Prognostic Nutritional Index as a Prognostic Factor for Very Early-Stage Hepatocellular Carcinoma

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INTRODUCTION: **Field factors play more important roles in predicting the outcomes of patients compared with tumor factors in early-stage hepatocellular carcinoma (HCC). However, the prognostic ability of noninvasive serum marker scores for hepatic fibrosis and liver functional reserve on very early-stage HCC is still not yet determined. We aimed to investigate the performance of these serum marker scores in predicting the prognoses of patients with very early-stage HCC.**

METHODS: **A total of 446 patients with very early-stage HCC from 2012 to 2022 were retrospectively enrolled. Serum biomarkers and prognostic scores determining overall survival (OS) were analyzed by Cox proportional hazards model. We compared the Akaike information criterion among the prognostic nutritional index (PNI), aspartate aminotransferase–to-platelet ratio index, albumin-bilirubin (ALBI) score, EZ (easy)-ALBI score, modified ALBI score, fibrosis-4 score, and lymphocyte-to-monocyte ratio to determine the predictability on the OS.**

RESULTS: **After a median follow-up of 41.0 months (interquartile range 36.9–45.1 months), 81 patients died, with a 5-year OS rate of 71.0%. Among the noninvasive serum marker scores, PNI had the best performance in predicting the OS with the lowest Akaike information criterion (846.407) compared with other scores. Moreover, we stratified the patients into high-risk (PNI <45) and low-risk (PNI ≥45) groups. It showed that the 5-year OS rates were 83.4% and 60.8% in the low-risk and high-risk PNI groups, respectively ($P < 0.001$).**

DISCUSSION: **PNI had the best performance in predicting the OS for patients with very early-stage HCC.**

KEYWORDS: hepatocellular carcinoma; nutrition; prognostic nutritional index

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/B71, http://links.lww.com/CTG/B72, http://links.lww.com/CTG/B73, http://links.lww.com/CTG/B74, http://links.lww.com/CTG/B75, http://links.lww.com/CTG/B76, and http://links.lww.com/CTG/B77

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INTRODUCTION

Liver cancer stands as one of the most prevalent forms of cancer globally and is ranked as the third leading cause of cancer-related deaths worldwide, with approximately 905,677 new cases diagnosed in 2020 (1). Hepatocellular carcinoma (HCC), the primary histologic type of liver cancer, is responsible for most diagnoses and fatalities associated with liver cancer (2). The Barcelona Clinic Liver Cancer (BCLC) clinical algorithm is the most commonly used system nowadays for patient stratification (3). Very early-stage HCC (BCLC stage 0) refers to a population of patients with Child-Pugh class A liver functional reserve, with a single tumor ≤2 cm and the absence of cancer-related symptoms, vascular invasion, or extrahepatic metastasis (3). Patients with very early-stage HCC typically exhibit satisfactory prognoses, boasting a median overall survival (OS) time exceeding 5 years (4,5). Nevertheless, the predictive models for outcomes of patients with BCLC stage 0 HCC are not well studied comprehensively till now.

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Several scores based on serum biomarkers have been developed to investigate the status of hepatic inflammation, fibrosis, and liver function and to predict the outcomes of patients with advanced chronic liver disease (ACLD) or HCC. The albumin-bilirubin (ALBI) score, based on serum albumin and bilirubin level, has been widely validated as a reliable tool to evaluate the grade of liver functional reserve (6,7). Recently, a simplified version of ALBI score, known as EZ-ALBI score, had showed noninferiority compared with the ALBI score (8,9). Aspartate aminotransferase–to-platelet ratio index (APRI) and fibrosis (FIB)–4 score had satisfactory ability to reflect the stage of liver fibrosis among patients with ACLD (10,11). Besides, the severity of systemic inflammation could determine the outcomes of patients with cancer. For example, lymphocyte-to-monocyte ratio (LMR) has been validated as a serum biomarker to reflect the severity of systemic inflammation and to predict the prognosis of the patients with various types of cancers, including HCC (12,13). Furthermore, nutritional status has been found to have a crucial impact on the tumor microenvironment that plays remarkable roles in tumor growth, progression, and metastasis. The prognostic nutritional index (PNI) allows physicians to assess the nutritional and inflammatory status of patients with cancer accurately and thus has been performed to predict the outcomes (14–19).

