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# Exploratory Study on the Association Between Pre-treatment Factors and Hematological Toxicity in Colorectal Cancer Patients Receiving CapeOX (Capecitabine Plus Oxaliplatin) Therapy

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## Abstract

**Background:** The capecitabine plus oxaliplatin (CapeOX) regimen is commonly used for adjuvant treatment and selected first-line treatment settings in colorectal cancer. However, hematologic toxicities, such as leukopenia, neutropenia, anemia, and thrombocytopenia, may adversely affect treatment continuity, resulting in treatment delays, dose reductions, or treatment discontinuation. If these toxicities could be predicted based on pre-treatment blood test results and markers of inflammation and nutrition, it would lead to improved treatment continuity. In this study, we explored potential associations related to hematologic toxicities that occur at the end of the first cycle of CapeOX therapy.

**Methods:** A retrospective analysis was conducted on 108 patients with colorectal cancer who began CapeOX therapy between September 2020 and October 2023. We evaluated hematologic toxicity (Grade  $\geq 1$ ) at the end of the first treatment cycle based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and examined its association with pre-treatment blood test results, nutritional indices (PNIs), and inflammatory markers (systemic inflammation response index (SIRI), systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR)). We performed multivariate logistic regression analysis on factors showing significant differences and calculated cutoff values using receiver operating characteristic (ROC) analysis.

**Results:** An SII value of  $\leq 496.8$  was identified as a significant pretreatment factor associated with the development of leukopenia. For hemoglobin reduction, age  $\geq 68$  years, red blood cell count  $\leq 394 \times 10^4/\mu\text{L}$ , and hemoglobin (Hb)  $\leq 11.7$  g/dL were associated; for thrombocytopenia, lymphocyte count  $\leq 12.41 \times 10^2/\mu\text{L}$  and SII  $\leq 477.9$  were significantly associated. The identified associations may help generate hypotheses for future prospective studies of pre-treatment risk assessment and supportive-care strategies.

**Conclusions:** Evidence suggests that some of the hematologic toxicities associated with CapeOX therapy show exploratory associations with pre-treatment blood tests and markers of inflammation and nutrition. These exploratory associations may help inform future hypothesis-generating research on pretreatment risk assessment and supportive-care strategies.

**Categories:** Therapeutics, Pharmacology, Oncology

**Keywords:** adverse effect, capeox therapy, colorectal cancer, cut-off value, hematologic toxicity, inflammatory marker, predictor

## Introduction

Colorectal cancer is one of the leading malignant tumors in Japan, with both incidence and mortality rates remaining high, partly because a substantial proportion of cases present with symptoms related to metastatic disease [1,2]. The capecitabine plus oxaliplatin (CapeOX) regimen is commonly used for adjuvant treatment and selected first-line treatment settings in colorectal cancer [3]. However, it has been reported that CapeOX therapy is associated with a variety of adverse effects, including peripheral neuropathy, hand-foot syndrome, gastrointestinal symptoms, and hematologic toxicity, which can lead to treatment delays, dose reductions, or discontinuation [4,5].

In recent years, efforts have been made to predict the occurrence of adverse effects using pre-treatment clinical data. For example, with regard to the prediction of early adverse effects in CapeOX therapy, factors such as age, body build, renal function, and muscle mass have been shown to be associated with these effects, and models using machine learning have achieved a certain level of predictive accuracy [4].

Furthermore, it has been suggested that pre-treatment blood test results and markers of inflammation and nutritional status may serve as predictive factors for non-hematologic adverse effects associated with CapeOX therapy, such as peripheral neuropathy, nausea, loss of appetite, and diarrhea [5].

However, there are few studies that have systematically examined have systematically examined predictive factors, focusing on hematologic toxicity (leukopenia, neutropenia, anemia, and thrombocytopenia), using

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pre-treatment blood test results and markers of inflammation and nutrition. Although several studies have examined pretreatment laboratory markers as predictors of non-hematologic adverse effects during CapeOX therapy, published research specifically evaluating hematologic toxicities using pretreatment blood tests is extremely limited. For example, Kishimoto et al. [5] investigated pretreatment predictors of peripheral neuropathy, nausea, anorexia, and diarrhea, but did not evaluate hematologic toxicity. Hematologic toxicity is a significant adverse effect that directly impacts treatment continuity; if its occurrence can be predicted in advance, treatment discontinuation can be avoided through enhanced supportive care and dose adjustments, thereby improving safety.

Therefore, this study aimed to explore potential associations between pre-treatment blood test results, inflammatory markers, and the development of hematologic toxicity in colorectal cancer patients undergoing CapeOX therapy. The primary objective was to examine associations between prespecified pre-treatment laboratory variables and grade  $\geq 1$  hematologic toxicity during the first CapeOX cycle. The secondary objectives were exploratory assessment of discriminative performance and internally derived candidate thresholds, which will require validation in independent cohorts.

## Materials And Methods

This study is a retrospective secondary analysis using existing data on colorectal cancer patients who received CapeOX therapy, and its objective was to exploratively identify pre-treatment factors associated with hematologic toxicity [5]. Although the dataset was constructed in a previous study, this study extracted only variables related to hematologic toxicity and constructed an independent analytical model. The dataset was originally developed in a previously published analysis of non-hematologic adverse effects associated with CapeOX therapy (Kishimoto M, Koinuma M, Tokunaga J: Exploratory investigation of predictive factors for reducing adverse effects in CapeOX therapy for colorectal cancer patients. *Cureus*. 2025, 17:95702 [5]). The present study represents an independent secondary analysis focusing specifically on hematologic toxicity. Neither the original study nor this secondary analysis was part of a registered clinical trial. In accordance with the institutional opt-out policy for retrospective studies with waived informed consent, patients who explicitly requested exclusion from research use of their clinical data were not included in the dataset. No patients discontinued CapeOX therapy before completing the first cycle; therefore, no patients were excluded for this reason. Although treatment discontinuation before completing the first cycle could theoretically introduce selection bias, because such discontinuation may be related to toxicity or clinical deterioration, no patients met this criterion in the present dataset. Therefore, the impact of this potential bias is considered minimal.

Patients with prior radiotherapy and previous chemotherapy, including adjuvant therapy, liver metastases, bone-marrow involvement, or baseline cytopenias (leukopenia, neutropenia, anemia, or thrombocytopenia before treatment initiation), were not included in this study. All patients were chemotherapy-naïve and received capecitabine plus oxaliplatin (CapeOX) as first-line treatment.

The analysis included 108 colorectal cancer patients who began CapeOX therapy at the Kirishima City Medical Association Medical Center between September 1, 2020, and October 31, 2023. All patients were chemotherapy-naïve at the start of treatment; the analysis included cases for which pre-treatment blood test results and adverse event assessments at the end of the first treatment cycle were available. Treatment intent was also documented. Among the 108 patients, 98 received CapeOX as adjuvant chemotherapy for Stage II-III colorectal cancer, while 10 patients with Stage IV disease received CapeOX as first-line therapy for metastatic colorectal cancer. All patients were chemotherapy-naïve at treatment initiation. Patients who refused to participate in the study, those who discontinued treatment on their own initiative, and cases with missing blood test results or adverse event information were excluded. A total of 108 patients were screened, and no cases were excluded. All patients had complete pretreatment laboratory data and cycle 1 adverse-event assessments; therefore, the final analysis included all 108 screened patients. One case involved a synchronous lesion located in the jejunum. Although the jejunum is not a colorectal site, chemotherapy was administered according to colorectal cancer treatment protocols; therefore, the case was retained in the colorectal cancer cohort for analysis.

This study did not involve any new interventions or additional data collection. Data collection was conducted within the scope of the ethical approval obtained for the previous study, and personal information was anonymized and managed accordingly. Ethical approval was obtained from the Ethics Review Committee of the Kirishima City Medical Association Medical Center (Receipt No.: 202301) and the Ethics Review Committee of Kyushu University of Health and Welfare (Approval No.: 23-015). Since this was a retrospective study, written informed consent was waived, and an opt-out procedure via the institution's website was adopted. In accordance with the institutional opt-out policy for retrospective studies with waived informed consent, patients who explicitly requested exclusion from research use of their clinical data were not included in the dataset. No patients discontinued CapeOX therapy before completing the first cycle; therefore, no patients were excluded for this reason.

The CapeOX regimen was administered in 21-day cycles, consisting of an intravenous infusion of 130 mg/m<sup>2</sup> of oxaliplatin on Day 1, followed by oral administration of 1,000 mg/m<sup>2</sup> of capecitabine twice daily from Day 1 through Day 14. Dose adjustments were made at the discretion of the treating physician. Dose (%) was defined as the percentage of the planned chemotherapy dose that was actually administered during the first cycle (relative dose intensity). No dose reductions or treatment delays occurred during Cycle 1. All patients received the planned CapeOX doses during the first cycle, and hematologic toxicity was assessed at the standard Day 21 evaluation.

