International Journal of Colorectal Disease (2019) 34:1303–1315
https://doi.org/10.1007/s00384-019-03316-z

ORIGINAL ARTICLE

Prognostic impact of the combination of neutrophil-to-lymphocyte ratio and Glasgow prognostic score in colorectal cancer: a retrospective cohort study

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Accepted: 10 May 2019 / Published online: 8 June 2019

Abstract

Purpose Although neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte count, and Glasgow prognostic score (GPS) are well-known prognostic markers in cancer, their prognostic importance is still controversial. We evaluated the prognostic value of NLR, PLR, monocyte count, and GPS in colorectal cancer (CRC).

Method We retrospectively evaluated 448 CRC patients undergoing curative resection. We compared overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS) between dichotomized groups by the optimal cutoff point. Univariate and multivariate analyses were applied to identify prognostic factors.

Result High NLR, high monocyte count, and high GPS exhibited significantly worse prognosis in OS, CSS, and DFS compared with low NLR, low monocyte count, and low GPS, respectively. In contrast, PLR was not significantly associated with OS, CSS, and DFS. The univariate and multivariate analyses indicated that poor OS was significantly associated with age ≥ 69 and high NLR; that poor CSS was significantly associated with age ≥ 69, M factor, high CA19-9, adjuvant chemotherapy, and high GPS; and that poor DFS was significantly associated with venous invasion, high NLR, and high GPS. When 448 patients were classified into three groups based on NLR and GPS, there was a significant difference in OS, CSS, and DFS between all the three groups. Patients with NLR ≥ 2.05 and GPS = 1/2 exhibited remarkably poorer prognosis, whereas those with both NLR < 2.05 and GPS = 0 exhibited remarkably better prognosis.

Conclusion Combination of NLR and GPS can be a novel scoring system to effectively stratify outcome in CRC.

Keywords Systemic inflammatory response · Colorectal cancer · Neutrophil-to-lymphocyte ratio · Glasgow prognostic score

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, and more than 600,000 people per year die from CRC [1]. TNM stage has been widely used as a predictor for the prognosis of patients with CRC. However, the prognosis of an individual patient varies, even within the same TNM stage, indicating that the current staging cannot correctly predict a patient's prognosis. Therefore, the optimal marker that can supplementarily stratify patients' prognosis is urgently needed.

As Rudolf Virchow first advocated in 1863, inflammation is a critical indicator of tumor progression [2]. Elevated systemic inflammatory response (SIR) is one of the crucial indicators of the status of the tumor microenvironment, which is correlated with poor prognosis [3–5]. In this decade, there have been increasing studies to highlight the prognostic value of various SIR-based scoring systems in several types of cancer. In particular, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte count, and Glasgow prognostic score (GPS) have been investigated in the prediction of clinical outcomes and prognosis [6–19]. NLR is defined as the neutrophil count divided by the lymphocyte count, and PLR is defined as the platelet count

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00384-019-03316-z) contains supplementary material, which is available to authorized users.

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divided by the lymphocyte count. GPS is categorized based on the C-reactive protein (CRP) level and albumin concentration, and represents not only SIR status but also nutritional status. Although a number of studies have investigated the prognostic value of these markers, their clinical importance remains to be elucidated.

In this study, we investigated the prognostic value of pretreatment NLR, PLR, monocyte count, and GPS in CRC patients undergoing curative resection. We also investigated the prognostic factors for overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS) using univariate and multivariate analyses. Both NLR and GPS were particularly associated with prognosis (OS, CSS, and DFS) in this cohort, and so we further explored the impact of the combination of NLR and GPS as a prognostic marker.

Materials and methods

Patients and samples

In total, consecutive 608 CRC patients underwent colorectal surgery at Kyoto University Hospital from 2005 to 2010. To investigate the pure effect of several markers on prognosis, patients with the following factors were excluded: recurrence tumor ($n = 20$), synchronous malignant disease ($n = 8$), histopathology other than adenocarcinoma ($n = 10$), palliative surgery case ($n = 10$), carcinoma in situ ($n = 30$), preoperative therapy case ($n = 41$), and non-curative resection case ($n = 41$). Finally, 448 patients were enrolled in this retrospective cohort study (Fig. 1).

Patients' blood samples were collected within 30 days before operation. Blood sample data included absolute neutrophil count, absolute monocyte count, absolute lymphocyte count, carcinoembryonic antigen (CEA) level, carbohydrate antigen 19-9 (CA19-9) level, C-reactive protein (CRP) level, and albumin concentration. NLR was calculated as the neutrophil count divided by the lymphocyte count. PLR was calculated as the platelet count divided by the lymphocyte count. GPS was estimated as previously described [20]. Briefly, patients with both high serum CRP level (> 1.0 mg/dL) and low albumin concentration (< 3.5 g/dL) were categorized as GPS = 2. Patients with only one of the abnormal values were categorized as GPS = 1, while patients with neither were as GPS = 0.

From the electronic patient record data, we collected other clinicopathological data, such as patients' age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, tumor location, TNM stage (UICC 7th edition) with each T-, N-, and M-status, histological grading, lymphatic invasion, venous invasion, number of resected lymph nodes, and adjuvant chemotherapy. This research protocol was approved by the institutional review board of Kyoto University (reference no. R0722).

Patients' follow-up, survival, and recurrence

We performed patients' postoperative follow-up in regular interval (outpatient visit; every 3 months in first year, every 6 months in years 2 to 3, and every 12 months in years 4 to 5). Physical examination and blood test were done in every visit. Patients also received chest and abdominal computed tomography in every 3 months for stage III/IV patients, and in every

