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CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

# A Systemic Inflammation Response Index (SIRI)-Based Nomogram for Predicting the Recurrence of Early Stage Hepatocellular Carcinoma After Radiofrequency Ablation

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**Abstract**
*Objective* To explore the prognostic value of the systemic inflammation response index (SIRI) defined as neutrophil count × monocyte count/lymphocyte count in the patients with early stage hepatocellular carcinoma (HCC) within the Milan criteria after radiofrequency ablation (RFA).
*Materials and Methods* The prognostic value of SIRI was evaluated in a primary cohort ($n$ = 403) and then further validated in an independent test cohort ($n$ = 140). A novel preoperative prognostic nomogram was constructed from a multivariate analysis and validated in an external validation cohort.
*Results* The optimal cutoff value of SIRI for patient stratification into a low SIRI group and a high SIRI group was 1.36. Survival analysis showed that the median overall survival (OS) and recurrence-free survival (RFS) were significantly higher in patients with a low SIRI compared to those with a high SIRI. The alpha-fetoprotein (AFP), SIRI, tumor number and size were independent predictors of RFS based on multivariate analysis. The nomogram including the SIRI, tumor number, tumor size, AFP could more accurately determine the prognosis of HCC patients than BCLC stage (0.74 vs. 0.62, $P < 0.001$). In addition, the dynamic changes in post-RFA SIRI also had prognostic significance and patients with a reduction in the SIRI by > 75% had a better prognosis.
*Conclusion* Preoperative SIRI was an independent predictor for RFS in patients with early stage HCC within the Milan criteria. The comprehensive nomogram can objectively and reliably help clinicians identify high-risk patients and develop individualized treatment plans.

**Keywords** Hepatocellular carcinoma · Radiofrequency ablation · Systemic inflammation response index · Recurrence-free survival

## Introduction

Hepatocellular carcinoma (HCC) represents 75% ∼ 85% of liver malignancies, which is the sixth most common type of cancer and the fourth leading cause of cancer-related deaths worldwide [1]. China accounts for nearly 50% of the global burden of HCC [2]. Currently, surgical resection and liver transplantation are recognized as the first-line treatments for early stage HCC [3]. Radiofrequency ablation (RFA) has been recommended as an alternative and potentially curative treatment for selected patients with early stage HCC within the Milan criteria [4, 5]. Nevertheless, the long-term survival of HCC is poor, due to the high incidence of tumor recurrence, which can occur in up to 70% within 5 years after radical therapies [6, 7]. Recent studies have found that patients with HCC after RFA exhibited a higher recurrence rate and poorer long-term

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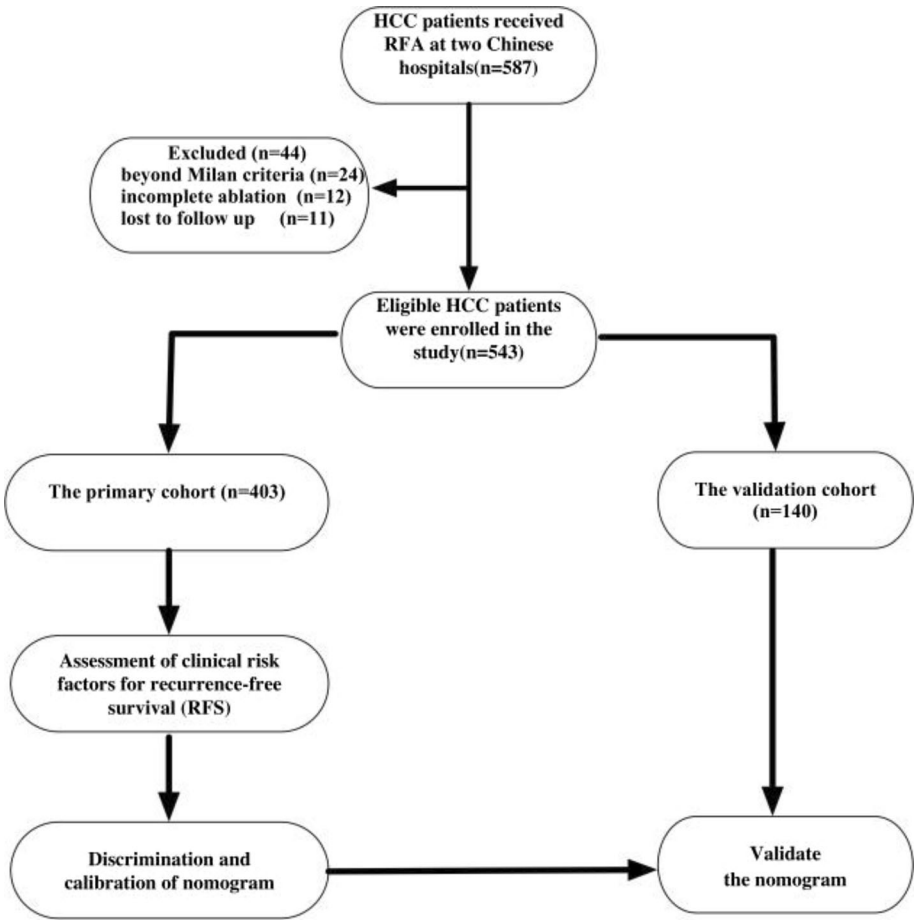


**Fig. 1** Flowchart showing patient selection and study design

survival compared to patients with HCC after curative treatment [8, 9]. So, effective and objective indicators may help clinicians make treatment decisions and improve prognosis.

