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Low Albumin and Mortality

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Scholarly Project

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Dedication

To my dad, Melvin Campbell, who pushed me to think deeper and to value higher education, as he has been a role model of life long learning. His advice to "not reinvent the wheel" was taken to heart.

To my husband Jay, my biggest fan, for without his constant support I would have never finished this process. He listened to the hair-brained ideas, offered suggestions when despair had taken over my good sense and hugged me when none of that worked.

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Abstract

Sepsis is a major epidemic worldwide and is a large unmet medical need in this country. Annual costs for the treatment of sepsis are over $3.4 billion dollars, and over 1.7 million people die each year from sepsis. Effective treatment of sepsis has two major obstacles: failure to recognize the early stages of sepsis and misjudging the severity of the disease. Identifying patients who are at higher risk for mortality and morbidity related to sepsis would be beneficial in keeping the numbers of deaths down, as well as decreasing the overall cost to the hospitals, as well as to the patient.

Albumin is a significant part of the plasma proteins that are important in maintaining oncotic pressure, permeability of the microvascular structures, acid base balance and prevent platelet aggregation. The aim of this study is to investigate the correlation between admission albumin levels and mortality in patients admitted from the emergency department with the diagnosis of sepsis.

The purpose of this quantitative, descriptive, retrospective, correlational study was to examine the relationship between low admission albumin levels and mortality in patients >18 years of age admitted through the emergency department with sepsis. Low admission albumin levels were evaluated for association and predictive ability to the outcome of mortality. In addition, age, gender and ethnicity were also evaluated for association and predictive ability in relation to low admission albumin levels and mortality.

There was a statistically significant correlation between low admission albumin levels and mortality. There was no statistical significant correlation between gender and mortality in regards to low admission albumin levels. There was significant negative correlation between age and mortality in patients with low albumin levels.

Chapter One

Background and Significance of Proposed Project/Intervention

Sepsis is a major epidemic, killing over 270,000 United States (US) citizens per year and is one of the largest unmet medical needs in this country. One in three deaths in a hospital are related to sepsis (Centers for Disease Control and Prevention [CDC], 2017). Annual costs for the treatment of sepsis has increased to over $3.4 billion dollars over a two-year period, and in 2013 sepsis accounted for nearly $24 billion dollars in annual costs, making it the most costly disorder to treat in the entire United States (U.S.) healthcare system. The Healthcare Cost and Utilization Project (HCUP) and the Agency for Healthcare Research and Quality, a division of the U.S. Department of Health and Human Services, reported that although total hospital care expenses have continued as fairly constant, the cost for sepsis care rose by 19% from 2011 to 2014. This more than doubles the rate for all hospitalizations. Sepsis was responsible for 6.2% of all hospital costs across the country, at nearly $24 billion dollars in 2013 (Sepsis Alliance News, 2016).

Sepsis is the most expensive reason for hospitalization. Every day approximately $55,616, 438 is spent on sepsis care in United States hospitals daily. This cost is nearly twice the amount for other diagnoses. Patients with sepsis stay in the hospital 75% longer than other patients, making it difficult for hospitals to transfer patients out of the emergency department and into available hospital beds. Those who survive sepsis are more likely to be discharged to another place besides their home and undergo readmissions at a higher rate (Sepsis Alliance News, 2016).

Sepsis mortality rates (Moore, et al., 2016) were evaluated at the county level for the US Age adjusted mortality was found to be 59.6 deaths per 100,000 persons (95% CI: 58.9 – 60.4). Among the counties categorized as strongly clustered around the county where the studied

hospital is located, the age-related sepsis mortality rate was 93.1 deaths per 100,000 persons (95% CI: 90.5- 95.7). Counties categorized as strongly clustered were more likely to be located in the South (92.6%, $p<0.001$), had lower educational levels, larger poverty populations, more individuals without medical insurance, and higher unemployment rate. The study concluded that sepsis mortality is prevalent in the Southern U.S. and found related characteristics of lower education, income, employment, and insurance coverage (Moore, et al, 2016).

Adjusted death rates in 2016 and 2071 respectively for septicemia in similar states in the region surrounding the state studied were as demonstrated in Table 1.

Table 1. Adjusted Death Rates for Septicemia 2016-2017

	Year 2016		Year 2017	
State	Deaths per/100,000	Total # of deaths	Deaths per/100,000	Total # of deaths
Alabama	17.7	1,025	17.3	1,036
Georgia	15.1	1,565	15.2	1,611
Kentucky	18.5	979	17.1	878
Tennessee	11.9	931	12.5	989

From January through May 2018, the available data from the studied facility demonstrated a total of 114 patients admitted with sepsis, and 13 expired, making a total of 11% expired. In addition, 202 patients were admitted with the diagnosis septic shock, with 64 who expired, making a total of 32% expired. This was compared with 9% and 35%, respectively, from the entire year of 2017. Tennessee reported 931 deaths (11.9%) in 2016 and 989 deaths (12.5%) in 2017. These statistics represent a significant impact on sepsis, not only in the facility reviewed, but also in the surrounding region (National Center for Health Statistics).

Two major obstacles to effective treatment of sepsis are the failure to recognize the early stages of the disease and underestimating its severity in regards to which patients may or may not develop more severe illness. Organ dysfunction has notably been seen as a way to foretell poor

outcomes and is a recurrent route to mortality in these patients. Innovative methods to assist healthcare providers to determine risk for these patients and enable timely and proper therapeutic interventions would improve patient outcomes. Using serum biomarker for diagnosing, stratifying risk and treating acute problems such as coronary artery disease (Creatinine phosphokinase and troponin), pulmonary emboli (D-dimer) and congestive heart failure (brain natriuretic peptide) have appreciably enhanced the provider's capacity to diagnose, prioritize risk potential. A number of lab measures have been proposed for clinical use for patients with sepsis (lactate, interleukin (IL-6), C-reactive protein, procalcitonin) however, there is no sole accepted biomarker for use in patients with suspected sepsis (Shapiro et al., 2009).

