Systemic Immune-Inflammation Index Predicts Prognosis of Patients after Curative Resection for Hepatocellular Carcinoma

Bo Hu1, Xin-Rong Yang1, Yang Xu1, Yun-Fan Sun1, Chao Sun1, Wei Guo1,2, Xin Zhang1, Wei-Min Wang1, Shuang-Jian Qiu1, Jian Zhou1,3, and Jia Fan1,3

Abstract

Purpose: We developed a novel systemic immune-inflammation index (SII) based on lymphocyte, neutrophil, and platelet counts and explored its prognostic value in hepatocellular carcinoma (HCC).

Experimental Design: The SII was developed based on a retrospective study of 133 patients with HCC undergoing resection between 2005 and 2006, and validated in a prospective study of 123 patients enrolled from 2010 to 2011. The circulating tumor cell (CTC) level in the validation cohort was measured using the CellSearch system. Prediction accuracy was evaluated with area under the receiver operating characteristic curve (AUC).

Results: An optimal cutoff point for the SII of $330 \times 10^3$ stratified the patients with HCC into high ($\geq 330$) and low SII (<$330$) groups in the training cohort. Univariate and multivariate analyses revealed the SII was an independent predictor for overall survival and relapse-free survival, and prognostic for patients with negative $\alpha$-fetoprotein and Barcelona Clinic Liver Cancer stage 0+A. The AUCs of the SII for survival and recurrence were higher than other conventional clinical indices. An SII $\geq 330$ was significantly associated with vascular invasion, large tumors, and early recurrence. CTC levels were significantly higher in the SII $\geq 330$ group ($1.71 \pm 0.34$ vs. $4.37 \pm 1.04$, $P = 0.029$). In patients with detectable CTCs, those with SII $\geq 330$ had higher recurrence rates and shorter survival time than patients with SII $< 330$.

Conclusion: The SII was a powerful prognostic indicator of poor outcome in patients with HCC and is a promising tool for HCC treatment strategy decisions. The dismal outcome in patients with high SII scores might be related to higher CTC levels. Clin Cancer Res; 20(23); 6212–22. ©2014 AACR.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and has the third highest mortality rate in the world (1, 2). Currently, surgery remains the main treatment for patients with HCC. However, in spite of “curative” resection, approximate 60% to 70% patients experience recurrence or distant metastasis within 5 years (3). Therefore, it is important to identify patient subpopulations with a high risk of recurrence and metastasis to optimize postoperative rational adjuvant treatments and provide these treatments to at-risk subpopulations without delay.

The reasons for the high recurrence/metastasis rate in HCC are complex and multifactorial. Hematogenous spread is an important cause of recurrence and metastasis in HCC, and circulating tumor cells (CTC) in the bloodstream play an important role in HCC metastasis (4, 5). In addition to the tumor cells, immune and inflammatory cells such as neutrophils, platelets, and lymphocytes also contribute to tumor cell invasion into the peripheral blood, where the tumor cells can survive and reseed distant organs (6).

Several studies have shown that platelets can protect CTCs from shear stresses during circulation, induce CTC epithelial–mesenchymal transition, and promote tumor cell extravasation to metastatic sites (7–10). Neutrophils can promote adhesion and seeding of distant organ sites through secretion of circulating growth factors such as VEGF and proteases (11–15). Lymphocytes play a crucial role in tumor defense by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration (16), thereby dictating the host immune response to malignancy (12). In consideration of these factors, several inflammation and immune-based prognostic scores have been developed to...
predict survival and recurrence, such as lymphocyte count, neutrophil–lymphocyte ratio (NLR), and platelet–lymphocyte ratio (PLR; refs. 17–19); however, an integrated indicator based on peripheral lymphocyte, neutrophil, and platelet counts, which might be better able to reflect the balance of host inflammatory and immune status, has not yet been reported in HCC. Moreover, the potential effects of peripheral lymphocytes, neutrophils, and platelets on HCC recurrence and metastasis have not been elaborated.

In this study, a novel index, defined as the systemic immune-inflammation index (SII), based on lymphocyte, neutrophil, and platelet counts, was developed. The prognostic value of the SII in patients with HCC who underwent surgery was evaluated in two independent cohorts. The correlation between the SII and CTC levels was also explored. We found that the SII was a promising independent predictive factor for prognosis of patients with HCC after surgery and that the high recurrence rate in patients with high SII scores might be due to increased release of CTCs from tumor sites.

