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Original Article

The predictive value of contrast-enhanced ultrasound parameters combined with inflammatory nutritional indicators for recurrence and survival of early liver cancer following radiofrequency ablation

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Abstract: This study aimed to explore the predictive value of contrast-enhanced ultrasound (CEUS) parameters combined with inflammatory-nutritional indices for recurrence and survival following radiofrequency ablation (RFA) in early-stage hepatocellular carcinoma (HCC). It also sought to provide evidence-based personalized treatment strategies for clinical practice. A retrospective analysis was conducted on the clinical data of 263 HCC patients who underwent RFA at Henan Provincial People's Hospital from January 2021 to June 2022. Comprehensive data on tumor angiogenesis and hemodynamics were collected using CEUS, and the Prognostic Inflammatory and Nutritional Index (PINI) was calculated. Multivariate Cox analysis was performed to assess the predictive efficacy of these parameters for tumor recurrence and long-term survival. The study found that a low PINI score was associated with a higher risk of postoperative tumor recurrence and mortality. Among the CEUS parameters, time to peak, peak intensity, enhancement rate, and PINI were significantly correlated with tumor recurrence and patient survival. The combined scoring system, integrating CEUS parameters and PINI (CEUS-PINI), effectively distinguished different risk groups and was significantly associated with both recurrence-free survival and overall survival. In conclusion, the combination of CEUS parameters and PINI provides a simple, non-invasive prognostic tool that helps predict recurrence risk and survival outcomes following RFA in early-stage HCC. This combined assessment system can aid in the early identification of high-risk patients and facilitate the development of postoperative monitoring and management strategies.

Keywords: Contrast-enhanced ultrasound, inflammatory nutritional index, hepatocellular carcinoma, radiofrequency ablation, recurrence

Introduction

Liver cancer is one of the most lethal malignancies worldwide, with high morbidity and mortality rates. It is estimated that over 90% of all liver cancer cases are hepatocellular carcinoma (HCC) [1]. In terms of clinical management, surgical resection or radiofrequency ablation (RFA) is typically recommended for patients with HCC at Barcelona Clinic Liver Cancer (BCLC) stage 0 or stage A [1, 2]. However, although the 5-year median survival rate for early HCC patients treated with RFA can reach 50% to 70%, the recurrence rate remains as high as 70% [3]. Postoperative recurrence remains a significant factor affecting patient survival [4]. Thus, identifying effective predictors for recurrence risk and survival in liver cancer patients after RFA is critical for clinical decision-making and patient management. Contrast-enhanced ultrasound (CEUS) is a non-invasive imaging technique that provides detailed information on tumor angiogenesis and hemodynamics by using microbubble contrast agents to enhance ultrasound signals [5]. Recent studies have demonstrated the potential value of CEUS parameters in evaluating tumor biological characteristics and predicting HCC recurrence [6, 7]. Additionally inflammation and malnutrition are significant contribu-

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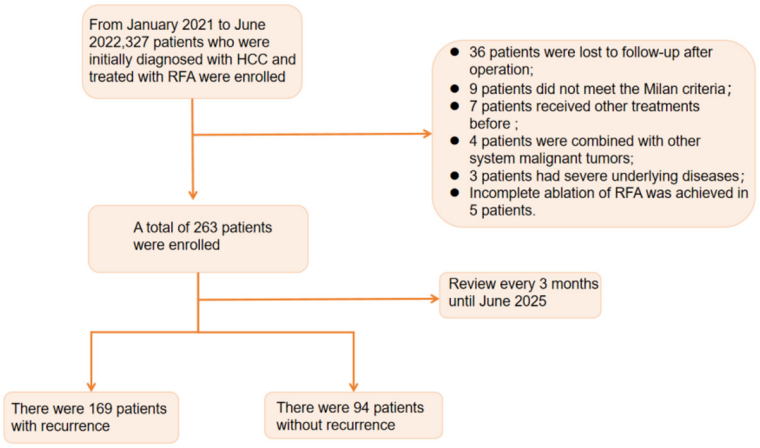

Figure 1. Flowchart of patient enrollment. Note: HCC, hepatocellular carcinoma; RFA, radiofrequency ablation.

tors to the progression of liver cancer. The Prognostic Inflammatory and Nutritional Index (PINI) has been utilized to assess morbidity and mortality risks in patients with inflammation and/or malnutrition, particularly in intensive care unit patients. It has been shown that inflammatory nutritional indicators are closely linked to the prognosis of liver cancer patients [8, 9]. While the prognostic value of CEUS parameters and inflammatory nutritional indicators in liver cancer has been explored individually, there is limited research on the combined use of these factors for predicting recurrence and survival following RFA. The objective of this study was to investigate the combined predictive value of CEUS parameters and PINI for recurrence risk and survival outcomes in early-stage liver cancer after RFA. This approach aims to enhance the accuracy of clinical outcome predictions and enable the development of more personalized treatment strategies for clinical practice.

Data and methods

Data source

A total of 263 patients with HCC who received their initial treatment at Henan Provincial People's Hospital between January 2021 and June 2022 were included in this study. The inclusion criteria were as follows: (1) All patients met the diagnostic criteria for HCC based on radiological or histological findings, according to the *Guidelines for the Diagnosis and Treatment of Primary Liver Cancer in China (2019 Edition)*; (2) Patients fulfilled the Milan criteria (a single tumor ≤5 cm in diameter or up to three tumors with each ≤3 cm in diameter), corresponding strictly to BCLC stage 0 or stage A; (3) No evidence of extrahepatic metastasis or major vascular invasion; (4) No prior anti-tumor treatment before surgery; (5) Recurrence was diagnosed by imaging examinations (e.g., CEUS) showing newly enhanced lesions with characteristics of liver cancer at the original ablation site or elsewhere within or outside the liver, accompanied by elevated alpha-fetoprotein (AFP) levels. The exclusion criteria were as follows: (1) Acute infection within two weeks before enrollment; (2) Presence of other systemic malignancies or severe underlying diseases; (3) Incomplete ablation (CEUS showing abnormal enhancement or unfilled defect areas in the ablation zone); (4) Incomplete clinical data (missing baseline characteristics, key parameters, or follow-up information). Patient screening and eligibility assessment were independently conducted by two authors of the research team. The detailed inclusion process is illustrated in **Figure 1**.

