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ORIGINAL ARTICLE

Retrospective Study

Interaction between the albumin-bilirubin score and nutritional risk index in the prediction of post-hepatectomy liver failure

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Abstract

BACKGROUND

Post-hepatectomy liver failure (PHLF) is the most common postoperative complication and the leading cause of death after hepatectomy. The albumin-bilirubin (ALBI) score and nutritional risk index (NRI) have been shown to assess end-stage liver disease and predict PHLF and patient survival. We hypothesized that the ALBI score and NRI interact in the prediction of PHLF.

AIM

To analyze the interaction between the ALBI score and NRI in PHLF in patients with hepatocellular carcinoma.

METHODS
This retrospective study included 186 patients who underwent hepatectomy for hepatocellular carcinoma at the Affiliated Hospital of Youjiang Medical University for Nationalities between January 2020 and July 2023. Data on patient characteristics and laboratory indices were collected from their medical records. Univariate and multivariate logistic regression were performed to determine the interaction effect between the ALBI score and NRI in PHLF.

RESULTS
Of the 186 patients included in the study, PHLF occurred in 44 (23.66%). After adjusting for confounders, multivariate logistic regression identified ALBI grade 2/3 [odds ratio (OR) = 73.713, 95% confidence interval (CI): 9.175-592.199] and NRI > 97.5 (OR = 58.990, 95%CI: 7.337-474.297) as risk factors for PHLF. No multiplicative interaction was observed between the ALBI score and NRI (OR = 0.357, 95%CI: 0.022-5.889). However, the risk of PHLF in patients with ALBI grade 2/3 and NRI < 97.5 was 101 times greater than that in patients with ALBI grade 1 and NRI ≥ 97.5 (95%CI: 56.445-523.839), indicating a significant additive interaction between the ALBI score and NRI in PHLF.

CONCLUSION
Both the ALBI score and NRI were risk factors for PHLF, and there was an additive interaction between the ALBI score and NRI in PHLF.

Key Words: Albumin-bilirubin score; Nutritional risk index; Post-hepatectomy liver failure; Interaction; Liver cancer

Core Tip: This study investigated the relationship between the albumin-bilirubin (ALBI) score and nutritional risk index (NRI) in post-hepatectomy liver failure (PHLF). Of the 186 patients who underwent hepatectomy for hepatocellular carcinoma and were included in the study, 44 (23.66%) developed PHLF. Both the ALBI score and NRI were risk factors for PHLF, and there was an additive interaction between the ALBI score and NRI in PHLF. Patients with either of these risk factors should receive preventive pharmacological treatment and help with nutrition to reduce the risk of PHLF.

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INTRODUCTION

Liver cancer is the seventh most common malignancy worldwide and its incidence is increasing annually. The high incidence and mortality of liver cancer make it an important global public health issue, with 906000 new cases and 830000 deaths being reported in 2020[1]. Hepatectomy is currently the main treatment for hepatocellular carcinoma and it significantly improves prognosis. However, the procedure carries a risk of postoperative complications. Post-hepatectomy liver failure (PHLF) occurs in 0.7%-32% of patients[2] and accounts for 40%-60% of the total postoperative mortality[3,4]. The albumin-bilirubin (ALBI) score, which combines these two objective indicators, is currently used to assess patients with end-stage liver disease and predict liver function, PHLF, and mortality after liver resection[5]. Previous studies have shown the ALBI score was superior to the Child-Pugh score for predicting PHLF[6,7].

Malnutrition has a significant impact on the prognosis of patients with hepatocellular carcinoma. Patients with a poor nutritional status before surgery are susceptible to postoperative complications[8]. The key to improving the nutritional status of patients is the use of nutritional risk screening tools to detect malnutrition and determine its severity as early as possible and enable a timely targeted intervention. The nutritional risk index (NRI) combines weight and serum albumin level and has the advantages of objectivity and simplicity. Preoperative NRI can predict serious postoperative complications and patient survival[9]. However, few studies have reported the use of the NRI in patients with hepatocellular carcinoma, and none has analyzed the relationship between the NRI and the ALBI score. Therefore, this study analyzed the relationship between the ALBI score and the NRI for predicting PHLF, identifying patients at high risk of PHLF and enabling the implementation of treatment strategies to reduce the risk.

