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ORIGINAL ARTICLE

Plenary Session

Evaluation of prognostic efficacy of liver immune status index in predicting postoperative outcomes in hepatocellular carcinoma patients: A multi-institutional retrospective study

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Abstract

Background: Hepatocellular carcinoma (HCC) ranks third in cancer-related deaths globally. Despite treatment advances, high post-hepatectomy recurrence rates (RR), especially with liver fibrosis and hepatitis C virus infection, remain challenging. Key prognostic factors include vascular invasion and perioperative blood loss, impacting extrahepatic recurrence. Natural killer (NK) cells are crucial in countering circulating tumor cells through TRAIL-mediated pathways. The aim of this study was to validate the liver immune status index (LISI) as a predictive tool for liver NK cell antitumor efficiency, particularly in HCC patients with vascular invasion.

Methods: A retrospective analysis of 1337 primary HCC hepatectomies was conducted by the Hiroshima Surgical Study Group of Clinical Oncology (HiSCO). Clinicodemographic data were extracted from electronic medical records.

Prognostic indices (FIB-4, ALBI, ALICE, GNRI, APRI, and LISI) were evaluated using area under the receiver operating characteristic curve values. Survival analyses employed Kaplan–Meier estimations and log-rank tests.

Results: LISI significantly correlated with other prognostic markers and stratified patients into risk groups with distinct overall survival (OS) and RR. It showed superior predictive performance for 2-year OS and RR, especially in patients with vascular invasion. Over longer periods, APRI and FIB-4 index reliabilities improved. The HISCO-HCC score, combining LISI, tumor burden score, and alpha-fetoprotein levels, enhanced prognostic accuracy.

Conclusion: LISI outperformed existing models, particularly in HCC with vascular invasion. The HISCO-HCC score offers improved prognostic precision, guiding immunotherapeutic strategies and individualized patient care in HCC.

KEYWORDS

antitumor activity, hepatectomy, hepatocellular carcinoma, natural killer cells

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) continues to be a global health burden, ranking third among cancer-related mortalities worldwide.[1] Despite therapeutic advancements, the management of HCC is complicated by high recurrence rates (RR) after curative interventions such as hepatectomy, with liver fibrosis exacerbating the risk of multicentric carcinogenesis.[2] It is imperative to acknowledge the complex interplay of factors influencing HCC prognosis, including patterns of vascular invasion, perioperative blood loss, quantity of skeletal muscle, blood infusion, renal function, and postoperative bile leakage,[3–8] which have been empirically recognized as contributory elements in extrahepatic recurrence and early recurrence due to circulating tumor cells (CTC).[9–12]

Natural killer (NK) cells are instrumental in the complex interplay of host defense mechanisms, serving as the vanguard of the immune system against pathogens and malignancies and crucially countering CTCs.[10,13,14] Unique in their apoptosis-inducing arsenal, notably through Fas ligand and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) expression, NK cells, especially liver-resident subsets, exhibit heightened antitumor activities via TRAIL-mediated pathways against liver tumor cells.[15–19] Previous investigations have highlighted TRAIL expression in liver NK cells as an antitumor efficacy marker for the direct killing of tumors.[20–22] We hypothesize that the antitumor activity of liver NK cells is related to early recurrence due to CTCs, as reported in a previous study.[23]

However, it becomes clear that the antitumor activity of liver NK cells varies among individuals, and noninvasive prognostic tools are required. To address this, the liver immune status index (LISI) was developed as a pioneering stratification tool for predicting the antitumor efficiency of liver NK cells, particularly in HCC patients with vascular invasion.[24] This study aimed to evaluate the prognostic efficacy of LISI for predicting the postoperative outcomes of hepatectomy for HCC in multiple institutions.

2 | METHODS

2.1 | Patients

This study retrospectively analyzed 1337 initial hepatectomies for primary HCC conducted within the Hiroshima Surgical Study Group of Clinical Oncology (HiSCO) from 2011 to 2021. The criteria for liver resection adhered to established protocols, factoring in the presence of ascites, serum total bilirubin levels, and indocyanine green retention rate at 15 min (ICG-R15).[25] Comprehensive clinicopathological data, including age, sex, body mass index (BMI), Child–Pugh classification, viral hepatitis markers, and pathological findings, were meticulously extracted from the electronic medical records. Longitudinal data on HCC recurrence and postoperative survival rates were also compiled. Postoperative surveillance entailed a regimented protocol utilizing ultrasonography, contrast-enhanced CT, or MRI, in conjunction with biannual serum alpha-fetoprotein (AFP) and des-gamma-carboxy

prothrombin (DCP) evaluations, extending up to 5 years post-hepatectomy. The diagnosis was histologically confirmed when necessary.

