediatric patients who were admitted to the pediatric ICUs with the diagnosis of sepsis at Boston Children's Hospital from 2014 to 2019. Patient information was collected on demographics, length of stay in the ICU, outcomes, types of microbes detected, types of antibiotics used, and blood laboratory tests. This information was used to derive an organ failure score using the pSOFA tool. The pSOFA score was obtained by totaling subscores for the respiratory, coagulation, hepatic, cardiovascular and renal systems.

Results: Each of the five pSOFA subscores, when elevated above average, was associated with meeting Sepsis-3 criteria in pediatric patients. An pSOFA score above average was also associated with a greater chance of mortality in children. An increased respiratory subscore above average was shown to be more significantly associated with mortality with an odds ratio of 1.71 in children. An above average hepatic and coagulation subscore were also showed to be positively associated with mortality with odds ratios of 1.38 and 1.34, respectively. An increased renal and cardiovascular subscores above average were not found to be a significant predictor of mortality.

Conclusions: The use of the Sepsis-3 criteria was better at predicting the outcome of pediatric patients diagnosed with sepsis than widely used Sepsis-2 definition in pediatric sepsis. Of the organ systems that were evaluated, respiratory dysfunction appears to be associated the most associated with increased mortality in pediatric patients.

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LIST OF ABBREVIATIONS

AKI………………………………………………………………... acute kidney injury

AP-1……………………………...……………………………… activator protein 1

ARDS………………………………………….. acute respiratory distress syndrome

BCH……………………………………...…………...… Boston Children's Hospital

BPAP………………………………………………….. bilevel positive airway pressure

CO……………………………………………………………………. cardiac output

CPAP………………………………………….. continuous positive airway pressure

DAMPs……………………………………..... damage-associated molecular patterns

dectin 1……………………………...…… C-type lectin domain family 7 member A

dectin 2………………………………...… C-type lectin domain family 6 member A

DIC………………………………………….. disseminated intravascular coagulation

ETT…………………………………………………………….. endotracheal tube

Fi_{O2}……………………………………...………………. fraction of inspired oxygen

ICU……………………………………...………………………... intensive care unit

IFN…………………………………………………………………………… interferon

IL-1……………………………………...………………………………… interleukin-1

IL-2……………………………………...………………………………… interleukin-2

IL-4……………………………………...………………………………… interleukin-4

IL-5……………………………………...………………………………… interleukin-5

IL-6……………………………………...………………………………… interleukin-6

IL-10……..………………………………...……………………………..… interleukin-10

IL-17……..……………………………...…………………………..… interleukin-17

IL-22……..……………………………...…………………………..… interleukin-22

IRF……………………………………...……………….. interferon regulatory factor

MAP…………………………………...………………... mean arterial pressure

NF-κB…………………………………….………..…...……… nuclear factor-κB

Pa_{O2}……………………………………….…………… partial pressure of oxygen

PAMP………………………………………... pathogen-associated molecular patterns

PELOD-2…………………………….…………… pediatric logistic organ dysfunction

PPRs……………………………………………………… pattern recognition receptors

pSOFA…………………………………... pediatric Sequential Organ Failure Assessment

ROS…………………………………...…..………………… reactive oxygen species

Sepsis-1…..... 1991 First International Consensus Definitions for Sepsis and Septic Shock

Sepsis-2.... 2001 Second International Consensus Definitions for Sepsis and Septic Shock

Sepsis-3…... 2016 Third International Consensus Definitions for Sepsis and Septic Shock

SIRS……………………………………… systemic inflammatory response syndrome

SOFA……………………...………………...….. Sequential Organ Failure Assessment

SVR…………………………………...…………….. systemic vascular resistance

Th ……………………………………...…………………………...…….. T helper

TLR…………………………………………………...…...……….... toll like receptor

TNF alpha……………………………………...………... tumor necrosis factor alpha

7S……………………………………………………………………………...7 South

11S………………………………………………………...………………11 South

INTRODUCTION

Significance of Sepsis

Sepsis is a severe disease that is loosely defined as the presence of an acute infection that leads to organ dysfunction (Rudd et al., 2020). By definition, sepsis is considered a severe disease that has a range of the short- and long-term consequences. Global hospital mortality rates for pediatric patients diagnosed with sepsis have been shown to have been as high as 25%, and for those children who did survive, about 17% went on to develop moderate disabilities or worse (Weiss et al., 2015). It has also been shown that sepsis can lead to additional poor health outcomes, such as long-term cognitive impairments and cardiovascular disease (Iwashyna et al., 2010; Mankowski et al., 2019). Early diagnosis and treatment of sepsis are considered important for potential outcome improvement. Mortality rates from continuous septic shock increase by greater than two-fold for each hour after diagnosis without ability for shock reversal (Han et al., 2003). In addition, sepsis is one of the greatest financial burdens on hospitals. In the United States alone, sepsis is a major strain on the healthcare system, accounting for more than $20 billion in hospital costs in 2011 and an estimated cost of about $5 billion for pediatric cases in 2005 (Hartman et al., 2013; Torio & Andrews, 2006). And despite sepsis mortality rates decreasing, sepsis rates are increasing in the United States (Hartman et al., 2013). This makes sepsis a great public health concern that needs to be further addressed.

Defining Sepsis

The modern definition of sepsis was first established in 1991 at the First International Consensus Definitions for Sepsis and Septic Shock (Sepsis-1), which included the American College of Chest Physicians and the Society of Critical Care Medicine. Sepsis-1 defined sepsis as a confirmed or suspected infection in the presence of two or more criteria for systemic inflammatory response syndrome (SIRS) (Gül et al., 2017). SIRS is defined as "an exaggerated defense response of the body to a noxious stress (infection, trauma, surgery, acute inflammation) to localize and then eliminate the… source of the insult" (Chakraborty & Burns, 2022). Patients with an underlying infection that presented with two or greater criteria for SIRS were defined as septic. This assessment primarily evaluated the level of inflammation of the body, a nonspecific response of the individual. This ultimately made the Sepsis-1 definition inadequate because the selection criteria that were used were too broad and could be present during many different conditions. The lack of specificity of Sepsis-1 resulted in most patients that had an infection along with some manifestations of systemic inflammation were diagnosed with sepsis. Even though all cases of sepsis do have an infection, not all infections can be classified as sepsis. In addition, although children that present with 2 or more SIRS criteria do have an increased risk of morbidity and mortality, it has also been shown that over 80% of children admitted to the intensive care unit (ICU) for any infection meet these guidelines (Schlapbach et al., 2018).

Then, in 2001, the American College of Chest Physicians, the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, the American Thoracic

Society and the Surgical Infection Society came together for the Second Consensus Definitions for Sepsis and Septic Shock (Sepsis-2) conference. Advanced understanding and clinical signs of sepsis allowed for a more fitting definition of the disease. Symptoms of sepsis were further characterized into the categories general, organ dysfunction and tissue perfusion variations, biochemical indicators, hemodynamic and inflammatory. Sepsis-2 used these current signs of sepsis in order to add to the previous Sepsis-1 definition of the disease by including a component of organ dysfunction. Despite these new clinical indicators and definition of the disease, the Sepsis-2 conference failed to update the clinical diagnostic tools used to evaluate sepsis. Ultimately, Sepsis-2 did not change any of the fundamental issues with distinguishing and diagnosing sepsis compared to other diseases of infection or inflammation.

In 2016, the definition and diagnosis of sepsis was revisited by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in order to more clearly define sepsis and its clinical criteria. Singer et al. went on to define sepsis as “life-threatening organ dysfunction caused by a dysregulated host response to infection.” As the primary tool to analyze organ system dysfunction, the sequential organ failure assessment (SOFA) tool was chosen (Singer et al., 2016**)**. This assessment easily allows clinicians to score organ dysfunction or failure using clinical values and relate the relative dysfunction to morbidity. The updated sepsis definition was significant because it was better associated with morbidity and mortality than the Sepsis 2 definition. SOFA evaluates the function of the cardiovascular, hepatic, renal, neurological, respiratory, and coagulation systems, and an overall score of 2 or greater is indicative of an overall mortality rate of about 10% (Singer et al., 2016).

However, a pediatric version of SOFA was not available at the time of Sepsis-3 conference. The SOFA criteria "focused on adult patients" and there is still a "need to develop similar updated definitions for pediatric populations and the use of clinical criteria that take into account their age-dependent variation" (Singer et al., 2016).

In order to further investigate and evaluate the Sepsis-3 definition, Matics et al. adapted and validated an age-adjusted SOFA score criteria called the pediatric Sequential Organ Failure Assessment (pSOFA) tool. Although other organ dysfunction rating systems do exist in pediatric populations, including the pediatric logistic organ dysfunction score-2 (PELOD-2) and the Pediatric Multiple Organ Dysfunction Score, the pSOFA has been shown to be equivalent or better at predicting in-hospital mortality. The pSOFA is the only scoring system that has been validated for children. Unlike previous studies, Matics et al. took into consideration age-dependent variables for the different organ systems, most specifically the renal and respiratory subscores, so that the SOFA score could be adapted to children. The cardiovascular and renal subscores were adjusted by using scoring cutoffs from the PELOD-2 scoring system that were previously validated (Matics & Sanchez-Pinto, 2017). In addition, the respiratory subscore was adjusted by using the ratio of peripheral oxygen saturation (Pa_{O2}) to the fraction of inspired oxygen (Fi_{O2}) (Matics & Sanchez-Pinto, 2017). The pSOFA score showed promising results when assessing critically ill pediatric patients with confirmed or suspected infection (Matics & Sanchez-Pinto, 2017). More accurately understanding and defining sepsis in children will lead to better diagnosis and treatment of these patients.

Clinical Manifestations

Despite the knowledge of sepsis having been improved dramatically over the past few decades, it is still a complex disease state that is not fully understood. The progression of sepsis can be characterized into two contradictory immune responses of a hyperinflammatory state and a hypoinflammatory state (Nedeva, 2021). It is still not clear as to why the immune systems of some individuals respond normally to fight an infection, whereas the immune systems of others break down into a dysregulated response that is seen in sepsis. The hyperinflammatory state is commonly referred to as the “cytokine storm.” Some important inflammatory cytokines that have been studied in the relationship to sepsis include tumor necrosis factor alpha (TNF alpha), interleukin-1 (IL-1) and interleukin-6 (IL-6). After this cytokine storm, the immune system is weakened, resulting in a hypoinflammatory state. At this stage of sepsis, immune cells are marked for degradation, which diminishes the immune system. This not only results in a decreased ability to fight the original infection but also leaves the patient vulnerable to secondary infections (Nedeva, 2021). In addition to a systemic immune response, sepsis can have organ system-specific consequences which can lead to different manifestations of the disease and ultimately different treatment plans.

Sepsis can significantly affect the cardiovascular system through vasodilation leading to hypotension. In adult populations, up to 60% of septic patients have also suffered from myocardial depression (Skrupky et al., 2012). Heart damage and sepsis have been linked through elevated troponin levels (Hotchkiss et al., 2016).

The respiratory system is also commonly affected during sepsis because of the increased permeability of the pulmonary endothelium leading to noncardiogenic pulmonary edema (Kim & Hong, 2016). This inhibits oxygenation and ventilation, which can lead to the development of hypoxia, metabolic acidosis and tachypnea. Oftentimes, these conditions require intubation and mechanical ventilation for support. Acute respiratory distress syndrome (ARDS) occurs in about 7% of sepsis patients (Mikkelsen et al., 2013).

Changes in hemodynamics, endothelial dysfunctions, and inflammation that occur during sepsis can lead to acute kidney injury (AKI) (Zarjou & Agarwal, 2011). Septic AKI has been associated with an increased mortality rate as well as an increased length of hospital stay (Bagshaw et al., 2007). Comorbidities of AKI include increased age, chronic kidney disease, and cardiovascular disease (de Mendonça et al., 2000).

Sepsis can cause a wide range of hematological effects including anemia, leukocytes, neutropenia, thrombocytopenia and disseminated intravascular coagulation (Font et al., 2020). Hematologic dysfunction is one of the most common clinical manifestations of the disease (Goyette et al., 2004). Thrombopoiesis inhibition and platelet damage caused by sepsis are often responsible for thrombocytopenia without disseminated intravascular coagulation (DIC). Inflammation, decreased lifespan of red blood cells, and hemolysis from sepsis typically lead to anemia.