To identify predictors of hematologic toxicity, we extracted pre-treatment hematologic parameters (white

blood cell count, neutrophil count, lymphocyte count, monocyte count, red blood cell count, hemoglobin, and platelet count; all measured in  $\times 10^3/\mu\text{L}$ , except hemoglobin in g/dL) and biochemical parameters (albumin in g/dL, C-reactive protein (CRP) in mg/dL, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) in U/L, serum creatinine in mg/dL, estimated glomerular filtration rate (eGFR) in mL/min/1.73 m<sup>2</sup>, and creatinine clearance in mL/min). Furthermore, we calculated the following inflammatory and nutritional indices: prognostic nutritional index (PNI) ( $10 \times \text{albumin} + 0.005 \times \text{lymphocytes}$ ), systemic inflammation response index (SIRI) ( $\text{neutrophils} \times \text{monocytes} / \text{lymphocytes}$ ), systemic immune-inflammation index (SII) ( $\text{platelets} \times \text{neutrophils} / \text{lymphocytes}$ ), neutrophil-to-lymphocyte ratio (NLR) ( $\text{neutrophils} / \text{lymphocytes}$ ), platelet-to-lymphocyte ratio (PLR) ( $\text{platelets} / \text{lymphocytes}$ ), and lymphocyte-to-monocyte ratio (LMR) ( $\text{lymphocytes} / \text{monocytes}$ ). Pre-treatment laboratory values were obtained on the day of Cycle 1 initiation (Day 1). Reference ranges for all laboratory, nutritional, and inflammatory indices used in this study are provided in Appendix A.

Smoking history was categorized using the Brinkman index as recorded in the electronic medical record. Drinking history categories were taken directly from the electronic medical record, where alcohol consumption is routinely documented using predefined clinical categories. These categories were not based on a numerical index.

Hematologic toxicity (leukopenia, neutropenia, anemia, and thrombocytopenia) was classified as Grade 0 or Grade  $\geq 1$  based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Japanese version) [6] using routine blood tests conducted at the end of each cycle. Post-treatment blood tests used to assess hematologic toxicity at the end of the first cycle were performed on Day 21, which is the standard timing for cycle-end laboratory evaluation in our institution. All hematologic parameters were Grade 0 at baseline, and patients with Grade  $\geq 1$  leukopenia, neutropenia, anemia, or thrombocytopenia before starting CapeOX were not included in the corresponding toxicity analyses. Baseline CTCAE grades were confirmed and reported to clarify that the outcomes represent abnormalities observed at the end of cycle 1. No supportive interventions such as G-CSF administration, blood transfusion, or other hematologic supportive measures were given during Cycle 1 before the end-of-cycle blood test. Therefore, hematologic toxicity grading reflects untreated laboratory values.

In the statistical analysis, we first evaluated the association between pre-treatment factors and each toxicity using univariate analysis. For continuous variables, we used the Wilcoxon two-sample test and reported the Z-statistic and p-value. For categorical variables, we used Pearson's  $\chi^2$  test or Fisher's exact test and reported the  $\chi^2$  statistic or exact probability and p-value. Factors that showed significant differences in the univariate analysis were included in multivariate logistic regression analysis, and the odds ratio (OR) and 95% confidence interval (CI) were reported. In addition, ROC analysis was performed to evaluate predictors of toxicity occurrence, and the AUC and cutoff values were calculated. Fisher's exact test was used to compare groups based on cutoff values. The significance level was set at  $p < 0.05$ . Cutoff values for each variable were determined using ROC curve analysis within the same dataset. Because no internal validation (e.g., bootstrapping or cross-validation) was performed, these cutoff values should be interpreted as exploratory and data-dependent rather than as established thresholds for clinical risk stratification.

In the multivariate logistic regression analysis, Grade 0 was coded as 0 and Grade  $\geq 1$  as 1. Therefore, the ORs indicate the likelihood of developing hematologic toxicity (Grade  $\geq 1$ ).

Some ORs in the multivariable analysis, particularly for basophils, SIRI, and CRP, showed extremely wide confidence intervals due to sparse data and separation. These values were retained for transparency, but their instability was acknowledged, and interpretation was limited accordingly.

We performed ROC analysis on the independent variables to calculate the cutoff value, AUC, sensitivity, and specificity. We stratified patients into two groups based on the cutoff value and compared the incidence rates of toxicity. Statistical analysis was performed using JMP® Student Edition version 19.0.5 (SAS Institute Inc., 2025, jmp.com). To maintain consistency with our previous report, continuous variables were summarized using mean  $\pm$  SD. The Wilcoxon rank-sum test was applied to reduce the influence of potential outliers rather than to address non-normality. Multiple univariate comparisons were performed across numerous variables and four hematologic toxicities. These analyses were considered exploratory, and no formal correction for multiple testing was applied. Because JMP does not provide confidence intervals for the area under the curve (AUC), the standard error (SE) of the AUC was estimated according to the method of Hanley and McNeil [7]. The 95% confidence interval (CI) for the AUC was calculated as  $\text{AUC} \pm 1.96 \times \text{SE}$ . Sensitivity and specificity were obtained from the ROC output in JMP at the cutoff value that maximized the Youden index ( $\text{sensitivity} - (1 - \text{specificity})$ ). In addition, several continuous predictors showed unstable ORs due to sparse data and separation. Therefore, we retained the original numerical estimates for transparency but simplified the multivariable model by reducing the number of predictors. The ORs for continuous variables were interpreted on their original scales; for example, the age OR represents a per-one-year increment.

## Results

Previous studies have suggested that pre-treatment blood test results and markers of inflammation and nutrition may be associated with nonhematologic adverse events of CapeOX therapy. In this study, using the same dataset, we focused on hematologic toxicity and analyzed the association between the occurrence of leukopenia, neutropenia, anemia, and thrombocytopenia and pre-treatment factors.

### Leukopenia

Table 1 and Table 2 show the results of a comparison of pre-treatment factors associated with leukopenia. The results of the multivariate logistic regression analysis are shown in Table 3A. In cases of leukopenia, the SII at the start of the first cycle was significantly lower in the Grade  $\geq 1$  group ( $334.52 \pm 92.71$ ) compared to the Grade 0 group ( $630.69 \pm 385.02$ ) ( $Z = -3.2606$ ,  $p = 0.0022$ ) (Table 2). Multivariate logistic regression analysis identified SII as the sole independent factor associated with the occurrence of leukopenia (OR = 0.9660,  $p = 0.0098$ ) (Table 3A). Lower baseline SII was associated with first-cycle leukopenia in the exploratory multivariable analysis; the internally derived threshold of 496.768 requires validation in an independent cohort. In the ROC analysis, this threshold demonstrated good discriminatory ability with an AUC of 0.8013 (Table 4A). Lower baseline SII was associated with first-cycle leukopenia in this cohort; however, this in-sample association does not establish clinical utility, and its potential role in pre-treatment risk assessment requires external validation. Based on the above, SII was identified as a pre-treatment factor associated with an increased risk of leukopenia. Additional baseline comparisons across all four hematologic toxicities are summarized in Appendix B.

| Variable                            |                  | Grade 0       | Grade ≥ 1     | Statistic (Z / $\chi^2$ ) | p-value |    |
|-------------------------------------|------------------|---------------|---------------|---------------------------|---------|----|
|                                     |                  | n = 97        | n = 11        |                           |         |    |
| Age (years)                         |                  | 66.68 ± 10.40 | 68.27 ± 8.58  | Z = 0.3863                | 0.6992  | a) |
| Sex                                 | Male             | 55            | 4             | $\chi^2$ = 1.7112         | 0.1991  | b) |
|                                     | Female           | 42            | 7             |                           |         |    |
| BMI (kg/m <sup>2</sup> )            |                  | 22.10 ± 3.72  | 22.64 ± 2.99  | Z = 0.4571                | 0.6476  | a) |
| Body surface area (m <sup>2</sup> ) |                  | 1.57 ± 0.20   | 1.55 ± 0.14   | Z = -0.5180               | 0.6044  | a) |
| General condition□PS□               | 0                | 85            | 10            | $\chi^2$ = 1.1357         | 0.5965  | b) |
|                                     | 1                | 8             | 1             |                           |         |    |
| Smoking history                     | 0                | 38            | 5             | $\chi^2$ = 0.0032         | 0.5965  | b) |
|                                     | 1-199            | 9             | 1             |                           |         |    |
|                                     | 200-399          | 6             | 2             |                           |         |    |
|                                     | 400-699          | 13            | 1             |                           |         |    |
|                                     | 700-             | 31            | 2             |                           |         |    |
| Drinking history                    | None             | 30            | 2             | $\chi^2$ = 5.8957         | 0.1912  | b) |
|                                     | Occasional       | 21            | 0             |                           |         |    |
|                                     | Weekly           | 17            | 1             |                           |         |    |
|                                     | Everyday         | 29            | 6             |                           |         |    |
|                                     | Upper colon      | 12            | 0             |                           |         |    |
| Cancer site                         | Lower colon      | 5             | 0             | $\chi^2$ = 8.1922         | 0.2790  | b) |
|                                     | Sigmoid colon    | 21            | 3             |                           |         |    |
|                                     | Transverse colon | 19            | 0             |                           |         |    |
|                                     | Jejunum          | 1             | 0             |                           |         |    |
|                                     | Rectum           | 32            | 4             |                           |         |    |
| Stage                               | Cecum            | 8             | 3             | $\chi^2$ = 4.3770         | 0.9702  | b) |
|                                     | Ila              | 23            | 1             |                           |         |    |
|                                     | Ilb              | 5             | 1             |                           |         |    |
|                                     | IIla             | 13            | 1             |                           |         |    |
|                                     | IIlb             | 36            | 7             |                           |         |    |
| Dose(%)                             | IIlc             | 10            | 1             | Z = -0.6094               | 0.5422  | a) |
|                                     | IV               | 10            | 0             |                           |         |    |
|                                     | Oxaliplatin      | 89.25 ± 7.74  | 87.36 ± 9.54  |                           |         |    |
| Capecitabine                        |                  | 92.90 ± 9.82  | 94.97 ± 11.59 | Z = 1.0462                | 0.2954  | a) |

