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Skeletal muscle index/systemic immune-inflammation index (SMI/SII) ratio predicts prognosis in patients with hepatocellular carcinoma

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Abstract

Background Systemic inflammation and skeletal muscle are associated with prognosis in hepatocellular carcinoma (HCC). The prognostic value of a combination of skeletal muscle index (SMI) and systemic immune-inflammation index (SII) remains unclear. The present study aims to investigate the prognostic value of combined SMI and SII in predicting overall survival (OS) for HCCs after liver resection (LR) or transarterial chemoembolization (TACE).

Methods This multi-institutional study included three retrospective datasets and one prospective dataset. The SMI/SII was calculated for each cohort. The performance of SMI/SII in predicting recurrence after LR was evaluated in the training cohort, and the optimal cut-off value was calculated. Based on optimal cut-off value, patients were stratified into low and high SMI/SII groups. Cox regression analysis were performed to determine the independent prognostic factors for poor OS. In prospective validation-3 cohort, peripheral blood samples were analyzed for correlation between SMI/SII and distribution of immune cells.

Results A total of 1504 patients were included. The AUC of SMI/SII was 0.701. The OS was significantly better in the high SMI/SII group than that in the low SMI/SII group in the training, validation-1, validation-2 cohorts, and combined those three cohorts. Furthermore, low SMI/SII level was an independent prognostic factor for poor OS. Additionally, findings in validation-3 cohort indicated that patients with HCCs and high SMI/SII display anti-tumor attributes in their peripheral blood composition.

Conclusion A decreased SMI/SII may be a distinct biomarker of unfavorable prognosis in patients with HCCs, which may be practical to develop personalized treatment strategies for HCC.

Keywords Hepatocellular carcinoma, Nutrition status, Systemic inflammation, Prognosis

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Introduction

Hepatocellular carcinoma (HCC) is a highly heterogeneous disease and individualized prognostication is essential to optimize the care for patients [1–4]. Currently, several staging or scoring systems are available to stratify the prognosis of HCC. These scoring systems consider predictive factors such as tumor burden, liver function, and performance status [5–7]. Nevertheless, there is considerable variability in survival rates within each risk subgroup, indicating that the current systems have limited accuracy in assessing the overall aggressiveness of tumors.

Immunonutrition is one of the key factors that can significantly influence the priming, proliferation, angiogenesis, and migration of cancer [8]. HCC can induce an inflammatory environment, and cause immunosuppression and nutritional deficiencies locally and systemically, which potentially affect the therapeutic outcomes [9, 10]. Systemic immune-inflammation index (SII) is a novel prognostic factor, constructed based on neutrophil, platelet, and lymphocyte counts, and high SII level is correlated with poor survival of patients with HCC [11]. Muscle mass, usually calculated as skeletal muscle index (SMI), is a key determinant of the nutritional status. The correlation of low SMI level and poor survival in HCC has been well investigated [12, 13]. Previous studies have showed that long-term systemic inflammation is associated with muscle loss, which may aggravate systemic inflammation and lead to higher risk of mortality [14, 15]. Given the association between of SII, and SMI and HCC, a new biomarker SMI to SII ratio (SMI/SII) which combines the advantages of SII and SMI can potentially improve the prognosis in patients with HCC.

Therefore, the present study aimed to (a) assess the predictive performance of SMI/SII ratio for identifying early recurrence in HCC patients who underwent liver resection (LR) and calculate the optimal cut-off value; (b) validate the predictive performance of SMI/SII ratio for estimating overall survival (OS) in two independent cohorts of patients with HCC who underwent either LR or transarterial chemoembolization (TACE); (c) prospectively analyze blood specimens obtained from patients with HCC, to accurately quantify the distribution of immune cells in the peripheral blood of individuals with varying SMI/SII ratio.

Materials and methods

Study population

This multi-institutional study included three retrospective datasets (a training cohort and two validation cohorts) and one prospective dataset (a validation cohort). For the training (from hospital A, between August 2013 and December 2020) and validation-1 cohort (from hospital B and C, between April 2013 and September 2021), consecutive untreated patients with HCC who underwent LR were included. For validation-2 cohort (from hospitals A, B, C, and D, between June 2014 and September 2020), consecutive untreated patients with unresectable HCC who underwent TACE were included. For validation-3 cohort (from hospital A, between August 2021 and September 2022), consecutive untreated patients with HCC who underwent LR or TACE were recruited. A flowchart of the study population is shown in Fig. 1A and B. The institutional review boards of all hospitals approved the study. Written informed consent was obtained from participants included in the prospective dataset only, and it was waived for the retrospective datasets because of the study design (Hospital A: Second Xiangya Hospital of Central South University; Hospital B: Affiliated Cancer Hospital of Guizhou Medical University; Hospital C: Hunan Cancer Hospital; Hospital D: Affiliated Hospital of Guizhou Medical University.).

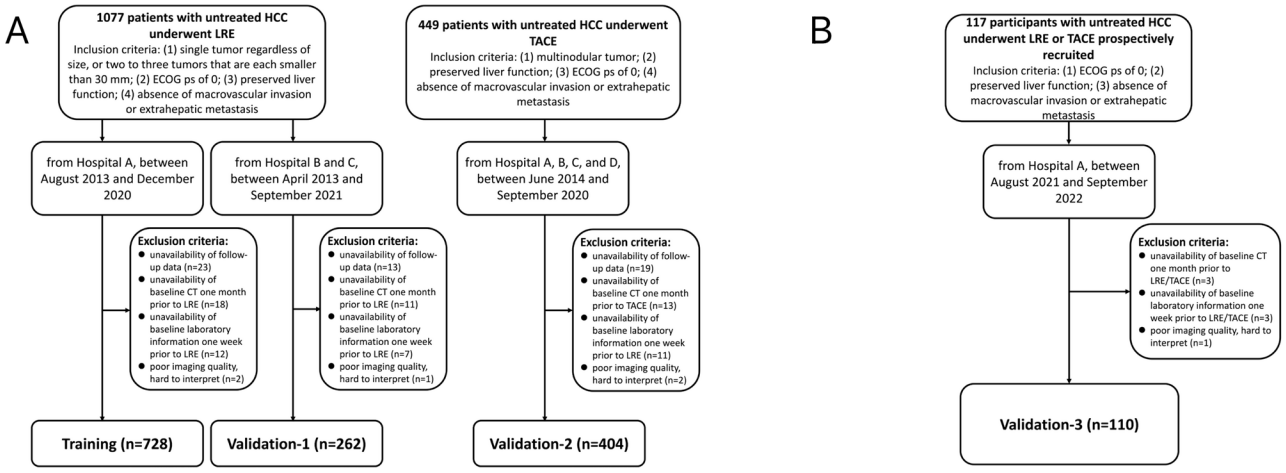

Fig. 1 Flowchart of the study population (**A**, **B**)

The inclusion criteria for training and validation-1 cohorts were: (1) single tumor regardless of size, or two to three tumors that were each < 30 mm; (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0; (3) preserved liver function; (4) absence of macrovascular invasion or extrahepatic metastasis. The exclusion criteria were: (1) unavailability of baseline computed tomography (CT) imaging one-month preceding LR; (2) unavailability of baseline laboratory information within one-week preceding LR; (3) poor imaging quality; (4) unavailability of follow-up data.

