Clinics of Surgery

Research Article ISSN 2638-1451|Volume 6

Laparoscopic Hepatectomy Reduces the Incidence of Postoperative Hypoalbuminemia: A Propensity Score Matching Analysis with Open Hepatectomy

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Keyword :
Laparoscopic hepatectomy; Hypoalbuminemia; Albumin

Received: 20 Oct 2021
Accepted: 05 Nov 2021
Published: 09 Nov 2021
J Short Name: COS

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Citation:

Jie Zhou, Chuanjiang Li, Kai Wang. Laparoscopic Hepatectomy Reduces the Incidence of Postoperative Hypoalbuminemia: A Propensity Score Matching Analysis with Open Hepatectomy. Clin Surg. 2021; 6(10): 1-13

List of Abbreviations

ALB, Albumin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; Cr, Creatinine; HGB, Hemoglobin; LH, Laparoscopic hepatectomy; LNHP, Laparoscopic non-hemihepatectomy group; LHP, Laparoscopic hemihepatectomy group; OH, Open hepatectomy; OHP, Open hemihepatectomy group; ONHP, Open non-hemihepatectomy group; OALP Patients without albumin supplement after laparoscopic hepatectomy group; OAOP, Patients without albumin supplement after open hepatectomy group; POD, Postoperative days; Preop, Preoperative; PLT, Platelet; ROC, Receiver operator characteristic; TB, Total bilirubin; WALP, Patients with albumin supplement after laparoscopic hepatectomy group; WAOP, Patients with albumin supplement after open hepatectomy group.

1. Abstract

1.1. Background: This study investigated the incidence of post-hepatectomy hypoalbuminemia and the necessity of intravenous albumin (ALB) supplement for hypoalbuminemia after laparoscopic hepatectomy (LH).

1.2. Methods: 980 patients with open hepatectomy (OH) and 198 patients with LH were matched on the propensity score by 2:1. The incidences of postoperative hypoalbuminemia and the usage of ALB injection on different postoperative days (POD) were compared. Preventive and risk factors of hypoalbuminemia were screened by logistic regression. Receiver operator characteristic (ROC) curve and nomogram were established to predict postoperative hypoalbuminemia.

1.3. Result: 175 patients of LH and 296 patients of OH were matched. The usage of ALB injection was significantly lower in the LH group than those in the OH group (60.0 vs. 75.3%, P=0.000; 6.71±6.99 vs. 8.62±7.18 g, P=0.005). The incidences of postoperative hypoalbuminemia in the LH group were significantly lower than those in the OH group [62.3 vs. 78.4% (P=0.000) on POD 1, 51.4 vs. 71.6% (P=0.000) on POD 3, 37.1 vs. 51.4% (P=0.003) on POD 5, and 27.4 vs. 39.9% (P=0.006) on POD 7]. Preoperative serum ALB level and serum alanine aminotransferase (ALT) level was identified as independent protective and risk factor of hypoalbuminemia after LH, respectively. Preoperative serum ALB level below 42.95 g/L and serum ALT level above 28.50 U/L were identified as the reliable cut-off value to predict postoperative hypoalbuminemia after LH. A nomogram for predicting the probability of hypoalbuminemia after LH was established.

1.4. Conclusion: LH with a reduced intravenous ALB supplement was still associated with a lower incidence of postoperative hypoalbuminemia.

2. Introduction

Hepatectomy is a primary treatment for benign and malignant liver diseases [1, 2]. Hypoalbuminemia is still a common complication that is caused by impairment of albumin (ALB) synthesis or loss of ALB after hepatectomy [3-5]. In adults, hypoalbuminemia is defined as an intravascular serum ALB level below 35 g/L [6], with an incidence of approximately 70% in patients received hepatectomy [7]. Hypoalbuminemia is reported to significantly increase postoperative complications, including deep vein thrombosis, pulmonary embolism, superficial and deep surgical site infection [8], which are further associated with higher mortality, more extended hospital stay, and increased readmitting [9]. With the advent of laparoscopic technology, laparoscopic hepatectomy (LH) has now been implicated to improve liver surgery with reduced operative blood loss, less postoperative pain, and shorter length of hospital stay [10]. Previous studies have reported that the serum ALB level of patients received LH was more stable than who received open hepatectomy (OH) [11-14]. However, whether LH decreased the incidence of postoperative hypoalbuminemia nor the risk factors of postoperative hypoalbuminemia after LH has not yet been investigated.

In this study, we evaluated the incidence of postoperative hypoalbuminemia and the necessity of intravenous ALB supplement for hypoalbuminemia in patents received LH. Furthermore, we developed a novel strategy to predict the hypoalbuminemia after LH.

3. Materials and Methods

3.1. Patients and Data Collection

Inclusion criteria: Patients underwent hepatectomy for liver disease. Exclusion criteria: (1) Patients with severe heart, lung, kidney and other organ dysfunction; (2) Patients transferred to Intensive Care Unit (ICU) after hepatectomy; (3) Patients had proteinuria or nephrotic syndrome; (4) Allergic to human serum albumin preparations. Clinical data were collected from a total of 1178 patients underwent hepatectomy at the Division of Hepatobiliopancreatic Surgery, Department of General Surgery, Nanfang Hospital, Southern Medical University, Guang Zhou, China from March 2012 to August 2017, including 980 patients underwent open surgery and 198 patients underwent laparoscopic surgery. The collection of clinical data includes gender, age, body mass index (BMI), histology, resected range of the liver, cirrhosis, preoperative (Preop) hemoglobin (HGB) levels, Preop platelet (PLT) levels, Preop albumin (ALB) levels, Preop alanine aminotransferase (ALT) levels, Preop aspartate aminotransferase (AST) levels, Preop total bilirubin (TB) levels, Preop creatinine (Cr) levels, intravenous ALB adminstration, duration of surgery, bleeding volume, and serum ALB levels on postoperative day (POD) 1, POD 3, POD 4, POD 5, POD 7. The histology of liver diseases is classified as benign and malignant. The resected range of the liver was grouped as hemihepatectomy and non-hemihepatectomy, which were defined according to the Brisbane 2000 standard [15]. Hypoalbuminemia was determined with serum ALB below 35g/L [6]. Hypoalbuminemia was stratified into three levels: 35-30 g/L as level 1 hypoalbuminemia, 30-25 g/L as level 2 hypoalbuminemia, and below 25 g/L as level 3 hypoalbuminemia.

3.2. Propensity Score Matching (PSM) and Groups

PSM was performed using the PSM extension program in Statistical Product and Service Solutions (SPSS) Statistics for Windows version 22.0 (IBM; Armonk, NY, USA). The nearest neighbor matching method was used for 2:1 matching (open group: laparoscopic group), and the caliper value was set at 0.05. After matching, the patients were further stratified into laparoscopic non-hemihepatectomy group (LNHP), open non-hemihepatectomy group (ONHP), laparoscopic hemihepatectomy group (LHP), open hemihepatectomy group (OHP), patients with intravenous ALB supplement after LH (WALP), patients with intravenous ALB supplement after OH group (WAOP), patients without intravenous ALB supplement after LH (OALP), patients without intravenous ALB supplement after OH group (OAOP).

