C-Reactive Protein as Predictor of Recurrence in Patients with Rectal Cancer Undergoing Chemoradiotherapy Followed by Surgery

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Abstract. *Background: The clinical significance of the systemic inflammatory response (SIR) in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy (CRT), to the best of our knowledge, has not been thus far investigated. Patients and Methods: The neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and C-Reactive protein (CRP) levels for 84 patients with rectal cancer undergoing CRT were available as indicators of SIR status. The impact of SIR status on the prognosis of these patients was assessed. Results: Elevated NLR, CRP, carcinoembryonic antigen (CEA) and pathological TNM stage III [ypN(+)] were identified as significant prognostic factors for poor overall survival (OS), with CRP and ypN(+) being validated as independent predictors of OS. Elevated CRP and CEA levels were significant predictive factors for poor disease-free survival (DFS), and an elevated CRP level was identified as the only independent predictive factor for DFS. In addition, an elevated CRP level predicted for poorer OS and DFS in patients with pathological TNM stage I-II [ypN(–)]. Conclusion: CRP is a promising predictor of recurrence and prognosis in patients with rectal cancer treated by CRT.*

Rectal cancer is one of the most common types of cancer in Japan and in the Western world. Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is currently recognized as one of the standard therapeutic strategies for locally advanced rectal cancer, and many clinical studies have shown that CRT improves the rate of sphincter preservation and reduces the rate of postoperative local recurrence (1, 2). However, despite significant improvements in the management of rectal cancer, distant recurrence remains the major cause of mortality in patients undergoing preoperative CRT followed by TME.

Many biomarkers have the potential to act as supplementary tools for the further classification of patients with colorectal cancer into subgroups based on the current standard TNM classification (3-5). The systemic inflammatory response (SIR), which is thought to be secondary to hypoxia or tumor necrosis, is associated with the anti-apoptotic characteristic of cancer cells (6) and has been shown to be a reliable biomarker of outcome in a variety of malignancies (7). C-Reactive protein (CRP) is an essential acute-phase reactant, acting as a surveillance molecule for activation of the adaptive immune system, and its levels correlate with outcome in patients undergoing cancer treatment (8, 9). CRP is an independent predictor of postoperative recurrence and prognosis in colorectal cancer (10), and has also been demonstrated as a predictor of chemosensitivity (11, 12).

The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) are two further representative indices of systemic inflammation, and their prognostic value has been studied in many types of cancer (13). A high NLR or PLR was shown to predict poor outcomes in patients with colorectal cancer undergoing primary resection, without lymph node metastases, and those undergoing hepatectomy for liver metastases (14-16). However, the clinical significance of SIR in patients with rectal cancer undergoing CRT followed by surgery has not been fully investigated.

In this study, we investigated the correlations between levels of the SIR markers CRP, NLR and PLR in pre-treatment blood tests, and clinicopathological features in patients undergoing CRT followed by TME for locally advanced rectal cancer, and evaluated their potential as biomarkers of outcome.

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Key Words: C-Reactive protein, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, rectal cancer, prognosis, chemoradiotherapy.

Table I. *Patients' characteristics*.

Variable	Category	N (%)
Age (median 64.5), years	≤64	42 (50%)
	≥65	42 (50%)
Gender	Male	62 (74%)
	Female	22 (26%)
Clinical T stage	T1	2 (2%)
	T2	14 (17%)
	T3	54 (64%)
	T4	24 (17%)
Clinical N stage	N0	27 (32%)
	N1-3	57 (68%)
Clinical TNM stage	I	13 (15%)
	II	15 (18%)
	III	56 (67%)
ypT stage	T0	5 (6%)
	T1	8 (9%)
	T2	26 (31%)
	T3	45 (54%)
yp N stage	N0	38 (45%)
	N1-3	46 (55%)
Pathological TNM stage	I	13 (15%)
	II	15 (18%)
	III	56 (67%)
Radiotherapy	Short course (20 Gy/4 fractions)	48 (57%)
	Long course (45 Gy/25 fractions)	36 (43%)
Pathological response	Non-responder (grade 0/1a/1b)	0 (0%)/27 (32%)/22 (26%)
	Responder (grade 2/3)	29 (35%)/6 (7%)
Histology	Well/moderate	73 (87%)
	Poorly/mucinous/signet	11(13%)
Recurrence	Absent	68 (81%)
	Local	4 (5%)
	Distant	12 (14%)

yp: Pathological status after neoadjuvant chemoradiotherapy, TNM: tumor node metastasis.

Patients and Methods

Patients. A total of 84 patients with rectal cancer received pre-operative CRT followed by TME at our Institute from 2001 to 2012. The criteria for pre-operative CRT were: age 80 years or younger, clinical stage I-III based on the International Union Against Cancer's TNM classification (17), and no evidence of deep venous thrombosis.

