SERUM ALBUMIN TREND AS OUTCOME PREDICTOR

IN ADULT ICU PATIENTS WITH SEPSIS

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DOCTOR OF PHILOSOPHY

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SERUM ALBUMIN TREND AS OUTCOME PREDICTOR
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ABSTRACT

Patients admitted to the hospital with sepsis are eight times more likely to die than patients with other diagnoses. Sepsis is associated with an intense and persistent stress response that can become dysfunctional, resulting in disease, organ failure, and death. Allostasis theory has emerged as an influential theory in describing the biological response to stress, focusing on individual differences. There is no diagnostic test that clearly identifies the presence of the dysregulated host response that is central to sepsis.

Serum albumin is a protein produced by the liver that has been identified by researchers as a possible predictor of mortality in a number of critically ill patient populations. However, these studies primarily focus on the levels on admission, neglecting the clinically significant decrease that occurs subsequently.

The purpose of this retrospective, correlational study was to examine the relationship between the trend of serum albumin over time and mortality in adults admitted to the ICU at a Midwestern regional medical center with sepsis. Serum albumin trend, admission, average, maximum, and minimum albumin levels were evaluated for association and predictive ability to each of the outcomes (mortality, length of stay, ICU length of stay, ventilator days, progression to a state of chronic critical illness, vasopressor use, presence of ICU delirium, and readmission to the ICU).

Low serum albumin trend, low admission albumin level, and low minimum albumin level significantly predicted mortality while controlling for age. The combination of serum albumin trend and minimum albumin level significantly predicted length of stay (LOS). Mortality was a moderator of the relationship between serum albumin trend and LOS. The combination of serum albumin trend and minimum albumin level significantly predicted ICU LOS. Minimum albumin level was a significant predictor of ventilator days. Minimum albumin was identified as the best predictor of progression to a state of chronic critical illness while controlling for mortality. Minimum albumin was found to be the best predictor of vasopressor use while controlling for mortality. There were no significant predictors of ICU delirium, but there was a relationship between mortality and ICU delirium. Minimum albumin was the best predictor of ICU readmission.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Nursing and Health Studies, have examined a dissertation titled "Serum Albumin as Outcome Predictor in Adult ICU Patients with Sepsis," presented by Heather Kendall, candidate for the Doctor of Philosophy degree, and hereby certify that in their opinion it is worth of acceptance.

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CHAPTER 1

INTRODUCTION AND PURPOSE

The Healthcare Cost and Utilization Project (HCUP) estimates that nearly 1.3 million patients were treated in United States hospitals for sepsis in 2013. Sepsis was identified as the most expensive condition treated, accounting for $23.7 billion and 6.2% of total hospitalization costs (Torio & Moore, 2016). The Agency for Healthcare Research and Quality (AHRQ) estimates the mortality rate for sepsis at 16% but others have estimated as high as 29.9% (Elixhauser, Friedman, & Stranges, 2011; Hall, Williams, DeFrances, & Golosinskiy, 2011). The National Center for Health Statistics (NCHS) states that patients admitted to the hospital with sepsis are eight times more likely to die in the hospital when compared with other diagnoses. According to the NCHS, the length of stay is 75% longer for those hospitalized with sepsis (Hall et al., 2011). Sepsis was the most expensive reason for hospitalization in 2009, costing $15.4 billion (Elixhauser et al., 2011). According to the NCHS, the length of stay is 75% longer for those hospitalized with sepsis (Hall et al., 2011). While sepsis cases have increased, mortality rates have declined over time most likely as a result of utilization of bundled care models proposed by the Surviving Sepsis Campaign (Gaieski, Edwards, Kallan, & Carr, 2013; Lagu et al., 2012). However, patients who survive sepsis tend to have sequelae such as multiple organ dysfunction/failure, myopathy, mood disorders and an increased risk of death in the months and years following the sepsis event (Angus & van der Poll, 2013).

Sepsis

Historically, definitions related to sepsis syndromes reflected a flawed understanding of the related pathophysiology (Singer et al., 2016). A great deal of emphasis was placed on

the overly sensitive and non-specific symptoms of systemic inflammatory response syndrome (SIRS) which are present in many patients without sepsis and are often not seen in patients with sepsis (Kleinpell, Schorr, & Balk, 2016). The diagnosis of sepsis was dependent upon the presence of two or more SIRS criteria, which are listed in Table 1 (Singer et al., 2016).

Table 1. SIRS Criteria.

Temperature <36^{o} C or >38^{o}C
Heart rate >90 beats per minute
Respiratory Rate >20 breaths per minute or PaCO2 <32 mmHg
White blood cell count <4000/mm^{3} or >12,000/mm^{3} or >10% immature bands

In addition, the definitions indicated that sepsis occurs on a continuum starting with an infection that leads to sepsis and severe sepsis, which may progress to septic shock (Singer et al., 2016). The Third International Consensus Definitions Task Force for Sepsis and Septic Shock (Sepsis-3) convened in 2014 to provide updated definitions which eliminate SIRS criteria and emphasize the dysfunctional host response to infection (Singer et al., 2016). Table 2 provides a comparison between the 2001 and new definitions published in 2016 (Levy et al., 2003; Singer et al., 2016). The term severe sepsis was found to be redundant and the Task Force recommended its elimination.

Table 2. Sepsis definitions.

Syndrome	2001 Definitions	2016 Definitions
Sepsis	A clinical syndrome characterized by a systemic inflammatory response to infection	Life-threatening organ dysfunction caused by a dysregulated host response to infection
Severe Sepsis	Sepsis plus the presence of organ dysfunction	Term eliminated from definitions
Septic Shock	Sepsis plus persistent hypotension despite adequate fluid resuscitation	A subset of sepsis in which circulatory, cellular, and metabolic abnormalities have the potential to increase mortality

Pathophysiology of Sepsis

The clinical manifestations of sepsis are a reflection of a systemic, damaging host response (Dellinger et al., 2013). The host response involves a widespread inflammatory response that is triggered by the infection but dependent upon individual differences (Angus & van der Poll, 2013). Ideally pro-inflammatory and anti-inflammatory reactions balance to destroy the pathogen while promoting tissue repair (Cawcutt & Peters, 2014). The release of inflammatory mediators such as cytokines, chemokines, prostaglandins, and histamines trigger responses including vasodilation, capillary permeability, and movement of neutrophils into tissues and local activation of the coagulation cascade (Baudouin, 2007). Tissue factor (TF), also known as thromboplastin, is a glycoprotein that is released by cells in response to the action of cytokines. The result of TF expression is coagulation, which occurs systemically and results in the formation of intravascular fibrin. This deposition of fibrin results in localized thrombosis and widespread microvascular thrombosis which occludes the vessels and interrupts tissue and organ perfusion. The previously mentioned processes

contribute to cellular hypoxia, cellular death, and organ dysfunction (Duran-Bedolla et al., 2014). Additionally, cell death results in a loss of barrier function that contributes to interstitial and organ edema (Angus & van der Poll, 2013) exacerbated by vascular permeability, which allows for the accumulation of protein-rich fluid (Baudouin, 2007; Duran-Bedolla et al., 2014). Tissue oxygenation is further inhibited by oxidative stress which results in mitochondrial dysfunction causing impaired cellular oxygen utilization (Angus & van der Poll, 2013; Cawcutt & Peters, 2014; Duran-Bedolla et al., 2014). Figure 1 is a depiction of the dysfunctional host response seen in sepsis (Angus & van der Poll, 2013; Baudouin, 2007; Cawcutt & Peters, 2014; Dellinger et al., 2013; Duran-Bedolla et al., 2014).

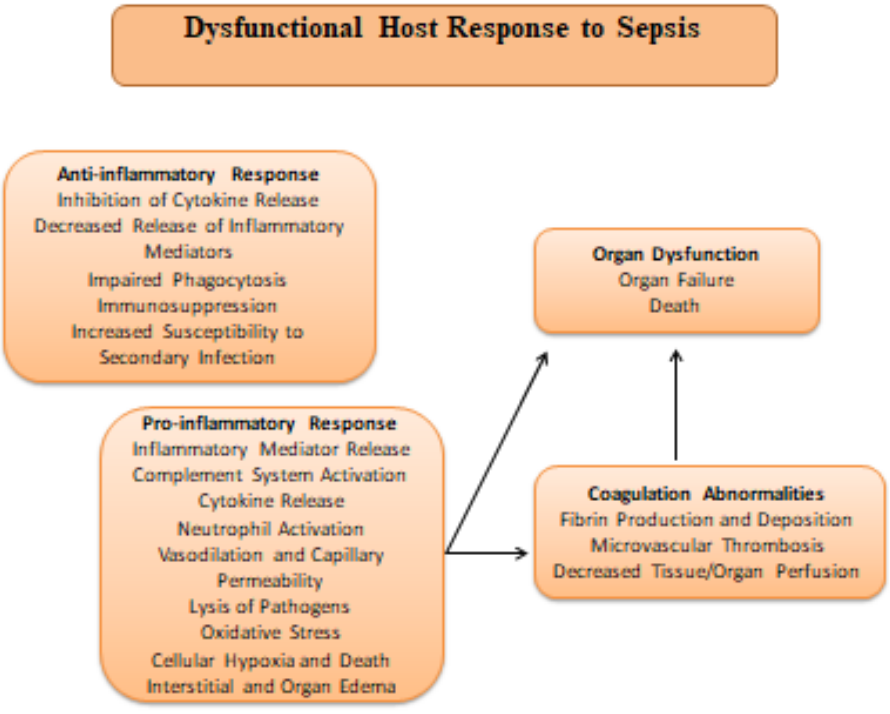

Figure 1. The Dysfunctional Host Response to Sepsis.

There is no clinical test or exam that can clearly identify the presence of the dysregulated host response that is central to the pathophysiology of sepsis (Singer et al., 2016). Therefore, the diagnosis of sepsis continues to hinge on clinical identification of symptoms that indicate infection and consequences of the damaging host response, namely organ dysfunction (Singer et al., 2016). Early recognition of patients who are at risk of death or unfavorable outcomes from sepsis could help to improve care and decrease costs.

Purpose

While researchers have established an association between admission serum albumin level and negative outcomes in critically ill populations, little has been done to examine the clinically significant decrease in serum albumin levels that occurs in the days after admission. Decreases in serum albumin are hypothesized to be associated with the intense stress response that is seen during critical illness, a response that is quite pronounced during sepsis. The purpose of this correlational research study is to examine the relationship between the trend of serum albumin and negative outcomes (in-hospital mortality, ICU length of stay, ventilator days, progression to a state of chronic critical illness, use of vasopressors, ICU delirium, and readmission to the ICU) in adults with sepsis admitted to an intensive care unit.

