Tohoku J. Exp. Med., 2023, **261**, 229-238

# Systemic Immune-Inflammation Index Predicts Tumor Recurrence after Radical Resection for Colorectal Cancer

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The systemic inflammatory response is associated with tumor promotion and suppression. Accumulating evidence shows that peripheral blood markers of inflammatory response predict clinical outcomes in various human cancers. The aim of this study was to investigate the prognostic relevance of the inflammation-based biomarkers in colorectal cancer (CRC). We retrospectively analyzed 118 CRC patients who underwent curative resection between 2012 and 2017. The inflammation-based biomarkers were evaluated by using preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), prognostic nutritional index (PNI), and Glasgow prognostic score (GPS). Prognostic values were assessed by the Kaplan-Meier analysis for cancer-specific recurrence-free survival (RFS) and Cox proportional-hazards model. There were significant differences in the levels of NLR, PLR, SII, and SIRI between recurrence and non-recurrence group. The area under the curve (AUC) for SII was 0.710, which showed the highest value in the inflammation-based biomarkers. Multivariate analysis identified that SII ($p = 0.0031$) and lymph node metastasis ($p = 0.0168$) were independent prognostic factors for recurrence. High SII exhibited more dismal RFS than low SII in CRC patients with non-metastatic lymph node ($p = 0.0002$). Our study suggests that SII and lymph node metastasis could be useful indicators in predicting the recurrence of CRC patients. Additionally, SII could accurately stratify CRC patients with tumor recurrence by combining with lymph node metastasis. This result would be beneficial for determining the optimal therapeutic strategies after surgical resection for CRC.

**Keywords:** colorectal cancer; lymph node metastasis; prognosis; recurrence; systemic immune-inflammation index
Tohoku J. Exp. Med., 2023 November, **261** (3), 229-238.
doi: 10.1620/tjem.2023.J074

## Introduction

Colorectal cancer (CRC) is the most common malignancy in digestive system. According to Cancer Statistics 2022 (Siegel et al. 2022), the patients were estimated as new cases of 151,030, and deaths of 52,580 in the United States. Surgical resection remains the only potentially curative treatment, while their prognosis of CRC patients is showing an improving trend by providing multidisciplinary treatment approach including novel molecular targeted agents in the last few decades (Cammà et al. 2000; Saltz et al. 2008; Douillard et al. 2010). However, postoperative patients with recurrence and metastasis culminate in dismal prognosis, and the risk factors affecting outcomes of their patients in CRC remain to be fully elucidated. Therefore, the effective molecular biomarkers for predicting these factors are highly demanded in clinical practice.

Growing evidence suggests that systemic inflammatory response is associated with the prognosis in various cancers, including esophagus, stomach, colorectum, liver, pancreas, bladder, and breast (Dolan et al. 2017; Inoue et al. 2021; Yamamoto et al. 2021). The tumor microenvironment and host immune system played a critical role in cancer development, and these behaviors might have involved in systemic inflammation (Coussens and Werb 2002; Mantovani et al. 2008). Several studies have demonstrated

Received July 10, 2023; revised and accepted August 29, 2023; J-STAGE Advance online publication September 7, 2023
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that inflammation-based prognostic markers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), prognostic nutritional index (PNI), and Glasgow prognostic scale (GPS) provide survival information on patients with colorectal cancer (Zou et al. 2016; Chen et al. 2017; Yamamoto et al. 2021; Cai et al. 2023). However, there have been relatively few studies which have explored tumor recurrence and metastasis of CRC patients after surgery by combining comprehensive inflammation-based biomarkers with clinicopathological factors.

The aim of this study was to examine the prognostic value for recurrence of the preoperative inflammation-based biomarkers in CRC patients, and further to clarify clinical significance of clinicopathological factors including these biomarkers.

## Materials and Methods

*Patient selection and study endpoint*

This study retrospectively collected the clinical data from 187 patients who underwent surgical resection for CRC between January 2012 and December 2017 at Sagamidai Hospital. Of those patients, we excluded 16 patients who had received transanal endoscopic microsurgery (TEM) or transanal tumor resection (TAR), 23 patients with distant metastasis diagnosed preoperatively, and 30 patients with unavailable or incomplete clinical data. Then, a total of 118 patients were eligible for analysis in this study (Fig. 1). The primary endpoint was to explore the inflammation-based biomarker associated with cancer-specific recurrence-free survival (RFS), which was defined as the duration from surgical resection to relapse of disease or the last follow up time without recurrence. The death from causes unrelated to CRC were censored. All procedures were performed in accordance with the Declaration of Helsinki and the present study was approved by the Ethics Committee of Sagamidai Hospital (No. 21-01). Informed consent for this study was obtained by opt-out method on our hospital website.