3.3. Statistical Analysis

Normal distribution continuous data were reported as the mean ± standard deviation ($\bar{x}$ ±SD) and compared using the two-sided Student's t-test. Non-normally distributed continuous data were reported as the median (IQR) and compared using the Mann–Whitney U test. Categorical variables were analyzed with the Chi-squared test or Fisher's exact test, depending on best applicability. Logistic regression was used to examine risk factors of hypoalbuminemia. Univariate logistic regression was used to examine the unadjusted risk factor of hypoalbuminemia. Multivariate logistic regression was applied to examine risk factors of hypoalbuminemia after adjusting for potentially confounding covariates. Independent variables with P <0.05 in univariate models were incorporated as covariates into the multivariate regression model.

Receiver operating characteristic (ROC) curve analysis was used to examine predictive factors of postoperative hypoalbuminemia. Univariate analysis was applied to determine which variables influenced postoperative hypoalbuminemia. Data analysis was performed using IBM SPSS Statistics for Windows version 22.0 (IBM; Armonk, NY, USA). A nomogram was formulated based on the results of multivariate logistic regression analysis and by using the rms package of R, version 3.6. *P* <0.05 was considered to be statistically significant.

4. Result

4.1. Patient Characteristics

A total of 1178 patients were enrolled according to inclusion and exclusion criteria, including 980 cases of OH and 198 cases of LH. Gender, BMI, histology, resected range of the liver, incidence of cirrhosis, Preop HGB levels, Preop ALB levels, Preop AST levels and bleeding volume were different between the two groups (*P* <0.05). After 2:1 propensity score matching, 471 cases were successfully matched, including 296 cases in the open group and 175 cases in the laparoscopic group. The general data of matched patients were listed in Table S1. The comparison of general characteristics showed no significant difference between the laparoscopic group and the open group after PSM (*P* >0.05) **(**Table S1**)**.

4.2. Serum ALB Levels in Laparoscopic Group and Open Group

There was no significant difference between the two groups in Preop ALB levels, Preop incidences of hypoalbuminemia, or Preop severity of hypoalbuminemia (*P* >0.05) **(**Table 1 and Table S2**)**. The amount of postoperative administration of ALB in the laparoscopic group was significantly lower than that in the open group (*P*<0.05) **(**Table 1**)**. Serum ALB levels in both groups reached its lowest point on POD 1, and gradually recovered after POD1. The serum ALB levels in the laparoscopic group were significantly higher than those in the open group on POD 1, 3, 5, and 7 (*P* <0.05) **(**Table 1**)**. The highest incidence of hypoalbuminemia occurred on POD 1 in both groups **(**Table 1**)**. The incidences of hypoalbuminemia in the laparoscopic group were significantly lower than those in the open group on POD 1, 3, 5, and 7 (*P* <0.05) **(**Table 1**)**. The severity of hypoalbuminemia in the open group were more severe on the POD 1, 3, and 5 (*P* <0.05) **(**Table S2**)**.

Supplementary Table 1: Comparison of covariates in the pre-matching and balanced cohort.

Characteristic	Pre-matching cohort N=1178			Balanced cohort N=471		
	LH N=198	**OH N=980**	***P* value**	**LH N=175**	**OH N=296**	***P* value**
Gender *			**0.004**†			0.281†
Male, n (%)	152 (76.8)	834 (85.1)		134 (76.6)	239 (80.7)	
Female, n (%)	46 (23.2)	146 (14.9)		41 (23.4)	57 (19.3)	
Age, (years), X±SD	52.55±12.46	50.88±11.63	0.072‡	53.24±12.72	53.60 11.98	0.244‡
BMI, (kg/m²), X±SD	22.00±3.12	22.84±3.29	**0.001**‡	22.19±3.13	22.15±3.13	0.902‡
Histology *			**0.000**†			0.350†
Benign, n (%)	27 (13.6)	37 (3.8)		20 (11.4)	26 (8.8)	
Malignant, n (%)	171 (86.4)	943 (96.2)		155 (88.6)	270 (91.2)	
Resection *			**0.020**†			0.712†
Non-hemihepatectomies, n (%)	163 (82.3)	731 (74.6)		146 (83.4)	243 (82.1)	
Hemihepatectomies, n (%)	35 (17.7)	249 (25.4)		29 (16.6)	53 (17.9)	
Cirrhosis *			**0.027**†			0.735†
Yes, n (%)	117 (59.1)	659 (67.2)		112 (64.0)	194 (65.5)	
No, n (%)	81 (40.9)	321 (32.8)		63 (36.0)	102 (34.5)	
Preop HGB (g/L), X±SD	141.50±55.96	135.85±19.55	**0.013**‡	141.56±59.25	137.04±17.92	0.222‡
Preop PLT (10^9/L), X±SD	185.37±75.19	186.29±81.97	0.884‡	189.51±80.88	181.66±81.92	0.313‡
Preop ALB (g/L), X±SD	40.07±4.26	38.52±4.59	**0.000**‡	39.89±3.96	39.69±4.55	0.618‡
Preop ALT (U/L), X±SD	37.43±44.28	40.67±36.32	0.271‡	35.11±35.89	44.48±98.11	0.224‡
Preop AST (U/L), X±SD	34.10±31.82	43.29±33.25	**0.000**‡	33.94±28.59	39.33±29.85	0.055‡
Preop TB (μmol/L), X±SD	14.29±17.58	13.44±7.57	0.506‡	12.95±7.13	14.01±15.46	0.393‡
Preop CR (μmol/L), X±SD	78.80±30.09	75.67±30.01	0.185‡	77.19±23.54	74.75±16.46	0.188‡
Duration of surgery (min), X±SD	202.60±101.13	195.08±84.52	0.275‡	208.72±98.20	209.76±91 .05	0.908‡
Bleeding volume (ml), X±SD	160.80±236.39	356.16±479.46	**0.000**‡	176.66±298.81	231.45±306.40	0.059‡

*Values in parentheses are percentages; †Chi-squared test or calibration Chi-square test; ‡Student's t-test

Table 1: Serum ALB levels of laparoscopic and open group.

