International Journal of Clinical Oncology (2019) 24:825–835
https://doi.org/10.1007/s10147-019-01402-4

ORIGINAL ARTICLE

Inflammation–nutrition score predicts prognosis of patients with resectable hepatocellular carcinoma

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Received: 31 October 2018 / Accepted: 17 January 2019 / Published online: 24 April 2019

Abstract

Background Various inflammation-based prognostic scores have been associated with poor survival in patients with hepatocellular carcinoma (HCC).

Methods Data were collected retrospectively from 674 HCC patients who underwent curative resection. The correlation between INS (inflammation–nutrition score), BCLC (Barcelona Clinic Liver Cancer) stage and inflammatory indices and overall survival (OS) and disease free survival (DFS) was examined.

Results An elevated INS was associated with both tumor and host clinical characteristics. The combination of INS and BCLC stage stratifies OS and DFS from 80% and 65% (INS = 0, stage A) to 0% (INS = 2, stage C). Univariate and multivariate analyses revealed that the INS was an independent predictor for OS and DFS, and was superior to inflammation-based scores. In addition, INS was demonstrated to be a prognostic factor for patients with early stage and had a higher AUC value in comparison with inflammation scores.

Conclusion This study demonstrates that the INS is an independent marker of poor prognosis in patients with resectable HCC, especially for those with early stage, and it provides complimentary prognostic information to BCLC stage, and may aid in treatment strategy.

Keywords Inflammation–nutrition score · Hepatocellular carcinoma · Prognosis

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and is the third leading cause of cancer-related death in the world [1, 2]. However, even after complete resection, the long-term prognosis of patients still remained unsatisfactory because of high rate of recurrence [3, 4]. Hence, it is critical to identify reliable prognostic factors to define patients with a high risk of recurrence, especially for patients with early stage disease.

In addition to tumor-based characteristics, there is increasing evidence that host systemic inflammatory response is recognized as an important determinant of disease progression and cancer-specific survival in several solid tumors [5–8]. In particular, various combinations of hematological parameters based on systemic inflammatory response, represented by Glasgow prognostic score (GPS), modified Glasgow prognostic score (mGPS), and neutrophil-to-lymphocyte ratio (NLR) have been reported to possess prognostic value in HCC [9–14]. Of these, the mGPS, a

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10147-019-01402-4) contains supplementary material, which is available to authorized users.

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cumulative score based on serum C-reactive protein (CRP) and albumin seems to have superior prognostic value compared to other inflammation scores in patients with HCC [6, 15]. However, it is of interest that a greater proportion of patients have elevated systemic inflammation scores in Western countries than that in Eastern Asian countries, as the GPS/mGPS studies in East Asia used lower CRP thresholds (7.5 mg/L, 5 mg/L and 3 mg/L) [16–20], while most western studies used original abnormal thresholds (CRP > 10 mg/L). In a Japanese study, Ishizuka et al. [21] assessed a new mGPS, which incorporated a lower CRP cut-off level, had a better predictive value and ability to classify patients than the GPS, mGPS, or even the CLIP score. Hence, the redefinition of CRP threshold due to such consistent East/West differences is essential for improving prognostic value of the scores composed of CRP (i.e., GPS/mGPS).

Apart from host inflammation, the patient's nutritional status has also been closely related to cancer prognosis [22–24]. Serum markers such as albumin and prealbumin are most used in practice for nutritional assessment. Although the albumin level may reflect the nutritional status, because of its long half-life (3 weeks), wide distribution, no close correlation to protein mass, some authors proposed to replace it with prealbumin, which is also recognized particularly as reverse acute-phase reactants with significantly shorter half-lives, and more correlated to recent nutritional status and liver protein production [25, 26]. Moreover, low prealbumin levels have been found to be associated with recurrence and poorer short-term outcome in various tumors [27–30].

In the present study, a novel inflammation–nutrition prognostic score (INS), based on prealbumin and adjusted cut-off value of CRP, was developed. The clinical prognostic assessment of the INS was examined in a large cohort of patients undergoing curative resection of HCC. We also evaluated the prognostic ability of different inflammation-based prognostic scores and BCLC (Barcelona Clinic Liver Cancer) stage to determine whether the INS could be a more useful prognostic marker.

Materials and methods

Patient selection

This retrospective study was conducted on 674 HCC patients who underwent curative hepatectomy as a first-line treatment at the Liver Cancer Institute of Zhongshan Hospital (Fudan University, Shanghai, China) between December 2010 and January 2012. Any patient with a synchronous cancer, clinical evidence of infection or who had received prior intervention or died within 30 days after surgery was excluded. This study was approved by the Ethics Committee of Zhongshan Hospital.

