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EXAMINING BODY MASS INDEX AND MORTALITY AT ONE YEAR AFTER SEPSIS

A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

JAMIE D. ROBINSON

Master of Science (Nursing),
University of Virginia, 2007
Bachelor of Science (Nursing),
Shenandoah University, 2004
Associate of Science (Nursing),
Shenandoah University, 1998

Advisor: Theresa Swift-Scanlan, Ph.D., RN, FAAN
Ellen Fontaine Winston Distinguished Professor, Director, Biobehavioral Laboratory Services,
Associate Professor, Department of Adult Health and Nursing Systems

Virginia Commonwealth University
Richmond, Virginia
April 2020

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Abstract

Introduction: Sepsis is a serious and life-threatening syndrome affecting 1.7 million Americans annually and resulting in approximately 270,000 deaths. An “obesity paradox” where obese individuals have lower sepsis mortality than their non-obese counterparts has been described. The problem is that the longevity of the effect is unknown, and few studies have examined the obesity paradox after 1-2 months post-diagnosis.

Methods: This retrospective cohort study examined clinical, demographic, and biomarker variables thought to affect sepsis mortality at three-time points: 30 days, 180 days, and at one year post-sepsis diagnosis in order to shed light on specific factors that might define a “sepsis survivor” phenotype. A convenience sample of adults age 18 and older admitted to an academic medical center between the years of 2007 to 2018 with a diagnosis of sepsis was identified. Simple logistic regression was used to test for significance between age, sex, race, c-reactive protein, lactate, white blood cells, body mass index, and sepsis severity on mortality at each of the three previously described time points. Variables with statistical and clinical significance were entered into multivariate logistic regression models to explore the contributions of each variable and interactions between variables at 30 days, 180 days, and one year after sepsis diagnosis.

Results: We found for every 5 unit increase in BMI, the odds of mortality were 0.92 (95% CI: 0.85, 0.99) times lower at 30 days since sepsis diagnosis. However, at 180-day and one-year post sepsis diagnosis, as BMI increased, there was an increase in odds of death for each sepsis type.

Discussion: In this dataset, it appears that the "obesity paradox" exists up to 30 days, but the protective effect of obesity on sepsis outcomes may not extend beyond one month. Future studies that control for comorbidities and other potential covariates, and that can test for the contributions of novel biomarkers on sepsis outcomes are needed.

Introductory Narrative

This dissertation represents a collection of scholarly work based on the preparation, implementation and analysis of a retrospective dataset that examined the association of body mass index on sepsis mortality at one year. This dissertation is formatted following the Virginia Commonwealth University School of Nursing's Manuscript Dissertation Option, which differs from the traditional dissertation format. With the manuscript option, the dissertation has four chapters, each of which each is styled to the requirements of the associated grant or journal and is summarized with a conclusive narrative. Chapter One is the literature review that describes the current state of the science of sepsis mortality in the context of obesity (Robinson, Swift-Scanlan, & Salyer, 2020). Chapter Two describes the conceptual framework developed for use in this dissertation. This framework demonstrates the relationships between demographic and biological variables that impact sepsis mortality. (Robinson, Swift-Scanlan, Salyer, & Jones, 2020). Chapter Three is the project proposal and includes the specific aims, significance of the study, research strategy and methods. Chapter Four is the results manuscript which is submission ready to the journal "Biological Research for Nursing" pending review of the committee members who are co-authors on this results paper. This introductory narrative that follows, along with the abstract and concluding narrative, together represent a comprehensive dissertation.

Chapter One

Obesity and One-Year Mortality in Adults After Sepsis: A Systematic Review

Jamie Robinson, Theresa Swift-Scanlan, Jeanne Salyer

Virginia Commonwealth University

Manuscript published in Biological Research for Nursing

(January 2020)

Abstract

Purpose: In recent years researchers have noted an "obesity paradox," where individuals with obesity survive sepsis at higher rates than their nonobese counterparts. This systematic review summarizes the literature on studies examining the association between obesity and 1-year mortality among patients admitted with sepsis, severe sepsis, or septic shock.

Materials and methods: Using a comprehensive search strategy, a systematic review was conducted to identify studies examining the association of obesity and sepsis mortality. PubMed, Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Elton B. Stephens Company (EBSCO) host databases were searched for the terms *sepsis, obesity, mortality,* and *adult.*

Results: The initial search identified 189 studies, 9 of which met inclusion criteria. Of these, 4 provide evidence that obese or very obese patients with sepsis have lower mortality than nonobese patients. Methodologic differences in the remaining 5 studies that report conflicting results limit generalizability.

Conclusion: This systematic review on the association of obesity and sepsis mortality revealed 3 studies that demonstrate lower mortality among obese patients in the first 30 days, and one study that shows this protection extends up to 1 year. The studies that showed inconsistent results were difficult to generalize due to methodological constraints. Given the increased number of patients surviving sepsis, it is important to consider long-term mortality and further describe the variables associated with increased survival.

Keywords: Obesity, Body Mass Index, Sepsis, Mortality

Obesity and One-Year Mortality in Adults After Sepsis: A Systematic Review

Background

Sepsis and obesity have high incidence and mortality rates independent of each other. When taken together, one might expect a perfect storm in which patient outcomes are exponentially worse than either diagnosis on its own. This notion is countered by the "obesity paradox" where obese individuals with sepsis survive at higher rates than non-obese individuals in the short term (Abbate et al., 2016; Arabi et al., 2013; Meyer et al., 2018; Nguyen et al., 2016; Sakr et al., 2013; Wacharasint et al., 2013).

Despite extensive research, optimizing sepsis outcomes remains challenging. Grim statistics indicate the magnitude of sepsis in the United States (US) is far reaching, with more than 1.5 million cases and 250,000 deaths occurring annually, and an estimated one out of every three hospital deaths that occur are due to sepsis (Centers for Disease Control and Prevention [CDC], 2017). Due to recent advances in early sepsis recognition and treatment more people survive the initial insult, yet many experience persistent residual symptoms of physical, psychological, cognitive, and functional frailty from sepsis associated tissue impairment, metabolic impairment, and organ dysfunction (Gardner et al., 2019; Winters et al., 2010). Subsequent increased utilization of healthcare, including hospital re-admission, has been reported along with increased late mortality (Iwashyna & Netzer, 2012; Yende, et al., 2016). Meanwhile the literature often examines mortality at 30, 60, or 90 days, omitting end points that may better estimate the long-term effects. Given the "obesity paradox," whereby obese patients survive inflammatory conditions at higher rates than non-obese patients, (Braun et al., 2017; De Schutter et al., 2016; Hafner, Hillenbrand, Knippschild, & Radermacher, 2013), it is important to explore the impact of obesity on long-term sepsis outcomes.

Obesity is a global epidemic associated with complex multi-system diseases affecting cardiovascular, endocrine, and mental health, and increased all-cause mortality (Keaver, Xu, Jaccard, & Webber, 2018). Complications of obesity can potentiate each other, such as type 2 diabetes and hypertension leading to chronic kidney disease, a potential cause of early disability. The physiologic consequences of obesity increase the risk for complications and likelihood of slowed recovery from sepsis. However, taken together sepsis and obesity are associated with better rather than worse survival in the short term, observations that have collectively identified the "obesity paradox."

Inconsistent results on the impact of obesity on other critical illness have indicated that obesity may be related to better, worse, or unchanged rates of hospital and intensive care unit (ICU) length of stay and mortality (Martino et al., 2011). A theme that many studies uncovered is that the consequences of critical illness continues for years after hospital discharge (Gardner et al., 2019; Winters et al., 2010). For instance, examining data from the Health and Retirement Study (HRS) researchers found a significant increase in the odds of cognitive dysfunction and physical dysfunction that continued through an 8-year follow up period (Iwashyna, Ely, Smith, & Langa, 2010). Narrowing the scope of investigation from critical illness to sepsis will be pivotal in order to establish relationships among variables affecting mortality and to identify a phenotype of sepsis survivors. Given the implications of obesity on sepsis mortality in the short term, and the resultant chronicity of sepsis following survival, the objective of this systematic review is to describe the association of obesity and one-year mortality in adults after sepsis.

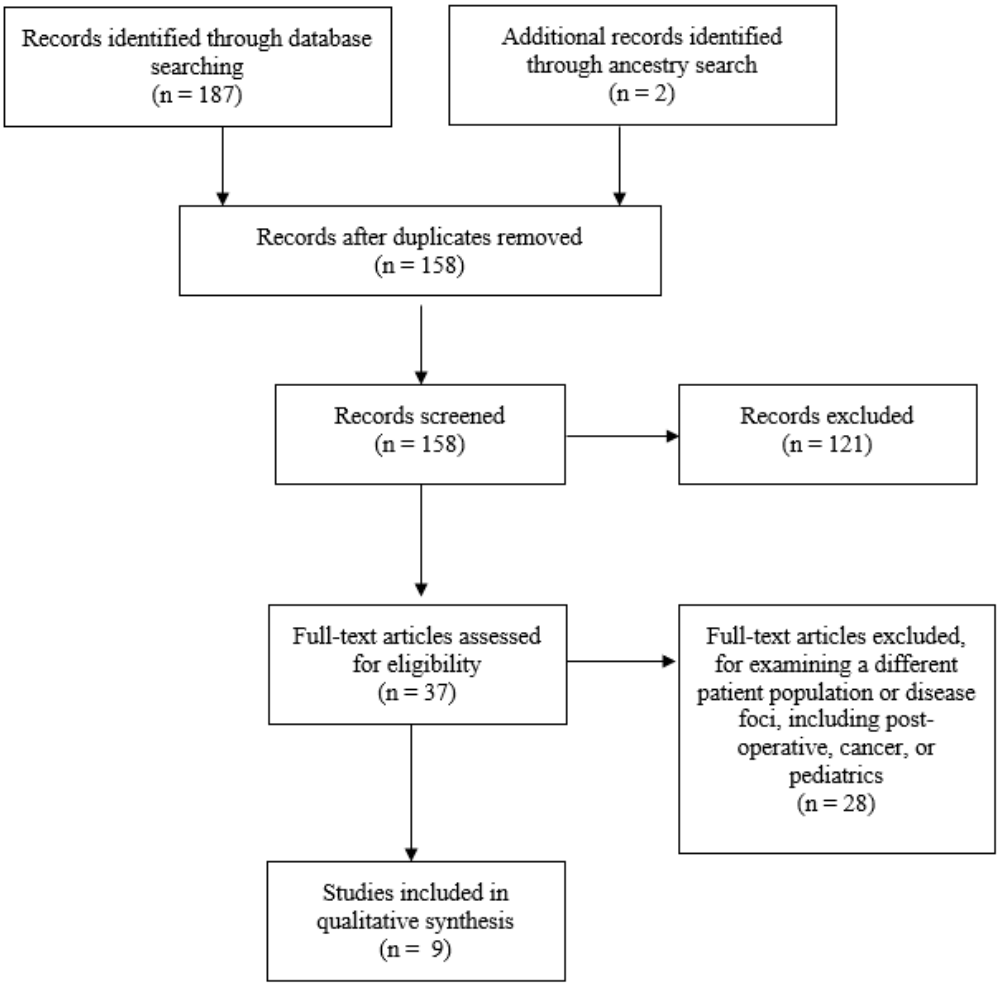
Methods

Using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Liberati et al., 2009) PubMed, Cumulative Index of Nursing and Allied Health

Literature (CINAHL), and Elton B. Stephens Company (EBSCO) host were searched to access research published between the years 2013 to 2018 to identify relevant articles. The review of the literature was conducted from November 2017 to May 2018 by the primary author. Studies were included in the review if they were published in the English language between 2013 and 2018 and reported mortality in subjects 18 years or older. This time period of 2013 to 2018 was chosen to reflect the current state of the literature. Each database was searched for the terms "sepsis," "obesity," "mortality," and "adult," with the additional limiters listed above. A total of 189 studies were identified from databases and two from ancestry searches. Publications were excluded from review if the study examined a disease other than sepsis or if the population included obstetric patients, children, or neonates because body mass index (BMI) is a poor correlate of adiposity in these populations. After 29 duplicate articles were removed 158 articles were screened. The initial screening eliminated 121 articles that focused on a different patient population or disease foci, including but not limited to post-operative, cancer, or pediatrics. An additional 28 articles were eliminated after reading the title, full abstract, introduction, and methodology sections of the articles due to a disparate focus of research, to include dose response to mechanical ventilation, the association of BMI to gram positive bacteremia, and focus on properties of visceral adipose tissue. The remaining 9 articles were read in their entirety and were included in this systematic review. The search and screening results are reported in the figure.

Figure 1:

Flow diagram of literature search and study selection.



The methodological quality of all of the articles that met inclusion criteria were evaluated against the Strengthening the Reporting of Observational (STROBE) criteria (STROBE, 2009). These criteria outline elements that should be included in cohort studies investigating health outcomes. A score of 1 was given for each criterion that was present in the articles, with the possible 0-22 score range, where 0 is methodologically unsound and 22 is the highest level of reporting. The scoring of each publication is included in the literature review matrix (N =9, mean (M) = 20.88, Standard deviation (SD) = 0.60) calculated with Microsoft Excel for Mac version 16.16.2, see Table. The topics identified for inclusion in the literature review matrix

included: (a) the first authors' name and year of publication; (b) the research design and timeframe of the study; (c) sample and setting; (d) statistical analysis, and; (e) the main outcomes of the study.

Results

We included nine studies in the systematic review, all of which were retrospective cohort studies. To define obesity, four studies used the World Health Organization (WHO) criteria (WHO, 2016; Arabi et al., 2013; Gaulton et al., 2014; Kuperman et al., 2013; Papadimitriou Olivgeris et al., 2016), one of which collapsed the categories into "obese" for BMI < 30 kg/m2 and "nonobese" for BMI < 30 kg/m2 (Papadimitriou-Olivgeris, 2016); two used the National Institutes of Health (NIH) criteria (NIH, n.d.; Gaulton et al., 2015; Wacharasint et al., 2013), one of which collapsed underweight and normal weight into a "< 25 kg/m2 BMI" category (Wacharasint et al., 2013); and three used binary Y/N based on International Classification of Diseases, 9th edition (ICD-9), coding (Abbate et al., 2016; (Nguyen, 2016; Prescott et al., 2014), one of which derived presence of obesity from Elixhauser comorbidity coding (Austin, Wong, Uzzo, Beck, & Egleston, 2015; Nguyen, 2016). Studies also defined sepsis using several methods: two used the 1992 American College of Chest Physicians/Society of Critical Care Medicine Consensus definitions (ACCP/SCCM; Arabi et al., 2013; Wacharasint et al., 2013), one used the 2001 ACCP/SCCM Consensus definitions (Gaulton et al., 2015), four used ICD-9 codes (Abbate et al., 2016; Kuperman et al., 2013; Nguyen et al., 2016; Prescott et al., 2014), one used diagnosis as the classification of sepsis (Papadimitriou-Olivgeris et al., 2016), and one used a presumed sepsis antibiotic algorithm (Gaulton et al., 2014). All of the studies examined mortality, with five reporting "in-hospital" mortality (Abbate et al., 2016; Arabi et al., 2013; Kuperman et al., 2013; Nguyen et al., 2016; Papadimitriou-Olivgeris et al., 2016), two reporting

28-day mortality (Gaulton et al., 2014; Wacharasint et al., 2013), one reporting 28-day, 60-day and 1-year mortality (Gaulton et al., 2015), and one reporting in-hospital, 90-day, and 1-year mortality (Prescott et al., 2014). All studies reported the association of obesity and sepsis mortality, while some also reported prevalence of source of sepsis infection (Arabi et al., 2013; Gaulton et al., 2015; Papadimitriou-Olivgeris et al., 2016) and associations between sepsis mortality and gender and comorbidities (Abbate et al., 2016; Gaulton et al., 2014; Gaulton et al., 2015; Nguyen et al., 2016; Prescott et al., 2014; Wacharasint et al., 2013).

In looking at the relationship between obesity and sepsis mortality, three of the studies provide evidence to support the obesity paradox, or the association of reduced mortality from sepsis in obese or very obese patients compared to nonobese patients (Abbate et al., 2016; Nguyen et al., 2016; Wacharasint et al., 2013). Abbate and colleagues (2016) analyzed data from the California State Inpatient Database (SID), a subset of the Association of Health Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) database, and found that in 2011 nonobese adults with sepsis had higher in-hospital mortality (27.4%) than obese adults (18.4%; absolute difference -9.0, 95% confidence interval [CI] -9.7−-8.3). These results are generalizable due to the large sample size, yet they are limited by the potential lack of full identification of obesity due to the use of administrative data. For instance, researchers identified obesity using the HCUP chronic-condition indicator as a Y/N variable rather than by using actual height and weight to calculate BMI. Nguyen and associates (2016) examined the 2011 Nationwide Inpatient Sample (NIS), which was also drawn from the HCUP SID and comprises data from more than 1,000 hospitals in the United States. The researchers concluded that, after adjustment, all-cause in-hospital mortality was lower (adjusted odds ratio [OR] = 0.84; 95% CI 0.81−0.88) for obese sepsis patients as compared to nonobese ones. Similar to Abbate et al.

(2013), Nguyen et al. (2016) used administrative data rather than clinical data to determine obesity. Wacharasint et al. (2013) conducted post-hoc analysis of the Vasopressin and Septic Shock Trial (VASST) and found that obese patients had the lowest 28-day mortality followed by overweight patients, while patients with BMI < 25 kg/m2 had the highest mortality ($p = 0.02$). For every 1-unit increase in BMI, hazard ratio (HR)-adjusted mortality was 2% lower (95% CI 0.97−0.99, $p = 0.04$). Variation in the remaining studies regarding examination of septic shock versus sepsis or severe sepsis limits ease of comparison among them. However, results regarding the association of obesity with reduced sepsis mortality across studies is promising.

In contrast to studies that examined mortality in the short term, Prescott et al. (2014) examined the association of obesity and 1-year mortality after sepsis. They used data from the University of Michigan Health and Retirement Study (HRS), a longitudinal nationwide study supported by the National Institute on Aging and the Social Security Administration. Multivariate logistic regression models showed that higher BMI was associated with lower 1 year mortality post sepsis. Compared with nonobese patients, obese (odds ratio = 0.59; 95% CI 0.39–0.88) and severely obese patients (OR = 0.46; 95% CI 0.26–0.80) had the lowest mortality (Prescott et al., 2014). The authors found the same effect of BMI when they categorized patients by age < 70 and > 70 years.

Of the remaining studies, five reported inconclusive results or conflicting evidence that there was no association between obesity and reduced short-term mortality from sepsis (Arabi, 2013; Gaulton et al., 2014; Gaulton et al., 2015; Kuperman, Showalter, Lehman, Leib, & Kraschnewski, 2013; Papadimitriou-Olivgeris et al., 2016). Of these, two studies with strong methodologic soundness initially found obesity to be protective, yet, after adjustment for confounders, the association became insignificant (Arabi, 2013; Kuperman et al., 2013). Arabi et

al. (2013) interrogated a clinical database with information from medical centers in Canada, the United States, and Saudi Arabia (Cooperative Antimicrobial Therapy of Septic Shock [CATTS] group) and reported that patients who were obese (unadjusted OR 0.80, 95% CI 0.66−0.97) and very obese (unadjusted OR 0.61, 95% CI 0.44−0.85) had lower in-hospital mortality compared to normal-weight patients. These associations were insignificant, however, after adjustment for confounders. Kuperman et al. (2013) reported a clinically significant association between lower BMI and higher mortality, but the association failed to reach statistical significance ($p = 0.06$). However, when the researchers used BMI as a continuous variable, survivors had a higher BMI (27.6 kg/m2) than non survivors (26.3 kg/m2; $p = 0.03$). Kuperman et al. further reported that incidence of Type 2 diabetes and chronic obstructive pulmonary disease (COPD) were associated with BMI category ($p < 0.01$; $p = 0.04$, respectively). They also found that Type 2 diabetes was protective against sepsis-related mortality (OR = 0.53, 95% CI 0.32–0.88, $p = 0.01$), an association that remained when they excluded underweight patients due to low incidence of diabetes in that category (OR 0.54, 95% CI 0.32–0.91, $p = 0.02$). Independent risk factors for increased mortality were increasing age (in 5-year increments) and greater disease severity, as indicated by higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score (adjusted ORs = 1.12 and 1.14, respectively, $p < 0.01$). Neither sex nor race were associated with BMI or mortality ($p < 0.01$ and $p = 0.03$, respectively).

The three studies that reported conflicting findings about the association between BMI and sepsis mortality and methodologic inconsistencies: all were conducted at a single medical center (Gaulton et al., 2014, 2015; Kuperman, Showalter, Lehman, Leib, & Kraschnewski, 2013; Papadimitriou-Olivgeris et al., 2016), one examined a population of presumed rather than confirmed sepsis (Gaulton et al., 2014), one was potentially underpowered in the BMI category

of morbid obesity (Gaulton et al., 2014), and one was conducted in a region with higher-than average rates of multidrug-resistant pathogens (Papadimitriou-Olivgeris et al., 2016). Gaulton et al. (2014) examined the Pennsylvania Integrated Clinical and Administrative Research Database (PICARD) and found that obesity was associated with higher sepsis-related mortality rates (24.4%) than non-obesity (21.2%; unadjusted OR 1.21, 95% CI 0.95–1.54, p = 0.12) and there was no linear association between BMI and mortality. In another study, Gaulton and colleagues (2015) found that 28-day sepsis-related mortality for normal weight was 22% versus for morbid obesity at 6.5% (p = 0.002). Indeed, these researchers found that obese and morbidly obese patients were less likely to die from sepsis-related causes within 28 days (OR 0.67, 95% CI 0.46–0.95, p = 0.04), though there was no difference in mortality rates between groups for 60 days and 1 year in adjusted and unadjusted models (Gaulton et al., 2015).

Papadimitriou-Olivgeris et al. (2016) examined the effects of obesity in critically ill patients in a Greek ICU, including a subset of patients with sepsis. Researchers grouped patients by diagnosis into the categories of trauma, spontaneous intracranial hemorrhage, sepsis, postoperative observation, respiratory insufficiency, and other, which included coma, epilepsy, and intoxication. Total ICU mortality (N = 834) was 22.5%, with a mortality rate for nonobese patients of 21% and for obese patients 28.8% (p = 0.036). For patients with sepsis (n = 125), more nonobese patients survived (76.3%) than obese patients (43.7%; p = 0.001), and multivariate analysis indicated increased risk of mortality for higher Sequential Organ Failure Assessment (SOFA) score upon admission (OR 1.3, 95% CI 1.1−1.5, p = 0.003), obesity (OR 5.3, 95% CI 1.4−20.2, p = 0.014), pneumonia (OR 3.5, 95% CI 1.1−11.3, p = 0.015), and development of septic shock (OR 3.4, 95% CI 1.3−9.1, p = 0.015) and decreased risk of mortality for urinary tract infection (OR 0.06, 95% CI 0.01−0.52, p = 0.038). These results

should be interpreted with caution given the small size of the sample of sepsis patients and the comparison with five other diagnoses with very different disease trajectories. Further, the associations of septic shock, pneumonia, and high SOFA with increased mortality among patients with sepsis are unsurprising given that these conditions are associated with increased disease severity.

Discussion

The current literature on the relationship between mortality in sepsis and obesity consists of retrospective cohort studies that primarily describe this association in hospital or at 30 days. Few studies that we found explored follow-up periods of 60 or 90 days, and only one study had a 1-year follow-up. These time frames leave significant gaps in data because, of patients that survive sepsis to 30 days, as many as one-third die before 6 months (Prescott, Osterholzer, Langa, Angus, & Iwashyna, 2016; Shankar-Hari & Rubenfeld, 2016; Yende, Austin, & Rhodes, 2016), and the risk of death extends up to 10 years after hospitalization (Linder et al., 2014). Prospective cohort studies or controlled longitudinal studies would provide a value-added contribution to this topic. In one such study, Prescott and colleagues (2016) examined longitudinal cohort data, comparing patients with sepsis against adults not currently hospitalized, hospitalized patients with non-sepsis infection, and hospitalized patients with acute sterile inflammation. Their goal was to assess the risk factors and confounders associated with late (31 days to 2 years) sepsis mortality. Sepsis patients experienced a 22.1% absolute increase (95% CI 17.5−26.7%) in late mortality when compared to non-hospitalized adults, a 10.4% increase when compared to hospitalized patients with non-sepsis infection (95% CI 5.4−15.4%), and a 16.2% increase compared to hospitalized patients with a sterile inflammatory diagnosis (95% CI 10.2−22.2%). These results support the need for similar research that incorporates the variable of

obesity to better understand the impact of obesity on long-term sepsis outcomes.

Despite criticism for its inability to discriminate between lean and fat mass (Nuttall, 2018), BMI is currently the most commonly used method to estimate obesity in adults (Shah & Braverman, 2012). WHO and NIH classify body mass categories using the same BMI ranges, which assists in interpretation of results across studies. ICD-9 codes, which are used to identify diagnoses for insurance reimbursement purposes, are a less reliable method for identifying obesity because they may not be accurately coded in administrative data (Mocarski, Tian, Smolarz, McAna, & Crawford, 2018). Chronic conditions are coded only when they apply to the patient's present treatment, not if those conditions are no longer actively being treated (Hill, 1999). Using derived clinical data from the electronic health record (EHR) is a more accurate method for determining body mass category (Mocarski, Tian, Smolarz, McAna, & Crawford, 2018). While indirect measures of body fat are more reliable, such as dual energy x-ray absorptiometry (DEXA) scans, computed tomography (CT) scans, bioelectric impendence analysis, underwater weighing, and air displacement and density measures (Bod Pod), they are expensive and impractical (Nuttall, 2018).

Investigators in the reviewed studies identified sepsis using a variety of methods, including the 1992 and 2001 consensus definitions (Bone et al., 1992; Levy et al., 2002), administrative identification via ICD-9 codes, physician diagnosis, and an antibiotic algorithm for presumed sepsis. The most problematic of these methods is inclusion of presumed sepsis to estimate mortality, as patients may have been inappropriately assigned to the antibiotic algorithm. Use of clinical data such as blood-culture results would strengthen this approach so that cases of confirmed sepsis could be compared against cases of unconfirmed sepsis. The ACCP/SCCM first published consensus definitions for systemic inflammatory response

syndrome (SIRS), sepsis, severe sepsis, septic shock, and multiple organ dysfunction along with scoring methods for determining severity and assess mortality in 1992 (Bone et al., 1992). In recognition of the limitations of applying these complex descriptions in practice, the ACCP/SCCM published revisions in 2001 that refined the definitions, expanded the list of diagnostic criteria, and proposed a classification scheme for sepsis to stratify patients called PIRO: Predisposing conditions, nature and extent of the Insult, nature and magnitude of the host Response, and degree of Organ dysfunction present (Levy et al., 2003). Accurate identification of sepsis remains challenging, as evidenced by the evolution of consensus statements, the latest of which (Sepsis-3) incorporate a refined understanding of the pathophysiology of sepsis, moving away from emphasizing SIRS as the underlying mechanism and recognizing the role of a maladaptive host response as the major issue that results in the tissue damage and altered organ function in sepsis (Singer et al., 2016). Using this new definition and incorporating severity scores such as SOFA to estimate the extent of organ dysfunction is a more precise way to identify the severity of sepsis.

While evidence supporting the association between obesity and lower sepsis mortality is promising, descriptions of causal mechanisms are still lacking. One commonly proposed mechanism that links obesity and sepsis is inflammation. Sepsis is an example of acute inflammation that is brief in duration and begins with the production and release of chemical mediators to destroy and remove pathogens as the initial normal response of the body to protect against infection or injury. Obesity, meanwhile, represents chronic inflammation that occurs as a result of a maladaptive process where persistent low-grade inflammation causes tissue destruction over time (Makki, Froguel, & Wolowczuk, 2013).

