ORIGINAL

New scoring system to create a prognostic criteria in colorectal carcinoma based on serum elevation of C-reactive protein and decrease in lymphocyte in peripheral blood

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Abstract : BACKGROUND. Both serum elevation of C-reactive protein (CRP) and reduction of lymphocyte in the peripheral blood has been known as indicator for malignant potential of human tumors. METHODS. Whether newly devised CLS (CRP/Lymphocyte Score), based on combined data of serum elevation of CRP and of lymphocyte percentage in the peripheral blood can be an indicator for progressive potential in colorectal carcinoma was examined in 280 cases who had been surgically treated. RESULTS. Significant difference in survival was observed both between CLS 0 and 1 and between CLS 1 and 2, in both cases when analyzed among whole patients and patient who had been treated with curative resection. Multivariate analysis among patients who had been treated with curative resection demonstrated that CLS (P < 0.0001), histologic type (P = 0.0003), and tumor stage (P = 0.039) were factors independently associated with worse prognosis of the patients. CONCLUSIONS. Newly devised criteria CLS could be an independent prognostic indicator in colorectal carcinoma and would be utilized as a helpful information. J. Med. Invest. 66 : 264-268, August, 2019

Keywords **:** *colorectal carcinoma, C-reactive protein, lymphocyte ratio, prognostic indicator*

INTRODUCTION

Serum elevation of C-reactive protein has been known as an indicator for aggressiveness of the tumor and/or patients' prognosis in malignant tumors of the digestive tracts such as gastric carcinoma (1) and esophageal carcinoma (2) as well as colorectal carcinoma (3, 4).

Decrease in lymphocyte in peripheral blood has been also reported to be correlated with malignant potential in colorectal carcinoma (5).

However, criteria based on the combined data of serum elevation of CRP and decrease in lymphocyte in peripheral blood in human tumors has not been presented.

In this study, we attempted to form a new scoring system to determine outcome of the patients with colorectal carcinoma based on combination of serum elevation of C-reactive protein and decrease in lymphocyte in peripheral blood.

PATIENTS AND METHODS

Patients, collection of blood samples, and measurement of C-reactive protein (CRP) and lymphocyte percentage in peripheral blood. Two hundred and eighty patients, composed of 165 men and 115 women, with colorectal carcinoma, which had been treated by surgical resection in our institute from 2004 to 2013, were enrolled in this study.

This study was approved by the institutional ethic committee of Fukuoka Higashi Medical Center.

Patients who have been suffering from other malignant tumors or other inflammatory diseases possibly causing the serum elevation of CRP were excluded from this study. Moreover there was no patients who had been treated with neoadjuvant therapy.

All blood samples to measure serum value of CRP were collected just before the operation. Patients who had the serum concentration of more than 1.0 mg/dL, as applied in our series of investigations (1-3), were regarded to have a serum elevation of CRP. And among Japanese, the normal range of lymphocyte percentage in peripheral blood has been described as 21.2-51.0% in male and 21.3-50.2% in female in Kanai's Manual of Clinical Laboratory Medicine widely utilized in most institution in Japan. Then. lymphocyte percentage in the peripheral blood of less than 20% were regarded to have a decrease in lymphocyte.

Pathologic investigation. Pathologic investigation was performed using TNM classification of malignant tumors prescribed by the International Union Against Cancer (6).

Definition of CLS (CRP/Lymphocyte Score). Patients who had both serum elevation of CRP and decrease in lymphocyte were allocated a CLS of 2. Patients who had each one and neither were allocated a CLS of 1 and 0, respectively (Table 1).

Follow-up of the Patients. The follow-up for patients was continued until their death and only patients who died of colorectal carcinoma were included in the tumor-related deaths. The period

Table 1. Chart to calculate CLS

	Serum elevation of C-reactive protein	
	Yes	No
Decrease in lymphocytes in peripheral blood		
Yes	2	1
No	1	0

CLS, CRP/Lymphocyte Score

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from the operation to the date of death was defined to be the survival time. The survival time ranged from one month to 8 years and 6 months with a mean of 3 years and 6 months.

