Published in final edited form as:

Surg Obes Relat Dis. 2015 ; 11(4): 912–918. doi:10.1016/j.soard.2014.10.010.

Hypoalbuminemia is Disproportionately Associated with Adverse Outcomes in Obese Elective Surgical Patients

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Abstract

Background—Protein deficiency (PD) is a known risk factor for surgical complications; however, the risks of PD by weight class have not been well described. We hypothesized that the combination of obesity and PD is associated with increased surgical complications, compared to normal weight and normoalbuminemic patients.

Objectives—85,833 general surgery patients undergoing elective operations within the 2011 National Surgical Quality Improvement Program were analyzed. Patients with conditions that could potentially confound serum albumin (SA) were excluded. Patients were stratified by normal (>3.0 g/dl) versus low (<3.0 g/dl) SA. The relative impact of SA and body mass index (BMI) (as individual and as combined variables) on surgical morbidity and mortality were assessed. Multivariate analyses were performed to identify independent risk factors for morbidity and mortality.

Setting—Multi-institution, United States.

Results—Overall, 2,088 (2.43%) of patients had low preoperative SA. 587 (28.1%) patients with low preoperative SA were obese (BMI >30), versus 39,299 (46.9%) with normal preoperative SA. Importantly, the interaction of hypoalbuminemia and BMI was independently associated with all complications among hypoalbuminemic patients with BMI>40, and mortality for patients with BMI>30 after controlling for appropriate demographics, comorbidities, surgical wound classification, operation type and complexity (c-statistic: 0.803 and 0.874 respectively).

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Previous Presentation: Surgical Infection Society Annual Meeting, Baltimore, MD, May 2, 2014.

Disclosure: The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the ACS NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Conflicts of Interest: The authors have no conflicts of interest.

Conclusions—PD and obesity appear to synergistically increase the risk of surgical complications. Paradoxically, malnutrition may be less easily recognized in obese individuals and surgeons may need to more carefully evaluate this population prior to surgery. Future studies should investigate therapy to correct PD specifically among obese patients prior to surgery.

INTRODUCTION

Malnutrition has long been recognized as a risk factor for poor surgical outcomes ⁽¹⁻⁴⁾. Protein plays a particularly important role in surgical recovery by facilitating wound healing and immunocompetence. Serum albumin (SA) has been frequently used as an index of protein status and has been shown to correlate with risk for surgical complications and mortality ^(3,5-8).

The purpose of the present study was to analyze the relationship between protein deficiency (PD) and surgical complications stratified by weight class. The high prevalence of obesity heightens the importance of delineating the unique risks associated with weight class, which may offer opportunities to mitigate risk with preoperative intervention. While the risks of malnutrition and PD have been well-described for surgical populations at large, we are not aware of previous studies that have examined whether the interaction of obesity and PD confers a distinct risk for adverse events after surgery. Furthermore, few studies have evaluated the prevalence of PD among obese patients ⁽⁹⁾ and surgeons do not routinely evaluate protein status in the typical preoperative risk assessment of obese patients. We hypothesized that PD is an under-recognized phenomenon among obese surgical patients that confers a unique and elevated risk for adverse outcomes over the risks associated with obesity and PD in isolation.

METHODS

Data Source

The 2011 American College of Surgeons National Surgical Quality Improvement Program (NSQIP) participant use file (PUF) was utilized for this study. Our Institutional Review Board exempted this study from formal review as NSQIP contains de-identified data, of which the use is not considered human subject research. The NSQIP PUF is a multi-institutional clinical outcomes database designed to allow innovations in surgical quality; its validity and reliability have been extensively described ⁽¹⁰⁻¹²⁾. NSQIP data is prospectively abstracted from patient charts by trained reviewers located at participating institutions. The database includes extensive pre-operative through 30-day postoperative data, which allows for risk-adjusted comparisons of outcomes among participating institutions.