TABLE 1: Pre-treatment factors associated with leukopenia (Grade ≥1)

Values marked with an asterisk (\*) are statistically significant (p < 0.05). Statistical tests used: a) Wilcoxon two-sample test; b) Pearson's chi-square test.

| Variable                             | Reference range (normal value) | Leukopenia   |              |               |         | Neutropenia  |              |               |         | Hemoglobin decrease |              |               |          | Thrombocytopenia |              |               |
|--------------------------------------|--------------------------------|--------------|--------------|---------------|---------|--------------|--------------|---------------|---------|---------------------|--------------|---------------|----------|------------------|--------------|---------------|
|                                      |                                | Grade 0      | Grade ≥ 1    | Statistic (Z) | p-value | Grade 0      | Grade ≥ 1    | Statistic (Z) | p-value | Grade 0             | Grade ≥ 1    | Statistic (Z) | p-value  | Grade 0          | Grade ≥ 1    | Statistic (Z) |
|                                      |                                | n = 97       | n = 11       |               |         | n = 93       | n = 15       |               |         | n = 71              | n = 37       |               |          | n = 82           | n = 26       |               |
|                                      |                                |              |              |               |         |              |              |               |         |                     |              |               |          |                  |              |               |
| Red blood cell (10 <sup>9</sup> /μL) | Male 420–570 / Female 380–     | 422.60±65.98 | 379.09±44.13 | -2.7986       | 0.0051* | 422.06±64.29 | 394.06±68.55 | -1.8124       | 0.0699  | 439.81±63.08        | 376.64±47.31 | -5.9335       | <0.0001* | 424.35±67.65     | 398.69±53.82 | -2.2931       |

|                                        |                                            |               |              |         |          |               |               |         |          |               |               |         |          |               |               |         |
|----------------------------------------|--------------------------------------------|---------------|--------------|---------|----------|---------------|---------------|---------|----------|---------------|---------------|---------|----------|---------------|---------------|---------|
|                                        | 500                                        |               |              |         |          |               |               |         |          |               |               |         |          |               |               |         |
| White blood cell (10 <sup>3</sup> /μL) | 35–90                                      | 62.27±41.07   | 35.81±7.41   | -4.6285 | <0.0001* | 62.44±42.02   | 41.86±10.23   | -3.8880 | 0.0001*  | 62.23±47.07   | 54.48±18.88   | -0.8710 | 0.3837   | 62.82±44.42   | 49.34±15.50   | -2.0767 |
| Basophil (10 <sup>3</sup> /μL)         | 0-2                                        | 0.32±0.27     | 0.17±0.09    | -1.9607 | 0.0499*  | 0.32±0.27     | 0.22±0.19     | -1.6970 | 0.0888   | 0.32±0.29     | 0.28±0.17     | -0.1521 | 0.8791   | 0.33±0.28     | 0.24±0.16     | -1.3871 |
| Eosinophil (10 <sup>3</sup> /μL)       | 0-6                                        | 2.23±2.21     | 1.29±0.74    | -1.9249 | 0.0542   | 2.22±2.26     | 1.63±0.88     | -0.7640 | 0.4449   | 2.42±2.45     | 1.58±1.15     | -2.8549 | 0.0043*  | 2.13±2.30     | 2.15±1.48     | 0.5317  |
| Neutrophil (10 <sup>3</sup> /μL)       | 40-75                                      | 38.45±28.88   | 20.32±4.32   | -4.4541 | <0.0001* | 38.95±29.35   | 22.09±6.28    | -4.4995 | <0.0001* | 37.54±32.33   | 34.81±16.78   | -0.5535 | 0.5799   | 38.89±31.11   | 29.41±11.53   | -2.2599 |
| Lymphocyte (10 <sup>3</sup> /μL)       | 20-50                                      | 17.30±10.20   | 11.44±3.12   | -2.9051 | 0.0037*  | 16.98±10.41   | 14.94±5.34    | -0.6040 | 0.5458   | 17.97±11.46   | 14.27±5.01    | -2.0618 | 0.0392*  | 17.66±10.94   | 13.68±4.12    | -2.0767 |
| Monocyte (10 <sup>3</sup> /μL)         | 2-10                                       | 3.95±2.23     | 2.57±0.60    | -3.1794 | 0.0015*  | 3.95±2.27     | 2.95±0.93     | -2.3764 | 0.0175*  | 3.96±2.48     | 3.52±1.33     | -0.6020 | 0.5471   | 3.80±2.28     | 3.85±1.79     | 0.0035  |
| Platelet (10 <sup>6</sup> /μL)         | 15-35                                      | 25.91±7.68    | 18.47±5.01   | -3.4792 | 0.0005*  | 25.50±7.74    | 23.02±7.83    | -1.3281 | 0.1841   | 24.08±6.75    | 27.22±9.16    | 1.6573  | 0.0974   | 26.70±6.95    | 20.28±8.31    | -4.8688 |
| Serum Albumin (g/dL)                   | 3.8-5.0                                    | 4.04±0.47     | 4.07±0.24    | -0.3007 | 0.7636   | 4.05±0.44     | 4.04±0.54     | 0.0490  | 0.9609   | 4.17±0.37     | 3.81±0.51     | -3.4171 | 0.0006*  | 4.07±0.44     | 3.97±0.49     | -0.7535 |
| CRP (mg/dL)                            | <0.3                                       | 0.38±1.15     | 0.06±0.07    | -2.2663 | 0.0234*  | 0.38±1.17     | 0.14±0.31     | -2.2811 | 0.0225*  | 0.22±0.38     | 0.60±1.78     | 0.7872  | 0.4311   | 0.39±1.24     | 0.22±0.30     | 1.0724  |
| AST (IU/L)                             | 13-33                                      | 21.30±11.68   | 18.63±5.86   | -0.7277 | 0.4668   | 21.00±11.48   | 21.26±10.01   | 0.0667  | 0.9468   | 19.38±7.34    | 24.21±15.97   | 1.1221  | 0.2618   | 21.43±12.38   | 19.76±6.46    | 0.0360  |
| ALT (IU/L)                             | 8-42                                       | 20.55±11.88   | 16.54±8.69   | -1.2916 | 0.1965   | 19.52±10.86   | 24.00±15.48   | 0.7960  | 0.4260   | 19.70±9.93    | 21.00±14.46   | -0.2463 | 0.8054   | 20.25±11.98   | 19.80±10.67   | 0.1007  |
| Hb (g/dL)                              | Male 13.0–17.0<br>/ Female 11.5–15.0       | 12.80±3.31    | 11.32±1.12   | -2.2151 | 0.0267*  | 12.78±3.34    | 11.84±1.91    | -1.3241 | 0.1855   | 13.67±3.46    | 10.70±0.97    | -7.6869 | <0.0001* | 12.87±3.54    | 11.96±1.51    | -1.5347 |
| eGFR (mL/min/1.73m <sup>2</sup> )      | ≥60                                        | 78.03±20.71   | 72.36±12.73  | -1.0923 | 0.2747   | 76.86±20.62   | 81.13±16.40   | 0.8930  | 0.3718   | 79.07±21.77   | 74.35±16.15   | -1.4343 | 0.1515   | 78.18±20.79   | 75.15±17.78   | -1.0782 |
| Cr (mg/dL)                             | Male 0.65–1.07<br>/ Female 0.46–0.79       | 0.70±0.17     | 0.70±0.15    | -0.0609 | 0.9514   | 0.71±0.17     | 0.67±0.12     | -0.7020 | 0.4826   | 0.71±0.17     | 0.69±0.17     | -1.1138 | 0.2653   | 0.69±0.16     | 0.74±0.17     | 0.9812  |
| Ccr (mL/min)                           | 80-130                                     | 162.49±44.09  | 159.89±33.49 | 0.1218  | 0.903    | 160.57±44.05  | 172.49±35.36  | 1.4835  | 0.1379   | 170.49±43.74  | 146.37±37.18  | -2.9196 | 0.0035*  | 163.73±42.33  | 157.46±45.58  | -0.4563 |
| PNI                                    | ≥45(Good)                                  | 49.12±7.00    | 46.45±2.70   | -1.6861 | 0.0918   | 49.01±6.93    | 47.87±5.44    | -0.3553 | 0.7223   | 50.68±6.71    | 45.32±5.27    | -4.3502 | <0.0001* | 49.57±7.04    | 46.57±5.13    | -2.1809 |
| SIRI                                   | 1.0-1.5(clinical cut-off)                  | 0.98±0.82     | 0.47±0.15    | -3.0676 | 0.0022*  | 1.00±0.82     | 0.46±0.21     | -3.8732 | 0.0001*  | 0.90±0.82     | 0.97±0.73     | 0.3884  | 0.6977   | 0.92±0.79     | 0.95±0.82     | -0.0610 |
| NLR                                    | 1.0-3.0                                    | 2.40±1.10     | 1.86±0.52    | -1.4830 | 0.1381   | 2.47±1.09     | 1.59±0.48     | -3.1714 | 0.0015*  | 2.21±0.93     | 2.61±1.27     | 1.3918  | 0.164    | 2.38±1.11     | 2.26±0.93     | -0.1760 |
| PLR                                    | 100-200                                    | 1.73±0.76     | 1.65±0.37    | 0.0914  | 0.9272   | 1.74±0.76     | 1.60±0.49     | -0.3820 | 0.7025   | 1.55±0.63     | 2.04±0.80     | 3.2562  | 0.0011*  | 1.77±0.77     | 1.56±0.57     | -1.1317 |
| LMR                                    | 3.0-5.0                                    | 4.79±2.08     | 4.49±0.97    | -0.0914 | 0.9272   | 4.70±2.08     | 5.14±1.30     | 1.5368  | 0.1243   | 4.89±1.94     | 4.52±2.10     | -1.2558 | 0.2092   | 4.98±2.06     | 4.08±1.64     | -2.0228 |
| SII                                    | ≤500(Increased by inflammation and tumors) | 630.69±385.02 | 334.52±92.71 | -3.2606 | 0.0022*  | 638.85±387.94 | 362.94±159.15 | -3.1892 | 0.0014*  | 525.47±257.28 | 744.56±510.51 | 1.7673  | 0.0772   | 651.68±404.45 | 439.20±204.17 | -2.6120 |

