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Systemic immune-inflammation index predicts postoperative acute kidney injury in hepatocellular carcinoma patients after hepatectomy

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Abstract

The systemic immune-inflammation index (SII) is an independent prognostic predictor of hepatocellular carcinoma (HCC). The present investigation examined whether an association exists between preoperative SII value and postoperative acute kidney injury (pAKI) in HCC patients.

The study included 479 hepatitis B virus (HBV)-associated HCC patients undergoing hepatectomy. The SII was calculated as P × N/L, where P, N, and L represent the counts of platelets, neutrophils, and lymphocytes in routine blood test, respectively. After propensity score matching, logistic regression analysis was used to explore independent predictors of pAKI in HCC patients.

pAKI was confirmed in 51 patients (10.8%). The average SII value was higher in patients with pAKI than patients without pAKI. After multivariate logistic regression analysis, SII, history of hypertension, and tumor size, among others, were found to be predictors of pAKI. The optimal threshold value of SII for predicting pAKI was found to be 547.84 × 109/L. Multivariate analysis performed after propensity score matching confirmed that SII ≥ 547.84 × 109/L was an independent predictor of pAKI.

The preoperative SII qualifies as a novel, independent predictor of pAKI in HCC patients with HBV infection who underwent hepatectomy.

Abbreviations: AFP = α-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinical Liver Cancer, CLIP = The Cancer of the Liver Italian Group Score, CT = computed tomography, CTP = Child-Turcotte-Pugh classification, GGT = γ-glutamyltransferase, Hb = hemoglobin, HBV = hepatitis B virus, HBV DNA = serum HBV DNA levels, HCC = hepatocellular carcinoma, KDIGO = Kidney Disease Improving Global Outcomes, MRI = magnetic resonance imaging, pAKI = postoperative acute renal injury, PLT = platelet, SII = systemic immune-inflammation index, TB = total bilirubin.

Keywords: hepatocellular carcinoma, postoperative acute kidney injury, propensity score matching, systemic immune-inflammation index

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most frequent type of carcinoma worldwide, and its mortality rate ranks third globally.[1,2] At present, surgery-based comprehensive treatment is still the primary therapeutic option for HCC patients. Postoperative acute renal injury (pAKI) is one of the main complications after abdominal surgery and its incidence increases continuously,[3,4] affecting approximately 15% of patients undergoing hepatectomy.[3] pAKI is associated with prolonged hospitalization, increased medical costs, higher mortality, and lower long-term survival rate.[5–9] It was estimated that pAKI causes approximately 10-fold increase in in-hospital mortality,

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This retrospective study was approved by the Tongji Medical College research ethics committee, Wuhan, China. (No: IORG0003571).

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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reduces postoperative survival by up to 15 years, and potentiates the risk of chronic renal diseases.[6,8,10,11] The extent and burden of pAKI are particularly evident in developing countries, including China, which has the largest number of patients with hepatitis B virus (HBV) infection.[4] Given the close link between HBV infection and HCC,[12] it is critical to explore new methods to identify the predictors of high risk of pAKI in HCC patients after hepatectomy and to design personalized approaches to the prevention and treatment of pAKI.

The etiology of pAKI is complex and multifactorial. Although ischemia is a major cause of this condition, growing evidence indicates that pAKI frequently occurs in the absence of clear signs of hypoperfusion, and may be related to immune and inflammatory responses.[13] Several studies have reported that the systemic immune-inflammation index (SII), based on a composite index of platelet (PLT), neutrophil, and lymphocyte counts in peripheral blood, has a prognostic value in a variety of malignancies, including HCC,[14,15] pancreatic cancer,[16,17] breast cancer,[18] gastric cancer,[19] esophageal squamous cell carcinoma,[20] oral cell carcinoma,[21] and cervical squamous cell carcinoma.[22] Elevated SII in patients with malignant tumor indicates worse prognosis.[14] However, the relationship between preoperative SII and pAKI after hepatectomy in HCC patients was not studied in detail. Therefore, the predictive value of preoperative SII for acute renal injury after hepatectomy in these patients needs to be determined.

The present study addressed the relationship between the novel SII score and postoperative acute renal injury in patients with HCC using retrospective data from a single-center cohort. The analysis demonstrated that the preoperative SII is an independent predictor of AKI in HCC patients undergoing hepatectomy.

2. Patients and methods

2.1. Patients

A total of 759 patients admitted to the Union Hospital of Tongji Medical College from September 2012 to April 2019 were enrolled in this study. All patients were diagnosed with HCC by liver dynamic enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI). Prior to diagnosis, none of the participants were on treatment for HCC, and on preoperative steroids, aspirin, chemotherapy or other treatments that could have affect the variables used to calculate the SII.