5-Fluorouracil (5-FU)-based chemoradiotherapy regimen. Patients with rectal cancer were treated at our Institute with short-course (20 Gy in four fractions) or long-course (45 Gy in 25 fractions) radiotherapy using a four-field box technique. Patients underwent concurrent pharmacokinetic modulation chemotherapy (intravenous infusion of 5-FU: 600 mg/m^2 for 24 h, and tegafur/uracil given as 400 mg/m^2 orally for five days) to take advantage of 5-FU-mediated radiosensitization (18). Forty-eight patients (57%) received short-course radiotherapy with chemotherapy over one week. The remaining 36 patients (43%) received long-course radiotherapy with chemotherapy for four weeks. The time interval between preoperative CRT and surgery was two to three weeks in short-course irradiation, and four to six weeks in long-course irradiation. All patients underwent standard surgery including TME, and received 5-FU-based adjuvant chemotherapy after surgery for six months to one year.

Laboratory measurement of neutrophils, lymphocytes, carcino-embryonic antigen (CEA) and CRP. Neutrophils, lymphocytes, CEA and CRP were analyzed in routine blood tests. Blood samples from each patient were obtained within one week prior to CRT. The NLR was defined as the neutrophil-to-lymphocyte ratio, and patients were divided into two groups using a cut-off value of 3 (19). The PLR was defined as the platelet count-to-lymphocyte ratio, and patients were categorized according to ratios of ≤150 or >150 (13). The cut-off value for CEA was ≤5 ng/μl and >5 ng/μl, according to the normal range at our Institute. The cut-off value for CRP was defined as 0.2 mg/dl because levels <0.2 mg/dl could not be demonstrated at our Institute. We obtained written informed consent from all patients according to guidelines approved by the Institutional Research Board.

Clinical response, tumor regression after CRT and pathological staging of surgical specimens. The clinical response after preoperative CRT was evaluated by barium enema, endoscopy, and magnetic resonance imaging. Response was graded as a complete

Table II. *Associations between tumor markers Carcinoembryonic antigen (CEA) and systemic inflammatory response (SIR) status and clinicopathological findings.*

	CEA (ng/μl)			NLR			PLR			CRP (mg/dl)		
Factor.	≤5	>5	*p*-Value	≤3	>3	*p*-Value	≤0.015	>0.015	*p*-Value	≤0.2	>0.2	*p*-Value
Age, years												
≤64	20	22	0.82	32	10	0.8	28	14	0.5	31	11	0.63
≥65	18	24		30	12		24	18		28	14	
Gender												
Male	22	40	0.0057	43	19	0.2	43	19	0.03	40	22	0.09
Female	16	6		19	3		9	13		19	3	
Clinical T												
I	2	0	0.008	2	0	0.004	2	0	0.11	2	0	0.002
II	10	4		12	2		9	5		14	0	
III	24	30		43	11		36	18		38	16	
IV	2	12		5	9		5	9		5	9	
Clinical N												
Positive	22	35	0.12	41	16	0.76	35	22	0.91	37	20	0.19
Negative	16	11		21	6		17	10		22	5	
Pathological T												
0	4	1	0.034	4	1	0.37	3	2	0.76	4	1	0.38
I	5	3		4	4		5	3		6	2	
II	15	11		21	5		14	12		21	5	
III	14	31		33	12		30	15		28	17	
Pathological N												
Positive	8	17	0.17	19	6	0.98	16	9	0.99	17	8	0.97
Negative	30	29		43	16		36	23		42	17	
Histology												
Well/moderate	32	41	0.73	54	19	0.78	47	26	0.38	53	20	0.39
Poorly/signet/mucinous	6	5		8	3		5	6		6	5	
Pathological response												
Non-responder (grade 0/1a/1b)	20	29	0.45	39	10	0.24	34	15	0.15	35	14	0.96
Responder (grade 2/3)	18	17		23	12		18	17		24	11	
Recurrence												
Absent	36	32	0.01	52	16	0.42	44	24	0.55	54	14	0.0007
Local	0	4		2	2		2	2		1	3	
Distant	2	10		8	4		6	6		4	8	

CRP: C-Reactive protein; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio. Analyzed by χ^2 tests.

response, partial response, no change, or progressive disease. After resection of the tumor, all specimens were analyzed histopathologically, and pathological TNM classification and staging were determined according to the classification established by the American Joint Committee on Cancer (17). The degree of histopathological tumor regression was based on the Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Colorectum, and was classified into four categories: grade 0, no necrosis or regressive changes; grade 1a, more than two-thirds vital residual tumor cells (VRTCs); grade 1b, approximately one-third to two-thirds VRTCs; grade 2, fewer than one-third VRTCs; and grade 3, no VRTCs (20). We defined non-responders as patients with histopathological tumor regression grade 0-1b, and responders as those with grades 2-3.