Although gastrointestinal dysfunction of sepsis is extremely rare, these complications can be significant. Liver failure is observed in about 2% of all sepsis cases and greatly increases morbidity and mortality (Angus et al., 2001). Bilirubin concentration and coagulopathy with an international normalized ratio are used to clinically assess gastrointestinal dysfunction. Bilirubin concentrations greater than 2 mg/dL and coagulopathy with an international normalized ratio greater than 1.5 are both required to diagnose septic hepatic dysfunction. Gastrointestinal dysfunction is caused by hemodynamic and immune dysfunction that ultimately cause parenchymal hypoxia. This condition can clinically present as hypoxic hepatitis, sepsis-induced cholestasis, coagulopathies, and hyperammonemia and can further cause hepatic encephalopathy.

The most common endocrine dysfunction in sepsis is hyperglycemia, which is caused by increased levels of cortisol, glucagon, catecholamines and growth hormone-combined insulin resistance due to the stress of the disease (Brierre et al., 2004). Adrenal insufficiency can also affect 8% to 9% of patients with severe sepsis, which can help exacerbate catecholamine insensitivity (Marik & Zaloga, 2003). In addition, septic patients oftentimes experience vasopressin deficiency because of depletion of stores, increased activity of vasopressinase (the enzyme that breaks down vasopressin), and inhibition of production of new vasopressin (Sharshar et al., 2003).

Neurologic complications of sepsis most often include septic encephalopathy, which presents with altered mental status, altered sleep/wake cycle, disorientation, agitation and hallucinations. Typically, focal deficits are not associated with septic encephalopathy. A rare complication of septic encephalopathy is the occurrence of seizures (Sonneville et al., 2013).

Similarities and Differences in Sepsis in Children Versus Adults

Although the definition of sepsis in children and adults is the same, its clinical manifestations and defining characteristics are sometimes different between the two populations. Recognizing these differences can help to more precisely define the disease. For both children and adults, early diagnosis and treatments of fluid resuscitation, antibiotics, and source control can significantly impact outcomes of patients (Carcillo et al., 2002). Comorbidities are significant risk factors for mortality in all patients with sepsis, and some significant conditions in children include "prematurity, congenital heart disease, solid and hematopoietic cancers, and immune deficiencies" (Prusakowski & Chen, 2017). In addition, an independent comorbidity for both pediatric and adult populations is acute kidney injury (Prusakowski & Chen, 2017).

Pediatric sepsis differs from adult sepsis in its pathophysiology and its etiology, which lead to differences in diagnosis and treatment. The most significant difference is the effect on the cardiovascular system of each population. Children tend to have higher systemic vascular resistance (SVR) and higher heart rates than adults. This can lead to a decreased cardiac output (CO) for children with sepsis. Because of these physiological differences, cardiovascular dysfunction plays a more significant role in morbidity for children. This also makes cold shock much more common and fatal in pediatric patients, whereas adult patients with sepsis are more often diagnosed with warm shock. Cold shock indications in children include high SVR, cold or cyanotic extremities, tachycardia or bradycardia, and reduced peripheral pulses; warm shock indications include low SVR, warm extremities, tachycardia, and wide pulse pressure (Prusakowski & Chen, 2017).

Thus, treatment for sepsis in children often warrants greater consideration of cardiovascular health with the use of inotropic support such as epinephrine, dobutamine, or epinephrine (Prusakowski & Chen, 2017). In addition, pediatric patients are at higher risk for respiratory complications from sepsis. Anatomical differences in size of airways can lead to greater resistance and more severe disease for children compared with adults (Wheeler et al., 2011). Newborns and young children are also at an increased risk of bleeding complications because of lower levels of vitamin K-dependent procoagulant factors, thrombin production and coagulation inhibitors (Wheeler et al., 2011). Lastly, mortality rates among children and adults are vastly different. The mortality rate among pediatric patients with sepsis is about 10% to 20%, whereas the mortality rates for adults range from 35% to 50% (Rudd et al., 2020)**.**

Pediatric sepsis can even differ among children of different age groups. Infant comorbidities are more often congenital heart disease and chronic lung disease while comorbidities of older children are more often neuromuscular disease and cancer (Prusakowski & Chen, 2017). In addition, sites of infection can also differ. The most common site of infection for infants is primary bacteremia, whereas older children are more likely to present with respiratory infections and secondary bacteremia (Prusakowski & Chen, 2017). Ultimately though, differences in sepsis between children and adults tend to diminish as the age of the child increases.

Signaling Pathways of Sepsis

Although sepsis is simply defined as organ dysfunction in the setting of an infection, the pathophysiological process in which this occurs is complex and involves changes in function of many different organ systems as well as changes at the cellular level. The current understanding of this disease has proven that sepsis is much more than a state of inflammation like was previously thought. Even though there are common signaling pathways and host responses, each case of sepsis is unique, and this uniqueness makes it more difficult to treat when compared with other, milder infections.

The host response to an infection that can lead to sepsis begins with the innate immune system. Pattern recognition receptors (PRRs) on the membranes of cells are able to recognize and bind to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). Most commonly, PAMPs and DAMPs associated with sepsis bind to PPRs including Toll-like receptors (TLRs), C-type lectin domain family 7 member A (dectin 1), and C-type lectin domain family 6 member A (dectin 2) (Zhang & Ning, 2021). These receptors ultimately activate inflammatory response pathways including interferon regulatory factor (IRF) and nuclear factor-κB (NF-κB). These two pathways are responsible for activating type I interferon (IFN) production and activator protein 1 (AP-1), respectively, which help activate the early inflammatory response.

The IRF and NF-κB pathways ultimately promote the release of many proinflammatory and proapoptosis cytokines including TNF alpha, IL-1, and IL-6. As sepsis progresses, these pathways lead to prolonged states of inflammation and stress that can have deleterious effects on cells including mitochondria distress and increased production of reactive oxygen species (ROS). IL-1 is a general regulator of proinflammatory responses. It acts by promoting the recruitment of leukocytes and inducing fever (Kaneko et al., 2019). IL-6 promotes inflammation by upregulating the production of acute phase proteins and effector T-cell maturation (Tanaka et al., 2014). TNF alpha is another proinflammatory cytokine that is responsible for a wide range of cell responses which ultimately lead to cell necrosis and apoptosis (Idriss & Naismith, 2000).

In addition to activating the innate immune system, sepsis activates the adaptive immune response through different pathways. The adaptive immune system responds with B and T cells. The unique function of B cells is to produce antibodies that can bind to antigens and mark them for degradation (Cano & Lopera, 2013). T cells are primarily broken into two categories: CD4 and CD8 T cells. CD4 T cells, also known as T helper (Th) cells, can help promote antigen production by B cells and activate CD8 T cells. (Cano & Lopera, 2013). CD8 T cells directly kill infected cells by inducing apoptosis (Cano & Lopera, 2013). CD4 T cells can further differentiate into specific types of Th cells including Th1, Th2, and Th17 (Martinez-Sanchez et al., 2018). The Th1 cells play a role in the activation of CD8 T cells, the proliferation of memory T cells by secreting interleukin 2 (IL-2) and the release of type II IFN (IFN- γ) which helps promote inflammation and phagocytosis (Tham et al., 2002). The primary function of Th2 is to produce interleukin-4 (IL-4) and interleukin-5 (IL-5), which promote the maturation of B lymphocytes, and interleukin-10 (IL-10), which acts to help resolve inflammation

(Mosmann et al., 1986). The Th17 cells act to help induce production of more cytokines, including TNF alpha, interleukin-17 (IL-17), and interleukin-22 (IL-22) (Zhang et al., 2009).

After the body mounts the immune response, the patient then enters a state of hypoimmune response. Normally, once the immune system resolves an infection, the body returns to homeostasis. Specific cytokines, including IL-10, act to suppress proinflammatory cytokines such as IFN-γ and IL-6. In addition, antagonists are produced to help further lower cytokine levels and ultimately return the immune system to baseline levels (Delano & Ward, 2016). In sepsis, the immune system fails to undergo the proper pathways to resolve inflammation. Both the innate and adaptive immune system become significantly inhibited by diminishing the survival of existing immune cells and the production of new immune cells leading to a state of hypoimmunity. This situation ultimately leaves the patient unable to fight the original infection and renders the individual susceptible to secondary infections as well (Skrupky et al., 2012).

Treatments of Sepsis

Diagnosing and treating sepsis early in the disease process can have a profound impact on the outcome of the patient. Initial treatment should be started if the patient has an elevated SOFA or pSOFA score, even if additional diagnostic studies are still pending. Blood cultures are expected to be drawn early, and suspicion for urinary tract infection should be ruled out with a urine culture. A chest X-ray should be used to rule out developing pneumonia, although it is not necessarily a diagnostic tool of sepsis. Initial procalcitonin levels should be measured within the first hour of diagnosis to help indicate antibiotic cessation for certain infections later (Pepper et al., 2019).

Administration of antibiotics early in the disease state of sepsis has been associated with better outcomes, which has led to the goal of beginning antibiotics within one hour of presentation according to the Surviving Sepsis Campaign Guidelines (Levy et al., 2018). Even before culture results are completed, broad-spectrum antibiotic therapy should be initiated, with consideration of the patient's comorbidities and presentation. In general, initial antibiotics should target gram-positive and gram-negative bacteria. More specific medications may be used depending on the case.

Because hypotension is a common symptom of sepsis, decreasing the amount of time the patient is hypotensive is an important aspect of treatment and is associated with decreased mortality (Kumar et al., 2006). To counteract vasodilation, the process of fluid resuscitation works to increase CO and mean arterial pressure (MAP). The current recommendation by the Surviving Sepsis Campaign Guidelines is an initial fluid bolus of 30 mL/kg; however, there is a growing concern that this recommendation has led to over-resuscitation.

Health records have shown that a MAP of less than 85 mmHg is associated with an increased risk of mortality and kidney injury in sepsis patients (Maheshwari et al., 2018). The Surviving Sepsis Guidelines Campaign currently recommend maintaining a target MAP of at least 65 mmHg. It is standard of care to use vasopressors if the patient is hypotensive after a bolus IV fluid resuscitation. Dopamine has been recommended as the initial blood pressure medical therapy in cases of septic shock. More recently, norepinephrine has been recommended by the Surviving Sepsis Campaign Guidelines as the first-line medical therapy. Secondary and tertiary medical therapies for hypotension include vasopressin and epinephrine, respectively (Evans et al., 2021).

SPECIFIC AIMS

Considering the current knowledge of sepsis, the definition was updated in 2016 to incorporate organ dysfunction as a part of the diagnosis as well as the use of an established evaluation guideline. This new definition, known as Sepsis-3, has been shown to be more predictive of mortality in adult patients. Previous papers have worked to adapt those established criteria of organ dysfunction to pediatric patients. Although these bodies of work were significant in creating relevant clinical laboratory values to allow for proper diagnosis of sepsis in children, a more thorough examination into the correlation between the new definition of sepsis and mortality in children has not been performed.

The purpose of this study is to further evaluate the use of the Sepsis-3 definition and pSOFA tool when diagnosing children with sepsis. This study aims to use this definition to help predict outcomes in pediatric patients and identify any risk factors that are associated with mortality.

METHODS

Study Population and Eligibility

To validate Sepsis-3 and help evaluate the relationship between Sepsis-3 and mortality in children, data were collected from when the diagnosed children were admitted to the ICU at Boston Children's Hospital's (BCH) (Boston, MA, USA). A retrospective study was performed looking at pediatric patients in the pediatric ICUs at BCH from 2014 to 2019. This study was approved by the BCH Institutional Review Board with the goal of assessing the association between sepsis and mortality in children admitted to the ICU. Because of the observational nature of the study, patient informed consent was waived.

Subjects who were eligible to participate in this study included any patient who was admitted to either the pediatric ICU and given a diagnosis of sepsis based on the Sepsis-2 definition. Patients who were diagnosed with cyanotic congenital heart disease were omitted from this study. Overall, there were 1040 cases were eligible for the study. A total of 806 cases were selected at random, including 665 unique patients. These cases were then enrolled in the study and their patient chart information was reviewed.

To determine whether the patients met the updated Sepsis-3 definition and to further assess mortality and risks factors, additional data were obtained on demographic information, length of stay in the ICU, outcomes, types of microbes detected, type of antibiotics used, and blood laboratory test results including peripheral oxygen saturation, fraction of inspired oxygen, platelet count, mean arterial pressure, vasoactive infusion, and bilirubin and creatinine levels. These data were pulled from the electronic medical record database PowerChart and T3 system and uploaded to Microsoft Excel (Version 16.69.1) in locked folders to be analyzed.