Adipose tissue, present in excess in obesity, is an active immune organ that produces

cytokines and chemokines, vasoactive and coagulation factors, regulators of lipoprotein metabolism and proteins that participate in the inflammatory response (Lehr et al., 2012; Mohamed-Ali, Pinkney, & Coppack 1998; Romacho, Elsen, Rohrborn, & Eckel, 2014). Chronic inflammation occurs as adipose cells hypertrophy, stimulating enhanced adipokine production and increased infiltration of pro-inflammatory immune cells (Sell, Habich, & Eckel, 2012) resulting in endothelial-cell dysfunction, oxidative stress, and the activation of circulating immune cells (Singer & Granger, 2007). Adipose-cell hypertrophy is associated with increased expression of the pro-inflammatory markers interleukin-6 and leptin, while the anti inflammatory marker adiponectin is decreased (Singer & Granger, 2007). Taken together, these actions contribute to a maladaptive inflammatory response.

The metabolic alterations seen in acute and chronic inflammation are similar, including insulin resistance and elevation of leptin, IL-6, and C-reactive protein (CRP; Wisse, 2004). Typically, leptin and adiponectin work in balanced opposition (Guzik, Mangalat, & Korbut, 2006; Trayhum & Wood 2004), but unique to chronic inflammation from obesity, leptin and IL-6 are upregulated, while adiponectin is downregulated (Fantuzzi, 2009; Fantuzzi, 2013). Subsequently, leptin and IL-6 spill over into peripheral tissues causing insulin-receptor resistance (Ye & McGuinness, 2013). Importantly, a similar effect occurs with leptin: leptin secretion increases as adipose tissue expands, and when this is coupled with leptin-receptor resistance there is increasing leptin mRNA expression, contributing to hyperleptinemia (Tschöp et al., 2010; Ye & McGuinness, 2013).

Summary and Conclusions

This review revealed conflicting results. Of the nine studies included, three support the association of lower mortality with obesity in sepsis (Abbate et al., 2016; Nguyen et al., 2016;

Wacharasint et al., 2013), and one found that obesity was associated with lower 1-year mortality in sepsis compared non obesity (Prescott et al., 2014). Each of the three studies whose findings refuted the obesity paradox were conducted at a single center (Gaulton et al., 2014; Gaulton et al., 2015; Papadimitriou-Olivgeris et al., 2016). Future research should be directed toward studying prospective cohorts and examining the effects of the association of obesity and sepsis on longer-term mortality and on related persistent residual symptoms of post sepsis frailty.

To summarize the inflammatory processes in obesity, the immune function of adipose tissue is upregulated. Cytokine and chemokine regulation is altered, resulting in increased expression of the pro-inflammatory markers IL-6 and leptin, while the anti-inflammatory marker adiponectin is decreased (Singer & Granger, 2007). When the excessive inflammation of sepsis is modulated due to the chronic inflammation of obesity, the result is a more balanced physiologic response that causes less endothelial damage, less capillary permeability and ultimately less organ dysfunction. Research that examines the associations among inflammatory biomarkers, sepsis, and obesity may help to uncover the nature of these relationships, furthering our understanding of these mechanisms and leading to innovative interventions and treatment strategies.

The obesity paradox is not unique to sepsis but has been seen in other inflammatory diseases including heart disease (De Schutter et al., 2016), pneumonia (Braun et al., 2017), and acute kidney injury (Hafner, Hillenbrand, Knippschild, & Radermacher, 2013). Research that seeks to describe the phenotype of sepsis survivors by stratifying risk factors and controlling for confounders will be instrumental in developing targeted interventions to improve sepsis outcomes.

References

Abbate, L. M., Perman, S. M., Ginde, A. A., Clambey, E. T., & Van Pelt, R. E. (2016). Age modifies the association between obesity and mortality in individuals hospitalized with severe sepsis. *Journal of the American Geriatrics Society, 64,* 882–883. doi:10.1111/jgs.14047

Arabi, Y. M., Dara, S. I., Tamim, H. M., Rishu, A. H., Bouchama, A., Khedr, M. K., … Kumar, A. (2013). Clinical characteristics, sepsis interventions and outcomes in the obese patients with septic shock: an international multicenter cohort study. *Critical Care, 17*(2), R72. doi: 10.1186/cc12680

Austin, S. R., Wong, Y., Uzzo, R. G., Beck, J. R., & Egleston, B. L. (2015). Why summary comorbidity measures such as the Charlson Comorbidity Index and Elixhauser score work. *Medical Care, 53*(9), e65-e72. doi: 10.1097/MLR.0b013e318297429c

Bone, R. C., Balk, R. A., Cerra, F. B., Dellinger, R. P., Fein, A. M., Knaus, W. A., … Sibbald, W. J. (1992). Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest, 101*(6), 1644–1655.

Braun, N., Hoess, C., Kutz, A., Christ-Crain, M., Thomann, R., Henzen, C., Zimmerli, W., Mueller, B., & Schuetz, P. (2017). Obesity paradox in patients with community-acquired pneumonia: Is inflammation the missing link? *Nutrition, 33*(304-310). doi: 10.1016/j.nut.2016.07.016

Centers for Disease Control and Prevention [CDC]. (2017). *Sepsis data & reports*. Retrieved from https://www.cdc.gov/sepsis/datareports/index.html

De Schutter, A., Kachur, S., Lavie, C. J., Boddepalli, R. S., Patel, D. A., & Milani, R. V. (2016).

The impact of inflammation on the obesity paradox in coronary heart disease. *International Journal of Obesity, 40*(11), 1730-1735. doi: 10.1038/ijo.2016.125

Fantuzzi, G. (2009). Three questions about leptin and immunity. *Brain, Behavior, and Immunity, 23*(4), 405–410. http://doi.org/10.1016/j.bbi.2008.10.007

Fantuzzi, G. (2013). Adiponectin in inflammatory and immune-mediated diseases. *Cytokine, 64*(1), 1–10. http://doi.org/10.1016/j.cyto.2013.06.317

Gaulton, T. G., Marshall MacNabb, C., Mikkelsen, M. E., Agarwal, A. K., Cham Sante, S., Shah, C. V., & Gaieski, D. F. (2015). A retrospective cohort study examining the association between body mass index and mortality in severe sepsis. *Internal and Emergency Medicine, 10*(4), 471–479. doi: 10.1007/s11739-015-1200-1

Gaulton, T. G., Weiner, M. G., Morales, K. H., Gaieski, D. F., Mehta, J., & Lautenbach, E. (2014). The effect of obesity on clinical outcomes in presumed sepsis: A retrospective cohort study. *Internal and Emergency Medicine, 9*(2), 213–221. doi: 10.1007/s11739 013-1002-2

Gardner, A. K., Ghita, G. L., Wang, Z., Ozrazgat-Baslanti, T., Raymond, S. L., Mankowski, R. T., . . . Brakenridge, S. C. (2019). The development of chronic critical illness determines physical function, quality of life, and long-term survival among early survivors of sepsis in surgical ICUs. *Critical Care Medicine, 47*(4), 566-573. doi: 10.1097/CCM.0000000000003655

Guzik, T. J., Mangalat, D., & Korbut, R. (2006). Adipocytokines- novel link between inflammation and vascular function? *Journal of Physiology and Pharmacology, 57*(4), 505-28.

Hafner, S., Hillenbrand, A., Knippschild, U., & Radermacher, P. (2013). The obesity paradox

and acute kidney injury: beneficial effects of hyper-inflammation? Critical Care, 17(6), 1023. doi: 10.1186/cc13152

Hill, E. (1999). Improve Your ICD-9 Coding Accuracy. *Family Practice Management, 6*(7), 27 31.

Iwashyna, T. J., Ely, E. W., Smith, D. M., & Lang, K. M. (2010). Long-term cognitive impairment and functional disability among survivors of severe sepsis. *Journal of the American Medical Association, 304*(16), 1787-1794. doi:10.1001/jama.2010.1553.

Iwashyna, T. J., & Netzer, G. (2012). The burdens of survivorship: an approach to thinking about long-term outcomes after critical illness. *Seminars in Respiratory and Critical Care Medicine, 33*(4), 327-38. doi: 10.1055/s-0032-1321982

Keaver, L., Xu, B., Jaccard, A., & Webber, L. (2018). Morbid obesity in the UK: a modelling projection study to 2035. *Scandinavian Journal of Public Health, Aug 30,* 140349481879481. doi: 10.1177/1403494818794814

Kuperman, E. F., Showalter, J. W., Lehman, E. B., Leib, A. E., & Kraschnewski, J. L. (2013). The impact of obesity on sepsis mortality: a retrospective review. *BMC Infectious Diseases, 13,* 377. doi:10.1186/1471-2334-13-377

Lehr, S., Hartwig, S., Lamers, D., Famulla, S., Müller, S., Hanisch, F.-G., … Eckel, J. (2012). Identification and validation of novel adipokines released from primary human adipocytes. *Molecular & Cellular Proteomics: MCP, 11*(1), M111.010504. http://doi.org/10.1074/mcp.M111.010504

Levy, M. M., Fink, M. P., Marshall, J. C., Abraham, E., Angus, D., Cook, D., … Ramsay, G. (2003). 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Intensive Care Medicine, 29*(4), 530–538. doi: 10.1097/01.CCM.0000050454.01978.3B

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J. P. A., … Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of Clinical Epidemiology. 2009 Oct;62*(10):e1-34. doi: 10.1016/j.jclinepi.2009.06.006

Linder, A., Guh, D., Boyd, J. H., Walley, K. R., Anis, A. H., & Russell, J. A. (2014). Long-term (10-year) mortality of younger previously healthy patients with severe sepsis/septic shock is worse than that of patients with nonseptic critical illness and of the general population. *Critical Care Medicine, 42*(10), 2211-8. doi: 10.1097/CCM.0000000000000503.

Makki, K., Froguel, P., & Wolowczuk, I. (2013). Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. *ISRN Inflammation, 2013*, 139239. http://doi.org/10.1155/2013/139239

Mohamed-Ali, V., Pinkney, J. H., & Coppack, S. W. (1998). Adipose tissue as an endocrine and paracrine organ. *International Journal of Obesity and Related Metabolic Disorders, 22*(12), 1145-58.

Mocarski, M., Tian, Y., Smolarz, B. G., McAna, J., & Crawford. (2018). Use of international classification of diseases, ninth revision codes for obesity: trends in the United States from an electronic health record derived database. *Population Health Management, 21*(3), 222-230. doi: 10.1089/pop.2017.0092

Martino, J. L., Stapleton, R. D., Wang, M., Day, A. G., Cahill, N. E., Dixon, A. E., … Heyland, D. K. (2011). Extreme obesity and outcomes in critically ill patients. *Chest, 140*(5), 1198–1206. doi: 10.1378/chest.10-3023.

National Institutes of Health (NIH). (n.d.) Classification of overweight and obesity by BMI,

waist circumference, and associated disease risks. National Heart Lung and Blood Institute. U.S. Department of Health and Human Services. https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_dis.htm

Nguyen, A. T., Tsai, C., Hwang, L., Lai, D., Markham, C., & Patel, B. (2016). Obesity and mortality, length of stay and hospital cost among patients with sepsis: A nationwide inpatient retrospective cohort study. *PLoS ONE, 11*(4), e0154599. doi: 10.1371/journal.pone.0154599

Papadimitriou-Olivgeris, M., Aretha, D., Zotou, A., Koutsileou, K., Zbouki, A., Lefkaditi, A., … Fligou, F. (2016). The role of obesity in sepsis outcome among critically ill patients: a retrospective cohort analysis. *BioMed Research International, 2016*(5941279). doi: 10.1155/2016/5941279

Prescott, H. C., Chang, V. W., O'Brien Jr, J. M., Langa, K. M., Iwashyna, T. J., & O'Brien, J. J. (2014). Obesity and 1-year outcomes in older Americans with severe sepsis. *Critical Care Medicine, 42*(8), 1766-1774. doi:10.1097/CCM.0000000000000336

Romacho, T., Elsen, M., Rohrborn, D., & Ecklel, J. (2014). Adipose tissue and its role in organ cross talk. *Acta Physiologica, 210*(4), 733-53. doi:10.1111/apha.12246

Sell, H., Habich, C., & Eckel, J. (2012). Adaptive immunity in obesity and insulin resistance. *Nature Reviews Endocrinology, 8*(12), 709-16. doi:10.1038/nrendo.2012.114

Shah, N. R., & Braverman, E. R. (2012). Measuring adiposity in patients: The utility of body mass index (BMI), percent body fat, and leptin. *PloS One, 7*(4), e33308. doi: 10.1371/journal.pone.0033308

Shankar-Hari, M. & Rubenfeld, G. D. (2016). Understanding long-term outcomes following sepsis: implications and challenges. *Current Infectious Disease Reports, 18*(11), 37. doi:

10.1007/s11908-016-0544-7

Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., . . . Angus, D. C. (2016). The third international consensus definitions for sepsis and septic shock (Sepsis-3). *Journal of the American Medical Association, 315*(8), 801-810. doi:10.1001/jama.2016.0287

Singer, G., & Granger, D. N. (2007). Inflammatory responses underlying the microvascular dysfunction associated with obesity and insulin resistance. *Microcirculation, 14*(4-5), 375-87.

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). (2009). Checklist for cohort studies. University of Bern. https://www.strobe statement.org/index.php?id=available-checklists

Tschöp, J., Nogueiras, R., Haas-Lockie, S., Kasten, K., Castañeda, T. R., Huber, N., … Tschöp, M. H. (2010). CNS leptin action modulates immune response and survival in sepsis. The Journal of Neuroscience: *The Official Journal of the Society for Neuroscience, 30*(17), 6036–6047. http://doi.org/10.1523/JNEUROSCI.4875-09.2010

Winters, B. D., Eberlein, M., Leung, J., Needham, D. M., Pronovost, P. J., & Sevransky, J. E. (2010). Long-term mortality and quality of life in sepsis: a systematic review. *Critical Care Medicine, 38*(5), 1276–83. doi: 10.1097/CCM.0b013e3181d8cc1d

Trayhum, P., & Wood, I. S. (2004). Adipokines: inflammation and the pleiotropic role of white adipose tissue. *British Journal of Nutrition, 92*(3), 347-55.

Wacharasint, P., Boyd, J. H., Russell, J. A., & Walley, K. R. (2013). One size does not fit all in severe infection: obesity alters outcome, susceptibility, treatment, and inflammatory response. *Critical Care, 17*(3), R122. doi: 10.1186/cc12794

Wisse, B. E. (2004). The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *Journal of the American Society of Nephrology, 15*(11), 2792-800.

World Health Organization (WHO). (November 2016). *BMI Classification*. Retrieved from http://apps.who.int/bmi/index.jsp?introPage=intro_3.html

Ye, J., & McGuinness, O. P. (2012). Inflammation during obesity is not all bad: evidence from animal and human studies. American Journal of Physiology: Endocrinology and Metabolism, 304, E466-E477. doi:10.1152/ajpendo.00266.2012

Yende, S., Austin, S., Rhodes, A., Finfer, S., Opal, S., Thompson, T., . . . Angus, D. C. (2016). Long-term quality of life among survivors of severe sepsis: analysis of two international trials. *Critical Care Medicine, 44*(8), 1461–1467. doi: 10.1097/CCM.0000000000001658

Table 1

Studies examining obesity and sepsis mortality in adults.

First Author, year, STROBE Score	Objective	Research design	Sample	Statistical analysis	Main outcomes
Abbate, 2016 STROBE Score: 21	To determine if age modifies the association between obesity and mortality in sepsis	Retrospective, cohort 2010 - 2011	N= 116,566 sepsis n = 13,991 (12%) coded as obese n = 30, 712 (26.3%) coded as death in hospital California State Inpatient Database Defined obesity has a binary Y/N variable using ICD-9 based chronic disease indicators Defined sepsis with ICD-9 codes for severe sepsis and septic shock	Multivariate logistic regression	Obesity 18.4% Non Obesity 27.4% (After adjusting for covariates absolute difference -9.0%, 95% CI, -9.7 to -8.3) Obesity and older age associated with decreased mortality (P < 0.001) Age < 50 years and obesity (OR 0.99, 95% CI, 0.87- 1.13) Age > 50 years and obesity (OR 0.65, 95% CI, 0.62-0.68)
Arabi, 2013 STROBE Score: 20	To examine the impact of obesity on hospital mortality in septic shock Secondary aim to examine ICU mortality and hospital length of stay	Retrospective, cohort 1996 - 2006	N= 8,670 n = 2, 882 with documented height and weight Cooperative Antimicrobial Therapy of Septic Shock (CATSS) (28 medical centers in Canada,	Analysis of variance (ANOVA) Chi-square Multivariate logistic regression	Unadjusted hospital mortality by weight group: Under weight 61.7%, Normal

	United States, Saudi Arabia) Defined sepsis using 1992 AACP Guidelines Defined obesity using WHO criteria	weight 56.9%, Overweight 54.4%, Obese 51.3%, Very Obese 44.7% (P = 0.003). Became insignificant when adjusted for confounders. Obese and Very Obese categories were associated with more gram positive infections, more skin/soft tissue infections, and less pneumonia Obese categories had more diabetes and related

					compli cations
Gaulton, 2014 STROBE Score: 21	To define a novel association between obesity and mortality in sepsis, and to identify a potential high-risk population for future targeted interventions	Retrospective, cohort March 1, 2007 – June 30, 2011	N = 1835 n = 1779 after exclusion for leg amputation, pregnancy, or missing height and weight 7.1% Underweight 60.6% Non-obese 32.2% Obese Pennsylvania Integrated Clinical and Administrative Research Database (PICARD) Used UPHS antibiotic algorithm for presumed sepsis treatment Defined obesity using WHO criteria	Wilcoxon Rank Sum Chi-square Forward selection logistic regression	28 day mortality overall 22.1% Non obese 21.1% Obese 24.4% (Unadjusted OR 1.21, 95% CI, 0.95-1.54, P = 0.12) No effect noted by gender (P = 0.59), admission to hospital (P = 0.54), or ICU location (P = 0.29) No linear association between BMI and mortality (P = 0.14) Severely obese higher odds of mortality after adjustment for sepsis severity compared to normal group (OR 1.53, 95% CI,

					0.96 0 2.36, P = 0.05)
Gaulton, 2015 STROBE Score: 21	to determine if BMI is associated with 28-day mortality in a patient population presenting to the emergency department with severe sepsis or septic shock	Retrospective, cohort January 2005 – October 2007	N = 1324 n = 1191 after excluding for missing or unreliable data 54.7% male 53.6% African American 57 median age (IQR 45-69) 25.1 median BMI Pennsylvania Integrated Clinical and Administrative Research Database (PICARD) Sepsis defined using 2001 consensus recommendations Obesity defined using NIH criteria	Wilcoxon Rank Sum Kruskal–Wallis Chi square Multivariate logistic regression 5 Knot restricted cubic spline regression	Overall cohort mortality 19.9% at 28 days; 24.4% at 60 days Mortality at 28 days for normal weight 22% vs morbid obesity 6.5% (P = 0.002) Obese and morbid obese were less likely to die (OR 0.67, 95% CI, 0.46 – 0.95, P = 0.04) No difference in mortality between groups for 60 days and 1 year in adjusted and unadjusted models Obese and morbidly obese more likely to have soft tissue infections Morbidly obese were younger

					Overweight, obese, morbidly obese had more comorbidity of diabetes, hypertension, chronic heart failure, and less comorbidity of cancer and immunosuppression
Kuperman, 2013 STROBE score: 21	To determine the association between BMI and survival in patients admitted with a diagnosis of sepsis	Retrospective, cohort July 1, 2007 - June 30, 2010	N = 792 24% obese 6% morbidly obese Penn State Milton S. Hershey Medical Center Defined obesity using WHO criteria Defined sepsis with ICD-9 codes for sepsis, severe sepsis, septic shock	Analysis of variance (ANOVA) Chi-square Cochran-Armitage Multivariate logistic regression	Odds ratio for mortality was 1.5 (95% CI 0.67-6.3) for underweight patients and 0.7 (95% CI 0.12 – 4.2) for those with morbid obesity (P = 0.19) BMI as a continuous variable, in-hospital sepsis survivors had a BMI of 27.6 kg/m^2,compared with 26.3 kg/m^2 among non- survivors (P = 0.03) Diabetes was protective against death, with an odds ratio for mortality of 0.53 (95% CI 0.32-0.88, P = 0.01)

Nguyen, 2016 STROBE Score: 21	To examine the association between obesity and all-cause mortality, length of stay and hospital cost among patients with sepsis 20 years of age or older	Retrospective, cohort 2011	N = 1,763,000 50.6% female 34.7% severe sepsis 20.9% septic shock Nationwide Inpatient Sample (NIS) of Healthcare Cost and Utilization Project (HCUP) Defined obesity as ≥ 30 using Elixhauser comorbidity measure Defined sepsis with ICD-9 codes for sepsis, severe sepsis, septic shock	Wilcoxon Rank Sum Chi-square tests Pearson's correlation Multivariate logistic regression	Overall sepsis mortality rate was 14.8% Sepsis 14.3% Severe sepsis 28.2% Septic shock 35.4% After adjustment obesity was association with 16% decrease in odds of dying (OR 0.84, 95% CI, 0.81-0.88). Obesity more likely to be female, younger, lower income area, less likely to have Medicare Obesity more likely to have chronic heart failure, pulmonary circulatory disorders, diabetes, hypertension, liver disease, renal failure, depression, psychoses, deficiency anemia, arthritis, hypothyroid Non obesity more likely to have AIDS, alcohol abuse, drug abuse, fluid and electrolyte disorders, coagulopathy, cancer, valvular heart disease, paralysis, neurological disorders
Prescott, 2014	To determine whether 1-year mortality, healthcare utilization, and	Retrospective, cohort 1998 – 2004 baseline data and claims based data for 1998 - 2005	N = 1524 n = 1404 after exclusion for missing	Kruskal-Wallis Chi-square test Multivariate logistic regression	Increasing BMI was associated with lower in hospital, 90 day and 1 year mortality. Normal weight 62%

STROBE Score: 22	functional outcomes following a severe sepsis hospitalization differ by body mass index		height and weight or underweight 42.5% normal weight 33.7% overweight 23.8% obese or severely obese Health and Retirement Study (HRS) Definition of sepsis based on ICD-9 claims Defined obesity using WHO criteria	Kaplan Meier Curve	Overweight 53.1% Obese 46% Severely Obese 44.7% (P < 0.001) Obese (OR 0.59, 95% CI, 0.39-0.88) Severely Obese (OR 0.46, 95% CI, 0.26 – 0.80) (P < 0.001) Obese patients were more like younger (P < 0.001), female (P < 0.001), less wealthy (P < 0.001), had diabetes (P< 0.001), had more renal dysfunction (P = 0.001), had more ADL baseline limits (P = 0.02) Kaplan Meier curve BMI was associated with lower morality (P < 0.001)
Wacharasint, 2013 STROBE Score: 21	To determine whether being overweight or obese altered (a) mortality and organ dysfunction outcomes of sepsis, (b) pattern of susceptibility to infection, (c) treatment received by patients, or (d) the inflammatory response to sepsis	Retrospective, cohort 2001-2006	N = 778 n = 730 with height and weight measured of which n = 250 BMI < 25 n = 209 BMI 25-29.9 n = 245 BMI ≥ 30 n = 396 vasopressin group of which n = 47 BMI < 25 n = 13 BMI 25-29.9 n = 16 BMI ≥ 30 n = 382 inflammatory	Kruskal-Wallis Chi Square Log rank (Mantel Cox) hazard ratio Kaplan Meier curve	Mortality at 28 days was lower in (BMI 25-29.9 and BMI ≥ 30 vs BMI < 25 (P = 0.02). BMI < 25 vs BMI 25-29.9 (P = 0.10). BMI < 25 vs BMI ≥ 30 (P = 0.01). BMI 25-29.9 vs BMI ≥ 30 (p = 0.2). For every 1 unit increase in BMI, HR adjusted mortality was 2% lower (95% CI, 0.97-0.99, P = 0.04) Median BMI: BMI < 25 = 23; BMI 25- 29.9 = 28; BMI ≥ 30 = 34 Obese patients less likely to be male (BMI < 25 = 62%;

	cytokine group of which n = 138 BMI < 25 n = 112 BMI 25-29.9 n = 132 BMI ≥ 30 Vasopressin and Septic Shock Trial (VASST) a multicenter randomized doubled blind controlled trial Defined obesity using NIH criteria and collapsed underweight and normal weight into BMI < 25 Defined sepsis using 1992 AACP Guidelines	BMI 25- 29.9 = 67.9%; BMI ≥ 30 = 55.5% (P = 0.03) Obese patients more likely to have diabetes (BMI < 25 = 14.9%; BMI 25- 29.9 = 20.6%; BMI ≥ 30 = 29.8% (P < 0.0001) Lower rates of lung infection found in overweight and obese (BMI < 25 = 49.8%; BMI 25- 29.9 = 45%; BMI ≥ 30 = 35% (P = 0.003) IL-6 was blunted in overweight and obesity in early septic shock (BMI < 25 = 235 (IQR 44- 1793 pg/ml); BMI 25- 29.9 = 190 (IQR 44-2339 pg/ml); BMI ≥ 30 = 106 (IQR 34 – 686 pg/ml) (P = 0.046) No differences in APACHE II, lactate, WBC, platelets, MCP-1, TNF-α, resistin

Chapter Two

The obesity paradox in sepsis: A theoretical framework

Jamie Robinson, Theresa Swift-Scanlan, Jeanne Salyer, Terry Jones

Virginia Commonwealth University

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Abstract

Sepsis is a life threatening syndrome that occurs in response to a severe infection. In recent years the understanding of the pathobiology of sepsis has been refined, with research describing the altered host response as the underlying cause. Survivors of sepsis often have long hospital stays and suffer from subsequent frailty and long-term health consequences. Predicting attributes of sepsis survivors remains challenging, however an "Obesity Paradox" exists wherein obese individuals survive sepsis at higher rates than their normal weight counterparts. We present a model that describes the relationships between sepsis and obesity, focusing on inflammation as a shared pathway for dysregulation in obese versus healthy weight adults. Understanding the interaction of these complex variables is an important first step toward developing interventions and treatments to augment sepsis survival.

Keywords: sepsis, obesity, mortality, survival

Introduction

Sepsis is a life-threatening syndrome in which complex biologic systems respond to pathogenic invaders with pro- and anti- inflammatory responses in a manner that evolves over time, typically resulting in a dysregulated, or exaggerated, host response (Singer et al., 2016). Not only is sepsis a public health priority in the United States (US), affecting 1.7 million adults per year (CDC, 2016), it is a global health burden with an estimated 30 million cases and 6 million deaths per year (Reinhart, Daniels, Kissoon, Machado, Schachter, & Finger, 2017). In response to this crisis The World Health Assembly (WHA) has published recommendations for researchers and clinicians centered on prevention, early diagnosis, and management of sepsis to reduce premature deaths and reduce effects of long-term disability for survivors (Reinhart et al., 2017). The National Institute of Nursing Research (NINR) supports nursing science aimed at developing new biological knowledge that will translate into improving patient health outcomes and reducing disabling effects of symptoms (NINR, 2016). Identifying sepsis phenotypes is critical to the goal of promoting early diagnosis and management support. In recent years an "obesity paradox" has been observed in sepsis where obese patients survive at higher rates than their non-obese counterparts (Abbate, 2016; Arabi, 2013; Meyer et al., 2018; Nguyen et al., 2016; Wacharasint, Boyd, Russell, & Walley, 2013). Identifying the causal mechanisms and teasing out characteristics of an obese-sepsis phenotype is one step toward meeting the goals of the WHA and the NINR. The causal mechanisms for the obesity paradox have not been fully described, nor is there an established theoretical framework in which to test the salient variables thought to contribute to this phenomenon. We present a model that describes the relationships between sepsis and obesity, focusing on inflammation as a shared pathway for dysregulation in obese versus healthy weight adults, that affects mortality rates. Research to explain this

phenomenon may lead to interventions that aid in early diagnosis by identifying patient phenotypes and may contribute to management algorithms that can reduce the burden of debilitation and persistent symptoms for survivors.

