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Original Research Article

C-reactive Protein-albumin-lymphocyte Index Is a Useful Indicator for Recurrence and Survival Following Curative Resection of Stage I-III Colorectal Cancer

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Abstract

Objectives: Recently, several simple inflammation-based prognostic scores that can be calculated easily from serum parameters, have been reported to be related to colorectal cancer prognosis. This study aimed to investigate factors influencing the prognosis of patients, including inflammation-based prognostic scores, with stage I-III colorectal cancer following curative resection.

Methods: This single-center study included 608 patients with stage I-III colorectal cancer who underwent curative resection between April 2010 and December 2018. A retrospective analysis was performed to identify the prognosis-associated variables in these patients. As a multi-center study, the Hiroshima Surgical study Group of Clinical Oncology database was used to analyze 1659 patients with stage I-III colorectal cancer who underwent curative resection to confirm the results of our single-center study.

Results: Of the inflammation-based prognostic scores, only preoperative C-reactive protein-albumin-lymphocyte index was revealed to predict a poor prognosis in patients with stage I-III colorectal cancer following curative resection. The low C-reactive protein-albumin-lymphocyte index was associated with poor overall survival and recurrence-free survival, which was similar in patients from multi-center database. The C-reactive protein-albumin-lymphocyte index was found to be associated with patient age, systemic condition, comorbidities, and tumor factors. The time-dependent area under the curve for the postoperative prognosis of the C-reactive protein-albumin-lymphocyte index was superior to those of other inflammation-based prognostic scores in most postoperative observation periods.

Conclusions: The preoperative C-reactive protein-albumin-lymphocyte index was independently associated with long-term prognosis in patients with stage I-III colorectal cancer following curative resection.

Keywords

colorectal cancer, curative resection, C-reactive protein-albumin-lymphocyte index, inflammation-based prognostic scores

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Introduction

Colorectal cancer (CRC) is the most frequently diagnosed gastrointestinal cancer and the second most common new cause of cancer-related deaths worldwide[1]. It accounts for approximately 10% of new cancer cases and cancer-related

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deaths worldwide[1]. The frequency at which CRC is encountered in clinical practice is increasing; it is critical to identify prognostic markers easily and to plan appropriate treatment strategies for CRC.

It has been reported that systemic inflammatory responses play a central role in carcinogenesis and cancer progression[2]. According to epidemiological studies, various types of cancers show predisposition to the development of chronic inflammation[3], and inflammation responses influence prognosis by providing a suitable environment for tumor progression[4]. C-reactive protein (CRP) is a common clinical indicator that reflects the inflammatory levels in patients[5]. Hypoalbuminemia is associated with inflammation[6]; albumin (Alb) is not an indicator of the nutritional condition of patients but rather an indicator of their recovery from inflammation[7]. Host immune function is also recognized as a pivotal factor influencing both carcinogenesis and progression of cancer; lymphocyte count is an indicator which reflects immune function of patients[8]. In patients with cancer, Alb values and lymphocyte counts are reduced, and CRP values are elevated owing to inflammation, poor nutrition, and a weakened immune system. Based on this principle, several simple indicators such as C-reactive protein/albumin ratio (CAR), prognostic nutritional index (PNI), and modified Glasgow prognostic score (mGPS), calculated from serum parameters, including lymphocytes, Alb, and CRP, have been reported to be related to CRC prognosis[9,10].

Recently, the C-reactive protein-albumin-lymphocyte (CALLY) index which is calculated from CRP, Alb, and lymphocyte counts drawn from blood examination results, was reported as a new inflammation-based prognostic scores (IBPS)[11]. As it is calculated from inflammatory responses and factors indicative of immune function, it is being increasingly reported as a prognostic indicator for various types of carcinomas[11-14]. However, a few studies have reported the effect of CALLY index on the prognosis of patients with CRC[15]. To date, there have been no studies detailing the prognostic impact of the CALLY index following curative resection for stage I-III CRC.

This retrospective study investigated prognostic factors, including preoperative IBPS such as CALLY index, PNI, and mGPS, which affect the prognosis of patients who underwent curative resection for stage I-III CRC.

Methods

Study population

This retrospective study evaluated 663 patients with stage I-III CRC who underwent R0 resection between April 2010 and December 2018 at the Hiroshima University Hospital. Patients with other primary malignancies during the same period, heterochronic CRC within 5 years, or coexisting colon and rectal cancers were excluded. Finally, 608 patients who underwent R0 resection were enrolled in this single-center study.

For the multi-center study, 1804 patients with stage I-III CRC who underwent R0 resection for the first time between January 2017 and December 2018 at 14 institutions, excluding Hiroshima University Hospital, which belongs to the Hiroshima Surgical study group of Clinical Oncology (HiSCO) were evaluated, and we analyzed 1659 patients, excluding 145 patients because of the exclusion criteria described above. Survival time and multivariate analyses to assess the factors influencing overall survival (OS) and recurrence-free survival (RFS) were performed in multi-center study to confirm the results of the single-center study.

This study was conducted in accordance with the guidelines of the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and was approved by the Institutional Review Board of Hiroshima University Hospital (approval no. E2012-0744, E2021-2527).