Statistical analysis. The associations between SIR status, CEA and clinicopathological findings were analyzed using χ^2 tests. OS and DFS curves were analyzed using the Kaplan–Meier method, and differences were examined using log-rank tests. Cox's proportional hazard regression test was used to estimate univariate and multivariate hazard ratios for recurrence and prognosis. Multivariate survival analyses were performed using the factors that were significant on univariate survival analyses. All *p*-values were two-sided, and $p<0.05$ was considered statistically significant. All statistical analyses were carried out using Medcalc 7.2 for Windows (Mariakerke, Belgium).

Results

Patients' characteristics. The general characteristics of the patients are shown in Table I. The median age was 64.5 years (range=33-80 years), and the male-to-female ratio was 2.8:1. The pre-CRT clinical T stages were T1 (n=2), T2 (n=14), T3 (n=54) and T4 (n=24). Clinical N stages before CRT were N0 (n=27) and N1-3 (n=57). The post-CRT pathological T stages

Table III. *Uni- and multivariate analysis for prognosis of curative rectal cancer after chemoradiotherapy.*

	Univariate			Multivariate		
Factor.	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (>64 *vs.* ≤64 years)	1.69	0.67-4.25	0.26	-	-	-
Gender (female *vs.* male)	1.36	0.45-4.07	0.56	-	-	-
Pre CRT Clinical TNM stage (III *vs.* I-II)	1.37	0.52-3.58	0.51	-	-	-
Pathological TNM stage (III *vs.* I-II)	3.26	1.33-7.97	0.0098	4.57	1.65-12.67	0.003
Pathology (poor *vs.* mod/well differentiated)	2.47	0.81-7.50	0.14	-	-	-
Radiation effect (grade 2-3 *vs.* 0-1)	0.79	0.32-1.96	0.61	-	-	-
CEA (>5 *vs.* ≤5 ng/μl)	7.36	1.71-31.61	0.007	2.78	0.60-12.74	0.18
CRP (>0.2 *vs.* ≤0.2 mg/dl)	7.73	2.90-20.63	<0.0001	8.04	2.48-26.08	0.0005
NLR (>3 *vs.* ≤3)	2.97	1.23-7.17	0.01	0.98	0.37-2.56	0.96
PLR (>150 *vs.* ≤150)	2.17	0.90-5.21	0.08	-	-	-

CEA: Carcinoembryonic antigen; CI: confidential interval; CRP:C-Reactive protein; CRT: chemoradiotherapy; HR: hazard ratio; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

Table IV. *Uni- and multivariate analysis for predictors of recurrence in curative rectal cancer after chemoradiotherapy.*

	Univariate			Multivariate		
Factor.	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age (>64 *vs.* ≤64 years)	1.71	0.67-4.33	0.25	-	-	-
Gender (female *vs.* male)	0.81	0.29-2.26	0.7	-	-	-
Pre CRT Clinical TNM stage (III *vs.* I-II)	1.61	0.58-4.46	0.35	-	-	-
Pathological TNM stage (III *vs.* I-II)	2.31	0.94-5.67	0.06	-	-	-
Pathology (poor *vs.* mod/well differentiated)	2.29	0.76-6.87	0.14	-	-	-
Radiation effect (grade 2-3 *vs.* 0-1)	1.02	0.41-2.52	0.96	-	-	-
CEA (>5 *vs.* ≤5 ng/μl)	4.14	1.21-14.1	0.02	2.48	0.61-14.28	0.16
CRP (>0.2 *vs.* ≤0.2 mg/dl)	5.91	2.25-15.55	0.0003	4.56	1.66-12.49	0.003
NLR (>3 *vs.* ≤3)	1.86	0.73-4.71	0.19	-	-	-
PLR (>150 *vs.* ≤150)	1.66	0.67-4.07	0.26	-	-	-

CEA: Carcinoembryonic antigen; CI: confidential interval; CRP:C-Reactive protein; CRT: chemoradiotherapy; HR: hazard ratio; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

were ypT0 (n=5), ypT1 (n=8), ypT2 (n=26) and ypT3 (n=45). A total of 46 patients (55%) had lymph node metastases (ypN1-3). Seventy-three tumors (87%) had well- or moderately-differentiated adenocarcinoma histology. A total of four patients (5%) had local recurrence alone, and 12 patients (14%) had distant recurrence. The 5-point historical tumor regression grades were as follows: grade 0 (n=0), grade 1a (n=27), grade 1b (n=22), grade 2 (n=29), and grade 3 (n=6). The median follow-up period was 56 months (range=2-147 months).

Associations between pre-CRT CEA, CRP, NLR and PLR, and clinicopathological features. An elevated CEA level was associated with an increasing clinical T stage (p=0.008) and pathological T stage (p=0.034), and postoperative tumor recurrence (p=0.01). Similarly, an elevated CRP level was associated with increasing clinical T stage (p=0.002) and postoperative tumor recurrence (p=0.0007). However, no markers were associated with tumor regression grade by CRT (Table II).