Tumor-related inflammation has been proven to play a vital role in tumor occurrence, development, and metastasis [10, 11]. HCC is characterized by chronic systemic inflammation due to its unique etiology with chronic hepatitis. The inflammatory markers composed of two types of leukocytes, such as the neutrophil–lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and monocyte-lymphocyte ratio (MLR), have been recognized as reliable prognostic factors for HCC patients [12–14]. Recently, a new immune-inflammation index, the systemic inflammation response index (SIRI), based on three types of leukocytes (peripheral blood neutrophil, monocyte and lymphocyte counts) was investigated in various cancers and its prognostic value is higher than that of only white blood cells [15–20]. Moreover, SIRI may comprehensively reflect the balance of host immune and inflammatory status compared with NLR, MLR, and PLR. These studies suggest that SIRI may be a more accurate and promising predictor than other inflammatory indices for HCC prognosis.

As far as we know, there is only one study on the relationship between SIRI and the prognosis of patients with middle and advanced stage HCC receiving local or systemic treatment. The correlation between the preoperative SIRI and the prognosis of patients with early stage HCC patients after RFA has not been evaluated. Hence, the purpose of the current study was to explore the prognostic value of the SIRI in early stage HCC patients after RFA and compare the predictive performance with conventional inflammatory indices. Subsequently, a new preoperative prognostic factor-based nomogram was established to select patients with high-risk recurrence and guide clinicians to design an individualized treatment plan, which may improve the prognosis of patients.

**Table 1** Baseline characteristics for patients in the two cohorts (SIRI ≤ 1.36 vs. SIRI > 1.36)

| Clinical parameter | Primary cohort | | | Validation cohort | | |
|---|---|---|---|---|---|---|
| | SIRI ≤ 1.36 ($n$ = 178) | SIRI > 1.36 ($n$ = 225) | $P$ | SIRI ≤ 1.36 ($n$ = 61) | SIRI > 1.36 ($n$ = 79) | $P$ |
| Age (> 50) | 41 (23.0%) | 44 (19.6%) | 0.467 | 16 (26.2%) | 13 (16.5%) | 0.228 |
| Sex (male) | 148 (83.1%) | 180 (80.0%) | 0.498 | 49 (80.3%) | 65(82.3%) | 0.940 |
| Tumor number (Multiple) | 67 (37.6%) | 114 (50.7%) | 0.012 | 22 (36.1%) | 43 (54.4%) | 0.050 |
| Tumor size (≥ 3 cm) | 58 (32.6%) | 98 (43.6%) | 0.032 | 17 (27.9%) | 30(38.0%) | 0.282 |
| Cirrhosis (Yes) | 161 (90.4%) | 206 (91.6%) | 0.833 | 54 (88.5%) | 71 (89.9%) | 1.000 |
| Child–Pugh (B) | 2 (1.1%) | 3 (1.3%) | 1.000 | 0 (0%) | 2 (2.5%) | 0.594 |
| HBV (Yes) | 143 (80.3%) | 186 (82.7%) | 0.638 | 45 (73.8%) | 64 (81.0%) | 0.413 |
| Antiviral therapy (Yes) | 89 (50.0%) | 112 (49.8%) | 0.964 | 45(73.8%) | 48 (60.8%) | 0.151 |
| BCLC | | | 0.002 | | | 0.323 |
| 0 | 71 (39.9%) | 79 (35.1%) | | 24(39.3%) | 28 (35.4%) | |
| A | 90 (50.6%) | 95 (42.2%) | | 31 (50.8%) | 36 (45.6%) | |
| B | 17 (9.6%) | 51 (22.7%) | | 6 (9.8%) | 15 (19.0%) | |
| ALBI grade | | | 0.719 | | | 0.912 |
| 1 | 93 (52.2%) | 110 (48.9%) | | 28 (45.9%) | 39 (49.4%) | |
| 2 | 83 (46.6%) | 111 (49.3%) | | 32 (52.5%) | 39 (49.4%) | |
| 3 | 2 (1.1%) | 4 (1.8%) | | 1 (1.6%) | 1 (1.3%) | |
| AFP (> 20 ng/mL) | 79 (44.4%) | 93 (41.3%) | 0.608 | 29 (47.5%) | 32 (40.5%) | 0.509 |
| AST (> 40U/L) | 28 (15.7%) | 37 (16.4%) | 0.954 | 13 (21.3%) | 13 (16.5%) | 0.608 |
| ALT (> 40U/L) | 40 (22.5%) | 59 (26.2%) | 0.452 | 18 (29.5%) | 16 (20.3%) | 0.286 |
| TBIL (> 17.1umol/L) | 69 (38.8%) | 77 (34.2%) | 0.402 | 22 (36.1%) | 32 (40.5%) | 0.719 |
| NLR (> 2.49) | 20 (11.2%) | 44 (19.6%) | 0.033 | 4 (6.6%) | 14 (17.7%) | 0.089 |
| PLR (> 101.79) | 87 (48.9%) | 170 (75.6%) | < 0.001 | 30 (49.2%) | 54 (68.4%) | 0.034 |
| MLR (> 0.36) | 32(18.0) | 112 (49.8) | < 0.001 | 10 (16.4%) | 38 (48.1%) | < 0.001 |
| Tumor recurrence (YES) | 139(78.1%) | 39 (17.3%) | < 0.001 | 15 (24.6%) | 51 (64.6%) | < 0.001 |

*HCC* hepatocellular carcinoma; *HBV* hepatitis B virus; *BCLC* barcelona clinical liver cancer; *ALBI* albumin-bilirubin; *AFP* alpha-fetoprotein; *AST* aspartic transaminase; *ALT* alanine aminotransferase; *TBIL* total bilirubin; *NLR* neutrophil to lymphocyte ratio; *PLR* platelet to lymphocyte ratio; *MLR* monocyte/lymphocyte ratio; *SIRI* systemic inflammation response index

