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Relationship Between Preoperative Erythrocyte Sedimentation Rate and Survival After Surgery in Patients with Colorectal Cancer

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Abstract. *Aim: To investigate the relationship between erythrocyte sedimentation rate (ESR) and postoperative survival of patients with colorectal cancer (CRC). Materials and Methods: Relationships between clinical characteristics and overall survival (OS) of patients with CRC were investigated using multivariate analysis. Receiver operating characteristics curve analysis was performed to decide the ideal cut-off values of clinical characteristics to divide patients into two groups, which were then compared using a survival curve analysis. Results: Three hundred and eleven patients with CRC undergoing surgery were enrolled. Multivariate analysis showed that ESR >40 mm/h (hazard ratio(HR)=2.601, 95% confidence interval(CI)=1.187-5.697; p=0.017) was associated with poorer OS, along with non-tubular pathology (p=0.034). Kaplan–Meier analysis revealed that patients with ESR >40 mm/h had poorer postoperative survival than those without ESR elevation (p<0.001). Conclusion: Preoperative elevation of ESR (>40 mm/h) can predict poorer postoperative survival in patients with CRC.*

In the past decade, several inflammation-based prognostic systems such as the Glasgow Prognostic Score (GPS) (1), modified GPS (mGPS) (2), neutrophil to lymphocyte ratio (NLR) (3) and reactive thrombocytosis have been established and investigated for their clinical roles in prognostication of a number of cancer types. McMillan and colleagues proposed that the systemic inflammatory response (SIR) reflects the magnitude of hypercytokinemia that underlies the interaction between a tumor and its host (4-6).

Although the erythrocyte sedimentation rate (ESR), like C-reactive protein (CRP), is a well-recognized marker of inflammation and inflammation-related diseases such as rheumatoid arthritis (7), Crohn's disease and ulcerative colitis (8), a similar relationship exists between ESR and cancer (9). Therefore, the ESR would also appear to have the potential to become part of an inflammation-based prognostic system. In fact, several studies have investigated this possibility. Although the results demonstrated that ESR can predict the postoperative survival of patients not only with Hodgkin's disease (10) but also renal cell cancer (RCC) (11, 12) and gastric cancer (13), few studies have investigated the clinical significance of ESR for prognostication of patients with colorectal cancer (CRC) (14, 15).

In the present study, we investigated the possibility of using the ESR as a novel and simple inflammation-based prognostic system for patients with CRC undergoing surgery at a Japanese university teaching hospital.

Materials and Methods

We conducted a retrospective review of a database comprising 311 patients (male: female=191: 120) who had undergone surgery for CRC. All procedures had been performed by the same surgical team at the Department of Gastroenterological Surgery, Dokkyo Medical University Hospital, between November 2009 and December 2014. Routine laboratory measurements including ESR and the serum levels of tumor markers such as carcinoembryonic antigen (CEA) (upper physiological value 5 ng/ml) (16) and carbohydrate antigen 19-9 (CA 19-9) (upper physiological value 37 U/ml) (17) were carried out on the day of admission in order to exclude any effects attributable to inflammation associated with sequential preoperative examinations. None of the patients had clinical evidence of infection or other inflammatory conditions except for one patient with ulcerative colitis severe dysplasia.

The ideal cut-off values for the clinical features were decided using receiver operating characteristic (ROC) curve analyses. These ideal cut-off values were based on the most prominent point on the

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Key Words: Colorectal cancer, erythrocyte sedimentation rate, inflammation-based prognostic system, systemic inflammatory response.

