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Prognostic significance of carbohydrate antigen 19-9 (CA19-9) change during immediate postoperative periods in patients with stage I–III colorectal cancer

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Purpose: Although carbohydrate antigen 19-9 (CA19-9) may exhibit low sensitivity in tumor screening, its prognostic significance has been highlighted. This study assessed the significance of preoperative CA19-9 and early postoperative CA19-9 levels in patients with nonmetastatic colorectal cancer (CRC).

Methods: Patients diagnosed with stage I–III CRC between January 2004 and April 2014 were included. Preoperative CA19-9 was assessed within 2 months of operation, whereas postoperative CA19-9 was measured 4 to 7 days after operation. The optimal cutoff values for preoperative and postoperative CA19-9 were established to maximize the differences in overall survival. Patients were categorized into 3 groups based on the CA19-9 change (CA19-9 trend): group 1, low preoperative CA19-9; group 2, high preoperative and low postoperative CA19-9; and group 3, high preoperative and postoperative CA19-9. The discriminatory powers of all variables were compared using the concordance index.

Results: A total of 816 patients were included. The determined cutoff values for preoperative and postoperative CA19-9 were 18.9 and 21.4 U/mL, respectively. Subgroup dichotomization revealed associations of preoperative CA19-9, postoperative CA19-9, and CA19-9 trend with overall survival in univariable analysis. The CA19-9 trend emerged as an independent prognostic factor in the multivariable analysis (group 1 vs. group 2: hazard ratio, 1.682 [95% confidence interval (CI), 1.043–2.710], P = 0.032; group 1 vs. group 3: hazard ratio, 2.882 [95% CI, 1.899–4.371], P < 0.001). The concordance index value of the CA19-9 trend (0.636; 95% CI, 0.509–0.682) surpassed those of preoperative and postoperative CA19-9.

Conclusion: The amalgamation of preoperative and postoperative CA19-9 levels demonstrated enhanced prognostic stratification, allowing for a more detailed classification of patients with nonmetastatic CRC.

Keywords: Colorectal neoplasms; CA-19-9 antigen; Survival

INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent type of cancer worldwide and the third leading cause of death in Korea [1, 2]. The treatment of CRC primarily involves surgery, chemotherapy, and radiation therapy. Presently, treatment strategies predominantly rely on accurate diagnosis before surgery and staging after surgery [3]. However, despite diverse alterations in postoperative chemotherapy for patients with stage IV CRC, treatment strategies for nonmetastatic CRC, such as stage II or III, have remained

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static over the last 2 decades [4]. Even with precise treatment according to the guidelines, a considerable number of patients with stage I–III disease experience recurrence [5, 6]. Furthermore, the prognosis may vary slightly, even among patients at the same stage, when examined in detail. Despite this awareness, the practice of confirming and selecting appropriate treatments is still not widely implemented [7, 8].

There is abundant research on numerous indicators for predicting the prognosis of patients with nonmetastatic CRC. Reports suggest that patient prognosis varies according to molecular genetic characteristics, and recent studies have increasingly focused on factors such as circulating tumor cells [9]. However, this recent trend faces practical limitations in its application to all patients due to the relatively high costs involved in conducting such tests. Conversely, readily measurable indicators, such as the well-known carcinoembryonic antigen (CEA) serum marker specific to CRC, as well as various inflammation-related markers and body composition metrics that are easily measurable on computed tomography scans of patients with CRC, are considered advantageous because of their relatively easy accessibility [10, 11].

