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Original Article

Preoperative Prognostic Nutritional Index is a significant predictive factor for posthepatectomy bile leakage

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Backgrounds/Aims: It is known that preoperative nutritional status can influence patient outcomes after hepatectomy. Prognostic Nutritional Index (PNI) is a useful parameter to reflect patient outcomes undergoing gastro-intestinal surgery. The aim of this study was to retrospectively evaluate relationships of nutritional parameters, demographics, and surgical records with postoperative outcomes in a cohort study.
Methods: Curative hepatectomy was performed for 182 patients at the University of Miyazaki between 2015 and 2018. Each preoperative level of albumin, prealbumin, lymphocyte, total cholesterol, or the comprehensively calculated Onodera's PNI was examined as a nutritional parameter.
Results: The mean PNI was 39.6 ± 5.1, with PNI below 40 observed in 91 (50.0%) patients. Nutritional parameters were not different among patients with various liver diseases. Serum albumin or prealbumin level was significantly correlated with each hepatic parameter ($p < 0.01$). Prealbumin and total cholesterol levels were significantly correlated with postoperative prothrombin activity ($p < 0.05$). Albumin or prealbumin levels and PNI were significantly lower in patients with posthepatectomy complications, particularly bile leakage in comparison those without such complications ($p < 0.05$). Multiple logistic analysis showed that albumin level was an independent risk factor for complications after hepatectomy (risk ratio [RR]: 1.33) and that lymphocyte count was an independent risk factor for bile leakage (RR: 1.28) ($p < 0.05$). The cut-off level of albumin was approximately 3.8 mg/dL and that of lymphocyte count was 1,320/mm^3.
Conclusions: Preoperative PNI reflected perioperative liver functional status. It was a predictive parameter for postoperative complications, particularly biliary leakage.

Key Words: Prognostic Nutritional Index; Postoperative nutritional parameters; Hepatectomy; Postoperative complications

INTRODUCTION

Perioperative management and recent advances in surgical techniques in hepatectomy have improved patient outcomes [1]. Although the mortality rate in major hepatectomy has been remarkably decreased, postoperative morbidity rate is still high in comparison with other gastro-intestinal surgeries [2]. Patients with advanced stage liver malignancies sometimes have low nutritional status, which can influence post-treatment outcomes. Various Prognostic Nutritional Indexes (PNIs) have been proposed so far [3-6]. Among them, the Onodera's PNI has been likely to apply evaluating operative risk in the field of gastro-intestinal surgeries in Japan since 1984 [4]. Onodera's PNI less than 40 or 45 indicates the impaired patient status

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relating to postoperative complications [4,7-10]. However, clinical significance of this index in the field of hepatectomy, particularly posthepatectomy complications, has not been fully elucidated yet. We hypothesize that PNI is closely related to perioperative patient demographics or nutritional status, surgical records, and postoperative outcomes.

The aim of the present study was to determine the significance of PNI influencing patient outcomes after various hepatectomies in patients with liver malignancies. Relationships between nutritional parameters including PNI and clinico-pathological factors, surgical records and post-hepatectomy complications in 182 consecutively selected patients were examined at a single academic institute for 3 years between April 2015 and April 2018.

PATIENTS AND METHODS

Patients

Clinical records of 182 consecutively selected patients undergoing hepatic resections at the Division of Hepato-Biliary-Pancreas Surgery, Department of Surgery in the University of Miyazaki Faculty of Medicine between April 2015 and April 2018 were collected. All patients' in-hospital data were consecutively collected during this follow-up period. There were no patient selection or matching criteria. All patients were enrolled for the present study. The study design was approved by the ethics review board at our institution. Data were retrieved from both anesthetic and patient charts by our database. On the basis of the Declaration of Helsinki 2013, the study design was approved by the Ethics Committee of University of Miyazaki Faculty of Medicine (no. O-0569 on April 24, 2020). An informed consent was obtained by the opt-out procedure at the website of our institute for approximately one month after ethical approval according to the planning documents of the study. There was no financial support or conflict of interest regarding the present study.

