ORIGINAL ARTICLE

The impact of low serum cholinesterase levels on survival in patients with colorectal cancer

Yasuhiro Takano[1] · Koichiro Haruki[2] · Shu Tsukihara[1] · Daisuke Ito[1] · Hironori Kanno[1] · Kyonsu Son[1] · Nobuyoshi Hanyu[1] · Ken Eto[2]

Abstract

Purpose Nutritional and inflammatory status have been associated with postoperative recurrence and poor survival in patients with colorectal cancer. The aim of the present study is to investigate the relationship between serum cholinesterase levels and postoperative outcomes among patients who underwent curative resection for colorectal cancer.

Methods The study comprised 174 patients who had undergone curative resection for colorectal cancer. We explored the relationship between preoperative serum cholinesterase levels and disease-free survival and overall survival after curative resection. Then patients were divided into the high-cholinesterase group ($n = 102$) and the low-cholinesterase group ($n = 72$) to analyze their clinicopathological variables including other nutritional markers and systemic inflammatory responses.

Results In multivariate analysis, lymph node metastasis ($P = 0.011$) and serum cholinesterase levels ($P < 0.01$) were independent predictors of disease-free survival, while lymph node metastasis ($P = 0.013$), serum cholinesterase levels ($P < 0.01$), and carbohydrate antigen19-9 ($P = 0.022$) were independent predictors of overall survival. In the low-cholinesterase group, neutrophil to lymphocyte ratio, ($P = 0.021$), C-reactive protein to albumin ratio ($P < 0.01$), and distant metastasis ($P < 0.01$) were higher, and prognostic nutritional index ($P < 0.01$) was lower compared with the high-cholinesterase group.

Conclusion Preoperative low serum cholinesterase levels can be a prognostic factor for postoperative recurrence and poor prognosis in patients after curative resection for colorectal cancer, suggesting an important role of cholinesterase in the assessment of nutritional and inflammatory status in cancer patients.

Abbreviations

ASA-PS	American Society of Anesthesiologists physical status
BMI	Body mass index
CAR	C-reactive protein to albumin ratio
CA19-9	Carbohydrate antigen 19–9
CEA	Carcinoembryonic antigen
ChE	Cholinesterase
CRC	Colorectal cancer
NLR	Neutrophil to lymphocyte ratio
N.S.	Not significant
PNI	Prognostic nutritional index

✉ Koichiro Haruki
haruki@jikei.ac.jp

[1] Department of Surgery, Tokyo General Hospital, Tokyo, Japan

[2] Department of Surgery, The Jikei University School of Medicine, 3-25-8, Nishi-Shinbashi, Minato-ku, Tokyo 105-8461, Japan

Introduction

Colorectal cancer (CRC) is the third most commonly cancer which seriously affects the health of people worldwide [1]. In recent decades, advances of surgical procedures and chemotherapy have decreased the mortality rate of CRC [2, 3], however 20–30% of patients with advanced CRC still experience postoperative recurrence even after curative resection, leading to poor prognosis [4–6]. Therefore, it is critically important to identify a prognostic factor that allow more accurate prediction of poor survival in patients undergoing curative resection for CRC.

Cholinesterase (ChE) is one of classical nutritional markers [7], which is synthesized by the liver and secreted into the blood [8]. Previous studies have shown that low serum

ChE levels have been associated with several clinical conditions, such as liver dysfunction, heart failure, and inflammation bowel disease [9–11], because serum ChE levels tend to decrease in the stress and inflammatory response sensitively [12, 13]. Furthermore, serum ChE level has been reported to be decreased in patients with advanced cancer, which can reflect cancer-related inflammation [14–16]. However, the prognostic role of ChE in patients with CRC has not been fully investigated compared with albumin and systemic inflammatory responses.

The aim of the present study is to evaluate the prognostic value of ChE for prognosis after curative resection for CRC, compared with other nutritional factors and systemic inflammatory responses.