	LH N=175	OH N=296	P value
Percentage of albumin supplement, n (%) *	105 (60.0)	223 (75.3)	**0.000**†
The average amount of albumin supplement (g), X±SD	6.71±6.99	8.62±7.18	0.005‡
Serum albumin levels (g/L), X±SD			
Preop	39.89±3.96	39.69±4.55	0.618‡
POD 1	33.61±3.62	31.88±4.18	**0.000**‡
POD 3	34.74±3.55	32.84±3.86	**0.000**‡
POD 5	36.62±4.10	34.77±4.62	**0.000**‡
POD 7	37.95±4.33	36.60±4.95	**0.**003‡
The incidences of hypoalbuminemia, n (%) *			
Preop	22 (12.6)	43 (14.5)	0.552†
POD 1	109 (62.3)	232 (78.4)	**0.000**†
POD 3	90 (51.4)	212 (71.6)	**0.000**†
POD 5	65 (37.1)	152 (51.4)	**0.**003†
POD 7	48 (27.4)	118 (39.9)	**0.**006†

*Values in parentheses are percentages; †Chi-squared test or calibration Chi-square test; ‡ Student's t-test

Supplementary Table 2: The severity of hypoalbuminemia in laparoscopic and open group.

	Laparoscopic group	Open group	P **value**
Preop hypoalbuminemia, n (%) *	22 (100.0)	43 (100.0)	0.690†
Level 1, n (%)	18 (81.8)	37 (86.0)	
Level 2, n (%)	4 (18.2)	5 (11.6)	
Level 3, n (%)	0 (0.0)	1 (2.3)	
POD 1 hypoalbuminemia, n (%) *	109 (100.0)	232 (100.0)	**0.**013†
Level 1, n (%)	78 (71.6)	137 (59.1)	
Level 2, n (%)	30 (27.5)	79 (34.1)	
Level 3, n (%)	1 (0.9)	16 (6.9)	
POD 3 hypoalbuminemia, n (%) *	90 (100.0)	212 (100.0)	**0.**010†
Level 1, n (%)	73 (81.1)	142 (67.0)	
Level 2, n (%)	17 (18.9)	62 (29.2)	
Level 3, n (%)	0 (0.0)	8 (3.8)	
POD 5 hypoalbuminemia, n (%) *	65 (100.0)	152 (100.0)	**0.**043†
Level 1, n (%)	55 (84.6)	110 (72.4)	
Level 2, n (%)	10 (15.4)	36 (23.7)	
Level 3, n (%)	0 (0.0)	6 (3.9)	
POD 7 hypoalbuminemia, n (%) *	48 (100.0)	118 (100.0)	0.361†
Level 1, n (%)	41 (85.4)	94 (79.7)	
Level 2, n (%)	7 (14.6)	21 (17.8)	
Level 3, n (%)	0 (0.0)	3 (2.5)	

*Values in parentheses are percentages; † Mann–Whitney U test

4.3. Serum ALB Levels and Incidence of Hypoalbuminemia in Patients Received Non-Hemihepatectomy and Hemihepatectomy

Stratified analysis was further performed according to the liver resection range. Serum ALB levels of patients received non-hemihepatectomy and hemihepatectomy in laparoscopic group and open group were correspondingly compared. The comparison of general data between the corresponding subgroups showed no significant difference (*P* >0.05) **(**Table S3**)**. There was no significant difference in the levels of Preop ALB, incidences of Preop hypoalbuminemia, or severity of Preop hypoalbuminemia between the corresponding subgroups (*P* >0.05) **(**Table 2 and Table S4**)**. In patients who received non-hemihepatectomy, the administration of albumin was significantly lower in the LNHP than that in the ONHP (*P* <0.05) **(**Table 2**)**. The serum ALB levels in the LNHP were significantly higher than those in the ONHP on POD 1, 3, 5, and 7 (*P* <0.05). The incidences of postoperative hypoalbuminemia were significantly lower in the LNHP than those in the ONHP on POD 1, 3, 5, and 7 (*P* <0.05) **(**Table 2**)**. The severity of postoperative hypoalbuminemia significantly attenuated in the LNHP on POD 1, 3, and 5 (*P* <0.05) **(**Table S4**)**. In patients received hemihepatectomy, there were no significant differences in the administration of ALB between the LHP and OHP groups (*P* >0.05) **(**Table 2**)**. The serum ALB level in the LHP was still significantly higher than that in the OHP only on POD 5 (*P* <0.05) **(**Table 2**)**. However, the incidences of postoperative hypoalbuminemia between these two groups showed no differences (*P* >0.05) **(**Table 2**)**. There was no significant difference in the severity of postoperative hypoalbuminemia between these two groups (*P* >0.05) **(**Table S4**)**. These data demonstrated that laparoscopic surgery stabilized postoperative serum ALB levels and reduced the incidence of hypoalbuminemia, mainly in non-hemihepatectomy.

Supplementary Table 3: Comparison of general data between the laparoscopic group and open group with the same range of hepatectomy.

Characteristic	**Non-hemihepatectomies N=389**			**Hemihepatectomies N=82**		
	LNHP N=146	**ONHP N=243**	***P* value**	**LHP N=29**	**OHP N=53**	***P* value**
Gender *			0.725†			0.073†
Male, n (%)	115 (78.8)	195 (80.2)		19 (65.5)	44 (83.0)	
Female, n (%)	31 (21.2)	48 (19.8)		10 (34.5)	9 (17.0)	
Age, (years), X±SD	51.90±12.53	53.75±11.83	0.146‡	53.93±13.76	52.94±12.78	0.746‡
BMI, (kg/m²), X±SD	21.95±3.18	22.13±3.07	0.586‡	23.39±2.59	22.24±3.47	0.129‡
Histology *			0.860†			0.166†
Benign, n (%)	14 (9.6)	22 (9.1)		6 (20.7)	4 (7.5)	
Malignant, n (%)	132 (90.4)	221 (90.9)		23 (79.3)	49 (92.5)	
Cirrhosis *			0.602†			0.893†
Yes, n (%)	96 (65.8)	166 (68.3)		16 (55.2)	28 (52.8)	
No, n (%)	50 (34.2)	77 (31.7)		13 (44.8)	25 (47.2)	
Preop HGB(g/L), X±SD	142.88±64.49	136.26±18.12	0.133‡	134.90±15.09	140.60±16.67	0.130‡
Preop PLT (10^9/L), X±SD	182.27±69.21	172.60±80.61	0.228‡	227.97±119.13	223.19±75.46	0.898‡
Preop ALB (g/L), X±SD	39.86±4.22	39.62±4.43	0.605‡	40.07±2.27	40.02±5.07	0.957‡
Preop ALT (U/L), X±SD	31.83±28.64	43.46±105.14	0.271‡	51.60±58.48	49.17±56.02	0.854‡
Preop AST (U/L), X±SD	32.87±28.54	38.05±26.53	0.071‡	39.34±28.71	45.21±41.66	0.501‡
Preop TB (μmol/L), X±SD	12.95±7.14	14.31±16.88	0.354‡	12.94±7.16	12.60±5.13	0.802‡
Preop CR (μmol/L), X±SD	78.00±22.98	75.17±16.49	0.172‡	73.17±21.13	72.79±16.29	0.928‡
Duration of surgery (min), X±SD	190.30±90.31	196.00±85.08	0.535‡	300.83±84.26	272.71±91.74	0.178‡
Bleeding volume (ml), X±SD	160.86±254.89	209.84±291.04	0.093‡	256.21±458.85	330.57±355.28	0.417‡