Specific Aims/Hypotheses

Trends identified by serial measurement of serum albumin may prove to be a better biomarker of allostasis and allostatic load in critically ill patient populations than a single albumin measure. Therefore, the aims of this research are: (a) to test 8 hypotheses concerning the trend of serum albumin and negative outcomes in adult patients admitted to the ICU with

sepsis using medical record data, (b) to propose a theoretical explanation for the correlation between trend of serum albumin and negative outcomes in adult ICU patients with sepsis, and (c) to identify future directions for research. The following hypotheses will be tested:

1. Negative trend in serum albumin measurement over time will be associated with increased mortality in patients admitted to the ICU with sepsis.
2. Negative trend in serum albumin measurement over time will be associated with increased hospital length of stay in patients admitted to the ICU with sepsis.
3. Negative trend in serum albumin measurement over time will be associated with increased ICU length of stay in patients admitted to the ICU with sepsis.
4. Negative trend in serum albumin measurement over time will be associated with increased ventilator days in patients admitted to the ICU with sepsis.
5. Negative trend in serum albumin measurement over time will be associated with increased incidence in progression to a state of chronic critical illness in patients admitted to the ICU with sepsis.
6. Negative trend in serum albumin measurement over time will be associated with increased use of vasopressors in patients admitted to the ICU with sepsis.
7. Negative trend in serum albumin measurement over time will be associated with increased incidence of ICU delirium in patients admitted to the ICU with sepsis.
8. Negative trend in serum albumin measurement over time will be associated with increased readmission to the ICU in patients admitted to the ICU with sepsis.

CHAPTER 2

REVIEW OF LITERATURE AND CONCEPTUAL FRAMEWORK

Review of the Literature

Albumin

Albumin is the most abundant plasma protein, with normal serum levels between 3.5 and 5 g/dL (Taverna, Marie, Mira, & Guidet, 2013). Albumin, which is produced by the liver, is the primary factor in the maintenance of colloid osmotic pressure. Ions such as calcium, zinc and copper are transported in the circulation by albumin. Albumin binds to molecules and drugs, having a significant effect on the action and half-life of these drugs. Toxic molecules, such as bilirubin, are carried to the liver by albumin for excretion (Merlot, Kalinowski, & Richardson, 2014).

Recognition of serum albumin as a predictor of morbidity and mortality began with research conducted as part of the National Veterans Affairs (VA) Surgical Risk Study (Gibbs et al., 1999). This prospective, observational study followed 54,215 patients with all major surgical procedures from 44 tertiary VA centers for 30 days postoperatively to evaluate serum albumin as a predictor of morbidity and mortality. Variables included in the study were preoperative serum albumin level and 61 other variables including 14 other laboratory values, patient characteristics such as age, sex, tobacco and alcohol use, functional status, weight loss, and comorbidities. Serum albumin level was the strongest predictor of morbidity and mortality and researchers concluded that serum albumin was a better predictor of surgical outcomes than many other variables. This large study served as a foundation for further research of serum albumin levels and mortality in other patient populations.

Surgical populations. Low serum albumin has been associated with negative postoperative outcomes in specific surgical cohorts. Turner, Ilano, Zhu, Johnson and Hanna (2011) found that, in a sample of 340 critically ill surgical patients, a lower preoperative serum albumin level was associated with increased postoperative mortality. Subjects in this study who had a preoperative serum albumin level of $\leq$2.5 g/dL demonstrated 36.8% mortality. A retrospective review of 1,320 radical cystectomy cases revealed that a low preoperative serum albumin (<4.0 g/dL) was associated with increased neurologic deficits, wound complications, and increased 90 day mortality. In addition, the researchers found that a decrease in serum albumin of 1.0 g/dL tripled the odds of death (Garg et al., 2014).

Several studies revealed associations between low serum albumin and undesirable outcomes in patients who underwent surgery for gastrointestinal cancer. Gohil, Rishi and Tan (2014) found that a lower preoperative serum albumin level was associated with an increased length of stay in patients undergoing colorectal cancer surgery. These researchers identified a serum albumin level of less than 3.45 g/dL to have the best discriminatory value. A study of 641 patients with gastrointestinal malignancy demonstrated statistically significant associations between a low preoperative serum albumin level and complications (infectious and noninfectious) as well as increased 30 day mortality (Lin et al., 2011). The researchers reported that serum albumin level below 3.2 g/dL increased the risk of postoperative complications by three times. In addition, infectious complications increased fivefold and mortality risk was twice as high as subjects above the threshold. Lai et al. (2011) found that low serum albumin was associated with higher rates of postoperative wound, pulmonary, urinary and anastomosis complications. Statistically significant associations were also found with 30 day postoperative mortality. A 15% reduction in serum

albumin within the first two postoperative days was associated with postoperative complications in patients following colorectal resection (Ge et al., 2017). Postoperative day one serum albumin level was associated with risk of complications, including pancreatic fistula, and length of stay in a study of 446 patients undergoing pancreaticoduodenectomy (Relles et al., 2013).

Cardiovascular populations. Researchers have found relationships between serum albumin levels and outcomes in cardiovascular patient cohorts. Low preoperative serum albumin level (<3.0 g/dL) was associated with increased mortality and length of stay in patients following cardiac surgery (Koertzen, Punjabi, & Lockwood, 2013). In patients undergoing coronary artery bypass grafting, body mass index, a known risk factor for undesired outcomes following cardiac surgery, was found to be less predictive than low serum albumin level (Bhamidipati et al., 2011; Montazerghaem, Safaie, & Samiei Nezhad, 2014). Montazerghaem et al. (2014) found associations between low serum albumin and postoperative mortality as well as reoperation due to bleeding and prolonged mechanical ventilation. Bhamidipati et al. found that higher serum albumin levels reduced the odds of death, complication rates and intra-aortic balloon pump use. Ejection fraction was also lower in heart failure patients with low serum albumin. Baranyi & Rothenhäusler (2012) found that lower serum albumin level at 24 and 48 hour postoperatively was associated with delirium following cardiopulmonary bypass. Preoperative serum albumin level was associated with mortality in patients undergoing left ventricular assist device implantation and postoperative mortality decreased by 4.8% for each 0.1 g/dl increase in preoperative serum albumin concentration (Kato et al., 2013). Serum albumin levels were associated with an increased

incidence of major adverse cardiac events and all-cause mortality in patients undergoing percutaneous coronary intervention (Wada et al., 2017).

Uthamalingam et al. (2010) found that patients with acutely decompensated heart failure who had serum albumin levels below 3.4 g/dL had an increased risk of death at one year. Outcomes such as symptom classification, leg edema, renal function, and brain natriuretic peptide (BNP) levels were worsened in the presence of low serum albumin level. Patients with heart failure with preserved ejection fraction were found to have an increased risk of cardiovascular death at one year in the presence of hypoalbuminemia (Liu et al., 2012). Hartopo, Gharini and Setianto (2010) found an increase in in-hospital adverse outcomes in hypoalbuminemic patients with acute coronary syndrome.

Pulmonary populations. Researchers have examined the relationship between serum albumin and outcomes in critically ill pulmonary patient populations. Viasus et al. (2013) found that serum albumin level measured within 24 hours of admission was a significant prognostic indicator in patients admitted with community acquired pneumonia (CAP). Specifically, lower levels of serum albumin were associated with prolonged time to reach clinical stability, increased length of stay, need for ICU admission and mechanical ventilation, and 30 day mortality. Complications, including bacteremia, septic shock, empyema, cardiac events and hospital acquired infection, were also negatively associated with serum albumin level. These findings were similar to the findings of Lee et al. (2011), who found increased 28 day mortality in patients with CAP who had low serum albumin levels. Ugajin, Yamaki, Iwamura, Yagi, and Asano (2012) found the blood urea nitrogen (BUN) to serum albumin ratio to be a prognostic indicator of mortality and illness severity in

patients with CAP. Lower initial serum albumin level was associated with in-hospital mortality among patients hospitalized with aspiration pneumonia (H. Kim et al., 2018).

A study of critically ill older patients requiring mechanical ventilation found associations between low admission serum albumin level and mortality (Wi, Kim, & Peck, 2014). When combined with high BUN levels, there was a synergistic impact on mortality prediction. Serum albumin level was also found to be a useful prognostic tool in patients with H1N1 influenza infections. Low admission serum albumin level was predictive of the need for intensive respiratory or vasopressor support in this cohort (Wi et al., 2014).

Neurologic populations. Serum albumin level may be a useful tool for outcome prediction in neurological patient populations. Ramesh et al. (2011) conducted multivariate logistic regression analyses to identify variables that could significantly predict survival in neurosurgical ICU patients. Serum albumin collected within 24 hours of admission was one of six variables that were identified as independent predictors of survival. Low serum albumin level was associated with poor outcome as measured by the Modified Rankin Scale (mRS) in patients following acute ischemic stroke (Abubakar, Sabir, Ndakotsu, Imam, & Tasiu, 2013). Using a receiver operating characteristics (ROC) curve, researchers identified cutoff points for serum albumin. Serum albumin level of 1.55 g/dL had 100% sensitivity in predicting survival or 30 day case fatality. Babu et al (2013) also found an association between low admission serum albumin and mRS in patients with acute ischemic stroke and its subtypes. Alvarez-Perez, Castelo-Branco, and Alvarez-Sabin (2011) compared serum albumin levels in patients with acute ischemic stroke of cardioembolic and non-cardioembolic origin. Low levels of serum albumin were associated with increased risk of mortality and poor functional outcome, regardless of origin type. Additionally, patients with

cardioembolic stroke had lower albumin levels than patients with non-cardioembolic stroke. In the context of status epilepticus, low serum albumin, collected on first day of hospitalization and on day of status epilepticus onset, was found to be associated with refractory epileptic activity and death during hospitalization (Sutter, Grize, Fuhr, Rüegg, & Marsch, 2013).

Chen, Bao, Lu, and Xu (2014) established serum albumin as an independent predictor of unfavorable outcome, defined as death or vegetative state, in patients with traumatic brain injury. A study by Bernard et al. (2008) is the only study found in the review of literature that utilized serial measurements of serum albumin in the analysis. The results of this study indicate that, in patients with unfavorable outcome, albumin levels stayed lower for longer. The multiple logistic regression results indicated that outcome improved with each single unit increase in serum albumin.