*Postoperative follow-up*

Follow-up was performed according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 (Japanese Society for Cancer of the Colon and Rectum 2019). Briefly, the patients were assessed every 3 months for 3 years, every 6 months during 3 to 5 years after surgery. They were followed up through routine peripheral blood test, computed tomography (CT), ultrasonography (US), magnetic resonance imaging (MRI), and colonoscopy. Follow-up information was obtained by medical records or direct communication with patients or their family. Eighteen patients were lost to follow-up during the observation period.

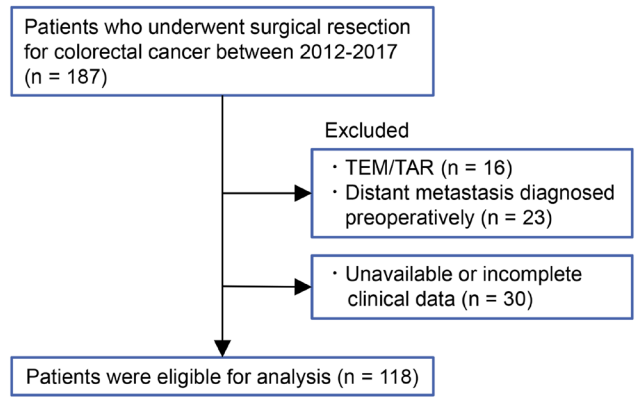


Fig. 1. Consort diagram showing the flow of participants. TEM, transanal endoscopic microsurgery; TAR, transanal tumor resection.

*The definitions of clinicopathological factors including inflammation markers*

Pathological stage was classified according to the 8th edition of the UICC/AJCC TNM staging system (Brierley et al. 2016). Surgical complication was assigned based on the Clavien-Dindo classification (Dindo et al. 2004). The NLR and PLR were defined as the absolute neutrophil count or platelet count divided by the absolute lymphocyte count measured in peripheral blood, respectively. The LMR was obtained by dividing the absolute lymphocyte count by the absolute monocyte count. The SII and SIRI were defined as neutrophil × platelet/lymphocyte count, and neutrophil × monocyte/lymphocyte count, respectively. The SII was expressed as $\times 10^3/\mu$l. The PNI was calculated by the following formula: 10 × albumin + 0.005 × lymphocyte count. The GPS was scored by the combination of C-reactive protein and serum albumin levels as follows. Patients with both an elevated CRP (> 1.0 mg/dl) and hypoalbuminemia (< 3.5 mg/dl) was assigned a score of 2. Those with either an elevated CRP or hypoalbuminemia alone was assigned a score of 1. Those with normal CRP and albumin was assigned a score of 0.

*Statistical analysis*

The clinical data were expressed as median and range for continuous variables. They were analyzed using Mann-Whitney's U test and Kruskal-Wallis test, as appropriate. Categorical variables were analyzed using the Chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) analysis was conducted to identify the optimal cut-off values for continuous variables. RFS was evaluated by Kaplan-Meier method, and log-rank test was used to compared RFS between groups. Variables suggesting potential prognostic factors on univariate analyses were subjected to a multivariate analysis using a Cox proportional-hazards model. P-value < 0.05 was considered to indicate statistical significance. All statistical analyses were conducted using the SAS software package (JMP Pro17, SAS Institute, Cary, NC, USA).

## Results

*Patient characteristics and clinical outcomes*

A total of 118 patients who underwent surgical resection for CRC were enrolled in this study. The median age was 70 years (range, 34-94), including 72 males (61.0%) and 46 females (39.0%). Tumor locations were as follow: 70 cases of colon and 48 of rectum. Based on the 8th TNM classification, there were 29, 48, and 41 patients classified as stage 0-I, II, and III, respectively. Postoperative complications of grade III or higher according to the Clavien-Dindo classification were detected in 7 patients: postoperative ileus (n = 3), anastomotic leakage (n = 3), and incisional hernia (n = 1). Perioperative mortality rate was 0%. Adjuvant chemotherapy was performed in 59 of 118 patients. The median duration of follow-up was 60 months. Twenty-two cases had recurrent diseases. The median of preoperative NLR, PLR, LMR, SII, SIRI, and PNI were 2.31 (range, 0.69-9.05), 156 (range, 68.9-422), 4.74 (range, 1.71-11.8), 559 (range, 126-3,614), 788 (range, 156-4,629), and 50.2 (range, 35.2-61.0), respectively. The GPS was 0 score in 100 patients (84.7%) and 1-2 score in 18 patients (15.3%). Preoperative blood tests measured 19.5 day (2-48) before surgery. The clinicopathologic characteristics of the patients are summarized in Table 1.