In contemporary CRC treatment, carbohydrate antigen 19-9 (CA19-9) serves as an additional tumor marker alongside CEA. Typically produced by normal human pancreatic and biliary ductal cells as well as by the gastric, colon, endometrial, and salivary epithelia, CA19-9 is found in minimal quantities in the bloodstream and may be upregulated in various benign gastrointestinal disorders [12]. Crucially, a significant increase in plasma levels was observed under neoplastic conditions. Although CA19-9 may exhibit lower sensitivity in tumor screening, certain studies have highlighted its prognostic importance. According to Lee et al. [13], for patients with elevated preoperative CA19-9, CA19-9 serves as a valuable prognostic and diagnostic indicator for CRC and can enhance sensitivity as a complementary marker alongside CEA. Several studies also have demonstrated that higher preoperative CA19-9 was associated with poor survival in patients with CRC [14, 15]. To date, research on CA19-9 levels has predominantly utilized preoperative CA19-9 levels. A recent study indicated that dynamic monitoring of the levels of CEA and CA19-9 could serve as a high-risk factor in patients with stage II colon cancer, with postoperative CEA/CA19-9 measured before commencing adjuvant chemotherapy or within 6 weeks of the surgery [16]. However, data on the effect of changes in CA19-9 levels immediately after surgery (within 7 days of surgery) on prognostic prediction are limited.

This study aimed to determine the cutoff values for preoperative CA19-9 and early postoperative CA19-9 levels in patients with nonmetastatic CRC. Primarily, we examined the prognostic importance of early changes in preoperative and postoperative CA19-9 levels in our study cohort.

METHODS

Ethics statement

This study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine, with a waiver of informed consent (No. 3-2023-0064). The study protocol followed the principles of the Declaration of Helsinki.

Study population

This was a retrospective, single-institution study of patients who underwent curative colorectal surgery at Gangnam Severance Hospital, Yonsei University College of Medicine (Seoul, Korea), between August 2004 and March 2014. A total of 1,674 patients who underwent surgery during the study period were initially selected. The exclusion criteria were as follows: (1) neuroendocrine tumor, gastrointestinal stromal tumor, or other types of carcinoma such as anal and appendiceal cancer; (2) stage 0, stage IV, or no information of stage; (3) underwent preoperative chemoradiotherapy or emergency operation, or diagnosed with familial adenomatous polyposis, hereditary nonpolyposis CRC, Crohn disease, or double primary cancer; and (4) unavailability of preoperative CEA or postoperative CA19-9 measured on postoperative days 4 to 7. Finally, 816 patients were included in this study (Fig. 1).

Measurement of CA19-9

CA19-9 values were measured before and after surgery. The preoperative CA19-9 level was usually measured within 2 months before the surgery, mostly with preoperative evaluation. Postoperative CA19-9 levels were measured 4 to 7 days after operation. The CA19-9 measurement immunologic analyzer was changed once during the study period. The Roche Modular E170 (Roche Diagnostics Operations) was used, and afterward, the Beckman Coulter UniCel DxI 800 (Beckman Coulter Inc) was used for the analysis. The agreement between the 2 machines is already well established [17]; therefore, in our study, we used both techniques without distinguishing.

Defining the cutoff value of CA19-9

We determined the cutoff values for preoperative and postoperative CA19-9 from our data (Supplementary Fig. 1). The maximally differentiated survival between patients was measured using the X-tile program (Rimm Lab, Yale University) [18]. The X-tile program is a well-known tool that identifies the most appropriate cutoff value for specific parameters.