MATERIALS AND METHODS

Participants

This retrospective study reviewed the data of patients who underwent partial hepatectomy for liver cancer at the Affiliated Hospital of Youjiang Medical University for Nationalities between January 2020 and July 2023. The inclusion criteria were: (1) Diagnosis of primary liver cancer suitable for radical resection according to the "Norms for the Diagnosis and Treatment of Primary Liver Cancer (2017 edition)" of the Medical Administration of the Health and Family Planning Commission of the People's Republic of China[10]; (2) Barcelona Liver Cancer Staging System stage B; (3) Elective open radical resection of liver cancer, performed under general anesthesia using the Pringle method to block the hepatic portal, with postoperative pathological examination; and (4) Complete clinical data and a postoperative survival time of more than 5 d.

The exclusion criteria were: (1) Incomplete basic information and clinical data; (2) Previous surgery; (3) Presence of preoperative distant metastases; (4) Severe liver or kidney dysfunction (Child-Pugh class B or higher) before surgery; and (5) Other organ insufficiency. Patients who underwent partial hepatectomy were divided into two groups depending on whether they developed PHLF. Figure 1 is a study flowchart.

Data collection

General patient information and laboratory data, including sex, age, height, weight, smoking status, alcohol consumption status, and levels of albumin, total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were collected from their medical records. Pathology indicators included tumor diameter, total liver volume, resected liver volume, Child-Pugh score, and presence of cirrhosis.

Diagnosis and definitions

PHLF was diagnosed either when the international normalized ratio (INR) and serum bilirubin levels were higher than normal on or after postoperative day 5 and the rise could not be explained by biliary obstruction or other nonhepatocellular pathology; or, in patients with a high preoperative INR and serum bilirubin level, when the INR and serum bilirubin levels were higher than preoperative values on or after postoperative day 5[10]. The ALBI score was calculated as: $-0.085 \times$ [albumin (g/L)] $+ 0.66 \times$ log[TBIL (μmol/L)]. ALBI scores were categorized as: grade 1, ≤ −2.6; grade 2, > −2.6 and ≤ −1.39; and grade 3, > −1.39[11]. The NRI was calculated as: $1.519 \times$ [albumin (g/L)] $+ 41.7 \times$ (current weight/usual weight) where the usual weight was based on the basal stabilized weight 6 mo before the onset of disease. An NRI of < 97.5 was considered to indicate malnutrition[12,13].

Statistical analysis

SPSS 26.0 (IBM Corp., Armonk, NY, United States) was used to perform the statistical analysis. Quantitative data with a normal distribution were reported as means ± standard deviations, and *t*-tests were used to compare between-group differences. Categorical data were reported as percentages and were compared using chi-squared tests. Factors associated with the occurrence of PHLF were identified by univariate logistic regression and significant factors were included in a multivariate logistic regression model. Logistic regression was used to analyze the multiplicative interaction between the ALBI score and NRI. Logistic regression and Excel tables compiled by Andersson *et al*[14] were used to analyze the additive interaction between the ALBI score and NRI. The interaction was evaluated by calculating the relative excess risk of the interaction (RERI), attribution ratio of the interaction (API), and synergy index (SI). If there was an additive interaction between the two risk factors, the 95% confidence interval (CI) for RERI and API could not contain 0, and the 95%CI for SI could not contain 1. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

RESULTS

Enrollment of patients

A total of 268 patients underwent partial hepatic tumor resection at our hospital between January 2020 and July 2023. Of these, 82 were excluded and the remaining 186 were included in the analysis. Forty-four patients (23.66%) developed PHLF and 142 (76.34%) did not.

Clinical characteristics

Comparing general patient characteristics revealed statistically significant differences of sex and history of hepatitis ($P < 0.05$) between the PHLF and non-PHLF groups. However, of age, smoking, drinking, diabetes, or hypertension in the two groups were not significant ($P > 0.05$) (Table 1). Comparing laboratory test results revealed that TBIL, DBIL, and albumin levels, the INR, ALBI grade, and NRI in the two groups were significantly different ($P < 0.05$). Differences in the ALT and AST levels were not significant ($P > 0.05$) (Table 2).

Multiplicative interaction between the ALBI score and NRI

After adjusting for the confounders sex, history of hepatitis, TBIL level, DBIL level, and INR, multivariate logistic regression analysis identified an ALBI grade of 2/3 (OR = 73.713, 95%CI: 9.175-592.199) and an NRI < 97.5 (OR = 58.990, 95%CI: 7.337-474.297) as risk factors for PHLF. There was no multiplicative interaction between the ALBI score and NRI (OR = 0.357, 95%CI: 0.022-5.889) (Table 3).