**Patients and Methods**

**Patients and specimens**

A retrospective study was conducted in a primary cohort of patients with HCC who underwent curative resection in our institute from 2005 to 2006 (n = 133). From July 2010 to June 2011, a validation cohort of patients with HCC (n = 123) undergoing resection was prospectively recruited, which was reported previously (5). The inclusion and exclusion criteria were the same as those previously described (20). Tumor stage was determined according to the Barcelona Clinic Liver Cancer (BCLC) stage (21). Tumor differentiation was graded by the Edmondson grading system (22). Liver function was assessed by the Child–Pugh scoring system. The blood sample (7.5 mL) used for CellSearch analysis was collected two days before resection as described in our previous report (5). A second blood sample (2 mL) for platelet, neutrophil, and lymphocyte counts was obtained at the same time and detected in laboratory department. Ethical approval for the use of human subjects was obtained from the Zhongshan Hospital Research Ethics Committee, and informed consent was obtained from all patients. The comparative baseline clinical characteristics of patients in both training and validation cohorts are described in Table 1.

**Follow-up and treatment for tumor recurrences**

Postoperative patient surveillance was performed as described previously (23). Patients were followed up every 2 months during the first postoperative year, and then every 3 to 4 months. All patients were prospectively monitored by serum a-fetoprotein (AFP), abdomen ultrasonography, and chest X-ray with an interval of 1 to 6 months depending on the postoperative time. A computed tomography scan of the abdomen was performed every 6 months. Bone scan or magnetic resonance imaging was done if localized bone pain was reported. If recurrence was suspected, a computed tomography scan or magnetic resonance imaging was done immediately. Most of death causes were recurrence, metastasis, or complicated liver cirrhosis. Patients with confirmed recurrence received further treatment, which followed a set protocol based on the size, site, number of tumor nodules, and liver function. Briefly, if the recurrent tumor was localized, a second liver resection, radiofrequency ablation, or percutaneous ethanol injection was suggested. If the recurrent tumor was multiple or diffused, transcatheter arterial chemoembolization was administered. External radiotherapy was given if lymph node or bone metastasis was found. Otherwise, symptomatic treatment was provided. Follow-up was terminated on February 7, 2012, in the training cohort and on November 1, 2013, in the validation cohort. Time to recurrence (TTR) and overall survival (OS) were defined as the interval between the surgery and recurrence or death, respectively. Using 12 months as the cutoff value, all recurrences were divided into early recurrence and late recurrence.

**Systemic immune-inflammation index**

The SII was defined as follows: SII = P × N/L, where P, N, and L were the preoperative peripheral platelet, neutrophil, and lymphocyte counts, respectively.

The X-tile 3.6.1 software (Yale University, New Haven, CT) was used for bioinformatic analysis of the training cohort data to determine the cutoff value of SII for tumor recurrence (24). Results from X-Tile analysis revealed an optimal cutoff point for the SII at 330 × 10^9 in the training cohort (Supplementary Fig. S1). Subsequently, the SII scores were stratified into <330 × 10^9 or ≥330 × 10^9 for all subsequent analyses.
Detection of CTCs

Epithelial cell adhesion molecule-positive (EpCAM+) CTC analysis was performed before resection using the CellSearch (Veridex) method, without knowledge of patient clinical characteristics (25). Briefly, the semiautomated CellSearch platform (Janssen Diagnostics) enriches the sample for cells expressing EpCAM with ferromagnetic beads. Fluorescently labeled monoclonal antibodies specific for cytokeratins and leukocyte (CD45) are used to distinguish epithelial cells from leukocytes. The identification and enumeration of CTCs were performed with the use of the CellSpotter Analyzer. The CTC results were expressed as the number of cells per 7.5 mL of blood.

Statistical analysis

Statistical analyses were performed using IBM SPSS 19.0 software (SPSS). Continuous variables were summarized as the median and range or the mean ± SEM. The cumulative

Table 1. The clinicopathologic characteristics of patients in the training and validation cohorts

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Abbreviation: HBsAg, hepatitis B surface antigen.

aFisher exact test.

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**Detection of CTCs**

Epithelial cell adhesion molecule-positive (EpCAM+) CTC analysis was performed before resection using the CellSearch (Veridex) method, without knowledge of patient clinical characteristics (25). Briefly, the semiautomated CellSearch platform (Janssen Diagnostics) enriches the sample for cells expressing EpCAM with ferromagnetic beads. Fluorescently labeled monoclonal antibodies specific for cytokeratins and leukocyte (CD45) are used to distinguish epithelial cells from leukocytes. The identification and enumeration of CTCs were performed with the use of the CellSpotter Analyzer. The CTC results were expressed as the number of cells per 7.5 mL of blood.