Materials and methods

Patient selection

Between March 2014 and December 2020, 216 patients with CRC of stage I to III underwent curative colorectal resection (R0 resection). Of these, 42 patients were excluded (16 for obstruction or perforation as emergency, 3 for intervention for a synchronous metastatic lesion, 4 for local recurrence, 4 for multiple or double cancer, and 15 for insufficient data), remaining 174 patients for the present study. We performed a retrospective review of a prospectively maintained database of patients. The present study was approved by the Ethics Committee of Tokyo General Hospital (No. 21–3).

Assessment of the nutrition and systemic inflammatory response

Hemogram and chemistry profile were routinely evaluated within 4 weeks before surgery. We measured albumin and ChE which is a classical nutritional marker, as previously described [17]. Additionally, the systemic inflammatory response was assessed as follows: neutrophil to lymphocyte ratio (NLR) [18], prognostic nutritional index (PNI) [19], and C-reactive protein to albumin ratio (CAR) [20]. NLR was calculated by dividing the neutrophil count (per mm^3) by the lymphocyte count (per mm^3) [18]. PNI was calculated as follows: $10 \times$ serum albumin level (g/dl) $+ 0.005 \times$ total peripheral lymphocyte count (per mm^3) [19]. CAR was calculated by dividing the serum C-reactive protein (CRP) level (mg/dl) by serum albumin level (g/dl) [20].

Treatment and patient follow-up

Postoperative complications were defined as those occurring within 30 days after primary surgery. Patients with Clavien-Dindo grade II or higher complications were included in the complication group [21]. Postoperatively, the patients were followed up every 3 months for 3 years, and then every 6 months until 5 years. At each follow-up, tumor biomarkers, including serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19–9, were measured. Contrast-enhanced computed tomography or magnetic resonance imaging and colonoscopy were performed during the follow-up period according to the NCCN Clinical Practice Guidelines in Oncology [22].

Statistical analysis

All statistical analyses were conducted using EZR software version 1.51 (Saitama Medical Center, Jichi Medical University, Japan), and all P-values were two-sided with α level of 0.05.

Data are expressed as a median value. Continuous and categorical variables were compared using the Mann–Whitney U or chi-square tests, as appropriate. The optimal cutoff value of clinical continuous variables was determined by a receiver-operating characteristic (ROC) analyses to overall survival event. Clinical continuous variables were classified into two groups for Cox proportional-hazard regression models using the cutoff value, and above or below the standard value.

We evaluated the prognostic significance of ChE in patients with CRC of stage I to III. Univariate and multivariate Cox proportional-hazard regression models were used to estimate the hazard ratios (HR) for disease-free and overall survival. The multivariable Cox regression model included sex (male vs. female), age (≥ 65 vs. < 65 years), surgical approach (laparoscopic vs. open), tumor location (rectum vs. colon), pathological depth of invasion (T3 or T4 vs. T1 or T2), pathological lymph node metastasis (positive vs. negative), serum albumin (< 3.5 vs. ≥ 3.5 g/dl), serum ChE (< 247 vs. ≥ 247 U/l), NLR (≥ 2.64 vs. < 2.64), PNI (< 45.2 vs. ≥ 45.2), CAR (≥ 0.119 vs. < 0.119), serum CEA (≥ 6.0 vs. < 6.0 ng/ml), serum CA19-9 (≥ 37 vs. < 37 U/ml), and postoperative complications (yes vs. no). A backward elimination stepwise approach was conducted with a threshold P-value of 0.05 to select variables for the final model. The Kaplan–Meier method was used to estimate cumulative survival probabilities, and the differences between groups were compared using the log-rank test.

Results

Patients' characteristics

Demographic and preoperative characteristics of patients ($n = 174$) are shown in Table 1. The median age was 74 (23–98) years and 97 patients were male. Fifty-nine patients (33.9%) developed postoperative complications and laparoscopic surgery was performed in 108 patients (62.1%). In the present study, the median follow-up time was 3.1 years and the 5-year overall survival rate after resection for CRC was 83.3%.