*Associations of the levels of inflammatory markers with the status of recurrence in CRC and the optimal cut-off values using ROC curve analysis*

To evaluate the accuracy of 7 candidate inflammatory markers for predicting postoperative recurrence in CRC, we compared the levels of inflammatory markers between the non-recurrent group and recurrent group. As shown in Fig. 2A, the levels of preoperative NLR, PLR, SII, and SIRI in the recurrence group were significantly higher than those in the non-recurrence group (NLR: $p = 0.0037$, PLR: $p = 0.0071$, SII: $p = 0.0022$, SIRI: $p = 0.0278$), whereas LMR and PNI were not significant difference between these

Table 1. Clinical characteristics of the patients.

| Patient characteristics | | Number |
|---|---|---|
| Age, year, median (range) | 70 (34-94) | |
| | ≥ 65 / < 65 | 8 /34 |
| Sex | male / female | 72/46 |
| Body mass index, kg/m², median (range) | 22.2 (13.4-34.2) | |
| | ≥ 25 / < 25 | 24/94 |
| Tumor location | Colon / Rectum | 70/48 |
| T stage | Tis, TI / T2 / T3 / T4 | 20/13/57/28 |
| N stage | N0/N1 | 77/41 |
| TNM stage | 0, I / II / III | 29/48/41 |
| Histology | differentiated / undifferenciated | 112/6 |
| Lymphatic invasion | absent/present | 47/71 |
| Vascular invasion | absent/present | 51/67 |
| Postoperative complications | | |
| Clavien-Dindo classification | 0-II/III-V | 111/7 |
| Postoperative length of stay, day, median (range) | 18 (7-65) | |
| | > 21 / ≤ 21 | 41/77 |
| Adjuvant chemotherapy | absent / present | 59/59 |
| Preoperative blood test | | |
| CRP, mg/dl | ≥ 0.3 / < 0.3 | 31/87 |
| CEA, ng/ml | ≥ 5.0 / < 5.0 | 34/84 |
| NLR, median (range) | 2.31 (0.69-9.05) | |
| PLR, median (range) | 156 (68.9-422) | |
| LMR, median (range) | 4.74 (1.71-11.8) | |
| SII, median (range) | 559 (126-3,614) | |
| SIRI, median (range) | 788 (156-4,629) | |
| PNI, median (range) | 50.2 (35.2-61.0) | |
| GPS | 0/1, 2 | 100/18 |

CRP, C-reactive protein; CEA, carcinoembryonic antigen; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; PNI, prognostic nutritional index; GPS, Glasgow prognostic score.