Definition

Blood samples were obtained for neutrophil, lymphocyte, platelet counts, albumin, prealbumin, and CRP, which were measured in the laboratory at the same time within 1 week before surgery. We determined an optimal cutpoint of CRP for predicting survival using the "minimum *P* value" approach called X-tile, Version 3.6.1 [31]. The optimal CRP cut-off value for both the overall survival (OS) and the disease-free survival (DFS) was 8.2 mg/L. The new score INS and other inflammatory scores, including GPS, mGPS, NLR, PLR, and PNI, were defined as follows (Table S1).

Follow-up

Follow-up procedures are described in our previous study [32]. DFS was defined as the interval between the date of surgery and the first recurrence, or the date of last follow-up without recurrence. OS was defined as the interval between the date of surgery and death, or last follow-up.

Statistical analysis

All data analyses were performed using SPSS for Windows version 19.0 (SPSS, Chicago, IL, USA). Associations between categorical variables were examined using the χ^2 test or Fisher exact test. The Kaplan–Meier method with log-rank test was used to compare survival curves. The Cox proportional hazards model was used for univariate and multivariate survival analyses. To avoid collinearity bias, the inflammation-based prognostic scores were preliminarily tested using a multivariate model that included the individual variables composing the BCLC stage. A receiver operating characteristics (ROC) curve was used to compare the discrimination ability for OS and DFS. A value of $P < 0.05$ was considered statistically significant.

Results

674 patients who underwent potentially curative resection of hepatocellular carcinoma were studied. Clinicopathological characteristics are shown in Table 1. The median age of patients was 54 years old at the time of surgery. One-sixth of patients were female, and more than 80% of patients had hepatitis B diseases. Overall, the majority of patients had early stage cancer, and 64% patients had BCLC stage 0/A.

Eleven percent of patients had CRP more than 8.2 mg/L, and 45% had a prealbumin less than 0.2 g/L before surgery. More than half patients were INS = 0, whereas 38% and 6%

Table 1 Relationship between INS and clinicopathological characteristics in patients

Clinicopathological characteristic	All ($n=674$)	INS = 0 ($n=373$)	INS = 1 ($n=258$)	INS = 2 ($n=43$)	P
Age (years)					
< 54	303	186	99	18	0.02
≥ 54	371	187	159	25	
Sex					
Female	108	41	60	7	< 0.001
Male	566	332	198	36	
HBsAg					
Positive	572	310	226	36	0.3
Negative	102	63	32	7	
Cirrhosis					
Positive	502	265	209	28	0.006
Negative	172	108	49	15	
BMI					
≤ 18.5	27	18	7	2	0.37
> 18.5	647	355	251	41	
ALT					
< 50	540	298	205	37	0.61
≥ 50	134	75	53	6	
Total serum bilirubin					
≤ 20	609	343	230	36	0.16
> 20	65	30	28	7	
GGT					
< 60	391	230	147	14	0.001
≥ 60	283	143	111	29	
AFP					
< 400	483	273	184	28	0.51
≥ 400	191	100	74	15	
Albumin					
< 40	215	75	110	30	< 0.001
≥ 40	459	298	148	13	
Child–Pugh grade					
A	672	373	257	42	0.05
B	2	0	1	1	
BCLC stage					
0/A	434	266	161	7	< 0.001
B	205	93	81	31	
C	35	14	16	5	
Tumor size					
< 5	395	234	155	6	< 0.001
≥ 5	279	139	103	37	
Tumor number					
Solitary	578	328	220	40	0.4
Multiple	96	55	38	3	
Tumor capsule					
Complete	429	247	161	21	0.07
None	245	126	97	22	
Microvenous invasion					
No	479	279	183	17	< 0.001
Yes	195	94	75	26	
Vascular thrombus					

Table 1 (continued)

Clinicopathological characteristic	All ($n=674$)	INS = 0 ($n=373$)	INS = 1 ($n=258$)	INS = 2 ($n=43$)	P
No	635	356	242	37	0.045
Yes	39	17	16	6	
Edmondson grade					
I–II	463	266	175	22	0.02
III	211	107	83	21	

HBsAg hepatitis B surface antigen, *BMI* body mass index, *ALT* alanine aminotransferase, *GGT* gamma glutamyl transferase, *AFP* a-fetoprotein level, *BCLC* Barcelona Clinic Liver Cancer Score

were INS = 1 and INS = 2, respectively. An elevated INS was associated with advancing BCLC stage, huge tumor size, poor tumor differentiation, and vascular involvement and thrombus ($P<0.05$). In addition, the INS was correlated with host characteristics such as age, gender, and cirrhosis. The relationships between other inflammation-based scores and clinicopathological characteristics are shown in Table S2.