Sepsis populations. Few studies have been conducted to evaluate the predictive ability of serum albumin level in patients with sepsis. Admission serum albumin level of less than 2.92 g/dL was associated with increased 28-day mortality in patients with severe sepsis in a prospective cohort study (Yin et al., 2016). The review of literature yielded no other studies of the association between serum albumin, as an independent measurement, and sepsis outcomes. Two studies utilized the C-Reactive Protein (CRP)/Albumin ratio in mortality prediction of septic patients. Ranzani, Zampieri, Forte, Azevedo, and Park (2013) found that the CRP/Albumin ratio measured on admission and discharge was predictive of 90 day mortality in patients with severe sepsis or septic shock. The CRP/Albumin ratio was also predictive of 180 day mortality in patients with severe sepsis or septic shock (M. H. Kim et al., 2015). While the researchers in both studies did not include serum albumin alone in the

prediction models, they found that a higher CRP/albumin ratio was associated with mortality. Larger CRP/albumin ratios were clearly a result of high CRP, low serum albumin or both. It is reasonable to suspect that serum albumin alone could have been a significant predictor in the models, had this analysis been conducted. Baseline serum albumin level was associated with mortality in a sample of 6045 ICU patients in Australia and New Zealand. While the sample population in this study was not limited to patients with sepsis, it represented a large proportion (Saline versus Albumin Fluid Evaluation Study Investigators, 2006).

Gaps in the research

Existing prediction models such as the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) are useful predictors of sepsis population outcomes but are not effective in outcome prediction in individual patients (Baudouin, 2007; Sweeney et al., 2018). In addition, they do not account for the dysregulated host response that is central to sepsis (Sweeney et al., 2018). The validity of these tools can vary based on the data collection methods and timing. In addition, the data collection process can be resource intensive and costly (Sadaka et al., 2017). Serum albumin is a low cost, readily available measure that may be a useful biomarker in outcome prediction (Lin et al., 2011). Serum albumin has not been studied independently in the prediction of outcomes in patients with sepsis, nor have studies adequately studied the utility of serial measurements of serum albumin in outcome prediction. Early recognition of patients who are at risk of death or unfavorable outcomes from sepsis could help to improve care and decrease costs. Repeated measures of serum albumin may be a novel biomarker of negative outcomes in patients with sepsis. This study could be useful in guiding future

research aimed at improving outcomes in sepsis patients through the targeted investigation of the clinically significant decreases in serum albumin levels.

Conceptual Framework of Stress during Sepsis

Homeostasis

Stress has been defined as a threat to homeostasis, a term that was first introduced by Walter B. Cannon (1932) to describe the physiological processes that maintain a steady state in an individual (Goldstein & McEwen, 2002). Homeostasis, according to Cannon, is responsible for maintaining constancy in the internal environment by producing compensatory and anticipatory adjustments that increase the likelihood of survival. Cannon was the first to describe the "fight or flight" response upon recognition that the primary mediator of homeostasis is the sympathetic nervous system (Koolhaas et al., 2011). Elements of homeostasis include pH, core temperature, blood glucose, oxygen tension, and blood pressure (Goldstein & McEwen, 2002; McEwen & Wingfield, 2003). Cannon emphasized that different insults produce the same physiologic homeostatic response (Goldstein, 2010).

General Adaptation Syndrome

Selye (1978) was the first to recognize the concept of stress-induced disease when he discovered that the stress response can cause more damage than the initial insult. Selye's research evolved from Cannon's work on homeostasis and culminated in the development of the General Adaptation Syndrome as a theoretical framework for stress research. The stress response was described as a common syndrome of non-specific physiologic reactions that are present regardless of the type of insult. The first phase of the stress response, the alarm reaction phase, involves a hormonal response within the adrenal cortex. The second phase,

the stage of resistance, is characterized by a plateau of the stress response that allows the body to compensate and restore homeostasis. The third phase, the stage of exhaustion, is characterized by a loss of the adaptive processes seen in the first two phases. The stage of exhaustion is associated with increased morbidity and mortality as the body becomes more susceptible to tissue damage (Brame & Singer, 2010). Selye was the first researcher to acknowledge that the stress response could cause disease of the cardiovascular, digestive, immune, metabolic and central nervous systems. It is intriguing that several organ systems were left unmentioned in his work, but his work certainly advanced the field of stress research beyond the relative weak knowledge and along with it, the acceptance that stress itself might be the trigger of disease.

Stress

Activation of the stress response, in most cases, is a beneficial process that helps to preserve tissue oxygenation and organ integrity (Dünser & Hasibeder, 2009). The stress response in sepsis is an important aspect of recovery but can be intense and persistent. "Stress that is prolonged, repetitive or that fails to switch off can, in itself, be detrimental" (Brame & Singer, 2010, p. S601).

Allostasis. Allostasis is the ability to adapt to stressors and maintain stability through change (Goldstein & McEwen, 2002). The term allostasis was first introduced by Sterling and Eyer in 1988 (Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002). Allostasis involves body processes that support homeostasis by responding to triggers in the environment and stressors such as illness (McEwen & Wingfield, 2003). Allostasis is a dynamic process that continually evaluates needs and adapts as necessary to support physiologic functioning in response to stress (Logan & Barksdale, 2008). Allostatic

responses may be physiologic or behavioral in nature. Allostatic processes involve interaction from the cardiovascular, metabolic, immune and central nervous systems (McEwen, 1998). The primary mediators of allostasis are the hypothalamic-pituitary-adrenal (HPA) axis, catecholamines, and cytokines. Allostatic systems are beneficial when rapidly mobilized during periods of stress and turned off quickly when the stressor has been resolved. Intense or prolonged activation of these systems can have dangerous consequences for health (McEwen & Wingfield, 2003; Papathanassoglou, Giannakopoulou, Mpouzika, Bozas, & Karabinis, 2010).

Allostatic load. Allostatic load refers to the accumulated toll of adaptation on the body's physiologic systems and is a result of a chronically activated stress response (Carlson & Chamberlain, 2005; McEwen, 1998). McEwen (1998) cites three physiological responses that cause allostatic load: frequent stress, failure to shut down the stress response, and inadequate response to stress. Two types of allostatic overload are described in allostasis theory. Type I allostatic overload occurs when energy demands exceed energy income and energy reserves. This type is typically seen in acute illness and is a protective, survival mechanism that is regulated by glucocorticoids and the HPA axis. Type II allostatic overload occurs when intake exceeds energy demands and typically occurs when poor diet and lack of exercise result from chronic life stress (McEwen & Wingfield, 2003). Higher allostatic load can cause disease and is associated with increased mortality (Beckie, 2012; Juster, McEwen, & Lupien, 2010).

Allostasis research. The MacArthur Study of Successful Aging was initiated in 1988 by the MacArthur Foundation to identify predictors of successful aging. The research, conducted by a multidisciplinary team led by John Rowe and Robert Kahn, is the most

extensive and comprehensive study of aging and also provided seminal research on allostasis (Rowe & Kahn, 1998; T. Seeman, Burton, Rowe, & McEwen, 1997) . This longitudinal, community-based study involved 1,189 subjects aged 70-79 years who were thought to be aging successfully. The objective was to examine the cumulative toll of allostasis and to develop an operational definition of allostatic load. Allostatic load was measured and scored based on 10 physiologic variables, also known as biomarkers: systolic and diastolic blood pressure, waist-hip ratio, serum high-density lipoprotein (HDL) and total cholesterol level, total glycosated hemoglobin level, serum dehydroepiandrosterone sulfate (DHEA-S), urinary cortisol, and urinary epinephrine and norepinephrine. Higher allostatic load scores were associated with poorer cognitive and physical functioning, as well as an increase in cardiovascular disease. Higher allostatic load scores were also predictive of decline in cognitive and physical functioning in subjects who were initially high functioning (T. Seeman et al., 1997). The MacArthur researchers later examined the initial allostatic load scores in relation to mortality and found that higher allostatic load scores were associated with increased 7 year all-cause mortality (T. E. Seeman, McEwen, Rowe, & Singer, 2001). Higher allostatic load scores in the same population were associated with lower socioeconomic status upon further analysis by the MacArthur researchers (T. E. Seeman et al., 2004).

The findings and developments from the MacArthur Study of Successful Aging have served as a framework for subsequent research on allostasis, leading to a refinement of the operational definition of allostatic load by that group. Some researchers were concerned that 6 of the 10 markers initially used to measure allostatic load (AL) were also markers of metabolic syndrome, also known as syndrome X, and that these specific risk factors would

not adequately represent allostatic load (Karlamangla et al., 2002). However, the AL panel was a better predictor of mortality and physical decline than only markers of the syndrome X or any individual components in the panel (Seeman et al., 2001). Other parameters have been included in that initial AL panel by other researchers, including CRP, tumor necrosis factor (TNF), fibrinogen, interleukin-6 (IL-6), serum albumin, stress neuropeptides, insulin-like growth factor-1, triglycerides, glucose, insulin, homocysteine, creatinine clearance and peak flow (Crimmins, Johnston, Hayward, & Seeman, 2003; Juster et al., 2010; Papathanassoglou et al., 2010; Schnorpfeil et al., 2003; T. E. Seeman et al., 2004). Overall, these continued additions to the panel demonstrate there is still much work to be done until a consensus of how to best evaluate allostatic load is reached. In addition, recent research implies that in a number of chronic diseases and also that lack of physical activity itself is manifested by a low grade systemic inflammation in the organism, suggesting that it is important to continue to explore the link between inflammation and allostasis (Pedersen & Febbraio, 2012).

Oxidative Stress. Oxidative stress occurs when free radicals are produced in excessive amounts or when antioxidant molecules are insufficient to neutralize free radicals (Duran-Bedolla et al., 2014). Free radicals are molecules with one or more free electrons, making them unstable and "highly reactive and toxic" (Duran-Bedolla et al., 2014, p. E61). Mitochondria within cells normally produce free radicals such as radical oxygen species (ROS) which are neutralized by internal antioxidant systems (Duran-Bedolla et al., 2014). When ROS are not completely neutralized by antioxidants within the cell, they may cause damage to intracellular proteins, DNA and lipids. Unrepaired oxidative damage can result in disease and death over time (Buffenstein, Edrey, Yang, & Mele, 2008). Sepsis is associated

with high levels of oxidative stress as a result of a profound inflammatory response which increases the production of free radicals. Cellular hypoperfusion and hypoxia during sepsis leads to the production of radical oxygen species and radical nitrogen species within cells, contributing to mitochondrial damage, multiple organ dysfunction syndrome and death (Duran-Bedolla et al., 2014).

Serum Albumin and Stress. Within the context of oxidative stress, serum albumin plays an important role. Albumin binds to substances such as fatty acids and lipoproteins, protecting them from oxidation (Merlot et al., 2014). Binding of albumin to molecules such as bilirubin and homocysteine may also help to prevent lipid peroxidation, contributing to its antioxidant properties (Taverna et al., 2013). Serum albumin has a high affinity for copper (Cu) and iron (Fe) ions, which tend to react with hydrogen peroxide to form ROS. Binding of these metal ions to albumin decreases their availability for this potentially destructive reaction (Taverna et al., 2013). Albumin is also a source of thiols, which scavenge radicals (Merlot et al., 2014). The capillary permeability seen in sepsis can contribute to low serum albumin levels through the third spacing of proteinaceous fluid into interstitial spaces and organs (Baudouin, 2007; Duran-Bedolla et al., 2014). The theoretical premise of this research is that the trend of serum albumin during sepsis is a biomarker of the intensity of the stress response.