**Statistical analysis**

Statistical analyses were performed using IBM SPSS 19.0 software (SPSS). Continuous variables were summarized as the median and range or the mean ± SEM. The cumulative
recurrence and survival rates were calculated using the Kaplan–Meier method, and the differences between the groups were assessed by the log-rank test. Univariate and multivariate analyses were calculated by the Cox proportional hazards regression model. The Student t test, Pearson χ² test, and the Fisher exact test were used to compare groups. The Pearson χ² test or Fisher exact test was used to compare qualitative variables; and quantitative variables were analyzed by the Pearson correlation test. Receiver operating characteristics (ROC) curves were used to define sensitivity, specificity, and the differences in the area under the curves (AUC) were detected using MedCalc version 13.0 (MedCalc Software). A P value <0.05 was considered statistically significant.

Results

Patient characteristics

The clinicopathologic characteristics of patients are shown in Table 1. In the training cohort, OS and recurrence rates were 87.2% and 26.3% at 1 year, 63.2% and 36.1% at 3 years, and 53.4% and 49.6% at 5 years, respectively. There were 71 (53.4%) patients confirmed dead and 70 (52.6%) patients confirmed with tumor recurrence at last follow-up. The mean age of the patients was 64.1 years (range, 32.0–150). Patients confirmed with tumor recurrence at last follow-up, with a median follow-up time of 28.8 months (range, 1.0–39.5), and 98 patients were still alive at a median follow-up of 30.4 months (range, 2.0–86.0). The median follow-up period was 61.3 months (range, 2.0–86.4).

In the validation cohort, 58 of 123 patients presented with tumor recurrence at the final follow-up, with a median follow-up time of 28.8 months (range, 1.0–39.5), and 98 patients were still alive at a median follow-up of 30.4 months (range, 2.0–86.0). SII ≥ 330 was present in 39.9% (53/133) of patients in the training cohort and 33.3% (41/123) of patients in the validation cohort (Supplementary Table S1). The clinicopathologic characteristics were similar between the two cohorts, with the exception of gender and BCLC stage. The validation cohort included more males, and patients in the training cohort had a more advanced BCLC stage (Supplementary Table S1).

The prognostic significance of SII in the training cohort

Results from our univariate analysis indicated that AFP level, tumor encapsulation, tumor differentiation, tumor size, vascular invasion, BCLC stage, NLR, PLR, and SII were prognostic factors for OS and/or TTR in the training cohort (Table 2), whereas age, gender, cirrhosis, Child–Pugh score, hepatitis history, alanine aminotransferase (ALT) level, and tumor number had no prognostic significance for OS and TTR. A low SII score was significantly associated with both prolonged TTR [HR, 2.78; 95% confidence interval (CI), 1.72–4.48; P < 0.001] and OS (HR, 2.62; 95% CI, 1.63–4.20; P < 0.001).

The Kaplan–Meier analysis indicated that the high SII, NLR, and PLR scores were all associated with shorter OS (P < 0.0001, P = 0.001, and P = 0.010, respectively) and TTR (P < 0.0001, P = 0.001, and P = 0.022, respectively; Fig. 1A; Supplementary Fig. S2A and S2B). The median TTR and OS were 61.3 and 63.3 months for patients with SII < 330 and 26.4 and 37.3 months for patients with SII ≥ 330, respectively. In addition, patients with an NLR < 5 had a median OS and TTR of 62.4 and 51.7 months, respectively, whereas patients with an NLR ≥ 5 had a median OS and TTR of 34.5 and 30.4 months, respectively. Patients with a PLR < 150 had a median OS and TTR of 61.3 and 47.1 months, respectively, compared with 55.2 and 47.1 months, respectively, for the patients with a PLR ≥ 150.

On the basis of our multivariate analysis, the SII was an independent prognostic factor for both TTR (HR, 1.92; 95% CI, 1.04–3.54; P = 0.037) and OS (HR, 2.10; 95% CI, 1.14–3.85; P = 0.017; Table 3). The discrimination ability of inflammation-based prognostic scores and clinical indices was compared by the AUC for OS and TTR (Fig. 1C; Supplementary Fig. S2C). The AUC for the SII was 0.66 (95% CI, 0.57–0.76) and 0.68 (95% CI, 0.59–0.77), which was the strongest factor among indices (NLR, PLR, tumor number, size, encapsulation, differentiation, vascular invasion, AFP, and BCLC stage) for predicting survival and recurrence in patients with HCC.