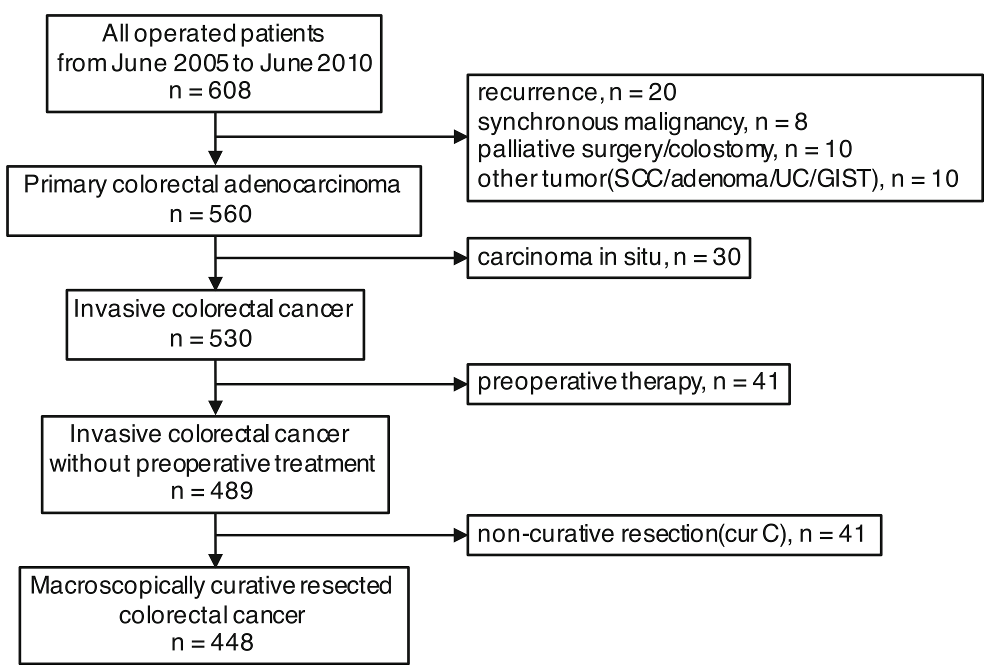


Fig. 1 Flow diagram of the cases analyzed in this study

Table 1 Clinicopathological characters of all 448 colorectal cancer patients

Variable	Number	%
Gender		
Male	268	60
Female	180	40
Age (years)		
< 69	211	47
≥ 69	237	53
Performance status		
0	355	79
≥ 1	93	21
Location		
Colon	333	74
Rectum/proctodeum	115	26
Histology		
tub1/tub2	424	95
por/sig/muc	24	5
T factor		
T1–2	142	32
T3–4	306	68
N factor		
Negative	292	65
Positive	156	35
M factor		
Negative	427	95
Positive	21	5
UICC-TNM stage		
I	123	27
II	165	37
III	139	31
IV	21	5
Lymphatic invasion		
Negative	288	64
Positive	160	36
Venous invasion		
Negative	209	47
Positive	239	53
No. of resected lymph node		
< 12	81	18
≥ 12	367	82
CEA levels (ng/mL)		
< 5.0	302	67
≥ 5.0	146	33
CA19-9 levels (U/mL)		
< 37.0	392	87
≥ 37.0	56	13
Adjuvant chemotherapy		
No	273	61
Yes	175	39
NLR		
< 2.05	190	42
≥ 2.05	258	58
Monocyte count		
< 400	322	72
≥ 400	126	28
PLR		
< 195	343	77
≥ 195	105	23
GPS		
0	382	85
1.2	66	15
Curability		
A	426	95
B	22	5

One stage II patient who had pathologically surgical margin positive included in curve

SD, standard deviation; *tubt*, well differentiated; *tub2*, moderately differentiated; *por*, poorly differentiated; *sig*, signet ring cell carcinoma; *muci*, mucinous carcinoma; *UICC-TNM*, Union of International Cancer Control - tumor node metastasis; *CEA*, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; *NLR*, neutrophil to lymphocyte ratio; *GPS*, Glasgow prognostic score

6 months for others, in the first 3 years, followed by annual surveillance until at least 5 years. Colonoscopy was performed in biannual.

Overall survival (OS) was calculated from the date of primary surgery to the date of death with any cause. Cancer-specific survival (CSS) was calculated from the date of primary surgery to the date of death due to primary CRC recurrences or metastases. Disease-free survival (DFS) was calculated from the date of primary surgery to the date of local/distant recurrence or the date of death with any cause.

Statistical analysis

The optimal cutoff values of preoperative NLR, PLR, and monocyte count were determined by receiver operating characteristic (ROC) curve. The continuous variables were shown as the mean ± standard deviation (SD). Categorical variables were analyzed by Fisher exact test. Mann-Whitney *U* test was employed to analyze the continuous variables. Clinical outcomes were analyzed using the log-rank test with Kaplan-Meier curve. The variables with a *P* value less than 0.05 in the preceding univariate analysis with the log-rank test proceeded into the following multivariate analysis using the Cox proportional hazard regression analyses to determine the predictive factors. Regarding the combination of NLR and GPS, subgroup analyses were done based on the stage: early stage (stage I/II) and advanced stage (stage III/IV). All analyses were two-sided, and P value of < 0.05 was defined as statistically significant. Statistical analyses were done using JMP® Pro software version 13.0.0 (SAS Institute Inc., NC, USA).

Results

Table 1 presents the clinicopathological characteristics of the 448 enrolled patients with CRC, consisting of 268 males (60%) and 180 females (40%), with a mean age of 69 years (range, 36–91). A total of 333 patients (74%) had colon cancer and the remaining 115 patients (26%) had rectal cancer. The patients were staged as follows: Stage I, $n = 123$ (27%), stage II, $n = 165$ (37%), stage III, $n = 139$ (31%), and stage IV, $n = 21$ (5%). Median follow-up duration was 60 months (range, 1–92). The 5-year OS, CSS, and DFS of all the 448 patients were 85.6%, 90.8%, and 75.0%, respectively.

