Systemic Immune-Inflammation Index and serum albumin predict prognosis in rectal cancer patients undergoing curative resection

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Research Article

Keywords: serum albumin, Systemic immune-inflammation index(SII), rectal cancer(RC)

Posted Date: April 14th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1541906/v1

Abstract

Background: Systemic nutrition and inflammation have been reported to be associated with the prognosis of various cancers. The aim of this study is to explore the predictive value of systemic immune-inflammation index (SII) and serum albumin in postoperative prognosis for patients with rectal cancer(RC) who received curative resection.

Methods: A total of 184 eligible RC patients were included in this retrospective study. X-tile software was used to determine the optimal cut-off values for SII and serum albumin. The relationship between serum albumin/SII and clinicopathological parameters was analyzed. The effects of serum albumin and SII on overall survival (OS) were assessed by univariate and multivariate Cox proportional hazards model analysis and Kaplan-Meier curves.

Results: The ideal preoperative cut-off points of NLR, PLR, and OPNI were 2.5, 133.3, and 39.5, respectively. Multivariate Cox regression analysis identified that the lymphocyte (P =0.011), Serum albumin (P=0.010), SII (P =0.012) and tumor diameter (P=0.032) were significant prognostic markers for OS. The median OS in the Serum albumin-low and Serum albumin-high groups was 22 months and and not observed (P < 0.001), and that in the SII-high and SII-low groups was 15 months and not observed (P < 0.001), respectively.

Conclusions: SII and serum albumin could be feasible and promising biomarkers for prognosis in RC patients who received curative resection.

Introduction

Rectal cancer accounts for about 29.7% of the total colorectal cancer incidence in United States[1], which has become the most common cancer in men and the second in women. This high incidence is also kept in China[2] and represents a major health care concern which is also attributed to high recurrence rates and the morbidity with local recurrence[3].

Surgery or adjuvant therapy is suggested for the majority of patients with stage II/III rectal cancer[4]. Identification of prognostic factors can predict overall survival (OS) and disease-free survival (DFS) and guide individualized treatment plans. A variety of studies have focused on the clinical factors that determine posttreatment survival in rectal cancer[5–8]. Clinical stage and nodal status were identified as independent variables of survival outcome in rectal cancer[8] and previous researches also provided the evidence for the prognostic value of radial margin[9] in this regard.

Inflammation is known to all that can promote tumorigenesis, progression and metastasis[10]. Inflammatory cells can produce an attractive environment for genomic instability and angiogenesis[11]. Therefore, several inflammatory response biomarkers including neutrophil-to lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio and the level of C-reactive protein, were observed to be

prognostic predictors for non-small cell lung cancer, renal cell carcinoma and hepatocellular carcinoma[12–15]. An integrated indicator defined as the systemic immune-inflammation index (SII), reflecting the balance of host inflammatory and immune status, was developed based on peripheral lymphocyte, neutrophil and platelet counts[16]. Moreover, the level of serum albumin reflects the risk of postoperative complications, which was also proved related to the prognosis of gastrointestinal tumors[17, 18].

To the best of our knowledge, few studies with large sample-size focused on SII and serum albumin in rectal cancer. The aim of this study was to investigate the prognostic value of SII and serum albumin in patients with stage II/III rectal cancer.

Materials And Methods

This retrospective study was approved by the institutional review board of the author's affiliated institution (Affiliated Hospital of Hebei University). All procedures involving patients were performed in accordance with the 1975 Helsinki declaration and its later amendments.

Patients

Patients with stage II/III rectal cancer between October 2017 and October 2018 were enrolled in this retrospective study (Fig. 1). Written informed consent was obtained from participants who met the inclusion criteria: (1) treatment-naïve when admitted to our hospital; (2) diagnosed with stage II/III rectal cancer by pathology; (3) received curative resection. Exclusion criteria were as follows: (1) previous surgery on colorectum; (2) active or chronic infections or autoimmune disease; (3) metastases at diagnosis; (4) complicated with other tumors or hematological diseases; (5) complicated with intestinal obstruction, gastrointestinal hemorrhage or perforation; (6) incomplete clinical or survival data.

Data Collection

Diagnosis and staging were performed according to the 8th edition of American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system[19]. We retrospectively collected clinical-pathologic data including sex, age, tumor size, tumor differentiation, the status of vascular invasion, TNM stage. Serum examination results including neutrophil, lymphocyte, platelet (PLT) counts and serum albumin were obtained within 3 day before surgery. The SII was calculated as PLT counts × nertrophil/lymphocyte.