While several studies have compared the predictability of these biomarkers in different patient groups with HCC (6,8,9,12,16,19–21), there remains a dearth of comprehensive studies focusing on patients with very early-stage HCC. This study aimed to compare the prognostic value of the serum biomarker scores in predicting the outcome of patients with very early (BCLC stage 0) HCC.

METHODS

Data sources

This noninterventional retrospective cohort study compared and analyzed the predictability of different serum biomarkers on OS of patients with very early-stage HCC in a real-world setting. We used data from the Taipei Veterans General Hospital HCC registration database (Figure 1). The study was executed in accordance with the Declaration of Helsinki and was approved by the joint institutional review board (IRB) (VGHIRB No. 2023-05-011BC). As a retrospective cohort study, informed consent was waived by the IRB. Patient information was deidentified before the initiation of this study.

Patients and follow-up

This study enrolled 446 consecutive patients with treatment-naïve BCLC stage 0 HCC who were diagnosed between 2012 and 2022 in Taipei Veterans General Hospital. All patients who were newly diagnosed with HCC at Taipei General Veterans Hospital were discussed to determine the treatment strategy by a multidisciplinary committee (22,23). The decision of therapy for HCC was shared with the patient and the physician by the multidisciplinary experts after discussing the efficacies, risks, and complications of the currently available treatment modalities (22).

All the demographic characteristics, baseline laboratory data, tumor factors, treatments, and outcomes of the enrolled patients were prospectively collected in the HCC registration system (22–25). We continued to follow-up the patients until patients had dead or lost to follow-up.

Biochemical and serologic markers

Patients were examined at the time when HCC was diagnosed. Age, gender, tumor number, tumor size, etiology, serum creatinine, alanine aminotransferase, aspartate aminotransferase (AST), total bilirubin, albumin, and alpha fetoprotein levels, white blood cell differential count, hemoglobin, and platelet (PLT) were examined. In our cohort, the interval between diagnosis and treatment was less than 1 month for all patients.

The serum biomarkers were calculated as follows:

1. LMR = serum lymphocyte/serum monocyte (13)
2. FIB-4 = age (years) × AST (U/L)/(PLT [10^9/L] × ALT$^{1/2}$ [U/L]) (10)
3. PNI = ([10 × serum albumin (g/dL)] + [0.005 × total lymphocyte count]) (14–16)
4. ALBI score = ($\log_{10}$ bilirubin [μmol/L] × 0.66) + (albumin [g/L] × −0.0852) (7)
5. EZ-ALBI score = total bilirubin (mg/dL) − (9 × albumin [g/dL]) (8)
6. APRI = (serum AST/upper limit of normal of AST)/PLT (10^9/L) (11)

Outcome events

The primary outcome of this study was OS. The index date was defined as the date of diagnosis for HCC. OS was defined from the index date to the date of death or last date of follow-up. The follow-up end point was set on January 30, 2022.

Statistical analysis

Categorical and ordinal variables are presented as frequency, and continuous variables are presented as median with interquartile range where appropriate. The selection of a PNI cutoff value in our study was based on the Youden index, which identified 44.6 as

