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Impact of Hypoalbuminemia on Outcomes Following Hepatic Resection: A NSQIP Retrospective Cohort Analysis of 26,394 Patients

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Abstract: Background/Objectives: Efforts to preoperatively risk stratify and optimize patients before liver resection allow for improvements in postoperative outcomes, with hypoalbuminemia being increasingly researched as a surrogate for nutrition, overall health and functional status. Given the paucity of studies examining the relationship between hypoalbuminemia and liver resection, this study aims to determine the impact of hypoalbuminemia on outcomes following liver resections using a large multicenter database. **Methods:** The American College of Surgeons–National Surgical Quality Improvement Program (2017–2021) database was used to extract the data of patients who underwent a hepatic resection. Two cohorts were defined; those with hypoalbuminemia (HA; <3.0 g/L) and those with normal albumin levels (≥3.0 g/L). Both baseline characteristics and 30-day postoperative complication rates were compared between the two cohorts. Multivariable logistic regression models were used to assess the independent effect of HA on various outcomes. Area under curve–receiver operating characteristic (AUC-ROC) curves were used to identify optimal albumin thresholds for both serious complications and mortality. **Results:** We evaluated 26,394 patients who underwent liver resections, with 1347 (5.1%) having preoperative HA. The HA patients were older (62.3 vs. 59.8; $p < 0.001$) and more likely to be of an ASA class ≥ 4 (13.0% vs. 6.5%; $p < 0.001$). The patients with HA had significantly more complications such as an increased length of stay, readmission, reoperation, sepsis, surgical site infection, bile leak, and need for transfusion. After controlling for demographics and comorbidities, HA remained a significant independent predictor associated with both 30-day serious complication rates (aOR 2.93 [CI 95% 2.36–3.65, $p < 0.001$]) and mortality (aOR 2.15 [CI 95% 1.38–3.36, $p = 0.001$]). The optimal cut-off for albumin with respect to predicting serious complications was 4.0 g/dL (sensitivity 59.1%, specificity 56.8%, AUC-ROC 0.61) and 3.8 g/dL (sensitivity 56.6%, specificity 68.3%, AUC-ROC 0.67) for mortality. **Conclusions:** In this large, retrospective database analysis, preoperative HA was significantly associated with 30-day morbidity and mortality rates following hepatic resection. Preoperative albumin may serve as a useful marker for risk stratification in conjunction with pre-existing calculators. Future studies evaluating the risk mitigation impact of nutrition and exercise prehabilitation in these patients and its capacity to modify hypoalbuminemia would be beneficial.

Keywords: hypoalbuminemia; hepatic resection; liver surgery; risk stratification

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1. Introduction

The risk of morbidity and mortality following a hepatic resection varies dramatically depending on the preoperative diagnosis, extent of resection, and patient factors [1]. Despite advances in surgical techniques, such as the increasing use of minimally invasive surgery [2,3], and perioperative care, such as the introduction and uptake of liver enhanced recovery after surgery (ERAS) protocols [4], the rates of complications and death after a liver resection still range from 20 to 45% and 2 to 4%, respectively [5,6]. Furthermore, while there are known predictors of poor outcomes following a liver resection (such as cirrhosis, American Society of Anesthesiologists (ASA score), or extent of resection), these factors

are often non-specific or not easily modifiable. Simple clinical tools and biomarkers that can be fluidly incorporated into clinical practice remain an area of study [7]. The ability to better identify patients at an increased risk of complications following a liver resection has important implications for patient selection, operative approach, and prehabilitation.

Albumin constitutes the majority of circulating plasma proteins and has long been recognized as a marker for lean muscle mass [8] and nutritional status [9]. Given its crucial role in oncotic pressure, postoperative wound healing, and inflammation, serum albumin has gained interest as a tool to help guide perioperative risk decision making [10–12]. Its role in hepatic surgery, however, may be more complicated given that preoperative hypoalbuminemia may reflect the adverse effects of pathologic liver diseases on synthetic function [13]. Furthermore, global liver disease (i.e., cirrhosis) can coexist or be caused by hepatic pathology, which can also influence albumin levels [14]. Given its relevance as a surrogate marker of both nutrition and synthetic liver function, hypoalbuminemia may have a more or less significant impact on complications compared to non-hepatic surgery. Thus far, several studies have shown associations between HA and postoperative complications following various types of surgery, including liver surgery [15–18]. However, studies focusing on hepatic resections have been limited by small sample sizes and single-center cohorts [19–23]. Furthermore, the relationship between albumin and patient functional status and nutrition is more complicated in patients with liver pathology compared to other diseases because albumin is synthesized by the liver. Such patients may be hypoalbuminemic due to their intrinsic liver disease, due to sarcopenia and malnutrition, or due to a combination thereof. Given the intrinsically more complicated relationship between HA and patients undergoing liver surgery compared to non-liver surgery, we aim to help address gaps in the literature by performing a large multicenter cohort study looking at key postoperative outcomes.