The inclusion criteria for validation-2 cohort were: (1) multinodular tumor; (2) preserved liver function; (3) ECOG performance status of 0; (4) absence of macrovascular invasion or extrahepatic metastasis. The exclusion criteria were: (1) unavailability of baseline CT imaging one-month prior to TACE; (2) poor imaging quality; (3) unavailability of baseline laboratory information within one week prior to TACE; (4) unavailability of follow-up data.

The inclusion and exclusion criteria for the validation-3 cohort were based on the training and validation-1 cohorts (for patients treated with LR) or validation-2 cohort (for patients treated with TACE).

Data collection

Clinical and laboratory data, including age, sex, liver cirrhosis, etiologies of hepatitis, tumor size, number of tumors, height, weight, creatine, total bilirubin, albumin, creatine, neutrophil, lymphocyte, monocyte, platelet, alpha-fetoprotein (AFP) level, and Barcelona clinic liver cancer staging were collected.

Systemic inflammatory biomarkers and anthropometric measurements

The neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), and SII were defined as: NLR = N/L, PLR = P/L, MLR = M/L, and SII = P × N/L, where "N" stands for neutrophil count, "P" stands for platelet count, "M" stands for monocyte count, and "L" stands for lymphocyte count.

Weight and height were measured before treatment. Body mass index (BMI) was calculated as weight (kg)/height (m^2). As previously described, total skeletal muscle area (SMA) was measured on unenhanced CT images at the third lumbar vertebrae level when both pedicles were visible, identified and quantified by thresholds of -29 to 150 HU, respectively,16 and the regions of interest were adjusted manually to match the actual muscle (Fig. 2A, B, C and D). The cross-sectional areas were automatically computed by summing tissue pixels and multiplying by pixel surface area. The CT images were independently reviewed and measured by two board-certified radiologists with 14 and 19 years of experience by using Slice-O-Matic software (version 6.0; Tomovision, Montreal, Canada). The SMI was defined as: SMI = SMA (cm^2)/height (m^2), and the SMI/SII ratio was calculated by the SMI divided by the SII.

Treatment approach and follow-up

The treatment approach was discussed by a tumor board including surgeons, interventional radiologists, oncologists, diagnostic radiologists, and hepatologists. The clinicians discussed the treatment recommendation with the patients, and a final decision was made after consensus. The detailed information for LR and TACE was illustrated in Supplementary Materials. Patients were followed-up via telephone interviews (December 2023) or during the last visit to the hospital if a telephone interview was unavailable. The primary outcome was early recurrence, characterized by the reappearance of tumor recurrence within two years following LR. Tumor recurrence was defined as the detection of HCC lesions, identifiable via CT or magnetic resonance imaging, either within the liver or at extrahepatic sites, irrespective of elevated AFP levels. The secondary outcome was OS, defined as the time interval between the date of LR/TACE and that of death or the last follow-up.

Determination of SMI/SII stratification and prognostic factors

In the training cohort, the predictive ability of early recurrence after LR for SMI/SII was evaluated, and the optimal cut-off value of SMI/SII was calculated. Additionally, the predictive ability of early recurrence among various systemic inflammatory or nutrition indices such as NLR, PLR, MLR, SII, BMI, SMA, and SMI were determined. Using the optimal cut-off value of SMI/SII, patients were stratified into high or low SMI/SII group in each cohort. The OS were compared between the high and low SMI/SII groups in the training, validation-1, and validation-2, as well as combined those three cohorts. The independent risk factor for poor OS was determined in a combination of training, validation-1, and validation-2 cohorts.

Blood sample collection and flow cytometric analysis

For the immune cell variables, peripheral blood samples were prospectively collected from validation-3 cohort within one week before LR/TACE. Whole-blood (10 mL) samples were collected into ethylenediaminetetraacetic acid-coated tubes, centrifuged in Ficoll-Paque, and peripheral blood mononuclear cells were isolated. Blood samples were processed fresh, and forward scatter/sideward scatter on a logarithmic scale was employed to delineate live cell populations. Subsequently, CD3+, CD3 + CD4+, CD3 + CD8 + T cells, natural killer cells

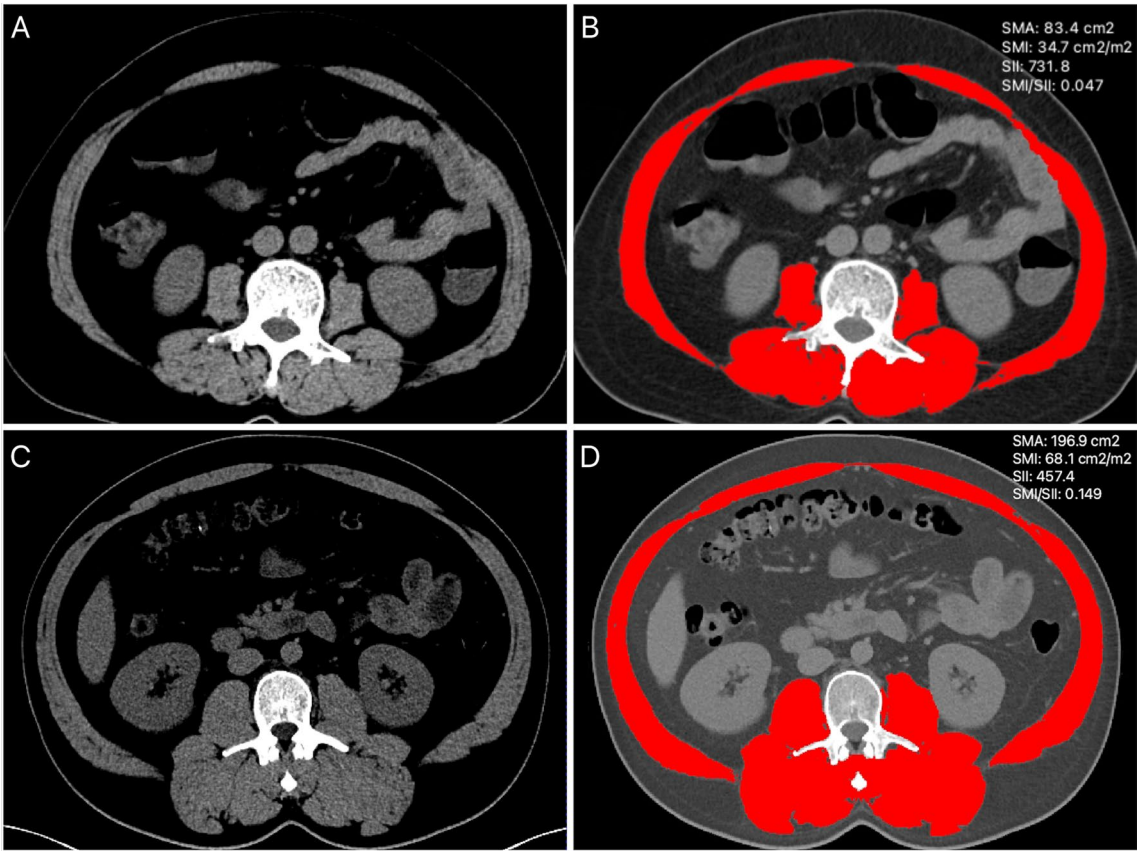

Fig. 2 Unenhanced axial CT scan before LR. A 48-year-old female with HCC in low SMI/SII group before (**A**) and after (**B**) segmentation of skeletal muscle. A 38-year-old male with HCC in high SMI/SII group before (**C**) and after (**D**) segmentation of skeletal muscle. The red outline represents the closed polygon drawn using the region of interest tool around the interior border of the skeletal muscle

(CD3-/CD56+), and Tregs (CD25 + CD4+) were sequentially examined through flow cytometry.