*Values in parentheses are percentages; †Chi-squared test or calibration Chi-square test; ‡Student's t-test

Supplementary Table 4: The severity of hypoalbuminemia between the laparoscopic group and open group with the same scope of hepatectomy

	Non-hemihepatectomies			Hemihepatectomies		
	LNHP	ONHP	P **value**	LHP	OHP	P **value**
Preop hypoalbuminemia, n (%) *	22 (100.0)	33 (100.0)	0.959†	0 (0.0)	8 (100.0)	——
Level 1, n (%)	18 (81.8)	27 (81.8)		0 (0.0)	8 (100.0)	
Level 2, n (%)	4 (18.2)	5 (15.2)		0 (0.0)	0 (0.0)	
Level 3, n (%)	0 (0.0)	1 (3.0)		0 (0.0)	0 (0.0)	
POD 1 hypoalbuminemia, n (%) *	88 (100.0)	187 (100.0)	0.043†	21 (100.0)	45 (100.0)	0.143†
Level 1, n (%)	63 (71.6)	113 (60.4)		15 (71.4)	24 (53.3)	
Level 2, n (%)	25 (28.4)	64 (34.2)		5 (23.8)	15 (33.3)	
Level 3, n (%)	0 (0.0)	10 (5.3)		1 (4.8)	6 (13.3)	
POD 3 hypoalbuminemia, n (%) *	77 (100.0)	179 (100.0)	0.015†	13 (100.0)	33 (100.0)	0.367†
Level 1, n (%)	62 (80.5)	118 (65.9)		11 (84.6)	24 (72.7)	
Level 2, n (%)	15 (19.5)	55 (30.7)		2 (15.4)	7 (21.2)	
Level 3, n (%)	0 (0.0)	6 (3.4)		0 (0.0)	2 (6.1)	
POD 5 hypoalbuminemia, n (%) *	58 (100.0)	128 (100.0)	0.033†	7 (100.0)	24 (100.0)	0.853†

Level 1, n (%)	49 (84.5)	90 (70.3)		6 (85.7)	20 (83.3)	
Level 2, n (%)	9 (15.5)	33 (25.8)		1 (14.3)	3 (12.5)	
Level 3, n (%)	0 (0.0)	5 (3.9)		0 (0.0)	1 (4.2)	
POD 7 hypoalbuminemia, n (%) *	42 (100.0)	102 (100.0)	0.300†	6 (100.0)	16 (100.0)	0.853†
Level 1, n (%)	36 (85.7)	80 (78.4)		5 (83.3)	14 (87.5)	
Level 2, n (%)	6 (14.3)	20 (19.6)		1 (16.7)	1 (6.3)	
Level 3, n (%)	0 (0.0)	2 (2.0)		0 (0.0)	1 (6.3)	

*Values in parentheses are percentages; † Mann–Whitney U test

Table 2: Comparison of ALB levels changed between the laparoscopic group and open group with the same scope of hepatectomy.

Characteristic	Non-hemihepatectomies N=389			Hemihepatectomies N=82		
	LNHP N=146	ONHP N=243	P value	LHP N=29	OHP N=53	P value
Percentage of albumin supplement, n (%) *	85 (58.2)	177 (72.8)	0.003†	20 (69.0)	46 (86.8)	0.051†
The average amount of albumin supplement (g), X±SD	6.15±6.69	7.97±7.04	0.012‡	9.53±7.88	11.59±7.13	0.232
Serum albumin levels (g/L), X±SD						
Preop	39.86±4.22	39.62±4.43	0.605‡	40.07±2.27	40.02±5.07	0.957‡
POD 1	33.79±3.64	32.10±4.06	0.002‡	32.72±3.46	30.85±4.58	0.059‡
POD 3	34.75±3.56	32.71±3.84	**0.000**‡	34.70±3.55	33.41±3.91	0.145‡
POD 5	36.45±4.11	34.63±4.66	**0.000**‡	37.47±4.00	35.44±4.40	0.043‡
POD 7	37.86±4.30	36.34±4.98	0.002‡	38.43±4.52	37.76±4.63	0.530‡
The incidences of hypoalbuminemia, n (%)*						
Preop	22 (15.1)	33 (13.6)	0.683†	0 (0.0)	8 (15.1%)	0.070†
POD 1	88 (60.3)	187 (77.0)	**0.000**†	21 (72.4)	45 (84.9)	0.172†
POD 3	77 (52.7)	179 (73.7)	**0.000**†	13 (44.8)	33 (62.3)	0.128†
POD 5	58 (39.7)	128 (52.7)	0.013†	7 (24.1)	24 (45.3)	0.059†
POD 7	42 (28.8)	102 (42.0)	0.009†	6 (20.7)	16 (30.2)	0.353†

*Values in parentheses are percentages; †Chi-squared test or calibration Chi-square test; ‡Student's t-test

4.4. Serum Albumin Levels and Incidence of Hypoalbuminemia in Patients Supplied with or Without ALB

Stratification analysis was performed according to the intravenous supplement of ALB. The serum ALB levels of patients supplied with or without ALB in the laparoscopic group and the open group were further compared. There were no significant differences between the corresponding subgroups in general data (*P* >0.05) **(**Table S5**)**. The levels of Preop ALB, incidence of Preop hypoalbuminemia, or severity of Preop hypoalbuminemia between the corresponding subgroups showed no significant differences **(**Table 3 and Table S6**)**. In patients supplied with ALB after surgery, the amount of ALB supplement showed no significant difference between the WALP group and the WAOP group (*P* >0.05) **(**Table 3**)**. The serum ALB levels in the WALP group were significantly higher than those in the WAOP group on POD 1, 3, 5, and 7 (*P* <0.05). The incidences of postoperative hypoalbuminemia were significantly lower in the WALP group than those in the WAOP group on POD 1, 3, 5, and 7 (*P* <0.05) **(**Table 3**)**. The severity of postoperative hypoalbuminemia between the two groups showed no significant difference (*P* >0.05) **(**Table S6**)**. In patients without supplement of ALB after surgery**,** the serum ALB levels in the OALP were significantly higher than that in the OAOP on POD 5 and 7 (*P* <0.05). The incidences of postoperative hypoalbuminemia were significantly lower in the OALP than those in the OAOP on POD 5 and 7 (*P* <0.05) **(**Table 3**)**. There were no significant differences in the severity of postoperative hypoalbuminemia between these two groups (*P* >0.05) **(**Table S6**)**. These data suggested that laparoscopic surgery prevented postoperative hypoalbuminemia regardless of intravenous ALB supplement.