As detailed in Figure 1, 280 of admitted patients were excluded from the analysis. The remaining 479 patients had the diagnosis of HCC confirmed by pathologic examination. All patients

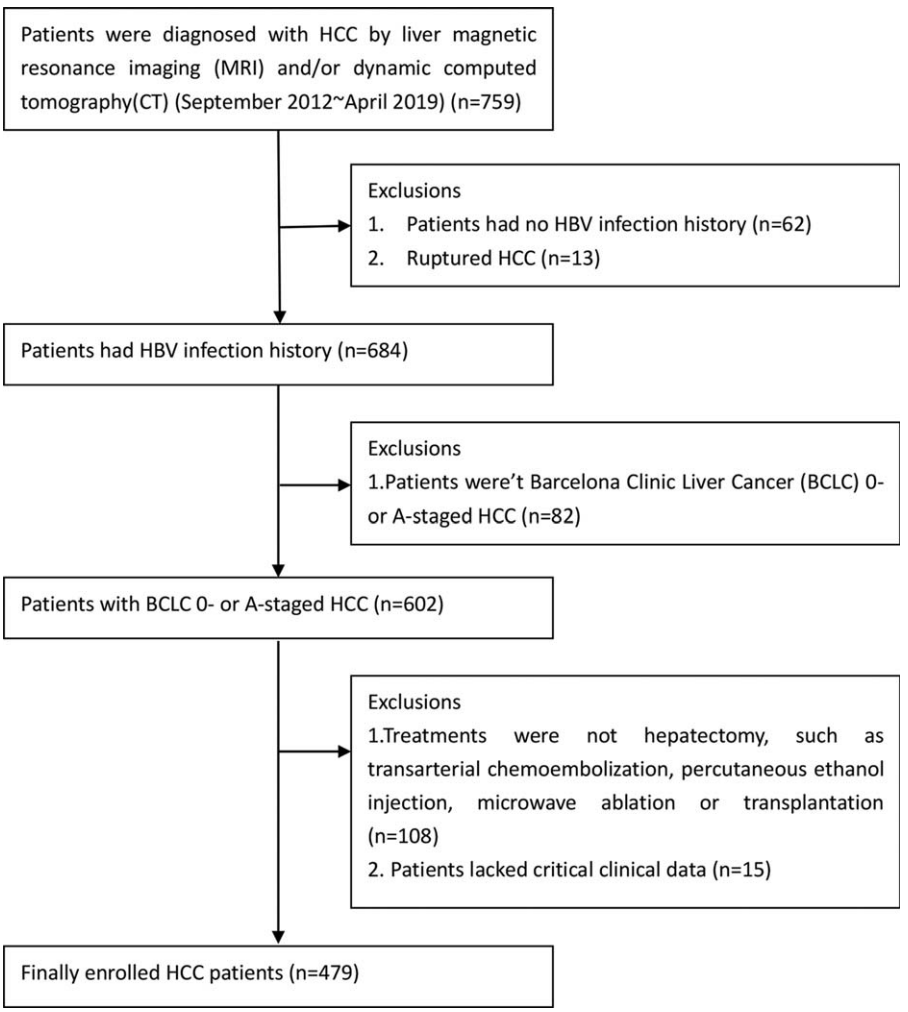

Figure 1. A total of 479 HCC patients was enrolled in this study. BCLC = Barcelona Clinic Liver Cancer, HBV = hepatitis B virus, HCC = hepatocellular carcinoma.

signed informed consent for the surgery before the procedure, and agreed that their clinical data and specimens could be used for scientific research. The protocol of the study was approved by the Human Experimental Ethics Committee of Tongji Medical College.

2.2. Data collection

Complete clinical data for all patients were obtained by retrieving the electronic data records for each case, including sex, age, the presence of hypertension, diabetes, and liver cirrhosis, length of postoperative hospital stay, serum levels of hemoglobin (Hb), albumin, total bilirubin (TB), γ-glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, blood urea nitrogen, α-fetoprotein (AFP). Additional information included serum HBV DNA levels (HBV DNA), The Cancer of the Liver Italian Group Score (CLIP), Child-Turcotte-Pugh classification (CTP), surgery type, tumor size, number of tumors, and their differentiation. Preoperative SII was calculated based on the results of routine blood test, according to the formula: $SII = P \times N/L$, where P, N, and L represent the count of platelets, neutrophils, and lymphocytes, respectively. All the data obtained by the test were the latest data before the operation. The Milan criteria for HCC, that is, a single lesion < 5 cm, or no more than 3 lesions ≤ 3 cm were used.[23] Clinical stages of HCC were defined according to the Barcelona Clinical Liver Cancer (BCLC) staging.[24]

2.3. Surgical treatment

All HCC patients with HCC were subjected to hepatectomy. Hepatectomy was considered minor if less than 4 liver segments were removed and major if 4 or more segments were removed.[25] Pathologic examination was performed for all surgically removed specimens. The Edmondson grading system was used to define the degree of carcinoma differentiation.[26]

2.4. Definition of postoperative AKI

The diagnostic classification of pAKI was based on the Kidney Disease Improving Global Outcomes (KDIGO) criteria. The KDIGO criteria are as follows:

1. Increase in blood creatinine within 48 hours after surgery greater than or equal to 0.3 mg/dL (26.5 mmol/L); and
2. Increase in blood creatinine within 7 days after surgery to more than 1.5 times of the preoperative value.