Concepts

Inflammation

As a protective mechanism the body responds to noxious stimuli, such as a pathogenic invader, with the inflammatory response to communicate exposure and to contain the foreign substance (Bennett, Reeves, Billman, & Sturmberg, 2018; Del Giudice & Gangestad, 2018). Governed by immune-regulatory pathways the sympathetic nervous system (SNS) triggers peripheral pro-inflammatory responses, while the parasympathetic nervous system (PNS) and the neuroendocrine hypothalamic-pituitary-adrenal (HPA) axis balance sympathetic effects by inhibiting inflammatory responses, and SNS, PNS and HPA pathways are mediated by cytokine and hormonal influences (Bennett et al., 2018). At the intersection of the immune and neuroendocrine systems, cytokines and immune mediators released during the immune response can activate neural responses that exaggerate local inflammation, but that can also activate neuroendocrine responses to restore homeostasis (Bennett et al., 2018).

The ubiquitous goal of non-specific inflammation is to increase blood flow, dispatch white blood cells to infiltrate the area and isolate the threat, and increase phagocytosis to remove the threat. Normally, this process is followed by down-regulation of inflammation to promote healing and maintain homeostasis (Bennett et al., 2018). When the body is invaded or injured the inflammatory response is activated causing monocyte-macrophage cells to be released, followed by the release of cytokines and chemokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), that mediate non-specific cellular, tissue, and vascular damage

(Bennett et al., 2018; Del Giudice & Gangestad, 2018). The activity of monocyte-macrophage cells is heightened in the state of obesity and is a likely confounding factor contributing to the obesity paradox.

Obesity

Characterized by excess adipose tissue, obesity is a global health concern that increases risk of comorbidities, decreases life expectancy, and results in 2.8 million deaths annually (Pal, Pal, Babu, & Lalitha, 2015). Antecedents of obesity include caloric energy intake and usage imbalance, decreased physical activity, and genetic predispositions (Pal et al., 2015). Recent observations point to socioeconomic status and environmental factors causing epigenetic modifications as well (Vecchié et al., 2018). Obesity is associated with several disorders such as metabolic syndrome, type 2 diabetes, cardiovascular disease, lipid disorders, stroke, sleep apnea, and cancer (CDC, 2018). In the US, middle aged (40.2%) and older adults (37%) as well as non-Hispanic blacks (48.1%) and Hispanics (42.5%) have higher rates of obesity than other groups (CDC, August 13, 2018). The economic burden of obesity was estimated at $147 billion in the US in 2008 (CDC, August 13, 2018).

Obesity definition.

The World Health Organization defines obesity as an accumulation of abnormal or excessive fat that is a risk to health (WHO, 2019). The Obesity Society elaborates, defining obesity as a chronic disease with multiple phenotypes resulting from long term positive energy balance and excess adiposity that leads to physiologic abnormalities (Kelly, Kahan, Heymsfield, Kotz, & Jastreboff, 2019). Obesity is a clinical diagnosis that is determined by Body Mass Index (BMI), a surrogate measure of body fat, (CDC, n.d.). BMI is an index of weight adjusted for height calculated as weight in kilograms divided by the square of the height in meters (kg/m^2).

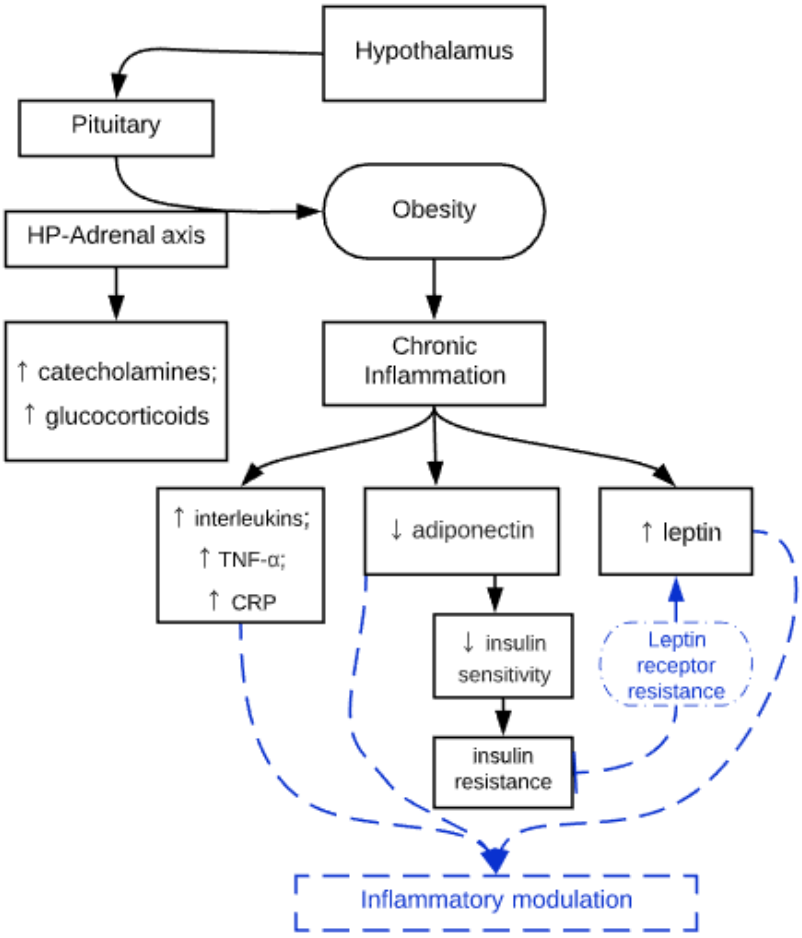
Based on range of BMI individuals are classified as underweight (BMI < 18.50 kg/m^2), normal weight (BMI = 18.50 to 24.99 kg/m^2), overweight (BMI = 25.0 to 29.99 kg/m^2), obese (BMI = 30.0 to 39.99 kg/m^2) or very obese (BMI > 40 kg/m^2) (WHO, November 2016). A limitation of BMI is that individuals with varying clinical and biochemical characteristics are in the same category, regardless of emerging evidence of obesity phenotypes (Vecchié et al., 2018). Despite this limitation, BMI is still accepted internationally by researchers as the standard method for identifying and defining obesity (Engin, 2017).

Neurophysiologic control of energy balance and regulation of body weight occurs along the HPA axis. In obesity, chronic low grade inflammation increases pro-inflammatory cytokines while alteration in the HPA axis increases catecholamine and glucocorticoid levels that together contribute to modulation of immune function (Pal et al., 2015), (Figure 1). The consequences of obesity stem from the activity of adipose tissue, which is up regulated when it is present in excess. Adipose tissue secretes a large number of adipokines that have integral roles in immunometabolism. For example, chronic low grade inflammation occurs when macrophages preferentially take up residence in adipose tissue (Na, Je, & Seok, 2018) leading to cytokine IL-6, CRP, and TNF-α up regulation, while parallel up regulation of the pro-inflammatory adipokine leptin and down regulation of the anti-inflammatory adipokine adiponectin takes place (Cottam et al., 2004). Despite the subsequent hyperleptinemia, leptin is biologically unavailable, thus the effects of leptin are often not observed in obesity and leptin resistance is independently associated with insulin resistance, suggesting that leptin receptor activity may be altered (Sudhakar, Silambanan, Chandran, Prabhakaran, & Ramakrishnan, 2018). CRP, a protein that increases significantly in concentration during inflammation and obesity, has been found to be independently associated with changes in leptin levels and researchers have hypothesized that

CRP interacts with the leptin receptor, linking CRP and leptin to immune function. Receptor resistance associated with obesity is not a novel concept. Insulin resistance has been widely accepted as a consequence of obesity for many years (Dandona, Aljada, & Bandyopadhyay, 2004; Jung, Jung, Reaven, & Kim, 2018)

Figure 1

A hypothesized model of inflammatory modulation. The hypothalamus-pituitary-adrenal axis exerts action on cellular mechanisms in both obesity and inflammation, adapted from Pal et al., (2015). In obesity there is heightened immunometabolic activity, inducing a state of chronic low grade inflammation. Macrophages/monocytes that take up residence in adipose tissue alter immunometabolic inflammation where the cytokines IL-6, CRP, TNF-α, and leptin are up regulated while parallel down regulation of the anti-inflammatory adipokine adiponectin occurs (Cottam et al., 2004). It has been established that there is a relationship between adipokines (adiponectin and leptin) and decreased insulin sensitivity and insulin resistance. Depicted in blue, this model hypothesizes that a similar mechanism occurs wherein there is increased, but biologically unavailable leptin, due to leptin receptor resistance, which contributes to inflammatory modulation.



Sepsis

Sepsis is a heterogeneous syndrome where the host response to inflammation and infection becomes excessive, causing harm to the epithelium and capillary leakage, leading to organ failure and death (Cohen et al., 2015). Sepsis with organ dysfunction (severe sepsis) and septic shock is associated with higher mortality rates, up to 50%, while general sepsis has a mortality rate of less than 20% (De La Rica, Gilsanz, & Maseda, 2016). Mansur et al. (2015) reported a 71% increase in cases of severe sepsis between 2003 and 2007 and reported that total costs for all patients with severe sepsis increased 57% in the same time period. The approximate cost of sepsis care in 2008 was $14.6 billion (Hall, Williams, DeFrances, & Golosinskiy, 2011).

The risk factors for sepsis are varied. More than half of the cases of severe sepsis occur in adults over age 65 (Mayr, Yende, & Angus, 2014). Although sepsis can occur in both sexes it is more common in males (De La Rica et al., 2016; Sakr et al., 2012). Black race has been reported to have a higher incidence of both sepsis and severe sepsis than their white counterparts (Barnato, Alexander, Linde-Zwirble, & Angus, 2008; Dombrovskiy, Martin, Sunderram, & Paz, 2007); in fact, De La Rica and colleagues (2016) found that in the United States blacks had a 2-fold greater probability of experiencing sepsis. Over half of the patients with sepsis have chronic comorbid conditions such as diabetes, congestive heart failure, chronic pulmonary disease, cancer, and chronic renal failure (De La Rica et al., 2016; Mayr et al., 2014).

Sepsis definition.

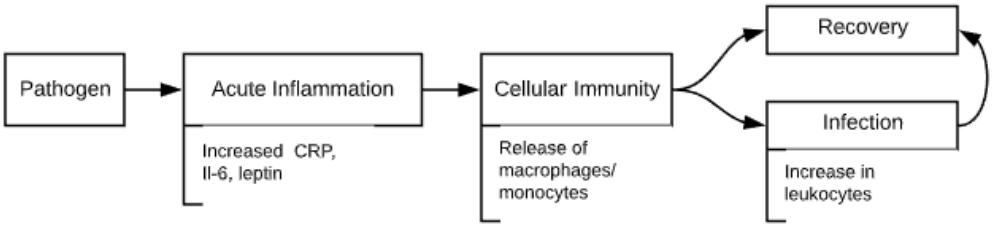
While systemic inflammatory response syndrome (SIRS) has been the focus of sepsis research for the last two decades (Bone et al., 1992; Levy et al., 2003), a refined understanding of the pathophysiology now points to an altered host response as the underlying cause of sepsis (Singer, Deutschman, Seymour, Shankar-Hari, et al., 2016). When the body encounters a pathogenic invader, an inflammatory and immune response occurs in attempt to isolate the threat. If not contained, the pathogenic invader can result in infection and the immune response will trigger the release of leukocytes to systemically counteract the pathogenic invader in an attempt to recover (Figure 2). However, in sepsis the host inflammatory response is so excessive that the cytokine storm causes epithelial damage, increased capillary permeability, organ dysfunction, and even death (Winters et al., 2010), (Figure 2). Of course, at any point in this process, recovery could either occur spontaneously, or more likely, due to aggressive medical treatment, but currently 1 in 3 hospital deaths are due to sepsis (CDC, 2016). However, an "obesity paradox", whereby obese patients with sepsis survive at higher rates than their non-

obese counterparts has been documented (Abbate, 2016; Nguyen et al., 2016; Prescott, Langa, Liu, Escobar, & Iwashyna, 2014; Wacharasint et al., 2013). In fact, increased BMI has been associated with decreased mortality from post-operative sepsis (Davenport et al., 2009; Memtsoudis et al., 2012), community acquired pneumonia (Braun et al., 2016), and septic shock (Arabi, 2013; Wacharasint et al., 2013).

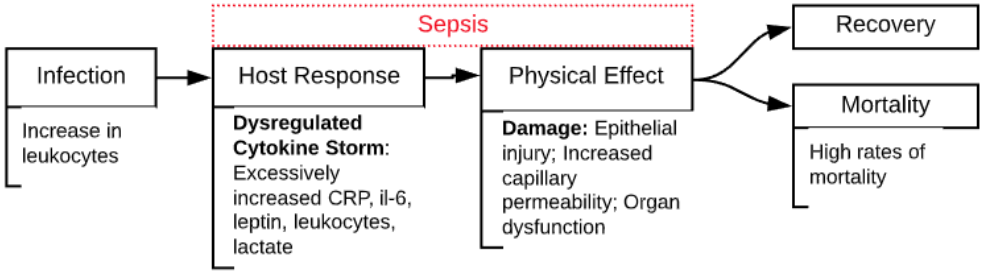
Figure 2

A comparison of the normal response to infection and the dysregulation response in sepsis. The normal response to infection is depicted**,** where a pathogen elicits the ubiquitous acute inflammatory response, which is followed by the activation of cellular immunity, including release of the leukocytes called macrophages/monocytes, followed by recovery, or a state of infection that typically leads to recovery. In sepsis (depicted in red) the body responds to infection in a dysregulated, over-active manner by releasing cytokines excessively. The physical effect to the cytokine storm is damage from epithelial injury, increased capillary permeability, and organ dysfunction. Together this damage is responsible for high mortality rates from sepsis.

Normal response to infection:



Dysregulated response to infection in sepsis:

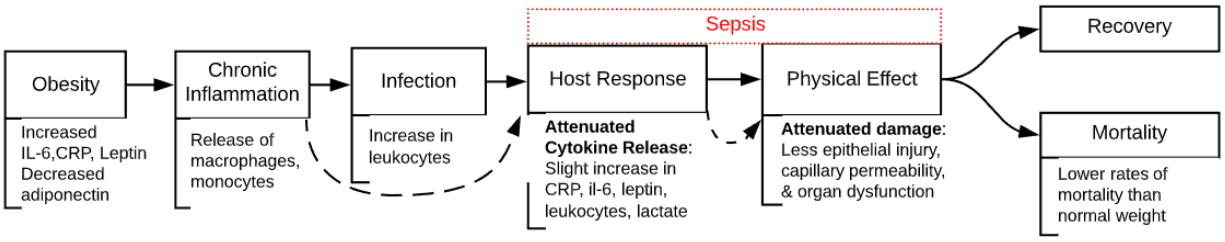


Relationship between Obesity and Sepsis

Inflammation is the common pathway shared by obesity and sepsis. Obesity is associated with chronic low grade inflammation whereas sepsis is an acute state of inflammation and dysregulated host response. Taken together, the model presented in Figure 3 hypothesizes this that obesity related chronic inflammation, characterized by up regulation of the pro-inflammatory markers IL-6, CRP, and leptin actually modulates the insult from sepsis. Therefore, when the excessive inflammation of sepsis occurs, the effect is less severe and the result is a more balanced physiologic response that causes less endothelial damage, less capillary permeability and ultimately less organ dysfunction (Figure 3).

Figure 3

The hypothesized relationship between obesity, sepsis, and sepsis mortality. The chronic inflammation that obesity is notorious for chronic inflammation and in this model chronic inflammation is hypothesized to modulate the sepsis (depicted in red) host response which results in an attenuated cytokine release and attenuated physical effect. Together the attenuated cytokine release and attenuated damage leads to lower mortality rates than in those individuals of normal weight.

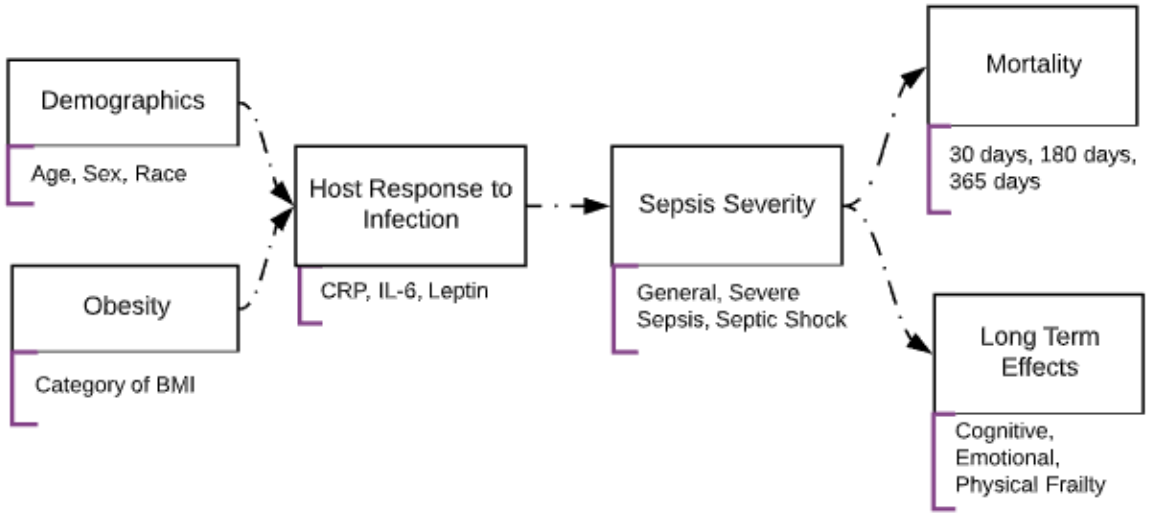


Discussion

The conceptual model presented here is a theoretical construct based on what is understood about pathophysiology and the reports of the obesity paradox in the literature. This model offers a sound base upon which to test the salient variables of obesity, sepsis and mortality, but allows for adaptability to also test for associations between variables that will help to distinguish sepsis phenotypes. For example, the relationships between obesity, demographic variables, biologic indicators of host response to infection, and degree of sepsis severity to the dependent variables of morality time points and long-term effects can be tested (Figure 4). This is important in order to fully understand risk factors for individuals based on their unique phenotypical context.

Figure 4

This figure illustrates an example of how to use the proposed model to test relationships. In this representation the base of the model remains constant, however different variables are added to further explicate potential relationships. This model tests the relationships between the independent variables of demographic information, obesity, biologic indicators of host response to infection, and sepsis severity with the dependent variables of mortality time points and long term effects.



An exploration of pathophysiology points to inflammation as the common characteristic shared by obesity and sepsis. Molecular mechanisms demonstrate the immunometabolic actions of adipose tissue while also describing how the phenomenon of insulin resistance could apply in the case of hyperleptinemia. Adipocytes produce the pro-inflammatory adipokine leptin and the pro-inflammatory cytokine IL-6, which are up regulated in obesity and sepsis, and leptin and IL-6 independently promote the synthesis of CRP, a protein released during inflammation (Hribal, Fiorentino, & Sesti, 2014). These same players are known to be elevated in obesity related insulin resistance, providing a physiologic precedence for receptor resistance (Figure 1) (D'Alessandris, Lauro, Presta, & Sesti, 2007; Osborn & Olefsky, 2012). Leptin receptor resistance causes hyperleptinemia, whereby higher than normal leptin levels are present, but the leptin is biologically unavailable. In other words, hyperleptinemia comes from a physiologic attempt to activate leptin receptors with increased leptin levels, causing the unexpected effect of an attenuated inflammatory response. This modulated physiologic response seems to provide protection whereby, when both obesity and sepsis are present, the inflammatory response is attenuated rather than excessive, resulting in less tissue damage, less severe systemic response, and ultimately lower rates of severe sepsis, septic shock, and death (Hillenbrand, Knippschild,

Weiss, Schrezenmeier, Henne-Bruns, Huber-Lang, & Wolf, 2010). Again, this conceptual model allows for the testing of these relationships to build upon the current body of knowledge (Figure 4).

Due to the serious nature of sepsis and its impact on the population, new theories are emerging and research into hypothesized sepsis etiologies is underway. The Persistent Inflammation, Immuosuppression, Catabolism Syndrome (PICS) hypothesis builds on the Chronic Critical Illness (CCI) model and attempts to define a phenotype of critical illness (Kamel, Rosenthal, Brakenridge, Croft, Moore, & Rosenthal, 2018). The main tenet is that given the excess energy stores in obesity, catabolism may not be as deleterious as it is in lean individuals. The researchers state that further research is needed to control for increased adiposity. This theory may offer an additional lens through which to view the complexity of sepsis mortality in obesity. We propose that this theory does not negate the conceptual model presented in this paper. Instead we agree that this theory has merit and could be tested within the model we propose.

The association between obesity and decreased sepsis mortality has been observed in several populations, yet the mechanism has not yet been fully described. For example, increased BMI and decreased mortality has been documented in post-operative sepsis in vascular surgery (Davenport et al., 2009), laparoscopic gastric bypass, (Villamere, Gebhart, Vu, Nguyen, & Nguyen, 2014), sepsis from pneumonia (Corrales-Medina, Valayam, Serpa, Rueda, & Musher, 2011; Kahlon et al., 2013; King et al., 2013; Nie et al., 2014; Reiner et al., 2009), and in septic shock (Arabi et al., 2013; Wacharasint et al., 2013). While obesity puts patients at higher risk of contracting adult respiratory distress syndrome (ARDS) after surgery, the risk of mortality is lower (Memtsoudis et al., 2012). It has been proposed that because obesity is associated with

less virulent gram positive infections such as from skin and soft tissue infection, the survival rate is higher. However, we suggest that obesity related chronic low-grade inflammation attenuates the host response resulting in lower mortality (Figure 3). The variability in post-operative sepsis mortality could be related to pathogenic virulence in combination with obesity related inflammation modulation (Figure 3). Sepsis from underlying respiratory causes, which are predominantly caused by virulent gram negative organisms, trends toward protection, with reduced 30 day mortality for obese patients with sepsis from pneumonia (Corrales-Medina, Valayam, Serpa, Rueda, & Musher, 2011; Kahlon et al., 2013; King et al., 2013; Nie et al., 2014; Reiner et al., 2009). In septic shock obesity has been found to be associated with increased survival, indicating that the host response may be as important as microbial virulence when it comes to sepsis mortality (Arabi et al., 2013; Wacharasint et al., 2013). However, the highly pathogenic H1N1 influenza was found to have higher 30 day mortality for obese patients with sepsis, which could be explained by the rapidity of the onset of illness associated with influenza, wherein an attenuated host response is not strong enough to halt its effects (Kwong, Campitelli, & Rosella, 2011).

While several studies present contrary evidence on the association between obesity in adults and decreased sepsis mortality, we propose that methodological stringency and use of this conceptual model would help to strengthen interpretability of the results. Gaulton et al. (2014) reported no difference in sepsis survival in obese individuals, but results stemmed from participants with presumed sepsis rather than confirmed sepsis, indicating individuals may not have had sepsis, severe sepsis or septic shock. Papadimitriou-Olivgeris et al. (2016) reported no difference in sepsis survival in obese individuals when comparing sepsis outcomes to other critical illnesses such as intracranial hemorrhage, respiratory insufficiency, trauma, and a

category of "others." Comparing survival from sepsis to other critical illnesses with different pathophysiology is difficult to interpret and limits generalizability of the findings.

Given the charge by the WHA (2017) to focus research and clinical practice on prevention, early diagnosis and treatment of sepsis, it is not surprising that sepsis treatment guidelines focus on advances in supportive care, source control, maintenance of hemodynamic stability, and anti-infective agents (Teng, Pourmand, & Mazer-Amirshahi, 2018). Indeed, the Surviving Sepsis Campaign (2018) recommends measuring biologic indicators, such as serum lactate to guide treatment and the administration of anti-infective drugs after obtaining blood cultures. Recently adjuvant targeted therapies such as activated protein C, toll like receptor 4 antagonist, tumor necrosis factor receptor antagonist, and interleukin receptor antagonist, have been shown to be ineffective or harmful (Teng, Pourmand, & Mazer-Amirshahi, 2018). Using the conceptual model described here to test relationships between the biologic indicators CRP, IL-6, and leptin may result in clinical practice changes, by providing a guide to risk stratification and early recognition or by providing a road map to reduce long term debilitation.

An adjuvant approach that warrants investigation is the administration of leptin (metreleptin) to non-obese sepsis patients to simulate the immunomodulatory effect that obesity has in sepsis (Figure 3). Currently leptin (metreleptin) is used to treat congenital leptin deficiency and lipodystrophy, but there is no Food and Drug Administration approval at this time for other uses (Blüher & Mantzoros, 2015). A fear of using leptin in non-obese individuals relates to the orexigenic, or loss of appetite, effect that leptin is known for, which could reduce energy stores. More research to better understand how exogenous leptin administration might affect non-obese individuals and sepsis mortality is needed.

Conclusion

In both obesity and sepsis inflammation is the common thread. While it may be unusual to describe the protective effects of obesity, it is important to acknowledge paradoxes in the human body that may converge to convey a benefit of obesity in sepsis survival. Whether for risk stratification, phenotype identification, or for new treatment development, understanding the complexities of the obesity paradox is of primary importance. The NINR explicitly cites symptom precursors, such as biologic indicators, as part of its strategic plan to determine symptom risk, disease severity, and disease duration (NINR, 2016). This reinforces the importance of biologically focused research in nursing science to provide a strong foundation upon which to close knowledge gaps in patient care, such as has been identified in the obesity paradox.

Harnessing known biologic mechanisms is the basis of research that identifies possible new drug targets and classification of disease (Darden, Kundu, Pal, & Moult, 2018). Consideration of new ways to exploit biologic mechanisms is needed to advance patient care. Models that provide a basis for discovering causal factors of complex biologic systems such as sepsis are needed to set forth a road map for systematic investigation of variables that affect sepsis outcomes.

References

Abbate, L. M., Perman, S. M., Clambey, E. T., Van Pelt, R. E., & Ginde, A. A. (2016). Age Modifies the Association Between Obesity and Mortality Among Hospitalizations for Severe Sepsis. *Journal of the American Geriatric Society*, *64*(4), 882–883. https://doi.org/10.1016/S2214-109X(16)30265-0.Cost-effectiveness

Abdullah, A. R., Hasan, H. A., & Raigangar, V. L. (2009). Analysis of the relationship of leptin, high-sensitivity C-reactive protein, adiponectin, insulin, and uric acid to metabolic syndrome in lean, overweight, and obese young females. *Metabolic Syndrome and Related Disorders*, *7*(1), 17–22. https://doi.org/10.1089/met.2008.0045

Arabi, Y. M., Dara, S. I., Tamim, H. M., Rishu, A. H., Bouchama, A., Khedr, M. K., Feinstein, D., Parrillo, J. E., Wood, K. E., Keenan, S. P., Zanotti, S., Martinka, G., Kumar, A., & Kumar, A. (2013). Clinical characteristics, sepsis interventions and outcomes in the obese patients with septic shock: an international multicenter cohort study. *Critical Care*, *17*(2), R72. https://doi.org/10.1186/cc12680

Bakker, J. (2017). Lactate is the target for early resuscitation in sepsis. *Revista Brasileira de Terapia Intensiva*, *29*(2), 124–127. https://doi.org/10.5935/0103-507X.20170021

Barnato, A. E., Alexander, S. L., Linde-Zwirble, W. T., & Angus, D. C. (2008). Racial variation in the incidence, care, and outcomes of severe sepsis: Analysis of population, patient, and hospital characteristics. *American Journal of Respiratory and Critical Care Medicine*, *177*(3), 279–284. https://doi.org/10.1164/rccm.200703-480OC

Bone, R. C., Balk, R. A., Cerra, F. B., Dellinger, R. P., Fein, A. M., Knaus, W. A., Schein, R. M. H., & Sibbald, W. J. (1992). Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*, *101*(6), 1644–1655.

https://doi.org/10.1378/chest.101.6.1644

Bornstein, S. R., Licinio, J., Tauchnitz, R., Engelmann, L., Negrao, A. B., Gold, P., & Chrousos, G. P. (1998). Plasma leptin levels are increased in survivors of acute sepsis: associated loss of diurnal rhythm in cortisol and leptin secretion. *Journal of Clinical Endrocrinology and Metabolism*, *83*(1), 280–283.