Study methods

Data collection: A total of 263 patients were included in this study, and clinical data were collected prior to RFA. The collected variables included sex, age, presence of cirrhosis or diabetes, etiology of liver disease, family history of liver cancer, complete blood count, liver function indices, and tumor marker AFP. Imaging data were obtained using CEUS. The PINI was calculated based on the above clinical data using the following formula: PINI = [Albumin (ALB) (g/dL)×0.9] - [Monocyte (mm^3) ×0.0007]. A PINI score of ≥1.48 was defined as normal immune-nutritional status, whereas a score <1.48 indicated immune malnutrition [10]. Informed consent was obtained from all participants prior to inclusion in the study.

Previous studies have identified several independent risk factors associated with the prognosis of HCC. In the study by Yang et al. [11],

Table 1. Baseline characteristics of patients with early-stage hepatocellular carcinoma

Variable	Number of patients	Percentage/Mean
Gender		
male	205	77.95%
female	58	22.05%
Age (years)		
≤55	69	26.24%
>55	194	73.76%
Cirrhosis	227	86.31%
Diabetes mellitus	61	23.19%
Etiology of liver disease		
hepatitis B	206	78.33%
hepatitis C	28	10.65%
alcohol-related liver disease	14	5.32%
other causes	15	5.70%
Family history of liver cancer	33	12.55%
Tumor differentiation		
poorly differentiated	161	61.22%
Moderate-well differentiated	102	38.78%
Maximum tumor diameter (cm)		
≤2.5	188	71.48%
>2.5	75	28.52%
Number of tumors		
1	200	76.05%
2	50	19.01%
≥3	13	4.94%
ALT (U/L)		
≤45	151	57.41%
>45	112	42.59%
AST (U/L)		
≤45	182	69.20%
>45	81	30.80%
ALB (g/L)		
≥35	30	11.41%
<35	233	88.59%
TBIL (μmol/L)		
≤20	163	61.98%
>20	100	38.02%
AFP/(ng/mL)		
≤15	149	56.65%
>15	114	43.35%
Monocyte count (mm^3)		
<1600	109	41.44%
≥1600	154	58.56%
PINI (points)	263	1.62±0.49
TTP (s)	263	16.87±2.14
PI (dB)	263	45.94±6.21

which established a prognostic model for HCC patients undergoing transarterial chemoembolization combined with RFA, tumor size (≤3 cm vs. >3 cm) and tumor number (single vs. multiple) were reported as independent predictors of progression-free survival and overall survival (OS). Similarly, in the predictive model developed by Zhang et al. [12] for early recurrence of HCC following RFA, univariate logistic regression analysis identified age (P=0.040; hazard ratio [HR]=1.043; 95% confidence interval [CI]: 1.002-1.087), serum ALB level (P=0.018; HR=0.913; 95% CI: 0.846-0.985), and tumor number (P=0.012; HR=4.889; 95% CI: 1.418-16.885) are significant variables (P<0.05). Further multivariate analysis confirmed that ALB level (P=0.037; HR=0.919; 95% CI: 0.850-0.995) and tumor number (P=0.041; HR=3.829; 95% CI: 1.058-13.851) were independent predictive factors for early recurrence in small HCC. Moreover, in a retrospective study by Han et al. [13], tumor diameter, tumor number, and AFP were identified as independent prognostic factors influencing RFS in HCC patients.

RFA treatment: RFA treatment was performed under real-time ultrasound guidance using the S-1500 tumor radiofrequency treatment system (Maide Medical Technology (Shanghai) Co., Ltd., Shanghai, China). Under local anesthesia, a surgical electrode was percutaneously inserted into the hepatic lesion, and ablation was conducted for approximately 10 minutes. The initial output power was set to 20 W and increased by 10 W at 1-minute intervals, up to a maximum of 90 W. Once the output power reached 90 W, ablation was maintained for an additional 2-3 minutes at a temperature of 90-95°C. When the tumor tissue became degenerated and necrotic and the impedance reached its peak value, the system automatically reduced the output power.

ER (dB/s)	263	2.12±0.36
ALBI grade		
grade 1	181	68.82%
grade 2	70	26.62%
grade 3	12	4.56%
BLCL stage		
stage 0	42	15.97%
stage A	221	84.03%

Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; AFP, alpha-fetoprotein; PINI, Prognostic Inflammatory and Nutritional Index; TTP, time to peak; PI, peak intensity; ER, enhancement rate; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer.

Each patient underwent three ablation sessions in total. The ablation range was designed to extend beyond the tumor margin by at least 1 cm, ensuring a safe boundary of no less than 0.5 cm to achieve complete tumor necrosis. All RFA procedures were performed by two senior physicians with extensive experience in interventional ultrasound.

CEUS inspection and analysis: A Siemens ACUSON Sequoia 512 color-Doppler ultrasound diagnostic system (ACUSON Sequoia 512; Siemens Healthineers, Germany) was employed. The hepatic examination mode was selected, using a convex-array transducer (4C1-S, 1-4 MHz). The maximum longitudinal section of each lesion was chosen for analysis. The CEUS examination was conducted in contrast-pulsed sequences mode with a mechanical index of 0.10. Imaging depth, image gain and acoustic output were kept constant during the imaging process. The ultrasound contrast agent SonoVue (sulphur hexafluoride microbubbles; Bracco, Milan, Italy) was used. According to the manufacturer's instructions, the lyophilised powder was reconstituted with sterile isotonic saline (5 mL), agitated thoroughly to yield a homogeneous milky-white suspension. The contrast was injected into a superficial vein of the forearm (2.0 mL), followed by a flush of isotonic saline (5 mL). The dynamic enhancement was recorded for approximately 2 minutes and contrast images were quantitatively analysed. Quantitative analysis was performed using the SonoLiver CAP software (TomTec Imaging Systems GmbH, Munich, Germany). A region of interest was placed either at the center of the lesion or at the most pronounced enhancement region. In cases of complete remission in which the lesion was no longer visible, the most significant area of peripheral echo enhancement was selected. The software automatically calculated quantitative CEUS parameters, including time to peak (TTP), peak intensity (PI), and enhancement rate (ER). The mean value over three independent measurements was recorded.

Postoperative follow-up: Postoperative evaluations were performed two months after RFA, including contrast-enhanced abdominal computed tomography/magnetic resonance imaging or CEUS, along with liver function tests and serum tumor marker assessments. These examinations were repeated monthly to confirm complete tumor ablation. Thereafter, follow-up assessments were conducted every three months until the completion of the observation period in June 2025. The primary endpoint of this study was tumor recurrence, and the secondary endpoint was all-cause mortality. RFS was defined as the interval from RFA to the first documented recurrence or the end of follow-up. OS was defined as the time from RFA to death from any cause or the end of follow-up.