Patients meeting one of these criteria are diagnosed with pAKI.[4]

2.5. Propensity score matching

All patients were divided into 2 groups based on the best threshold value of SII predicting pAKI: the high SII ($\geq 547.84 \times 109$/L) group and the low SII ($< 547.84 \times 109$/L) group. The propensity score matching (PSM) introduced by Rubin and Rosenbaum was used to pair the patients.[27] The propensity score was calculated using logistic regression model in which sex, age, hypertension, diabetes, cirrhosis, Hb, albumin, TB, GGT, ALT, creatinine, AFP, CLIP, CTP, surgery type, tumor size, number of tumors, BCLC stage, fulfillment of Milan criteria, and differentiation of carcinoma were all considered. To minimize conditional bias, 1:1 matching was adopted. By this approach, patients in the high SII group were matched with patients in the low SII group having the closest propensity score. Subsequently, both subjects were eliminated from the next round of matching. Patients selected by PSM were enrolled in a new cohort and subjected to further analysis.

2.6. Statistical analyses

Continuous variables and categorical variables are described by mean (range), and frequency (percentage), respectively. If the variance in the 2 groups was the same, the continuous variables were compared by the t test, otherwise, the Welch's t test was used. Categorical variables were compared by the χ^2 test or Fisher's exact test. After univariate logistic regression analysis, variables with P-value less than .05 were selected for multivariate analysis to obtain predictors of pAKI. The best threshold value of SII was obtained using the Youden index. The two-sided P-value $< .05$ was considered to indicate a statistically significant difference. The computing process of PSM was performed using the Empower Stats software. SPSS24.0 software was used for statistical analysis.

3. Results

3.1. Patient characteristics

A total of 479 HCC patients with HBV infection were enrolled in this study (Fig. 1); their clinical data are listed in Table 1. There were 424 (88.5%) males and the mean age of all patients was 54.3 years (15–84 years). The population under study included 155 (32.4%) patients with hypertension, 54 (11.3%) patients with a history of diabetes, and 309 (73.2%) patients with liver cirrhosis. The average length of hospital stay after hepatectomy was 15.1 days (3–50 days). In routine blood tests, the average values of Hb, PLT, neutrophils, lymphocytes, white blood cells, and SII were 132.3 (69–181) g/L, 151.6 (25–375) × 109/L, 3.43 (0.76–13.45) × 109/L, 1.41 (0.28–3.70) × 109/L, 5.49 (1.49–16.03) × 109/L, and 438.3 (38.2–3461.0) × 109/L, respectively. In biochemical tests, the mean levels of albumin, TB, GGT, ALT, AST, creatinine, and BUN were 39.3 (24.8–64.3) g/L, 16.6 (3.4–143.8) μmol/L, 115.3 (10–2777) IU/L, 48.6 (1–477) IU/L, 48.3 (15–489) IU/L, 70.7 (37.1–234.1) mmol/L, and 5.69 (1.01–81.50) mmol/L. Low CLIP score was diagnosed in 424 (88.5%) patients, and CTP class A liver function in 461 (96.2%) patients. Major liver resection was performed in 116 (24.2%) patients. The mean carcinoma size was 6.1 cm (1–26 cm). A small amount of ascites was present in 37 (7.7%) participants. The BCLC stage A HCC was identified in 450 (93.9%) participants, and the Milan criteria were met in 272 (56.8%) cases. According to the Edmondson grading system, HCC differentiation I–II and III–IV were confirmed in 324 (67.6%) and 155 (32.4%) patients, respectively.

3.2. Comparison of clinical characteristics with regard to pAKI

A total of 51 (10.6%) HCC patients suffered from pAKI (Table 1). Table 1 indicates also that the patients with pAKI were 5.8 years older than in participants not affected by pAKI (59.5 vs 53.7 years, $P = .001$). HCC patients with pAKI had a higher rate of concurrent hypertension (52.9% vs 29.9%, $P = .001$) and

Table 1

Distribution of patients according to AKI based on the "KDIGO" criteria.