The median follow-up of survivors was 69 months (range 2–79 months), with 233 cancer-related deaths and 331 patients with tumor recurrence. OS and DFS at 5 years were 68% and 54%, respectively. The relationship between clinicopathological characteristics, preoperative INS, and survival is shown in Table 2. The following clinicopathological characteristics were associated with reduced OS on univariate analysis: INS ($P<0.001$), GPS ($P<0.001$), mGPS ($P<0.001$), NLR ($P=0.02$), GGT ($P<0.001$), AFP ($P<0.001$), BCLC stage ($P<0.001$), tumor size ($P<0.001$), tumor number ($P=0.001$), tumor capsule ($P=0.04$), poor differentiation ($P<0.001$), microvenous invasion ($P<0.001$), and vascular thrombus ($P<0.001$). On multivariate survival analysis, INS was associated with reduced OS (HR 1.571, $P<0.001$), independent of GGT ($P=0.008$), tumor size ($P<0.001$), tumor number ($P=0.04$), microvenous invasion ($P<0.001$), and vascular thrombus ($P=0.01$). Poor differentiation showed a trend toward reduced overall survival on multivariate analysis ($P=0.06$), whereas inflammation scores such as GPS, Mgps, and NLR were not associated with OS (Fig. 1 and Figure S1).

The following clinicopathological characteristics were associated with reduced DFS on univariate analysis: INS ($P<0.001$), GPS ($P<0.001$), mGPS ($P<0.001$), GGT ($P<0.001$), AFP ($P=0.02$), ALT ($P=0.004$), liver cirrhosis ($P=0.005$), BCLC stage ($P<0.001$), tumor size ($P<0.001$), tumor number ($P=0.002$), poor differentiation ($P=0.001$), microvenous invasion ($P<0.001$), and vascular thrombus ($P<0.001$) (Fig. 1 and Figure S2). On multivariate analysis, INS was associated with reduced DFS (HR 1.454, $P<0.001$), independent of GGT ($P=0.003$), liver cirrhosis ($P=0.03$), tumor size ($P=0.003$), microvenous invasion ($P=0.004$), and vascular thrombus ($P=0.008$). Tumor number showed a trend toward reduced DFS ($P=0.07$), whereas GPS and mGPS were not associated with disease-free survival. In addition, we further assessed the independent prognostic ability of BCLC stage. The multivariate analysis showed that INS still remained significant prognostic factors for OS and DFS (Table 2 and Table S3).

The relationship between preoperative INS, BCLC stage, OS, and DFS is shown in Fig. 1 and Table 3. OS varied from about 75% in patients with early stage (BCLC 0/A) liver cancer to 26% in patients with advanced stage (BCLC C) and from 72% in patients with INS 0 to 27% in patients with INS 2. When combined, OS varied from 80% in patients with early stage disease and INS 0, to 0% in patients with advanced stage disease and INS 2 ($P<0.001$). A similar relationship between BCLC stage, INS, and DFS was also observed; whereas survival ranged from about 58–17% and from 56 to 21% with BCLC stage or INS alone, the combination of stage and INS stratified DFS from 65% (BCLC 0/A, INS 0) to 0% (BCLC C, INS 2). The synergistic nature of the relationship between BCLC stage and INS is, for example, shown for early stage in Fig. 2 ($P<0.001$).

To date, it still lack of precise biomarkers to predict the outcome of HCC with early stage subgroups. Therefore, we stratified the patients according to BCLC stage, and we found that the INS was significantly correlated with OS and DFS in BCLC 0/A stage subgroups (Fig. 2, OS: BCLC 0/A: $P<0.001$; DFS: BCLC 0/A: $P<0.001$). In addition, GPS and mGPS were also significantly related to OS and DFS in both BCLC 0/A stage subgroups. (OS: GPS: $P=0.001$, mGPS: $P=0.003$; DFS: GPS: $P=0.005$, mGPS: $P=0.001$, respectively). While PLR and PNI were not significantly associated with OS and DFS in early stage, apart from a close association between NLR and OS (Figures S3 and S4).

Finally, predictive ability of the INS was compared with other inflammatory parameters and clinical stages by ROC curves. Although the discrimination ability of the INS, as assessed by AUC, was 0.606 for OS, which was higher than other clinical parameters, the BCLC stage was superior to INS. However, the AUC for the INS was 0.598, which was the strongest index among inflammatory parameters, and similar to the BCLC stage (Fig. 3; Table 4).