Having the ability to identify patients who are at higher risk for mortality and morbidity related to sepsis would be beneficial in keeping the numbers of deaths down, as well as decreasing the overall cost to the hospitals, and subsequently to the patient. Currently, the use of lactate levels, hypotension and target organ function has been used as a predictor of outcomes for those with sepsis as a diagnosis (Rhodes, et al., 2017). In addition, scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE) or quick Sepsis Related Organ Failure (qSOFA) aid in providing healthcare providers in emergency departments and intensive care unites a mechanism to identify patients who are at higher risk for poor outcomes. The APACHE score generates a score ranging from 0-71 founded on physiologic variables, such as age, and underlying health (Goldwasser & Feldman, 1997). The aSOFA score can be done quickly at the bedside to identify patients with suspected infection with potential higher risk for poor outcomes. It evaluates three criteria, assigning points for low blood pressure (SBP$\leq$ 100 mmHg), respiratory rate $\geq$ 22 or altered mental status with Glasgow coma scale <15 (qSOFA, n.d.).

Pollak, Strong, Gribbon and Shah (1991) proposed although the APACHE II score predicts mortality in a severely ill patient, the score does not take into consideration the serum albumin level. Patients who had severe hypoalbuminemia had almost double the mortality rate of patients with normal levels (54% compared with 29%). Death rates in patients with severe hypoalbuminemia were 5.1-fold higher than what could be predicted by only the APACHE II score. The APACHE II scores did not predict well enough the outcomes for patients who had low albumin levels.

Low albumin levels can occur in a number of disease processes and are connected with an increased rate of complications during hospitalization, resulting in a subsequent prolongation of the time a patient stays in the hospital. Albumin is a transport protein of various substances, such as fatty acids, metals, hormones and exogenous drugs. One of the most important physiological roles of albumin is the maintenance of oncotic pressure inside the vascular compartments, which controls the leaking of fluid into the extravascular compartments. A concern of low albumin levels may be that certain drugs, which are usually bound to the protein, could result in higher drug levels (toxicity) or more rapid hepatic metabolism, or both. Another concern of low albumin levels is its ability to alter platelet function (Peralta & Rubery, 2018). Albumin demonstrates anticoagulation action by neutralizing coagulation factor Xa and inhibiting platelet aggregation. On the other hand, albumin can have a pro-coagulation action by inducing tissue factor (TF) production in monocytes, which can be linked with the activation of clotting (Paar, et al, 2017). While hypoalbuminemia can be caused by a variety of pathophysiological problems, should it be connected to an increase in mortality and morbidity, it could help health care providers recognize high-risk groups who may benefit from more intense

care, as in the case of sepsis, as well as nutritional support (Herrmann, Safran, Levkoff, & Minaker, 1992).

Do low admission albumin levels correlate with mortality in an individual 18 years of age or older that presents to the emergency department (ED) in Southeast Tennessee with the diagnosis of sepsis?

P: Population of Interest

Individuals 18 years of age or older who present to the ED with sepsis

I: Intervention

- Review the electronic health record for clinical factors of admission and discharge albumin level indicative of mortality.
- Assess for correlation between low admission albumin levels and mortality.
- Develop recommendations based on this correlation in regards to nutritional consults, enteral and parental nutrition, as well as exogenous albumin administration to correct albumin deficiency and decrease mortality.

C: Comparison of Interest

Items of interest include: admission albumin levels, discharge albumin levels, age, ethnicity and gender as factors of interest in correlation with mortality rate for those admitted with sepsis. Comparison of the same items of interest could be completed with those who were discharged having had the admission diagnosis of sepsis.

O: Outcome of Interest

Recognizing a clinical indicator that identifies those who are at most risk for adverse outcomes from initial assessment in order that interventions are rigorous and timely enough to prevent progression to mortality. Consideration could be also be paid to 1) patients who may

receive nutritional consults and follow up in order to provide adequate attention to low albumin levels and decrease poor outcome 2) patients who receive enteral or parenteral nutrition in response to diagnosis and low albumin levels 3) patients who receive exogenous albumin in response to low albumin levels, but not as part of resuscitation procedure.

Project Objectives

The objectives of this project are the following:

1. identify if there is a correlation between low admission albumin levels in patients admitted through the emergency department with the diagnosis of sepsis and mortality.
2. identify if there is a correlation between other variables, such as age, gender, and ethnicity and mortality in the same population of patients.

The studied acute care facility routinely admits to its ED, patients who meet the criterion and experiences situations where patients who have presented with these criterion, progress to develop adverse outcomes. By having information/research on the notable contributing factors to patient's morbidity/mortality, key players can be trained/educated on early detection and intervention to decrease the incidence.

Identify Key Stakeholders

Emergency room providers and nurses serve as the front line to assessment of patients and serve to identify those patients at risk for or who already have sepsis. Facilities have in place screening tools and nursing protocols for early identification and treatment of sepsis and septic shock. These protocols guide the healthcare provider to assessment, respond and intervene in a timely manner (Rhodes, et al., 2017). Implementation of these protocols are monitored and reported on a quarterly basis for compliance and outcomes.

Concepts and Definition of terms

Sepsis is defined as the presence of infection, either possible or recognized, along with some other indicators of infection. A toxic condition resulting from the spread of bacteria or their toxins from a focus of infection (Sepsis, n.d.).

Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or low tissue perfusion (Tedesco,Whiteman, Heuston, Swanon-Biearman, & Stephens, 2017).

Septic shock is defined as having the causal cardiovascular and cellular metabolism dysfunction overwhelming enough to significantly increase mortality (Tedesco, et al. 2017).

Mortality is defined as death, especially on a large scale as measured by the relative frequency of deaths or death rate in a certain population; in this case those with defined sepsis (Mortality, n.d.).

Morbidity is defined as the condition of having a disease or the rate of disease in a population. Morbidity can also refer to the physical or psychological state as a result of a disease, illness or injury (Morbidity, n.d.)

