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The Influence of Body Mass Index on Survival and Length of Stay in Patients with Septic Shock

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The influence of body mass index on survival and length of stay in patients with septic shock

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Abstract

Background

Obesity is one of the most widespread epidemics of our time. In fact, currently 65.7% of US adults age 20 and older are overweight, while 30.6% are obese. It has been well-established that obesity has numerous adverse effects on long-term health, however the specific effect on patients treated for sepsis and septic shock is unclear. Body Mass Index (BMI) is a measure of total body fat content and surrogate marker for obesity. In our study, we aimed to identify if BMI was an independent risk factor for poor survival or increased length of stay (LOS) in patients with sepsis.

Methods

We retrospectively selected patients with diagnostic codes of sepsis and septic shock who were admitted to the ICU over three years. These patients were further separated into groups of alive and deceased. Based on their perceived association with mortality in sepsis, numerous variables were investigated, such as BMI, LOS, age, cirrhosis, chronic kidney disease (CKD), lactate level, age, multiple organ dysfunction syndrome (MODS), and APACHE II scores. Specifically, BMI was classified into sub-groups.

The alive and deceased groups were initially compared for any significant differences with univariate analysis. Thereafter, the significant variables were analyzed using multivariate analysis to assess whether any were able to independently predict mortality in sepsis.

Results

Our study selected 293 patients with sepsis, including 185 alive and 108 deceased. Interestingly, our univariate analysis revealed that underweight and obese patients exhibited slightly less mortality in sepsis compared to normal and overweight patients. However, these results did not reach statistical significance, with a p-value of 0.30; this was confirmed in multivariate analysis, which resulted in a p-value of 0.08. Additionally, underweight, overweight, and obese patients had a slightly decreased median LOS in the ICU and hospital compared to patients with normal BMI. Nevertheless, these results were not significant either, with ICU LOS p-value of 0.22 and hospital LOS p-value of 0.45.

Univariate analysis identified certain variables that reached statistical significance, including cirrhosis ($p<0.01$), CKD ($p= 0.05$), MODS>2 ($p=0.03$), median lactate level ($p=0.05$), age ($p<0.01$), and APACHE II scores ($p<0.01$). Multivariate analysis of these variables established that only the presence of cirrhosis ($p=0.03$), age ($p<0.01$), and APACHE II scores ($p<0.01$) were independent predictors of mortality in sepsis.

Conclusion

The data suggests that normal BMI in patients with sepsis may result in increased mortality and LOS both in the ICU and hospital, though this was not statistically significant. Other variables that were significant independent predictors for mortality in sepsis were cirrhosis, mean age, and

mean APACHE II score. As the obesity epidemic continues to rise, further inquiry into the association of BMI and mortality in sepsis is needed.

Keywords

Body Mass Index, Septic Shock, Survival

Introduction

Approximately 30% of the population in the United States is obese.[1] This is particularly alarming since obesity is known to be directly related to conditions such as cardiovascular disease, diabetes, and hypertension.[2,3,4] However, the effects of obesity are not only limited to metabolic conditions, since there is also an increased incidence in cancer and in all-cause mortality.[5] Body mass index (BMI) is a surrogate marker for obesity, currently the best standard by which to measure patient adiposity, and may be sub-classified into underweight, normal, overweight, and obese.[6]

As the prevalence of obesity is on the rise, the number of obese patients admitted to the hospital has increased in turn as well. This has further led to increased costs incurred and greater national health expenditure in the US.[2,3,7] Many obese patients suffer from multiple comorbidities, which has led to an increase in the prevalence of the obese patient population in the ICU. Sepsis is considered to be a major contributing condition to the morbidity and mortality in the ICU.[8] Sepsis and obesity are both considered to result in an increased length of stay (LOS) and overall cost of medical treatment. Past studies on patients with sepsis have advocated that there is no significance in morbidity and mortality after adjustment of the data has been done with regard to BMI.[8,9] Our study aimed to elucidate the relationship between obesity, morbidity and mortality outcomes, and LOS in patients with septic shock.

Methods

This is an Institutional Review Board (IRB) approved study by Cooper University Hospital. The aim of this study is to identify whether BMI is an independent predictor of mortality or greater length of stay (LOS) in patients with septic shock. We specifically focused on BMI due to its prevalence in the population,[10] as well as its clinical correlation with poorer outcomes, while also attempting to assess for indicators of overall health and other comorbidities.