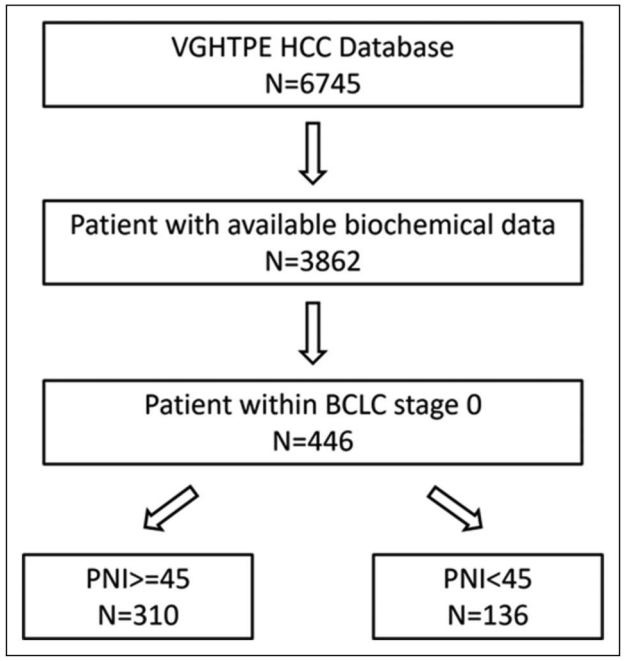

Figure 1. Study flowchart. BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; PNI, prognostic nutritional index.

the optimal value. For enhanced clinical applicability and convenience, we rounded this to 45 as our chosen cutoff. This cuff-off value was compatible with the established practices in the literature (14,17–19,26). The optimal cutoff value of LMR, FIB-4, ALBI, EZ-ALBI, and APRI were determined by consensus according to previous studies, which yield 3.6, 3.25, -2.6, -34.4, and 1.5, respectively (14,21,27–29). The cutoff value of other variables was based on the normal value of clinical laboratory examination: albumin was 4 g/dL, bilirubin was 1 mg/dL, alanine aminotransferase was 40 U/L, AST was 45 U/L, platelet was 100,000/mm^3, and alpha fetoprotein was 20 ng/mL.

The baseline characteristics were compared using the Pearson χ^2 test or Fisher exact test for categorical variables, whereas continuous variables were compared with the Mann-Whitney *U* test. The cumulative OS rates were estimated by the Kaplan-Meier method and compared by the Cox proportional hazards model. The assumption of proportional hazards was confirmed by the log minus log plot of survival in the Cox regression analysis (30). The performance of serum-based scores to predict the OS were compared using homogeneity and Akaike Information Criterion (AIC). A 2-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS Statistics for Windows, version 24.0 (IBM, Armonk, NY) and R version 3.6.3.

RESULTS

Basic characteristics

The clinical characteristics of enrolled patients are summarized in Table 1. Among the 446 patients, 431 underwent curative treatments, including 190 patients with surgical resection, 6 patients with liver transplantation, 226 patients with radiofrequency ablation (RFA), and the remaining 9 patients with percutaneous ethanol injection therapy (PEIT). Besides, among the 15 patients who received noncurative therapy, 14 patients underwent transarterial chemoembolization (TACE), and the remaining 1 patient received best supportive treatment.

In our cohort, 273 (61.2%) patients were male, and the remaining 173 (38.8%) patients were female. Compared with the female patients, male patients were younger in age, more with hepatitis B virus (HBV) infection, less with chronic hepatitis C virus (HCV) infection, and had higher serum albumin levels. Other demographic characteristics, tumor factors, liver functional reserve, serum marker scores, and treatment modalities were comparable between male and female patients.

Comparison of selected biomarkers and scores

After a median follow-up of 41.0 months (interquartile range 36.9–45.1 months), 81 patients died, and the 5-year OS rate was 71.0%. As summarized in Table 2, univariate analysis showed that older in age, lower serum albumin, higher AST levels, longer prothrombin time international normalized ratio (PT INR), and lower platelet count were associated with poorer OS. Moreover, all serum biomarker scores, including ALBI grade, modified ALBI grade, EZ-ALBI grade, APRI, LMR, PNI, and FIB-4 could predict the outcomes of patients with very early-stage HCC (Figure 2 and Supplementary Figure S1 A–F, Supplementary Digital Contents 1–6, http://links.lww.com/CTG/B71, http://links.lww.com/CTG/B72, http://links.lww.com/CTG/B73, http://links.lww.com/CTG/B74, http://links.lww.com/CTG/B75, http://links.lww.com/CTG/B76). Because these marker scores were composed of serum markers in the univariate analysis, they were not enrolled into multivariate analysis. By the multivariate Cox regression analysis, age older than 65 years (hazard ratio [HR] 1.591, 95% confidence interval [CI] 1.003–2.523, $P = 0.048$), platelet count <100,000/mm^3 (HR 1.617, 95% CI 1.016–2.574, $P = 0.043$), and serum albumin level <4 g/dL (HR 2.217, 95% CI 1.330–3.694, $P = 0.002$) were the independent risk factors to determine the poor OS in patients with very early-stage HCC.