2.2 | Evaluation of prognostic indices

The FIB-4 index was computed as described in the literature and originally intended for HIV/hepatitis C virus (HCV) coinfected patients.[26] The albumin–bilirubin (ALBI) grade was determined through a proprietary logarithmic equation encompassing serum bilirubin and albumin concentrations, yielding a gradation from grades 1 to 3.[27] Concurrently, the albumin-indocyanine green evaluation (ALICE) score incorporated parameters such as ICG R15 and serum albumin levels, which were segmented further into three distinct grades according to the ALICE grading system.[28]

The geriatric nutritional risk index (GNRI) employs a formula integrating serum albumin levels with a ratio of present to ideal bodyweight (PBW/IBW), with BMI serving as a surrogate marker for the latter component.[29,30] The AST to platelet ratio index (APRI) was calculated using the standard methodology.[31] Notably, LISI was extrapolated from a complex formula incorporating albumin levels, BMI, and the FIB-4 index[26] to approximate the prevalence of TRAIL-positive liver NK cells in living-donor liver transplants.[24] LISI was calculated using the following formula: $36.39-(6.18\times\text{ALB})-(0.50\times\text{BMI})+(2.91\times\text{FIB-4 index})$.[24] Patients were categorized into three groups, namely the low group (<4.55; $N=321$), the moderate group (4.55–15.33), and the high group (15.33 <, $N=267$), based on the cutoff value utilized in a prior study.[24]

The ASAP score was calculated using the following equation: $\text{ASAP score}=-7.58+0.05\times\text{age}-0.58\times\text{gender}+0.42\times\ln\text{AFP (ng/mL)}+1.11\times\ln\text{PIVIKA-II (mAU/mL)}$, where gender = 0 for males and 1 for females.[32]

The HALT HCC score assessed the utility of a continuous risk score in predicting overall survival (OS) following liver transplantation for HCC and was generated as $(1.27\times\text{TBS})+(1.85\times\ln\text{AFP})+(0.26\times\text{MELD-Na})$.[33]

2.3 | Statistical analysis

Comparative analyses between independent groups were performed using the nonparametric Mann–Whitney U test, with a p-value threshold of <.05, denoting statistical significance. Data are expressed as median values with minimum and maximum ranges. Spearman's Rho was used to assess correlations among LISI and alternative prognostic indices. Survival curves were generated using Kaplan–Meier estimations and contrasted using log-rank tests. Comparative evaluations of different prognostic frameworks factored in metrics, such as the area under the receiver operating characteristic curve (AUROC), consistency across various risk strata, discriminatory prowess, and informational parsimony per the Akaike criterion. AUROC comparisons between the models were performed using the DeLong test. All statistical procedures were conducted using JMP statistical software (version 17; SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Correlation between LISI and clinical characteristics

This study included 1337 patients, including 1025 (76.6%) males and 312 (23.4%) females. The median age of the patients was 73.0 years (67–79). The median total tumor size and tumor burden score (TBS) were 2.6 cm (1.8–4.2) and 3.16 (2.23–4.6). In 453 cases (33.8%), vascular invasion was identified. The specific distribution of vascular invasion included Vp1 (23.7%), Vp2 (1.6%), Vp3 (1.2%), Vp4 (0.0%), Va1 (1.1%), Vv1 (12.1%), Vv2 (0.4%), and Vv3 (0.2%). The median of LISI was 8.45 (4.61–13.67) (Figure S1). The medians of other markers, such as APRI, FIB-4 index, GNRI, ALICE, and ALBI, were 0.51 (0.33–0.89), 2.90 (1.97–4.41), 100.7 (95.3–105.3), −2.15 (−2.44–1.86), and −2.70 (−2.43–2.43), respectively.

The low LISI group (<4.55; $N=321$) was defined, which was expected to have high antitumor activity in liver NK cells. Meanwhile, the high LISI group (>15.33; $N=267$) was identified as a high-risk group with lower antitumor activity of liver NK cells. The distribution of the characteristics is summarized in Table 1. The high-risk group included a larger number of patients with poor liver function, higher AFP levels, and larger tumor sizes. There were significant correlations between LISI and other markers, including the APRI, FIB-4 index, GNRI, ALICE, and ALBI (Spearman's Rho: 0.69, 0.84, −0.66, 0.63, and 0.63; $p<.01$).

3.2 | Overall patient outcomes

The three LISI grades also stratified the OS and RR risks (low group; <4.55, moderate group; 4.55–15.33, high group; 15.33<) The survival rates at 1, 3, and 5 years were 98.7%,90.1%, and 84.3% in the low group; 95.0%, 82.9%, and 71.7% in the moderate group; and 88.3%, 70.6%, and 54.8% in the high group, respectively ($p<.01$; Figure 1a). The 1-, 3-, and 5-year RR were 13.8%, 32.9%, and 46.4% in the low group; 21.3%, 44.8%, and 53.4% in the moderate

TABLE 1 Background data according to LISI grade.