Variables	Total	AKI (−)	AKI (+)	*P*
Total	479 (100)	428 (89.4)	51 (1.6)	
Sex (male)	424 (88.5)	376 (87.9)	48 (94.1)	.184
Age (yr)	54.3 (15–84)	53.7 (15–79)	59.5 (41–84)	.001*
Hypertension	155 (32.4)	128 (29.9)	27 (52.9)	.001*
Diabetes	54 (11.3)	42 (9.8)	12 (23.5)	.003*
Liver cirrhosis	358 (74.7)	319 (74.5)	39 (76.5)	.763
Splenomegaly	103 (21.5)	90 (21.0)	13 (25.5)	.463
Postoperative hospital stay (d)	15.1 (3–50)	14.9 (3–50)	17.2 (9–26)	.001*
Hb (g/L)	132.3 (69–181)	133.6 (73–181)	121.7 (69–151)	.001*
PLT (G/L)	151.6 (25–375)	148.8 (25–375)	175.6 (87–323)	.008*
Neutrophil (G/L)	3.43 (.76–13.45)	3.33 (.76–13.45)	4.32 (2.44–8.20)	.001*
Lymphocyte (G/L)	1.41 (.28–3.70)	1.47 (.32–3.70)	.86 (.28–2.06)	.001*
SII (G/L)	438.3 (38.2–3461.0)	383.4 (38,2–3461.0)	899.2 (283.7–1488.9)	.001*
WBC (G/L)	5.49 (1.49–16.03)	5.38 (1.49–16.03)	6.40 (3.24–1.70)	.001*
Albumin (g/L)	39.3 (24.8–64.3)	39.4 (24.8–5.4)	38.6 (29.8–64.3)	.451
TB (μmol/L)	16.6 (3.4–143.8)	15.8 (3.4–143.8)	23.0 (7.2–66.3)	.001*
GGT (IU/L)	115.3 (10–2777)	105.2 (10–2777)	20.1 (24–820)	.001*
ALT (IU/L)	48.6 (1–477)	5.8 (11–477)	29.5 (1–66)	.005*
AST (IU/L)	48.3 (15–489)	48.5 (15–489)	46.3 (21–94)	.568
Baseline Cr, (mmol/L)	7.7 (37.1–234.1)	7.2 (37.1–234.1)	75.3 (44.2–175.1)	.106
BUN (mmol/L)	5.69 (1.01–81.50)	5.62 (1.01–81.50)	6.22 (2.70–9.44)	.073
AFP (ng/mL)	4765.5 (1.4–80005.1)	4968.5 (1.4–80005.1)	3085.0 (1.5–22331.0)	.366
HBV DNA, ≥2000/<2000	97/131 (42.4/57.5)	85/116 (42.3/57.7)	12/15 (44.4/55.6)	0.832
CLIP score, 0–1/2–3	424/55 (88.5/11.5)	391/37 (91.4/8.6)	33/18 (64.7/35.3)	.001*
CTP, A/B	461/18 (96.2/3.8)	416/12 (97.2/2.8)	45/6 (88.2/11.8)	.001*
Surgery type, major/minor	116/363 (24.2/75.8)	92/336 (21.5/78.5)	24/27 (47.1/52.9)	.001*
Tumor size (cm)	6.1 (1.0–26.0)	5.9 (1–22)	8.2 (3–26)	.001*
Tumor number, 1/2–3	440/39 (91.1/8.9)	389/39 (9.9/9.1)	51/0 (100/0)	0.999
Ascites	37 (7.7)	31 (7.2)	6 (11.8)	.253
BCLC stage, 0/A	29/450 (6.1/93.9)	29/399 (6.8/93.2)	0/51 (0/100)	0.999
Within Milan criteria, n (%)	272 (56.8)	254 (59.3)	18 (35.3)	.001*
Resection, R0/R1	389/90 (81.2/18.8)	356 (83.2)	33 (64.7)	.001*
Differentiation, I–II/III–IV, n (%)	324/155 (67.6/32.4)	285/143 (66.6/33.4)	39/12 (76.5/23.5)	.154
Microwave	281 (58.7)	256 (59.8)	25 (49.0)	.139

AFP = α-fetoprotein, AKI = acute kidney injury, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinical Liver Cancer, BUN = blood urea nitrogen, CLIP = The Cancer of the Liver Italian Group Score, Cr = creatinine, CTP = Child-Turcotte-Pugh classification, GGT = γ-glutamyltransferase, Hb = hemoglobin, HBV DNA = serum HBV DNA levels, HBV = hepatitis B virus, KDIGO = Kidney Disease Improving Global Outcomes, PLT = platelet, SII = systemic immune-inflammation index, TB = total bilirubin, WBC = white blood cell.

* *P* values < .05 were considered statistically significant.

diabetes (23.5% vs 9.8%, *P* = .003), a lower level of Hb (121.7 vs 133.6 g/L, *P* = .001), and stayed in hospital longer after the surgery (17.2 days vs 14.9 days, *P* = .001). They had also higher counts of PLT (175.6 vs 148.8 × 109/L, *P* = .008) and neutrophils (4.32 vs 3.33 × 109/L, *P* = .001), lower count of lymphocytes (0.86 vs 1.47 × 109/L, *P* = .001), and higher of SII values (899.2 vs 383.4 × 109/L, *P* = .001). Participants with pAKI had higher levels of TB (23.0 vs 15.8 μmol/L, *P* = .001)and GGT (200.1 vs 105.2 IU/L, *P* = .001), and lower levels of ALT (29.5 vs 50.8 μmol/L, *P* = .005). The CLIP score was higher in HCC patients with pAKI (35.3% vs 8.6%, *P* = .001), and higher fraction of them underwent major hepatectomy (47.1% vs 21.5%, *P* = .001). The mean tumor diameter of HCC patients with pAKI was larger (8.2 cm vs 5.9 cm, *P* = .001), lower fraction of them fulfilled the Milan criteria (35.3% vs 59.3%, *P* = .001), or underwent the R0 resection (64.7% vs 83.2%, *P* = .001).