Pre-CRT serum CRP is an independent predictor of poor prognosis in patients with rectal cancer undergoing CRT followed by TME. OS curves for patients classified on the basis of CEA and NLR, PLR and CRP values prior to CRT are shown in Figure 1. Patients with elevated CRP, NLR and CEA levels had significantly poorer OS than patients with levels below the cut-off values (log-rank test: CRP, p<0.0001; NLR, p=0.01; CEA, p<0.001) (Figure 1 A, B and D). Patients with elevated PLR also had poorer OS than those with lower PLR, but the difference was not significant (log-rank test: p=0.07) (Figure 1 C). Univariate analysis identified pathological TNM stage III [ypN(+)] (p=0.0098), elevated CEA (p=0.007),

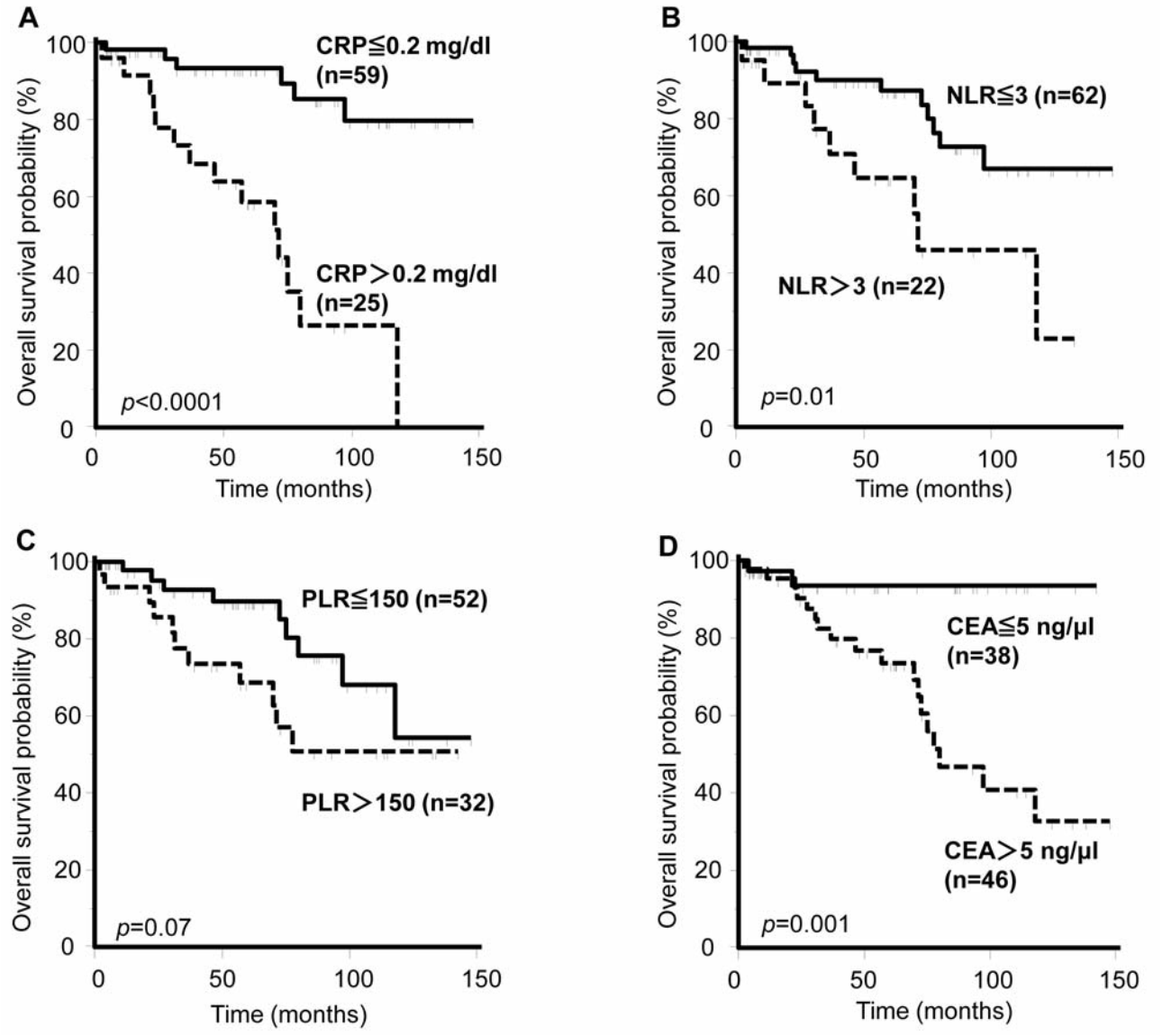

Figure 1. *Kaplan–Meier curves for overall survival (OS) classified according to systemic inflammatory response (SIR) status and carcinoembryonic antigen (CEA) level prior to chemoradiotherapy in patients with rectal cancer. OS rates subdivided by C-Reactive protein (CRP) level (A), neutrophil/lymphocyte ratio (NLR) (B), platelet/lymphocyte ratio (PLR) (C) and CEA level (D).*

elevated NLR (p=0.01) and elevated CRP (p<0.0001) as significant prognostic factors for poor OS. Multivariate analysis using a Cox proportional hazards model showed that pathological TNM stage III [ypN(+)] (Hazard Ratio (HR)=4.57 [95% confidence interval (CI)=1.65-12.67]; p=0.003) and elevated CRP (HR=8.04 [95% CI=2.48-26.08]; p=0.0005) were independent predictors of poor prognosis in patients with rectal cancer treated with CRT followed by TME (Table III).

