Prognostic value and association of sarcopenic obesity and systemic inflammatory indexes in patients with hepatocellular carcinoma following hepatectomy and the establishment of novel predictive nomograms

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Background: The specific impacts of sarcopenic obesity (SO) on hepatocellular carcinoma (HCC) and the association between SO and systemic inflammation remain unclear. This study aimed to investigate the prognostic value and association of SO and systemic inflammation with outcomes after hepatectomy for HCC and develop novel nomograms based on SO and inflammatory indexes for survival prediction.

Methods: We retrospectively enrolled 452 patients with HCC who underwent radical hepatectomy between January 2012 and March 2015 in Fujian Provincial Hospital as the training cohort. In addition, 275 patients during the same period were enrolled as the external validation cohort. Patients were classified into different groups according to the presence of sarcopenia and obesity. Different inflammation indexes were evaluated to select the best predictor of overall survival (OS) and recurrence-free survival (RFS). Univariate and multivariate logistic regression were performed to investigate the associations between inflammatory indexes and SO. The inflammatory indexes with the highest predictive values and SO were selected for subgroup analyses to establish a novel classification system: the SOLMR grade. SOLMR grades identified in the multivariate Cox analysis were selected to construct novel nomograms for OS and RFS.

Results: SO (P<0.001) was an independent risk factor for OS and RFS. The lymphocyte monocyte ratio (LMR) had the highest areas under the receiver operating characteristic (ROC) curves (AUCs) for OS (P<0.001) and RFS (P<0.001) and was identified as an independent factor of SO (P=0.001). SO and the LMR were selected to establish the SOLMR grade. Multivariate Cox analysis revealed that SOLMR grade was a significant independent predictor of OS (P<0.001) and RFS (P<0.001). Nomograms based on SOLMR grades were generated and accurately predicted 1-, 3- and 5-year OS and RFS in HCC patients. The C-index of the novel nomograms was higher than those of the other conventional staging systems (P<0.001).

Conclusions: Both SO and the LMR were independent risk factors for OS and RFS in HCC patients after hepatectomy. The LMR was an independent factor of SO. The novel nomograms developed from the SOLMR grading system combining SO with the LMR provide good prognostic estimates of the outcomes of HCC patients.

Keywords: Hepatocellular carcinoma (HCC); sarcopenic obesity (SO); sarcopenia; inflammatory indexes; nomogram; prognostic value

Introduction

Hepatocellular carcinoma (HCC) is a common tumor that leads to poor survival outcomes even though the surgical techniques and adjuvant therapy has great advancements. In the era of individualized treatment with precision medicine, how to accurately identify various risk factors in early-stage HCC patients and establish corresponding individualized treatment have become clinical challenges. Recently, both sarcopenia and systemic inflammation have been proven to be closely associated with poor survival outcomes in HCC patients (1). Sarcopenia is a progressive syndrome that is characterized by skeletal muscle dysfunction involving the accelerated loss of muscle mass and function, which is associated with an increased risk of adverse outcomes (2). Sarcopenic obesity (SO) is defined as the coexistence of sarcopenia and obesity (3). Sarcopenia is associated with a poor HCC prognosis (4-14). However, studies on the specific impacts of SO on HCC are scarce, and there are still disagreements about the influence of SO on the survival prognosis in HCC patients (1,15-22). SO is a complex nutritional condition and a new syndrome, and its mechanisms are unknown to the research field of HCC (23). With the decrease in muscle mass and simultaneous accumulation of fat, SO is considered to have more complex mechanisms than sarcopenia alone. A series of evidence has demonstrated that the mechanism of sarcopenia may be related to systemic inflammation, in which resulting in imbalance of protein synthesis and catabolism by activating many of the molecular pathways involved in skeletal muscle loss (24,25). Lin *et al.* proved an association between the inflammatory index and sarcopenia, and both are considered good prognostic indicators in gastric cancer patients (26). But it is not clear whether SO has similar mechanisms and associations with inflammation in HCC patients. Different inflammatory indexes reflecting systemic inflammation and related inflammatory levels have been reported to play a key role in the development and progression of cancer (27). Different inflammatory indexes based on blood neutrophil, lymphocyte, monocyte, and platelet ratios, such as the neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), and platelet-lymphocyte ratio (PLR), the prognostic

nutritional index (PNI) and the systemic immune-inflammation index (SII) were reported to be closely related to the progression and prognosis of HCC (28). What is the intricate relationship among SO, these inflammatory indexes and HCC?

The specific impacts of SO on HCC and the association between SO and systemic inflammation remain unclear, especially in the HCC population with an extremely high infection rate of hepatitis B virus in China. Thus, this study attempted to investigate the relationships among SO, systemic inflammation and HCC. Furthermore, we aimed to evaluate the prognostic abilities of preoperative SO and systemic inflammatory indexes and their combined prognostic ability in predicting outcomes after hepatectomy for HCC to establish a novel prediction system involving nomograms for survival prediction. We present the study in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-341).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The protocol was approved by the institutional review boards of Fujian Provincial Hospital and Fujian Medical University Union Hospital (No. K2019-12-025; 2019KY022), and Informed consent was obtained from all patients before inclusion in the study.

Study population

This was a retrospective study performed in the Fujian Provincial Hospital and Fujian Medical University Union Hospital affiliated with Fujian Medical University from January 2012 to March 2015. We retrospectively reviewed data collected from patients who underwent radical hepatectomy at Fujian Provincial Hospital from January 2012 to March 2015; these patients were considered the training cohort. Patients who underwent radical hepatectomy at Fujian Medical University Union Hospital during the same period were enrolled in the study as the external validation cohort. The inclusion criteria were as follows: (I) patients with histologically confirmed HCC;
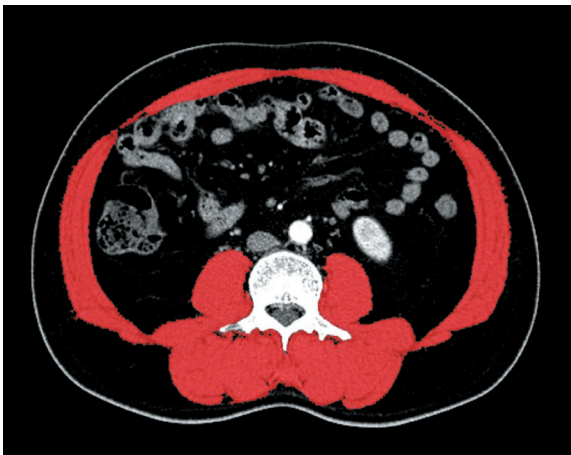
Figure 1 Cross-sectional CT image at the third lumbar vertebra level. The red shadows show the skeletal muscle areas, which were identified and quantified at –29 to 150 Hu. CT, computed tomography; Hu, Hounsfield units.

(II) patients who had not received any other curative treatment before radical hepatectomy (R0); and (III) patients with available preoperative computed tomography (CT) images within 30 days. The exclusion criteria were as follows: (I) other malignant tumors or metastatic disease; (II) unavailable preoperative CT images or incomplete or inaccurate medical records; or (III) death within 30 days after surgery. In total, 452 patients were enrolled in the training cohort, and 275 patients were enrolled in the external validation cohort in this study.

Image analysis and definition of SO

In this study, CT-based measurements were performed with ImageJ (v1.52q, RRID:SCR_003070) by a single trained researcher who was blinded to the outcomes. We measured the cross-sectional skeletal muscle area at the level of the third lumbar vertebra (L3) based on attenuation thresholds of –29 to +150 Hounsfield units (Hu) (19). Muscle area (cm^2), which was calculated as the average surface of two consecutive transverse slices, was normalized for the height of the patient (m^2) to obtain the L3 skeletal muscle index (SMI; cm^2/m^2) (29). SMI cutoff values were defined according to the area under the curve (AUC), receiver operating characteristic (ROC) curve and Youden index. SMI cutoff values were 40.86 cm^2/m^2 for males and 30.71 cm^2/m^2 for females (*Figure 1*).

Obesity was defined as a body mass index (BMI) ≥25 kg/m^2 (30). Patients were classified into 1 of 2 body composition categories according to the presence of both sarcopenia and obesity: the nonsarcopenic obesity (NSO) group and the SO group.

Markers of systemic inflammation

After a literature review, the following inflammatory indexes calculated from laboratory parameters obtained within 1 week before surgery were included in the analysis: the NLR, PLR, LMR, PNI and SII (31). The optimal cutoff values for the NLR, PLR, LMR, PNI and SII were calculated based on the ROC curves and defined by calculating the Youden index in SPSS. The predictive values of the inflammatory indexes were evaluated by the AUC in SPSS (version 23.0). To avoid collinearity, the index with the highest predictive ability was entered into the multivariate analysis to establish a novel prognostic nomogram.

Follow-up

The patients were followed for 1 month after initial surgical treatment and every 3 months thereafter. The final follow-up evaluation was conducted in March 2020. Follow-up surveillance included routine blood tests, liver function tests, alpha-fetoprotein (AFP) levels, dynamic CT, and magnetic resonance imaging (MRI).

Statistical analysis

Continuous variables were analyzed using the Kruskal-Wallis test or Mann-Whitney U-test, and categorical variables were analyzed using the Pearson chi-square or Fisher's exact test, as appropriate. Cumulative overall survival (OS) and recurrence-free survival (RFS) rates were calculated using the Kaplan-Meier method, and differences between curves were evaluated using the log-rank test. To investigate the association of prognostic factors with OS and RFS, we used the Cox proportional hazard model for the univariate and multivariate analyses, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Univariate and multivariate logistical regression analyses were performed to assess the relationship between preoperative SO and systemic inflammation. A nomogram was generated by Rstudio (v1.2.1335, RRID:SCR_000432) and R software (v3.6.3, RRID:SCR_001905) using the "rms, survival, survminer, rmda" packages. The predictive accuracy and discriminative ability of the nomogram

were evaluated by the concordance index (C-index) and calibration curves and compared with those of conventional staging systems. P<0.05 was considered significant. All statistical data were generated using SPSS (v23.0, RRID:SCR_002865), R software and Rstudio.

