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ORIGINAL ARTICLE

Preoperative HALP score is a prognostic factor for intrahepatic cholangiocarcinoma patients undergoing curative hepatic resection: association with sarcopenia and immune microenvironment

Katsuya Toshida[1] · Shinji Itoh[1] · Yuki Nakayama[1] · Yuriko Tsutsui[1] · Yukiko Kosai-Fujimoto[1] · Takahiro Tomino[1] · Shohei Yoshiya[1] · Yoshihiro Nagao[1] · Noboru Harada[1] · Kenichi Kohashi[2] · Yoshinao Oda[2] · Tomoharu Yoshizumi[1]

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Abstract

Background The hemoglobin–albumin–lymphocyte–platelet (HALP) score is a combination index that assesses nutritional status and systemic inflammatory response and is reported to predict prognosis in several cancer types. However, researches about the usefulness of the HALP score in intrahepatic cholangiocarcinoma (ICC) are limited.

Methods This was a single-center, retrospective study of 95 patients who underwent surgical resection for ICC between 1998 and 2018. We divided patients into two groups by calculating the cutoff value of the HALP score and examined clinicopathological characteristics, prognosis, and sarcopenia. Tumor-infiltrating lymphocytes (TILs), CD8 + TILs, and FOXP3 + TILs were evaluated by immunohistochemical staining of resected tumors.

Results Of 95 patients, 22 were HALP-low. The HALP-low group had significantly lower hemoglobin ($p = 0.0007$), lower albumin ($p = 0.0013$), higher platelet counts ($p < 0.0001$), fewer lymphocytes ($p < 0.0001$), higher CA19-9 levels ($p = 0.0431$), and more lymph node metastasis ($p = 0.0013$). Multivariate analysis revealed that the independent prognostic factors for disease-free survival were maximum tumor size (≥ 5.0 cm) ($p = 0.0033$), microvascular invasion ($p = 0.0108$), and HALP score (≤ 25.2) ($p = 0.0349$), and that factors for overall survival were lymph node metastasis ($p = 0.0020$) and HALP score (≤ 25.2) ($p = 0.0014$). The HALP-low group contained significantly more patients with sarcopenia ($p = 0.0015$). Immunohistochemistry showed that counts of CD8 + TILs were significantly lower in the HALP-low group ($p = 0.0075$).

Conclusions We demonstrated that low HALP score is an independent prognostic factor for ICC patients undergoing curative hepatic resection and is associated with sarcopenia and the immune microenvironment.

Keywords Hemoglobin, albumin, lymphocyte, and platelet (HALP) score · Intrahepatic cholangiocarcinoma · Immune microenvironment · Sarcopenia

Abbreviations

CA19-9	Carbohydrate antigen 19-9
CEA	Carcinoembryonic antigen
CI	Confidence interval
CT	Computed tomography
DFS	Disease-free survival
γ-GTP	γ-Glutamyl transpeptidase
HALP	Hemoglobin, albumin, lymphocyte and platelet
HR	Hazard ratio
HBV-Ag	Hepatitis B surface-antigen
HCV-Ab	Hepatitis C virus-antibody
ICC	Intrahepatic cholangiocarcinoma
OS	Overall survival
PLR	Platelet-to-lymphocyte ratio
PNI	Prognostic nutritional index
ROC	Receiver operating characteristic
SMI	Skeletal muscle mass index
TILs	Tumor-infiltrating lymphocytes

✉ Shinji Itoh
itoh.shinji.453@m.kyushu-u.ac.jp

[1] Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1, Maidashi, Fukuoka 812-8582, Japan

[2] Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary hepatic malignancy after hepatocellular carcinoma, with a high rate of advanced disease at initial presentation, and the number of cases is increasing worldwide [1]. Surgical resection is the only potentially curative treatment, but many patients develop recurrence [2, 3]. In addition, systemic therapy is performed in locally advanced or metastatic cases, but there are few regimens available and the response rate remains low [4, 5].

Systemic inflammatory response and nutritional status are recognized as hallmarks to predict the tumor microenvironment or prognosis, and the impact of preoperative immunonutritional status on surgical outcomes has been explored in ICC [6–8]. Recently, the index calculated by hemoglobin–albumin–lymphocyte–platelet (HALP) levels, the HALP score, has been demonstrated as an indicator of nutritional status and systemic inflammation, and its predictions are vital to survival in several cancer types [9, 10]. Zhang D, et al. reported the prognostic role of the HALP score in ICC patients, but research focusing on the association between HALP score and systemic status or tumor microenvironment is lacking [11]. The aim of the present study was to demonstrate the prognostic effect of the HALP score as a biomarker in ICC patients undergoing curative hepatic resection and its association with sarcopenia and the immune microenvironment.

