Research Article

The Change of Systemic Immune-Inflammation Index Independently Predicts Survival of Colorectal Cancer Patients after Curative Resection

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Background. The systemic immune-inflammation index (SII) has an important role in predicting survival in some solid tumors. However, little information is available concerning the change of the SII (ΔSII) in colorectal cancer (CRC) after curative resection. This study was designed to evaluate the role of ΔSII in CRC patients who received surgery. Methods. A total 206 patients were enrolled in this study. Clinicopathologic characteristics and survival were assessed. The relationships between overall survival (OS), disease-free survival (DFS), and ΔSII were analyzed with both univariate Kaplan-Meier and multivariate Cox regression methods. Results. Based on the patient data, the receiver operating characteristic (ROC) optimal cutoff value of ΔSII was 127.7 for OS prediction. The 3-year and 5-year OS rates, respectively, were 60.4% and 36.7% in the high-ΔSII group (>127.7) and 87.6% and 79.8% in the low-ΔSII group (≤127.7). The 3-year and 5-year DFS rates, respectively, were 54.1% and 34.1% in the high-ΔSII group and 80.3% and 78.5% in the low-ΔSII group. In the univariate analysis, smoking, pathological stages III-IV, high-middle degree of differentiation, lymphatic invasion, vascular invasion, and the high-ΔSII group were associated with poor OS. Adjuvant therapy, pathological stages III-IV, vascular invasion, and ΔSII were able to predict DFS. Multivariate analysis revealed that pathological stages III-IV (HR = 0.442, 95% CI = 0.236-0.827, p = 0.011), vascular invasion (HR = 2.182, 95% CI = 1.243-3.829, p = 0.007), and the high-ΔSII group (HR = 4.301, 95% CI = 2.517-7.350, p < 0.001) were independent predictors for OS. Adjuvant therapy (HR = 0.415, 95% CI = 0.250-0.687, p = 0.001), vascular invasion (HR = 3.305, 95% CI = 1.944-5.620, p < 0.001), and the high-ΔSII group (HR = 4.924, 95% CI = 2.992-8.102, p < 0.001) were significant prognostic factors for DFS. Conclusions. The present study demonstrated that ΔSII was associated with the clinical outcome in CRC patients undergoing curative resection, supporting the role of ΔSII as a prognostic biomarker.

1. Introduction

Colorectal cancer (CRC) is one of the most common malignant diseases [1, 2]. The clinical outcome of CRC is still unsatisfactory because of recurrence or metastasis. In addition, despite significant advances in CRC treatment with intense research activity and outcomes, the appropriate stratification of CRC patients remains a challenge. There is still heterogeneity in the prognosis between CRC with the same tumor nodal metastasis (TNM) stage and CRC with the same Dukes’ classification [3, 4], which indicates that they are not sufficient to correctly stratify patients in terms of the risk of mortality [5, 6]. Other conventional prognostic biomarkers, such as tumor differentiation and pathological type, have been used for predicting CRC outcomes [7, 8]. However, these are tumor tissue dependent and the detections are
usually costly and time-consuming. Therefore, it is very urgent to develop auxiliary biomarkers to help clinicians to identify individualized treatment.

In recent years, a lot of inflammation-based prognostic systems are gradually getting attention [9, 10], with the role of inflammation in angiogenesis promotion, DNA damage, and tumor invasion and metastasis [11–13]. Several immune-inflammation systems, such as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), have been reported to predict the prognosis for some malignant solid tumors [14–17]. Systemic immune-inflammation index (SII) is a novel parameter related to the platelet, neutrophil, and lymphocyte. Recently, SII has been reported for its prognostic role in some solid tumors such as liver cancer, non-small-cell lung cancer, renal cell cancer, and esophageal squamous cell carcinoma [18–20]. Although many studies also indicated the prognostic role of SII in CRC patients, the results were inconsistent [21–23]. Noteworthy, some studies have found that the dynamic change in the SII represents a new indicator for predicting the prognosis in renal cell cancer [20] and hepatocellular carcinoma [24]. However, the role of the change in SII (ΔSII) before and after treatment is unknown for patients undergoing curative surgery for CRC.