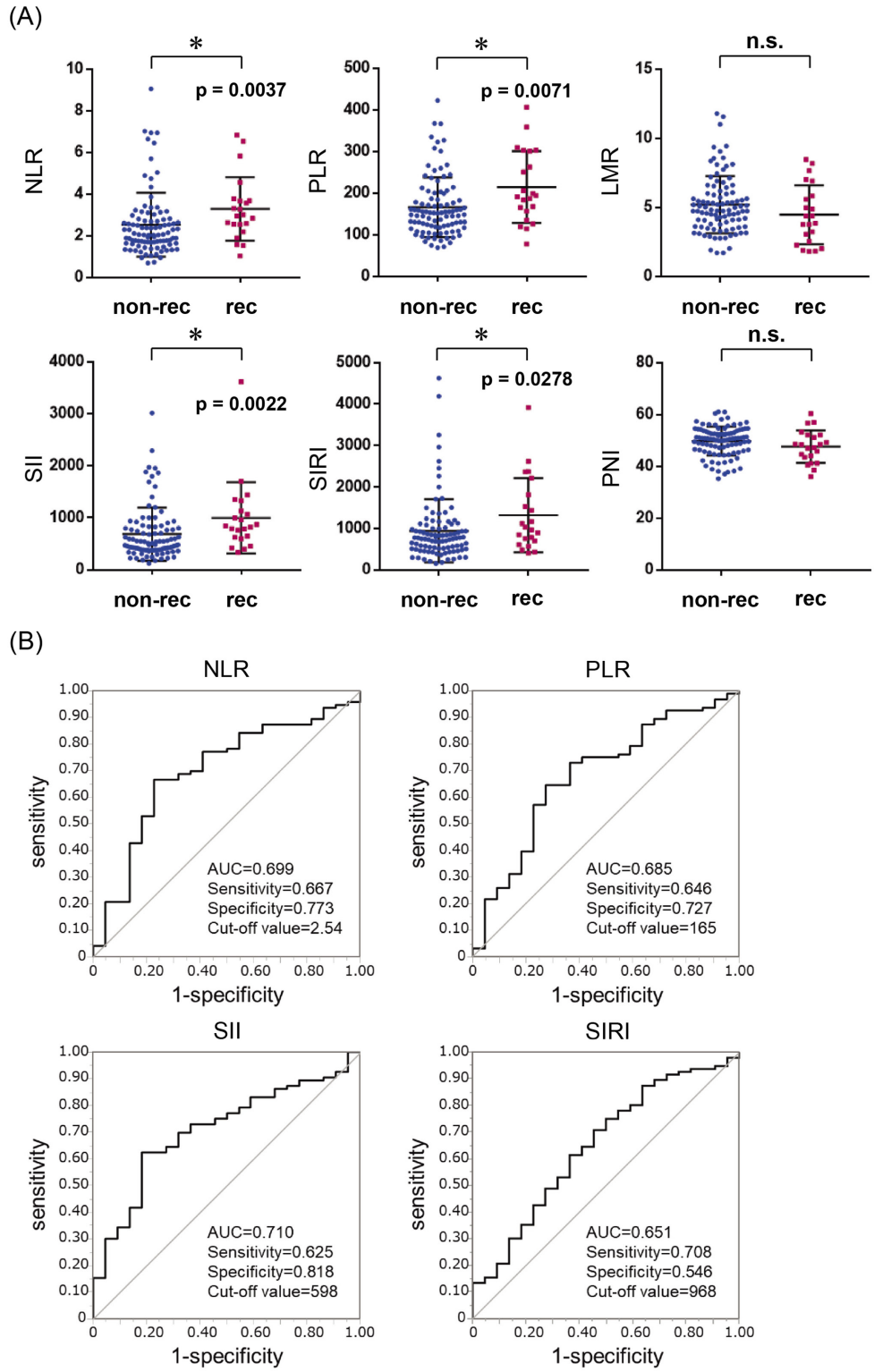


Fig. 2. Association between the levels of inflammatory markers and tumor recurrence and determination of their cut-off values.

(A) The levels of inflammatory markers, neutrophil-to-lymphocyte ratio (NLR) platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI) and prognostic nutritional index (PNI), depending on tumor recurrence. Data are expressed as the median and the interquartile range. non-rec, non-recurrence group; rec, recurrence group; n.s., not significant. *significant ($p < 0.05$). (B) Receiver Operating Characteristic (ROC) curve of NLR, PLR, SII, and SIRI for detection of tumor recurrence in colorectal cancer (CRC).

Table 2. Correlation of clinicopathological characteristics and systemic immune-inflammation index (SII) levels in colorectal cancer (CRC).

| Patient characteristics | | SII ≥ 598 (n = 54) | SII < 598 (n = 64) | p value |
|---|---|---|---|---|
| Age | ≥ 65 | 38 | 46 | 0.8574 |
| | < 65 | 16 | 18 | |
| Sex | male | 31 | 41 | 0.4604 |
| | female | 23 | 23 | |
| Tumor location | Colon | 36 | 34 | 0.1344 |
| | Rectum | 18 | 30 | |
| T stage | Tis, T1 | 4 | 16 | 0.0043 |
| | T2 | 3 | 10 | |
| | T3 | 29 | 28 | |
| | T4 | 18 | 10 | |
| N stage | N0 | 33 | 44 | 0.3856 |
| | N1 | 21 | 20 | |
| TNM stage | 0, I | 7 | 22 | 0.0217 |
| | II | 26 | 22 | |
| | III | 21 | 20 | |
| Histology | differentiated | 49 | 63 | 0.0507 |
| | undifferenciated | 5 | 1 | |
| Lymphatic invasion | absent | 15 | 32 | 0.0133 |
| | present | 39 | 32 | |
| Vascular invasion | absent | 13 | 38 | < 0.0001 |
| | present | 41 | 26 | |
| Postoperative complications | | | | |
| Clavien-Dindo classification | 0-II | 52 | 59 | 0.3371 |
| | III-V | 2 | 5 | |
| Postoperative length of stay | > 21 | 22 | 19 | 0.2093 |
| | ≤ 21 | 32 | 45 | |
| Adjuvant chemotherapy | absent | 22 | 37 | 0.0640 |
| | present | 32 | 27 | |
| Preoperative blood test | | | | |
| CRP | ≥ 0.3 | 21 | 10 | 0.0041 |
| | < 0.3 | 33 | 54 | |
| CEA | ≥ 5.0 | 22 | 12 | 0.0084 |
| | < 0.5 | 32 | 52 | |
| GPS | 0 | 40 | 60 | 0.0026 |
| | 1, 2 | 14 | 4 | |

