Validation of the conventional Glasgow Prognostic Score and development of the improved Glasgow Prognostic Score in patients with stage 0-III colorectal cancer after curative resection

Satoshi Ishikawa\(^1\) | Norikatsu Miyoshi\(^1,2\) | Shiki Fujino\(^1\) | Takayuki Ogino\(^1\) | Hidekazu Takahashi\(^1\) | Mamoru Uemura\(^1\) | Hirofumi Yamamoto\(^1\) | Tsunekazu Mizushima\(^1\) | Yuichiro Doki\(^1\) | Hidetoshi Eguchi\(^1\)

\(^1\)Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita City, Japan
\(^2\)Department of Innovative Cancer Research and Translational Medicine, Osaka International Cancer Institute, Osaka, Japan

Correspondence
Norikatsu Miyoshi, Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita-City, Osaka 565-0871, Japan.
Email: nmiyoshi@gesurg.med.osaka-u.ac.jp

Abstract
Aim: Many inflammation-nutrition scores, including the Glasgow Prognostic Score (GPS), have been reported as prognostic biomarkers in patients with colorectal cancer (CRC). We aimed to examine the predictive ability of the GPS and to improve the GPS.

Methods: We included a total of 438 patients with stage 0-III CRC who underwent curative surgery from 2010 to 2013. They were divided into a training set comprising 221 patients and a validation set comprising 227 patients, according to the date of surgery. In the training set, the GPS was verified using a Cox regression model, and cut-off values for C-reactive protein (CRP) and albumin for relapse-free survival (RFS) were calculated using receiver operating characteristics (ROC) curves. The improved GPS (iGPS) was developed with additional optimal cut-off values. We also compared the iGPS with the conventional GPS in the validation set.

Results: The high GPS (GPS: 1-2) was correlated with RFS and overall survival (OS) in the training set. Cut-off values of CRP and albumin for RFS were 1.6 and 3.9, and we modified the GPS accordingly, adding the cut-off values of 2 and 3.9 to CRP and albumin, respectively. In the validation set, a high iGPS was an independent prognostic factor for RFS (hazard ratio [HR]: 2.273; 95% confidence interval [CI]: 1.212-4.364; \(P = .011\)), although the conventional GPS was not.

Conclusion: The iGPS was a more accurate prognostic predictor for patients with stage 0-III CRC.

Keywords
biomarkers, colorectal cancer, inflammation, nutrition, prognosis
Colorectal cancer (CRC) was the third most common malignancy and the fourth most frequent cause of cancer-related death worldwide in 2012. Despite advances in therapeutic strategies, including surgical procedures, chemotherapy, and immunotherapy, the relapse and mortality rates of CRC remain high. Therefore, it is crucial to predict the risk of recurrence in patients with CRC and to identify patients who will require additional therapeutic interventions even after curative resection. Currently, the tumor-node-metastasis (TNM) classification is widely used as a prognostic prediction system in various cancers, including CRC. However, TNM staging system reflects only tumor characteristics and does not convey patient status. In particular, the TNM staging system for CRC does not accurately apply to patients without metastasis.

A growing body of studies has indicated that the inflammatory, nutritional, and immunological status of a patient has important functions in cancer progression and is associated with the prognosis of malignant tumors. Increasingly, inflammatory scores such as the neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), prognostic nutritional index (PNI), Glasgow prognostic score (GPS), controlling nutritional status (CONUT), and systemic inflammation score (SIS) have been reported to be prognostic indicators. All of these comprise some combination of blood cell counts, serum albumin level, total cholesterol concentration, and C-reactive protein (CRP) concentration. Among these, CRP is a critical factor in the prognosis of patients with CRC.

The GPS consists of CRP and albumin and reflects both the inflammatory and nutritional status of the patient. The GPS was first reported as a prognostic indicator in patients with non-small-cell lung cancer in 2003. Since then, many studies have shown the utility of the GPS in predicting prognoses for various cancers types. Typically, these studies have utilized the common cut-off values for CRP and albumin, although some studies have used the modified GPS, which regards patients with only hypoalbuminemia as low risk. However, the optimal cut-off values for inflammatory scores should vary between cancers because the degree of inflammation and malnutrition depends on the types of cancer. For example, one study utilizing PNI in the investigation of T1-2N1 breast cancer used a cut-off value of 52.0, another study of unresectable advanced gastric cancer used 36.1, and a study of resectable CRC used 45.5.

In the present study, we sought to investigate the predictive capacity of the GPS for the risk of relapse in patients with CRC undergoing curative resection without distant metastasis. To the best of our knowledge, this is the first report on the GPS that focused on relapse-free survival (RFS) in patients with stage 0-III CRC. Moreover, we developed the improved GPS (iGPS) with additional cut-off values for CRP and albumin. We validated the iGPS in a separate data set and compared it with the conventional GPS.