Statistical analysis

Continuous variables were presented as the median with IQR or range using the Mann–Whitney U test or t test, as appropriate. Categorical variables were presented as numbers with percentages and compared using the χ2 test or Fisher's exact test, as appropriate. The inter-reader agreements between the two radiologists were evaluated using intraclass correlation coefficient. The predictive performance was evaluated by analyzing the areas under receiver operating characteristic (AUCs) curve. The optimal cut-off value for SMI/SII was calculated based on the maximum value of the Youden index. The OSs were compared between the groups in each cohort using log-rank test. Moreover, to reduce potential confounding and selection bias between the two groups, propensity score matching was performed in training, validation-1, and validation-2, as well as combination of those three cohorts, with a matching tolerance of 0.05. The OS was also compared after matching. Univariable and multivariable Cox regression analyses using forward LR method were performed to determine independent risk factor of poor OS. Significant factors from univariable analysis were included in the multivariable model. Sample sizes were evaluated for the validation-3 cohort using the priori method in G-power software, setting a moderate effect size d (0.7) with $\alpha = 0.05$ and a power of 0.8 with two independent groups. Statistical analyses were performed using R software version 4.0.2; a two-sided $P < 0.05$ denoted statistical significance.

Results

Baseline characteristics of patients

The entire study population included 1504 patients (1292 men and 212 women; mean age, 54.1 ± 12.1 years). Of whom 728 patients were in training cohort, 262 patients were in valdation-1 cohort, 404 patients in validation-2 cohort, and 110 patients in validation-3 cohort. The diagnosis of HCC was based on typical imaging features according to the LI-RADS criteria ($n = 344$) or pathology ($n = 1102$). The baseline characteristics of the patients are summarized in Table 1. By the end of the follow-up, 316 patients (43.4%, 316/728) had died in training cohort, 127 patients (48.5%, 127/262) had died in validation-1 cohort,

Table 1 Baseline characteristics of patients

Characteristics	Training (*n* = 728)	Validation-1 (*n* = 262)	Validation-2 (*n* = 404)	Validation-3 (*n* = 110)
Age (years)*	53.0±11.7	54.5±13.4	55.9±11.5	53.9±13.9
Sex (n, %)				
Male	621 (85.3)	215 (82.1)	358 (88.6)	98 (89.1)
Female	107 (14.7)	47 (17.9)	46 (11.4)	12 (10.9)
Height (m) #	1.66 (1.61–1.71)	1.67 (1.60–1.72)	1.65 (1.60–1.70)	1.67 (1.59–1.72)
Weight (kg) #	62.0 (55.0–68.0)	63.0 (53.0–70.0)	62.0 (55.0–69.0)	64.0 (57.5–69.0)
BMI (kg/m^2) #	22.4 (20.3–24.8)	22.6 (20.1–25.8)	22.5 (20.3–25.0)	23.2 (20.8–25.7)
BCLC staging (n, %)				
0	51 (7.0)	20 (7.6)	-	6 (5.4)
A	677 (93.0)	242 (92.4)	-	52 (47.3)
B	-	-	404 (100.0)	52 (47.3)
Etiologies of hepatitis (n, %)				
None	77 (10.6)	67 (25.6)	54 (13.4)	14 (12.7)
HBV	558 (76.6)	188 (71.7)	324 (80.2)	89 (80.9)
Others	93 (12.8)	7 (2.7)	26 (6.4)	7 (6.4)
Liver cirrhosis (n, %)				
Absence	354 (48.6)	126 (48.1)	153 (37.9)	41 (37.3)
Presence	374 (51.4)	136 (51.9)	251 (62.1)	69 (62.7)
Tumor size (n, %)				
≤ 50 mm	351 (48.2)	146 (55.7)	211 (52.2)	57 (51.8)
> 50 mm	377 (51.8)	116 (44.3)	193 (47.8)	53 (48.2)
Number of tumors (n, %)				
Solitary	617 (84.8)	224 (85.5)	-	47 (42.7)
Multinodular	111 (15.2)	38 (14.5)	404 (100.0)	63 (57.3)
Up-to-seven criteria (n, %)				
Within	418 (57.4)	160 (61.1)	210 (52.0)	63 (57.3)
Beyond	310 (42.6)	102 (38.9)	194 (48.0)	47 (42.7)
Creatine (umol/L) #	71.3 (61.3–80.6)	66.0 (57.5–77.0)	71.9 (62.0-81.1)	71.9 (62.4–81.3)
Total bilirubin (umol/L) #	13.7 (10.1–18.5)	13.2 (9.7–19.2)	16.1 (11.9–22.8)	14.5 (10.6–19.6)
Albumin (g/L) #	38.7 (35.8–41.2)	41.2 (37.2–44.0)	37.9 (34.0-41.1)	39.8 (35.6–42.5)
ALBI grade (n, %)				
I	306 (42.0)	172 (65.6)	142 (35.1)	53 (48.2)
II	422 (58.0)	90 (34.4)	262 (64.9)	57 (51.8)
Neutrophil ($\times 10^9$) #	3.40 (2.47–4.50)	3.13 (2.21–4.21)	2.85 (2.01–4.11)	3.58 (2.68–4.24)
Lymphocyte ($\times 10^9$) #	1.37 (1.04–1.73)	1.34 (1.02–1.80)	1.24 (0.92–1.68)	1.36 (1.04–1.75)
Platelet ($\times 10^9$) #	162.0 (113.0-218.0)	148.5 (101.0-213.0)	133.5 (86.0-187.0)	157.5 (132.0-207.5)
Monocyte ($\times 10^9$) #	0.32 (0.24–0.43)	0.45 (0.34–0.60)	0.38 (0.27–0.53)	0.41 (0.28–0.56)
NLR #	2.42 (1.81–3.30)	2.21 (1.64–3.18)	2.38 (1.62–3.22)	2.53 (1.98–3.20)
PLR #	116.6 (83.2-158.2)	103.4 (76.4-150.2)	99.6 (69.8-147.1)	121.1 (93.8-161.5)
MLR #	0.23 (0.18–0.32)	0.33 (0.26–0.44)	0.29 (0.22–0.40)	0.29 (0.22–0.41)
SII #	383.6 (236.0-627.0)	323.9 (192.6-578.4)	283.9 (164.1–542.0)	389.4 (331.5-448.4)
SMA (cm^2) #	114.2 (95.0-130.3)	113.7 (93.8-132.4)	116.3 (97.0-131.6)	116.0 (94.6–131.0)
SMI (cm^2/m^2) #	41.6 (35.1–46.3)	41.7 (35.0-47.3)	42.3 (35.6–47.3)	41.9 (35.3–47.4)
SMI/SII #	0.11 (0.06–0.18)	0.11 (0.07–0.22)	0.14 (0.07–0.26)	0.10 (0.08–0.13)
AFP level (n, %)				
≤ 200ng/mL	446 (61.3)	160 (61.1)	234 (57.9)	65 (59.1)
> 200ng/mL	282 (38.7)	102 (38.9)	170 (42.1)	45 (40.9)
Follow-up duration (months) #	38.8 (17.1–59.4)	42.3 (21.6–63.1)	24.3 (10.2–47.6)	-