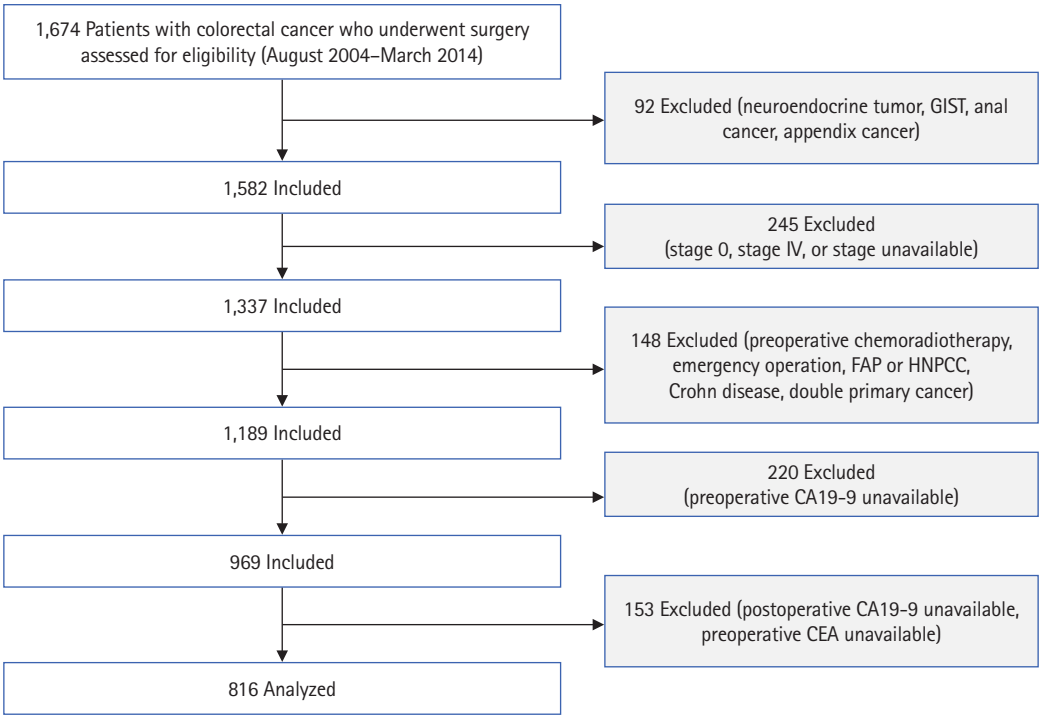

Fig. 1. Study flowchart. GIST, gastrointestinal stromal tumor; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

Defining of CA19-9 trend

Based on the combinations of preoperative and postoperative CA19-9 into low and high groups, the patients were initially classified into 4 groups. Subsequently, there was no significant difference in survival between the low preoperative CA19-9 with low postoperative CA19-9 group and the low preoperative CA19-9 with high postoperative CA19-9 group (Supplementary Fig. 2). Based on this result, we categorized the patients into 3 groups, defined with the CA19-9 trend: group 1, low preoperative CA19-9; group 2, high preoperative and low postoperative CA19-9; and group 3, high preoperative and postoperative CA19-9.

Statistical analysis

The primary endpoint was overall survival (OS), which was defined as the time from the initial day of surgery to death from any cause or the last follow-up date, with a limit of 5 years. Patients with OS periods exceeding 5 years were considered censored. The association between OS and clinicopathological factors was examined using univariable and multivariable analyses. Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model. Variables with a significance level of $P < 0.05$ in the univariable analysis were included in the multivariable analysis with backward elimination of variables. The Kaplan-Meier method and log-rank test were used to analyze the dependence of OS on preoperative CA19-9, postoperative CA19-9, and CA19-9 trend. Disease-free survival (DFS) was defined as the time from the date of surgery to the date of detection of recurrence or any cause of death or last follow-up date.

The prognostic predictive capabilities of preoperative CA19-9, postoperative CA19-9, and CA19-9 trend were assessed and compared using Harrell concordance index (C-index). Variations in predictive performance among different CA19-9 categories were determined using bootstrapping.

All analyses were performed using R ver. 4.2.1 (R Foundation for Statistical Computing). Statistical significance was set at $P < 0.05$.

RESULTS

Restricted cubic spline curve of OS according to preoperative and postoperative CA19-9

To clarify the relationship between CA19-9 levels and survival rates, we constructed restricted cubic spline curves. We observed that higher CA19-9 levels before and after surgery corresponded to an increased hazard ratio (Fig. 2). From this graph, we can infer that the levels of CA19-9 are associated with survival rate.