## Materials and Methods

### Patients

This retrospective study was approved by the Institutional Review Boards of the National Cancer Center of China. Each patient provided written informed consent for the treatment. Ethics committee approval was obtained 20 March 2019. We included primary early stage HCC adult patients (18 ∼ 80 years) within Milan criteria treated by RFA between July 2012 to December 2017. The inclusion criteria were as follows: (1) HCC confirmed by histology or noninvasive diagnostic criteria recommended by the European Association for the Study of Liver (EASL) [21]; (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (3) solitary tumor ≤ 5 cm or up to 3 tumors ≤ 3 cm; (4) no extrahepatic metastasis or major vessel invasion; and (5) patients who underwent RFA with complete tumor ablation. The exclusion criteria were as follows: (1) patients who received surgery as the primary treatment for HCC; (2) patients who were lost to follow up; (3) patients with tumor(s) beyond Milan criteria; and (4) patients with other tumors, infectious diseases, or systematic inflammatory disease.

### Data Collection

Neutrophil, lymphocyte, monocyte, and platelet counts, as well as other clinically relevant variables, were measured from the peripheral blood ≤ 1 week before RFA and 4–8 weeks after RFA. In this study, four scoring systems (NLR, MLR, PLR, and SIRI) were analyzed and were computed as follows:

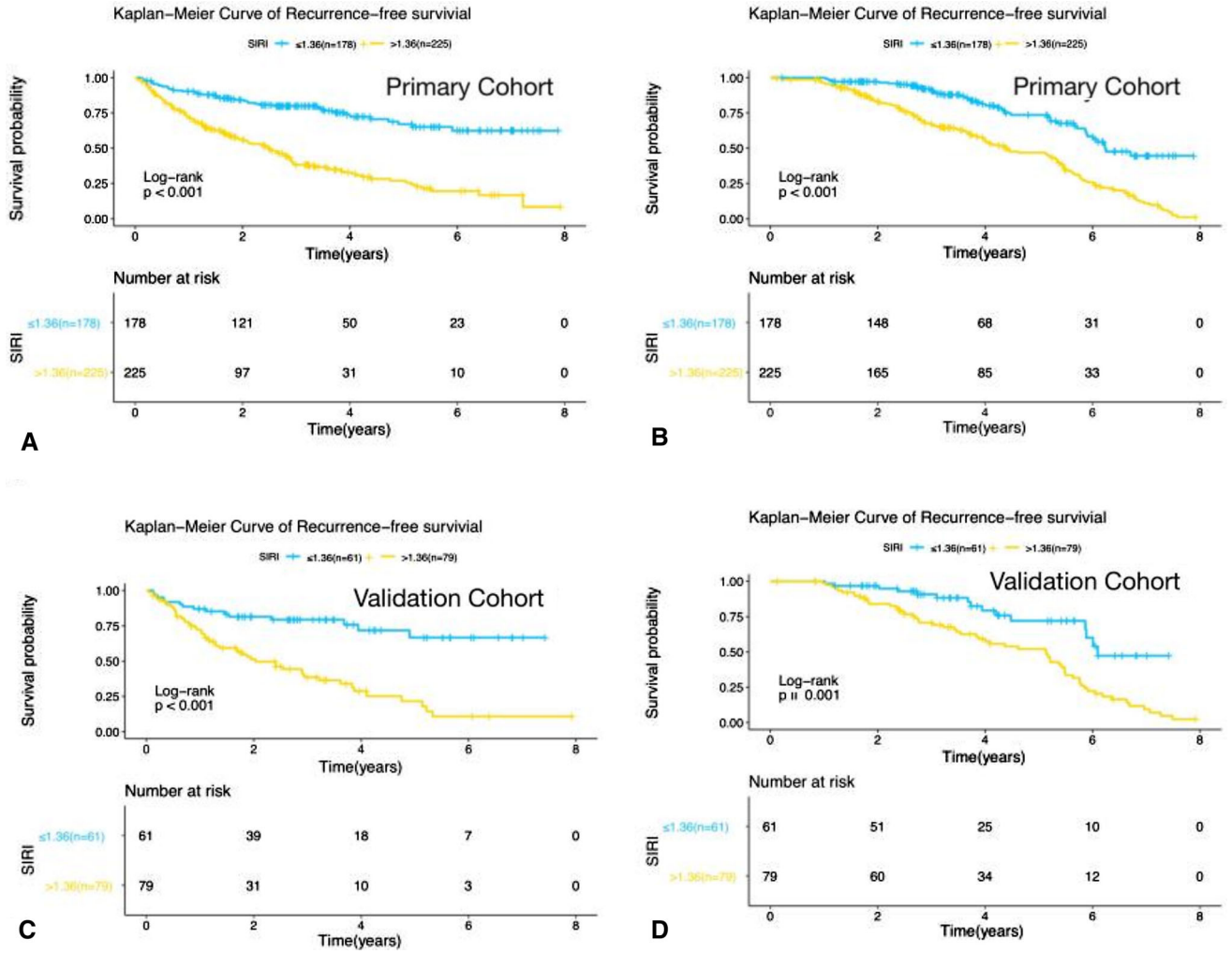


**Fig. 2** Kaplan–Meier curves for OS and RFS based on SIRI in the primary cohort before **A**, **B** and after PSM analysis (**C**, **D**), and in the validation cohort (**E**, **F**)

1. NLR = neutrophil count/lymphocyte count
2. MLR = monocyte count/lymphocyte count
3. PLR = platelet count/lymphocyte count
4. SIRI = neutrophil count × monocyte count/lymphocyte count

## RFA Procedure

All RFA procedures were performed under ultrasound or computed tomography (CT) guidance by doctors with at least 5 years of RFA experience. Expanding or overlapping ablation was performed such that all the tumors were ablated with a safety margin of at least 0.5 cm [22, 23]. Postoperative contrast-enhanced (CE) imaging, such as magnetic resonance imaging (MRI) or ultrasound, was performed immediately after the RFA procedure to confirm complete ablation. If a residual tumor was present, an additional RFA session was performed to ensure complete ablation. After the lesions were ablated, the ablation path was cauterized to avoid tumor seeding and hemorrhage.