Statistical analysis: All statistical analyses were performed using SPSS software, version 27.0 (IBM Corp., Armonk, NY, USA). The predictive performance of the models was evaluated using sensitivity, specificity, and the area under the curve (AUC). Sensitivity served as the primary evaluation metric, emphasizing the model's ability to identify high-risk patients for recurrence, while specificity was also considered to minimize overdiagnosis. Differences in sensitivity between the new model (CEUS combined with PINI) and the conventional model were compared using the chi-square test. Receiver operating characteristic (ROC) curve analysis was used to determine optimal diagnostic cut-off values for PINI, TTP, PI and ER with respect to recurrence. All continuous variables were dichotomized according to the optimal cut-off points derived from the ROC curve of RFS. When ROC analysis was not statistically significant ($P \geq 0.05$), reference thresholds were adopted from established clinical guidelines. Categorical variables were compared using the

Table 2. Correlations between PINI, TTP, PI, and ER and liver tumor characteristics

Variable	PINI	TTP	PI	ER
Tumor differentiation	*r*=0.028	*r*=-0.221*	*r*=0.223*	*r*=0.062
Number of tumors	*r*=0.043	*r*=-0.114	*r*=-0.038	*r*=0.061
Maximum tumor diameter (cm)	*r*=-0.039	*r*=-0.039	*r*=0.063	*r*=-0.064

Note: * indicates P<0.05. PINI, Prognostic Inflammatory and Nutritional Index; TTP, time to peak; PI, peak intensity; ER, enhancement rate.

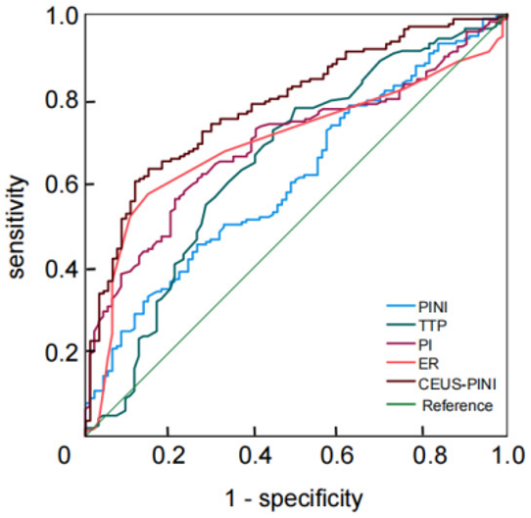

Figure 2. ROC curves for RFS in PINI, TTP, PI, ER, and CEUS-PINI. Note: ROC, receiver operating characteristic; RFS, recurrence-free survival; PINI, Prognostic Inflammatory and Nutritional Index; TTP, time to peak; PI, peak intensity; ER, enhancement rate; CEUS, contrast-enhanced ultrasound.

chi-square test. Kaplan-Meier survival analysis and the log-rank test were employed to assess differences in RFS and OS among groups stratified by CEUS-PINI grade. Cox proportional hazards regression analysis was performed to identify independent predictors of RFS and OS, with variables entered using a forward stepwise likelihood-ratio method. A two-sided *P*<0.05 was considered statistically significant. Categorical data are presented as n (%). Survival outcomes are expressed as survival rates (%), with corresponding HRs and 95% CIs. Predictive efficacy metrics are reported with 95% CIs, and *P*-values are presented as exact numerical values.

Results

Baseline characteristics of patients with early-stage HCC

The baseline characteristics of the 263 patients with early-stage HCC who underwent RFA are summarized in **Table 1**. The majority of patients were male (77.95%), with a mean age of 55 years. Cirrhosis was present in 86.31% of patients, and 23.19% had diabetes mellitus. The predominant etiology of liver disease was hepatitis B virus (HBV) (78.33%), followed by hepatitis C, alcoholic liver disease, and other causes. A family history of liver cancer was reported in 12.55% of patients. Histologically, most tumors were poorly differentiated (61.22%). In 71.48% of cases, the maximum tumor diameter was ≤2.5 cm, and 76.05% of patients had a single lesion. According to the Albumin-Bilirubin (ALBI) grading system, 68.82% of patients were classified as grade 1. The mean PINI score was 1.62±0.49, and the mean values for TTP, PI, and ER were 16.87±2.14 seconds, 45.94±6.21 dB, and 2.12±0.36 dB/s, respectively. These baseline data provide a comprehensive overview of the study population and establish a foundation for subsequent analyses of the associations between clinical, biochemical, and imaging parameters and patient outcomes following RFA.

Correlation between PINI, TTP, PI, ER, and liver tumor characteristics

As shown in **Table 2**, TTP was negatively correlated with the degree of tumor differentiation (r=-0.221, P<0.05), indicating that a higher TTP was associated with a greater degree of tumor differentiation. Conversely, PI demonstrated a positive correlation with tumor differentiation (r=0.223, P<0.05), suggesting that higher PI values were associated with lower tumor differentiation.

ROC curves for PINI, TTP, PI, ER, and CEUS-PINI in predicting RFS and OS

ROC curves were constructed for the PINI, TTP, PI, ER, and the combined CEUS-PINI model to evaluate their diagnostic performance in predicting RFS (**Figure 2**). The AUCs were as follows: PINI=0.610 (95% CI: 0.541-0.680),

Table 3. Diagnostic values of CEUS parameters (TTP, PI, and ER) combined with PINI for predicting RFS

Index	AUC	95% CI	Cut-off value	Sensitivity (%)	Specificity (%)	*P*-value
PINI	0.610	0.541-0.680	1.48	0.438	0.745	0.003
TTP (s)	0.663	0.579-0.723	17.65	0.740	0.553	<0.001
PI (dB)	0.693	0.629-0.756	47.25	0.562	0.769	<0.001
ER (dB/s)	0.695	0.631-0.760	2.15	0.574	0.851	<0.001
CEUS-PINI	0.792	0.737-0.847	0.72	0.604	0.872	<0.001

Note: CEUS, contrast-enhanced ultrasound; PINI, Prognostic Inflammatory and Nutritional Index; TTP, time to peak; PI, peak intensity; ER, enhancement rate; CEUS, contrast-enhanced ultrasound; RFS, recurrence-free survival; AUC, area under the curve; 95% CI, 95% confidence interval.