Sepsis and Stress. Figure 2 is a model of the relationship between sepsis and stress. Individual differences in genetics, epigenetics, environment, co-morbidities, cultural, economic, and social factors affect the sepsis event and associated stress response, which includes physiological and behavioral responses. The stress response leads to allostasis. Successful allostasis leads to recovery from critical illness. The accumulated effect of

allostasis, allostatic load, can cause disease which can lead to chronic illness or death. Identification of biomarkers of allostasis and allostatic load during critical illness has proved challenging. Albumin may be a useful biomarker of the stress response, allostasis and/or allostatic load.

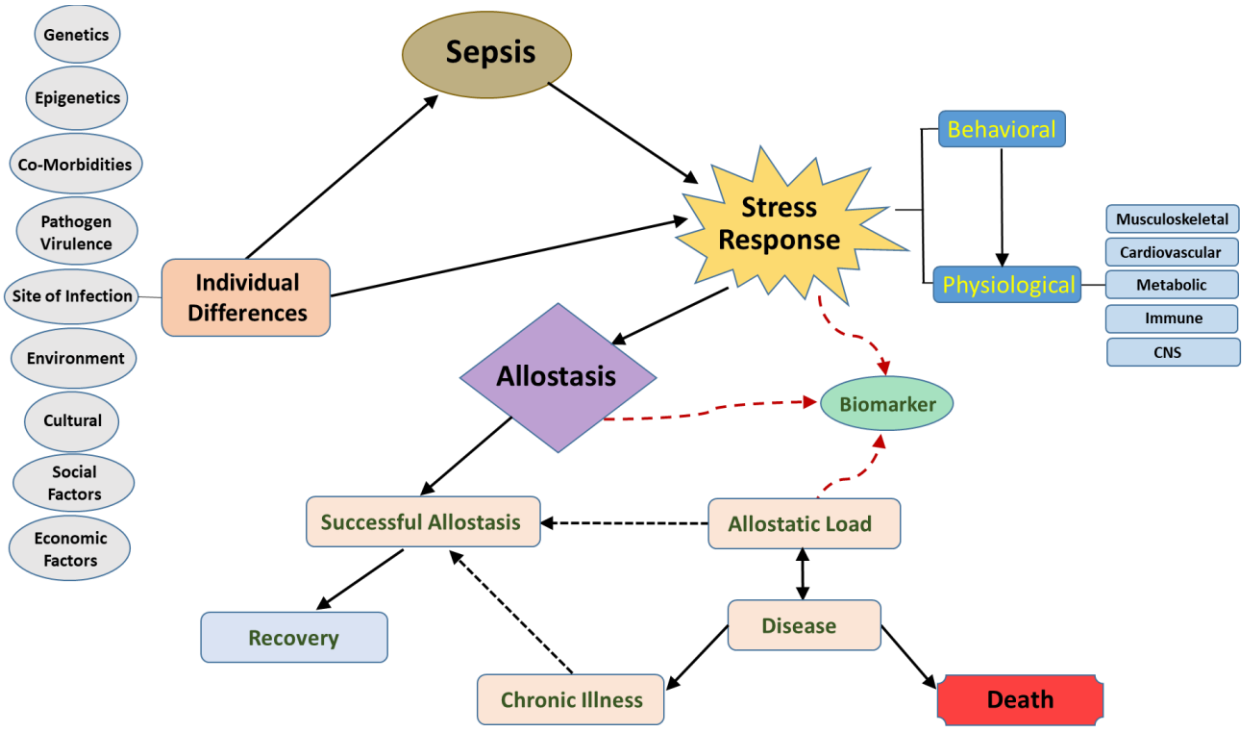

Figure 2. A Model of the Relationship between Sepsis and Stress.

CHAPTER 3

METHODS

Research Design

This study uses a retrospective, correlational design to examine the relationship between the trend of serum albumin and negative outcomes (in-hospital mortality, hospital length of stay, ICU length of stay, ventilator days, progression to a state of chronic critical illness, use of vasopressors, ICU delirium and readmission to the ICU in adults admitted to the ICU with sepsis.

Subjects and Setting

The setting for data collection is Mosaic Life Care, a non-profit acute care medical center with a total of 352 staffed in-patient beds located in St. Joseph, Missouri. This Level II trauma center serves a 21 county area in northwest Missouri, northeast Kansas, and southeast Nebraska. The 21 county service area 2015 demographics are as follows: 89.9% white, 3.4% Black, 3.4% Hispanic, 0.8% Asian/Pacific Islander, and 2.5% other. The Intensive Care Unit (ICU) is a general/combined ICU with 21 beds that is staffed with board certified intensivists. The sample consists of all adult patients admitted to the ICU between January 2014 and May 2017 with a primary sepsis diagnosis who had three or more serum albumin measurements. Table 3 provides a list of International Classification of Diseases-9 (ICD-9) and International Classification of Diseases-10 (ICD-10) diagnostic codes that were used to query the patient population by primary diagnosis. These ICD codes provide an exhaustive list of diagnoses that meet the most current sepsis definitions.

Table 3. ICD-9 and ICD-10 Sepsis Codes.

ICD-9 Code	Description	ICD-10 Code	Description
995.91	Sepsis	A021	Salmonella sepsis
995.92	Severe Sepsis	A227	Anthrax sepsis
785.52	Septic Shock	A267	Erysipelothrix sepsis
003.1	Salmonella Septicemia	A327	Listerial sepsis
020.2	Septicemic plague	A400	Sepsis due to streptococcus, group A
022.3	Anthrax septicemia	A401	Sepsis due to streptococcus, group B
038.0	Streptococcal septicemia	A403	Sepsis due to Streptococcus pneumoniae
038.10	Staphylococcal Septicemia unspecified	A408	Other streptococcal sepsis
		A409	Streptococcal sepsis, unspecified
038.11	Methicillin Susceptible Staphylococcus aureus septicemia	A4101	Sepsis due to Methicillin susceptible Staphylococcus aureus
		A4102	Sepsis due to Methicillin resistant Staphylococcus aureus
038.12	Methicillin Resistant Staphylococcus aureus septicemia	A411	Sepsis due to other specified staphylococcus
038.19	Other Staphylococcal septicemia	A412	Sepsis due to unspecified staphylococcus
		A413	Sepsis due to Hemophilus influenza
038.2	Pneumococcal septicemia	A414	Sepsis due to anaerobes
038.3	Septicemia due to anaerobes	A4150	Gram-negative sepsis, unspecified
		A4151	Sepsis due to Eschericia coli
038.40	Septicemia due to gram-negative organism unspecified	A4152	Sepsis due to Pseudomonas
		A4153	Sepsis due to Serratia
		A4159	Other Gram-negative sepsis
038.41	Septicemia due to hemophilus influenza	A4181	Sepsis due to enterococcus
		A4189	Other specified sepsis
038.42	Septicemia due to Eschericia coli	A419	Sepsis, unspecified organism
		A427	Actinomycotic sepsis
038.43	Septicemia due to pseudomonas	A5486	Gonococcal sepsis
		B377	Candidal sepsis
038.44	Septicemia due to serratia	R6520	Severe sepsis without septic shock
038.49	Other septicemia due to gram-negative organisms	R6521	Severe sepsis with septic shock
038.8	Other specified septicemias		
038.9	Unspecified septicemia		
054.5	Herpetic septicemia		

The initial sample included 1136 subjects with a primary sepsis diagnosis. A total of 559 subjects met the exclusion criteria. Exclusion criteria with frequencies are listed in Table 4.

Table 4. Exclusion Criteria.

Characteristic	Frequency n
Transfer to another acute care facility	17
Exogenous albumin administration	181
Less than 3 serum albumin measurements	361

Measures

All measures were collected retrospectively from existing electronic medical record data. Albumin level, which has a normal reference range of 3.5-5.5 mg/dL, was used to compute the predictor variables. Specimens were collected and analyzed using standard hospital procedures. The hospital laboratory is accredited by the College of American Pathologists and specimens were collected by registered nurses in the ICU before being sent to the laboratory for analysis. The Siemans Dimension Vista 500 system was used to analyze albumin levels throughout the data collection period, with daily quality controls performed in compliance with the College of American Pathologists' requirements by checking high and low values using a liquid containing a known value. All albumin measurements and collection time (in hours) were included in the analysis and used to establish the trend. Other laboratory measurement results with collection time were collected but not used in this analysis. These measurements are listed in Table 5.

Table 5. Other Laboratory Variables Collected.

White blood cell count (WBC)
C-Reactive Protein (CRP)
Lactate level
Total protein
Calcium
Sodium
Potassium
Chloride
Glucose
Total bilirubin
Direct bilirubin
Blood urea nitrogen (BUN)
Creatnine
Glomerular filtration rate
Alkaline phosphatase
Alalanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Total cholesterol
High density lipoprotein (HDL)
Low density lipoprotein (LDL)
Triglycerides

Demographic variables collected were age, gender, race, ethnicity, payor source, and primary and secondary International Classification of Diseases (ICD) codes. Attributes of the demographic variables are described in Table 6.

Table 6. Demographic Variables.

Variable	Level of Measurement	Measurement Characteristics
Age	Continuous	Reported in years Calculated by the EMR using date of birth and date of admission
Gender	Dichotomous	Reported as male or female
Race	Nominal	Reported as white, black or African American, Latin American, Native Hawaiian/Pacific Islander, Asian, Native American/Alaska Native, Multiracial, Patient Declined or other
Expected payment source	Nominal	Reported as Medicare, Medicaid, private insurance, self-pay or other
Comorbidities and Procedures	Nominal	All diagnosis related groups (DRGs) assigned to the patient were collected and coded

Dependent variables measured include mortality, hospital length of stay, ICU length of stay, ventilator days, progression to a state of chronic critical illness, vasopressor use, ICU delirium, and readmission to ICU. Table 7 provides a description of each dependent variable. Specifically, ICU delirium was classified based upon the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) tool, which was instituted in this facility in October, 2013. Clinical practice guidelines for the management of delirium in ICU patients include recommendations for routine monitoring for delirium using a standardized tool. The CAM-ICU tool is among the most valid and reliable tools for assessing delirium in ICU patients (Barr et al., 2013).

Table 7. Dependent Variables.