Mean age for patients at the time of surgery was 66.2 ± 10.2 years (range, 24–85 years). There were 127 males and 55 females. Background diseases included alcoholic liver injury in 3 patients, chemotherapy associated hepatitis in 17, fatty liver injury in two, non-alcoholic steatohepatitis in six, chronic viral hepatitis in 30, liver cirrhosis in 20, icteric liver in 11, and normal in 93. Main diseases included hepatocellular carcinoma in 90 patients, intrahepatic cholangiocarcinoma in 12, extrahepatic cholangiocarcinoma in 12, metastatic liver carcinoma in 46, gall bladder carcinoma in 16, and benign liver diseases in six. There were 181 patients with Child-Pugh A and one with Child-Pugh B. Procedures performed included trisectionectomy or extended hemi-hepatectomy in eight patients, hemi-hepatectomy in 31, segmentectomy or sectionectomy in 50, and limited resection in 93. Thus, anatomical hepatectomy was performed for 89 (48.9%) patients in this series. Combined vascular resection was performed for eight patients and radical operation was achieved without leaving any residual tumor or diseases for all patients. All bile duct reconstructions were performed with hepaticojejunostomy.

Table 1. Laboratory data and complications in 182 patients

Variable	Number
Preoperative laboratory parameter	
Platelet count, $\times 10^4$/mL	20.2 ± 8.1
Prothrombin activity, % (n = 177)	92.9 ± 17.9
Albumin, g/dL	3.89 ± 0.41
Prealbumin, g/dL (n = 98)	21.8 ± 6.4
Total bilirubin, mg/dL	0.80 ± 0.46
Total cholesterol, mg/dL (n = 175)	179 ± 49
PNI	39.6 ± 5.1
PNI < 40	91 (50.0)
White blood cells, per mm^3	555 ± 1,746
Lymphocyte counts, per mm^3	1,571 ± 597
Lymphocyte ratio of the blood, %	29.4 ± 9.8
Functional liver parameter	
Indocyanine green retention rate at 15 min, %	11.7 ± 7.5
LHL15, %	92.2 ± 3.5
Serum hyaluronic acid, ng/mL (n = 154)	100.1 ± 114.7
Surgical record	
Blood loss, mL	886 ± 1,270
Transfusion, mL	302 ± 810
Transfusion, yes	37 (20.3)
Operation time (min)	397 ± 188
Transection time (min)[a]	43.4 ± 37.4
Postoperative impaired liver functional parameter[b]	
Total bilirubin, mg/dL	1.85 ± 1.44
Alanine aminotransferase, IU/L	329 ± 257
Prothrombin activity, %	63.1 ± 12.1
Platelet counts, per mm^3	13.4 ± 8.1
C-reactive protein, mg/dL	11.2 ± 5.0
Postoperative adverse events and outcome	
In-hospital mortality, yes/no	1 (0.5)/181
Total morbidity, yes/no	45 (24.7)/137
Hepatectomy-related complications, yes/no	28 (15.4)/154
Hepatic failure, yes/no	4 (2.2)/178
Intra-abdominal infection, yes/no	13 (7.1)/169
Uncontrolled ascites, yes/no	13 (7.1)/169
Bile leakage, yes/no	16 (8.8)/166
Hospital stay (day)	18.5 ± 19.2

Values are presented as mean ± standard deviation or number (%).
PNI, Onodera et al. [4]'s Prognostic Nutritional Index; LHL15, liver uptake ratio of 99m-technetium galactosyl serum albumin scintigraphy between 3 and 15 minutes.
[a]This data was equivalent to inflow occlusion time. [b]Within day 7 after hepatectomy.

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Operative indications, evaluated parameters, surgical procedures

The volume of the liver to be resected was determined preoperatively based on the indocyanine green retention rate at 15 minutes (ICGR15) using the formula of Takasaki et al. [11]. The estimated resected liver volume, excluding tumor volume (cm^3), was measured by computed tomography volumetry [12]. Essentially, for cases where the permitted resected volume of the liver calculated by Takasaki's formula was greater than the estimated resected volume of the liver, planned hepatectomy was scheduled. Liver uptake ratio of 99m-technetium galactosyl serum albumin scintigraphy between 3 and 15 minutes (LHL15) was complementarily performed preoperatively to define operative indications and evaluate functional hepatic volumes [13].

Investigated nutritional parameters included Onodera's PNI [4] (calculated using the formula of *10 × serum albumin value (g/dL) + 0.005 × total lymphocyte count in peripheral blood*, with PNI less than 40 indicating impaired nutrition [9]) and preoperative serum levels of albumin (g/dL), total cholesterol (mg/dL), prealbumin (g/dL), lymphocyte ratio, and actual lymphocyte counts (per mm^3) as nutritional parameters.