Note: *, data are presented as mean ± SD; #, data are presented as median and IQR

Abbreviations: BMI, body mass index; BCLC, Barcelona clinic liver cancer; HBV, hepatitis B virus; ALBI, albumin-bilirubin; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic immune-inflammation index; SMA, skeletal muscle area; SMI, skeletal muscle index; SMI/SII, SMI to SII ratio; AFP, alpha-fetoprotein

and 277 patients (68.6%, 277/404) had died in validation-2 cohort.

Determination of early recurrence among systemic inflammatory or nutrition indices

The inter-reader agreements in measuring the tumor size and SMA were excellent, with intraclass correlation coefficients of 0.912 and 0.884, respectively. In the training cohort, 352 patients (48.3%, 352/728) had an early recurrence after LR. The AUCs for predicting early recurrence in NLR was 0.626, PLR was 0.680, MLR was 0.613, SII was 0.676, BMI was 0.596, SMA was 0.595, SMI was 0.654, and SMI/SII was 0.701, and the corresponding optimal cut-off value of SMI/SII was 0.106 (Supplementary Figure S1). Furthermore, we integrated SMI/SII with other independent prognostic factors to enhance the prediction of early recurrence of HCC following resection, resulting in improved predictive accuracy, and the AUC was 0.757 (Supplementary Figure S2).

Comparison in OS between low and high SMI/SII groups

Based on the cut-off value of SMI/SII, patients were divided into low and high SMI/SII groups (Table 2). The OS rates were significantly better in the high SMI/SII group than that in the low SMI/SII group in the training cohort ($P < 0.001$), the validation-1 cohort ($P = 0.008$), the validation-2 cohort ($P < 0.001$), and the combined cohorts ($P < 0.001$) (Fig. 3A, C, E and G). Subsequently, 230 pairs, 89 pairs, 101 pairs, and 483 pairs were matched in training, validation-1, validation-2, and the combined cohorts, accordingly (Supplementary Table S1). The OSs were also significantly better in high SMI/SII group than those of low SMI/SII group after matching in training ($P < 0.001$), validation-1 ($P = 0.038$), validation-2 ($P < 0.001$), and the combined cohorts ($P < 0.001$) matching (Fig. 3B, D, F and H). Simultaneously, we conducted a comparative analysis of OS prognosis between individuals with high and low SMI and SII within the total population (Supplementary Figure S3). Our findings indicate that patients exhibiting low SII and high SMI demonstrate superior OS outcomes ($P < 0.001$).

Prognostic factors of poor OS

The evaluation of prognostic factors of poor OS was performed in the combination cohorts of training, validation-1, and validation-2. In the univariable Cox analysis, age ($P = 0.027$), SMI/SII level (low/high) ($P < 0.001$), up-to-seven criteria (within/beyond) ($P < 0.001$), liver cirrhosis (absence/presence) ($P = 0.029$), albumin-bilirubin (ALBI) grade (I/II) ($P < 0.001$), and AFP level (≤ 200/> 200 ng/mL) ($P < 0.001$) were factors that affected the OS. Therefore, these six parameters were included in the multivariable Cox regression analysis, and the results showed that low SMI/SII ($P < 0.001$), beyond up-to-seven criteria ($P < 0.001$), liver cirrhosis ($P = 0.002$), ALBI grade of II ($P < 0.001$), and AFP level greater than 200 ng/mL ($P = 0.002$) were independent prognostic factors of poor OS. The univariable and multivariable analysis is illustrated in Table 3.

Distribution of peripheral blood lymphocytes in validation-3 cohort

Based on the sample size calculation, a total of 110 participants were recruited, of whom, 59 patients were in low SMI/SII group and 51 patients were in high SMI/SII group (Table 4). Cytotoxic T lymphocytes were identified based on the expression of CD3 and CD8 cells, natural killer cells based on expression of CD3-CD56 + cells, and Tregs were identified based on expression of CD4 + CD25 + cells. The high SMI/SII group exhibited significantly higher frequencies of CD3+, CD3 + CD4+, CD3 + CD8 + T cells, and natural killer cells in the peripheral blood compared to those exhibited by the low SMI/SII group. Conversely, the high SMI/SII group demonstrated significantly lower frequencies of Tregs compared to those exhibited by the low SMI/SII group (Fig. 4A, B, C, D and E).

Discussion

To date, the therapeutic approaches for HCC predominantly rely on factors such as tumor burden, liver function, and performance status; [5–7] however, the inclusion of patients' inflammation and immune status in the clinical guidelines is lacking. In the present study, a novel index SMI/SII ratio combining the systemic inflammatory and the quantity of skeletal muscle was introduced. The ratio of SMI/SII, which combines the strengths of both SMI and SII, demonstrated the highest performance for evaluating early recurrence of HCC patients after LR among various inflammatory index or nutrition index. In general, an elevated SII signifies an exaggerated inflammatory reaction, whereas a diminished SMI signifies suboptimal nutritional condition. As a result, HCCs exhibiting low SMI/SII frequently exhibit a robust inflammatory response (high SII), and owing to their compromised nutritional status (low SMI), they are unable to effectively self-regulate, resulting in the persistence of inflammatory response. The prolonged presence of inflammation further compromises immune function, ultimately culminating in tumor recurrence, invasion, and metastasis [17].