The aim of this study is to assess the association between HA and post-hepatic resection complications, including assessing its association with the 30-day serious complication rate and mortality using a multicenter cohort study. Furthermore, we aim to identify the prevalence of HA in the hepatic resection population and determine the optimal preoperative albumin cut-off values for predicting serious complications and mortality following a liver resection.

2. Methods

2.1. Data Source

The patient cohort of this study was derived from the National Surgical Quality Improvement Program (NSQIP). This North American database prospectively collects standardized preoperative variables for patients and outcomes up to 30 days after operation. Collection of data is performed by certified and trained Surgical Clinical Reviewers, promoting high reliability and accuracy. Furthermore, the collected data undergoes regular audits to ensure accuracy [24]. This study was exempt from ethics approval.

2.2. Study Design, Patient Population, and Variable Definitions

Adult patients undergoing all-type liver resections between 2016 and 2021 who had preoperative albumin data within 30 days of operation were included in this retrospective cohort study. The primary objective of this study was to assess the association of HA with postoperative complications in liver resection patients. Secondary objectives included evaluating the prevalence of HA in patients undergoing hepatic resection and determining optimal cut-off values for albumin in association with 30-day complication rate. For the purposes of this study, we defined HA as a preoperative serum albumin level of $\leq$3.0 g/dL. The definition of HA has varied significantly in the liver resection literature, with levels from 2.5 to 3.5 g/dL [7,25–28]. Furthermore, other hepatobiliary surgery literature has used a definition of $\leq$3.0 [29]. We selected the value of $\leq$3.0 to define HA for this study as it represents an intermediate value among previous levels examined in the aforementioned liver resection literature. In addition, due to heterogeneity in HA definitions, further a priori subgroup analyses using cut-offs from 2 to 4 g/dL were also completed to explore the association between the extent of HA and its impact on outcomes.

To accomplish this study, patients were divided into HA and non-HA cohorts. We evaluated demographic factors, overall well-being measures (e.g., functional status) and comorbidities. Preoperative and disease factors including preoperative sepsis, tumor invasion (defined as T3 or T4 pathological staging), tumor size, liver disease, and minimally invasive operative approach (with conversion to open being considered open) were included (Table 1). A comprehensive list of postoperative outcomes occurring within 30 days of surgery were investigated including infectious complications, wound complications, medical (e.g., myocardial infarction) and surgical (e.g., reoperation) critical perioperative events, and other complications (venous thromboembolism) (Table 2). Finally, we evaluated an aggregate measure of serious complications. This included development of one or more of the following: unplanned intubation, cardiac arrest, myocardial infarction, stroke, acute kidney failure, liver failure, bile leak, death, readmission, length of stay >30 days, reoperation, sepsis or septic shock, venous thromboembolism, and transfusion need. All other outcomes were defined as per the NSQIP 2021 Participant Use Data File [24].

Table 1. Demographics of patients with low (HA) and normal (non-HA) serum albumin levels prior to hepatic resection.

	Normal Serum Albumin (n = 25,047)	**Hypoalbuminemia (n = 1347)**	***p*-Value**
Patient factors			
Female sex	12,199 (48.7%)	657 (48.8)	0.960
Age	59.8 ± 13.6	62.3 ± 14.1	<0.001
BMI	28.8 ± 6.3	27.8 ± 7.1	<0.001
ASA class			<0.001
1	217 (0.87)	7 (0.52)	
2	5654 (22.6)	172 (12.9)	
3	17,499 (70.0)	983 (73.6)	
4	1632 (6.5)	174 (13.0)	
5	9 (0.04)	10 (0.7)	
None assigned	36 (0.1)	1 (0.1)	
Functional status			<0.001
Partially dependent	190 (0.8)	38 (2.8)	
Totally dependent	7 (0.03)	6 (0.5)	
Unknown	61 (0.2)	5 (0.4)	
Comorbidities			
COPD	890 (3.6)	63 (4.7)	0.031
CHF	161 (0.6)	24 (1.8)	<0.001
Hypertension	11,996 (47.9)	651 (48.3)	0.755
Diabetes			<0.001
Non-insulin dependent	3160 (12.6)	164 (12.2)	
Insulin-dependent	1589 (6.3)	131 (10.5)	
Smoker	3531 (14.1)	234 (17.4)	0.001
Dialysis	92 (0.4)	21 (1.6)	<0.001
Steroid use	947 (3.8)	79 (5.9)	<0.001
Bleeding disorder	841 (3.4)	102 (7.6)	<0.001
SIRS/sepsis/septic shock	240 (1.0)	191 (14.2%)	<0.001