Subject	Low group (<4.55) $N=321$	Moderate group (4.55–15.33) $N=749$	High group (15.33<) $N=267$	p-value
Gender male	278 (86.6)	589 (78.6)	158 (59.2)	<.01
Age (years)	69 [63–74]	74 [68–79]	74 [68–80]	<.01
Hepatitis B/B+C/C/non-virus	80/5/103/133	105/4/302/338	22/3/160/82	<.01
BMI (%)	24.8 [22.9–27.0]	23.0 [21.1–25.3]	22.3 [20.2–24.7]	<.01
Fibrosis-4 index	1.75 [1.38–2.19]	2.95 [2.28–3.84]	6.66 [5.09–8.68]	<.01
T-bilirubin (mg/dL)	0.8 [0.6–1.0]	0.7 [0.6–1.0]	0.8 [0.7–1.2]	<.01
Albumin (mg/dL)	4.4 [4.2–4.6]	4 [3.8–4.2]	3.6 [3.3–3.9]	<.01
Platelet (10^4/L)	200 [161–241]	157 [127–200]	93 [71–118]	<.01
AST (IU/L)	26 [20–32]	30 [23–42]	47 [35–67]	<.01
ALT (IU/L)	26 [18–38]	25 [16–38]	32 [21–49]	<.01
PT (%)	93 [84–100]	88 [80–97]	80 [70–89]	<.01
ICGR15 (%)	10.2 [6.9–14.5]	12.5 [8.3–18.4]	20.3 [13.9–29.2]	<.01
AFP (ng/mL)	5.2 [2.7–28]	7.0 [3.3–44]	14 [5.7–86]	<.01
DCP (mAU/mL)	59 [25–334]	80 [25–637]	47 [20–347]	.04
Operation time (min)	314 [248–389]	300 [229–388]	276 [197–351]	<.01
Bleeding volume (mL)	230 [100–512]	290 [122–578]	300 [120–650]	.06
Tumor size (mm)	27 [18–40]	28 [19–45]	22 [16–35]	<.01
Multiple tumors, yes	76 (23.8)	180 (24.4)	69 (25.9)	.82
Vascular invasion, yes	94 (29.3)	268 (35.8)	91 (34.1)	.12

Abbreviations: AFP, α-fetoprotein; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DCP, des-γ-carboxy protein; ICG, indocyanine green; LISI, the liver immune status index; PT, prothrombin time.

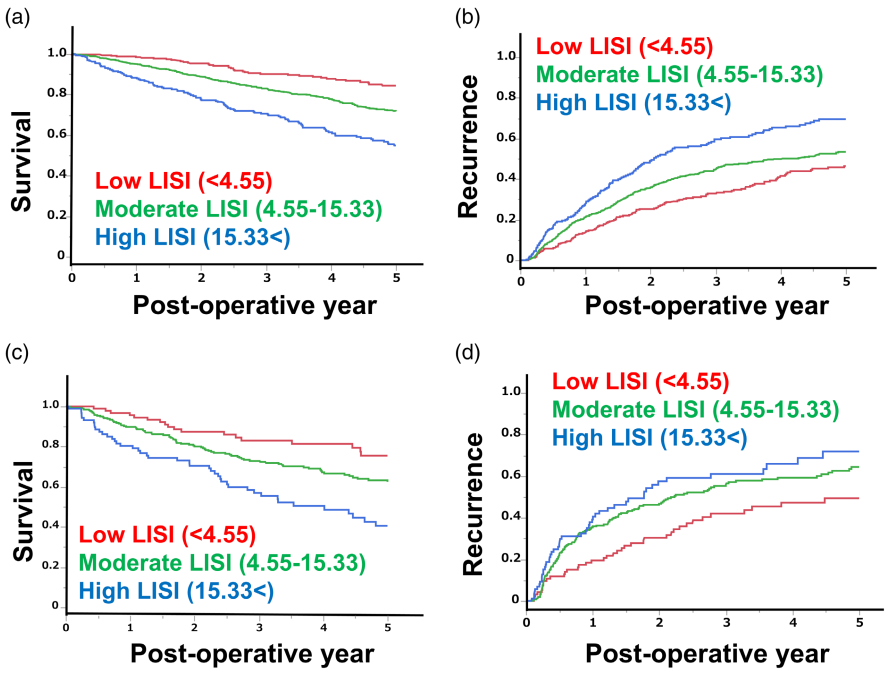

FIGURE 1 The outcomes according to the liver immune status index (LISI) grades. (a) The 5-year overall survival (OS) in all cases. (b) The 5-year recurrence rates (RR) in all cases. (c) The 5-year OS in vascular invasion cases. (d) The 5-year RR in vascular invasion cases.

group; and 27.7%, 59.6%, and 69.5% in high group ($p<.01$; Figure 1b). Next, we compared the recurrence pattern based on the LISI grade. The overall 2-year RR for intra- and extrahepatic regions were 30.5% and 6.0%, respectively. The 2-year intrahepatic recurrence rate demonstrated a significant increase with rising LISI grade

($p < .01$, low LISI group: 21.3%, moderate LISI group: 30.8%, high LISI group: 40.4%). However, the 2-year extrahepatic recurrence rate exhibited no increase depending on LISI groups ($p = .88$, low LISI group: 6.6%, moderate LISI group: 5.9%, high LISI group: 5.7%). The cumulative intra- and extrahepatic RR are shown in Figure S2a,b.

On the other hand, among vascular invasion cases, the survival rates at 1, 3, and 5 years were 95.6%,83.0%, and 75.5% in the low group; 89.8%, 72.9%, and 62.5% in the moderate group; and 80.3%, 56.9%, and 40.5% in the high group, respectively ($p < .01$; Figure 1c). The 1-, 3-, and 5-year RR were 19.5%, 41.9%, and 49.3% in the low group; 35.4%, 55.2%, and 64.4% in the moderate group; and 39.2%, 61.0%, and 71.9% in the high group ($p < .01$; Figure 1d).