Pre-CRT serum CRP is an independent predictor of recurrence in patients with rectal cancer undergoing CRT followed by TME. DFS curves for patients classified according to CEA and SIR markers before CRT are shown in Figure 2. Patients with elevated CRP and CEA levels had significantly poorer DFS than patients with levels below the cut-off values (log-rank test: CRP, p<0.0001; CEA, p=0.01) (Figure 2 A and D). In contrast, patients with elevated NLR or PLR also had poorer OS than those with lower values, but differences were not significant (log-rank test: NLR, p=0.1; PLR, p=0.26) (Figure 2 B and C). In univariate analysis, both elevated CEA (p=0.02) and CRP (p=0.0003) were significant predictive factors for poor DFS. Multivariate analysis using a Cox proportional hazards model showed that only elevated CRP (HR=4.56; 95% CI=1.66-12.49; p=0.003)

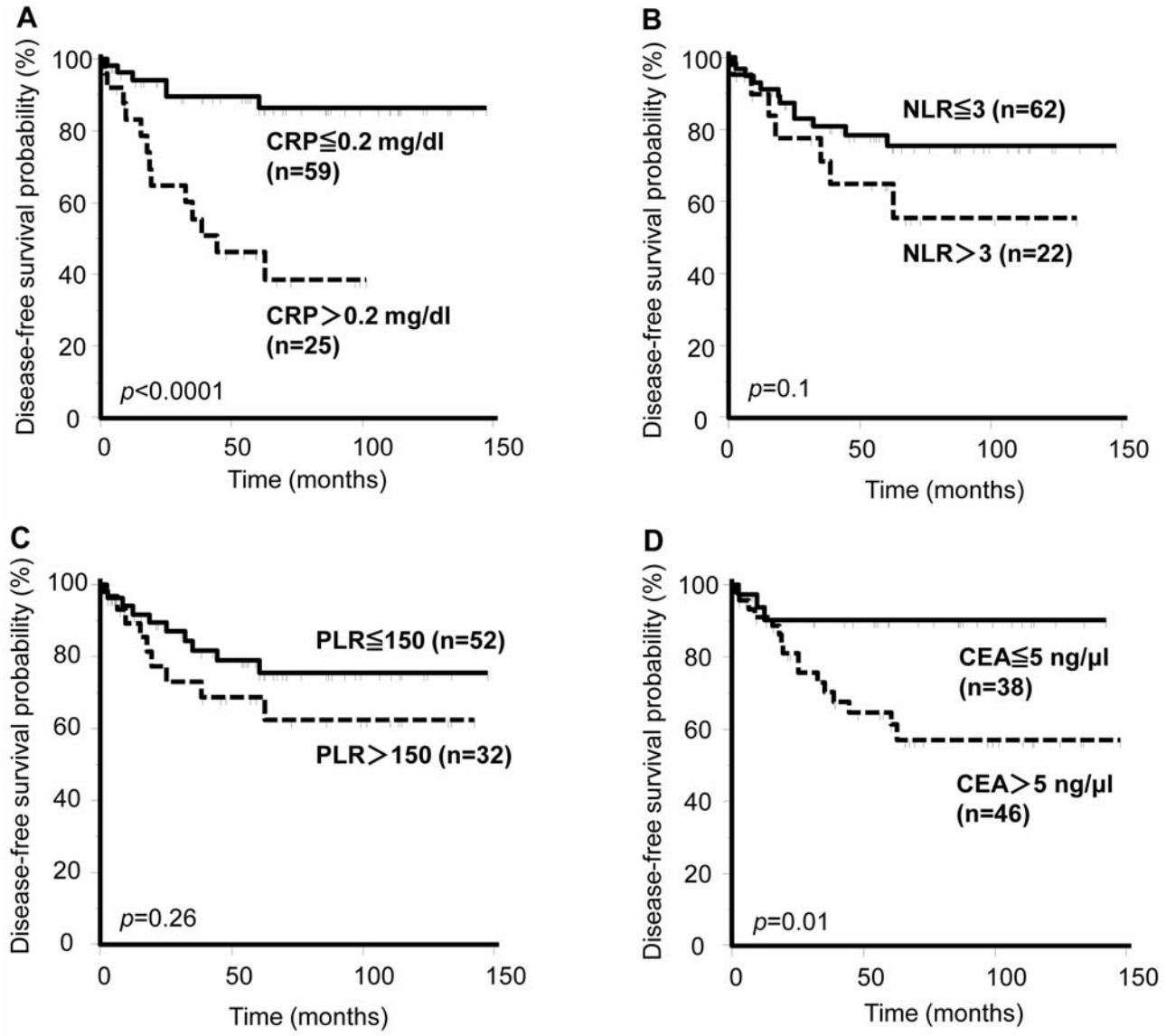

Figure 2. *Kaplan–Meier curves for disease-free Survival (DFS) classified according to Systemic Inflammatory Response (SIR) status and Carcinoembryonic antigen (CEA) level prior to chemoradiotherapy in patients with rectal cancer. DFS rates subdivided by C-reactive protein (CRP) level (A), neutrophil/lymphocyte ratio (NLR) (B), platelet/lymphocyte ratio (PLR) (C) and CEA level (D).*