4.5. Preventive and Risk Factors of Postoperative Hypoalbuminemia

Multivariate logistical regression analysis was carried out based on the significant variables (*P* <0.05) of univariate logistical regression analysis. Preop ALB and Preop ALT were identified as independent preventive and risk factors of hypoalbuminemia after LH, respectively **(**Table 4**)**. Preop ALB was also identified as a preventive factor of hypoalbuminemia after OH **(**Table 5**)**. Since the highest incidence of hypoalbuminemia occurred on POD 1, we performed univariate and multivariate analyses to evaluate the preventive and risk factors of hypoalbuminemia on POD 1. Preop ALB levels were identified as a preventive factor of hypoalbuminemia on POD 1. However, Preop AST, duration of surgery, and bleeding volume were identified as independent risk factors of hypoalbuminemia after LH on POD 1 **(**Table S7**)**. Preop ALB was a preventive factor of hypoalbuminemia after OH on POD 1 **(**Table S8**)**.

Table 3: Comparison of ALB levels changed between the laparoscopic group and open group with or without albumin supplement

Characteristic	With supplement of albumin N=328			Without supplement of albumin N=143		
	WALP N=105	WAOP N=223	P value	OALP N=70	OAOP N=73	P value
The average amount of albumin supplement (g), X±SD	11.18±5.60	11.44±6.00	0.711‡	——	——	——
Serum albumin levels (g/L), X±SD						
Preop	39.23±4.09	39.30±4.70	0.905‡	40.89±3.57	40.91±3.86	0.968‡
POD 1	32.86±3.71	31.08±3.95	**0.000**‡	34.73±3.19	34.32±3.91	0.498‡
POD 3	35.02±3.87	32.68±3.93	**0.000**‡	34.32±2.98	33.33±3.59	0.077‡
POD 5	37.38±4.42	35.05±4.74	**0.000**‡	35.48±3.27	33.92±4.16	0.014‡
POD 7	38.76±4.42	37.15±5.04	0.005‡	36.73±3.92	34.92±4.24	0.009‡
The incidences of hypoalbuminemia, n (%)*						
Preop	18 (17.1)	39 (17.5)	0.939†	4 (5.7)	4 (5.5)	1.000†
POD 1	76 (72.4)	190 (85.2)	0.006†	33 (47.1)	42 (57.5)	0.214†
POD 3	51 (48.6)	162 (72.6)	**0.000**†	39 (55.7)	50 (68.5)	0.115†
POD 5	34 (32.4)	105 (47.1)	0.012†	31 (44.3)	47 (64.4)	0.016†
POD 7	23 (21.9)	76 (34.1)	0.025†	25 (35.7)	42 (57.5)	0.009†

*Values in parentheses are percentages; †Chi-squared test or calibration Chi-square test; ‡Student's t-test

Supplementary Table 5: Comparison of general data between the laparoscopic group and the open group with or without albumin supplement

Characteristic	**Albumin supplementation after hepatectomy N=328**			**No albumin supplementation after hepatectomy N=143**		
	WALP N=105	**WAOP N=223**	***P* value**	**OALP N=70**	**OAOP N=73**	***P* value**
Gender *			0.723†			0.258†
Male, n (%)	83 (79.0)	180 (80.7)		51 (72.9)	59 (80.8)	
Female, n (%)	22 (21.0)	43 (19.3)		19 (27.1)	14 (19.2)	
Age, (years), X±SD	54.55±12.38	55.06±11.19	0.710‡	48.77±12.52	49.15±13.26	0.861‡
BMI, (kg/m^2), X±SD	22.33±3.10	22.11±3.11	0.562‡	21.97±3.18	22.26±3.22	0.596‡
Histology *			0.651†			0.910†
Benign, n (%)	8 (7.6)	14 (6.3)		12 (17.1)	12 (16.4)	
Malignant, n (%)	97 (92.4)	209 (93.7)		58 (82.9)	61 (83.6)	
Resection			0.739†			0.535†
Non-hemihepatectomies, n (%)	85 (81.0)	177 (79.4)		61 (87.1)	66 (90.4)	
Hemihepatectomies, n (%)	20 (19.0)	46 (20.6)		9 (12.9)	7 (9.6)	
Cirrhosis *			0.485†			0.508†
Yes, n (%)	67 (63.8)	151 (67.7)		45 (64.3)	43 (58.9)	
No, n (%)	38 (36.2)	72 (32.3)		25 (35.7)	30 (41.1)	
Preop HGB (g/L), X±SD	137.31±17.62	136.81±18.33	0.818‡	147.94±91.20	137.74±16.70	0.349‡
Preop PLT (10^9/L), X±SD	177.14±60.12	173.71±74.00	0.656‡	208.06±102.31	205.92±99.10	0.899‡
Preop ALB (g/L), X±SD	39.23±4.09	39.30±4.69	0.905‡	40.89±3.57	40.91±3.86	0.968‡
Preop ALT (U/L), X±SD	36.27±40.88	49.75±112.10	0.233‡	33.36±26.93	28.37±18.57	0.198‡
Preop AST (U/L), X±SD	36.58±33.18	41.34±31.82	0.214‡	29.99±19.38	33.21±21.86	0.354‡
Preop TB (μmol/L), X±SD	12.44±6.24	14.41±17.38	0.260‡	13.71±8.27	12.77±6.70	0.456‡
Preop CR (μmol/L), X±SD	76.57±19.96	74.01±15.63	0.210‡	78.13±28.22	76.99±18.68	0.775‡
Length of surgery (min), X±SD	238.41±97.23	223.28±93.22	0.179‡	163.55±81.52	168.81±70.16	0.682‡
Bleeding volume (ml), X±SD	215.14±369.92	251.08±326.94	0.374‡	118.93±115.22	171.51±224.18	0.082‡

*Values in parentheses are percentages; †Chi-squared test or calibration Chi-square test; ‡Student's t-test

Supplementary Table 6: The severity of hypoalbuminemia between the laparoscopic group and open group with or without human serum albumin.