Braun, N., Hoess, C., Kutz, A., Christ-Crain, M., Thomann, R., Henzen, C., Zimmerli, W., Mueller, B., & Schuetz, P. (2016). Obesity paradox in patients with community-acquired pneumonia: Is inflammation the missing link? *Nutrition*, *33*, 1–7. https://doi.org/10.1016/j.nut.2016.07.016

Bujang, M. A., Sa'At, N., Tg Abu Bakar Sidik, T. M. I., & Lim, C. J. (2018). Sample size guidelines for logistic regression from observational studies with large population: Emphasis on the accuracy between statistics and parameters based on real life clinical data. *Malaysian Journal of Medical Sciences*, *25*(4), 122–130. https://doi.org/10.21315/mjms2018.25.4.12

Center for Clinical and Translational Research [CCTR]. (2020). Cite the Grant. https://cctr.vcu.edu/cite-us/

Chaudhary, N. S., Donnelly, J. P., & Wang, H. E. (2018). Racial differences in sepsis mortality at U.S. academic medical center-affiliated hospitals. *Critical Care Medicine*, *46*(6), 878–883. https://doi.org/10.1097/CCM.0000000000003020

Cheng, H. H., Chen, F. C., Change, M. W., Kung, C. Te, Cheng, C. Y., Tsai, T. C., Hsiao, S. Y., & Su, C. M. (2018). Difference between elderly and non-elderly patients in using serum lactate level to predict mortality caused by sepsis in the emergency department. *Medicine*, *97*(13), 1–6. https://doi.org/10.1097/MD.0000000000010209

Christopher, K. B. (2015). The body mass index paradox. *Critical Care Medicine*, *43*(12), 2693–2694. https://doi.org/10.1097/CCM.0000000000001344

Coopersmith, C. M., De Backer, D., Deutschman, C. S., Ferrer, R., Lat, I., Machado, F. R., Martin, G. S., Martin-Loeches, I., Nunnally, M. E., Antonelli, M., Evans, L. E., Hellman, J., Jog, S., Kesecioglu, J., Levy, M. M., & Rhodes, A. (2018). Surviving sepsis campaign: research priorities for sepsis and septic shock. *Intensive Care Medicine*, *44*(9), 1400–1426. https://doi.org/10.1007/s00134-018-5175-z

De Backer, D., & Dorman, T. (2017). Surviving Sepsis Guidelines A Continuous Move Toward Better Care of Patients With Sepsis. *Journal of the American Medical Association*, *317*(8), 807–808. https://doi.org/10.1007/s00134

De Schutter, A., Kachur, S., Lavie, C. J., Boddepalli, R. S., Patel, D. A., & Milani, R. V. (2016). The impact of inflammation on the obesity paradox in coronary heart disease. *International Journal of Obesity*, *40*(11), 1730–1735. https://doi.org/10.1038/ijo.2016.125

Duman, A., Akoz, A., Kapci, M., Ture, M., Orun, S., Karaman, K., & Turkdogan, K. A. (2016). Prognostic value of neglected biomarker in sepsis patients with the old and new criteria: predictive role of lactate dehydrogenase. *American Journal of Emergency Medicine*, *34*(11), 2167–2171. https://doi.org/10.1016/j.ajem.2016.06.012

Engin, A. (2017). The Pathogenesis of Obesity-Associated Adipose Tissue Inflammation. In A. B. Engin & A. Engin (Eds.), *Obesity and Lipotoxicity* (pp. 221–245). Springer International Publishing. https://doi.org/10.1007/978-3-319-48382-5_9

Florez, H., Castillo-Florez, S., Mendez, A., Casanova-Romero, P., Larreal-Urdaneta, C., Lee, D., & Goldberg, R. (2006). C-reactive protein is elevated in obese patients with the metabolic syndrome. *Diabetes Research and Clinical Practice*, *71*(1), 92–100.

https://doi.org/10.1016/j.diabres.2005.05.003

Fowler, R. A., Filate, W., Hartleib, M., Frost, D. W., Lazongas, C., & Hladunewich, M. (2009). Sex and critical illness. *Current Opinion in Critical Care*, *15*(5), 442–449. https://doi.org/10.1097/MCC.0b013e3283307a12

Gardner, A. K., Ghita, G. L., Wang, Z., Ozrazgat-baslanti, T., Raymond, S. L., Mankowski, R. T., Brumback, B. A., Efron, P. A., Bihorac, A., Moore, F. A., Anton, S. D., & Brakenridge, S. C. (2019). The Development of Chronic Critical Illness Determines Physical Function, Quality of Life, and Long-Term Survival Among Early Survivors of Sepsis in Surgical ICUs. *Critical Care Medicine*, *47*(4), 566–573. https://doi.org/10.1097/CCM.0000000000003655

Gradel, K. O., Jensen, T. G., Kolmos, H. J., Pedersen, C., Vinholt, P. J., & Lassen, A. T. (2013). Does C-reactive protein independently predict mortality in adult community-acquired bacteremia patients with known sepsis severity? *Apmis*, *121*(9), 835–842. https://doi.org/10.1111/apm.12040

Gucyetmez, B., & Atalan, H. K. (2016). C-reactive protein and hemogram parameters for the non-sepsis systemic inflammatory response syndrome and sepsis: What do they mean? *PLoS ONE*, *11*(2), 1–9. https://doi.org/10.1371/journal.pone.0148699

Hafner, S., Hillenbrand, A., Knippschild, U., & Radermacher, P. (2013). The obesity paradox and acute kidney injury: Beneficial effects of hyper-inflammation? *Critical Care*, *17*(6). https://doi.org/10.1186/cc13152

Herrán-Monge, R., Muriel-Bombín, A., García-García, M. M., Merino-García, P. A., Martínez-Barrios, M., Andaluz, D., Ballesteros, J. C., Domínguez-Berrot, A. M., Moradillo-Gonzalez, S., Macías, S., Álvarez-Martínez, B., Fernández-Calavia, M. J., Tarancón, C., Villar, J.,

Blanco, J., & on behalf of the GRECIA Network. (2019). Epidemiology and Changes in Mortality of Sepsis After the Implementation of Surviving Sepsis Campaign Guidelines. *Journal of Intensive Care Medicine*, *34*(9), 740–750. https://doi.org/10.1177/0885066617711882

Hribal, M., Fiorentino, T., & Sesti, G. (2014). Role of C Reactive Protein (CRP) in Leptin Resistance. *Current Pharmaceutical Design*, *20*(4), 609–615. https://doi.org/10.2174/13816128113199990016

Iwashyna, T. J., Ely, E. W., Smith, D. M., & Langa, K. M. (2010). Long-term cognitive impairment and functional disability among survivors of severe sepsis. *Journal of the American Medical Association*, *304*(16), 1787–1794. https://doi.org/10.1001/jama.2010.1553.Long-term

Iwashyna, T. J., & Netzer, G. (2012). The Burdens of Survivorship : An Approach to Thinking about Long-Term Outcomes after Critical Illness. *Seminars in Respiratory and Critical Care Medicine*, *33*, 327–338. https://doi.org/DOI: 10.1055/s-00000075

Jones, T. K., Fuchs, B. D., Small, D. S., Halpern, S. D., Hanish, A., Umscheid, C. A., Baillie, C. A., Kerlin, M. P., Gaieski, D. F., & Mikkelsen, M. E. (2015). Post-acute care use and hospital readmission after sepsis. *Annals of the American Thoracic Society*, *12*(6), 904–913. https://doi.org/10.1513/AnnalsATS.201411-504OC

Karampela, I., Christodoulatos, G. S., & Dalamaga, M. (2019). The Role of Adipose Tissue and Adipokines in Sepsis: Inflammatory and Metabolic Considerations, and the Obesity Paradox. *Current Obesity Reports*, *8*(4), 434–457. https://doi.org/10.1007/s13679-019-00360-2

Karlsson, S., Ruokonen, E., Varpula, T., Ala-Kokko, T. I., & Pettilä, V. (2009). Long-term

outcome and quality-adjusted life years after severe sepsis. *Critical Care Medicine*, *37*(4), 1268–1274. https://doi.org/10.1097/CCM.0b013e31819c13ac

Keaver, L., Xu, B., Jaccard, A., & Webber, L. (2018). Morbid obesity in the UK: A modelling projection study to 2035. *Scandinavian Journal of Public Health*, *January*, 1–6. https://doi.org/10.1177/1403494818794814

Klein, S. L. (2000). The effects of hormones on sex differences in infection: From genes to behavior. *Neuroscience and Biobehavioral Reviews*, *24*(6), 627–638. https://doi.org/10.1016/S0149-7634(00)00027-0

Levy, M. M., Fink, M. P., Marshall, J. C., Abraham, E., Angus, D., Cook, D., Cohen, J., Opal, S. M., Vincent, J. L., & Ramsay, G. (2003). 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Medicine*, *29*(4), 530–538. https://doi.org/10.1007/s00134-003-1662-x

Li, S., Hu, X., Xu, J., Huang, F., Guo, Z., Tong, L., Lui, K. Y., Cao, L., Zhu, Y., Yao, J., Lin, X., Guan, X., & Cai, C. (2019). Increased body mass index linked to greater short- and long-term survival in sepsis patients: A retrospective analysis of a large clinical database. *International Journal of Infectious Diseases*, *87*, 109–116. https://doi.org/10.1016/j.ijid.2019.07.018

Mayr, F. B., Yende, S., & Angus, D. C. (2014). Epidemiology of severe sepsis. *Virulence*, *5*(1), 4–11. https://doi.org/10.4161/viru.27372

Meyer, N., Harhay, M. O., Small, D. S., Prescott, H. C., Bowles, K. H., Gaieski, D. F., & Mikkelsen, M. E. (2018). Temporal Trends in Incidence, Sepsis-Related Mortality, and Hospital-Based Acute Care After Sepsis. *Critical Care Medicine*, *46*(3), 354–360. https://doi.org/10.1097/CCM.0000000000002872

Mustafić, S., Brkić, S., Prnjavorac, B., Sinanović, A., Porobić-Jahić, H., & Salkić, S. (2018). Diagnostic and prognostic value of procalcitonin in patients with sepsis. *Medicinski Glasnik, 15*(2), 93–100. https://doi.org/10.17392/963-18

Nachtigall, I., Tafelski, S., Rothbart, A., Kaufner, L., Schmidt, M., Tamarkin, A., Kartachov, M., Zebedies, D., Trefzer, T., Wernecke, K. D., & Spies, C. (2011). Gender-related outcome difference is related to course of sepsis on mixed ICUs: A prospective, observational clinical study. *Critical Care*, *15*(3). https://doi.org/10.1186/cc10277

Negrin, L. L., Jahn, A., & van Griensven, M. (2017). Leptin Protects Against Mortality and Organ Dysfunction in A Two-Hit Trauma/Sepsis Model and is IL-6-Dependent. *Shock, 48*(1), 130–137. https://doi.org/10.1097/SHK.0000000000000837

Nguyen, A. T., Tsai, C.-L., Hwang, L.-Y., Lai, D., Markham, C., & Patel, B. (2016). Obesity and Mortality, Length of Stay and Hospital Cost among Patients with Sepsis: A Nationwide Inpatient Retrospective Cohort Study. *PloS One, 11*(4), e0154599. https://doi.org/10.1371/journal.pone.0154599

Papadimitriou-olivgeris, M., Aretha, D., Zotou, A., Koutsileou, K., Zbouki, A., Lefkaditi, A., Sklavou, C., Marangos, M., & Fligou, F. (2016). The Role of Obesity in Sepsis Outcome among Critically Ill Patients : A Retrospective Cohort Analysis. *BioMed*, *5941279*.

Pepper, D. J., Demirkale, C. Y., Sun, J., Rhee, C., Fram, D., Eichacker, P., Klompas, M., Suffredini, A. F., & Kadri, S. S. (2019). Does Obesity Protect Against Death in Sepsis? A Retrospective Cohort Study of 55,038 Adult Patients. *Critical Care Medicine*, *47*(5), 643–650. https://doi.org/10.1097/CCM.0000000000003692

Pepper, D. J., Sun, J., Welsh, J., Cui, X., Suffredini, A. F., & Eichacker, P. Q. (2016). Increased body mass index and adjusted mortality in ICU patients with sepsis or septic shock: a

systematic review and meta-analysis. *Critical Care*, *20*(1), 181. https://doi.org/10.1186/s13054-016-1360-z

Prescott, H. C., & Angus, D. C. (2018). Enhancing Recovery from Sepsis. *Journal of the American Medical Association*, *319*(1), 62–75. https://doi.org/10.1001/jama.2017.17687

Prescott, H. C., Chang, V. W., O'Brien, J. M., Langa, K. M., & Iwashyna, T. J. (2014). Obesity and 1-year outcomes in older Americans with severe sepsis. *Critical Care Medicine*, *42*(8), 1766–1774. https://doi.org/10.1097/CCM.0000000000000336

Prevention, C. for D. C. and. (2016). *Data & Reports*. Data & Reports. https://www.cdc.gov/sepsis/datareports/index.html

Reinhart, K., Daniels, R., Kissoon, N., Machado, F., Schachter, R., & Finfer, S. (2017). Recognizing Sepsis as a Global Health Priority — A WHO Resolution. *New England Journal of Medicine*, *377*(5), 411–414. https://doi.org/10.1056/NEJMp1704633

Robinson, J., Swift-Scanlan, T., & Salyer, J. (2020). Obesity and 1-Year Mortality in Adults After Sepsis: A Systematic Review. *Biological Research for Nursing*, *22*(1), 103–113. https://doi.org/10.1177/1099800419876070

Robinson, J., Swift-Scanlan, T., Salyer, J., & Jones, T. (2020). The Obesity Paradox in Sepsis: A Theoretical Framework. *Biological Research For Nursing*. https://doi.org/10.1177/1099800420905889

Sandoval, E., & Chang, D. W. (2016). Association between race and case fatality rate in hospitalizations for sepsis. *Journal of Racial and Ethnic Health Disparities*, *3*(4), 625–634. https://doi.org/10.1007/s40615-015-0181-0

Schröder, J., Kahlke, V., Staubach, K. H., Zabel, P., & Stüber, F. (1998). Gender differences in human sepsis. *Archives of Surgery*, *133*(11), 1200–1205.

https://doi.org/10.1001/archsurg.133.11.1200

Shankar-Hari, M., Harrison, D. A., Ferrando-Vivas, P., Rubenfeld, G. D., & Rowan, K. (2019). Risk Factors at Index Hospitalization Associated With Longer-term Mortality in Adult Sepsis Survivors. *Journal of the American Medical Association*, *2*(5), e194900. https://doi.org/10.1001/jamanetworkopen.2019.4900

Shankar-Hari, M., & Rubenfeld, G. D. (2018). Race, Ethnicity, and Sepsis. *Critical Care Medicine*, *46*(6), 1009–1010. https://doi.org/10.1097/CCM.0000000000003060

Sherwin, R., Winters, M. E., Vilke, G. M., & Wardi, G. (2017). Does Early and Appropriate Antibiotic Administration Improve Mortality in Emergency Department Patients with Severe Sepsis or Septic Shock? *Journal of Emergency Medicine*, *53*(4), 588–595. https://doi.org/10.1016/j.jemermed.2016.12.009

Shukeri, W. F. W. M., Ralib, A. M., Abdulah, N. Z., & Mat-Nor, M. B. (2018). Sepsis mortality score for the prediction of mortality in septic patients. *Journal of Critical Care*, *43*, 163–168. https://doi.org/10.1016/j.jcrc.2017.09.009

Siegl, D., Annecke, T., Johnson, B. L., Schlag, C., Martignoni, A., Huber, N., Conzen, P., Caldwell, C. C., & Tschöp, J. (2014). Obesity-induced Hyperleptinemia Improves Survival and Immune Response in a Murine Model of Sepsis. *Anesthesiology*, *121*(1), 98–114. https://doi.org/10.1097/ALN.0000000000000192

Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., Bellomo, R., Bernard, G. R., Chiche, J.-D., Coopersmith, C. M., Hotchkiss, R. S., Levy, M. M., Marshall, J. C., Martin, G. S., Opal, S. M., Rubenfeld, G. D., van der Poll, T., Vincent, J., & Angus, D. C. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Journal of the American Medicine Association*, *315*(8), 801–810.

https://doi.org/10.1001/jama.2016.0287

Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-hari, M., Annane, D., Bauer, M., Bellomo, R., Bernard, G. R., Chiche, J., Craig, M., Hotchkiss, R. S., Levy, M. M., Marshall, J. C., Martin, G. S., Opal, S. M., Rubenfeld, G. D., Vincent, J., Angus, D. C., Park, N. H., … Centrum, A. M. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Journal of the American Medical Association*, *315*(8), 801–810. https://doi.org/10.1001/jama.2016.0287.The

Vecchié, A., Dallegri, F., Carbone, F., Bonaventura, A., Liberale, L., Portincasa, P., Frühbeck, G., & Montecucco, F. (2018). Obesity phenotypes and their paradoxical association with cardiovascular diseases. *European Journal of Internal Medicine*, *48*, 6–17. https://doi.org/10.1016/j.ejim.2017.10.020

Vellinga, N. A. R., Boerma, E. C., Koopmans, M., Donati, A., Dubin, A., Shapiro, N. I., Pearse, R. M., van der Voort, P. H. J., Dondorp, A. M., Bafi, T., Fries, M., Akarsu-Ayazoglu, T., Pranskunas, A., Hollenberg, S., Balestra, G., van Iterson, M., Sadaka, F., Minto, G., Aypar, U., … Ayhan, B. (2017). Mildly elevated lactate levels are associated with microcirculatory flow abnormalities and increased mortality: A microSOAP post hoc analysis. *Critical Care*, *21*(1), 1–9. https://doi.org/10.1186/s13054-017-1842-7

Villar, J., Short, J. H., & Lighthall, G. (2019). Lactate Predicts Both Short- and Long-Term Mortality in Patients With and Without Sepsis. *Infectious Diseases: Research and Treatment*, *12*, 1–6. https://doi.org/10.1177/1178633719862776

Vlassopoulos, A., Combet, E., & Lean, M. E. J. (2014). Changing distributions of body size and adiposity with age. *International Journal of Obesity*, *38*(6), 857–864. https://doi.org/10.1038/ijo.2013.216

Wacharasint, P., Boyd, J. H., Russell, J. A., & Walley, K. R. (2013). One size does not fit all in severe infection: obesity alters outcome, susceptibility, treatment, and inflammatory response. *Critical Care*, *17*(3), R122. https://doi.org/10.1186/cc12794

Weniger, M., Dhaese, J. G., Angele, M. K., & Chaudry, I. H. (2015). Potential therapeutic targets for sepsis in women. *Expert Opinion on Therapeutic Targets*, *19*(11), 1531–1543. https://doi.org/10.1517/14728222.2015.1057570

Widick, P., & Winer, E. S. (2016). Leukocytosis and Leukemia. *Primary Care - Clinics in Office Practice*, *43*(4), 575–587. https://doi.org/10.1016/j.pop.2016.07.007

Winters, B. D., Eberlein, M., Leung, J., Needham, D. M., Pronovost, P. J., & Sevransky, J. E. (2010). Long-term mortality and quality of life in sepsis: a systematic review. *Critical Care Medicine*, *38*(5), 1276–1283. https://doi.org/10.1097/CCM.0b013e3181d8cc1d

Yende, S., Austin, S., Rhodes, A., Finfer, S. R., Opal, S. M., Thompson, B. T., Bozza, F. A., LaRosa, S. P., Ranieri, V. M., & Angus, D. C. (2016). Long-Term Quality of Life Among Survivors of Severe Sepsis. *Critical Care Medicine*, 1. https://doi.org/10.1097/CCM.0000000000001658

Yousef, A. A. A., Amr, Y. M., & Suliman, G. A. (2010). The diagnostic value of serum leptin monitoring and its correlation with tumor necrosis factor- a in critically ill patients : a prospective observational study. *Critical Care*, *6*. https://doi.org/doi: 10.1186/cc8911

Zhang, K., Mao, X., Fang, Q., Jin, Y., Cheng, B., Xie, G., Li, H., Yu, L., Zhu, T., Wang, H., Liu, X., Zhang, Y., Jin, Y., Zhang, N., Lou, T., & Fang, X. M. (2013). Impaired long-term quality of life in survivors of severe sepsis: Chinese multicenter study over 6 years. *Anaesthesist*, *62*(12), 995–1002. https://doi.org/10.1007/s00101-013-2257-8

Chapter Three

Dissertation Proposal:

Examining BMI and Mortality at One Year After Sepsis

Jamie Robinson

Virginia Commonwealth University

Abstract

Sepsis is a life-threatening syndrome in which complex biologic systems respond to pathogenic invaders with pro- and anti-inflammatory responses in a manner that evolves over time, typically resulting in a dysregulated, or exaggerated host response (Singer et al., 2016). A public health priority, sepsis affects 1.7 million adults and results in 270,000 deaths in the United States (US) annually (Centers for Disease Control and Prevention [CDC], 2016). However, in recent years researchers have documented an "obesity paradox" where obese adults experience lower sepsis mortality than those with normal weight (Abbate, Perman, Clambey, Van Pelt, & Ginde, 2016; Arabi et al., 2013; Meyer et al., 2018; Nguyen et al., 2016; Wacharasint, Boyd, Russell, & Walley, 2013). The majority of the literature describes the association between obesity and sepsis mortality in-hospital and at 30 days. The single study that examined the obesity paradox at one year was limited to older adults, limiting generalizability to other age groups (Prescott, Chang, O'Brien, Langa, & Iwashyna, 2014). The hypothesis central to this project is that the chronic inflammation of obesity attenuates the body's response to the extreme inflammation seen in sepsis, resulting in a more balanced physiologic response that causes less endothelial damage, capillary permeability, organ dysfunction, and ultimately less death. The problem is that our understanding of the obesity paradox in patients who survive sepsis at up to one year is very limited. To address this gap, the primary research aim is to test whether the relationship between obesity and all-cause mortality at up to one year after sepsis holds true. The secondary, exploratory aims of this project that will provide information for future work are to describe the relationships among demographic factors and biologic contributors linked to sepsis severity and outcomes within the context of obesity and mortality after sepsis. Data from this project will be

used to increase understanding of the nature of the obesity paradox as a first step toward developing interventions to improve sepsis mortality.

Specific Aims

Despite extensive research, optimizing sepsis outcomes remains challenging. Grim statistics indicate the magnitude of sepsis is far-reaching, with more than 1.7 million cases and 270,000 deaths annually in the United States (US) (CDC, 2016), and an estimated 30 million cases and 6 million deaths per year globally (Reinhart, Daniels, Kissoon, Machado, Schachter, & Finger, 2017). Due to recent advances in early sepsis recognition and treatment, more people survive the initial insult, yet many experience persistent residual symptoms of physical, psychological, cognitive and functional frailty, as well as late mortality (Gardner et al., 2019; Iwashyna & Netzer, 2012; Winters et al., 2010). The literature primarily examines sepsis outcomes in the short term, omitting endpoints that may better estimate the long-term effects, despite the Surviving Sepsis Campaign call for new research to describe predictors of sepsis long-term morbidity and mortality as a top priority (Coopersmith et al., 2018). Precedence for the obesity paradox in inflammatory conditions (Braun et al., 2017; De Schutter et al., 2016; Hafner, Hillenbrand, Knippschild, & Radermacher, 2013) and for short term sepsis mortality (Abbate et al., 2016; Arabi et al., 2013; Meyer et al., 2018; Nguyen et al., 2016; Sakr et al., 2013; Wacharasint et al., 2013) has been established. What is not well understood is the effect of obesity on long term sepsis outcomes. The demographic variables of age, sex, and race have been shown to affect mortality in the general population of sepsis patients. However, the relationship between these variables with obesity and mortality *after* sepsis has not yet been fully explored.

Similarly, biomarkers that indicate sepsis and severity, such as white blood cells (WBC), c-reactive protein (CRP), and lactate, have not yet been examined in the context of obesity and mortality after sepsis. It is expected that distinctive differences between obese and non-obese physiologic states will be associated with varied sepsis outcomes. Descriptive research of this nature is the first step toward understanding the relationships of the above variables and their contributions to sepsis outcomes. Once these relationships are better understood, future research can focus on understanding causative factors that contribute to decreased sepsis mortality and thereby guide the development of future interventions.

In this descriptive study we aim to interrogate existing data from administrative and medical record databases at a large academic medical center,

Aim 1: To examine the relationship between body mass index (BMI) and mortality at 30 days, 180 days, and 1 year after sepsis diagnosis in adults age 18 and older. A sub-aim is to examine the relationship between BMI and mortality at 30 days, 180 days, and 1 year after sepsis diagnosis in adults age 18 and older with sepsis severity (sepsis, severe sepsis, septic shock).

Hypothesis: BMI > 30 (obesity) is associated with lower mortality in adults at 30 days, 180 days, and 1 year after diagnosis, and BMI may be associated with sepsis severity.

R1: What is the relationship between BMI and mortality at the time points 30 days, 180 days, and 1 year one year after sepsis in adults age 18 and older?

R2: What is the relationship between BMI and mortality after sepsis at the same time points, stratified by severity of sepsis (sepsis, severe sepsis, septic shock)?

Aim 2: To describe the relationship between the demographic variables (sex, age, race) and biologic variables (CRP, WBC, lactate) with BMI and mortality at 30 days, 180 days, and 1 year after sepsis diagnosis in adults age 18 and older.

Hypothesis: BMI, demographic characteristics, and biologic variables are potential confounding variables affecting mortality in adults at 30 days, 180 days, and 1 year after diagnosis.

R3: What is the relationship between BMI categories and mortality after sepsis at the same time points, by demographic variables (age, sex, race)?

R4: What is the relationship between BMI categories and mortality after sepsis at the same time points, by biological factors (WBC, CRP, lactate)?

Significance

Sepsis and obesity have high incidence and mortality rates independent of each other. When taken together, one might expect a perfect storm in which patient outcomes are exponentially worse than either diagnosis on its own. This notion is countered by the "obesity paradox" where obese individuals with sepsis survive at higher rates than non-obese individuals in the short term (Abbate et al., 2016; Arabi et al., 2013; Meyer et al., 2018; Nguyen et al., 2016; Sakr et al., 2013; Wacharasint et al., 2013).

Obesity is a global epidemic associated with complex multi-system diseases affecting cardiovascular, endocrine, and mental health, and increased all-cause mortality (Keaver, Xu, Jaccard, & Webber, 2018). Complications of obesity can potentiate each other, such as type 2 diabetes and hypertension leading to chronic kidney disease. The physiologic consequences of obesity increase the risk of complications and the likelihood of slowed recovery from sepsis. However, when they co-occur, sepsis and obesity are associated with better rather than worse survival in the short term, observations that have collectively been described as the "obesity paradox." Inconsistent results on the impact of obesity on other critical illnesses have indicated that obesity may be related to better, worse, or unchanged rates of hospital and intensive care unit (ICU) length of stay and mortality (Martino et al., 2011). Narrowing the scope of

investigation from critical illness to sepsis will be pivotal to establish relationships among variables affecting mortality and to identify a phenotype of sepsis survivors. Given the implications of the obesity paradox in the short term and the resultant chronicity of sepsis following survival, the main objective is to describe the association of obesity and mortality at 30 days, 180 days and at 1 year in adults after sepsis.

Theoretical Framework

The central concepts involved in the conceptual framework for this project are inflammation, obesity, and sepsis. Each concept and their interactions are described below.