Table 2 Relationship between and clinicopathological characteristics and survival of patients undergoing potentially curative resection

Clinicopathological characteristic	OS				DFS			
	Univariate analysis	*P*	Multivariate analysis	*P*	Univariate analysis	*P*	Multivariate analysis	*P*
Age (< 54, ≥ 54), years	1.222 (0.846–1.767)	0.285			1.246 (0.915–1.697)	0.16		
Sex (female/male)	1.034 (0.798–1.339)	0.8			1.199 (0.963–1.493)	0.1		
HBsAg (positive/negative)	0.963 (0.675–1.374)	0.84			1.161 (0.846–1.597)	0.35		
Cirrhosis (positive/negative)	1.096 (0.939–1.278)	0.25			1.21 (1.058–1.383)	0.005	1.163 (1.016–1.321)	0.03
BMI (≤ 18.5, > 18.5)	0.822 (0.406–1.664)	0.574			0.679 (0.362–1.273)	0.227		
ALT (< 50, ≥ 50)	1.345 (0.997–1.813)	0.05			1.442 (1.121–1.855)	0.004		
Total serum bilirubin (≤ 20, > 20)	1.213 (0.801–1.838)	0.36			1.293 (0.915–1.828)	0.146		
GGT (< 60, ≥ 60)	2.028 (1.566–2.626)	< 0.001	1.447 (1.101–1.901)	0.008	1.793 (1.445–2.226)	< 0.001	1.406 (1.12–1.765)	0.003
AFP (< 400, ≥ 400)	1.609 (1.23–2.106)	0.001			1.32 (1.046–1.666)	0.02		
Albumin (< 40, ≥ 40)	0.763 (0.583–0.993)	0.045			0.826 (0.660–1.035)	0.097		
Prealbumin (< 0.2, ≥ 0.2)	1.978 (1.407–2.781)	< 0.001			1.623 (1.243–2.119)	< 0.001		
CRP (< 8.2, ≥ 8.2)	2.905 (2.107–4.004)	< 0.001			2.473 (1.853–3.3)	< 0.001		
Child–Pugh grade (A/B)	1.800 (0.252–12.836)	0.56			3.995 (0.99–16.119)	0.05		
BCLC stage (A/B/C)	2.434 (2.011–2.946)	< 0.001			1.89 (1.593–2.243)	< 0.001		
Tumor size (< 5, ≥ 5)	2.615 (2.013–3.398)	< 0.001	1.802 (1.358–2.393)	< 0.001	1.93 (1.555–2.395)	< 0.001	1.426 (1.124–1.809)	0.003
Tumor number (solitary, multiple)	1.758 (1.276–2.421)	0.001	1.447 (1.02–1.975)	0.04	1.572 (1.186–2.084)	0.002	1.306 (0.979–1.744)	0.07
Tumor capsule (complete/none)	1.31 (1.008–1.7020)	0.04			1.157 (0.926–1.444)	0.2		
Microvenous invasion (no/yes)	2.665 (2.057–3.453)	< 0.001	1.74 (1.293–2.342)	< 0.001	1.984 (1.587–2.481)	< 0.001	1.444 (1.122–1.857)	0.004
Vascular thrombus (no/yes)	4.074 (2.754–6.027)	< 0.001	1.749 (1.113–2.709)	0.01	3.255 (2.255–4.696)	< 0.001	1.749 (1.16–2.636)	0.008
Edmondson grade (I–II/III)	1.758 (1.353–2.285)	< 0.001	1.309 (0.994–1.724)	0.06	1.477 (1.181–1.848)	0.001		
INS (0/1/2)	1.945 (1.59–2.379)	< 0.001	1.571 (1.285–1.921)	< 0.001	1.702 (1.432–2.022)	< 0.001	1.454 (1.222–1.729)	< 0.001
GPS (0/1/2)	1.938 (1.487–2.527)	< 0.001			1.65 (1.298–2.099)	< 0.001		
mGPS (0/1/2)	2.164 (1.634–2.865)	< 0.001			1.893 (1.467–2.443)	< 0.001		
NLR (0/1)	2.194 (1.164–4.135)	0.02			1.561 (0.832–2.93)	0.17		
PLR (0/1)	1.387 (0.894–2.152)	0.14			1.148 (0.779–1.691)	0.49		
PNI (0/1)	1.291 (0.93–1.792)	0.13			1.225 (0.926–1.62)	0.16		

HBsAg hepatitis B surface antigen, *BMI* body mass index, *ALT* alanine aminotransferase, *GGT* gamma glutamyl transferase, *AFP* a-fetoprotein level, *CRP* C-reactive protein, *BCLC* Barcelona Clinic Liver Cancer Score, *INS* Inflammation–Nutrition Prognostic Score, *GPS* Glasgow Prognostic Score, *mGPS* modified Glasgow Prognostic Score, *NLR* neutrophil–lymphocyte ratio, *PLR* platelet–lymphocyte ratio, *PNI* prognostic nutritional index

Discussion

This study shows that the INS is an independent indicator of outcome for HCC patients who undergo surgery, especially for those with early stage disease. When compared with previously developed prognostic systems, the INS shows the best prognostic performance nearly matching the BCLC-staging system. Moreover, the combination of INS and BCLC stage effectively stratifies outcome in patients undergoing curative resection.