Table 1. *Cont.*

	Normal Serum Albumin (n = 25,047)	Hypoalbuminemia (n = 1347)	*p*-Value
Preoperative factors			
Thrombocytopenia	592 (2.4)	61 (4.5)	<0.001
Weight loss	627 (3.2)	145 (13.0)	<0.001
Disease factors			
Invasion			
Yes	1095 (10.1%)	142 (20.5%)	<0.001
Liver texture			
Cirrhotic	1941 (9.5%)	113 (10.5%)	<0.001
Congested	377 (1.9%)	38 (3.5%)	
Fatty	2801 (13.7%)	97 (9.0%)	
Fibrosis	707 (3.5%)	48 (4.5%)	
Normal	5564 (27.3%)	240 (22.3%)	
Not documented	9012 (44.2%)	541 (50.2%)	
Tumor size			
No lesion	13,100 (52.3%)	885 (65.7%)	<0.001
<2 cm	2852 (11.4%)	80 (5.9%)	<0.001
2–5 cm	5290 (21.1%)	148 (11.0)	<0.001
>5 cm	3804 (15.2%)	232 (17.4%)	<0.001
Invasive disease (≥T3)	1095 (10.1)	142 (20.5)	<0.001
Neoadjuvant therapy	6357 (31.3)	272 (25.3)	<0.001
Operative factors			
MIS	4675 (18.7)	166 (12.3)	<0.001
Open	20,372 (81.3)	1181 (87.7)	

Hypoalbuminemia defined as ≤ 3.5 g/dL. Significant *p*-values are italicized. Data represented as n (%) or mean ± SD. Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; MIS, minimally invasive surgery; n, sample size; SD, standard deviation.

Table 2. Outcomes of patients with low (HA) and normal (non-HA) serum albumin levels prior to hepatic resection.

	Normal Serum Albumin (n = 25,047)	Hypoalbuminemia (n = 1347)	*p*-Value
Operative outcomes			
Major liver resection			
Yes	17,559 (70.1%)	794 (59.0%)	<0.001
No	7488 (29.9%)	553 (41.1%)	<0.001
Operative time (min)	241.5 ± 124.9	263.1 ± 148.9	<0.001
Length of stay (d)	5.9 ± 4.8	11.1 ± 9.2	<0.001
Hospital stay >30d	246 (1.0)	62 (4.6)	<0.001
Readmission	2386 (9.5)	230 (17.1)	<0.001
Unplanned intubation	455 (1.8)	68 (5.1)	<0.001
Reoperation	736 (2.9)	91 (6.8)	<0.001

Table 2. *Cont.*

	Normal Serum Albumin (n = 25,047)	Hypoalbuminemia (n = 1347)	*p*-Value
Wound and infection complications			
Superficial surgical site infection	728 (2.9)	57 (4.23)	0.005
Deep surgical site infection	76 (0.3)	5 (0.4)	0.661
Organ space surgical site infection	1756 (7.0)	250 (18.6)	<0.001
Wound disruption	131 (0.5)	9 (0.7)	0.048
Pneumonia	689 (2.8)	79 (5.86)	<0.001
Urinary tract infection	426 (1.7)	20 (1.5)	0.05
Sepsis	797 (3.2)	147 (10.9)	<0.001
Septic shock	353 (1.4)	70 (5.2)	<0.001
Other complications			
Pulmonary embolism	247 (1.0)	29 (2.2)	<0.001
Deep vein thrombosis, thrombophlebitis	358 (1.4)	51 (3.8)	<0.001
Bleeding requiring transfusion	3965 (15.8)	560 (41.6)	<0.001
Acute renal failure	207 (0.83)	23 (2.6)	<0.001
Stroke	42 (0.2)	5 (0.4)	0.084
Cardiac arrest	163 (0.7)	25 (1.9)	<0.001
Myocardial infarction	203 (0.8)	13 (1.0)	0.539
Liver failure	797 (3.9)	96 (8.9)	<0.001
Bile leak	1330 (6.6)	164 (15.5)	<0.001
Serious complication	7235 (28.9)	830 (61.6)	<0.001
Death	320 (1.28)	74 (5.49)	<0.001

Hypoalbuminemia defined as $\leq$ 3.5 g/dL. Significant *p*-values are italicized. Data represented as n (%) or mean $\pm$ SD. Abbreviations: d, day(s); min, minute(s); n, sample size; SD, standard deviation.

2.3. Statistical Analysis

As previously mentioned, the patient population was divided into two cohorts based on preoperative albumin levels. Absolute values were expressed as mean $\pm$ standard deviation for continuous data. For categorical variables, data were represented with absolute values (percentages). Comparisons between cohorts were performed with ANOVA tests for continuous data. For categorical data, chi-squared tests were performed.