Statistical Analysis. All statistical analyses were performed using StatView (SAS Institute Inc, Cary, NC). Chi-square test and *t* test were used to compare the difference regarding values in each CLS score. Survival curves were made by the Kaplan-Meier method, and the Mantel-Cox test was used to analyze the equality of the survival curves. Cox proportional hazards model in a forward stepwise manner was used to perform a multivariate analysis to determine the independent prognosticators. A *P* value of less than 0.05 was considered to demonstrate a significant difference.

RESULTS

Correlation of the CLS with clinicopathologic features was shown in Table 2. Significant difference was observed regarding depth of tumor ($P = 0.003$), stage of the tumor ($P = 0.0053$), and similarly, the rate of curative resection ($P = 0.021$).

The survival of CLS 1 patients with 5-year survival rate of 73.3% was significantly more unfavorable than that of CLS 0 patients with 5-year survival rate of 90.8% ($P = 0.003$). Prognosis of CLS 2 patients with 5-year survival rate of 43.2% was significantly worse than that of TRHRS 1 patients ($P = 0.015$, Fig. 1).

An analysis restricted to patients who had been treated with

Table 2. Relationship Between CLS and Patients' Clinicopathologic Characteristics

	CLS 0 (n = 178)	CLS 1 (n = 63)	CLS 2 (n = 39)	*P*-value
Sex				
Male	105 (59.0)	33 (52.4)	27 (69.2)	0.243
Female	73 (41.0)	30 (47.6)	12 (30.8)	
Age	69.6 ± 11.7	70.8 ± 10.9	71.0 ± 9.2	0.477
Location of tumor				
Colon	122 (68.5)	46 (73.0)	33 (84.6)	0.126
Rectum	56 (31.5)	17 (27.0)	6 (15.4)	
Depth of tumor				
T1, 2	62 (34.8)	12 (19.0)	4 (10.3)	0.0005
T3, 4	114 (65.2)	51 (81.0)	35 (89.7)	
Histology*				
Well	58 (32.6)	15 (23.8)	10 (25.6)	0.127
Moderately	109 (61.2)	41 (65.1)	26 (66.7)	
Poorly	11 (6.2)	7 (11.1)	3 (7.7)	
Nodal metastasis				
No	103 (57.9)	39 (61.9)	18 (46.2)	0.083
Yes	75 (42.1)	24 (38.1)	21 (53.8)	
Lymphatic invasion				
No	105 (59.0)	39 (61.9)	17 (43.6)	0.153
Yes	73 (41.0)	24 (38.1)	22 (56.4)	
Venous invasion				
No	133 (74.7)	50 (79.4)	28 (71.8)	0.654
Yes	45 (25.3)	13 (20.6)	11 (28.2)	
Tumor stage				
I	57 (32.0)	12 (19.1)	2 (5.2)	0.0053
II	45 (25.3)	21 (33.3)	14 (35.9)	
III	67 (37.6)	25 (39.7)	16 (41.0)	
IV	9 (5.1)	5 (7.9)	7 (17.9)	
Curability for resection				
Curative	169 (94.9)	58 (92.1)	32 (82.1)	0.021
Non-curative	9 (5.1)	5 (7.9)	7 (17.9)	

CLS, CRP/Lymphocyte Score
Values in the parenthesis are the percentages.
*Well, well differentiated adenocarcinoma ; Moderately, moderately differentiated adenocarcinoma ; Poorly, pooyly differentiated adenocarcinoma;