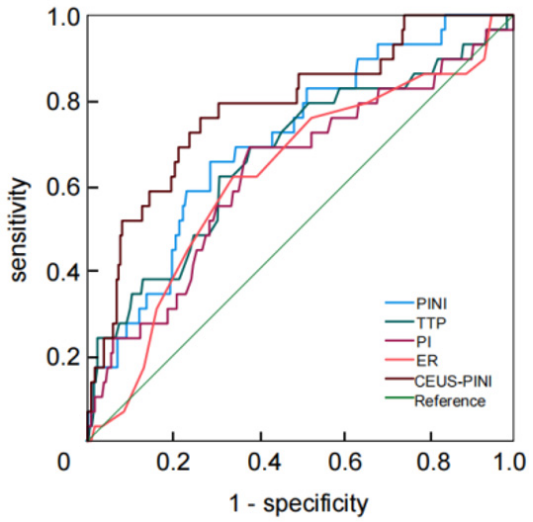

Figure 3. ROC curves for OS in PINI, TTP, PI, ER, and CEUS-PINI. Note: ROC, receiver operating characteristic; OS, overall survival; PINI, Prognostic Inflammatory and Nutritional Index; TTP, time to peak; PI, peak intensity; ER, enhancement rate; CEUS, contrast-enhanced ultrasound.

TTP=0.663 (95% CI: 0.579-0.723), PI=0.693 (95% CI: 0.629-0.756), ER=0.695 (95% CI: 0.631-0.760), and CEUS-PINI=0.792 (95% CI: 0.737-0.847). All of these AUC values were statistically significant (all *P*<0.05). The optimal cut-off values for the diagnosis of RFS were as follows: PINI, 1.48; TTP, 17.65 s; PI, 47.25 dB; ER, 2.15 dB/s; and CEUS-PINI, 0.72. Detailed grouping information is provided in **Table 3**.

ROC curves were also constructed for the PINI, TTP, PI, ER, and the combined CEUS-PINI model to evaluate their diagnostic performance in predicting OS (**Figure 3**). The AUCs were as follows: PINI=0.705 (95% CI: 0.599-0.811), TTP=0.669 (95% CI: 0.545-0.793), PI=0.632 (95% CI: 0.517-0.747), ER=0.626 (95% CI: 0.516-0.737), and CEUS-PINI=0.784 (95% CI: 0.693-0.876). All AUC values were statistically significant (all *P*<0.05). The optimal cut-off value for the continuous CEUS-PINI score was determined using ROC analysis and then stratified according to clinically practical risk categories. The optimal cut-off values for PINI, TTP, PI, ER, and CEUS-PINI in predicting OS were 1.43, 16.05 s, 47.55 dB, 2.25 dB/s, and 0.12, respectively. Detailed grouping information is provided in **Table 4**.

Comparison of RFS rates in patients with different CEUS-PINI levels

Among the 263 patients followed up for a mean period of 38.09±6.22 months, 169 patients experienced tumor recurrence. The 1-year, 2-year, and 3-year RFS rates were 80.2%, 51.6%, and 24.33%, respectively, with a median RFS of 28 months. There were significant differences in RFS rates based on TTP, PI, ER, and CEUS-PINI levels across the different patient groups (*all* P<0.05) (**Figure 4**; **Table 5**).

Comparison of OS rates in patients with different CEUS-PINI levels

Among the 263 patients followed up, 29 deaths were recorded. The 1-year, 2-year, and 3-year OS rates for all patients were 98.48%, 93.16%, and 90.11%, respectively. The cumulative OS differed significantly between the high and low groups for TTP, PI, ER, PINI, and CEUS-PINI (*all P*<0.05) (all *P*<0.05) (**Figure 5**; **Table 6**).

Analysis of risk factors influencing RFS

A Cox proportional hazards regression model was constructed to evaluate the influence of various clinical and imaging factors on RFS (**Table 7**). Univariate analysis revealed that family history of liver cancer, number of tumors,

Table 4. Prognostic values of CEUS parameters (TTP, PI, and ER) combined with PINI for predicting OS

Index	AUC	95% CI	Cut-off value	Sensitivity (%)	Specificity (%)	*P*-value
PINI	0.705	0.599-0.811	1.43	0.655	0.709	0.002
TTP (s)	0.669	0.545-0.793	16.05	0.621	0.688	0.008
PI (dB)	0.632	0.517-0.747	47.55	0.690	0.620	0.020
ER (dB/s)	0.626	0.516-0.737	2.25	0.621	0.658	0.027
CEUS-PINI	0.784	0.693-0.876	0.12	0.795	0.735	<0.001

Note: CEUS, contrast-enhanced ultrasound; PINI, Prognostic Inflammatory and Nutritional Index; TTP, time to peak; PI, peak intensity; ER, enhancement rate; CEUS, contrast-enhanced ultrasound; OS, overall survival; AUC, area under the curve; 95% CI, 95% confidence interval.

AFP level, ALBI grade, and CEUS-PINI classification were significantly associated with tumor recurrence (all $P<0.05$). Multivariate analysis further identified family history of liver cancer (HR=2.007, 95% CI: 1.245-3.238), number of tumors (HR=1.448, 95% CI: 1.129-1.857), ALBI grade (HR=1.880, 95% CI: 1.404-2.516), and CEUS-PINI classification (HR=1.279, 95% CI: 1.067-1.534) as independent risk factors for RFS (all $P<0.05$).

Analysis of risk factors influencing OS

A Cox proportional hazards regression model was constructed to identify factors associated with OS (**Table 8**). Univariate analysis showed that the number of tumors, ALBI score, and CEUS-PINI classification were significantly correlated with mortality in patients with HCC (all $P<0.05$). Multivariate analysis further demonstrated that the number of tumors (HR=2.046, 95% CI: 1.256-3.335), ALBI score (HR=2.603, 95% CI: 1.501-4.514), and CEUS-PINI classification (HR=2.661, 95% CI: 1.957-3.619) were independent risk factors for OS (all $P<0.05$).

Model prediction formula

Based on the results of multivariate Cox regression analysis, CEUS parameters with independent predictive value were identified and integrated to construct a combined predictive model, referred to as the CEUS-PINI model. The corresponding risk score was calculated using the following formula: Risk Score =0.38 × PINI value +0.23 × TTP value +0.42 × PI value +0.25 × ER value (**Table 9**).