Table 1 Patient characteristics

Characteristic	All ($n=174$)
Sex, male	97 (55.7%)
Age (year)	74 (23–98)
BMI (kg/m^2)	22.1 (12.1–32.0)
ASA-PS ≥ 3	30 (17.2%)
Surgical approach	
Laparoscopic	108 (62.1%)
Open	66 (37.9%)
Location	
Colon	112 (64.4%)
Rectum	62 (35.6%)
Depth of invasion	
T1-2	57 (32.8%)
T3-4	117 (67.2%)
Lymph node metastasis, positive	65 (37.4%)
Stoma construction	28 (16.1%)
Operation time	241 (60–510)
Blood loss	40 (0–1100)
Postoperative complications (C-D classification)	59 (33.9%)
Grade II	49 (28.2%)
Grade III-IV	6 (3.45%)
Serum cholinesterase levels (U/l)	265 (54–461)
NLR	2.64 (0.87–13.5)
PNI	46.6 (26.5–64.4)
CAR	0.058 (0.002–4.003)

ASA-PS American Society of Anesthesiologists physical status, *BMI* body mass index, *CAR* C-reactive protein to albumin ratio, *C-D* Clavien-Dindo, *NLR* neutrophil to lymphocyte ratio, *PNI* prognostic nutritional index

Survival curve in patients after curative resection for CRC according to preoperative serum ChE levels

The optimal cutoff value of serum ChE levels determined by a ROC analysis was 247 U/l, and the area under the curve (AUC) was 0.684 (95% confidence interval [CI]: 0.578–0.790). Preoperative serum ChE levels were significantly associated with disease-free survival (Fig. 1a; log-rank test, $P < 0.01$) and overall survival (Fig. 1b; log-rank test, $P < 0.01$) after curative resection for CRC.

Univariate and multivariate analyses of clinicopathologic variables in relation to disease-free survival after curative resection for CRC

Table 2 lists the relationship between the clinical variables and disease-free survival after curative resection for CRC. In univariate analysis, disease-free survival was significantly worse in patients with depth of invasion T3 or T4 ($P=0.029$), lymph node metastasis ($P < 0.01$), albumin < 3.5 g/dl ($P=0.011$), ChE < 247 g/dl ($P < 0.01$), PNI < 45.2 ($P=0.026$), CAR ≥ 0.119 ($P < 0.01$), CEA ≥ 6.0 ng/ml ($P < 0.01$), and postoperative complication occurrence ($P=0.037$). In multivariate analysis, lymph node metastasis ($P=0.011$) and ChE < 247 g/dl ($P < 0.01$) were independent predictors of disease-free survival.

Univariate and multivariate analyses of clinicopathologic variables in relation to overall survival after curative resection for CRC

Table 3 lists the relationship between the clinical variables and overall survival after curative resection for CRC. In univariate analysis, overall survival was significantly worse in patients with lymph node metastasis ($P < 0.01$), albumin < 3.5 g/dl ($P < 0.01$), ChE < 247 g/dl ($P < 0.01$), PNI < 45.2 ($P=0.020$), CAR ≥ 0.119 ($P < 0.01$), CEA ≥ 6.0 ng/ml ($P < 0.01$), and CA19-9 ≥ 37 ng/ml ($P=0.017$). In multivariate analysis, lymph node metastasis ($P=0.013$), ChE < 247 g/dl ($P < 0.01$), and CA19-9 ≥ 37 ng/ml ($P=0.022$) were independent predictors of overall survival.

Patients' characteristics according to preoperative serum ChE levels

The clinical perioperative characteristics of patients according to ChE levels are shown in Table 4. Body mass index (BMI) ($P < 0.01$), surgical approach (laparoscopic) ($P < 0.01$), serum albumin levels ($P < 0.01$), and PNI ($P < 0.01$) were significantly lower in the low-ChE group. On the other hand, age ($P < 0.01$), NLR ($P=0.021$), CAR ($P < 0.01$), and distant metastasis ($P < 0.01$) were significantly higher in the low-ChE group. There was no difference in local recurrence ($P=0.79$) between the two groups.