CRP, C-reactive protein; CEA, carcinoembryonic antigen; GPS, Glasgow prognostic score.

group. The GPS divided by 0 score and 1-2 score was analyzed by the Fisher's exact test, and there was no significant difference (p = 0.7430). Subsequently, the optimal cut-off values of NLR, PLR, SII, and SIRI excluding LMR and PNI with no significant difference by Mann-Whitney test (p > 0.05) were determined using ROC curve analysis. The individual areas under the curve (AUC) for NLR, PLR, SII, and SIRI were 0.699, 0.685, 0.710, and 0.651, respectively. The most optimal cut-off values were defined as 2.54 for NLR (sensitivity = 0.667, specificity = 0.773), 165 for PLR (sensitivity = 0.646, specificity = 0.727), 598 for SII (sensitivity = 0.625, specificity = 0.818), and 968 for SIRI (sensitivity = 0.708, specificity = 0.546) (Fig. 2B).

*Correlation between clinicopathological factors and SII levels divided by the optimized cut-off value in CRC*

Focusing on SII which showed the highest AUC in inflammatory markers, we analyzed the correlation between clinicopathological factors and SII divided by a cut-off value of 598 in primary CRC, which was determined by the Chi-square test or Fisher's exact test. SII was associated with T stage, TNM stage, lymphatic invasion, vascular invasion, CRP, CEA, and GPS, indicating that SII reflected the degree of tumor invasion and inflammatory response

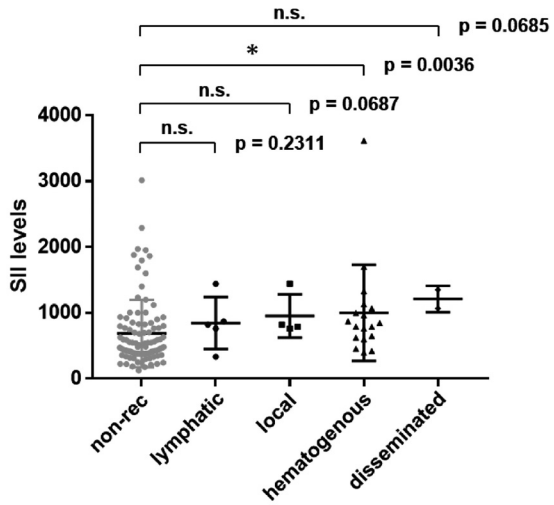


Fig. 3. Recurrence patterns according to systemic immune-inflammation index (SII) values in colorectal cancer (CRC) patients.
non-rec, non-recurrence group; lymphatic, lymphatic metastasis (n = 5); local, local recurrence (n = 4); hematogenous; hematogenous metastasis (n = 18); disseminated, peritoneal dissemination (n = 2); n.s., not significant. *significant ($p < 0.05$).

(Table 2).

*Patterns of initial recurrence and SII values*

We investigated the relationship between the patterns of initial recurrence and SII values in 22 patients with post-operative recurrence. Twenty-nine recurrence patterns were observed in 22 patients, which had hematogenous metastasis in 18 cases, lymphatic metastasis in 5 cases, local recurrence in 4 cases, and peritoneal dissemination in 2 cases. Hematogenous metastasis showed significantly higher SII values than patients without recurrence ($p = 0.0036$). Local recurrence and peritoneal dissemination exhibited marginally significant ($p = 0.0687$ and $p = 0.0685$, respectively) (Fig. 3).

*Univariate and multivariate prognostic analysis including inflammatory markers in primary CRC*

Univariate analysis revealed that lymph node metastasis (N stage) ($p = 0.0049$), TNM stage ($p = 0.0079$), vascular invasion ($p = 0.0066$), preoperative CEA ($p = 0.0085$), preoperative NLR ($p = 0.0001$), preoperative PLR ($p = 0.0022$), preoperative SII ($p = 0.0002$), and preoperative SIRI ($p = 0.0202$) were significantly associated with tumor

Table 3. Univariate and multivariate analysis for recurrent-free survival in colorectal cancer (CRC).