Patients and Outcomes

The 2011 NSQIP PUF contained entries for 240,474 general surgical encounters. Patients with any of the following NSQIP variables were excluded from study since SA could be artificially or pathologically decreased: inpatient status at time of operation, emergent operation, American Society of Anesthesiologists Physical Status score (ASA) of five, evidence of systemic infection or systemic inflammatory response syndrome, cirrhosis, and pregnancy. Patients without a recorded preoperative SA were also excluded. After

exclusions, 85,833 patients remained and were stratified by normal (≥ 3.0 g/dL) versus low (<3.0 g/dL) preoperative SA, and by body mass index (BMI) within each group. Demographic variables, as well as additional data on individual comorbidities, were recorded. Incidences of complications as captured by NSQIP, including morbidity and mortality, were recorded for each patient. The primary outcomes of interest were the risk-adjusted associations between preoperative SA and surgical complications by weight class. Secondary outcomes included the association between SA and weight class – as individual variables – and adverse events.

Statistical Analysis

Data analyses were designed to test the null hypothesis that hypoalbuminemia (HA) and weight class – as individual and combined variables – are not associated with an increase in surgical complications. Statistical significance was determined using the standard alpha value of <0.05 . All data analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC).

Descriptive Statistics and Univariate Analyses

Descriptive, univariate statistics were utilized to characterize baseline demographic characteristics, co-morbid disease states, operative and 30-day postoperative complications. Continuous data are reported as median values [interquartile range] and were compared using Wilcoxon rank-sum or Kruskal-Wallis tests for non-parametric data where appropriate. Categorical values are reported as a percentage of the total population of each group, and were compared using Fisher's Exact or Chi-square tests where appropriate. All calculated test statistics were used to derive reported two-tailed p-values.

Multivariable Analysis

Multivariable analysis was performed using logistic regression to estimate adjusted associations between various potential variables and adverse outcomes, including infectious complications, all-cause complications, and mortality. The recently published NSQIP Universal Surgical Risk Calculator includes 21 variables, and two separate variables for a colon-specific model, which formed the foundation for our multivariable analysis, with several exceptions⁽¹⁰⁾. First, our study excluded patients with sepsis or ascites at the time of surgery, therefore, these variables were not included in the multivariate analysis. Second, relative value units (RVUs) were used as a surrogate for case-complexity. Finally, while we included colon surgery as a variable, we did not include indication for colon surgery as a unique variable as does the NSQIP colon-specific calculator. Our model included the following variables: age, sex, BMI, SA, history of unintentional weight loss of greater than 10% body weight in the six months prior to surgery, diabetes, smoking status, presence of dyspnea at baseline, chronic obstructive pulmonary disease, acute renal failure, dialysis dependence, disseminated cancer, chronic steroid use, transfusion within 72 prior to surgery, ventilator dependence, history of myocardial infarction, congestive heart failure, inpatient admission after surgery, ASA class, operative wound classification, colon surgery, preoperative functional status, and RVU. Modeled factor likelihood ratios (Wald 2 statistic) were utilized to estimate the predictive strength and relative contribution of each covariate with the odds of complications, including mortality. Results are reported as adjusted odds

ratios (AOR) with 95% confidence intervals (CI). Model performance was assessed using the calculated Area Under the Receiver Operating Characteristic Curve.

RESULTS

Select patient characteristics, including select co-morbidities, are represented in **Table 1**, by preoperative SA status. A large majority of patients presented with normal preoperative SA levels. Patients with preoperative HA were significantly older than patients with normal preoperative SA. Higher percentages of patients with HA were male and normal weight or underweight. Expectedly, the hypoalbuminemic cohort had higher rates of all comorbidities, including diabetes, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), dialysis dependence, and disseminated cancer.

Select operative details are presented in **Table 2**. More patients with preoperative HA were listed as ASA scores of 3 or 4 and a higher percentage was admitted after surgery than in the normoalbuminemic group. Normal albumin levels were associated with clean wound classification.