Follow-up

After resection, patients were followed up and tumor recurrence was screened by means of digital rectal examination, serum carcinoma embryonic antigen (CEA) level, colonoscopy and contrast-enhanced CT or MRI of the chest and abdomen every 3 months during the first 2 years and then every 6 months

thereafter. The data were censored on October 15, 2021. Overall survival was determined from the date of surgery to the death of patients.

Statistical Analysis

Statistical analysis was performed with R software (version 4.0.2, http://www.r-project.org). Continuous and categorical variables were compared by using the Student *t* test and χ^2 test, respectively. OS was presented by using the Kaplan-Meier curve and compared with the log-rank test. Variables with statistical significance for OS in the univariable Cox regression analysis were included in the multivariable Cox model. A Nomogram was constructed to provide a more understandable outcome measure. The prediction performance was evaluated with the concordance index (C index) and a calibration plot by means of 1000 bootstrap resamples. The optimal cutoff point for continuous prognostic variables was obtained by using X-tile software (version 3.6.1, Yale University School of Medicine, New Haven, Conn). P values less than 0.05 indicated statistical significance.

Result

Baseline patient characteristics

A total of 184 patients were included in this study finally. The general clinical characteristics of the RC patients are shown in Table 1. Of these patients, 108(41.3%)were male and 76 (58.7%) were female, with the average age was 60.9 ± 10.1 years. The median serum albumin level was 38.2 ± 5.6 g/L. The average neutrophil, lymphocyte, and plate counts were (4.6 ± 2.5)109/L, (1.7 ± 0.6)109/L, and (240.7 ± 95.6)109/L, respectively. The mean SII was 828.0 ± 959.2. The mean tumor diameter was 4.6 ± 1.7 cm. Moreover, a total of 164 patients had TNM stage I-III (89.1%), and 20 patients had TNM stage IV (10.9%). (Table 1).

Table 1
The clinicopathological variables in patients with RC (n = 184)

Variables	Values (n = 184)
Gender	
Male	108 (58.7)
Female	76 (41.3)
Age (years),mean(SD)	60.9 (10.1)
Neutrophil (10^9/L),mean(SD)	4.6 (2.5)
Lymphocyte (10^9/L),mean(SD)	1.7 (0.6)
PLT (10^9/L),mean (SD)	240.7 (95.6)
Serum albumin (g/L),mean(SD)	38.2 (5.6)
SII (mean (SD))	828.0 (959.2)
T stage (%)	
T_{1-3}	146 (79.3)
T_4	38 (20.7)
N stage (%)	
N_{0-1}	152 (82.6)
N_2	32 (17.4)
M stage (%)	
M_0	162 (88.0)
M_1	22 (12.0)
TNM stage (%)	
I-III	164 (89.1)
IV	20 (10.9)
Blood_sugar(mmol/L),mean(SD)	6.1 (1.5)
Tumor diameter(cm),mean (SD)	4.6 (1.7)
Tumor volume (mean(SD)	31.8 (17.2)
Vascular_invasion (%)	

Variables	Values (n = 184)
Negative	158 (85.9)
Positive	26 (14.1)
Nerve_infiltration (%)	
Negative	160 (87.0)
Positive	24 (13.0)

PLT platelet, SII systemic immune-inflammation index, TNM tumor-node-metastasis

X-tile analysis:

SII and Serum albumin were used as test variables and OS as state variables. The X-tile program determined the optimal cut-off values of SII and Serum albumin. The analysis results demonstrated that the optimal cut-off points of SII and Serum albumin were 939.9 and 36.0. (Figs. 1a-1b).

Univariate and Multivariate Analyses for the RC Patients:

Univariate and multivariate analyses were performed for age, gender, neutrophil, lymphocyte, serum albumin, platelet, serum albumin, SII, tumor diameter, and other clinicopathologic variables.

The univariate Cox regression analysis identified that neutrophil (HR = 1.10; 95% CI = 1.10–1.20; P < 0.001), lymphocyte (HR = 0.28; 95% CI = 0.17–0.44; P < 0.001), serum albumin (HR = 0.30; 95% CI = 0.20–0.46; P < 0.001), tumor diameter (HR = 1.30; 95% CI = 1.20–1.50; P < 0.001), and SII (HR = 5.80; 95% CI = 3.70–9.10; P < 0.001) were significant prognostic factors associated with OS (Table 2).