## Follow-up

After RFA, the patients were followed-up with every third month during the first year and every sixth month in subsequent years until tumor recurrence or death. Each follow-up visit consisted of collecting information on clinical history, routine blood investigations, liver function tests, determining AFP level, and performing ultrasonography, contrast-enhanced computed tomography (CT) of the chest, and magnetic resonance imaging or CT of the abdomen.

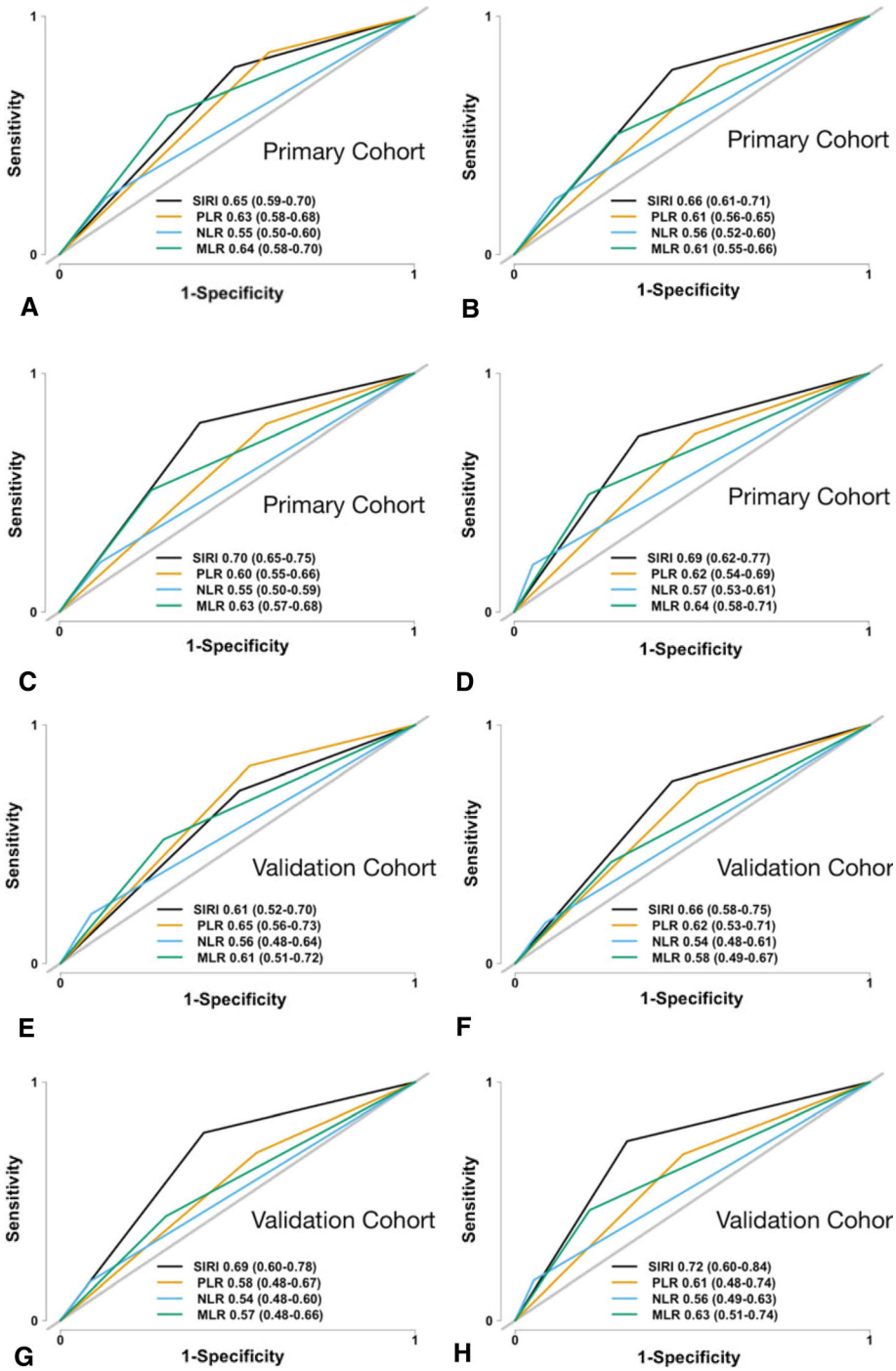


**Fig. 3** The predictive ability of the SIRI in early stage HCC patients was compared with that of NLR, PLR, and MLR by ROC curves at 1-year (**A**), 2-year (**B**), 3-year (**C**), and 5-year (**D**) in the primary cohort and by ROC curves at 1-year (**E**), 2-year (**F**), 3-year (**G**), and 5-year (**H**) in the validation cohort

## Oncological Outcomes

The primary outcome measurement of this study was recurrence-free survival (RFS), and the secondary outcome was overall survival (OS). Tumor recurrence was confirmed by dynamic CT or MR imaging. Recurrence was classified as local tumor progression (LTP), intrahepatic distant progression (IDP), or extrahepatic progression (EP).