Compared parameters included clinicopathological parameters (age, sex, background liver disease, main liver diseases, and related parameters), laboratory data including conventional liver parameters, advanced liver functional reserve tests such as ICGR15 (%) and LHL15 [13]. Surgical records included transection time (minutes; equivalent to inflow occlusion time), blood loss (mL), existence of administration of allo-red cell blood transfusion, post-hepatectomy laboratory data, postoperative hepatectomy-related complications (hepatic failure, bile leakage, uncontrolled ascites or intraabdominal infection), and period of hospital stay (days). Correlations between nutritional parameters and other parameters or independent risk parameter associated with post-hepatectomy severe complications were analyzed.

Statistical analysis

Continuous data are expressed as a median value with range. Data for different groups were compared using one-way analysis of variance. Wilcoxon-test was used to compare two groups. A chi-squared test was used to compare categorical variables. Differences between groups were analyzed by Fisher exact test or Scheffé multiple comparison test. Correlations between two parameters were examined by calculating Pearson correlation coefficient. In addition, 95% confidence intervals were calculated for each correlation. The cut-off value was calculated by the area under the receiver operating characteristics (AUROC) analysis. The odds ratio was calculated by multivariate logistic analysis. A two-tailed p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences software, version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient's laboratory data, surgical records, and outcomes

Table 1 summarizes all clinical data in 182 patients. Mean Onodera's PNI was 39.6 ± 5.1, with 91 patients (50.0%) having PNI less than 40 indicating impaired preoperative nutritional status. Mean blood loss was 886 mL (range: 10–9,850 mL). Transfusion was performed in 20.3% of patients.

In the patient outcomes, in-hospital mortality rate was 0.5%, morbidity rate was 24.7% and hepatectomy related complication rate was 15.4%, respectively. In hepatectomy-related complications, rate of hepatic failure was 2.2%, intra-abdominal infection in 7.1%, uncontrolled ascites in 7.1%, and bile leakage in 8.8%, respectively. The mean duration of hospital stay was 18.5 days (range: 5–135 days).

Compared nutritional parameters with other clinical features

Correlation in each nutritional parameter is shown in Table 2. Serum albumin level was significantly correlated with prealbumin level, lymphocyte ratio, actual counts of lymphocytes, and PNI (all $p < 0.01$). Prealbumin level was significantly correlated with albumin, leukocyte ratio, lymphocyte counts, and PNI (all $p < 0.05$). Total cholesterol level was significantly correlated with PNI ($p < 0.05$). The lymphocyte ratio was significantly correlated with prealbumin level and lymphocyte actual count (both $p < 0.05$). The lymphocyte count was significantly correlated with other all parameters (all $p < 0.05$). The PNI was

Table 2. Relationship between each nutritional parameters

Nutritional parameter	Albumin	Prealbumin	Total cholesterol	LN rate	LN counts	PNI
Albumin (g/dL)	-	0.577**	0.125	0.128	0.255**	0.997**
Prealbumin	0.577**	-	0.124	0.224*	0.232*	0.582**
Total cholesterol (mg/dL)	0.125	0.124	-	–0.092	0.232*	0.182*
LN rate (%)	0.128	0.224*	–0.092	-	0.648**	0.120
LN counts (per mm^3)	0.255**	0.232*	–0.023	0.648**	-	0.251**
PNI	0.997**	0.582**	0.182*	0.120	0.251**	-

LN, lymphocyte; PNI, Onodera et al. [4]'s Prognostic Nutritional Index; -, not available.
Statistically significant (* $p < 0.05$, ** $p < 0.01$).