From the multivariate analyses, we found that lymphocyte (HR = 0.50; 95% CI = 0.30–0.85; P = 0.011), serum albumin (HR = 0.52; 95% CI = 0.32–0.86; P = 0.010), SII (HR = 2.56; 95% CI = 1.23–5.29; P = 0.012), and tumor diameter (HR = 1.97; 95% CI = 1.06–3.68; P = 0.032) were significant prognostic markers for OS (Table 2).

Table 2
Univariate and multivariate analyses for OS in patients with RC

Variables	OS	
	HR(95% CI)	*P* value
Univariate analysis		
Age	1.00 (0.98-1.00)	0.880
Gender(male vs.female)	1.50 (0.99–2.40)	0.056
Neutrophil	1.10 (1.10–1.20)	< 0.001
Lymphocyte	0.28 (0.17–0.44)	< 0.001
PLT	1.00 (1.00–1.00)	0.770
Serum albumin (high group vs.low group)	0.30 (0.20–0.46)	< 0.001
SII(high group vs.low group)	5.80 (3.70–9.10)	< 0.001
T stage(T_{1-3} vs.T_4)	2.60 (1.70–4.10)	< 0.001
N stage(N_{0-1} vs.N_2)	1.10 (0.66–1.90)	0.700
M stage(M_0 vs.M_1)	2.70 (1.60–4.60)	< 0.001
TNM stage(I-III vs. IV)	3.00 (1.70–5.10)	< 0.001
Blood_sugar	0.91 (0.77–1.10)	0.220
Tumor diameter	1.30 (1.20–1.50)	< 0.001
Tumor volume	1.00 (1.00–1.00)	< 0.001
Vascular_invasion(Negative vs. Positive)	0.65 (0.34–1.30)	0.200
Nerve_infiltration(Negative vs. Positive)	1.10 (0.57–1.90)	0.870
Multivariate analysis		
Neutrophil	1.01 [0.91, 1.13]	0.828
Lymphocyte	0.50 [0.30, 0.85]	0.011
Serum albumin (high group vs.low group)	0.52 [0.32, 0.86]	0.010
SII(high group vs.low group)	2.56 [1.23, 5.29]	0.012
T stage(T_{1-3} vs.T_4)	1.85 [1.08, 3.17]	0.025
M stage(M_0 vs.M_1)	0.53 [0.07, 4.27]	0.554
TNM stage(I-III vs. IV)	2.41[0.29, 19.68]	0.412

Variables	OS	
Tumor diameter	1.97 [1.06, 3.68]	0.032
Tumor volume	0.94 [0.89, 1.00]	0.054

PLT platelet, SII systemic immune-inflammation index, TNM tumor-node-metastasis

The Prognostic Value of Serum albumin and SII in RC Patients

Finally, we evaluated the prognostic value of Serum albumin and SII in RC patients who received curative resection. The median OS times in the Serum albumin-low was 22 months, and Serum albumin-high groups was not observed (P < 0.001, Fig. 2a), and the median OS in the SII- high was 15 months, and SII-low groups was not observed (P < 0.001, Fig. 2b).

Discussion

A large number of studies have found that serum albumin and SII play a critical role in the occurrence, development and prognosis of tumors. In this study, we divided the patients into two groups: high albumin (SII) group and low albumin (SII) group. Finally, we found that serum albumin and SII could predict the prognosis of RC after curative resection, and serum albumin and SII were independent risk factors for OS in RC patients.

TNM staging system occupies the central role in prognosis and therefore treatment allocation[19]. However, quantifiable risk measures cannot be provided and the accuracy was affected by tumor heterogeneity. Therefore, it is necessary to find a novel biomarker to identify patients with poor prognosis and guide the personalized treatment. The important role of inflammation in tumorigenesis, progression and metastasis has become as a hot topic in medical research. Because the immune and nutritional status of the system contributed to the inflammatory response, multiple studies focused on the predictive values of biochemical indices related to the immune and nutritional status in cancer patients[20, 21].

SII can accurately provide measures of the systemic inflammation, which is calculated based on neutrophil, lymphocyte and platelet counts. Patients with an elevated SII usually have thrombocytopenia, neutrophilia or lymphopenia, indicating an elevated inflammatory status and weak immune response[16]. Neutrophils can stimulate premalignant epithelial cell to enhance cancer cell invasion and release cytokines such as vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β) and platelet derived growth factor (PDGF) to promote tumor proliferation and angiogenesis[22, 23]. Neutrophils can assist cancer cells with evading immune surveillance[24]. Several studies revealed that platelets have the ability of interacting with cancer cells and facilitate tumor metastasis through various pathways[25, 26]. Activated T cells and other lymphocytes contribute to the immune response and inhibit tumor cell

proliferation, and thus a lower lymphocyte count can lead to the easier escape of tumor cells from immune surveillance[27].