According to the total score, patients were stratified into three risk categories: (1) Low-risk group (0-2 points): indicating low local tumor invasiveness, good systemic condition, and a low recurrence risk. (2) Medium-risk group (3-4 points): indicating one high-risk factor in either local or systemicdomains, corresponding to a moderate recurrence risk. (3) High-risk group (5-6 points): indicating high tumor invasiveness, poor systemic condition, multiple high-risk factors, and a high probability of recurrence.

Discussion

HCC remains one of the most common and aggressive malignancies worldwide, characterized by high morbidity and mortality rates and generally poor prognosis [14]. RFA is recognized as an effective local curative therapy for early-stage HCC, offering favorable short-term outcomes compared with surgical resection. However, its major limitation lies in the high rate of postoperative recurrence, which continues to compromise long-term survival [15, 16]. In this study, we integrated CEUS parameters with inflammatory-nutritional indices, providing a comprehensive predictive framework that combines both tumor biological activity and systemic host condition. This dual approach reflects recent advances in prognostic research, emphasizing the complementary value of imaging biomarkers and systemic inflammatory-nutritional status in predicting recurrence after RFA.

CEUS is a real-time imaging technique that effectively characterizes the hemodynamic properties of hepatic lesions by visualizing contrast enhancement during the arterial, portal venous, and late phases [17]. Previous studies have shown that quantitative parameters derived from CEUS imaging are closely associated with the pathological characteristics of HCC and with gene expression profiles related to tumor proliferation and apoptosis [18]. The TTP represents the interval between the injec-

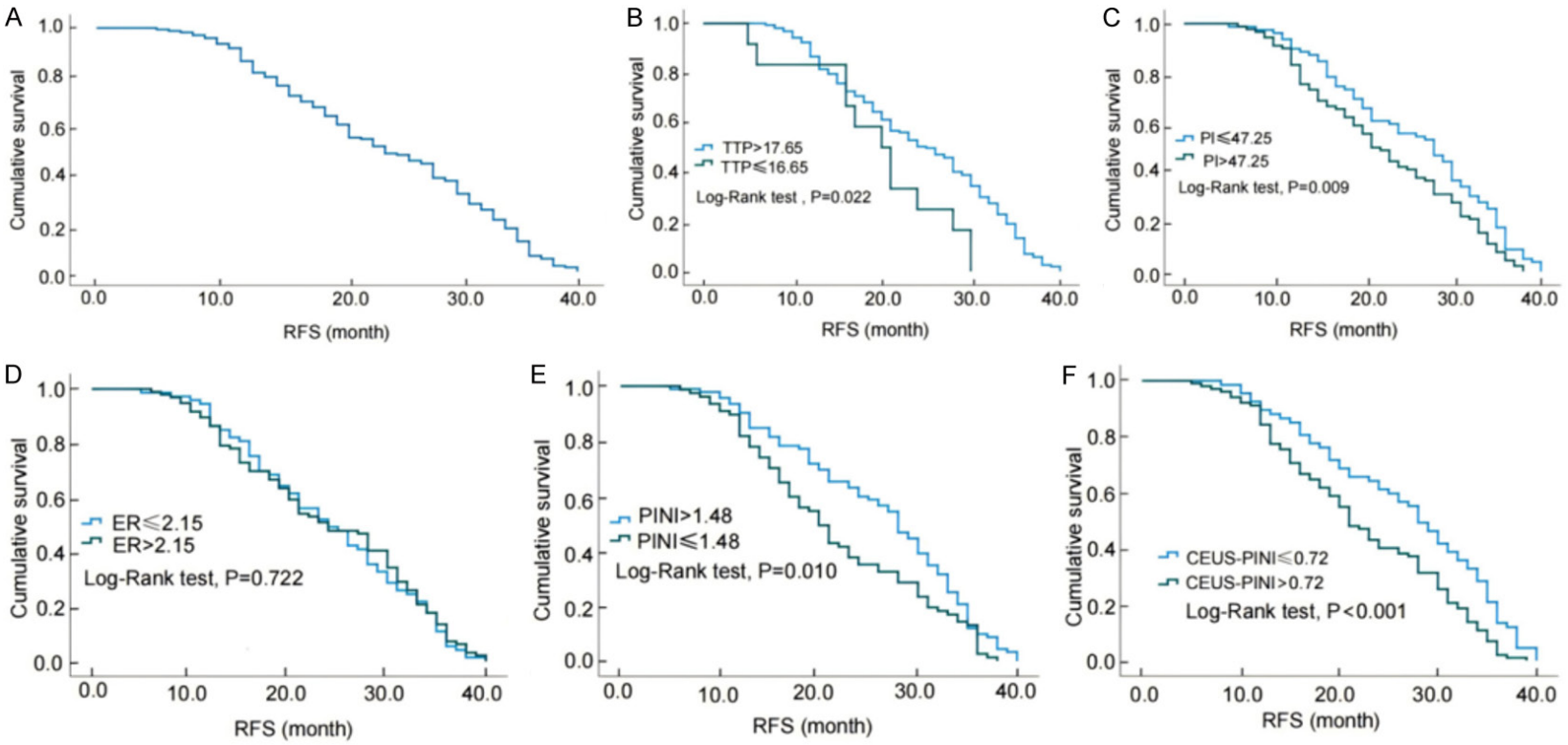

Figure 4. RFS curves for patients with different TTP, PI, ER, PINI, and CEUS-PINI levels. A. Overall RFS; B. RFS comparison by TTP grade groups; C. RFS comparison by PI grade groups; D. RFS comparison by ER grade groups; E. RFS comparison by PINI grade groups; F. RFS comparison by CEUS-PINI grade groups. Note: PINI, Prognostic Inflammatory and Nutritional Index; TTP, time to peak; PI, peak intensity; ER, enhancement rate; CEUS, contrast-enhanced ultrasound; RFS, recurrence-free survival.