Table 3. Relationship between PNI and clinico-pathological parameters

Variable	Albumin	Prealbumin	TC	LN%	LNC	PNI	PNI < 40/≥ 40[a]
Age	−0.243**	−0.218*	−0.106	−0.013	−0.152*	−0.249**	68.5 ± 9.1/ 63.9 ±10.9**
Sex							
Male (n = 127)	4.0 ± 0.4	22.9 ± 5.6	179 ± 39	29 ± 10	1569 ± 566	40.0 ± 5.5	57/70 (56)
Female (n = 55)	3.8 ± 0.4*	20.0 ± 7.3	199 ± 63**	31 ± 11	1578 ± 668	38.9 ± 4.1	34/21 (48)
Disease							
HCC (n = 90)	3.9 ± 0.4	19.8 ± 5.7	165 ± 31	31 ± 10	1645 ± 654	39.6 ± 6.0	47/43
ICC (n = 12)	3.8 ± 0.4	23.9 ± 5.2	177 ± 34	29 ± 10	1532 ± 510	38.6 ± 3.5	8/4
Liver metastasis (n = 46)	3.9 ± 0.4	23.5 ± 5.4	199 ± 64	27 ± 9	1554 ± 494	39.8 ± 4.5	20/26
ECC (n = 12)	3.7 ± 0.4	17.2 ± 5.3	197 ± 94	25 ± 13	1298 ± 680	38.2 ± 4.0	8/4
GBC (n = 16)	4.0 ± 0.4	25.8 ± 8.0	187 ± 26	28 ± 10	1382 ± 384	40.4 ± 3.5	7/9
Other (n = 6)	4.0 ± 0.4	22.8 ± 10.5	186 ± 31	29 ± 10	1664 ± 774	41.5 ± 4.9	1/5
Liver functional parameter							-
ICGR15	−0.296**	−0.335**	−0.203**	0.181*	−0.078	−0.339**	
LHL15	0.184**	0.204*	−0.226**	−0.225**	−0.020	0.197**	
Prothrombin activity (%)	0.133	0.213*	0.305**	−0.009	0.068	0.159*	
Total bilirubin (mg/dL)	0.090	0.090	0.037	0.043	−0.100	0.093	
Hyaluronic acid (ng/mL)	−0.340**	0.212*	−0.088	0.086	−0.080	−0.399**	
Surgical record							
Extent of hepatectomy							
Major (n = 31)	3.7 ± 0.4	18.9 ± 6.7	188 ± 74	26 ± 11	1429 ± 562	38.0 ± 4.0	30/12
Minor (n = 143)	4.0 ± 0.4	22.6 ± 6.2	176 ± 38	31 ± 9	1620 ± 607	40.2 ± 5.4	58/78
Transection time	0.085	−0.162	0.010	0.021	0.027	0.092	-
Operation time (min)	−0.139	−0.171	0.159	−0.204	−0.085	−0.057	-
Blood loss (mL)	−0.122	−0.080	0.026	−0.120	−0.172*	−0.097	-
Transfusion	−0.091	−0.068	0.024	−0.127	−0.170*	−0.085	-
No	3.9 ± 0.4	22.3 ± 6.3	177 ± 43	31 ± 10	1644 ± 604	40.2 ± 4.0	
Yes (n = 37)	3.8 ± 0.5*	19.7 ± 6.5	189 ± 68	26 ± 10*	1329 ± 540**	37.6 ± 7.9	
Postoperative function[b]							-
Total bilirubin	−0.055	−0.003	−0.063	0.083	−0.028	−0.026	
Alanine aminotransferase	0.013	0.043	0.077	−0.125	0.041	0.032	
Prothrombin activity	0.133	0.277**	0.178*	−0.024	−0.015	−0.014	
Platelet	0.056	0.119	0.087	−0.130	−0.069	0.057	
C-reactive protein	0.020	−0.007	0.083	−0.061	0.090	0.032	
Postoperative coarse							
Total complication							
No	4.0 ± 0.4	22.9 ± 6.3	177 ± 40	31 ± 9	1,612 ± 545	40.1 ± 5.4	59/72 (55)
Yes (n = 45)	3.8 ± 0.4**	19.1 ± 6.2**	187 ± 68	28 ± 12	1,480 ± 740	38.5 ± 4.2*	28/17 (38)
HT-related complication							
No	4.0 ± 0.4	22.7 ± 6.3	177 ± 39	30 ± 10	1,597 ± 606	40.1 ± 5.3	66/82 (75)
Yes (n = 28)	3.7 ± 0.4**	17.4 ± 4.8**	189 ± 84	27 ± 10	1,482 ± 581	37.7 ± 4.0**	21/7 (46)**
Liver failure							
No	3.9 ± 0.4	21.9 ± 6.4	180 ± 49	30 ± 10	1,590 ± 600	39.4 ± 5.3	84/88
Yes (n = 4)	3.7 ± 0.3	18.5 ± 6.8	148 ± 37	24 ± 6	1,063 ± 490	38.9 ± 6.0	3/1
Intra-abdominal infection							
No	3.9 ± 0.4	22.0 ± 6.5	178 ± 46	30 ± 10	1,589 ± 596	39.8 ± 5.2	79/84
Yes (n = 13)	3.8 ± 0.4	19.4±5.5	197 ± 75	30 ± 12	1,452 ± 686	38.7 ± 4.3	8/5
Ascites							
No	3.9 ± 0.4	21.8 ± 6.6	180 ± 50	30 ± 10	1,567 ± 606	39.7 ± 5.2	78/85
Yes (n = 13)	3.8 ± 0.4	20.8 ± 1.4	164 ± 33	29 ± 13	1,718 ± 548	38.9 ± 3.8	9/4