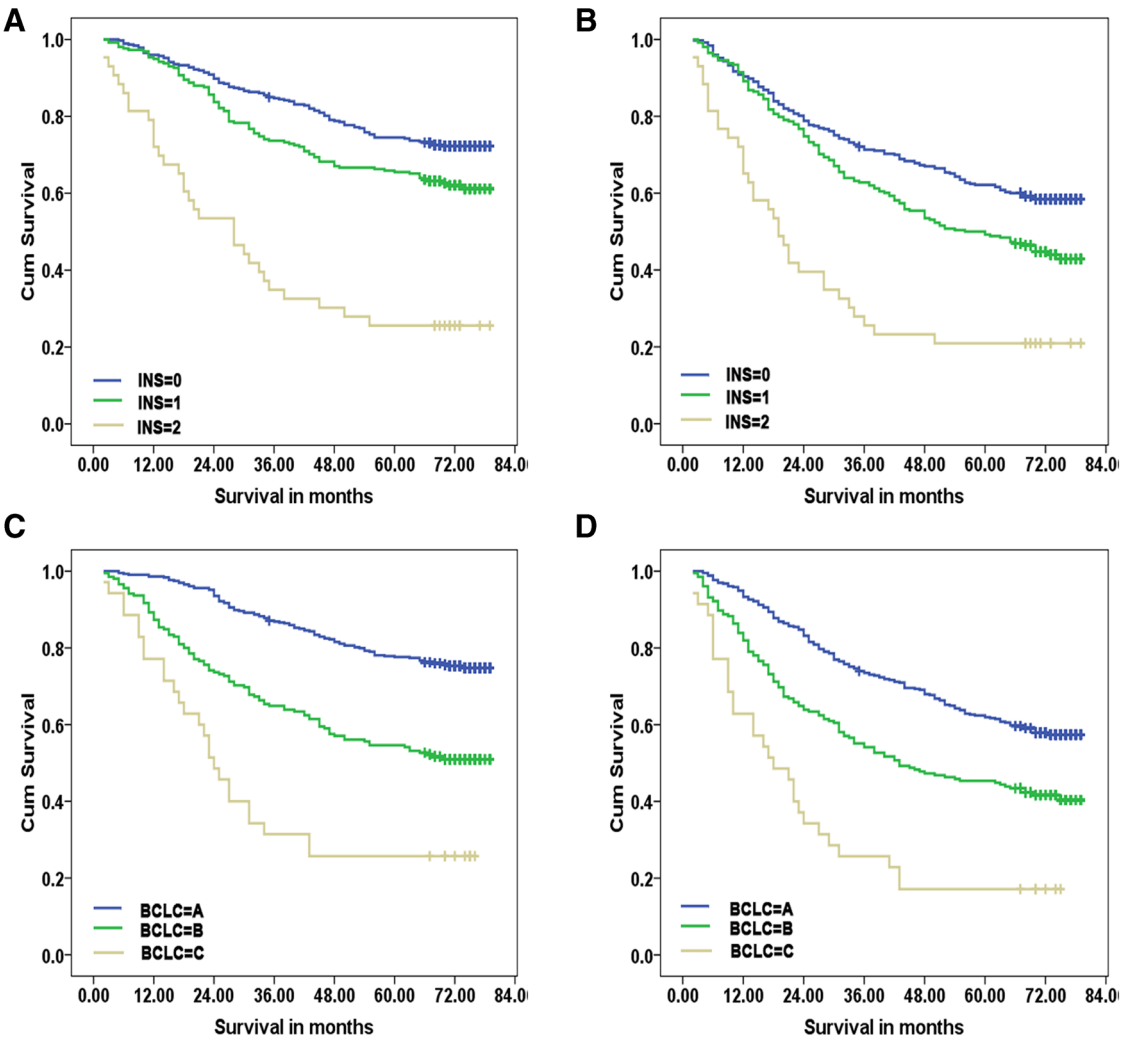

Fig. 1 **a** Relationship between INS and OS of patients undergoing resection ($P<0.001$). **b** Relationship between INS and DFS of patients undergoing resection ($P<0.001$). **c** Relationship between BCLC stage and OS of patients undergoing resection ($P<0.001$). **d** Relationship between BCLC stage and DFS of patients undergoing resection ($P<0.001$)

Table 3 Relationship between INS and OS and DFS in patients undergoing curative resection

BCLC	INS = 0		INS = 1		INS = 2		All	
	n	OS	*n*	OS	*n*	OS	*n*	OS
0/A	266	79.7	161	70.2	7	28.6	434	75.3
B	93	58.1	81	51.9	31	29	205	51.2
C	14	28.2	16	31.2	5	0	35	25.7
ALL	373	72.4	258	62	43	26.6	674	65.4
BCLC	INS = 0		INS = 1		INS = 2		All	
	n	DFS	*n*	DFS	*n*	DFS	*n*	DFS
0/A	266	65	161	48.4	7	14.3	434	58.1
B	93	45.2	81	43.2	31	25.8	205	41.5
C	14	28.6	16	12.5	5	0	35	17.1
ALL	373	56.3	258	44.6	43	20.9	674	50.9