Patient outcomes stratified by preoperative SA status are shown in **Table 3**. Total complications, including mortality, occurred at a higher rate among patients with low preoperative SA. Infectious complications also occurred at a notably higher rate within the hypoalbuminemic cohort. Transfusion was a relatively frequent event that occurred approximately 4-fold more frequently among hypoalbuminemic patients.

Table 4 presents patient outcomes by BMI class. Mortality, all-cause complications, and infectious complications occurred with the highest frequency among underweight patients, while the frequency of similar events was lowest among patients with BMI 40.

Many variables were independently associated with adverse outcomes on multivariate analysis due to the size of the study population, however many of these variables, such as dialysis dependence and chronic steroid use, may not be considered actionable in the preoperative period. The independent relationships of HA and BMI with outcomes are presented in Table 5 because HA may be considered actionable in the preoperative setting. Results of the complete multivariate analysis are provided in supplementary materials. Over the entire study population, HA was associated with an increased risk of infectious and all complications, but not mortality. As an independent variable, increasing BMI demonstrated a protective association with infectious complications, all-cause complications, and mortality. The association between HA and the risk for surgical complications stratified by BMI demonstrated significance for infectious complications, all-cause complications, and mortality with higher BMI. This increased risk for infectious and total complications was demonstrated for patients with BMI>40, while an increased risk for mortality was observed among patients with BMI 30-39 and BMI>40. Otherwise stated, HA was associated with disproportionately worse outcomes among patients with higher BMI.

DISCUSSION

This study identifies large, risk-adjusted increases in adverse outcomes for obese patients with preoperative HA undergoing elective general surgery. The methodology used in this study controlled for many potentially confounding variables on preoperative serum albumin status. As a result, we believe that HA in this study population may reflect protein deficiency, which results in a disproportionate share of adverse outcomes among obese patients. These findings may suggest that protein-calorie malnutrition is an under-recognized phenomenon which predisposes obese surgical patients to additional risk for adverse outcomes. We believe this relationship warrants further study to investigate the efficacy of preoperative assessment of protein status and intervention for at-risk patients to reduce potentially modifiable complications.

HA has long been recognized as a risk factor for adverse outcomes after surgery^(1,8,13,14); however, whether HA can be used as a surrogate marker of nutrition status remains controversial. Albumin is a single peptide chain protein with a half-life of 3 weeks. It is synthesized by hepatocytes and rapidly secreted into plasma where its two primary functions include maintenance of osmotic pressure and transport of circulating substances such as bilirubin, fatty acids, and exogenous drugs. SA depends on rates of synthesis and secretion, degradation, and exchange between intra- and extravascular compartments⁽¹⁵⁾. Factors known to influence SA synthesis include nutritional protein intake and illness⁽¹⁵⁾. Low nutritional protein has been shown to slow the rate of albumin synthesis and reduce serum levels, while slowing the rate of degradation to a lesser degree^(15,16). Similarly, inflammatory disorders and other disease states have been shown to lower SA by several possible mechanisms, including down regulated synthesis, increased catabolism, and increased vascular permeability^(17,18).

The potentially confounding influence of inflammatory disorders and other disease states and the frequent coexistence of underlying illness among malnourished patients complicate the interpretation of SA as an index of nutrition status. Indeed, many authors who identify malnutrition as a causal variable for adverse outcomes assume that HA reflects PD without adequately controlling for other potentially confounding variables⁽¹⁹⁾.

Despite the challenges of interpreting SA, that protein-calorie malnutrition is associated with HA has been well-established, for example, in studies of patients with kwashiorkor, in healthy volunteers receiving protein-restricted diets, and bariatric surgical patients whose postoperative courses were marked by protein malnutrition^(9,20-23). More recently, Dutheil et al. randomized patients with metabolic syndrome to calorie-restricted diets with either normal protein content or high protein content, defined as 1.0g/kg/day and 1.2g/kg/day, respectively. After 90 days, patients receiving the normal protein diet developed HA whereas the high protein cohort maintained normoalbuminemia⁽⁹⁾. These examples suggest that well-designed studies with adequate power to control for potentially confounding variables can use SA as a surrogate for protein status. For example, Gibbs et al. analyzed a large sample of patients (>50,000) from the National VA Surgical Risk Study, controlling for 61 other variables to isolate the effect of malnutrition – using SA as an index – on

surgical outcomes. The authors found HA to be associated with large, risk-adjusted increases in morbidity and mortality ⁽²⁴⁾.