3.3 | Assessment of model efficacy in prognostic stratification

The efficacy of the predictive models, including LISI, APRI, FIB-4, GNRI, ALBI grade, and ALICE, was evaluated using AUROC values, highlighting each model's performance in various scenarios. For the 2-year OS, the AUROC values were: APRI (0.61), LISI (0.67), FIB-4 index (0.62), GNRI (0.67), ALBI grade (0.65), and ALICE (0.66). While the performance of LISI was comparable to that of other systems, the AUROC of the FIB-4 index was lower, indicating its inferiority to LISI (Figure 2a). In cases with vascular invasion, associated with higher CTC risk and recurrence, the AUROC values for 2-year OS were: APRI (0.58), LISI (0.62), FIB-4 index (0.56), GNRI (0.63), ALICE (0.60), and ALBI grade (0.63) (Figure 2b). For tumors larger than 5.0 cm, the AUROC values for 2-year OS were: APRI (0.74), LISI (0.76), FIB-4 index (0.69), GNRI (0.69), ALICE (0.67), and ALBI grade (0.69).

The AUROC values for the 2-year RR were APRI (0.59), LISI (0.59), FIB-4 index (0.57), GNRI (0.57), ALICE (0.57), and ALBI grade (0.58), where all models, including LISI (0.59), exhibited similar AUROC values (Figure 2c). For patients with vascular invasion, prone to CTC emergence and recurrence, the 5-year RR AUROC values were APRI (0.58), LISI (0.59), FIB-4 index (0.57), GNRI (0.55), ALICE (0.52), and ALBI grade (0.55) (Figure 2d). These findings underscore LISI's consistent performance of LISI, particularly in stratifying patients with vascular invasion, although its advantage was limited to other tumor scenarios, such as in patients with advanced tumor markers (AFP > 500 [ng/mL] or DCP > 500 [mAU/mL]) (Figure S2a,b) and patients with a larger tumor >5 cm or a higher TBS (>5) (Figure S3c,d).

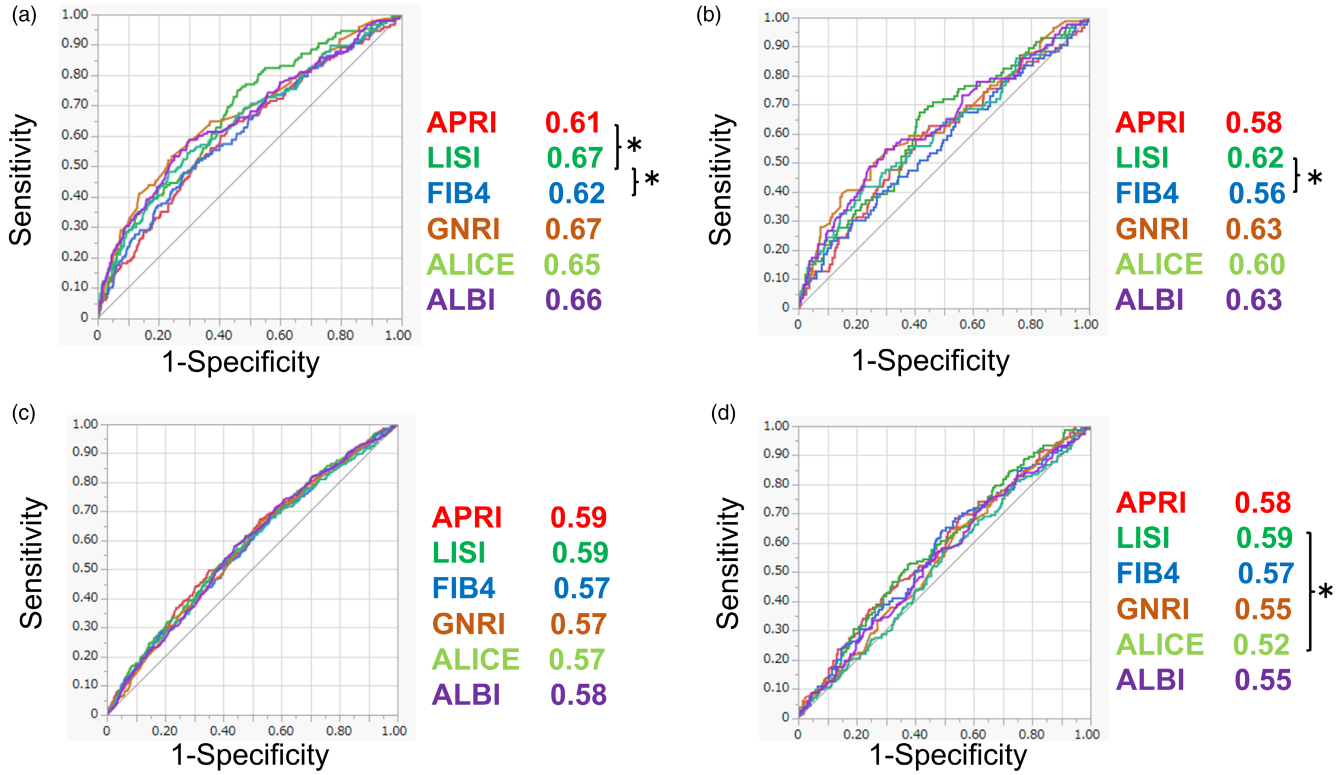

FIGURE 2 The area under the receiving operating characteristic curve (AUROC) of markers for the outcomes. (a) The 2-year overall survival (OS) in all cases. (b) The 2-year OS in vascular invasion cases. (c) The 2-year recurrence rates (RR) in all cases. (d) The 2-year RR in vascular invasion cases. *$p < .05$.