Variable	Level of Measurement	Measurement Characteristics
Mortality	Dichotomous (died/survived)	Collected from discharge disposition in EMR. A discharge disposition of "expired" or "hospice" indicates mortality.
Hospital length of stay	Continuous	Reported in days and calculated using hospital admission date and hospital discharge date
ICU length of stay	Continuous	Reported in days and calculated using ICU admission date and ICU discharge date
Ventilator days	Continuous	Reported in days and calculated using mechanical ventilation start date and mechanical ventilation end date
Progression to a state of chronic critical illness	Dichotomous (yes/no)	Defined as mechanical ventilator dependence for >10 days and/or admission to a long-term acute care unit following the ICU or hospital stay. Mechanical ventilator dependence for > 10 days identified from ventilator days. Patients with >10 ventilator days were coded as progressing to a state of chronic critical illness. Admission to a long-term acute care unit following ICU or hospital stay identified from the discharge disposition.
Vasopressor use	Dichotomous (yes/no)	Identified using the code for therapeutic drug class for vasopressors
Presence of ICU delirium	Dichotomous (yes/no)	Identified using CAM-ICU criteria
Readmission to ICU	Dichotomous (yes/no)	Identified using the ICD code for readmission to the ICU during a single hospital stay

Procedure

Institutional review board (IRB) approval was obtained at the University of Missouri - Kansas City and Mosaic Life Care prior to conducting the study. All data was collected

from the existing electronic medical record database. A decision support analyst used the query codes necessary to gather the data and the file was de-identified prior to being delivered to primary investigator (PI) in a password protected excel file. Data was entered into Statistical Package for the Social Sciences (SPSS) software for analysis by the PI.

Human Subjects Protection

This study does not involve the use of human subjects as defined by the Common Rule (ASH, n.d.-a). Although human subjects were not involved in this research, there is no violation of the ethical principles of respect for persons, beneficence or justice as explained in the Belmont Report (ASH, n.d.-b). Internal review board (IRB) approval was obtained from the University of Missouri – Kansas City and Mosaic Life Care. The PI was required to enter into a data use agreement with Mosaic Life Care. This agreement prohibits use of the data for purposes other than the approved research. Informed consent was not necessary from subjects due to the de-identified nature of the data. Data was delivered and stored in a password protected excel file. The data file was not shared with anyone else.

Data Analysis

Descriptive statistics for all sample variables were conducted to describe the study sample. Procedures for data analysis are outlined in Table 8. All analyses were performed using SPSS with a p value of less than .05 indicating statistical significance. The primary predictor variable, serum albumin trend, was calculated by producing a Pearson's correlation coefficient using the individual measurements and the time of specimen collection (in hours). Admission, lowest (minimum), highest (maximum), and average albumin level were also identified as possible predictors in the analysis. Each independent variable was evaluated for association with the dependent variables using either Mann-Whitney or Pearson's

correlation, depending upon the level of measurement for the dependent variable. Regression modeling was performed for each predictor that demonstrated a significant association with an outcome variable. Logistic regression was conducted for dichotomous dependent variables and linear regression was used for those that were continuous measures. An optimal prediction model was developed for each dependent variable based on level of significance and R square estimates after evaluating and excluding predictors that demonstrated multicollinearity. Demographic variables were evaluated as possible covariates and included in the models as appropriate.

Table 8. Procedures for Data Analysis.

Hypothesis	Independent Variables	Dependent Variable	Statistical Test
Negative trend in serum albumin measurement over time will be associated with increased in-hospital mortality in ICU patients with sepsis.	Serum albumin trend (Pearson's r) Average albumin level (g/dL) Admission albumin level (g/dL) Minimum albumin level (g/dL) Maximum albumin level (g/dL)	In-hospital mortality (died/survived)	Mann Whitney Logistic regression
Negative trend in serum albumin measurement over time will be associated with increased hospital length of stay in ICU patients with sepsis.	Serum albumin trend (Pearson's r) Average albumin level (g/dL) Admission albumin level (g/dL) Minimum albumin level (g/dL) Maximum albumin level (g/dL)	Hospital length of stay (days)	Pearson's correlation Linear regression Multiple regression
Negative trend in serum albumin measurement over time will be associated with	Serum albumin trend (Pearson's r) Average albumin level (g/dL)	ICU length of stay (days)	Pearson's correlation Linear regression Multiple

Hypothesis	Independent Variables	Dependent Variable	Statistical Test
increased ICU length of stay in ICU patients with sepsis.	Admission albumin level (g/dL) Minimum albumin level (g/dL) Maximum albumin level (g/dL)		regression
Negative trend in serum albumin measurement over time will be associated with increased ventilator days in ICU patients with sepsis.	Serum albumin trend (Pearson's r) Average albumin level (g/dL) Admission albumin level (g/dL) Minimum albumin level (g/dL) Maximum albumin level (g/dL)	Ventilator days (days)	Pearson's correlation Linear regression
Negative trend in serum albumin measurement over time will be associated with progression to a state of chronic critical illness in ICU patients with sepsis.	Serum albumin trend (Pearson's r) Average albumin level (g/dL) Admission albumin level (g/dL) Minimum albumin level (g/dL) Maximum albumin level (g/dL)	Progression to a state of chronic critical illness (yes/no)	Mann Whitney Logistic regression
Negative trend in serum albumin measurement over time will be associated with increased vasopressor use in ICU patients with sepsis.	Serum albumin trend (Pearson's r) Average albumin level (g/dL) Admission albumin level (g/dL) Minimum albumin level (g/dL) Maximum albumin level (g/dL)	Vasopressor use (yes/no)	Mann Whitney Logistic regression
Negative trend in serum albumin measurement over time will be associated with development of ICU delirium in ICU patients with sepsis.	Serum albumin trend (Pearson's r) Average albumin level (g/dL) Admission albumin level (g/dL) Minimum albumin level	Development of ICU delirium (yes/no)	Mann Whitney Logistic regression

Hypothesis	Independent Variables	Dependent Variable	Statistical Test
	(g/dL) Maximum albumin level (g/dL)		
Negative trend in serum albumin measurement over time will be associated with readmission to the ICU in ICU patients with sepsis.	Serum albumin trend (Pearson's r) Average albumin level (g/dL) Admission albumin level (g/dL) Minimum albumin level (g/dL) Maximum albumin level (g/dL)	Readmission to the ICU (yes/no)	Mann Whitney Logistic regression

Receiver operating characteristic (ROC) analyses were conducted for each of the albumin variables to assess suitability for mortality prediction. Optimal cutoff values were identified for each albumin variable based on maximum sensitivity and specificity. The cutoff values were then used to create new dichotomous variables in order to improve clinical application. Each of the new variables was evaluated for association with mortality using the Chi Square statistic. The dichotomous albumin variables were evaluated for multicollinearity prior to formulation of the final regression model. Low average albumin level and low maximum albumin level were found to be highly correlated with low admission albumin level and with one another. For this reason, these two variables were excluded from the final prediction model. Low admission albumin level, low minimum albumin level, and low serum albumin trend did not demonstrate multicollinearity.

CHAPTER 4

RESULTS

One hundred twenty-two of the 577 subjects in the final sample population did not survive (21.1%), which is consistent with national data cited in Chapter 1. Sample population demographic characteristics are described in Table 9. The subjects ranged in age from 19 to 98 years, split nearly even on the gender line. The racial background of the sample population was consistent with the makeup of the community population as reported by the institution to the PI.

Table 9. Sample Characteristics.

Characteristic	Mean (SD) or n (%)
Age (years)	65.6 (15.09)
Gender	
Male	286 (49.6%)
Female	291 (50.4%)
Race	
White	539 (93.4%)
Black or African American	15 (2.6%)
Latin American	4 (0.7%)
American Indian/Alaska Native	3 (0.5%)
Asian	1 (0.2%)
Other	12 (2.1%)
Patient declined	3 (0.5%)
Ethnicity	
Hispanic/Latino	13 (2.3%)
Non-Hispanic/Latino	561 (97.2%)
Declined	3 (0.5%)
Payor	
Commercial insurance	115 (19.9%)
Medicare	278 (48.2%)
Medicaid	67 (11.6%)
Accountable Care Organization (ACO)	90 (15.6%)
Medicaid pending	4 (<1%)

Characteristic	Mean (SD) or n (%)
Self-Pay	22 (3.8%)
Missing data	1 (<1%)
Primary admitting diagnosis	
Streptococcal sepsis	15 (2.6%)
Sepsis due to staphylococcus	3 (<1%)
Sepsis due to MSSA	17 (2.9%)
Sepsis due to MRSA	30 (5.2%)
Sepsis due to Streptococcus pneumoniae	8 (1.4%)
Sepsis due to anaerobes	2 (<1%)
Sepsis due to unspecified gram-negative organism	12 (2.1%)
Sepsis due to Eschericia coli	37 (6.4%)
Sepsis due to pseudomonas	4 (<1%)
Sepsis due to serratia	5 (<1%)
Other gram-negative sepsis	6 (1.0%)
Other specified sepsis	11 (1.9%)
Sepsis, unspecified organism	420 (72.8%)
Sepsis due to enterococcus	3 (<1%)
Sepsis due to candida	1 (<1%)
Severe sepsis with septic shock	3 (<1%)

Note: Abbreviations were used for methicillin resistant Staphylococcus aureus (MRSA) and methicillin-sensitive Staphylococcus aureus (MSSA).

Subjects averaged 5.7 serum albumin measurements. The minimum number of measurements for individuals was 3 and the maximum was 42. The measures ranged in value from 0.7 mg/dL to 4.5 mg/dL.

Research Question 1

What is the relationship between trend of serum albumin measurement over time and mortality in adult patients admitted to the ICU with sepsis? Each of the albumin predictor variables was found to have a significant association with the mortality on the univariate analysis and these results are described in Table 10. The serum albumin trend was more

negative and the individual albumin measures were higher in patients who survived versus those who did not.

Table 10. Univariate Analysis of Factors Associated with Mortality.

Variable	**Lived (n=455)**	**Died (n=122)**	**p value**
Serum albumin trend (Pearson's r)	-.6773	-.7967	.000
Average albumin level (g/dL)	2.3	2.1	.000
Maximum albumin level (g/dL)	2.8	2.7	.000
Admission albumin level (g/dL)	2.8	2.65	.000
Minimum albumin level (g/dL)	2.0	1.8	.000

Note: values expressed as median

Each of the albumin variables was a significant independent predictor of mortality using binary logistic regression and these results are available in Table 11. A strong negative trend in albumin over time decreased the chance of living. For each one unit increase in admission serum albumin level, the odds of living increased 100%. An increase of one unit in minimum (lowest) serum albumin resulted in a 150% increase in the odds of living.