| Patient characteristics | | Univariate analysis | Multivariate analysis | | |
|---|---|---|---|---|---|
| | | p value | HR | 95% CI | p value |
| Age | ≥ 65 / < 65 | 0.8543 | | | |
| Sex | male / female | 0.4849 | | | |
| Body mass index | ≥ 25 / < 25 | 0.1465 | | | |
| Tumor location | Colon/Rectum | 0.5417 | | | |
| T stage | Tis, TI/T2/T3/T4 | 0.0584 | | | |
| N stage | N0/N1 | 0.0049 | 2.82 | 1.20-6.64 | 0.0168 |
| TNM stage | 0, I/II/III | 0.0079 | | | |
| Histology | differentiated/ undifferenciated | 0.9063 | | | |
| Lymphatic invasion | absent/present | 0.0677 | | | |
| Vascular invasion | absent/present | 0.0066 | | | |
| Postoperative complications | | | | | |
| Clavien-Dindo classification | 0-II/III-V | 0.9030 | | | |
| Postoperative length of stay | > 21 / ≤ 21 | 0.4458 | | | |
| Adjuvant chemotherapy | absent / present | 0.4889 | | | |
| Preoperative blood test | | | | | |
| CRP | ≥ 0.3 / < 0.3 | 0.1561 | | | |
| CEA | ≥ 5.0 / < 0.5 | 0.0085 | 2.05 | 0.87-4.86 | 0.1048 |
| NLR | ≥ 2.54 / < 2.54 | 0.0001 | | | |
| PLR | ≥ 165 / < 165 | 0.0022 | | | |
| SII | ≥ 598 / < 598 | 0.0002 | 4.56 | 1.48-14.0 | 0.0031 |
| SIRI | ≥ 968 / < 968 | 0.0202 | | | |
| GPS | 0/1, 2 | 0.5128 | | | |

CRP, C-reactive protein; CEA, carcinoembryonic antigen; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; GPS, Glasgow prognostic score.