Organ Failure Criteria

As a part of the Sepsis-3 conference, the SOFA tool was established as the selection criteria for evaluating organ dysfunction to diagnose sepsis in adult patients. The SOFA score was determined to be better at predicting in-hospital morbidity mortality in adults when compared with other organ dysfunction scoring systems (Matics & Sanchez-Pinto, 2017). This organ injury assessment tool was later adapted and validated to pediatric patients with age-appropriate markers of organ dysfunction for the respiratory, coagulatory, hepatic, cardiovascular, neurological, and renal systems. Scores for each subcategory were calculated individually based on the respective lab values and cutoffs. Each subcategory could score from 0 to 4 points. If a subscore lab value was not measured or if there was a value of zero, it was considered within normal range and a subscore of zero was given. The pSOFA score was calculated for a single 24-hour period by totaling the highest score from each of the six subcategories in that respective time. Total scores could range from 0 to 24 points, and a higher score indicated a more severe disease state.

Respiratory Subscore

The respiratory subscore was based on the values of Pa_{O2}, Fi_{O2}, and the presence of respiratory support that was extracted from the patient chart. Respiratory support was defined as the use of any device or system that provided oxygenation to the patient and most commonly included, but was not limited to, ventilators, bilevel positive airway pressure (BPAP) machines, continuous positive airway pressure (CPAP) machines, hand-bag endotracheal tube (ETT), nasal cannula, trach collar, and blow-by. The Pa_{O2}: Fi_{O2} ratio was then calculated using the values from the patient chart. If either Pa_{O2} or Fi_{O2} or both had a value of zero in their chart, the parameter was considered to be normal and a subscore of zero was given. Patients who were on respiratory support but had a Pa_{O2}: Fi_{O2} ratio that was greater than 220 were given a score of 2.5. Patients who were not on respiratory support but had a Pa_{O2}: Fi_{O2} ratio that was lower than 220 were given a score of 2.5.

Coagulation Subscore

The coagulation subscore was based on the lowest value of the platelet count for a given 24-hour period that was extracted from the patient chart. Units of platelets per microliter were used.

Hepatic Subscore

The hepatic subscore was based on the highest value of the bilirubin measurement for a given 24-hour period that was extracted from the patient chart. Units of milligrams per deciliter were used.

Cardiovascular Subscore

The cardiovascular subscore was based on the lowest MAP measured within a 24-hour period and/or the highest concentration of vasoactive infusion that was given in the respective time period. Vasoactive infusions were extracted in milligrams given intravenously in the 24-hour period. These values were then converted into micrograms per kilogram of bodyweight per minute. The vasoactive infusions that were considered included dopamine hydrochloride, epinephrine, and norepinephrine bitartrate. If multiple vasoactive infusions were given within the same 24-hour time period, the drug or concentration that resulted in the highest subscore based on the pSOFA criteria was used.

Neurological Subscore

The neurological subscore was based on the pediatric scale of the Glasgow Coma Score (Matics & Sanchez-Pinto, 2017). Because of the nature of the cases that were cared for in the 7-south (7S) and 11-south (11S) ICUs, all cases were assumed to be within normal limits and values of zero were given.

Renal Subscore

The renal subscore was established based on the highest creatinine concentration measured within a 24-hour period. Units of milligram per deciliter were used. For any creatinine level that fell between the maximum limit of the lower subscore and the lower limit of the higher subscore, the average of the two subscores was given.

Microbe Classification

To further evaluate the types of infections that composed each case, the organisms were divided into the following categories: gram-positive, gram-negative, fungal, yeast, viral, mixed single, mixed multiple and suspected/undefined. Gram-positive, gram-negative, fungal, yeast, and viral categories composed cases with a single microbe of that respective category. The mixed single category was composed of cases with confirmed mixed flora of a single organism classification. The mixed multiple category was composed of cases with a confirmed mixed flora of two or more organism classifications. The suspected/undefined category was composed of cases with no confirmed microbe type.

Statistical Analysis

The data was collected and analyzed using Microsoft Excel (Version 16.69.1), StataCorp Stata (Version 13.0), and BoxPlotR.

The data were first split into categories of meeting Sepsis-3 criteria and failing to meet Sepsis-3 criteria (Sepsis-2). Univariate analysis was performed on the following variables: age, weight, sex, length of stay, mortality, maximum and average subscores for each of the five organ systems, maximum and average pSOFA scores, and infection type. Multivariate analysis was performed on length of stay, mortality, and the maximum subscores for each of the five organ systems.

The data were then split into outcome categories including death during ICU stay and survived ICU stay. Univariate analysis was performed on the following variables: age, weight, sex, length of stay, maximum and average subscores for each of the five organ systems, maximum and average pSOFA scores, and infection type. Multivariate analysis was performed on length of stay, mortality, and the maximum subscores for each of the five organ systems.

Next, we broke the data into categories of children and adults. Pediatric cases included anyone that was under 18 years old while adult cases were 18 years and older. Univariate analysis was performed on the following variables: age, weight, sex, length of stay, mortality, maximum and average subscores for each of the five organ systems, maximum and average pSOFA scores, and infection type. Multivariate analysis was performed on length of stay, mortality, and the maximum subscores for each of the five organ systems.

Last, the pediatric patients were split into outcome categories of death during ICU stay and survived ICU stay. Univariate analysis was performed on the following variables: age, weight, sex, length of stay, maximum and average subscores for each of the five organ systems, maximum and average pSOFA scores, and infection type.

Multivariate analysis was performed on length of stay and the maximum subscores for each of the five organ systems.

Mortality and maximum subscores for each organ system were the primary independent variables that were assessed, and Sepsis-3 criteria were used as the primary dependent variables. First, univariate analysis was performed for each of the variables to compare the Sepsis-3 and Sepsis-2 groups for both the adult and pediatric cases using an independent two-sided independent *t*-test and $p<.05$ for significance. Second, multivariable analysis was performed for each of the variables to compare the Sepsis-3 and Sepsis-2 groups for both the adult and pediatric cases using logistic regression. Odds ratios, 95% confidence intervals and *p*-values were calculated for each variable.

Analysis was also completed using the maximum subscores for each organ system as the dependent variable and using outcome as the independent variable for both the pediatric and adult cases. Univariate analysis was performed for each of the variables to compare the death and survived groups using an independent two-sided independent *t*-test and $p<.05$ for significance. Next, multivariable analysis was performed for each of the variables to compare the died and survived groups for both the adults and pediatric cases using logistic regression. Odds ratios, 95% confidence intervals and *p*-values were calculated for each variable.

RESULTS

Population Variable Information

There were a total of 806 cases included in this study with 665 unique patients. Of these cases, 419 were males, and 387 were females. The age for the population was an average of 10.4 years and ranged from 0 days to 40 years. The population had an average weight of 35.7 kilograms. Sixty-five cases, all of which met Sepsis-3 criteria, died during their stay in the ICU. The cases were then compared by categorizing them into Sepsis-3 versus Sepsis-2 and death versus survived. Last, the cases were compared by categorizing them into adults versus children. There were a total of 641 cases under the age of 18 years, which was comprised of 329 males, and 312 females. The category had an average age of 7.2 years and an average weight of 30.0 kilograms. The pediatric population had a total of 46 cases that died during their stay in the ICU.

Sepsis-3 Versus Sepsis-2

Table 1 shows a comparison of the results for Sepsis-3 and non-Sepsis-3 patients. Of the 806 cases that were included in this study, 724 cases met the updated Sepsis-3 criteria, and 82 cases did not. The Sepsis-3 category was 51.7% male, and the Sepsis-2 category was 54.9% male. For cases that met Sepsis-3 criteria, the average age and weight were 10.5 years and 36.1 kilograms, respectively (Figures 1 and 2). The differences in sex distribution, age and weight differences were not statistically significant between the two groups. However, the average length of stay in the ICU of

12.3 days for Sepsis-3 patients was significantly longer than the average length of stay in the ICU of 1.4 days for Sepsis-2 patients (Figure 3).

Table 1

Population Statistics of Sepsis-3 Versus Sepsis-2 Patients

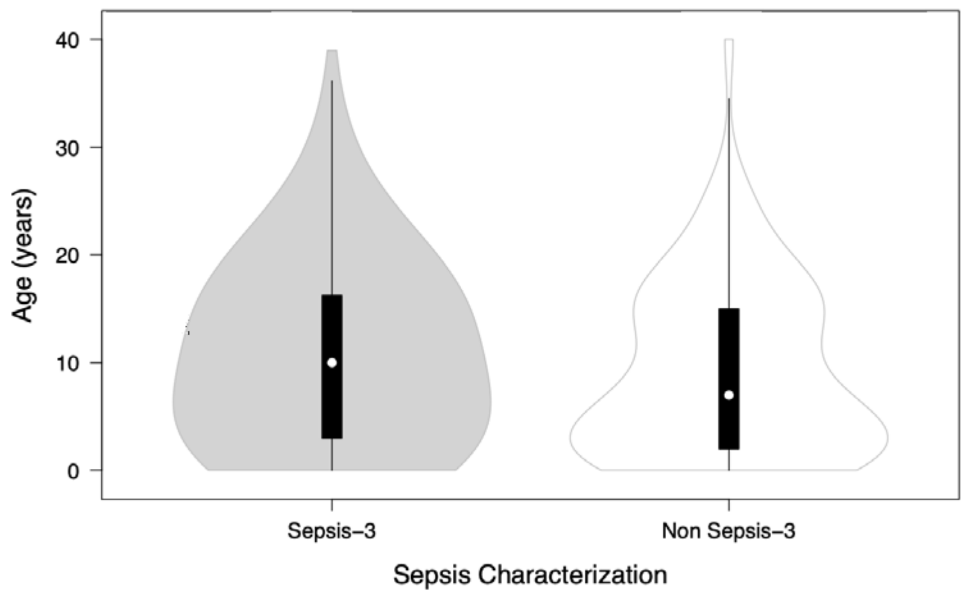
Variable	Sepsis-3	Sepsis-2	*t*-Test *p*-Value	Odds Ratio	Log Regression *p*-Value	Confidence Interval
Total No.	724	82				
Age (years)	10.5	9.1	1.67E-01			
Weight (kilograms)	36.1	31.7	1.04E-01			
Male, No. (% of total)	374 (51.7)	45 (54.9)	5.82E-01			
Length of ICU Stay (days)	12.3	1.4	3.83E-26	1.10E+00	0.857	[0.39, 3.12]
No. of Death in ICU (% of total)	65 (9.0)	0.0 (0)	1.66E-16			
Avg Renal Score	0.26	0.01	1.59E-21			
Avg Respiratory Score	2.02	0.00	1.13E-218			
Avg Hepatic Score	0.23	0.00	2.29E-24			
Avg Coagulation Score	0.77	0.00	5.29E-71			
Avg Cardiovascular Score	1.15	0.64	1.56E-19			
Avg Sum Score	4.43	0.65	9.40E-177			
Max Renal Score	0.57	0.02	1.22E-31	3.55E+15	<0.001	[1.13E+14, 1.12]
Max Respiratory Score	2.91	0.00	2.46E-264	1.00E+00		
Max Hepatic Score	0.51	0.00	7.38E-38	1.00E+00		
Max Coagulation Score	1.41	0.01	3.33E-103	5.01E+16	<0.001	[4.46E+15, 5.65]

Max Cardiovascular Score	2.10	0.82	6.17E-61	2.22E+17	<0.001	[3.03E+14, 1.63]
Max Sum Score	6.88	0.83	1.10E-222			
Mixed Single No. (% of total)	157 (21.7)	2 (2.4)	4.43E-15	6.47E+10	0.95	
Mixed Multiple No. (% of total)	89 (12.3)	2 (2.4)	5.59E-06	1.00E+00		
Gram Positive No. (% of total)	44 (6.1)	2 (2.4)	6.17E-02			
Gram Negative No. (% of total)	21 (2.9)	2 (2.4)	8.01E-01			
Viral No. (% of total)	1 (0.1)	0 (0.0)	3.18E-01			
Yeast No. (% of total)	8 (1.1)	0 (0.0)	4.61E-03			
Suspected/Undefined No. (% of total)	404 (55.8)	74 (89.0)	1.25E-26	3.93E+5		

Note. Each category is broken down into the means of age, weight, sex, and length of ICU stay. The average subscores and average maximum subscores for each of the five organ systems are also shown. Average pSOFA and average maximum pSOFA scores are calculated for each category. A t-test p-value is calculated to determine the statistical significance of the difference between death versus survival groups for each category. Log regression is then calculated and shown for t-test p-values that are statistically significant. ICU = intensive care unit; pSOFA = pediatric Sequential Organ Failure Assessment; Sepsis-3 = Third International Consensus Definitions for Sepsis and Septic Shock. $N = 806$.