Multivariable logistic regression models were created to isolate the effect of HA on various complications, including 30-day serious complication and 30-day mortality rates. Variables were included if they met a threshold upon univariate analysis ($p < 0.1$) or in a hypothesis-driven purposeful selection methodology. To assess model fit, Brier scores and receiver operating characteristic (ROC) curves were calculated. STATA 17 was used to conduct the above analyses.

Furthermore, we performed additional analyses to identify cut-off values that were most optimal for predicting serious complications and mortality. Bamber and Hanley confidence intervals were used to perform a non-parametric estimation of area under the curve–ROC. A product of the sensitivity and specificity was used to determine the optimal cut-off value using Liu method [30], and these values, along with positive likelihood ratio and negative likelihood ratio, are reported.

3. Results

3.1. Patient Characteristics

A total of 26,394 patients were included in our analysis. Of those, 1347 (5.1%) patients were identified as having preoperative HA. The HA patients were found to be older (62.3 $\pm$ 14.1 vs. 59.8 $\pm$ 13.6 $p < 0.001$), had a lower BMI (27.8 $\pm$ 7.1 kg/m^2 vs. 28.8 $\pm$ 6.3 kg/m^2;

$p < 0.001$), and were significantly more likely to be classified as an ASA class 4 or higher (13.0% vs. 6.5%; $p < 0.001$). Likewise, the HA patients were found to have a higher incidence of medical comorbidities including diabetes (21.9% vs. 19.0%; $p < 0.001$), COPD (4.7% vs. 3.6%; $p = 0.031$), CHF (1.8% vs. 0.6%; $p < 0.001$), coagulopathy (7.6% vs. 3.4%; $p < 0.001$), dialysis dependence (1.6% vs. 0.4%; $p < 0.001$), and preoperative sepsis (SIRS, sepsis, and septic shock) (14.2% vs. 1.0%; $p < 0.001$). Further, the HA patients were more likely to have a dependent or totally dependent functional health status (3.3% vs. 0.8%; $p < 0.001$), be a smoker (17.4% vs. 14.1%; $p = 0.01$), and use chronic steroids (5.9% vs. 3.8%; $p < 0.001$).

The patients with HA had differences in their liver texture (10.5% cirrhotic and 4.5% fibrosis versus 9.5% and 3.5%, respectively) and were less likely to have normal livers (22.3% vs. 27.3%, $p < 0.001$). Of note, liver texture was not documented in 50.2% of the HA and 44.2% of the non-HA cohorts. Tumor size also varied, with more patients in the HA cohort having no size documented/no lesion (65.7% vs. 52.3%) and less having lesions < 2 cm and 2–5 cm in size (5.9% vs. 11.4% and 11.0 vs. 21.1%, respectively). Lesions > 5 cm occurred in 17.4% of the HA cohort and 15.2% of the non-HA cohort ($p < 0.001$). The HA patients were more likely to have major liver procedures (41.1% vs. 29.9%, $p < 0.001$).

3.2. Association of HA on Post Liver Resection Outcomes

The patients with HA had longer operative times (263.1 min vs. 241.5 min; $p < 0.001$), a longer length of hospital stay (11.1 days vs. 5.9 days; $p < 0.001$), and higher rates of reoperation (6.8% vs. 2.9%; $p < 0.001$) and readmission (6.8% vs. 2.9%; $p < 0.001$). A significantly higher proportion of the HA patients remained in the hospital for >30 days postoperatively (4.6% vs. 1.0%; $p < 0.001$). Notably, the HA patients experienced a two-fold increase in all types of serious complications (61.6% vs. 28.9%; $p < 0.001$).

The patients with HA also had significantly increased rates of wound healing complications including wound disruption (0.7% vs. 0.5%; $p = 0.0475$), postoperative SSI (4.2% vs. 2.9%; $p = 0.005$), and organ space SSI (18.6% vs. 7.0%; $p < 0.001$) (Table 2). The HA patients were also found to have higher rates of systemic and other infections postoperatively, including sepsis (10.9% vs. 3.2%; $p < 0.001$), septic shock (5.2% vs. 1.4%; $p < 0.001$), and pneumonia (5.9% vs. 2.8%; $p < 0.001$). Complications specific to liver function were also found to be significantly higher in the HA group, including bile leaks (15.5% vs. 6.6%; $p < 0.001$) and liver failure (8.9% vs. 3.0%; $p < 0.001$).