	Used **human serum albumin**			Non-used **human serum albumin**		
	UHLP	UHOP	P **value**	NUHLP	NUHOP	P **value**
Preop hypoalbuminemia, n (%) *	18 (100.0)	39 (100.0)	0.400†	4 (100.0)	4 (100.0)	0.317†
Level 1, n (%)	14 (77.8)	34 (87.2)		4 (100.0)	3 (75.0)	
Level 2, n (%)	4 (22.2)	4 (10.3)		0 (0.0)	1 (25.0)	
Level 3, n (%)	0 (0.0)	1 (2.6)		0 (0.0)	0 (0.0)	
POD 1 hypoalbuminemia, n (%) *	76 (100.0)	190 (100.0)	0.075†	33 (100.0)	42 (100.0)	0.236†
Level 1, n (%)	50 (65.8)	106 (55.8)		28 (84.8)	31 (73.8)	
Level 2, n (%)	25 (32.9)	69 (36.3)		5 (15.2)	10 (23.8)	
Level 3, n (%)	1 (1.3)	15 (7.9)		0 (0.0)	1 (2.4)	
POD 3 hypoalbuminemia, n (%) *	51 (100.0)	162 (100.0)	0.058†	39 (100.0)	50 (100.0)	0.356†
Level 1, n (%)	39 (76.5)	102 (63.0)		34 (87.2)	40 (80.0)	
Level 2, n (%)	12 (23.5)	53 (32.7)		5 (12.8)	9 (18.0)	
Level 3, n (%)	0 (0.0)	7 (4.3)		0 (0.0)	1 (2.0)	
POD 5 hypoalbuminemia, n (%) *	34 (100.0)	105 (100.0)	0.124†	31 (100.0)	47 (100.0)	0.334†
Level 1, n (%)	28 (82.4)	73 (69.5)		27 (87.1)	37 (78.7)	
Level 2, n (%)	6 (17.6)	27 (25.7)		4 (12.9)	9 (19.1)	
Level 3, n (%)	0 (0.0)	5 (4.8)		0 (0.0)	1 (2.1)	
POD 7 hypoalbuminemia, n (%) *	23 (100.0)	76 (100.0)	0.413†	25 (100.0)	42 (100.0)	0.991†
Level 1, n (%)	19 (82.6)	57 (75.0)		22 (88.0)	37 (88.1)	
Level 2, n (%)	4 (17.4)	16 (21.1)		3 (12.0)	5 (11.9)	
Level 3, n (%)	0 (0.0)	3 (3.9)		0 (0.0)	0 (0.0)	

*Values in parentheses are percentages; † Mann–Whitney U test

Table 4: Univariate and multivariate analysis of postoperative hypoalbuminemia in the laparoscopic group.

Variables	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P **value**	**OR (95%CI)**	P **value**
Gender (Male vs. Female)	0.891 (0.402-1.973)	0.776	——	——
Age	1.008 (0.982-1.036)	0.541	——	——
BMI	0.977 (0.876-1.090)	0.674	——	——
Histology (Malignant vs. Benign)	0.758 (0.272-2.110)	0.596	——	——
Resection (Non-hemihepatectomies vs. Hemihepatectomies)	1.750 (0.624-4.905)	0.288	——	——
Cirrhosis (No vs. Yes)	1.323 (0.656-2.667)	0.434	——	——
Preop HGB	1.003 (0.992-1.013)	0.632	——	——
Preop PLT	1.001 (0.997-1.005)	0.670	——	——
Preop ALB	0.834 (0.751-0.927)	0.001	0.821 (0.733-0.920)	0.001
Preop ALT	1.022 (1.001-1.043)	0.044	1.025 (1.001-1.049)	0.042
Preop AST	1.019 (0.997-1.041)	0.087	——	——
Preop TB	1.013 (0.963-1.066)	0.610	——	——
Preop CR	0.987 (0.972-1.001)	0.075	——	——
Duration of surgery	1.006 (1.002-1.011)	0.004	1.003 (0.998-1.008)	0.190
Bleeding volume	1.005 (1.001-1.009)	0.020	1.004 (1.000-1.008)	0.073

Table 5: Univariate and multivariate analysis of postoperative hypoalbuminemia in the open group

Variables	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P **value**	OR (95%CI)	P **value**
Gender (Male vs. Female)	0.819 (0.314-2.132)	0.682	——	——
Age	1.024 (0.991-1.057)	0.152	——	——
BMI	0.887 (0.772-1.019)	0.090	——	——
Histology (Malignant vs Benign)	1.224 (0.273-5.488)	0.791	——	
Resection (Non-hemihepatectomies vs. Hemihepatectomies)	1.281 (0.424-3.871)	0.661	——	——
Cirrhosis (No vs. Yes)	0.946 (0.409-2.189)	0.897	——	——
Preop HGB	0.983 (0.960-1.007)	0.160	——	——
Preop PLT	0.999 (0.995-1.004)	0.793	——	——
Preop ALB	0.817 (0.737-0.905)	**0.000**	0.825 (0.743-0.916)	**0.000**
Preop ALT	1.009 (0.992-1.027)	0.300	——	——
Preop AST	1.027 (0.997-1.058)	0.079	——	——
Preop TB	1.015 (0.956-1.079)	0.624	——	——
Preop CR	0.981 (0.958-1.005)	0.118	——	——
Duration of surgery	1.007 (1.001-1.012)	0.025	1.006 (1.000-1.012)	0.055
Bleeding volume	1.003 (1.000-1.006)	0.078		

Supplementary Table 7: Univariate and multivariate analysis of hypoalbuminemia on POD 1 in the laparoscopic group

Variables	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P **value**	OR (95%CI)	P **value**
Gender (Male vs. Female)	0.626 (0.308-1.271)	0.195	——	——
Age, (years), X±SD	1.019 (0.994-1.044)	0.133	——	——
BMI, (kg/m^2), X±SD	0.989 (0.897-1.091)	0.829	——	——
Histology (Malignant vs. Benign)	0.566 (0.222-1.442)	0.233	——	——
Resection (Non-hemihepatectomies vs. Hemihepatectomies)	1.730 (0.718-4.168)	0.222	——	——
Cirrhosis (NO vs. Yes)	1.265 (0.671-2.383)	0.467	——	——
Preop HGB	1.003 (0.994-1.011)	0.555	——	——
Preop PLT	0.999 (0.996-1.003)	0.785	——	——
Preop ALB	0.860 (0.787-0.941)	0.001	0.855 (0.776-0.942)	0.002
Preop ALT	1.012 (0.999-1.026)	0.061	——	——
Preop AST	1.024 (1.004-1.044)	0.019	1.021 (1.003-1.041)	0.025
Preop TB	1.011 (0.967-1.056)	0.635	——	——
Preop CR	0.998 (0.985-1.011)	0.774	——	——
Length of surgery	1.008 (1.004-1.012)	**0.000**	1.005 (1.001-1.010)	0.022
Bleeding volume	1.005 (1.002-1.009)	0.004	1.004 (1.000-1.007)	0.049

Supplementary Table 8: Univariate and multivariate analysis of hypoalbuminemia on POD 1 in the open group.