Figure 1

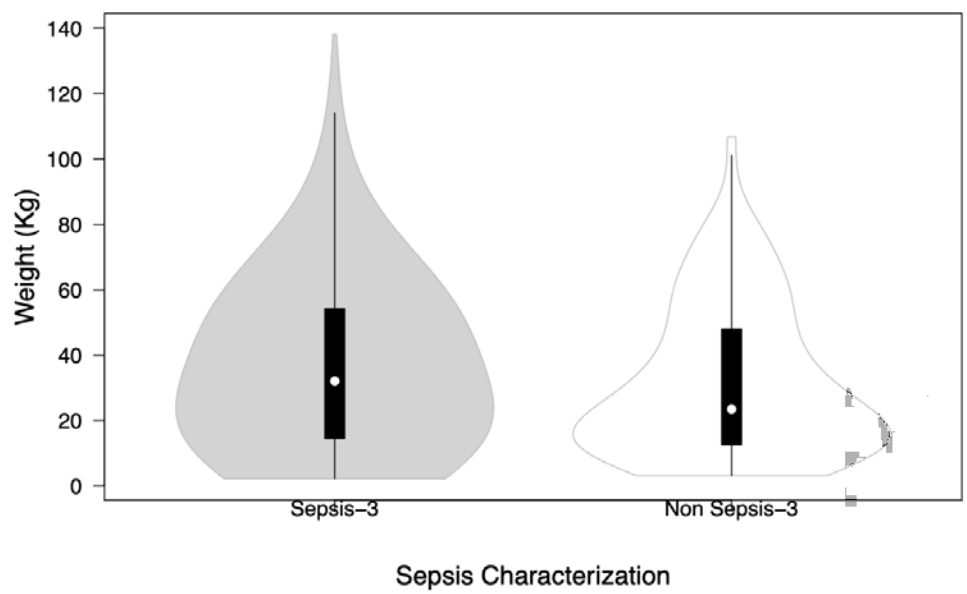
Age Distribution of Sepsis-3 Patients Versus Sepsis-2 Patients



Note. This plot shows the distribution of age in years for each patient depending on the individual's Sepsis-3 characterization. The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines. Sepsis-3 = Third International Consensus Definitions for Sepsis and Septic Shock.

Figure 2

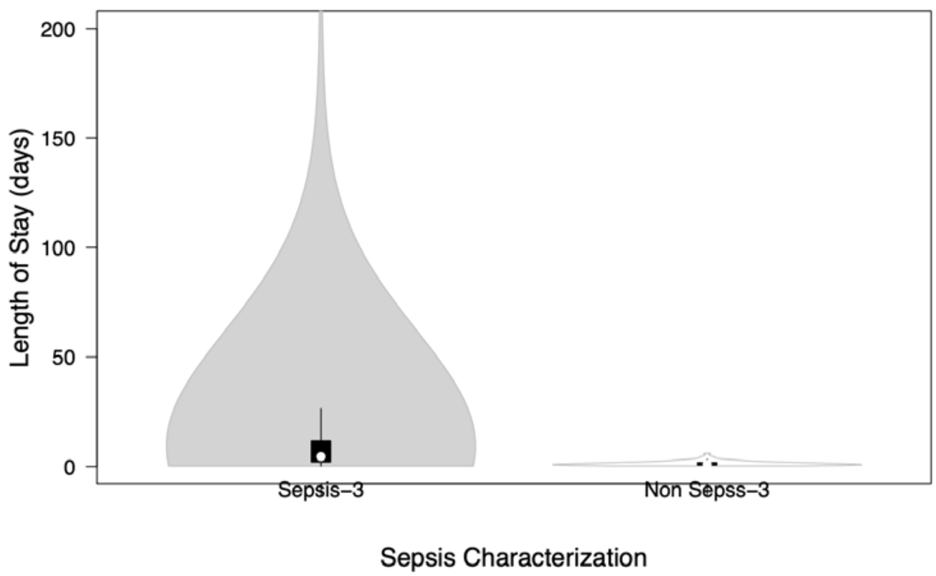
Weight Distribution of Sepsis-3 Patients Versus Sepsis-2 Patients



Note. This plot shows the distribution of weight in kilograms for each patient depending on the individual's Sepsis-3 characterization. The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines. Sepsis-3 = Third International Consensus Definitions for Sepsis and Septic Shock.

Figure 3

Length of Stay Distribution of Sepsis-3 Patients Versus Sepsis-2 Patients



Note. This plot shows the distribution of length of stay in days for each patient depending on the individual's Sepsis-3 characterization. The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines. Sepsis-3 = Third International Consensus Definitions for Sepsis and Septic Shock.

pSOFA Scores of Sepsis-3 Versus Sepsis-2

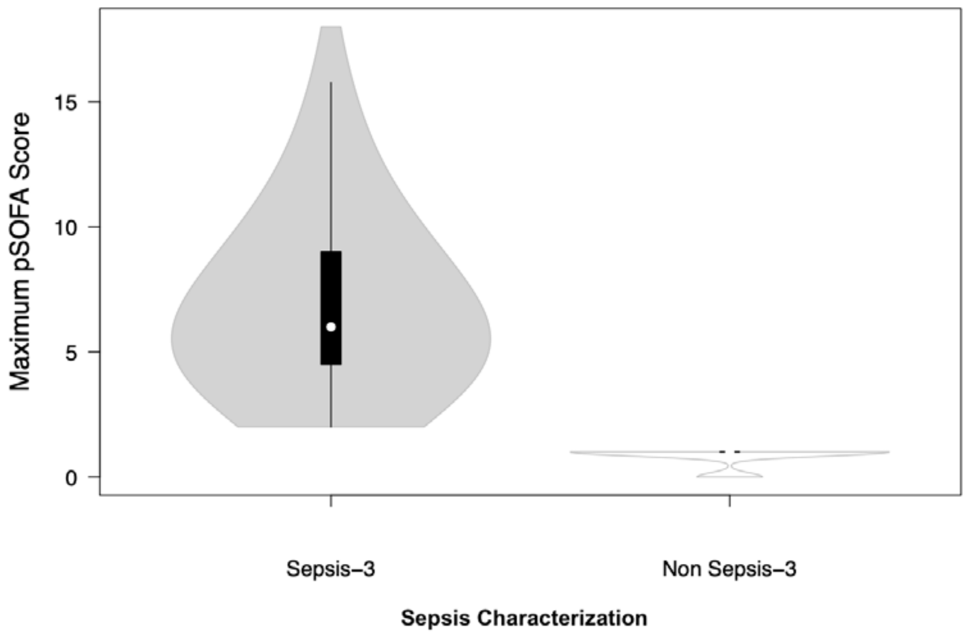
The average and maximum subscores for each of the five organ systems (renal, respiratory, hepatic, coagulation and cardiovascular) were calculated, and the results are summarized in Table 1. The average maximum total pSOFA score for Sepsis-3 cases was significantly higher than the average maximum total pSOFA score for Sepsis-2 cases (6.88 versus 0.83; $p < .001$). The distributions of the maximum total pSOFA scores for both Sepsis-3 and non-Sepsis-3 cases are shown in Figure 4.

The highest average maximum subscores for Sepsis-3 cases were the respiratory and cardiovascular values of 2.91 and 2.10, respectively. The average maximum coagulation subscore was 1.41 for Sepsis-3 cases. The renal and hepatic subscores were the lowest average maximum values of 0.57 and 0.51, respectively, for Sepsis-3 cases. The distributions of the maximum subscores for Sepsis-3 cases for each organ system are shown in Figure 5.

For Sepsis-2 cases, the cardiovascular and renal subscores were the highest average maximum values at 0.82 and 0.02, respectively. The average maximum coagulation subscore was 0.01 for Sepsis-2 cases, and the respiratory and hepatic systems both had average maximum subscores of 0. The distributions of the maximum subscores for Sepsis-2 cases for each organ system are shown in Figure 6.

Figure 4

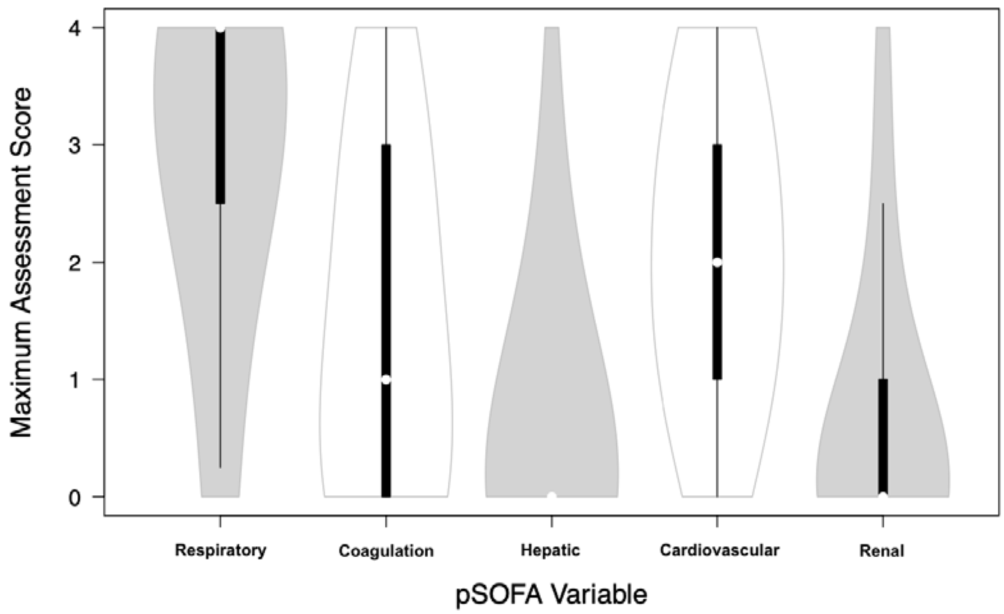
Distribution of Maximum pSOFA Scores of Sepsis-3 Versus Sepsis-2 Patients



Note. This plot shows the distribution of the maximum pSOFA subscores of patients meeting Sepsis-3 criteria for each of the five organ systems (respiratory, coagulation, hepatic, cardiovascular, and renal). The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines. pSOFA = pediatric Sequential Organ Failure Assessment; Sepsis-3 = Third International Consensus Definitions for Sepsis and Septic Shock.

Figure 5

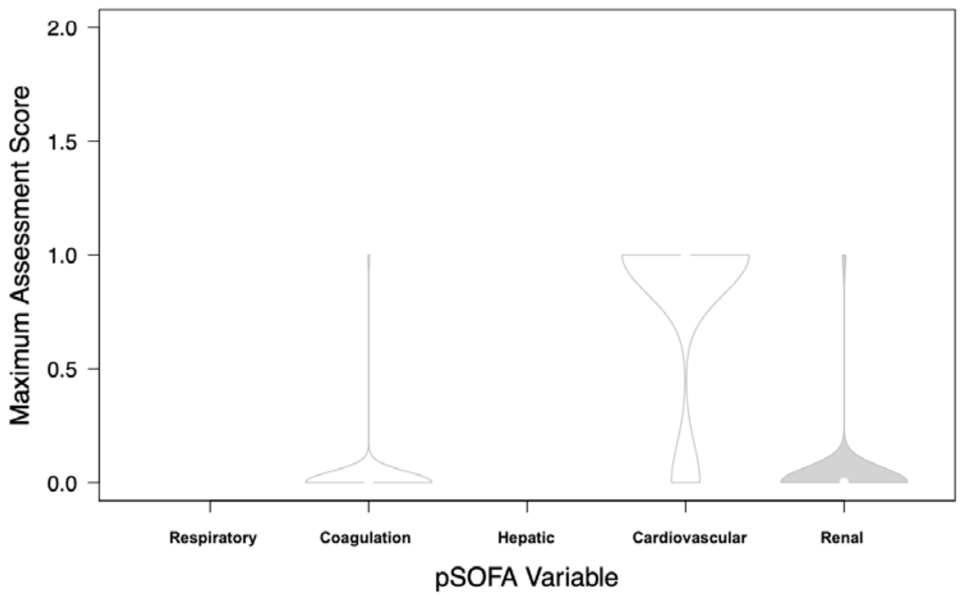
Distribution of Maximum pSOFA Subscores for Patients Meeting Sepsis-3 Criteria



Note. This plot shows the distribution of the maximum pSOFA subscores of patients meeting Sepsis-3 criteria for each of the five organ systems (respiratory, coagulation, hepatic, cardiovascular, and renal). The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines. pSOFA = pediatric Sequential Organ Failure Assessment; Sepsis-3 = Third International Consensus Definitions for Sepsis and Septic Shock.

