Original Paper

Systemic Immune-Inflammation Index (SII) is Useful to Predict Survival Outcomes in Patients After Liver Transplantation for Hepatocellular Carcinoma within Hangzhou Criteria

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Key Words

Hepatocellular carcinoma • Systemic immune-inflammatory index • Liver transplantation

Abstract

Background: There is growing evidence that the systemic immune-inflammation index (SII), a novel prognostic biomarker based on peripheral lymphocyte, neutrophil, and platelet counts, is associated with poor prognosis for several tumors. However, the prognostic value of SII in patients with hepatocellular carcinoma (HCC) who undergo liver transplantation (LT) remains unclear. The aim of this study was to determine the correlation between SII and prognosis in these patients. **Methods:** This retrospective study involved 150 patients with HCC who underwent LT within the Hangzhou criteria. The optimal cut-off value was determined by receiver-operating characteristic (ROC) curve analysis to stratify the patients into those with a high SII and those with low SII. The Kaplan-Meier method and the Cox proportional hazards model were used to evaluate the prognostic value of SII. Finally, we calculated the area under the ROC curve to compare the prognostic power of SII, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and monocyte-to-lymphocyte ratio (MLR). **Results:** Patients were divided into high SII (≥ 226) and low SII (< 226) groups. Five-year overall survival (OS) was lower in the high SII group than in the low SII group (56.1% vs. 82.4%, $p = 0.002$). SII $\geq 226 \times 10^9/L$, maximum tumor size > 5 cm, microvascular invasion, and poor differentiation were independent prognostic factors for OS. However, SII did not predict 5-year recurrence-free survival (high vs. low SII: 64.1% vs. 78.4%, $p = 0.073$). The area under the ROC curve was

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greater for SII than for PLR, NLR, and MLR. **Conclusions:** Preoperative SII may be a powerful prognostic biomarker in patients with HCC who undergo LT within the Hangzhou criteria. SII is superior to PLR, NLR, and MLR for prediction of OS in these patients.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant neoplasm and second most common cause of tumor-related deaths worldwide [1, 2]. HCC is a heterogeneous disease with various etiologies, but chronic infection with a hepatitis virus is the major causative factor. Most cases in developing countries are associated with hepatitis B virus [3] whereas the leading cause in western countries is hepatitis C virus [4]. There are many treatments available for HCC, but liver transplantation (LT) is considered to be the radical treatment of choice, especially in patients with underlying cirrhotic liver disease [5], because it not only removes liver tumors completely but also removes the underlying cirrhotic liver. LT has proven to be the best treatment for selected patients with HCC, but how to select those patients remains controversial, especially in the face of a global organ shortage. The strict Milan criteria devised by Mazzaferro et al. [5] in 1965 have been expanded in recent decades so that more patients with HCC can benefit from LT [6-8]. The Hangzhou criteria based on a Chinese population were proposed by Zheng et al [9] in 2008 to address the fact that the main etiology of HCC in China is different from that in western countries. According to the Hangzhou criteria, candidates for LT must have (1) a total tumor size ≤ 8 cm or (2) a total tumor diameter > 8 cm with a histopathologic grade of I or II and a preoperative alpha-fetoprotein (AFP) level ≤ 400 ng/mL. In this respect, the Hangzhou criteria are similar to other criteria used to predict the prognosis of HCC patients after LT in that they enroll patients according to factors such as preoperative tumor size and degree of tumor differentiation. However, patients with HCC who meet the Hangzhou criteria often have variable outcomes. Therefore, simple, easily obtained, and dependable prognostic factors are required.

There is abundant evidence that inflammation is associated with carcinogenesis and tumor progression [10-12]. Furthermore, a growing number of studies have demonstrated that circulating immune-inflammatory cells, such as platelets, neutrophils, and lymphocytes, play a prominent role in promoting proliferation, invasion, and migration of cancer cells by changing the tumor microenvironment. These cells are thought to affect outcome in various ways, including shielding circulating tumor cells from destruction by the immune system [13], secreting cytokines and chemokines [14, 15], and inducing cytotoxic cell death [16, 17].