Other postoperative complications found to be significantly higher in the HA patients included DVT (3.8% vs. 1.4%; $p < 0.001$), PE (2.2% vs. 1.0%; $p < 0.001$), acute renal failure (2.6% vs. 0.8%; $p < 0.001$), postoperative bleeding requiring transfusion (41.6% HA vs. 15.8% non-HA; $p < 0.001$), unplanned intubation (5.1% vs. 1.8%; $p < 0.001$), and cardiac arrest (1.9% vs. 0.7% ($p < 0.001$).

3.3. Multivariable Model Assessing Impact of HA on 30-Day Serious Complication Rate and Mortality

A multivariable logistic regression modeling demonstrated HA as the second strongest independent factor associated with the 30-day serious complication rate after adjusting for comorbidities (aOR 2.93, $p < 0.001$). Among other variables considered, the following were identified to be most strongly associated with the 30-day serious complication rate: preoperative sepsis (aOR 3.30, $p < 0.001$), neoadjuvant therapy (aOR 2.11; $p < 0.001$), preoperative functional health status (aOR 1.95, $p = 0.005$), tumor invasion (aOR 1.56, $p < 0.001$), insulin dependent diabetes (aOR 1.34, $p = 0.002$), and non-insulin dependent diabetes (aOR 1.20, $p = 0.011$). Comorbidities generally increased the odds of complications (Table 3). Minimally invasive surgery was identified as a protective factor against serious complications occurring within 30 days (Table 3). The calculated ROC area and BS value for the model predicting serious complications (ROC 0.667, BS 0.213) demonstrated a satisfactory predictive capability for the desired outcomes.

Table 3. Multivariable logistic regression model for factors predictive of 30-day serious complication rate and mortality.

	OR Complications	*p*-Value	OR Mortality	*p*-Value
HA	2.93 (2.36–3.65)	<0.001	2.15 (1.38–3.36)	0.001
Age	1.00 (1.00–1.01)	0.148	1.05 (1.03–1.07)	<0.001
BMI	1.00 (0.99–1.01)	0.760	0.98 (0.95–1.01)	0.190
Female sex	0.99 (0.89–1.11)	0.894	0.72 (0.52–1.00)	0.051
COPD	1.06 (0.85–2.29)	0.599	1.33 (0.76–2.32))	0.319
CHF	1.40 (0.81–2.39)	0.224	2.89 (1.25–6.70)	0.013
Hypertension	1.07 (0.95–1.21)	0.251	0.98 (0.69–1.39)	0.907
Diabetes				
Non-insulin dependent	1.20 (1.04–1.39)	0.011	1.38 (0.94–2.02)	0.104
Insulin dependent	1.34 (1.11–1.61)	0.002	2.45 (1.61–3.73)	<0.001
Smoker	1.00 (0.87–1.16)	0.954	1.02 0.76–1.55)	0.921
Dialysis	1.49 (0.74–2.98)	0.264	0.44 (0.05–1.55)	0.443
Steroid use	0.94 (0.71–1.24)	0.649	0.79 (0.34–1.83)	0.587
Bleeding disorder	1.16 (0.89–1.51)	0.268	1.73 (1.00–3.00)	0.052
Preoperative sepsis	3.30 (1.93–5.66)	<0.001	3.35 (1.51–7.46)	0.003
Functional status	1.95 (1.22–3.13	0.005	2.96 (1.44–6.07)	0.003
Neoadjuvant	2.11 (1.81–2.45)	<0.001	1.41 (0.95–2.10)	0.092
MIS (vs. open)	0.39 (0.33–0.45)	<0.001	0.46 (0.29–0.73)	0.001
Invasive (≥T3)	1.56 (1.37–1.78)	<0.001	1.08 (0.75–1.55)	0.684

Significant *p*-values are italicized. Values presented as odds ratio (95% confidence interval). Brier score 0.2129, ROC area under curve 0.6674 ($p < 0.001$) for serious complications. Brier score 0.027, ROC area under curve 0.721 ($p < 0.001$) for mortality. Abbreviations: HA, Hypoalbuminemia ≤ 3.5 g/dL; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MIS, minimally invasive surgery); ROC, receiver operating curve.

In the multivariable logistic regression model assessing 30-day mortality, HA was again a significant independent predictor (aOR 2.15, $p < 0.001$; Table 4). Preoperative sepsis had the greatest likelihood of mortality among patients undergoing a liver resection (aOR 3.35, $p = 0.003$). Other variables found to be independently associated with 30-day postoperative mortality included age, CHF, insulin-dependent diabetes, and preoperative functional health status. Minimally invasive surgery was shown to be a protective factor against 30-day mortality. The calculated ROC area and BS value for the model predicting serious complications (ROC 0.721, BS 0.027) demonstrated a satisfactory fit.

Table 4. Logistic regression model and subgroup analysis controlling for tumor size for factors predictive of 30-day serious complication rate and mortality.