We retrospectively selected a sample of patients admitted to the Cooper University Hospital (New Jersey) ICU under the diagnostic codes of septic shock over a period of 3 years. The total number of patients sampled were 293, which were subsequently separated into groups of 185 alive patients and 108 deceased patients based on their status by the end of their hospitalization. Variables thought to be associated with mortality in septic shock were collected and analyzed, including BMI, cirrhosis, chronic kidney disease (CKD), albumin, lactate level, age, multiple organ dysfunction syndrome (MODS), and APACHE II scores.

Our inclusion criteria defined patients with septic shock as those in need of vasopressors in spite of adequate fluid resuscitation while having at least two signs of systemic inflammation. Our exclusion criteria were patients less than 18 years of age, pregnant women, and patients with no

recorded height or weight. BMI was classified into sub-groups, including underweight (BMI<18), normal (BMI 18-24.9), overweight (BMI 25-29.9), and obese (BMI>30).

Initially, the two groups (alive and deceased patients) were compared for any significant differences using univariate analysis, including chi-squared and t-tests as appropriate. Subsequently, each variable found to be significant ($p<0.05$) was analyzed using multivariate analysis, including logistic regression, to evaluate whether any were independent predictors of mortality in patients with septic shock. Finally, a Kruskal-Wallis comparison of the weight categories was done to determine if there was any significant difference in the ICU LOS, which was then repeated for hospital LOS.

Results

A total of 293 patients were selected for the study between January 2008 and January 2011; these were further divided into 185 alive and 108 deceased. Numerous pertinent variables were identified among the two groups and analyzed initially using univariate analysis, after which the statistically significant variables were further analyzed using multivariate analysis. In the total sample of patients, the mean age was 61.27 years old, with 51.9% men and 48.1% women. Interestingly, our univariate analysis revealed that underweight and obese patients exhibited slightly less mortality in septic shock compared to normal and overweight patients. However, these results did not reach statistical significance (p=0.30, Pearson's chi-squared test; Table 1), which was then confirmed in multivariate analysis (OR 0.97, 95% CI 0.94-1.00, p=0.08; Table 2).

Table 1. Body Mass Index in Univariate Analysis

Variables	Alive		Deceased		P-Value
Body Mass Index (Mean/SD)	28.7	9.90	27.61	6.97	0.3
Body Mass Index (n/%)					
Underweight	9	69.2%	4	30.8%	0.53
Normal	48	60.0%	32	40.0%	0.55
Overweight	42	58.3%	30	41.7%	0.84
Obese	56	64.4%	31	35.6%	0.56

Table 2. Complete Multivariate Analysis

Variables	P-Value	Odds Ratio	95% Confidence Interval
Age	<0.01	1.03	1.01-1.05
Multiple Organ Dysfunction Syndrome	0.39	1.43	0.63-3.21
Chronic Kidney Disease	0.34	1.43	0.69-3.00
Lactate	0.94	1.00	1.00-1.00
Albumin	0.98	1.00	0.71-1.42
Cirrhosis	0.03	11.43	1.25-104.92
APACHE II	<0.01	1.07	1.04-1.11
Body Mass Index	0.08	0.97	0.94-1.00

Univariate analysis identified certain variables that reached statistical significance, including:

- cirrhosis ($p<0.01$, Fisher's exact test) in 0.7% of alive and 9.4% of deceased patients
- CKD ($p=0.05$, Pearson's chi-squared test) in 15.7% of alive and 25.0% of deceased patients
- MODS>2 ($p=0.03$, Pearson's chi-squared test) in 76.2% of alive and 87.0% of deceased patients
- median lactate level within 24 hours ($p=0.05$, Mann-Whitney U test) with interquartile range of 1.6-4.8 (median of 2.70) in alive patients and 1.9-5.4 (median of 3.50) in deceased patients
- age ($p<0.01$, independent samples) with mean of 58.49 (SD 16.42) in alive and 66.03 (SD 14.71) in deceased patients
- APACHE II scores ($p<0.01$, independent samples T-test) with mean of 17.24 (SD 9.31) in alive and 23.95 (SD 10.39) in deceased patients (Table 3)