TABLE 2: Comparison of blood test values, nutritional and inflammatory indices before treatment by adverse effect after one cycle

Values marked with an asterisk (\*) are statistically significant (p < 0.05). Statistical tests used: Wilcoxon two-sample test.

CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Hb: hemoglobin; eGFR: estimated glomerular filtration rate; Cr: creatinine; Ccr: creatinine clearance; PNI: prognostic nutrition index; SIRI: systemic inflammatory response index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; SII: systemic immune inflammatory index

|                                        | Odds ratio | 95%CI         | p-value |
|----------------------------------------|------------|---------------|---------|
| (A) Leukopenia                         |            |               |         |
| Red blood cell (10 <sup>6</sup> /μL)   | 1.0063     | 0.9531-1.0728 | 0.8454  |
| White blood cell (10 <sup>3</sup> /μL) | 0.7853     | 0.1656-2.8359 | 0.7154  |

|                                        |                         |                                               |                |        |
|----------------------------------------|-------------------------|-----------------------------------------------|----------------|--------|
| Basophil (10 <sup>3</sup> /μL)         | 1.0275×10 <sup>-4</sup> | 0.03693-3.82×10 <sup>12</sup>                 | 0.1623         |        |
| Neutrophil (10 <sup>3</sup> /μL)       | 1.8830                  | 0.3430-14.2900                                | 0.4675         |        |
| Lymphocyte (10 <sup>3</sup> /μL)       | 0.2138                  | 0.0182-1.2930                                 | 0.0961         |        |
| Monocyte (10 <sup>3</sup> /μL)         | 11.6200                 | 0.0222-1.0000×10 <sup>4</sup>                 | 0.4591         |        |
| Platelet (10 <sup>4</sup> /μL)         | 1.7640                  | 0.9283-4.2670                                 | 0.0854         |        |
| CRP (mg/dL)                            | 1.3310×10 <sup>-8</sup> | 3.1400×10 <sup>-21</sup> -1.3950              | 0.0583         |        |
| Hb (g/dL)                              | 0.6370                  | 0.10850-1.4940                                | 0.5940         |        |
| SIRI                                   | 2.9000×10 <sup>-4</sup> | 6.29×10 <sup>-20</sup> -37490×10 <sup>4</sup> | 0.5790         |        |
| SII                                    | 0.9660                  | 0.9180-0.9930                                 | 0.0098*        |        |
| (B) Neutropenia                        |                         |                                               |                |        |
| BMI (kg/m <sup>2</sup> )               | 1.1507                  | 0.9614-1.4080                                 | 0.1285         |        |
| White blood cell (10 <sup>3</sup> /μL) | 0.8850                  | 0.6080-1.2020                                 | 0.4537         |        |
| Neutrophil (10 <sup>3</sup> /μL)       | 1.0264                  | 0.6140-1.8860                                 | 0.9249         |        |
| Monocyte (10 <sup>3</sup> /μL)         | 1.4680                  | 0.2200-17.0200                                | 0.7207         |        |
| CRP (mg/dL)                            | 0.6840                  | 0.02050-7.6500                                | 0.8000         |        |
| SIRI                                   | 0.1705                  | 7.03×10 <sup>-7</sup> -2.941×10 <sup>2</sup>  | 0.7175         |        |
| NLR                                    | 0.4120                  | 0.0080-9.4200                                 | 0.5959         |        |
| SII                                    | 0.9996                  | 0.9930-1.0055                                 | 0.9071         |        |
| (C) Hemoglobin decrease                |                         |                                               |                |        |
| Age (years)                            | 1.3410                  | 1.0300-2.8500                                 | 0.0229*        |        |
| Sex                                    | 6.2300                  | 0.3860-151.5000                               | 0.0605         |        |
| BMI (kg/m <sup>2</sup> )               | 0.7950                  | 0.2790-1.4510                                 | 0.457          |        |
| Body surface area (m <sup>2</sup> )    | 0.5560                  | 0.0225-10.6700                                | 0.1933         |        |
| Smoking history                        | 1-199                   | 0.5540                                        | 0.0280-10.9300 | 0.6984 |
|                                        | 200-399                 | 1.4380                                        | 0.0737-2.8090  | 0.8105 |
|                                        | 400-699                 | 0.1930                                        | 0.0089-4.1800  | 0.2943 |
|                                        | 700-                    | 0.1880                                        | 0.0085-4.1300  | 0.289  |
|                                        | Occasional              | 0.5540                                        | 0.0280-10.9300 | 0.6984 |
| Drinking history                       | Weekly                  | 1.0360                                        | 0.0737-28.0900 | 0.8105 |
|                                        | Everyday                | 0.1930                                        | 0.0089-4.1800  | 0.2943 |
| Red blood cell (10 <sup>6</sup> /μL)   | 0.9420                  | 0.9370-0.9997                                 | 0.0420*        |        |
| Eosinophil (103/μL)                    | 0.6410                  | 0.2530-1.3450                                 | 0.2710         |        |
| Lymphocyte (10 <sup>3</sup> /μL)       | 0.9390                  | 0.7650-1.1400                                 | 0.5230         |        |
| Serum albumin (g/dL)                   | 1.4180                  | 0.1460-10.9900                                | 0.7419         |        |
| Hb (g/dL)                              | 0.0623                  | 0.0098-0.2198                                 | 0.0003*        |        |
| Ccr                                    | 0.9831                  | 0.9460-1.0168                                 | 0.3491         |        |
| PNI                                    | 1.1180                  | 0.8680-1.4490                                 | 0.3730         |        |
| PLR                                    | 0.6490                  | 0.3530-1.2440                                 | 0.1649         |        |
| (D) Thrombocytopenia                   |                         |                                               |                |        |
| Capecitabine dose (%)                  | 1.0496                  | 0.9880-1.1197                                 | 0.1206         |        |
| Red blood cell (10 <sup>6</sup> /μL)   | 0.9914                  | 0.9782-1.0041                                 | 0.1856         |        |

|                                  |        |               |         |
|----------------------------------|--------|---------------|---------|
| White blood cell (103/μL)        | 1.4480 | 0.9140-2.3730 | 0.1155  |
| Neutrophil (10 <sup>3</sup> /μL) | 0.7470 | 0.4400-1.2580 | 0.2708  |
| Lymphocyte (10 <sup>3</sup> /μL) | 0.4810 | 0.2250-0.9430 | 0.0326* |
| Platelet (10 <sup>4</sup> /μL)   | 1.0218 | 0.8167-1.2530 | 0.8406  |
| PNI                              | 0.8780 | 0.7320-1.0400 | 0.1351  |
| LMR                              | 0.9310 | 0.4090-1.9370 | 0.8553  |
| SII                              | 0.9910 | 0.9820-0.9996 | 0.0382* |

TABLE 3: Multivariable logistic regression analysis of significant factors

Values marked with an asterisk (\*) are statistically significant (p < 0.05). Statistical tests used: multivariable logistic regression analysis.

Sex was treated as a categorical variable, with “female” as the reference category. Odds ratios (ORs) were calculated relative to females. Smoking status was treated as a categorical variable, with “non-smoker” as the reference category. Odds ratios (ORs) were calculated relative to non-smokers. Drinking status was treated as a categorical variable, with “non-drinker” as the reference category. Odds ratios (ORs) were calculated relative to non-drinkers.