Table 1 Comparison of general patient characteristics in the two study groups, *n* (%)

Variable	PHLF group, *n* = 44	Non-PHLF group, *n* = 142	t/χ^2	*P* value
Sex			5.699	0.017
Male	27 (61.36)	58 (40.85)		
Female	17 (38.64)	84 (59.15)		
Age in yr, mean ± SD	59.95 ± 10.37	61.15 ± 10.17	-0.681	0.497
Smoking			0.080	0.777
Yes	14 (31.82)	42 (29.58)		
No	30 (68.18)	100 (70.42)		
Drinking			0.051	0.821
Yes	16 (36.36)	49 (34.51)		
No	28 (63.64)	93 (65.49)		
Diabetes			0.005	0.943
Yes	14 (31.82)	46 (32.39)		
No	30 (68.18)	96 (67.61)		
Hypertension			0.118	0.732
Yes	18 (40.91)	54 (38.03)		
No	26 (59.09)	88 (61.97)		
History of hepatitis			4.654	0.031
Yes	16 (36.36)	29 (20.42)		
No	28 (63.64)	113 (79.58)		
Diameter of tumor in cm, mean ± SD	5.86 ± 3.12	4.16 ± 1.37	5.113	< 0.001
Total liver volume in cm^3, mean ± SD	1586.25 ± 485.26	1591.03 ± 467.80	0.059	0.953
Resected liver volume in cm^3, mean ± SD	573.25 ± 102.58	436.33 ± 98.72	7.965	< 0.001
Child-Pugh score as grade, mean ± SD	8.60 ± 1.34	8.52 ± 1.25	0.365	0.716
Liver cirrhosis			0.208	0.648
Yes	13 (29.55)	37 (26.06)		
No	31 (70.45)	105 (73.94)		

PHLF: Post-hepatectomy liver failure; SD: Standard deviation.

Additive interaction between the ALBI score and NRI

Univariate logistic regression indicated that the risk of PHLF in patients with an ALBI grade of 2/3 and an NRI < 97.5 was 86 times greater than that in patients with an ALBI of grade 1 and an NRI ≥ 97.5 (95%CI: 62.453-251.936). After adjusting for confounders, multivariate logistic regression indicated that the risk was 101 times greater in patients with an ALBI grade of 2/3 and an NRI < 97.5 than that in patients with an ALBI grade of 1 and an NRI ≥ 97.5 (95%CI: 56.445-523.839) (Table 4). Further analysis indicated a significant additive interaction between the ALBI score and NRI (RERI = 13.564, 95%CI: 10.176-26.331; API = 13.340, 95%CI: 9.665-23.023; SI = 1.156, 95%CI: 1.013-1.294) as shown in Table 5.

DISCUSSION

PHLF is the most common complication after hepatectomy in patients with hepatocellular carcinoma and is the most important cause of death[15]. In this study, the incidence of PHLF was 23.66%, which is within the range of 0.7%-32% reported in the literature[2]. The occurrence of PHLF has previously been shown to be influenced by various factors including liver reserve function and postoperative residual liver volume[3]. It has also been reported that the occurrence of PHLF may be influenced by intraoperative and postoperative patient management[16].

In this study, the ALBI score and NRI were found to be risk factors for PHLF, which may be explained by the fact that both reflect hepatic reserve function. Albumin, a plasma protein that can maintain normal blood osmotic pressure,

Table 2 Comparison of laboratory test results in the two study groups

Variable	PHLF group, *n* = 44	Non-PHLF group, *n* = 142	χ^2	*P* value
ALT in U/L, mean ± SD	28.26 ± 7.8	27.64 ± 7.33	0.487	0.627
AST in U/L, mean ± SD	35.6 ± 10.27	34.07 ± 10.93	0.823	0.412
TBIL in μmol/L, mean ± SD	22.68 ± 6.99	19.5 ± 6.38	2.690	0.009
DBIL in μmol/L, mean ± SD	7.26 ± 2.07	4.49 ± 1.48	8.239	< 0.001
INR, mean ± SD	1.96 ± 0.59	1.70 ± 0.55	2.619	0.011
ALB in g/L, mean ± SD	35.57 ± 8.35	40.35 ± 10.1	-3.150	0.002
ALBI score, *n* (%)			61.176	< 0.001
Grade 1	11 (25)	122 (85.92)		
Grade 2/3	33 (75)	20 (14.08)		
NRI, *n* (%)			58.453	< 0.001
< 97.5	30 (68.18)	16 (11.27)		
≥ 97.5	14 (31.82)	126 (88.73)		

ALB: Albumin; ALBI: Albumin-bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; DBIL: Direct bilirubin; INR: International normalized ratio; NRI: Nutritional risk index; PHLF: Post-hepatectomy liver failure; TBIL: Total bilirubin.