Obesity

Characterized by excess adipose tissue, obesity is a global health concern that increases the risk of comorbidities, decreases life expectancy, and results in 2.8 million deaths annually (Pal, Pal, Babu, & Lalitha, 2015). Antecedents of obesity include caloric energy intake and usage imbalance, decreased physical activity, and genetic predispositions (Pal et al., 2015). Recent observations point to socioeconomic status and environmental factors causing epigenetic modifications as well (Vecchié et al., 2018). Obesity is associated with several disorders such as metabolic syndrome, type 2 diabetes, cardiovascular disease, lipid disorders, stroke, sleep apnea, and cancer (CDC, 2018). In the US, middle-aged (40.2%) and older adults (37%), as well as non-Hispanic blacks (48.1%) and Hispanics (42.5%), have higher rates of obesity than other groups (CDC, August 13, 2018). The economic burden of obesity was estimated at $147 billion in the US in 2008 (CDC, August 13, 2018).

Obesity definition.

Obesity has been defined as an accumulation of abnormal or excessive fat that is a risk to health (WHO, 2019) and as a chronic disease with multiple phenotypes where excess adiposity

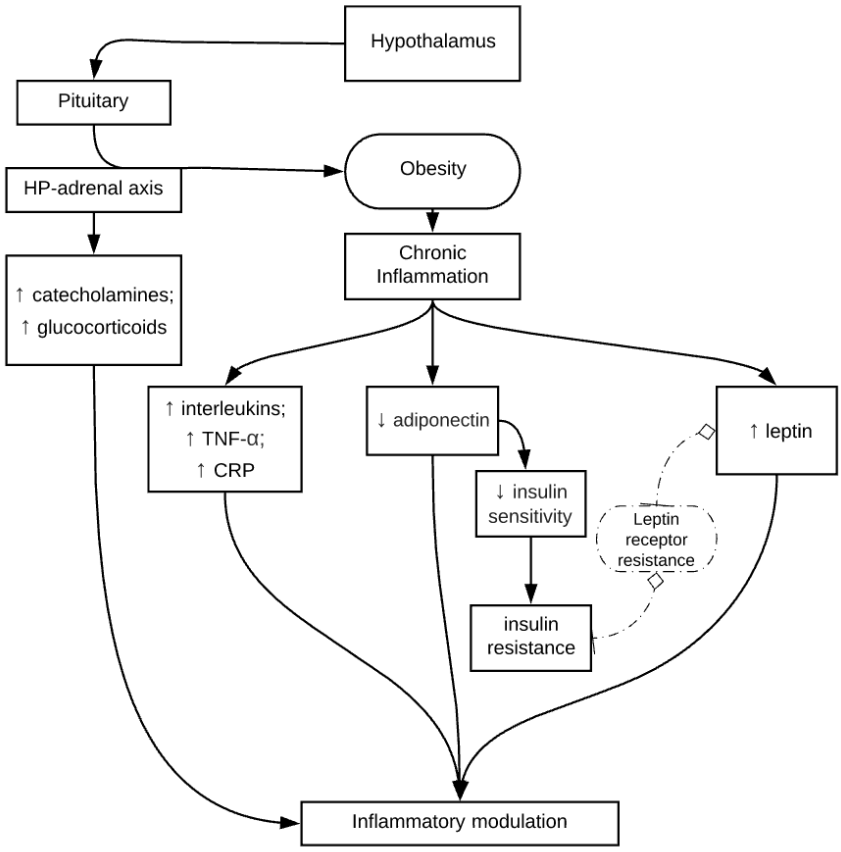
leads to physiologic abnormalities (Kelly, Kahan, Heymsfield, Kotz, & Jastreboff, 2019). Obesity is a clinical diagnosis that is determined by the surrogate measure of body fat, BMI, an index of weight adjusted for height that only indirectly estimates body fat. A limitation of BMI is that individuals with varying clinical and biochemical characteristics are categorized similarly, regardless of emerging evidence of obesity phenotypes (Vecchié et al., 2018). Despite this limitation, BMI is still accepted internationally by researchers as the standard method for identifying and defining obesity (Engin, 2017).

The consequences of obesity stem from heightened endocrine activity that occurs when there is excess adipose tissue. Chronic low-grade inflammation occurs when macrophages take up residence in adipose tissue causing dysregulation of cytokines IL-6, CRP, and TNF-α, while parallel down regulation of the anti-inflammatory adipokine adiponectin and up regulation of the pro-inflammatory adipokine leptin occurs (Cottam et al., 2004). As in acute inflammation, neurophysiologic control of energy balance and regulation of body weight occurs along the HPA axis. Specifically, obesity states can impair neuronal function that can alter homeostatic feedback loops, compounding inflammatory modulation (Pal et al., 2015). Chronic low-grade inflammation increases pro-inflammatory cytokines, while alteration in the HPA axis increases catecholamine and glucocorticoid levels that together contribute to the modulation of immune function (Pal et al., 2015), see Figure 1.

Figure 1

Hypothesized relationships between HPA dysregulation and obesity-associated factors: The hypothalamus-pituitary-adrenal (HPA) axis becomes dysregulated in obese states where heightened endocrine activity causes chronic low-grade inflammation resulting in chronically interleukins, tumor necrosis factor-alpha, and c-reactive protein. The anti-inflammatory

adipokine adiponectin is decreased contributing to decreased insulin sensitivity and insulin resistance. It is hypothesized that the pro-inflammatory adipokine leptin is increased due to leptin receptor resistance, which is related to and contributes to insulin resistance, and taken together result in inflammatory modulation. Adapted from Pal et al., (2015).



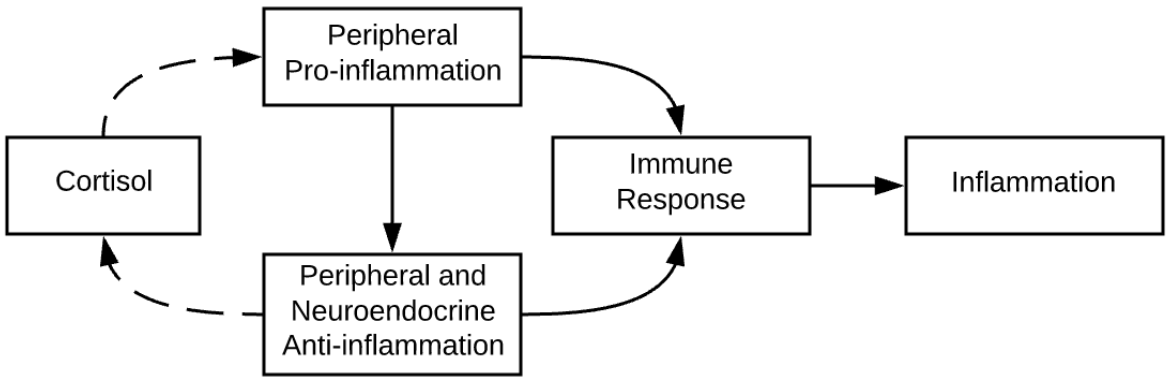
Inflammation

The body is an integrated system that uses inflammation to communicate exposure to foreign substances, tissue damage, or pathogen invasion (Bennett, Reeves, Billman, & Sturmberg, 2018; Del Giudice & Gangestad, 2018). Governed by immune-regulatory pathways, the sympathetic nervous system (SNS) triggers peripheral pro-inflammatory responses, while the parasympathetic nervous system (PNS) and the neuroendocrine hypothalamic-pituitary-adrenal (HPA) axis balance sympathetic effects by inhibiting inflammatory responses. These pathways

are mediated by cytokine and hormonal influences in healthy or “normal” inflammatory responses (Bennett et al., 2018), see Figure 2. At the intersection of the immune and neuroendocrine systems, cytokines and immune mediators released during the immune response activate neural responses that exaggerate local inflammation, and that enable neuroendocrine responses to restore homeostasis (Bennett et al., 2018).

Figure 2

The normal immune response: consists of immune regulatory pathways that govern peripheral sympathetic pro-inflammatory responses as well as peripheral parasympathetic and neuroendocrine anti-inflammatory responses to elicit a balanced inflammatory response, adapted from Bennett et al. (2018).



The ubiquitous goal of non-specific inflammation is to increase blood flow, dispatch white blood cells to infiltrate the area and contain the threat, followed by phagocytosis to remove the threat. When the body is invaded or injured, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), respectively, lead to activation of the inflammatory system where monocyte-macrophage cells are released, followed by the release of cytokines and chemokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), that mediate non-specific cellular, tissue, and vascular damage (Bennett et al., 2018; Del

Giudice & Gangestad, 2018). Meanwhile, CRP, a protein released during inflammation, is upregulated due to the abundance of monocytic cells and IL-6. Normally, this process is followed by down-regulation of inflammation to promote healing and maintain homeostasis (Bennett et al., 2018).

Sepsis

Sepsis is a heterogeneous syndrome where a dysregulated host response to infection occurs in response to widespread inflammation (Cohen et al., 2015). In patients with sepsis without organ dysfunction, the mortality rate is less than 20%, whereas in those with organ dysfunction mortality has been reported as over 50% (De La Rica, Gilsanz, & Maseda, 2016). Mansur et al. (2015) reported a 71% increase in cases of severe sepsis between 2003 and 2007 and reported that total costs for all patients with severe sepsis increased 57% in the same period. The approximate cost of sepsis care in 2008 was $14.6 billion (Hall, Williams, DeFrances, & Golosinskiy, 2011).

The risk factors for sepsis are varied. More than half of the cases of severe sepsis occur in adults over age 65 (Mayr, Yende, & Angus, 2014). Sepsis is more common in males (De La Rica et al., 2016; Sakr et al., 2012) and blacks versus whites (Barnato, Alexander, Linde-Zwirble, & Angus, 2008; Dombrovskiy, Martin, Sunderram, & Paz, 2007). De La Rica and colleagues (2016) found that in the US, African Americans had a 2-fold higher probability of experiencing sepsis. Over half of the patients with sepsis have chronic comorbid conditions such as diabetes, congestive heart failure, chronic pulmonary disease, cancer, and chronic renal failure (De La Rica et al., 2016; Mayr et al., 2014).

Sepsis definition.

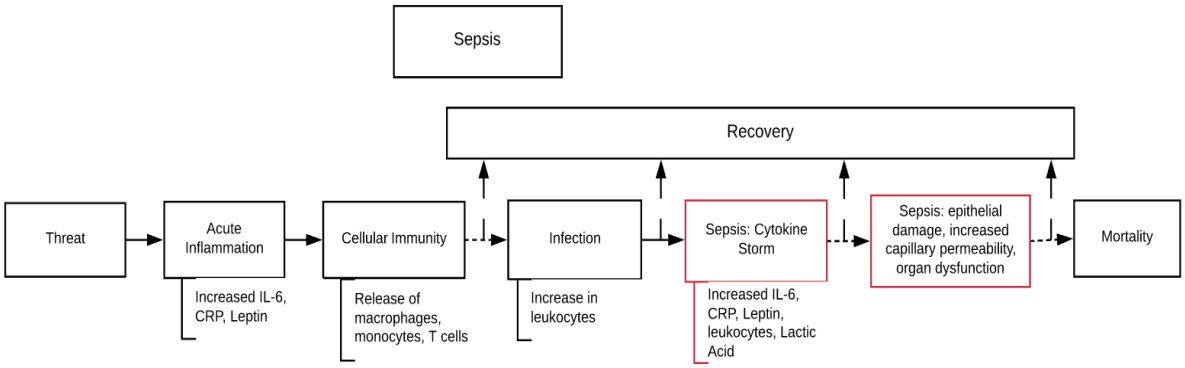
While systemic inflammatory response syndrome (SIRS) has been the focus of sepsis research for the last two decades (Bone et al., 1992; Levy et al., 2003), a refined understanding of the pathophysiology now points to an altered host response as the underlying cause of sepsis (Singer, Deutschman, Seymour, Shankar-Hari, et al., 2016). The new "Sepsis-3" definitions suggest removal of the diagnosis of "severe sepsis" from the lexicon (Singer et al., 2016) despite this term differentiating the phenotype and its use over the past two decades in International Classification of Disease, ninth edition (ICD-9) coding.

Sepsis pathophysiology.

When the body encounters a pathogen, an inflammatory and immune response occurs in an attempt to isolate the threat. If not contained, the pathogen can result in infection and the immune response will trigger the release of leukocytes to systemically counteract the pathogen in an attempt to recover. However, in some cases the inflammatory response is over-zealous, leading to the excessive inflammation that causes epithelial damage, increased capillary permeability, organ dysfunction, and even death (Winters et al., 2010), see Figure 3.

Figure 3

Comparison of biomarker changes in healthy normal versus dysregulated immune responses: The normal immune response from threat to infection, diagrammed left to right, consists of a balanced effect of acute inflammation, cellular immunity and physiologic response to infection. In sepsis, in red, the host response becomes over-zealous resulting in a cytokine storm that causes epithelial damage, increased capillary permeability, organ dysfunction, and sometimes death.



Sepsis Diagnosis.

Rapid identification of sepsis includes assessing patient presentation along with laboratory markers to assist in determining disease severity and prognosis (Fan, Miller, Lee, & Remick, 2016). CRP levels reflect the degree of inflammation and disease severity (Gradel, Jensen, Kolmos, Pedersen, Vinholt, & Lassen, 2013). WBC levels indicate immune system activation due to a pathogen (Castelli, Pognani, Cita, Stuani, Sgarbi, & Paladini, 2006). Lactate is measured to identify the degree of hypoperfusion present and as a prognostic marker, where elevated levels indicate more severe disease and a higher likelihood of mortality (Anderson, Mackenhauer, Roberts, Berg, Cocchi, & Donnino, 2013).

Relationship between obesity and sepsis

Inflammation is the common pathway shared by obesity and sepsis. In obesity, up-regulation of the pro-inflammatory markers IL-6, CRP, and leptin, along with down-regulation of the anti-inflammatory marker adiponectin, leads to chronic inflammation (Singer & Granger, 2007). It is hypothesized that in obese individuals where there is chronic inflammation, the excessive inflammation of sepsis causes less endothelial damage and organ dysfunction, and results in lower mortality, see Figure 4. While all the variables in the conceptual model merit study, some data were not available to fully examine these inflammatory processes retrospectively. Therefore, future prospective studies will be undertaken to further explore these

variables in more detail. Nevertheless, one advantage of this hospital-based dataset is that WBC and lactate, both indicators of disease severity, and CRP, an important marker of inflammation, were available. Therefore, these biomarkers and their associations with mortality and BMI will be included in the statistical analyses for this proposed research, see Figure 4b.

Figure 4

The **Hypothesized relationship between obesity-related factors and sepsis mortality:** In blue, the chronic inflammation of obesity, with upregulated pro-inflammatory adipokines (leptin), interleukins, tumor necrosis factor-alpha, and c-reactive protein modulate the effect of sepsis, in red. The result is a modulated, rather than over-zealous, host response that results in lower mortality.

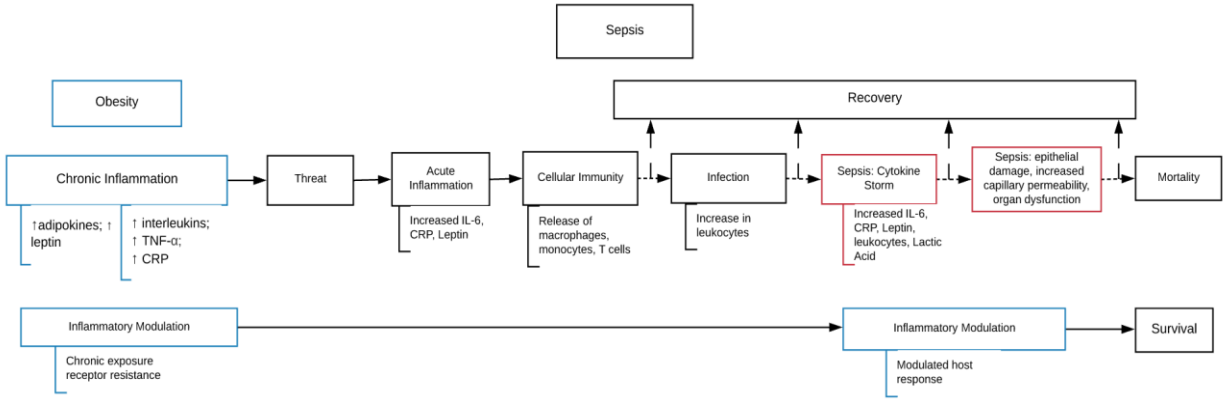
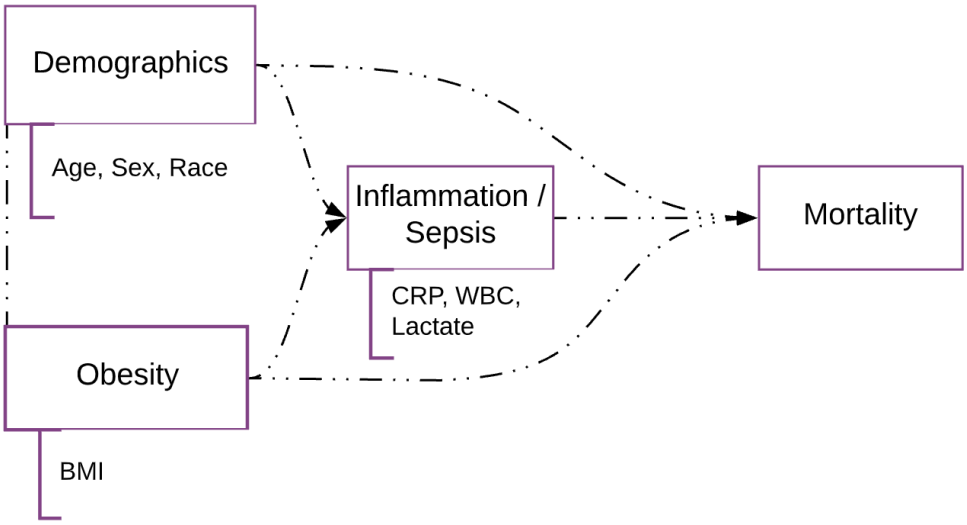


Figure 4b

Variables included in this research. The main association between obesity, measured by BMI, and sepsis mortality after one year, will be examined. The relationships between demographics (age, sex, race) with obesity and mortality at one year after sepsis will be examined. Additionally, the relationships between markers of inflammation and/or sepsis (CRP, WBC, lactate) with obesity and mortality at one year after sepsis will be examined.



Study Design

A retrospective cohort study was designed to examine the primary endpoint of mortality at up to one year after sepsis diagnosis and to compare characteristics of individuals by BMI. To determine the feasibility and availability of data on the variables of interest three databases were examined. First, the Medical Information Mart for Intensive Care, 3rd edition (MIMIC-III) database, which integrates deidentified, clinical data of patients admitted to the Beth Israel Deaconess Medical Center in Boston, Massachusetts was examined for the presence of the variables of interest (Johnson et al., 2016). Next, the Virginia Commonwealth University (VCU) Center for Clinical and Translational Research (CCTR) was consulted, resulting in the examination of the TriNetX database and the electronic health record and administrative billing database of VCU were to determine the availability of biomarker data. While none of the databases had biomarker data for infrequently ordered clinical tests such as leptin and IL-6, the VCU database contained sufficient numbers of some markers of inflammation and infection (WBC, lactate, and CRP). Demographic variables, BMI, and laboratory data were obtained from the electronic health record, while the administrative database was used to identify admission

dates and diagnosis codes. The administrative database was matched to the Social Security Administration (SSA) Death Master File by the data analyst at the academic medical center to identify dates of death. The primary aim of this proposal is to examine the relationship between obesity and mortality at 30 days, 180 days, and at 1 year after sepsis diagnosis in adults over age 18. The secondary aims are to describe the relationships between the outcomes in Aim 1 with age, sex, and race, and with WBC, lactate, and CRP. The 30-day time point is necessary to compare results of this study with findings from the literature showing a protective effect of obesity on mortality, while the 180 day and 1-year time points will enable exploration of the longevity of protection ascribed to obesity on mortality after sepsis. Institutional Review Board approval has already been received (IRB-hm20010673_ame) for this project and was determined to be exempt.

Sample

A convenience sample comprised of adults age 18 and older with one or more diagnoses of sepsis within the years 2007- 2018 was identified (N = 11,981). Sepsis was identified using ICD-9 codes. Individuals were identified initially by medical record number (MRN), date of birth (DoB), and date of admission, and then anonymized by the primary investigator, by organizing the data by descending MRN, assigning a consecutive number beginning with "1" to each record and removing all identifiers. Dates of admission, discharge, and death will be retained for subsequent research that is in alignment with the aims of this study. Records without BMI will not be included, n = 6,216, and only the first admission for a diagnosis of sepsis will be included in the study, resulting in n = 4,756 to be used for analysis. Laboratory data reported below the detectable limit (i.e., < X) were imputed. Results will be reported in

aggregate to eliminate the possibility of identifying an individual point or combination of data points.

Data collection, cleaning, and storage

Data were received from the academic medical center data analyst in a password protected encrypted Excel file via the Research Electronic Data Capture (REDCap) hosted by the Virginia Commonwealth University (VCU). The data were subsequently parsed by the identifiers of medical record number (MRN), date of birth (DoB), and date of admission (DoA). The Excel add-in extension Ablebits was used to merge data across spreadsheets together using the MRN as the match-point. Each variable was merged onto one spreadsheet using an exact date match to the date of admission. To complete the data merge hand-sorting of data for the variables was conducted to include all data points that occurred 1 day before the admission date and up to 5 days after the admission date. To meet the statistical assumption of independence among the observations the data were further parsed by MRN and DoA to identify if more than one admission existed for an MRN. The Ablebits "Quick Dedupe" option was used to select "MRN" and "move to a new worksheet." This action transferred 2,685 rows of data to a new workbook and left only the first DoA for each MRN. The remaining 9,296 unique rows of data were filtered largest to smallest, and a unique identification number was assigned. A master list with patient identifiers is kept in a password-protected external hard drive that is stored in a locked file cabinet in the office of the primary investigator.

Measures

Obesity: BMI will be used to categorize individuals based on height and weight. BMI was collected in the EHR as a continuous variable, and for this project, BMI will be categorized into the WHO BMI classifications (2019).

Sepsis: Individual records were identified using the ICD-9 diagnosis codes related to infection, sepsis, and systemic inflammatory response syndrome, see Table 1. Only records with a diagnosis code for sepsis (785.52; 995.91; 995.92) will be included in the analysis.

Mortality: To compute all-cause mortality overall survival reported in days will be examined where all-cause mortality may include death from sepsis, from co-morbidities, or some unknown cause. Despite this limitation, this is an essential first step toward describing mortality rates at up to 1 year after sepsis. Mortality time points will include the time period of the date of admission and the end-point(s) will be 30 days, 180 days, and 1-year after sepsis diagnosis. The SSA Death Master file was queried in 2019 for the dates of 2007-2018 to ensure that if death occurred within 1 year 2018 that death date was included.

Data Point Definitions

- Date of admission: This is the date the individual was admitted to the academic medical center.
- Date of death: This is the date of individual death identified by the SSA Death Master File. The cause of death is not identified within this dataset. This limitation will be reported.
- Age: DoB was used to identify individuals' age at the time of admission and time of death. DoB was removed from the dataset using the anonymization procedure described previously. Records for individuals under the age of 18 were excluded.
- Sex: Sex is reported by the individual as either male or female and is recorded in the medical record at the academic medical center. There is a risk that this data is entered incorrectly, potentially affecting results. This limitation will be reported.

- Race: Race is reported by the individual and recorded in the EHR at the academic medical center. There is a risk that this data is entered incorrectly, potentially affecting results. This limitation will be reported.
- BMI: BMI was recorded in the EHR as a continuous variable, but will be collapsed into WHO categories as follows: < 18.5 Underweight; 18.50-24.99 Normal Weight; ≥ 25.00 Overweight; ≥ 30.00 Obese. Further stratification of these classifications are as follows: < 16 Severe thinness; 16-16.99 Moderate thinness; 17-18.49 Mild thinness; 25- 29.99 Pre-obese; 30 – 34.99 Obese Class I; 35-39.99 Obese Class II; ≥ 40.00 Obese Class III (WHO, 2019). BMI distribution of this subset ranged from 10.47 to 84.72; BMI < 14 (n = 15) will be excluded from the analysis.
- Biomarkers. Sepsis is a syndrome without a specific test to confirm its presence. The use of several biomarkers together, along with physical examination, is the standard for diagnosing sepsis. Diagnostic features suggestive of sepsis include elevated WBC, CRP, and lactate.
    - White blood cells (WBC): WBCs can be elevated for several systemic indications; however, a count >12,000/mm^3 or <4,000/mm^3 is one parameter of several that indicates sepsis. Data reported as less than the detectable limit was imputed by dividing the reported value by 2 and using the subsequent value (i.e., < 0.1/2 = 0.05).
    - Lactate is a marker of endogenous catecholamines. Lactate levels equal to or greater than 2 mmol/L at presentation is indicative of hypoperfusion, such as in septic shock, and decreasing or normalized lactate levels indicate recovery (Gomez & Kellum, 2015).

- CRP is an acute-phase reactant that is frequently elevated in acute inflammation, and though not specific for sepsis CRP can indicate sepsis severity. Data reported as less than the detectable limit was imputed by dividing the reported value by 2 and using the subsequent value (i.e.: < 0.3/2 = 0.15), with the exception of a value reported as < 31.7, which was kept in the dataset as 31.7 since this is an elevation from normal that is biologically plausible.

Inclusion and Exclusion Criteria

BMI is a required study variable; therefore, only patients with BMI information were included (n = 6,216). Values for BMI, WBC, lactate, and CRP were included if recorded within the time period of 1 day before the admission date and 5 days after the admission date. BMI values of < 14 and > 90 will be excluded from analysis *a priori* to reduce the inclusion of possible spurious values and to reduce the likelihood of extreme BMI values biasing the results. Medical records with BMI not recorded within the time period of 1 day before the admission date and 5 days after the admission date were excluded.

Missing Data

Missing data is a known challenge in the use of electronic health records for research. The patterns of missingness are generally considered to be missing at random (MAR) rather than missing completely at random (MCAR). To handle the missing data in this dataset the method of listwise deletion will be used, whereby only observations with complete data will be used for analysis (Raghunathan, 2004; Meeyai, 2016). This method has been reported to be robust in regression analysis even when violations of MCAR or MAR may exist for the predictor variables, given that the missingness does not depend on the dependent variable. The risks of listwise deletion include potential Type II error and potential for bias, though the loss of

statistical power is unlikely in large datasets (Raghunathan, 2004; Meeyai, 2016). Other methods for handling missing data, such as mean substitution and regression imputation, were considered and deemed unsuitable due to loss of accuracy in the data.

Data Density

For the time period of 2007 to 2018, N = 11,981 admissions for sepsis were identified. Each of these was matched with the SSA Death Master File. A total of n = 6,216 had data for BMI. From this sample, the first admission for a diagnosis of sepsis will be included in the study, resulting in n = 4,756 to be used for analysis. Next, the total number of observations with age, sex, and race is n = 4,709. Lastly, the total number of observations with CRP, WBC, and Lactate is n = 210.

Total observations with sepsis diagnosis and death date	N = 11,981
+ BMI	n = 6,216
+ Restricted to first sepsis diagnosis	n = 4,756
+ Age, Sex, Race	n = 4,709
+ CRP, WBC, Lactate	n = 210

Statistical Plan:

A quantitative study using logistic regression will be conducted to analyze the relationships among the variables and their ability to predict the likelihood of the dichotomous dependent variable of mortality (alive vs. dead) at the three-time points identified.

Descriptive Statistics

The data, from a sample of individuals with a diagnosis of sepsis, will be examined descriptively and graphically. For continuous variables, distributions will be assessed with histograms and outlier box plots, and the means and standard errors will be calculated and

reported in tabular form. For categorical variables, frequencies and percentages will be calculated and reported in tabular form. Further, the means with standard deviations and frequencies with percentages will be presented for BMI <30 (not obese) and ≥ 30 (obese) and pooled to initially describe the data.