Variables	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P **value**	OR (95%CI)	P **value**
Gender (Male vs. Female)	1.043 (0.514-2.115)	0.908	——	——
Age	1.028 (1.005-1.052)	0.018	1.021 (0.996-1.047)	0.095
BMI	0.980 (0.892-1.076)	0.672	——	——
Histology (Malignant vs Benign)	0.589 (0.243-1.424)	0.240	——	——
Resection (Non-hemihepatectomies vs. Hemihepatectomies)	1.684 (0.750-3.783)	0.207	——	——
Cirrhosis (NO vs. Yes)	0.910 (0.506-1.638)	0.754	——	——
Preop HGB	0.982 (0.966-0.999)	0.036	0.995 (0.977-1.014)	0.627
Preop PLT	0.997 (0.994-1.001)	0.117	——	——
Preop ALB	0.861 (0.803-0.924)	**0.000**	0.896 (0.827-0.971)	0.007
Preop ALT	1.005 (0.995-1.014)	0.328	——	——
Preop AST	1.028 (1.007-1.049)	0.007	1.018 (0.998-1.038)	0.085
Preop TB	0.990 (0.973-1.007)	0.251	——	——
Preop CR	0.997 (0.980-1.013)	0.684	——	——
Duration of surgery	1.006 (1.002-1.009)	0.004	1.004 (1.000-1.008)	0.059
Bleeding volume	1.002 (1.000-1.004)	0.034	1.001 (0.999-1.003)	0.335

4.6. Prediction of Hypoalbuminemia After LH

ROC curve was performed to estimate the cut-off values of relevant Preop factors for postoperative hypoalbuminemia after LH. The analysis identified that Preop ALB levels below 42.95 g/L (AUC=0.678; sensitivity=47.7%; specificity=85.5%, *P*=0.000) **(**Figure 1**)** and Preop ALT levels above 28.50 U/L (AUC=0.630; sensitivity=49.6%; specificity=77.3%, *P*=0.010) **(**Figure 2**)** were the most reliable cut-off values to predict postoperative hypoalbuminemia in the laparoscopic group. A nomogram was developed from the total points accumulated by Preop ALB levels and Preop ALT levels to predict the probability of hypoalbuminemia after LH **(**Figure 3**)**. The nomogram demonstrated medium accuracy in estimating the probability of hypoalbuminemia after LH, with C index of 0.724 (95% CI, 0.642-0.807). In addition, calibration plots graphically showed good agreement on the presence of hypoalbuminemia between the probability estimation by the nomogram and actual situation **(**Figure 4**)**.

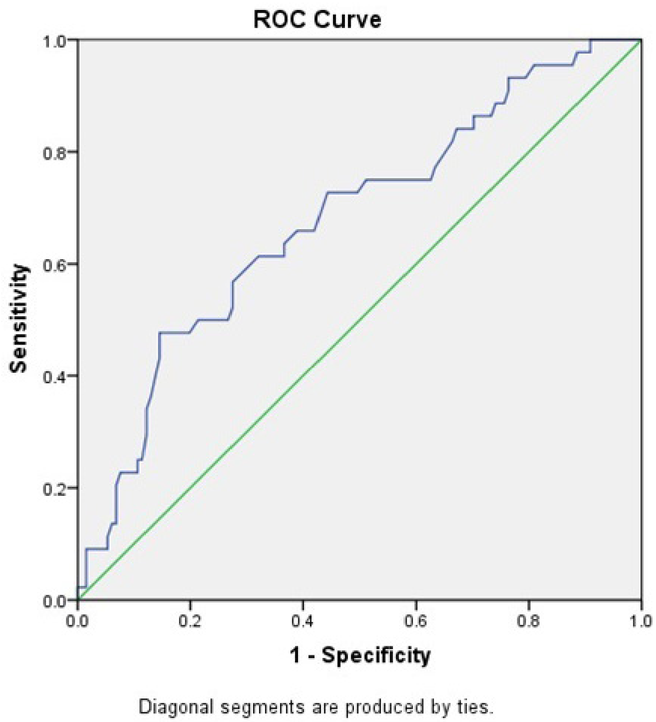

Figure 1: The ROC curve of Preop ALB for postoperative hypoalbuminemia after LH.

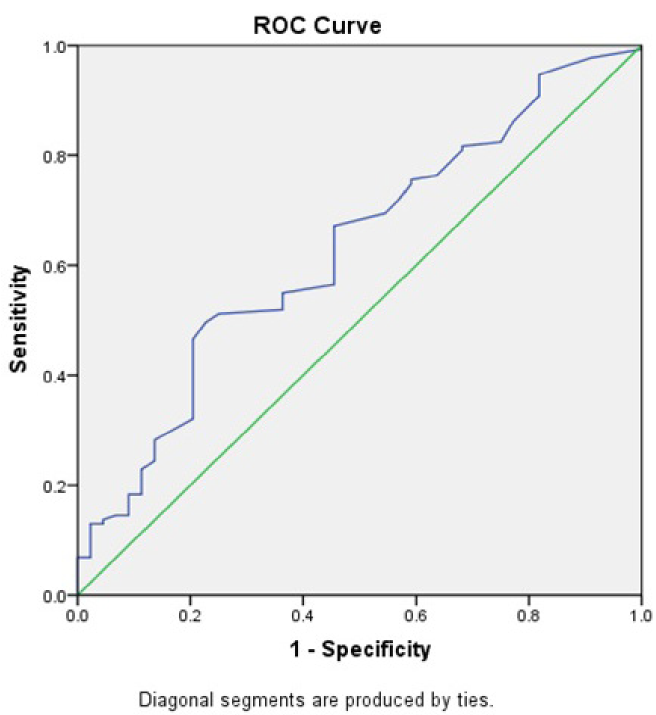

Figure 2: The ROC curve of Preop ALT for postoperative hypoalbuminemia after LH.

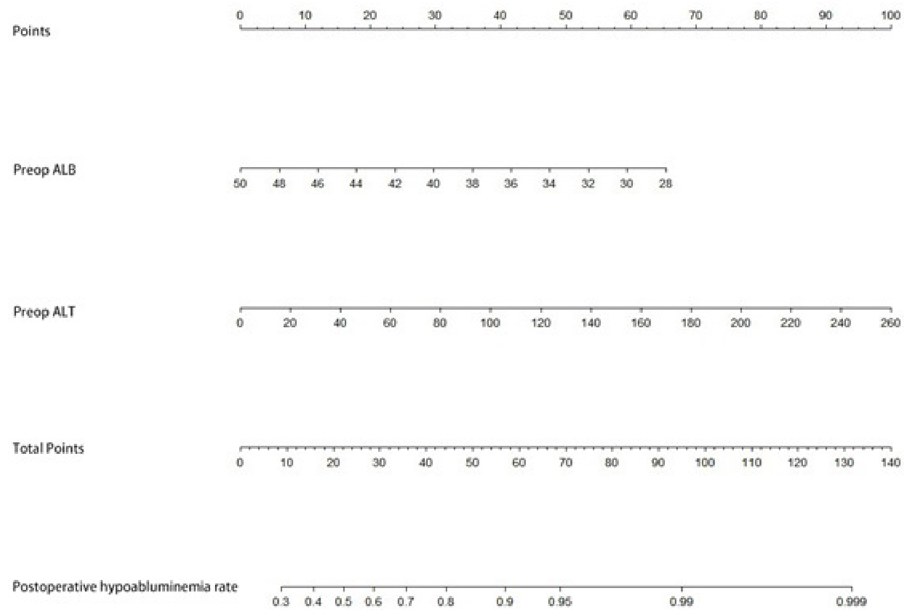

Figure 3: Nomogram.