Validation of the SII in an independent cohort

The prognostic value of the SII score was further confirmed in an independent validation cohort of 123 patients. The results were similar to those obtained from the training cohort (Fig. 1B). The SII but not PLR remained associated with shorter OS (P = 0.003 and P = 0.184, respectively) and TTR (P < 0.0001 and P = 0.215, respectively; Fig. 1B; Supplementary Fig. S3B). The NLR also significantly correlated with TTR (P = 0.007; Supplementary Fig. S3A). Univariate and multivariate analyses demonstrated that the SII correlated was significantly prognostic OS (HR, 2.56; 95% CI, 1.17–5.76; P = 0.019) and TTR (HR, 2.32; 95% CI, 1.28–4.23; P = 0.006; Tables 2 and 3). The discrimination ability of the SII, as assessed by AUC, was 0.66 (95% CI, 0.53–0.78) and 0.67 (95% CI, 0.58–0.78) for OS and TTR (Fig. 1D) respectively, which was higher than other clinical indexes (Supplementary Fig. S2D).

Association of the SII with clinicopathologic parameters

In the training cohort, we found that patients with an SII ≥ 330 were more likely to have liver cirrhosis (P = 0.006), large tumor size (P < 0.001), presence of vascular invasion (P = 0.020), high BCLC stage (P = 0.002), and early recurrence (P = 0.015; Supplementary Table S1). NLR ≥ 5 was associated with elevated ALT (P = 0.047); PLR ≥ 150 was associated with liver cirrhosis (P = 0.001) and tumor size (P = 0.009; Supplementary Table S2).

The relationship between the scores and clinicopathologic parameters for the validation cohort is shown in Supplementary Tables S1 and S2. An SII ≥ 330 was associated with liver cirrhosis (P = 0.016), poor tumor differentiation (P = 0.021), tumor size > 5 cm (P < 0.001), and early recurrence (P < 0.001). NLR ≥ 5 was associated with tumor size > 5 cm (P = 0.038) and vascular invasion (P = 0.009). PLR ≥ 150 was associated with tumor size > 5 cm (P = 0.021).
The correlation between the SII and CTCs and its prognostic significance in patients with HCC who had CTCs

The correlation between perioperative SII score and CTC level was further investigated. Scatter plot analyses revealed a significant positive correlation between the SII and CTC level ($r = 0.306; P = 0.001$, Fig. 3A). The level of CTCs was significantly higher in patients in the SII $\geq 330$ group than those in the SII $< 330$ group (1.71 vs. 0.34 vs. 4.37 vs. 1.04; $P = 0.029$, Fig. 3B).
Figure 1. Prognostic significance of SII in patients with HCC undergoing resection. The Kaplan-Meier analysis of OS and TTR for the SII in the training (A) and validation (B) cohorts. Predictive ability of the SII was compared with other clinical parameters by ROC curves in the training (C) and validation (D) cohorts.
In light of the close relationship between CTCs and the SII, we further explored the prognostic significance of the SII in subgroups of patients presenting with CTCs. In patients with detectable CTCs, patients with an SII ≥ 330 had higher recurrence rates (78.1% vs. 36.0%; P < 0.001) and a shorter TTR (median, 3.6 months vs. not reached; P < 0.001) compared with patients with SII < 330 (Fig. 3C). In terms of OS, we found that the OS rates were significantly lower in the SII ≥ 330 group than in the SII < 330 group (65.6% vs. 84.0%; P = 0.033, Fig. 3D).

Discussion

Several studies have shown the prognostic significance of NLR, PLR, and percentage of lymphocytes in postsurgery patients with HCC (26–28). In the present study, a novel immune-inflammation–based prognostic score (SII) was constructed based on lymphocyte, neutrophil, and platelet counts and was shown to be an independent predictor of recurrence and survival for patients with HCC after surgery in two independent cohorts. Its prediction ability was shown to be higher than that of the NLR, PLR, and other conventional parameters such as BCLC staging, tumor differentiation, and tumor number (Fig. 1C and D). Meanwhile, the measure of SII is based on standard laboratory measurements of total platelet, neutrophil, and lymphocyte counts, which are routinely performed in the clinical setting. Thus, there is a potential for the SII to be used as a marker for tumor recurrence and treatment response surveillance, which might provide a powerful test enabling accurate and early decision making to tailor the most effective therapy according to characteristics of individual tumors.