Much research effort has been devoted to identifying indicators based on these immune-inflammatory circulating cells that can predict prognosis in immune-mediated diseases. In the last decade, more and more evidence has emerged showing that the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) could be useful for predicting prognosis in various types of cancer, including HCC [18-20]. However, these indicators involve only two types of circulating immune-inflammatory cells and might not accurately reflect the inflammatory and immune responses in the host body. A novel indicator known as the systemic immune-inflammation index (SII) was developed recently and has been demonstrated to be an effective and powerful prognostic indicator for several types of tumors, including HCC, colorectal cancer, and small cell lung cancer [21-23]. SII differs from other indicators in that it combines peripheral lymphocyte, neutrophil, and platelet counts. This combination could have a stronger prognostic ability in some diseases. However, the relationship between preoperative SII and prognosis in patients with HCC after LT remains unclear. The aim of this study was to investigate the prognostic value of SII in patients undergoing LT for HCC within the Hangzhou criteria and to compare its prognostic ability with that of the NLR, PLR, and MLR.

Materials and Methods

Patients

This retrospective study involved patients who underwent LT at the Third Affiliated Hospital of Sun Yat-sen University (Guangdong, China) since October 2003. Handwritten and electronic medical records were screened carefully until December 2016. Patients were eligible for inclusion in the study if they met the following criteria: recipient age older than 18 years; a histopathologic diagnosis of HCC that met the Hangzhou criteria [9]; no pre-transplant radiofrequency ablation, liver resection, or transarterial chemoembolization; no pre-transplant sepsis or massive gastrointestinal hemorrhage; no history of taking hematopoietic agents within the month before LT; and availability of complete and authentic clinicopathologic and follow-up data. One hundred and fifty patients who underwent LT between October 2003 and December 2015 met these criteria and were enrolled.

Follow-up

After LT, the patients underwent regular follow-up in our outpatient clinics. A physical examination was routinely performed at all follow-up appointments. Serum AFP levels were measured and hepatobiliary ultrasonography was performed at monthly intervals in the first year and then every 3 months thereafter if no recurrence was suspected. Plain/enhanced abdominal computed tomography (CT) scans or magnetic resonance imaging was performed every 3 months in the first 2 years, and then every 6 months thereafter. An enhanced CT scan of the lung, positron emission tomography-CT scan, or a bone scan was carried out immediately when necessary if a metastasis was suspected. Overall survival (OS) was calculated from the time of LT to the date of death or last follow-up. Recurrence-free survival (RFS) was defined as the interval between LT and recurrence or last tumor evaluation/last follow-up or death. The last follow-up was performed at the end of March 2017.

Study design and data collection

We obtained neutrophil, lymphocyte, monocyte, and platelet counts from each patient's peripheral venous blood sample during the week before LT, usually in the morning before surgery. Cell counts in these morning fasting venous blood samples were measured using a fully automatic hematology analyzer. Information on other potential prognostic factors was also collected and evaluated, including demographic data (including age and sex), clinical and laboratory data obtained within the week before surgery (including AFP, albumin, and HBV DNA), preoperative imaging data (tumor size, number of tumors, and macrovascular invasion), and postoperative histopathologic data (microvascular invasion and tumor cell differentiation grade). The relevant indicators were calculated as follows: $SII = P \text{ (absolute platelet count)} \times N \text{ (absolute neutrophil count)} / L \text{ (absolute lymphocyte count)}$, $PLR = P \text{ (absolute platelet count)} / L \text{ (lymphocyte count)}$, $NLR = N \text{ (absolute neutrophil count)} / L \text{ (absolute lymphocyte count)}$, and $MLR = M \text{ (absolute monocyte count)} / L \text{ (absolute lymphocyte count)}$.