Figure 6

Distribution of Maximum pSOFA Subscores for Patients Meeting Sepsis-2 Criteria



Note. This plot shows the distribution of the maximum pSOFA subscores of patients meeting Sepsis-2 criteria for each of the five organ systems (respiratory, coagulation, hepatic, cardiovascular, and renal). The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines. pSOFA = pediatric Sequential Organ Failure Assessment; Sepsis-3 = Third International Consensus Definitions for Sepsis and Septic Shock.

Univariate Analysis of Sepsis-3 Versus Sepsis-2

In the comparison of the Sepsis-3 and Sepsis-2 groups, both the average maximum subscores and the average subscores were calculated. The average maximum subscores were used for further analysis instead of the average subscores and total pSOFA scores. To assess the differences between the average maximum subscores of Sepsis-3 and Sepsis-2 cases, univariate analysis was first performed using *t*-tests. All of the differences in subscores were statistically significant between the two groups. The average maximum respiratory subscores gave the most statistically significant different between the two groups (p = 2.46E-246). The difference between the average maximum coagulation scores had a p -value of 3.33E-103. The p-values of the renal, hepatic, and cardiovascular subscores were 1.22E-31, 7.38E-38 and 6.17E-61, respectively.

Multivariate Analysis of Sepsis-3 Versus Sepsis-2

Length of stay, death, and all five of the organ system subscores were positively correlated with meeting Sepsis-3 definition. Logistic regression was then performed using average maximums to compare each subscore. The average maximum respiratory and hepatic scores were unable to be determined because the Sepsis-2 group had average maximums of 0. Of the renal, coagulation, and cardiovascular subscores, the cardiovascular subscore was determined to be the most significant predictor of meeting Sepsis-3 definition with an odds ratio of 2.22E+17 ($p < .001$, 95% CI [3.03E+14, 1.63]). The coagulation subscore had an odds ratio of 5.01E+16 ($p < .001$, 95% CI [4.46E+15, 5.65]), and the renal subscore had an odds ratio of 3.55E+15 ($p < .001$, 95% CI

[1.13E+14, 1.12]).

Died Versus Survived

Table 2 shows a comparison of the results for those patients who survived and those patients who died during their stay in the ICU. Of the 806 cases that were included in this study, 65 cases died during their ICU stay, and 741 cases survived. Males made up 52.3% of the cases that died and 52.0% of the cases that survived. For cases that died, the average age and weight were 11.7 years and 40.5 kilograms, respectively (Figures 7 and 8). The differences in sex distribution, age and weight differences were not statistically significant between the two groups. However, there was an average length of stay in the ICU of 23.8 days for patients who died, and this was significantly longer than the average length of stay in the ICU of 10.1 days for patients who survived (Figure 9).

Table 2

Population Statistics of Died Versus Survived Patients

Variable	Died	Survived	*t*-Test *p*-Value	Odds Ratio	Log Regression *p*-Value	Confidence Interval
Total No.	65	741				
Age (years)	11.7	10.2	2.15E-01			
Weight (kilograms)	40.5	35.2	1.77E-01			
Male, No. (% of total)	34 (52.3)	385 (52.0)	9.57E-01			
Length of ICU Stay (days)	23.8	10.1	8.19E-03	1	0.365	[0.99, 1.00]
Avg Renal Score	0.49	0.19	6.19E-05			
Avg Respiratory Score	3.01	1.71	7.25E-23			
Avg Hepatic Score	0.89	0.15	2.34E-06			
Avg Coagulation Score	1.63	0.61	1.00E-07			
Avg Cardiovascular Score	1.61	1.05	4.78E-05			
Avg Sum Score	7.84	3.71	9.16E-13			
Max Renal Score	1.49	0.43	3.67E-07	1.31	0.019	[1.05, 1.65]
Max Respiratory Score	3.73	2.52	5.63E-29	1.77	0.004	[1.20, 2.61]
Max Hepatic Score	1.40	0.38	3.95E-07	1.33	0.022	[1.04, 1.70]
Max Coagulation Score	2.42	1.16	6.10E-09	1.29	0.029	[1.03, 1.63]
Max Cardiovascular Score	2.89	1.89	2.15E-08	1.28	0.078	[0.97, 1.68]
Max Sum Score	10.8	5.86	1.97E-14			

Mixed Single No. (% of total)	22 (33.8)	137 (18.5)	1.38E-02	1.74	0.285	[0.63, 4.79]
Mixed Multiple No. (% of total)	13 (20.0)	78 (10.5)	6.87E-02	1.36	0.582	[0.46, 4.01]
Gram Positive No. (% of total)	4 (6.2)	42 (5.7)	8.77E-01			
Gram Negative No. (% of total)	2 (3.1)	21 (2.8)	9.14E-01			
Viral No. (% of total)	1 (1.5)	0 (0.0)	3.21E-01			
Yeast No. (% of total)	0 (0.0)	8(1.1)	4.61E-03			
Suspected/Undefined No. (% of total)	11 (16.9)	351 (47.4)	3.79E-08	1.38	0.519	[0.51, 3.72]

Note. Each category is broken down into the means of age, weight, sex, and length of ICU stay. The average subscores and average maximum subscores for each of the five organ systems are shown. Average pSOFA and average maximum pSOFA scores are calculated for each category. A *t*-test *p*-value is calculated to determine the statistical significance of the difference between died versus survived groups for each category. Log regression is then calculated and shown for *t*-test *p*-values that are statistically significant. ICU = intensive care unit; pSOFA = pediatric Sequential Organ Failure Assessment. $N = 806$.

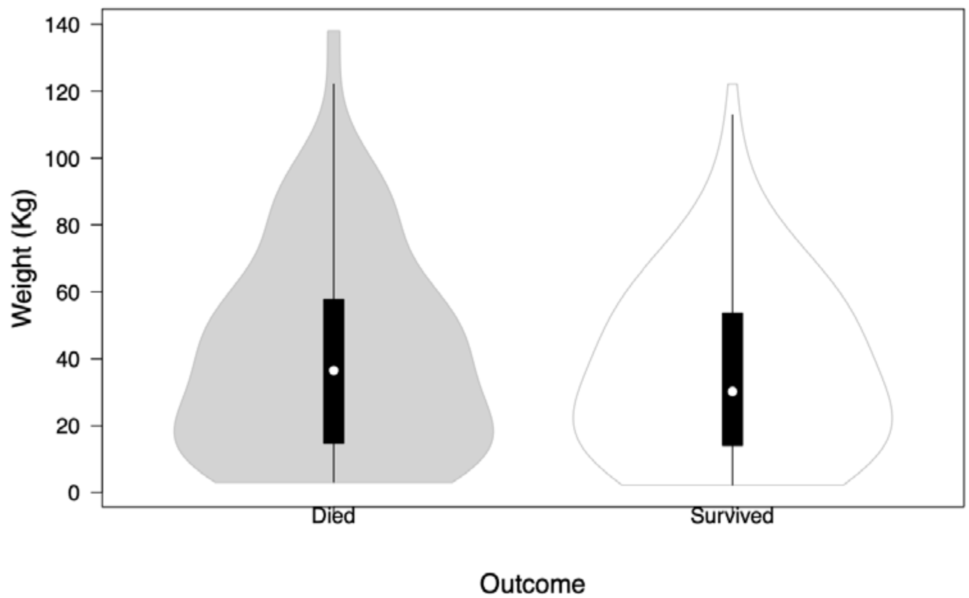
Figure 7

Age Distribution Based on Outcome

Note. This plot shows the distribution of age in years for patients who died during ICU stay compared with patients who survived. The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines.

Figure 8

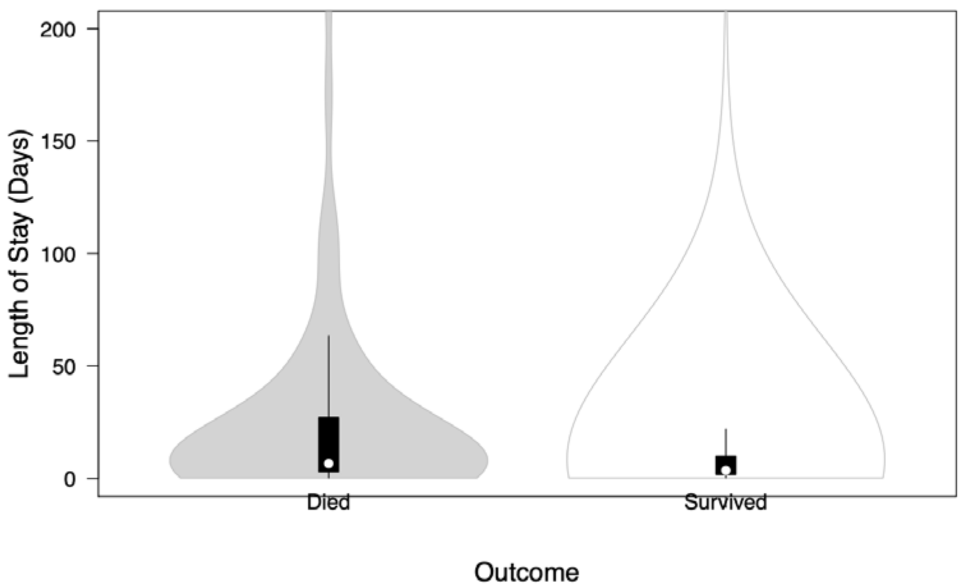
Weight Distribution Based on Outcome



Note. This plot shows the distribution of weight in kilograms for patients who died during ICU stay compared with patients who survived. The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines.

Figure 9

Length of Stay Distribution Based on Outcome



Note. This plot shows the distribution of length of stay in days for patients who died during ICU stay compared with patients who survived. The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box. respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines.

pSOFA Scores of Died Versus Survived

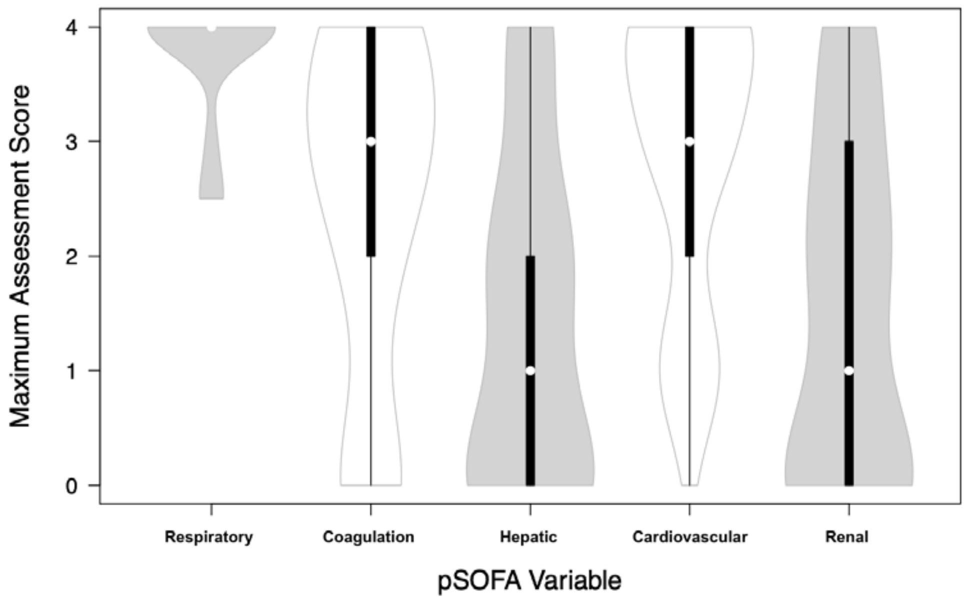
The average and maximum subscores for each of the five organ systems (renal, respiratory, hepatic, coagulation, and cardiovascular) were calculated, and the results are shown in Table 2. The average maximum total pSOFA score for patients who died was significantly higher than the average maximum total pSOFA score for patients who survived (10.8 versus 5.86; $p < .001$).

The highest average maximum subscores for patients who died were the respiratory and cardiovascular values of 3.73 and 2.89, respectively. Their average maximum coagulation subscore was 2.42. The renal and hepatic subscores were the lowest average maximum of 1.49 and 1.40, respectively. The distributions of the maximum subscores for each organ system for patients who died are shown in Figure 10.

For patients who survived, the respiratory and cardiovascular subscores were the highest at 2.52 and 1.89, respectively. The average maximum coagulation subscore was 1.16. The renal and hepatic maximum subscores had averages of 0.43 and 0.38, respectively. The distributions of the maximum subscores for each organ system for patients who survived are shown in Figure 11.