Table 3. Continued

Variable	Albumin	Prealbumin	TC	LN%	LNC	PNI	PNI < 40/≥ 40
Bile leak							
No	3.9 ± 0.4	22.4 ± 6.2	175 ± 39	30 ± 10	1,598 ± 597	39.9 ± 5.2	76/84
Yes (n = 16)	3.6 ± 0.5*	16.7 ± 6.0*	215 ± 99	24 ± 11	1,386 ± 636	37.5 ± 4.4*	11/5
Hospital stay (day)	−0.194*	−0.267**	−0.098	−0.131	−0.123	−0.155*	

Values are presented as the mean ± standard deviation. Correlation was indicated as r by Pearson co-efficiency test. Categorical data were examined by chi-squared test. Major hepatectomy included hemihepatectomy or more extended hepatectomy, minor included others.
PNI, Onodera et al. [4]'s Prognostic Nutritional Index; TC, total cholesterol; LN%, lymphocyte rate; LNC, lymphocyte counts; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; GBC, gall bladder carcinoma; ICGR15, indocyanine green retention rate at 15 minutes; LHL15, liver uptake ratio of 99m-technetium galactosyl serum albumin scintigraphy between 3 and 15 minutes; HT, hepatectomy; -, not available.
Statistically significant (*$p < 0.05$, **$p < 0.01$).
[a]Parenthesis showed the prevalence of PNI over 40. [b]Maximum or minimum value within 7 days after hepatectomy.

significantly correlated with most of other parameters ($p < 0.05$), but not with lymphocyte ratio.

Correlations of nutritional parameters with other preoperative clinical or hepatic parameters, surgical records, postoperative liver functions, and postoperative outcomes are shown in Table 3. Among nutritional parameters, serum albumin and prealbumin levels, and lymphocyte counts showed significant negative correlations with increased patient age ($p < 0.05$). Total cholesterol level was significantly higher in females than in males ($p < 0.01$). Nutritional parameters were not significantly associated with liver diseases. Serum albumin level was significantly lower in patients with liver damage grade B than in those with grade A ($p < 0.01$). Serum albumin level showed significant positive correlation with LHL15 and significant negative correlations with ICGR15 and hyaluronic acid level (all $p < 0.01$). The prealbumin level was significantly correlated with ICGR15, prothrombin activity, and hyaluronic acid level (all $p < 0.05$). The total cholesterol level was significantly correlated with ICGR15, LHL15, and prothrombin activity (all $p < 0.01$). The lymphocyte ratio was significantly correlated with LHL15 ($p < 0.01$). Albumin and prealbumin levels were significantly higher in patients undergoing minor hepatectomy than those undergoing major hepatectomy ($p < 0.05$). The lymphocyte count showed significant negative correlations with blood loss and related blood cell transfusion ($p < 0.05$). Prealbumin and total cholesterol levels were significantly correlated with postoperative prothrombin activity (both $p < 0.05$). Albumin and prealbumin levels were significantly lower in patients with postoperative complications or hepatectomy related complications than in those without such complications ($p < 0.01$). Among all complication, these levels were significantly lower in patients with bile leakage than in those without ($p < 0.05$). Albumin and prealbumin levels were negatively correlated with hospital stay period ($p < 0.05$).

Relationship with Prognostic Nutritional Index

Correlations of PNI with clinical factors, laboratory data, surgical records, and patient outcomes are shown in Table 3. PNI was negatively correlated with ICGR15, LHL15, prothrombin activity, and hyaluronic acid (all $p < 0.01$). PNI was not correlated with surgical records or postoperative liver functions. PNI was significantly lower in patients with hepatectomy related complication, particularly bile leakage ($p < 0.05$). PNI also showed significant negative correlation with postoperative hospital stay period ($p < 0.05$).