## Statistical Analysis

Categorical and continuous variables were compared using a Fisher's exact or $\chi^2$ test and a Mann–Whitney U or a t-test, respectively, when appropriate. The Kaplan–Meier curve analysis was used to determine the cumulative incidence rates of OS and RFS. The log-rank test was used to compare the survival curves of the two groups. The risk

**Table 2** Univariate Cox regression analyses for the recurrence-free survival of HCC patients in the primary cohorts

| | HR | 95%CI | *P* |
|---|---|---|---|
| Age (> 50) | 1.35 | 0.96–1.90 | 0.082 |
| Sex (male) | 1.28 | 0.85–1.91 | 0.232 |
| Tumor number (Multiple) | 2.18 | 1.62–2.92 | < 0.001 |
| Tumor size (≥ 3 cm) | 2.05 | 1.53–2.75 | < 0.001 |
| BCLC | | | < 0.001 |
| 0 | – | | – |
| A | 0.98 | 0.69–1.40 | 0.920 |
| B | 3.90 | 2.68–5.69 | < 0.001 |
| ALBI | | | 0.700 |
| 1 | – | | – |
| 2 | 1.14 | 0.85–1.52 | 0.391 |
| 3 | 1.25 | 0.40–3.96 | 0.702 |
| Cirrhosis (Yes) | 0.95 | 0.57–1.59 | 0.843 |
| Child–Pugh (B) | 1.29 | 0.32–5.22 | 0.720 |
| HBV (Yes) | 0.89 | 0.61–1.30 | 0.544 |
| AFP (> 20 ng/mL) | 1.85 | 1.38–2.47 | < 0.001 |
| PLR (> 101.79) | 2.28 | 1.62–3.21 | < 0.001 |
| NLR (> 2.49) | 1.82 | 1.26–2.61 | 0.001 |
| SIRI (> 1.36) | 3.63 | 2.58–5.10 | < 0.001 |
| MLR (> 0.36) | 2.41 | 1.80–3.23 | < 0.001 |

*HCC* hepatocellular carcinoma; *HBV* hepatitis B virus; *BCLC* barcelona clinical liver cancer; *ALBI* albumin-bilirubin; *AFP* alpha-fetoprotein; *NLR* neutrophil to lymphocyte ratio; *PLR* platelet to lymphocyte ratio; *MLR* monocyte/lymphocyte ratio; *SIRI* systemic inflammation response index

**Table 3** Multivariate Cox regression analyses for recurrence-free survival of HCC patients in the primary cohorts

| | HR | 95%CI | *P* |
|---|---|---|---|
| Tumor number (Multiple) | 1.78 | 1.29–2.45 | < 0.001 |
| Tumor size (≥ 3 cm) | 1.89 | 1.38–2.57 | < 0.001 |
| AFP (> 20 ng/mL) | 1.63 | 1.20–2.23 | 0.002 |
| PLR (> 101.79) | 1.36 | 0.90–2.06 | 0.147 |
| NLR (> 2.49) | 1.26 | 0.84–1.87 | 0.262 |
| SIRI (> 1.36) | 2.72 | 1.88–3.93 | < 0.001 |
| MLR (> 0.36) | 1.29 | 0.87–1.90 | 0.204 |

*HCC* hepatocellular carcinoma; *AFP* alpha-fetoprotein; *NLR* neutrophil to lymphocyte ratio; *PLR* platelet to lymphocyte ratio; *MLR* monocyte/lymphocyte ratio; *SIRI* systemic inflammation response index

factors for RFS were obtained with Cox proportional hazards models. A multivariable Cox hazard model was constructed using the significant variables ($P < 0.1$) from the univariate Cox regression analysis. The optimal cutoff value for the SIRI, PLR, MLR, and NLR was determined with the X-tile 3.6.1 software (https://medicine.yale.edu/lab/rimm/research/software/) [24]. A two-tailed 95% confidence interval (CI) was applied to reveal the accuracy of the hazard ratio (HR), and the statistical significance level was set as 0.05. The R software (version 3.6.2) was used to perform the statistical analyses.

The nomogram was plotted by selecting significant variables with $P < 0.05$ from the multivariate analysis. Five hundred bootstrap resamples were performed for internal validation. The concordance index (C-index) was computed to evaluate the performance of these models for prognosis prediction. The nomogram for 1-year, 2-year, 3-year, and 5-year RFS was calibrated by comparing the observed and predicted survival. The predictive power of the model was analyzed by examining the time-dependent receiver operating characteristic (t-ROC) curve.

## Results

### Patient Characteristics

Ultimately, 403 patients with HCC who underwent RFA at the National Cancer Center were selected as the primary cohort. Another 140 patients with HCC from the First Hospital of Shanxi Medical University were included as the validation cohort. The flowchart of patient selection and study design is shown in Fig. 1. The demographics of the patients are displayed in Table 1. The median age of the HCC patients was 58 (range: 30–80) years old. The median follow-up period was 44.5 (range: 12.6–95.0) months. Briefly, elevated preoperative SIRI was associated with larger tumor size, multiple tumors, BCLC B stage, and high recurrence rate in the primary cohort. The optimal cutoff value, as calculated using X-tile software, for the SIRI, NLR, PLR, and MLR scores was 1.36, 2.49, 101.79, and 0.36, respectively.

### Survival Analysis of HCC Patients After RFA

In the primary cohort, the median OS was 5.42 years and the median RFS was 4.04 years, and recurrence occurred in 178 HCC patients. The Kaplan–Meier curves illustrated that patients with low-SIRI had a longer RFS and OS than patients with high SIRI ($P = 0.001$, Fig. 2A–B). In the validation cohort, the survival curves of SIRI also showed similar trends (Fig. 2C–D). Besides, the t-AUC indicated that the SIRI had the largest AUC among the previously mentioned systemic inflammatory indexes, regardless of the 1-year, 2-year, 3-year, and 5-year RFS in the primary cohort (Fig. 3A–D) and validation cohorts (Fig. 3E–H).