Definition of IBPS

IBPS were calculated using preoperative blood examinations at initial visit. The CALLY index was calculated as serum Alb level (g/dL) multiplied by the peripheral lymphocyte count and divided by serum CRP level (mg/dL) multiplied by 10000 [(Alb × lymphocyte) ÷ (CRP × 10^4)][11]. The neutrophil/lymphocyte ratio (NLR) was calculated as a ratio: relative neutrophil (%)/relative lymphocyte (%)[16]. The PNI was calculated as 10 × Alb level (g/dL) + 0.005 × total lymphocyte count (per mm^3)[17]. The mGPS was calculated as previously described[18]. Patients with both an increased CRP level (> 1.0 mg/dL) and hypoalbuminemia (< 3.5 g/dL) were allocated a score of 2. Patients showing one or neither of these blood chemistry abnormalities were allocated a score of 1 or 0, respectively.

Treatment and follow-up

Follow-up blood examinations to identify tumor markers were performed every 3-6 months, 5 years after surgery. Simple or enhanced abdominal computed tomography was performed to rule out recurrence every 6-12 months, and colonoscopy was performed in the first, third, and fifth years after surgery. Patients with high-risk stage II or III CRC underwent postoperative adjuvant chemotherapy (ACT). Postoperative ACT for older patients or those with severe comorbidities was performed at the discretion of the primary surgeon based on the patients' general condition.

Statistical analysis

Continuous variables are presented as medians and interquartile ranges. Nominal variables are expressed as numbers (%). Nonparametric quantitative data were analyzed using

Table 1. Patient Characteristics in Single-Center Study.

Characteristics	Patients (n = 608)
Male/Female	371/237
Age (years)	67 (61-75)
BMI (kg/m^2)	22.6 (20.4-24.6)
ASA-PS ≥ 3	33 (5.4%)
CCI	0 (0-1)
Medication: antiplatelet or coagulation agent	74 (12.2%)
CEA (ng/mL)	2.9 (1.8-5.6)
CA19-9 (U/mL)	6.0 (3.0-13.0)
PNI	51.4 (47.1-54.7)
CALLY index	8.4 (2.5-19.8)
NLR	2.3 (1.7-3.2)
mGPS 0/1/2	495/87/26
Tumor localization: colon/rectum	335/273
pT ≥ 4	32 (5.3%)
pN (+)	177 (19.1%)
TNM classification (I/II/III)	255/176/177
Histology: other than differentiated carcinoma	76 (12.6%)

Continuous variables are expressed as medians (interquartile ranges). Qualitative variables are expressed as numbers (%). Abbreviations: BMI, body mass index; ASA-PS, American Society of Anesthesiologists Physical Status; CCI, Charlson Comorbidity Index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; PNI, prognostic nutrition index; CALLY index, C-reactive protein-albumin-lymphocyte index; NLR, neutrophile/lymphocyte ratio; mGPS, modified Glasgow prognostic score

the Mann-Whitney *U*-test. The chi-square test or Fisher's exact test was performed to determine the relationships among nominal variables. For continuous variables such as operative time and intraoperative blood loss, median values were used as cutoff values. The cutoff values for IBPS were set using receiver operating characteristic (ROC) curve analysis with reference to OS after surgery. The performance of the prognostic systems was evaluated in terms of the area under the ROC (AUROC) curve. The Kaplan-Meier method was used to analyze OS and RFS, and the log-rank test was used to compare parameters between different groups. Multivariate analyses were performed to assess the factors influencing OS and RFS using the Cox regression model. All variables in univariate analysis were included in the multivariate models, and the backward elimination method with a removal criterion of $P = 0.10$ was used to select the covariates.

The prognostic capabilities of the CALLY index, PNI, NLR, and mGPS were compared using time-dependent ROC curves and the area under the curve (AUC). Harrell's concordance index (C-index) was calculated for each model to determine which index had a predictive association with the endpoints. Bootstrapping method was used to calculate 95% confidence intervals (CI). P-values < 0.05 were considered statistically significant. Calculations were performed using JMP v17 (SAS Institute, Cary, NC, USA) and EZR Ver 1.61 (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[19].

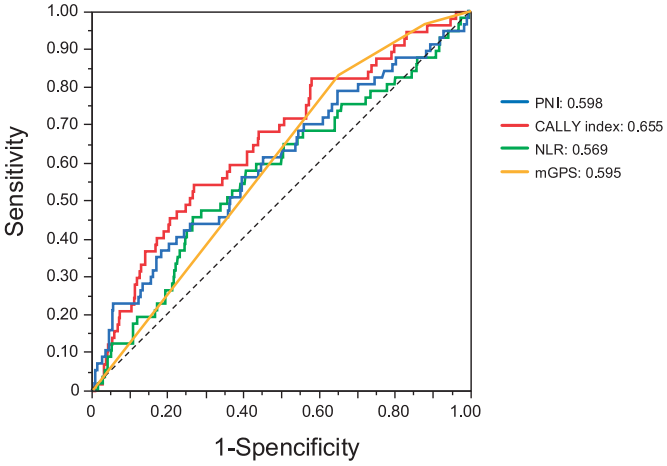

Figure 1. Comparison of the areas under receiver operating curves for survival prediction among the IBPS.

Results

Characteristics of patients with CRC in single-center study

Among 663 patients who underwent R0 curative resection of stage I-III CRC between April 2010 and December 2018 at our institute, 608 patients were enrolled in single-center study, excluding 55 patients because of the exclusion criteria. Table 1 summarizes the characteristics of the patients in single-center study. The median age of the patients was 67 years, with more men than women among the patients enrolled. The median CEA and CA19-9 were 2.9 ng/mL and 6.0 U/mL, respectively. Overall, 87 patients (14.3%) experienced recurrence. Figure 1 presents a comparison of ROC curve analysis for each IBPS with reference to OS after surgery. The AUROC value of the CALLY index was 0.655, which was higher than that of the other indices (PNI, 0.598; NLR, 0.569; mGPS, 0.595).