Table I. *Relationships between categorical clinical characteristics and the erythrocyte sedimentation rate (ESR) in patients with colorectal cancer.*

Variable	Patients, n (%)		*p*-Value*
	ESR≤40 mm/h (n=243)	ESR>40 mm/h (n=68)	
Age			
≤70 Years	144 (46)	34 (11)	0.173
>70 Years	99 (32)	34 (11)	
Gender			
Male	158 (51)	33 (11)	0.014
Female	85 (27)	35 (11)	
BMI			
≤25 kg/m^2	195 (63)	57 (18)	0.506
>25 kg/m^2	48 (15)	11 (4)	
Number of tumors			
1	216 (69)	64 (21)	0.203
≥2	27 (9)	4 (1)	
Maximum tumor diameter			
≤33 mm	78 (25)	10 (3)	<0.001
>33 mm	155 (50)	47 (15)	
Undetermined	10 (3)	11 (4)	
Tumor location			
Colon	154 (49)	49 (16)	0.184
Rectum	89 (29)	19 (6)	
Tumor type†			
0, 1, 2	197 (63)	43 (14)	<0.001
3, 4, 5	39 (13)	15 (5)	
Undetermined	7 (2)	10 (3)	
Type of surgery			
Open	101 (32)	39 (13)	0.021
Laparoscopic	142 (46)	29 (9)	
Chemotherapy			
Adjuvant	55 (18)	9 (3)	
Systemic	35 (11)	22 (7)	0.002
None	153 (49)	37 (12)	
Operative curability†			
A	201 (65)	37 (12)	
B	14 (4)	7 (2)	<0.001
C	28 (9)	24 (8)	
TNM stage			
0	7 (2)	3 (1)	
I	48 (16)	7 (2)	
II	61 (20)	15 (5)	
III	88 (28)	17 (5)	0.001
IV	37 (12)	26 (8)	
Undetermined	2 (1)	0 (0)	

BMI: Body mass index, TNM: tumor-nodes-metastasis. †According to the Japanese Classification of Colorectal Carcinoma (19). *Chi-squared test.

Table II. *Relationships between continuous clinicolaboratory characteristics and the erythrocyte sedimentation rate (ESR) in patients with colorectal cancer. Data are the mean±SD.*

Variable	ESR≤40 mm/h (n=243)	ESR>40 mm/h (n=68)	*p*-Value*
Age (years)	68±12	71±10	0.07
Number of tumors	1.1±0.5	1.1±0.4	0.946
Maximum tumor diameter (mm)	43±21	68±26	<0.001
WBC (×10^3/mm^3)	6.8±2.7	7.7±2.9	0.006
CRP (mg/dl)	0.5±1.2	3.1±4.1	<0.001
Albumin (g/dl)	3.7±0.5	3.2±0.7	<0.001
CEA (ng/ml)	25±148	68±193	<0.001
CA19-9 (U/ml)	104±595	302±820	0.094
BMI (kg/m^2)	23±3.2	22±3.8	0.002
Survival period (days)	1414±841	1104±1031	0.001

BMI: Body mass index, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, CRP: C-reactive protein, WBC: white blood cell count. *Mann-Whitney *U*-test.

ROC curve for sensitivity and 1−specificity, respectively. The ideal cut-off values were then defined using the Youden index [maximum (sensitivity−(1−specificity))] (18). The area under the ROC (AUROC) curve was also calculated.

The ideal cut-off value for ESR was based on the most prominent point on the ROC curve for sensitivity (0.471) and specificity (0.812), respectively. Because these two parameters indicated 41.5, the ideal cut-off value for ESR was defined as 40. The area under the ROC curve was 0.690.

Univariate analysis was performed to evaluate clinical characteristics including age (>70/≤70, years), sex (female/male), body mass index (BMI), number of tumors, maximum tumor diameter, tumor location, tumor type, pathology, lymphatic invasion, venous invasion, operation time, bleeding volume, white blood cell (WBC) count, platelet count, ESR and the serum levels of CRP, albumin, CEA and CA19-9 in relation to overall survival (OS).

Multivariate analysis was then performed using preoperative clinical characteristics with a p value of less than 0.05 that had been selected by univariate analysis to assess those that were predictive of OS.

Kaplan–Meier analysis and log-rank test were used to compare the survival curves of the two groups divided by the ideal ESR cut-off value (>40/≤40 mm/h).