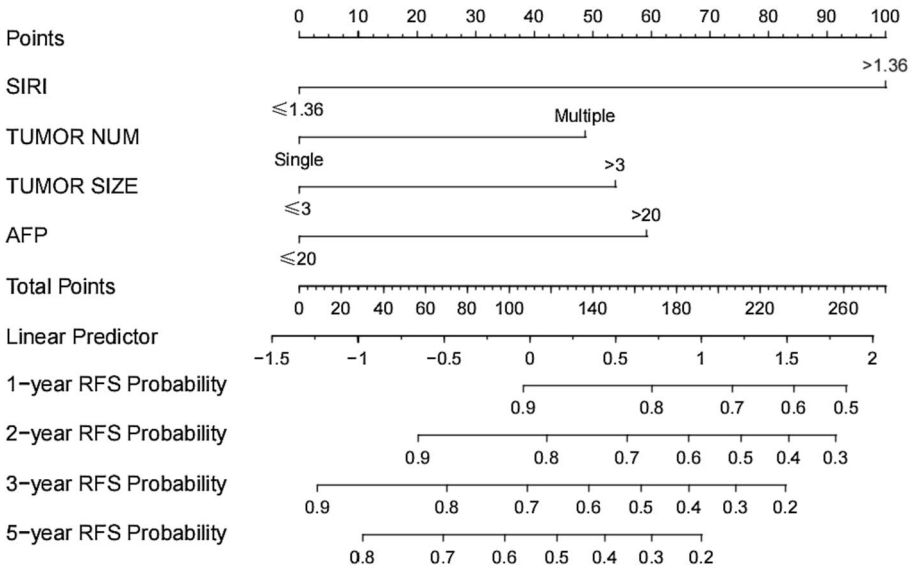


**Fig. 4** Nomogram for predicting 1-, 2-, 3-, and 5-year RFS probability based on the SIRI, tumor number, tumor size, and AFP in HCC patients

These results demonstrate that the prognostic value of SIRI was better than that of NLR, PLR, and MLR.

### Risk Factors for Recurrence

The univariate survival analysis indicated that multiple tumors, larger tumor size, BCLC stage B, and high levels of AFP, NLR, SIRI, MLR, and PLR were all poor prognostic factors for early stage HCC patients in the primary cohort (Table 2). From the multivariate Cox proportional hazards model analysis, the SIRI, AFP, tumor size, and tumor number were associated with RFS (Table 3). The SIRI was the only predictive factor that was significantly associated with survival among the inflammatory markers examined (HR = 2.72, 95% CI: 1.88–3.93, $P < 0.001$).

### Establishment and Verification of the Nomogram

A comprehensive nomogram including tumor number, tumor size, AFP, and SIRI in the primary cohort was constructed to predict the 1-year, 2-year, 3-year, and 5-year RFS (Fig. 4). The C-index of the comprehensive nomogram was significantly higher than that of BCLC staging system (0.74 vs. 0.62, $P < 0.001$). The calibration curves for predicting 1-year, 2-year, 3-year, and 5-year RFS in the primary cohort and validation cohort are shown in Fig. 5A–B. The nomogram achieves better 1-year, 2-year, 3-year, and 5-year t-AUCs than the BCLC staging system (Fig. 5C–E, Fig. 5G–J, respectively), indicating that the nomogram is more accurate in predicting the RFS of early stage HCC patients than the traditional BCLC staging system.

### Prognostic Role of Dynamic Changes in SIRI

In order to analyze the relationship between the dynamic changes of the SIRI and the HCC prognosis, 202 HCC patients with SIRI levels measured at 4–8 weeks after RFA were identified and divided into five groups: increase > 75%, increase of 25–75%, no change (decrease or increase < 25%), decrease of 25–75% and decrease > 75%. The Kaplan–Meier curves illustrated that the dynamic changes in the post-RFA SIRI were related to the prognosis of HCC patients (Fig. 6A). The forest plot indicates that a decrease in SIRI > 75% after RFA was the most significant protective factor for RFS (HR = 0.29, 95% CI: 0.13–0.68, $P = 0.004$).

### Recurrence Patterns and Therapies After Recurrence

The recurrence patterns, their characteristics, and therapies after recurrence are shown in Table 4. Among the 178 patients with recurrence after RFA in the primary cohort, although the recurrence rate of patients with high SIRI level was higher than that of patients with low SIRI level (77.2% vs. 16.8%, $P < 0.01$), there was no significant difference in recurrence pattern between the two groups ($P = 0.783$).

## Discussion

The role of inflammatory factors in mediating the occurrence, progression, and metastasis of malignant tumors has been widely recognized [10, 11]. This study is the first to explore the relationship between SIRI and prognosis of