Materials and methods

Patients and specimen preparation

This retrospective study was approved by the ethics committee of Kyushu University Hospital (approval code: 2021–467), which was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients. We retrospectively selected 95 patients who had undergone hepatic resection for primary ICC without preoperative treatment. We conducted this study by reviewing their medical records from May 1993 to November 2019 at Kyushu University Hospital, Japan. When distant metastases, tumor dissemination, and/or multiple tumors in the bilateral hepatic lobes were present, patients were considered to have unresectable tumors. The details of surgical procedure for hepatic resection have been described previously [12, 13]. Major hepatic resection with bile duct resection was performed when bile duct invasion by ICC was suspected to affect the first branch of the hepatic duct. Partial hepatic resection was performed in patients with peripheral ICC. If the surgical margin was suspected to be infiltrated by carcinoma cells, the resected stump was sent to the pathology department for frozen sectioning. Lymph node dissection was performed if lymph node metastasis was suspected on preoperative abdominal computed tomography or during surgery. Lymph node dissection was performed within the hepatoduodenal mesentery, around the common hepatic artery, and the posterior pancreatic head lymph node. The specimens were fixed in 10% formalin solution, embedded in paraffin, and sectioned into 4-μm-thick slices to evaluate the histological characteristics.

Data collection of clinicopathological characteristics

Data of patients' clinicopathological factors (age, sex, hepatitis B surface-antigen positivity, hepatitis C virus-antibody positivity, γ-glutamyl transpeptidase, albumin, platelet count, carcinoembryonic antigen, carbohydrate antigen 19–9 (CA19-9), maximum tumor size, tumor localization, poor differentiation, microvascular invasion, intrahepatic metastasis, lymph node metastasis, and histological liver cirrhosis) and perioperative factors (laparoscopic surgery, blood transfusion during surgery, blood loss, duration of surgery and postoperative adjuvant chemotherapy) were recorded. The HALP score was calculated as follows, hemoglobin (g/L) × albumin (g/L) × lymphocytes (/L)) / platelets (/L) [9]. PNI (prognostic nutritional index) and PLR (platelet-to-lymphocyte ratio) were calculated as follows, PNI: 10 × serum albumin (g/dL) + 0.005 × lymphocytes (cells/mm^3) and PLR: platelets (/L) / lymphocytes (/L), [14].

Evaluation of sarcopenia

We calculated the skeletal muscle mass index (SMI) by dividing skeletal muscle mass at lumbar vertebral body 3 (cm^2) by the square of the height (cm^2/m^2) using abdominal preoperative computed tomography (CT). The cutoff values were based on the Japan Society of Hepatology guidelines for sarcopenia in liver disease, defined as an SMI < 42 cm^2/m^2 and < 38 cm^2/m^2 in men and women, respectively [15].

Follow-up strategy

After the discharge, we performed screening for recurrence by abdominal CT and tumor markers every 3 months. If

we suspected recurrence, we performed magnetic resonance imaging and diagnosed the presence or absence of recurrence. We defined overall survival (OS) as death from any cause and disease-free survival (DFS) as first recurrence after hepatic resection.

Histological evaluation of tumor-infiltrating lymphocytes (TILs)

We stained sections with hematoxylin and eosin. The number of TILs was assessed using standardized methods for TILs analysis in solid tumors [16]. All sections obtained from each patient were reviewed using light microscopy (200 × magnification, 20 × objective lens and 10 × ocular lens; 0.950 mm^2 per field) by three independent observers (S.I., K.Y., and K.K.) who were blinded to the clinical data. If TILs counted by the three observers differed by more than 10%, the sections were reevaluated. The average of the counts was used as the final TIL count.

Immunohistochemistry (IHC)

IHC was performed as previously described [17, 18]. Formalin-fixed, paraffin-embedded tissue sections from patients with ICC were stained with mouse monoclonal anti-CD8 antibody (Clone C8/144B; Agilent Technologies, Santa Clara, CA, USA) and mouse monoclonal anti-FOXP3 antibody (236A/E7; Abcam, Cambridge, UK). Average CD8 + and FOXP3 + TIL counts were calculated for the five areas with the highest density of staining in the intratumoral area under light microscopy (×400 magnification). The capture of microscopic images and quantitative analyses was undertaken on the NanoZoomer platform (Hamamatsu Photonics), and immunohistochemical evaluations were performed independently by three independent observers (K.T., S.I., and K.K.) blinded to the clinical data.