Figure 10

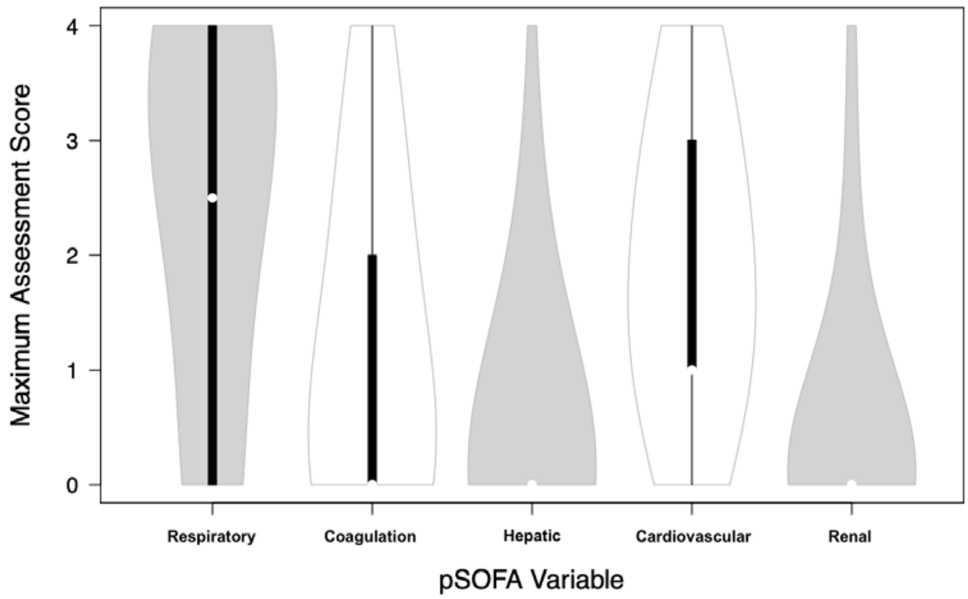
Distribution of Maximum pSOFA Subscores for Patients Who Died



Note. This plot shows the distribution of the maximum pSOFA subscores of patients who died during the ICU stay for each of the five organ systems (respiratory, coagulation, hepatic, cardiovascular, and renal). The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines. pSOFA = pediatric Sequential Organ Failure Assessment.

Figure 11

Distribution of Maximum pSOFA Subscores for Patients Who Survived



Note. This plot shows the distribution of the maximum subscores of patients who survived the ICU stay for each of the five organ systems (respiratory, coagulation, hepatic, cardiovascular, and renal). The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines. pSOFA = pediatric Sequential Organ Failure Assessment.

Univariate Analysis of Died Versus Survived

In the comparison of the patients who died versus the patients who survived while in the ICU, both the average maximum subscores and the average subscores were calculated for the two groups. The average maximum subscores were used for further analysis instead of the average subscores and total pSOFA scores. To assess the differences between the average maximum subscores of death and survival cases, univariate analysis was first performed using *t*-tests. All of the differences in subscores were statistically significant between the two groups. The difference between the average maximum respiratory subscores gave the most statistically significant difference between the two groups (p=5.63E-29). The difference between the average maximum coagulation scores had a p-value of 6.10E-9. The p-values of the renal, hepatic, and cardiovascular subscores were 3.67E-7, 3.95E-7, and 2.15E-8, respectively.

Multivariate Analysis of Died Versus Survived

Length of stay and all five of the organ system subscores were positively correlated with patients who died. Logistic regression was then performed using average maximums to compare each subscore. The average maximum cardiovascular subscore was not found to be a statistically significant predictor of death. Of the respiratory, hepatic, renal, and coagulation subscores, the respiratory subscore was determined to be the most significant predictor of death with an odds ratio of 1.77 (p=0.004, 95% CI [1.20, 2.61]). The hepatic subscore had an odds ratio of 1.33 (p = .022, 95% CI [1.04, 1.70]) and the renal subscore had an odds ratio of 1.31 (p = .019, 95% CI [1.05, 1.65]). The coagulation subscore was the least predictive of death with an odds ratio of 1.29 (p = .029, 95% CI [1.03, 1.63]).

Pediatric Sepsis-3 Versus Sepsis-2 Populations

Table 3 shows a comparison of the results for Sepsis-3 and Sepsis-2 pediatric patients. Of the 806 cases that were included in this study, 641 cases were under 18 years old. Of the pediatric patients, 572 cases met the updated Sepsis-3 criteria, and 69 cases did not. The Sepsis-3 category was 50.7% male, and the Sepsis-2 category was 56.5% male. For cases that met Sepsis-3 criteria, the average age and weight were 7.2 years and 30.3 kilograms, respectively (Table 3). The differences in sex distribution, age and weight differences were not statistically significant between the two groups. However, the average length of stay in the ICU of 12.7 days for Sepsis-3 pediatric patients was significantly longer than the average length of stay in the ICU for Sepsis-2 pediatric patients of 1.3 days (Table 3).

Table 3

Population Statistics of Sepsis-3 Versus Sepsis-2 in Children

Variable	Sepsis-3	Sepsis-2	*t*-Test *p*-Value	Odds Ratio	Log Regression *p*-Value	Confidence Interval
Total No.	572	69				
Age (Years)	7.2	6.6	3.54E-01			
Weight (Kilograms)	30.3	27.3	2.88E-01			
Male, No. (% of total)	290 (50.7)	39 (56.5)	3.63E-01			
Length of ICU Stay	12.7	1.3	3.00E-21	3.08E+00	0	[2.16, 4.38]
No. of Death in ICU (% of total)	46 (8.0)	0 (0.0)	4.65E-12			
Avg Renal Score	0.27	0.01	1.78E-16			
Avg Respiratory Score	2.00	0.00	2.94E-169			
Avg Hepatic Score	0.24	0.00	6.23E-21			
Avg Coagulation Score	0.80	0.00	4.48E-58			
Avg Cardiovascular Score	1.15	0.62	1.93E-16			
Avg Sum Score	4.47	0.64	6.69E-139			
Max Renal Score	0.60	0.03	3.12E-25	4.28E+00	0.033	[1.13, 16.2]
Max Respiratory Score	2.90	0.00	5.93E-204	1.00E+00		
Max Hepatic Score	0.55	0.00	7.24E-32	1.00E+00		

Max Coagulation Score	1.43	0.01	4.86E-82	1.43E+01	0.004	[2.37, 85]
Max Cardiovascular Score	2.10	0.80	9.16E-50	5.88E+00	0	[3.22, 10.7]
Max Sum Score	6.95	0.81	1.52E-173			
Mixed Single No. (% of total)	120 (21.0)	2 (2.9)	1.28E-10			
Mixed Multiple No. (% of total)	64 (11.2)	1 (1.4)	1.39E-06			
Gram Positive No. (% of total)	37 (6.5)	2 (2.9)	1.20E-01			
Gram Negative No. (% of total)	19 (3.3)	2 (2.9)	8.46E-01			
Viral No. (% of total)	1 (0.2)	0 (0.0)	3.18E-01			
Yeast No. (% of total)	6 (1.0)	0 (0.0)	1.42E-02			
Suspected/Undefined No. (% of total)	325 (56.8)	62 (89.9)	2.17E-12			

Note. Each category is broken down into the means of age, weight, sex, and length of ICU stay. The average subscores and average maximum subscores for each of the five organ systems are also shown. Average pSOFA and average maximum pSOFA scores are calculated for each category. A *t*-test *p*-value is calculated to determine the statistical significance of the difference between death versus survival groups for each category. Log regression is then calculated and shown for *t*-test *p*-values that are statistically significant. ICU = intensive care unit; pSOFA = pediatric Sequential Organ Failure Assessment; Sepsis-3 = Third International Consensus Definitions for Sepsis and Septic Shock. $N = 641$.

pSOFA Scores of Pediatric Sepsis-3 Versus Sepsis-2 Patients

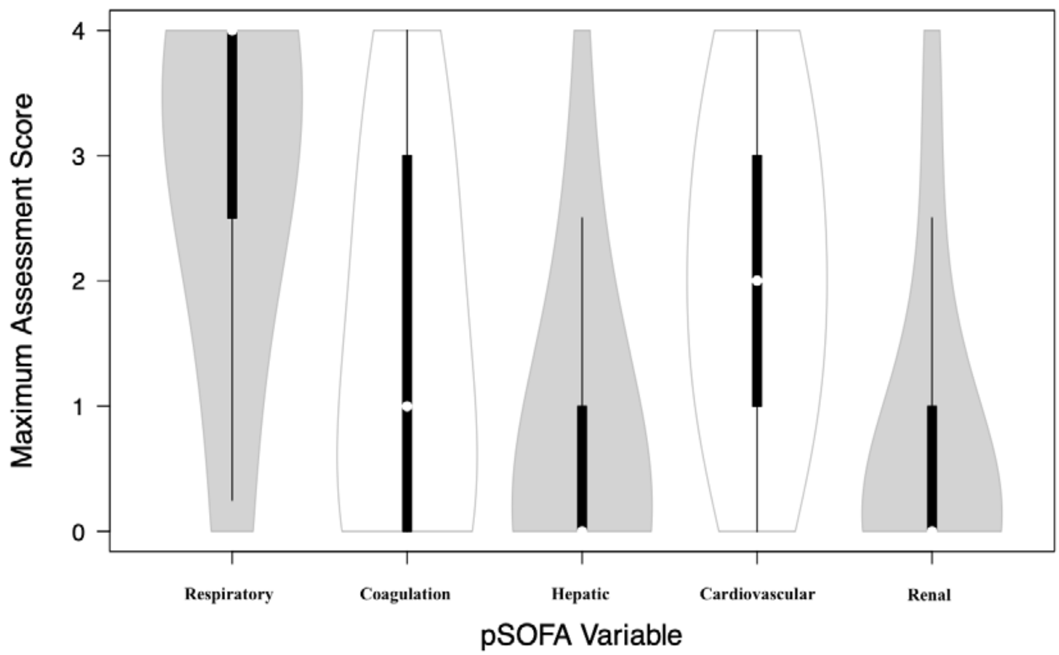
The average and maximum subscores for each of the five organ systems (renal, respiratory, hepatic, coagulation, and cardiovascular) in children were calculated and the results are summarized in Table 3. The average maximum total pSOFA score for Sepsis-3 cases was significantly higher than the average maximum total pSOFA score for Sepsis-2 cases (6.95 versus 0.81; $p < .001$).

The highest average maximum subscores for Sepsis-3 pediatric cases were the respiratory and cardiovascular values of 2.90 and 2.10, respectively. Their average maximum coagulation subscore was 1.43 for children meeting Sepsis-3 criteria. The renal and hepatic subscores were the lowest average maximum values of 0.60 and 0.55, respectively, for Sepsis-3 cases. The distributions of the maximum subscores for children meeting Sepsis-3 criteria for each organ system are shown in Figure 12.

For Sepsis-2 pediatric cases, the cardiovascular and renal subscores were the highest average maximum values at 0.80 and 0.03, respectively. The average maximum coagulation subscore was 0.01 for Sepsis-2 pediatric cases, and the respiratory and hepatic systems both had average maximum subscores of 0. The distributions of the maximum subscores for children meeting Sepsis-2 criteria for each organ system are shown in Figure 13.