3.3. Predictive factors of pAKI

To explore predictors of pAKI, the logistic regression model was used for univariate analysis to evaluate multiple clinical parameters (Table 2). The univariate analysis identified the following variables with *P* < .05: age (odds ratio, OR = 1.054, *P* = .001), hypertension (OR = 2.637, *P* = .001), diabetes (OR = 2.828, *P* = .005), Hb (OR = 0.970, *P* = .001), PLT (OR = 1.006, *P* = .007), neutrophil (OR = 1.228, *P* = .001), lymphocyte (OR = 0.025, *P* = .001), SII (OR = 1.002, *P* = .001), WBC (OR = 1.193, *P* = .002), TB (OR = 1.047, *P* = .001), GGT (OR = 1.001, *P* = .022), ALT (OR = 0.967, *P* = .001), CLIP score (OR = 5.764, *P* = .001), CTP (OR = 4.622, *P* = .003), surgery type (OR = 3.246, *P* = .010), carcinoma size (OR = 1.103, *P* = .001), within Milan criteria (OR 2.676, *P* = .001), and surgical margin (OR 2.697, *P* = .002). On this basis, these variables were included in multivariate regression analysis which documented that SII, history of hypertension, Hb, PLT, neutrophil, lymphocyte, WBC, GGT, ALT, surgery type and tumor size were independent predictors of pAKI after hepatectomy in HCC patients.

The receiver operating curve analysis indicated that the optimal threshold value of preoperative SII for predicting pAKI in HCC patients was 547.84 × 109/L. The area under the curve, reflecting the accuracy of predicting pAKI by SII was 0.907 ((95%CI: 0.877–0.937) (Fig. 2)). Sensitivity, specificity, positive

Table 2

Univariate and multivariate analysis of postoperative AKI based on the "KDIGO" criteria.

Patient characteristics	Univariate analysis			Multivariate analysis		
	OR	95%CI	P	OR	95%CI	P
Sex	.452	.136–1.503	.195			
Age	1.054	1.023–1.086	.001	.990	.927–1.057	.762
Hypertension	2.637	1.465–4.745	.001	9.366	2.260–38.805	.002*
Diabetes	2.828	1.375–5.816	.005	.395	.066–2.352	.307
Liver cirrhosis	1.111	.561–2.198	.763			
Hb	.970	.957–.984	.001	.974	.946–1.002	.067
PLT	1.006	1.001–1.010	.007	1.025	1.005–1.045	.012*
Neutrophil	1.228	1.089–1.386	.001	.062	.009–427	.005*
Lymphocyte	.025	.009–.069	.001	.001	.001–001	.001*
SII	1.002	1.002–1.003	.001	.997	.994–1.001	.110
WBC	1.193	1.066–1.335	.002	3.099	5.190–174.537	.001*
Albumin	.969	.913–1.028	.291			
TB	1.047	1.021–1.074	.001	.995	.955–1.036	.793
GGT	1.001	1.000–1.002	.022	1.010	1.005–1.015	.001*
ALT	.967	.949–.985	.001	.928	.895–962	.001*
AST	.999	.992–1.006	.750			
Baseline Cr	1.009	.998–1.020	.114			
BUN	1.024	.974–1.077	.345			
AFP	1.000	1.000–1.000	.374			
HBV DNA, ≥2000/<2000	1.000	1.000–1.000	.411			
CLIP score, 0–1/2–3	5.764	2.962–11.219	.001	1.495	.108–19.638	.776
CTP, A/B	4.622	1.655–12.910	.003	1.401	.107–18.316	.797
Surgery type, major/minor	3.246	1.788–5.893	.001	31.585	5.654–176.435	.001*
Tumor size	1.103	1.044–1.165	.001	.855	.734–997	.045*
Ascites	1.599	.655–3.899	.302			
Within Milan criteria	2.676	1.460–4.905	.001	2.146	.242–19.040	.493
Resection, R0/R1	2.697	1.440–5.052	.002	.787	.147–4.200	.779
Differentiation, I–II/III–IV	.613	.311–1.207	.157			
Microwave	1.548	.865–2.770	.141			

AFP = α-fetoprotein, AKI = acute kidney injury, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CLIP = The Cancer of the Liver Italian Group Score, Cr = creatinine, CTP = Child-Turcotte-Pugh classification, GGT = γ-glutamyltransferase, Hb = hemoglobin, HBV DNA = serum HBV DNA levels, HBV = hepatitis B virus, KDIGO = Kidney Disease Improving Global Outcomes, PLT = platelet, SII = systemic immune-inflammation index, TB = total bilirubin, WBC = white blood cell.