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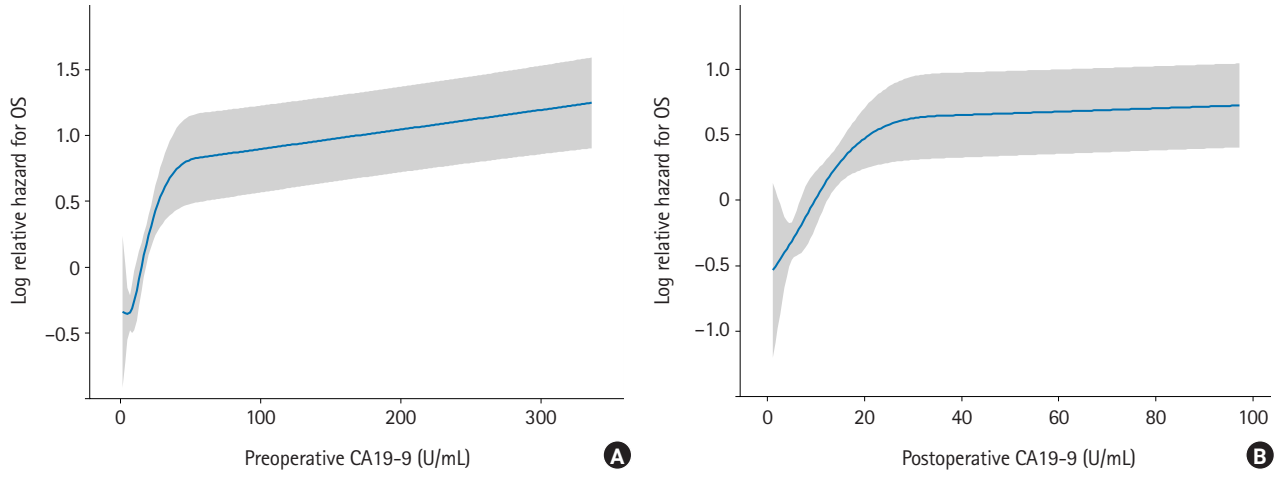

Fig. 2. Restricted cubic spline curve of overall survival (OS) according to (A) preoperative and (B) early postoperative carbohydrate antigen 19-9 (CA19-9) levels.

Optimal cutoff values

The determined cutoff values for preoperative and postoperative CA19-9 were 18.9 and 21.4 U/mL, respectively (Supplementary Fig. 1).

Comparison of patient characteristics according to preoperative and postoperative CA19-9

Between the low and high preoperative CA19-9 groups, age (P = 0.010), CEA level (P < 0.001), tumor size (P < 0.001), histologic grade (P = 0.003), lymphovascular invasion (LVI; P = 0.004) and tumor stage (P < 0.001) were significantly different. For the low and high postoperative CA19-9 groups, CEA (P < 0.001), histologic grade (P = 0.010), LVI (P = 0.004), and tumor stage (P = 0.003) had differed (Supplementary Table 1).

Patient characteristics according to CA19-9 trend

Baseline characteristics were compared among the 3 CA19-9 trend groups. Patients in groups 2 and 3 had a higher proportion of elevated preoperative CEA levels, larger tumor size, and more frequent LVI (all P < 0.001) compared to group 1. High-grade histology was also more common in group 3 (P = 0.003), and the proportion of stage III disease increased from group 1 to group 3 (P < 0.001). Other factors, including sex, body mass index (BMI), tumor location, complications, lymph node retrieval, and chemotherapy status, showed no significant differences (Table 1).

Kaplan-Meier survival curve analysis

Kaplan-Meier survival curve analysis confirmed that higher CA19-9 levels, both before and after surgery, were associated with lower survival rates. There were significant differences in the 5-year OS rates between the low and high groups based on preoperative CA19-9 (88.2% vs. 71.3%, P < 0.001) and postoperative CA19-9 (86.3% vs. 67.6%, P < 0.001) (Supplementary Fig. 2). The CA19-9 trends showed that the survival rate decreases in the order of group 1, group 2, and group 3 (88.2% vs. 77.6% vs. 64.1%, P < 0.001) (Fig. 3).

In the Kaplan-Meier analysis of DFS according to CA19-9 trend groups, group 3 showed the poorest prognosis, followed by group 2 and group 1. The overall difference among the 3 groups was statistically significant (P < 0.001). Pairwise comparisons revealed that group 1 had significantly better DFS than both group 2 (P = 0.019) and group 3 (P < 0.001), and group 2 also had significantly better outcomes compared to group 3 (P = 0.006) (Supplementary Fig. 3).