Our study was designed with a similar goal in mind, therefore, we excluded potentially confounding disease states. Furthermore, by restricting our sample to outpatients without acute illness who underwent elective, non-urgent operations, we sought to eliminate the known confounding effects of the stress response on SA since in patients with acute illness, HA may better represent severity of illness than nutrition status ^(6,25-27). In addition, our regression analysis controlled for many disease states – in particular, end-stage renal disease – where the use of SA as a nutrition index has been questioned ^(19,28-30).

Severe protein-calorie malnutrition is recognized as a rare occurrence among the general population of developed countries and is rarely reported in the literature ⁽³¹⁾. Not surprisingly, only a small fraction of patients who met inclusion criteria in our study were found to have preoperative HA. Consistent with previous literature, we found that these hypoalbuminemic patients faced a risk-adjusted increase for adverse outcomes, though not for mortality.

However, our results also demonstrated that the interaction of obesity and HA is disproportionately associated with adverse outcomes compared to each variable in isolation. The effect of this interaction is particularly well-illustrated among patients with BMI ≥ 40 . When controlling for BMI class alone, our multivariate analysis demonstrated a protective effect of having a BMI ≥ 40 . After controlling for the combination of BMI and HA, however, we found that this interaction demonstrated large, across-the-board increases in risk for adverse outcomes among obese patients. The increases in risk of mortality were especially notable; 3-fold and 19-fold increases were observed for patients with BMI of 30-39 and ≥ 40 , respectively. Significant increases in risk for infectious and all-cause complications were also observed for patients with HA and BMI ≥ 40 .

To our knowledge, this study represents the first effort to quantify the surgical risks associated with PD by BMI. Our results suggest that PD is a phenomenon that not only occurs among the obese, but also one that adds significant risk for surgical morbidity and mortality in comparison to lean or normoalbuminemic comparators.

This study has several important limitations. As previously noted, SA may not directly reflect protein status in many patients with confounding disease states. While the size of NSQIP has allowed us to exclude or control for many variables that are known to affect SA, HA in our study population could be attributable to patient characteristics or comorbidities that have not been captured by NSQIP. For example, although we controlled for the effect of case-mix on outcomes using procedure-specific RVU as a surrogate for case-complexity, this variable may not fully account for procedure variation that could explain some of the observed differences in outcomes versus risk attributable to HA. Furthermore, despite the use of a large dataset; the obese, hypoalbuminemic cohort was relatively small, likely as a result of the study's exclusionary criteria and the low baseline prevalence of HA in non-hospitalized, obese patients. The small size of these cohorts may explain, to some extent, the relatively dramatic odds ratios, and the results should be interpreted with this limitation in

mind. In addition, NSQIP data is prospectively collected observational data from which we can establish association but not a causal relationship. The association between obesity and PD; and adverse surgical outcomes would need to be tested in a randomized, prospective manner to evaluate a potential causal relationship. Finally, NSQIP is a large, clinical database that may contain errors or omissions that could distort or alter our findings. The impact of potential errors, however, is presumably small as NSQIP has been shown to have high interrater reliability^(11,12).

In summary, we have demonstrated that HA is disproportionately associated with adverse outcomes among obese patients undergoing elective general surgery, although the low prevalence of HA in the obese cohort prevents a precise estimation of this risk. After controlling for confounding factors affecting SA, we believe that HA in this population could reflect PD. Further studies should be conducted to prospectively evaluate the efficacy of preoperative nutrition screening and intervention on protein status among obese surgical patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

The authors thank Timothy McMurry, PhD, of the Division of Patient Outcomes, Policy & Population Research, Department of Public Health Sciences of the University of Virginia, for his assistance with statistical analysis.