Definition of operative curability. The Japanese Classification of Colorectal Carcinoma (Japanese Society for Cancer of the Colon and Rectum, Second English Edition) (19) uses the following categories for residual tumor status: R0, No residual tumor; R1, no residual tumor, but tumor suspected at the resection margin; R2, macroscopically evident residual tumor. On the basis of this definition, operative curability is defined as: Curability A, R0 in tumor-nodes-metastasis (TNM) stage I, II or III; curability B, R0 in TNM stage IV or R1 in any TNM stage; curability C, R2 in any TNM stage.

Definition of macroscopic tumor types. Similarly, according to the Japanese Classification of Colorectal Carcinoma (19), macroscopic tumor types are classified as: Type 0, superficial type; type 1, polypoid type; type 2, ulcerated type with a clear margin; type 3, ulcerated type with infiltration; type 4, diffusely infiltrating type; and type 5, unclassified type.

Statistical analysis. Data are presented as mean±SD (standard deviation). Differences among the groups were analyzed using the chi-squared test and Mann–Whitney *U*-test. Hazard ratios (HRs)

Table III. *Univariate analysis in relation to overall survival of patients with colorectal cancer.*

Variable	Comparator *vs*. referent	Hazard ratio	95% CI	*p*-Value
Age	>70 *vs*. ≤70 Years	1.047	0.523-2.095	0.896
Gender	Female *vs*. male	1.408	0.715-2.773	0.322
BMI	>25 *vs*. ≤25 kg/m^2	0.653	0.252-1.692	0.381
Number of tumors	≥2 *vs*. 1	0.470	0.112-1.967	0.301
Maximum tumor diameter	>33 *vs*. ≤33 mm	3.705	1.104-12.43	0.034
Tumor location	Colon *vs*. rectum	2.006	0.906-4.440	0.086
Tumor type	3, 4, 5 *vs*. 0 1 2	2.571	1.114-5.778	0.022
Pathology	Other *vs*. tub1 or tub2	3.803	1.439-10.05	0.007
Lymphatic invasion	ly1, 2, 3 *vs*. ly0	3.948	0.930-16.76	0.063
Venous invasion	v1, 2, 3 *vs*. v0	2.527	0.865-7.380	0.090
Operative time	>125 *vs*. ≤125 min	0.217	0.103-0.455	<0.001
Bleeding volume	>80 *vs*. ≤80 ml	2.005	1.017-3.952	0.045
WBC	>7.25 *vs*. ≤7.25×10^3/mm^3	2.486	1.267-4.879	0.008
CRP	>0.48 *vs*. ≤0.48 mg/dl	7.627	3.407-17.08	<0.001
Albumin	≥3.5 *vs*. <3.5 g/dl	0.222	0.112-0.438	<0.001
CEA	>9.4 *vs*. ≤9.4 ng *vs*. ml	4.026	2.040-7.923	<0.001
CA19-9	>35 *vs*. ≤35 U/ml	3.695	1.863-7.328	<0.001
Platelet count	>30 *vs*. ≤30×104/mm^3	1.544	0.787-3.030	0.206
ESR	>40 *vs*. ≤40 mm/h	4.754	2.406-9.393	<0.001

95% CI: 95% Confidence interval, BMI: body mass index, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, WBC: white blood cell.

Table IV. *Multivariate analysis in relation to overall survival of patients with colorectal cancer.*

Variable		Hazard ratio	95% CI	*p*-Value
Pathology	Other *vs*. tub1 or tub2	2.904	1.082-7.793	0.034
WBC	>7.25 *vs*. ≤7.25×10^3/mm^3	1.475	0.691-3.147	0.315
CEA	>9.4 *vs*. ≤9.4 ng *vs*. ml	2.041	0.849-4.908	0.111
CA19-9	>35 *vs*. ≤35 U/ml	1.768	0.711-4.398	0.220
ESR	>40 *vs*. ≤40 mm/h	2.601	1.187-5.697	0.017

CEA: Carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, WBC: white blood cell.

with 95% confidence interval (95% CI) were calculated by uni-or multivariate analysis using the Cox proportional hazards model.