Logistic Regression Models

Logistic regression will be used to build prediction models using the method proposed by Hosmer and Lemeshow (2013). In this analysis, three dependent variables defined by time (30 days, 180 days, and 1 year) for which logistic regression will be used to assess the effect of BMI by category on mortality. Thus, the analysis steps that follow will apply to each of the dependent variables.

Assumptions for logistic regression include a binary dependent variable, independence among the observations, linearity in the logit for continuous predictors, and no multicollinearity among the predictors. Finally, it assumed that the sample size is sufficient as defined by n = 100 +50*i*, where *i* is the number of predictor variables (Bujang, Sa'at, Tg, Sidik, & Lim, 2018). The assumption of linearity of the logit for continuous predictors, i.e., age, will be tested by forming three design variables based on quartiles of age. The linearity assumption is satisfied if the ordered logits are linear.

Steps to Model Building

Step 1: Using the model-building strategy proposed by Hosmer and Lemeshow (2013), the first step is to explore bivariate associations between the independent variable and each of the dependent variables using simple logistic regression. A p-value cut off of < 0.25 will make that predictor eligible for the multiple regression model in the next step.

Step 2: In the second step, a multivariable model will be formed using all variables, as identified in the first step.

Step 3: Variables with a p-value > 0.05 will be eliminated from the model one at a time using a backward stepwise approach, with the least significant variable being removed first.

Step 4: Interactions between the remaining main effects will be added to the model in Step 2. Only interactions deemed of clinical interest will be added in this step. It is anticipated that interaction terms of WBC and lactate; lactate and CRP; age and disease severity; and lactate and disease severity will be of clinical interest.

Step 5: Similar to the approach in Step 2, a backward stepwise approach will be used to remove those interactions with a p-value > 0.05.

The resultant model from Step 5 will be considered the final predictive model. Note that this process will be used three times; one for each dependent variable defined above. Data analysis will be completed on JMP Pro version 14.2.0 (64-bit).

References

Abbate, L. M., Perman, S. M., Clambey, E. T., Van Pelt, R. E., & Ginde, A. A. (2016). Age modifies the association between obesity and mortality in individuals hospitalized with severe sepsis. *Journal of the American Geriatric Society*, *4*(11), 882–883. DOI:10.1111/jgs.14047

Anderson, L. W., Mackenhauer, J., Roberts, J. C., Berg, K. M., Cocchi, M. N., & Donnino, M. W. (2013). Etiology and therapeutic approach to elevated lactate. *Mayo Clinic Proceedings, 88*(10), 112701140. doi: 10.1016/j.mayocp.2013.06.012

Arabi, Y. M., Dara, S. I., Tamim, H. M., Rishu, A. H., Bouchama, A., Khedr, M. K., . . . Kumar, A. (2013). Clinical characteristics, sepsis interventions and outcomes in obese patients with septic shock: an international multicenter cohort study. *Critical Care*, *17*(2), R72. doi: 10.1186/cc12680

Barnato, A. E., Alexander, S. L., Linde-Zwirble, W. T., & Angus, D. C. (2008). Racial variation in the incidence, care, and outcomes of severe sepsis: analysis of population, patient, and hospital characteristics. *American Journal of Respiratory and Critical Care Medicine*, *177*(3), 279–284. https://doi.org/10.1164/rccm.200703-480OC

Bennett, J. M., Reeves, G., Billman, G. E., & Sturmberg, J. P. (2018). Inflammation–nature's way to efficiently respond to all types of challenges: implications for understanding and managing "the epidemic" of chronic diseases. *Frontiers in Medicine*, *5*(November), 1–30. https://doi.org/10.3389/fmed.2018.00316

Bone, R. C., Balk, R. A., Cerra, F. B., Dellinger, R. P., Fein, A. M., Knaus, W. A., … Sibbald, W. J. (1992). Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*, *101*(6), 1644–1655.

https://doi.org/10.1378/chest.101.6.1644

Braun, N., Hoess, C., Kutz, A., Christ-Crain, M., Thomann, R., Henzen, C., Zimmerli, W., Mueller, B., & Schuetz, P. (2017). Obesity paradox in patients with community-acquired pneumonia: Is inflammation the missing link? *Nutrition, 33*(304-310). doi: 10.1016/j.nut.2016.07.016

Bujang, M. A., Sa'at, N., Tg, A. B., Sidik, T. M. I., & Lim, C. J. (2018). Sample size guidelines for logistic regression from observational studies with large population: emphasis on the accuracy between statistics and parameters based on real-life clinical data. *Malaysian Journal of Medical Science, 25(4),* 122-130. https://doi.org/10.21315/ mjms2018.25.4.12

Castelli, G. P., Pognani, C., Cita, M., Stuani, A., Sgarbi, L., & Paladini, R. (2006). Procalcitonin, c-reactive protein, white blood cells and SOFA score in ICU: diagnosis and monitoring of sepsis. *Minervera Anestesiology, 72*(1-2), 69-80.

Centers for Disease Control and Prevention. (2016). *Data & reports.* Retrieved from https://www.cdc.gov/sepsis/datareports/index.html

Centers for Disease Control and Prevention. (2018). *What is sepsis?* Retrieved from https://www.cdc.gov/sepsis/what-is-sepsis.html

Cohen, J., Vincent, J. L., Adhikari, N. K. J., Machado, F. R., Angus, D. C., Calandra, T., … Pelfrene, E. (2015). Sepsis: A roadmap for future research. *The Lancet Infectious Diseases*, *15*(5), 581–614. https://doi.org/10.1016/S1473-3099(15)70112-X

Coopersmith, C. M., De Backer, D., Deutschman, C. S., Ferrer, R., Lat, I., Machado, F. R., . . . Rhodes, A. (2018). Surviving sepsis campaign: research priorities for sepsis and septic shock. *Intensive Care Medicine, 44*(9), 1400-1426. https://doi.org/10.1007/s00134-018-5175-z

Cottam, D. R., Mattar, S. G., Barinas-Mitchell, E., Eid, G., Kuller, L., Kelley, D. E., & Schauer, P. R. (2004). The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effect of weight loss. *Obesity Surgery*, *14*(5), 589–600. https://doi.org/10.1381/096089204323093345

Del Giudice, M., & Gangestad, S. W. (2018). Rethinking IL-6 and CRP: why they are more than inflammatory biomarkers, and why it matters. *Brain, Behavior, and Immunity*, *70*, 61–75. https://doi.org/10.1016/j.bbi.2018.02.013

De La Rica, A. S., Gilsanz, F., & Maseda, E. (2016). Epidemiologic trends of sepsis in western countries. *Annals of Translational Medicine*, *4*(17), 325–325. https://doi.org/10.21037/atm.2016.08.59

De Schutter, A., Kachur, S., Lavie, C. J., Boddepalli, R. S., Patel, D. A., & Milani, R. V. (2016). The impact of inflammation on the obesity paradox in coronary heart disease. *International Journal of Obesity, London*, *40*(11), 1730-1735. doi: 10.1038/ijo.2016.125

Davenport, D. L., Xenos, E. S., Hosokawa, P., Radford, J., Henderson, W. G., & Endean, E. D. (2009). The influence of body mass index obesity status on vascular surgery 30-day morbidity and mortality. *Journal of Vascular Surgery*, *49*(1), 140–147.e1. https://doi.org/10.1016/j.jvs.2008.08.052

Dombrovskiy, V. Y., Martin, A. A., Sunderram, J., & Paz, H. L. (2007). Occurrence and outcomes of sepsis: influence of race. *Critical Care Medicine*, *35*(3), 763–768. https://doi.org/10.1097/01.CCM.0000256726.80998.BF

Engin, A. (2017). The pathogenesis of obesity-associated adipose tissue inflammation. In A. B. Engin & A. Engin (Eds.), *Obesity and Lipotoxicity* (pp. 221–245). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-319-48382-5_9

Fan, S. L., Miller, N. S., Lee, J., & Remick, D. G. (2016). Diagnosing sepsis - The role of laboratory medicine. *Clinica chimica acta; international journal of clinical chemistry, 460*, 203–210. doi:10.1016/j.cca.2016.07.002

Gardner, A. K., Ghita, G. L., Wang, Z., Ozrazgat-Baslanti, T., Raymond, S. L., Mankowski, R. T., . . . Brakenridge, S. C. (2019). The development of chronic critical illness determines physical function, quality of life, and long-term survival among early survivors of sepsis in surgical ICUs. *Critical Care Medicine, 47*(4), 566-573. doi: 10.1097/CCM.0000000000003655.

Gomez, H. & Kellum, J. A. (2015). Lactate in sepsis. *JAMA, 313*(2):194-195. doi:10.1001/jama.2014.13811

Gradel, K. O., Jensen, T. G., Kolmos, H. J., Pedersen, C., Vinholt, P. J., & Lassen, A. T. (2013). Does c-reactive protein independently predict mortality in adult community-acquired bacteremia patients with known sepsis severity? *APMIS, 121*(9), 835-842. doi: 10.1111/apm.12040

Hafner, S., Hillenbrand, A., Knippschild, U., & Radermacher, P. (2013). The obesity paradox and acute kidney injury: beneficial effects of hyper-inflammation? *Critical Care, 17*(6), 1023. doi: 10.1186/cc13152

Hall, M. J., Williams, S. N., DeFrances, C. J., & Golosinskiy, A. (2011). Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. *NCHS Data Brief*, (62), 1–8. https://doi.org/10.1111/j.1468-3083.2011.04279.x

Hosmer, D. W., & Lemeshow, S. (1989). Applied Logistic Regression, 1st. ed. John Wiley & Sons, Inc.

Iwashyna, T. J., & Netzer, G. (2012). The burdens of survivorship: an approach to thinking

about long-term outcomes after critical illness. *Seminars in Respiratory and Critical Care Medicine,* 33(4), 327-38. doi: 10.1055/s-0032-1321982

Iwashyna, T. J., Ely, E. W., Smith, D. M., & Langa, K. M. (2010). Long-term cognitive impairment and functional disability among survivors of severe sepsis. *Journal of the American Medical Association, 304*(16), 1787-1794. DOI:10.1001/jama.2010.1553.

Johnson, A. E. W., Pollard, T. J., Shen, L., Lehman, L., Feng, M., Ghassemi, M. . . . Mark, R. G. (2016). MIMIC-III A freely accessible critical care database. *Scientific Data, 3,* 160035. doi:10.1038/sdata.2016.35.

Keaver, L., Xu, B., Jaccard, A., & Webber, L. (2018). Morbid obesity in the UK: a modeling projection study to 2035. *Scandinavian Journal of Public Health, Aug 30,* 140349481879481. doi: 10.1177/1403494818794814

Kelly, A. S., Kahan, S., Heymsfield, S. B., Kotz, C. M., & Jastreboff, A. M. (2019). Obesity as a disease: the Obesity Society 2018 position statement. *Obesity*, *27*(1), 7–9. https://doi.org/10.1002/oby.22378

Levy, M. M., Fink, M. P., Marshall, J. C., Abraham, E., Angus, D., Cook, D., … Ramsay, G. (2003). 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Intensive Care Medicine*, *29*(4), 530–538. https://doi.org/10.1007/s00134-003-1662-x

Mayr, F. B., Yende, S., & Angus, D. C. (2014). Epidemiology of severe sepsis. *Virulence*, *5*(1), 4–11. https://doi.org/10.4161/viru.27372

Mansur, A., Liese, B., Steinau, M., Ghadimi, M., Bergmann, I., Tzvetkov, M., … Tzeng, S. (2015). The CD14 rs2569190 TT genotype is associated with an improved 30-day survival in patients with sepsis: a prospective observational cohort study. *Plos One*, *10*(5), e0127761. https://doi.org/10.1371/journal.pone.0127761

Martino, J. L., Stapleton, R. D., Wang, M., Day, A. G., Cahill, N. E., Dixon, A. E., … Heyland, D. K. (2011). Extreme obesity and outcomes in critically ill patients. *Chest*, *140*(5), 1198–1206. doi: 10.1378/chest.10-3023.

Meeyai, S. (2016). Logistic regression with missing data: A comparison of handling methods, and effects of percent missing values. *Journal of Traffic and Logistics Engineering, 4*(2). doi: 10.18178/jtle.4.2.128-134

Memtsoudis, S. G., Bombardieri, A. M., Ma, Y., Walz, J. M., Chiu, Y. L., & Mazumdar, M. (2012). Mortality of patients with respiratory insufficiency and adult respiratory distress syndrome after surgery: the obesity paradox. *Journal of Intensive Care Medicine*, *27*(5), 306–311. https://doi.org/10.1177/0885066611411410

Meyer, N., Harhay, M. O., Small, D. S., Prescott, H. C., Bowles, K. H., Gaieski, D. F., & Mikkelsen, M. E. (2018). Temporal trends in incidence, sepsis-related mortality, and hospital-based acute care after sepsis. *Critical Care Medicine*, *46*(3), 354–360. doi: 10.1097/CCM.0000000000002872

Nguyen, A. T., Tsai, C.-L., Hwang, L.-Y., Lai, D., Markham, C., & Patel, B. (2016). Obesity and mortality, length of stay and hospital cost among patients with sepsis: a nationwide inpatient retrospective cohort study. *PloS One*, *11*(4), e0154599. https://doi.org/10.1371/journal.pone.0154599

Pal, G., Pal, P., Babu, M., & Lalitha, V. (2015). Neuroimmunomodulation in obesity *International Journal of Clinical and Experimental Physiology*, *2*(2), 97. https://doi.org/10.4103/2348-8093.161530

Prescott, H. C., Osterholzer, J. J., Langa, K. M., Angus, D. C., & Iwashyna, T. J. (2016). Late mortality after sepsis: a propensity-matched cohort study. *BMJ*, *353*, 1–8.

https://doi.org/10.1136/bmj.i2375

Raghunathan, T. (2004). What do we do with missing data? Some options for analysis of incomplete data. *Annual Reviews of Public Health, 25*; 99-117. doi: 10.1146/annurev.publhealth.25.102802.124410

Sakr, Y., Elia, C., Mascia, L., Barberis, B., Cardellino, S., Livigni, S., … Ranieri, V. M. (2012). Being overweight or obese is associated with decreased mortality in critically ill patients: a retrospective analysis of a large regional Italian multicenter cohort. *Journal of Critical Care*, *27*(6), 714–721. https://doi.org/10.1016/j.jcrc.2012.08.013

Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., … Centrum, A. M. (2016). The third international consensus definitions for sepsis and septic shock (Sepsis-3). *Journal of the American Medical Association, 315*(8), 801–810. https://doi.org/10.1001/jama.2016.0287.

Singer, G., & Granger, D. N. (2007). Inflammatory responses underlying the microvascular dysfunction associated with obesity and insulin resistance. *Microcirculation, 14*(4-5), 375-87.

Vecchié, A., Dallegri, F., Carbone, F., Bonaventura, A., Liberale, L., Portincasa, P., … Montecucco, F. (2018). Obesity phenotypes and their paradoxical association with cardiovascular diseases. *European Journal of Internal Medicine, 48*, 6–17. https://doi.org/10.1016/j.ejim.2017.10.020

Wacharasint, P., Boyd, J. H., Russell, J. A., & Walley, K. R. (2013). One size does not fit all in severe infection: obesity alters outcome, susceptibility, treatment, and inflammatory response. *Critical Care, 17*(3), R122. https://doi.org/10.1186/cc12794

World Health Organization (WHO). (2019). *BMI Classification*. Retrieved from

http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi

Winters, B. D., Eberlein, M., Leung, J., Needham, D. M., Pronovost, P. J., & Sevransky, J. E. (2010). Long-term mortality and quality of life in sepsis: a systematic review. *Critical Care Medicine*, *38*(5), 1276–83. https://doi.org/10.1097/CCM.0b013e3181d8cc1d

Chapter Four

Examining Body Mass Index and Sepsis Mortality at One Year

Jamie Robinson

Manuscript to be submitted to Biological Research for Nursing

Abstract

Sepsis is a serious and life-threatening syndrome affecting 1.7 million Americans annually and resulting in approximately 270,000 deaths. An “obesity paradox” where obese individuals have lower sepsis mortality than their non-obese counterparts has been described. The problem is that the longevity of the effect is unknown, and few studies have examined the obesity paradox after 1-2 months post-diagnosis. Therefore, this retrospective cohort study examined clinical, demographic, and biomarker variables thought to affect sepsis mortality at three-time points: 30 days, 180 days, and one year in order to shed light on specific factors that might define a “sepsis survivor” phenotype. A convenience sample of adults age 18 and older admitted to an academic medical center between the years of 2007 to 2018 with a diagnosis of sepsis was identified. Simple logistic regression was used to test for significance between age, sex, race, c-reactive protein, lactate, white blood cells, body mass index, and sepsis severity on mortality at each of the three previously described time points. Variables with statistical and clinical significance were entered into multivariate logistic regression models to explore the contributions of each variable and interactions between variables at 30 days, 180 days, and one year. We found for every 5 unit increase in BMI, the odds of mortality are 0.92 (95% CI: 0.85, 0.99) times lower at 30 days since sepsis diagnosis. However, at 180-day and one-year post sepsis diagnosis, as BMI increased, there was an increase in odds of death for each sepsis type. In this dataset, it appears that the "obesity paradox" exists up to 30 days, but the protective effect of obesity on sepsis outcomes may not extend beyond one month.

Keywords: Sepsis, Obesity, Mortality, Body Mass Index

Examining Body Mass Index and Mortality at One Year After Sepsis

Sepsis is a serious and life-threatening syndrome affecting 1.7 million Americans annually, resulting in approximately 270,000 deaths (Centers for Disease Control and Prevention [CDC], 2016). In recent years early detection and treatment of sepsis have been a priority for clinicians and researchers (De Backer & Dorman, 2017). Recent data suggests that now more people are surviving the initial sepsis diagnosis, and in those individuals, residual symptoms of physical, psychological, cognitive and functional frailty, and late mortality persist (Gardner et al., 2019; Iwashyna & Netzer, 2012; Winters et al., 2010). Indeed, research to describe predictors of sepsis long-term morbidity and mortality has been identified as a top priority by the Surviving Sepsis Campaign (Coopersmith et al., 2018) and the World Health Assembly (Reinhart et al., 2017).

Obesity is a condition known to cause deleterious health consequences (Keaver et al., 2018). Nevertheless, when obese individuals experience sepsis, they have better short-term survival rates, which has been described as the "obesity paradox," referring to the ostensible protective effect of obesity (Abbate et al., 2016; Arabi et al., 2013; Meyer et al., 2018; Nguyen et al., 2016; Wacharasint et al., 2013). Not unique to sepsis, the obesity paradox has been reported in other in inflammatory conditions, such as pneumonia, coronary artery disease, and acute kidney injury (Braun et al., 2016; De Schutter et al., 2016; Hafner et al., 2013). The problem is that few studies to date have explored the duration of the obesity paradox in sepsis after 1-2 months and certainly not out to one year (Li et al., 2019; Pepper et al., 2019; Prescott et al., 2014). Describing the relationships between variables that affect sepsis outcomes and exploring the magnitude of long-term mortality is essential in order to develop interventions, given the documented chronicity of symptoms in sepsis survivors (Iwashyna & Netzer, 2012).

The physiologic basis for the advantage of obesity in sepsis is unclear. However, the hypothesis central to this project is that the chronic inflammation of obesity attenuates the body's response to the extreme inflammation seen in sepsis, resulting in a more balanced physiologic response that causes less endothelial damage, capillary permeability, organ dysfunction, and ultimately lower mortality. The theoretical framework for testing the relationship between obesity and sepsis mortality has been described elsewhere (Robinson, Swift-Scanlan, Salyer, & Jones, 2020).

Other variables purported to impact sepsis outcomes are demographic and biological factors. For example, associations of sex, age, and race have been described in the short-term, but not the long-term, after sepsis. Biomarkers such as white blood cells (WBC), c-reactive protein (CRP), and lactate are useful in diagnosing infection, inflammation, and septic shock, respectively, but have not yet been examined as potential predictors of long-term survival in the context of obesity and mortality after sepsis. It is expected that distinctive differences between obese and non-obese physiologic states are associated with varied sepsis outcomes.

This research project was designed to address the dearth of knowledge about obesity and long-term sepsis mortality. The aim was to test whether the relationship between increased body mass index (BMI) and all-cause mortality at 30 days, 180 days, and up to one year after sepsis remains protective. We explored the interactions between BMI and sepsis severity at each time point. Additionally, we tested the relationships between demographic variables (sex, age, race) and biologic variables (CRP, WBC, lactate) with BMI and sepsis mortality at 30 days, 180 days, and one year after sepsis diagnosis in adults age 18 and older. The hypothesis is that BMI, demographic characteristics, and biologic variables are potential contributing factors affecting mortality in adults at 30 days, 180 days, and one year after diagnosis.

Methods

A retrospective cohort study was designed to examine factors affecting mortality at 30 days, 180 days, and one year. Through a partnership with the C. Kenneth and Dianne Wright Center (Center for Clinical and Translational Research [CCTR], 2020) data were collected from the electronic health record and the administrative database of a tertiary care academic medical center for a ten year period. Demographic variables, BMI, and laboratory data were obtained from the electronic health record. Admission dates and diagnosis codes were collected from the administrative database, which was matched to the Social Security Administration Death Master File to identify dates of death.

Data were cleaned by merging each variable into one spreadsheet using an exact date match to the date of admission. Hand-sorting of the variables was conducted to include all data points that occurred one day before the admission date and up to 5 days after the admission date. Listwise deletion was used to handle missing data. The data were then parsed by medical record number (MRN) and date of admission (DoA) to identify if more than one admission existed for an MRN, and if so, only the first date of admission was used to satisfy the assumption of independence between observations. Each MRN included was then assigned a unique identification number and de-identified in the analysis file. Data were secured in a password protected encrypted Excel file via the Research Electronic Data Capture (REDCap) platform hosted by Virginia Commonwealth University (VCU) (CCTR, 2020). Institutional Review Board approval was obtained for this study.

Sample.

A convenience sample of adults age 18 and older admitted to the academic medical center between the years of 2007 to 2018 with a diagnosis of sepsis was identified (N = 11,981).

Only the first admission for a diagnosis of sepsis was included in the study, and records without BMI were excluded (n = 4,756). Laboratory data reported below the detectable limit (i.e., < X) were imputed. WBC reported as less than the detectable limit was imputed by dividing the reported value by two and using the subsequent value (i.e., < 0.1/2 = 0.05). CRP reported as less than the detectable limit was imputed by dividing the reported value by two and using the subsequent value (i.e., < 0.3/2 = 0.15), except for a value reported as < 31.7, which was retained based on the rationale that this value is an elevation from normal that is biologically plausible. Results were reported in aggregate.

Inclusion and Exclusion Criteria. To ensure that the values for BMI, WBC, lactate, and CRP were captured as close as possible to the time of sepsis diagnosis, values were included if they were recorded within one day before the admission date and five days after the admission date. BMI values of < 14 and > 90 kg/m^2 were excluded from analysis *a priori* to reduce the inclusion of possible spurious values and to reduce the likelihood of extreme BMI values biasing the results. BMI in this dataset was recorded by the pharmacy. Medical records with BMI not recorded within the time period of 1 day before the admission date and five days after the admission date were excluded. WBC values > 30,000 $cells/mm^3$ were excluded to reduce the chance of inclusion of conditions other than sepsis (Widick & Winer, 2016). Lactate values > 6 mmol/L were excluded due to small numbers in that range. Race other than white non-Hispanic and black non-Hispanic were excluded due to small sample size. For the study flow diagram, see figure 1.

Variables

The variables included in the study were defined as follows:

- Sepsis was identified using **International Classification of Diseases, 9th ed. (**ICD-9) diagnosis codes for sepsis, severe sepsis, and septic shock (785.52; 995.91; 995.92).
- BMI was derived from the medical record as recorded by the pharmacy rather than being calculated from height and weight, due to inconsistently documented height and weight. BMI was defined as an index of weight adjusted for height (kg/m^2) that indirectly estimates body fat.
- Age was calculated from the date of birth.
- The date of death was identified through the Social Security Administration Death Master File and defined as death from any cause.
- Biologic sex was self-reported by the individual.
- Race and ethnicity were self-reported by the individual.
- WBC value was obtained from a laboratory report. Severe infection and sepsis can result in elevation ranging from 12,000 to 30,000 cells/mm^3. Values > 30,000 were excluded since values higher than this level could be resultant from congenital or malignant conditions rather than from sepsis (Widick & Winer, 2016).
- Lactate value was obtained from a laboratory report. Values in the range of 2 - 4 mmol/L indicate septic shock (Bakker, 2017; Vellinga et al., 2017).
- CRP value was obtained from a laboratory report. Values > 10 mg/L can indicate inflammation, and a range of 10-50 mg/L can indicate infection (Kusher et al., 2019).

Statistical Plan

A quantitative study using logistic regression was conducted to analyze the relationships among the variables and their ability to predict the likelihood of the dichotomous dependent variable of mortality at the three-time points described.

Descriptive Statistics. The data were examined descriptively and graphically. For continuous variables, distributions were assessed with histograms and outlier box plots, and the means and standard errors were calculated and reported in tabular form. For categorical variables, frequencies and percentages were calculated and reported in tabular form. Further, the means with standard deviations and frequencies with percentages are presented for BMI < 30 (not obese) and ≥ 30 (obese) and pooled to describe the data.

Logistic Regression Models. Logistic regression was used to build prediction models using the method proposed by Hosmer and Lemeshow (1989). In this analysis, there are three dependent mortality variables defined by time (30 days, 180 days, and one year) for which logistic regression was used to assess the effect of BMI on mortality, the effect of demographic (age, race, sex) and biologic (CRP, lactate, WBC) covariates on mortality and the interaction of BMI and demographic and biologic covariates on mortality. Thus, the analysis steps that follow applied to each of the dependent variables.

Assumptions for logistic regression include a binary dependent variable, independence among the observations, linearity in the logit for continuous predictors, and no multicollinearity among the predictors. Finally, it assumes that the sample size is sufficient as defined by n = 100 +50*i*, where *i* is the number of predictor variables (Bujang et al., 2018).

Steps to Model Building. Using the model-building strategy proposed by Hosmer and Lemeshow (1989), the first step was to explore associations between each independent variable, to include age, race, sex, c-reactive protein, lactate, and white blood cells and mortality using simple logistic regression. Independent variables with *p*-values < 0.25 made the variable eligible for inclusion in a subsequent multiple regression model. In the second step, a multivariable model was formed using all eligible variables from the first step. Variables with a *p*-value > 0.05

were eliminated from the model one at a time using a backward stepwise approach, with the least significant variable being removed first. In the third step, interactions between the remaining main effects deemed of clinical interest were added to the model in the second step. The interaction terms of BMI and sepsis type, BMI and age, BMI and sex, BMI and race, BMI and CRP, BMI and lactate, and BMI and WBC were entered into each model. Similar to in the second step, a backward stepwise approach was used to remove those interactions with a *p*-value > 0.05. The resultant model was considered the final predictive model. Note that this process was used three times, one for mortality at 30 days, 180 days and one year. Wald's test was used to assess the contribution of individual predictors in each model and the c-index was used to measure goodness of fit. Data analysis was carried out using JMP Pro version 14.2.0 (64-bit) and SAS.

Results

Descriptive statistics are presented for the variables of age, sex, race, BMI, CRP, lactate, and WBC. Each predictor variable is summarized with sample sizes, with means, and standard deviations (SD) for continuous variables and percentages for categorical variables, see Table 1. Age ranged from 18 to 97, (M = 56.56, SD = 16.17). The range of BMI was 14.26 to 84.72 kg/m^2; 65% had a BMI < 30 and 35% had a BMI > 30. CRP ranged from 0.15 to 0.63 mg/dl. Lactate ranged from 0.1 to 5.9 mmol/L. Within the total sample, 52% were black non-Hispanic, 48% were white non-Hispanic, 44% were female, and 56% were male. Diagnoses were 21% Severe Sepsis, 35% Septic Shock, and 44% Sepsis. WBC results ranged from 0.05 to 29.8 (5,000 to 29,800 cells/mm^3).