As an integrated indicator based on peripheral lymphocyte, neutrophil, and platelets counts, the predictive value of the SII for tumor recurrence and metastasis might be elucidated by the function of the three kinds of cells, and their close relationship with CTCs, which play an important role in the initiation of recurrence and metastases after surgery (29–31). The patients with an elevated preoperative SII usually have thrombocytopenia, neutrophilia, or lymphopenia, suggesting an elevated inflammatory status and weak immune response in patients. Recent evidence indicates that neutrophils can enhance cancer cell invasion, proliferation, and metastasis as well as assist cancer cells with evading immune surveillance (16, 32). Platelets could interact with tumor cells and facilitate tumor cell survival and metastasis via different mechanisms (8, 9). Activated T cells and other lymphocytes play a fundamental role in cell-mediated immunologic destruction of host cancer cells. Meanwhile, elevated levels of cytokines released by lymphocytes, such as IFN-γ and TNF-α, that promote tumor control have been associated with an improved prognosis for patients with many different cancers. All of these might cause more tumor cells disseminating into the circulation, escaping immune surveillance, and finally increasing the peripheral CTC level. When analyzed only the subgroup of patients with detectable CTCs, patients with an SII ≥ 330 had a higher recurrence rate (78.1% vs. 36.0%, P <
and a shorter TTR (median, 3.6 months vs. not reached, \( P < 0.001 \)) than patients with an SII < 330. This suggests that CTCs are unable to complete vascular transport and reseed without assistance from immune and inflammatory cells. In addition, we also found that an elevated SII was associated with vascular invasion, early recurrence, and a larger tumor size, indicating a more aggressive phenotype (4, 33). Subsequently, more CTCs might migrate into the bloodstream and ultimately colonize distant tissues.

These results parallel the well-established association between cancer and host immune and inflammation environments and lend support through clinical evidence. These results suggest the SII could be a more objective marker that reflects the balance between host inflammatory and immune response status than indexes such as the PLR and NLR.
bogger understanding of the role of neutrophils, platelets, and lymphocytes in cancer will help elucidate the association between cancer, immunity, and inflammation. Furthermore, patients with HCC who have a high SII might benefit from targeted antiinflammatory and immunotherapy after surgery with agents such as aspirin and thymosin (34, 35).

In clinical practice, it is difficult to predict which individuals will have tumor relapse after surgical treatment for early-stage HCC, such as BCLC 0+ A stage patients. When we stratified the patient cohort according to BCLC stage, we found that the prognostic significance of the SII was still strong in BCLC 0+ A stage patients with HCC (Fig. 2C and D). To date, AFP is still the most widely used marker for HCC diagnosis and management. However, there has been no ideal tumor marker to provide information about the prognosis and treatment of the 30% to 40% of patients with HCC who had normal serum AFP after surgery. When we further explored the predictive prognostic potential of the SII in the normal AFP group, we found that patients can be stratified according to SII status into two groups with substantially different 5-year TTR (29.0% vs. 57.1%; \( P = 0.033 \)). Taken together, our data indicate that the SII may be a powerful prognostic marker for HCC, especially for patients with early-stage disease and normal AFP as well as those whose prognoses are very difficult to predict by conventional clinical indexes (36). The predictive significance of the SII in those subgroups should help clinicians identify patients at high risk of recurrence and enable targeted rational adjuvant therapy after surgery.

There are a few limitations of this study. It should be noted that most patients with HCC in China have a hepatitis B virus–positive background (85.9% of our study population was hepatitis B virus–positive), which differs greatly from the patient population in previous studies in the United States, Europe, and Japan. Therefore, the prognostic significance of the SII needs to be validated in patients with HCC from those geographic areas. Second, because C-reactive protein (CRP) is not routinely measured in our daily practice, we did not compare our data with the predictive performance of CRP. Routine examination of blood requires less than a 100 \( \mu L \) blood sample, which is an easy technique and requires no pretreatment, in contrast with the requirements for CRP testing. On the basis of EpCAM and cytokeratin expression, CellSearch system might fail to capture some CTC subsets, such as CTCs undergoing EMT or without EpCAM expression, which might cause underestimation of the CTC level and result in the moderate correlation (\( r = 0.306 \)) between SII score and CTC level. Thus, to explore a novel CTC detection platform, using marker-independent enrichment method and multimarker approach for CTC detection will improve the sensitivity of CTC detection, and be helpful to clarify the true relationship between SII score and CTC level (37).

To our knowledge, this is the first report to demonstrate the prognostic value of the SII for patients with HCC after surgery in two independent cohorts. Our results confirmed that the SII qualifies as a novel, independent prognostic predictor of patients after curative resection for HCC. The high recurrence rate in patients with high SII scores may be related to the increased level of CTCs in the bloodstream along with reduced CTC clearance. The low cost, easy
determination, and reproducibility of a full blood count make the SII a promising tool for assessing HCC prognosis in future clinical practice.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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