Subsequently, we compared the prognostic performance of the serum-based scores for HCC, and the result is summarized in Table 3. Among all the scores, PNI had the best performance with the lowest AIC value of 846.407. When stratified by the etiologies of HCC, PNI consistently displayed a robust prognostic capability across various subgroups, with the lowest AIC values observed in HCV-related HCC (see Supplementary Table S1, Supplementary Digital Content 7, http://links.lww.com/CTG/B77). By contrast, the modified ALBI score, despite showing the lowest AIC in patients with HBV-related HCC, exhibited poor discriminative ability for individuals with HCV-related HCC. In addition, although APRI had the lowest AIC in nonviral HCC, its predictive performance was unsatisfactory in both cases with HBV-related HCC and HCV-related HCC.

Characteristics of patients according to their PNI status

Because PNI was the most significant prognostic score to predict the OS, we then divided the patients into high (PNI ≥45) and low (PNI <45) PNI groups. It showed that age, sex, viral etiology, platelet count, PT INR, serum albumin, total bilirubin, AST levels, treatment modalities, ALBI grade, EZ-ALBI grade and modified ALBI-grade were different significantly between the two groups of patients (Table 4).

Patients with lower PNI had significantly shorter OS compared with patients with higher PNI ($P < 0.001$, Figure 2). The 1-year, 3-year, and 5-year OS rates were 98.2%, 91.6%, and 83.4%, respectively, for high PNI group; 89.9%, 72.5%, and 60.8%, respectively, for low PNI group.

DISCUSSION

There are several major findings in this study. First, compared with those with advanced stage HCC, patients with very early-stage HCC had more favorable outcomes, with a 5-year OS rate of 71.0%. Second, we discovered serum-based scores such as FIB-4, LMR, PNI, ALBI grade, EZ-ALBI grade, modified ALBI grade, and APRI could predict the outcomes of patients with very early-stage HCC. Third, among these scores, PNI had the best performance in predicting the OS of patients and can accurately stratify patients into different prognostic groups. The results confirmed the theory that liver function reserve and inflammatory, fibrosis, and nutritional status had a great impact on the outcome of patients with very early-stage HCC.

Nutritional status has been proven to be correlated with prognosis with various types of malignancies, including HCC (26,31,32). A better nutritional status can lead to a more favorable outcome in patients with cancer because they can promote immune response and indicate a better reserve of body function against the disease burden (32,33). Serum albumin level has long been considered as a reliable marker for liver function reserve and nutritional status. Besides, immune and inflammatory status have also been considered as important

