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ORIGINAL ARTICLE

Preoperative serum cholinesterase as a prognostic factor in patients with colorectal cancer

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Abstract

Aim: Serum cholinesterase (ChE) levels are considered to reflect nutritional status. Although ChE has been well documented as a prognostic factor for some cancers, no clear consensus on its use for colorectal cancer (CRC) has been reached. The aim of this study was to investigate the relationship between preoperative serum ChE and postoperative long-term prognosis in CRC patients.

Methods: A total of 1053 CRC patients who underwent curative surgery were included in this study. The correlations between the preoperative ChE value and overall survival (OS) or cancer-specific survival (CSS) were assessed. By dividing patients into two groups according to their ChE value, OS and CSS were compared between the groups.

Results: Multivariate analysis revealed that the continuous ChE value was a significant predictor of OS (hazard ratio, 0.996; 95% CI, 0.993–0.998; $p=0.002$) and CSS (hazard ratio, 0.994; 95% CI, 0.991–0.998; $p=0.001$), independent of other variables. The low-ChE (≤234 U/L) group had a significantly poorer prognosis than the high-ChE (>234 U/L) group for both OS (5-year OS for low ChE and high ChE: 79.8% and 93.3%, respectively; $p<0.001$) and CSS (5-year CSS for low ChE and high ChE: 84.8% and 95.6%, respectively; $p<0.001$).

Conclusions: Lower preoperative serum ChE levels are a predictive factor of poor prognosis for CRC patients. As serum ChE levels can be measured quickly and evaluated easily, ChE could become a useful marker for predicting the postoperative long-term outcomes of CRC patients.

KEYWORDS
cholinesterase, colorectal cancer, nutrition, prognosis, surgery

1 | INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer death worldwide.[1] Despite the performance of curative surgery and adjuvant chemotherapy for nonmetastatic or endoscopically unresectable CRC as a standard treatment, recurrence and cancer death can occur postoperatively.[2]

Patient demographics and tumor characteristics are the main factors for predicting the prognosis of patients with CRC. However, some preoperative laboratory parameters have been reported to correlate with prognosis and are considered hematological biomarkers.[3] In particular, preoperative nutritional status has been well documented as a prognostic predictor.[4,5] To estimate nutritional status, the usefulness of several scores, such as the Glasgow prognostic score or the prognostic nutritional index, has been reported.[5,6] However, these scores need several factors to be calculated and are not necessarily widely used in clinics.

Cholinesterase (ChE) is a group of enzymes that hydrolyze acetylcholine, and classified broadly into two groups, Acetylcholinestrase and serum ChE (Butyrylcholinestrase). Serum ChE can be measured quickly and easily preoperatively via standard serum laboratory testing. Serum ChE levels are considered to reflect nutritional status, and their relationship with the prognosis of wasting diseases (inflammatory bowel disease, acute heart failure, etc.), including malignant tumors such as pancreatic cancer, hepatocellular carcinoma, and urologic cancer, has been well documented.[7–11] However, no clear consensus on the relationship between serum ChE and the prognosis of CRC patients has been reached.

The aim of our study was to investigate the relationship between preoperative serum ChE and postoperative long-term prognosis using data from a large number of CRC patients.

2 | METHODS

2.1 | Search strategy

This is a retrospective analysis of prospectively collected data from a single institution. We applied the opt-out method to obtain consent for this study, and the protocol for this research project was approved by a suitably constituted ethics committee of the institution in our hospital (20150148) and conforms to the provisions of the Declaration of Helsinki. A total of 2309 consecutive patients who underwent surgery for CRC at Keio University Hospital from January 2003 to December 2019 were retrospectively reviewed in this study. As shown in Figure 1, patients with colitic or hereditary CRC (69 patients); stage 0, IV or noncurative surgery (≥R1 surgery including perforated cases) (155 patients); synchronous or metachronous cancer (111 patients); preoperative therapy (20 patients); or inadequate data (901 patients) were excluded. Consequently, 1053 patients were eligible for this study.

2.2 | Clinical parameters

The following clinical parameters were collected preoperatively: carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), total protein (TP), serum albumin (Alb), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), creatine kinase (CK), ChE, C-reactive protein (CRP), white blood cell count (WBC), neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and platelet/lymphocyte ratio (PLR). All clinical data were obtained within 1 month prior to surgery.