Statistical analyses

All statistical analyses were performed using SAS software (JMP Pro 16; SAS Institute Inc.). The Shapiro–Wilk test was used to assess whether continuous variables were normally distributed. Continuous variables were presented as the median and were compared using the Mann–Whitney U test. Categorical variables were reported as percentages and compared using the χ^2 test or Fisher's exact test. Cumulative DFS and OS rates were calculated using the Kaplan–Meier method, and differences between the curves were evaluated using the log-rank test. Survival data were used to establish a univariate Cox proportional hazards model. Cut-off values for the HALP score were determined by receiver operating characteristic (ROC) curves 5 years after surgery for OS. Covariates that were significant at $p < 0.05$ were included in the multivariate Cox proportional hazards model.

Results

Patients characteristics

Of 95 patients who underwent curative hepatic resection for ICC in present study, 63 patients were male (66.3%), and the median age of the patients was 66 years (range, 33–87 years). The best cutoff point for the HALP score was 25.2, although the area under the ROC curve (AUC) was of limited value (0.63) (Supp Fig. 1). We divided ICC patients into two groups (HALP-high/low) according to this cutoff value. Clinicopathological characteristics of ICC patients with HALP-high and -low are shown in Table 1. The HALP-low group had significantly lower albumin ($p = 0.0004$), lower hemoglobin ($p = 0.0007$), higher platelet counts ($p < 0.0001$), fewer lymphocytes ($p < 0.0001$), higher CA19-9 levels ($p = 0.0431$), more lymph node metastasis ($p = 0.0013$), more blood loss ($p = 0.0447$) and more blood transfusion ($p = 0.0095$).

Univariate survival analysis of ICC patients according to the HALP score

We assessed the association between the HALP score and postoperative survival after curative hepatic resection using the Kaplan–Meier method (Fig. 1A, B). Kaplan–Meier analysis showed a trend toward significantly impaired DFS ($p = 0.0116$) and OS ($p = 0.0070$) in the HALP-low group. Median DFS was 1.74 years (95% confidence interval (CI) 1.03–9.12) in the HALP-high group and 0.68 years (95% CI 0.36–0.98) in the HALP-low group. Median OS was 4.29 years (range, 2.43–5.49) in the HALP-high group and 1.08 years (95% CI 0.56–1.61) in the HALP-low group.

Risk factors associated with DFS and OS

Table 2 lists the univariate and multivariate analyses results associated with DFS in patients with ICC after curative hepatic resection. Univariate analysis of the association between DFS and patient characteristics showed that the significant prognostic factors were CA19-9 (≥ 72 U/mL) (hazard ratio (HR) 2.44; 95% CI 1.40–4.26; $p = 0.0074$), maximum tumor size (≥ 5.0 cm) (HR 2.13; 95% CI 1.17–3.91; $p = 0.0004$), intrahepatic metastasis (HR 2.13; 95% CI 1.17–3.91; $p < 0.0001$), microvascular invasion (HR 2.13; 95% CI 1.17–3.91; $p = 0.0001$), lymph node metastasis (HR 2.13; 95% CI 1.17–3.91; $p < 0.0001$), and HALP score (≤ 25.2) (HR 2.13; 95% CI 1.17–3.91; $p = 0.0043$). Multivariate analysis also showed that the