3.4 | Analyzing longitudinal predictive efficacy of prognostic markers in patients with vascular invasion

LISI has been associated with the antitumor activity of liver NK cells which can eliminate cancer-derived CTCs. To utilize LISI as a predictor of liver NK cell antitumor efficacy, we concentrated on HCC cases with vascular invasion, as these cases are more likely to produce CTCs. To examine the evolution of OS and RR predictions for existing markers and LISI over time, we conducted a comprehensive analytical process that included time-dependent AUROC analysis. Visual representations of these temporal progressions are shown in Figure 3. Our investigation uncovered a nuanced trajectory of predictive accuracy. Within the initial two-year timeframe, LISI emerged as a superior prognostic tool for delineating RR, attaining the highest AUROC value (0.59). However, this supremacy appeared to diminish in the AUROC values beyond the third year. Conversely, an interesting inverse dynamic was observed for both the APRI (5Y-RR, 0.60) and the FIB-4 index (5Y-RR, 0.57). Unlike LISI, these markers exhibited an upward trajectory in their predictive reliability (Figure 3a).

On the other hand, as for predicting OS, the LISI showed the highest AUROC value as a tool to predict OS after the second year (0.62–0.65). This suggests that LISI can be utilized as a versatile marker for RR and OS compared to other markers (Figure 3b).

3.5 | Development of a new score using a combination of LISI, TBS, and AFP levels

However, LISI's prognostic AUROC value was insufficient on its own, and it is crucial to incorporate a combination of morphology, tumor biology, and background liver background to more accurately predict patient outcomes.

To develop a new predictive model, we utilized a stratified random sampling method, dividing the training set into 874 cases and the validation set into 437 cases. Table 2 illustrates the patients' backgrounds, and no significant disparities were discovered between the two sets.

A multivariate logistic analysis was performed using LISI (OR 1.02, CI: 1.01–1.03, $p < .01$), TBS[33] (OR 1.07, CI: 1.05–1.10, $p < .01$), and log (AFP) (OR 1.37, CI: 1.23–1.52, $p < .01$) in the training set, with 2-year RR as the outcome (Table 3). Additionally, the hepatocellular carcinoma index for survival and clinical outcomes (HISCO-HCC score) was calculated.

The formula used for the predictive model in the training set was as follows:

$$2.16 \times \text{LISI} + 31.4 \times \log(\text{AFP}) + 7.23 \times \text{TBS}$$

The AUROC for predicting recurrence within 2 years in the training set was 0.67 for all patients and 0.66 for patients with vascular invasion. In the validation set, the HISCO-HCC score was compared with the ASAP and HALT-HCC scores, and time-dependent AUC analysis was performed to assess the temporal dynamics of OS and RR predictions. The HISCO-HCC score demonstrated a better predictive value for both OS and RR in all patients and in those with vascular invasion. Specifically, the AUCROC values for 1- to 5-year OS in vascular invasion cases were 0.74, 0.67, 0.68, 0.68, and 0.70, respectively (Figure 4a). The AUROC for 1- to 5-year RR were 0.67, 0.64, 0.63, 0.62, and 0.61, respectively (Figure 4b). The AUCROC values for the 1- to 5-year OS in all cases were 0.77, 0.70, 0.71, 0.70, and 0.70, respectively (Figure 4c). The AUROC for 1- to 5-year RR were 0.67, 0.64, 0.64, 0.62, and 0.62, respectively (Figure 4d).

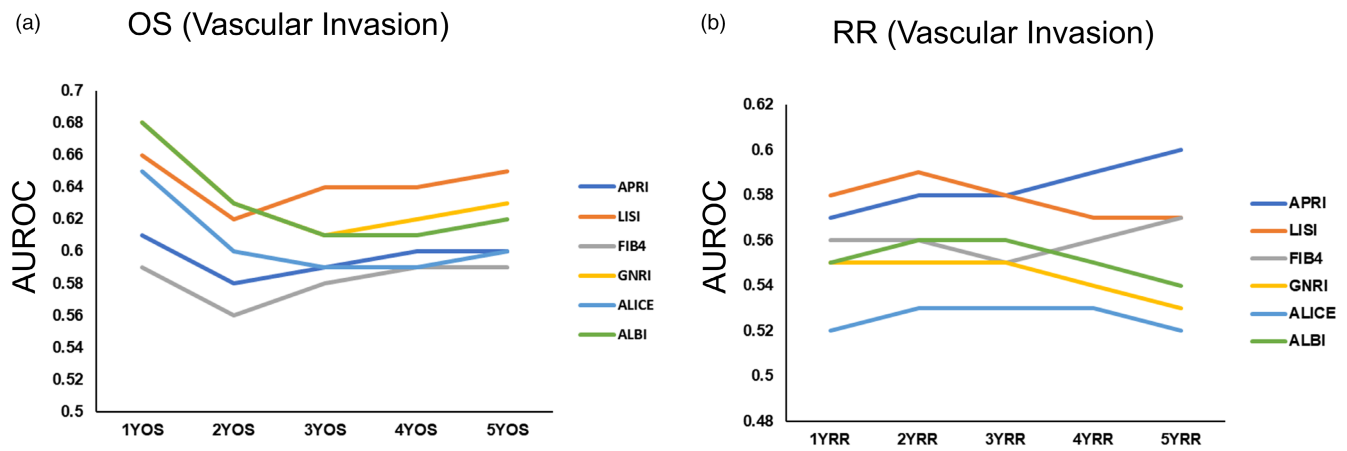

FIGURE 3 The time-dependent area under the receiving operating characteristic curve (AUROC) analysis using the liver immune status index (LISI). (a) The 5-year overall survival (OS) in vascular invasion cases. (b) The 5-year RR in vascular invasion cases.