The findings of this study indicated that HCC with pretreatment high SMI/SII exhibit improved OS compared to those of HCC with low SMI/SII after LR. Moreover, this study revalidated the prognostic significance of SMI/SII ratio in the TACE cohort showing that the SMI/SII ratio is favorable for prognosis in patients treated with TACE. These results suggest that the SMI/SII ratio holds

Table 2 Clinical characteristics of patients between the low and high SMI/SII groups

Characteristics	Training ($n=728$)			Validation-1 ($n=262$)			Validation-2 ($n=404$)			Combined cohorts ($n=1394$)		
	Low ($n=365$)	High ($n=363$)	*P*	Low ($n=123$)	High ($n=139$)	*P*	Low ($n=157$)	High ($n=247$)	*P*	Low ($n=645$)	High ($n=749$)	*P*
Age (years)*	53.3±12.1	52.8±11.3	0.622	53.5±13.3	55.4±13.5	0.241	54.4±11.9	56.8±11.1	0.039	53.6±12.3	54.6±11.8	0.105
Sex			0.050			0.050			0.778			0.596
Male	302 (82.7)	319 (87.9)		107 (87.0)	108 (77.7)		140 (89.2)	218 (88.3)		549 (85.1)	645 (86.1)	
Female	63 (17.3)	44 (12.1)		16 (13.0)	31 (22.3)		17 (10.8)	29 (11.7)		96 (14.9)	104 (13.9)	
BMI (kg/m^2) #	21.9 (19.8–24.3)	22.9 (20.8–25.5)	< 0.001	22.5 (20.2–25.8)	22.9 (19.9–25.8)	0.976	22.0 (19.6–24.7)	22.7 (20.8–25.5)	0.010	21.0 (18.0-23.7)	21.9 (18.6–24.8)	< 0.001
BCLC staging (n, %)			< 0.001			0.776			-			< 0.001
0	12 (3.3)	39 (10.7)		10 (8.1)	10 (7.2)		0	0		22 (3.4)	49 (6.5)	
A	353 (96.7)	324 (89.3)		113 (91.9)	129 (92.8)		0	0		466 (72.2)	453 (60.5)	
B	-	-		-	-		157	247		157 (24.3)	247 (33.0)	
Etiologies of hepatitis (n, %)			0.034			0.646			0.032			0.006
None	48 (13.2)	29 (8.0)		34 (27.6)	33 (23.7)		29 (18.5)	25 (10.1)		111 (17.2)	87 (11.6)	
HBV	266 (72.9)	292 (80.4)		85 (69.1)	103 (74.1)		121 (77.1)	203 (82.2)		472 (73.2)	598 (79.8)	
Others	51 (14.0)	42 (11.6)		4 (3.3)	3 (2.2)		7 (4.5)	19 (7.7)		62 (9.6)	64 (8.5)	
Liver cirrhosis (n, %)			< 0.001			< 0.001			< 0.001			< 0.001
Absence	200 (54.8)	154 (42.4)		38 (30.9)	88 (63.3)		90 (57.3)	63 (25.5)		328 (50.9)	305 (40.7)	
Presence	165 (45.2)	209 (57.6)		85 (69.1)	51 (36.7)		67 (42.7)	184 (74.5)		317 (49.1)	444 (59.3)	
Tumor size (n, %)			< 0.001			0.909			< 0.001			< 0.001
≤ 50 mm	108 (29.6)	243 (66.9)		69 (56.1)	77 (55.4)		37 (23.6)	174 (70.4)		214 (33.2)	494 (66.0)	
> 50 mm	257 (70.4)	120 (33.1)		54 (43.9)	62 (44.6)		120 (76.4)	73 (29.6)		431 (66.8)	255 (34.0)	
Number of tumors (n, %)			0.893			0.955			-			0.005
Solitary	310 (84.9)	307 (84.6)		105 (85.4)	119 (85.6)		0	0		415 (64.3)	426 (56.9)	
Multinodular	55 (15.1)	56 (15.4)		18 (14.6)	20 (14.4)		157	247		230 (35.7)	323 (43.1)	
Up-to-seven criteria (n, %)			< 0.001			0.632			< 0.001			< 0.001
Within	142 (38.9)	276 (76.0)		77 (62.6)	83 (59.7)		33 (21.0)	163 (66.0)		252 (39.1)	522 (69.7)	
Beyond	223 (61.1)	87 (24.0)		46 (37.4)	56 (40.3)		124 (79.0)	84 (34.0)		393 (60.9)	227 (30.3)	
Creatine (umol/L) #	70.2 (59.6–79.6)	72.2 (63.0-83.5)	0.006	66.0 (59.0-79.7)	66.0 (55.4–75.8)	0.110	71.8 (61.9–79.3)	72.7 (62.0-81.9)	0.582	70.1 (60.0-79.3)	71.2 (61.0–81.0)	0.098
Total bilirubin (umol/L) #	13.0 (9.3–17.6)	14.6 (11.0-19.2)	< 0.001	14.4 (10.5–20.2)	11.6 (8.7–17.1)	0.004	14.7 (11.4–21.0)	16.5 (12.6–24.2)	0.045	13.7 (10.1–19.1)	14.8 (11.0–20.0)	0.007
Albumin (g/L) #	38.6 (35.6–41.4)	38.7 (36.1–41.1)	0.662	41.5 (37.5–44.6)	40.9 (37.1–43.5)	0.126	38.3 (35.2–41.2)	37.5 (33.2–41.0)	0.148	39.0 (35.7–42.1)	38.7 (35.6–41.6)	0.197
ALBI grade (n, %)			0.698			0.845			0.698			0.508
I	156 (42.7)	150 (41.3)		80 (65.0)	92 (66.2)		57 (36.3)	85 (34.4)		293 (45.4)	327 (43.7)	
II	209 (57.3)	213 (58.7)		43 (35.0)	47 (33.8)		100 (63.7)	162 (65.6)		352 (54.6)	422 (56.3)	
Neutrophil (× 10^9) #	4.33 (3.40–5.35)	2.64 (2.04–3.38)	< 0.001	3.51 (2.26–4.55)	3.05 (2.18–3.94)	0.103	4.36 (3.30–5.53)	2.29 (1.71–3.01)	< 0.001	4.20 (3.18–5.24)	2.60 (1.90–3.36)	< 0.001
Lymphocyte (× 10^9) #	1.32 (1.03–1.63)	1.41 (1.06–1.84)	0.019	1.25 (0.97–1.77)	1.37 (1.05–1.86)	0.161	1.21 (0.90–1.61)	1.27 (0.92–1.70)	0.575	1.30 (1.01–1.66)	1.36 (1.02–1.80)	0.026
Platelet (× 10^9) #	210.0 (163.0-258.5)	122.0 (86.0-159.0)	< 0.001	157.0 (101.0-215.0)	147.0 (101.0-209.0)	0.924	199.0 (154.5-250.5)	99.0 (68.0-136.0)	< 0.001	196.5 (148.9-251.1)	118.2 (81.0-159.1)	< 0.001

Table 2 (continued)