Table 1. Baseline characteristics

	All patients (n = 446)	Male (n = 273)	Female (n = 173)	*P* value
Baseline characteristics				
Age (yr)	65.0 (58.0–74.0)	63.0 (55.0–71.0)	71.0 (62.0–77.0)	0.001
Tumor size (cm)	1.60 (1.30–1.80)	1.60 (1.40–1.90)	1.60 (1.30–1.80)	0.276
Etiology				
HBsAg (+/−)	222/224 (49.8%/50.2%)	160/113 (58.6%/41.4%)	62/111 (35.8%/64.2%)	<0.001
Anti-HCV (+/−)	149/297 (33.4%/66.6%)	70/203 (25.6%/74.4%)	79/94 (45.7%/54.3%)	<0.001
Serum biomarkers				
Platelet (/mm^3)	133,000 (92,000–180,000)	140,000 (97,000–181,000)	120,000 (82,000–178,500)	0.499
INR	1.07 (1.02–1.13)	1.07 (1.02–1.13)	1.08 (1.02–1.15)	0.611
Albumin (g/dL)	4.0 (3.7–4.3)	4.1 (3.8–4.3)	4.0 (3.6–4.2)	0.011
Total bilirubin (mg/dL)	0.71 (0.51–1.04)	0.72 (0.51–1.05)	0.67 (0.48–1.04)	0.492
ALT (U/L)	29.5 (20.0–44.0)	30.0 (21.0–43.0)	28.0 (18.0–49.0)	0.489
AST (U/L)	32.0 (24.0–46.3)	30.0 (23.0–43.0)	34.0 (25.0–51.0)	0.228
AFP (ng/mL)	9.51 (3.56–60.13)	7.88 (3.26–48.6)	12.2 (4.53–71.7)	0.402
Curative treatment (yes/no)	431/15 (96.6%/3.4%)	264/9 (96.7%/3.3%)	167/6 (96.5%/3.5%)	0.922
Serum marker scores				
ALBI (1/2/3)	266/174/6 (59.6%/39.0%/1.3%)	167/103/3 (61.2%/37.7%/1.1%)	99/71/3 (57.2%/41.0%/1.7%)	0.640
Modified ALBI (1/2A/2B/3)	266/103/71/6 (59.6%/23.1%/15.9%/1.3%)	167/68/35/3 (61.2%/24.9%/12.8%/1.1%)	99/35/36/3 (57.2%/20.2%/20.8%/1.7%)	0.120
EZ-ALBI (1/2/3)	272/171/3 (61.0%/38.3%/0.7%)	172/100/1 (63.0%/36.6%/0.4%)	100/71/2 (57.8%/41.0%/1.2%)	0.370
APRI	0.58 (0.33–1.05)	0.48 (0.31–0.98)	0.69 (0.36–1.33)	0.542
LMR	3.34 (2.46–4.34)	3.19 (2.33–4.20)	3.52 (2.56–4.55)	0.470
PNI	48.3 (43.8–51.9)	49.2 (44.6–52.5)	47.1 (41.7–51.2)	0.454
FIB-4	2.99 (1.89–5.28)	2.51 (1.77–4.18)	4.01 (2.34–6.90)	0.478

Continuous variables are expressed as the median with the 25th and 75th percentiles.
AFP, alpha fetoprotein; ALB, albumin; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; FIB-4, fibrosis-4 index; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; LMR, lymphocyte-to-monocyte ratio; PLT, platelet; PNI, prognostic nutritional index; PT INR, prothrombin time international normalized ratio.

factors on tumor growth. Lymphocyte has been known as an important character in the immune response against malignancies. Adequate lymphocyte action is considered favorable because they can control tumor growth through cytokine secretion or direct cytotoxic effect by B and T lymphocytes (19,33,34).

PNI, a biochemical indicator that was composed of the patients' lymphocyte and albumin level, could indicate the patient's nutritional and inflammatory status. It has been validated to predict the prognosis of patients with cancer (14,15,19,32,33,35). Several studies have assessed the impact of PNI on patients with HCC who underwent surgical resection (14,17–19). However, there remains a notable gap in research concerning the role of PNI in predicting outcomes for patients with BCLC stage 0 HCC, extending beyond the context of surgical resection. The novelty of our research is to compare the ability of the current serum marker scores to predict the outcomes of patients with BCLC stage 0 HCC undergoing diverse treatment modalities. In our study, patients with a higher PNI level were younger in age, were more in male patients, had more HBV infection, had less HCV infection, had higher platelet counts, had shorter PT INR, had higher serum albumin level, had lower bilirubin level, and had lower AST level when compared with their counterparts. It indicated that patients with a higher PNI level had a better liver function reserve and milder hepatic necroinflammation than those with a lower PNI level. Besides, our study evaluated the prognostic ability of several serum marker scores in patients with HCC. It revealed PNI had the best performance in predicting the outcomes of patients with BCLC stage 0 HCC. Of note, patients with a high PNI level yield an excellent 5-year OS of 83.4%. Our finding revealed that PNI surpasses other serum-based scores in terms of predictability and patient stratification among patients with very early-stage HCC and varying etiologies. This revelation not only advances our comprehension of predictive markers but also equips clinicians with a valuable tool to identify high-risk patients within the realm of very early-stage HCC.