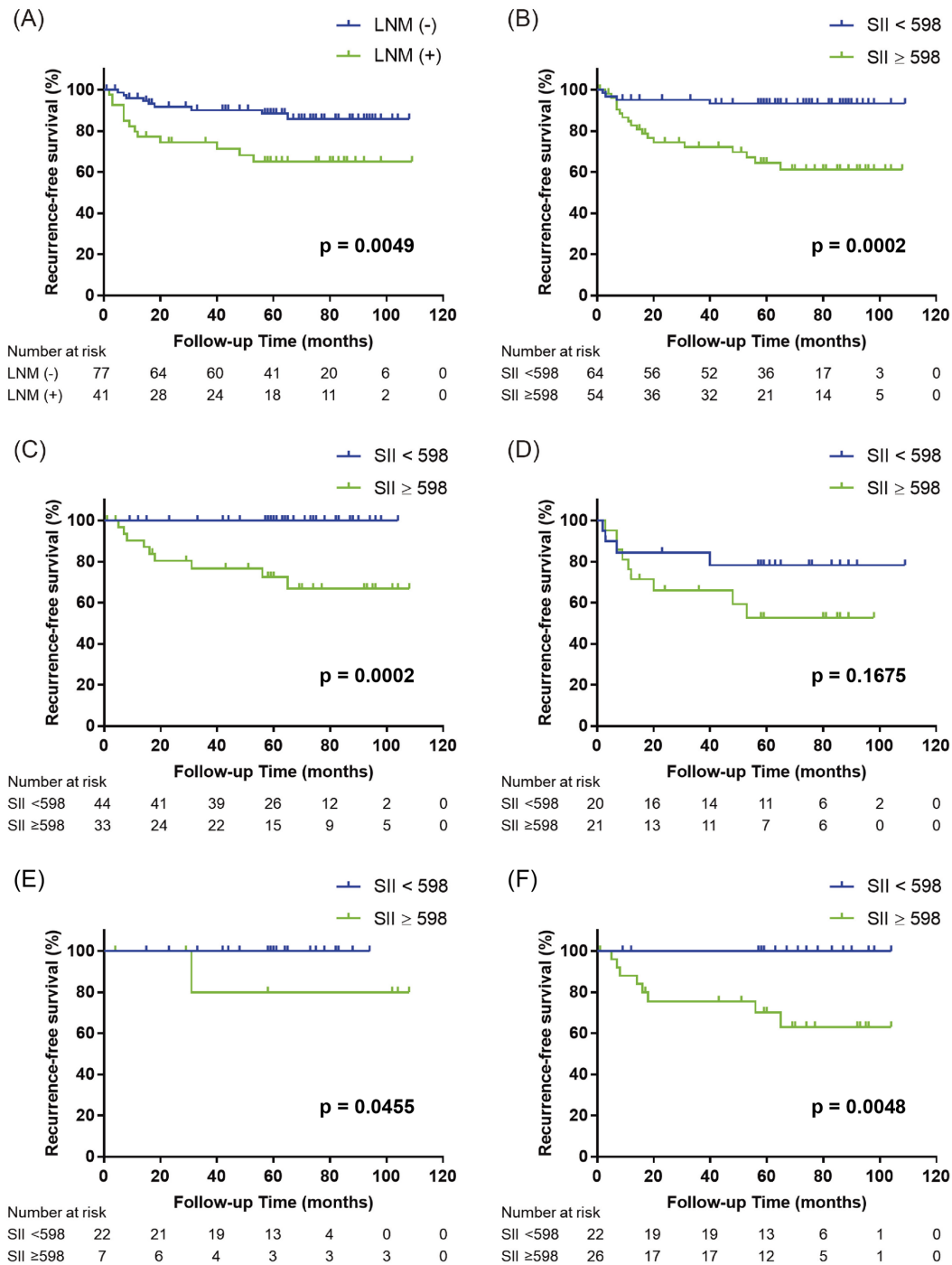


Fig. 4. Kaplan-Meier curves for recurrence-free survival (RFS).
Kaplan-Meier curves for RFS stratified by (A) lymph node metastasis (LNM), and (B) systemic immune-inflammation index (SII) levels in patients with colorectal cancer (CRC). Kaplan-Meier curves for RFS stratified by SII levels in patients without LNM (stage 0-II) (C) and with LNM (stage III) (D). Kaplan-Meier curves for RFS stratified by SII levels in stage 0, I (E) and stage II (F).

recurrence in CRC. The identified univariate prognostic factors were subject to multivariate analysis, in which TNM stage and vascular invasion were excluded due to confounding factor and emphasis on outcome relevance. Additionally, SII showing the highest AUC was used as the representative of inflammatory markers for multivariate analysis. Multivariate analysis indicated that lymph node metastasis (HR 2.82, 95% CI 1.20-6.64, p = 0.0168) and preoperative SII (HR 4.56, 95% CI 1.48-14.0, p = 0.0031) were finally remnant independent prognostic factors related

RFS in CRC (Table 3).

*Predicting recurrence of combined lymph node metastasis and SII levels*

Kaplan-Meier analysis for RFS stratified by lymph node metastasis and SII levels are shown in Fig. 4A, B, respectively. We further examined the association of the combination of independent risk factors, that is lymph node metastasis and SII levels with RFS in CRC. Kaplan-Meier curves showed that low SII group with non-metastatic lymph nodes meaning stage 0-II had significantly much better RFS rather than high SII group without metastatic lymph nodes ($p = 0.0002$) (Fig. 4C). On the other hand, there was a significant trend between those groups with metastatic lymph nodes meaning stage III ($p = 0.1675$) (Fig. 4D). In addition, we analyzed Kaplan-Meier curves for RFS stratified by SII levels in stage 0, I and stage II, respectively. High SII exhibited significantly more dismal RFS than low SII in both stage 0, I ($p = 0.0455$, Fig. 4E) and stage II ($p = 0.0048$, Fig. 4F).

*Effect of adjuvant chemotherapy on SII levels*

We investigated whether adjuvant chemotherapy for SII levels affected survival benefits. Kaplan-Meier analysis for CSS (cancer-specific survival) and RFS showed no significant benefits in both patients with high and low SII (Supplementary Fig. S1).

## Discussion

The systemic inflammatory response has been suggested to be associated with potential prognosis in CRC. Our data demonstrated that preoperative SII was more accurate predictor for recurrence in 7 candidate inflammation-based biomarkers (NLR, PLR, LMR, SII, SIRI, PNI, and GPS). In addition, high SII and lymph node metastasis were independently related to dismal RFS in CRC patients after curative resection. Previous studies have reported that high SII negatively affect the prognosis for overall survival (OS), disease-fee survival (DFS), and RFS in various cancers (Hu et al. 2014; Chen et al. 2017; Inoue et al. 2021), and this can also predict tumor response after neoadjuvant chemoradiotherapy for locally advanced rectal cancer (Eraslan et al. 2021). In addition, there has been shown that the dynamic change between pre and postoperative SII, defined as the delta-SII was associated with clinical outcome for overall survival (OS) and DFS in CRC (Chen et al. 2020). These studies have robustly supported the hypothesis that SII could be a simple and excellent biomarker for postoperative recurrence in primary CRC.