Table 1 Clinicopathological and perioperative characteristics of ICC patients

Factors	HALP-high (n = 73)	HALP-low (n = 22)	P Value
Age (years)	65 (33–87)	69 (41–87)	0.1438
Sex, male/female	51/22	12/10	0.1827
HBs-Ag positive	9 (12.3%)	1 (4.6%)	0.2971
HCV-Ab positive	6 (8.2%)	3 (13.6%)	0.4280
Total bilirubin (mg/dL)	0.7 (0.2–1.8)	0.7 (0.4–2.8)	0.2301
γ-GTP (IU/L)	78 (12–1071)	91 (16–515)	0.8264
Albumin (g/dL)	4.2 (3.2–5.3)	3.8 (2.9–4.5)	0.0004
Hemoglobin (g/dL)	13.2 (9.9–16.7)	12.3 (9.2–14.4)	0.0007
Platelet count (10^4 μL)	18.3 (6.1–40.2))	27.1 (14.9–54.3)	< 0.0001
Lymphocyte (/μL)	1585 (363–3960)	1120 (417–1998)	< 0.0001
CEA (ng/mL)	2.6 (0.1–117.5)	2.6 (0.6–30.7)	0.6328
CA19-9 (U/mL)	36.3 (0.3–58,307)	156.2 (0.6–98,106)	0.0431
Maximum tumor size (cm)	4.0 (0.5–10.0)	5.5 (1.1–12.0)	0.2663
Tumor localization (peripheral type/perihilar type)	55/18	13/9	0.1785
Poor differentiation (%)	45 (61.6%)	11 (50.0%)	0.3305
Microvascular invasion (%)	41 (56.2%)	11 (50.0%)	0.6106
Intrahepatic metastasis (%)	45 (61.6%)	13 (59.1%)	0.8296
Lymph node metastasis (%)	12 (16.4%)	11 (50.0%)	0.0013
Histological liver cirrhosis (%)	9 (12.3%)	2 (9.1%)	0.6774
Laparoscopic surgery	0 (0%)	4 (18.2%)	0.5702
Duration of surgery (minutes)	353 (142–765)	401 (168–740)	0.2168
Blood loss (ml)	420 (5–4000)	880 (80–5500)	0.0447
Blood transfusion during surgery	8 (11.0%)	8 (36.4%)	0.0095
Adjuvant chemotherapy	24 (32.9%)	3 (13.6%)	0.1070

Data are presented as *n* (%) or the median (range)

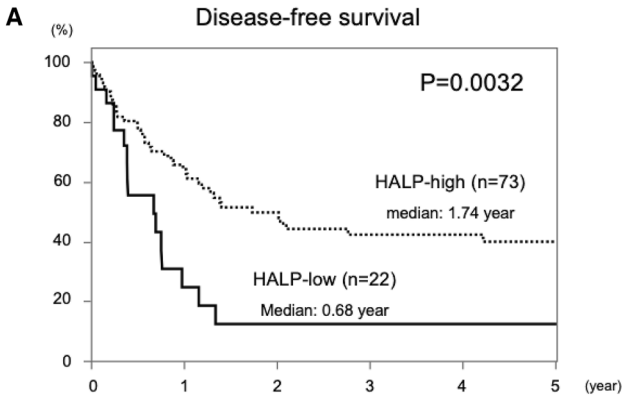
ICC Intrahepatic cholangiocarcinoma, *HALP* hemoglobin, albumin, lymphocyte, and platelet, *HBs-Ag* hepatitis B surface antigen, *HCV-Ab* hepatitis C virus antibody, *γ-GTP* γ-glutamyl transpeptidase, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19–9

independent prognostic factors for DFS were maximum tumor size (≥ 5.0 cm) (HR 2.27; 95% CI 1.27–4.05; p = 0.0033), microvascular invasion (HR 2.45; 95% CI 1.24–4.83; p = 0.0108), and HALP score (≤ 25.2) (HR 2.05; 95% CI 1.05–3.99; p = 0.0349).

Table 3 lists the univariate and multivariate analyses results associated with OS in patients with ICC after curative hepatic resection. Univariate analysis of the association between OS and patient characteristics showed that the significant prognostic factors were CA19-9 (≥ 37 U/mL) (HR 2.05; 95% CI 1.05–3.11; p = 0.0048), maximum tumor size (≥ 5.0 cm) (HR 1.87; 95% CI 1.12–2.98; p = 0.0132), intrahepatic metastasis (HR 1.98; 95% CI 1.20–3.25; p = 0.0071), microvascular invasion (HR 1.68; 95% CI 1.01–2.80; p = 0.0458), lymph node metastasis (HR 4.54; 95% CI 2.53–8.15; p < 0.0001), and HALP score (≤ 25.2) (HR 3.42; 95% CI 1.94–6.04; p < 0.0001). Multivariate analysis also showed that the independent prognostic factors were lymph node metastasis (HR 3.28; 95% CI 1.67–6.43; p = 0.0020) and HALP score (≤ 25.2) (HR 3.10; 95% CI 1.54–6.21; p = 0.0014).

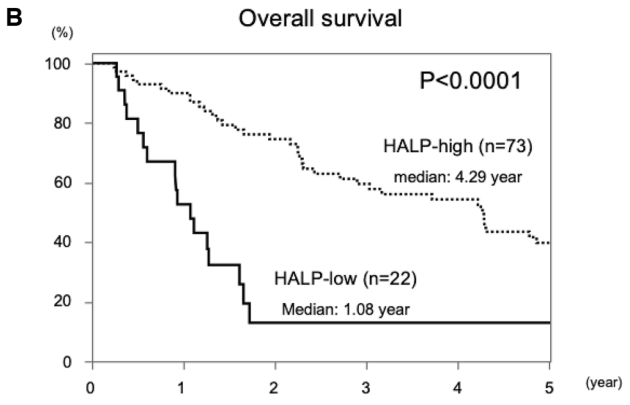
Proportion of patients with sarcopenia according to HALP high/low