Albumin is defined as a simple form of protein that is water-soluble and heat coagulated. It is synthesized by the liver and is the main protein in human blood. Albumin is key to regulation of osmotic pressure. Normal range for albumin is 3.5 to 5.5 mg/dL or 35-55 g/L with variances possible, dependent on laboratories (Lyons, Whelan, Bennett, O'Riordan, & Silke, 2010).

Hypoalbuminemia is defined as an abnormally low level of albumin. Low levels can be detected in shock, malnutrition and inflammation. The range for mild hypoalbuminemia

is 2.5-3.5 mg/dL and marked hypoalbuminemia <2.5 mg/dL (Akirov, Masri-Iraqi, Atamna & Shimon, 2017).

Theoretical Framework

The theoretical framework for this scholarly project is a combination of Levine's Conservation Model (1973) and the CREATION Health Model, (n.d.). Levine's model includes four principles, of which two will be highlighted within this paper: conservation of structural integrity and conservation of energy. Three overlying, conceptual elements will be highlighted from the construct of the CREATION Health Model: rest, environment, and nutrition (Figure 1).

In the context of sepsis, the environment of the patient has had disruption in the ability to maintain structural integrity with a "resultant suspected or proven infection." (Grossman & Porth, 2014, p. 888) In an attempt at self-protection to remove harmful stimuli and begin healing, inflammation is triggered. Inflammation is the body's way of trying to conserve and adapt in order to protect itself to remove stimuli and begin healing. It is generally a positive response and is what returns structural integrity to the body environment. However, it is these same components of the inherent immune response that can cause cellular and tissue damage, leading to multiple organ failure, which is a hallmark feature of sepsis (Cohen, 2002). Sepsis triggers a response that causes the body's immune system to release of proinflammatory mediators, such as TNF-α and interleukein-1. These mediators are involved in leukocytes adhesion, local inflammation, neutrophil activation, erythropoiesis suppression, fever, tachycardia, lactic acidosis, ventilation-perfusion abnormalities and other symptoms consistent with sepsis (Grossman & Porth, 2014, p. 889).

While activated neutrophils are key in killing microorganisms, they also cause endothelium injury by releasing mediators that increase vascular permeability. Nitric oxide is

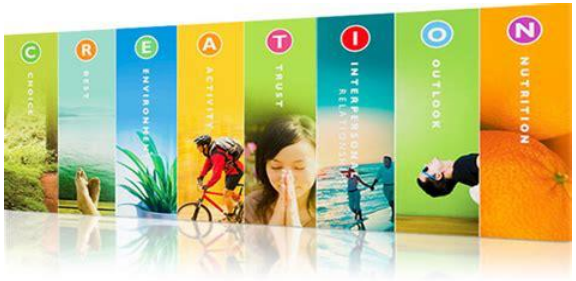
released from activated endothelial cells and is a potent vasodilator. Endothelial cells are stimulated by lipopolysaccharide on the surface of a microorganism to increase production of tissue factor, which activates coagulation (Remick, 2007).

When viewing the patient as an environment of cellular function, four characteristics can be designated as a staging system for sepsis. The first is predisposition, which would include pre-existing co-morbidities, such as diabetes, that would decrease the potential for adaptation and conservation. The second is the insult or infection that suggests that some organisms are more lethal than others. The third represents the individual's response to the infectious challenge, including progression to Systemic Inflammatory Response Syndrome (SIRS). The final one represents dysfunction and/or failure of organs or a system such as the coagulation system (Remick, 2007).

During times of physiological stress, threats to structural and energy integrity such as infection and subsequent sepsis, the body responds to the situation by releasing cortisol and adrenaline from the adrenal glands. This response causes an increase in heart rate, respiratory rate, as well as release of glucose stores to boost energy. This fight or flight response is part of the persons capacity to adapt to the environmental conditions.

There can also be an increase in energy demands from the inflammatory response demonstrated by fever and other metabolic consequences. In reaction to stress, neuroendocrine responses create a hyperglycemic state characterized by gluconeogenesis, glycogenolysis and insulin resistance. This conservation of ready fuel provides the immune system and brain with a ready source of fuel (Marik & Bellomo, 2013).

Figure 1 Theoretical Framework



Sepsis is illustrated by early substantial catabolism, loss of lean body mass (LBM), and heightening hypermetabolism leading to rapid mobilization of energy stores. Without appropriate nutrition, either via enteral or parenteral routes, patients end up with a fast developing nutritional deficit, which can worsen the outcome. During the course of sepsis, nutritional needs change and attention should focus on the stage the individual is in and what immediate nutritional needs he/she may have at that time. Screening for pre-illness malnutrition and nutritional risk at the time of admission is essential for patients with sepsis (Wischmeyer, 2017).

While rest can be viewed in the context of relaxation and sleep, in sepsis the focus of rest would be on the conservation of energy within the body environment. Rest allows the individual to function at his/her best (CREATION, 2019). Normal maintenance energy expenditure may be 25-28 kcal/kg/day, where as patients under duress related to a significant illness expend energy upwards of 50-60 kcal/kg/day (Uehara, Plank & Hill, 1999). The physiological demand of the illness itself can interfere with the patient's ability to perform activities of daily living. Interventions should focus on decreasing the physical demand on the individual through conservation of energy (rest). Mediations such as bed rest, limiting interruptions to sleep, administration of oxygen and intravenous fluids allows the body the opportunity to expend the energy in fighting the disease process.

Interventions aimed at augmenting the patient's ability to adapt to the physiological processes involved in the response to sepsis are conceptualized by the CREATION Health Model (n.d.) elements of rest, environment, and nutrition.