Table 3 Multiplicative interaction between the albumin-bilirubin score and nutritional risk index in post-hepatectomy liver failure

Variable	β	SE	Wald	*P* value	OR	95%CI
ALBI score	4.300	1.063	16.361	< 0.001	73.713	(9.175, 592.199)
NRI	4.077	1.064	14.698	< 0.001	58.990	(7.337, 474.297)
ALBI score × NRI	-1.031	1.432	0.519	0.471	0.357	(0.022, 5.889)

The confounding factors sex, history of hepatitis, total bilirubin, direct bilirubin, and international normalized ratio were adjusted for. ALBI: Albumin-bilirubin; CI: Confidence interval; NRI: Nutritional risk index; OR: Odds ratio; PHLF: Post-hepatectomy liver failure; SE: Standard error.

Table 4 Additive interaction between the albumin-bilirubin score and nutritional risk index in post-hepatectomy liver failure

ALBI grade 2/3: NRI < 97.5	PHLF, *n* (%)	Non-PHLF, *n* (%)	Univariate analysis		Multivariate analysis	
			OR (95%CI)	*P* value	OR (95%CI)	*P* value
No: No	3 (6.82)	108 (76.06)	1		1	
Yes: No	11 (25.00)	18 (12.68)	22.000 (5.587, 86.634)	< 0.001	57.574 (6.629, 300.037)	< 0.001
No: Yes	8 (18.18)	14 (9.86)	20.571 (4.879, 86.736)	< 0.001	31.495 (3.738, 265.349)	0.002
Yes: Yes	22 (50.00)	2 (1.41)	86.000 (62.453, 251.936)	< 0.001	101.633 (56.445, 523.839)	< 0.001

The confounding factors sex, history of hepatitis, total bilirubin, direct bilirubin, and international normalized ratio were adjusted for. ALBI: Albumin-bilirubin; CI: Confidence interval; NRI: Nutritional risk index; OR: Odds ratio; PHLF: Post-hepatectomy liver failure.

contains many charged amino acids and can increase the uptake of organic anions by liver cells[17]. Duran-Güell *et al*[18] found that albumin is required for the effective protection of hepatocytes against tumor necrosis factor alpha-induced mitochondrial oxidative stress, which is related to the breakpoint recovery between isocitrate and α-ketoglutarate in the tricarboxylic acid cycle and the upregulation of antioxidant-activated transcription factor 3. Thus, albumin reduces oxidative stress in the liver, thereby reducing liver injury. Engelmann *et al*[19] reported that dysfunctional albumin exacerbated inflammation in patients and that the more severe the dysfunction, the more severe the cirrhosis. This is a typical feature of patients with acute liver failure. Serum bilirubin is produced by the disassembly of heme present in hemoglobin and myoglobin. Bilirubin is an indicator of hepatic dysfunction and a strong predictor of infection in patients undergoing surgery and of mortality in patients who have experienced trauma[20]. The ALBI score combines the levels of albumin and bilirubin to reflect hepatic functional reserve and it accurately predicts PHLF in patients with hepatocellular

Table 5 Analysis of the additive effect of the albumin-bilirubin score and nutritional risk index in post-hepatectomy liver failure

Parameter	Estimated value	95%CI
RERI	13.564	(10.176, 26.331)
API, %	13.340	(9.665, 23.023)
SI	1.156	(1.013, 1.294)

API: Attribution ratio of the interaction; CI: Confidence interval; RERI: Relative excess risk of the interaction; SI: Synergy index.