Funding/Support: This work was supported by National Institutes of Health grant T32 AI078875.

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Table 1

Select Patient Characteristics and Co-morbidities Stratified By Albumin Status

Variable	<i>n</i>	NA, % ^a	HA, % ^a	<i>p</i>
Total	85,833	83,745 (97.6%)	2,088 (2.4%)	
Age				
<65	60,724	71.1%	56.7%	<0.0001
65-75	15,489	17.9%	22.8%	<0.0001
75-85	8,131	9.3%	16.4%	<0.0001
>85	1,889	2.1%	5.2%	<0.0001
Female	54,206	63.4%	51.6%	<0.0001
White	60,985	71.0%	72.3%	0.20
Black	10,240	11.9%	12.9%	0.15
Asian	2,524	2.9%	3.2%	0.46
Native American	529	0.6%	0.7%	0.75
Hispanic	6,028	7.1%	6.1%	0.11
Body Mass Index				
<18.5	1,815	2.0%	6.1%	<0.0001
18.5-24	20,444	23.5%	37.0%	<0.0001
25-29	23,688	27.6%	28.8%	0.22
30-39	24,900	29.2%	21.9%	<0.0001
40	14,986	17.7%	6.2%	<0.0001
Select NSQIP Co-Morbidities				
Recent Weight Loss	1,826	1.95%	9.39%	<0.0001
All Diabetes	14,016	16.2%	22.2%	<0.0001
Smoker	13,668	15.8%	20.1%	<0.0001
Dyspnea	7,221	8.3%	12.0%	<0.0001
Acute Renal Failure	95	0.1%	0.7%	<0.0001
Ventilator Dependence	6	0.0%	0.0%	1
COPD	2,985	3.4%	7.4%	<0.0001
CHF	178	0.2%	0.9%	<0.0001
History of MI	74	0.1%	0.2%	0.02
HTN Med ^b	40,736	47.3%	52.9%	<0.0001
Dialysis Dependent	894	0.9%	5.7%	<0.0001
Disseminated Cancer	2,530	2.9%	6.1%	<0.0001
Chronic Steroid Use	2,778	3.1%	7.4%	<0.0001
Preoperative Transfusion	132	0.1%	0.7%	<0.0001

^a NA = normoalbuminemia, HA = hypoalbuminemia^b Hypertension requiring medication

Table 2Select Procedure Details Stratified By Preoperative Albumin Status ^a

Variable	<i>n</i>	NA, % ^b	HA, % ^b	<i>p</i>
Total	85,833	83,745 (97.6%)	2,088 (2.4%)	
Inpatient Admission After Surgery	50,344	58.3%	72.9%	<0.0001
Colon	10,016	11.5%	17.3%	<0.0001
ASA Class				
ASA Class 1	4,656	5.5%	2.4%	<0.0001
ASA Class 2	41,186	48.4%	29.5%	<0.0001
ASA Class 3	37,710	43.6%	58.9%	<0.0001
ASA Class 4	2,101	2.3%	9.0%	<0.0001
ASA Class 5	0	0.0%	0.0%	-
Wound Classification				
Clean	37,698	44.4%	25.5%	<0.0001
Clean Contaminated	43,183	50.1%	58.3%	<0.0001
Contaminated	3,753	4.2%	10.2%	<0.0001
Infected	1,199	1.3%	6.1%	<0.0001
Operative Time, in minutes^c		95 [55-160]	118 [63-214]	

^aNo significant difference observed in anesthesia technique^bNA = normoalbuminemia, HA = hypoalbuminemia^cResults reported as median value [interquartile range]