Table 5. Number at risk for CEUS parameters (TTP, PI and ER) combined with PINI in relation to RFS

Index	Group classification	0 mo	10 mo	20 mo	30 mo	40 mo	*P*-value
PINI	>17.65	169 (100%)	155 (91.7%)	100 (59.2)	68 (40.2%)	10 (5.9%)	0.022
	≤17.65	169 (100%)	135 (79.9%)	67 (39.6)	13 (7.7%)	0 (0.0%)	
TTP (s)	>47.25	169 (100%)	160 (94.7%)	89 (52.7%)	37 (21.9%)	8 (4.7%)	0.009
	≤47.25	169 (100%)	165 (97.6%)	105 (62.1)	68 (40.2%)	0 (0.0%)	
PI (dB)	>2.15	169 (100%)	163 (96.4%)	101 (59.8%)	68 (40.2%)	3 (1.8%)	0.722
	≤2.15	169 (100%)	165 (97.6%)	102 (60.4%)	62 (36.7%)	4 (2.4%)	
ER (dB/s)	>1.18	169 (100%)	165 (97.6%)	121 (71.6%)	84 (49.7%)	4 (2.4%)	0.010
	≤1.48	169 (100%)	160 (94.7%)	101 (59.8%)	62 (36.7%)	3 (1.8%)	
CEUS-PINI	>0.72	169 (100%)	160 (94.7%)	85 (50.3%)	40 (23.7%)	3 (1.8%)	<0.001
	≤0.72	169 (100%)	169 (100%)	118 (69.8%)	83 (49.1%)	10 (5.9%)	

Note: CEUS, contrast-enhanced ultrasound; PINI, Prognostic Inflammatory and Nutritional Index; TTP, time to peak; PI, peak intensity; ER, enhancement rate; CEUS, contrast-enhanced ultrasound; RFS, recurrence-free survival.

tion of the contrast agent and the attainment of maximum enhancement within a region of interest [19]. Studies have demonstrated that TTP is positively correlated with the degree of tumor differentiation, suggesting that a longer TTP reflects higher differentiation and, consequently, lower malignancy potential. Therefore, TTP serves as a valuable parameter for predicting the risk of HCC recurrence following RFA [20]. The PI and ER quantify, respectively, the maximum signal intensity and the rate of signal increase in CEUS imaging [21]. A retrospective cohort study of 125 patients with HCC treated with RFA in China identified PI as an independent predictor of intrahepatic recurrence (HR= 0.3, 95% CI: 0.1-0.9). The optimal cut-off PI value for predicting recurrence was 58.8% (AUC=0.72, 95% CI: 0.63-0.81) [22].

Within the tumor microenvironment of HCC, inflammatory mediators constitute a major component that plays a crucial role in tumor progression, metastasis and recurrence [23]. Various inflammation-based indices have been widely utilized in clinical practice to assess systemic inflammatory responses and predict patient outcomes [24-26]. Furthermore, mounting evidence indicates a strong association between nutritional status and the prognosis of liver cancer patients [27]. The PINI was initially proposed to evaluate systemic inflammation and nutritional status in patients undergoing colorectal cancer surgery [28]. Since its introduction in 2022, PINI demonstrated significant prognostic value in several conditions, including anti-neutrophil cytoplasmic antibody-associated vasculitis and metastatic colorectal cancer [29, 30]. Mechanistically, monocytes act as sentinel and effector cells during infection and play a pivotal role in initiating inflammatory responses [31], whereas ALB serves as an indicator of both nutritional and hepatic functional status [32]. A reduction in the PINI score reflects impaired nutritional or immune function, thereby increasing the risk of recurrence and mortality following RFA. In the present study, inflammatory-nutritional indicators, as represented by the PINI score, were identified as key risk factors for postoperative disease progression and overall survival in HCC patients treated with RFA.

This study also identified family history of liver cancer as an independent risk factor for recurrence following RFA in patients with HCC. In addition, both the number of tumors and the ALBI score were confirmed as independent predictors of recurrence and overall survival. A positive family history of HCC is known to increase susceptibility to liver cancer within certain populations [33]. Individuals with such a history may harbor specific genetic variants that impair hepatic metabolic pathways, weaken tumor-suppressive mechanisms, and alter cellular responses to oncogenic stress, thereby predisposing them to disease recurrence [34]. The ALBI score is a quantitative tool that combines serum ALB and bilirubin levels to assess hepatic function and disease severity [35]. A study by Ho et al. [36] demonstrated a significant association between ALBI score, tumor recurrence, and survival outcomes, and further showed that the score maintains its prognostic validity across different levels of hepatic func-