In this retrospective study, we enrolled 531 patients with stage 0-III CRC who underwent curative resection at Osaka University Hospital between January 2010 and December 2013. We excluded 52 patients who underwent surgery after endoscopic resection, three with inflammatory bowel syndrome, and 38 for whom there was no available.
laboratory data for CRP or albumin within the 30 days prior to surgery. The remaining 438 patients were divided into two groups: a training set, consisting of 211 patients who underwent surgery between 2010 and 2011, and a validation set, consisting of 227 patients who underwent surgery between 2012 and 2013 (Figure 1). We utilized the most recently obtained laboratory data within the 30 days prior to surgery, including CRP, albumin, and CEA. The clinicopathological findings were evaluated based on the eighth edition of the Union International Contra Cancrum (UICC) TNM classification. The Institutional Review Boards of Osaka University granted ethical approval for this study.

2.2 | The GPS and the iGPS

The GPS was estimated using CRP and albumin, as described in previous reports. Patients with both an elevated CRP (>10 mg/L) and hypoalbuminemia (<35 g/L) were given a GPS of 2, those with only one of these conditions were given a GPS of 1, and those with neither of these were given a GPS of 0. Receiver operating characteristics (ROC) curve analyses were used to determine the best cut-off values for CRP and albumin to predict relapse or death in the training set. We constructed the iGPS by adding the cut-off values to the conventional GPS.

2.3 | Survival data

After surgery, patients were followed up with a computed tomography (CT) scan and laboratory analysis of serum CEA and CA19-9 concentrations every 3-6 months, as well as a colonoscopy annually or biannually in accordance with Japanese national guidelines. Data regarding patient survival and recurrence were collected from the medical records to calculate overall survival (OS), defined as the time in months from the date of surgery to the date of death from any cause, and relapse-free survival (RFS), defined as the time in months from the date of surgery to either the date of relapse or death.

2.4 | Statistical analysis

Patient characteristics are presented as mean ± standard deviation for continuous variables and the number of patients (as a percentage) for categorical variables. The difference between the two groups was analyzed using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. Univariate and multivariate analyses were performed using a Cox proportional hazards model. Kaplan-Meier analyses were used to compare survival with the log-rank test. Receiver operating characteristics (ROC) curves for relapse or death were used to determine the CRP and albumin cut-off values in the training set. These statistical analyses were performed using JMP® software version 14 (SAS Institute Inc.). The predictive performance of GPS and iGPS was calculated using the concordance-index (c-index) with the R software program, v. 3.1.3 (CRAN; the R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Patient characteristics

The characteristics of 211 patients in the training set and 227 patients in the validation set are summarized in Table S1. The training set, consisting of 211 patients who underwent surgery between 2010 and 2011, and a validation set, consisting of 227 patients who underwent surgery between 2012 and 2013 (Figure 1). We utilized the most recently obtained laboratory data within the 30 days prior to surgery, including CRP, albumin, and CEA. The clinicopathological findings were evaluated based on the eighth edition of the Union International Contra Cancrum (UICC) TNM classification. The Institutional Review Boards of Osaka University granted ethical approval for this study.

**TABLE 1** The relationship between GPS (0/1, 2) and patient characteristics in the training set

| Variable                  | Number (%) | GPS 0 (%) | 1-2 (%) | P-value |
|---------------------------|------------|-----------|---------|---------|
| GPS                       |            | 157 (74.4) | 54 (25.6) |         |
| Agea (years)              |            | 65.0 ± 11.1 | 70.4 ± 13.5 | .002    |
| Gender                    |            |           |         |         |
| Male                      |            | 128 (60.7) | 96 (75.0) | 32 (25.0) | .807    |
| Female                    |            | 83 (39.3)  | 61 (73.5) | 22 (26.5) |         |
| Primary tumor site        |            |           |         |         |
| Colon                     |            | 155 (73.5) | 113 (74.2) | 40 (25.8) | .906    |
| Rectum                    |            | 56 (26.5)  | 42 (75.0) | 14 (25.0) |         |
| Histological grade        |            |           |         |         |
| Pap, Tub1 or Tub2         |            | 197 (93.4) | 152 (77.2) | 45 (22.8) | .002    |
| Othersb                   |            | 14 (6.6)   | 5 (35.7)  | 9 (64.3) |         |
| Tumor invasion            |            |           |         |         |
| Tis, T1 or T2             |            | 95 (45.0)  | 82 (86.3) | 13 (13.7) | <.001   |
| T3 or T4                  |            | 116 (55.0) | 75 (64.7) | 41 (35.3) |         |
| Lymph node metastasis     |            |           |         |         |
| Absent                    |            | 148 (70.5) | 114 (77.0) | 34 (23.0) | .166    |
| Present                   |            | 62 (29.5)  | 42 (67.7) | 20 (32.3) |         |
| Lymphatic invasion        |            |           |         |         |
| Absent                    |            | 63 (30.0)  | 54 (85.7) | 9 (14.3) | .010    |
| Present                   |            | 147 (70.0) | 102 (69.4) | 45 (30.5) |         |
| Venous invasion           |            |           |         |         |
| Absent                    |            | 145 (69.4) | 116 (80.0) | 29 (20.0) | .005    |
| Present                   |            | 64 (30.6)  | 39 (60.9) | 25 (39.1) |         |
| Preoperative CEA          |            |           |         |         |
| CEA < 5                   |            | 142 (78.4) | 116 (81.7) | 26 (18.3) | <.001   |
| CEA ≥ 5                   |            | 39 (21.6)  | 19 (48.7) | 20 (51.3) |         |
| TNM stage                 |            |           |         |         |
| 0, I                      |            | 79 (37.4)  | 69 (87.3) | 10 (12.7) | <.001   |
| II, III                   |            | 132 (62.6) | 88 (66.7) | 44 (33.3) |         |