* *P* values < .05 were considered statistically significant.

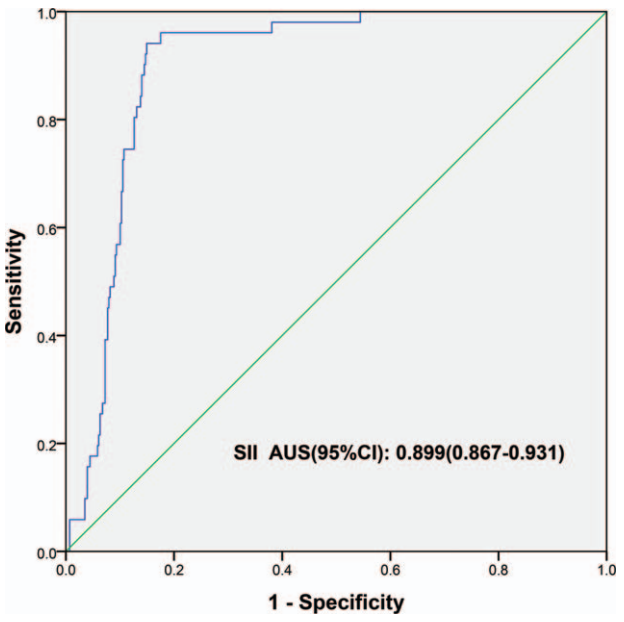

Figure 2. Receiver operating curve (ROC) of predicting postoperative AKI with SII. AKI = acute kidney injury, SII = systemic immune-inflammation index.

predictive value, and negative predictive value were 0.96 (95% CI: 0.85–0.99), 0.84 (95%CI: 0.80–0.87), 0.41 (95%CI: 0.32–0.51), and 0.99 (95%CI: 0.98–0.99), respectively.

According to the optimal cut-off value of SII, all patients enrolled in the study were divided into 2 groups: the high SII (≥547.84 × 109/L) group (n = 119) and the low SII (<547.84 × 109/L) group (n = 360). After univariate analysis, the SII grouping variables with $P < .05$ were included in the multivariate regression analysis, which indicated that the SII ≥ 547.84 × 109/L was still an independent predictor of pAKI after hepatectomy in HCC patients.

3.4. Predictive factors of pAKI after propensity score matching

The variables that were statistically different between the high SII and low SII groups, included gender, history of diabetes, Hb, PLT, neutrophil, lymphocyte, WBC, TB, GGT, AST, CLIP score, surgery type, tumor size, BCLC stage, and Milan criteria (Table 3). Ninety-three propensity score-matched pairs of HCC patients pairs with HCC were selected using the Empower Stats software. Their clinical data were compared, and no significant differences in the matched variables between the 2 groups were found ($P > .05$). After univariate analysis, the variables with $P < .05$, including age

Table 3

Comparison of clinical parameters between the low and high SII groups.

Clinical parameters	SII ≥ 547.84	SII < 547.84	P
Total	119 (24.8)	360 (75.2)	
AKI	49 (41.2)	2 (.6)	.001*
Gender (male)	113 (95.0)	311 (86.4)	.011*
Age (y)	53.6 (15.0–84.0)	54.6 (21.0–79.0)	.415
Hypertension	44 (37.0)	111 (3.8)	.214
Diabetes	21 (17.6)	33 (9.2)	.011*
Liver cirrhosis	86 (72.3)	272 (75.6)	.474
Hb (g/L)	129.0 (69.0–162.0)	133.4 (73.0–181.0)	.043*
PLT (G/L)	195.1 (6.0–375.0)	137.3 (25.0–33.0)	.001*
Neutrophil (G/L)	5.5 (2.4–13.5)	2.8 (.8–8.9)	.001*
Lymphocyte (G/L)	1.1 (.3–2.1)	1.5 (.5–3.7)	.001*
WBC (G/L)	7.5 (3.2–16.0)	4.8 (1.5–11.7)	.001*
Albumin (g/L)	38.9 (24.8–64.3)	39.4 (27.9–5.4)	.405
TB (μmol/L)	19.4 (3.4–143.8)	15.6 (4.3–58.9)	.013*
GGT (IU/L)	189.0 (12.0–2777.0)	91.0 (1.0–962.0)	.005*
ALT (IU/L)	56.4 (1.0–477.0)	46.0 (11.0–19.0)	.192
AST (IU/L)	63.0 (15.0–489.0)	43.5 (15.0–258.0)	.009*
Baseline Cr, (mmol/L)	7.8 (4.4–175.1)	7.7 (37.1–234.1)	.953
CLIP score, 0–1/2–3	94/25 (79.0/21.0)	330/30 (91.7/8.3)	.001*
CTP, A/B	112/7 (94.1/5.9)	349/11 (96.9/3.1)	.160
Surgery type, major/minor	51/68 (42.9/57.1)	65/295 (18.1/81.9)	.001*
Tumor size (cm)	8.2 (1.5–26.0)	5.4 (1.0–21.0)	.001*
Tumor number, 1/2–3	110/9 (92.4/7.6)	330/30 (91.7/8.3)	.790
Ascites	9 (7.6)	28 (7.8)	.939
BCLC stage, 0/A	1/118 (.8/99.2)	28/332 (7.8/92.2)	.006*
Within Milan criteria	41 (34.5)	231 (64.2)	.001*
Resection, R0/R1	91/28 (76.5/23.5)	298/62 (82.8/17.2)	.127
Differentiation, I–II/III–IV	82/37 (68.9/31.1)	242/118 (67.2/32.8)	.733