**Because of missing data, the total number for independent variables may not add up to the total sample 293*

Table 3. Complete Univariate Analysis *

Variables	Alive		Deceased		P-Value
Age (Mean/SD)	58.49	16.42	66.03	14.71	<0.01
Gender (n/%)					1.00
Male	96	51.9%	56	51.9%	
Female	89	48.1%	52	48.1%	
Coagulation (n/%)	19	10.3%	15	13.9%	0.36
Platelets (n/%)	13	7.1%	13	12.0%	0.15
Organ Dysfunction (n/%)	179	96.8%	107	99.1%	0.21
Multiple Organ Dysfunction Syndrome (n/%)	141	76.2%	94	87.0%	0.03
Body Mass Index (Mean/SD)	28.7	9.90	27.61	6.97	0.3
Body Mass Index (n/%)					
Underweight	9	69.2%	4	30.8%	0.53
Normal	48	60.0%	32	40.0%	0.55
Overweight	42	58.3%	30	41.7%	0.84
Obese	56	64.4%	31	35.6%	0.56
Fatty Liver (n/%)	18	11.8%	8	8.4%	0.39
Cirrhosis (n/%)	1	0.7%	9	9.4%	<0.01
Diabetes Mellitus (n/%)	76	41.1%	43	39.8%	0.83
Hypertension (n/%)	119	64.3%	67	62.0%	0.70
Congestive Heart Failure (n/%)	59	31.9%	41	38.0%	0.29
Chronic Kidney Disease (n/%)	29	15.7%	27	25.0%	0.05
Chronic Obstructive Pulmonary Disease (n/%)	20	10.9%	9	8.3%	0.49
Time of Antibiotics Institution from Sepsis Onset (n/%)	123	66.5%	61	56.5%	0.08
Albumin (Mean/SD)	2.51	0.95	2.34	0.79	0.15
APACHE II (Mean/SD)	17.24	9.31	23.95	10.39	<0.01
Lactate (Median/IQR)	2.70	1.6-4.8	3.50	1.9-5.4	0.05
Days on Mechanical Ventilator (Median/IQR)	7.43	3.8-13.1	6.28	1.9-12.5	0.21

Thereafter, multivariate analysis using logistic regression of the aforementioned variables yielded statistical significance in:

- cirrhosis (OR 11.43, 95% CI 1.25-104.92, p=0.03)
- age (OR 1.03, 95% CI 1.01-1.05, p<0.01)
- APACHE II scores (OR 1.07, 95% CI 1.04-1.11, p<0.01)

Despite the lack of significance using univariate analysis, since it was the focus of our study, BMI was further evaluated with multivariate analysis, which confirmed again that it was not significant (OR 0.97, 95% CI 0.94-1.00, p=0.08).

Finally, underweight, overweight, and obese patients had a slightly decreased median LOS in the ICU and hospital compared to patients with normal BMI. Nevertheless, these results were not significant either (ICU LOS p=0.22, hospital LOS p=0.45) (Table 4).

Table 4. Length of Stay Comparison

	ICU LOS (Median/IQR)	Hospital LOS (Median/IQR)
Underweight	3.93 (1.79-10.77)	10.00 (7.5-22)
Normal	7.47 (3.28-14.58)	20.50 (10.25-31.25)
Overweight	5.28 (2.15-9.91)	18.50 (8.75-30.50)
Obese	6.89 (3.28-12.24)	20.50 (9.25-38.50)
P-Value	0.22	0.45

Discussion

Medical paradoxes arise when surprising findings contradict the expected logical or conventional wisdom. The obesity paradox with regard to sepsis states that obesity should increase mortality in sepsis due to the fact that it is a chronically heightened inflammatory state with increased oxidative stress. Numerous studies have revealed that while obese patients have high morbidity, they interestingly have lower mortality outcomes as compared to patients with normal BMI.[11,12] A meta-analyses by Pepper et al, showed that patients in the ICU due to septic parameters that had overweight or obese BMIs had a reduced adjusted mortality compared to those with a normal BMI..[13] While this benefit may not be completely understood, it can still be explained by a number of reasons. Firstly, hypertension in obese patients from increased renin-angiotensin activity may confer hemodynamic protection during sepsis and decrease the necessity for fluid or vasopressor support.[13] Furthermore, hormones secreted from adipose tissue may have an immunomodulatory effect that limits the inflammatory response and improves host survival.[14] Finally, it may be that the previous studies, such as the ones reviewed in the aforementioned meta-analysis, may have weak methodologies.