Results

Patient characteristics

Of the 452 patients included in the training cohort, 386 (85.4%) were men and 66 (14.6%) were women. The cohort was divided into two body composition groups: the NSO group, with 370 (81.9%) patients, and the SO group, with 82 (18.1%) patients. The clinical characteristics of each group are shown in *Table 1*. The median age was 54.00 years. The median SMI was 46.14 (cm^2/m^2). Men comprised the majority in each group (87.0%, 78.0%). HBsAg-positive patients (n=385) accounted for 85.2% of the training cohort. We found that the SO group had a higher rate of cardiovascular disease than the NSO group (P<0.025). Unlike the NSO group, the SO group had higher rates of multiple tumors, microvascular invasion, moderate differentiation and satellite lesions. The clinical characteristics of the validation cohort are shown in *Table 1*. These characteristics were not significantly different between the training cohort and validation cohort.

OS and RFS rates after hepatectomy for HCC

The median survival time was 47.0 months in the training cohort and 43.0 months in the validation cohort. The 1-, 3-, and 5-year OS rates in the entire cohort were 85.4%, 58.5%, and 45.5%, respectively. The 1-, 3-, and 5-year RFS rates in the entire cohort were 59.8%, 41.9%, and 31.8%, respectively. The 1-, 3-, and 5-year OS rates in the training cohort and validation cohort were 80.8%, 56.4%, and 45.3% and 86.2%, 61.8%, and 44.2%, respectively (P=0.713). The 1-, 3-, and 5-year RFS rates in the training cohort and validation cohort were 57.9%, 39.8%, and 29.6% and 62.8%, 45.4%, and 35.5%, respectively (P=0.220).

The 1-, 3-, and 5-year OS rates in the SO group and NSO group in the training cohort were 81.7%, 34.1%, and 17.3% and 84.3%, 61.9%, and 51.5%, respectively. The 1-, 3-, and 5-year RFS rates in the SO group and NSO group in the training cohort were 52.4%, 27.8%, and 12.4% and 60.3%, 43.4%, and 33.5%, respectively. The OS and RFS rates in the SO group were significantly lower than those in the NSO group in the training cohort (P<0.0001 and P=0.00037, respectively) (*Figure 2A,B*). The 1-, 3-, and 5-year OS rates in the SO group and NSO group in the validation cohort were 78.0%, 48.8%, and 25.9% and 87.6%, 64.1%, and 49.3%, respectively. The 1-, 3-, and 5-year RFS rates in the SO group and NSO group in the validation cohort were 43.9%, 21.3%, and 12.8% and 66.1%, 49.5%, and 39.2%, respectively. The OS and RFS rates in the SO group were significantly lower than those in the NSO group in the validation cohort (P=0.00028 and P<0.0001, respectively) (*Figure 2C,D*).

Inflammatory indexes

The following parameters were chosen for analysis: NLR, PLR, LMR, PNI and SII. The definitions and optimal cutoffs identified by calculating the AUCs are shown in *Table 2*. A higher NLR, higher PLR, higher SII, lower LMR, and lower PNI were correlated with poor OS and RFS (*Table 3*). The LMR had the highest AUC (0.624) for OS and the highest AUC (0.642) for RFS. The AUC values for the same inflammatory indexes in the validation cohort also followed a similar pattern. Some of the components of each inflammatory index were derived from the same laboratory test values; thus, if all these indexes were entered into the multivariate analysis, the problem of collinearity would be unavoidable. Thus, the LMR was selected for entry into the multivariate analysis to establish a novel prognostic nomogram for OS and RFS to account for collinearity.

Prognostic factors for OS and RFS after hepatectomy for HCC

The univariate analysis showed that cardiovascular disease, AFP level, tumor size, number of tumors, microvascular invasion, macrovascular invasion, the presence of satellite lesions, the NLR, the PLR, the LMR (HR, 2.297; 95% CI, 1.762–2.995; P<0.001), the PNI, the SII, body composition (HR, 2.096; 95% CI, 1.548–2.773; P<0.001) and American Joint Committee on Cancer (AJCC) stage (8th edition) were prognostic factors of OS in patients who underwent hepatectomy for HCC (*Table 3*). The univariate analysis of RFS showed that the AFP level, the tumor size, the number of tumors, microvascular invasion, macrovascular invasion, the presence of satellite lesions, the NLR, the PLR, the LMR (HR, 1.896; 95% CI, 1.513–2.376; P<0.001), the

Table 1 Characteristics of the patients (SO and NSO group)

Characteristic	Training cohort				Validation cohort				
	Total (n=452)	NSO (n=370)	SO (n=82)	P	Total (n=275)	NSO (n=234)	SO (n=41)	P	P*
Age (y), mean (SD)	53.15 (11.70)	52.95 (11.70)	54.05 (11.73)	0.456	54.07 (11.30)	54.34 (11.32)	52.51 (11.25)	0.396	0.336
Sex, n (%)				0.037				0.996	0.099
Male	386 (85.4)	322 (87.0)	64 (78.0)		223 (81.1)	189 (80.8)	33 (80.5)		
Female	66 (14.6)	48 (13.0)	18 (22.0)		53 (19.3)	45 (19.2)	8 (19.5)		
BMI (kg/m^2), mean (SD)	23.10 (3.13)	22.49 (3.06)	25.84 (1.59)	<0.001	23.42 (3.31)	22.88 (3.26)	26.53 (1.32)	<0.001	0.243
SMI (cm^2/m^2), mean (SD)	47.17 (9.78)	49.44 (9.4)	36.92 (4.64)	<0.001	44.77 (9.06)	46.47 (8.59)	35.06 (4.58)	<0.001	<0.001
Comorbidity, n (%)									
Diabetes	51 (11.3)	38 (10.3)	13 (15.9)	0.148	31 (11.3)	23 (9.9)	8 (19.5)	0.072	0.997
Cardiovascular disease	99 (21.9)	62 (16.8)	37 (45.1)	<0.001	69 (25.1)	59 (25.2)	17 (41.5)	0.032	0.079
WBC count (10^9/L), mean (SD)	6.69 (2.56)	6.71 (2.58)	6.60 (2.50)	0.724	6.35 (2.15)	6.31 (2.21)	6.61 (1.82)	0.199	0.202
Neutrophil count (10^9/L), mean (SD)	4.26 (2.40)	4.32 (2.46)	4.00 (2.06)	0.244	3.89 (2.00)	3.89 (1.99)	3.94 (2.05)	0.803	0.079
Lymphocyte count (10^9/L), mean (SD)	1.79 (0.69)	1.76 (0.73)	1.90 (0.46)	0.005	1.77 (0.63)	1.73 (0.60)	2.00 (0.72)	0.019	0.997
Monocyte count (10^9/L), mean (SD)	0.49 (0.26)	0.50 (0.27)	0.46 (0.23)	0.042	0.47 (0.17)	0.47 (0.18)	0.49 (0.13)	0.246	0.930
Platelet count (10^9/L), mean (SD)	191.51 (79.98)	191.22 (77.52)	192.80 (90.78)	0.567	193.85 (81.14)	194.15 (82.42)	192.17 (74.34)	0.972	0.852
Albumin (g/L), mean (SD)	42.25 (5.86)	42.03 (6.06)	43.22 (4.74)	0.110	42.38 (5.28)	42.18 (5.52)	43.53 (3.48)	0.288	0.886
NLR, mean (SD)	2.96 (3.30)	2.15 (3.59)	2.12 (0.98)	0.021	2.56 (2.14)	2.61 (2.15)	2.25 (2.06)	0.194	0.098
PLR, mean (SD)	119.45 (64.79)	122.44 (66.60)	105.86 (54.26)	0.200	119.70 (61.71)	123.16 (64.82)	99.98 (33.77)	0.096	0.777
LMR, mean (SD)	4.19 (2.00)	4.05 (1.99)	4.85 (1.93)	<0.001	4.06 (1.52)	4.00 (1.41)	4.37 (2.02)	0.992	0.916
PNI, mean (SD)	51.19 (7.64)	50.84 (7.89)	52.76 (6.20)	0.200	50.57 (8.60)	50.04 (8.98)	53.55 (5.14)	0.017	0.820
SII, mean (SD)	552 (597.59)	579.54 (634.11)	432.69 (372.48)	0.031	486.64 (419.81)	502.87 (432.93)	394.02 (324.73)	0.265	0.330
Child-Pugh classification, n (%)				0.549				0.138	0.859
A	431 (95.4)	353 (95.4)	78 (95.1)		263 (95.6)	222 (94.9)	12 (5.1)		
B	21 (4.6)	17 (4.6)	4 (4.9)		12 (4.4)	12 (100.0)	0		
HBsAg, n (%)				0.096				0.494	0.174
Positive	385 (85.2)	320 (86.5)	65 (79.3)		244 (88.7)	207 (88.5)	37 (90.2)		
Negative	67 (14.8)	50 (13.5)	17 (20.7)		31 (11.3)	27 (11.5)	4 (9.8)		