was an independent predictive marker for early recurrence in patients with rectal cancer treated with CRT followed by TME (Table IV).

High pre-CRT CRP predicts recurrence in patients with pathological TNM stage I-II [ypN(–)] rectal cancer. We demonstrated that the clinical TNM stage before CRT was unable to predict for OS and DFS in patients with rectal cancer (Figure 3 A and B). In contrast, only pathological TNM stage predicted for early recurrence and poor prognosis in such patients undergoing CRT followed by surgery. Kaplan–Meier survival curves showed that pathological TNM stage III [ypN(+)] was associated with significantly lower probabilities of OS and DFS than pathological TNM stage I-II [ypN(–)] (OS, p=0.006; DFS, p=0.05; log-rank test) (Figure 3 C and D).

We also analyzed whether pre-CRT CRP could predict for early recurrence or poor prognosis in pathological TNM stages I-II [ypN(–)] and III [ypN(+)]. An elevated CRP level was associated with significantly poorer OS than a normal CRP level in pathological TNM stage III [ypN(+)] (p=0.0004; log-rank test) (Figure 4 B). Similarly, an elevated CRP level was associated with poorer DFS than a normal CRP level, although the difference was not significant

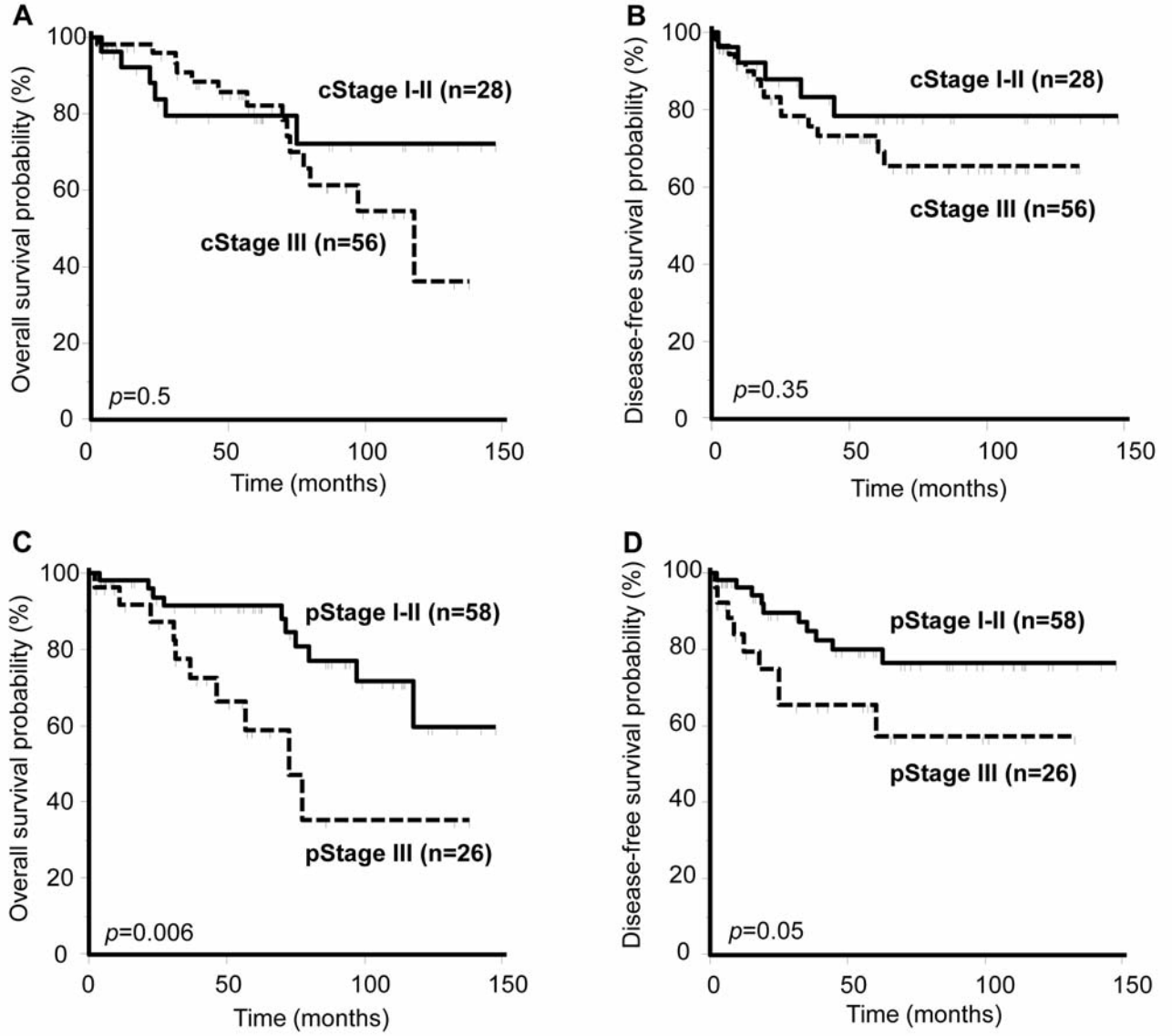

Figure 3. *Kaplan–Meier curves for Overall Survival (OS) and Disease-Free Survival (DFS) in patients with rectal cancer classified according to clinical TNM stage prior to chemoradiotherapy and pathological TNM stage of resected specimens. OS (A) and DFS (B) rates for patients with rectal cancer with clinical TNM stage I-II and those with stage III disease. OS (C) and DFS (D) rates for patients with rectal cancer with pathological TNM stage III [ypN(+)] and those with stage I-II [ypN(–)].*

(p=0.21, log-rank test) (Figure 4 D). However, an elevated CRP level was associated with significantly poorer OS and DFS than a normal CRP level in pathological TNM stage I-II [ypN(–)] (OS, p=0.0002; DFS, p<0.0001; log-rank test) (Figure 4 A and C).

Discussion

The pathological lymph node status in surgical specimens is known to be the most important factor predicting for long-term oncological outcomes in patients with rectal cancer treated with surgery alone (21-23). However, ypN stage remains the most important predictor of long-term outcomes in patients treated with pre-operative CRT (21-23). The German Intergroup trial showed that ypT, ypN, yp stage, tumor regression grade, and histological grade were significantly associated with DFS in univariate analysis, and ypN stage was the strongest prognostic factor for DFS in multivariate analysis (21). Similarly, Bujko *et al*. (22) and Kim *et al*. (24) reported that ypN was an independent prognostic factor for DFS and OS. We also demonstrated that patients with ypN-positive (pathological stage III) disease