Chapter Two

Review of Literature

The vast majority of patients diagnosed with sepsis present initially to the emergency department (ED). Few laboratory tests for indicators of sepsis are available: C-reactive protein (CRP), lactic acid, procalcitonin, and semi quantitative IL-6 levels. Serum lactate acid levels can contribute assistance with identifying and predicting patients with severe sepsis (Malmir, Bolvardi, & Aghaee, 2014). With access to these particular indicators such as lactate levels, BP, and other diagnostic tests, are healthcare providers able to adequately identify those who are higher risk for subsequent morbidity and mortality? Specifically, in addition to lactate levels between 2 and 4 mM, what other indicators are present that would contribute to a higher incidence of mortality? Patients who are admitted with intermediate lactate levels between 2 and 4 mM are still at risk for poor outcomes in relationship to those with a normal lactate level <2mM. These outcomes can include death with 24-48 hours (Tang, et al., 2015).

One solution that has been created to aid in the early identification of patients who are at risk for mortality has been the development of multiple scoring systems, such as The Mortality in Emergency Department Sepsis (MEDS) score. The Mortality in Severe Sepsis in the Emergency Department (MISSED) score was proposed in the United Kingdom to predict mortality risk in sepsis. The MISSED score includes the variables of: albumin 27 g/L or less, international normalized ratio (INR) 1.3 or greater, and age 65 years or older. This MISSED score was comparable to the Acute Physiology and Chronic Health Evaluation II (APACHE II) score in predicting sepsis mortality. While the MISSED score can be used in the ICU setting, as well as in the emergency room setting, this scoring system includes three variables and does not focus on

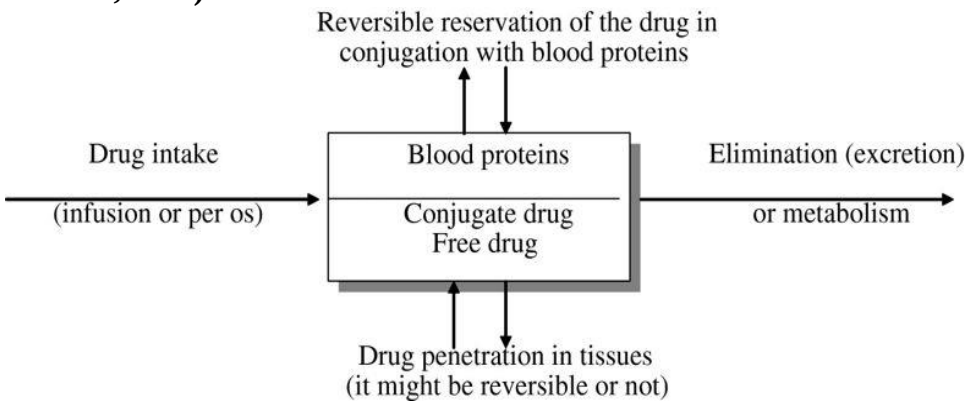
low albumin levels as a singular predictor of mortality risk in patients with sepsis (McCormick, et al., 2016).

Albumin contributes to 75-80% of the oncotic pressure of the plasma and comprises about 50% of the plasma protein content. Oncotic pressure is the osmotic pressure generated by large molecules (proteins) in a solution. This is an important force involved in fluid movement across capillaries as the body exchanges fluids between body compartments. During situations where plasma proteins are reduced, as in the case of sepsis inducing inflammation, there will be a decrease in the oncotic pressure and an increase in the filtration of fluid across the capillary membranes, resulting in an increase in fluid build up in the tissues, causing edema and loss of intravascular circulation (Peralta & Rubery, 2018).

Albumin serves as a carrier protein to many important hormones such as thyroxine, cortisol and testosterone. In addition, other compounds such as fatty acids, bilirubin and exogenous drugs are transported by the albumin molecule (Gounden & Jialal, 2018). Serum albumin's ability to transport such a wide variety of molecules is due to the numerous binding sites. Not only does albumin travel within the bloodstream, but can travel further into the lymphatic system, facilitating deep-tissue delivery of therapeutic agents, such as anti-cancer drugs (Czub, et al., 2019). The free drug concentration has curative activity, but can also have potential toxic side effects. The binding of a drug with albumin or other blood proteins is not a predictable state and can vary in many different situations, such as hypoalbuminemia. Blood concentrations of proteins are very important in adapting how clinicians adapt their dosing regimens. In a situation such as with terminal patients or other patients with poor nutrition, low albumin levels are common. Drugs with a high protein affinity will no longer have adequate binding sites and will create a toxic effect in the individual. Albumin also influences how drugs

penetrate into tissues, as well as drug elimination and metabolism. (Figure 2) Any change in this activity can change the free drug concentration and influence both therapeutic and non-therapeutic effects (Gurevich, 2013). This could be a significant negative for a patient with sepsis with low albumin levels who have been prescribed antibiotics, which rely on protein binding for metabolism for activation, as well as tissue penetration for the pharmacological action.

Figure 2. (Gurevich, 2013)



Albumin has different effects on the ability of the body to coagulate. Albumin binds with antithrombin, is associated with neutralization of coagulation factor Xa, and it has an inhibitory influence on platelet aggregation. On the other hand, albumin has been reported to exert a procoagulant action with anionic form of albumin inducing tissue factor (TF) production in monocytes, which is linked with initiation of coagulation (Paar, et. al, 2017).

Normal range reference for albumin is 3.4- 5.4 g/dL and a reduced level is found in a fifth of patients admitted with acute medical conditions. The cause of the hypoalbuminemia can be attributed to several factors. It can be due to inadequate protein intake or mal-absorption problems. It is common in conditions where there is decreased liver synthesis, such as cirrhosis or other chronic liver disorders. As a negative acute-phase protein, reduced levels are noted in acute inflammatory processes, such as sepsis. This can be related to the breakdown of albumin

during heightened catabolism and leakage of albumin from the vascular space to extra-vascular space due increased permeability of the venous system in response to inflammation. Lyons et al., (2009), pointed to serum albumin as a predictor of 30-day mortality in emergency patients, mortality is non-linearly related to albumin baseline admission measurements and could be used as a clinical tool for identifying patients at risk for poor outcomes. A univariate analysis identified the subset group with < 10% and >10 and <25% of the frequency distribution at presentation to have increased mortality rates of 31.7% and 15.4% respectively; with unadjusted odds rates of 6.35 (5.68, 7.09) and 2.11 (1.90, 2.34) respectively (Lyons, et al., 2009).