Patient characteristics (age at surgery, sex, body mass index [BMI], smoking history, and drinking habits), oncological factors

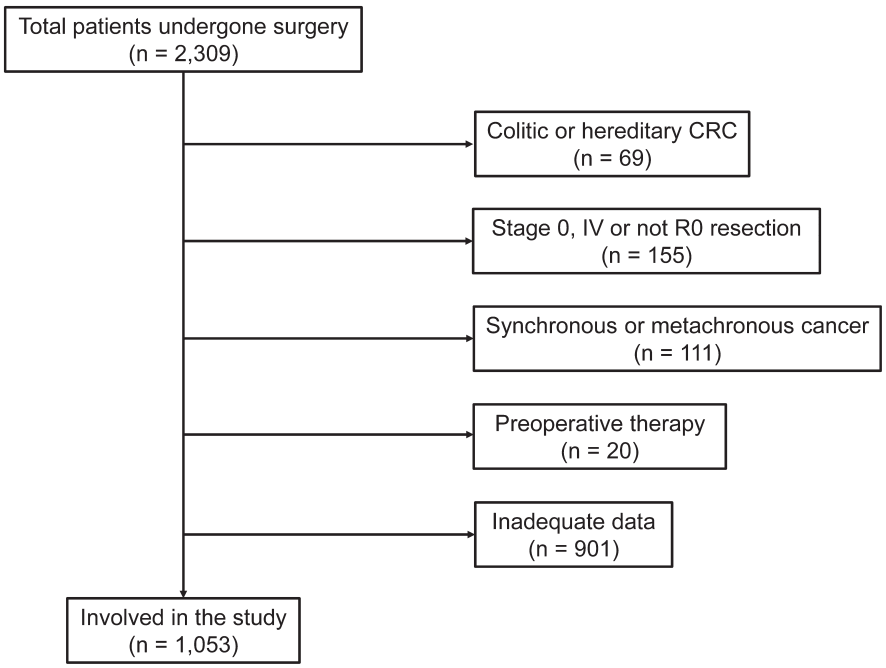

FIGURE 1 The CONSORT diagram of the study.

TABLE 1 Patients' pre- and postoperative demographic and clinicopathological findings.

Patients characteristics	Total ($n = 1053$)
Age (y/o)	67 (58–75)
Sex [male]	566 (53.8%)
BMI	22.5 (20.3–24.7)
ASA-PS	
1	424 (40.3%)
2	563 (53.5%)
3	66 (6.2%)
Smoking history [+][a]	373 (35.4%)
Drinking habit [+][a]	478 (45.4%)
Oncological factors	
Tumor location	
Right Colon	378 (35.9%)
Left Colon	432 (41.0%)
Rectum	243 (23.1%)
pStage	
I	374 (35.5%)
II	340 (32.3%)
III	339 (32.2%)
Histological grade [wel – mod]	992 (94.2%)
Lymphatic invasion [+][a]	569 (54.0%)
Venous invasion [+][a]	634 (60.2%)
Surgical factors	
Surgical time (min)	244 (200–304)
Blood loss (mL)	10 (10–100)
Surgical procedure	
Open	275 (26.1%)
Laparoscopy	764 (72.6%)
Robot	14 (1.3%)
Postoperative factors	
Postoperative therapy [+]	379 (36.0%)
Postoperative complication [+]	288 (27.3%)
Follow-up period (month)	60 (33–87)
Clinical parameters	
CEA	2.4 (1.4–4.5)
CA19-9	9.0 (2.0–17.5)
TP	6.9 (6.5–7.2)
Alb[a]	4.1 (3.8–4.3)
LDH	181 (160–208)
AST	20 (17–25)
ALT[a]	16 (12–22)
γ-GTP[a]	23 (16–36)
CK[a]	80 (54–113)
CRP	0.07 (0.03–0.26)
Ch-E	283 (237–334)
WBC	5.7 (4.8–6.9)

Note: All of the continuous variables are shown by median (interquartile range).

Abbreviations: Alb, albumin (g/dL); ALT, alanine aminotransferase (U/L); ASA-PS, American Society of Anesthesiologists Physical status; AST, aspartate aminotransferase (U/L); BMI, body mass index (kg/m^2); CA19-9, carbohydrate antigen 19-9 (ng/mL); CEA, carcinoembryonic antigen (ng/mL); Ch-E, choline esterase (U/L); CK, creatine kinase (U/L); CRP, C-reactive protein (mg/dL); LDH, lactate dehydrogenase (U/L); TP, total protein (g/dL); WBC, white blood cell count ($10^3/\mu L$); γ-GTP, γ-glutamyl transpeptidase (U/L).

[a]Missing values excluded from the analysis.