TABLE 2 Background data after the stratified random sampling.

Subject	Training set $N=874$	Validation set $N=473$	p-value
Gender male	668 (76.4)	340 (77.8)	.57
Age (years)	72 [66–78]	74 [68–79]	.06
Hepatitis B/B + C/C/non-virus	132/9/374/359	688/3/181/185	.87
BMI (%)	23.5 [21.2–25.7]	23.2 [21.2–25.6]	.58
Fibrosis-4 index	2.88 [1.95–4.51]	2.97 [2.06–4.35]	.54
T-bilirubin (mg/dL)	0.8 [0.6–1.0]	0.8 [0.6–1.0]	.21
Albumin (mg/dL)	4 [3.7–4.3]	4 [3.7–4.3]	.47
Platelet (10^4/L)	154 [116–206]	153 [118–199]	.60
AST (IU/L)	31 [24–46]	30 [23–42]	.08
PT (%)	88 [79–97]	88 [78–98]	.50
ICGR15 (%)	13.0 [8.9–20]	12.3 [8.0–19.8]	.42
AFP (ng/mL)	7.6 [3.6–46]	6.8 [3.2–46]	.28
DCP (mAU/mL)	70 [24–517]	62 [24–378]	.30
Operation time (min)	299 [231–380]	295 [230–390]	.93
Bleeding volume (mL)	269 [115–555]	279 [120–580]	.51
Tumor size (mm)	26 [18–41]	27 [18–42]	.76
Multiple tumors, yes	230 (26.3)	95 (21.7)	.07
Vascular invasion, yes	290 (33.2)	153 (35.0)	.50

Abbrevitions: AFP, alpha-fetoprotein; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DCP, des-gamma-carboxy protein; ICG, indocyanine green; PT, prothrombin time.

TABLE 3 Multivariate logistic analysis for prediction of 2Y-RR.

Variables	Coefficient	OR	95% CI	p-value
LISI	0.0216	1.02	1.01–1.03	<.01
TBS	0.0723	1.07	1.05–1.10	<.01
log (AFP)	0.3140	1.37	1.23–1.52	<.01

Abbreviations: 2Y-RR, two-year recurrence rate; AFP, alpha-fetoprotein; CI, confidence interval; LISI, liver immune status index; OR, odds ratio; TBS, tumor burden score.

A multivariate Cox-hazard analysis was conducted using LISI (HR 1.01, 95% CI: 1.01–1.01, $p<.01$), larger blood loss (HR 1.02, 95% CI: 1.01–1.03, $p<.01$), and HCV (HR 1.46, 95% CI: 1.06–2.01, $p=.02$) and non-HBV/non-HCV (NBNC) (HR 1.39, 95% CI: 1.01–1.91, $p=.046$) in comparison to hepatitis B (HBV)-related HCC for 2-year RR (Table 4).

4 | DISCUSSION

This study underscores the significance of LISI, a composite index comprising BMI, serum albumin levels, and FIB-4 indices, for predicting mid- to long-term survival and early recurrence in patients with high-risk HCC and vascular invasion. The prognostic ability of LISI is noteworthy as it surpasses that of existing markers in predicting OS and recurrence. These results suggest that NK cells play a crucial role in targeting CTCs, leading to early recurrence and distant metastasis. However, LISI alone does not provide accurate predictive results. To address this limitation, we developed a HISCO-HCC score that incorporates LISI, TBS, and AFP levels, resulting in a high predictive power (Figure 5).

Liver NK cells can play an important role in preventing the spread of CTCs into the circulation in the early stages within the liver sinusoids and subsequently preventing early and distant recurrence. Single nucleotide polymorphisms in TRAIL, which is one of the important molecules for the direct killing of tumor cells,[15,17,20,34] are significantly associated with extrahepatic recurrences.[35] While liver NK cells are known for their diverse antitumor effector molecule expression, their antitumor activity typically requires invasive procedures like liver biopsy for evaluation preoperatively. The antitumor effects of liver NK cells are reduced by conditions such as liver fibrosis,[36] hepatectomy,[17] portal hypertension,[37] and coexisting tumors.[38–40] Consequently, direct assessment of liver NK cells in HCC-bearing conditions is crucial. We propose that utilizing LISI for prognostication and noninvasive risk stratification of liver NK cell function could significantly improve the management of high-risk HCC cases, particularly those with vascular invasion. LISI score,