Hsu, Hwang, Lin, Lin, and Tjung (2014) discovered that the in-hospital mortality rate in patients 82.0 +/- 5.4 years with severe hypoalbuminemia were 25.8%. If that patient in the same age group had mild hypoalbuminemia, the mortality rate was 6.6%, and if the albumin level was normal the mortality rate was 2.0% ($p < 0.01$). " When comparing the normal level albumin group, the adjusted odds ratios of albumin level associated with in-hospital mortality were 3.9 (2.4-6.3) in the mild hypoalbuminemia group and 17.4 (10.4-28.8) in the severe albuminemia group." (p. 221)

The utilization of albumin levels as a predictor of poor outcomes has been used in other areas of practice. Hypoalbuminemia has been a predictor of poor postoperative outcomes in surgical patients. First, patients with poor nutritional states undergoing surgery may experience post-operative complications/outcomes. There is evidence that plasma proteins support tissue repair, specifically facilitate wound healing. In the absence of adequate protein, post-operative wound healing could be delayed. Second, albumin has several pharmacological activities, such as transporter, antiplatelet and antioxidant characteristics. Should a patient be low in albumin, it could be logically assumed that there would be a lack in those functions, resulting in poor post-

surgical outcomes. Thirdly, low albumin levels might potentially lead to poor outcomes mainly due to the presence of increased inflammation (Kim, McCleve, Martindale, Miller, & Hurt, 2017).

In the area of systolic heart failure (HF), patients with hypoalbuminemia is a common finding. Potential mechanisms could be identified as poor nutrition, chronic inflammation, infection, etc. This occurrence is associated with increased mortality within a one-year time frame. Patients with systolic heart failure studied by Hussein (2012) had a mean serum albumin level of 3.9 (+/- 0.7) g/dL (range 1.7-5.6 g/dL), and 27.2% of patients had hypoalbuminemia (serum albumin $\leq$ 3.4 g/dL). One- year survival rate was 64.71% in patients with hypoalbuminemia and 85.72% in patients with normal albumin levels.

Additionally, low albumin and acute kidney injury (AKI) has been connected with noteworthy morbidity and mortality in critically ill patients. Hypoalbuminemia has been recognized as an independent risk factor, but as a predictor of AKI specifically it remains poorly described. There has also been the thought that hypoalbuminemia augments the risk of AKI. In a meta-analysis of observational clinical studies, 17 clinical studies were reviewed. Eleven studies appraised the influence of serum albumin on AKI, as well as the correlation between serum albumin levels and the development of AKI. The remaining six studies looked at lower levels of albumin serving as an independent prognosticator of both AKI and mortality after the AKI developed. With each 1.0 mg/dL of serum albumin decrease, the odds of AKI increased by 134%. Among the patients who had developed AKI, the odds of death rose 147% with each decrease of 1.0 mg/dL of albumin decrement. Using serum albumin determinations may be useful in determining patients at increased risk for AKI or death after AKI (Wiedermann, Wiedermann, & Joannidis, 2010).

Hypoalbuminemia has been established as a "dose-dependent and independent predictor of poor outcome in patients with acute illness." (Vincent, et al., 2014, p. 319). With each decrease of 1.0 g/dL albumin concentration, the odds of mortality increase by 137%, and morbidity by 89%. Albumin has several physiological properties such as binding and transportation of various substances, (medications and hormones), antioxidant components, modulation of nitric oxide and buffering capabilities, which can have significant application for patients who are critically ill (Vincent, et al., 2014). Low albumin levels secured within 48 hours of admission corresponded with longer lengths of stay in the hospital and higher in-hospital mortality. Even though problematic concerns of hypoalbuminemia have been identified, it is often overlooked in the patient care process with the main focus of care on the primary reason the patient was hospitalized (Herrmann, et al., 1992).

The link of albumin levels on admission and changes in those levels during hospitalization in regards to outcomes was investigated by Akirov et al., (2017). Patients who had normal albumin levels on admission had a 29% mortality rate, compared with mild hypoalbuminemia (67%) and marked hypoalbuminemia (83%). This pattern was similar when analyzed individually in different age groups. In-hospital mortality was appreciably greater in patients with mild hypoalbuminemia (12%) and marked (34%). At the end of follow up, mortality for patients with mild hypoalbuminemia was (67%) and marked (83%) (Akirov, et al., 2017).

Gaps in the literature originate in attempting to establish a causal relationship between low albumin and mortality directly. And while the correlation between the two can be found in numerous studies, there has not been significant evidence in clinical trials that raising the albumin concentration through exogenous albumin administration improves the outcomes in

patients with low albumin levels (Goldwasser & Feldman, 1997). Further unsolved questions such as timing of albumin administration, concentration of albumin administered and dose of albumin pose perplexing as to the validity of the intervention of exogenous albumin administration (Jiang, Jiang, Zhang, Zheng, & Ma, 2014).

Attempts to identify patients who are at risk for mortality have used a variety of methods to do so. Low albumin levels have been found correlating with poor outcomes in trauma patients, patients with acute kidney injury (AKI) and heart failure. Studies (Al-Khafaji & Webb, 2003), (Caraceni, Tufoni, & Bonavita, 2013) and (Jiang, et al., 2014) have examined whether or not administration of exogenous albumin reduces this risk, without compelling results. However, the consensus still is that serum albumin is a predictive variable for mortality and could be used as a clinical tool to identify patients who are at high risk for poor outcomes.

Chapter Three

Methodology

Research Design

This Scholarly Project study is a quantitative, descriptive retrospective design to establish the relationship between the variables of low admission albumin levels and mortality in patients 18 years of age and older who have been admitted through the emergency department with a specified diagnosis of sepsis.