Kaplan–Meier analysis and log-rank test were used for comparison of survival curves. Deaths prior to 31st December 2014 were included in this analysis.

Statistical analyses were performed using the SPSS statistical software package, version 20 (IBM, Armonk, NY, USA) at a significance level of $p<0.05$.

Results

A total of 311 patients were enrolled [male: female=191 (61.4%): 120 (38.6%)]. There were 243 (78.1%) patients with ESR ≤40 mm/h and 68 (21.9%) with ESR >40 mm/h.

Table I shows the distribution of the categorical background clinical characteristics of the studied patients in the two groups divided according to the ESR. There were no significant differences between the groups, except for there being more males ($p=0.014$), greater maximum tumor diameter ($p<0.001$), tumor types 0, 1, 2 and 3 ($p<0.001$), more frequent laparoscopic surgery ($p=0.021$), lack of chemotherapy ($p=0.002$), operative curability A ($p<0.001$) and TNM stages I-III ($p<0.001$) in the group with ESR ≤40 mm/h (chi-squared test).

Table II shows the relationships between the continuous clinicolaboratory characteristics and ESR. There were no significant differences between the groups except maximum tumor diameter ($p<0.001$), WBC count ($p=0.006$), serum CRP ($p<0.001$) and CEA ($p<0.001$) were significantly lower, while BMI ($p=0.002$) and serum albumin ($p<0.001$) were higher, and the survival period ($p=0.001$) was significantly longer (Mann–Whitney *U*-test).

During the observation period, 34 (10.9%) patients died, among whom 10 (29.4%) died of intercurrent disease.

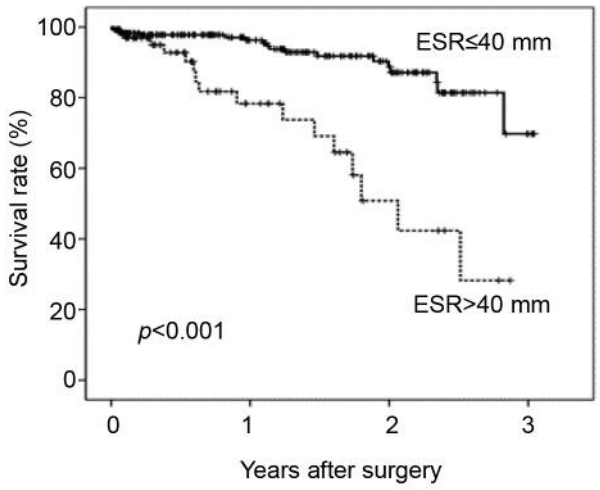

Figure 1. *Overall survival of patients with colorectal cancer undergoing surgery according to erythrocyte sedimentation rate (ESR).*

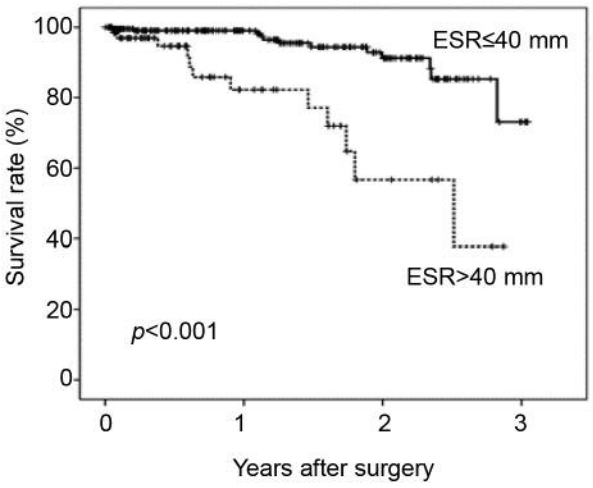

Figure 2. *Cancer-specific survival of patients with colorectal cancer undergoing surgery according to erythrocyte sedimentation rate (ESR).*

Univariate and multivariate analyses were performed to evaluate the relationship between clinical characteristics and OS.