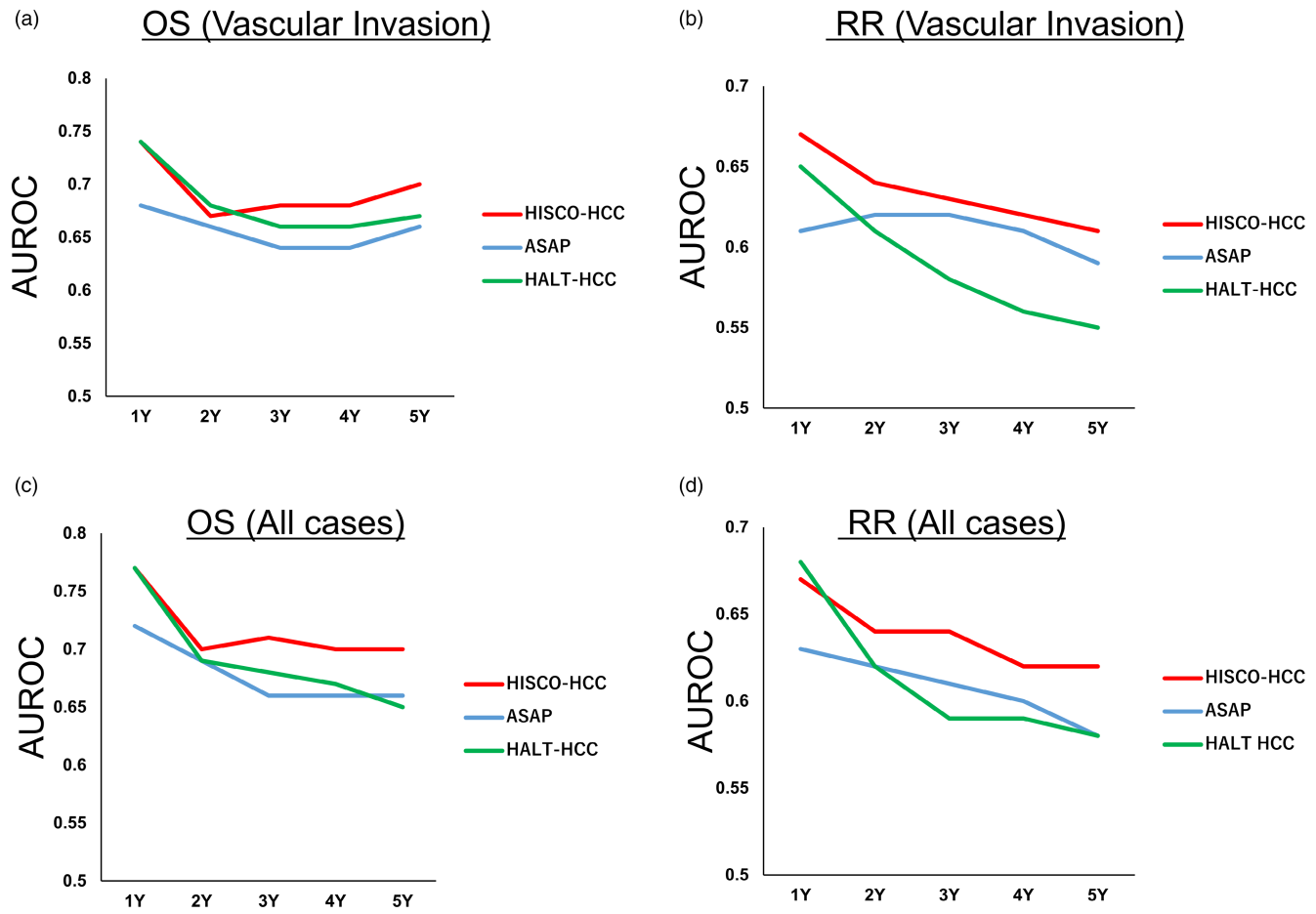

FIGURE 4 The time-dependent area under the receiving operating characteristic curve (AUROC) analysis in the validation set. (a) The 5-year overall survival (OS) in vascular invasion cases. (b) The 5-year recurrence rates (RR) in vascular invasion cases. (c) The 5-year OS in all cases. (d) The 5-year RR in all cases.

which predicts the antitumor efficacy of liver NK cells, was a valuable parameter for stratifying high-risk patients with vascular invasion after liver resection[24] and living donor liver transplantation for HCC.[41] The results of our study show that LISI has a higher AUROC in mid- to long-term OS and early recurrence than existing markers, and this holds even in a multicenter study.

This study evaluated the effectiveness of various predictive models, including LISI, APRI, FIB-4, GNRI, ALBI grade, and ALICE, using AUROC values. While LISI showed strong performance in predicting 2-year OS and recurrence, especially in patients with vascular invasion, the FIB-4 index fell behind. Over longer periods, LISI's predictive power for LISI decreased, whereas APRI and FIB-4 index reliability improved, showing the varying strengths of these models over different prognostic timelines. According to various factors, for instance, the APRI is effective in predicting RR but not OS; on the other hand, LISI serves as a dual predictor for both RR and OS. It remains challenging to differentiate between multicentric recurrence and intrahepatic metastasis.[42] The recurrences resulting from CTC are more likely to occur in the initial stages, which is within 2 years after hepatectomy, as they are intrahepatic metastases or extrahepatic recurrence. Our study revealed that LISI was able to predict early recurrence, particularly in intrahepatic metastases, with a higher degree of accuracy than other scores, thus lending

TABLE 4 Multivariate Cox hazard analysis for prediction of 2Y-RR.