Subgroup analysis according to the tumor-node classification

Subgroup analysis was performed to further investigate the predictive value of preoperative serum ChE levels. In the subgroup of T3-4 patients, the low-ChE group had worse disease-free survival and overall survival than the high-ChE group. Similar associations were observed in the subgroup of T1-2 (Fig. 2a–d). Also, in the subgroup of lymph node metastasis-positive patients, the low-ChE group had worse disease-free survival and overall survival than the high-ChE group. Similar associations were observed in the subgroup of lymph node metastasis-negative patients (Fig. 3a–d).

a

b
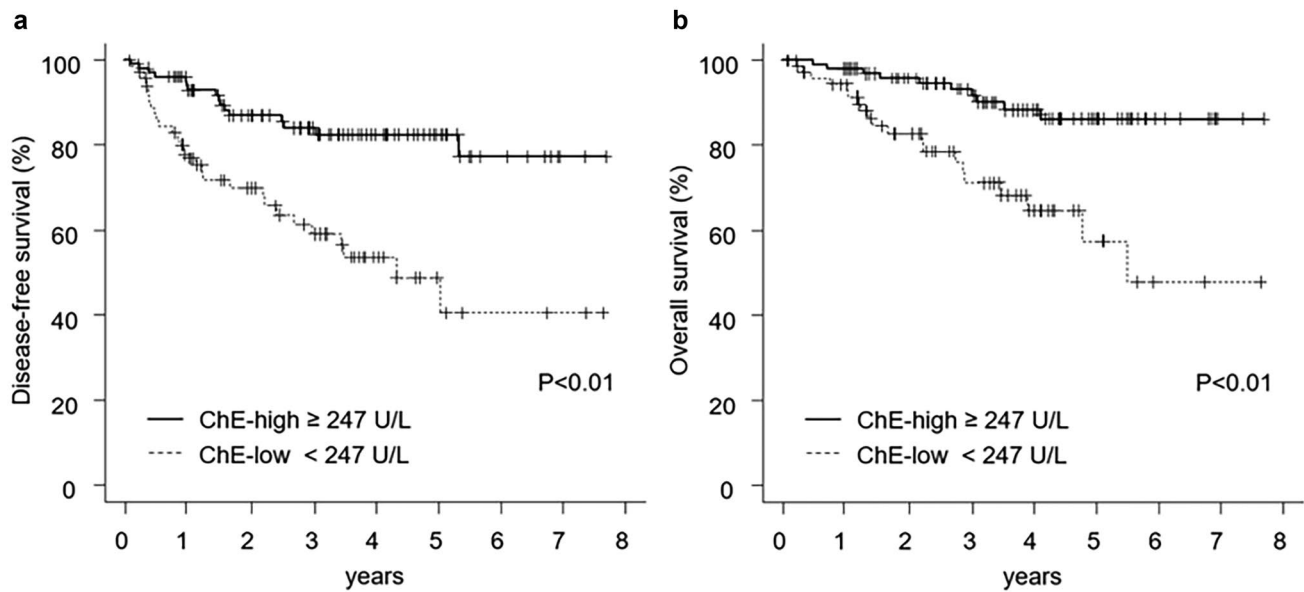
Fig. 1 Kaplan–Meier curves according to preoperative serum ChE levels for disease-free survival (**a**) and overall survival (**b**) after curative resection for colorectal cancer. Preoperative serum ChE levels were significantly associated with disease-free survival ($P < 0.01$) and overall survival ($P < 0.01$)

Table 2 Univariate and multivariate analyses of factors associated with disease-free survival