Serum albumin was found negatively associated with OS in this study. The level of serum albumin cannot accurately reflect nutritional status but the negative relationship with postoperative complications might affect the postoperative inflammatory status[28]. A recent study also showed that serum albumin can protect the tissues against inflammatory injury[29]. Several studies concluded that serum albumin can be regarded as an independent prognostic biomarker for tumors[30, 31].

Several limitations should be noted in this study. First, inherent selection biases cannot be avoided because of the retrospective nature of this study. Second, inaccurate data recording and medication might affect the quality of blood-circulating cell counts. Third, several patients might receive additional postoperative treatments to improve the prognosis. Therefore, further multicenter or prospective studies are warranted to validate these results.

In conclusion, SII and serum albumin were feasible and promising biomarkers for prognosis in stage II/III rectal cancer. Our established nomogram model can successfully identify patients with high risk of poor prognosis, which can help clinical decision making and potentially provide benefits for clinicians and selected patients.

Declarations

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

Data Availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yating Qiao and Tao Zhang. The first draft of the manuscript was written by Tao Zhang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

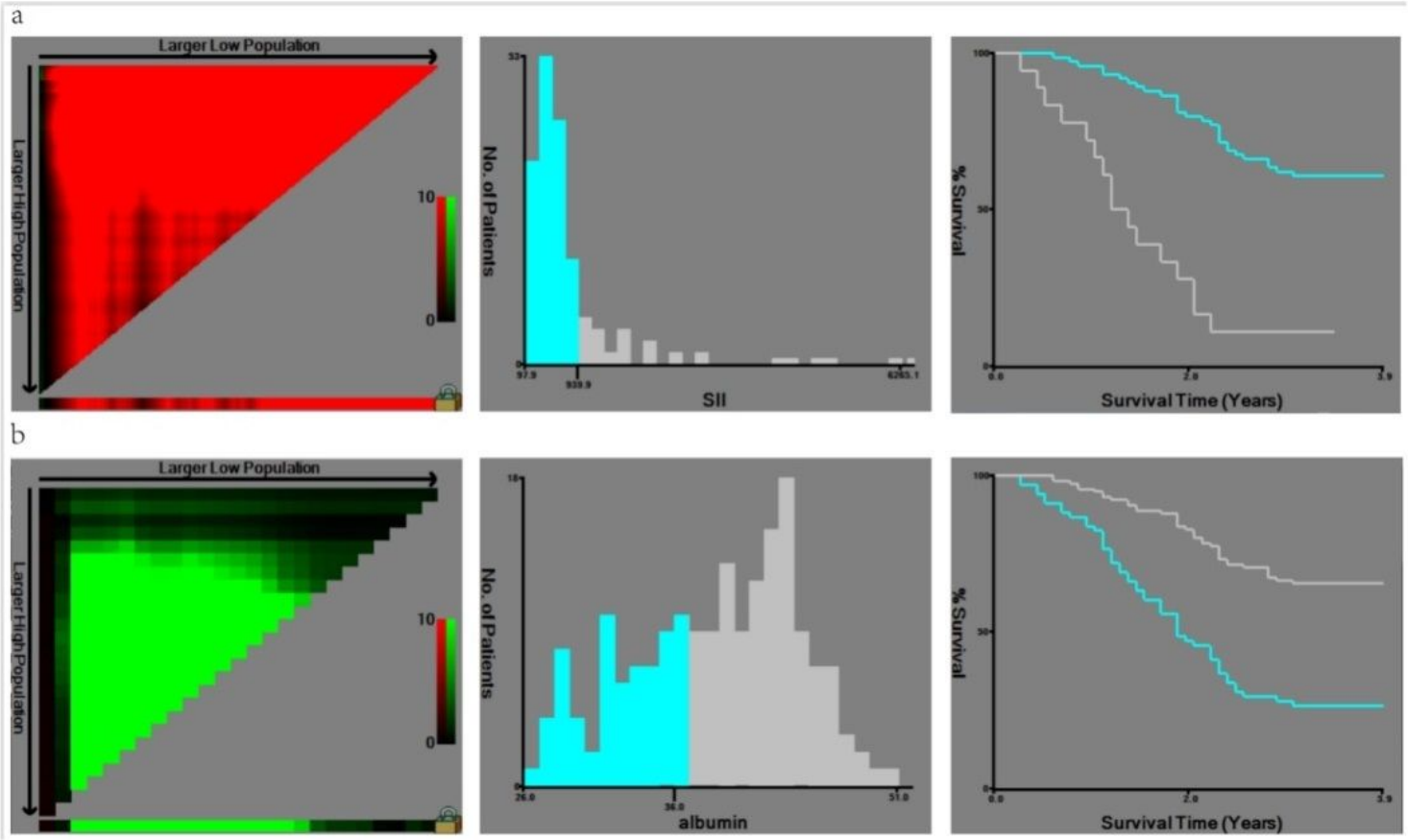
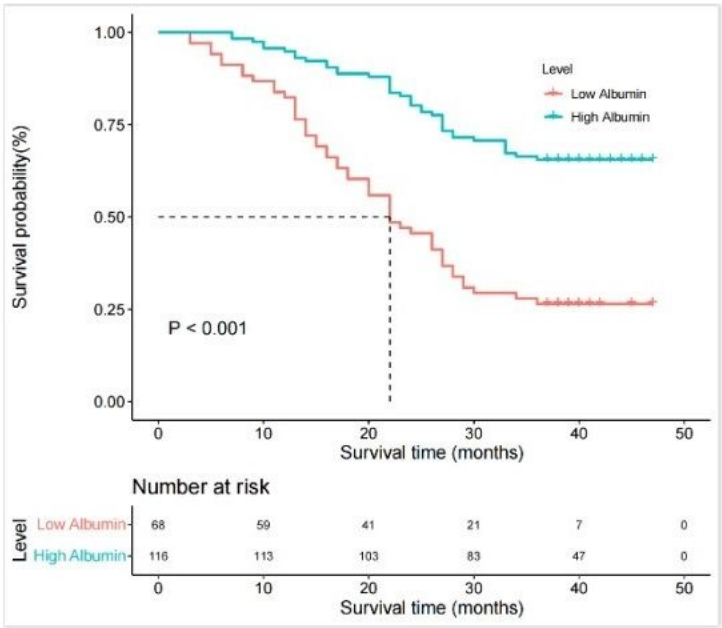