In 1987, adipose tissue was first recognized as a major endocrine organ by Siiteri et al.[15] Thereafter, Ahima et al stated that adipose tissue functions as a complex endocrine organ.[16] The major hormones secreted by adipose tissue include adiponectin and leptin. Moreover, the non-adipose portion of adipose tissue is responsible for the secretion of several proteins participating in the renin-angiotensin aldosterone system. These include angiotensinogen, angiotensin I, angiotensin II, angiotensin II receptor type 1, angiotensin II receptor type 2, and angiotensin-converting enzyme.[17,18] In normal individuals, this leads to hypertension; however, in states of hemodynamic instability this has a protective effect, resulting in decreased need for pressor support and less fluid required for volume resuscitation. Recent multicenter trials ARISE and PROMISE have shown no mortality benefit with liberal fluid management as compared to conservative fluid treatment.[19]

In addition to the aforementioned proteinaceous secretions, adipose tissue is also responsible for the secretion of lipoproteins. Lipoproteins, in particular high-density lipoprotein (HDL), have been linked with the delipidation of lipopolysaccharides (LPS). The delipidated version of the LPS, with density of less than 1.2 g/cm^3 has been shown to have low virulence when compared to the native LPS molecule. The low-density LPS was shown to have decreased activation of the complement pathway and pyrogenicity in animal models.[20,21] Kim and Nishida have also demonstrated that apoliporotein A1 has binding sites for plasma disaggregated LPS, and hence disintegrated LPS can bind to these sites further inhibiting the systemic effects.[22] Interestingly, obesity has been linked with increased TNF-alpha production, which is cytokine associated with hypotension and endothelial damage. On the other hand, obesity is also associated with increased lipoproteins, which act as soluble TNF receptors with the potential to blunt the effect of increased TNF production in sepsis.[23,24]

Pepper et al state that the methodology of studies may have contributed to an apparent but not real reduction in mortality in septic patients with overweight and obese BMIs.[14] For example, mortality may not have been adjusted for factors that predict a favorable outcome in this population. Additionally, selection bias may have altered results, as obese patients may have undergone earlier intubation and mechanical ventilation due to hypoventilation.[25,26] The inability to administer care on the general medical wards prompted early ICU admission for obese patients with less severe diseases.[3] Moreover, inaccurate height and weight measurement in the ICU may have led to assignment of patients into the wrong BMI category.[27-29] The measurement of weight after fluid resuscitation may have also led to inaccurate stratification of patients in different BMI categories.[30] Finally, BMI does not differentiate between muscle and adiposity. Decreased BMI may be associated with sarcopenia and secondary protein-calorie malnutrition with decreased albumin and low oncotic pressure, all of which increase mortality in sepsis.[31]

We conducted a post hoc power analysis for our main outcome variable that was analyzed using chi-square. We used an alpha error probability of 0.05 and a medium effect size of 0.3 with a total sample size of 252 (excluding individuals with missing values) which produced a power of 98.7%. This shows our study was sufficiently powered to detect a significant difference in our main outcome variable.

There are, however, a few limitations to keep in mind about our study. The inclusion of patients from a single center reduces generalizability. This is a retrospective study that does not demonstrate causality but only suggests associations. The results from our analysis did align with

the trend of other studies, however, this was not statistically significant. Other studies that we have cited had more statistically significant results. The weight, height and BMI were obtained from documentation in the electronic medical records, the accuracy of which cannot be confirmed. Also, our study has not accounted for the possibility of measurement bias that may come from measuring weight and height across different BMI groups. Our study adds more evidence to the contingent of studies examining the obesity paradox.

Conclusion

Even though abnormal BMI has a strong association with increased overall morbidity, our retrospective study has shown that in our sample it resulted in equal or lower mortality as compared to normal control subjects. This seemingly paradoxical result, as suggested above, is due to the underlying immunophysiology and endocrine function of the adipose tissue. Additionally, the discrepancies in the methodologies of previous studies may have also led to an apparent reduction in mortality. One issue of particular interest is whether lipoproteins, which confer a protective effect against cytokines and LPS, can be of use as therapeutic pharmacologic agents in sepsis. Further studies in the future will be required to elaborate more on this association.

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