Note: P < .05 indicated in bold.

Abbreviations: CEA, carcinoembryonic antigen; Pap, papillary adenocarcinoma; Tub1, well differentiated adenocarcinoma; Tub2, moderately differentiated adenocarcinoma.

aContinuous variable.
bOthers: poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or endocrine cell carcinoma.
cUnknown in one case.
dUnknown in one case.
eUnknown in two cases.
fUnknown in 30 cases.
set consisted of 155 patients with colon cancer and 56 patients with rectal cancer, and the validation set consisted of 154 patients with colon cancer and 73 patients with rectal cancer. There were 157 patients with a GPS of 0, 43 patients with a GPS of 1, and 11 patients with a GPS of 2 in the training set, and the corresponding values were 169, 34, and 24, respectively, in the validation set.

### TABLE 2
Univariate and multivariate analyses of relapse-free survival and overall survival by GPS in the training set

| Variable | Univariate | | Multivariate | |  |
|----------|------------|---|------------|---|---|
|          | HR         | 95% CI | P-value    | HR   | 95% CI | P-value   |
|          |            |        |            |            |        |            |
| A. Analyses of relapse-free survival | | | | | | |
| Age (≥65/<65 years) | 1.272 | 0.728-2.222 | .397 | | | |
| Gender (male/female) | 1.255 | 0.710-2.218 | .435 | | | |
| Preoperative CEA (≥5/<5) | 1.948 | 0.993-3.821 | .052 | | | |
| Primary tumor site (Rectum/Colon) | 1.566 | 0.878-2.791 | .129 | | | |
| Histological grade (Others/Pap, Tub1 or Tub2) | 1.602 | 0.637-4.027 | .316 | | | |
| Tumor invasion (T3-4/Tis, T1-2) | 2.615 | 1.419-4.819 | <.002 | 1.643 | 0.839-3.217 | .148 |
| Lymph node metastasis (present/absent) | 1.959 | 1.129-3.399 | .017 | 1.241 | 0.685-2.249 | .477 |
| Venous invasion (present/absent) | 1.673 | 0.879-3.183 | .117 | | | |
| BMI | 2.891 | 1.676-4.986 | <.001 | 2.020 | 1.096-3.723 | .024 |
| GPS (1-2/0) | 2.434 | 1.400-4.234 | <.001 | 1.877 | 1.052-3.349 | .033 |
| B. Analyses of overall survival | | | | | | |
| Age (≥65/<65 years) | 2.532 | 1.235-5.192 | .011 | 2.574 | 1.205-5.502 | .015 |
| Gender (male/female) | 2.009 | 0.981-4.111 | .056 | | | |
| Preoperative CEA (≥5/<5) | 1.982 | 0.086-4.331 | .086 | | | |
| Primary tumor site (Rectum/Colon) | 1.593 | 0.822-3.090 | .168 | | | |
| Histological grade (Others/Pap, Tub1 or Tub2) | 1.606 | 0.570-4.520 | .370 | | | |
| Tumor invasion (T3-4/Tis, T1-2) | 2.575 | 1.258-5.269 | .010 | 1.612 | 0.732-3.549 | .236 |
| Lymph node metastasis (present/absent) | 1.811 | 0.961-3.410 | .066 | | | |
| Lymphatic invasion (present/absent) | 1.562 | 0.743-3.282 | .239 | | | |
| Venous invasion (present/absent) | 2.550 | 1.360-4.780 | .004 | 1.975 | 0.994-3.923 | .052 |
| GPS (1-2/0) | 3.042 | 1.628-5.684 | <.001 | 2.107 | 1.077-4.123 | .030 |

Note: P < .05 indicated in bold.

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; GPS, Glasgow prognostic score; HR, hazard ratio; Pap, papillary adenocarcinoma; Tub1, well differentiated adenocarcinoma; Tub2, moderately differentiated adenocarcinoma.