The setting for data collection was a large acute care medical center in the southeastern region of the United States. The medical facility has over 800 acute-care beds and serves patients from 50 counties. This Level I trauma center services a 50 county area, with more than 345,000 outpatient visits and more than 36,000 adult inpatient admissions. Sample consisted patient records for those admitted through the emergency department between January 1, 2018 and December 31, 2018. Table 2 provides a list of International Classification of Diseases-10 (ICD 10) diagnostic codes that were used to query patient population by primary diagnosis. These ICD codes provided a basic list of diagnoses that meet the most current sepsis definitions.

Electronic health records (EHR) for patient admitted through the emergency department with a diagnosis of sepsis were identified and reviewed. Data collection was based on identified variables, such as age, gender, race, admission and discharge albumin levels and condition on discharge. Each variable was compared with the others to determine a correlation between the variables, with focus on admission albumin levels and condition on discharge.

Table 2. ICD-10 Sepsis Codes

ICD-10 Code	Description
R65.10	Systemic inflammatory response syndrome (SIRS)
A41.9	Sepsis, unspecified organism
R65.20	Severe sepsis without septic shock
R65.11	Systemic inflammatory response syndrome (SIRS) of non-infectious origin with acute organ dysfunction

The initial sample included 995 patient records with the specified diagnoses codes that met the inclusion criteria of 18 years of age or older, admitted with specified diagnoses codes and through the emergency department. Demographic variables collected were age, gender and race/ethnicity. Attributes of demographic variables are described in Table 3.

Table 3. 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 Asian Indian, Black or African American, Chinese, Filipino, Other, Other Asian, Other Pacific Islander, Unknown, Vietnamese and White

The measurement characteristic was the variable collected from the discharged disposition in the electronic health records, and a discharge disposition of "expired" indicated mortality. Any other discharge indication other than expired was reviewed as "living." The outcome variable was condition on discharge and was a dichotomous level of measurement. The measurement characteristic was the variable collected from the discharged disposition in the electronic health record, and a discharge disposition of "expired" indicated mortality. Any other discharge indication other than expired was reviewed as "living."

An Institutional Review Board (IRB) procedure was followed and approved through the academic institution of study, as well as through the acute care facility. No use of human subjects was involved in this study. All data was collected from the existing electronic health record database and the primary investigator (PI) was required to only use the data for purposes outlined in the IRB agreement. Informed consent was not necessary from subjects due to the de-identified nature of the data. A decision support analyst used the query codes necessary to gather the data and the file was de-identified prior to being delivered to the PI.

Descriptive statistics for all sample variables were conducted to describe the study sample. Procedures for data analysis were performed using SPSS with a *p* value of less than .05 indicating statistical significance. The primary predictor, admission albumin level, was calculated using an independent *t* test, using patient lab values and condition on discharge. Age, gender and ethnicity were also identified as possible predictors in the analysis. Each independent variable was appraised for association with the dependent variable using Pearson's correlation. Regression modeling was performed for the independent variable of admission albumin. Logistic regression was conducted for the dichotomous dependent variable and the independent variable. Demographic variables were evaluated as possible covariates and were included as appropriate.

Chapter Four

Analysis of Results

This Scholarly Project study is a quantitative, descriptive retrospective design to establish the relationship between the variables of low admission albumin levels and mortality in patients 18 years of age and older who have been admitted through the emergency department with a specified diagnosis of sepsis. A total of 995 patient data records were identified as meeting the inclusion criteria. The ethnicity recorded on the patient record included 83% white, 12.26% Black or African American, with Asian Indian, Pacific Islander or Vietnamese, Chinese, Filipino, or other Asian comprising the other 5.48%. Patient data for gender included, 534 (54%) males and 452 (46%) females. Ages ranged from 18 to above 95, with the mean age (SD) 60.9 (16.22). Of the total 995 patient records, 828 (83%) subjects were discharged living to home, hospice or other long-term care facility and 167 (17%) subjects were noted as expired at time of discharge. Albumin levels were divided by range marked hypoalbuminemia, < 2.5 mg/dL, mild hypoalbuminemia, 2.5 – 3.5 mg/dL, normal albumin 3.5 – 4.5 mg/dL and hyperalbuminemia, > 4.5 mg/dL. The mean first (admission) albumin level was 2.98 (.596). The mean last (prior to discharge) albumin level was 2.85 (.584).

Primary Hypothesis Testing

An independent-samples *t* test comparing the dependent variable of admission albumin and the independent (grouping) variable of living versus expired status on discharge was performed. The *t* test demonstrated the admission albumin level of the expired and living groups as significantly different between the two groups (t (984) = 2.252, p = .025). The mean admission albumin level of the expired group (n=163) was significantly lower (M = 2.880, sd =

.6812) than the mean admission albumin level (n=823) of the discharged group (M = 2.995, sd = .5759).

Additionally, a t test was utilized to compare ethnicity and admission albumin levels. White and Black/African American groups were used, as these were the groups with the greatest number of subjects in the category. An independent-samples t test was calculated comparing the mean admission albumin score of participants who identified themselves as White (n= 823) ethnicity to the mean score of participants who identified themselves as Black/African American (n= 122). No significant different was found (t (945) = .099, p =.*092*). The mean of the White group (M = 2.984, sd = .593) was not significantly different from the mean of the Black/African American group (M = 2.979, sd = .644). Ethnicity does not appear to impact baseline albumin levels.

A Pearson correlation coefficient was calculated for the relationship between patient's age and admission albumin. A negative correlation was found (r (958) = -.071, p = .029), indicating a very weak negative correlation between the two variables. Older patients were somewhat more likely to have lower admission albumin levels.

An independent-samples t test comparing the mean last albumin level of both discharged and expired groups found a significant difference between the means of the two groups (t (980) = 4.449, p < .001). The mean of the discharged group was significantly higher (M = 2.995, sd = .574) than the mean of the expired group (M = 2.660, sd = .600).

Exploratory data analysis was done to compare the means of admission and last (discharge) albumin levels for those who expired. In the group of patients who expired, the mean admission albumin level was 2.83, (sd = .718), and the mean last albumin level was 2.48,

(*sd* = .585). A significant decrease from admission albumin level to last albumin level was found (*t* (153) = 6.74, *p* = <.001).