Predictive risk of postoperative complications

To avoid confounding influences, the PNI was not included in the predictive risk analysis of relationship between nutritional or liver functional parameters and postoperative complications (Table 4). The albumin level was an independent risk factor of total complications and hepatectomy related complications (Table 4, risk ratio: 1.33 and 1.28, respectively; $p < 0.05$). The lymphocyte count was a significantly independent risk factor for bile leakage (risk ratio: 1.19; $p < 0.05$). AUROC analysis showed that cut-off levels of albumin for total complications and hepatectomy related complications were 3.88 and 3.84 mg/dL, respectively. The cut-off level of lymphocyte counts for bile leakage was 1,320/mm^3.

DISCUSSION

Preoperative poor nutritional status is related to operative risk. For example, it can increase morbidity rate in digestive surgeries [14,15]. Therefore, we attempted to improve nutritional status of patients by monitoring nutritional parameters. Comprehensive indices or parameters for evaluating nutrition or predicting operative risks have been reported worldwide [3-10,16]. In these indices, PNI was proposed by Lowe et al. [3] first. Subsequently, Onodera et al. [4] proposed the modified PNI in Japanese patient series. These reports showed that PNI less than 40 indicated impaired nutritional status associated with postoperative morbidities [9]. Major hepatectomy, particularly when it is combined with vascular or biliary reconstruc-

Table 4. Risk ratio of nutritional and liver functional for postoperative morbidities calculated by the multiple variable logistic analysis

Model	Non-standardization factor		Standardization coefficient	t-value	Significance probability (*p*-value)	Risk ratio	95% confidence interval	
	B	SE	β				Lower-limit	Upper-limit
Total postoperative complications								
(Constant)	0.212	0.073	-	2.894	0.005*	-	0.066	0.358
Age	–0.069	0.122	–0.076	–0.569	0.571	0.93	–0.312	0.174
Prealbumin	–0.015	0.139	–0.015	–0.105	0.917	0.99	–0.293	0.264
Albumin	0.288	0.130	0.297	2.208	0.031*	1.33	0.028	0.548
ICGR15	–0.008	0.219	–0.006	–0.036	0.971	0.99	–0.445	0.429
LHL15	–0.055	0.213	–0.047	–0.256	0.799	0.95	–0.480	0.370
Prothrombin activity	0.181	0.276	0.082	0.658	0.513	1.20	–0.369	0.732
Hyaluronic acid	0.231	0.227	0.132	1.017	0.313	1.26	–0.222	0.684
Hepatectomy related postoperative complications								
(Constant)	0.120	0.056	-	2.131	0.037*	-	0.008	0.232
Age	–0.030	0.094	–0.041	–0.316	0.753	0.97	–0.217	0.157
Prealbumin	–0.046	0.107	–0.059	–0.433	0.666	0.96	–0.261	0.168
Albumin	0.245	0.100	0.324	2.443	0.017*	1.28	0.045	0.445
ICGR15	–0.014	0.169	–0.015	–0.083	0.934	0.99	–0.350	0.323
LHL15	–0.060	0.164	–0.067	–0.368	0.714	0.94	–0.387	0.267
Prothrombin activity	–0.110	0.109	–0.143	–1.006	0.318	0.90	–0.328	0.108
Hyaluronic acid	–0.053	0.212	–0.031	–0.252	0.802	0.95	–0.477	0.370
Bile leakage								
(Constant)	0.032	0.041	-	0.788	0.433	-	–0.049	0.114
Age	–0.087	0.067	–0.139	–1.300	0.197	0.92	–0.220	0.046
Prealbumin	0.136	0.079	0.196	1.727	0.087	1.15	–0.020	0.293
Albumin	0.092	0.075	0.139	1.226	0.223	1.10	–0.057	0.240
Lymphatic counts	0.171	0.071	0.239	2.422	0.017*	1.19	0.031	0.312

SE, standard error; ICGR15, indocyanine green retention rate at 15 minutes; LHL15, liver uptake ratio of 99m-technetium galactosylserum albumin scintigraphy between 3 and 15 minutes; -, not available.
*Statistically significant (p<0.05).

tion, has a higher risk of severe postoperative morbidity and mortality than gastrectomy or colectomy because of its more invasiveness [17]. The relationship between nutritional status or its management and postoperative outcomes after major hepatectomy has not been fully examined yet to the best of our knowledge. PNI could be calculated with a simple formula using albumin and total lymphocyte counts [4]. Alteration of nutritional status, and PNI are associated with postoperative complications and administrative costs [18,19]. Recently, controlling nutrional status (CONUT) score using albumin level and total cholesterol level has also been found to be useful for evaluating postoperative status [7]. However, categorical score seems to be difficult to analyze. Accomplished scoring system reflecting clinical significance has not been reported yet. To achieve successful results for such patients, preoperative nutritional managements are often required.