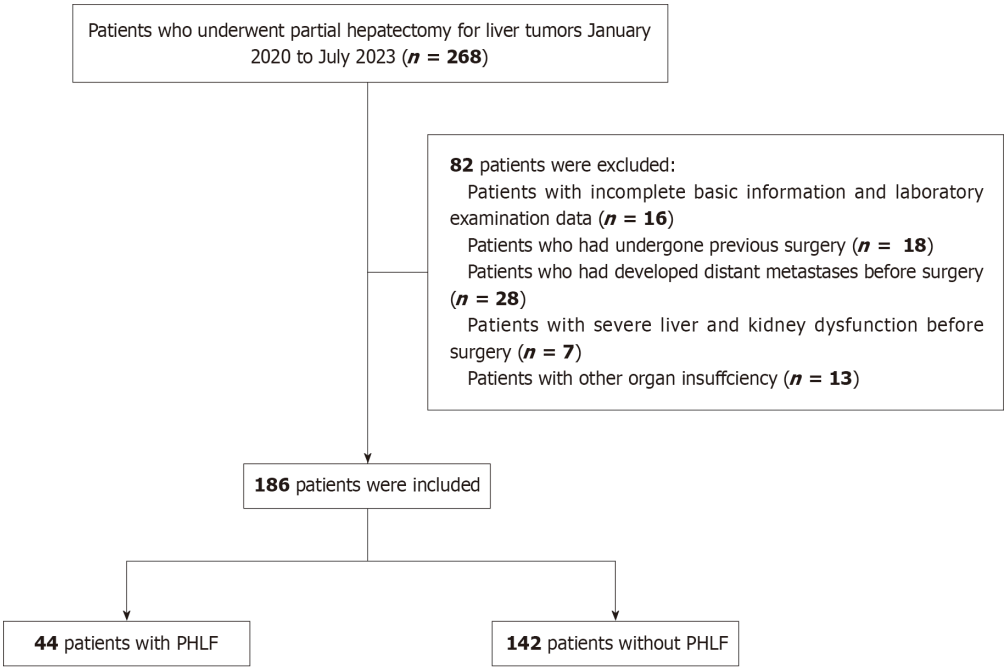

Figure 1 Study flowchart. PHLF: Post-hepatectomy liver failure.

carcinoma. Marasco *et al*[21] found the ALBI score to be superior to the Model for End-Stage Liver Disease score as a predictor of PHLF in patients with hepatocellular carcinoma undergoing extensive hepatectomy. The ALBI score has also been combined with other measures to improve its prediction ability[22].

The NRI is influenced by serum albumin and body weight and reflects the nutritional status of patients. Malnutrition is common in patients with liver cancer and can contribute to morbidity and mortality. Nutritional deficiencies can accelerate catabolic reactions, resulting in reduced protein synthesis and liver regeneration. Malnutrition thus inhibits the recovery of liver function after hepatectomy[23,24]. Rosen *et al*[25] concluded that the main mechanism of liver dysfunction in malnourished individuals is starvation-induced autophagy in hepatocytes, which can lead to hepatocyte injury and death. Therefore, determining the nutritional status of patients with hepatocellular carcinoma undergoing hepatectomy is necessary to enable nutritional intervention and thus reduce the risk of PHLF.

In this study, a positive additive interaction was observed between the ALBI score and NRI, which produced a synergistic effect. The mechanism underlying this interaction requires further investigation. However, we speculate that it may occur as follows. The ALBI score, a novel indicator of liver function, is a continuous variable, and as such reflects small changes in liver function. It has therefore been increasingly used to predict cirrhosis and its complications. The NRI is used to assess nutritional status. As albumin is a component of both the ALBI score and NRI, both fluctuate with albumin levels. When other variables are fixed, changes of the trends of the ALBI score and NRI are consistent regardless of the increase or decrease in the albumin level. That is, they increase or decrease at the same time. Albumin has been shown to have therapeutic effects in patients with liver failure. For example, Sommerfeld *et al*[26] reported that extracorporeal albumin dialysis enhanced bile acid clearance or albumin binding in the livers of patients with severe liver failure, thus protecting against further damage.

In conclusion, the combined detection of the ALBI score and NRI can more effectively identify high-risk patients with PHLF, help to improve the clinical detection rate of PHLF, and thus enable early intervention. However, this study has some limitations. As a retrospective analysis, it was inherently affected by a research question that is not clearly defined, an unconsidered sampling link, and data collection that may be subject to insufficient researcher control. In addition, the study participants were selected at a single center and the sample size and selection range were therefore limited and which may have led to bias in the research results. It is therefore necessary to increase the sample size and further verify the findings in multiple centers.

CONCLUSION

An ALBI grade of 2/3 and an NRI < 97.5 are risk factors for PHLF. The interaction between these two indices further increases the risk of developing PHLF. Patients who exhibit these risk factors should receive preventive pharmacological treatment and nutritional help and education to reduce the risk of PHLF.

FOOTNOTES

Author contributions: Qin FF and Deng FL, as co-first authors, designed and performed the research and wrote the manuscript; Huang CT and Lin SL collected experimental data and conducted statistical analyses; Huang H collected pathological specimens; Nong JJ and Wei MJ, as co-corresponding authors, provided funding and administrative support, provided guidance for the research, and revised the manuscript.

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