Characteristics	Training (*n* = 728)			Validation-1 (*n* = 262)			Validation-2 (*n* = 404)			Combined cohorts (*n* = 1394)		
	Low (*n* = 365)	High (*n* = 363)	*P*	Low (*n* = 123)	High (*n* = 139)	*P*	Low (*n* = 157)	High (*n* = 247)	*P*	Low (*n* = 645)	High (*n* = 749)	*P*
Monocyte ($\times 10^9$) #	0.38 (0.27–0.51)	0.28 (0.21–0.37)	< 0.001	0.43 (0.34–0.57)	0.46 (0.34–0.62)	0.294	0.48 (0.36–0.62)	0.33 (0.23–0.46)	< 0.001	0.41 (0.29–0.54)	0.32 (0.23–0.44)	< 0.001
SII #	623.6 (469.2-915.1)	236.9 (154.8-307.6)	< 0.001	592.3 (446.8-840.7)	203.3 (146.8-284.8)	< 0.001	659.9 (479.7-1029.5)	190.7 (120.7-252.7)	< 0.001	628.1 (466.1-931.5)	209.6 (141.0-289.0)	< 0.001
SMA (cm^2) #	107.9 (88.5–124.0)	119.9 (104.3-137.2)	< 0.001	109.3 (82.9-124.8)	118.1 (102.1-137.6)	< 0.001	109.1 (85.8-125.7)	118.6 (102.3-136.6)	< 0.001	108.3 (86.2-124.7)	119.2 (103.8-136.9)	< 0.001
SMI (cm^2/m^2) #	38.9 (32.7–44.2)	43.6 (38.0-49.2)	< 0.001	39.2 (30.6–45.1)	43.6 (37.4–49.7)	< 0.001	40.4 (32.5–44.9)	43.2 (37.3–49.0)	< 0.001	39.1 (32.4–44.4)	43.5 (37.5–49.1)	< 0.001
AFP level (n, %)			0.011			0.121			< 0.001			< 0.001
≤ 200ng/mL	207 (56.7)	239 (65.8)		69 (56.1)	91 (65.5)		72 (45.9)	162 (65.6)		348 (54.0)	492 (65.7)	
> 200ng/mL	158 (43.3)	124 (34.2)		54 (43.9)	48 (34.5)		85 (54.1)	85 (34.4)		297 (46.0)	257 (34.3)	

Note: *, data are presented as mean ± SD; #, data are presented as median and IQR

Abbreviations: SMI/SII, SMI to SII ratio; BMI, body mass index; BCLC, Barcelona clinic liver cancer; HBV, hepatitis B virus; ALBI, albumin-bilirubin; SII, systemic immune-inflammation index; SMA, skeletal muscle area; SMI, skeletal muscle index; AFP, alpha-fetoprotein

predictive significance HCC patients who undergo LR, as well as prognostic significance across TACE. Existing literature shows a robust association between nutrition, inflammation, and the progression of malignancies [18]. The loss of skeletal muscle exacerbates postoperative functional impairment and disability in patients undergoing surgery, as it hampers mobilization, compromises respiratory function, and diminishes physical performance [19]. A loss of skeletal muscle has been shown to be associated with the prognosis of HCC. [20] For instance, Yang et al. [21] demonstrated an association between sarcopenia and unfavorable outcomes following LR for HCC, and Yamasaki et al. [22] have reported an association between sarcopenia and adverse clinical outcomes in patients with HCC undergoing treatment with Sorafenib or Lenvatinib. The SII scoring tool was established for the assessment of lymphocytes, neutrophils, and platelet counts, and it can be used as a prognostic factor for both recurrence and survival in patients with HCC following LR. [11] Given that the SII ratio considers the peripheral blood composition including lymphocytes, neutrophil, and platelet counts, the predictive capacity of SII for tumor recurrence and metastasis can be better understood by examining the complex interplay of these three cells types the tumor microenvironment.23 For example, it has been demonstrated that the tumor-promoting activity of neutrophils could be attributed to the ability of these cells to migrate to the tumor microenvironment and secrete various pro-angiogenic factors, thereby facilitating tumor progression [24]. Lymphocytes play a pivotal role in the pathogenesis and advancement of tumors, and studies have indicated that increased infiltration of lymphocytes in tumors is associated with extended survival among patients with HCC [25]. The CD8 + cytotoxic lymphocytes can identify tumor antigens and initiate apoptosis in cancer cells by generating cytotoxins like perforin and granzyme [26]. While peripheral platelets are important for primary hemostasis, platelets can also release pro-angiogenic cytokines such as vascular endothelial growth factor and endothelial cell growth factor, which facilitate tumor angiogenesis [27]. Given the correlation between an increased inflammatory index (indicative of a robust inflammatory response) and a decreased quantity of skeletal muscle (indicative of insufficient immunonutrition), a novel composite indicator which combines these two metrics, namely SMI/SII, was developed. Our study showed that the predictive accuracy of the combination of SMI and SII (SMI/SII) surpassed that of SMI or SII individually, suggesting that the combined SMI/SII ratio could be a good prognostic measure of HCC. Notably, this study exclusively examined the role of SMI/SII in the HCC prognosis following LR and TACE, without investigating its prognostic significance in the context of HCC immunotherapy or