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Training cohort				Validation cohort				
	Total (n=452)	NSO (n=370)	SO (n=82)	P	Total (n=275)	NSO (n=234)	SO (n=41)	P	P*
AFP group (ng/mL), n (%)									
≥400	158 (35.0)	128 (34.6)	30 (36.6)	0.732	104 (34.8)	87 (37.2)	17 (41.5)	0.602	0.436
<400	294 (65.0)	242 (65.4)	52 (63.4)		171 (62.2)	147 (62.8)	24 (58.5)		
Surgery type, n (%)				0.316				0.365	0.003
≥ Lobectomy	198 (43.8)	158 (42.7)	40 (48.8)		152 (55.3)	132 (56.4)	20 (48.8)		
< Lobectomy	254 (56.2)	212 (57.3)	42 (51.2)		123 (44.7)	102 (43.6)	21 (51.2)		
Postoperative hospital stay (d), mean (SD)	13.43 (7.45)	13.32 (7.20)	13.89 (8.52)	0.886	12.16 (7.59)	12.40 (8.11)	10.78 (2.95)	0.935	<0.001
Tumor size (cm), mean (SD)	6.95 (4.71)	6.81 (4.61)	7.59 (5.16)	0.285	6.50 (4.46)	6.52 (4.52)	6.36 (4.20)	0.923	0.344
Number of tumors, n (%)				0.001				0.530	0.870
Solitary	356 (78.8)	303 (81.9)	53 (64.6)		218 (79.3)	187 (79.9)	31 (75.6)		
Multiple	96 (21.2)	67 (18.1)	29 (35.4)		57 (20.7)	47 (20.1)	10 (24.4)		
Macrovascular invasion, n (%)				0.225				0.054	<0.001
Negative	386 (85.4)	314 (84.9)	72 (87.8)		244 (88.7)	212 (90.6)	32 (78.0)		
PVTT	50 (11.1)	43 (11.6)	7 (8.5)		9 (3.3)	7 (3.0)	2 (4.9)		
HVTT	8 (1.8)	5 (1.4)	3 (3.7)		20 (7.3)	13 (5.6)	7 (17.1)		
PVTT + HVTT	8 (1.8)	8 (2.2)	0		2 (0.7)	2 (0.9)	0		
Microvascular invasion, n (%)				0.003				0.836	0.261
Positive	167 (36.9)	125 (33.8)	42 (51.2)		165 (60.0)	93 (39.7)	17 (41.5)		
Negative	285 (63.1)	245 (66.2)	40 (48.8)		107 (38.9)	141 (60.3)	24 (58.5)		
Tumor differentiation, n (%)				0.016				0.263	0.022
Well	42 (9.3)	34 (9.2)	8 (9.8)		12 (4.4)	12 (5.1)	0		
Moderate	327 (72.3)	259 (70.0)	68 (82.9)		199 (72.4)	170 (72.6)	29 (70.7)		
Poor	83 (18.4)	77 (20.8)	6 (7.3)		61 (23.3)	52 (22.2)	12 (29.3)		
Satellite lesions, n (%)				0.007				0.163	0.424
Positive	24 (5.3)	24 (6.5)	0		5 (4.0)	11 (4.7)	0		

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Training cohort				Validation cohort				P*
	Total (n=452)	NSO (n=370)	SO (n=82)	P	Total (n=275)	NSO (n=234)	SO (n=41)	P	
Negative	428 (94.7)	346 (93.5)	82 (100.0)		264 (96.0)	223 (95.3)	41 (100.0)		
Complete encapsulation, n (%)				0.116				0.443	0.500
Positive	7 (1.5)	4 (1.1)	3 (3.7)		5 (1.8)	5 (2.1)	0		
Negative	445 (98.5)	366 (98.9)	79 (96.3)		270 (98.2)	229 (97.9)	41 (100.0)		
AJCC stage, n (%)				0.363				0.636	0.124
I	208 (46.0)	180 (48.6)	31 (40.2)		119 (43.3)	105 (44.9)	14 (34.1)		
II	103 (22.8)	75 (20.3)	23 (28.0)		69 (25.1)	57 (24.4)	12 (29.3)		
III	135 (29.9)	110 (29.7)	25 (30.5)		77 (28.0)	64 (27.4)	13 (31.7)		
IV	6 (1.3)	5 (1.4)	1 (1.2)		10 (3.6)	8 (3.4)	2 (4.9)		
BCLC stage, n (%)				0.019				0.542	<0.001
0	24 (5.3)	24 (6.5)	0		12 (4.4)	12 (5.1)	0		
A	274 (60.6)	225 (60.8)	49 (59.8)		107 (38.9)	89 (38.0)	18 (43.9)		
B	14 (3.1)	13 (3.5)	1 (1.2)		87 (31.6)	75 (32.1)	12 (29.3)		
C	140 (31.0)	108 (29.2)	32 (39.0)		69 (25.1)	58 (24.8)	11 (26.8)		

P*, training cohort versus validation cohort. NSO, nonsarcopenic obesity; SO, sarcopenic obesity; BMI, body mass index; SMI, skeletal muscle index; WBC count, white blood cell count; NLR, neutrophil-lymphocyte ratio, PLR, platelet-lymphocyte ratio, LMR, lymphocyte-monocyte ratio, PNI, prognostic nutritional index; SII, systemic immune-inflammation index. AFP, alpha-fetoprotein; HBsAg, hepatitis B surface antigen; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus; BDTT, bile duct tumor thrombus; AJCC, American Joint Committee Cancer 8th edition; BCLC, Barcelona Clinic Liver Cancer staging systems.
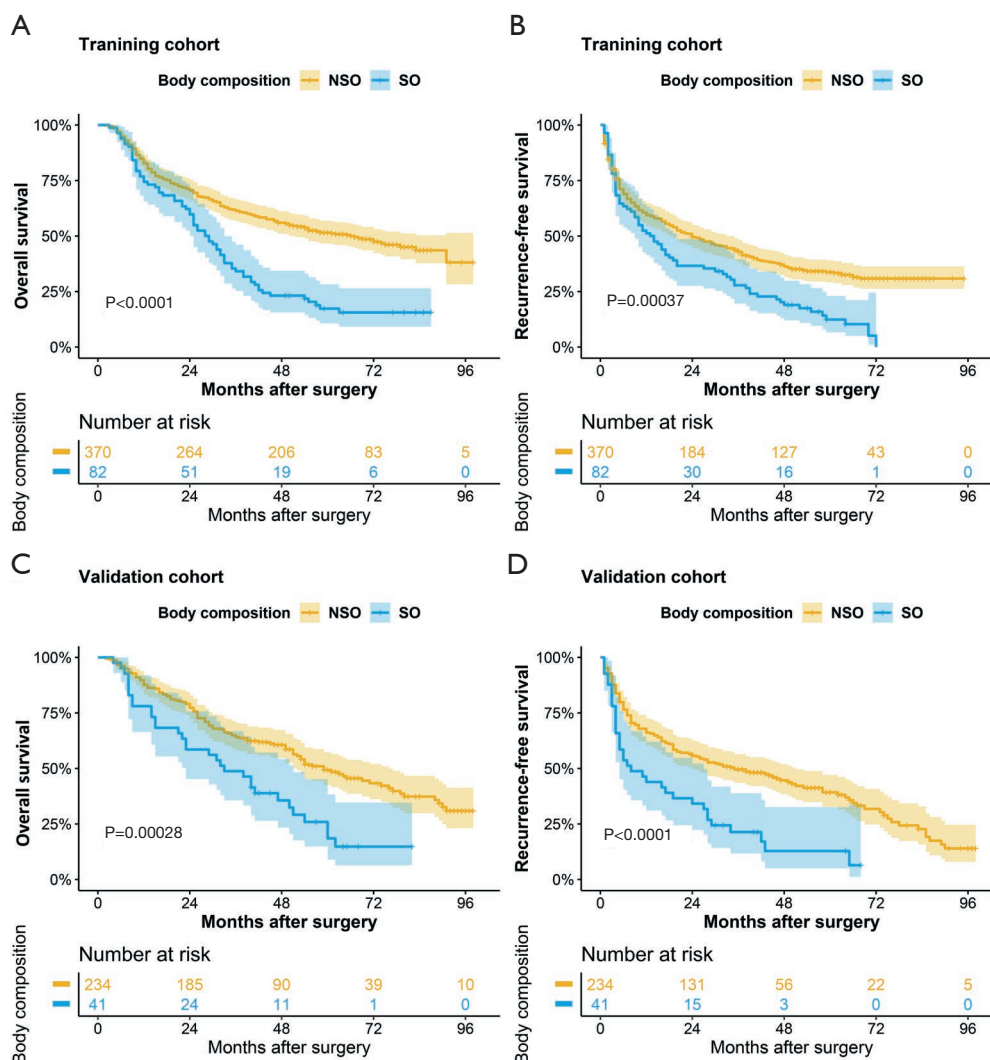
Figure 2 OS rates and RFS rates of patients after hepatectomy for HCC classified according to the two body composition categories: NSO and SO. (A) OS rates in the NSO group and SO group in the training cohort. (B) RFS rates in the NSO group and SO group in the training cohort. (C) OS rates in the NSO group and SO group in the validation cohort. (D) RFS rates in the NSO group and SO group in the validation cohort. OS, overall survival; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; NSO, nonsarcopenic obesity; SO, sarcopenic obesity.

PNI, the SII, body composition (HR, 1.520; 95% CI, 1.169–1.977; P=0.002) and the AJCC stage (8th edition) were prognostic factors of RFS in patients who underwent hepatectomy for HCC (*Table 3*).

According to the results of the multivariate analysis, SO (HR, 3.024; 95% CI, 2.239–4.084; P<0.001), a low LMR (HR, 2.103; 95% CI, 1.552–2.850; P<0.001), an AFP level ≥400 ng/mL (HR, 1.823; 95% CI, 1.410–2.359; P<0.001) and AJCC stage (8th edition) were independent prognostic factors of OS. Furthermore, SO (HR, 1.923; 95% CI,

1.461–2.530; P<0.001), a low LMR (HR, 2.161; 95% CI, 1.664–2.807; P<0.001), an AFP level ≥400 ng/mL (HR, 1.759; 95% CI, 1.391–2.226; P<0.001) and AJCC stage (8th edition) were also independent prognostic factors of RFS (*Figure 3A,B*).