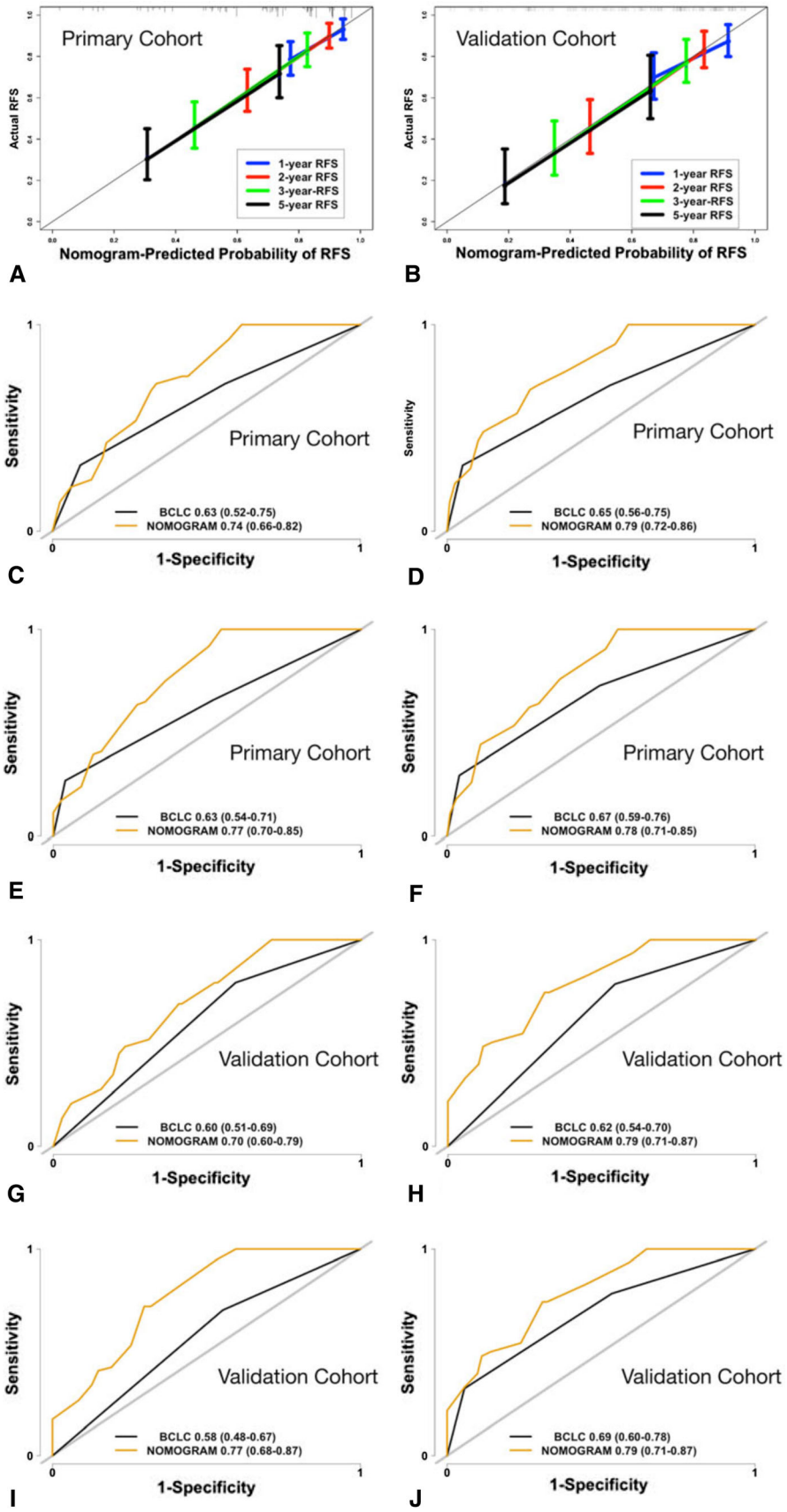


**Fig. 5** Comparison of the recurrence survival rates of HCC patients predicted by the nomogram with the actual values in the primary (**A**) and validation cohort (**B**). Comparison of the AUC between the nomogram and BCLC staging system for the prediction of 1-year (**C**), 2-year (**D**), 3-year (**E,**) and 5-year (**F**) recurrence-free survival in the primary cohort and 1-year (**G**), 2-year (**H**), 3-year (**I**), and 5-year (**J**) recurrence-free survival in the validation cohort

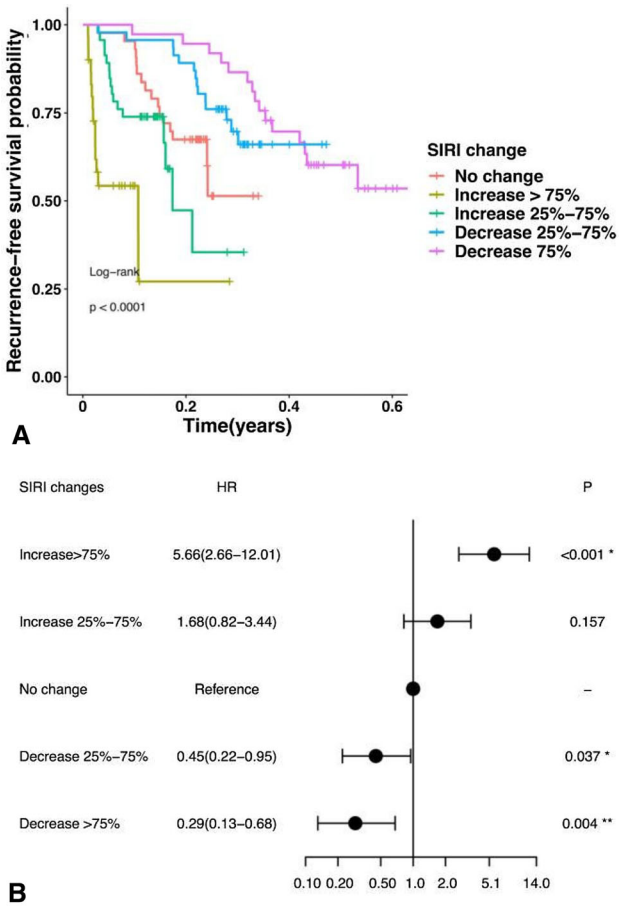


**Fig. 6** Association between the dynamic changes in the SIRI and HCC recurrence after RFA. **A** Kaplan–Meier curves showing RFS of five groups based on changes in the SIRI. **B** Compared to HCC patients with unchanged SIRI (absolute value of variation $< 2$ 5%), those with $> 75\%$ increase in the SIRI exhibited higher recurrence ($P < 0.001$), while patients with a decrease in SIRI $> 75\%$ exhibited lower recurrence ($P < 0.001$)

patients with early stage HCC underwent RFA, which showed that SIRI is an independent risk factor of recurrence in patients with HCC, and the established nomograms including SIRI, tumor number, tumor size and AFP were efficient to predict the RFS of patients with HCC, which can help clinicians develop individualized follow-up strategies and adjuvant treatment after RFA.