Using the ROC curve analysis to assess OS, we determined the optimal cutoff values for NLR, monocyte count, and PLR as 2.05, 400, and 195, respectively (Supplementary Fig. 1a, b, and c). The areas under the curve (AUC) of NLR, monocyte count, and PLR were 0.61, 0.61, and 0.50, respectively. In this cohort, the high NLR group (NLR ≥ 2.05; $n = 258$) exhibited worse prognosis than the low NLR group (NLR < 2.05; $n = 190$) in OS, CSS, and DFS ($P < 0.01$, $P < 0.01$, and $P < 0.01$, respectively) (Fig. 2a, b, and c). The high monocyte count group (monocyte count ≥ 400; $n = 126$) also exhibited worse prognosis than the low monocyte count group (monocyte count < 400; $n = 322$) in OS, CSS, and DFS ($P < 0.01$, $P < 0.01$, and $P = 0.012$, respectively) (Fig. 2d, e, and f). On the other hand, PLR was not significantly associated with OS,

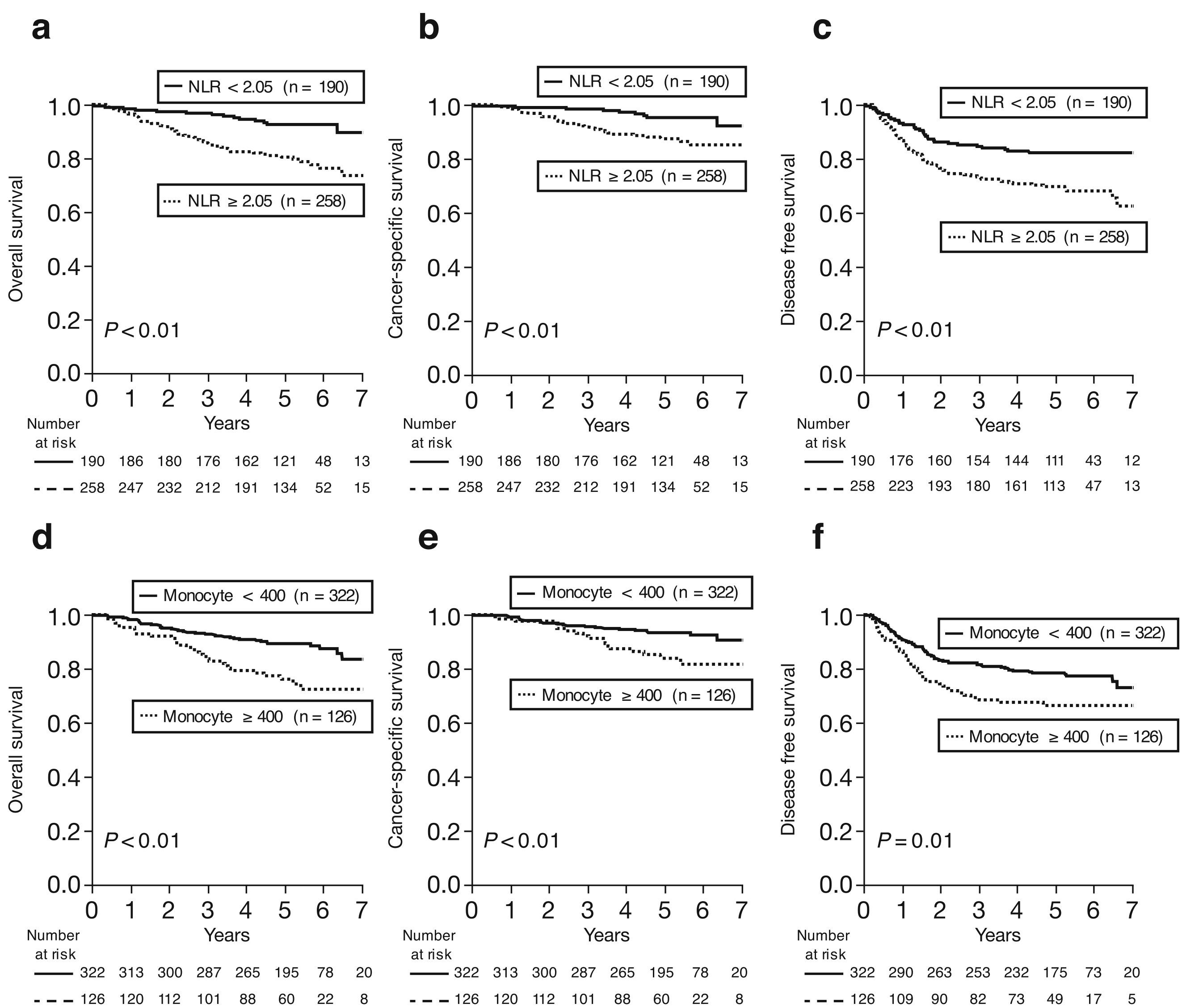


Fig. 2 Overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS) curves according to NLR and monocyte count. **a** OS curve of NLR. **b** CSS curve of NLR. **c** DFS curve of NLR. **d** OS curve of monocyte count. **e** CSS curve of monocyte count. **f** DFS curve of monocyte count

CSS, and DFS ($P = 0.28$, $P = 0.14$, and $P = 0.08$, respectively) (Fig. 3a, b, and c). Regarding the relationship between GPS and prognosis, the high GPS group (GPS = 1/2; $n = 66$) exhibited worse prognosis than low GPS group (GPS = 0; $n = 382$) in OS, CSS, and DFS ($P < 0.01$, $P < 0.01$, and $P < 0.01$, respectively) (Fig. 3d, e, and f).

Next, we investigated the prognostic factors for OS, CSS, and DFS. Univariate and multivariate analyses revealed that poor OS was significantly associated with age ≥69 (hazard ratio (HR) 3.19, $P < 0.01$) and high NLR (HR 2.04, $P = 0.02$) (Table 2). In addition, there was a tendency for high GPS to worsen OS (HR 1.73, $P = 0.06$), whereas monocyte count and PLR were not associated with OS. Univariate and multivariate analyses for CSS revealed that poor CSS was significantly associated with age ≥69 (HR 2.79, $P < 0.01$), M factor (HR 2.58, $P = 0.047$), high CA19-9 (HR 2.45, $P = 0.047$), adjuvant chemotherapy (HR 2.94, $P = 0.01$), and high GPS (HR 2.17, $P = 0.04$) (Table 3). NLR tended to worsen CSS with a P value of 0.06, whereas monocyte count and PLR did not. Furthermore, univariate and multivariate analyses for DFS indicated that poor DFS was significantly associated with venous invasion (HR 1.54, $P = 0.048$), high NLR (HR 1.71, $P = 0.01$), and high GPS (HR 1.68, $P = 0.04$) (Table 4). DFS was not associated with monocyte count and PLR.