Table 11. Results of Logistic Regression for Mortality.

Variable	B	SE	Odds ratio	p value
Serum albumin trend (Pearson's r)	.458	.232	1.6	.048
Average albumin level (g/dL)	.876	.225	2.4	.000
Maximum albumin level (g/dL)	.787	.181	2.2	.000
Admission albumin level (g/dL)		.174	2.0	.000
Minimum albumin level (g/dL)	.716	.237	2.5	.000
	.934			

The results of the ROC analysis are shown in Table 12. Values for the area under the curve (AUC) for each albumin variable were similar in the ability to predict mortality and each measure was significant with a high degree of sensitivity and specificity. In particular, minimum albumin level and serum albumin trend were highly specific for the prediction of mortality with sensitivity of .89 and .82 respectively.

Table 12. Receiver Operating Characteristic Analysis.

	Serum albumin trend	**Average albumin level**	**Maximum albumin level**	**Admission albumin level**	**Minimum albumin level**
Area under the curve (AUC)	.610	.609	.610	.605	.616
p value	.000	.000	.000	.000	.000
95% Confidence Interval	.550-.669	.552-.667	.552-.668	.548-.643	.559-.673
Optimal cut point	-.91	1.95	2.45	2.45	1.45
Sensitivity	.82	.77	.76	.72	.89
Specificity	.64	.58	.57	.57	.71

The optimal cut point was used to dichotomize each of the albumin measures. The new dichotomous predictor variables are described in Table 13.

Table 13. Dichotomous Predictor Variables.

Variable	**Variable definition**	**n (%)**
Low serum albumin trend	≤ -.91	126 (21.8%)
Low average albumin level	≤ 1.95 mg/dL	155 (26.9%)
Low maximum albumin level	≤ 2.45 mg/dL	161 (27.9%)
Low admission albumin level	≤ 2.45 mg/dL	178 (30.8%)
Low minimum albumin level	≤ 1.45 mg/dL	85 (14.7%)

Demographic variables were evaluated as possible covariates using univariate analysis. Age was the only demographic variable that showed a significant association with mortality (p=.000; r=-.19; U=20115). The median age for those who expired was 74 versus 65 for those who survived. The final model was determined to be the best fit by considering p values and R^2 estimates after excluding average albumin and maximum albumin for multicollinearity. Three predictor variables (low serum albumin trend, low admission albumin level, and low minimum albumin level) significantly predicted mortality while controlling for age. The model was significant ($\chi 2$=66.665, df=4, N=577, p=.000). The pseudo R^2 estimates indicate that between 10-17% of the variance in mortality can be predicted by the combination of variables. Each of the predictor variables were unique significant predictors of mortality.

Research Question 2

What is the relationship between trend of serum albumin measurement over time and hospital length of stay in adult patients admitted to the ICU with sepsis? The mean hospital length of stay (LOS) was 10.2 days. The serum albumin trend, average albumin, and minimum albumin level showed significant correlations with length of stay. The results of the Pearson's correlation for LOS are shown in Table 14. Serum albumin trend was positively correlated with LOS. Average and minimum albumin level were negatively correlated with LOS, indicating that as these values decrease the length of stay increases.

Table 14. Results of Pearson's Correlation for LOS.

Variable	LOS	Albumin Trend	Average Albumin	Maximum Albumin	Admission Albumin	Minimum Albumin
LOS	--	.322**	-.169**	-.020	-.073	-.243**
Albumin Trend		--	-.134**	-.219**	-.326**	-.087*
Average Albumin			--	.850**	.830**	.936**
Maximum Albumin				--	.982**	.679**
Admission Albumin					--	.666**
Minimum Albumin						--

Note: *p<.05; **p<.01; N=577

Linear regression was conducted to evaluate the predictive ability of each of the significantly correlated variables to LOS. The results of the simple linear regression models for LOS are shown in Table 15. Serum albumin trend, average albumin, and minimum albumin level were significant predictors of LOS.

Table 15. Results of Linear Regression Models Predicting Length of Stay.

Variable	F	B	Constant	R Square	p value
Serum albumin trend (Pearson's r)	66.46	4.271	12.45	.10	.000
Average albumin level (g/dL)	16.92	-2.33	15.46	.03	.000
Minimum albumin level (g/dL)	35.95	-3.51	17.02	.06	.000

Note: N=577

Post hoc analysis revealed that mortality is a moderator of the relationship between serum albumin trend and LOS. The mean LOS for patients who died is 7.6 days as compared to 10.9 days for those who survived. The mean serum albumin trend for those who expired is -.61 versus -.51 for those who lived.

Due to the presence of multicollinearity between average albumin and the other predictors, it was not included in the multiple regression models. The combination of serum albumin trend and minimum albumin level significantly predicted length of stay (F=50.67; p=000), with a moderate effect size (R^2=.15). Evaluation of the relationship between mortality and serum albumin trend revealed a significant interaction effect between the two in the prediction of LOS (F=49.07; p=.000). For this reason, the interaction was included in the final regression model. The best model was selected based on significance and R square estimates. The combination of serum albumin trend, minimum albumin level, mortality, and the interaction term was significant for the prediction of LOS (F=36.943; p=.000; R^2=.205). The final prediction model is LOS = 9.925 + (-1.071)(albumin trend) + (-3.562)(minimum albumin) + 5.130(mortality) + 2.729(interaction).

Research Question 3

What is the relationship between trend of serum albumin measurement over time and ICU length of stay in adult patients admitted to the ICU with sepsis? The mean ICU LOS was 4.16 days. Serum albumin trend, average albumin, and minimum albumin level showed significant correlations with ICU LOS. The results of the Pearson's correlation for ICU LOS are shown in Table 16. Serum albumin trend was positively correlated with ICU LOS. Average and minimum albumin level were negatively correlated with ICU LOS, indicating that as these values decrease the length of stay increases.

Table 16. Results of Pearson's Correlation for ICU LOS.

Variable	ICU LOS	Albumin Trend	Average Albumin	Maximum Albumin	Admission Albumin	Minimum Albumin
ICU LOS	--	.116**	-.188**	-.006	-.002	-.242**
Albumin Trend		--	-.134**	-.219**	-.326**	-.087*
Average Albumin			--	.850**	.830**	.936**
Maximum Albumin				--	.982**	.679**
Admission Albumin					--	.666**
Minimum Albumin						--

Note: *p<.05; **p<.01; N=577

Linear regression was conducted to evaluate the predictive ability of each of the significantly correlated variables to ICU LOS. The results of the simple linear regression models for ICU LOS are shown in Table 17. Serum albumin trend, average albumin, and minimum albumin level were significant predictors of ICU LOS.

Table 17. Results of Linear Regression Models Predicting ICU LOS.

Variable	F	B	Constant	R Square	p value
Serum albumin trend (Pearson's r)	7.82	0.856	4.616	.013	.005
Average albumin level (g/dL)	21.18	-1.45	7.43	.036	.000
Minimum albumin level (g/dL)	35.81	-1.95	7.96	.059	.000

Note: N=577

There was not a significant difference in ICU LOS between those who survived and those who did not (p=.270). The ICU LOS for those who did not survive was 4.49 days versus 4.08 days for those who survived. Therefore, mortality was not a significant moderator of the relationship between ICU LOS and serum albumin trend and there was no significant interaction effect (p=.247).

Due to multicollinearity with other predictor variables, average albumin level was not used in the multiple regression. The best model was selected using level of significance and R squared estimates. The combination of serum albumin trend and minimum albumin level significantly predicted ICU LOS (F=20.84; p=.000), with a small to medium effect size (R^2=.068). The final prediction model is ICU LOS = 8.201 + (0.706)(albumin trend) + (-1.881)(minimum albumin).

Research Question 4

What is the relationship between trend of serum albumin measurement over time and ventilator days in adult patients admitted to the ICU with sepsis? A total of 205 subjects were on the ventilator at any time during the hospitalization. The mean number of ventilator days for these subjects was 4.18 days. Minimum albumin level was the only predictor variable that had a significant correlation with ventilator days (r=-0.144; p=.039). Minimum albumin level was a significant predictor of ventilator days in the linear regression (F=4.3; p=.039), with a small effect size (R^2=.021). There were no significant covariates identified in this relationship. The final prediction model is ventilator days = 6.54 + (-1.27)(minimum albumin level).

Research Question 5

What is the relationship between trend of serum albumin measurement over time and progression to a state of chronic critical illness in adult patients admitted to the ICU with sepsis? Eighty-one of the 577 subjects progressed to a state of chronic critical illness as defined by discharged to long-term acute care hospital or greater than 10 days on the ventilator. Average albumin, maximum albumin, and minimum albumin level showed a significant association with progression to a chronic state of critical illness on the univariate analysis and these results are shown in Table 18.

Table 18. Univariate Analysis of Factors Associated with Chronic Critical Illness.

Variable	Positive (n=81)	Negative (n=496)	p value
Average albumin level (g/dL)	1.98	2.3	.000
Maximum albumin level (g/dL)	2.6	2.8	.047
Minimum albumin level (g/dL)	1.6	2.0	.000

Note: values expressed as median

Average and minimum albumin level were significant independent predictors of progression to a state of chronic critical illness using binary logistic regression and these results are available in Table 19. Lower average and minimum albumin levels increased the odds of progression to a state of chronic critical illness.

Table 19. Results of Logistic Regression Models Predicting Chronic Critical Illness.

Variable	B	SE	Odds ratio	p value
Average albumin level (g/dL)	-1.105	.267	.331	.000
Minimum albumin level (g/dL)	-1.312	.287	.269	.000

Due to the presence of multicollinearity between average and minimum albumin level, these variables cannot be used simultaneously in a prediction model. Mortality was found to have an association with the dependent variable using Chi-Square analysis and was included as a covariate in the final prediction model (χ^2=10.66; p=.001). Mortality rate for those who progressed to a state of chronic critical illness was 7.4% and was 23.4% for those who did not. Minimum albumin was identified as the best predictor of progression to a state of chronic critical illness while controlling for mortality (p=.000). The pseudo R^2 estimates indicate that between 7.1 and 12.8% of the variance in progression to a state of chronic critical illness can be predicted by minimum albumin level while controlling for mortality.

Research Question 6

What is the relationship between trend of serum albumin measurement over time and use of vasopressors in adult patients admitted to the ICU with sepsis? Vasopressors were required in 404 subjects. Average, maximum, admission, and minimum albumin levels had significant associations with vasopressor use on the univariate analysis and the results are shown in Table 20. Lower albumin levels were seen in patients who required vasopressors.

Table 20. Univariate Analysis of Factors Associated with Vasopressor Use.