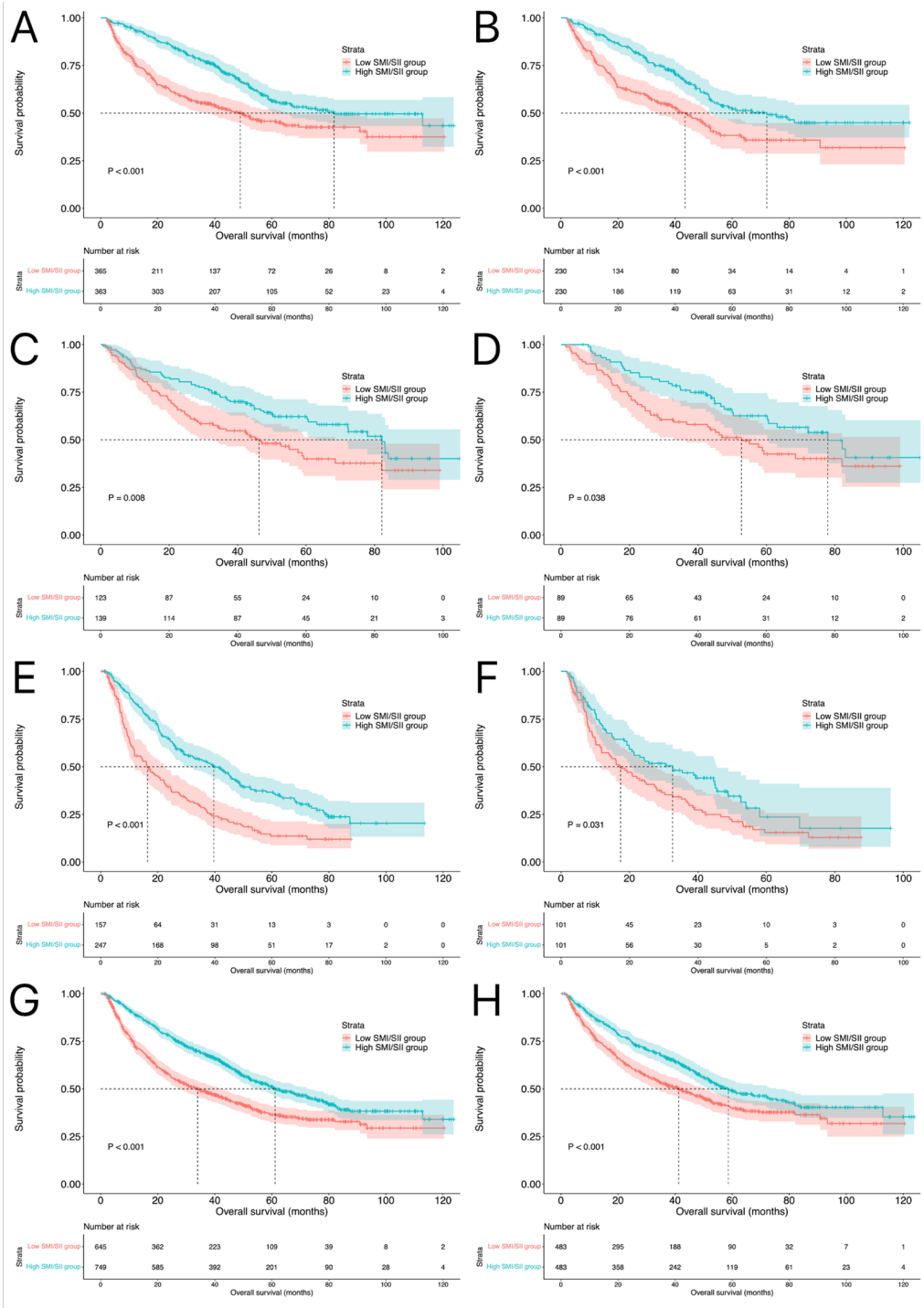

Fig. 3 Survival curves of the high and low SMI/SII groups in training (**A** before matching, **B** after matching), validation-1 (**C** before matching, **D** after matching), and validation-2 (**E** before matching, **F** after matching), as well as in the combined those three cohorts (**G** before matching, **H** after matching)

Table 3 Prognostic factors of OS in combination of training, validation-1, and validation-2 cohorts

Variables	Univariable			Multivariable	
	N	HR	P	HR	P
Age	1394	1.007 (1.001–1.013)	0.027		
Sex					
Male	1194				
Female	200	0.834 (0.671–1.036)	0.101		
Up-to-seven criteria					
Within	785				
Beyond	609	2.024 (1.747–2.344)	< 0.001	1.838 (1.574–2.147)	< 0.001
Etiologies of hepatitis					
None	198				
HBV	1070	0.882 (0.716–1.085)	0.234		
Others	126	0.928 (0.683–1.259)	0.630		
Liver cirrhosis					
Absence	633				
Presence	761	1.179 (1.017–1.367)	0.029	1.273 (1.095–1.479)	0.002
ALBI					
I	620				
II	774	1.389 (1.197–1.612)	< 0.001	1.321 (1.136–1.535)	< 0.001
AFP level					
≤ 200ng/mL	840				
> 200ng/mL	554	1.356 (1.169–1.573)	< 0.001	1.269 (1.093–1.474)	0.002
SMI/SII level					
High	749				
Low	645	1.629 (1.407–1.886)	< 0.001	1.389 (1.191–1.620)	< 0.001

Abbreviations: OS, overall survival; HR, hazard ratio; HBV, hepatitis B virus; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; SMI/SII, skeletal muscle index to systemic immune-inflammation index ratio

radiotherapy (e.g., yttrium-90). Should future research establish its prognostic value in immunotherapy and radiotherapy, SMI/SII could potentially serve as a comprehensive prognostic indicator for HCC, warranting its inclusion in clinical guidelines.

Importantly, in the prospective cohort in our study, HCC patients with a high SMI/SII ratio were characterized by elevated levels of CD8 + T cells and natural killer cells, and reduced levels of Tregs in peripheral blood, suggesting that these patients had increased anti-tumor activity based on their peripheral blood composition. Conversely, patients with low SMI/SII were characterized by decreased levels of CD8 + T cells and natural killer cells, and increased levels of Tregs in peripheral blood, indicating a tumor-promoting characteristic in these patients. The findings imply that SMI/SII has the potential to serve as an indicator of the body's anti-tumor immune status and may function as a prognostic biomarker for assessing the efficacy of immune checkpoint therapy. For example, individuals with low SMI/SII exhibit a reduced presence of immune killer cells in their peripheral blood. This deficiency may contribute to an immunosuppressive tumor microenvironment in HCC, characterized by an insufficient infiltration of CD8 + T cells and natural killer cells. Consequently, these individuals experience an immunosuppressive state. However, the application of immune checkpoint therapy may alleviate this immunosuppressive condition, potentially leading to improved prognostic outcomes.

This study had several limitations. First, it was conducted in a region with a high prevalence of hepatitis B, which is not the principal etiology of HCC in Europe or America. Second, the retrospective design of the study might have introduced selection biases. Third, this study primarily focused on muscle as a nutritional index; however, other nutritional indices such as adipose tissue and bone density, which could be correlated with prognosis were not examined.

In conclusion, the present study demonstrates that a reduced SMI/SII ratio functions as an independent risk factor for poor prognosis in patients with HCC undergoing LR. This biomarker, whether utilized independently or alongside other clinical predictors, can be seamlessly incorporated into clinical practice and may provide a novel framework for the personalized application of LR.

Table 4 Clinical characteristics of patients between the low and high SMI/SII groups in validation-3 cohort

Characteristics	Low (*n* = 59)	High (*n* = 51)	*P*
Age (years)*	53.9±14.5	54.0±13.3	0.981
Sex			0.338
Male	51 (86.4)	47 (92.2)	
Female	8 (13.6)	4 (7.8)	
BMI (kg/m^2) #	21.8 (20.2–24.9)	23.9 (21.7–26.4)	0.004
BCLC staging (n, %)			0.292
0	3 (5.1)	3 (5.9)	
A	32 (54.2)	20 (39.2)	
B	24 (40.7)	28 (54.9)	
Etiologies of hepatitis (n, %)			0.137
None	11 (18.6)	3 (5.9)	
HBV	44 (74.6)	45 (88.2)	
Others	4 (6.8)	3 (5.9)	
Liver cirrhosis (n, %)			0.234
Absence	25 (42.4)	16 (31.4)	
Presence	34 (57.6)	35 (68.6)	
Tumor size (n, %)			0.033
≤ 50 mm	25 (42.4)	32 (62.7)	
> 50 mm	34 (57.6)	19 (37.3)	
Number of tumors (n, %)			0.489
Solitary	27 (45.8)	20 (39.2)	
Multinodular	32 (54.2)	31 (60.8)	
Up-to-seven criteria (n, %)			0.143
Within	30 (50.8)	33 (64.7)	
Beyond	29 (49.2)	18 (35.3)	
Creatine (umol/L) #	71.9 (61.3–83.3)	72.0 (63.0-78.8)	0.936
Total bilirubin (umol/L) #	12.8 (10.4–19.5)	15.6 (11.6–21.1)	0.238
Albumin (g/L) #	40.3 (34.9–42.6)	39.6 (37.1–42.1)	0.708
ALBI grade (n, %)			0.827
I	29 (49.2)	24 (47.1)	
II	30 (50.8)	27 (52.9)	
Neutrophil (× 10^9) #	3.77 (3.05–5.03)	2.97 (2.39–3.77)	0.001
Lymphocyte (× 10^9) #	1.33 (1.03–1.77)	1.41 (1.05–1.73)	0.959
Platelet (× 10^9) #	172.0 (148.0-244.0)	142.0 (113.0-187.0)	< 0.001
Monocyte (× 10^9) #	0.44 (0.32–0.65)	0.35 (0.27–0.52)	0.037
SII #	434.8 (389.0-694.5)	331.6 (261.2–380.0)	< 0.001
SMA (cm^2) #	105.1 (88.7-122.4)	125.8 (110.4-139.7)	< 0.001
SMI (cm^2/m^2) #	36.9 (32.7–43.5)	45.5 (41.3–49.5)	< 0.001
AFP level (n, %)			0.133
≤ 200ng/mL	31 (52.5)	34 (66.7)	
> 200ng/mL	28 (47.5)	17 (33.3)	
Treatment modalities			0.136
LR	35 (59.3)	23 (45.1)	
TACE	24 (40.7)	28 (54.9)	