Univariable and multivariable analysis

Univariable Cox proportional hazards regression revealed that older age (≥ 70 years), lower BMI (< 25 kg/m^2), elevated CEA levels, larger tumor size (≥ 5 cm), postoperative complications, poor histologic differentiation (grade 3, mucinous adenocarcinoma, signet-ring cell), presence of LVI, advanced tumor stage (stage III), and the CA19-9 trend were significantly associated with OS (Table 2). Among the CA19-9 trend groups, group 3 demonstrated the highest risk of mortality in the univariable analysis (HR, 4.033; P < 0.001).

In the multivariable analysis, which adjusted for all variables significant in the univariable analysis, the CA19-9 trend remained an independent prognostic factor for OS. Compared to group 1 (reference), group 3 exhibited the highest risk (HR, 2.882; P < 0.001), while group 2 also showed a significantly increased risk (HR, 1.682; P = 0.032). Additionally, older age, lower BMI, postoperative complications, and stage III disease remained significant predic-

Table 1. Patient characteristics according to the CA19-9 trend (n = 816)

Characteristic	Group 1 (n = 589)	Group 2 (n = 121)	Group 3 (n = 106)	P-value
Sex				0.996
Female	232 (39.4)	58 (47.9)	44 (41.5)	
Male	357 (60.6)	63 (52.1)	62 (58.5)	
Age (yr)				0.015
< 70	413 (70.1)	77 (63.6)	60 (56.6)	
≥ 70	176 (29.9)	44 (36.4)	46 (43.4)	
Body mass index (kg/m^2)	23.6 ± 3.0	23.3 ± 3.4	23.8 ± 3.6	0.450
CEA (ng/mL)				< 0.001
< 5	485 (82.3)	60 (49.6)	47 (44.3)	
≥ 5	104 (17.7)	61 (50.4)	59 (55.7)	
Tumor location				0.093
Right colon	132 (22.4)	27 (22.3)	33 (31.1)	
Left colon	255 (43.3)	62 (51.2)	38 (35.8)	
Rectum	202 (34.3)	32 (26.4)	35 (33.0)	
Tumor size (cm)				< 0.001
< 5	374 (63.5)	55 (45.5)	56 (52.8)	
≥ 5	215 (36.5)	66 (54.5)	50 (47.2)	
Complication				0.313
No	448 (76.1)	96 (79.3)	75 (70.8)	
Yes	141 (23.9)	25 (20.7)	31 (29.2)	
Histologic grade				0.003
Grades 1, 2	560 (95.1)	110 (90.9)	92 (86.8)	
Grade 3, MC, SRC	29 (4.9)	11 (9.1)	14 (13.2)	
Lymphovascular invasion				< 0.001
Absent	409 (69.4)	83 (68.6)	53 (50.0)	
Present	106 (18.0)	30 (24.8)	35 (33.0)	
Unknown	74 (12.6)	8 (6.6)	18 (17.0)	
No. of retrieved LNs				0.829
< 12	101 (17.1)	18 (14.9)	18 (17.0)	
≥ 12	488 (82.9)	103 (85.1)	88 (83.0)	
Tumor stage				< 0.001
I, II	372 (63.2)	63 (52.1)	45 (42.5)	
III	217 (36.8)	58 (47.9)	61 (57.5)	
Chemotherapy				0.169
No	231 (39.2)	38 (31.4)	35 (33.0)	
Yes	358 (60.8)	83 (68.6)	71 (67.0)	

Values are presented as number (%) or mean ± standard deviation.
CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; MC, mucinous adenocarcinoma; SRC, signet-ring cell; LN, lymph node.

tors of decreased OS (Table 2).

Prognostic impact of CA19-9 trend

While deriving the cutoff value alone was significant, dividing the groups into group 1, group 2, and group 3 and observing the trend proved to be more effective for prognostic prediction (Table 3). The C-index value of the CA19-9 trend (0.636 [95% CI, 0.509–0.682]) surpassed those of preoperative CA19-9 (0.625 [95% CI, 0.579–0.667]; bootstrap C-index mean difference, 0.012 [95% CI, 0.003–0.020]) and postoperative CA19-9 (0.592 [95% CI, 0.551–0.630]; bootstrap C-index mean difference, 0.044 [95% CI, 0.014–0.075]).