Statistical analysis

Patients' baseline characteristics are shown as the mean $\pm$ standard deviation for normally distributed continuous variables and as the median and interquartile range for non-normally distributed continuous variables. Categorical variables are reported as proportions. Receiver-operating characteristic (ROC) curves were plotted to determine the optimal cut-off values for SII, PLR, NLR, and MLR. The independent samples t-test, Pearson's chi-squared test, and Fisher's exact test were used to assess the correlations between SII and other clinicopathologic characteristics as appropriate. Univariate and multivariate Cox proportional hazards regression were used to identify independent risk factors. The survival curves were plotted using the Kaplan-Meier method and tested by the log-rank statistic. Finally, we plotted the ROC curves and calculated the area under the ROC curve to compare the discriminative ability of SII, PLR, NLR, and MLR as inflammatory indicators. A p-value < 0.05 was accepted to be statistically significant. All p-values were based on two-sided testing. The statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY), GraphPad Prism version 5.0 (GraphPad Software, La Jolla, CA), and MedCalc version 13.0 (Mariakerke, Belgium).

Ethics

The study was approved by the Institutional Review Board of the Third Affiliated Hospital of Sun Yat-sen University and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Results

Patient demographics and outcomes

The 150 patients in the study were 8 (5.3%) women and 142 (94.7%) men (Table 1). Median age was 51.0 (interquartile range 45.0–59.0) years. During a median follow-up of 41 months, 39 patients died and 37 were confirmed to have a tumor recurrence. The 1-, 3- and 5-year OS rates were 89.9%, 76.6%, and 69.9%, respectively; the 1-, 3- and 5-year RFS rates were 86.1%, 75.0%, and 71.6%, respectively.

Comparison of variables when patients were stratified by SII

We plotted a ROC curve to determine the optimal cut-off SII for predicting survival after LT for HCC (Fig. 1). The area under the ROC curve was 0.632 and the Youden index was highest when SII was $226 \times 10^9/L$; the sensitivity and specificity were 69.2% and 58.6%, respectively. Therefore, we divided the patients into a high SII group ($\geq 226 \times 10^9/L$, $n = 73$) and a low SII group ($< 226 \times 10^9/L$, $n = 77$). Demographic and clinicopathologic characteristics were compared between the two groups. Patients with high SII were more likely to have larger tumor size ($p = 0.043$), greater total tumor volume ($p=0.034$), higher AFP level ($p = 0.047$), and poor differentiation ($p = 0.040$). No significant differences in the other variables were found between the groups (Table 2).

Table 1. Baseline Characteristics in HCC patients

Characteristic	Values
Gender	
Male	142(94.7%)
Female	8(5.3%)
Age(years)	51.0(45.0-59.0)
Child-Pugh Class	
A	81(54.0%)
B	48(32.0%)
C	21(14.0%)
HBsAg	
Positive	139(92.7%)
Negative	11(7.3%)
Tumor No. (n)	1(1-2)
Largest Tumor Size(cm)	3.1(2.3-4.8)
Total Tumor Size(cm)	4.2(3.0-6.1)
TTV(cm^3)	18.8(7.9-65.4)
AFP(ng/ml)	37.1(5.9-269.0)
MVI	
Positive	24(16.0%)
Negative	126(84.0%)
Differentiation	
Well	31(20.7%)
Moderate/Poor	119(79.3%)
Neutrophil($10^9/L$)	2.49(1.67-3.61)
Lymphocyte($10^9/L$)	1.03(0.73-1.44)
Monocyte($10^9/L$)	0.34(0.23-0.50)
Platelet($10^9/L$)	92.0(54.8-151.3)
SII	210.1(109.7-427.0)
PLR	86.2(58.8-124.0)
NLR	2.26(1.40-3.79)
MLR	0.34(0.21-0.53)

Fig. 1. ROC curve for the SII values to predict HCC survival after LT within Hangzhou Criteria.