BCLC Barcelona Clinic Liver Cancer Score, *INS* Inflammation–Nutrition Prognostic Score, *OS* overall survival, *DFS* disease-free survival

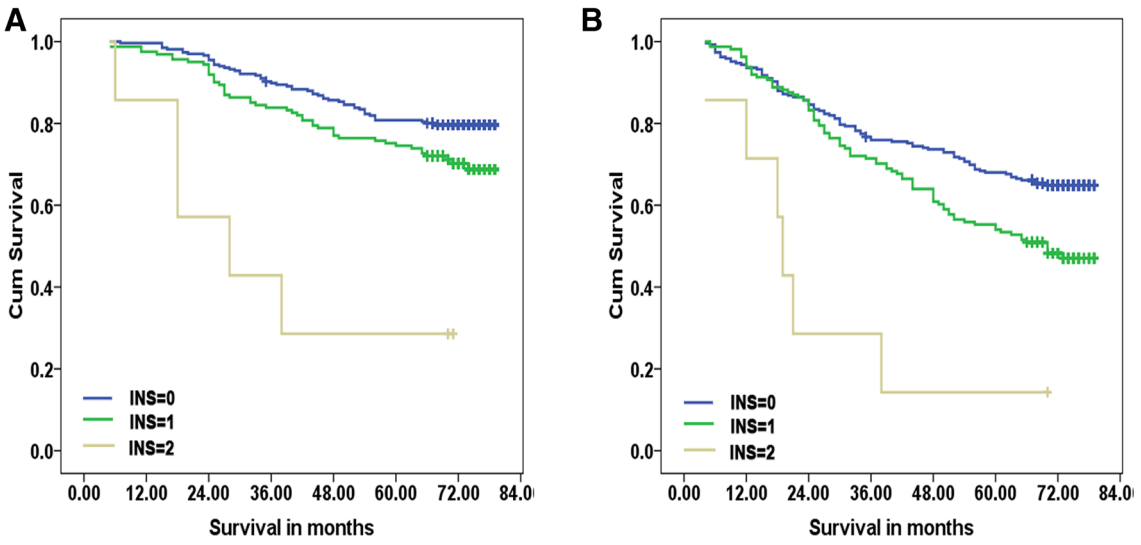

Fig. 2 **a** Relationship between INS and BCLC A stage and OS of patients undergoing resection ($P < 0.001$). **b** Relationship between INS and BCLC A stage and DFS of patients undergoing resection ($P < 0.001$)

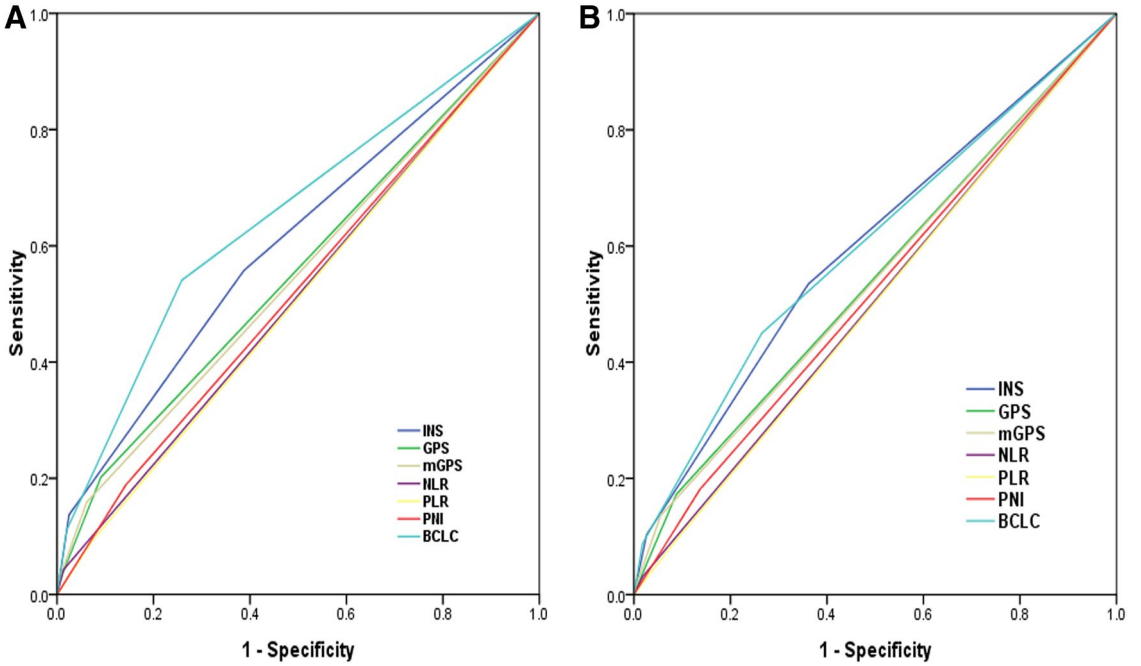

Fig. 3 **a** Predictive OS ability of the INS was compared with other inflammation-based scores and BCLC stage by ROC curves. **b** Predictive DFS ability of the INS was compared with other inflammation-based scores and BCLC stage by ROC curves