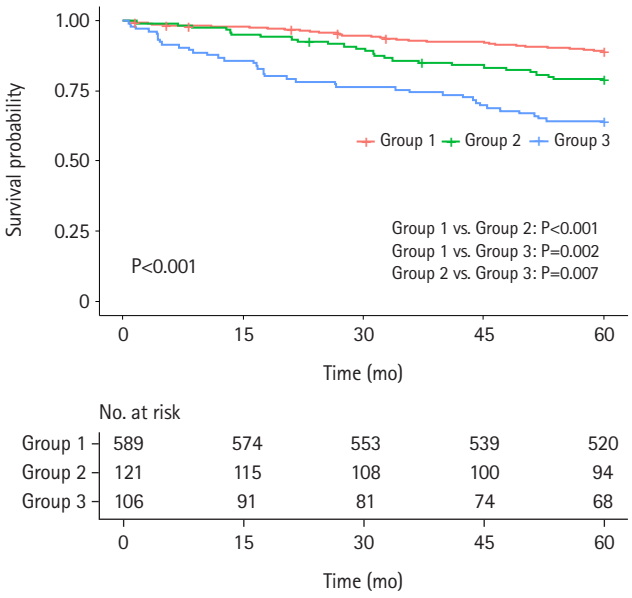

Fig. 3. Kaplan-Meier survival curve of overall survival according to the carbohydrate antigen 19-9 (CA19-9) trend. Group 1, low preoperative CA19-9; group 2, high preoperative and low postoperative CA19-9; and group 3, high preoperative and postoperative CA19-9.

In order to determine the role of CA19-9 trend in patients with preoperative CEA levels within the normal range of < 5 ng/mL, we conducted a subgroup analysis. Even among patients with CEA levels < 5 ng/mL, differences in survival were observed based on the CA19-9 trend, and these differences were somewhat noticeable. When investigating patients with CEA levels ≥ 5 ng/mL, we found that the group corresponding to group 3 had the poorest prognosis (Supplementary Fig. 4).

DISCUSSION

This study revealed that both preoperative and early postoperative CA19-9 levels are indicative of the prognosis in patients with CRC. Notably, analyzing the trends at these levels, rather than relying solely on individual values, proved to be more effective for prognostication. These findings are expected to enhance the clinical utility of CA19-9 in patients diagnosed with stage I–III colorectal cancer.

Presently, CA19-9 is not commonly used for diagnostic pur-

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Table 2. Univariable and multivariable analysis of factors associated with overall survival

	Univariable analysis		Multivariable analysis	
Factor	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex		0.915	-	-
Female	1			
Male	0.980 (0.688–1.399)			
Age (yr)		< 0.001		< 0.001
< 70	1		1	
≥ 70	2.714 (1.912–3.853)		2.613 (1.833–3.723)	
Body mass index (kg/m^2)		0.003		0.005
< 25	1		1	
≥ 25	0.517 (0.333–0.801)		0.532 (0.342–0.827)	
CEA (ng/mL)		< 0.001	-	-
< 5	1			
≥ 5	2.022 (1.418–2.883)			
Tumor location		0.333	-	-
Colon	1			
Rectum	1.196 (0.832–1.719)			
Tumor size (cm)		0.001		0.123
< 5	1		1	
≥ 5	1.754 (1.236–2.489)		1.334 (0.924–1.923)	
Complication		0.002		0.015
No	1		1	
Yes	1.757 (1.216–2.539)		1.593 (1.093–2.320)	
Histologic grade		0.001		0.098
Grades 1, 2	1		1	
Grade 3, MC, SRC	2.303 (1.363–3.892)		1.576 (0.919–2.700)	
Lymphovascular invasion			-	-
Absent	1	-		
Present	2.279 (1.557–3.334)	< 0.001		
Unknown	1.275 (0.728–2.232)	0.395		
Tumor stage		< 0.001		< 0.001
I, II	1		1	
III	2.705		2.414 (1.666–3.496)	
Chemotherapy		0.576	-	-
No	1			
Yes	0.902 (0.631–1.292)			
Preoperative CA19-9		< 0.001	-	-
Low	1			
High	2.906 (2.049–4.121)			
Postoperative CA19-9		< 0.001	-	-
Low	1			
High	2.982 (2.044–4.352)			
CA19-9 trend				
Group 1[a]	1	-	1	-
Group 2[b]	2.041 (1.284–3.243)	0.002	1.682 (1.043–2.710)	0.032
Group 3[c]	4.033 (2.695–6.033)	< 0.001	2.882 (1.899–4.371)	< 0.001

HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; MC, mucinous adenocarcinoma; SRC, signet-ring cell; CA19-9, carbohydrate antigen 19-9.
[a]Low preoperative CA19-9. [b]High preoperative and low postoperative CA19-9. [c]High preoperative and postoperative CA19-9.