(tumor location, tumor size, UICC pathological tumor stage, number of metastasized lymph nodes, histological grade, lymphatic invasion, and venous invasion), surgical factors (surgical time, intraoperative blood loss, and type of surgical procedure) and postoperative factors (performance of postoperative therapy and postoperative complications) were also collected.[12] Drinking habits were defined as alcohol intake occurring at least once a week, irrespective of the amount of alcohol consumed. Surgical time was measured from the start of the incision to the time of closure of all the wounds. Intraoperative blood loss was measured by subtracting the amount of saline used during surgery from the volume of the suction bottle and adding the weight increment of blood-soaked gauze. The type of surgical procedure was classified as open, laparoscopic, or robotic, and conversion of the surgical procedure was considered the last procedure. Complications were graded according to the Clavien–Dindo grading system, and complications greater than Grade I were counted as a complication. Based on the guidelines from the Japanese Society for Cancer of the Colon and Rectum, postoperative therapy was recommended for all patients with high-risk pStage II disease (pT4, poorly differentiated histology, less than 12 harvested lymph nodes, diagnosed as bowel obstruction/perforation, or lymphatic/venous invasion) and pStage III disease, and postoperative therapy was performed for 6 months according to the patient's wishes and tolerance. The chemotherapeutic agents used were capecitabine, capecitabine + oxaliplatin, S-1, fluorouracil, fluorouracil + oxaliplatin, and uracil/tegafur + leucovorin.[13,14]

2.3 | Follow-up

Postoperative follow-up included physical assessments, blood tests and image diagnoses (computed tomography and gastrointestinal endoscopy) at fixed intervals. All evidence of recurrence was obtained from the patients' medical records. The primary outcomes of this study were overall survival (OS) and cancer-specific survival (CSS). These parameters were calculated from the date of surgery until death.

2.4 | Statistical analysis

Survival was calculated from the date of surgery. Continuous variables were analyzed by the Mann–Whitney *U*-test, and categorical variables were analyzed by Pearson's chi-squared test. Clinical parameters with a p value < 0.10 in univariate analysis for OS or CSS were further analyzed together in multivariate analysis using the Cox proportional hazard regression model to determine prognostic factors. Laboratory test results or nutritional scores, which are considered confounding factors, were excluded from the analysis. Kaplan–Meier survival analysis with the log-rank test was performed to evaluate differences in prognosis among the groups. p values < 0.05 were considered statistically significant. Correlations were explored using Spearman's correlation coefficient. The optimal cutoff value was assessed by survival classification and regression tree (CART) analysis using R Statistical Software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). The remaining statistical analyses were conducted with Stata MP 11 (Stata Corporation, College Station, TX, USA).

3 | RESULTS

3.1 | Patient characteristics

The pre- and postoperative demographic and clinicopathological data of the 1053 CRC patients are summarized in Table 1. The selected patients included 566 (53.8%) men and 487 (46.2%) women, and the median age was 67 (interquartile range [IQR], 58–75) years. Pathological stage (pStage) was distributed equally, with 374 (35.5%) patients with pStage I, 340 (32.3%) patients with pStage II, and 339 (32.2%) patients with pStage III. Postoperative therapy was administered to 379 (36.0%) patients. The median preoperative ChE value of all patients was 283 (237–334) U/L. The median follow-up period was 60 (33–87) months from the date of surgery.

3.2 | Prognostic impact of ChE on long-term survival

To estimate the prognostic impact of preoperative ChE in CRC patients who underwent curative surgery, a Cox proportional hazard model was performed. For OS, univariate analysis identified the continuous ChE value as a significant prognostic factor (HR, 0.994; 95% CI, 0.992–0.996; $p < 0.001$). Age, sex, tumor location, postoperative complication, pStage, histological grade, lymphatic invasion, venous invasion, and postoperative therapy were also identified as significant factors (Table S1). Furthermore, according to multivariate analysis, the continuous ChE value was identified as a significant predictor of OS (HR, 0.996; 95% CI, 0.993–0.998; $p = 0.002$) independent of other variables (Table 2). Similarly, for CSS, the continuous ChE value was identified as a significant prognostic factor by univariate analysis (HR, 0.993; 95% CI, 0.990–0.996; $p < 0.001$). Age, sex, pStage, histological grade, and postoperative therapy were also identified as significant factors (Table S1). Multivariate analysis revealed that the continuous ChE value was a significant predictor of CSS (HR, 0.994; 95% CI, 0.991–0.998; $p = 0.001$) independent of other variables (Table 2).

3.3 | Comparison of long-term survival between ChE value classifications

Since ChE was identified as an independent significant predictor for both OS and CSS as a continuous variable, we sought to assess its clinical utility. The cutoff value of ChE was calculated to be 234 U/L via survival CART analysis. We then classified all patients into two groups according to the ChE level: "low" for patients with ChE ≤234 U/L and "high" for patients with ChE >234 U/L.