These aforementioned results indicated that poor prognosis was associated with high NLR and high GPS in this cohort. Therefore, we further explored the prognostic value of the combination of NLR and GPS. We also investigated the TNM stage-based classification of NLR and GPS, and found that they were not correlated to the stage progression (Fig. 4a

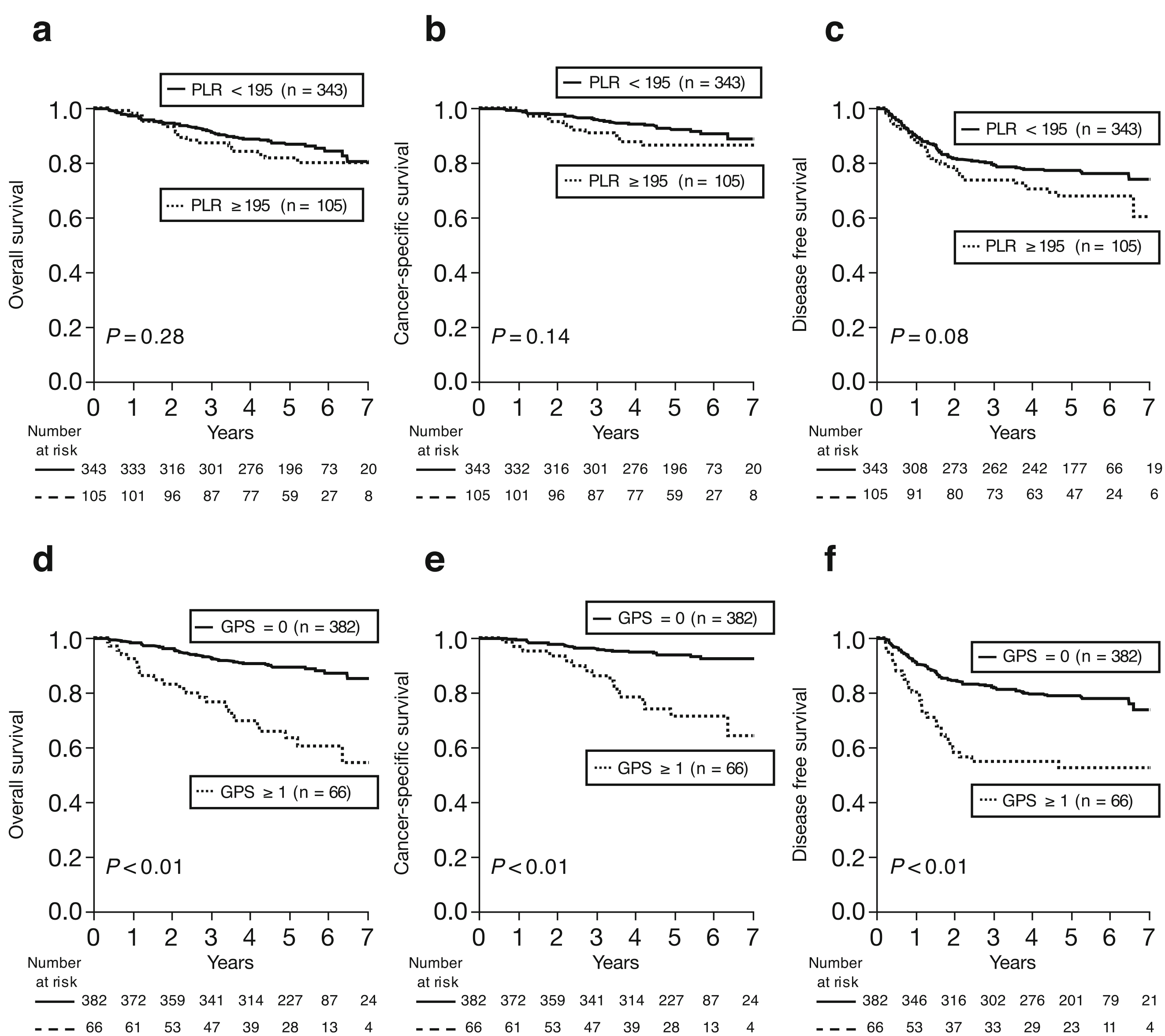


Fig. 3 Overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS) curves according to PLR and GPS. **a** OS curve of PLR. **b** CSS curve of PLR. **c** DFS curve of PLR. **d** OS curve of GPS. **e** CSS curve of GPS. f, DFS curve of GPS

Table 2 Univariate and multivariate analyses of clinicopathological factors for overall survival in all 448 colorectal cancer patients

		Univariate analysis (log-rank)	Multivariate analysis (Cox proportional hazard model)		
Variable	*n* (%)	*P* value	HR	95% CI	*P* value
Gender					
Male	268 (60)				
Female	180 (40)	0.77	–	–	–
Age (years)					
< 69	211 (47)				
≥ 69	237 (53)	*< 0.01*	3.19	1.820–5.934	*< 0.01*
Performance status					
0	355 (79)				
≥ 1	93 (21)	*< 0.01*	1.64	0.951–2.760	0.07
Location					
Colon	333 (74)				
Rectum/proctodeum	115 (26)	0.47	–	–	–
Histology					
tub1/tub2	424 (95)				
por/sig/muci	24 (5)	*< 0.01*	2.09	0.943–4.243	0.07
T factor					
T1–2	142 (32)				
T3–4	306 (68)	*< 0.01*	1.33	0.659–2.910	0.44
N factor					
Negative	292 (65)				
Positive	156 (35)	*< 0.01*	1.66	0.932–2.949	0.09
M factor					
Negative	427 (95)				
Positive	21 (5)	*< 0.01*	2.18	0.969–4.514	0.06
Lymphatic invasion					
Negative	288 (64)				
Positive	160 (36)	*< 0.01*	1.34	0.783–2.303	0.28
Venous invasion					
Negative	209 (47)				
Positive	239 (53)	0.23	–	–	–
No. of resected lymph node					
< 12	81 (18)	0.12	–	–	–
≥ 12	367 (82)				
CEA levels (ng/mL)					
< 5.0	302 (67)				
≥ 5.0	146 (33)	0.10	–	–	–
CA19-9 levels (U/mL)					
< 37.0	392 (87)				
≥ 37.0	56 (13)	*0.02*	1.68	0.881–3.005	0.11
Adjuvant chemotherapy					
No	273 (61)				
Yes	175 (39)	0.09	–	–	–
NLR					
< 2.05	190 (42)				
≥ 2.05	258 (58)	*< 0.01*	2.04	1.114–3.957	*0.02*
Monocycle count					
< 400	322 (72)				
≥ 400	126 (28)	*< 0.01*	1.60	0.94–2.668	0.08
PLR					
< 195	343 (77)				
≥ 195	105 (23)	0.28			
GPS					
0	382 (85)				
1.2	66 (15)	*< 0.01*	1.73	0.974–3.022	0.06