Note: *, data are presented as mean ± SD; #, data are presented as median and IQR

Abbreviations: SMI/SII, SMI to SII ratio; BMI, body mass index; BCLC, Barcelona clinic liver cancer; HBV, hepatitis B virus; ALBI, albumin-bilirubin; SII, systemic immune-inflammation index; SMA, skeletal muscle area; SMI, skeletal muscle index; AFP, alpha-fetoprotein; LR, liver resection; TACE, transarterial chemoembolization

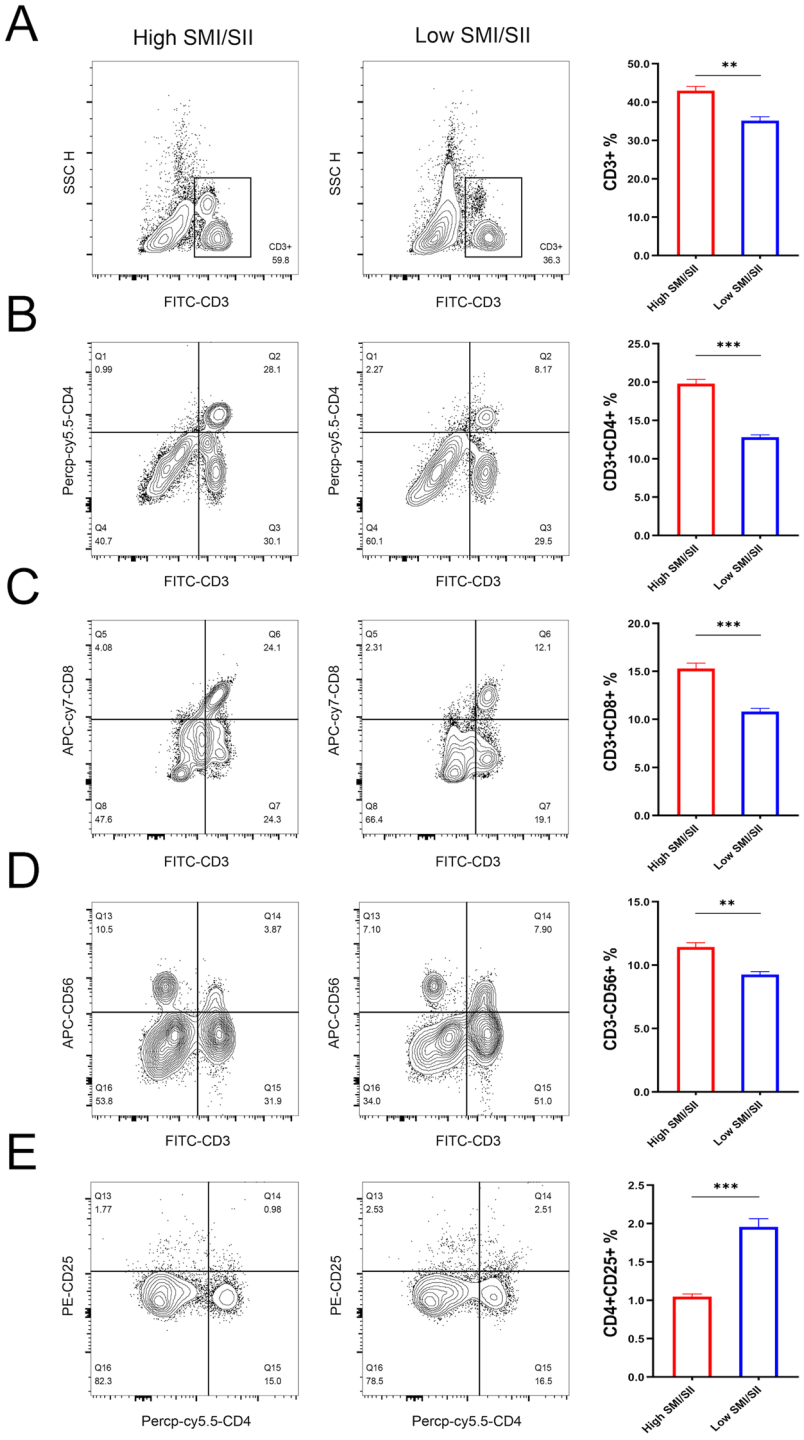

Fig. 4 Distribution of immune cells in peripheral blood between high SMI/SII group and low SMI/SII group. CD3 + T cells were higher in the high SII/SMI group than low SII/SMI group (**A**). CD3 + CD4 + T cells were higher in the high SII/SMI group than low SII/SMI group (**B**). CD3 + CD8 + T cells were higher in the high SII/SMI group than low SII/SMI group (**C**). CD3-CD56 + NK cells were higher in the high SII/SMI group than low SII/SMI group (**D**). CD4 + CD25 + Tregs were lower in the high SII/SMI group than low SII/SMI group (**E**). Note: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$;

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions
Guarantors of integrity of entire study, Y.D.X., T.C.W.; literature research, X.S.L., W.H., T.C.W.; clinical studies, J.X.L., T.Z.A., H.Z.L., X.S.L., C.H., T.C.W.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for im-portant intellectual content, all authors; approval of finalversion of submittedmanuscript, all authors; agrees to ensure any questions related to the work areappropriately resolved, all authors.

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Data availability
Data is available upon reasonable request from Tian-Cheng Wang.

Declarations

Ethical approval
The study was approved by the institutional review boards of the Second Xiangya Hospital of Central South University, the Affiliated Cancer Hospital of Guizhou Medical University, the Hunan Cancer Hospital and the Affiliated Hospital of Guizhou Medical University. This study was conducted in accordance with the Helsinki Declaration. The requirement of written informed consent was obtained for the prospective dataset only, while it was waived for the retrospective datasets owing to the study design.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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