Comparison of univariate and multivariate analyses of prognostic factors for OS and RFS in patients with stage I-III CRC in single-center study

Table 2 summarizes the results of univariate and multivariate analyses of prognostic factors for OS in a single-center study. Among the IBPS examined in this study, PNI and mGPS were excluded from the univariate and multivariate analysis, considering multicollinearity of the relevant clinical variables associated with the CALLY index. In the univariate analysis, statistically significant prognostic factors for poor OS were age ≥ 75 (year) ($P = 0.007$), American society of Anesthesiologists Physical Status (ASA-PS) ≥ 3 ($P = 0.005$), Charlson Comorbidity Index (CCI) ≥ 1 ($P < 0.001$), carcinoembryonic antigen (CEA) > 5 (ng/mL) ($P <$

Table 2. Univariate and Multivariate Analyses of Prognostic Factor for Overall Survival in Single-Center Study.

Variables	N = 608	Univariate			Multivariate		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
Male	371	1.221	0.70-2.12	0.476			
Age (year) ≥ 75	153	2.138	1.23-3.73	**0.007**			
BMI (kg/m^2) < 25	131	1.764	0.83-3.73	0.137			
ASA-PS ≥ 3	33	3.397	1.45-7.96	**0.005**	2.522	1.03-6.19	**0.044**
CCI ≥ 1	236	2.485	1.47-4.21	**< 0.001**	1.625	0.93-2.84	0.089
CEA (ng/mL) > 5	165	3.133	1.86-5.28	**< 0.001**			
CA19-9 (U/mL) > 37	38	5.083	2.68-9.65	**< 0.001**	3.645	1.87-7.10	**< 0.001**
CALLY index ≤ 3.35	177	2.909	1.73-4.90	**< 0.001**	1.901	1.11-3.29	**0.020**
NLR > 3.0	177	2.070	1.23-3.49	**0.006**			
Open surgery	108	1.932	1.08-3.44	**0.026**			
Operative time (min) ≥ 280	297	1.500	0.87-2.57	0.141	1.679	0.97-2.91	0.064
Blood loss (mL) ≥ 60	309	1.447	0.85-2.48	0.177			
Tumor localization: Rectum	273	1.350	0.80-2.27	0.258			
TNM classification: stage I	255	Ref.			Ref.		
stage II	176	3.899	1.55-9.83	**0.004**	3.453	1.33-8.98	**0.011**
stage III	177	6.928	2.89-16.6	**< 0.001**	10.43	3.93-27.7	**< 0.001**
Histology: other than differentiated carcinoma	76	1.527	0.77-3.03	0.226			
Postoperative chemotherapy (-)	411	0.857	0.50-1.46	0.570	2.670	1.42-5.03	**0.002**
Postoperative complications CD ≥ 3 (+)	45	1.672	0.76-3.70	0.204			

The variables in bold are statistically significant ($P < 0.05$). Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA-PS, American Society of Anesthesiologists Physical Status; CCI, Charlson Comorbidity Index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CALLY index, C-reactive protein-albumin-lymphocyte index; NLR, neutrophil/lymphocyte ratio; CD, Clavien-Dindo

0.001), carbohydrate antigen 19-9 (CA19-9) > 37 (U/mL) ($P < 0.001$), CALLY index ≤ 3.35 ($P < 0.001$), NLR > 3.0 ($P = 0.006$), open surgery ($P = 0.026$), and TNM classification (stage II; $P = 0.004$, stage III; $P < 0.001$: reference to stage I). In the multivariate analysis, the following five factors were identified as prognostic factors for poor OS in patients: ASA-PS ≥ 3 (hazard ratio [HR] = 2.522; 95% CI = 1.03-6.19, $P = 0.044$), CA19-9 > 37 (U/mL) (HR = 3.645; 95% CI = 1.87-7.10, $P < 0.001$), CALLY index ≤ 3.35 (HR = 1.901; 95% CI = 1.11-3.29, $P = 0.020$), TNM classification (stage II; HR = 3.453; 95% CI = 1.33-8.98, $P = 0.011$, stage III; HR = 10.43; 95% CI = 3.93-27.7, $P < 0.001$: reference to stage I), and no postoperative chemotherapy (HR = 2.670; 95% CI = 1.42-5.03, $P = 0.002$).