*Others: poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or endocrine cell carcinoma
3.2 | Clinicopathological factors and GPS

Clinicopathological factors in the training set were classified according to the GPS (low group: 0, high group: 1-2), as shown in Table 1. The high GPS group were older and had higher preoperative CEA levels than the low GPS group. Analysis of tumor factors revealed that the high GPS group had significantly deeper tumor invasion, more vascular invasion, and worse TNM stage than the low GPS group. Neoadjuvant and adjuvant chemotherapy regimens in the training set are shown in Table S2. Neoadjuvant chemotherapy was more frequently performed in the high GPS group than the low GPS group.

3.3 | Survival analyses according to GPS groups

Univariate and multivariate analyses for RFS and OS, according to the GPS groups in the training set, are shown in Table 2. RFS was significantly related to elevated CEA levels, deeper tumor invasion, presence of lymph node metastasis, presence of venous invasion, and a high GPS. Of these, a high GPS was the only independent prognostic factor for RFS in the multivariate analysis. OS was significantly related to age, deeper tumor invasion, presence of venous invasion, and a high GPS. Age and a high GPS were independent prognostic factors for OS. The high GPS group also had a worse prognosis than the low GPS group in Kaplan-Meier analyses for RFS and OS (Figure S1A,B). The difference in Kaplan-Meier curves for RFS between the GPS 0 and GPS 1-2 groups was more pronounced in stages II-III than in stages 0-I, as shown in Figure S2.

3.4 | Development of iGPS

The ROC curve analyses of CRP and albumin for relapse or death from any cause are shown in Figure S3A,B. The CRP and albumin values, which maximize the Youden indices (sensitivity + specificity - 1), were calculated using these analyses. The cut-off values of CRP and albumin were 1.6 and 3.9, and the area under the curve (AUC) of the ROC curves were 0.659 and 0.608, respectively. We then modified the existing GPS, adding cut-off values of 2 (1.6 rounded up) to CRP and 3.9 to albumin, to improve the prognostic ability of GPS for recurrence (Table 3).

3.5 | Survival analyses according to iGPS groups in the training and validation sets

Table 4 displays the univariate and multivariate analyses for RFS and OS using the iGPS in the training set. A high iGPS was also an independent prognostic factor and was a more powerful predictor for RFS (hazard ratio [HR]: 2.393) and OS (HR: 2.903) than a high GPS (RFS HR: 1.982, OS HR: 2.269) in the multivariate analyses. We further examined the prognostic ability of iGPS for RFS in the validation set, as shown in Table 5. A high iGPS was a significant independent predictor for RFS (HR: 2.273; 95% CI: 1.212-4.264; \( P = .011 \)), although conventional GPS was not an independent factor in the validation set (HR: 1.817; 95% CI: 0.962-3.432; \( P = .066 \)). The Kaplan-Meier curves for RFS according to the GPS and the iGPS in the validation set are illustrated in Figure 2. Five-year RFS rates were 85.4% and 61.6% in the low iGPS group and the high iGPS group, respectively, compared to 83.1% and 64.8% in the low GPS group and the high GPS group, respectively. In addition, we compared the predictive accuracy between conventional GPS and iGPS using C-indices. The C-index of iGPS for RFS (0.644) was superior to that of GPS (0.621) in the validation set (Table 6). A high iGPS was also a significant independent predictor for OS (Table S3), and the iGPS had a higher C-index for OS (0.705) than the conventional GPS (0.677) in the validation sets (Table 6).

4 | DISCUSSION

Multiple studies have reported that the GPS is associated with prognosis in patients with various types of gastrointestinal cancers, including CRC. The GPS divides patients into three groups based on their CRP and albumin levels: patients at high-risk, those at intermediate-risk, and those at low-risk. The conventional GPS utilizes only one cut-off value for each: 10 mg/L for CRP; and 35 g/L for albumin. However, this model can be too simple to precisely predict the prognosis in patients with differing types of cancers. In this study, roughly three-quarters of patients were classified as GPS 0, but some of these had a poor prognosis. Therefore, we added the cut-off values to the conventional GPS and developed the iGPS to predict RFS in patients with stage 0-III CRC with better accuracy. The resulting scores demonstrated an improved correlation with both RFS and OS compared to the conventional GPS. On the other hand, the modified GPS was not superior to the GPS as a prognostic indicator in these data sets, although some studies have shown that

| TABLE 3 | The GPS and the improved GPS based on CRP and albumin |
|----------------|----------------|
| **GPS** | **CRP (mg/L)** |
| ≤10 | 10< |
| **Albumin (g/L)** | 35≤ | <35 |
| 0 | 1 |
| 1 | 2 |
| **iGPS** | **CRP (mg/L)** |
| ≤2 | 2<, ≤10 | 10< |
| **Albumin (g/L)** | 39≤ | 35, <39 | <35 |
| 0 | 1 | 1 |
| 1 | 1 | 2 |