CRP: C-reactive protein; Hb: hemoglobin; Ccr: creatinine clearance; PNI: prognostic nutrition index; SIRI: systemic inflammatory response index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; SII: systemic immune inflammatory index

|                                      | Cut-off value | AUC    | AUC 95%CI     | Sensitivity | Specificity |          | Grade0      | Grade ≥ 1   | p-value |
|--------------------------------------|---------------|--------|---------------|-------------|-------------|----------|-------------|-------------|---------|
| (A) Leukopenia                       |               |        |               |             |             |          |             |             |         |
| SII                                  | 496.768       | 0.8013 | 0.628 - 0.975 | 0.9091      | 0.5361      | □496.768 | 40 (80.00%) | 10 (20.00%) | 0.0025* |
|                                      |               |        |               |             |             | >496.768 | 57 (98.28%) | 1 (1.72%)   |         |
| (B) Hemoglobin decrease              |               |        |               |             |             |          |             |             |         |
| Age (years)                          | 68.0          | 0.6917 | 0.561 - 0.822 | 0.8378      | 0.5493      | <68.00   | 39 (86.67%) | 6 (13.33%)  | 0.0001* |
|                                      |               |        |               |             |             | □68.00   | 32 (50.79%) | 31 (49.21%) |         |
| Red blood cell (10 <sup>6</sup> /μL) | 394.0         | 0.8491 | 0.714 - 0.984 | 0.6757      | 0.8873      | □394.0   | 8 (24.24%)  | 25 (75.76%) | 0.0001* |
|                                      |               |        |               |             |             | >394.0   | 63 (84.00%) | 12 (16.00%) |         |
| Hb (g/dL)                            | 11.70         | 0.9520 | 0.894 - 1.000 | 0.9459      | 0.8592      | □11.7    | 10 (22.22%) | 35 (77.78%) | 0.0001* |
|                                      |               |        |               |             |             | >11.7    | 61 (96.83%) | 2 (3.17%)   |         |
| (C) Thrombocytopenia                 |               |        |               |             |             |          |             |             |         |
| Lymphocyte (10 <sup>3</sup> /μL)     | 12.41         | 0.6358 | 0.446 - 0.826 | 0.5385      | 0.7199      | □12.4100 | 23 (62.16%) | 14 (37.84%) | 0.0194* |
|                                      |               |        |               |             |             | >12.4100 | 59 (83.10%) | 12 (16.90%) |         |
| SII                                  | 477.901       | 0.6707 | 0.516 - 0.825 | 0.7692      | 0.6098      | □477.901 | 32 (61.54%) | 20 (38.46%) | 0.0013* |
|                                      |               |        |               |             |             | >477.901 | 50 (89.29%) | 6 (10.71%)  |         |

TABLE 4: Significant predictors and cutoff values by adverse effect and comparisons before and after cutoff

Values marked with an asterisk (\*) are statistically significant (p < 0.05). Statistical tests used: Fisher’s exact test.

Hb: hemoglobin; SII: systemic immune inflammatory index

Neutropenia

The results of the univariate analysis of neutropenia are shown in Table 2 and Table 5, and the results of the multivariate logistic regression analysis are shown in Table 3B.

| Variable                            |                  | Grade 0       | Grade ≥ 1     | Statistic (Z / $\chi^2$ ) | p-value |    |
|-------------------------------------|------------------|---------------|---------------|---------------------------|---------|----|
|                                     |                  | n = 93        | n = 15        |                           |         |    |
| Age (years)                         |                  | 67.46 ± 10.21 | 63.00 ± 9.65  | Z = -1.8007               | 0.0717  | a) |
| Sex                                 | Male             | 52            | 7             | $\chi^2$ = 0.1500         | 0.5044  | b) |
|                                     | Female           | 41            | 8             |                           |         |    |
| BMI (kg/m <sup>2</sup> )            |                  | 22.05 ± 3.72  | 23.41 ± 4.3   | Z = 1.9632                | 0.0496* | a) |
| Body surface area (m <sup>2</sup> ) |                  | 1.57 ± 0.19   | 1.59 ± 0.21   | Z = 0.7639                | 0.4449  | a) |
| General condition (PS□              | 0                | 85            | 12            | $\chi^2$ = 3.5447         | 0.1756  | b) |
|                                     | 1                | 8             | 3             |                           |         |    |
| Smoking history                     | 0                | 38            | 5             | $\chi^2$ = 5.0055         | 0.2366  | b) |
|                                     | 1-199            | 8             | 2             |                           |         |    |
|                                     | 200-399          | 6             | 2             |                           |         |    |
|                                     | 400-699          | 10            | 4             |                           |         |    |
|                                     | 700-             | 31            | 2             |                           |         |    |
| Drinking history                    | None             | 31            | 3             | $\chi^2$ = 1.9445         | 0.5847  | b) |
|                                     | Occasional       | 18            | 3             |                           |         |    |
|                                     | Weekly           | 16            | 2             |                           |         |    |
|                                     | Everyday         | 28            | 7             |                           |         |    |
|                                     | Upper colon      | 12            | 0             |                           |         |    |
| Cancer site                         | Lower colon      | 5             | 1             | $\chi^2$ = 7.7881         | 0.2540  | b) |
|                                     | Sigmoid colon    | 23            | 1             |                           |         |    |
|                                     | Transverse colon | 17            | 2             |                           |         |    |
|                                     | Jejunum          | 1             | 0             |                           |         |    |
|                                     | Rectum           | 28            | 8             |                           |         |    |
| Stage                               | Cecum            | 8             | 3             | $\chi^2$ = 10.1572        | 0.2946  | b) |
|                                     | Ila              | 21            | 3             |                           |         |    |
|                                     | Ilb              | 3             | 3             |                           |         |    |
|                                     | IIla             | 12            | 2             |                           |         |    |
|                                     | IIlb             | 36            | 7             |                           |         |    |
|                                     | IIlc             | 11            | 0             |                           |         |    |
| Dose (%)                            | IV               | 10            | 0             | Z = -0.0355               | 0.9717  | a) |
|                                     | Oxaliplatin      | 89.10 ± 7.98  | 89.09 ± 7.75  |                           |         |    |
|                                     | Capecitabine     | 92.8 ± 9.47   | 95.23 ± 12.86 | Z = 0.9239                | 0.3555  | a) |

**TABLE 5: Pre-treatment factors associated with neutropenia (grade ≥1)**

Values marked with an asterisk (\*) are statistically significant (p < 0.05). Statistical tests used: a) Wilcoxon two-sample test; b) Pearson's chi-square test.

In patients with neutropenia, SIRI, NLR, and SII at the start of the first cycle were significantly lower in the Grade > 1 group than in the Grade 0 group in univariate analysis (SIRI: Z = -3.8732, p = 0.0001; NLR: Z = -3.1714, p = 0.0015; SII: Z = -3.1892, p = 0.0014) (Table 2). However, in multivariate logistic regression analysis, none of the factors, including SIRI and NLR, showed a significant association as independent predictors (p > 0.05) (Table 3B). Based on the above, no independent predictors that increase the risk of neutropenia were identified.

## Hemoglobin decrease

Pre-treatment factors associated with decreased hemoglobin are shown in Table 2 and Table 6, and the results of the multivariate logistic regression analysis are shown in Table 3C. In cases of decreased hemoglobin, the age at the start of the first cycle was significantly higher in the Grade  $\geq 1$  group than in the Grade 0 group, while the red blood cell count ( $\times 10^4/\mu\text{L}$ ) and Hb (g/dL) were significantly lower (age:  $Z = 3.2595$ ,  $p = 0.0011$ ; red blood cell count:  $Z = -5.9335$ ,  $p < 0.0001$ ; Hb:  $Z = -7.6869$ ,  $p < 0.0001$ ) (Tables 2, 6). The results of the multivariate logistic regression analysis identified age (OR = 1.3410,  $p = 0.0229$ ), red blood cell count (OR = 0.9420,  $p = 0.0420$ ), and Hb (OR = 0.0623,  $p = 0.0003$ ) as independent factors associated with the occurrence of decreased hemoglobin (Table 3C). In the ROC analysis, cutoff values of age  $\geq 68$  years, red blood cell count  $\leq 394 \times 10^4/\mu\text{L}$ , and Hb  $\leq 11.7$  g/dL were identified; the AUC values were 0.69, 0.78, and 0.95, respectively, with Hb demonstrating particularly high discriminatory power (Table 4B). Based on the above, age, red blood cell count, and Hb were identified as pre-treatment factors associated with an increased risk of decreased hemoglobin levels.