Table 2. The relationship between SII and clinical characteristics in HCC patients. HCC: hepatocellular carcinoma; SII:immune-inflammation index; TTV: total tumor volume; AFP: α -fetoprotein; MVI: micro-vascular invasion

Variables	SII<226(n=77)	SII $\geq$ 226(n=73)	t or χ^2 or Z	P value
Gender(Male)	75(97.4%)	67(91.8%)	1.364	0.243
Age, yr (mean)	51.38	51.01	0.222	0.824
Child-Pugh Class			-1.953	0.051
A	35(45.5%)	46(63.0%)		
B	30(39.0%)	18(24.7%)		
C	12(15.6%)	9(12.3%)		
HBsAg(+)	74(96.1%)	65(89.0%)	2.751	0.097
Tumor No. (n>3)	6(7.8%)	2(2.7%)	1.026	0.311
Largest Tumor Size(>5cm)	10(13.0%)	19(26.0%)	4.086	0.043*
Total Tumor Size(>7cm)	11(14.3%)	16(21.9%)	1.479	0.224
TTV(>20 cm^3)	32(41.6%)	43(58.9%)	4.510	0.034*
AFP($\geq$ 400)	11(14.3%)	20(27.4%)	3.929	0.047*
MVI(+)	14(18.2%)	10(13.7%)	0.560	0.454
Differentiation(M/P)	56(72.7%)	63(86.3%)	4.211	0.040*

OS and RFS in patients according to SII

The 1-, 3-, and 5-year OS rates were significantly lower in the high SII group (83.4%, 68.1%, and 56.1%, respectively) than in the low SII group (92.0%, 84.7%, and 82.4%, respectively; $p = 0.002$). There were no significant differences in RFS rates between the two groups ($p = 0.073$); the 1-, 3-, and 5-year RFS rates were respectively 81.2%, 69%, and 64.1% in the high SII group and 90.6%, 80.4%, and 78.4% in the low SII group. We also determined the cut-off values for PLR, NLR, and MLR using the same method (137, 2.64, and 0.27, respectively). Finally, OS curves were plotted by the Kaplan-Meier method and compared using the log-rank test. High PLR, NLR, and MLR scores were also associated with poor OS ($p = 0.017$, $p = 0.036$, and $p = 0.026$, respectively; Fig. 2A–2D).

Fig. 2. Kaplan-Meier survival curves for patients classified by (A) SII, (B) NLR, (C) PLR and (D) MLR.

Table 3. Univariate and multivariate analyses of OS in HCC patients. ^aThe variables (AFP, Largest Tumor Size, Total Tumor Size, TTV, Differentiation, MVI and SII) were tested in a multivariate analysis. ^bThe variables (AFP, Largest Tumor Size, Total Tumor Size, TTV, Differentiation, MVI and PLR) were tested in a multivariate analysis. ^cThe variables (AFP, Largest Tumor Size, Total Tumor Size, TTV, Differentiation, MVI and NLR) were tested in a multivariate analysis. ^dThe variables (AFP, Largest Tumor Size, Total Tumor Size, TTV, Differentiation, MVI and MLR) were tested in a multivariate analysis