Besides, for patients with advanced stage HCC, tyrosine kinase inhibitors (TKIs) and immunotherapy could provide

Table 2. Univariate and multivariate survival analyses of patients (n = 446)

Variable		Univariate		Multivariate	
		HR	*P* value	HR	*P* value
Age (yr)	>65	1.838 (1.165–2.900)	0.009	1.591 (1.003–2.523)	0.048
Sex	Male/female	1.333 (0.859–2.070)	0.213		
Tumor size (cm)	>1.5	0.813 (0.518–1.277)	0.369		
ALB (g/dL)	<4	2.830 (1.756–4.562)	<0.001	2.217 (1.330–3.694)	0.002
BILI (mg/dL)	>1	1.270 (0.799–2.019)	0.313		
ALT (U/L)	>40	1.213 (0.772–1.905)	0.402		
AST (U/L)	>45	2.165 (1.395–3.358)	0.001		
PLT (/L)	<100,000	2.206 (1.424–3.420)	<0.001	1.617 (1.016–2.574)	0.043
INR	>1.1	1.666 (1.070–2.596)	0.024		
AFP (ng/mL)	>20	1.130 (0.724–1.765)	0.590		
Curative treatment	Yes	0.749 (0.274–2.049)	0.574		
ALBI	2 + 3	2.598 (1.636–4.125)	<0.001		
Modified-ALBI	2B + C	2.609 (1.652–4.122)	<0.001		
EZ-ALBI	2 + 3	2.638 (1.668–4.172)	<0.001		
APRI	>1.5	2.197 (1.361–3.546)	0.001		
LMR	<3.6	2.433 (1.488–3.978)	<0.001		
PNI	<45	2.926 (1.888–4.533)	<0.001		
FIB-4	>3.25	2.393 (1.512–3.787)	<0.001		

AFP, alpha fetoprotein; ALB, albumin; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; FIB-4, fibrosis-4 index; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HR, hazard ratio; LMR, lymphocyte-to-monocyte ratio; PLT, platelet; PNI, prognostic nutritional index; PT INR, prothrombin time international normalized ratio.

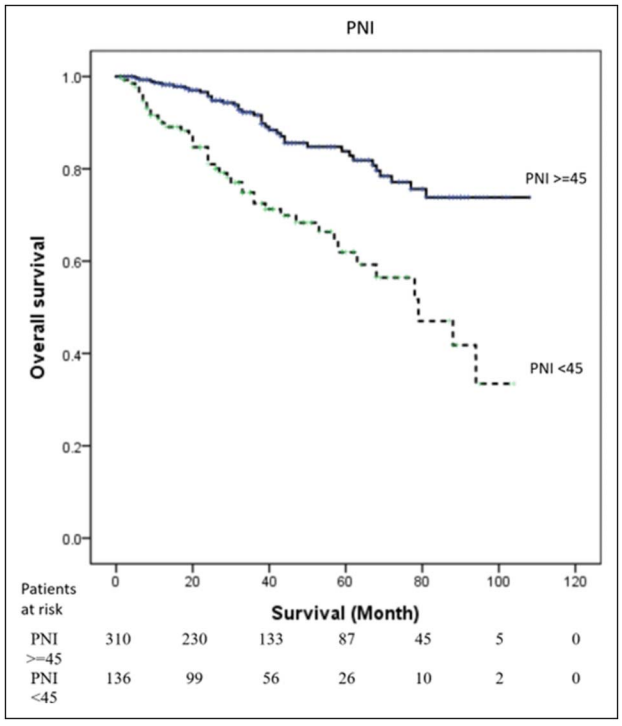

Figure 2. Comparison of OS between high PNI group and low PNI group. OS, overall survival; PNI, prognostic nutritional index.

a promising OS and could be served as the front-line therapy for such patients in the recent years (36). Caputo et al (37) further demonstrated the effective predictive capability of PNI in determining OS among patients with unresectable HCC following TKI therapy with sorafenib. These findings collectively affirm the potential of PNI as a promising prognostic factor applicable to patients with HCC at various tumor stages and undergoing different treatment modalities, such as the