The correlations between SO and inflammatory indexes

Univariate and multivariate logistic regression analyses were performed to investigate whether the inflammatory indexes were associated with SO. The multivariate analysis showed

Table 2 The optimal cutoffs and AUCs of the inflammatory indexes

Inflammatory indexes	OS			RFS		
	Cutoff value	AUC (training cohort)	AUC (validation cohort)	Cutoff value	AUC (training cohort)	AUC (validation cohort)
NLR (H/L)	2.116	0.615 (0.562–0.667)	0.561 (0.493–0.629)	1.800	0.605 (0.544–0.666)	0.551 (0.478–0.623)
PLR (H/L)	127.589	0.622 (0.570–0.673)	0.562 (0.494–0.630)	128.307	0.591 (0.532–0.651)	0.544 (0.473–0.616)
LMR (H/L)	4.399	0.624 (0.572–0.677)	0.601 (0.534–0.669)	4.601	0.642 (0.581–0.703)	0.559 (0.487–0.631)
PNI (H/L)	51.419	0.612 (0.559–0.664)	0.579 (0.512–0.647)	55.378	0.580 (0.517–0.643)	0.548 (0.475–0.621)
SII (H/L)	459.294	0.615 (0.563–0.667)	0.567 (0.499–0.634)	445.172	0.606 (0.546–0.665)	0.556 (0.484–0.627)

When an inflammation index was greater than or equal to its cutoff value, it was defined as H (high). When an inflammation index was lower than its cutoff value, it was defined as L (low). AUC, area under the ROC curve; ROC, receiver operating characteristic; OS, overall survival; RFS, recurrence-free survival; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index.

that cardiovascular disease (HR, 3.707; 95% CI, 2.184–6.291; P<0.001), multiple tumors (HR, 2.754; 95% CI, 1.567–4.840; P<0.001), and a low LMR (HR, 2.336; 95% CI, 1.388–3.930; P=0.001) were independent predictors of SO (*Table 4*). The other four inflammatory indexes—the NLR, PLR, PNI and SII—were not independently associated with an increased risk of SO.

Subgroup analysis and SOLMR grades

Both SO and a low LMR were associated with poor OS (*Figure 4A,B,C,D*). To further investigate the relationship between SO and the LMR and their different prognoses, we attempted to combine SO and the LMR to generate four subgroups [SO high (SOH), SO low (SOL), NSO high (NSOH), and NSO low (NSOL)] (*Figure 4E,F,G,H*). The subgroup of patients with SO and a low LMR had the worst survival rate, and the subgroup of patients with NSO and a high LMR had the longest OS (P<0.0001). The SOH and NSOL subgroups did not have significantly different OS rates (P=0.691). Similar results were observed for RFS (P=0.364) (*Figure 4E,F,G,H*). Therefore, they were included in the validation cohort. There were no significant differences in prognostic outcomes between the two subgroups; thus, it was not necessary to separate the two subgroups for prognostic evaluation. Consequently, we combined these two subgroups to establish a new classification system called SOLMR grading. Patients with both NSO and a high LMR were classified as grade A. Patients with neither SO nor a low LMR were classified

as grade B. Patients with both SO and a low LMR were classified as grade C. We also applied SOLMR grades to RFS (*Table 5*).

Kaplan-Meier OS curves and RFS curves were generated for the SOLMR grades. The SOLMR grades showed clearly different prognostic associations with OS and RFS in the training cohort and validation cohort (P<0.0001 and P<0.0001, respectively) (*Figure 4I,J,K,L*).

To further explore whether the SOLMR grade can replace SO and the LMR as a new independent prognostic factor for OS and RFS, SOLMR grade replaced SO and LMR in the univariate analysis and was found to be a prognostic factor of OS and RFS (P<0.001 and P<0.001, respectively) (*Table 6*). The multivariate analysis also revealed that the SOLMR grade was an independent prognostic factor for OS (SOLMR grade B: HR, 2.291; P<0.001, SOLMR grade C: HR, 6.535; P<0.001. *Figure 5A*) and an independent prognostic factor for RFS (SOLMR grade B: HR, 2.357; P<0.001, SOLMR grade C: HR, 3.979; P<0.001) (*Figure 5B*).

AUCs were evaluated to compare the prognostic accuracy of the SOLMR grade and each of its components—SO and the LMR. The AUCs of the SOLMR grade, SO and the LMR for OS were 0.688, 0.594 and 0.624, respectively (P<0.05). The AUCs of the SOLMR grade, SO and the LMR for OS were 0.687, 0.581 and 0.631, respectively (P<0.05).

Establishment of nomograms based on the SOLMR grade

A nomogram for OS prediction was established based on

Table 3 Univariate analysis results of OS and RFS

Variables	OS univariate			RFS univariate		
	HR	95% CI	P	HR	95% CI	P
Sex						
Female (n=66)	1.000		0.294	1.000		0.392
Male (n=386)	1.219	0.842–1.766		1.152	0.833–1.595	
Patient age (y)						
<65 (n=377)	1.000		0.618	1.000		0.837
≥65 (n=75)	1.084	0.790–1.486		1.032	0.768–1.386	
Diabetes						
No (n=401)	1.000		0.327	1.000		0.413
Yes (n=51)	0.819	0.550–1.221		0.864	0.608–1.227	
Cardiovascular disease						
No (n=353)	1.000		0.027	1.000		0.239
Yes (n=99)	1.370	1.036–1.811		1.169	0.901–1.515	
HBsAg						
Negative (n=67)	1.000		0.377	1.000		0.205
Positive (n=385)	1.175	0.822–1.678		1.227	0.887–1.698	
Child-Pugh classification						
A (n=431)	1.000		0.512	1.000		0.228
B (n=21)	1.214	0.680–2.168		1.363	0.824–2.254	
AFP (ng/mL)						
<400 (n=294)	1.000		<0.001	1.000		<0.001
≥400 (n=158)	2.151	1.682–2.751		1.896	1.513–2.376	
Tumor size (cm)						
<5.0 (n=200)	1.000		<0.001	1.000		<0.001
≥5.0 (n=252)	2.824	2.166–3.681		2.418	1.918–3.049	
Number of tumors						
Solitary (n=356)	1.000		<0.001	1.000		<0.001
Multiple (n=96)	1.743	1.326–2.291		1.702	1.324–2.189	
Tumor differentiation						
Well (n=42)	1.000		0.305	1.000		0.243
Moderate (n=327)	1.334	0.850–2.094	0.211	1.032	0.866–1.230	0.725
Poor (n=83)	1.493	0.897–2.487	0.123	1.196	0.965–1.484	0.103
Microvascular invasion						
Negative (n=290)	1.000		<0.001	1.000		<0.001
Positive (n=162)	2.293	1.791–2.935		1.764	1.407–2.212	
Macrovascular invasion						
Negative (n=386)			<0.001	1.000		<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Variables	OS univariate			RFS univariate		
	HR	95% CI	P	HR	95% CI	P
PVTT (n=50)	4.042	2.914–5.606	<0.001	3.097	2.239–4.238	<0.001
HVTT (n=8)	4.113	1.929–8.770	<0.001	5.562	2.720–11.377	<0.001
PVTT + HVTT (n=8)	3.641	1.708–7.763	<0.001	2.888	1.360–6.132	0.006
Complete encapsulation						
Positive (n=7)	1.000		0.927	1.000		0.382
Negative (n=445)	1.047	0.390–2.812		1.398	0.660–2.961	
Satellite lesions						
Negative (n=428)	1.000		0.001	1.000		<0.001
Positive (n=24)	2.230	1.411–3.524		2.532	1.650–3.886	
NLR						
Low (OS: n=230; RFS: n=173)	1.000		<0.001	1.000		<0.001
High (OS: n=222; RFS: n=279)	2.123	1.657–2.721		1.337	1.189–1.504	
PLR						
Low (OS: n=304; RFS: n=307)	1.000		<0.001	1.000		<0.001
High (OS: n=148; RFS: n=145)	1.481	1.309–1.675		1.392	1.241–1.560	
LMR						
High (OS: n=267; RFS: n=173)	1.000		<0.001	1.000		<0.001
Low (OS: n=185; RFS: n=279)	2.297	1.762–2.995		2.269	1.783–2.888	
PNI						
High (OS: n=248; RFS: n=129)	1.000		<0.001	1.000		<0.001
Low (OS: n=204; RFS: n=323)	1.995	1.530–2.498		1.748	1.345–2.272	
SII						
Low (OS: n=265; RFS: n=255)	1.000		<0.001	1.000		<0.001
High (OS: n=187; RFS: n=197)	1.443	1.278–1.631		1.359	1.217–1.519	
AJCC						
I (n=213)	1.000		<0.001	1.000		<0.001
II (n=98)	1.711	1.217–2.404	<0.001	1.559	1.160–2.096	0.003
III (n=135)	4.979	3.728–6.650	<0.001	4.606	3.573–5.998	<0.001
IV (n=6)	13.093	5.613–30.539	<0.001	5.852	2.369–14.454	<0.001
Body composition						
NSO (n=370)	1.000			1.000		0.002
SO (n=82)	2.096	1.548–2.773	<0.001	1.520	1.169–1.977	

OS, overall survival; RFS, recurrence-free survival; BMI, body mass index; NLR, neutrophil-lymphocyte ratio, PLR, platelet-lymphocyte ratio, LMR, lymphocyte-monocyte ratio, PNI, prognostic nutritional index; SII, systemic immune-inflammation index. AFP, alpha-fetoprotein; HBsAg, hepatitis B surface antigen; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus; BDTT, bile duct tumor thrombus; AJCC, American Joint Committee Cancer 8th edition; NSO, nonsarcopenic obesity; SO, sarcopenic obesity.
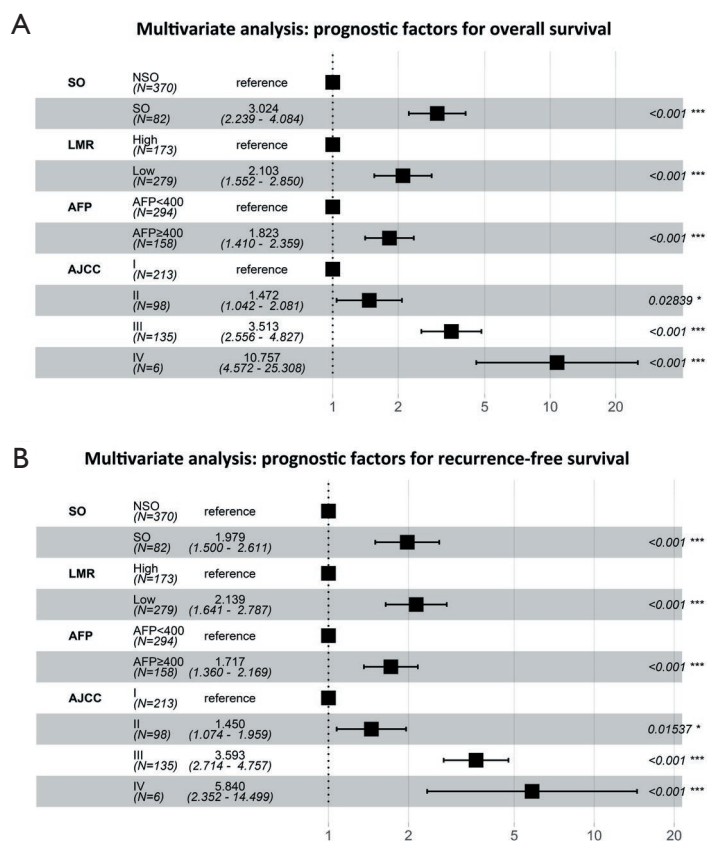
Figure 3 Forest plots of prognostic factors for OS and RFS in HCC patients. (A) The optimal prognostic factors for OS in the multivariate analysis in the training cohort. (B) The optimal prognostic factors for RFS in the multivariate analysis in the training cohort. OS, overall survival; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; SO, sarcopenic obesity; LMR, lymphocyte-monocyte ratio; AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer 8th edition.