	OR Complications	*p*-Value	OR Mortality	*p*-Value
HA	2.87 (2.50–3.28)	<0.001	2.29 (1.64–3.21)	<0.001
Age	1.00 (1.00–1.01)	0.004	1.04 (1.03–1.06)	<0.001
BMI	0.99 (0.99–1.00)	0.049	0.99 (0.97–1.01)	0.483
Female sex	0.98 (0.92–1.04)	0.479	0.86 (0.68–1.09)	0.212
COPD	1.12 (0.95–1.32)	0.165	1.36 (0.88–2.13)	0.165
CHF	1.35 (0.94–1.94)	0.110	2.77 (1.40–5.49)	0.004
Hypertension	1.06 (0.99–1.14)	0.101	1.31 (1.00–1.71)	0.048

Table 4. *Cont.*

	OR Complications	*p*-Value	OR Mortality	*p*-Value
Diabetes				
Non-insulin dependent	1.16 (1.0–1.27)	0.003	1.18 (0.87–1.61)	0.293
Insulin dependent	1.37 (1.21–1.55)	<0.001	1.61 (1.12–2.30)	0.009
Smoker	1.08 (0.99–1.18)	0.096	1.17 (0.8–1.61)	0.332
Dialysis	2.29 (1.44–3.64)	<0.001	1.52 (0.57–4.01)	0.402
Steroid use	1.23 (1.06–1.43)	0.006	0.88 (0.50–1.57)	0.673
Bleeding disorder	1.42 (1.22–1.65)	<0.001	1.87 (1.24–2.82)	0.003
Preoperative sepsis	3.20 (2.46–4.17)	<0.001	3.24 (1.90–5.54)	<0.001
Functional status	1.83 (1.32–2.54)	<0.001	3.29 (1.86–5.80)	<0.001
Neoadjuvant	1.50 (1.40–1.61)	<0.001	1.47 (1.12–1.93)	0.006
MIS (vs. open)	0.38 (0.35–0.41)	<0.001	0.3 (0.38–0.74)	<0.001
Tumor size				
<2 cm	0.49 (0.44–0.54)	<0.001	0.24 (0.14–0.41)	<0.001
2–5 cm	0.60 (0.55–0.65)	<0.001	0.29 (0.19–0.42)	<0.001
>5 cm	0.97 (0.89–1.05)	0.423	0.42 (0.29–0.63)	<0.001

Significant *p*-values are italicized. Values presented as odds ratio (95% confidence interval). Brier score 0.197, ROC area under curve 0.665 ($p < 0.001$) for serious complications. Brier score 0.014, ROC area under curve 0.786 ($p < 0.001$) for mortality. Abbreviations: HA, Hypoalbuminemia $\leq$ 3.5 g/dL; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MIS, minimally invasive surgery); ROC, receiver operating curve.

In addition to the above multivariable logistic regressions, two subgroup analyses were performed. The first excluded all of the patients with cirrhosis to control for the impact that liver texture might play on outcomes and its impact on hypoalbuminemia—in this subgroup analysis hypoalbuminemia remained independently associated with serious complications (aOR 2.87, $p < 0.001$) and mortality (aOR 2.30, $p < 0.001$; Supplementary Materials Table S1). Secondly, a subgroup analysis evaluated the impact of a preoperative albumin level $\leq$2.5 and demonstrated an even larger impact of severe hypoalbuminemia on serious complications (aOR 3.62, $p < 0.001$) and mortality (aOR 3.09, $p = 0.002$; Supplementary Materials Table S2).

3.4. Optimal Albumin Cut-Off Values for Predicting Serious Complications and Mortality

The optimal cut-off value for albumin to predict serious complications was found to be 4.0 g/dL. This value showed an AUC-ROC analysis sensitivity of 59.14% and a specificity of 56.84%. The positive likelihood ratio is 1.37 and negative likelihood ratio is 0.72. The AUC-ROC analysis demonstrated that preoperative hypoalbuminemia alone within 30 days of surgery had a ROC area of 0.61 (95% CI, 0.61–0.62) for the classification of serious complications (Table 5).

For mortality, this value was determined to be 3.8 g/dL. The sensitivity and specificity of this value are 56.6% and 68.3%, respectively, while the positive likelihood ratio and negative likelihood ratio are 1.78 and 0.64, respectively. The AUC-ROC is 0.67 (95% CI, 0.64–0.70) (Table 5).