Variable	Positive (n=404)	Negative (n=173)	p value
Average albumin level (g/dL)	2.18	2.43	.000
Maximum albumin level (g/dL)	2.7	2.9	.000
Admission albumin level (g/dL)	2.7	2.9	.001
Minimum albumin level (g/dL)	1.9	2.1	.000

Note: values expressed as median

Each of the associated albumin levels were significant independent predictors of vasopressor use in the binary logistic regression and these results are available in Table 21. Lower albumin levels increased the odds of vasopressor use.

Table 21. Results of Logistic Regression Models Predicting Vasopressor Use.

Variable	B	SE	Odds ratio	p value
Average albumin level (g/dL)	-1.085	.207	.338	.000
Maximum albumin level (g/dL)	-0.632	.162	.532	.000
Admission albumin level (g/dL)	-0.571	.156	.565	.000
Minimum albumin level (g/dL)	-1.161	.216	.313	.000

Mortality was found to have an association with the dependent variable using Chi-Square analysis and was included as a covariate in the final prediction model (χ^2=5.54; p=.019). Mortality for those who required vasopressors was 23.8% and 17.7% for those who did not. Minimum albumin was found to be the best predictor of vasopressor use while controlling for mortality (p=.000). The R^2 estimates indicate that 5.6-8% of the variance in vasopressor use can be predicted by minimum albumin level while controlling for mortality.

Research Question 7

What is the relationship between trend of serum albumin measurement over time and incidence of ICU delirium in adult patients admitted to the ICU with sepsis? A total of 62 subjects were coded as positive for ICU delirium as indicated by the CAM-ICU assessment. However, a large number of subjects had missing data relative to this variable (n=189). None of the albumin variables had a significant association with ICU delirium on the univariate analysis. Therefore, no predictors were identified for this variable. However, a relationship was identified between mortality and ICU delirium on Chi-Square analysis

(χ^2=6.936; p=.031). Subjects who were identified as positive for ICU delirium had a mortality rate of 33.9% while those who were negative experienced a 19% mortality rate.

Research Question 8

What is the relationship between trend of serum albumin measurement over time and readmission to the ICU in adult patients admitted to the ICU with sepsis? A total of 70 subjects were readmitted to the ICU during the hospitalization. Average and minimum albumin level were found to have significant associations with ICU readmission on the univariate analysis and those results are in Table 22. Lower average and minimum albumin levels were associated with ICU readmission.

Table 22. Univariate Analysis of Factors Associated with ICU Readmission.

Variable	**Yes (n=70)**	**No (n=507)**	**p value**
Average albumin level (g/dL)	2.04	2.28	.017
Minimum albumin level (g/dL)	1.7	2.0	.001

Note: values expressed as median

Average and minimum albumin levels were significant predictors of ICU readmission. The results of the logistic regression are in Table 23. Lower average and minimum albumin levels increased the odds of readmission to the ICU.

Table 23. Results of Logistic Regression Models Predicting ICU Readmission.

Variable	B	SE	Odds ratio	p value
Average albumin level (g/dL)	-0.662	.274	.516	.016
Minimum albumin level (g/dL)	-0.994	.294	.389	.001

Due to multicollinearity, average and minimum albumin cannot be used as predictors in the same logistic regression model. The best model was identified using significance and R^2 estimates. No significant covariates were identified. Mortality was not significantly different between those readmitted to the ICU versus those who were not. Minimum albumin was the best predictor of ICU readmission (p=.001), with pseudo R^2 estimates indicating that 1.8-3.5% of the variance in ICU readmission can be predicted using minimum albumin levels.

CHAPTER 5

DISCUSSION

This research was inspired by a clinical observation in the course of critical care nursing practice. The review of literature revealed an association between admission levels of serum albumin and outcomes in a number of patient populations. Limiting the serum albumin measurement to those taken on admission neglects the frequent significant decreases observed in clinical practice. It was hypothesized that the trend of serum albumin over time would predict outcomes in ICU patients with sepsis. Admission serum albumin was confirmed as a predictor of mortality but not for other outcomes. Serum albumin trend and/or minimum albumin level demonstrated better predictive ability than admission serum albumin in other outcomes studied.

The observed decrease in serum albumin levels in sepsis may be associated with high levels of oxidative stress and capillary leak (Duran-Bedolla et al., 2014; Merlot et al., 2014), which is consistent with the dysregulated host response central to the pathophysiology of sepsis (Angus & van der Poll, 2013). Clinical severity scoring systems such as the Acute Physiology and Chronic Health Evaluation III (APACHE III) and the Sequential Organ Failure Assessment (SOFA) are reliable predictors of mortality in groups of patients but do not account for the dysfunctional host response in individuals. These scoring systems were not designed to predict outcomes in individuals (Sweeney et al., 2018; Vincent & Moreno, 2010). The validity of these tools can also vary based on the data collection methods and timing. The data collection process can be resource intensive and costly (Sadaka et al., 2017). Albumin is a low-cost, readily available measure (Lin et al., 2011) that has important clinical applications in predicting outcomes in individual patients with sepsis.

Research Question 1

What is the relationship between trend of serum albumin measurement over time and in-hospital mortality in adult patients admitted to the ICU with sepsis? The research hypothesis was supported by the results of the analysis, which revealed significant associations between mortality and serum albumin trend, average albumin, maximum albumin, admission albumin, and minimum albumin levels. In addition, each of these variables was a significant predictor of mortality using logistic regression. The variables were dichotomized according to the optimal cutoff values identified by the ROC analysis for improved clinical application. The cutoff for admission serum albumin identified by Yin, et al. (2016) of 2.92 g/dL did not demonstrate adequate sensitivity (.395) or specificity (.254) in this sample. However, the cutoff for admission albumin level was consistent with the value of 2.5 g/dL established by the Saline versus Albumin Fluid Evaluation Study Investigators (2006), who found a 1.3 increase in the odds of death in ICU patients with baseline albumin level below the cutoff.

Serum albumin trend, admission albumin, and minimum albumin measurement were unique significant independent predictors of mortality and the combination of variables, while controlling for age, had a moderate effect size using pseudo R^2 estimates. Each of the predictor variables were unique significant predictors of mortality. The probability of living decreased significantly (70.6%) when there was a strong negative trend (<-.91) in serum albumin level over time (p=.000). The probability of living decreased by 63.4% when admission serum albumin was ≤2.45 mg/dL (p=.027). The probability of living decreased by 76.4% when serum albumin measured ≤1.45 mg/dL at any time (p=.000). The R^2 estimates

indicate that between 10-17% of the variance in mortality can be predicted by the combination of variables, improving the prediction ability over any single variable.

Serum albumin was shown to be an effective predictor of mortality. Mortality for subjects above the cutoff for the individual predictor variables was 17% universally. Mortality was 35% for subjects with serum albumin trend below the cutoff, 30% with admission albumin below the cutoff, and 41% with minimum albumin below the cutoff. Subjects who fell below the cutoff for serum albumin trend, admission albumin, and minimum albumin had a mortality rate of 60%. Subjects who were above the cutoff for all three variables had an 87.7% survival rate. The observed decrease in serum albumin levels in sepsis may be associated with high levels of oxidative stress and capillary leak (Duran-Bedolla et al., 2014; Merlot et al., 2014), which is consistent with the dysregulated host response central to the pathophysiology of sepsis that contributes to death (Angus & van der Poll, 2013).

Research Question 2

What is the relationship between trend of serum albumin measurement over time and hospital length of stay in adult patients admitted to the ICU with sepsis? Previous research has not examined the relationship between serum albumin levels and LOS in patients with sepsis. Lower baseline albumin levels were associated with increased length of stay in studies of other patient populations (Gohil et al., 2014; Koertzen et al., 2013; Relles et al., 2013; Viasus et al., 2013). Lower average albumin and minimum albumin levels were associated with increased LOS, which is consistent with the research hypothesis. However, the relationship with serum albumin trend and LOS was positive, indicating that a more negative trend in serum albumin measurements was associated with a shorter LOS. This

finding was not consistent with the hypothesized relationship. Upon further investigation, it was discovered that mortality was a moderator of the relationship between serum albumin trend and LOS. Patients who died had a shorter length of stay than those who survived. The interaction between serum albumin trend and mortality was tested and shown to be significant in the linear regression and, thus, was included in the final model. Since less negative albumin trend is associated with survival and survival is associated with longer LOS, the findings of the linear regression are logical.

Research Question 3

What is the relationship between trend of serum albumin measurement over time and ICU length of stay in adult patients admitted to the ICU with sepsis? No studies were found that used serum albumin levels to predict ICU LOS. The APACHE scoring system provides ICU length of stay equations, but is intended to provide benchmarks regarding efficiency and resource utilization, rather than prediction in individual patients (Vincent & Moreno, 2010). A systematic review of 31 prediction models found that none provided suitable prediction of long ICU LOS (Verburg et al., 2017).

The serum albumin trend showed a positive correlation with ICU LOS. This was contrary to the hypothesized relationship. While ICU LOS was shorter in patients who died than those who survived, the difference was not statistically significant. Therefore, mortality was not used as a moderator in the final prediction model. The relationship between minimum albumin level and ICU LOS was consistent with the hypothesis, indicating that a lower minimum albumin level is associated with an increase in ICU LOS. The final model supports the theorized relationship between serum albumin, sepsis, and allostatic load.

Research Question 4

What is the relationship between trend of serum albumin measurement over time and ventilator days in adult patients admitted to the ICU with sepsis? No studies were identified that used serum albumin levels to predict ventilator days. A study of 155 general ICU patients found that intensivists had limited accuracy in predicting duration of mechanical ventilation using clinical judgement and the researchers concluded that an objective tool for this purpose would be useful (Figueroa-Casas, Connery, Montoya, Dwivedi, & Lee, 2013). The ability to accurately predict ventilator days has the potential to influence treatment decisions and allocation of resources. In this analysis, minimum albumin level was the only significant predictor of ventilator days but the effect size was small. This relationship, while significant, requires further study.

Research Question 5

What is the relationship between trend of serum albumin measurement over time and progression to a state of chronic critical illness in adult patients admitted to the ICU with sepsis? Chronic critical illness is associated with long term sequelae such as malnutrition, wounds, myopathy, neuropathy, cognitive impairment, psychological distress, neuroendocrine dysfunction, and infections (Bellar, Kunkler, & Burkett, 2009; Nelson, Cox, Hope, & Carson, 2010). Outcomes in patients who progress to a state of chronic critical illness are poor, with high mortality rates and poor quality of life (Schulman & Mechanick, 2012). Early recognition of patients who are at risk for this condition may help to instigate more aggressive management in order to avoid progression. No prediction models for the development of chronic critical illness were found in the review of literature. Contrary to the research hypothesis, the serum albumin trend was not a significant predictor of chronic

critical illness. Minimum albumin level was the best predictor of progression to a state of chronic critical illness while controlling for mortality. The effect size of the logistic regression model was small to moderate, using pseudo R^2 estimates. Chronic critical illness is associated with allostatic load and an increased risk of death (Bellar et al., 2009; Schulman & Mechanick, 2012). The relationship between minimum albumin level and development of chronic critical illness provides further evidence to support the conceptual framework. Further investigation of serum albumin levels in chronic critical illness is warranted by these findings. Serum albumin level should be evaluated as a possible predictor of long-term outcomes in patients who are experiencing chronic critical illness.