The clinicopathological factors of the two groups are summarized in Table 3. There were significant differences in age, BMI, tumor size, pStage, histological grade, venous invasion, intraoperative blood loss, surgical procedure, postoperative complication, and CEA, TP, Alb, ALT, γ-GTP, CK, and CRP levels between the two groups. We compared survival curves between the groups by using Kaplan–Meier survival analysis with the log-rank test. As expected, the low-ChE group had a significantly poorer prognosis than the high-ChE group for both OS (5-year OS for low-ChE and high-ChE: 79.8% and 93.3%, respectively; $p < 0.001$) and CSS (5-year CSS for low-ChE and high-ChE: 84.8% and 95.6%, respectively; $p < 0.001$) (Figures 2A and 3A). As there are a few reports that ChE varies between sexes, survival was also analyzed for each sex, with the result of poor prognosis in the low-ChE group regardless of sex (Figure S1A, Figure 1B).[15] We then compared them at each pStage. In pStage II, low-ChE patients

TABLE 2 Multivariate analysis on continuous serum ChE value associated with long-term survival.

	Crude		Adjusted	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
OS	0.994 (0.992–0.996)	<0.001	0.996 (0.993–0.998)	0.002*
CSS	0.993 (0.990–0.996)	<0.001	0.994 (0.991–0.998)	0.001**

Abbreviations: ChE, cholinesterase; CSS, cancer-specific survival; OS, overall survival.

*OS: Adjusted for age, sex, tumor location, postoperative complication, pStage, histological grade, lymphatic invasion, venous invasion and postoperative therapy. **CSS: Adjusted for age, sex, postoperative complication, pStage, histological grade, lymphatic invasion, venous invasion and postoperative therapy.

TABLE 3 Comparison of clinicopathological factors between ChE low and high group.

Patients characteristics	Low ($n=251$)	High ($n=802$)	p value
Age (y/o)	73 (62–80)	65 (57–73)	<0.001*
Sex [male]	132 (52.6%)	434 (54.1%)	0.672***
BMI (kg/m^2)	21.2 (18.9–23.5)	23.0 (20.8–25.1)	<0.001*
ASA-PS			
1	67 (26.7%)	357 (44.5%)	<0.001**
2	156 (62.1%)	407 (50.8%)	
3	28 (11.2%)	38 (4.7%)	
Smoking history [+][a]	78 (31.1%)	80 (51.3%)	0.074***
Drinking habit [+][a]	100 (39.8%)	92 (59.0%)	0.070***
Oncological factors			
Tumor size (cm)	5.5 (3.5–8.0)	4.0 (2.5–6.5)	<0.001*
Tumor location			
Right colon	92 (36.7%)	286 (35.7%)	0.950**
Left colon	101 (40.2%)	331 (41.3%)	
Rectum	58 (23.1%)	185 (23.0%)	
pStage			
I	52 (20.7%)	322 (40.1%)	<0.001**
II	103 (41.1%)	237 (29.6%)	
III	96 (38.2%)	243 (30.3%)	
Histological grade [wel – mod]	229 (91.2%)	763 (95.1%)	0.021***
Lymphatic invasion [+][a]	143 (57.0%)	426 (53.1%)	0.282***
Venous invasion [+][a]	170 (67.7%)	464 (57.9%)	0.006***
Surgical factors			
Surgical time (min)	248 (197–304)	244 (200–304)	0.932*
Blood loss (mL)	50 (10–234)	10 (10–80)	<0.001*
Surgical procedure			
Open	118 (47.0%)	157 (19.6%)	<0.001**
Laparoscopy	132 (52.6%)	632 (78.8%)	
Robot	1 (0.4%)	13 (1.6%)	
Postoperative factors			
Postoperative therapy [+][b]	95 (50.5%)	277 (62.4%)	0.006***
Postoperative complication [+]	85 (33.9%)	203 (25.3%)	0.008***
Clinical parameters			
CEA	3.1 (1.8–6.2)	2.3 (1.4–4.1)	<0.001*
CA19-9	10 (5–23)	9 (5–17)	0.331*
TP	6.6 (6.2–7.0)	7.0 (6.7–7.2)	<0.001*
Alb[a]	3.7 (3.2–4.0)	4.1 (3.9–4.3)	<0.001*
LDH	178 (157–215)	181 (161–207)	0.436*
AST	20 (16–25)	21 (17–25)	0.143*
ALT[a]	14 (10–20)	16 (12–23)	<0.001*
γ-GTP[a]	20 (15–33)	24 (16–37)	0.005*
CK[a]	65 (32–98)	83 (59–119)	<0.001*
CRP	0.16 (0.04–0.86)	0.06 (0.03–0.18)	<0.001*
ChE	200 (167–220)	303 (272–346)	<0.001*

TABLE 3 (Continued)

Patients characteristics	Low ($n=251$)	High ($n=802$)	p value
WBC	5.8 (4.7–7.1)	5.7 (4.9–6.8)	0.525*

Note: All of the continuous variables are shown by median (interquartile range).