the identified independent prognostic factors: the SOLMR grade, AFP level, and AJCC stage. A nomogram for RFS prediction was established in the same way (*Figure 6*, *Figure 7*). The calibration plots for the probability of OS and RFS at 1, 3, and 5 years showed good correlation between the nomogram prediction and actual observations in the training cohort and validation cohort (*Figure 6*, *Figure 7*). Decision curves were plotted to compare the nomograms with other conventional staging systems (*Figure 6*, *Figure 7*). The nomograms resulted in the best net benefits. The clinical impact curves clearly revealed the true positive rates of the nomograms (*Figure 6*, *Figure 7*). The C-indexes of these two nomograms were 0.761 (95% CI, 0.734–0.788) and 0.736 (95% CI, 0.710–0.762), respectively, which were higher than those of any other system (P<0.0001 for all comparisons with each conventional staging system, *Table 6*). The same results were observed in the external validation cohort (*Table 7*).

Discussion

Most European and American studies have found that sarcopenia is an independent risk factor for the prognosis of HCC in patients undergoing surgical resection (32). However, there is a relative lack of research on sarcopenia and SO in Chinese HCC populations. This study is the first to study the relationship between SO and HCC in a Chinese population. Our study identified preoperative SO as an independent risk factor of poor OS and RFS in patients undergoing hepatectomy for HCC. Furthermore, similar to most studies in Europe and the United States, this study found that sarcopenia also had significant effects on the prognosis of HCC in patients undergoing radical surgical resection in the Chinese population (Figures S1,S2;

Table 4 Univariate and multivariate analysis results for SO

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Sex						
Female (n=66)	1.000		0.040			0.066
Male (n=386)	1.887	1.031–3.453				
Patient age (y)						
<65 (n=377)	1.000		0.897			
≥65 (n=75)	1.043	0.551–1.973				
Diabetes						
No (n=401)	1.000		0.151			
Yes (n=51)	1.646	0.833–3.253				
Cardiovascular disease						
No (n=353)	1.000		<0.001	1.000		<0.001
Yes (n=99)	4.085	2.444–6.825		3.707	2.184–6.291	
HBsAg						
Negative (n=67)	1.000		0.099			
Positive (n=385)	1.674	0.908–3.085				
Child-Pugh classification						
A (n=431)	1.000		0.912			
B (n=21)	0.939	0.307–2.868				
AFP (ng/mL)						
<400 (n=294)	1.000		0.732			
≥400 (n=158)	1.91	0.663–1.794				
Tumor size (cm)						
<5.0 (n=200)	1.000		0.945			
≥5.0 (n=252)	1.017	0.628–1.647				
Number of tumors						
Solitary (n=356)	1.000		0.001	1.000		<0.001
Multiple (n=96)	2.475	1.465–4.180		2.754	1.567–4.840	
Tumor differentiation						
Well (n=42)	1.000		0.024			0.054
Moderate (n=327)	1.116	0.494–2.521	0.792			0.025
Poor (n=42)	0.331	0.107–1.028	0.056			0.023
Microvascular invasion						
Negative (n=290)	1.000		0.054			

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Positive (n=162)	1.612	0.992–2.618				
Macrovascular invasion						
Negative (n=386)	1.000		0.496			
Positive (n=66)	1.284	0.625–2.638				
Complete encapsulation						
Positive (n=7)	1.000		0.107			
Negative (n=445)	0.288	0.063–1.311				
NLR						
Low (n=230)	1.000		0.077			
High (n=222)	1.550	0.954–2.521				
PLR						
Low (n=304)	1.000		0.318			
High (n=148)	1.309	0.772–2.219				
LMR						
High (n=185)	1.000		0.001	1.000		0.001
Low (n=267)	2.258	1.389–3.669		2.336	1.388–3.930	
PNI						
High (n=248)	1.000		0.087			
Low (n=204)	1.539	0.939–2.521				
SII						
Low (n=265)	1.000		0.008			0.118
High (n=187)	2.042	1.210–3.448				
AJCC						
I (n=213)	1.000		0.412			
II (n=98)	0.917	0.104–8.100	0.938			
III (n=135)	1.533	0.170–13.801	0.703			
IV (n=6)	1.136	0.127–10.159	0.909			

SO, sarcopenic obesity; HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; NLR, neutrophil-lymphocyte ratio, PLR, platelet-lymphocyte ratio, LMR, lymphocyte-monocyte ratio, PNI, prognostic nutritional index; SII, systemic immune-inflammation index; AJCC, American Joint Committee on Cancer 8th edition.
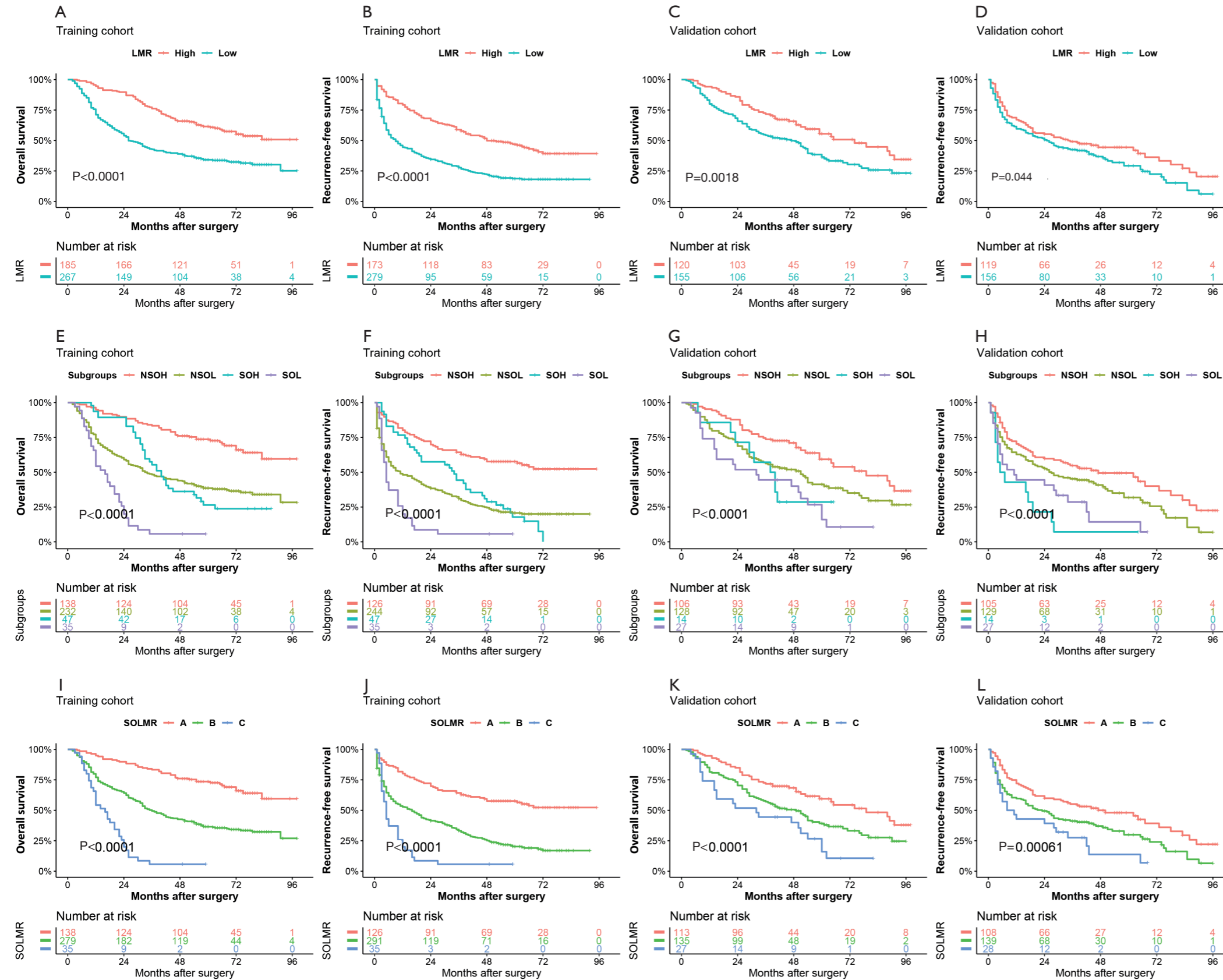
Figure 4 OS rates and RFS rates classified according to LMR subgroups and SOLMR grades. (A,B,C,D) OS rates and RFS rates classified according to the LMR in the training cohort and validation cohort. (E,F,G,H) OS rates and RFS rates according to subgroup analysis in the training cohort and validation cohort. (I,J,K,L) OS rates and RFS rates according to different SOLMR grades in the training cohort and validation cohort. Subgroups: NSOH, patients with both NSO and a high LMR; NSOL, patients with both NSO and a low LMR; SOH, patients with both SO and a high LMR; SOL, patients with both SO and a low LMR. OS, overall survival; RFS, recurrence-free survival; LMR, lymphocyte-monocyte ratio; SOLMR, SOLMR grade; LMR, lymphocyte-monocyte ratio; NSO, nonsarcopenic obesity; SO, sarcopenic obesity.