The tumor-related inflammatory response is caused by inflammatory cells and a series of inflammatory mediators. Many studies have indicated that systemic inflammatory responses destroy the host immune response, promote the escape of tumor cells from immune surveillance, inhibit cell apoptosis, and promote genomic instability, tumor angiogenesis, invasion and metastasis in cancer patients [25–27]. The prognostic role of HCC patients may be elucidated by the function of these inflammatory cells [28, 29]. Neutrophils promote the invasion, proliferation, and metastasis of cancer cells and help cancer cells escape immune surveillance. In addition, tumor-associated inflammatory cytokines such as IL-6 and tumor necrosis factor increase the neutrophil count [30]. On the other hand, lymphocytes control tumor growth by inducing cytotoxic cell death and secreting cytokines, and a reduced lymphocyte level damages the immunity of the host and accelerates tumor progression [31, 32]. Tumor-activated macrophages are derived from the circulating monocytes, which can destroy the host's immune system and promote tumor invasion, proliferation, angiogenesis, and metastasis [33]. The peripheral blood monocyte count indirectly represents the concentration of tumor-activated macrophages, and a high macrophage concentration is associated with heavy tumor burden [34, 35]. Therefore, cancer-associated inflammation leads to an elevated SIRI and promotes tumorigenesis and cancer progression, eventually resulting in adverse outcomes in HCC patients.

Nomograms have been widely used as a visualization tool to predict the recurrence and survival of patients with various types of tumors, including HCC [36]. In this study, the nomogram including tumor number, tumor size, AFP, and SIRI was proposed to predict the 1-, 2-, 3-, and 5-year RFS based on the results of multivariate Cox proportional hazards model, and the C-index of the nomogram was 0.74 and the t-AUCs of the nomogram of 1-, 2-,3-, and 5-year RFS were 0.74, 0.79, 0.77, and 0.78, respectively. This trend indicates that this nomogram is more accurate in predicting the RFS of early stage HCC patients than the traditional BCLC staging system. In clinical practice, clinicians can directly and conveniently predict the RFS by calculating the variable scores in the prediction model. Moreover, the nomogram can help clinicians to identify high-risk recurrent patients and perform targeted and reasonable adjuvant therapy after RFA.

The strengths of this study can be concluded into two points. Firstly, we evaluated and validated the predictive performance of SIRI in predicting RFS in patients with early stage HCC in two independent cohorts. SIRI is based on peripheral neutrophil, monocyte, and lymphocyte counts can better and more comprehensively reflect the balance of host inflammation and immune status, which is confirmed to be related to liver function and tumor burden. And SIRI is based on routine measurements of peripheral blood cells, thus providing a noninvasive, easily accessible, reproducible, cost-effective, and feasible approach for predicting the RFS of patients with early stage HCC after RFA and exhibited better predictive ability for RFS compared with conventional inflammatory markers (PLR, NLR or MLR). Secondly, we first explored the relationship between SIRI and recurrence of early HCC after ablation and provided a valuable predictive marker for HCC patients.

**Table 4** Recurrence patterns and therapies after recurrence of HCC patients in the two groups of the primary cohort

| | Total ($n$ = 178) | High SIRI ($n$ = 139) | Low SIRI ($n$ = 39) | $P$ value |
|---|---|---|---|---|
| Recurrence Patterns | | | | 0.783 |
| LTP | 8 (4.5%) | 6 (4.3%) | 2 (5.1%) | |
| IDP | 117 (65.7%) | 92 (66.2%) | 25 (64.1%) | |
| IDP + EP | 5 (2.8%) | 3 (2.2%) | 2 (5.1%) | |
| EP | 21 (11.8%) | 15 (10.8%) | 6 (15.4%) | |
| LTP + EP | 5 (2.8%) | 4 (2.9%) | 1 (2.6%) | |
| LTP + IDP | 22 (12.4%) | 19 (13.7%) | 3 (7.7%) | |
| Intrahepatic recurrent type | | | | 0.300 |
| Single | 113 | 91 (65.5%) | 22 (56.4%) | |
| Multiple | 65 | 48 (34.5%) | 17 (43.6%) | |
| Therapies after recurrence | | | | 0.033 |
| Hepatectomy | 25 (14.0%) | 10 (5.6%) | 15 (8.4%) | |
| Ablation | 95 (53.4%) | 35 (19.7%) | 60 (33.7%) | |
| Transarterial chemoembolization | 30 (16.9%) | 21 (11.8%) | 9 (5.1%) | |
| Systemic therapy | 20 (11.2%) | 12 (6.7%) | 8 (4.5%) | |
| Best supportive care | 8 (4.5%) | 5 (2.8%) | 3 (1.7%) | |

*HCC* hepatocellular carcinoma; *LTP* tumor progression; *IDP* intrahepatic distant progression; *EP* extrahepatic progression

Despite promising results, this study has several possible limitations. First, the study was retrospective in nature with a limited sample size and inherent bias. Second, some heterogeneity existed in the treatment of HCC recurrence after RFA at the various study centers, which may directly affect the long-term prognosis of the patients. Third, most of the study patients had HBV-related HCC. Hence, the results cannot be extrapolated to other populations. Future prospective multicenter studies with large sample sizes and HCC with other etiologies are required to validate the findings of this study.

## Conclusion

This study demonstrated that SIRI is an independent predictor for RFS in early stage HCC patients. The comprehensive nomogram can objectively and reliably help clinicians identify high-risk patients and develop individualized treatment plans.

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**Declarations**

**Conflict of interest** The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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