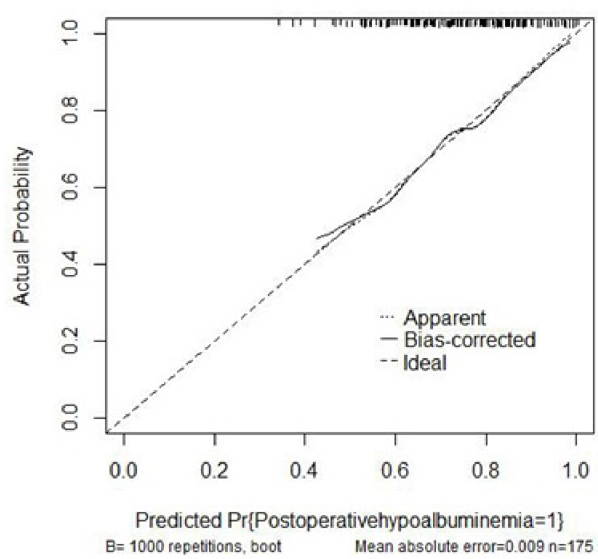

Figure 4: Calibration plots.

5. Discussion

Postoperative hypoalbuminemia is a common complication after various surgeries [4, 16-20], and it is associated with poor outcome in patients undergoing major surgery [18, 19, 21, 22]. In this study, we reported that LH with less intravenous serum ALB supplement was still significantly associated with a lower incidence of postoperative hypoalbuminemia than OH, suggesting that LH was capable of preventing postoperative hypoalbuminemia. By analyzing the risk factors of hypoalbuminemia after LH, we identified Preop ALB levels as a independent preventive factor, and Preop AST, duration of surgery, and bleeding volume as independent risk factors for hypoalbuminemia after LH, indicating that patients with reduced ALB and elevated ALT levels were more likely to develop postoperative hypoalbuminemia.

Post-hepatectomy hypoalbuminemia is known to be attributed to the impaired ALB synthesis and abnormal loss of ALB. Animal experiments showed that the rate of liver ALB synthesis in rats after hepatectomy was significantly reduced [3]. ALB accounts for half of the protein production by the liver. After hepatectomy, the liver synthesizes a large amount of acute-phase protein, but the ALB synthesis is inhibited in the liver [23]. Intraoperative bleeding can cause ALB loss. In addition, patients after surgery are in a state of fast metabolism, with increased consumption of protein and negative nitrogen balance, which also contribute to hypoalbuminemia [24]. Increase of the transcapillary escape rate (TER) can also increase the loss of ALB. Surgery is known to induce systemic inflammatory response syndrome (SIRS) [25]. Inflammatory factors can lead to increase vascular permeability and eventually increase he TER, such as tumor necrosis factor (TNF), interleukin 6 (IL-6), arachidonic acid metabolites [26, 27]. Although LH has been previously reported to stabilize the serum ALB levels after surgery, the mechanism by which LH prevents hypoalbuminemia is still unclear. Previous studies have shown that laparoscopic surgery alleviated the SIRS by reducing the local and systemic production of cytokines and acute-phase reactants, thus reduced the TER or promoted ALB synthesis [26, 27]. Moreover, LH with less intraoperative bleeding and liver tissue injury might also reduce ALB lost and alleviated liver dysfunction to promote ALB synthesis [28]. Altogether, LH with a less invasive technique can prevent hypoalbuminemia through multiple mechanisms.

The effects of LH with different resection range on posthepatectomy hypoalbuminemia has not yet been well studied. We performed stratified analysis according to the liver resection range, our data demonstrated that LH significantly improved postoperative serum ALB levels and reduced incidence of posthepatectomy hypoalbuminemia in non-hemihepatectomy patients. This result suggested that LH mainly prevented posthepatectomy hypoalbuminemia in patients who received partial hepatectomy with resection range less than hemihepatectomy. It was also reported that the duration of surgery was longer in laparoscopic hemihepatectomy than that in open hemihepatectomy, which might exaggerate systemic inflammatory response to worsen posthepatectomy hypoalbuminemia [29 -31]. However, the duration of surgery was not significantly different between the LH group and OH group in our study. Importantly, resection range of hepatectomy is a critical factor associated with post-hepatectomy liver dysfunction [32], including the function of producing ALB. The residual liver function is related to residual liver volume was reported in patients who received hepatectomy [32, 33]. Although LH has been reported to prevent system inflammation and local injury [26, 27], LH might not be sufficient to reduce the TER or promote the recovery of ALB production in regenerating liver after hemihepatectomy because of the more severe surgical trauma and longer duration of surgery.

Intravenous ALB supplement is essential for the therapy of hypoalbuminemia [34]. Our data demonstrated that LH prevented posthepatectomy hypoalbuminemia with less ALB supplement, and the stratification analysis according to the supplement of ALB supplement further verified that LH prevented posthepatectomy hypoalbuminemia indeed regardless of ALB supplement. These results indicated that the preventive effect of LH on posthepatectomy hypoalbuminemia did not rely on ALB supplement, limiting ALB supplement could be recommended in patients received partial hepatectomy with normal liver function. However, the safety of LH without postoperative ALB supplement seeks further investigation. Importantly, hepatic dysfunction is a critical reason of posthepatectomy hypoalbuminemia [35]. We identified low Preop ALB levels and high Preop ALT levels as independent risk factors for postoperative hypoalbuminemia, which were also indicators of liver dysfunction. Therefore, intervention should be implemented for patients with risk factors of liver dysfunction to prevent hypoalbuminemia after LH.

Our study has certain limitations. Obviously, the data of some patients were lost after PSM and selected from a single center. The results need to be verified in a larger, multi-center study. Secondly, we did not consider the effect of postoperative parenteral nutritional support on serum albumin. Thirdly, our study was retrospective and might fail to control for unknown confounders.

In conclusion, LH was associated with a lower incidence of postoperative hypoalbuminemia, particularly in patients who received partial hepatectomy with resection range less than hemihepatectomy. Limiting intravenous ALB supplement could be proposed in patients received partial hepatectomy with normal liver function.

6. Financial Support

This work was supported by Guangdong Province Science and Technology Program (2020A1515011205) to KW and (2021A1515012146) to CJL, National Natural Science Foundation of China (82070642) to JZ.

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