Table 3. Comparison of C-index

Variable	CA19-9 trend	Preoperative CA19-9	Postoperative CA19-9
Bootstrapped C-index (95% CI)	0.636 (0.509–0.682)	0.625 (0.579–0.667)	0.592 (0.551–0.630)
Estimated mean difference	-	0.012 (0.003–0.020)	0.044 (0.014–0.075)

C-index, concordance index; CA19-9, carbohydrate antigen 19-9; CI, confidence interval.

poses in clinical settings; instead, it is primarily used as a supplementary marker along with CEA. Recent studies have suggested that CA19-9 may be helpful for predicting the prognosis of patients with CRC [13–16, 19, 20]. For patients with CRC and peritoneal metastases undergoing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), preoperative CA19-9 levels alone, and not CEA or CA125 levels, are linked to poor prognosis [21]. Although our study specifically targeted patients with stage I–III disease without metastasis, CA19-9 also demonstrated significant results in patients with metastasis.

Considerable research has been conducted on the optimal CA19-9 cutoff value for assessing patient risk. Typically, 37 U/mL is considered the upper normal limit [22]. Several studies have utilized the widely adopted threshold of 37 U/mL to distinguish between high and low levels of CA19-9 and analyze the prognosis [14, 23, 24]. This threshold has also been employed in studies analyzing stage IV disease and in patients undergoing CRS/HIPEC procedures [21, 25]. Similar to our study, some studies have directly specified cutoff values. Mizuno et al. [15] identified an optimal cutoff value for preoperative CA19-9 of 22.4 U/mL in patients with stage II/III colon cancer. Hou et al. [26], considering factors such as diet, lifestyle, and patient-selection criteria, set a cutoff value of 20.0 U/mL. In a study of patients with CRC with liver metastasis, a preoperative optimal cutoff point of 35.24 U/mL was established [27]. Numerous studies have used a standard threshold of 37 U/mL to categorize CA19-9 levels. Although various prognostic analyses have suggested cutoff points, the emphasis has mainly been on preoperative values rather than postoperative values. Given the variability in cutoff values across studies, it seems challenging to propose an ideal value, which could limit the clinical utility of CA19-9. A notable feature of our study is the selection of appropriate values during both the preoperative and early postoperative periods, which best indicate prognosis in our group. Further research is necessary to identify more appropriate cutoff values for prognostic prediction.

Another aspect highlighted by our research is the timing of the CA19-9 measurements. Typically, patients undergo follow-up for tumor markers during outpatient evaluations or to assess their chemotherapy response after surgery. At our institution, in addition to measuring CA19-9 levels during follow-up, we confirmed changes in CA19-9 levels immediately before discharge. To the best of our knowledge, there is a scarcity of data from measurements taken 4 to 7 days after surgery, similar to that at our institution. A unique feature of our study was the ability to promptly assess changes in CA19-9 levels immediately after surgery, potentially allowing for a slightly earlier prognostic prediction. In most studies, the initiation of postoperative chemotherapy for at least 8 weeks after surgery is highly recommended [28, 29]. Therefore, factors measurable within postoperative 8 weeks could determine the necessity of postoperative chemotherapy. However, when making decisions based on observed postoperative changes, curiosity inevitably arises about the most appropriate timing for measuring these changes. Establishing a consistent timeframe for this period may be crucial to make such tests more accessible. In a recent study that monitored changes in CA19-9, the retrospective nature of the research inherently introduced a drawback due to the relatively wide interval between measurement periods, typically before the initiation of adjuvant chemotherapy or up to postoperative 6 weeks [29]. The very short measurement, specifically 4 to 7 days after surgery, as proposed in our study, offers the advantage of clinicians conducting the assessment before discharge, compared to measurements taken during outpatient visits, making it relatively easy to implement in a standardized manner. This consistency may have been advantageous. As mentioned earlier for group 3, more frequent monitoring in outpatient clinics or adjusting the chemotherapy duration could be advantageous for patients with a poor prognosis. This information is expected to assist in determining additional treatment strategies. However, as our study did not address these points, further investigations are warranted to confirm these findings.