Italicized entries indicate statistical significance $P < 0.05$

HR, hazard ratio; *CI*, confidence interval; *tub1*, well differentiated; *tub2*, moderately differentiated; *por*, poorly differentiated; *sig*, signet ring cell carcinoma; *muci*, mucinous carcinoma; *No*, number; *CEA*, carcinoembryonic antigen; CA19-19, carbohydrate antigen 19-9; *NLR*, neutrophil to lymphocyte ratio; *GPS*, Glasgow prognostic score

Table 3 Univariate and multivariate analyses of clinicopathological factors for cancer-specific survival in all 448 colorectal cancer patients

		Univariate analysis (log-rank)	Multivariate analysis (Cox proportional hazard model)		
Variable	*n* (%)	*P* value	HR	95% CI	*P* value
Gender					
Male	268 (60)				
Female	180 (40)	0.68	–	–	–
Age (years)					
< 69	211 (47)				
≥ 69	237 (53)	*0.02*	2.79	1.398–5.792	*< 0.01*
Performance status					
0	355 (79)				
≥1	93 (21)	0.07	–	–	–
Location					
Colon	333 (74)				
Rectum/proctodeum	115 (26)	0.87	–	–	–
Histology					
tub1/tub2	424 (95)				
por/sig/muci	24 (5)	*0.01*	1.57	0.505–4.046	0.40
T factor					
T1–2	142 (32)				
T3–4	306 (68)	*< 0.01*	2.77	0.759–17.900	0.13
N factor					
Negative	292 (65)				
Positive	156 (35)	*< 0.01*	2.17	0.939–5.343	0.07
M factor					
Negative	427 (95)				
Positive	21 (5)	*< 0.01*	2.58	1.013–6.136	*0.047*
Lymphatic invasion					
Negative	288 (64)				
Positive	160 (36)	*< 0.01*	1.97	0.956–4.271	0.07
Venous invasion					
Negative	209 (47)				
Positive	239 (53)	*< 0.01*	1.16	0.515–2.789	0.73
No. of resected lymph node					
< 12	81 (18)				
≥ 12	367 (82)	0.16	–	–	–
CEA levels (ng/mL)					
< 5.0	302 (67)				
≥ 5.0	146 (33)	*0.04*	0.72	0.336–1.491	0.38
CA19-9 levels (U/mL)					
< 37.0	392 (87)				
≥ 37.0	56 (13)	*0.03*	2.45	1.012–5.472	*0.047*
Adjuvant chemotherapy					
No	273 (61)				
Yes	175 (39)	*< 0.01*	2.94	1.246–7.476	*0.01*
NLR					
< 2.05	190 (42)				
≥ 2.05	258 (58)	*< 0.01*	2.11	0.959–5.054	0.06
Monocycle count					
< 400	322 (72)				
≥ 400	126 (28)	*< 0.01*	1.40	0.690–2.814	0.34
PLR					
< 195	343 (77)				
≥ 195	105 (23)	0.14	–	–	–
GPS					
0	382 (85)				
1.2	66 (15)	*< 0.01*	2.17	1.026–4.488	*0.04*

Italicized entries indicate statistical significance $P < 0.05$

HR, hazard ratio; *CI*, confidence interval; *tub1*, well differentiated; *tub2*, moderately differentiated; *por*, poorly differentiated; *sig*, signet ring cell carcinoma; *muci*, mucinous carcinoma; *No*, number; *CEA*, carcinoembryonic antigen; *CA19-19*, carbohydrate antigen 19-9; *NLR*, neutrophil to lymphocyte ratio; *GPS*, Glasgow prognostic score

Table 4 Univariate and multivariate analyses of clinicopathological factors for disease-free survival in all 448 colorectal cancer patients

Variable	*n* (%)	Univariate analysis (log-rank)	Multivariate analysis (Cox proportional hazard model)		
		P value	HR	95% CI	*P* value
Gender					
Male	268 (60)				
Female	180 (40)	1.00	–	–	–
Age (years)					
< 69	211 (47)				
≥ 69	237 (53)	0.12	–	–	–
Performance status					
0	355 (79)				
≥ 1	93 (21)	*0.05*	1.14	0.722–1.769	0.56
Location					
Colon	333 (74)				
Rectum/proctodeum	115 (26)	0.48	–	–	–
Histology					
tub1/tub2	424 (95)				
por/sig/muci	24 (5)	*< 0.01*	1.79	0.901–3.247	0.09
T factor					
T1–2	142 (32)				
T3–4	306 (68)	*< 0.01*	1.57	0.898–2.862	0.12
N factor					
Negative	292 (65)				
Positive	156 (35)	*< 0.01*	1.52	0.937–2.465	0.09
M factor					
Negative	427 (95)				
Positive	21 (5)	*< 0.01*	1.88	0.951–3.462	0.07
Lymphatic invasion					
Negative	288 (64)				
Positive	160 (36)	*< 0.01*	1.16	0.773–1.745	0.47
Venous invasion					
Negative	209 (47)				
Positive	239 (53)	*< 0.01*	1.54	1.005–2.390	*0.048*
No. of resected lymph node					
< 12	81 (18)	0.27	–	–	–
≥ 12	367 (82)				
CEA levels (ng/mL)					
< 5.0	302 (67)				
≥ 5.0	146 (33)	*< 0.01*	1.08	0.715–1.631	0.710
CA19-9 levels (U/mL)					
< 37.0	392 (87)				
≥ 37.0	56 (13)	*0.05*	1.34	0.780–2.187	0.28
Adjuvant chemotherapy					
No	273 (61)				
Yes	175 (39)	*< 0.01*	1.36	0.850–2.189	0.20
NLR					
< 2.05	190 (42)				
≥ 2.05	258 (58)	*< 0.01*	1.71	1.123–2.656	*0.01*
Monocycle count					
< 400	322 (72)				
≥ 400	126 (28)	*0.01*	1.22	0.800–1.837	0.35
PLR					
< 195	343 (77)				
≥ 195	105 (23)	0.08	–	–	–
GPS					
0	382 (85)				
1.2	66 (15)	*< 0.01*	1.68	1.031–2.673	*0.04*