We ran similar models to determine the effect of various hypoalbuminemia cut-offs on the specificity and sensitivity for serious complications, including cut-off values examined in previous literature. For serious complications, our analysis demonstrates that defining hypoalbuminemia at 2 g/dL yields a sensitivity of 0.99% and a specificity of 99.81%, at 2.5 g/dL a sensitivity of 3.57% and a specificity of 99.29%, at 3 g/dL a sensitivity 10.29% and a specificity of 97.18%, and at 3.5 g/dL a sensitivity of 25.05% and a specificity of 88.31%. For mortality, our analysis demonstrates that defining hypoalbuminemia at 2 g/dL yields a sensitivity of 4.97% and a specificity of 99.63%, at 2.5 g/dL a sensitivity of 9.64%

and a specificity of 98.54%, at 3 g/dL a sensitivity of 18.78% and a specificity of 95.10%, and at 3.5 g/dL a sensitivity of 38.32% and a specificity of 84.57%.

Table 5. Optimal albumin cut-off values determined from the area under the curve of receiver operating characteristics curves using the Liu method and the associated sensitivity and specificity of these values.

	Serious Complications	**Mortality**
Cut-off	4.0 (optimal)	3.80 (optimal)
Sensitivity	59.14%	56.60%
Specificity	56.84%	68.25%
Cut-off	3.5	3.5
Sensitivity	25.05%	38.32%
Specificity	88.31%	84.57%
Cut-off	3.0	3.0
Sensitivity	10.29%	18.78%
Specificity	97.18%	95.10%
Cut-off	2.5	2.5
Sensitivity	3.57%	9.64%
Specificity	99.29%	98.54%
Cut-off	2.0	2.0
Sensitivity	0.99%	4.97%
Specificity	99.81%	99.63%

Serious complications ROC area 0.61 (95% CI 0.61–0.62); Mortality ROC area 0.67 (95% CI 0.64–0.70).

4. Discussion

The current study is the largest studying the association of hypoalbuminemia with postoperative outcomes and complications in patients undergoing a liver resection. Among the 26,394 patients included in the analysis, the HA patients were more likely to be older, be functionally impaired, and be more comorbid. HA was significantly associated with numerous complications such as organ space SSI, liver failure, reoperation, and liver failure, and was independently associated with the 30-day serious complication rate and death.

Our analysis is consistent with previous studies showing an independent association between HA and serious complications among liver resection patients [22]. Our study reinforces these findings with a larger cohort and expands on previous studies by also demonstrating an independent association between HA and mortality among liver resection patients, which was not previously shown in other studies [22]. There are numerous potential explanations for this association. One explanation is our use of a lower serum albumin cut off. It stands to reason that more profound HA is likely to confer a greater risk of complications following surgery. In addition, the larger sample size of this study increased its power and resulted in a signal of mortality that was more likely to reach statistical significance.

The complications associated with HA identified in this study are consistent with previous understandings of albumin's physiology. Albumin plays a crucial role in maintaining oncotic pressure, achieving hemostasis, modulating systemic inflammation, and promoting wound healing [10]. HA patients in our study experienced more complications associated with decreased intravascular volume (acute renal failure), bleeding requiring transfusion, sepsis, and wound disruption. These results are consistent across studies that have examined HA among patients undergoing other surgical procedures, including cardiac surgery [31] and spinal surgery [32]. However, albumin may play a more nuanced role in hepatic resection compared to other operations, as preoperative HA may reflect both nutritional status and the effects of the liver pathology that is being resected. When

comparing to another large multicentre retrospective cohort study using NSQIP databases, HA also predicted complications in hepatobiliary patients (i.e., Whipple procedures) but the odds ratios were not as predictive as the current results [29]. There may be a relatively increased importance of hypoalbuminemia as a preoperative risk factor for complications in patients undergoing a hepatic resection.

Our research also adds to the existing literature by identifying absolute values for the optimal albumin cut-off, which we determined to be 4 g/dL for serious complications and 3.8 g/dL for mortality. The AUC of the ROC of albumin alone shows moderate predictive ability despite being a single preoperative patient factor, which might be due to its role as a surrogate marker for overall health. However, these values do not predict that it alone is a strong predictor and thus the utilization of albumin in conjunction with other preoperative risk stratification methods will likely hold the most utility, as suggested by studies in cardiac surgery [28].

The clinical utilization of preoperative serum albumin would be as an adjunct to risk calculator tools. Currently, the NSQIP-ACS calculator incorporates other measures of possible liver dysfunction (e.g., ascites) and overall morbidity (e.g., functional status and ASA classification) but does not incorporate hypoalbuminemia [33]. HA remained significant in the multivariate analysis for outcomes despite the presence of other important surrogates of overall health including age and functional status, which may emphasize its importance in risk stratification; the NSQIP database unfortunately did not allow for further assessment of hypoalbuminemia as marker of overall health or evaluating if it has a direct causal relationship with postoperative complications. Supplementing the NSQIP-ACS with hypoalbuminemia as a continuous variable may add more value than as a categorical variable alone and would improve surgeon–patient discussions regarding operative risks.