Among 96 patients, 73 could be evaluated for the presence of sarcopenia by preoperative CT, and 16 were diagnosed with sarcopenia. Ten of 62 patients (16.1%) in the HALP-high



Number at risk

Year	0	1	2	3	4	5
HALP-high	73	44	28	23	20	14
HALP-low	22	5	3	2	2	1



Number at risk

Year	0	1	2	3	4	5
HALP-high	73	62	47	36	31	22
HALP-low	22	13	3	3	3	2

Fig. 1 Kaplan–Meier curves for DFS **A** and OS **B** in the two groups according to HALP score in ICC patients who underwent hepatic resection

group and 6 of 11 (54.5%) in the HALP-low group had sarcopenia, with significantly more patients in the HALP-low group having sarcopenia (p = 0.0045) (Fig. 2).

Relationships between TILs, CD8 + TILs, FOXP3 + TILs, and HALP high/low

Next, we evaluated the relationships between TILs (Fig. 3A, B), CD8 + TILs (Fig. 3C, D), FOXP3 + TILs (Fig. 3E, F), and HALP-high/low. The median TIL values were as follows: 25 cells/0.950 mm^2 HALP-high and22 cells/0.950 mm^2 HALP-low; there was no significant difference between the two groups. The median CD8 + TIL values were as follows: 29 cells/0.237mm^2 HALP-high and 20 cells/0.237mm^2 HALP-low; this was significantly lower in the HALP-low group (p = 0.0075). The median FOXP3 + TIL values were as follows: 5 cells/0.237mm^2 HALP-high and 6 cells/0.237mm^2 HALP-low; there was no significant difference between the two groups.

Discussion

We retrospectively examined the prognostic impact of the HALP score in ICC and demonstrated that low HALP score was a powerful predictor of prognosis in ICC patients who underwent curative hepatic resection and was associated with sarcopenia and low CD8 + TIL infiltration.

The HALP score is a combination measure that has received much attention in recent years [9]. Anemia has impacts on patient disease progression, treatment and survival [19]. Low preoperative albumin levels and lymphocyte count are related to the prognosis of ICC [6, 20], and elevated platelet predicted poor OS [21]. The HALP score combines these indicators of systemic inflammatory response and nutritional status and is particularly convenient because it is often measured routinely in hospital. In order to demonstrate the usefulness of the HALP score, we compared it with PNI and PLR, known as nutritional and inflammation indicators in Tables 2 and 3. PNI and PLR were not significant as prognostic factors in univariate analysis, and only HALP score was an independent poor prognostic factor in multivariate analysis, clinical significance of the HALP score, which combines systemic inflammatory response and nutritional status, was demonstrated. In the present study, there were significantly fewer CD8 + TILs in the tumor micro environment of the HALP-low group. Systemic inflammation has been reported to correlate with immune status in the tumor microenvironment, and our laboratory has shown that biomarkers such as lymphocyte–C-reactive protein ratio and lymphocyte–monocyte ratio are not only prognostic factors for hepatocellular carcinoma and ICC, but also correlate and predict immune cell infiltration in the tumor microenvironment [6, 22–24]. Although there has been no previous report showing a relationship between the HALP score and TILs, there is no question that the HALP-score, a biomarker of systemic inflammatory response and nutritional status, was correlated with CD8 + TILs in the tumor microenvironment, as in previous reports. Considering the above findings, it is suggested that a decrease in anti-tumor immune cells may lead to differences in tumor factors between the two groups and may be related to ICC

Table 2 Univariate and multivariate analyses of factors related to DFS in ICC patients