Italicized entries indicate statistical significance $P < 0.05$

HR, hazard ratio; *CI*, confidence interval; *tub1*, well differentiated; *tub2*, moderately differentiated; *por*, poorly differentiated; *sig*, signet ring cell carcinoma; *muci*, mucinous carcinoma; *No*, number; *CEA*, carcinoembryonic antigen; *CA19-19*, carbohydrate antigen 19-9; *NLR*, neutrophil to lymphocyte ratio; *GPS*, Glasgow prognostic score and b). We classified 448 patients into three groups based on NLR and GPS: (i) high NLR/high GPS group (NLR ≥ 2.05 and GPS = 1/2; $n = 51$), (ii) low NLR/low GPS group (NLR < 2.05 and GPS = 0; $n = 175$), and (iii) residual case group ($n = 222$). Kaplan-Meier curves of the three groups are shown in Fig. 5. Of note, we observed that there was a significant difference between all the three groups. The high NLR/high GPS group exhibited remarkably poorer prognosis in OS, CSS, and DFS compared with the low NLR/low GPS group ($P < 0.01$, $P < 0.01$, $P < 0.01$, respectively) and the residual cases group ($P < 0.01$, $P < 0.01$, $P < 0.01$, respectively). The low NLR/low GPS group exhibited significantly better prognosis in OS, CSS, and DFS compared with the residual cases group ($P < 0.01$, $P = 0.014$, $P = 0.02$, respectively). The 5-year OS, CSS, and DFS were 58.0%, 67.7%, and 47.0% in the high NLR/high GPS group; 85.8%, 91.3%, and 75.0% in the residual cases group; and 93.2%, 96.1%, and 83.1% in the low NLR/low GPS group. Furthermore, we analyzed the prognostic impact in the two separate stages: early stage (stage I/II) and advanced stage (stage III/IV). Importantly, we found that the difference between all the three groups was much more pronounced in stage III/IV, whereas it was not in stage I/II (Fig. 6). The 5-year OS, CSS, and DFS of stage III/IV were 30.4%, 34.2%, and 26.3% in the high NLR/high GPS group; 75.5%, 77.9%, and 55.0% in the residual cases group; and 94.8%, 96.3%, and 80.9% in the low NLR/low GPS group. These results indicated that the combination of NLR and GPS could be a useful scoring system to effectively stratify the prognosis of CRC patients, especially in the advanced stage.

Discussion

Cancer-associated inflammation, both in the tumor immune microenvironment and in the systemic circulation, has attracted recent intense attention as important determinants of disease progression [21]. High microsatellite instability (MSI-high) in CRC is more susceptible to immune checkpoint inhibitors, because the MSI-high status is associated with a high mutational burden and increased immune infiltration [22]. The active immune system reflects the systemic and local inflammatory status. The SIR-based scores have been revealed as negative prognostic markers in several types of cancer, including CRC. NLR is one of the best-studied SIR-related markers, and has been reported as a poor prognostic factor [6–11]. The mechanism underlying the prognostic value of NLR remains poorly understood. Lymphocytes and neutrophils are pivotal players in the tumor microenvironment. Although neutrophils were originally viewed as the first responders of the innate immune system against pathogens, recent evidence has revealed a new aspect of neutrophils to accelerate tumor growth, invasion, metastasis, and angiogenesis by secreting several inflammatory, immunoregulatory, and angiogenic factors (e.g., elastase, matrix metalloproteinases, and vascular endothelial growth factor) [23]. We have recently reported that loss of SMAD4 from CRC cells resulted in the recruitment of tumor-associated neutrophils via the CCL15-CCR1 and CXCL1/8-CXCR2 axes [24–27]. On the other hand, anti-tumor activity is considered to be mediated mainly by lymphocyte-dependent reactions. A high density of tumor-infiltrating lymphocytes has been reported to be strongly correlated with a favorable prognosis in CRC [28]. Lymphopenia is associated with disease severity and immunosuppression state [29]. Thus, elevated NLR is considered to reflect a shift in the balance from anti-tumor immune status to pro-tumor inflammatory status, which can result in worse prognosis.

GPS, composed of serum CRP level and albumin concentration, has been reported to be effective in predicting the prognosis of a variety of cancers, including CRC [14–17]. The prognostic value of several SIR-related markers in cancer has been compared [30–35]. Park et al. reported that the

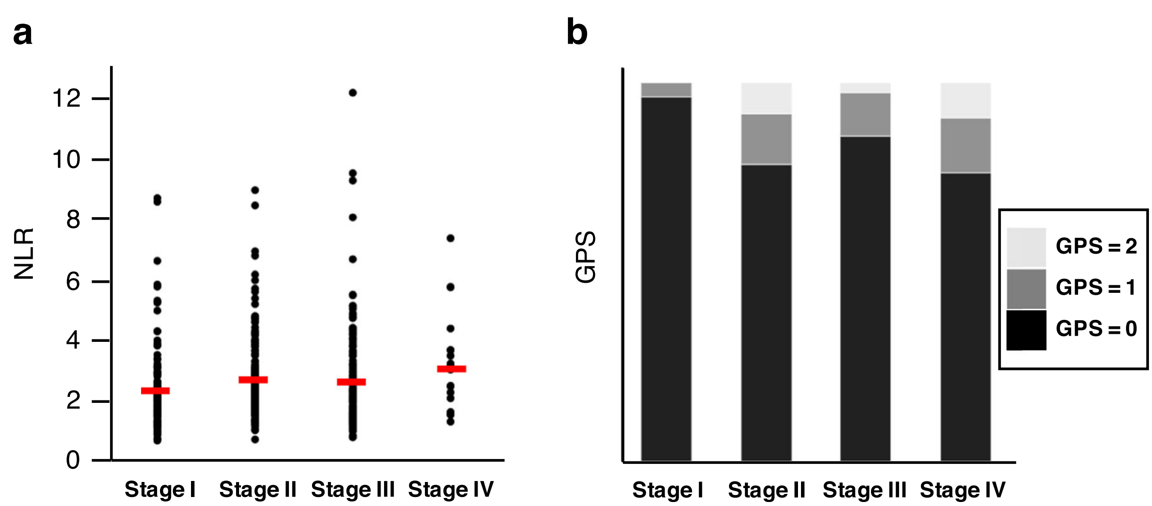


Fig. 4 Stage-based classification. **a** NLR according to the stage-based classification. Means; bars. **b** GPS according to the stage-based classification