In addition to studying albumin as a risk factor, studies have sought to assess if albumin supplementation in patients with HA would improve postoperative outcomes. In a highly specific patient population, administering albumin to patients with HA (<4 g/dL) prior to coronary artery by-pass surgery decreased the incidence of postoperative acute kidney injury [34]. However, Schaller et al. randomized a diverse group of surgical patients with serum albumin < 3 g/dL to either receive albumin infusions to maintain their serum albumin above 3 g/dL or to standard care, yet they found no difference in postoperative complications [35]. These results suggest that the relationship between HA and the risk of postoperative complications is complex. Albumin is more likely a surrogate marker of a combination of deconditioning, malnutrition, and chronic inflammatory states that increase a patient's postoperative risk, rather than an individually and independently casual factor.

Support for nutritional prehabilitation prior to surgery exists in the literature. For example, a multicenter prospective cohort study showed that preoperative nutritional support reduced the risk of complications in malnourished patients [36]. Other studies have used serum albumin in combination with other screening tools to identify optimal candidates for prehabilitation. For instance, Bojesen et al. treated select patients scheduled for colorectal surgery with a multimodal prehabilitation program and showed a decrease in severe complications [37]. Similarly, Ferrandis et al. used hypoalbuminemia to select patients undergoing bowel resection for Crohn's disease for prehabilitation [38]. The authors demonstrated that serum albumin, in combination with other factors, successfully selected patients for prehabilitation and reduced the incidence of anastomotic complications and reoperation rates. Notably, prehabilitation also resulted in a statistically significant increase in preoperative serum albumin. This suggests that albumin may be able to be measured before and after prehabilitation to help assess the protocol's effectiveness. Beyond prehabilitation, surgeons in gynecological oncology have used preoperative albumin to reduce morbidity and mortality associated with the surgical treatment of advanced endometrial cancer. Narasimhulu et al. included preoperative HA in an algorithm to triage patients to primary debulking surgery or to neoadjuvant therapy prior to surgery. In doing so, they demonstrated a decrease in both 90-day postoperative morbidity and mortality [39] Numerous other studies have examined prehabilitation programs in patients undergoing

liver [40] and other abdominal surgeries [41,42], and while the concept of prehabilitation to improve postoperative outcomes seems promising [42,43], the optimal selection of patients and protocol designs remain to be determined [41]. To the authors' knowledge, no studies have used serum albumin to select patients for prehabilitation prior to liver surgery. Given serum albumin's ability to predict patients at a high risk of postoperative complications, we hypothesize that it may help identify patients who would most benefit from surgical prehabilitation programs and/or triage patients to different preoperative care pathways.

The limitations of our study include the use of a database, which lends itself to a selection bias secondary to the inclusion of self-selected sites. It also suffers from the lack of inclusion of important variables that may not be captured, such as liver texture, presence of portal hypertension, cirrhosis severity, and detailed tumor characteristics. Variables such as statin use have also been shown to have implications for survival in patients undergoing a resection for hepatocellular carcinoma [44]. Such variables should be considered for NSQIP inclusion, especially as patients are receiving increasingly individualized care and may benefit from more nuanced information about preoperative and operative factors. However, the detailed data collection by trained reviewers with a high validity and inter-rater reliability with respect to other variables, which is assessed for consistency, helps reliably account for other factors. In addition, NSQIP does not collect data beyond 30 days, and therefore the effect of HA on longer term complications, including clinically relevant end-outcomes such as mortality, are not able to be assessed.

Nonetheless, our paper provides important insights into the role of hypoalbuminemia in hepatic surgery, highlighting its prognostic significance for predicting serious complications, as well as mortality. Future prospective studies should assess the impact of prehabilitation and nutritional strategies on albumin levels and sarcopenia in surgical candidates.

5. Conclusions

This large multicentre study demonstrates that a minority of liver resection patients have preoperative HA. Furthermore, preoperative HA is independently associated with an increased rate of 30-day serious complications and mortality. Optimal cut-off values for albumin to predict complications are 3.8 and 4.0 for serious complications and mortality, and signify the utility of serum albumin for preoperative risk stratification in liver resection patients.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/livers4040036/s1, Table S1: Logistic regression model for factors predictive of 30-day serious complication rate and mortality while controlling for cirrhosis; Table S2: Logistic regression model for factors predictive of 30-day serious complication rate and death where hypoalbuminemia is defined as $\leq$ 2.5 g/dL.

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Informed Consent Statement: This study was exempt from ethics review.

Data Availability Statement: The original data presented in the study are available through request from the American College of Surgeons National Surgical Quality Improvement Program for participating institutions at https://www.facs.org/quality-programs/data-and-registries/acs-nsqip/participant-use-data-file/.

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