Research Question 6

What is the relationship between trend of serum albumin measurement over time and use of vasopressors in adult patients admitted to the ICU with sepsis? Norepinephrine is the vasopressor of choice in the treatment of hypotension in sepsis that is unresponsive to fluid volume replacement (Backer & Dorman, 2017). The dysfunctional host response seen in sepsis is associated with hypotension, vasodilation, and poor tissue perfusion (Angus & van der Poll, 2013). For this reason, the need for vasopressors may be an indication of an exaggerated host response. The analysis demonstrated an association between lower serum albumin measurements and vasopressor use. The trend of serum albumin was not associated with vasopressor use. Therefore, the hypothesis was not supported. Minimum albumin was the best predictor of vasopressor use while controlling for mortality using logistic regression. While the effect size of this model was small, the findings support the conceptual relationship between sepsis and stress. High levels of oxidative stress are associated with

vasodilation and loss of capillary integrity (Duran-Bedolla et al., 2014), increasing the likelihood for vasopressor use.

Research Question 7

What is the relationship between trend of serum albumin measurement over time and incidence of ICU delirium in adult patients admitted to the ICU with sepsis? The research hypothesis was not supported by the findings of the analysis. However, large numbers of subjects with missing data relative to ICU delirium resulted in a much smaller sample for this particular analysis. In a correlational study, patients who experienced delirium following cardiopulmonary bypass had significantly lower albumin levels measured at 24 and 48 hours postoperatively (Baranyi & Rothenhäusler, 2012). Further investigation of this phenomenon is warranted, especially given the statistically significant relationship between ICU delirium and mortality in this study.

Research Question 8

What is the relationship between trend of serum albumin measurement over time and readmission to the ICU in adult patients admitted to the ICU with sepsis? There was no relationship between serum albumin trend and readmission to the ICU, contrary to the hypothesis. Minimum albumin level was the best predictor of readmission to the ICU but the effect size was small. While readmission to the ICU is an important measure of quality of care, there are many reasons for an individual to be readmitted. The readmission rate in this sample was 12%, which is consistent with published readmission rates (J.-I. Lai et al., 2012). Patients who are readmitted to the ICU have longer length of stay and higher mortality rates (Brown, Ratcliffe, Kahn, & Halpern, 2012; Kareliusson, De Geer, & Tibblin, 2015). In this sample, there was not a difference in mortality among those patients who were readmitted to

the ICU and those who were not. There, however, was a significant difference in LOS and ICU LOS between the groups. Patients who were readmitted to the ICU averaged a 4 day increase in LOS and 3 day increase in ICU LOS. Given the relationship between length of stay and cost of hospitalization, the ability to predict of this phenomenon could prove useful. Patients who are at high risk for readmission should be evaluated carefully prior to discharge and monitored closely following as a means of risk reduction (J.-I. Lai et al., 2012).

Limitations

The correlational study design using retrospective data is a limitation of this study, limiting conclusions to that of association. The next step is to conduct a prospective cohort study in which patients could be tracked throughout the hospitalization, providing consistency regarding the timing and frequency of measurement. Due to the homogeneity of demographics of the available population and the use of a single facility to obtain data, generalizability of results is limited. A study using a larger sample size at multiple facilities that provides nationally representative demographic characteristics should provide better generalizability of results.

The transition from ICD-9 to ICD-10 in 2015 may have created differences in coding of diagnoses. There is, however, a clear crosswalk that aligns ICD-9 to ICD-10 codes. The difficulty in defining sepsis populations is a limitation that many researchers face (Seymour CW, Liu VX, Iwashyna TJ, & et al, 2016) and the method used to identify sample populations can create variability (Gaieski et al., 2013). The utilization of ICD codes for identification of retrospective sample populations, as done in this study, has been shown to be highly sensitive (Gaieski et al., 2013). Recent changes in defining sepsis may have also impacted the subject pool. This factor was mitigated by using an exhaustive list of sepsis

diagnostic categories that meet the current definition of sepsis. As studies are conducted in the future, the population will be coded using only ICD-10.

It is possible that excluding patients with less than 3 serum albumin measurements may have had an influence on the outcomes. It is difficult to know what impact the individual albumin measures may have had on mortality in this group of patients. It is reasonable to conclude that patients who had less than three serum albumin measurements had a shorter length of stay and/or higher mortality rates. While it is not possible to establish a serum albumin trend with fewer than three measurements, admission and minimum albumin level should be evaluated in this group in a future study.

Clinical Implications

Hypotension, hypoxia, and impaired coagulation lead to the production of radical oxygen and nitrogen species, resulting in oxidative stress. The pro-inflammatory processes that are central to the dysfunctional host response in sepsis further contribute to oxidative stress (Duran-Bedolla et al., 2014). Oxidative stress contributes to mitochondrial damage, which results in energy depletion. This is a self-perpetuating cycle in which mitochondrial damage results in further production of radical oxygen species, exacerbating oxidative stress. This process is likely a major contributor in the development of organ failure in sepsis (Galley, 2011). Death from sepsis is most likely to be the result of multiple organ dysfunction and failure (Duran-Bedolla et al., 2014).

Human serum albumin has potent antioxidant effects, with particular affinity for radical oxygen and nitrogen species in the plasma. In addition, serum albumin may protect against vascular endothelial dysfunction by suppressing the production of certain pro-inflammatory substances. In summary, serum albumin is vital to the preservation of

intravascular homeostasis (Anraku, Chuang, Maruyama, & Otagiri, 2013). Albumin accounts for 80% plasma proteins but has relatively low intracellular concentrations. Cells may increase uptake of albumin, however, during times of increased metabolism (Merlot, Kalinowski, & Richardson, 2014). Low serum albumin levels are theorized in this research to be a result of a combination of capillary leak and oxidative stress, which are consequences of the dysfunctional pathophysiologic mechanisms seen in sepsis. Low serum albumin concentration results in a significant reduction in colloid osmotic pressure, further exacerbating the capillary leak. Increased fluid accumulation in the extravascular spaces contributes to cellular edema and organ congestion, leading to organ dysfunction and failure (Baudouin, 2007; Duran-Bedolla et al., 2014).

Clinicians are encouraged to obtain serum albumin levels on admission and track them throughout the hospitalization. Patients who are diagnosed with sepsis and have a baseline serum albumin level of 2.45 mg/dL or less may be at an increased risk of death. Serial measurements of serum albumin should be used to track the trend following admission. Patients with sepsis who are experiencing a dramatic negative trend in serum albumin measurements may be at an increased risk of death and for prolonged length of stay in the ICU and hospital. Patients whose serum albumin level drops to 1.45 mg/dL or below at any time during the hospitalization should be considered at an increased risk of death. In addition, lower serum albumin levels at any time during the hospitalization may be associated with increased length of hospital stay, length of ICU stay and time on the ventilator. They may also be more likely to require vasopressors, to be readmitted to the ICU, and to progress to a state of chronic critical illness.

Clinicians can use prognostic biomarkers in sepsis to predict outcomes, calculate risk, and stratify patients into subgroups based on pathophysiologic traits (van Engelen, Wiersinga, Scicluna, & van der Poll, 2018). Patients who are identified as at risk for negative outcomes as defined by the findings of this research should be subjected to closer monitoring and more aggressive treatment as soon as the risk is identified. In addition, supportive care such as artificial nutrition should be started early in order to decrease the risk of malnutrition and associated sequelae. When combined with other indicators, clinicians may also consider extremely low serum albumin levels as evidence of medical futility. This knowledge may assist clinicians in conversations with patients and families about end of life decisions.

Future Directions

The results of this research contribute to the body of knowledge related to prediction of outcomes in sepsis. The results confirm the utility of admission serum albumin level as a predictor of mortality, consistent with previous research. Serum albumin trend and minimum albumin level were significant predictors of outcomes in this study as well. In addition to performing a prospective multi-center study using these predictors, future research should be conducted to compare the predictive ability of the regression models identified in this study to existing prediction models. Further study is also needed to determine the optimal timing and frequency of albumin measurements.

Ultimately, the goal of this research was to identify a cost-effective, readily available predictor that could be used by clinicians to improve outcomes and reduce mortality in sepsis. After further confirmation of the predictive ability of the identified models, additional studies should be conducted to test the influence of the models in clinician

behavior in order to evaluate the efficacy of the models in instigating clinical responses that change outcomes in patients with sepsis. Serum albumin may prove useful as an indicator of the efficacy of treatments and should be evaluated as such in a future study.

Sepsis is the leading cause of death and is the most costly condition in hospitalized patients. Early recognition of those who are at risk for mortality or other negative outcomes could lead to improved care for those with sepsis.

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VITA

Heather Kendall was born on July 1, 1974 in St. Joseph, Missouri. She graduated from Savannah High School in Savannah, Missouri in 1992. She attended Missouri Western State University on an academic scholarship and was granted a Bachelor of Science in Nursing degree in 1996. She was named the outstanding graduate by the College of Professional Studies.

Mrs. Kendall practiced as a critical care nurse at Mosaic Life Care, formerly Heartland Regional Medical Center, from 1996 to 2014. She nominated for the Nurse Excellence Award in 2002 and 2007. She served as interim nurse manager for the Intensive Care Unit in 2003 and for the Emergency Department from 2004 to 2006. She served as a staff development support educator from 1998 to 2007, developing and teaching critical care classes to nurses.

Mrs. Kendall attended the University of Missouri – Kansas City from 2005 to 2007, when she was awarded a Master of Science degree in Nursing with emphasis in nursing education. She served as an adjunct clinical instructor for Missouri Western State University from 2004 to 2007. In 2008, she started working as a full-time tenure track faculty member at the rank of assistant professor. She was awarded tenure and promoted to associate professor in 2015. She became the BSN Pre-licensure Program Coordinator in 2015 and still serves in that capacity. In 2017, she was granted graduate faculty status. In 2018, she was awarded the Missouri Western State University Foundation Award for Teaching Excellence.

Mrs. Kendall presented at the annual Professional Nurse Educator Group national conference in 2008 and 2013. She presented at the Midwest Nursing Research Society annual conference in 2015. She published a paper in *Critical Care Nurse* journal in 2010.

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