Recently, more and more studies have indicated that inflammation plays an important role in cancer development and progression [33]. The presence of an elevated systemic inflammatory response as evidenced by an alteration in circulating acute-phase proteins, such as C-reactive protein and albumin (GPS/mGPS), is associated not only with poorer outcome in HCC [34], but it is prognostic of all-cause mortality in a large incidentally sampled cohort [35]. Although serum C-reactive protein (CRP) is widely used as a systemic inflammatory response index, the standard abnormal thresholds of CRP varied among various studies. Whether an universally standardised threshold (CRP > 10 mg/L), or thresholds based on ethnic differences should be utilized, remains to be investigated. Thus,

Table 4 Comparison of the AUC between inflammatory prognostic scores and staging systems

	Overall survival AUC	Disease-free survival AUC
INS	0.605	0.598
GPS	0.556	0.542
Modified GPS	0.549	0.54
NLR	0.515	0.506
PLR	0.51	0.503
PNI	0.523	0.522
BCLC stage	0.65	0.6

AUC the area under the ROC curve, *INS* Inflammation–Nutrition Prognostic Score, *GPS* Glasgow Prognostic Score, *mGPS* modified Glasgow Prognostic Score, *NLR* neutrophil–lymphocyte ratio, *PLR* platelet–lymphocyte ratio, *PNI* prognostic nutritional index, *BCLC* Barcelona Clinic Liver Cancer Score

in the present study, we performed optimal cut-off values of CRP for DFS and OS after curative resection and found that the two cut-off values were the same. Elevated pretreatment serum CRP, based on this same cut-off value (8.2 mg/L), tended to correlate with poor OS and DFS, consistent with the previous studies [15–17, 36]. Therefore, our results may indicated that a rational threshold of CRP should be further investigated and to be part of the preoperative routine workup of patients with operable cancer.

Preoperative nutritional status is one of critical factors for patient outcomes in a variety of cancers. The BMI, serum albumin, and prealbumin are important markers for the clinical evaluation of the nutritional status. It had been reported that the BMI and albumin associated with the surgical outcomes and survival in HCC, colorectal cancer, pancreatic cancer, and so on [37–42]. However, in our study, hypoalbuminemia and lower BMI were not prognostic factors for DFS in univariate analysis. On the contrary, the multivariate analysis revealed that only the prealbumin, rather than other nutritional indices, was independently associated with both OS and DFS. Therefore, prealbumin may have a more sensitive value for predicting survival of HCC patients than others, which is consistent with other cancers [28–30, 43]. This result is a reflection of the current trend that prealbumin became the research focus as a serum index for assessment of nutritional status especially during the perioperative period, as prealbumin is a negative acute-phase protein and affected earlier in acute metabolism state change than albumin. Furthermore, from the relationship of serum prealbumin levels and clinicopathologic characteristics, we found that it was significantly correlated with host-related characteristics such as age, sex, and liver cirrhosis, but not tumor-related characteristics. Therefore, the clinical utility of combining such markers as prealbumin with tumor-based factors or BCLC stage to more effectively predict patient prognosis is becoming increasingly recognized.

In the present study, we found that CRP levels were strongly and independently correlated (in an inverse manner) with prealbumin levels. Such correlations underline the complex interplay between systemic inflammation and malnutrition. Since CRP and prealbumin are both creditable factors to identify the most complex clinical situations characterized by the compounding effect of inflammation and malnutrition, as especially documented in cancer [7, 24, 27, 28], we hypothesize that above markers in combination may provide more effective prognostic value for HCC patients. Then, we constructed a new score model based on CRP and prealbumin called INS to evaluate the prognosis of HCC patients. Noteworthiness, concerning the correlationship between INS and clinical characteristics, we found that the new INS was associated with both tumor and host characteristics, while other inflammation scores were linked to either tumor-related factors or patient-related factors. This result suggested that the INS was a comprehensive and accurate reflection of host and tumor status, and it is a strong case for the INS to be incorporated into preoperative workup of patients undergoing surgery for cancer. Using univariate analysis, we discovered some inflammation prognostic factors for DFS and OS including INS and GPS/mGPS. However, after multivariate analysis, we revealed that INS, rather than other inflammation-based prognostic scores, was significantly associated with long-term outcome and recurrence rate independent of tumor stage. Moreover, we further evaluated the discrimination ability of the inflammation-based prognostic scores, the analysis of the estimated AUCs confirmed that the INS had higher values than the other scoring systems including the GPS, mGPS, NLR, PLR, and PNI, and it was only slightly less than that of the BCLC-staging system in terms of prognostic ability. Taken together, our data suggested that the INS, its prognostic performance turned out to be a more sensitive and promising predictor of poor outcome in patients with HCC compared with other previous inflammation scores, almost equaling the BCLC-staging system. In addition, the combination of BCLC stage and INS increased the range of survival compared to either BCLC or INS alone.