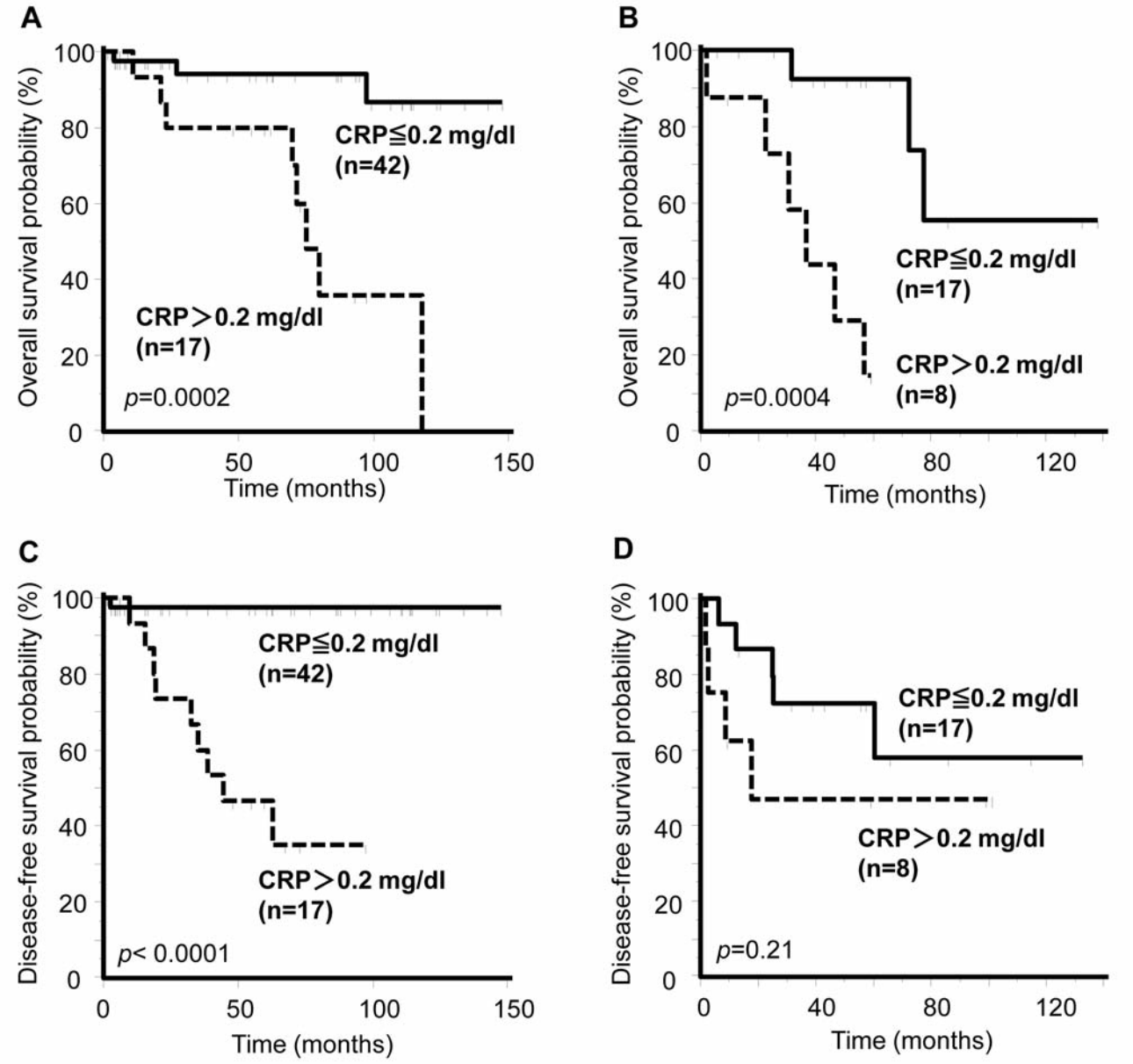

Figure 4. *Kaplan–Meier curves for Overall Survival (OS) and Disease-Free Survival (DFS) in patients with ypN(–) and ypN(+) rectal cancer classified according to C-Reactive protein (CRP) level before chemoradiotherapy. OS rates in ypN(–) (A) and ypN(+) (B) rectal cancer subdivided by CRP level. DFS rates in ypN(–) (C) and ypN(+) (D) rectal cancer subdivided by CRP level.*

had significantly poorer DFS and OS than those with ypN-negative (pathological stage I-II) disease, and ypN status was an independent prognostic factor predicting OS.

However, the oncological outcomes of patients who respond well to preoperative CRT for locally advanced rectal cancer (ypT1-2N0) are significantly poorer in terms of DFS and OS than those of patients with early rectal cancer (pT1-2N0), even if the final TNM stages are the same (25). Thus, some patients treated with CRT will be faulsely assessed as having good outcomes because their pathological N stage is modified from ypN-positive to -negative as a result of effective CRT. There is, therefore, a clear need to identify pre-CRT biomarkers for rectal cancer that do not depend on this staging system, and which will facilitate the identification of patients with a poor prognosis, and thus permit personalized treatment strategies in patients at high risk of tumor recurrence.

Previous investigators demonstrated the significance of the tumor marker CEA (26-29), absolute lymphocyte count (30), platelet count (31), NLR (32) and fibrinogen (33, 34) as potential pre-CRT biomarkers for predicting oncological

outcomes in patients with rectal cancer treated with CRT followed by TME. However, to the best of our knowledge, no studies have compared the prognostic values of pre-CRT SIR status markers (CRP, NLR and PLR) and CEA. The results of this study clearly demonstrate that elevated pre-CRT CRP, NLR and CEA levels in patients with rectal cancer treated with preoperative CRT were predictive of poorer OS. Multivariate analysis revealed that elevated CRP and ypN-positivity (pathological