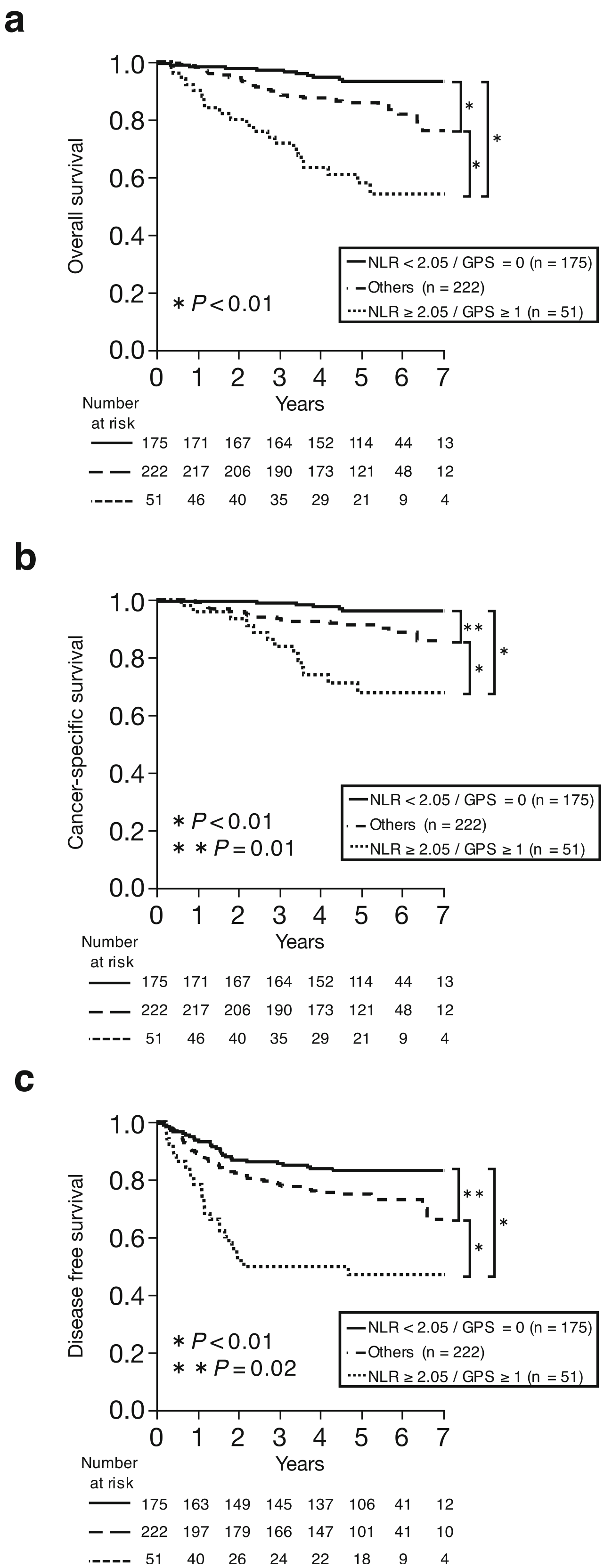


Fig. 5 Overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS) curves of stage I–IV according to the combination of NLR and GPS (Kaplan-Meier estimates). **a** OS curve. **b** CSS curve. **c** DFS curve

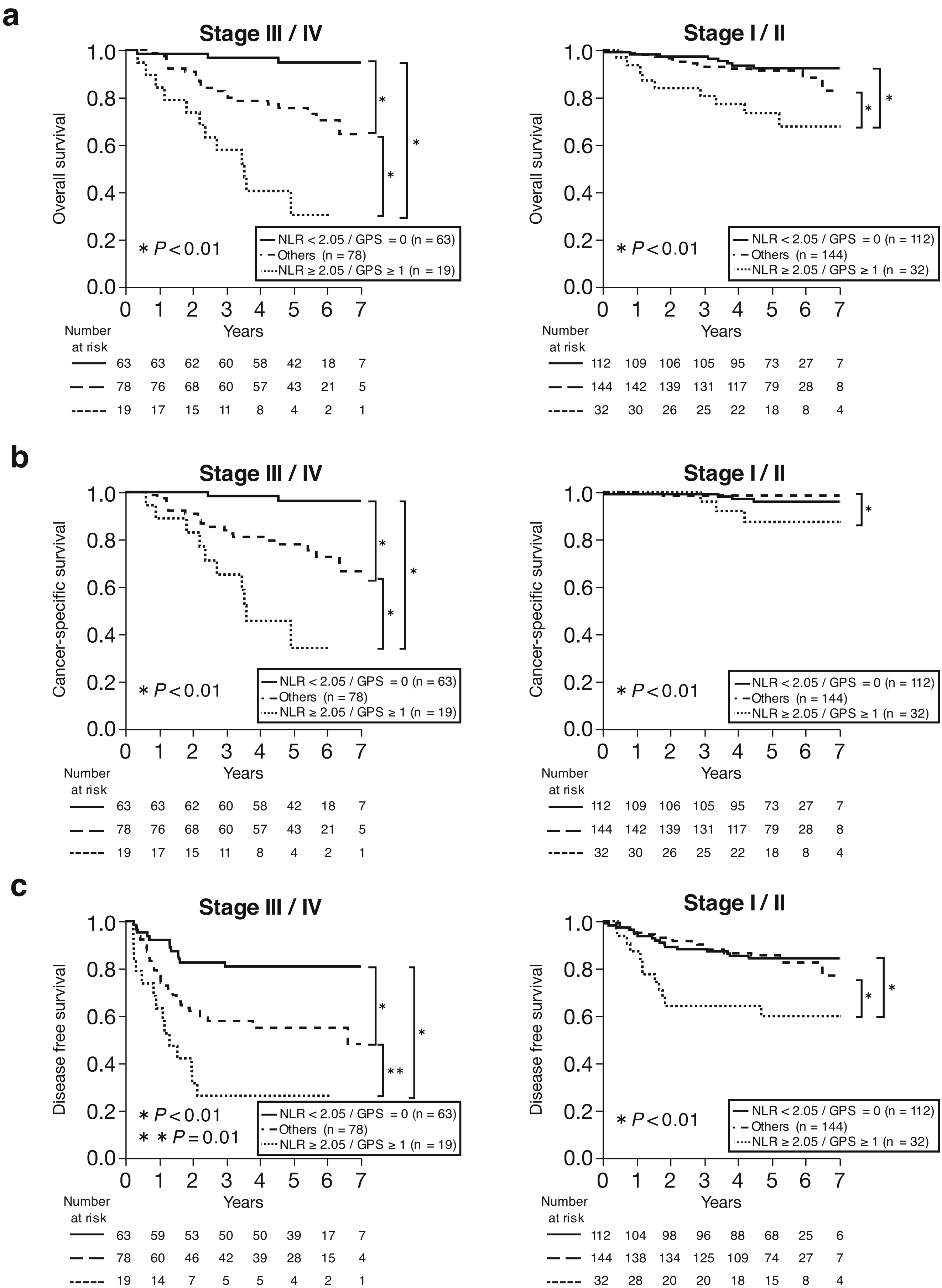
Fig. 6 Overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS) curves of stage I/II (right) and stage III/IV (left) according to the combination of NLR and GPS (Kaplan-Meier estimates). **a** OS curve. **b** CSS curve. **c** DFS curve