AKI = acute kidney injury, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinical Liver Cancer, CLIP = The Cancer of the Liver Italian Group Score, Cr = creatinine, CTP = Child-Turcotte-Pugh classification, GGT = γ-glutamyltransferase, Hb = hemoglobin, PLT = platelet, SII = systemic immune-inflammation index, TB = total bilirubin, WBC = white blood cell.

* *P* values < .05 were considered statistically significant.

(OR = 1.070, *P* = .001), history of hypertension (OR = 2.644, *P* = .008), lymphocyte count (OR = 0.119, *P* = .001), SII group (OR = 18.94, *P* = .001), GGT (OR = 1.003, *P* = .043), ALT (OR = 0.962, *P* = .001), carcinoma size (OR = 0.903, *P* = .043), surgical margin (OR = 2.525, *P* = .026), and carcinoma differentiation (OR = 0.375, *P* = .040), were included in the multivariate analysis (Table 4). Multivariate regression analysis confirmed that SII ≥ 547.84 × 109/L was an independent predictor of pAKI in HCC patients (Table 4).

4. Discussion

The retrospective analysis performed in the present investigation demonstrated that HCC patients infected by HBV with pAKI, defined according to the KDIGO criteria, had a higher preoperative value of blood SII value than patients without pAKI. Moreover, multivariate regression documented that SII was an independent predictor of pAKI after hepatectomy in these patients. Based on the receiver operating curve analysis, the best threshold truncation value of SII predicting pAKI was found to be 547.84 × 109/L. Multivariate analysis performed following the PSM confirmed that the SII ≥547.84 × 109/L was an independent predictor of pAKI after hepatectomy in HCC patients. This value of SII correctly predicted pAKI in 96.1% (95% CI: 85.4–99.3%) of participants with pAKI, and absence of pAKI in 83.6% (95% CI: 79.7–87.0%) of patients not affected by this condition. The positive predictive value of SII was slightly lower.

These results indicate that preoperative SII may be a novel, low-cost, and simple biomarker for predicting pAKI. Among HCC patients with concurrent HBV infection, preoperative SII may serve as a new prognostic tool to assess the risk of pAKI. Thus, preoperative SII may help to identify HCC patients that are at high risk of pAKI, enabling timely prevention and treatment of pAKI in high-risk patients and improving their prognosis.

The incidence of pAKI in patients undergoing hepatectomy is approximately15%.[3] pAKI causes a 10-fold increase in in-hospital mortality and reduces long-term survival.[6,8] In agreement with a previous report,[3] the current analysis showed that HCC patients with pAKI had a longer postsurgical hospital stay than patients without pAKI. A worse prognosis for surgically treated HCC patients with elevated preoperative value of SII was also reported.[14] This present investigation found that SII is an independent predictor of pAKI in HCC patients, suggesting that HCC patients with elevated SII value may have a worse prognosis due to the occurrence of pAKI. In this study, the presence of cirrhosis and ascites was not an independent predictor of pAKI. The reasonable explanations are as follows. According to the inclusion and exclusion criteria, the patients who were eventually included in the study had BCLC stage 0/A and Child-Turcotte-Pugh classification A/B. Therefore, the degree of cirrhosis and ascites in the vast majority of patients is relatively mild.

Immune and inflammatory responses, reflected by the SII index, have a significant role in the development of pAKI and may be related to the presence of HBV.[13] HBV infection is associated with the occurrence of kidney disease.[28] In addition, the presence of HBV DNA and HBV antigen in renal tubular epithelial cells has been well-documented,[28,29] and immune complexes released from the kidney may participate in the pathogenesis of HBV-associated nephropathy.[28] Experimentally, HBV replication in infected tubular cells may induce apoptosis of tubular cells.[30] In fact, serum from patients infected with HBV promotes apoptosis of renal tubular epithelial cells by a mechanism involving upregulation of Fas.[30] Apoptosis might promote cell loss and aggravate organ damage in acute kidney injury.[30] Tissue damage may be also promoted by excessive and unresolved inflammation.[31] Recent studies indicated that T cells are also involved in the early AKI reaction.[32] Activated dendritic cells and renal parenchymal cells secrete several chemokines, including CXCL8, CXCL1, CCL5, and CCL2, which promote acute neutrophil-dependent inflammatory responses in AKI[33,34] by recruiting cells to the site of injury. Consistent with these findings, experimental blockade of chemokines and cytokines can abrogate the AKI response.[35]