Abbreviations: Alb, albumin (g/dL); ALT, alanine aminotransferase (U/L); ASA-PS, American Society of Anesthesiologists Physical status; AST, aspartate aminotransferase (U/L); BMI, body mass index (kg/m^2); CA19-9, carbohydrate antigen 19-9 (ng/mL); CEA, carcinoembryonic antigen (ng/mL); Ch-E, choline esterase (U/L); CK, creatine kinase (U/L); CRP, C-reactive protein (mg/dL); LDH, lactate dehydrogenase (U/L); TP, total protein (g/dL); WBC, white blood cell count (10^3/μL); γ-GTP, γ-glutamyl transpeptidase (U/L).

[a]Missing values excluded from the analysis.

[b]Patients with no indication for postoperative therapy were excluded from the analysis.

*Mann–Whitney test. **Kruskal-Wallis test. ***Pearson's chi-squared test.

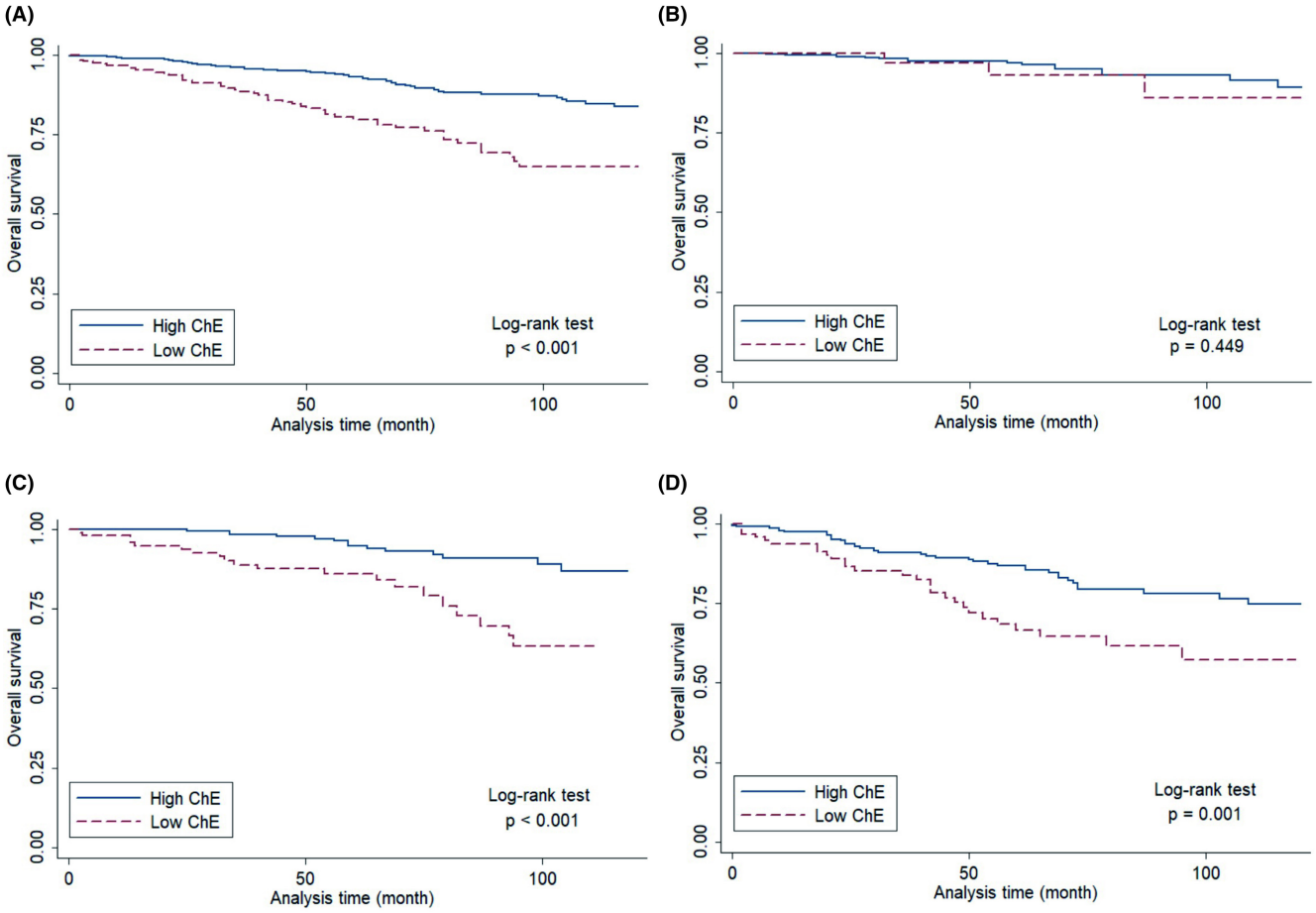

FIGURE 2 Kaplan–Meier curves for OS comparing the low-ChE group and high-ChE group for (A) all stages, (B) pStage I, (C) pStage II, and (D) pStage III CRC patients. ChE, cholinesterase; CRC, colorectal cancer; OS, overall survival.

had a significantly poorer prognosis than did high-ChE patients (5-year OS for low-ChE and high-ChE patients: 86.1% and 94.9%, respectively; $p<0.001$; 5-year CSS for low-ChE patients and high-ChE patients: 90.2% and 98.2%, respectively; $p<0.001$) (Figures 2C and 3C). There was also a significant difference in pStage III (5-year OS for low ChE and high ChE: 66.6% and 86.9%, respectively; $p=0.001$; 5-year CSS for low ChE and high ChE: 71.6% and 89.0%, respectively; $p=0.002$) (Figures 2D and 3D). However, there was no significant difference in pStage I (OS; $p=0.449$, CSS; $p=0.463$) (Figures 2B and 3B). Table 4 shows the results of the univariate and multivariate analyses assessing serum ChE as a categorical variable. Low-ChE was also an independent negative prognostic factor for OS (HR, 1.874; 95% CI, 1.285–2.732; $p=0.001$) and for CSS (HR, 2.507; 95% CI, 1.584–3.968; $p<0.001$).

Notably, we also investigated the correlation with recurrence-free survival (RFS). As shown in Table S2, both continuous ChE value and ChE classification showed strong associations but with no significance.