combination of TNM stage and GPS could stratify the postoperative prognosis in CRC patients undergoing curative resection [14]. Suzuki et al. recently reported that the systemic inflammation score, which is composed of the lymphocyte-to-monocyte ratio and albumin concentration, was more informative than GPS, and could be a novel prognostic marker in CRC [15]. To date, there is no consensus as to which biomarker is the best predictive for the prognosis of CRC patients. In our cohort, we evaluated the prognostic value of preoperative NLR, PLR, monocyte count, and GPS, and found that NLR and GPS were superior to monocyte count and/or PLR for predicting patients' prognosis (Tables 2, 3, and 4; Figs. 2 and 3).

There is a growing evidence indicating NLR can be a prognostic marker in cancer. However, the results of individual reports are inconsistent across tumor types and disease stages. In addition, published data suggest that there is a high variability in the NLR cutoff values used to predict prognosis [6–11]. Although an NLR cutoff value often used is 5.0, only 31 (7%) patients displayed NLR > 5.0 in our cohort. Therefore, we did not adopt this value. To identify the optimal cutoff value, we used the ROC curve analysis. The optimal cutoff value can be highly variable based on the time at which survival was assessed.

There are limitations in the present study. First, this is a retrospective study conducted at a single institution with a relatively small sample size, which might include case selection bias. Further studies with a large sample size and/or prospective design are needed. Second, there is no consensus as to the NLR cutoff value. In the present study, an NLR cutoff value of 2.05 was selected using ROC analysis. This lack of consensus as to the cutoff value makes NLR difficult for clinical use. NLR is a non-specific marker of inflammation, indicating that another systemic disease can affect the NLR value. Third, approximately 40% of all patients received routine adjuvant chemotherapy after resection in this study. We could not thoroughly investigate any possible association between patients' prognosis and use of adjuvant chemotherapy.

In conclusion, we examined the associations of several SIR-related markers with the prognosis of CRC patients, and found that both NLR and GPS could be useful predictors of prognosis in our cohort. In addition, this study identified the possibility that the combination of NLR and GPS could be a novel scoring system to effectively stratify the postoperative prognosis of CRC patients undergoing curative resection. To our knowledge, this is the first


a
Stage III / IV
Overall survival
* P < 0.01
NLR < 2.05 / GPS = 0 (n = 63)
Others (n = 78)
NLR ≥ 2.05 / GPS ≥ 1 (n = 19)
Years
Number at risk
63 63 62 60 58 42 18 7
78 76 68 60 57 43 21 5
19 17 15 11 8 4 2 1
Stage I / II
Overall survival
* P < 0.01
NLR < 2.05 / GPS = 0 (n = 112)
Others (n = 144)
NLR ≥ 2.05 / GPS ≥ 1 (n = 32)
Years
Number at risk
112 109 106 105 95 73 27 7
144 142 139 131 117 79 28 8
32 30 26 25 22 18 8 4
b
Stage III / IV
Cancer-specific survival
* P < 0.01
NLR < 2.05 / GPS = 0 (n = 63)
Others (n = 78)
NLR ≥ 2.05 / GPS ≥ 1 (n = 19)
Years
Number at risk
63 63 62 60 58 42 18 7
78 76 68 60 57 43 21 5
19 17 15 11 8 4 2 1
Stage I / II
Cancer-specific survival
* P < 0.01
NLR < 2.05 / GPS = 0 (n = 112)
Others (n = 144)
NLR ≥ 2.05 / GPS ≥ 1 (n = 32)
Years
Number at risk
112 109 106 105 95 73 27 7
144 142 139 131 117 79 28 8
32 30 26 25 22 18 8 4
c
Stage III / IV
Disease free survival
* P < 0.01
* * P = 0.01
NLR < 2.05 / GPS = 0 (n = 63)
Others (n = 78)
NLR ≥ 2.05 / GPS ≥ 1 (n = 19)
Years
Number at risk
63 59 53 50 50 39 17 7
78 60 46 42 39 28 15 4
19 14 7 5 5 4 2 1
Stage I / II
Disease free survival
* P < 0.01
NLR < 2.05 / GPS = 0 (n = 112)
Others (n = 144)
NLR ≥ 2.05 / GPS ≥ 1 (n = 32)
Years
Number at risk
112 104 98 96 88 68 25 6
144 138 134 125 109 74 27 7
32 28 20 20 18 15 8 4

report to reveal the prognostic impact of the combination of NLR and GPS in CRC. NLR and GPS are easily calculated through routine blood tests, thus providing opportunities for further investigation.

Grant supports This work was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan (to KK and SI).

Authors' contribution KK, SI and YS planned the study concept and design. Acquisition of data was done by SI. Analysis and interpretation of data was done by SI, KK, RO, and HK. KK and SI wrote the manuscript, and edited by all the authors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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