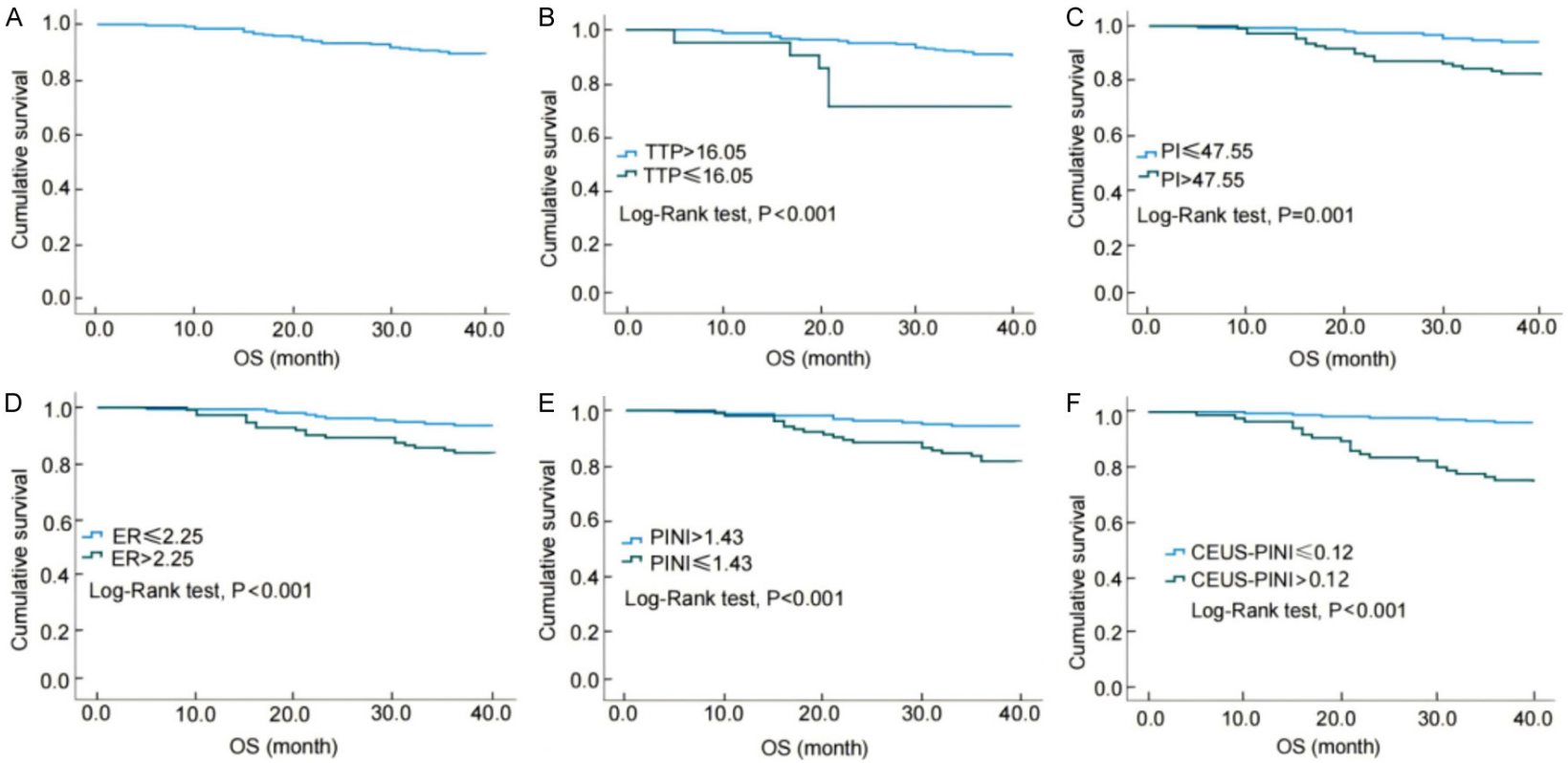

Figure 5. OS curves for patients with different TTP, PI, ER, PINI, and CEUS-PINI levels. A. Overall OS; B. OS comparison by TTP groups; C. OS comparison by PI groups; D. OS comparison by ER groups; E. OS comparison by PINI groups; F. OS comparison by CEUS-PINI groups. Note: PINI, Prognostic Inflammatory and Nutritional Index; TTP, time to peak; PI, peak intensity; ER, enhancement rate; CEUS, contrast-enhanced ultrasound; OS, overall survival.

Table 6. Number at risk for CEUS parameters (TTP, PI and ER) combined with PINI in relation to OS

Index	Group classification	0 mo	10 mo	20 mo	30 mo	40 mo	*P*-value
PINI	>16.05	169 (100%)	165 (97.6%)	163 (96.4%)	160 (94.7%)	159 (94.7%)	<0.001
	≤16.05	169 (100%)	152 (89.9%)	118 (69.8%)	118 (69.8%)	118 (69.8%)	
TTP (s)	>47.55	169 (100%)	167 (98.8%)	163 (96.4%)	159 (94.7%)	157 (92.9%)	0.001
	≤47.55	169 (100%)	166 (98.2%)	152 (89.9%)	150 (88.8%)	132 (78.1%)	
PI (dB)	>2.25	169 (100%)	160 (94.7%)	155 (91.7%)	148 (87.6%)	136 (80.5%)	<0.001
	≤2.25	169 (100%)	166 (98.2%)	163 (96.4%)	157 (92.9%)	152 (89.9%)	
ER (dB/s)	>1.43	169 (100%)	165 (97.6%)	162 (95.9%)	160 (94.7%)	158 (93.5%)	<0.001
	≤1.43	169 (100%)	164 (97.0)	152 (89.9%)	135 (79.9%)	130 (76.9%)	
CEUS-PINI	>0.12	169 (100%)	160 (94.7%)	152 (89.9%)	135 (79.9%)	130 (76.9%)	<0.001
	≤0.12	169 (100%)	165 (97.6%)	162 (95.9%)	160 (94.7%)	158 (93.5%)	

Note: CEUS, contrast-enhanced ultrasound; PINI, Prognostic Inflammatory and Nutritional Index; TTP, time to peak; PI, peak intensity; ER, enhancement rate; CEUS, contrast-enhanced ultrasound; OS, overall survival.

Table 7. Cox regression analysis of factors influencing RFS

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender (male/female)	0.912 (0.628-1.327)	0.631		
Age (≤55 years/>55 years)	0.786 (0.555-1.114)	0.176		
Cirrhosis	0.813 (0.503-1.315)	0.399		
Diabetes mellitus	1.131 (0.809-1.582)	0.471		
Etiology of liver disease (hepatitis B/hepatitis C/alcoholic/other)	0.929 (0.715-1.208)	0.584		
Family history of liver cancer	2.011 (1.273-3.177)	0.003	2.007 (1.245-3.238)	0.004
Tumor differentiation (poor/moderate-high)	0.908 (0.655-1.260)	0.564		
Maximum tumor diameter (cm)	0.756 (0.550-1.041)	0.087		
Number of tumors	1.315 (1.030-1.679)	0.028	1.448 (1.129-1.857)	0.004
ALT (U/L)	0.989 (0.961-1.017)	0.441		
AST (U/L)	1.084 (0.786-1.495)	0.622		
TBIL (μmol/L)	1.151 (0.848-1.562)	0.369		
AFP (ng/mL)	1.553 (1.146-2.106)	0.005		
ALBI grade (1/2/3)	1.944 (1.452-2.603)	<0.001	1.880 (1.404-2.516)	<0.001
CEUS-PINI	1.350 (1.132-1.611)	<0.001	1.279 (1.067-1.534)	0.008

Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin grade; CEUS, contrast-enhanced ultrasound; PINI, Prognostic Inflammatory and Nutritional Index; RFS, recurrence-free survival; HR, hazard ratio; 95% CI, 95% confidence interval.

tional reserve. Moreover, integrating the ALBI score with the tumor burden score has been shown enhance prognostic accuracy and improve individualized recurrence risk assessment in patients with HCC.

Furthermore, the number of tumors was identified as an independent risk factor for both RFS and OS. An increased tumor count was associated with a higher risk of recurrence and mortality following RFA, consistent with findings from previous studies [37, 38]. This association may be attributed to a greater likelihood of intrahepatic satellite lesions in patients with multiple tumors, which predisposes them to postoperative recurrence. In contrast, this study did not observe a significant correlation between tumor size and either RFS or OS. This may be explained by the relatively small tumor burden among enrolled patients, with a maximum diameter of ≤3 cm, and by the achievement of complete ablation in all cases. Under these conditions, the probability of in situ recurrence or incomplete ablation due to intrahepatic metastasis was correspondingly low.