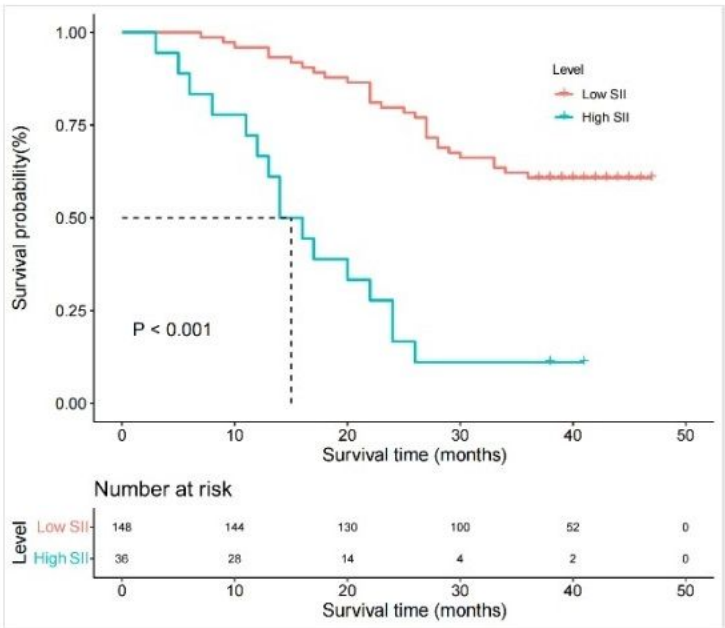
Figure 1

1a: X-tile analysis of the SII. The optimal cut-off value of SII is 939.9

1b: X-tile analysis of the Serum albumin. The optimal cut-off value of Serum albumin is 36.0



2a



2b

Figure 2

The Kaplan-Meier survival curves for OS in RC patients.

a. The median OS times in the Serum albumin-low and Serum albumin-high groups were 24 months and not observed, respectively ($P < 0.001$). b. The median OS times in the SII-low and SII-high groups was 36 months and not observed, respectively ($P < 0.001$)