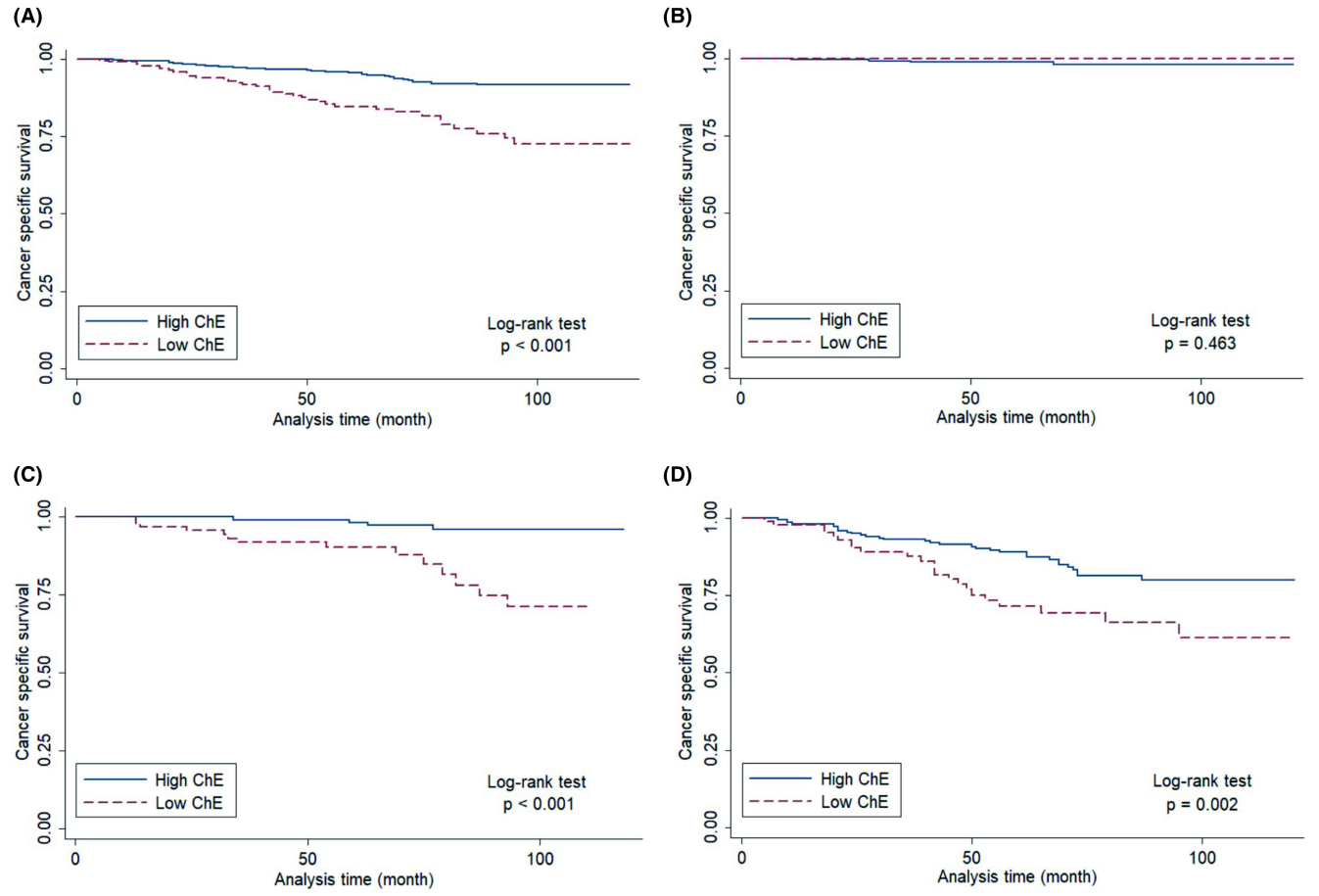

FIGURE 3 Kaplan–Meier curves for CSS comparing the low-ChE group and high-ChE group for (A) all stages, (B) pStage I, (C) pStage II, and (D) pStage III CRC patients. ChE, cholinesterase; CRC, colorectal cancer; CSS, cancer-specific survival.

TABLE 4 Multivariate analysis on ChE classification associated with long-term survival.

	Crude		Adjusted	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
OS	2.680 (1.878–3.824)	<0.001	1.874 (1.285–2.732)	0.001*
CSS	3.388 (2.183–5.256)	<0.001	2.507 (1.584–3.968)	<0.001**

Abbreviations: ChE, cholinesterase; CSS, cancer-specific survival; OS, overall survival.

*OS: Adjusted for age, sex, tumor location, postoperative complication, pStage, histological grade, lymphatic invasion, venous invasion, and postoperative therapy. **CSS: Adjusted for age, sex, postoperative complication, pStage, histological grade, lymphatic invasion, venous invasion, and postoperative therapy.

3.4 | Clinicopathological factors associated with ChE

Overall, the survival analysis showed that ChE was a significant prognostic factor for OS and CSS but not for RFS. To explore the causes of these results, we evaluated whether ChE is more strongly related to nutritional or oncological factors. Table 5 and Table S3 show the correlation coefficient matrix of various clinicopathological factors. Continuous ChE values were strongly associated with Alb levels and tumor size, whereas other factors were not as strongly associated with these two variables.

4 | DISCUSSION

In the current study, we showed that preoperative serum ChE is a significant prognostic factor for CRC patients. To consider the clinical utility of this method, we grouped the patients as low ChE levels for ChE ≤234 U/L and patients with high ChE levels for ChE >234 U/L according to survival CART analysis. Independent of other clinicopathological factors, low-ChE was a significant poor prognostic factor and may be a simpler biomarker than other nutritional scores.

TABLE 5 Correlation coefficient values of various clinicopathological factors associated with ChE.