Table 3 summarizes the results of univariate and multivariate analyses of prognostic factors for RFS in a single-center study. In the univariate analysis, statistically significant prognostic factors for poor RFS were as follows: male ($P = 0.020$), ASA-PS ≥ 3 ($P = 0.004$), CCI ≥ 1 ($P = 0.049$), CEA > 5 (ng/mL) ($P < 0.001$), CA19-9 > 37 (U/mL) ($P < 0.001$), CALLY index ≤ 3.35 ($P = 0.002$), NLR > 3.0 ($P = 0.008$), open surgery ($P = 0.011$), operative time ≥ 280 (min) ($P = 0.001$), blood loss ≥ 60 (mL) ($P = 0.003$), rectal cancer ($P = 0.001$), TNM classification (stage II; $P = 0.014$, stage III; $P < 0.001$: reference to stage I), and no postoperative chemotherapy ($P = 0.004$). In the multivariate analysis, the following seven factors were identified as prognostic factors for poor RFS: male (HR = 1.803; 95% CI = 1.18-2.75, $P = 0.006$), ASA-PS ≥ 3 (HR = 2.678; 95% CI = 1.36-5.29, $P = 0.005$), CEA > 5 (ng/mL) (HR = 2.025; 95% CI = 1.35-3.05, $P < 0.001$), CA19-9 > 37 (U/mL) (HR = 1.986; 95% CI = 1.12-3.53, $P = 0.019$), CALLY index ≤ 3.35 (HR = 1.522; 95% CI = 1.02-2.27, $P = 0.039$), rectal cancer (HR = 1.878; 95% CI = 1.27-2.77, $P = 0.002$), and TNM classification (stage III; HR = 3.271; 95% CI = 1.97-5.43, $P < 0.001$: reference to stage I). Figure 2 summarizes the Kaplan-Meier analysis showing OS and RFS in a single-center study using the CALLY index. The low CALLY index was associated with poor OS and RFS (OS: $P < 0.001$; log-rank test; Figure 2a, RFS: $P = 0.002$; log-rank test; Figure 2b). Survival analysis was performed for each stage to examine the impact of the CALLY index on the long-term postoperative prognosis in more detail. Supplemental Figure 1, 2 summarize the Kaplan-Meier analysis, showing each stage's OS and recurrence rate (RR) in a single-center study using the CALLY index. A low CALLY index was associated with poor OS for each stage (stage I, $P = 0.046$; stage II, $P = 0.019$; stage III, $P = 0.022$; log-rank test; Supplemental Figure 1a-c). However, it was only associated with a high RR in stage III (stage I, $P = 0.877$; stage II, $P = 0.196$; stage III, $P = 0.048$; log-rank test; Supplemental Figure 2a-c).

Table 3. Univariate and Multivariate Analyses of Prognostic Factor for Recurrence-Free Survival in Single-Center Study.

Variables	N = 608	Univariate			Multivariate		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
Male	371	1.627	1.08-2.45	**0.020**	1.803	1.18-2.75	**0.006**
Age (year) ≥ 75	153	0.987	0.63-1.54	0.953			
BMI (kg/m^2) < 25	131	1.536	0.93-2.54	0.096			
ASA-PS ≥ 3	33	2.578	1.34-4.94	**0.004**	2.678	1.36-5.29	**0.005**
CCI ≥ 1	236	1.455	1.00-2.11	**0.049**			
CEA (ng/mL) > 5	165	2.873	1.98-4.17	**< 0.001**	2.025	1.35-3.05	**< 0.001**
CA19-9 (U/mL) > 37	38	2.915	1.69-5.03	**< 0.001**	1.986	1.12-3.53	**0.019**
CALLY index ≤ 3.35	177	1.812	1.24-2.65	**0.002**	1.522	1.02-2.27	**0.039**
NLR > 3.0	177	1.681	1.15-2.46	**0.008**			
Open surgery	108	1.745	1.14-2.68	**0.011**			
Operative time (min) ≥ 280	297	1.894	1.28-2.81	**0.001**			
Blood loss (mL) ≥ 60	309	1.801	1.22-2.65	**0.003**			
Tumor localization: Rectum	273	1.943	1.33-2.85	**0.001**	1.878	1.27-2.77	**0.002**
TNM classification: stage I	255	Ref.			Ref.		
stage II	176	1.964	1.15-3.36	**0.014**	1.321	0.75-2.33	0.336
stage III	177	3.788	2.33-6.16	**< 0.001**	3.271	1.97-5.43	**< 0.001**
Histology: other than differentiated carcinoma	76	1.061	0.60-1.86	0.836			
Postoperative chemotherapy (-)	411	0.576	0.40-0.84	**0.004**			
Postoperative complications CD ≥ 3 (+)	45	1.413	0.76-2.64	0.277			

The variables in bold are statistically significant ($P < 0.05$). Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA-PS, American Society of Anesthesiologists Physical Status; CCI, Charlson Comorbidity Index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CALLY index, C-reactive protein-albumin-lymphocyte index; NLR, neutrophil/lymphocyte ratio; CD, Clavien-Dindo