Table 3. Prognostic performance of serum-based scores in 446 patients with HCC

	Homogeneity	AIC	*P* value
PNI	23.325	846.407	<0.001
EZ-ALBI	24.324	851.218	<0.001
Modified-ALBI	21.675	853.847	<0.001
ALBI	20.513	854.235	<0.001
APRI	5.082	855.617	0.051
FIB-4	12.039	864.784	0.001
LMR	3.209	866.016	0.077

ALBI, albumin–bilirubin; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; FIB-4, fibrosis-4 index; HCC, hepatocellular carcinoma; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index.

Table 4. Patients' characteristics according to PNI

	All patients (n = 446)	PNI ≥45 (n = 310)	PNI <45 (n = 136)	*P* value
Baseline characteristics				
Age	65.0 (58.0–74.0)	64.0 (57.0–71.0)	71.0 (61.0–77.8)	0.001
Sex (M/F)	273/173 (61.2%)	200/110 (64.5%)	73/63 (53.7%)	0.031
Tumor size (cm)	1.60 (1.30–1.80)	1.60 (1.40–1.80)	1.60 (1.30–1.90)	0.242
Etiology				
HBsAg (+/−)	222/224 (49.8%)	166/144 (53.5%)	56/80 (41.2%)	0.016
Anti-HCV (+/−)	149/297 (33.4%)	91/219 (29.4%)	58/78 (42.6%)	0.006
Serum biomarkers				
Platelet (/mm^3)	133,000 (92,000–180,000)	147,000 (113,000–196,000)	87,000 (59,000–122,000)	0.005
PT INR	1.07 (1.02–1.13)	1.05 (1.00–1.10)	1.13 (1.07–1.21)	<0.001
Albumin (g/dL)	4.0 (3.7–4.3)	4.2 (4.0–4.4)	3.6 (3.2–3.8)	<0.001
Total bilirubin (mg/dL)	0.71 (0.51–1.04)	0.64 (0.45–0.94)	0.92 (0.65–1.38)	0.041
ALT (U/L)	29.5 (20.0–44.0)	28.5 (19.8–42.0)	31.0 (20.0–53.8)	0.143
AST (U/L)	32.0 (24.0–46.3)	28.0 (22.0–40.0)	42.0 (28.0–64.0)	0.007
AFP (ng/mL)	9.51 (3.56–60.13)	9.22 (3.50–60.0)	10.7 (3.93–60.2)	0.458
Curative treatment (yes/no)	431/15 (96.6%)	305/5 (98.4%)	126/10 (92.6%)	0.002
Prognostic score				
ALBI (1/2/3)	266/174/6 (59.6%/39.0%/1.3%)	246/64/0 (79.4%/20.6%/0%)	20/110/6 (14.7%/80.9%/4.4%)	<0.001
EZ-ALBI (1/2/3)	266/103/71/6 (59.6%/23.1%/15.9%/1.3%)	256/54/0 (82.6%/17.4%/0%)	16/117/3 (11.8%/86.0%/2.2%)	<0.001
mALBI (1/2A/2B/C)	272/171/3 (61.0%/38.3%/0.7%)	246/56/8/0 (79.4%/18.1%/2.6%/0%)	20/47/63/6 (14.7%/34.6%/46.3%/4.4%)	<0.001
APRI	0.58 (0.33–1.05)	0.44 (0.29–0.73)	1.17 (0.66–2.04)	0.383
LMR	3.34 (2.46–4.34)	3.73 (2.98–4.66)	2.43 (1.83–3.09)	0.390
FIB-4	2.99 (1.89–5.28)	2.37 (1.59–3.63)	6.38 (3.63–10.3)	0.478

Continuous variables are expressed as the median with the 25th and 75th percentiles.
Abbreviations: AFP, alpha fetoprotein; ALB, albumin; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; FIB-4, fibrosis-4 index; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; LMR, lymphocyte-to-monocyte ratio; LT, liver transplantation; OP, surgical operation; PEI, percutaneous ethanol injection; PLT, platelet; PNI, prognostic nutritional index; PT INR, prothrombin time international normalized ratio; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; TKI, tyrosine kinase inhibitor.

combination of TKI plus immune checkpoint inhibitors. Nevertheless, further prospective studies are needed to validate this concept.