Therefore, we designed the study to evaluate the prognostic value of ΔSII in CRC patients who received curative resection.

2. Materials and Methods

2.1. Patients. In total, 206 sequential patients diagnosed with CRC who were treated at our institute from February 2010 to May 2015 were collected. The tumor stage was classified according to the seventh edition of the American Joint Committee on Cancer (AJCC) TNM classification system. The clinicopathological characteristics and laboratory data were collected for each patient. Patients were included if they underwent surgical resection and had sufficient laboratory data and follow-up data available. Patients with infection and emergency cases or patients using anti-inflammatory or immunosuppressive medicines were excluded. We also excluded the patients who received neoadjuvant therapy, chemotherapy, or radiotherapy. Follow-up assessments included routine laboratory and physical examinations as well as imaging examinations every 3 months in the first 3 years and every 6 months thereafter. The end points were overall survival (OS) and disease-free survival (DFS).

2.2. Ethical Statement. All procedures performed were in accordance with the ethical standards of the responsible committee for human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This study was approved by the Institutional Review Board of Nanjing Medical University Affiliated Suzhou Hospital (No. KL901056).

2.3. Calculation and Definition of SII and ΔSII. The platelet, neutrophil, and lymphocyte count at 7-day preoperative and postoperative. The SII was calculated as follows:

\[ SII = \text{platelet counts} \cdot \text{neutrophil counts}/\text{lymphocyte counts} \]

The ΔSII (change in SII) was calculated as the postoperative SII minus the preoperative SII.

2.4. Statistical Analysis. Association analysis was performed with the Fisher exact test or the chi-squared test, when appropriate. The Kaplan-Meier method and log-rank test were used for subsistence analysis. OS was the time between surgery and death or the last follow-up. DFS was the time between surgery and the first relapse (local recurrence and/or distant metastases). Univariate and multivariate Cox regression analyses were used to evaluate independent prognostic value. The optimal cutoff value was calculated with receiver

| Variables               | n  | %   |
|-------------------------|----|-----|
| Age (years)             |    |     |
| >60                     | 73 | 35.4|
| ≤60                     | 133| 64.6|
| Gender                  |    |     |
| Male                    | 108| 52.4|
| Female                  | 98 | 47.6|
| Smoking status          |    |     |
| Yes                     | 63 | 30.6|
| No                      | 143| 69.4|
| KPS                     |    |     |
| >80                     | 148| 71.8|
| ≤80                     | 58 | 28.2|
| Localization            |    |     |
| Rectum                  | 121| 58.7|
| Colon                   | 85 | 41.3|
| Surgical approach       |    |     |
| Laparoscopy             | 117| 56.8|
| Open                    | 89 | 43.2|
| Adjuvant therapy        |    |     |
| Yes                     | 101| 49.0|
| No                      | 105| 51.0|
| CEA (ng/ml)             |    |     |
| >5                      | 89 | 43.2|
| ≤5                      | 117| 56.8|
| Pathological stage      |    |     |
| Stages I–II             | 109| 52.9|
| Stages III–IV           | 97 | 47.1|
| Differentiated degree   |    |     |
| High-middle             | 173| 84.0|
| Minor                   | 33 | 16.0|
| Lymphatic invasion      |    |     |
| Yes                     | 99 | 48.1|
| No                      | 107| 51.9|
| Vascular invasion       |    |     |
| Yes                     | 99 | 48.1|
| No                      | 107| 51.9|

KPS: Karnofsky Performance Status; CEA: carcinoembryonic antigen.