In addition, a paired-sample *t* test compared the mean admission and last albumin levels in the group who were discharged (n=826). The mean admission albumin level was 3.01 (*sd* = .562), and the mean last albumin level was 2.91 (*sd* = .557). A significant decrease in albumin levels was also found in this group (*t* (7.63), *p* = .000).

Age, first albumin, and change in albumin level over admission were significant independent predictors of mortality using multiple logistic regression, ($X_2(4) = 97.557$, p< 0.001). These results can be found in Table 4. The Wald test was used to determine statistical significance with age (*p* = .017), first albumin (*p* = <0.001) and albumin change (*p* = <0.001) as being significant predictors of mortality, but sex (*p* = .673) was not a significant predictor of mortality. The odds of an individual dying were 3.545 times greater in those individuals with a low first albumin. The explained variation in the dependent variable ranged from 10% to 17% based on Cox & Snall and Nagelkerke R_2 method. Use of this prediction model resulted in an overall 85.3% correct classification of whether or not a patient would survive or expire based on their age, first albumin or change in albumin. The highest percent of accuracy was for prediction of those who survived and were able to be discharged to home or a facility.

Table 4. Results of Multiple Regression for Mortality

Variable	B	SE	Wald	df	Sig.	Exp (B)
Age	**-.015**	**.006**	**5.672**	**1**	**.017**	**.985**
Sex	**-.081**	**.192**	**.178**	**1**	**.673**	**.922**
First albumin	**1.266**	**.196**	**41.688**	**1**	**.000**	**3.545**
Albumin change	**-2.050**	**.244**	**70.610**	**1**	**.000**	**.129**
Constant	**-.520**	**.687**	**.594**	**1**	**.441**	**.589**

CHAPTER 5

Discussion of Findings

The overall purpose of this study was to investigate whether or not there was a correlation between low admission albumin levels and mortality in patients who are >18 admitted through the ED with sepsis related diagnoses. What was found was a statistically significant correlation between the two in the particular population reviewed. Patients with low admission albumin levels were more likely to die compared with those who had normal or higher albumin levels.

In addition, patients who are older and had a decrease in their albumin levels during the hospitalization were also more likely to die. When reviewing the outcomes of the study, an interesting note was the seemingly no difference between Black/African American and White subjects in albumin levels and mortality. Also, a negative correlation between age and low albumin levels, which in turn led to higher mortality rates, was also noteworthy. In a study on the impact of serum albumin on functional status and hospital outcomes in oldest-old inpatients, lower albumin levels was statistically significantly (p <0.01) correlated with lesser functional ability, longer hospital stays and higher mortality rate in-hospital (Hsu, et al., 2014).

Sepsis is a prevalent and significant issue with patients in the United States. This fact on it's own is worrisome. With outcomes of a noted correlation between low admission albumin levels and mortality in patients with sepsis the concern is exponential. Whether or not early intervention can correct the issue is an important question as the research looks forward to solutions.

There are very limited studies that discussed using albumin as restorative to normal levels as part of the helpful treatment in sepsis patients. Many studies (Al-Khafaji & Webb, 2003),

(Carceni, et al., 2013) and (Jiang et al., 2014) have focused on using albumin as a resuscitative component with treating patients with sepsis, which in turn would suggest a restoration to near normal albumin levels, thus improving overall mortality rates. These studies were without definitive results that indicate an improvement in mortality rates. The Surviving Sepsis Guidelines (Levy, Evans & Rhodes, 2018) recommend crystalloids as a fluid of choice of initial resuscitation and ongoing fluid replacement in patients with shock. In addition, the recommendation to use albumin in addition to the crystalloids was suggested by the Guidelines, with weak recommendation and low quality of evidence. There was some evidenced of improving mortality in patients with septic shock when albumin was used, but the use of albumin in sepsis was not noted as significant. When comparing crystalloids to albumin, there wasn't a significant reduction in mortality with moderate quality of evidence (Patel, Laff, Waheed, & Brett, 2014).

Limitations

Using retrospective data in a correlational study design is a limitation of this study, curbing conclusions to that of association and not causation. A prospective cohort study would be a viable next step in which patients would be followed throughout the hospitalization, with documentation of enteral and parenteral intervention. Due to the use of a single facility to obtain data, generalizability of results is limited. A study using a larger sample size at several facilities that affords data that represent a wider range of demographic characteristics would better provide generalizability of results.

The method of sampling attempted to decrease the potential for selection bias by choosing only those subjects who met the specific inclusion criteria. Subject who met the criteria of >18 years of age, admitted through the ED, as well as having the specific ICD 10 codes in

question were only included in the sample. There was no intervention or exposure bias due to the nature of the retrospective study. Using a wider range of ICD 10 codes specific to sepsis would bring in a larger sampling size and provide better generalizability of results.

Implications for Future Projects/Research

Sepsis is a significant source of morbidity and mortality globally. It is associated with very high in-hospital mortality rates in adult patients, ranging from 23-39%. Notwithstanding significant improvements on the detection and treatment of sepsis, it continues to be the second most common cause for mortality in intensive care units (ICUs) (Yin, et al., 2018).

Albumin is a major plasma protein that functions as regulator for osmotic pressure and carrier for endogenous and exogenous compounds. It also serves a buffer for acid/base balance, as well as having substantial anti-inflammatory and anti-oxidative features. Hypoalbuminemia is associated with a higher level of poor prognoses in patents with chronic and acute disease processes, and yet there is limited data on the affects of low albumin and sepsis (Yin, et al., 2018).

The results of this project help contribute to this body of knowledge in relation to the prediction of outcomes in sepsis, specifically. The results confirm using admission serum albumin levels as a predictor of mortality, as has been seen in what limited information there is available. Future research should be conducted using a multi-center study using these same predictors. Additional research should also include these particular questions and data collection:

1. What was the exact or proposed source of infection? For example, UTI, pneumonia, etc.
2. Did these patients receive exogenous albumin at the time of admission or any time during the hospitalization period?