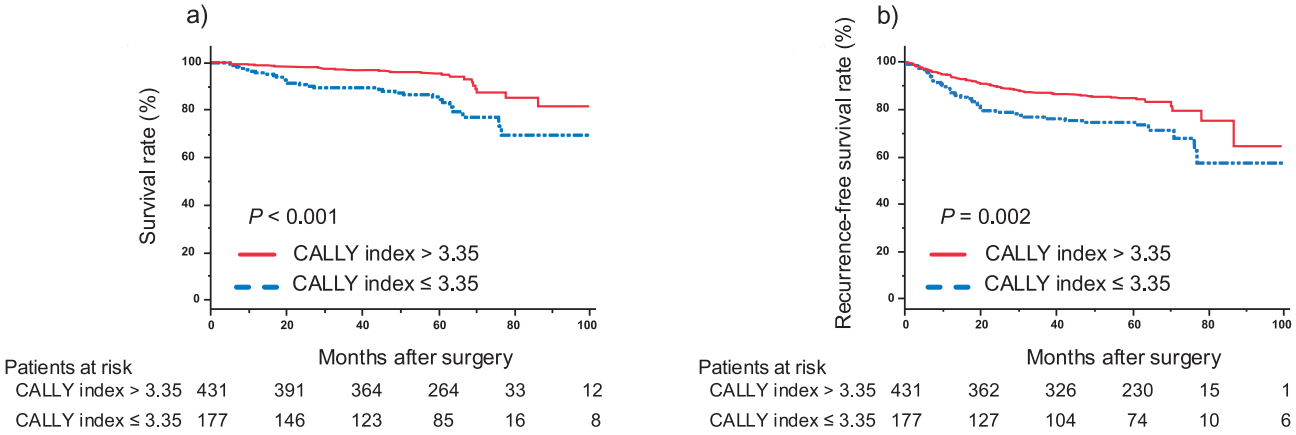

Figure 2. a, b. Kaplan-Meier curves for overall survival and recurrence-free survival in patients used to compare the high- and low-CALLY index groups in single-center study.

Comparison of backgrounds by preoperative CALLY index in single-center study

Supplemental Table 1 summarizes the characteristics of the patients in the high- and low-CALLY index groups in this single-center study. Compared with the low-CALLY index group, the high-CALLY index group included younger patients ($P < 0.001$), higher body mass index ($P = 0.016$), less patients with ASA-PS ≥ 3 ($P < 0.001$), less patients with CCI ≥ 1 ($P < 0.001$), less patients who underwent open surgery ($P < 0.001$) and less patients with stage II and III ($P < 0.001$). Intraoperative blood loss ($P < 0.001$) and the number of patients with deeper tumor invasion ($P < 0.001$) were higher in the low-CALLY index group than in the high-CALLY index group. Tumor marker levels were higher in the low-CALLY index group than in the high-CALLY index group (CEA: $P < 0.001$, CA19-9: $P < 0.001$).

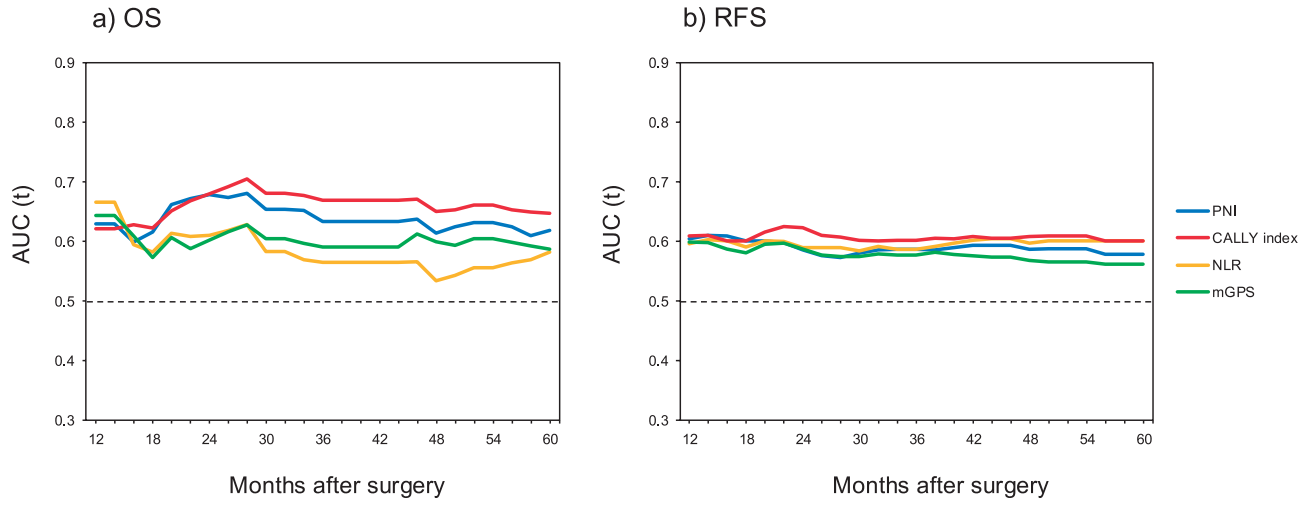

Figure 3. a, b. Comparison of the time-dependent areas under receiver operating curves for overall survival and recurrence-free survival between CALLY index and other indices in single-center study.

Comparison of IBPS for OS and RFS in single-center study

Figure 3 summarizes the comparison of time-dependent ROC curve of IBPS for OS and RFS in single-center study. A time-dependent ROC curve was used to calculate the AUC values at different time points. In terms of both OS and RFS, Harrell's concordance index (C-index) values for the CALLY index were superior than those for other IBPS after surgery (OS: CALLY index, 0.655; 95% CI = 0.571-0.739, standard error [SE] = 0.043; PNI, 0.616; 95% CI = 0.522-0.803, SE = 0.046; NLR, 0.574; 95% CI = 0.487-0.663, SE = 0.046; mGPS, 0.593; 95% CI = 0.520-0.665, SE = 0.037; Figure 3a, RFS: CALLY index, 0.598; 95% CI = 0.542-0.656, SE = 0.030; PNI, 0.580; 95% CI = 0.521-0.637, SE = 0.030; NLR, 0.586; 95% CI = 0.530-0.641, SE = 0.023; mGPS, 0.564; 95% CI = 0.520-0.612, SE = 0.023; Figure 3b).