Factors	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P Value	HR (95%CI)	P Value
Age (≥ 70 years)	1.08 (0.61–1.90)	0.7852		
Sex, Male	1.49 (0.85–2.61)	0.1604		
Albumin (≤ 4.0 g/dL)	1.47 (0.87–2.48)	0.1452		
CA19-9 (≥ 37 U/mL)	2.08 (1.22–3.56)	0.0074	1.08 (0.60–2.00)	0.6527
Maximum tumor size (≥ 5.0 cm)	2.63 (1.45–4.20)	0.0004	2.27 (1.27–4.05)	0.0033
Tumor localization (perihilar type)	1.81 (1.08–3.20)	0.0306	1.49 (0.74–3.00)	0.2442
Poor differentiation	1.43 (0.84–2.46)	0.1543		
Intrahepatic metastasis	2.91 (1.75–5.05)	< 0.0001	1.59 (0.87–3.07)	0.1552
Micro vascular invasion	3.18 (1.76–5.71)	0.0001	2.45 (1.24–4.83)	0.0108
Lymph node metastasis	3.77 (2.14–6.63)	< 0.0001	1.86 (0.87–3.97)	0.1582
Histological liver cirrhosis	1.02 (0.44–2.40)	0.9499		
Laparoscopic surgery	0.40 (0.06–2.90)	0.3658		
Duration of surgery (≥ 240 min)	1.41 (0.71–2.79)	0.3248		
Blood loss (≥ 250 ml)	1.90 (0.98–3.61)	0.0612		
Blood transfusion during surgery	1.34 (0.68–2.66)	0.3976		
Adjuvant chemotherapy	0.82 (0.46–1.47)	0.5076		
PNI (≤ 48.2)	1.58 (0.93–2.68)	0.0845		
PLR (≥ 80.0)	1.64 (0.74–3.63)	0.2202		
HALP score (≤ 25.2)	2.39 (1.31–4.36)	0.0043	2.05 (1.05–3.99)	0.0349

DFS disease-free survival, *ICC* Intrahepatic cholangiocarcinoma, *CA19-9* carbohydrate antigen 19–9, *PNI*, prognostic nutritional index, *PLR* platelet-to-lymphocyte ratio, *HALP* hemoglobin, albumin, lymphocyte, and platelet

Table 3 Univariate and multivariate analyses of factors related to OS in ICC patients

Factors	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P Value	HR (95%CI)	P Value
Age (≥ 70 years)	1.48 (0.87–2.51)	0.1416		
Sex, Male	1.33 (0.79–2.25)	0.2744		
Albumin (≤ 4.0 g/dL)	1.52 (0.93–2.48)	0.0928		
CA19-9 (≥ 37 U/mL)	2.05 (1.22–3.31)	0.0048	1.47 (0.86–2.52)	0.1540
Maximum tumor size (≥ 5.0 cm)	1.87 (1.12–2.98)	0.0132	1.57 (0.95–2.50)	0.0792
Tumor localization (perihilar type)	1.70 (0.99–2.95)	0.0592		
Poor differentiation	1.16 (0.71–1.91)	0.5459		
Intrahepatic metastasis	1.98 (1.20–3.25)	0.0071	1.40 (0.81–2.43)	0.2278
Micro vascular invasion	1.68 (1.01–2.80)	0.0458	1.42 (0.80–2.51)	0.2320
Lymph node metastasis	4.54 (2.53–8.15)	< 0.0001	3.28 (1.67–6.43)	0.0020
Histological liver cirrhosis	1.03 (0.47–2.26)	0.9463		
Laparoscopic surgery	0.76 (0.18–3.19)	0.7165		
Duration of surgery (≥ 240 min)	1.10 (0.57–2.11)	0.7698		
Blood loss (≥ 250 ml)	1.16 (0.66–2.02)	0.6052		
Blood transfusion during surgery	1.28 (0.65–2.53)	0.4617		
Adjuvant chemotherapy	0.73 (0.43–1.27)	0.2758		
PNI (≤ 48.2)	1.53 (0.93–2.51)	0.0927		
PLR (≥ 80.0)	1.53 (0.76–3.12)	0.2363		
HALP score (≤ 25.2)	3.42 (1.94–6.04)	< 0.0001	3.10 (1.54–6.21)	0.0014

OS overall survival, *ICC* Intrahepatic cholangiocarcinoma, *CA19-9* carbohydrate antigen 19–9, *PNI* prognostic nutritional index, *PLR* platelet-to-lymphocyte ratio, *HALP* hemoglobin, albumin, lymphocyte, and platelet