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Gender(M/F)	0.045	0-14.027	0.290			-
Age,yr(≥60/<60)	0.878	0.387-1.989	0.754			-
HBsAg(P/N)	0.448	0.175-1.147	0.085			-
Child-Pugh Class(A/B/C)	0.793	0.504-1.249	0.317			-
AFP(<400/≥400)	3.252	1.708-6.192	<0.001*	1.594	0.767-3.312	0.217
Tumor No. (≤3/>3)	1.309	0.402-4.255	0.654			-
Largest Tumor Size(>5cm)	2.916	1.488-5.712	0.002*	2.821	1.391-5.720	0.004*
Total Tumor Size(>7cm)	2.090	1.058-4.126	0.034*	1.064	0.464-2.440	0.802
TTV(>20cm ³)	3.670	1.785-7.545	<0.001*	1.976	0.849-4.597	0.087
Differentiation(W/M/P)	11.593	1.591-84.453	0.016*	8.391	1.145-61.515	0.036*
MVI	4.117	2.101-8.067	<0.001*	5.113	2.526-10.351	<0.001*
SII(≥226)	2.801	1.416-5.540	0.003*	2.538	1.276-5.046	0.008*a
PLR(≥137)	2.203	1.131-4.291	0.020*	1.592	0.791-3.203	0.213 ^b
NLR(≥2.64)	1.943	1.030-3.665	0.040*	1.776	0.909-3.470	0.063 ^c
MLR(≥0.27)	2.349	1.079-5.112	0.031*	1.604	0.710-3.624	0.182 ^d

Univariate and multivariate survival analyses

Univariate analysis revealed largest tumor size, total tumor size, microvascular invasion, AFP level, tumor cell differentiation, total tumor volume, SII, PLR, NLR, and MLR to be significant prognostic factors for OS. To avoid multicollinearity, we conducted multivariate analysis using four models separately. Each multivariate model included only one immune-inflammatory indicator (SII, PLR, NLR, or MLR) or other significant predictor identified in

Fig. 3. Predictive effect of the SII (categorical) was compared with PLR (categorical), NLR (categorical) and MLR (categorical) by ROC curves in 3-years (A) and 5-years (B) survival. Predictive effect of the SII (continuous) was compared with PLR (continuous), NLR (continuous) and MLR (continuous) by ROC curves in 3-years (C) and 5-years (D) survival.

univariate analysis. After multivariate analysis, SII $\geq 226 \times 10^9/L$ (hazard ratio [HR] 2.538, 95% confidence interval [CI] 1.276–5.046; $p = 0.008$), microvascular invasion (HR 5.113, 95% CI 2.526–10.351; $p < 0.001$), poor tumor cell differentiation (HR 8.391, 95% CI 1.145–61.515; $p = 0.036$), and maximum tumor size > 5 cm (HR 2.821, 95% CI 1.391–5.720; $p = 0.002$) were revealed to be independent predictors of OS after LT in patients with HCC, but PLR, NLR, and MLR were not ($p = 0.213$, $p = 0.063$, and $p = 0.182$, respectively; Table 3). We also performed univariate and multivariate survival analyses for RFS and did not identify any immune-inflammatory indicator as an independent predictor of RFS.

Comparison of prognostic significance of SII, NLR, PLR, and MLR

ROC curve analysis was performed after 3 and 5 years of follow-up. The discriminative ability of SII, PLR, NLR, and MLR were compared using the area under the ROC curve. At the 3-year follow-up, of all the factors tested, SII had the largest area under the ROC curve (Fig. 3). Furthermore, at the 5-year follow-up, the area under the ROC curve for SII was still higher than those for PLR, NLR, and MLR for predicting survival (Fig. 3A, 3B). Similar results were found when SII was treated as a continuous variable (Fig. 3C, 3D), indicating that SII was better than NLR, PLR and MLR for predicting OS in HCC patients after LT.

Discussion

To our knowledge, no previous study has investigated the predictive value of SII after LT in patients with HCC. This study is the first to demonstrate an association between SII and clinical outcomes in these patients and provides a new option for predicting their prognosis and for selecting appropriate recipients for LT. As mentioned earlier, SII is widely accepted to be useful for predicting the prognosis of several types of cancer [21–23], but the optimal cut-off values for SII remain controversial. However, it is known that these values may be treatment-dependent even in patients with the same disease. For example, SII $> 330 \times 10^9/L$ was reported to be associated with poorer prognosis after curative resection of HCC [21], whereas Casadei et al. [24] found that SII of $360 \times 10^9/L$ was the optimal cut-off value in patients with advanced HCC receiving sorafenib. ROC curve analysis in the present study identified the optimal cut-off value for SII as $230 \times 10^9/L$ after LT in patients with HCC. The patients were then grouped according to whether they had a high SII or a low SII. Our results showed that a higher preoperative SII ($\geq 226 \times 10^9/L$) was associated with larger tumor size, a higher AFP level, and poor pathologic differentiation. We demonstrated that SII was an independent prognostic factor for OS and RFS in patients who underwent LT for HCC.