SII = platelet counts • neutrophil counts/lymphocyte counts. The ΔSII (change in SII) was calculated as the postoperative SII minus the preoperative SII.
operating characteristic (ROC) curves. All tests were two-sided, and \( p < 0.05 \) was considered to be significant. The SPSS 25.0 statistical software (IBM Corporation, Armonk, NY, USA) was used for statistical analysis.

### 3. Results

#### 3.1. Patient Characteristics.
A total of 206 CRC patients received surgical were enrolled in the study. The median age was 56.8 years (27-83 years). The median follow-up duration was 46.5 months (8-98 months). The male and female patients were 108 (52.4%) and 98 (47.6%), respectively. In total, the number of early-stage (I-II) patients was 109 (52.9%) and the number of advanced-stage (III-IV) patients was 97 (47.1%). A total of 101 (49.0%) patients received adjuvant therapy (radiation, chemotherapy, or radiochemotherapy). The baseline of patient characteristics is shown in Table 1.

#### 3.2. Survival Results and Prognostic Values.
For all patients, before the last follow-up, 64 (31.1%) patients died, and 74 (35.9%) patients developed recurrence. The median DFS and OS were 44.6 months (2-80 months) and 51.6 months (8-98 months), respectively. The 3-year and 5-year OS rates were 60.4% and 36.7% in the high-\( \Delta SII \) group and 87.6% and 79.8% in the low-\( \Delta SII \) group. The 3-year and 5-year DFS rates, respectively, were 54.1% and 34.1% in the high-\( \Delta SII \) group and 80.3% and 78.5% in the low-\( \Delta SII \) group.

#### 3.3. Overall Survival Prediction with ROC Curve.
We attempted to select the optimal cutoff for the \( \Delta SII \) in our study with ROC curve analysis. The optimal cutoff value for the \( \Delta SII \) was 127.7 for the OS prediction, with an AUC of 0.774 (sensitivity = 65.6% and specificity = 77.5%) (Figure 1). Consequently, the patients were divided into two groups, the high \( \Delta SII \) group (\( \Delta SII > 127.7 \)) or low \( \Delta SII \) group (\( \Delta SII \leq 127.7 \)). 74 patients (35.9%) with high \( \Delta SII \) were considered the high-risk group, and 132 patients (64.1%) with low \( \Delta SII \) were considered the low-risk group.

#### 3.4. The \( \Delta SII \) and Clinicopathological Characteristics.
The clinicopathological characteristics in the high-\( \Delta SII \) group (\( \Delta SII > 127.7 \)) and low-\( \Delta SII \) group (\( \Delta SII \leq 127.7 \)) are shown in Table 2. There were no significant differences between the two groups, except for age (\( p < 0.001 \)), adjuvant therapy (\( p = 0.016 \)), and vascular invasion (\( p = 0.013 \)).

#### 3.5. Overall Survival and Disease-Free Survival according to the \( \Delta SII \).
The OS and DFS was estimated with the Kaplan-Meier method (Figures 2 and 3). The 3-year and 5-year OS rates, respectively, were 60.4% and 36.7% in the high-\( \Delta SII \) group and 87.6% and 79.8% in the low-\( \Delta SII \) group. The 3-year and 5-year DFS rates, respectively, were 54.1% and 34.1% in the high-\( \Delta SII \) group and 80.3% and 78.5% in the low-\( \Delta SII \) group.

#### 3.6. Univariate and Multivariate Cox Regression Survival Analyses.
In the univariate analysis, smoking (HR = 1.890, 95% CI = 1.028-3.476, \( p = 0.040 \)), pathological stages III-IV (HR = 0.451, 95% CI = 0.270-0.755, \( p = 0.002 \)), a high-middle degree of differentiation (HR = 0.476, 95% CI = 0.262-0.862, \( p = 0.014 \)), lymphatic invasion (HR = 1.934,
Table 2: Clinicopathological variables of 206 colorectal cancer patients according to the ΔSII.