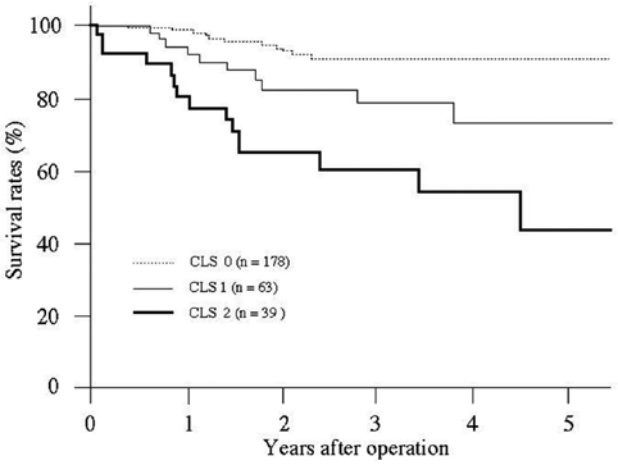

Fig. 1. CLS and survival curves among whole patients.
Significant difference was observed between survival of CLS 0 and 1 patients ($P = 0.030$) and between survival of CLS 1 and 2 patients ($P = 0.015$).

curative resection was additionally done (Table 3). A significant difference was observed regarding depth of tumor ($P = 0.003$) and stage of the tumor ($P = 0.013$).

The survival of CLS 1 patients with 5-year survival rate of 75.3% was significantly more unfavorable than that of CLS 0 patients with 5-year survival rate of 93.6% ($P = 0.002$). Prognosis of CLS 2 patients with 5-year survival rate of 45.2% was significantly worse than that of CLS 1 patients ($P = 0.030$, Fig. 2).

In univariate analysis among patients who had been treated with curative resection, CLS ($P < 0.0001$), lymphatic invasion ($P = 0.0005$), venous invasion ($P = 0.038$), histologic type ($P < 0.0001$) and tumor stage ($P = 0.0004$) were factors possibly to determine patients' prognosis. Multivariate analysis including all these factors demonstrated that CLS ($P < 0.0001$) as well as histologic type ($P = 0.0003$) and tumor stage ($P = 0.039$) were found to be factors independently associated with worse prognosis of the patients (Table 4).

Table 3. Relationship Between CLS and Clinicopathologic Characteristics of Patients Treated with Curative Resection

	CLS 0 (n = 169)	CLS 1 (n = 58)	CLS 2 (n = 32)	*P*-value
Sex				
Male	103 (60.9)	31 (53.4)	21 (65.6)	0.468
Female	66 (39.1)	27 (46.6)	11 (34.4)	
Age	70.0 ± 11.8	70.5 ± 11.2	72.0 ± 8.1	0.204
Location of tumor				
Colon	119 (70.4)	43 (74.1)	27 (84.4)	0.258
Rectum	50 (29.6)	15 (25.9)	5 (15.6)	
Depth of tumor				
T1, 2	62 (36.7)	12 (20.7)	4 (12.5)	0.005
T3, 4	107 (63.3)	46 (79.3)	28 (87.5)	
Histology*				
Well	56 (33.1)	15 (25.9)	9 (28.1)	0.679
Moderately	103 (61.0)	37 (63.8)	20 (62.5)	
Undifferentiated	10 (5.9)	6 (10.3)	3 (9.4)	
Nodal metastasis				
No	102 (60.4)	33 (56.9)	16 (50.0)	0.536
Yes	67 (39.6)	25 (43.1)	16 (50.0)	
Lymphatic invasion				
No	102 (60.4)	36 (62.1)	14 (43.8)	0.182
Yes	67 (39.6)	22 (37.9)	18 (56.2)	
Venous invasion				
No	130 (76.9)	48 (82.8)	24 (75.0)	0.592
Yes	39 (23.1)	10 (17.2)	8 (25.0)	
Tumor stage				
I	57 (33.7)	12 (20.7)	2 (6.2)	0.013
II	45 (26.6)	21 (36.2)	14 (43.8)	
III	67 (39.7)	25 (43.1)	16 (50.0)	

CLS, CRP/Lymphocyte Score
Values in the parenthesis are the percentages.