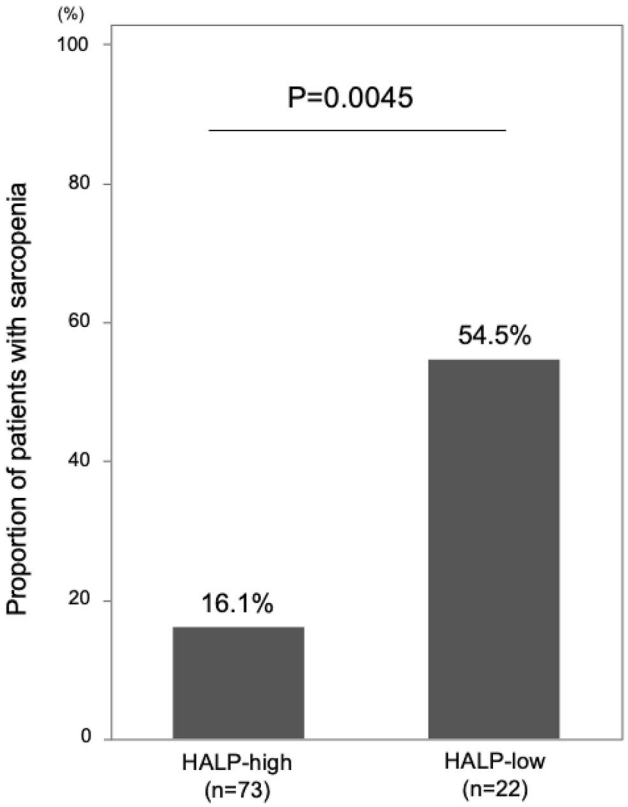


Fig. 2 Proportion of patients with sarcopenia in the HALP-high/-low groups

disease progression. In this study, lymph node metastasis, which is known to be one of the strongest factors to predict prognosis, was a significant factor not in DFS but in OS by multivariate analysis. There are three possible reasons for this. One is that 71.6% of the patients in this study were peripheral type. Second, the fact that a higher percentage of patients in the high HALP group tended to receive postoperative adjuvant therapy ($p = 0.1070$) may have influenced DFS. Third, which is most important, is that lymph node metastasis was significantly more in the HALP-low group ($p = 0.0013$) as shown in Table 1. Since the HALP score reflects not only systemic inflammation but also nutritional status, patients with lymph node metastasis were likely to have poorer nutritional status than those without it after surgery. Therefore, it was possible that patients with lymph node metastasis, many of whom were classified as the HALP-low group, due to worse general condition were less likely to receive treatment for recurrence, and even if they did receive treatment, their tolerability for it was worse.

Body composition is a topic that has received much attention recently, and the presence of sarcopenia has been studied as a prognostic factor for surgery and chemotherapy in some cancer types [15, 25]. Sarcopenia strongly reflects systemic nutritional and immune statuses and has been reported to be associated with biomarkers such as the prognostic nutritional index and neutrophil-to-lymphocyte ratio [8, 26]. Although there has been no report on the relationship between the HALP score and sarcopenia, the HALP score is considered to be strongly correlated with sarcopenia because it includes albumin, which represents nutritional status, and lymphocyte count, which represents systemic immune status, as indicators. In a study of extrahepatic cholangiocarcinoma, patients with sarcopenia had significantly fewer CD8 + TILs in their tumors than those without sarcopenia, suggesting that sarcopenia affects not only systemic inflammation but also the local immune system [27]. In the current study, the number of CD8 + TILs in tumors was higher in the HALP-high group, which also had significantly more sarcopenia, consistent with previous reports.

When we use the HALP score, we need to keep in mind that ICC is a primary liver tumor [28]. Hepatitis B and C viruses are risk factors for ICC as well as hepatocellular carcinoma; in addition, non-alcoholic fatty liver disease, whose incidence rate has recently rapidly increased, can also be a risk factor of ICC [29, 30]. Therefore, it is likely that a certain number of ICC patients have liver fibrosis and low platelet counts due to the progression of chronic hepatitis [31]. Although patients with liver cirrhosis are usually considered to have poorer immune and nutritional statuses than those of normal liver patients, the HALP score is calculated by dividing the platelet value by multiplied values of hemoglobin, albumin, and lymphocytes, which may result in a higher apparent HALP score in patients with cirrhosis and poor general condition [32]. In this study, 10% of the total cases were hepatitis B surface-antigen-positive and 10% were hepatitis C virus-antibody-positive, and there was no significant difference between the two groups. Moreover, histological liver cirrhosis in the surgical specimens also showed no significant difference.

This study had several limitations. First, it was a single-center retrospective study with a relatively small study cohort. A larger number of patients may have resulted in a significant difference in DFS by the HALP score. Second, this study included some very old cases, and hence it is undeniable that the surgical technique (laparotomy vs laparoscopic) and the presence or absence of systemic therapy after recurrence may have affected prognosis.

In conclusion, we demonstrated that low HALP score was a significant predictor in ICC patients who underwent surgical resection and was associated with sarcopenia and the immune microenvironment. Long-term and large-scale observations will be expected to validate these results.