30-Day Mortality. The overall model goodness of fit was adequate, with a c-index of 0.726. In the initial analysis for 30-day mortality, higher levels of lactate were associated with

mortality in simple logistic regression. While lower levels of BMI were associated with mortality. Race (p = 0.09), CRP (p = 0.39) and WBC (p = 0.74) were not statistically significant and did not meet criteria for inclusion into the full model. Sex (p =0.35) was not statistically significant but was retained in the full model due to biological importance.

The final 30-day logistic regression model included sepsis type, age, lactate, BMI, and sex (n = 1,554), see Table 2B. Odds ratios with 95% confidence intervals are presented for each variable, see Table 2C. For every 5 unit increase in BMI, the odds of survival are 0.92 (95% CI: 0.85, 0.99) times lower, or for every 5 unit decrease in BMI, the odds of death are lower. Age, lactate, and sepsis type were associated with increased odds of death. For every five year increase in age, the odds of death are 1.14 times higher (95% CI: 1.09, 1.19). We found 3.56 times higher odds of death for a patient with septic shock versus sepsis and 1.63 times greater odds of death for a patient with severe sepsis versus sepsis at 30 days. For every one-unit increase in lactate, the odds of death were 1.34 times higher.

180-Day Mortality. The c-index was 0.74, indicating good goodness of fit. Simple logistic regression analysis for each independent variable and the dependent variable of 180-day mortality indicated that age, sepsis type, WBC, lactate, race, and BMI held a statistically significant association. These significant variables and sex (p = 0.29), which was not significant but was retained due to biologic importance, were eligible for entry into the full logistic regression model. Backward stepwise regression was used to eliminate variables one at a time for significance > 0.05, except for sex, which was retained in the model despite lack of significance due to biological importance. The final 180-day model included age, lactate, WBC, sex, and the interaction term of BMI and sepsis type (n = 3,720) see Table 2B. Odds ratios with 95% confidence intervals are presented for each variable, see Table 2C. For every five year

increase in age, the odds of death are 1.16 times (95% CI: (1.14, 1.19) higher. For every 10 unit increase in WBC, the odds ratio was 0.82 times (95% CI: 0.74, 0.90) lower. Males had a slightly higher odds of death than females at this time point. The main effect of BMI was statistically significant, indicating that higher levels of BMI were associated with lower mortality (p <0.0001). However, the interaction term of BMI and septic shock was also significant, demonstrating that in the context of septic shock increasing BMI was associated with higher mortality (p = 0.0006).

1-Year Mortality. The c-index was 0.73, indicating good goodness of fit. Initial analysis at 1-year (365 days) indicated that age, sepsis type, WBC, lactate, race, and BMI were significant in simple logistic regression. Backward stepwise regression was performed, and the final model included age, sex, WBC, and the interaction term of BMI and sepsis type (n= 3,720) see Table 2B. Odds ratios with 95% confidence intervals are presented for each variable, see Table 2C. For every 10 unit increase in WBC, the odds of death were 0.74 (95% CI: 0.67, 0.82). For every five year increase in age, the odds of death were 1.22 (95% CI: 1.19, 1.24). As with the other time points, sex was not statistically significant. The main effect of BMI was statistically significant, indicating that higher levels of BMI were associated with lower mortality (p <0.0001). However, the interaction term of BMI and septic shock was also significant, demonstrating that in the context of septic shock increasing BMI was associated with higher mortality (p = 0.001), and in the context of severe sepsis increasing BMI was associated with higher mortality (p = 0.041).

Discussion

In this study, we aimed to gain insight into the relationship between BMI, demographic, and biologic factors with sepsis mortality at three-time points using data over a ten year period

from a large academic medical center. Consistent with other studies, we found that increasing BMI was protective in the context of sepsis at 30-days. We hypothesize that the chronic inflammation observed in obesity causes an attenuated response in sepsis, resulting in lower mortality. However, this effect did not continue to hold constant at 180-days or 1 year after diagnosis. In our sample, we used BMI as recorded in an electronic health record to define obesity. We also limited our analysis to patients with a BMI > 14 and < 90 kg/m^2. The small number of patients at the extreme ranges of BMI offered insufficient statistical power to draw meaningful conclusions. Therefore, results cannot be related to individuals outside of this BMI range.

These results were corroborated by two recent large retrospective studies and one prospective study. Mewes et al. (2019) examined obesity in septic shock at 90 days using a prospective cohort (N=352) where 24% were obese compared to 75% non-obese patients and found lower 90-day mortality (31% vs. 43%; $p = 0.0436$) in obese patients. Li and colleagues (2019) found that obese patients showed a survival advantage at 30 days. However, the benefit was not significant at the end of one year for both severe sepsis and septic shock subsets in a sample (n = 5,563) drawn from the Multiparameter Intelligent Monitoring in Intensive Care (MIMIC-III) database (Li et al., 2019). Pepper et al. (2019) used the Cerner electronic health record database to garner a cohort of 55,038 adults hospitalized with sepsis and found that 30-day mortality was lower in overweight and obese patients compared with those with normal weight BMIs. The distribution of BMI across categories was similar between our study and the two recent retrospective studies while the prospective study categorized individuals as "obese" or "not obese." Given the similarity between sample characteristics, these results may represent the association between BMI and mortality adequately for similar populations. Although obesity

may be protective in the context of sepsis in the short-term, future prospective studies that follow patients over the long-term are needed to elucidate phenotypes of sepsis survivors.

The rationale for the protective effect of obesity has not been fully described. Physiologically, adipose tissue has several functions, including inflammation and immunity. One proposed theory is that the chronic inflammation of obesity creates a type of resistance to further inflammatory insults (Robinson, Swift-Scanlan, & Salyer, 2020). In other words, when there is a state of chronic inflammation, an acute insult such as sepsis may not have a less harmful effect on obese versus non-obese individuals (Robinson, Swift-Scanlan, Salyer, et al., 2020). Abbate et al. (2016) expanded upon this concept and proposed that obese adults may be chronically immune stimulated, which might improve pathogen clearance and reduce mortality.

While BMI is accepted internationally as the standard method for identifying obesity (Engin, 2017), there are limitations to the use of BMI to estimate adiposity. BMI is an index of weight adjusted for height that indirectly estimates body fat. Overall, body composition of fat and muscle and distribution of body weight are not accounted for in this metric, which does not take into account sex and racial differences, age differences, or waist circumference (Christopher, 2015; Vlassopoulos et al., 2014). Individuals with varying clinical and biochemical characteristics can be categorized similarly, regardless of emerging evidence of obesity phenotypes (Vecchié et al., 2018). Methods that better quantify adiposity, such as measuring waist circumference and waist-to-hip ratio, are valid, low-cost methods that could be considered for inclusion in future studies.

BMI and Sepsis Severity. It has been reported that sepsis has a high risk of death, 10-30%, and that increases to greater than 40% for septic shock (Karampela et al., 2019). We found that BMI and sepsis severity was significantly associated with mortality at 6-months and 1-year

after sepsis. There was a stepwise increase in odds of death for every 5 unit increase in BMI for sepsis, severe sepsis, and septic shock. Given our results, increasing BMI was not protective per category of sepsis severity. Perhaps the biological processes underlying obesity and sepsis severity may be more complicated than can be explained in this statistical model that does not take into account confounding factors such as chronic comorbidities. For example, obese people suffer from chronic diseases that can increase mortality, such as type 2 diabetes, chronic obstructive pulmonary disease (Papadimitriou-Olivgeris et al., 2016), hypertension, heart failure, and renal failure (Nguyen et al., 2016). Future studies that control for comorbidities is needed.

Criteria for diagnosis and algorithms for sepsis treatment have evolved over time and still may differ between medical centers (Pepper et al., 2016). Our study was unable to examine time to antibiotic therapy, types of microbe and cause of infection, or sepsis treatment algorithm. Antibiotic administration after the recommended 6-hour window has been associated with sepsis mortality, with up to a 7.6% decrease in sepsis survival for every one hour of delay (Sherwin et al., 2017). Skin and soft tissue infections, which respond to well to treatment, are more common causes of sepsis in those with higher BMI versus normal BMI (Arabi et al., 2013; Wacharasint et al., 2013). Consensus criteria for sepsis diagnosis have changed three times in the past two decades (Bone et al., 1992; Levy et al., 2003; Singer et al., 2016), owing to advancing science, and associated changes in clinical practice guidelines which have evolved, resulting in better outcomes overall (Coopersmith et al., 2018).

Sepsis and Demographic Contributors

Sepsis and age. We examined several models by logistic regression, including age as a predictor variable. We found that there was only a minor difference in odds of mortality at 30 days and 180 days, but that as time went on, the odds of death increased. For every 5 year

increase in age the odds of death were 1.15 (95% CI: 1.09, 1.19) at 30 days, 1.16 (95% CI: 1.14, 1.19) at 180 days, and 1.22 (95% CI: 1.19, 1.24) at 365 days. The results of our study were similar to those found by other researchers (Herrán-Monge et al., 2019; Li et al., 2019; Pepper et al., 2019). As the population of the United States is changing toward a large elderly population, understanding how conditions such as sepsis are affected by age is important. Particularly, since of those that survive sepsis, new cognitive and functional limitations may occur among those with no previous limitations and those who had mild to moderate limitations before sepsis (Iwashyna et al., 2010). As improved early diagnosis and treatment occurs, and more people survive sepsis, there is an increased need to understand the long-term impact.

Sepsis and sex. Biologic sex and the role of sex in sepsis outcomes is complicated due to physiologic differences between males and females and because of potential sex-related social and environmental differences. While our study did not show sexual dimorphism regarding sepsis mortality, other studies have demonstrated this phenomenon (Nachtigall et al., 2011). The role of sex steroid hormones is thought to influence the expression and outcome of many diseases, such as autoimmune disorders, which are about 9-times more common in females as compared with males (Weniger et al., 2015). Estrogens have pro- and anti-inflammatory properties, while androgens are primarily anti-inflammatory (Klein, 2000). The enhanced immune response during the proestrus cycle in females has been found to be protective against developing sepsis and for the survival of sepsis (Mayr et al., 2014; Weniger et al., 2015). Whereas in males, testosterone has an integral role in immune depression after trauma and sepsis (Schröder et al., 1998). Beyond biological contributors, sex is also a social construct. Social and environmental factors and chronic disease burden may contribute to the increased susceptibility of sepsis in males (Mayr et al., 2014). It is unclear if females have a survival advantage, if there

is under-diagnosis of sepsis in females, or if there are differences in healthcare access and delivery (Fowler et al., 2009; Schröder et al., 1998).

Sepsis and race. Race represents genetic, social, and environmental factors that influence health, such as access to healthcare, quality of care received, and environmental exposures (Shankar-Hari & Rubenfeld, 2018). As opposed to epidemiologic studies that reported a higher risk of mortality for black versus white patients (Barnato et al., 2008; Mayr et al., 2014; Sandoval & Chang, 2016), our study showed no association between race and sepsis mortality. However, a recent study that used data solely from academic medical centers reported that blacks had lower mortality than whites (OR 0.85; 95 % CI: 0.84–0.86) (Chaudhary et al., 2018). Conflicting data such as this reflects the need for further research to explicate the relationship between race and sepsis mortality.

Social and environmental factors play important roles in healthcare access and disease mortality. Our study underscores population characteristics that drive regional sepsis outcomes rather than national norms. The Richmond metropolitan area is one of the three most densely populated areas of Virginia. Rather than mirroring the racial distribution of the population of Virginia, which is 71.5% white and 20.7% black, the racial distribution of Richmond is approximately 50.6% black and 45.9% white (Virginia Department of Health [VDH], 2020). However, the catchment area of the academic medical center is regional, reflecting relatively lower percentages of uninsured individuals and moderate percentages of poverty among individuals the surrounding counties.

Sepsis and Biologic Contributors

Sepsis and lactate. Hyperlactatemia is an indicator of septic shock and a predictor of in-hospital mortality (Singer et al., 2016). It is thought that anaerobic metabolism and oxidative

stress, hallmarks of septic shock, contribute to hyperlactatemia (Duman et al., 2016). However, few studies describe an association between hyperlactatemia and late mortality from sepsis. Villar and colleagues (2019) examined the prognostic ability of lactate to predict mortality at 30-day and 1-year and found an odds of 1.5 higher for 30-day mortality (95% CI: 1.1-2.1) and an odds of 1.3 for 1-year mortality (95% CI: 1.1-1.6). Lower lactate levels were associated with long-term mortality, and higher lactate levels were associated with short-term mortality (Villar et al., 2019). Our study confirmed that hyperlactatemia is associated with short-term mortality, but we were unable to see the effect on late mortality.

Age was not significantly associated with lactate in our models that examined late mortality. However, when the prognostic value of lactate in the elderly (> 65 years of age) for 28-day mortality was investigated researchers found that lactate was significantly lower in elderly septic patients (5.5 ± 4.9) versus those under age 65 (6.6 ± 6.7, $p = 0.001$) (Cheng et al., 2018). The physiologic changes that occur with aging may be responsible for this difference. In our sample age was normally distributed between 18 and 97, but 31% of the sample was age 65 or older, perhaps affecting the impact of lactate on mortality at the two later time points.

Sepsis and WBC. White blood cells are described as the biomarker most often used along with clinical parameters to diagnose sepsis (Shukeri et al., 2018), but WBCs have low sensitivity and specificity for sepsis (Gucyetmez & Atalan, 2016). We found that for 30-day mortality, WBCs were not significantly associated with sepsis mortality. One reason for this may be that leukocytosis is a normal physiologic reaction that is mounted to combat infection. Therefore, leukocytosis may indicate a robust immune system and a superior ability to fight off infection in the short-term. In our sample, we found that for every 10 unit increase in WBC, the odds of death were 0.82 (95% CI: 0.74, 0.90) times lower for 180-day mortality and 0.74 (95%

CI: 0.67, 0.82) times lower for 365-day mortality. This could be an indication of less severe sepsis in our population, as lower levels of WBC may be associated with less severe infection, which may translate into lower mortality.

Sepsis and CRP. As an acute-phase reactive protein, CRP is elevated in states of inflammation. In chronic inflammation, such as obesity, the elevation is mild, but in an acute condition such as sepsis, the elevation is marked (Hribal et al., 2014). CRP has been studied as a successful prognostic indicator in sepsis (Gradel et al., 2013; Mustafić et al., 2018), yet in our research, we found no association between CRP and mortality at any time point. Several factors could influence the level of CRP, including co-morbidities, sepsis recurrence, and obesity. Our findings may reflect our decision to use only the first admission date for sepsis as an inclusion criterion and to use only one value of CRP rather than examining values serially. Additionally, in our data there were relatively few (n=441) observations with a CRP value recorded. Biomarkers other than CRP may better assess for obesity-related protection in sepsis. CRP is chronically elevated in obesity, along with other biomarkers such as interleukin-6 (IL-6) and leptin, due to heightened endocrine and immunologic activity when there is excess adipose tissue (Abdullah et al., 2009; Florez et al., 2006). Increased adiposity causes dysregulation resulting in the up-regulation of CRP, IL-6, tumor necrosis factor-α (TNF-α), and leptin along with the simultaneous downregulation of adiponectin. Leptin and adiponectin are opposing adipokines; leptin is pro-inflammatory and adiponectin is anti-inflammatory. It is leptin's involvement in immunity and inflammation, particularly related to the activation of immune cells and cytokine expression that makes it an attractive biomarker to demonstrate protection from

sepsis (Yousef et al., 2010). Low leptin and high IL-6 levels have been observed in sepsis patients with unfavorable outcomes (Bornstein et al., 1998), and animal models have

shown that hyperleptinemia was associated with better sepsis outcomes (Negrin et al., 2017; Siegl et al., 2014). As there was little to no IL-6, TNF-α, or leptin biomarker measures in our retrospective dataset, we recommend prospective studies that include a series of biomarkers, including leptin, to test associations with sepsis outcomes and mortality.

Long-Term Outcomes

Sepsis survivors often experience morbidity, destabilizing health, and increased healthcare utilization, hospital readmission, and even mortality (Jones et al., 2015; Mayr et al., 2014). The risk of long-term mortality may be overshadowed by the characteristics of acute illness, which may not be representative of late mortality (Shankar-Hari et al., 2019). Recently, Demerle et al. (2017) reported that two-thirds of rehospitalizations after sepsis were due to infection and that among those readmitted for sepsis within 90 days, the mortality rate was 21.2% versus 10.5% for those readmitted for a different diagnosis ($p = 0.002$). Among those who survive sepsis, many experience persistent residual symptoms of physical, psychological, cognitive, and functional frailty (Gardner et al., 2019; Iwashyna & Netzer, 2012; Winters et al., 2010), such as fatigue, muscle weakness, difficulty swallowing, difficulty concentrating, poor memory, sadness, and anxiety (Prescott & Angus, 2018).

In addition to the physical deterioration seen after sepsis, survivors of sepsis experience lower quality of life for up one and half years afterward. In the Finnsepsis study, researchers found that patients recover slowly from severe sepsis and have a low quality of life when compared with controls, and had 1.5 times higher mortality at two years than in-hospital (Karlsson et al., 2009). A Chinese prospective multi-center study showed that severe sepsis

survivors had impaired quality of life at up to 6 years after hospital discharge (Zhang et al., 2013). Secondary analysis of the large-scale ACCESS and PROWESS-SHOCK trials

showed that about one-third of 6-month survivors reported poor quality of life, problems with mobility and self-care, and most required residency at a rehabilitation center, nursing home, or acute facility (Yende et al., 2016). Fears of medical setbacks in the weeks to months after sepsis have also been documented (Prescott & Angus, 2018). Sepsis is proving to be more than an acute syndrome; it has chronic consequences that can result in a declining physical function and quality of life measures over time (Winters et al., 2010).

Limitations

The use of retrospective medical record data is helpful for examining a large population over a long period of time. However, there are several limitations. First, the study population is drawn from a single academic medical center, so it may not generalize to community hospitals or areas with different sociogeographical characteristics. This study used all-cause mortality rather than disease specific mortality due to limitations of available data. Our reliance upon electronic health records holds a potential for the inaccuracy of information entered into the medical record and may reflect differences in diagnostic and treatment protocols over the ten year time period. In particular, the availability of laboratory data for newly recognized and investigative biomarkers such as leptin was not available in this sample. There were few observations with CRP values documented, which may have impacted results. The sample size was reduced by nearly half due to lack of BMI documentation in the dataset; height and weight were inconsistently available and BMI documented by pharmacy was all that was available. Additionally, using ICD-9 codes to identify the presence of sepsis may not accurately account for all cases of sepsis, and this method lacks granular detail about the timing of sepsis.

Using only the first admission date for sepsis promoted independence between observations but may not adequately capture the increasing magnitude of illness that can occur

with sepsis recurrence. Lastly, our data did not include co-morbidities, which may be an essential missing piece that, if present, would help to discriminate between sepsis phenotypes.

Conclusion

Sepsis is a serious health concern resulting in high rates of mortality. Our study demonstrates that increasing BMI is associated with reduced sepsis mortality at 30 days, but not at longer time points. Overall, after taking into account the strengths and limitations of this study design, it appears that the "obesity paradox" may exist at 30 days, but the protective effect does not extend beyond that time point. Our findings regarding demographic characteristics and biologic contributors were consistent with other published reports. Given the importance of long-term sepsis sequelae and the increasing rates of obesity, research that characterizes the phenotype of sepsis survivors based on BMI is needed to identify and meet the needs of this growing population.

References

Abbate, L. M., Perman, S. M., Clambey, E. T., Van Pelt, R. E., & Ginde, A. A. (2016). Age Modifies the Association Between Obesity and Mortality Among Hospitalizations for Severe Sepsis. *Journal of the American Geriatric Society*, *64*(4), 882–883. https://doi.org/10.1016/S2214-109X(16)30265-0.Cost-effectiveness

Abdullah, A. R., Hasan, H. A., & Raigangar, V. L. (2009). Analysis of the relationship of leptin, high-sensitivity C-reactive protein, adiponectin, insulin, and uric acid to metabolic syndrome in lean, overweight, and obese young females. *Metabolic Syndrome and Related Disorders*, *7*(1), 17–22. https://doi.org/10.1089/met.2008.0045

Arabi, Y. M., Dara, S. I., Tamim, H. M., Rishu, A. H., Bouchama, A., Khedr, M. K., Feinstein, D., Parrillo, J. E., Wood, K. E., Keenan, S. P., Zanotti, S., Martinka, G., Kumar, A., & Kumar, A. (2013). Clinical characteristics, sepsis interventions and outcomes in the obese patients with septic shock: an international multicenter cohort study. *Critical Care*, *17*(2), R72. https://doi.org/10.1186/cc12680

Bakker, J. (2017). Lactate is the target for early resuscitation in sepsis. *Revista Brasileira de Terapia Intensiva*, *29*(2), 124–127. https://doi.org/10.5935/0103-507X.20170021

Barnato, A. E., Alexander, S. L., Linde-Zwirble, W. T., & Angus, D. C. (2008). Racial variation in the incidence, care, and outcomes of severe sepsis: Analysis of population, patient, and hospital characteristics. *American Journal of Respiratory and Critical Care Medicine*, *177*(3), 279–284. https://doi.org/10.1164/rccm.200703-480OC

Bone, R. C., Balk, R. A., Cerra, F. B., Dellinger, R. P., Fein, A. M., Knaus, W. A., Schein, R. M. H., & Sibbald, W. J. (1992). Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*, *101*(6), 1644–1655.

https://doi.org/10.1378/chest.101.6.1644

Bornstein, S. R., Licinio, J., Tauchnitz, R., Engelmann, L., Negrao, A. B., Gold, P., & Chrousos, G. P. (1998). Plasma leptin levels are increased in survivors of acute sepsis: associated loss of diurnal rhythm in cortisol and leptin secretion. *Journal of Clinical Endrocrinology and Metabolism*, *83*(1), 280–283.

Braun, N., Hoess, C., Kutz, A., Christ-Crain, M., Thomann, R., Henzen, C., Zimmerli, W., Mueller, B., & Schuetz, P. (2016). Obesity paradox in patients with community-acquired pneumonia: Is inflammation the missing link? *Nutrition*, *33*, 1–7. https://doi.org/10.1016/j.nut.2016.07.016

Bujang, M. A., Sa'At, N., Tg Abu Bakar Sidik, T. M. I., & Lim, C. J. (2018). Sample size guidelines for logistic regression from observational studies with large population: Emphasis on the accuracy between statistics and parameters based on real life clinical data. *Malaysian Journal of Medical Sciences*, *25*(4), 122–130. https://doi.org/10.21315/mjms2018.25.4.12

Center for Clinical and Translational Research [CCTR]. (2020). Cite the Grant. https://cctr.vcu.edu/cite-us/

Chaudhary, N. S., Donnelly, J. P., & Wang, H. E. (2018). Racial differences in sepsis mortality at U.S. academic medical center-affiliated hospitals. *Critical Care Medicine*, *46*(6), 878–883. https://doi.org/10.1097/CCM.0000000000003020

Cheng, H. H., Chen, F. C., Change, M. W., Kung, C. Te, Cheng, C. Y., Tsai, T. C., Hsiao, S. Y., & Su, C. M. (2018). Difference between elderly and non-elderly patients in using serum lactate level to predict mortality caused by sepsis in the emergency department. *Medicine*, *97*(13), 1–6. https://doi.org/10.1097/MD.0000000000010209

Christopher, K. B. (2015). The body mass index paradox. *Critical Care Medicine*, *43*(12), 2693–2694. https://doi.org/10.1097/CCM.0000000000001344

Coopersmith, C. M., De Backer, D., Deutschman, C. S., Ferrer, R., Lat, I., Machado, F. R., Martin, G. S., Martin-Loeches, I., Nunnally, M. E., Antonelli, M., Evans, L. E., Hellman, J., Jog, S., Kesecioglu, J., Levy, M. M., & Rhodes, A. (2018). Surviving sepsis campaign: research priorities for sepsis and septic shock. *Intensive Care Medicine*, *44*(9), 1400–1426. https://doi.org/10.1007/s00134-018-5175-z

De Backer, D., & Dorman, T. (2017). Surviving Sepsis Guidelines A Continuous Move Toward Better Care of Patients With Sepsis. *Journal of the American Medical Association*, *317*(8), 807–808. https://doi.org/10.1007/s00134

De Schutter, A., Kachur, S., Lavie, C. J., Boddepalli, R. S., Patel, D. A., & Milani, R. V. (2016). The impact of inflammation on the obesity paradox in coronary heart disease. *International Journal of Obesity*, *40*(11), 1730–1735. https://doi.org/10.1038/ijo.2016.125

Duman, A., Akoz, A., Kapci, M., Ture, M., Orun, S., Karaman, K., & Turkdogan, K. A. (2016). Prognostic value of neglected biomarker in sepsis patients with the old and new criteria: predictive role of lactate dehydrogenase. *American Journal of Emergency Medicine*, *34*(11), 2167–2171. https://doi.org/10.1016/j.ajem.2016.06.012

Engin, A. (2017). The Pathogenesis of Obesity-Associated Adipose Tissue Inflammation. In A. B. Engin & A. Engin (Eds.), *Obesity and Lipotoxicity* (pp. 221–245). Springer International Publishing. https://doi.org/10.1007/978-3-319-48382-5_9

Florez, H., Castillo-Florez, S., Mendez, A., Casanova-Romero, P., Larreal-Urdaneta, C., Lee, D., & Goldberg, R. (2006). C-reactive protein is elevated in obese patients with the metabolic syndrome. *Diabetes Research and Clinical Practice*, *71*(1), 92–100.

https://doi.org/10.1016/j.diabres.2005.05.003

Fowler, R. A., Filate, W., Hartleib, M., Frost, D. W., Lazongas, C., & Hladunewich, M. (2009). Sex and critical illness. *Current Opinion in Critical Care*, *15*(5), 442–449. https://doi.org/10.1097/MCC.0b013e3283307a12

Gardner, A. K., Ghita, G. L., Wang, Z., Ozrazgat-baslanti, T., Raymond, S. L., Mankowski, R. T., Brumback, B. A., Efron, P. A., Bihorac, A., Moore, F. A., Anton, S. D., & Brakenridge, S. C. (2019). The Development of Chronic Critical Illness Determines Physical Function, Quality of Life, and Long-Term Survival Among Early Survivors of Sepsis in Surgical ICUs. *Critical Care Medicine*, *47*(4), 566–573. https://doi.org/10.1097/CCM.0000000000003655

Gradel, K. O., Jensen, T. G., Kolmos, H. J., Pedersen, C., Vinholt, P. J., & Lassen, A. T. (2013). Does C-reactive protein independently predict mortality in adult community-acquired bacteremia patients with known sepsis severity? *Apmis*, *121*(9), 835–842. https://doi.org/10.1111/apm.12040

Gucyetmez, B., & Atalan, H. K. (2016). C-reactive protein and hemogram parameters for the non-sepsis systemic inflammatory response syndrome and sepsis: What do they mean? *PLoS ONE*, *11*(2), 1–9. https://doi.org/10.1371/journal.pone.0148699

Hafner, S., Hillenbrand, A., Knippschild, U., & Radermacher, P. (2013). The obesity paradox and acute kidney injury: Beneficial effects of hyper-inflammation? *Critical Care*, *17*(6). https://doi.org/10.1186/cc13152

Herrán-Monge, R., Muriel-Bombín, A., García-García, M. M., Merino-García, P. A., Martínez-Barrios, M., Andaluz, D., Ballesteros, J. C., Domínguez-Berrot, A. M., Moradillo-Gonzalez, S., Macías, S., Álvarez-Martínez, B., Fernández-Calavia, M. J., Tarancón, C., Villar, J.,