Abbreviations: CRP, C-reactive protein; GPS, Glasgow Prognostic Score; iGPS, improved Glasgow Prognostic Score.
Several studies have shown the relationship between systemic inflammation and cancer progression. Pro-inflammatory cytokines, such as tumor necrosis factor \( \alpha \), interleukin (IL)-6, and IL-8 are elevated during the course of inflammatory responses.\(^{15}\) These cytokines, in particular IL-6, stimulate hepatocytes to increase the synthesis of acute-phase proteins including CRP and decrease the synthesis of albumin.\(^{27}\) Thus, hypoalbuminemia is an indicator of not only nutrition and liver function but also systemic inflammation. In addition, CRP is involved in the function of infiltrating immune cells, including dendritic cells, natural killer cells, and T-lymphocytes.\(^{28-30}\) The findings of this study indicate that even a mild increase in CRP level of \(<10\) mg/L can reflect an inflammatory response.

This study has some limitations. It was a retrospective, single-center study, and the iGPS was validated in an internal cohort of different periods. Although the iGPS was examined in different independent patients, external cohorts are required to verify the validity of the iGPS further. Furthermore, we investigated only Japanese patients and the utility of the iGPS may differ according to race. However, a previous study showed that the GPS had a similar prognostic value between Asian and non-Asian patients, and this also appears to be the case with the iGPS.\(^{16}\) Finally, we did not compare the iGPS with other inflammation scores. Although previous studies have claimed superiority for each prognostic score in patients with CRC,

**TABLE 4** Univariate and multivariate analyses of relapse-free survival and overall survival by iGPS in the training set

| Variable | Univariate | Multivariate |
|----------|------------|--------------|
|          | HR | 95% CI | P value | HR | 95% CI | P value |
| **A. Analyses of relapse-free survival** | | | | | | |
| Age (≥65/<65 years) | 1.272 | 0.728-2.222 | .397 | 1.556 | 0.795-3.043 | .197 |
| Gender (male/female) | 1.255 | 0.710-2.218 | .435 | 1.257 | 0.692-2.284 | .453 |
| Preoperative CEA (≥5/<5) | 1.948 | 0.993-3.821 | .052 | 1.257 | 0.692-2.284 | .453 |
| Primary tumor site (Rectum/Colon) | 1.566 | 0.878-2.791 | .129 | | | |
| Histological grade (Others\(^9\)/Pap, Tub1 or Tub2) | 1.602 | 0.637-4.027 | .316 | | | |
| Tumor invasion (T3-4/Tis, T1-2) | 2.615 | 1.419-4.819 | .002 | 1.556 | 0.795-3.043 | .197 |
| Lymph node metastasis (present/absent) | 1.959 | 1.129-3.399 | .017 | 1.257 | 0.692-2.284 | .453 |
| Lymphatic invasion (present/absent) | 1.673 | 0.879-3.183 | .117 | | | |
| Venous invasion (present/absent) | 2.891 | 1.676-4.986 | <.001 | 2.079 | 1.129-3.829 | .019 |
| iGPS (1-2/0) | 2.634 | 1.533-4.524 | <.001 | 2.191 | 1.248-3.849 | .006 |
| **B. Analyses of overall survival** | | | | | | |
| Age (≥65/<65 years) | 2.532 | 1.235-5.192 | .011 | 2.422 | 1.131-5.186 | .023 |
| Gender (male/female) | 2.009 | 0.981-4.111 | .056 | | | |
| Preoperative CEA (≥5/<5) | 1.982 | 0.086-4.331 | .086 | | | |
| Primary tumor site (Rectum/Colon) | 1.593 | 0.822-3.090 | .168 | | | |
| Histological grade (Others\(^9\)/Pap, Tub1 or Tub2) | 1.606 | 0.570-4.520 | .370 | | | |
| Tumor invasion (T3-4/Tis, T1-2) | 2.575 | 1.258-5.269 | .010 | 1.523 | 0.695-3.340 | .293 |
| Lymph node metastasis (present/absent) | 1.811 | 0.961-3.410 | .066 | | | |
| Lymphatic invasion (present/absent) | 1.562 | 0.743-3.282 | .239 | | | |
| Venous invasion (present/absent) | 2.550 | 1.360-4.780 | .004 | 2.031 | 1.032-3.997 | .040 |
| iGPS (1-2/0) | 4.080 | 2.138-7.785 | <.001 | 2.683 | 1.376-5.229 | .004 |

Note: P < .05 indicated in bold.

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; iGPS, improved Glasgow prognostic score; Pap, papillary adenocarcinoma; Tub1, well differentiated adenocarcinoma; Tub2, moderately differentiated adenocarcinoma.