We also concluded that SII was a more powerful prognostic indicator than other systemic inflammatory indicators, such as PLR and NLR. Given that it is inexpensive, is easily obtained, and has good predictive accuracy, SII could be a promising biomarker for predicting the prognosis in patients after LT for HCC within the Hangzhou criteria.

Although SII was demonstrated to be correlated with prognosis of HCC patients after LT, the mechanism has not been elucidated. The reason might be that SII predicts prognosis from levels of inflammatory and immune response markers in the host. A higher SII indicates relative hyperthrombocytopenia, neutrophilia, and lymphopenia, and an imbalance of neutrophils, platelets, and lymphocytes leads to disorders in the host's immune system. Vascular endothelial growth factor (VEGF) plays an important role in angiogenesis and tumor progression [25] and can be secreted by both neutrophils and platelets. Elevated levels of VEGF promote tumor progression. Furthermore, lymphocytes are important immune cells that are considered to promote tumor control by secreting cytokines and inducing cytotoxic cell death [26]. A decreased lymphocyte level will impair the host's immunity and encourage tumor progression. Several studies have demonstrated that tumors are usually infiltrated by various lymphocytes, and tumor-infiltrating lymphocyte levels correlate with the progression and aggressiveness of a tumor [27-29]. There were strong links between circulating lymphocytes and tumor-infiltrating lymphocytes. Targeted agents that regulate inflammation and immunity may improve the prognosis of patients with immune-mediated diseases. Aspirin was demonstrated to be helpful in protecting patients with chronic hepatitis from HCC [30] and could also be effective as secondary prevention in patients with colorectal cancer [31]. Thymosin has shown antitumor effects via enhancement of the Th1 immune response [32]. In the future, HCC patients might also benefit from drugs that target inflammation and immunity.

This study has several limitations. First, SII may be affected by many factors, including unidentified acute infection and gastrointestinal hemorrhage. Second, the majority of patients enrolled in this study had a background of hepatitis B infection, while hepatitis C virus-associated HCC is more common in western countries. It should be noted that SII is a dynamic index that changes during the course of a disease, and changes in SII during the treatment course may provide more information about the host's inflammatory and immune response status. Therefore, further study is needed to observe the dynamic changes in SII before and after LT. Furthermore, SII may have a role in mediating cytokines, so detecting cytokine levels in the patient's blood or tissues may help to reveal the possible mechanism. Subsequent studies should focus on the relationship between the patient's cytokine levels and the prognosis. Finally, this study had a retrospective design and included a relatively small number of patients. Further prospective studies in larger samples are needed to verify the prognostic value of SII in HCC patients after LT.

In conclusion, the results of this study indicate that patients with HCC meeting the Hangzhou criteria and an elevated preoperative SII have poorer OS after LT. Because of its attributes of comprehensiveness, simplicity, easy determination, and low cost, SII appears to be a promising tool for assessing prognosis after LT in patients with HCC who meet the Hangzhou criteria.

Abbreviations

OS (overall survival); HCC (hepatocellular carcinoma); TTV (total tumor volume); AFP (α -fetoprotein); MVI (micro-vascular invasion); SII (immune-inflammation index); PLR (platelet lymphocyte ratio); NLR (neutrophil lymphocyte ratio); MLR (monocyte lymphocyte ratio).

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Disclosure Statement

The authors who have been engaged in this clinical research declared that they did not have any conflict of interests.

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