TNM stage III) were significant independent prognostic factors for poor OS, while elevated pre-CRT CRP and CEA levels also predicted for early recurrence of rectal cancer. Furthermore, multivariate analysis showed that only serum CRP was an independent predictor of DFS. Collectively, these results suggest that the pre-CRT CRP level is a promising biomarker for predicting early recurrence, and consequently poor prognosis, in patients with potentially curable rectal cancer undergoing CRT followed by TME.

Although systemic postoperative adjuvant chemotherapy has a clear role to play in the management of pathological stage III colon cancer, its value in locally advanced rectal cancer remains unclear, especially when pathological staging may be affected by preoperative CRT. In addition, the preoperative evaluation of tumor invasiveness and involved lymph nodes remains poor (35, 36), uncertainties over patient selection, poor compliance with adjuvant postoperative treatment (2), and lack of clarity over postoperative therapeutic utility in patients receiving CRT (37), indicate that alternative intensified preoperative treatment strategies may be needed. However, such approaches may be associated with toxicity, and careful patient selection is, therefore, clearly important. We demonstrated that elevated pre-CRT CRP levels were associated with postoperative recurrence or cancer-specific death in patients with pathological TNM stage I-II [ypN(–)] rectal cancer, and this may help to guide the selection of patients likely to benefit from postoperative chemotherapy. However, the value of CRP requires validation in a prospective, stratified phase III study prior to being accepted into routine clinical practice.

In conclusion, CRP, as a pre-CRT marker of SIR, can be determined from routine blood tests without the need for special techniques or expertise, and may represent an effective biomarker for predicting recurrence or poor prognosis in patients with rectal cancer undergoing CRT followed by TME.

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