3. Did these patients receive enteral or parental nutrition specifically designed for protein replacement?
4. What was the APACHE II or III score for these patients?
5. What other comorbidities did these patients have?
6. What could be the underlying cause of the low albumin? Vascular permeability loss, nutritional deficit, or other organ dysfunction?
7. What was the relationship between CRP levels and albumin levels?
8. What was the average length of stay? Was the mortality rate higher in specific units?

The results of this research contributed to the body of knowledge related to prediction of outcomes in patients who are admitted through the ED with the diagnosis of sepsis. Consistent with prior research, low albumin levels were significant predictors of poor outcomes in the study performed. Focus on this diagnostic test can be employed by the advanced nurse practitioner to improve patient outcomes and decrease mortality in patients with sepsis. With sepsis being a significant cause of poor outcomes, using serum albumin levels to indicate those at risk for future problems can prompt advanced practice nurse to focus interventions not only on the cause of the sepsis, but on raising albumin levels. These interventions could improve care and decrease negative outcomes.

Future Directions

The results of this research contribute to the body of knowledge related to prediction of outcomes in sepsis. The results confirm that admission low albumin levels do correlate with an increase in mortality risk, consistent with prior research. Negative change in albumin level trends and age were also significant predictors of outcomes. In addition to performing this study on multiple hospitals, additional research should be conducted to include co-morbidities, sources of

the specific cause of the sepsis, length of stay and whether or not the patient received exogenous albumin administration.

Decisively, the goal of this research was to discover a correlation between low admission albumin levels and mortality and whether or not that could be a predictor used by clinicians to improve the outcome and decrease mortality in patients with sepsis. Should the predictive value of admission albumin levels be confirmed, additional studies could be done in evaluating clinician interventions and the clinical response patients experienced, specifically decreases mortality. The albumin level could demonstrate a valuable tool as meter of merit of those interventions.

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Appendix A

Scholarly Project End of Program Student Learning Objectives

In response to the ever increasing patient demand, improving the quality of care, as well as attaining senior-level leadership positions in clinical care and nursing systems, obtaining the Doctor of Nursing Practice (DNP) degree can demonstrate proficiency, excellence and a level of credibility for nurses. At Southern Adventist University, the doctoral prepared nurse will provide personalized, compassionate care for the whole patient. Management of care within the healthcare team achieves a high level of patient care. Fulfilling the role as member of the discipline through active professional organization membership, advocacy, legal and ethical practice, life-long learning and many other behaviors, reveal Christ centered excellence through caring, connecting and empowering (School of Nursing Handbook, 2018). Through the exercise of this scholarly project the role competencies set by Southern Adventist University can demonstrate the essential role components needed to achieve degree of Doctor of Nursing Practice.

Cultural Competence

Sepsis is a global concern and care for one's fellow man is an integral part of the practice of nursing. Even within the setting of the facility studied in this project, there was an array of cultural differences to which the DNP graduate should show sensitivity. Seeking timely and appropriate ways to identify sepsis early benefits all cultures and races.

Evidenced-based Practice

Scholarship and research are the hallmarks of doctoral education, as outlined in The Essentials of Doctoral Education for Advanced Nursing Practice. Reviewing the current literature and translating research findings is part of scholarly nursing practice. Through

literature review, the doctoral prepared nurse can uncover new phenomena and apply these findings to practice situations. It is through integrating knowledge and applying that knowledge to practice situations that health outcomes can be improved. In the process of discovery of information for this project, considerable amount of research and practice guidelines were reviewed and utilized as a basis for the study. It is through this process and application that patients with sepsis who exhibit particular risk factors may be identified earlier, with interventions focused on improving outcomes, names decreasing mortality.

Health Promotion

While this particular study did not focus on health promotion, there was discussion in the literature reviewed that nutritionally sound patients are more apt to survive sepsis and less likely to succumb to disease progression.

Patient-centered care

The primary focus on this study is to identify if low admission albumin levels were a risk factor for mortality in patients who are diagnosed with sepsis. Sepsis is a potentially life-threatening disease, with an average mortality rate of about 40 percent. Recognizing those who are higher risk for mortality is unquestionably a patient-centered intervention.

Quality and safety

Delivery of health care services that meet professional standards of care and are based on current evidence minimize harm to individuals is a part of quality and safety. Researching sepsis and the risk factors patients may have is a part of developing standards of care. Through the scholarly project process research and identification of risk factors that may decrease mortality in patients was completed. Interventions were suggested that could serve to better patient outcomes.

Informatics and Innovation

Management of patient data was completed ethically and innovatively using de-identified patient information. The primary investigator, appropriate hospital personnel and faculty supervisor only reviewed the patient data set. Utilizing nursing knowledge, computer and information sciences, such as a library data search, Mendeley and SPSS, contributed to the ethical and innovative management of data, information and technology. When there was an area of weakness and confusion, collaboration and counsel were offered, as well as recommendations for support services.

Teamwork and Collaboration

Effective inter- and intra-professional support through the academic facility faculty, as well as the facility resource personnel promoted quality health outcomes through coaching and provision of patient information. Discussion with physician providers at the facility studied proved to be invaluable with guiding the direction of this study. Going forward, it will be through the completion of the project and feedback to the facility providers where promotion of quality health outcomes and risk reduction can take place in the future. Initially, this researcher was not comfortable in the role of team leader when establishing interprofessional teams, but has gained a greater appreciation for what it takes to implement the role in the future. Communication and collaboration with the interprofessional team members at the facility facilitated growth in leadership skills.

Professionalism

Throughout the process of this project, the faculty encouraged the student to complete deadlines in a timely manner. Any interaction with the facility and with the educational institution was to follow the specific guidelines set up by that institution, for example,

completion of the institutional review board documents and approval. Professionally through this project this DNP graduate should be able to “assess risk and collaborate with others to manage risks ethically, based on professional standards.” (The Essentials, p. 10)