Treatment modality is an important factor to determine the outcomes of patients with HCC. According to the current guidelines for the management of HCC, curative therapy is the recommended treatment modality for patients with very early-stage HCC (3). However, several previous studies showed that substantial patients with BCLC stage 0 HCC underwent noncurative treatments, such as TACE, systemic therapy, or supportive treatment (5,38,39). For example, one Korean cohort study that enrolled patients between 2003 and 2008 showed that TACE and best supportive treatment were performed in 62.9% and 1.2%, respectively, among patients with BCLC stage 0 HCC. Our previous study that enrolled cases with HCC from 2007 to 2015 disclosed that 10% of patients with BCLC stage 0 HCC underwent noncurative treatment modality (5). In our current study, only 15 (3.4%) patients received noncurative treatments. Because most of the patients underwent curative treatment, treatment modality was not an independent risk factor to predict the outcomes of patients with HCC in our study. Moreover, among the 235 patients who received local ablation therapy, 226 patients underwent RFA and only 9 patients received PEIT. It was compatible with the trend by the previous nationwide report from Italy (40). Because RFA could provide a better local tumor control compared with PEIT for early-stage HCC (41), the outcomes of the patients in our cohort were acceptable with a 5-year OS rate of 71.0%.

Besides, we have calculated the median time to recurrence for curative treatments and time to progression for noncurative treatments. Specifically, for patients who underwent surgical resection, RFA, and TACE, the median times to recurrence or progression were 25.0 months (10.0–50.0),

15.0 months (7.5–32.5), and 13.0 months (10.0–18.0), respectively. However, the difference in disease progression was not statistically significant between patients who underwent curative treatment and those who received TACE. Nevertheless, this observation might be influenced by the relatively small number of patients (only 14) who underwent TACE in our cohort.

There are still several limitations in this study. First, the research is a single-center retrospective cohort study, and further validation on prospective cohorts would be needed to confirm the predictability of serum-based biomarker scores in determining the outcomes of patients with very early-stage HCC. Second, most of the patients in our study cohort had viral-related HCC; whether other etiologies of HCC will interfere the results or not should be studied further. Third, some of the biomarkers involved in this study still lack universal acknowledgment of cutoff value and clinical applicability. Hence, further studies with larger scale and more detailed information will be needed. Last, other cofounding factors such as cirrhosis and portal hypertension, viral hepatitis treatment, and alcohol consumption were not included in the initial database design (42). Further studies should be conducted to evaluate the effect of these factors on the prognosis of patients with BCLC stage 0 HCC.

For patients with very early-stage HCC, PNI had the best performance in predicting the OS of the patients and can accurately stratify patients into different prognostic groups.

CONFLICTS OF INTEREST

Guarantor of the article: Chien-Wei Su, MD, PhD.

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Study Highlights

WHAT IS KNOWN

- ✓ Field factors such as inflammatory, nutritional, and fibrotic status can interfere tumor growth and thus have effect on patients' outcome.
- ✓ Lymphocytes, which can suppress tumor growth by secreting cytokine and direct cytotoxic effect, play an important role in immune response against malignancies.
- ✓ Tools for risk stratification in patients with very early-stage hepatocellular carcinoma (HCC) is not yet fully developed.

WHAT IS NEW HERE

- ✓ Better nutritional status and greater lymphocytes are associated with a favorable outcome in patients with very early-stage HCC because field factors play more important role in early malignancies.
- ✓ Prognostic nutritional index, consisting of lymphocyte count and serum albumin, can serve as a quantitative indicator of patients' inflammatory and nutritional status. Moreover, it can predict patients' outcome and stratify patients into different risk groups.
- ✓ Prognostic nutritional index outperformed other serum-based score and biomarkers on predictability and patient stratification for patients with very early-stage HCC. It can assist physicians to identify high-risk patients at early stages and help develop personalized care.

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