\(^9\)Others: poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or endocrine cell carcinoma.
including the NLR, LMR, PNI (albumin and total lymphocyte), Osaka Prognostic Score (the mGPS and total lymphocyte), SIS (albumin and LMR), CONUT (albumin, total cholesterol concentration, and total lymphocyte), and NPS (albumin, total cholesterol, the NLR, and the LMR), which of these scores is the optimal one remains controversial.7 - 9, 31 - 34 A previous study showed that the prognostic performance of the NPS was better than that of the SIS, CONUT, and PNI and almost equal to that of the TNM staging system for determining OS.34 It is notable that the iGPS was an independent prognostic factor for both RFS and OS, although the T factor and the N factor were not independent.

### TABLE 5

| Variable                    | Univariate |          |          |          |          |          |          |
|-----------------------------|------------|----------|----------|----------|----------|----------|----------|
|                             | HR         | 95% CI   | P-value  | HR       | 95% CI   | P-value  | HR       | 95% CI   | P-value |
| Analyses of relapse-free survival |            |          |          |          |          |          |          |          |        |
| Age (≥65/<65)                | 1.930      | 1.051-3.547 | .034   | 2.038    | 1.062-3.911 | .032   | 1.956    | 1.015-3.767 | .045   |
| Gender (male/female)         | 1.437      | 0.798-2.589 | .227   |          |          |          |          |          |        |
| CEA level (≥5/<5)            | 2.989      | 1.686-5.298 | <.001  | 1.628    | 0.857-3.093 | .136  | 1.540    | 0.803-2.954 | .194  |
| Primary tumor site (Rectum/Colon) | 0.992   | 0.546-1.804 | .992   |          |          |          |          |          |        |
| Histological grade (Others/Pap, Tub) | 1.694    | 0.671-4.274 | .264   |          |          |          |          |          |        |
| Tumor invasion (T3-4/Tis,T1-2) | 3.217    | 1.677-6.172 | <.001  | 1.460    | 0.663-3.216 | .347  | 1.477    | 0.668-3.265 | .335  |
| Lymph node metastasis (N1-3/N0) | 2.414    | 1.378-4.229 | .002   | 1.414    | 0.716-2.793 | .318  | 1.433    | 0.731-2.809 | .295  |
| Lymphatic invasion (Present/Absent) | 2.937  | 1.498-5.761 | .002   | 1.178    | 0.483-2.869 | .719  | 1.144    | 0.470-2.784 | .766  |
| Venous invasion (Present/Absent) | 3.307 | 1.865-5.866 | <.001  | 2.140    | 1.091-4.198 | .027  | 2.176    | 1.108-4.274 | .024  |
| GPS (1-2/0)                  | 2.712      | 1.544-4.763 | <.001  | 1.548    | 0.831-2.883 | .168  | —        | —        | —       |
| iGPS (1-2/0)                 | 3.166      | 1.805-5.551 | <.001  | —        | —        | —        | 1.879    | 1.020-3.461 | .043  |

Note: P < .05 indicated in bold.

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; GPS, Glasgow prognostic score; HR, hazard ratio; iGPS, improved Glasgow prognostic score; Pap, papillary adenocarcinoma; Tub, Tubular adenocarcinoma.

*Others: poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or endocrine cell carcinoma.

### FIGURE 2

Kaplan-Meier curves for relapse-free survival (RFS) according to (A) the Glasgow Prognostic Score (GPS) and (B) the improved GPS (iGPS) in the validation set. (A) The RFS rate of the high GPS group (GPS: 1-2, n = 58) was significantly worse than that of the low GPS group (GPS: 0, n = 169) in the log-rank test (P < .001). (B) The RFS rate of the high iGPS group (iGPS: 1-2, n = 66) was significantly worse than that of the low iGPS group (GPS: 0, n = 161) in the log-rank test (P < .001)
TABLE 6  C-indices of the GPS and iGPS for RFS and OS in the training and validation sets

| C-index  | GPS | iGPS |
|---------|-----|------|
| RFS     |    |      |
| Training set | 0.596 | 0.613 |
| Validation set | 0.621 | 0.644 |
| OS      |    |      |
| Training set | 0.650 | 0.677 |
| Validation set | 0.687 | 0.705 |

Abbreviations: GPS, Glasgow Prognostic Score; iGPS, improved Glasgow Prognostic Score; OS, overall survival; RFS, relapse-free survival.

Prognostic factors in this study. The P-value of the iGPS for OS was less than that of TNM staging in multivariate analysis both in the training and validation sets (data not shown). Moreover, given that the iGPS is derived from only two serum laboratory measures, it is more straightforward than the SIS, CONUT, and NPS.

In conclusion, this study demonstrated that the iGPS correlated with recurrence and mortality in patients with stage 0-III CRC. The iGPS may be useful to identify patients who need careful follow-up and adjuvant chemotherapy even after curative surgery.