Multi-center Study of the CALLY index associated with prognosis of stage I-III CRC following curative resection

To confirm the applicability of the cut-off value of the CALLY index, which was identified as a prognostic factor following curative resection for CRC based on our institutional study, we conducted survival time and multivariate analyses to assess the factors influencing postoperative prognosis using the HiSCO multi-center dataset, which included a larger population. Table 4 summarizes the results of univariate and multivariate analyses of prognostic factors for OS in a multi-center study. In the multivariate analysis, the following seven factors were identified as prognostic factors for poor OS in patients: age ≥ 75 (year) (HR = 1.556; 95% CI = 1.18-2.06, P = 0.018), ASA-PS ≥ 3 (HR = 1.594; 95% CI = 1.15-2.21, P = 0.005), CCI ≥ 1 (HR = 1.612; 95% CI = 1.21-2.15, P = 0.001), CEA > 5 (ng/mL) (HR = 1.919; 95% CI = 1.45-2.53, P < 0.001), CALLY index ≤ 3.35 (HR = 1.446; 95% CI = 1.09-1.92, P = 0.010), TNM classification (stage II; HR = 2.042; 95% CI = 1.29-3.22, P = 0.002, stage III; HR = 3.656; 95% CI = 2.27-5.88, P < 0.001: reference to stage I), and no postoperative chemotherapy (HR = 1.777; 95% CI = 1.28-2.47, P < 0.001). Table 5 summarizes the results of univariate and multivariate analyses of prognostic factors for RFS in a multi-center study. In the multivariate analysis, the following ten factors were identified as prognostic factors for poor RFS: age ≥ 75 (year) (HR = 1.278; 95% CI = 1.01-1.61, P = 0.038), ASA-PS ≥ 3 (HR = 1.430; 95% CI = 1.07-1.90, P = 0.014), CCI ≥ 1 (HR = 1.418; 95% CI = 1.12-1.79, P = 0.004), CEA > 5 (ng/mL) (HR = 2.043; 95% CI = 1.63-2.56, P < 0.001), CALLY index ≤ 3.35 (HR = 1.264; 95% CI = 1.01-1.59, P = 0.045), open surgery (HR = 1.335; 95% CI = 1.05-1.69, P = 0.016), operative time ≥ 280 (min) (HR = 1.302; 95% CI = 1.03-1.64, P = 0.026), TNM classification (stage II; HR = 2.307; 95% CI = 1.56-3.41, P < 0.001, stage III; HR = 4.400; 95% CI = 2.94-6.59, P < 0.001: reference to stage I), no postoperative chemotherapy (HR = 1.464; 95% CI = 1.12-1.91, P = 0.005), and postoperative complications CD ≥ 3 (HR = 1.622; 95% CI = 1.17-2.25, P = 0.004). Figure 4 summarizes the Kaplan-Meier analysis showing OS and RFS in a multi-center study using the CALLY index with a cutoff value determined in a single-center study. A low CALLY index was associated with poor OS and RFS (OS: P < 0.001, log-rank test; Figure 4a; RFS: P < 0.001, log-rank test; Figure 4b). Supplemental Table 2 summarizes the characteristics of the patients in the high- and low-CALLY index groups in the multi-center study. Compared with the low-CALLY index group, the high-CALLY index group included younger patients (P < 0.001), less patients with ASA-PS ≥ 3

Table 4. Univariate and Multivariate Analyses of Prognostic Factor for Overall Survival in Multi-Center Study.

Variables	N = 1659	Univariate			Multivariate		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
Male	865	0.985	0.76-1.27	0.906			
Age (year) ≥ 75	684	2.166	1.67-2.80	**< 0.001**	1.556	1.18-2.06	**0.018**
BMI (kg/m^2) < 25	1276	1.300	0.94-1.80	0.114			
ASA-PS ≥ 3	229	2.657	1.97-3.58	**< 0.001**	1.594	1.15-2.21	**0.005**
CCI ≥ 1	676	2.352	1.81-3.06	**< 0.001**	1.612	1.21-2.15	**0.001**
CEA (ng/mL) > 5	547	2.892	2.23-3.76	**< 0.001**	1.919	1.45-2.53	**< 0.001**
CA19-9 (U/mL) > 37	169	1.988	1.40-2.82	**< 0.001**			
CALLY index ≤ 3.35	687	2.358	1.82-3.05	**< 0.001**	1.446	1.09-1.92	**0.010**
NLR > 3.0	606	1.610	1.25-2.08	**< 0.001**			
Open surgery	392	1.791	1.36-2.34	**< 0.001**			
Operative time (min) ≥ 280	457	1.334	1.02-1.75	**0.037**	1.327	0.99-1.77	0.053
Blood loss (mL) ≥ 60	575	1.580	1.22-2.04	**< 0.001**			
Tumor localization: Rectum	539	0.954	0.73-1.25	0.737			
TNM classification: stage I	476	Ref.			Ref.		
stage II	599	2.707	1.72-4.25	**< 0.001**	2.042	1.29-3.22	**0.002**
stage III	584	3.923	2.53-6.08	**< 0.001**	3.656	2.27-5.88	**< 0.001**
Histology: other than differentiated carcinoma	226	1.496	1.07-2.08	**0.017**			
Postoperative chemotherapy (-)	1120	1.163	0.88-1.53	0.282	1.777	1.28-2.47	**< 0.001**
Postoperative complications CD ≥ 3 (+)	151	1.602	1.09-2.35	**0.016**			

The variables in bold are statistically significant ($P < 0.05$). Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA-PS, American Society of Anesthesiologists Physical Status; CCI, Charlson Comorbidity Index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CALLY index, C-reactive protein-albumin-lymphocyte index; NLR, neutrophil/lymphocyte ratio; CD, Clavien-Dindo

Table 5. Univariate and Multivariate Analyses of Prognostic Factor for Recurrence-Free Survival in Multi-Center Study.