| Variable               |                  | Grade 0       | Grade ≥ 1     | Statistic (Z / χ²) | p-value  |    |
|------------------------|------------------|---------------|---------------|--------------------|----------|----|
|                        |                  | n = 71        | n = 37        |                    |          |    |
| Age (years)            |                  | 64.54 ± 10.81 | 71.24 ± 7.25  | Z = 3.2595         | 0.0011*  | a) |
| Sex                    | Male             | 46            | 13            | χ² = 7.5776        | 0.0033*  | b) |
|                        | Female           | 25            | 24            |                    |          |    |
| BMI (kg/m²)            |                  | 23.24 ± 3.75  | 20.31 ± 3.17  | Z = -3.9748        | <0.0001* | a) |
| Body surface area (m²) |                  | 1.62 ± 0.18   | 1.47 ± 0.17   | Z = -4.0201        | <0.0001* | a) |
| General condition□PS□  | 0                | 66            | 31            | χ² = 22.8371       | 0.0663   | b) |
|                        | 1                | 5             | 6             |                    |          |    |
| Smoking history        | 0                | 23            | 20            | χ² = 25.4196       | 0.0463*  | b) |
|                        | 1-199            | 1             | 4             |                    |          |    |
|                        | 200-399          | 8             | 0             |                    |          |    |
|                        | 400-699          | 12            | 2             |                    |          |    |
|                        | 700-             | 22            | 11            |                    |          |    |
| Drinking history       | None             | 16            | 18            | χ² = 8.6613        | 0.0330*  | b) |
|                        | Occasional       | 15            | 6             |                    |          |    |
|                        | Weekly           | 12            | 6             |                    |          |    |
|                        | Everyday         | 28            | 7             |                    |          |    |
|                        | Upper colon      | 4             | 8             |                    |          |    |
| Cancer site            | Lower colon      | 4             | 2             | χ² = 9.4878        | 0.2133   | b) |
|                        | Sigmoid colon    | 19            | 5             |                    |          |    |
|                        | Transverse colon | 12            | 7             |                    |          |    |
|                        | Jejunum          | 0             | 1             |                    |          |    |
|                        | Rectum           | 25            | 9             |                    |          |    |
| Stage                  | Cecum            | 7             | 4             | χ² = 6.5384        | 0.1722   | b) |
|                        | Ila              | 19            | 5             |                    |          |    |
|                        | Ilb              | 5             | 1             |                    |          |    |
|                        | IIla             | 10            | 4             |                    |          |    |
|                        | IIlb             | 27            | 16            |                    |          |    |
|                        | IIlc             | 6             | 5             |                    |          |    |
| Dose (%)               | IV               | 4             | 6             | Z = -0.7638        | 0.4449   | a) |
|                        | Oxaliplatin      | 89.55 ± 7.59  | 88.10 ± 8.50  |                    |          |    |
|                        | Capecitabine     | 93.49 ± 9.41  | 92.40 ± 11.08 |                    |          |    |

**TABLE 6: Pre-treatment factors associated with hemoglobin decrease (Grade ≥1)**

Values marked with an asterisk (\*) are statistically significant (p < 0.05). Statistical tests used: a) Wilcoxon two-sample test; b) Pearson's chi-square test.

## Thrombocytopenia

The results of the comparison of pre-treatment factors associated with thrombocytopenia are shown in Table 2 and Table 7, and the results of the multivariate logistic regression analysis are shown in Table 3D. In patients with thrombocytopenia, the lymphocyte count ( $\times 10^2/\mu\text{L}$ ) and SII at the start of the first cycle showed significant differences between the Grade ≥1 group and the Grade 0 group (lymphocyte: Z = -2.0767, p = 0.0378; SII: Z = -2.6120, p = 0.0090) (Table 2). The results of multivariate logistic regression analysis identified lymphocyte count (OR = 0.4810, p = 0.0326) and SII (OR = 0.9910, p = 0.0382) as independent factors associated with the occurrence of thrombocytopenia (Table 3D). In the ROC analysis, lymphocyte

counts  $\leq 12.41 \times 10^2/\mu\text{L}$  and SII  $\leq 477.901$  were identified as cutoff values, and the AUC ranged from 0.63 to 0.67 (Table 4C). Based on the above, lymphocyte count and SII were identified as pre-treatment factors associated with an increased risk of thrombocytopenia. The results of the ROC analysis for each toxicity (cutoff values, AUC, sensitivity, and specificity) are shown in Table 4.

| Variable                            |                  | Grade 0           | Grade $\geq 1$    | Statistic (Z / $\chi^2$ ) | p-value |    |
|-------------------------------------|------------------|-------------------|-------------------|---------------------------|---------|----|
|                                     |                  | n = 82            | n = 26            |                           |         |    |
| Age (years)                         |                  | 66.98 $\pm$ 10.40 | 66.38 $\pm$ 9.76  | Z = -0.4495               | 0.6530  | a) |
| Sex                                 | Male             | 73                | 24                | $\chi^2 = 7.7125$         | 0.7189  | b) |
|                                     | Female           | 9                 | 2                 |                           |         |    |
| BMI (kg/m <sup>2</sup> )            |                  | 22.32 $\pm$ 3.98  | 21.95 $\pm$ 3.62  | Z = -0.3090               | 0.7573  | a) |
| Body surface area (m <sup>2</sup> ) |                  | 1.56 $\pm$ 0.18   | 1.59 $\pm$ 0.21   | Z = 0.4670                | 0.6404  | a) |
| General condition (PS)              | 0                | 73                | 24                | $\chi^2 = 7.7125$         | 0.6296  | b) |
|                                     | 1                | 9                 | 2                 |                           |         |    |
| Smoking history                     | 0                | 32                | 11                | $\chi^2 = 1.3772$         | 0.8478  | b) |
|                                     | 1-199            | 9                 | 1                 |                           |         |    |
|                                     | 200-399          | 6                 | 2                 |                           |         |    |
|                                     | 400-699          | 11                | 3                 |                           |         |    |
|                                     | 700-             | 24                | 9                 |                           |         |    |
| Drinking history                    | None             | 27                | 7                 | $\chi^2 = 1.4117$         | 0.7027  | b) |
|                                     | Occasional       | 17                | 4                 |                           |         |    |
|                                     | Weekly           | 12                | 6                 |                           |         |    |
|                                     | Everyday         | 26                | 9                 |                           |         |    |
| Cancer site                         | Upper colon      | 12                | 0                 | $\chi^2 = 7.6996$         | 0.2166  | b) |
|                                     | Lower colon      | 5                 | 1                 |                           |         |    |
|                                     | Sigmoid colon    | 15                | 9                 |                           |         |    |
|                                     | Transverse colon | 13                | 6                 |                           |         |    |
|                                     | Jejunum          | 1                 | 0                 |                           |         |    |
| Stage                               | Rectum           | 27                | 9                 | $\chi^2 = 2.8166$         | 0.6707  | b) |
|                                     | Cecum            | 10                | 1                 |                           |         |    |
|                                     | IIa              | 20                | 4                 |                           |         |    |
|                                     | IIb              | 4                 | 2                 |                           |         |    |
|                                     | IIIa             | 12                | 2                 |                           |         |    |
|                                     | IIIb             | 30                | 13                |                           |         |    |
| Dose (%)                            | IIc              | 8                 | 3                 | Z = 0.1113                | 0.9113  | a) |
|                                     | IV               | 8                 | 2                 |                           |         |    |
|                                     | Oxaliplatin      | 88.96 $\pm$ 8.04  | 89.35 $\pm$ 7.63  |                           |         |    |
| Capecitabine                        |                  | 92.43 $\pm$ 9.42  | 95.27 $\pm$ 11.51 | Z = 1.9617                | 0.0498* | a) |

**TABLE 7: Pre-treatment factors associated with thrombocytopenia (Grade  $\geq 1$ )**

Values marked with an asterisk (\*) are statistically significant ( $p < 0.05$ ). Statistical tests used: a) Wilcoxon two-sample test; b) Pearson's chi-square test.

## Discussion

In this study, we conducted an exploratory analysis to examine how pre-treatment hematological, inflammatory, and immune markers are associated with the development of hematological toxicity in

colorectal cancer patients receiving CapeOX therapy. The results suggested that certain pre-treatment factors may serve as predictors for leukopenia, anemia, and thrombocytopenia.

With regard to leukopenia, SII was identified as the sole independent pre-treatment factor. SII is a composite inflammatory marker calculated from platelet, neutrophil, and lymphocyte counts and is known to reflect tumor-associated inflammation and immune status [5]. However, because SII is calculated directly from platelet, neutrophil, and lymphocyte counts and the outcomes include leukopenia and thrombocytopenia, the observed association may partly reflect low baseline hematologic reserve or mathematical coupling with the outcome rather than an independent inflammatory mechanism. Correlation analyses showed strong associations between SII and its component blood counts, supporting the need for cautious mechanistic interpretation. Therefore, the role of SII in hematologic toxicity should be considered exploratory and may primarily reflect baseline hematologic status rather than a distinct inflammatory pathway. In addition, lower pretreatment SII may indicate reduced marrow proliferative capacity or subclinical hematologic vulnerability, making patients more susceptible to chemotherapy-induced leukocyte depletion. This provides a biological rationale for the observed association between low SII and leukopenia. In the field of gastrointestinal cancers, including colorectal cancer, SII has been reported to be associated with prognosis and chemotherapy toxicity [8]; its identification as a predictor of leukopenia in this study is consistent with existing findings. Since the pre-treatment inflammatory state may influence susceptibility to bone marrow suppression, SII is considered useful for risk stratification prior to the start of treatment.