The results of univariate analyses demonstrated that maximum tumor diameter >33 mm (p=0.034), tumor type 3-5 (p=0.022), non-tubular pathology (p=0.007), operative time >125 min (p<0.001), bleeding volume >80 ml (p=0.045), WBC count >7.25×10^3/mm^3 (p=0.008), serum CRP >0.48 mg/dl (p<0.001), albumin ≥3.5 g/dl (p<0.001), CEA >9.4 ng/ml (p<0.001) and CA19-9 >35 U/ml (p<0.001) and ESR >40 mm/h (p<0.001) were associated with poorer OS (Table III).

Multivariate analysis was performed using the preoperative characteristics shown to have statistical significance (p<0.05) by univariate analysis, except for CRP and albumin because clinical evidence had been established by previous studies for these two inflammation-related variables (1, 4, 20). The results of multivariate analysis demonstrated that ESR >40 mm/h was associated with poorer OS (p=0.017) along with non-tubular pathology (p=0.034) (Table IV).

The mean±SD follow-up period was 390±312 days; the median and maximum follow-up periods for survivors were 317 and 1111 days, respectively.

The mean±SD duration of survival after surgery was significantly longer for the group of patients with ESR≤40 mm/h (1414±841 days) than that for those with ESR of >40 mm/h (1104±1031 days) groups (p=0.001, Mann–Whitney *U*-test).

Kaplan–Meier analysis and log-rank test demonstrated OS (Figure 1) and cancer-specific survival (Figure 2) to be significantly better for those with ESR≤40 mm/h (p<0.001). Thus, ESR was able to clearly classify patients into two independent groups before surgery.

Discussion

Serum CEA is a well-known and broadly used tumor marker for patients with CRC (21,22). However, although the results of ROC curve analysis revealed that the AUROC for ESR and CEA were almost the same (ESR=0.690, CEA=0.694, data not shown), multivariate analysis demonstrated that, as well as non-tubular pathology, ESR was superior to CEA as a preoperative prognostic factor. A recent study showed that approximately 55% (271/491) of patients with CRC undergoing elective surgery had a normal preoperative serum level of CEA (23) and among them, some had a poor outcome due to advanced stage. Therefore, ESR would be capable of distinguishing such patients with CRC with a normal CEA level before surgery, because patients with CRC with ESR>40 mm/h had a significantly poorer outcome than those with ESR≤40 mm/h.

Estimation of ESR is not only simple but also less costly than commonly used tumor markers such as CEA and CA19-9. However, it is difficult to diagnose a specific disease on the basis of ESR elevation alone because this is observed in various pathophysiological conditions. At present, ESR elevation can be estimated quickly within 1 min (13). The cut-off value of ESR is known to show a gender difference (24). However, the effect of such difference was ignored in the present study because the ESR cut-off value for patients with CRC was much higher than that for patients with normal ESR. In this study, the ideal cut-off value for ESR was defined as 40 mm/h. A recent study of patients with gastric cancer used an ESR cut-off value of 10 mm/h in men and 20 mm/h in women and found there was a significant difference in survival between patients with increased and decreased ESR (p=0.023) (13). On the other hand, another

study of patients with RCC defined an abnormal ESR as more than 22 mm/h in males and more than 29 mm/h in females (12). Thus, the recommend cut-off value for ESR differed not only in relation to gender but also the type of cancer studied. However, a meta-analysis of RCC concluded that the cut-off value range was 20-50 mm/h (11). Therefore, the ESR cut-off value defined in the present study was considered to be within the acceptable range.