	Age	Alb	BMI	WBC	NLR	LMR	PLR	CRP	CEA	CA19-9	Tumor Size	Number of LNM
ChE	−0.226	**0.550**	0.291	−0.001	−0.232	0.154	−0.229	−0.266	−0.101	−0.076	**−0.307**	−0.027

Note: Coefficients <−0.3 and >0.3 are shown in bold.

Abbreviations: Alb, albumin; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ChE, choline esterase; CRP, C-reactive protein; LMR, lymphocyte/monocyte ratio; LNM, lymph node metastasis; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; WBC, white blood cell count.

As serum ChE is synthesized and secreted into the blood stream by the liver, the plasma level of serum ChE decreases in acute and chronic liver damage, cirrhosis, and liver metastases. Thus, it is a biochemical marker of organ damage. Moreover, a decrease in serum ChE levels is found in protein-energy malnutrition, since serum ChE is also distributed in the lung, heart, brain, small intestine, and adipose tissue.[16] Accordingly, serum ChE levels are considered to reflect nutritional status.[7,17] In the present study, according to the results of the correlation coefficient matrix, ChE was most strongly correlated with Alb, which is a major nutritional marker. Alb is the most abundant circulating protein found in plasma and is synthesized by the liver and secreted into the bloodstream, similar to ChE. Although the underlying mechanism of Alb is controlled by alterations in colloid osmotic pressure and the osmolality of the extravascular hepatic space, this is an expected result considering the pathway of synthesis.[18] When discussing nutritional status, we might have to consider rapid turnover proteins (RTPs). RTPs, such as retinol binding protein (RBP), transthyretin or prealbumin (PA) and transferrin (TF), are circulating proteins with short half-lives and are used to assess the effectiveness of nutritional interventions on a timely basis. The serum half-life of albumin is approximately 21 days, whereas it is 8–12 days for ChE, 7 days for TF, 1.9 days for PA, and 12 h for RBP.[19,20] At present, although there are few reports on the association between TF and gastrointestinal cancer prognosis, a consensus has not been reached.[21,22]