There have been many studies on the relationship between innate immune cells and cancer; however, the mechanism by which SII correlates with prognosis have not been well clarified. There are the following possible explanations for correlation. Neutrophils play an important role in tumor development and progression. Elevated neutrophils upregulate the expression of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha), promoting tumor proliferation, invasion, and metastasis (Balkwill and Mantovani 2001; Kim and Bae 2016). Besides, they accelerate tumor growth through pro-angiogenic factors including vascular endothelial growth factor (VEGF) and create a tumor microenvironment (Kusumanto et al. 2003; Gregory and Houghton 2011). Neutrophil extracellular traps released by neutrophil may be also engaged in distant metastasis by trapping tumor cells (Khan et al. 2021). In addition, platelets are involved in promoting tumorigenesis. Platelets can accelerate tumor growth and angiogenesis by secreting cellular growth factors such as VEGF and platelet-derived growth factor (PDGF). Moreover, platelets play a protective role in cancer cells by adhering to tumors and evading mechanical forces and immune surveillance (Schlesinger 2018). On the other hand, lymphocytes act to eliminate tumorigenesis by inducing cytotoxic immune response, helping to attack residual and micrometastatic tumor cells. A decrease of peripheral lymphocyte counts lead to dismal prognosis for cancer patients by impairing immune function (Ropponen et al. 1997; Grivennikov et al. 2010). Therefore, SII indicates a balance between the protumor inflammatory response of neutrophils or platelets and anti-tumor immune system of lymphocytes, and it may reflect the potential prognosis in cancer patients.

In this study, we focused on recurrence in CRC patients after surgery since the importance of prognostic improvement by early detection has been demonstrated in postoperative CRC surveillance (van der Stok et al. 2017). There have been several reports on the correlation between SII levels and recurrence after curative resection for CRC. Chen et al. (2017) have first described that SII might predict survival prognosis for OS and DFS after surgery for CRC. However, few papers have examined the association between clinicopathological factors including comprehensive inflammatory markers and recurrence. Accordingly, we revealed that SII was an indicator with highest accuracy among 7 inflammatory biomarkers. The optimal cut-off value of SII was 598 in present study, which was consistent with the range of 340 to 1,505 in previous studies (Chen et al. 2017; Lu et al. 2019). This variation may have been influenced by the study population, race, region, setting of endpoints, etc. We also examined the SII values in the recurrence group and the time to recurrence, but no significant correlation was shown.

According to the NCCN guidelines (Benson et al. 2021), the adjuvant chemotherapy has been recommended for the purpose of suppressing recurrence in stage III CRC; however, the efficacy has not been established in stage II CRC. We suggest that SII identified by multivariate analysis may be an excellent biomarker for determining the indication of adjuvant chemotherapy in stage 0-II CRC which has no lymph node metastasis. In present study, we also showed that adjuvant chemotherapy for SII levels has limited effect on survival benefits (Supplementary Fig. S1).

However, these results may be attributed to the chemoresistance to SII levels and the difference in TNM stage between two groups because high-risk patients are eligible for adjuvant chemotherapy. Further verification is required to determine the effects of adjuvant chemotherapy for SII levels due to different types of anticancer agents and small sample sizes.

Recent studies have proposed the importance of host immune cells in various cancers. Pagès et al. (2018) have reported the usefulness of Immunoscore, which shows that the number of CD3 and CD8 positive cells in tumor specimens correlates with tumor recurrence for CRC, suggesting that this score is more useful in combination with the TNM classification. The present study has demonstrated that SII which was an index of inflammation and immune response facilitated the selection of high-risk patients for recurrence by combining lymph node metastasis status. In addition, SII can be measured in peripheral blood and clinically applied as an inexpensive and safe examination method. These results may be a promising predictor of recurrence that complements both the tumor and host side factors.

The limitations of this study are a retrospective study design and low statistical power in CRC patients. This study may suffer from some biases, i.e., calculation of cut-off value for single center data and tumor location and timing of preoperative blood sampling, and treatment strategy such as surgical procedure, range of lymph node dissection and application of chemoradiotherapy. Prospective validation is thus further needed to clarify our findings.

In conclusion, our study provided evidence that SII among 7 inflammation-based biomarkers could be a potential biomarker for predicting recurrence in CRC. Additionally, the combination of SII and lymph node metastasis could effectively enrich CRC patients who indicated tumor recurrence after curative surgery. These markers would be beneficial for clinical clarification of the optimal strategies and postoperative surveillance in CRC.

## Acknowledgments

We thank the staff at Sagamidai Hospital and Kitasato University Hospital for their important contributions.

## Conflict of Interest

The authors declare no conflict of interest.

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## Supplementary Files

Please find supplementary file(s);
https://doi.org/10.1620/tjem.2023.J074