Variables	N = 1659	Univariate			Multivariate		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value
Male	865	0.920	0.75-1.13	0.433			
Age (year) ≥ 75	684	1.578	1.28-1.95	**< 0.001**	1.278	1.01-1.61	**0.038**
BMI (kg/m^2) < 25	1276	1.143	0.88-1.47	0.308			
ASA-PS ≥ 3	229	2.130	1.65-2.75	**< 0.001**	1.430	1.07-1.90	**0.014**
CCI ≥ 1	676	1.798	1.46-2.22	**< 0.001**	1.418	1.12-1.79	**0.004**
CEA (ng/mL) > 5	547	2.981	2.41-3.69	**< 0.001**	2.043	1.63-2.56	**< 0.001**
CA19-9 (U/mL) > 37	169	1.672	1.23-2.27	**0.001**			
CALLY index ≤ 3.35	687	2.006	1.62-2.48	**< 0.001**	1.264	1.01-1.59	**0.045**
NLR > 3.0	606	1.352	1.09-1.67	**0.005**			
Open surgery	392	1.947	1.56-2.43	**< 0.001**	1.335	1.05-1.69	**0.016**
Operative time (min) ≥ 280	457	1.305	1.04-1.63	**0.020**	1.302	1.03-1.64	**0.026**
Blood loss (mL) ≥ 60	575	1.653	1.34-2.04	**< 0.001**			
Tumor localization: Rectum	539	1.135	0.91-1.41	0.257			
TNM classification: stage I	476	Ref.			Ref.		
stage II	599	3.065	2.11-4.44	**< 0.001**	2.307	1.56-3.41	**< 0.001**
stage III	584	5.165	3.62-7.38	**< 0.001**	4.400	2.94-6.59	**< 0.001**
Histology: other than differentiated carcinoma	226	1.474	1.12-1.94	**0.006**	1.312	0.99-1.74	0.059
Postoperative chemotherapy (-)	1120	0.835	0.67-1.04	0.101	1.464	1.12-1.91	**0.005**
Postoperative complications CD ≥ 3 (+)	151	1.785	1.31-2.43	**< 0.001**	1.622	1.17-2.25	**0.004**

The variables in bold are statistically significant ($P < 0.05$). Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA-PS, American Society of Anesthesiologists Physical Status; CCI, Charlson Comorbidity Index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CALLY index, C-reactive protein-albumin-lymphocyte index; NLR, neutrophil/lymphocyte ratio; CD, Clavien-Dindo

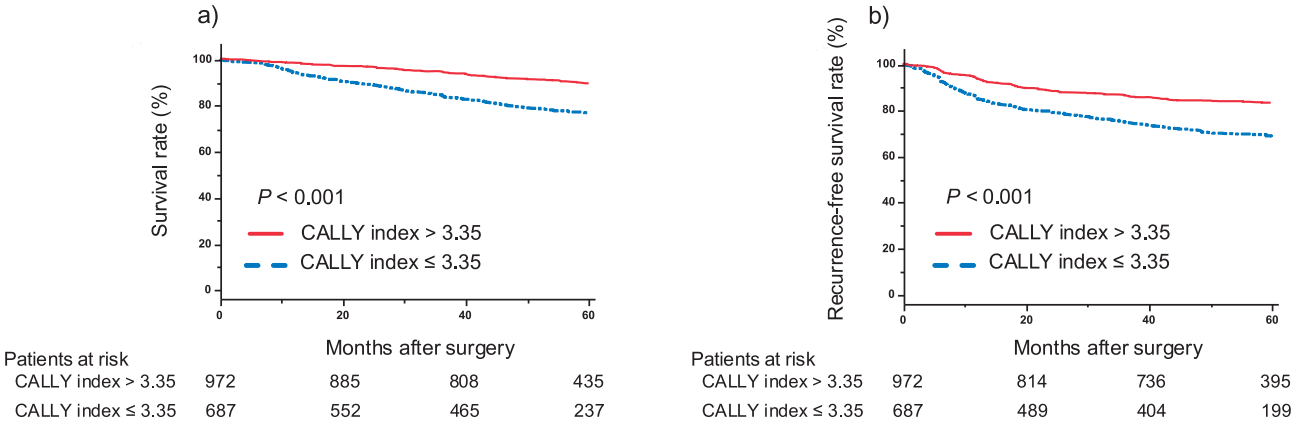

Figure 4. a, b. Kaplan-Meier curves for overall survival and recurrence-free survival in patients used to compare the high- and low-CALLY index groups in multi-center study.

($P < 0.001$) and less patients with CCI ≥ 1 ($P < 0.001$). The number of patients with deeper tumor invasion ($P < 0.001$) and high TNM classification ($P < 0.001$) were higher in the low-CALLY index group than in the high-CALLY index group. Tumor marker levels were higher in the low-CALLY index group than in the high-CALLY index group (CEA, $P < 0.001$; CA19-9, $P < 0.001$). The above results of the multi-center study were similar to those of the single-center study.