As we know, the prognosis of very early/early stage HCC (BCLC stage 0/A) with generally curative treatments is far from homogenous [44–46], and approximately one-quarter of patients with BCLC stage 0/A HCC experience tumor relapse within the first year after surgical resection [47]. While in clinical practice, it is still difficult to predict which individuals at high risk of tumor relapse after surgery, especially for patients with early stage HCC. Therefore, it is urgent to seek to subdivide this stage for purposes of individualizing surveillance and follow-up strategies after surgery. Subsequently, we assessed the

prognostic value of preoperative INS in subgroup of HCC patients in BCLC 0/A and revealed that patients with a higher grade (INS = 2) would have a worse outcome after curative resection compared with those with lower grades (INS = 0/1). Therefore, considering the lack of consensus on the follow-up strategies for detection of recurrent HCC after resection [48], our present results highlighted the role of the INS in predicting tumor relapse in patients with early HCC, and suggested that those early stage HCCs with high INS levels may receive postoperative monitoring and appropriate adjuvant therapy for better clinical outcome. In addition, given apparent the superior prognostic value of the GPS/mGPS [49, 50] in the previous studies and similar data for the GPS/mGPS appeared in subgroup of early stage in our study, it is likely that inflammation scores based on CRP apparently had more accurate prognostic value in patients with resectable HCC than other scores based on the ratio of components of a white cell count including NLR, PLR, and PNI.

This study has the limitation that it is based on a single institutional and retrospective data set of patients with resectable HCC. The results identify several points for further consideration. First, whereas conventional BCLC staging has been standardised universally to aid in the clinical trials, similar should occur with regard to the systemic inflammatory response. The easy-to-use and routinely available scores, such as the INS, allow us to utilize our current understanding of the systemic inflammatory responses in patients with cancer, and has important clinical implications. However, it remains to be determined if prognostic value of a lower threshold (i.e., CRP < 10 mg/L) utilized would be more rational compared with the standardised threshold (CRP > 10 mg/L). Next, there is no widely accepted score for determining nutritional status and predicting poor-nutrition-related outcomes, with a great diversity of assessment tools available in clinical practice. To overcome this problem, because of a potential of inflammatory markers to indirectly quantify a patient's nutritional status, the combination of the components of inflammation and nutrition parameters has been proposed as a solution and is superior to any of the parameters alone (prealbumin or CRP), as confirmed in present study. Finally, the BCLC stage incorporates efficient predictors of recurrence such as tumor size, multifocality, and macroscopic vascular invasion, and has been widely validated to determine patient prognosis. While how to accurately stratify early stage (BCLC 0/A) for patients with high risk of recurrence and poor prognosis is a great challenge. Although molecular or genomic pathological biomarkers have been supposed to predict outcomes accurately, it is far from practical application. Hence, establishing novel scoring systems based on simple and available parameters in practice will aid to conventional stage systems, and is helpful for clinicians to formulate surveillance and treatment strategies.

Conclusions

Our study has demonstrated that the INS score that is based on systemic inflammatory and nutritional status can be used as an effective factor for predicting the prognosis of patients with resectable HCC, especially in early stage. The INS provides complimentary prognostic information to current BCLC staging and may also aid in future therapeutic strategies. Given that the INS is clinical feasible, this score has much to commend in future research.

Acknowledgements This work was in part supported by National Key Sci-Tech Special Project of China (Grant 2012ZX10002010-001/002), the National Natural Science Foundation of China (Grant 81302102), and the Basic Research Programs of Science and Technology Commission Foundation of Shanghai (Grants 13JC1401800, XBR2013074, and 13CG04).

Author contributions Conception/Design: X-CN, JX, and S-JQ. Provision of study material or patients: YY, Y-PF, and X-CN. Collection and/or assembly of data: Y-PF, J-LH, and X-YC. Data analysis and interpretation: GL, J-LH, WG, Y-PF, X-CN, and S-JQ. Manuscript writing: X-CN, JX, and S-JQ. Final approval of manuscript: X-CN and S-JQ.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Ethics Committee of Zhongshan Hospital.

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