Inflammation status has been reported to be closely linked to nutritional status. Inflammatory cells, cytokines, and chemokines play important roles in the tumor microenvironment. They also contribute to systemic inflammation, which may affect laboratory data, including increased peripheral blood cells.[23,24] Hence, peripheral blood cell-based prognostic biomarkers, such as the NLR, LMR, and PLR, have been reported to predict patient prognosis in various cancers, including CRC.[25–27] Although the detailed underlying mechanism has not been clarified, the presence of proinflammatory cytokines produced by tumor cells may lead to malnutrition.[28] There are reports that elevated levels of proinflammatory cytokines, such as interleukin (IL)-6 and IL-17, are correlated with larger tumor sizes.[29,30] Accordingly, tumor size may have some effect on nutritional status but rather reflects inflammatory status. In addition, although still controversial, a negative correlation between ChE and cytokines such as IL-6 has been reported.[31] In the present study, serum ChE showed a relatively high correlation with tumor size, which is considered consistent with these previous reports. Thus, serum ChE may be a unique biomarker that reflects both nutritional status and inflammation status. The reason for the significant differences found for OS and CSS but not for RFS may be that ChE does not simply reflect oncological factors.

In addition to serum ChE, which reflects both nutritional status and inflammation status, serum ChE has several advantages compared with other prognostic markers. First, it is easy to test ChE by adding it to the general laboratory test. Second, ChE is much more common than RTP, and its serum half-life is much shorter than that of Alb, indicating that ChE is the most feasible marker among the

laboratories that are commonly used in actual clinical practice. Third, calculations are unnecessary for evaluating ChE compared to other nutritional assessment markers, such as the NLR, LMR, or PLR. Fourth, ChE has a relatively greater value than other nutritional markers and may reflect nutritional status more sensitively. In fact, ChE is gaining new attention as a prognostic marker. Takano et al. reported that a low ChE group was related to a strong systemic inflammatory response and distant metastasis regardless of the T or N stage in CRC patients.[32] Although the sample size of the study was limited, it strongly supports our findings. The clinical utility of ChE should continue to be discussed.

There are several limitations in this study. First, although a large number of CRC patients were registered, this was a retrospective single-center study. Second, we did not measure patients' RTP, which might be an important factor for further analysis of patients' nutritional status. Additional randomized controlled studies are needed to confirm the results. Third, preoperative cases of obstruction or infection were not excluded, which might have affected the ChE values and limited the insight on pure oncological impact. Despite these limitations, this study revealed that lower preoperative serum ChE levels were a significant poor prognostic factor for CRC patients, suggesting that patients with lower ChE levels should be treated with caution. As ChE reflects both the nutritional and oncological status of patients, perioperative nutritional management or a shorter surveillance interval with respect to postoperative follow-up could be considered.

5 | CONCLUSION

We demonstrated that lower preoperative serum ChE levels are a poor prognostic factor for CRC patients. As serum ChE levels can be measured quickly and evaluated easily, ChE can become a useful marker for predicting the postoperative long-term outcomes of CRC patients.

AUTHOR CONTRIBUTIONS

Conceptualization: KN and RS. Data curation: KN and RS. Formal analysis: KN and RS. Funding acquisition: N/A. Investigation: KN and RS. Methodology: KN and RS. Project administration: All authors. Resources: All authors. Software: N/A. Supervision: RS, KS, KO, and YK. Validation: KN and RS. Visualization: KN and RS. Writing—original draft: KN and RS. Writing—review & editing: KN, RS, KS, KO, and YK.

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CONFLICT OF INTEREST STATEMENT

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ETHICS STATEMENT

Approval of the research protocol: This retrospective study was approved by the institutional ethics committee of Keio University Hospital (20150148). The study was conducted in accordance with the Declaration of Helsinki and good clinical practice.

Informed Consent: Written informed consent for the use of clinicopathological data was obtained from all patients.

Registry and Registration No. of the study/Trial: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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