In this study, the mean PNI of patients was close to 40. Other nutritional parameters including serum albumin level were maintained in their normal levels. Therefore, many patients had a good nutritional status in comparison with those who underwent pancreatectomy or esophagectomy [4,6,14,18]. White blood cells or lymphocytes were examined in the status of released inflammation or biliary obstruction in case of biliary diseases just before hepatectomy. Surgical and posthepatectomy results were compabale with results of other reports [20,21]. Prealbumin is precisely reflected the present nutritional status in comparison with serum albumin level [22]. Both levels were well correlated with the ratio and actual counts of peripheral lymphocytes. These results suggest that lymphocyte level might reflect not only immunological status, but also the host's nutrition status.

In the present results, nutritional parameters showed lower levels in the elderly and female patients. However, they showed no differences between those with different liver diseases. Previous reports have shown that posthepatectomy outcomes in male patients are relatively worse [23]. Recently, major hepa-

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tectomy is accepted for selected elderly patients. With respect to relationship with liver functional parameters, the presently selected nutritional parameters except lymphocyte counts were well correlated with liver functional parameters as well as previous reports [24,25]. The comprehensive index of PNI was also correlated with reliable liver functional parameters. Therefore, such a scoring index can be also applied as a liver functional reserve as well.

With respect to surgical records, only lymphocyte count was correlated with blood loss and related transfusion in this study. However, predictive factors of increased blood loss might be reflected by background liver texture, hemodynamics, liver dysfunction, and operative invasiveness [26]. Therefore, lymphocyte count was supposed to be a reference parameter at this stage. Most nutritional parameters might not be associated with postoperative liver functions. While nutritional parameters and PNI, and the low PNI (<40) were associated with bile leakage in this study. This result is relatively optimal and reasonable because bile leakage maybe associated with wound healing process related to nutritional status [27]. In 16 patients showing significant bile leakage after hepatectomy, hepaticojejunostomy was performed only in two. Therefore, bile leakage mostly occurred at the peripheral transection-plane of the hepatic parenchyma. Considering wound healing, more careful ligation or closing of the entire biliary system during hepatectomy should be accomplished regardless of the existence of intestinal anastomosis in patients with low PNI. Although liver functional complication might not be influenced by the preoperative nutritional status, the comprehensive PNI might reflect wound healing in hepatectomy. In the contributed degree to PNI, serum albumin level was the mostly correlated with PNI (r = 0.997) and an independent risk parameter of postoperative complications in our results. In patients with sarcopenia, preoperative nutritional intervention or prehabilitation improving nutritional status may improve prevalence of postoperative complications [28]. In logistic analysis, lymphocyte count showed more association with risk of bile leak than albumin level. Wound healing mechanism with lymphocyte has been reported previously [29]. Immunological inducing agents are expected in the future [30]. Results of this study suggest that albumin level lower than 3.8 g/dL or lymphocyte count less than 1,300/mm^3 could predict the occurrence of posthepatectomy complications. As shown in Table 3, increased blood loss and related allo-blood transfusion were both negatively correlated with lymphocyte counts. The immunological impairment or stress is supposed to be a cause of biliary healing. Comprehensively, preoperative PNI less than 39 was a useful index to realize as the novel PNI for hepatectomy. However, the limitation of the present study was that the basic role or mechanism of each parameter of Onodera's PNI in each complication was still unclear, although this comprehensive index is widely used to enhance postoperatively poor results in previous studies [3-6]. This nutritional or immunological mechanism must be elucidated by future basic or clinical research. In addition, a larger size of cohort is needed to have adequate statistical power to address limitations of this study.

In conclusion, we examined preoperative nutritional parameters and PNI as well as their relationships with patient demographics, perioperative liver functions, surgical records and postoperative complications in a retrospective analysis using clinical records of 182 patients who underwent elective hepatectomy for various liver diseases at an academic cancer institute. Albumin or prealbumin level, total cholesterol, and lymphocyte level were useful for predicting posthepatectomy bile leakage complication. The comprehensive PNI was also useful for predicting morbidity.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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