Table 3

Select Patient Outcomes Stratified By Preoperative Albumin Status

Variable	<i>n</i>	NA, % ^{<i>a</i>}	HA, % ^{<i>a</i>}	<i>p</i>
Total	85,833	83,745 (97.6%)	2,088 (2.4%)	
Mortality	345	0.4%	1.9%	<0.0001
All Complications	9,652	10.8%	28.9%	<0.0001
Postoperative Length of Stay, in days^{<i>b</i>}		1 [0-4]	4 [1-7]	<0.0001
Unplanned Reoperation	2,419	2.8%	5.3%	<0.0001
All Infectious Complications	6,092	6.9%	16.1%	<0.0001
All Surgical Site Infections	4,285	4.9%	10.8%	<0.0001
Pneumonia	759	0.8%	2.6%	<0.0001
Urinary Tract Infection	1,138	1.3%	3.5%	<0.0001
Postoperative Sepsis	1,424	1.6%	3.8%	<0.0001
Postoperative Septic Shock	431	0.5%	2.1%	<0.0001
Intraoperative or Postoperative Transfusion	3,731	4.1%	16.2%	<0.0001

^{*a*} NA = normoalbuminemia, HA = hypoalbuminemia^{*b*} Results reported as median value [interquartile range]

Table 4

Select Patient Outcomes Stratified By Body Mass Index

Variable	<i>n</i>	Body Mass Index					<i>p</i> ^a
		<18.5	18.5-24	25-29	30-39	40	
Total	85,833	1,815 (2.1%)	20,444 (23.8%)	23,688 (27.6%)	24,900 (29.0%)	14,986 (17.5%)	
Mortality	345	1.2%	0.6%	0.4%	0.3%	0.3%	<0.0001
All Complications	9,652	17.7%	13.2%	11.5%	11.0%	7.9%	<0.0001
Postoperative Length of Stay, in days^b		2 [0-6]	1 [0-5]	1 [0-4]	1 [0-4]	2 [1-3]	<0.0001
Unplanned Reoperation	2,419	4.1%	3.3%	2.7%	2.7%	2.5%	<0.0001
All Infectious Complications	6,092	9.9%	7.9%	7.2%	7.2%	5.3%	<0.0001

^a Outcomes varies significantly across range of BMI values^b Results reported as median value [interquartile range]

Table 5Select results of multivariable logistic regression^a

Variable	All Infections^b		All Complications^c		Mortality^d	
	P-Value	Odds Ratio	P-Value	Odds Ratio	P-Value	Odds Ratio
HA^e	0.0042	1.40 (1.11-1.77)	<.0001	1.59 (1.30-1.94)	0.8849	
BMI^f	<.0001		<.0001		0.0064	
<18.5		1.10 (0.90-1.34)		1.16 (0.99-1.37)		1.62 (0.87-3.01)
18.5-24		1.00		1.00		1.00
25-29		0.98 (0.91-1.06)		0.93 (0.87-0.99)		0.73 (0.53-1.00)
30-39		1.05 (0.97-1.14)		0.95 (0.88-1.01)		0.67 (0.48-0.95)
40		0.54 (0.49-0.60)		0.44 (0.41-0.48)		0.56 (0.36-0.88)
HA + BMI^f	0.0032		<.0001		<.0001	
HA + BMI <18.5		0.73 (0.38-1.38)		1.02 (0.61-1.71)		1.62 (0.35-7.49)
HA + BMI 18.5-24		1.00		1.00		1.00
HA + BMI 25-29		1.22 (0.87-1.71)		1.37 (1.02-1.82)		1.19 (0.35-4.05)
HA + BMI 30-39		0.93 (0.63-1.36)		1.05 (0.76-1.44)		3.14 (1.03-9.60)
HA + BMI 40		2.59 (1.50-4.47)		3.13 (1.95-5.01)		18.98 (5.61-64.16)

^a All model covariates included in Methods and Appendix^b c-statistic = 0.768^c c-statistic = 0.803^d c-statistic = 0.874^e HA = hypoalbuminemia^f BMI = Body Mass Index