J Gastrointest Oncol 2021;12(2):669-693 | http://dx.doi.org/10.21037/jgo-20-341

Table 5 Characteristics of patients in different SOLMR grades

Characteristic	Cutoff of LMR for OS				Cutoff of LMR for RFS			
	A (n=138)	B (n=279)	C (n=35)	P	A (n=126)	B (n=291)	C (n=35)	P
Age (y), mean (SD)	53.29 (11.41)	52.84 (12.08)	55.03 (9.64)	0.778	52.91 (11.18)	53.02 (12.15)	55.03 (9.64)	0.766
Sex, n (%)				0.005				0.005
Male	112 (81.2)	249 (89.2)	25 (71.4)		102 (81.0)	259 (89.0)	25 (71.4)	0.005
Female	26 (5.8)	30 (6.6)	10 (2.2)		24 (19.0)	32 (11.0)	10 (28.6)	
BMI (kg/m^2), mean (SD)	22.50 (3.17)	23.07 (3.05)	25.65 (2.32)	<0.001	22.56 (3.25)	23.12 (3.02)	25.65 (2.32)	<0.001
SMI (cm^2/m^2), mean (SD)	48.29 (9.64)	47.96 (9.52)	36.43 (4.86)	<0.001	48.41 (9.77)	47.92 (9.46)	36.43 (4.86)	<0.001
Comorbidities, n (%)								
Diabetes	14 (10.1)	36 (12.9)	1 (2.9)	0.183	14 (11.1)	36 (12.4)	1 (2.9)	0.243
Cardiovascular disease	25 (18.1)	63 (13.9)	11 (2.4)	0.213	112 (88.9)	255 (87.6)	34 (97.1)	0.238
Child-Pugh classification, n (%)				<0.001				0.005
A	138 (100.0)	262 (93.9)	31 (88.6)		126 (100.0)	274 (94.2)	31 (88.6)	
B	0	17 (6.1)	4 (11.4)		0	17 (5.8)	4 (11.4)	
HBsAg, n (%)				0.984				0.870
Positive	118 (85.5)	237 (84.9)	30 (85.7)		109 (86.5)	246 (84.5)	30 (85.7)	
Negative	20 (14.5)	42 (15.1)	5 (14.3)		17 (13.5)	45 (15.5)	5 (14.3)	
AFP group (ng/mL)				0.875				0.788
≥400	46 (33.3)	99 (35.5)	22 (62.9)		41 (32.5)	104 (35.7)	13 (37.1)	
<400	92 (66.7)	180 (54.5)	22 (62.9)		85 (67.5)	187 (64.3)	22 (62.9)	
Surgery type, n (%)				0.001				<0.001
≥ Lobectomy	49 (35.5)	124 (44.4)	25 (71.4)		43 (34.1)	130 (44.7)	25 (71.4)	
< Lobectomy	89 (64.5)	155 (55.6)	10 (28.6)		83 (65.9)	161 (55.3)	10 (28.6)	
Postoperative hospital stay (d), mean (SD)	11.91 (5.08)	14.09 (8.33)	14.14 (7.10)	0.030	11.66 (4.63)	14.11 (8.32)	14.14 (7.10)	0.025
Tumor size (cm), mean (SD)	5.30 (3.94)	7.54 (4.80)	8.77 (5.22)	<0.001	5.21 (3.91)	7.49 (4.77)	8.77 (5.22)	<0.001
Number of tumors, n (%)				<0.001				<0.001
Solitary	118 (85.5)	221 (79.2)	17 (48.6)		106 (84.1)	233 (80.1)	17 (48.6)	
Multiple	20 (14.5)	58 (20.8)	18 (51.4)		20 (15.9)	58 (19.9)	18 (51.4)	
Macrovascular invasion, n (%)				0.002				0.008
Negative	130 (94.2)	228 (81.7)	28 (80.0)		118 (93.7)	240 (82.5)	28 (80.0)	
Positive	8 (5.8)	51 (18.3)	7 (20.0)		8 (6.3)	51 (17.5)	7 (20.0)	
Microvascular invasion, n (%)				0.015				0.009
Positive	38 (27.5)	106 (38.0)	18 (51.4)		33 (26.2)	111 (38.1)	18 (51.4)	
Negative	100 (72.5)	173 (62.0)	17 (48.6)		93 (73.8)	180 (61.9)	17 (48.6)	
Tumor differentiation, n (%)				0.196				0.124

Table 5 (*continued*)

Table 5 (*continued*)

Characteristic	Cutoff of LMR for OS				Cutoff of LMR for RFS			
	A (n=138)	B (n=279)	C (n=35)	P	A (n=126)	B (n=291)	C (n=35)	P
Well	13 (9.4)	28 (10.0)	1 (2.9)		9 (7.1)	32 (11.0)	1 (2.9)	
Moderate	102 (73.9)	194 (69.5)	31 (88.6)		95 (75.4)	201 (69.1)	31 (88.6)	
Poor	23 (16.7)	57 (20.4)	3 (8.6)		22 (17.5)	58 (19.9)	3 (8.6)	
Satellite lesions, n (%)				0.295				0.289
Positive	6 (4.3)	18 (6.5)	0		6 (4.8)	18 (6.2)	0	
Negative	132 (95.7)	261 (93.5)	35 (100.0)		120 (95.2)	273 (93.8)	35 (100.0)	
Complete capsule, n (%)				0.020				0.020
Positive	1 (0.7)	3 (1.1)	3 (8.6)		1 (0.8)	3 (1.0)	3 (8.6)	
Negative	137 (99.3)	276 (98.9)	32 (91.4)		125 (99.2)	276 (99.0)	32 (91.4)	
AJCC stage, n (%)				<0.001				<0.001
I	90 (65.2)	113 (40.5)	10 (28.6)		82 (65.1)	121 (26.8)	10 (28.6)	
II	33 (23.9)	60 (21.5)	5 (14.3)		30 (23.8)	63 (21.6)	5 (14.3)	
III	14 (10.1)	102 (36.6)	19 (54.3)		13 (10.3)	103 (35.4)	19 (54.3)	
IV	1 (0.7)	4 (1.4)	1 (2.9)		1 (0.8)	4 (1.4)	1 (2.9)	

BMI, body mass index; SMI, skeletal muscle index; AFP, alpha-fetoprotein; HBsAg, hepatitis B surface antigen; BDTT, bile duct tumor thrombus; AJCC, American Joint Committee on Cancer 8th edition.

Table S1).

To date, the cutoff value for SO defined by the SMI has not been agreed upon. In this study, a new cutoff value based on the best discriminatory index in the Chinese population was proposed via the ROC curve method; this cutoff value was compared with other SMI cutoff values frequently cited in studies (8,19,29,32-35) (Tables S1,S2; Figures S1,S2). Our SMI cutoff values of 40.86 cm^2/m^2 for males and 30.71 cm^2/m^2 for females were very close to those proposed by Kobayashi *et al.* for the Japanese HCC population (18), which were 40.31 cm^2/m^2 for males and 30.88 cm^2/m^2 for females; these similarities may be due to racial similarities or similarity between the Chinese HCC population and the Japanese HCC population. For the specific definition of obesity in SO, some scholars have suggested that the visceral fat area (VFA) measured on CT be used as the new definition of obesity (36,37). The VFA represents only visceral fat; notably, it is a type of obesity distribution but not a comprehensive representation of obesity (38). Diagnosing obesity considering the World Health Organization's (WHO's) obesity definition based on BMI is the most recognized and convenient method

worldwide. Therefore, this study applied the WHO definition of obesity.

Previous studies have identified an association between systemic inflammation and HCC prognosis (39-41). Whether there is a correlation between SO and systemic inflammation in HCC and its prognostic value remains unclear. In this study, five inflammatory indexes were evaluated, and the LMR was proven to be the best independent predictor of OS and RFS. A low LMR, cardiovascular disease and multiple tumors were closely associated with the occurrence of SO. In the past, many inflammatory indexes, such as the NLR and PLR, have been proposed, but they are rarely applied in clinical practice. This paper further explored their value and their utility when combined with SO, which was calculated by analyzing the clinical data of nonintraperitoneal tissues obtained from imaging examinations, as a new prediction model. Based on the results of our study, we inferred that there is a triangular relationship among SO, a low LMR and a poor HCC prognosis.

Recent studies have shown that skeletal muscle loss with adipose tissue gain leads to increased levels of inflammatory

Table 6 Univariate analysis results of OS and RFS

Variables	OS univariate			RFS univariate		
	HR	95% CI	P	HR	95% CI	P
Sex						
Female (n=66)	1.000		0.294	1.000		0.392
Male (n=386)	1.219	0.842–1.766		1.152	0.833–1.595	
Patient age (y)						
<65 (n=377)	1.000		0.618	1.000		0.837
≥65 (n=75)	1.084	0.790–1.486		1.032	0.768–1.386	
Diabetes						
No (n=401)	1.000		0.327	1.000		0.413
Yes (n=51)	0.819	0.550–1.221		0.864	0.608–1.227	
Cardiovascular disease						
No (n=353)	1.000		0.027	1.000		0.239
Yes (n=99)	1.370	1.036–1.811		1.169	0.901–1.515	
HBsAg						
Negative (n=67)	1.000		0.377	1.000		0.205
Positive (n=385)	1.175	0.822–1.678		1.227	0.887–1.698	
Child-Pugh classification						
A (n=431)	1.000		0.512	1.000		0.228
B (n=21)	1.214	0.680–2.168		1.363	0.824–2.254	
AFP (ng/mL)						
<400 (n=294)	1.000		<0.001	1.000		<0.001
≥400 (n=158)	2.151	1.682–2.751		1.896	1.513–2.376	
Tumor size (cm)						
<5.0 (n=200)	1.000		<0.001	1.000		<0.001
≥5.0 (n=252)	2.824	2.166–3.681		2.418	1.918–3.049	
Number of tumors						
Solitary (n=356)	1.000		<0.001	1.000		<0.001
Multiple (n=96)	1.743	1.326–2.291		1.702	1.324–2.189	
Tumor differentiation						
Well (n=42)	1.000		0.305	1.000		0.243
Moderate (n=327)	1.334	0.850–2.094	0.211	1.032	0.866–1.230	0.725
Poor (n=83)	1.493	0.897–2.487	0.123	1.196	0.965–1.484	0.103
Microvascular invasion						
Negative (n=290)	1.000		<0.001	1.000		<0.001
Positive (n=162)	2.293	1.791–2.935		1.764	1.407–2.212	