| Variables                  | ΔSII > 127.7 | ΔSII ≤ 127.7 | p     |
|----------------------------|--------------|--------------|-------|
| Age (years)                |              |              |       |
| >60                        | 38 (51.4)    | 35 (26.5)    | <0.001|
| ≤60                        | 36 (48.6)    | 97 (73.5)    |       |
| Gender                     |              |              |       |
| Male                       | 33 (44.6)    | 75 (56.8)    | 0.092 |
| Female                     | 41 (55.4)    | 57 (43.2)    |       |
| Smoking status             |              |              |       |
| Yes                        | 20 (27.0)    | 43 (32.6)    | 0.407 |
| No                         | 54 (73.0)    | 89 (67.4)    |       |
| 'KPS                       |              |              |       |
| >80                        | 51 (68.9)    | 97 (73.5)    | 0.485 |
| ≤80                        | 23 (31.1)    | 35 (26.5)    |       |
| Localization               |              |              |       |
| Rectum                     | 46 (62.2)    | 75 (56.8)    | 0.455 |
| Colon                      | 28 (37.8)    | 57 (43.2)    |       |
| Surgical approach          |              |              |       |
| Laparoscopy                | 42 (56.8)    | 75 (56.8)    | 0.993 |
| Open                       | 32 (43.2)    | 57 (43.2)    |       |
| Adjuvant therapy           |              |              |       |
| Yes                        | 28 (37.8)    | 73 (35.4)    | 0.016 |
| No                         | 46 (62.2)    | 59 (64.6)    |       |
| 'CEA (ng/ml)               |              |              |       |
| >5                         | 33 (44.6)    | 56 (42.4)    | 0.763 |
| ≤5                         | 41 (55.4)    | 76 (57.6)    |       |
| Pathological stage         |              |              |       |
| Stages I-II                | 42 (56.8)    | 67 (50.8)    | 0.408 |
| Stages III-IV              | 32 (43.2)    | 65 (49.2)    |       |
| Differentiated degree      |              |              |       |
| High-middle                | 61 (82.4)    | 112 (84.8)   | 0.650 |
| Minor                      | 13 (17.6)    | 20 (15.2)    |       |
| Lymphatic invasion         |              |              |       |
| Yes                        | 32 (43.2)    | 67 (50.8)    | 0.300 |
| No                         | 42 (56.8)    | 65 (49.2)    |       |
| Vascular invasion          |              |              |       |
| Yes                        | 27 (36.5)    | 72 (54.5)    | 0.013 |
| No                         | 47 (63.5)    | 60 (45.5)    |       |

1KPS: ΔSII; change in the systemic immune-inflammation index; KPS: Karnofsky Performance Status; CEA: carcinoembryonic antigen.

95% CI = 1.159-3.227, p = 0.012), vascular invasion (HR = 3.508, 95% CI = 1.771-5.279, p < 0.001), and the ΔSII (HR = 4.281, 95% CI = 2.553-7.719, p < 0.001) were associated with poor OS (Table 3). Adjuvant therapy (HR = 0.627, 95% CI = 0.395-0.993, p = 0.047), pathological stages III-IV (HR = 0.512, 95% CI = 0.321-0.814, p = 0.005), vascular invasion (HR = 3.572, 95% CI = 2.118-6.024, p < 0.001), and the ΔSII (HR = 4.041, 95% CI = 2.514-6.496, p < 0.001) were able to predict DFS (Table 4). The multivariate analysis revealed that pathological stages III-IV (HR = 0.442, 95% CI = 0.236-0.827, p = 0.011), vascular invasion (HR = 2.182, 95% CI = 1.243-3.829, p = 0.007), and the ΔSII (HR = 4.301, 95% CI = 2.517-7.350, p < 0.001) were independent predictors of OS (Table 3). Adjuvant therapy (HR = 0.415, 95% CI = 0.250-0.687, p = 0.001), vascular invasion (HR = 3.305, 95% CI = 1.944-5.620, p < 0.001), and the ΔSII (HR = 4.924, 95% CI = 2.992-8.102, p < 0.001) were significant prognostic factors for DFS (Table 4).