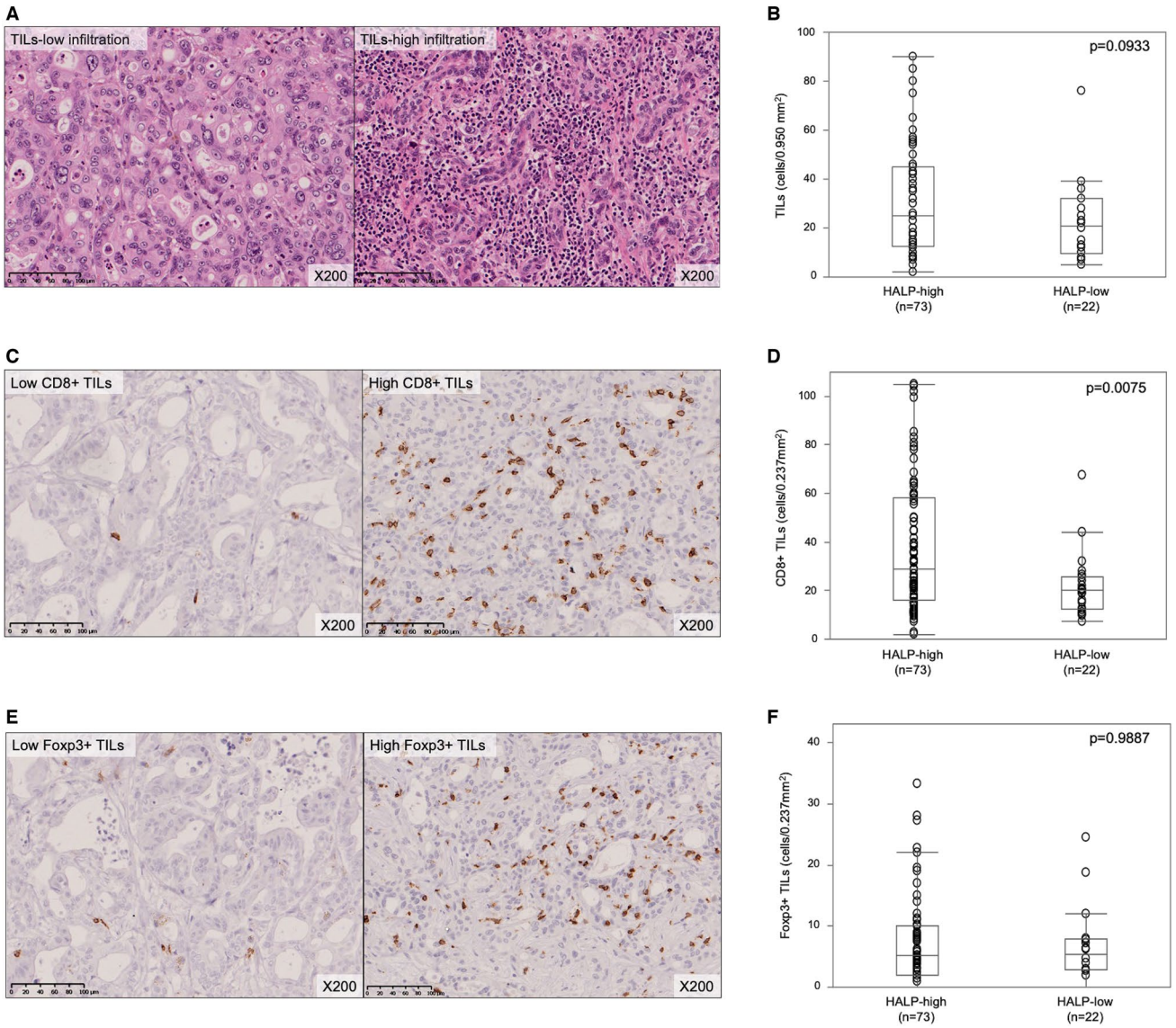


Fig. 3 Representative features of TILs **A** There was no significant difference between the two groups in terms of infiltration of TILs according to HALP high/low **B** Representative features of CD8 + TILs **C** The counts of CD8 + TILs were significantly lower in the HALP-low group (p = 0.0075) **D** Representative features of FOXP3 + TILs **E** There was no significant difference between the two groups in terms of infiltration of FOXP3 + TILs according to HALP high/low **F**

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Author contribution KT participated in the study conception and design, analysis, and drafting of the article. SI participated in the study conception and design, and in the critical revision of the manuscript. YN, TT, SY, YN, NH, and KK participated in the data acquisition, analysis, and interpretation. YO and TY participated in the analysis and in the critical revision of the manuscript.

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Declarations

Conflict of interest K.T. and the other co-authors have no conflict of interest.

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