Oxidative stress may represent another mechanism that might participate in renal tubular cells injury because renal tubular epithelial cells are very susceptible to reactive oxygen species.[36] Some experimental studies suggested that exposure of cells to superoxide anion leads to an increase in intracellular calcium concentration, resulting in renal vasoconstriction, and decreased renal blood flow and glomerular filtration rate, ultimately generating kidney damage.[37,38] The role of reactive oxygen in renal injury is supported by the demonstration that antioxidant therapy can prevent kidney damage and improve renal dysfunction.[39]

The majority of thus far performed clinical trials on the prevention or treatment of AKI was negative. The unfavorable outcomes may be related to the multifactorial nature and dynamic progression of AKI, as well as the difficulty in

Table 4

Univariate and multivariate analysis of predictors of postoperative AKI after propensity score matching.

	Univariate analysis			Multivariate analysis		
Patient data	**OR**	**95%CI**	***P***	**OR**	**95%CI**	***P***
Age	1.070	1.032–1.108	.001	1.014	.962–1.068	.612
Hypertension	2.644	1.286–5.436	.008	2.773	1.019–7.550	.046*
Diabetes	2.294	.933–5.644	.071			
Liver cirrhosis	1.424	.624–3.247	.401			
Hb	.991	.974–1.009	.338			
PLT	1.003	.998–1.008	.213			
Neutrophil	1.064	.928–1.220	.375			
Lymphocyte	.119	.042–.335	.001	.241	.060–.974	.046*
High SII vs low SII	18.947	5.574–64.412	.001	15.723	3.595–68.766	.001*
WBC	1.080	.949–1.229	.245			
Albumin	.991	.931–1.056	.781			
TB	1.022	.981–1.064	.301			
GGT	1.003	1.000–1.006	.043	1.010	1.005–1.016	.001*
ALT	.962	.940–.985	.001	.943	.904–.983	.005*
AST	.987	.972–1.002	.081			
Baseline Cr	1.008	.997–1.020	.159			
AFP	1.000	1.000–1.000	.220			
CLIP score, 0–1/2–3	1.390	.508–3.802	.521			
CTP, A/B	2.367	.540–1.369	.253			
Surgery type, major/minor	.987	.478–2.038	.971			
Tumor size	.903	.818–.997	.043	.873	.763–.999	.048*
Ascites	.945	.275–3.246	.929			
Within Milan criteria	1.043	.505–2.153	.910			
Resection, R0/R1	2.525	1.115–5.717	.026	1.145	.342–3.834	.826
Differentiation, I–II/III–IV	.375	.147–.956	.040	.480	.143–1.610	.235

AFP = α-fetoprotein, AKI = acute kidney injury, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CLIP = The Cancer of the Liver Italian Group Score, Cr = creatinine, CTP = Child-Turcotte-Pugh classification, GGT = γ-glutamyltransferase, Hb = hemoglobin; PLT = platelet, SII = systemic immune-inflammation index, TB = total bilirubin, WBC = white blood cell.

* *P* values < .05 were considered statistically significant.

establishing extent of tissue damage that has occurred.[40,41] This present work demonstrates that SII is an independent predictor of pAKI in HCC patients, and HCC patients with elevated SII value are at high risk of pAKI. The identification of a predictor of pAKI creates an opportunity to provide individualized treatment for high-risk patients, including measures to prevent pAKI and treat a subclinical condition. The availability of these options might improve the prognosis of patients.

It should also be recognized that the current study has some limitations. First, this work is a single-center retrospective study with a low incidence of pAKI (10.8%), and relatively few pAKI cases were included in the study. Therefore, large-scale multicenter prospective cohort studies are necessary to strengthen the results. Second, it should be noted that most HCC patients in China are infected by HBV, which is not the case in patient populations in the United States, Japan, and Europe. Therefore, the predictive significance of the SII needs to be validated in HCC patients with HCC from those geographic regions. Third, the best threshold value of SII identified here may not be suitable for other studies. Prospective validation or a meta-analysis of various studies focused on SII is required to confirm the optimal cut-off value of SII. Despite these limitations, to the best of our knowledge, this study provides the first demonstration of the predictive value of SII for pAKI in HCC patients who underwent hepatectomy.

5. Conclusions

The results of this study indicate that SII qualifies as a novel, independent predictor of pAKI in HCC patients with HBV infection who underwent hepatectomy.

Author contributions

Jianjun Xu, Shaobo Hu, Suzhen Li, Xiang Cheng, and Qichang Zheng researched literature and conceived the study. Weimin Wang, Yuzhe Wu, Zhe Su, Xing Zhou, and Yang Gao were involved in protocol development, gaining ethical approval, patient recruitment, and data analysis. Jianjun Xu, Shaobo Hu, and Suzhen Li wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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