Predicting the prognosis based solely on CA19-9 levels is meaningful, the combination of CA19-9 with the currently utilized CEA values is also worth exploring. Lee et al. [13] suggested that the sensitivity for recurrence increased to 31.4% with the combined follow-up of CEA and CA19-9, representing a 5% difference compared to the sensitivity of CEA alone. In their study, patients whose initially elevated CEA or CA 19-9 levels demonstrated superior survival outcomes compared to those who maintained elevated levels postoperatively. Our research data involved distinguishing between high and low CEA levels using a threshold of 5 ng/mL, followed by examining the survival trend of CA19-9 trends (Supplementary Fig. 2). The 2 groups exhibited slightly dif-

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ferent trends, with the group with elevated CEA levels showing less favorable survival. The poorest prognosis was observed in group 3 patients with high CEA levels. This aspect aligns somewhat with recent research findings, suggesting that considering CEA and CA19-9 levels simultaneously may best select patients with poor survival outcomes [16].

Our study has some limitations. As our study had a retrospective single-center design, selection bias may have been inherent in the research process. Additionally, there was a single change in the CA19-9 measurement equipment during the study period. Because the agreement between the 2 measurement machines was expected to be quite high, this may not have posed a significant issue. However, consistency in the data may have been enhanced if the same machine had been used throughout. CA19-9 is a glycolipid antigen formed by the modification of the Lewis blood group antigen. In individuals with the Lewis a-b genotype, CA19-9 levels may not increase, leading to lower levels even in the presence of CRC, which could produce false-negative outcomes. If the patient had a benign disease in the biliary tract, there would have been an increase in CA19-9 levels, potentially resulting in false-positive outcomes [30]. Finally, our study specifically targeted patients for whom CA19-9 measurements were feasible. Patients with very low CA19-9 levels, indicated as CA19-9 <0.14 U/mL, were excluded from our study, potentially introducing a limitation owing to the exclusion of a considerable number of patients. Additionally, the inability to apply our algorithm to patients with the Lewis a–b– genotype, as their CA19-9 levels do not increase, presents another drawback. Research on evaluating such patients using appropriate algorithms is also necessary.

In conclusion, we recommend defining optimal CA19-9 thresholds both preoperatively and immediately postoperatively in CRC patients. Integrating preoperative and postoperative CA19-9 values enhances prognostic stratification, allowing for more precise categorization in nonmetastatic CRC. Patients who demonstrate unfavorable CA19-9 trends may require closer postoperative monitoring and might be strong candidates for trials exploring intensified adjuvant chemotherapy. Nevertheless, further validation through larger, prospective studies is needed to confirm these findings.

ARTICLE INFORMATION

Conflict of interest
No potential conflict of interest relevant to this article was reported.

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Author contributions
Conceptualization: JK; Data curation: WC, YP; Formal analysis: WC, JK; Investigation: JK; Methodology: YP, JK; Supervision: JK; Visualization: WC, JK; Writing–original draft: WC, JK; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Supplementary materials
Supplementary Table 1. Patient characteristics according to preoperative and postoperative CA19-9

Supplementary Fig. 1. Defining the CA19-9 cutoff values using the X-tile program.

Supplementary Fig. 2. Kaplan-Meier survival curve of overall survival.

Supplementary Fig. 3. Kaplan-Meier curve of disease-free survival according to CA19-9 trend.

Supplementary Fig. 4. Kaplan-Meier survival curve of overall survival according to the CEA levels.

Supplementary materials are available from https://doi.org/10.3393/ac.2025.00528.0075.

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