Discussion

This retrospective study investigated prognostic factors, which include IBPS, affecting long-term prognosis in patients who underwent curative resection for stage I-III CRC. In addition to severe systemic condition and tumor factors such as tumor markers and tumor stage, preoperative low CALLY index, an inflammation-based marker, was associated with poor long-term prognosis in patients with stage I-III CRC following curative resection. The CALLY index, which is calculated from CRP and Alb reflecting inflammation, and lymphocyte counts reflecting immune function, was reported as an IBPS, and as a postoperative prognostic predictor for hepatocellular carcinoma[11]. In this study, the CALLY index was strongly related to age and tumor factors. This index reflects inflammation and may be a sensitive indicator of preoperative systemic status, and it can be considered useful in predicting postoperative outcomes for patients with various types of cancers.

Cancer development and progression have been shown to be closely associated with the host nutritional status and inflammatory responses within the tumor microenvironment[2,20,21]; high CRP and low Alb levels were reported as factors for poor survival in patients with CRC[22,23]. Peripheral lymphocyte count has also been reported as a prognostic indicator of patients with CRC[24]. In patients with cancer, Alb values and lymphocyte counts are reduced, and the CRP values are elevated owing to inflammation, poor nutrition, and a weakened immune system; various IBPS calculated from CRP and Alb which are called inflammatory markers, and lymphocyte, which is a surrogate marker of immunocompetence, were already reported as prognostic indicators for CRC following curative resection[9,10,25]. Because the CALLY index is calculated from three factors mentioned above, it more accurately reflects the inflammatory responses within the tumor microenvironment and may be a more sensitive marker for the prognosis of various cancers than other IBPS. This study revealed that the CALLY index is associated with tumor markers and progression and was the most sensitive prognostic indicator for patients with stage I-III CRC after curative resection among the IBPS examined in this study. When examined by stage, the CALLY index was a good predictor of postoperative OS, whereas it was not a good predictor of recurrence in stages I and II CRC. However, in advanced stage III CRC, it reflects tumor inflammation and was a good predictor of OS and recurrence. Based on these results, the CALLY index can serve as a survival indicator that reflects systemic inflammation in early-stage cancer. In addition, as cancer progresses, the CALLY index not only continues to reflect systemic inflammation but also captures tumor-associated inflammation, making it a valuable predictor of both survival and recurrence. The CALLY index is considered as an extremely useful marker to identify the patients at risk of poor prognosis and to establish appropriate treatment strategies. In addition, another reason why the CALLY index is considered a valuable prognostic indicator for patients with stage I-III CRC following curative resection is its susceptibility to the influence of age.

The prevalence of cancer in older patients is increasing, and by 2030, approximately 70% of all new cancer cases will be diagnosed in individuals aged ≥ 65 years[26]. Generally, older patients have age-related declines in organ function and immunity[27], and a relation between aging and

decreased lymphocyte counts has been reported[28]. Recently, frailty has also been reported as a poor prognostic factor for stage I-III CRC following curative resection[29]; elevated CRP and hypoalbuminemia, which lead to chronic inflammation in older patients, have been suggested as candidate indicators for frailty[30]. In other words, the three factors mentioned above, which are components of the CALLY index, are also considered to be affected by not only tumor factors but also frailty caused by aging. This study confirmed that age is associated with the CALLY index in both single- and multi-center studies. Moreover, the CALLY index was confirmed to be a more sensitive prognostic indicator in older patients (data not shown). Based on the above, the CALLY index, which is influenced by age, may be considered as an accurate prognostic indicator after surgery for various types of cancers, including CRC.

This study has several limitations. First, its retrospective design. Second, all common postoperative prognostic factors for CRC reported in previous studies were not included in the analysis. Third, the cohorts for biological markers such as RAS, BRAF, and MSI had a limited sample size and could not be included in the analysis. It is challenging to assess how the absence of biological markers in the variables may introduce bias into the analysis, and a more detailed study by stage is necessary. Therefore, more analyses are needed to confirm whether these results are similar to those of the present study after accumulating more cases of these biological markers. However, the results of this study, including single- and multi-center studies, show that the CALLY index is a good prognostic indicator for patients with CRC following curative resection.

Conclusions

Low preoperative CALLY index was found to be independently associated with poor prognosis in patients with stage I-III CRC after curative resection. Preoperative CALLY index was a useful assessment index for predicting the prognosis of patients who underwent curative resection of stage I-III CRC.

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Conflicts of Interest

There are no conflicts of interest.

Author Contributions

TB, TY, SA and MS drafted the manuscript. MH contributed to the interpretation of data and analysis. HO substantively revised the manuscript. All the authors have cooperated in the accumulation of cases and approved the final manuscript.

Approval by Institutional Review Board (IRB)

There is no need for consent to participate to be obtained due to retrospective study. Administrative permissions were not required to access and use the medical records described in this study. This study was authorized in advance by the institutional review board of the Hiroshima University Hospital (approval number: E2012-0744, E2021-2527).

Data Availability

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

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Supplementary Files

Supplemental Table 1. Comparison of patient characteristics with high- and low-CALLY index group in single-center study.

Supplemental Table 2. Comparison of patient characteristics with high- and low-CALLY index group in multi-center study.

Supplemental Figure 1a-c. Kaplan-Meier curves of overall survival by patients' stage used to compare the high- and low-CALLY index groups in single-center study.

Supplemental Figure 2a-c. Kaplan-Meier curves of recurrence rate by patients' stage used to compare the high- and low-CALLY index groups in single-center study.

Please find supplementary file(s);
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