Figure 12

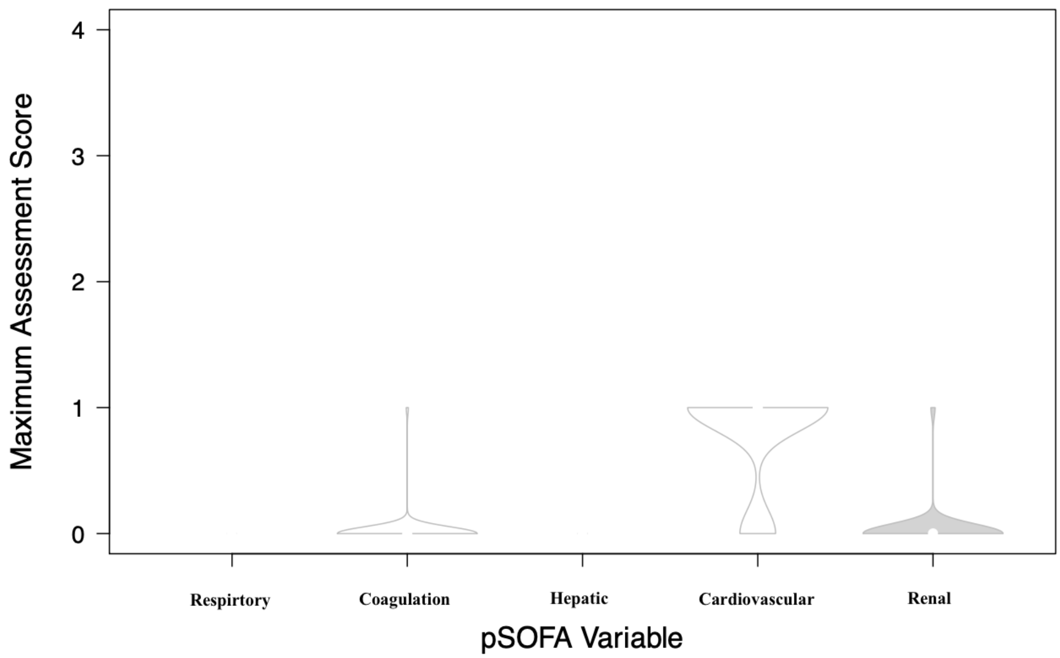
Distribution of Maximum pSOFA Subscores for Children Meeting Sepsis-3 Criteria



Note. This plot shows the distribution of the maximum pSOFA subscores of pediatric patients meeting Sepsis-3 criteria for each of the five organ systems (respiratory, coagulation, hepatic, cardiovascular, and renal). The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines. pSOFA = pediatric Sequential Organ Failure Assessment; Sepsis-3 = Third International Consensus Definitions for Sepsis and Septic Shock.

Figure 13

Distribution of Maximum pSOFA Subscores for Children Meeting Sepsis-2 Criteria



Note. This plot shows the distribution of the maximum pSOFA subscores of pediatric patients meeting Sepsis-2 criteria for each of the five organ systems (respiratory, coagulation, hepatic, cardiovascular, and renal). The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines. pSOFA = pediatric Sequential Organ Failure Assessment; Sepsis-3 = Third International Consensus Definitions for Sepsis and Septic Shock.

Univariate Analysis of Pediatric Sepsis-3 Versus Sepsis-2

In the comparison of the Sepsis-3 and Sepsis-2 pediatric groups, both the average maximum subscores and the average subscores were calculated. The average maximum subscores were used for further analysis instead of the average subscores and total pSOFA scores. To assess the differences between the average maximum subscores of Sepsis-3 and Sepsis-2 cases in children, univariate analysis was first performed using *t*-tests. All of the differences in subscores were statistically significant between the two groups. The average maximum respiratory subscores gave the most statistically significant difference between the two groups (p = 5.63E-204). The difference between the average maximum coagulation scores had a p-value of 4.86E-82. The p-values of the renal, hepatic, and cardiovascular subscores were 3.12E-25, 7.24E-32 and 9.16E-50, respectively.

Multivariate Analysis of Pediatric Sepsis-3 Versus Sepsis-2

In the pediatric cases, length of stay and all five of the organ system subscores were positively correlated with meeting Sepsis-3 definition. Logistic regression was then performed using average maximums to compare each subscore. The average maximum respiratory and hepatic scores were unable to be determined because the Sepsis-2 group had average maximums of 0. Of the renal, coagulation, and cardiovascular subscores, the coagulation subscore was determined to be the most significant predictor of meeting Sepsis-3 definition with an odds ratio of 1.43E+01 (p =.004, 95% CI [2.37, 85]). The cardiovascular subscore had an odds ratio of 5.88E+0 ($p < .001$, 95% CI [3.22, 10.7]), and the renal subscore had an odds ratio of 4.28E+00 (p = .033, 95% CI [1.13, 16.2]).

Children that Died Versus Survived

Table 4 shows a comparison of the results for those pediatric patients who survived and those patients who died during their stay in the ICU. Of the 641 pediatric cases that were included in this study, 46 pediatric patients died during their ICU stay, and 595 pediatric patients survived. Males made up 47.8% of the pediatric patients who died and 51.6 % of the pediatric patients who survived. For pediatric patients that died, the average age and weight were 6.8 years and 31.4 kilograms, respectively (Table 4). The differences in sex distribution, age and weight differences were not statistically significant between the two groups. However, there was an average length of stay in the ICU of 23.3 days for pediatric patients that died, and this was significantly longer than the 10.6 days average length of stay in the ICU for pediatric patients that survived.

Table 4

Population Statistics of Children that Died Versus Survived

Variable	Died	Survived	*t*-Test *p*-Value	Odds Ratio	Log Regression *p*-Value	Confidence Interval
Total No.	46	595				
Age (years)	6.8	7.2	6.96E-01			
Weight (kilograms)	31.4	29.9	7.33E-01			
Male, No. (% of total)	22 (47.8)	307 (51.6)	6.27E-01			
Length of ICU Stay (days)	23.3	10.6	1.76E-02	1.01	0.01	[1.00, 1.01]
Avg Renal Score	0.80	0.20	4.21E-04			
Avg Respiratory Score	3.05	1.69	1.30E-17			
Avg Hepatic Score	0.96	0.16	2.08E-05			
Avg Coagulation Score	1.80	0.63	5.52E-07			
Avg Cardiovascular Score	1.62	1.05	5.66E-04			
Avg Sum Score	8.23	3.73	4.48E-10			
Max Renal Score	1.61	0.45	8.16E-06	1.22	0.11	[0.96, 1.50]
Max Respiratory Score	3.74	2.50	4.01E-22	1.71	0.017	[1.10, 2.66]
Max Hepatic Score	1.57	0.40	2.55E-06	1.38	0.023	[1.04, 1.81]
Max Coagulation Score	2.57	1.18	7.97E-08	1.34	0.038	[1.02, 1.74]
Max Cardiovascular Score	2.91	1.89	9.91E-07	1.27	0.16	[0.91, 1.75]
Max Sum Score	11.30	5.90	1.46E-11			

Mixed Single No. (% of total)	13 (28.3)	109 (18.3)	1.56E-01			
Mixed Multiple No. (% of total)	10 (21.7)	55 (9.2)	5.17E-02			
Gram Positive No. (% of total)	3 (6.5)	36 (6.1)	9.02E-01			
Gram Negative No. (% of total)	2 (4.3)	19 (3.2)	7.13E-01			
Viral No. (% of total)	1 (2.2)	0 (0.0)	3.23E-01			
Yeast No. (% of total)	0 (0.0)	6 (1.0)	1.42E-02			
Suspected/Undefined No. (% of total)	17 (37.0)	370 (62.2)	1.38E-03			

Note. Each category is broken down into the means of age, weight, sex, and length of ICU stay. The average subscores and average maximum subscores for each of the five organ systems are shown. Average pSOFA and average maximum pSOFA scores are calculated for each category. A *t*-test *p*-value is calculated to determine the statistical significance of the difference between died versus survived groups for each category. Log regression is then calculated and shown for *t*-test *p*-values that are statistically significant. ICU = intensive care unit; pSOFA = pediatric Sequential Organ Failure Assessment. $N = 641$.

pSOFA Scores of Children that Died Versus Survived

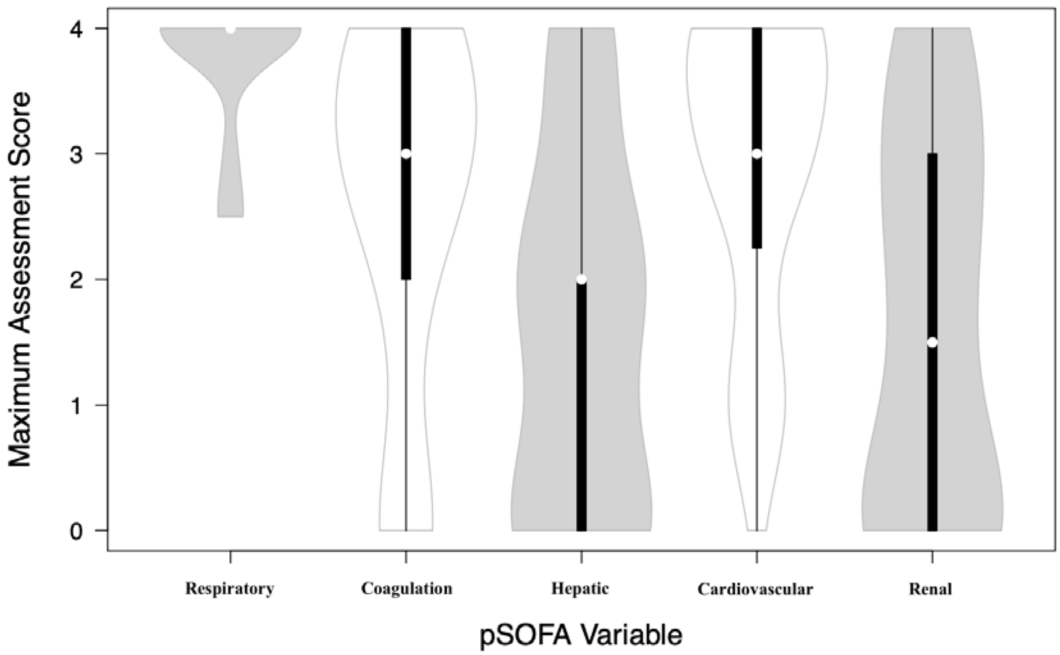
The average and maximum subscores for each of the five organ systems (renal, respiratory, hepatic, coagulation, and cardiovascular) were calculated and are shown in Table 4. The average maximum total pSOFA score for pediatric patients who died was significantly higher than the average maximum total pSOFA score for pediatric patients who survived (11.3 versus 5.9; $p < .001$).

The highest average maximum subscores for pediatric patients died were the respiratory and cardiovascular values of 3.74 and 2.91, respectively. The average maximum coagulation subscore was 2.57. The renal and hepatic subscores were the lowest average maximum values of 1.61 and 1.57, respectively. The distributions of the maximum subscores for each organ system for pediatric patients who died for each organ system are shown in Figure 14.

For pediatric patients who survived, the respiratory and cardiovascular subscores were the highest at 2.50 and 1.89, respectively. The average maximum coagulation subscore was 1.18. The renal and hepatic maximum subscores were 0.45 and 0.40, respectively. The distributions of the maximum subscores for each of the organ systems for pediatric patients who survived for each organ system are shown in Figure 15.

Figure 14

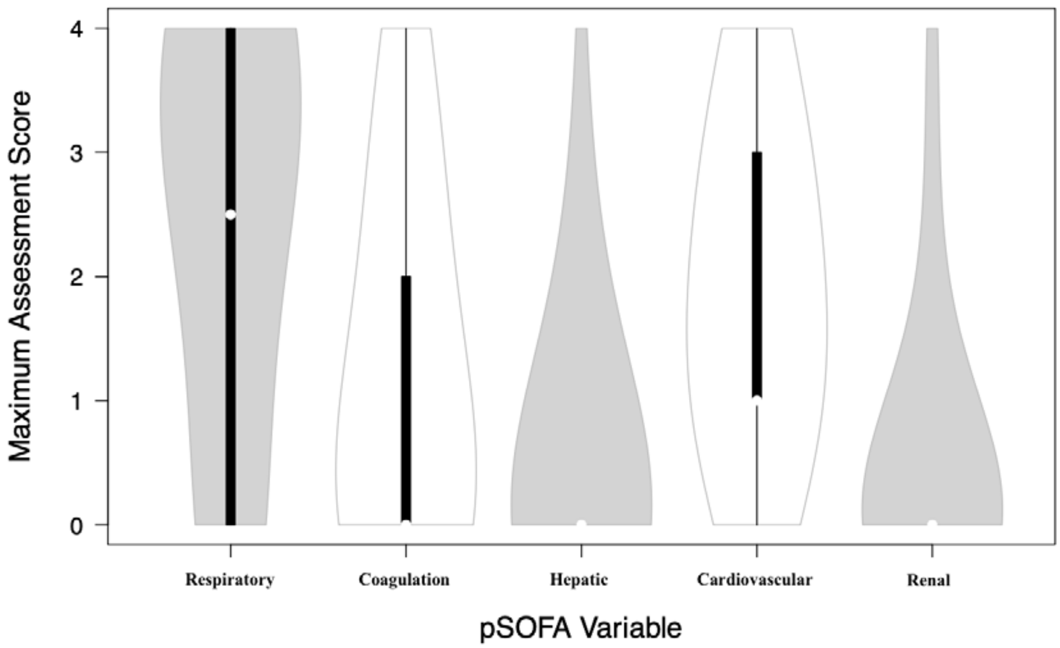
Distribution of Maximum pSOFA Subscores for Children Who Died



Note. This plot shows the distribution of the maximum pSOFA subscores of pediatric patients who died during the ICU stay for each of the five organ systems (respiratory, coagulation, hepatic, cardiovascular, and renal). The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines. pSOFA = pediatric Sequential Organ Failure Assessment.