Table 6 (*continued*)

Table 6 (*continued*)

Variables	OS univariate			RFS univariate		
	HR	95% CI	P	HR	95% CI	P
Macrovascular invasion						
Negative (n=386)			<0.001	1.000		<0.001
PVTT (n=50)	4.042	2.914–5.606	<0.001	3.097	2.239–4.238	<0.001
HVTT (n=8)	4.113	1.929–8.770	<0.001	5.562	2.720–11.377	<0.001
PVTT + HVTT (n=8)	3.641	1.708–7.763	<0.001	2.888	1.360–6.132	0.006
Complete encapsulation						
Positive (n=7)	1.000		0.927	1.000		0.382
Negative (n=445)	1.047	0.390–2.812		1.398	0.660–2.961	
Satellite lesions						
Negative (n=428)	1.000		0.001	1.000		<0.001
Positive (n=24)	2.230	1.411–3.524		2.532	1.650–3.886	
AJCC						
I (n=213)	1.000		<0.001	1.000		<0.001
II (n=98)	1.711	1.217–2.404	<0.001	1.559	1.160–2.096	0.003
III (n=135)	4.979	3.728–6.650	<0.001	4.606	3.573–5.998	<0.001
IV (n=6)	13.093	5.613–30.539	<0.001	5.852	2.369–14.454	<0.001
SOLMR grade						
A (OS: n=138; RFS: n=126)	1.000		<0.001	1.000		<0.001
B (OS: n=279; RFS: n=291)	2.890	2.077–4.020		2.664	1.989–3.569	
C (n=35)	8.671	5.439–13.821		5.219	3.360–8.107	

OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus; BDTT, bile duct tumor thrombus; AJCC, American Joint Committee Cancer 8th of HCC; HCC, hepatocellular carcinoma.

adipokines such as leptin, chemerin, and resistin and cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and interferon (INF)-γ as well as decreased concentrations of adiponectin or myokines such as IL-15 (42-44). In addition, liver cirrhosis patients experience reduced insulin inactivation, resulting in a certain amount of insulin resistance. This unfavorable adipokine/cytokine profile further increases insulin resistance, which amplifies inflammation and oxidative stress and contributes to ectopic fat deposition. Wannamethee *et al.* observed a continuous cycle involving "decline in physical activity-sarcopenia-insulin resistance-inflammation-oxidative stress", which results in the development of SO (45). All these changes contribute to the progression of HCC.

This study is the first to combine SO and the LMR to obtain a SOLMR grade in HCC research. Based on the above conclusions in this study, we developed a novel classification system called SOLMR grading via subgroup analysis. The multivariate analysis suggested that the SOLMR grade was an independent prognostic factor for patients with HCC. The OS and RFS of patients with SOLMR grade C disease were far worse than those with grades B and A disease. According to the 8th edition AJCC and the Barcelona Clinic Liver Cancer (BCLC) staging systems, we plotted survival curves stratified by different stages (Figure S3). The results suggested that SOLMR grade had better discrimination in each AJCC stage than BCLC stage. Considering that the BCLC staging systems contains
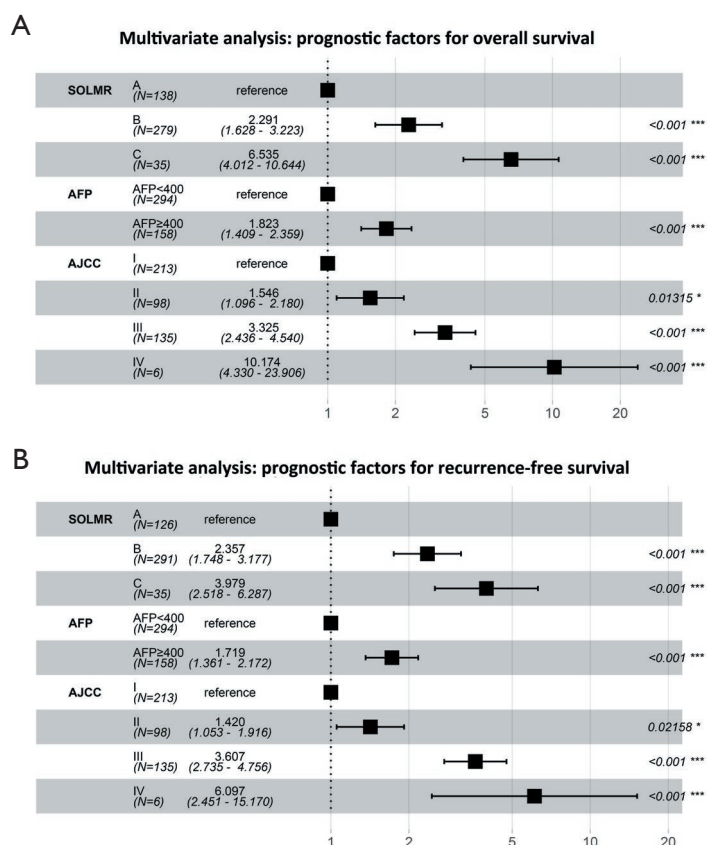
Figure 5 Forest plots of prognostic factors for OS and RFS in HCC patients. (A) The optimal prognostic factors for OS in the multivariate analysis in the training cohort. (B) The optimal prognostic factors for RFS in the multivariate analysis in the training cohort. OS, overall survival; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; SOLMR, SOLMR grade; AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer 8th edition.

performance status (PS) scores, if we use SOLMR grade to further subdivide the general physical condition, it may lead to bias. Therefore, we recommend use the SOLMR grade for stratification on the basis of the AJCC staging systems instead of the BCLC staging systems. Among the clinical characteristics associated with the SOLMR grade, the factors that were considered to be related to poor prognosis, such as age, cardiovascular disease, liver function classification, AFP level, liver resection volume, length of hospital stay, tumor size, number of tumors, occurrence of vascular invasion and tumor stage, were all highest in grade A and lowest in grade C (*Table 5*). Therefore, the SOLMR grade is quite representative. In clinical practice, the SOLMR grade can be used as a risk stratification tool to supplement the TNM staging system to better stratify patients by risk and to provide an accurate basis for postoperative follow-up and treatment guidance. Close

follow-up and aggressive postoperative adjuvant therapies, such as transarterial chemoembolization (TACE), targeted therapy and immunotherapy, are recommended for HCC patients with SOLMR grades B and C.