ACKNOWLEDGMENT
We would like to thank Editage (www.editage.com) for English language editing.

DISCLOSURE
Conflicts of Interest: Authors declare no conflicts of interest for this article.

Author Contribution: All authors are in agreement with the content of the manuscript.

Ethical Approval: The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. The Ethics Committee of Osaka University Hospital, Approval No. 08226. All informed consent was obtained from the subject(s) and/or guardian(s).

ORCID
Satoshi Ishikawa https://orcid.org/0000-0002-6015-8921
Norikatsu Miyoshi https://orcid.org/0000-0003-1113-8884
Shiki Fujino https://orcid.org/0000-0003-0302-5337
Takayuki Ogino https://orcid.org/0000-0001-5435-4144
Hidekazu Takahashi https://orcid.org/0000-0003-0779-407X
Mamoru Uemura https://orcid.org/0000-0001-6285-5619
Hirofumi Yamamoto https://orcid.org/0000-0001-6959-9574
Tsunezaku Mizushima https://orcid.org/0000-0002-0825-6823
Yuichiro Doki https://orcid.org/0000-0001-7346-0209
Hidetoshi Eguchi https://orcid.org/0000-0002-2318-1129

REFERENCES
1. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683–91.
2. DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin. 2014;64(4):252–71.
3. Benson AB, Venook AP, Cederquist L, Chan E, Chen Y-J, Cooper HS, et al. Colon cancer, version 1.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2017;15(3):370–98.
4. Zito A, Pietrocola F, Kroemer G. Nutrition, inflammation and cancer. Nat Immunol. 2017;18(8):843–50.
5. Shalapour S, Karin M. Pas de deux: Control of anti-tumor immunity by cancer-associated inflammation. Immunity. 2019;51(1):15–26.
6. Guo G, Wang Y, Zhou Y, Quan Q, Zhang Y, Wang H, et al. Immune cell concentrations among the primary tumor microenvironment in colorectal cancer patients predicted by clinicopathologic characteristics and blood indexes. J Immunother Cancer. 2019;7(1):179.
7. Pine JK, Morris E, Hutchins GG, West NP, Jayne DG, Quirke P, et al. Systemic neutrophil-to-lymphocyte ratio in colorectal cancer: the relationship to patient survival, tumour biology and local lymphocytic response to tumour. Br J Cancer. 2015;113(2):204–11.
8. Chan JCY, Chan DL, Diakos CI, Engel A, Pavlakis N, Gill A, et al. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. Ann Surg. 2017;265(3):539–46.
9. Sasaki M, Miyoshi N, Fujino S, Ishikawa S, Saso K, Takahashi H, et al. Development of novel prognostic prediction models including the Prognostic Nutritional Index for patients with colorectal cancer after curative resection. J Anus Rectum Colon. 2019;3(3):106–15.
10. Liu Y, He X, Pan J, Chen S, Wang L. Prognostic role of Glasgow Prognostic Score in patients with colorectal cancer: evidence from population studies. Sci Rep. 2017;7(1):6144.
11. Li L, Liu C, Yang J, Wu H, Wen T, Wang W, et al. Early postoperative controlling nutritional status (CONUT) score is associated with complication III-V after hepatectomy in hepatocellular carcinoma: a retrospective cohort study of 1,334 patients. Sci Rep. 2018;8(1):e13406.
12. Chang Y, An H, Xu L, Zhu Y, Yang Y, Lin Z, et al. Systemic inflammation score predicts postoperative prognosis of patients with clear-cell renal cell carcinoma. Br J Cancer. 2015;113(4):626–33.
13. Suzuki S, Akiyoshi T, Oka B, Otsuka F, Tominaga T, Nagasaki T, et al. Comprehensive comparative analysis of prognostic value of systemic inflammatory biomarkers for patients with stage II/III colon cancer. Ann Surg Oncol. 2020;27(3):844–52.
14. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer. 2003;89(6):1028–30.
15. Ishizuka M, Nagata H, Takagi K, Horie T, Kubota K. Inflammation-based prognostic score is a novel predictor of postoperative outcome in patients with colorectal cancer. Ann Surg. 2007;246(6):1047–51.
16. He L, Li H, Cai J, Chen L, Yao J, Zhang Y, et al. Prognostic value of the Glasgow Prognostic Score or Modified Glasgow Prognostic Score for patients with colorectal cancer receiving various treatments: a systematic review and meta-analysis. Cell Physiol Biochem. 2018;51(3):1237–49.
17. Park JH, Fuglestad AJ, Kastner AH, Oliwa A, Graham J, Horgan PG, et al. Systemic inflammation and outcome in 2295 patients with stage I-III colorectal cancer from Scotland and Norway: first results from the ScotsCan colorectal cancer group. Ann Surg Oncol. 2020;27(8):2784–94.
18. Hua X, Long Z-Q, Huang X, Deng J-P, He Z-Y, Guo L, et al. The value of prognostic nutritional index (PNI) in predicting survival and guiding radiotherapy of patients with T1-2N1 breast cancer. Front Oncol. 2020;30(9):1562.
19. Namikawa T, Ishida N, Tsuda S, Fujisawa K, Munekage E, Iwabu J, et al. Prognostic significance of serum alkaline phosphatase and...
lactate dehydrogenase levels in patients with unresectable advanced gastric cancer. Gastric Cancer. 2019;22(4):684–91.