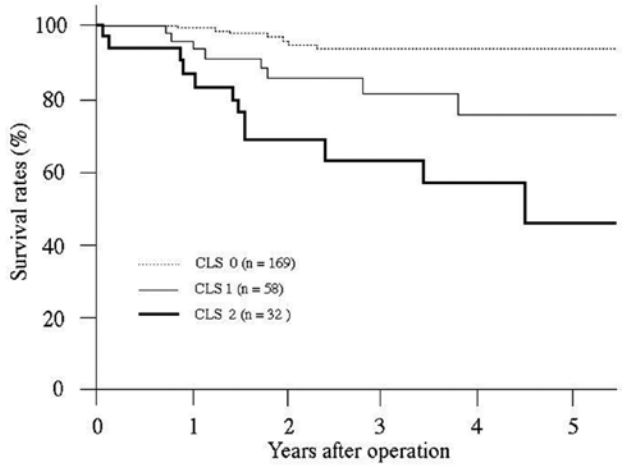

Fig. 2. CLS and survival curves among patients who had been treated with curative resection.
Significant difference was observed between survival of CLS 0 and 1 patients (P = 0.003) and between survival of CLS 1 and 2 patients (P = 0.030).

Table 4. Factors independently correlated with prognosis of the patients treated with curative resection

Variable	Hazard Ratio	P-value
CLS (0, 1 vs 2)	6.17 (2.74-13.9)	< 0.0001
Histologic type (Differentiated vs Undifferentiated)	5.88 (2.25-15.4)	0.0003
Stage of tumors (I, II vs III)	2.85 (1.05-7.76)	0.040

DISCUSSION

Serum elevation of C-reactive protein, an acute phase protein, has been known as a definitive indicator for aggressiveness of the tumor and/or patients' prognosis in malignant tumors including colorectal carcinoma (3, 4). Also other than the individual significance of serum elevation of CRP, cumulative scoring system, namely Glasgow prognostic score that can be constructed by serum elevation of CRP and hypoalbuminemia, has been demonstrated to stratify prognosis of patients with colorectal carcinoma (7-10). Moreover prognostic nutritional index constructed by the value of serum albumin and lymphocyte counts in the peripheral blood has been emphasized to be a prognostic indicator of colorectal carcinoma (11).

On the other hand, decrease in lymphocyte in the peripheral blood has been reported also to be an indicator to predict worse prognosis of patients with colorectal carcinoma (12).

A significant correlation between serum elevation of CRP and decrease in lymphocyte in the peripheral blood was found in this study, which is concomitant with the result reported in the previous investigation (13). Immunosuppressive condition of the tumor-bearing patients might cause both decrease in lymphocyte in the peripheral blood and serum elevation of CRP.

These findings promoted us to possibly construct a new criteria to determine a malignant potential and/or prognosis of patients with colorectal carcinoma based on the two elements, serum elevation of CRP and decrease in lymphocyte in peripheral blood, which similarly influence the prognosis of the patients with colorectal carcinoma.

Significant correlation between CLS and curability was observed, which could demonstrate an utility of CLS as an indicator for malignant potential of the tumor and preoperative predictor for possible curative resection of colorectal carcinoma.

Moreover, in this study, indeed, a significant correlation was found between CLS and an incidence of non-curative resection due to the co-existence of distant metastasis or peritoneal dissemination. Suppressed physical condition caused by the cachexia derived from far advanced carcinoma with distant metastasis could influence the both the values of serum level of CRP and lymphocyte ratio in the peripheral blood. Therefore, analysis restricted to the cases who had been treated with curative resection was additionally done and nevertheless the significance of CLS as an independent prognostic indicator in colorectal carcinoma was elucidated.

Incidentally, also from the multivariate analysis in the current study, pathological incidence of poorly differentiated colorectal carcinoma could contain more progressive potential, as having been reported in the previous study (4, 14).

In conclusion, this newly devised simple and convenient criteria, CLS, can be measured using a basic examinations would strictly classify the prognosis in colorectal carcinoma and would provide a beneficial information regarding the clinical course of patients with colorectal carcinoma.

DISCLOSURE

Authors declare that we have no financial interest or conflict of interest.

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