Figure 15

Distribution of Maximum pSOFA Subscores for Children Who Survived



Note. This plot shows the distribution of the maximum subscores of pediatric patients who survived the ICU stay for each of the five organ systems (respiratory, coagulation, hepatic, cardiovascular, and renal). The medians are represented by white circles. The 25th percentile and the 75th percentile are represented by the lower edge and the upper edge of the black box, respectively. Whiskers that extend to 1.5x the interquartile range from the 25th to the 75th percentile are represented by black lines. pSOFA = pediatric Sequential Organ Failure Assessment.

Univariate Analysis of Children that Died Versus Survived

In the comparison of the pediatric patients who died versus the pediatric patients who survived while in the ICU, both the average maximum subscores and the average subscores were calculated for the two groups. The average maximum subscores were used for further analysis instead of the average subscores and total pSOFA scores. To assess the differences between the average maximum subscores of death and survival cases, univariate analysis was first performed using *t*-tests. All of the differences in subscores were statistically significant between the two groups. The average maximum respiratory subscores gave the most statistically significant difference between the two groups (p = 4.01E-22). The difference between the average maximum coagulation scores had a p-value of 7.97E-08. The p-values of the renal, hepatic, and cardiovascular subscores were 8.16E-06, 2.55E-06, and 29.91E-07, respectively.

Multivariate Analysis of Children that Died Versus Survived

Length of stay and all five of the organ system subscores were positively correlated with pediatric patients who died. Logistic regression was then performed using average maximums to compare each subscore. The renal and cardiovascular subscores were not found to be a statistically significant predictor of death in children. Of the respiratory, hepatic, renal, and coagulation subscores, the respiratory subscore was determined to be the most significant predictor of death in children with an odds ratio of 1.71 (p = .017, 95% CI [1.10, 2.66]). The hepatic subscore had an odds ratio of 1.38 (p = .023, 95% CI [1.04, 1.81]), and the coagulation subscore had an odds ratio of 1.34 (p =

.038, 95% CI [1.02, 1.74]).

Types of Microbes

Based on the microbes detected in the patient's culture, each case was categorized into one of the following groups: gram-positive bacteria, gram-negative bacteria, yeast, fungus, virus, mixed single, mixed multiple and suspected/undefined. Table 5 shows the results of this categorization. The most common bacteria were *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The gram-positive *Staphylococcus aureus* was detected in 7.94% (64/806) of cases, and the gram-negative *Pseudomonas aeruginosa* was detected in 8.31% (67/806) of cases. *Enterococcus faecalis* and *Staphylococcus epidermidis* were the second and third most common gram-positive bacteria detected in 3.72% (30/806) and 1.99% (16/806) of cases, respectively. *Klebsiella pneumoniae* and *Escherichia coli* were the second and third most common gram-negative bacteria detected in 3.60% (29/806) and 3.35% (27/806) of cases, respectively. *Candida albicans* was the most common yeast found in cases and comprised 3.85% (31/806) of cases. Fungi and viruses were much more rare compared with bacteria and yeast. *Penicillium* species, *Scedosporium apiospermum*, cytomegalovirus, and respiratory syncytial virus were each detected in one case. Of the 806 cases that were included in this study, 478 cases did not have a confirmed microbe, and they were included in the suspected/undefined category.

Table 5

Most Common Organisms Detected

Type of Infection	Organism	Number of Patients Infected	Percentage of Total Infected
Gram-Positive	*Staphylococcus aureus*	64	7.94
Gram-Positive	*Enterococcus faecalis*	30	3.72
Gram-Positive	*Staphylococcus epidermidis*	16	1.99
Gram-Negative	*Pseudomonas aeruginosa*	67	8.31
Gram-Negative	*Klebsiella pneumoniae*	29	3.60
Gram-Negative	*Escherichia coli*	27	3.35
Yeast	*Candida albicans*	31	3.85
Yeast	*Candida parapsilosis*	10	1.24
Yeast	*Candida krusei*	4	0.50
Fungus	*Aureobasidium species*	1	0.12
Fungus	*Penicillium species*	1	0.12
Fungus	*Scedosporium apiospermum*	1	0.12
Virus	Cytomegalovirus	1	0.12
Virus	Respiratory syncytial virus	1	0.12

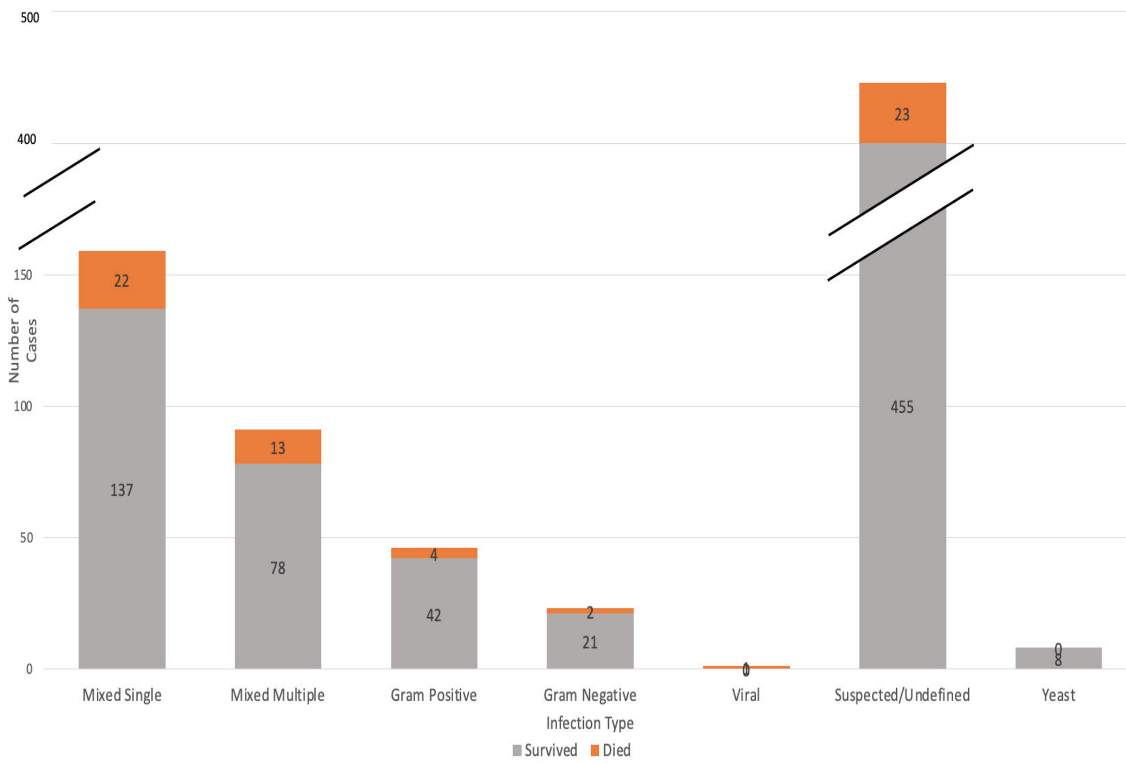
Note. This table shows the total number of patients and the percentage of the total cohort that were confirmed to be infected by the three most common microbes based on type. $N = 806$.

Microbe Type Related to Death

Figure 16 shows the total number of cases that survived and died for each infection type. For a single gram-positive bacteria detected, 8.70% (4/46) of cases died. For a single gram-negative bacteria detected, 8.70% (2/23) of cases died. For mixed cultures, including mixed single and mixed multiple, 14% (35/250) of cases died. Of the 478 of cases that were undefined, 4.81% (23/478) died. Yeast had none of its eight cases die. In the case of a single virus detected, the patient died.

Figure 16

Total Patients Categorized by Type of Infection



Note. This plot shows the total number of patients categorized by the type of infection that was established during the ICU stay. Gray bars represent patients who survived during their ICU stay; orange bars represent patients who died during their ICU stay. Mixed multiple = mixed flora of two or more organism classifications; mixed single = mixed flora of a single organism classification; suspected/undefined infection = no microbe type. *N* = 806.

Statistical Analysis of Microbe Types

Single and multivariate analyses were performed to further assess the correlation between infection type and meeting Sepsis-3 criteria. Table 1 shows the relationship between infection type and Sepsis-3. Univariate analysis indicated a statistically significant difference between the number of mixed single, mixed multiple, and suspected/undefined cases for Sepsis-3 and Sepsis-2. Multivariate analysis showed that there was no significant predictability between any type of infection and meeting Sepsis-3 criteria.

Table 3 shows the relationship between infection type and Sepsis-3 in the pediatric population. Univariate analysis incidcated a statistically significant difference between the number of mixed single, mixed multiple, yeast, and suspected/undefined cases for Sepsis-3 and Sepsis-2. Multivariate analysis showed that there was no significant predictability between any type of infection and meeting Sepsis-3 criteria in children.

These statistical tests were repeated to assess the relationship between infection type and death during ICU stay (Table 2). Univariate analysis found that there was a significant difference between the number of mixed single, mixed multiple, yeast, and suspected/undefined cases for patients who died compared with patients who survived. Multivariate analysis was not performed on yeast because the number of deaths for yeast was zero. None of the other three infection types were shown to be predictive of outcome based on multivariate analysis.

Table 4 shows the relationship between infection type and death in children. Univariate analysis found that there was a significant difference between the number of mixed multiple, yeast, and suspected/undefined cases for patients who died compared with patients who survived. Multivariate analysis was not performed on yeast because the number of deaths for yeast was zero. None of the other three infection types were shown to be predictive of outcome based on multivariate analysis.

DISCUSSION

The Sepsis-3 definition of sepsis has established and validated the SOFA score as the criteria for determining organ dysfunction because of its ability to better predict outcomes in adult populations. These guidelines previously failed to consider pediatric patients and the unique manifestations of organ dysfunction in different ages of children. Matics and Sanchez-Pinto (2017) were the first to adapt the SOFA tool to pediatric patients, known as the pSOFA, to better coincide with more updated and accurate definitions of sepsis. The purpose of this study was to validate the use of Sepsis-3 and pSOFA in children and to further assess the relationship of the disease to patient outcome in pediatric populations.

Sepsis-3 Criteria and its Relationship to Outcome in Pediatric Patients

The results of this study showed that in pediatric patients the updated Sepsis-3 definition, which includes a component of organ dysfunction in the diagnosis, was clearly associated with worse outcomes when compared with pediatric patients who met the previous Sepsis-2 definition. This study is consistent with previous findings in adult populations and highlights the significance of incorporating organ dysfunction into the sepsis definition.

In the pediatric patients with an elevated subscore in any of the pSOFA categories, including renal, respiratory, coagulatory, or hepatic, the patient's outcome was more likely to be associated with death according to multivariate analysis. More specifically, an elevated respiratory subscore was shown to be most associated with death in pediatric patients compared with the other covariates. An increase in renal and cardiovascular pSOFA subscores did not significantly show a correlation to death in pediatric patients according to multivariate analysis. This is significant because the study showed that the Sepsis-3 definition in children can indicate a more severe disease state to providers and can give more insight into morbidity and mortality.

Type of Microbe and Outcome in Pediatric Patients

The results of this study also found that the type of infection detected was not a good predictor of outcome in pediatric patients. In the cases that were observed in this study, the most common microbes were *Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa, Klebsiella pneumonia, Escherichia coli,* and *Candida albicans*. Nevertheless, this study helped showcase common infections in pediatric septic patients and might allow for more targeted therapeutics. As a result, more studies should be done in order to assess the relationship between specific microbes and deaths in pediatric patients.

Limitations and Future Studies

One limitation of this study is that only patients were evaluated who were diagnosed with sepsis under the previous Sepsis-2 definition. No assessment was made of critically ill pediatric patients who did not meet Sepsis-2 and their relationship to meeting

Sepsis-3 criteria. Future studies should look to include the totality of critically ill patients to help evaluate Sepsis-3 criteria in pediatric patients.

Another limitation of this study is the failure to consider patients who were experiencing neurological dysfunction that could have influenced the use of Sepsis-3. By nature of the ICUs that were used in this study, all of the patients who were included were assumed to have normal Glasgow Coma Scores. The validity of this test was not evaluated in respect to diagnosing sepsis according to the updated definition. In addition, no conclusions were formed about neurological dysfunction and its relationship to patient outcome. These are areas that should be investigated in future studies.

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CURRICULUM VITAE

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