Variables	HR	95% CI	*p*-value
HISCO score per 1	1.01	1.01–1.01	<.01
Blood loss, per 100 mL	1.02	1.01–1.03	<.01
HBV	(1)		
HCV	1.46	1.06–2.01	.02
NBNC	1.39	1.01–1.91	.046

Abbreviations: 2Y-RR, two-year recurrence rate; CI, confidence interval; HISCO, Hiroshima Surgical Study Group of Clinical Oncology; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV/non-HCV.

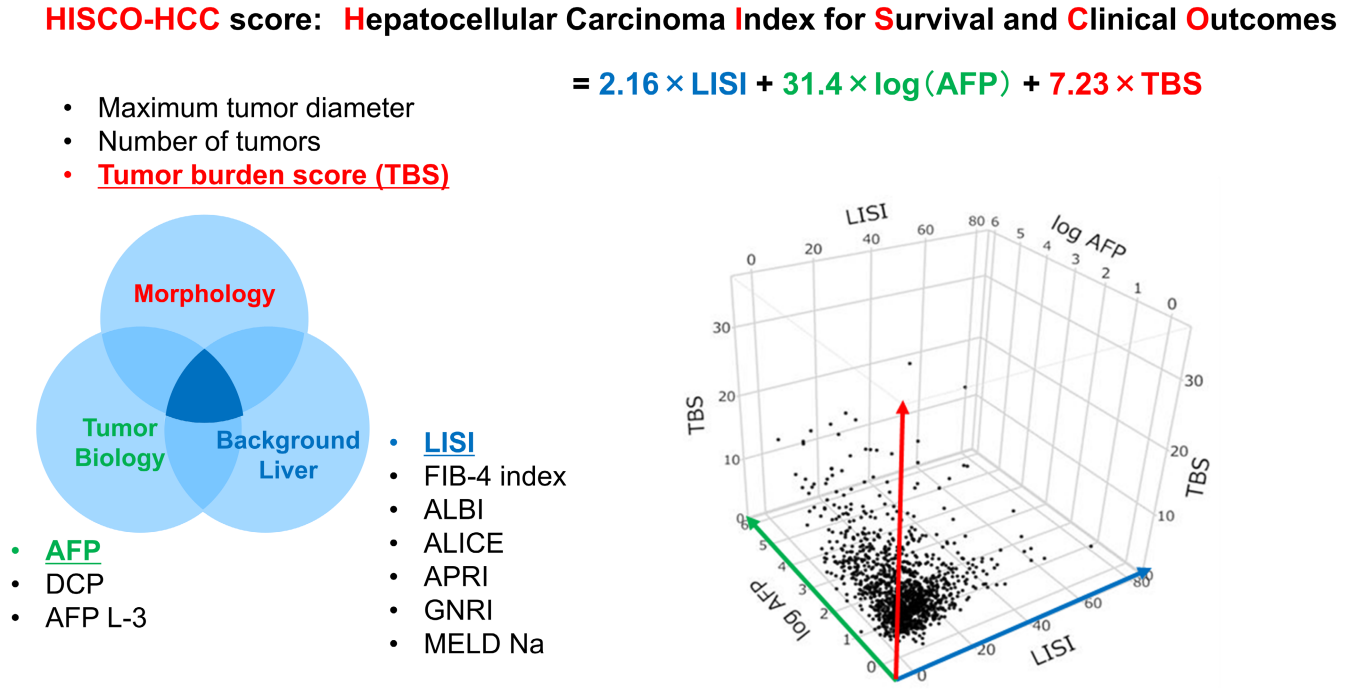

FIGURE 5 HISCO-HCC score.

further support to our hypothesis that the antitumor activity of liver NK cells is highly correlated with early recurrence caused by CTCs.

However, the results of the precise analysis raised the issue that LISI alone has a lower predictive ability for RR after 2 years. One reason for this is that it is challenging to predict recurrence at 5 years based on liver background factors alone. Therefore, to further improve predictive ability, it is necessary to develop a valid model based on three critical aspects: morphology, tumor biology, and background liver condition. LISI also showed a better predictive ability than existing markers as a liver background factor in this study. Therefore, a new score was developed by adding AFP and TBS. Although additional pathological factors, including vascular invasion, were originally considered, only preoperative factors were included in this new score, allowing for preoperative stratification and prediction of prognostic risk.

This study had several limitations that should be acknowledged. The LISI utilized in this study was computed from living-donor livers exhibiting moderate to mild liver fibrosis.[24] Therefore, it is crucial to include more liver samples with severe fibrosis and HCC in future studies. Currently, efforts are being undertaken to reconfirm LISI in patients undergoing liver resection for HCC, and the application of the revised LISI score may enhance the predictive value of the HISCO-HCC score.

In conclusion, LISI is a more versatile index for both OS and early recurrence after HCC hepatectomy than the existing indices, especially in cases of HCC with vascular invasion. The introduction of the HISCO-HCC score holds substantial promise for enhancing individualized patient care strategies, optimizing treatment approaches, and ultimately improving prognostic outcomes in HCC.

AUTHOR CONTRIBUTIONS

YI and MO conceived and designed the study. Y.I., M.O., T.K., N.H., M.H., T.O., D.T., K.O., and T.A. acquired the data and performed all the experiments. Y.I., T.N., M.A., K.S., and M.O. analyzed and interpreted the data. Y.I. and M.O. drafted the manuscript. All authors have revised the manuscript critically and approved the final version of the manuscript for publication.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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