The ESR is affected by several conditions. Firstly, in order for the ESR to increase, there must be an increase in positively charged molecules such as immunoglobulin and fibrinogen (25). B-Cells differentiate into plasma cells, which produce immunoglobulins as a result of the SIR, which results from tumor *versus* host interaction. Fibrinogen is also produced as a result of tumor necrosis. In fact, patients who have an elevated ESR are more likely to have tumors with adverse pathological features, such as coagulative tumor necrosis, than those in whom the ESR is normal (46.7% *vs*. 11.5%; $p<0.001$) (12). Secondly, in order for the ESR to decrease, there must be an increase in negatively charged molecules such as albumin (26). Thirdly, the ESR is also affected by anemia. In a study of patients with clear-cell RCC, Sengupta *et al*. reported that a higher proportion of those with anemia had an elevated ESR relative to those with a normal ESR (66% *vs*. 12%; $p<0.001$) (12). Consequently, it is suggested that an elevated ESR indicates not only chronic inflammation, but also hypercytokinemia-hyperglobulinemia due to tumor *versus* host interaction.

An elevated ESR suggests that a patient is more likely to have more advanced cancer than one in whom the ESR is not elevated; Table II shows that patients with ESR >40 mm/h had a larger tumor diameter, higher levels of CEA and CRP, and a lower level of albumin than those with ESR ≤40 mm/h. Moreover, patients with ESR >40 mm/h had a significantly poorer outcome than those with ESR≤40 mm/h (Figures 1 and 2). Therefore, ESR would appear to be an independent prognostic factor for patients with CRC.

A recent study also reported that ESR was significantly increased in patients with Dukes' C or D than in those with Dukes' A or B CRC, and that patients with an elevated ESR had a significantly poorer outcome than those without an elevated ESR (14). Although multivariate analysis in another study using a low ESR cut-off value (15 mm/h) demonstrated no relationships between ESR and disease-related survival parameters, there were significant differences in disease-free survival and disease-specific survival between patients with ESR >15 mm/h and those with ESR ≤15 mm/h, respectively (15). The result of our multivariate analysis clearly demonstrated that ESR was associated with OS.

It has been reported that obesity (27), intake of red meat (28), alcohol consumption and smoking (29) are well-known risk factors for CRC. Chronic inflammation has also been pointed out as a CRC risk factor (30, 31). Kantor *et al*. reported that adolescent males with an elevated ESR had a 63% higher risk of CRC than those without an elevated ESR (HR=1.63, 95% CI=1.08-2.45; $p=0.006$) (32). Thus, ESR would be useful for not only prognostication in patients with CRC, but also as an indicator of increased risk for CRC development.

In the clinical field, because patients with a preoperative ESR of >40 mm/h are considered to be a high-risk group for CRC, the preoperative treatment strategy employed for them is very important. We propose the following treatment strategies for such patients with ESR >40 mm/h: Patients with stage I CRC should undergo postoperative surveillance at frequent intervals; those with stage II should receive adjuvant chemotherapy using capecitabine or tegafur-uracil; those with stage III should receive stronger adjuvant chemotherapy such as folinic acid-fluorouracil-oxaliplatin (FOLFOX); and those with stage IV should receive neoadjuvant chemotherapy for colon cancer or neoadjuvant chemoradiation therapy for rectal cancer, and then systemic chemotherapy and strict surveillance should also be performed after surgery. All of these strategies should improve the prognosis of patients with CRC, especially those with a preoperative ESR of >40 mm/h.

In conclusion, preoperative elevation of the ESR (>40 mm/h) can predict poorer postoperative survival in patients with CRC. The present findings may be significant in the context of surgical decision making for such patients.

Disclosure of Ethical Statements

This study had the approval of the Institutional Review Board (provided ID number: 28025) and conformed to the Ethical Guidelines for Clinical Research of the Ministry of Health, Labour and Welfare, Japan (http://www.mhlw.go.jp/seisakunitsuite/bunya/hokabunya/kenkyujigyou/i-kenkyu/index.html).

Conflicts of Interest

All Authors have no conflicts of interest in regard to this study.

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