4. Discussion

In this study, we investigated the association between the ΔSII and the clinical outcome of CRC. Our study demonstrated that the ΔSII had an independent prognostic value in CRC patients who underwent curative resection. Our study suggested that the ΔSII could independently predict survival in colorectal cancer after curative resection.

Some inflammatory index, such as the NLR, LMR, and PLR, have been indicated to be valid prognosticators for CRC [17, 25–27]. However, these prognosticators are typically based on two immunoinflammation cell types, and their predictive reliability for clinical outcomes was limited. The SII has been widely investigated and was demonstrated to be an effective predictor of the prognosis of various malignant tumors [18–20, 28, 29]. Hu et al. [19] initially revealed the prognostic value of the SII in liver cancer and demonstrated that higher preoperative SII heralded shorter survival times. Tong et al. [28] also demonstrated that a high SII was associated with poor outcomes in non-small-cell lung cancer. Jiang et al. [29] conducted a propensity score-matched analysis, which showed that the SII could predict OS in nasopharyngeal carcinoma patients independently.

However, most previous studies only indicated the preoperative value and the results were not consistent. Some studies indicate that SII was proposed as a significant prognostic factor in CRC [21, 22, 30], whereas other studies were not significant [23, 31]. Few studies focused on the changes of inflammatory markers before and after treatment, which might reflect the correlation between the host’s inherent inflammatory state and immune response. Wang et al. [24] reported that dynamic changes in the SII represent new prognosis indicators for liver cancer that received surgery. As far as we know, this present study was the first to explore the role of the ΔSII in CRC. These results revealed that the ΔSII (p < 0.001) was an independent risk factor that predicted OS. Furthermore, we confirmed the significant predictive value of the ΔSII (p < 0.001) for DFS. We also observed that the surgical approach, CEA level, differentiation degree, and lymphatic invasion were not significantly associated with OS and DFS for CRC patients. Adjuvant therapy was only associated with DFS. These results revealed that the ΔSII reflects the systemic immune-inflammatory changes before and after surgery, which may indicate a more accurate prognosis.

The underlying mechanism by which ΔSII predicts the survival of CRC may be related to platelets, neutrophils, and lymphocytes. Elevated platelet counts can protect circulating tumor cells (CTCs) and promote metastasis by...
inducing CTC epithelial-mesenchymal transition [32, 33]. Neutrophils have been reported to have the potential to promote tumor progression by establishing a tumor microenvironment, including a lot of inflammatory index, such as growth factors (CXCL8), proangiogenic factors (VEGF), and antiapoptotic factors (NF-κB) [34–36]. Lymphocytes
can inhibit tumor cell proliferation and migration by secreting cytokines, inducing cytotoxic cell death [37]. Therefore, a higher SII indicates a stronger inflammatory reaction while weaker immune defense, leading to poor clinical outcomes.

There are several limitations of this study. Firstly, the current study used a retrospective design with a small population. Although we utilized data that was obtained from the electronic medical records, biases such as selection bias may exist. Secondly, the impact of treatment after recurrence on survival has not been analyzed due to lack of sufficient information. Therefore, further studies with larger sample sizes and prospective research designs are necessary to demonstrate the relationship between the ΔSII and prognosis for CRC patients.

In conclusion, our study demonstrated ΔSII was an independent prognostic factor for CRC patients undergoing curative resection. The patients with CRC would receive more individualized treatment according to the ΔSII in the future.

**Data Availability**

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

**Conflicts of Interest**

The authors declared that no conflicts of interest exist with respect to the authorship and/or publication of this article.
Authors’ Contributions

Qingqing Chen, Haohao Wu, and Xinwei Guo contributed equally to this work.

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