Blanco, J., & on behalf of the GRECIA Network. (2019). Epidemiology and Changes in Mortality of Sepsis After the Implementation of Surviving Sepsis Campaign Guidelines. *Journal of Intensive Care Medicine*, *34*(9), 740–750. https://doi.org/10.1177/0885066617711882

Hribal, M., Fiorentino, T., & Sesti, G. (2014). Role of C Reactive Protein (CRP) in Leptin Resistance. *Current Pharmaceutical Design*, *20*(4), 609–615. https://doi.org/10.2174/13816128113199990016

Iwashyna, T. J., Ely, E. W., Smith, D. M., & Langa, K. M. (2010). Long-term cognitive impairment and functional disability among survivors of severe sepsis. *Journal of the American Medical Association*, *304*(16), 1787–1794. https://doi.org/10.1001/jama.2010.1553.Long-term

Iwashyna, T. J., & Netzer, G. (2012). The Burdens of Survivorship : An Approach to Thinking about Long-Term Outcomes after Critical Illness. *Seminars in Respiratory and Critical Care Medicine*, *33*, 327–338. https://doi.org/DOI: 10.1055/s-00000075

Jones, T. K., Fuchs, B. D., Small, D. S., Halpern, S. D., Hanish, A., Umscheid, C. A., Baillie, C. A., Kerlin, M. P., Gaieski, D. F., & Mikkelsen, M. E. (2015). Post-acute care use and hospital readmission after sepsis. *Annals of the American Thoracic Society*, *12*(6), 904–913. https://doi.org/10.1513/AnnalsATS.201411-504OC

Karampela, I., Christodoulatos, G. S., & Dalamaga, M. (2019). The Role of Adipose Tissue and Adipokines in Sepsis: Inflammatory and Metabolic Considerations, and the Obesity Paradox. *Current Obesity Reports*, *8*(4), 434–457. https://doi.org/10.1007/s13679-019-00360-2

Karlsson, S., Ruokonen, E., Varpula, T., Ala-Kokko, T. I., & Pettilä, V. (2009). Long-term

outcome and quality-adjusted life years after severe sepsis. *Critical Care Medicine*, *37*(4), 1268–1274. https://doi.org/10.1097/CCM.0b013e31819c13ac

Keaver, L., Xu, B., Jaccard, A., & Webber, L. (2018). Morbid obesity in the UK: A modelling projection study to 2035. *Scandinavian Journal of Public Health*, *January*, 1–6. https://doi.org/10.1177/1403494818794814

Klein, S. L. (2000). The effects of hormones on sex differences in infection: From genes to behavior. *Neuroscience and Biobehavioral Reviews*, *24*(6), 627–638. https://doi.org/10.1016/S0149-7634(00)00027-0

Levy, M. M., Fink, M. P., Marshall, J. C., Abraham, E., Angus, D., Cook, D., Cohen, J., Opal, S. M., Vincent, J. L., & Ramsay, G. (2003). 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Medicine*, *29*(4), 530–538. https://doi.org/10.1007/s00134-003-1662-x

Li, S., Hu, X., Xu, J., Huang, F., Guo, Z., Tong, L., Lui, K. Y., Cao, L., Zhu, Y., Yao, J., Lin, X., Guan, X., & Cai, C. (2019). Increased body mass index linked to greater short- and long-term survival in sepsis patients: A retrospective analysis of a large clinical database. *International Journal of Infectious Diseases*, *87*, 109–116. https://doi.org/10.1016/j.ijid.2019.07.018

Mayr, F. B., Yende, S., & Angus, D. C. (2014). Epidemiology of severe sepsis. *Virulence*, *5*(1), 4–11. https://doi.org/10.4161/viru.27372

Meyer, N., Harhay, M. O., Small, D. S., Prescott, H. C., Bowles, K. H., Gaieski, D. F., & Mikkelsen, M. E. (2018). Temporal Trends in Incidence, Sepsis-Related Mortality, and Hospital-Based Acute Care After Sepsis. *Critical Care Medicine*, *46*(3), 354–360. https://doi.org/10.1097/CCM.0000000000002872

Mustafić, S., Brkić, S., Prnjavorac, B., Sinanović, A., Porobić-Jahić, H., & Salkić, S. (2018). Diagnostic and prognostic value of procalcitonin in patients with sepsis. *Medicinski Glasnik, 15*(2), 93–100. https://doi.org/10.17392/963-18

Nachtigall, I., Tafelski, S., Rothbart, A., Kaufner, L., Schmidt, M., Tamarkin, A., Kartachov, M., Zebedies, D., Trefzer, T., Wernecke, K. D., & Spies, C. (2011). Gender-related outcome difference is related to course of sepsis on mixed ICUs: A prospective, observational clinical study. *Critical Care, 15*(3). https://doi.org/10.1186/cc10277

Negrin, L. L., Jahn, A., & van Griensven, M. (2017). Leptin Protects Against Mortality and Organ Dysfunction in A Two-Hit Trauma/Sepsis Model and is IL-6-Dependent. *Shock, 48*(1), 130–137. https://doi.org/10.1097/SHK.0000000000000837

Nguyen, A. T., Tsai, C.-L., Hwang, L.-Y., Lai, D., Markham, C., & Patel, B. (2016). Obesity and Mortality, Length of Stay and Hospital Cost among Patients with Sepsis: A Nationwide Inpatient Retrospective Cohort Study. *PloS One, 11*(4), e0154599. https://doi.org/10.1371/journal.pone.0154599

Papadimitriou-olivgeris, M., Aretha, D., Zotou, A., Koutsileou, K., Zbouki, A., Lefkaditi, A., Sklavou, C., Marangos, M., & Fligou, F. (2016). The Role of Obesity in Sepsis Outcome among Critically Ill Patients : A Retrospective Cohort Analysis. *BioMed, 5941279*.

Pepper, D. J., Demirkale, C. Y., Sun, J., Rhee, C., Fram, D., Eichacker, P., Klompas, M., Suffredini, A. F., & Kadri, S. S. (2019). Does Obesity Protect Against Death in Sepsis? A Retrospective Cohort Study of 55,038 Adult Patients. *Critical Care Medicine*, *47*(5), 643–650. https://doi.org/10.1097/CCM.0000000000003692

Pepper, D. J., Sun, J., Welsh, J., Cui, X., Suffredini, A. F., & Eichacker, P. Q. (2016). Increased body mass index and adjusted mortality in ICU patients with sepsis or septic shock: a

systematic review and meta-analysis. *Critical Care*, *20*(1), 181. https://doi.org/10.1186/s13054-016-1360-z

Prescott, H. C., & Angus, D. C. (2018). Enhancing Recovery from Sepsis. *Journal of the American Medical Association*, *319*(1), 62–75. https://doi.org/10.1001/jama.2017.17687

Prescott, H. C., Chang, V. W., O'Brien, J. M., Langa, K. M., & Iwashyna, T. J. (2014). Obesity and 1-year outcomes in older Americans with severe sepsis. *Critical Care Medicine*, *42*(8), 1766–1774. https://doi.org/10.1097/CCM.0000000000000336

Prevention, C. for D. C. and. (2016). *Data & Reports*. Data & Reports. https://www.cdc.gov/sepsis/datareports/index.html

Reinhart, K., Daniels, R., Kissoon, N., Machado, F., Schachter, R., & Finfer, S. (2017). Recognizing Sepsis as a Global Health Priority — A WHO Resolution. *New England Journal of Medicine*, *377*(5), 411–414. https://doi.org/10.1056/NEJMp1704633

Robinson, J., Swift-Scanlan, T., & Salyer, J. (2020). Obesity and 1-Year Mortality in Adults After Sepsis: A Systematic Review. *Biological Research for Nursing*, *22*(1), 103–113. https://doi.org/10.1177/1099800419876070

Robinson, J., Swift-Scanlan, T., Salyer, J., & Jones, T. (2020). The Obesity Paradox in Sepsis: A Theoretical Framework. *Biological Research For Nursing*. https://doi.org/10.1177/1099800420905889

Sandoval, E., & Chang, D. W. (2016). Association between race and case fatality rate in hospitalizations for sepsis. *Journal of Racial and Ethnic Health Disparities*, *3*(4), 625–634. https://doi.org/10.1007/s40615-015-0181-0

Schröder, J., Kahlke, V., Staubach, K. H., Zabel, P., & Stüber, F. (1998). Gender differences in human sepsis. *Archives of Surgery*, *133*(11), 1200–1205.

https://doi.org/10.1001/archsurg.133.11.1200

Shankar-Hari, M., Harrison, D. A., Ferrando-Vivas, P., Rubenfeld, G. D., & Rowan, K. (2019). Risk Factors at Index Hospitalization Associated With Longer-term Mortality in Adult Sepsis Survivors. *Journal of the American Medical Association*, *2*(5), e194900. https://doi.org/10.1001/jamanetworkopen.2019.4900

Shankar-Hari, M., & Rubenfeld, G. D. (2018). Race, Ethnicity, and Sepsis. *Critical Care Medicine*, *46*(6), 1009–1010. https://doi.org/10.1097/CCM.0000000000003060

Sherwin, R., Winters, M. E., Vilke, G. M., & Wardi, G. (2017). Does Early and Appropriate Antibiotic Administration Improve Mortality in Emergency Department Patients with Severe Sepsis or Septic Shock? *Journal of Emergency Medicine*, *53*(4), 588–595. https://doi.org/10.1016/j.jemermed.2016.12.009

Shukeri, W. F. W. M., Ralib, A. M., Abdulah, N. Z., & Mat-Nor, M. B. (2018). Sepsis mortality score for the prediction of mortality in septic patients. *Journal of Critical Care*, *43*, 163–168. https://doi.org/10.1016/j.jcrc.2017.09.009

Siegl, D., Annecke, T., Johnson, B. L., Schlag, C., Martignoni, A., Huber, N., Conzen, P., Caldwell, C. C., & Tschöp, J. (2014). Obesity-induced Hyperleptinemia Improves Survival and Immune Response in a Murine Model of Sepsis. *Anesthesiology*, *121*(1), 98–114. https://doi.org/10.1097/ALN.0000000000000192

Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., Bellomo, R., Bernard, G. R., Chiche, J.-D., Coopersmith, C. M., Hotchkiss, R. S., Levy, M. M., Marshall, J. C., Martin, G. S., Opal, S. M., Rubenfeld, G. D., van der Poll, T., Vincent, J., & Angus, D. C. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Journal of the American Medicine Association*, *315*(8), 801–810.

https://doi.org/10.1001/jama.2016.0287

Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-hari, M., Annane, D., Bauer, M., Bellomo, R., Bernard, G. R., Chiche, J., Craig, M., Hotchkiss, R. S., Levy, M. M., Marshall, J. C., Martin, G. S., Opal, S. M., Rubenfeld, G. D., Vincent, J., Angus, D. C., Park, N. H., … Centrum, A. M. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Journal of the American Medical Association*, *315*(8), 801–810. https://doi.org/10.1001/jama.2016.0287.The

Vecchié, A., Dallegri, F., Carbone, F., Bonaventura, A., Liberale, L., Portincasa, P., Frühbeck, G., & Montecucco, F. (2018). Obesity phenotypes and their paradoxical association with cardiovascular diseases. *European Journal of Internal Medicine*, *48*, 6–17. https://doi.org/10.1016/j.ejim.2017.10.020

Vellinga, N. A. R., Boerma, E. C., Koopmans, M., Donati, A., Dubin, A., Shapiro, N. I., Pearse, R. M., van der Voort, P. H. J., Dondorp, A. M., Bafi, T., Fries, M., Akarsu-Ayazoglu, T., Pranskunas, A., Hollenberg, S., Balestra, G., van Iterson, M., Sadaka, F., Minto, G., Aypar, U., … Ayhan, B. (2017). Mildly elevated lactate levels are associated with microcirculatory flow abnormalities and increased mortality: A microSOAP post hoc analysis. *Critical Care*, *21*(1), 1–9. https://doi.org/10.1186/s13054-017-1842-7

Villar, J., Short, J. H., & Lighthall, G. (2019). Lactate Predicts Both Short- and Long-Term Mortality in Patients With and Without Sepsis. *Infectious Diseases: Research and Treatment*, *12*, 1–6. https://doi.org/10.1177/1178633719862776

Vlassopoulos, A., Combet, E., & Lean, M. E. J. (2014). Changing distributions of body size and adiposity with age. *International Journal of Obesity*, *38*(6), 857–864. https://doi.org/10.1038/ijo.2013.216

Wacharasint, P., Boyd, J. H., Russell, J. A., & Walley, K. R. (2013). One size does not fit all in severe infection: obesity alters outcome, susceptibility, treatment, and inflammatory response. *Critical Care*, *17*(3), R122. https://doi.org/10.1186/cc12794

Weniger, M., Dhaese, J. G., Angele, M. K., & Chaudry, I. H. (2015). Potential therapeutic targets for sepsis in women. *Expert Opinion on Therapeutic Targets*, *19*(11), 1531–1543. https://doi.org/10.1517/14728222.2015.1057570

Widick, P., & Winer, E. S. (2016). Leukocytosis and Leukemia. *Primary Care - Clinics in Office Practice*, *43*(4), 575–587. https://doi.org/10.1016/j.pop.2016.07.007

Winters, B. D., Eberlein, M., Leung, J., Needham, D. M., Pronovost, P. J., & Sevransky, J. E. (2010). Long-term mortality and quality of life in sepsis: a systematic review. *Critical Care Medicine*, *38*(5), 1276–1283. https://doi.org/10.1097/CCM.0b013e3181d8cc1d

Yende, S., Austin, S., Rhodes, A., Finfer, S. R., Opal, S. M., Thompson, B. T., Bozza, F. A., LaRosa, S. P., Ranieri, V. M., & Angus, D. C. (2016). Long-Term Quality of Life Among Survivors of Severe Sepsis. *Critical Care Medicine*, 1. https://doi.org/10.1097/CCM.0000000000001658

Yousef, A. A. A., Amr, Y. M., & Suliman, G. A. (2010). The diagnostic value of serum leptin monitoring and its correlation with tumor necrosis factor- a in critically ill patients : a prospective observational study. *Critical Care*, *6*. https://doi.org/doi: 10.1186/cc8911

Zhang, K., Mao, X., Fang, Q., Jin, Y., Cheng, B., Xie, G., Li, H., Yu, L., Zhu, T., Wang, H., Liu, X., Zhang, Y., Jin, Y., Zhang, N., Lou, T., & Fang, X. M. (2013). Impaired long-term quality of life in survivors of severe sepsis: Chinese multicenter study over 6 years. *Anaesthesist*, *62*(12), 995–1002. https://doi.org/10.1007/s00101-013-2257-8

Figure 1: Study flow diagram.

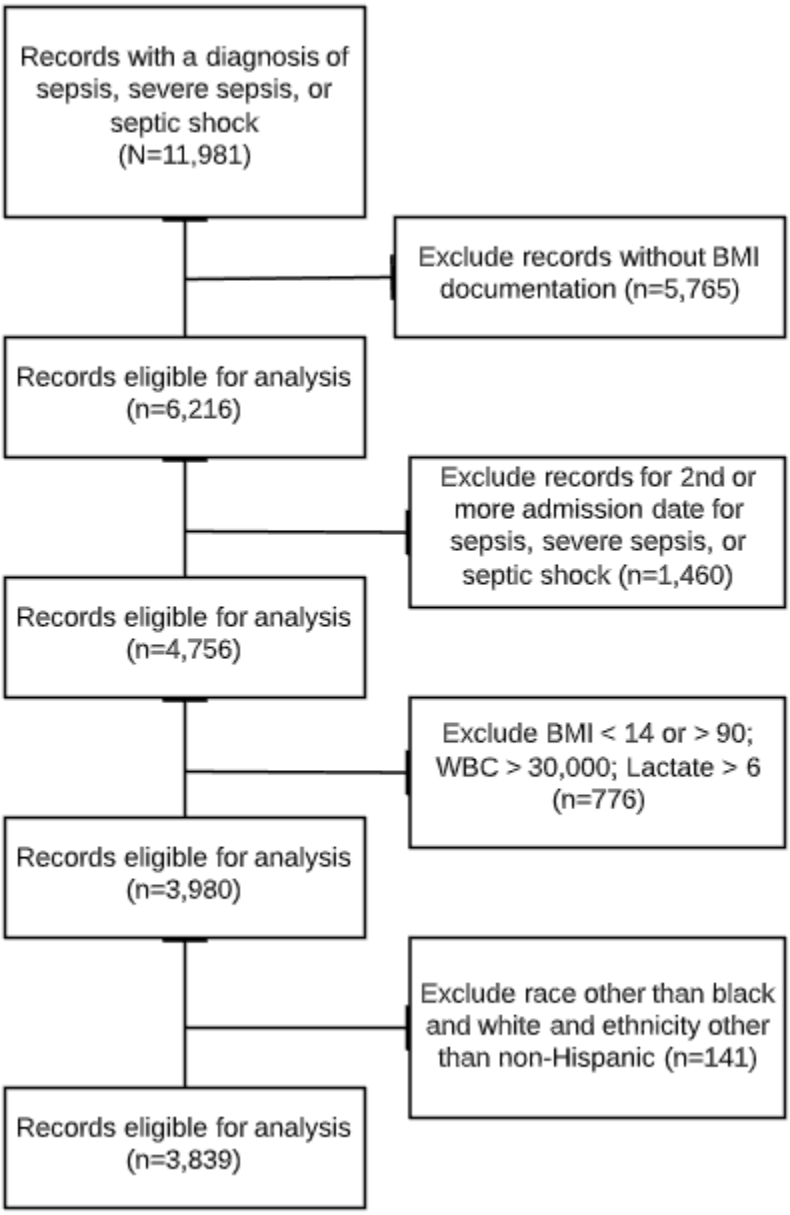


Figure 2: For 180 day mortality, the interaction terms of sepsis type and BMI is reported to further demonstrate the relationship between these predictor variables. For Sepsis versus Severe Sepsis there is little change as BMI increases. For Sepsis versus Sepsis Shock as BMI increases there are increased odds of mortality; for a BMI of 15 the OR=2.64 (CI: 1.92, 3.61) while for a BMI of 40 the OR = 6.80 (CI: 4.92, 9.39).

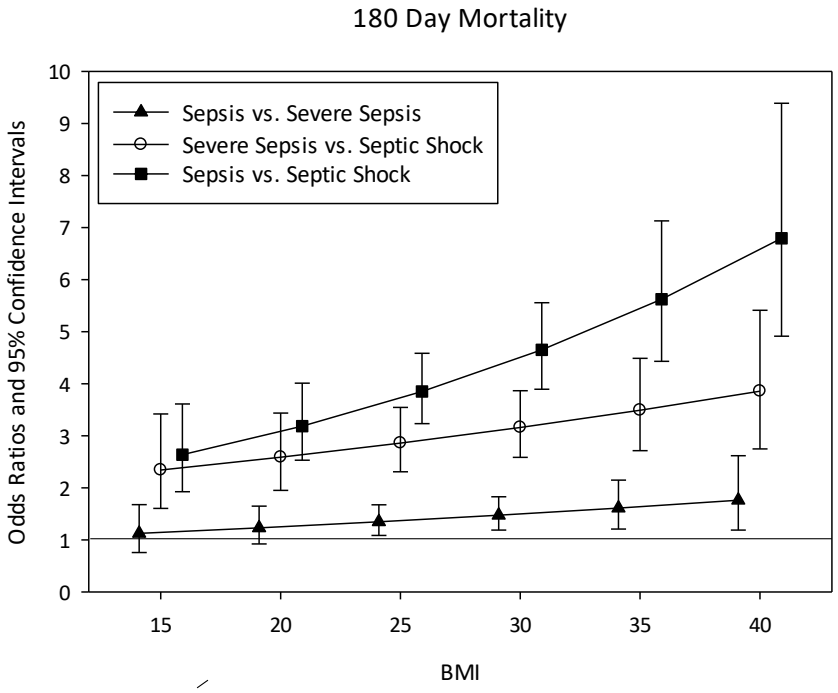


Figure 3: For 1-year mortality, the interaction terms of sepsis type and BMI is reported to further demonstrate the relationship between these predictor variables. For Sepsis versus Severe Sepsis and for Severe Sepsis versus Septic Shock there is little change as BMI increases. For Sepsis versus Sepsis Shock as BMI increases there are increased odds of mortality; for a BMI of 15 the OR=2.34 (CI: 1.73, 3.18) while for a BMI of 40 the OR = 5.52 (CI: 4.08, 7.47).

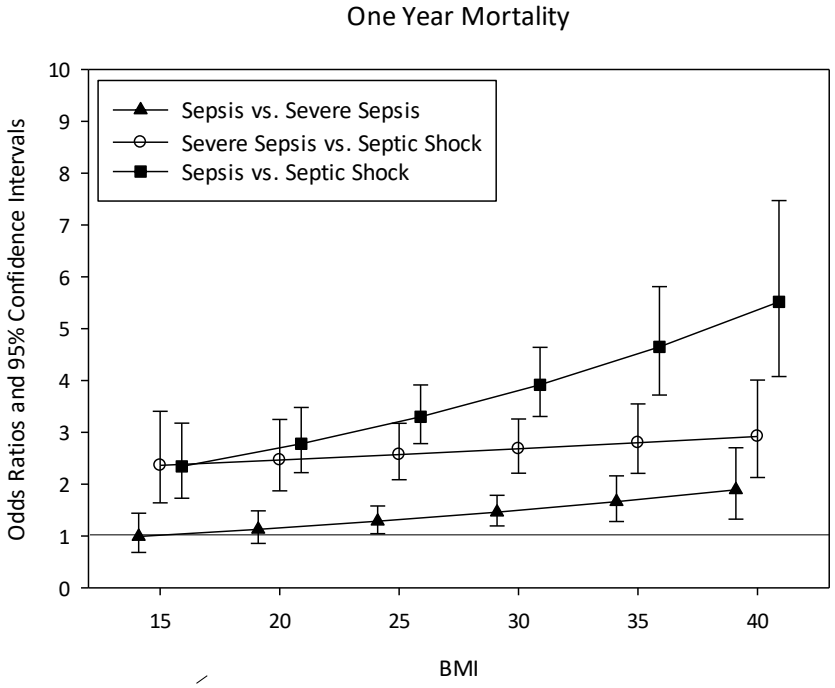


Table 1: Descriptive Statistics of the Variables in the Sample for this Study.

	N	Means	SD	Percentage	Missing
Age	3832	56.56	16.71		7
BMI	3839	28.63	8.8		0
CRP	441	15.42	33.4		3398
Lactate	1556	1.95	1.92		2284
Race	3839			100%	0
Black, Non-Hispanic	1993			52%	0
White, Non-Hispanic	1846			48%	0
Sepsis Type	3839			100%	0
Sepsis	1696			44%	0
Severe Sepsis	789			21%	0
Septic Shock	1354			35%	0
Sex	3839			100%	0
Female	1698			44%	0
Male	2141			56%	0

*Cells are empty when the variable is not described by the method indicated by the column header (i.e.: continuous variable are not described by percentages; categorical variables are not described by means and SD).

Table 2: Logistic regression modeling of predictors at three time points of mortality. Bivariate analysis identified predictors eligible for testing in subsequent multivariable logistic regression models; those with a p value of value of < 0.25, see Table 2A. Eligible predictors for the multivariable models were used to generate models through backward stepwise logistic regression, along with the interaction terms of each predictor variable and BMI (i.e.: BMI and sepsis type), see Table 2B. Odds ratios and confidence intervals for each significant predictor, along with the significant interaction term of sepsis type and BMI are described with odds ratios and confidence intervals, see Table 2C. **The interaction terms of sepsis type at a BMI of 25 (normal weight) is reported to further demonstrate the relationship between these predictor variables on mortality at 180 days and 365 days**

Predictor	N	**2A: Bivariate Models**			**2B: Final Multivariable Models**		
		30 Days *p*-value	180 Days *p*-value	365 Days *p*-value	30 Days (n=1554) *p*-value	180 Days (n=3720) *p*-value	365 Days (n=3720) *p*-value
CRP	441	0.3922	0.0673	0.0256			
Race	3839	0.0873	0.0342	0.0204			
Age	3832	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Sex	3839	0.3553	0.2907	0.9629	0.7764	0.2852	0.7724
Lactate	1556	<0.0001	<0.0001	<0.0001	<0.0001		
Sepsis Type	3839	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
BMI	3839	<0.0001	<0.0001	<0.0001	0.0212	<0.0001	<0.0001
WBC	3726	0.7465	0.0012	<0.0001		0.0064	<0.0001
BMI*Sepsis Type	-	-	-	-		0.0023	0.0044
Parameter					**2C: Odds Ratio and 95% Confidence Intervals**		
					30 Days	180 Days	365 Days
Age, per 5 year increase					1.14 (1.09, 1.19)	1.16 (1.14, 1.19)	1.22 (1.19, 1.24)
Sex, Female					1.03 (0.97, 0.99)	0.92 (0.79, 1.07)	1.02 (0.88, 1.18)
Lactate, per 1 unit increase					1.34 (1.22, 1.47)		
Sepsis vs. Severe Sepsis					1.63 (1.12, 2.38)		
Severe Sepsis vs. Septic Shock					2.18 (1.60, 2.98)		
Sepsis vs. Septic Shock					3.56 (2.60, 4.90)		
BMI, per 5 unit increase					0.92 (0.85, 0.99)		
Sepsis vs. Severe Sepsis at BMI=25						1.35 (1.08, 1.67)	1.28 (1.04, 1.58)

Severe Sepsis vs. Septic Shock at BMI=25	2.86 (2.31, 3.54)	2.57 (2.08, 3.17)
Sepsis vs. Septic Shock at BMI-25	3.85 (3.23, 4.59)	3.30 (2.78, 3.91)
WBC, per 10 unit increase	0.82 (0.74, 0.90)	0.74 (0.67, 0.82)

*The symbol “- ”represents an untested interaction term in bivariate testing. Empty cells within the table represent variables that were not found to be significant and were excluded from analysis.

Concluding Narrative

This dissertation shed light on some of the contributing factors that influence mortality at 30 days, 60 days, and 1 year post-sepsis diagnosis. The systematic review of the literature in Chapter One described the current state of knowledge about the "obesity paradox" e.g., the association between obesity and sepsis mortality. A gap in the literature was identified, where long term sepsis outcomes after 30 days had not yet been described. Chapter Two outlines a conceptual model that links the main concepts of inflammation, sepsis and obesity through pathophysiologic mechanisms, and describes how to use the model for testing relationships between antecedents, the main concepts, and multiple sepsis outcomes. This conceptual model was the framework for the dissertation proposal in Chapter Three and the results "manuscript ready" study presented in Chapter Four. We used a large dataset that spanned a 10 year time frame to characterize a population of individuals diagnosed with sepsis at a large academic medical center. Our findings supported previous studies of short-term post-sepsis mortality, but highlights that there is more research needed to understand obesity and longer term sepsis mortality. The lack of available laboratory data on specific novel biomarkers is a limitation of this study that comes from using a secondary, retrospective, clinical dataset.

While this initial study did not show a connection between obesity and long-term sepsis mortality, there is literature that suggests this is still an area worthy of research. This researcher plans to seek funding to conduct a prospective study that follows patients from the time of diagnosis to one year after diagnosis. A strength of this approach is that comorbidities can be identified and controlled for, adiposity related metrics to augment body mass index can be included and testing of specific novel biomarkers can be incorporated. There is ample opportunity for research in the area of obesity and sepsis outcomes. Of patients that survive the

initial sepsis insult, long-term cognitive, emotional, and physical frailty is an emerging concern. Considering the aging population, research that aims to improve the lives of patients post sepsis is highly needed.

Vita

Jamie D. Robinson was born on February 22, 1971 in Winchester, Virginia, and is an American citizen. She graduated from Strasburg High School in Strasburg Virginia in 1989. She received her Associate Degree in Nursing from Shenandoah University in 1998, a Bachelor's Degree in nursing from Shenandoah University in 2004, and a Master's Degree in Nursing from the University of Virginia in 2007.