20. Tokunaga R, Sakamoto Y, Nakagawa S, Miyamoto Y, Yoshida N, Oki E, et al. Prognostic nutritional index predicts severe complications, recurrence, and poor prognosis in patients with colorectal cancer undergoing primary tumor resection. Dis Colon Rectum. 2015;58(11):1048–57.

21. Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajoka Y, Hamaguchi T, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2020;25(1):1–42.

22. McMillan DC, Crozier JEM, Canna K, Angerson WJ, McArdle CS. Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. Int J Colorectal Dis. 2007;22(8):881–6.

23. Vashist YK, Loos J, Dedow J, Tachezy M, Uzunoglu G, Kutup A, et al. Glasgow Prognostic Score is a predictor of perioperative and long-term outcome in patients with only surgically treated esophageal cancer. Ann Surg Oncol. 2011;18(4):1130–8.

24. Jamieson NB, Denley SM, Logue J, MacKenzie DJ, Foulis AK, Dickson EJ, et al. A prospective comparison of the prognostic value of tumor- and patient-related factors in patients undergoing potentially curative surgery for pancreatic ductal adenocarcinoma. Ann Surg Oncol. 2011;18(8):2318–28.

25. Wang D, Ren C, Qiu M, Luo H, Wang Z, Zhang D, et al. Comparison of the prognostic value of various preoperative inflammation-based factors in patients with stage III gastric cancer. Tumor Biol. 2012;33(3):749–56.

26. Pinato DJ, Stebbing J, Ishizuka M, Khan SA, Wasan HS, North BV, et al. A novel and validated prognostic index in hepatocellular carcinoma: the inflammation based index (IBI). J Hepatol. 2012;57(5):1013–20.

27. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K. Combination of platelet count and neutrophil to lymphocyte ratio is a useful predictor of postoperative survival in patients with colorectal cancer. Br J Cancer. 2013;109(2):401–7.

28. Van Vré EA, Bult H, Hoymans VY, Van Tendeloo VFI, Vrints CJ, Bosmans JM. Human C-reactive protein activates monocyte-derived dendritic cells and induces dendritic cell-mediated T-cell activation. Arterioscler Thromb Vasc Biol. 2008;28(3):511–8.

29. Inatsu A, Kinoshita M, Nakashima H, Shimizu J, Saitoh D, Tamai S, et al. Novel mechanism of C-reactive protein for enhancing mouse liver innate immunity. Hepatology. 2009;49(6):2044–54.

30. Alifano M, Mansuet-Lupo A, Lococo F, Roche N, Bobbio A, Canny E, et al. Systemic inflammation, nutritional status and tumor immune microenvironment determine outcome of resected non-small cell lung cancer. PloS One. 2014;9(9):e106914.

31. Fujino S, Miyoshi N, Saso K, Sasaki M, Ishikawa S, Takahashi Y, et al. The inflammation–nutrition score supports the prognostic prediction of the TNM stage for colorectal cancer patients after curative resection. Surg Today. 2020;50(2):163–70.

32. Suzuki Y, Okabayashi K, Hasegawa H, Tsuruta M, Shigeta K, Kondo T, et al. Comparison of preoperative inflammation-based prognostic scores in patients with colorectal cancer. Ann Surg. 2018;267(3):527–31.

33. Ahiko Y, Shida D, Horie T, Tanabe T, Takamizawa Y, Sakamoto R, et al. Controlling nutritional status (CONUT) score as a preoperative risk assessment index for older patients with colorectal cancer. BMC Cancer. 2019;19(1):946.

34. Galizia G, Lieto E, Auricchio A, Cardella F, Mabilia A, Podzemny V, et al. Naples Prognostic Score, based on nutritional and inflammatory status, is an independent predictor of long-term outcome in patients undergoing surgery for colorectal cancer. Dis Colon Rectum. 2017;60(12):1273–84.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Ishikawa S, Miyoshi N, Fujino S, et al. Validation of the conventional Glasgow Prognostic Score and development of the improved Glasgow Prognostic Score in patients with stage 0–III colorectal cancer after curative resection. Ann Gastroenterol Surg. 2021;5:345–353. https://doi.org/10.1002/ags3.12426