Regarding neutropenia, although SIRI and NLR showed an association in univariate analysis, they did not remain as independent factors in multivariate analysis. First, it has been reported that neutropenia is strongly influenced by drug exposure, and it has been suggested that individual differences in the pharmacokinetics and exposure levels of anticancer drugs may contribute to the manifestation of toxicity [9]. Furthermore, it has been shown that impaired renal function affects drug clearance and exacerbates bone marrow suppression [10]. In addition, it is known that genetic background (polymorphisms in drug-metabolizing enzymes and transporters) is involved in the development of neutropenia [10]. Based on these findings, neutropenia is likely a multifactorial toxicity that is difficult to predict using pre-treatment factors alone. The results of this study suggest that it is difficult to adequately predict neutropenia based solely on pre-treatment inflammatory and immune markers.

Age, red blood cell count, and Hb were identified as independent predictors of hemoglobin decline. First, it has been reported that older adults are more prone to developing anemia during chemotherapy due to reduced bone marrow reserve and the effects of nutritional status [11]. Furthermore, it has been suggested that age-related fragility of hematopoietic function may influence chemotherapy toxicity [12]. Second, it has been shown that patients with low pre-treatment red blood cell counts are more susceptible to bone marrow suppression caused by anticancer drugs [13]. Similarly, multiple studies have reported that a low pre-treatment Hb level is a significant risk factor for the development of anemia during chemotherapy [14,15]. The results of this study indicate that a tendency toward anemia prior to treatment is a significant risk factor for a decrease in hemoglobin during treatment, reaffirming the importance of hematological evaluation before the start of treatment.

However, because baseline hemoglobin lies close to the CTCAE Grade 1 threshold used to define first-cycle anemia, the observed association may partly reflect baseline status or mathematical coupling with the outcome rather than treatment-induced toxicity. Lower baseline Hb was strongly associated with meeting the study's anemia definition, and this relationship should not be interpreted as an independent causal marker of CapeOX-induced anemia without analyses accounting for baseline anemia and absolute Hb change. Therefore, the finding should be considered exploratory and requires validation using clinically meaningful toxicity thresholds.

With regard to thrombocytopenia, lymphocyte count and SII were identified as independent factors. First, it has been reported that a low lymphocyte count prior to treatment is associated with the development of hematologic toxicity during chemotherapy [16]. Furthermore, it has been suggested that lymphocytopenia reflects immunological vulnerability and may contribute to the exacerbation of chemotherapy-related toxicity [17]. In addition, it has been shown that patients with low pre-treatment lymphocyte counts are more prone to myelosuppression, including thrombocytopenia [18]. This study suggested that low pre-treatment SII levels are associated with thrombocytopenia and that the pre-treatment inflammatory and immune status may be involved in the development of thrombocytopenia. The results of this study indicate that thrombocytopenia is a toxicity susceptible to the influence of immune and inflammatory states, suggesting that assessment of the pre-treatment immune status may be useful.

This study has several statistical limitations. Given its exploratory nature, this study conducted univariate analyses on numerous pre-treatment factors and included those showing statistically significant differences in the multivariate logistic regression analysis. Therefore, the possibility of Type I errors (false positives) associated with multiple comparisons cannot be ruled out. Furthermore, the number of events for some hematologic toxicities was small, particularly leukopenia (11 events) and neutropenia (15 events), raising concerns about the stability and robustness of the multivariable logistic regression estimates. In addition, the AUC values obtained from the ROC analysis were sometimes moderate, suggesting that the predictive model has limitations in terms of accuracy.

In addition, some categorical comparisons involved sparse cell counts, for which ordinary chi-square testing is not optimal. These univariate results were therefore interpreted only as exploratory screening, and the potential impact of sparse data on the robustness of the p-values represents a limitation of this study. Because extensive univariate testing increases the risk of type I error, these findings should be interpreted as

exploratory and hypothesis-generating.

The cutoff values derived in this study were obtained and evaluated using the same small dataset without internal or external validation. This approach may lead to optimistic AUC estimates and data-specific thresholds. Therefore, the cutoff values should be considered exploratory and require independent validation in larger cohorts before being applied for clinical risk stratification.

A single Day 21 measurement may not necessarily capture the hematologic nadir, and this limitation should be considered when interpreting the association between pretreatment laboratory values and hematologic toxicity. Baseline dose reductions may have influenced the occurrence of hematologic toxicity, and this factor should be considered when interpreting the association between pretreatment laboratory values and toxicity.

In addition, because hematologic toxicity was defined by the absolute CTCAE grade at the end of cycle 1, the present analysis does not distinguish between new-onset and worsening abnormalities. This is particularly relevant for hemoglobin, where the baseline value is also used as a predictor. Future studies should define toxicity based on new-onset or worsening from baseline and incorporate clinically meaningful thresholds.

Furthermore, this study is a single-center retrospective analysis, and patient characteristics, treatment strategies, and the use of supportive care may vary depending on the specific characteristics of the institution. Therefore, caution is required when interpreting the results for generalization to other institutions, and validation through prospective studies involving a more diverse patient population is needed.

However, as an exploratory analysis, this study presents clinically useful hypotheses suggesting that pre-treatment factors may contribute to the development of hematologic toxicity. These findings serve as an important starting point that should be validated in future prospective and multicenter studies, and are expected to lead to the development of more accurate predictive models.

In addition, the multivariable logistic regression models in this exploratory analysis were developed with a limited number of events relative to the number of candidate predictors, and several hematologic and inflammatory variables (e.g., white blood cell count, neutrophil count, lymphocyte count, platelet count, SII, SIRI, NLR, red blood cell count, and hemoglobin) are mathematically and biologically correlated. These factors raise concerns about overfitting and multicollinearity, and the resulting ORs and cutoff values should be interpreted very cautiously as data-driven, exploratory estimates rather than definitive clinical thresholds. Future studies should adopt more parsimonious prespecified models and consider penalized logistic regression or other shrinkage approaches to improve model stability and generalizability.

Based on the above, it was suggested that some of the hematologic toxicities associated with CapeOX therapy can be predicted based on pre-treatment hematologic markers and inflammatory and immune markers, and that this may contribute to risk stratification prior to treatment initiation and the consideration of individualized supportive care.

## Conclusions

In this exploratory single-center cohort, lower baseline SII was associated with Cycle 1 leukopenia, while lower baseline lymphocyte count and SII were associated with thrombocytopenia. Baseline hemoglobin and red blood cell count were strongly associated with meeting the study's anemia definition. Because the models were data-driven, the outcomes were predominantly Grade  $\geq 1$ , and no external validation was performed, these findings should be considered hypothesis-generating rather than clinically actionable predictors. Prospective multicenter studies with prespecified, parsimonious models and external validation are needed before these markers can be used to guide supportive care or treatment modification.

## Appendices

| Variable                               | Reference range (normal value)              |
|----------------------------------------|---------------------------------------------|
| Red blood cell (10 <sup>6</sup> /μL)   | Male 420–570 / Female 380–500               |
| White blood cell (10 <sup>3</sup> /μL) | 35–90                                       |
| Basophil (10 <sup>3</sup> /μL)         | 0-2                                         |
| Eosinophil (10 <sup>3</sup> /μL)       | 0-6                                         |
| Neutrophil (10 <sup>3</sup> /μL)       | 40-75                                       |
| Lymphocyte (10 <sup>3</sup> /μL)       | 20-50                                       |
| Monocyte (10 <sup>3</sup> /μL)         | 2-10                                        |
| Platelet (10 <sup>4</sup> /μL)         | 15-35                                       |
| Serum albumin (g/dL)                   | 3.8-5.0                                     |
| CRP (mg/dL)                            | <0.3                                        |
| AST (IU/L)                             | 13-33                                       |
| ALT (IU/L)                             | 8-42                                        |
| Hb (g/dL)                              | Male 13.0–17.0 / Female 11.5–15.0           |
| eGFR (mL/min/1.73m <sup>2</sup> )      | ≥60                                         |
| Cr (mg/dL)                             | Male 0.65–1.07 / Female 0.46–0.79           |
| Ccr (mL/min)                           | 80-130                                      |
| PNI                                    | ≥45(Good)                                   |
| SIRI                                   | 1.0-1.5 (clinical cut-off)                  |
| NLR                                    | 1.0-3.0                                     |
| PLR                                    | 100-200                                     |
| LMR                                    | 3.0-5.0                                     |
| SII                                    | ≤500 (increased by inflammation and tumors) |

TABLE 8: Reference ranges for blood test values and nutritional and inflammatory indices

CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Hb: hemoglobin; eGFR: estimated glomerular filtration rate; Cr: creatinine; Ccr: creatinine clearance; PNI: prognostic nutrition index; SIRI: systemic inflammatory response index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; SII: systemic immune inflammatory index

| Variable               |        | Leukopenia    |              |                    |         | Neutropenia   |              |                    |         | Hemoglobin decrease |              |                    |          | Thrombocytopenia |              |                    |         |    |
|------------------------|--------|---------------|--------------|--------------------|---------|---------------|--------------|--------------------|---------|---------------------|--------------|--------------------|----------|------------------|--------------|--------------------|---------|----|
|                        |        | Grade 0       | Grade ≥ 1    | Statistic (Z / χ²) | p-value | Grade 0       | Grade ≥ 1    | Statistic (Z / χ²) | p-value | Grade 0             | Grade ≥ 1    | Statistic (Z / χ²) | p-value  | Grade 0          | Grade ≥ 1    | Statistic (Z / χ²) | p-value |    |
|                        |        |               |              |                    |         |               |              |                    |         |                     |              |                    |          |                  |              |                    |         |    |
|                        |        |               |              |                    |         |               |              |                    |         |                     |              |                    |          |                  |              |                    |         |    |
| Age (years)            |        | 66.68 ± 10.40 | 68.27 ± 8.58 | Z = 0.3863         | 0.6992  | 67.46 ± 10.21 | 63.00 ± 9.65 | Z = -1.8007        | 0.0717  | 64.54 ± 10.81       | 71.24 ± 7.25 | Z = 3.2595         | 0.0011*  | 66.98 ± 10.40    | 66.38 ± 9.76 | Z = -0.4495        | 0.6530  | a) |
| Sex                    | Male   | 55            | 4            | χ² = 1.7112        | 0.1991  | 52            | 7            | χ² = 0.1500        | 0.5044  | 46                  | 13           | χ² = 7.5776        | 0.0033*  | 73               | 24           | χ² = 7.7125        | 0.7189  | b) |
|                        | Female | 42            | 7            |                    |         | 41            | 8            |                    |         | 25                  | 24           |                    |          | 9                | 2            |                    |         |    |
| BMI (kg/m²)            |        | 22.10 ± 3.72  | 22.64 ± 2.99 | Z = 0.4571         | 0.6476  | 22.05 ± 3.72  | 23.41 ± 4.3  | Z = 1.9632         | 0.0496* | 23.24 ± 3.75        | 20.31 ± 3.17 | Z = 3.9748         | <0.0001* | 22.32 ± 3.98     | 21.95 ± 3.62 | Z = 0.3090         | 0.7573  | a) |
| Body surface area (m²) |        | 1.57 ± 0.20   | 1.55 ± 0.14  | Z = -0.5180        | 0.6044  | 1.57 ± 0.19   | 1.59 ± 0.21  | Z = 0.7639         | 0.4449  | 1.62 ± 0.18         | 1.47 ± 0.17  | Z = 4.0201         | <0.0001* | 1.56 ± 0.18      | 1.59 ± 0.21  | Z = 0.4670         | 0.6404  | a) |
| General condition: PS  | 0      | 85            | 10           | χ² = 1.1357        | 0.5965  | 85            | 12           | χ² = 3.5447        | 0.1756  | 66                  | 31           | χ² = 22.8371       | 0.0663   | 73               | 24           | χ² = 7.7125        | 0.6296  | b) |
|                        | 1      | 8             | 1            |                    |         | 8             | 3            |                    |         | 5                   | 6            |                    |          | 9                | 2            |                    |         |    |

|                  |                  |              |               |                      |        |              |               |                       |        |              |               |                       |         |              |               |                      |         |    |
|------------------|------------------|--------------|---------------|----------------------|--------|--------------|---------------|-----------------------|--------|--------------|---------------|-----------------------|---------|--------------|---------------|----------------------|---------|----|
|                  | 0                | 38           | 5             |                      | 38     | 5            |               | 23                    | 20     |              | 32            | 11                    |         |              |               |                      |         |    |
|                  | 1-199            | 9            | 1             |                      | 8      | 2            |               | 1                     | 4      |              | 9             | 1                     |         |              |               |                      |         |    |
| Smoking history  | 200-399          | 6            | 2             | $\chi^2 =$<br>0.0032 | 0.5965 | 6            | 2             | $\chi^2 =$<br>5.0055  | 0.2366 | 8            | 0             | $\chi^2 =$<br>25.4196 | 0.0463* | 6            | 2             | $\chi^2 =$<br>1.3772 | 0.8478  | b) |
|                  | 400-699          | 13           | 1             |                      |        | 10           | 4             |                       |        | 12           | 2             |                       |         | 11           | 3             |                      |         |    |
|                  | 700-             | 31           | 2             |                      |        | 31           | 2             |                       |        | 22           | 11            |                       |         | 24           | 9             |                      |         |    |
| Drinking history | None             | 30           | 2             |                      |        | 31           | 3             |                       |        | 16           | 18            |                       |         | 27           | 7             |                      |         |    |
|                  | Occasional       | 21           | 0             | $\chi^2 =$<br>5.8957 | 0.1912 | 18           | 3             | $\chi^2 =$<br>1.9445  | 0.5847 | 15           | 6             | $\chi^2 =$<br>8.6613  | 0.0330* | 17           | 4             | $\chi^2$<br>=1.4117  | 0.7027  | b) |
|                  | Weekly           | 17           | 1             |                      |        | 16           | 2             |                       |        | 12           | 6             |                       |         | 12           | 6             |                      |         |    |
|                  | Everyday         | 29           | 6             |                      |        | 28           | 7             |                       |        | 28           | 7             |                       |         | 26           | 9             |                      |         |    |
| Cancer site      | Upper colon      | 12           | 0             |                      |        | 12           | 0             |                       |        | 4            | 8             |                       |         | 12           | 0             |                      |         |    |
|                  | Lower colon      | 5            | 0             |                      |        | 5            | 1             |                       |        | 4            | 2             |                       |         | 5            | 1             |                      |         |    |
|                  | Sigmoid colon    | 21           | 3             |                      |        | 23           | 1             |                       |        | 19           | 5             |                       |         | 15           | 9             |                      |         |    |
|                  | Transverse colon | 19           | 0             | $\chi^2 =$<br>8.1922 | 0.2790 | 17           | 2             | $\chi^2 =$<br>7.7881  | 0.2540 | 12           | 7             | $\chi^2 =$<br>9.4878  | 0.2133  | 13           | 6             | $\chi^2$<br>=7.6996  | 0.2166  | b) |
|                  | Jejunum          | 1            | 0             |                      |        | 1            | 0             |                       |        | 0            | 1             |                       |         | 1            | 0             |                      |         |    |
|                  | Rectum           | 32           | 4             |                      |        | 28           | 8             |                       |        | 25           | 9             |                       |         | 27           | 9             |                      |         |    |
|                  | Cecum            | 8            | 3             |                      |        | 8            | 3             |                       |        | 7            | 4             |                       |         | 10           | 1             |                      |         |    |
| Stage            | Ila              | 23           | 1             |                      |        | 21           | 3             |                       |        | 19           | 5             |                       |         | 20           | 4             |                      |         |    |
|                  | Ilb              | 5            | 1             |                      |        | 3            | 3             |                       |        | 5            | 1             |                       |         | 4            | 2             |                      |         |    |
|                  | IIla             | 13           | 1             | $\chi^2 =$<br>4.3770 | 0.9702 | 12           | 2             | $\chi^2 =$<br>10.1572 | 0.2946 | 10           | 4             | $\chi^2 =$<br>6.5384  | 0.1722  | 12           | 2             | $\chi^2 =$<br>2.8166 | 0.6707  | b) |
|                  | IIlb             | 36           | 7             |                      |        | 36           | 7             |                       |        | 27           | 16            |                       |         | 30           | 13            |                      |         |    |
|                  | IIlc             | 10           | 1             |                      |        | 11           | 0             |                       |        | 6            | 5             |                       |         | 8            | 3             |                      |         |    |
|                  | IV               | 10           | 0             |                      |        | 10           | 0             |                       |        | 4            | 6             |                       |         | 8            | 2             |                      |         |    |
| Dose (%)         | Oxaliplatin      | 89.25 ± 7.74 | 87.36 ± 9.54  | Z = - 0.6094         | 0.5422 | 89.10 ± 7.98 | 89.09 ± 7.75  | Z = - 0.0355          | 0.9717 | 89.55 ± 7.59 | 88.10 ± 8.50  | Z = - 0.7638          | 0.4449  | 88.96 ± 8.04 | 89.35 ± 7.63  | Z = 0.1113           | 0.9113  | a) |
|                  | Capecitabine     | 92.90 ± 9.82 | 94.97 ± 11.59 | Z = 1.0462           | 0.2954 | 92.8 ± 9.47  | 95.23 ± 12.86 | Z = 0.9239            | 0.3555 | 93.49 ± 9.41 | 92.40 ± 11.08 | Z = - 0.4466          | 0.6551  | 92.43 ± 9.42 | 95.27 ± 11.51 | Z = 1.9617           | 0.0498* | a) |

TABLE 9: Baseline patient information by adverse effect observed at the end of one treatment cycle
Values marked with an asterisk (\*) are statistically significant (p < 0.05). Statistical tests used: a) Wilcoxon two-sample test; b) Pearson's chi-square test. One case involved a synchronous jejunal lesion. Although the jejunum is not a colorectal site, the patient received chemotherapy according to colorectal cancer protocols; therefore, the case was retained in the colorectal cancer cohort.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Makoto Kishimoto, Jin Tokunaga

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Disclosures

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