In this study, HBV-related cirrhosis accounted for 65.8% of cases, which is consistent with the predominant etiology of HCC patients in China. Cirrhosis secondary to chronic HBV infection is

Table 8. Cox regression analysis of factors influencing OS

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender (male/female)	1.093 (0.445-2.684)	0.847		
Age (≤55 years/>55 years)	0.929 (0.412-2.098)	0.859		
Cirrhosis	0613 (0.249-1.504)	0.285		
Diabetes mellitus	0.852 (0.347-2.092)	0.852		
Etiology of liver disease (hepatitis B/hepatitis C/alcoholic/other)	0.832 (0.430-1.607)	0.583		
Family history of liver cancer	1.418 (0.541-3.716)	0.478		
Tumor differentiation (low/moderate-high)	0.481 (0.206-1.127)	0.092		
Maximum tumor diameter (cm)	1.797 (0.858-3.762)	0.120		
Number of tumors	2.107 (1.266-3.509)	0.004	2.046 (1.256-3.335)	0.004
ALT (U/L)	1.298 (0.627-2.690)	0.482		
AST (U/L)	1.622 (0.774-3.395)	0.200		
TBIL (μmol/L)	0.848 (0.394-1.824)	0.674		
AFP (ng/mL)	1.700 (0.818-3.534)	0.155		
ALBI grade (1/2/3)	2.631 (1.517-4.560)	<0.001	2.603 (1.501-4.514)	0.001
CEUS-PINI	2.779 (2.045-3.778)	<0.001	2.661 (1.957-3.619)	<0.001

Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin grade; CEUS, contrast-enhanced ultrasound; PINI, Prognostic Inflammatory and Nutritional Index; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 9. Multivariate Cox regression analysis and coefficients for constructing the CEUS-PINI prognostic model

Factor	Univariate analysis		Multivariate analysis
	HR (95% CI)	*P*-value	β coefficient
Gender (male/female)	0.912 (0.628-1.327)	0.631	
Age (≤55 years/>55 years)	0.786 (0.555-1.114)	0.176	
Cirrhosis	0.813 (0.503-1.315)	0.399	
Diabetes mellitus	1.131 (0.809-1.582)	0.471	
Etiology of liver disease (hepatitis B/hepatitis C/alcoholic/other)	0.929 (0.715-1.208)	0.584	
Family history of liver cancer	2.011 (1.273-3.177)	0.003	
Tumor differentiation (low/moderate-high)	0.908 (0.655-1.260)	0.564	
Maximum tumor diameter (cm)	0.756 (0.550-1.041)	0.087	
Number of tumors	1.315 (1.030-1.679)	0.028	
ALT (U/L)	0.989 (0.961-1.017)	0.441	
AST (U/L)	1.084 (0.786-1.495)	0.622	
TBIL (μmol/L)	1.151 (0.848-1.562)	0.369	
AFP (ng/mL)	1.553 (1.146-2.106)	0.005	
ALBI grade (1/2/3)	1.944 (1.452-2.603)	<0.001	
CEUS-PINI	1.350 (1.132-1.611)	<0.001	
PINI	2.45 (1.61-3.73)	<0.001	0.38
TTP (s)	1.86 (1.21-2.85)	0.005	0.23
PI (dB)	2.68 (1.75-4.09)	<0.001	0.42
ER (dB/s)	2.03 (1.32-3.12)	0.001	0.25

Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin grade; CEUS, contrast-enhanced ultrasound; PINI, Prognostic Inflammatory and Nutritional Index; TTP, time to peak; PI, peak intensity; ER, enhancement rate; HR, hazard ratio; 95% CI, 95% confidence interval.

frequently accompanied by persistent intrahepatic inflammation and ongoing viral replication, both of which can promote tumor angiogenesis and immune suppression thereby increasing the risk of recurrence. In contrast, alcohol-related cirrhosis is more strongly influ-

enced by metabolic disturbances and oxidative stress, which adversely affect prognosis. Notably, the proportion of early-stage HCC patients with cirrhosis included in most previous studies has been relatively low [11, 13]. The predictive model developed in this study integrates CEUS parameters with the PINI. In the context of cirrhosis, this combined approach offers a more comprehensive assessment of recurrence risk than any single parameter alone. This integrated evaluation framework represents a key distinction of the present study compared with previous research that focused solely on tumor characteristics or serum biomarkers.

The CEUS-PINI model, although slightly costlier than models such as the ALBI and neutrophil-to-lymphocyte ratio scores, remains equally non-invasive while offering broader diagnostic coverage. Unlike traditional single-dimensional models - where the ALBI score fails to reflect vascular invasiveness and the neutrophil-to-lymphocyte ratio score cannot assess local lesion biology - CEUS-PINI incorporates both local tumor characteristics and systemic inflammatory-nutritional status, providing a multidimensional assessment framework.

Notably, this study has several limitations in its analysis of recurrence risk factors in HCC. First, no subgroup analysis was performed based on recurrence timing; however, early and late recurrences are known to differ in biological behavior and clinical determinants, as supported by prior literature [37]. Second, the study cohort was derived predominantly from a single domestic center, with most patients having HBV-related cirrhosis, which may limit the generalizability of the findings to other etiological backgrounds. Third, the relatively small number of OS events reduced the statistical power of the multivariate Cox regression model, potentially affecting the precision of HR estimates. Lastly, the cohort included a disproportionately high proportion of patients with tumor diameters ≤2.5 cm, limiting its representativeness for early-stage HCC cases with tumors measuring 3-5 cm. Future studies should aim to include a larger and more diverse patient population encompassing multiple liver disease etiologies, perform stratified analyses by recurrence timing, and incorporate additional clinical and imaging covariates. Expanding the number of patients with 3-5 cm tumors would further help validate the conclusions of this study and improve the robustness and generalizability of the CEUS-PINI model.

Conclusion

The CEUS-PINI scoring system, which integrates CEUS parameters with inflammatory-nutritional indices, provides a promising, simple, and non-invasive tool for evaluating recurrence and survival risks in patients with early-stage HCC following RFA. Its predictive performance has been validated in the cohort from our center, demonstrating its potential clinical utility. However, broader clinical application requires further verification through multicenter studies and external validation in diverse patient populations.

Disclosure of conflict of interest

None.

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