Although those traditional staging systems provide good guidance for clinical treatment, most of them focus on tumor progression and ignore the general physical condition of the patient, resulting in a biased assessment of the prognosis. In the era of individualized precision medicine, a nomogram was constructed by incorporating both the SOLMR grade and the AJCC stage; this nomogram resulted in better in predictive accuracy and discriminative ability than AJCC staging alone. The nomograms were comprehensive, as they accounted for general body-inflammation status, serological indicators, and tumor stage. Moreover, regarding their convenience in clinical practice, the nomograms utilized three variables that were easy to
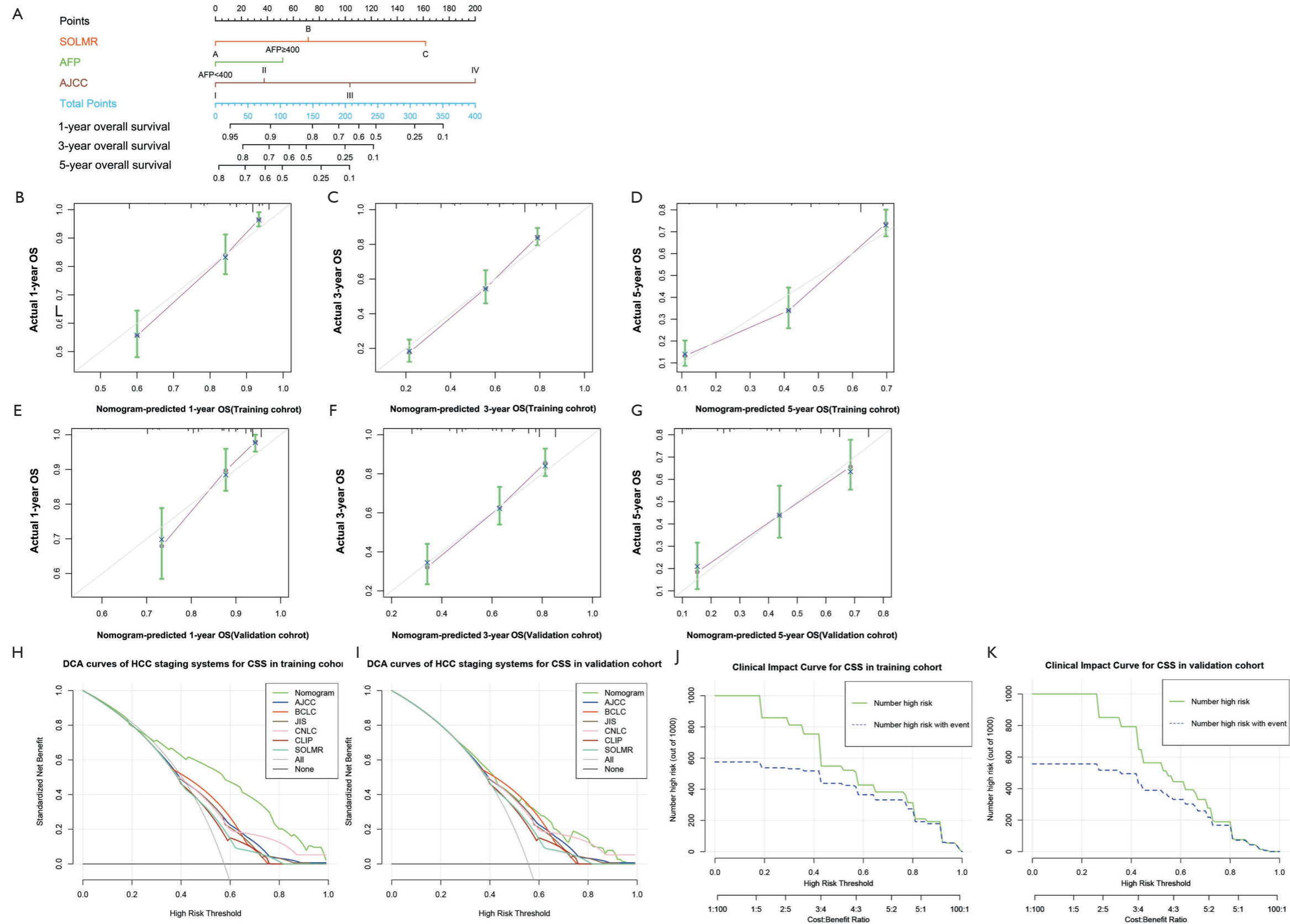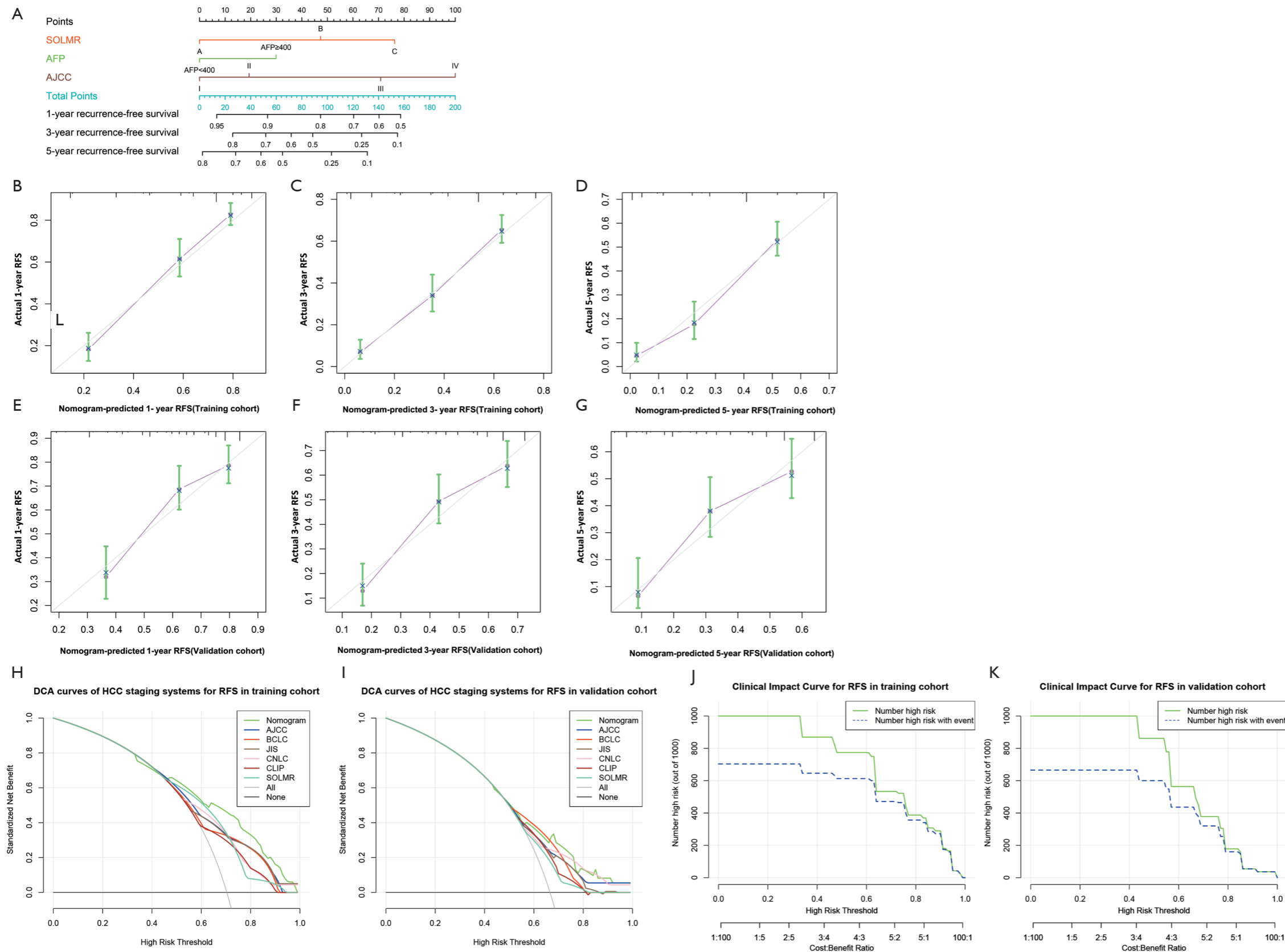
Figure 6 Nomogram for OS prediction and its calibration plots, decision curve analyses, and clinical impact curves. (A) The nomogram for predicting 1-, 3- and 5-year OS in patients with HCC after surgery. (B,C,D) Calibration plots of the nomogram for 1-, 3- and 5-year OS in the training cohort. (E,F,G) Calibration plots of the nomogram for 1-, 3- and 5-year OS in the validation cohort. (H,I) Decision curve analysis for the nomogram and the other conventional staging systems. (J,K) The clinical impact curves of the nomogram in the training cohort and validation cohort. OS, overall survival; HCC, hepatocellular carcinoma; SOLMR, SOLMR grade; AFP, alpha-fetoprotein; AJCC, the American Joint Committee on Cancer 8th edition; BCLC, Barcelona Clinic Liver Cancer; JIS, Japan Integrated Staging; CNLC, China Liver Cancer staging; CLIP, Cancer of the Liver Italian Program.

Figure 7 Nomogram for RFS predictions and calibration plots, decision curve analysis, and clinical impact curves. (A) The nomogram for predicting 1-, 3- and 5-year RFS in patients with HCC after surgery. (B-D) Calibration plots of the nomogram for 1-, 3- and 5-year RFS in the training cohort. (E,F,G) Calibration plots of the nomogram for 1-, 3- and 5-year RFS in the validation cohort. (H,I) Decision curve analysis for the nomogram and the other conventional staging systems. (I,J,K) The clinical impact curves of the nomogram in the training cohort and validation cohort. RFS, recurrence-free survival; HCC, hepatocellular carcinoma; SOLMR, SOLMR grade; AFP, alpha-fetoprotein; AJCC, the American Joint Committee on Cancer 8th edition; BCLC, Barcelona Clinic Liver Cancer; JIS, Japan Integrated Staging. CNLC, China Liver Cancer staging; CLIP, Cancer of the Liver Italian Program.

Table 7 The C-indexes of the established nomograms and other conventional staging systems

C-index	OS		RFS	
	Training cohort	Validation cohort	Training cohort	Validation cohort
Nomogram	0.761 (0.734–0.788)	0.715 (0.676–0.754)	0.736 (0.710–0.762)	0.683 (0.643–0.723)
AJCC	0.710 (0.681–0.739)*	0.686 (0.646–0.726)*	0.700 (0.674–0.726)*	0.643 (0.602–0.684)*
BCLC	0.674 (0.647–0.701)*	0.643 (0.600–0.686)*	0.665 (0.640–0.690)*	0.609 (0.566–0.652)*
JIS	0.690 (0.660–0.720)*	0.684 (0.643–0.725)*	0.679 (0.654–0.704)*	0.649 (0.608–0.690)*
CNLC	0.693 (0.664–0.722)*	0.655 (0.610–0.700)*	0.673 (0.645–0.701)*	0.622 (0.582–0.662)*
CLIP	0.635 (0.606–0.664)*	0.655 (0.614–0.696)*	0.636 (0.608–0.664)*	0.641 (0.600–0.682)*
SOLMR	0.647 (0.620–0.674)*	0.593 (0.550–0.636)*	0.615 (0.589–0.641)*	0.576 (0.537–0.615)*

*, $P<0.001$ when compared with nomogram. AJCC, American Joint Committee on Cancer 8th edition; BCLC, Barcelona Clinic Liver Cancer; JIS, Japan Integrated Staging; CNLC, China Liver Cancer staging; CLIP, Cancer of the Liver Italian Program.

obtain and required only the basic AJCC stage. The BCLC and China Liver Cancer (CNLC) staging systems also include PS scores to indicate general physical condition. However, PS scores are easily affected by subjective patient factors, and indications for surgery in the BCLC staging seem to be too conservative. With the development of HCC surgery, almost all areas are now accessible, and the relatively conservative indication for surgery in the BCLC system seems to contrast with that development, especially in China where there are many cases of large-volume and advanced-stage HCC. As a new predictive tool in HCC, the application value of our nomograms in China requires long-term evaluation.

There were several limitations in our study. First, as a retrospective, small-sample study, it may have been subject to selection bias, and validation in a larger sample could be more convincing. Second, calculating the SMI requires relatively complex imaging calculations, and a convenient, automated software program needs to be further developed. Finally, the preoperative stress state of the patient or comorbidities may have affected the variation in the LMR. Thus, the optimal time window and physiological status for obtaining blood samples have yet to be determined.

Conclusions

Our study is the first to demonstrate that the preoperative LMR was significantly associated with SO in HCC patients and the first to proposed SOLMR grading in HCC. The novel visualized nomograms developed from the SOLMR

grading system combining SO with the inflammatory index provided better prognostic estimates than the traditional staging systems. Thus, more in-depth studies on SO and inflammation and a better understanding of specific molecular mechanisms and pathways may lead to the development of novel therapies to improve HCC outcomes.

Footnote

(as revised in 2013). The study was approved by the institutional review boards of Fujian Provincial Hospital and Fujian Medical University Union Hospital (No. K2019-12-025; 2019KY022) and Informed consent was obtained from all patients before inclusion in the study.

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