Variables	Univariate		Multivariate[*]	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex (male)	1.25 (0.74–2.44)	0.33		N.S
Age (≥ 65 years)	1.51 (0.67–3.38)	0.32		N.S
Surgical approach (laparoscopic)	0.67 (0.38–1.21)	0.19		N.S
Tumor location (rectum)	1.40 (0.76–2.57)	0.28		N.S
Depth of invasion (T3-4)	2.26 (1.08–4.70)	0.029		N.S
Lymph node metastasis, positive	2.72 (1.50–4.91)	<0.01	2.27 (1.21–4.28)	0.011
Serum albumin (<3.5 g/dl)	2.21 (1.20–4.07)	0.011		N.S
Serum cholinesterase (<247 U/l)	3.29 (1.78–6.08)	<0.01	2.70 (1.42–5.12)	<0.01
NLR (≥2.64)	1.43 (0.80–2.57)	0.23		N.S
PNI (<45.2)	1.96 (1.09–3.52)	0.026		N.S
CAR (≥0.119)	2.47 (1.36–4.47)	<0.01		N.S
Serum CEA (≥6.0 ng/ml)	2.85 (1.53–5.31)	<0.01		N.S
Serum CA19-9 (≥37 ng/ml)	1.42 (0.66–3.08)	0.37		N.S
Postoperative complication, yes	1.87 (1.04–3.37)	0.037		N.S

*The multivariable Cox regression model included sex (male vs. female), age (≥ 65 vs. < 65 years), surgical approach (laparoscopic vs. open), tumor location (rectum vs. colon), pathological depth of invasion (T3 or T4 vs. T1 or T2), pathological lymph node metastasis (positive vs. negative), serum albumin (< 3.5 vs. ≥ 3.5 g/dl), serum ChE (< 247 vs. ≥ 247 U/L), NLR (≥ 2.64 vs. < 2.64), PNI (< 45.2 vs. ≥45.2), CAR (≥ 0.119 vs. <0.119), serum CEA (≥ 6.0 vs. < 6.0 ng/ml), serum CA19-9 (≥ 37 vs. < 37 U/ml) and postoperative complications (yes vs. no). A backward elimination was conducted with a threshold P of 0.05 to select variables for the final models

CAR C-reactive protein to albumin ratio, *CA19-9* carbohydrate antigen 19–9, *CEA* carcinoembryonic antigen, *NLR* neutrophil to lymphocyte ratio, *N.S.* not significant, *PNI* prognostic nutritional index

Table 3 Univariate and multivariate analyses of factors associated with overall survival

Variables	Univariate		Multivariate[*]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex (male)	1.74 (0.82–3.73)	0.15		N.S
Age (≥ 65 years)	1.45 (0.56–3.80)	0.44		N.S
Surgical approach (laparoscopic)	0.70 (0.34–1.43)	0.33		N.S
Tumor location (rectum)	1.13 (0.53–2.42)	0.75		N.S
Depth of invasion (T3-4)	2.07 (0.84–5.08)	0.11		N.S
Lymph node metastasis, positive	3.43 (1.60–7.33)	< 0.01	2.81 (1.25–6.31)	0.013
Serum albumin (< 3.5 g/dl)	3.38 (1.64–6.98)	< 0.01		N.S
Serum cholinesterase (< 247 U/l)	3.77 (1.76–8.09)	< 0.01	3.17 (1.43–7.02)	< 0.01
NLR (≥ 2.64)	1.78 (0.86–3.66)	0.12		N.S
PNI (< 45.2)	2.39 (1.15–4.96)	0.020		N.S
CAR (≥ 0.119)	3.71 (1.75–7.87)	< 0.01		N.S
Serum CEA (≥ 6.0 ng/ml)	3.04 (1.43–6.45)	< 0.01		N.S
Serum CA19-9 (≥ 37 ng/ml)	2.70 (1.20–6.12)	0.017	2.80 (1.16–6.75)	0.022
Postoperative complication, yes	1.84 (0.90–3.77)	0.096		N.S

*The multivariable Cox regression model included sex (male vs. female), age (≥ 65 vs. < 65 years), surgical approach (laparoscopic vs. open), tumor location (rectum vs. colon), pathological depth of invasion (T3 or T4 vs. T1 or T2), pathological lymph node metastasis (positive vs. negative), serum albumin (< 3.5 vs. ≥ 3.5 g/dl), serum ChE (< 247 vs. ≥ 247 U/L), NLR (≥ 2.64 vs. < 2.64), PNI (< 45.2 vs. ≥45.2), CAR (≥ 0.119 vs. <0.119), serum CEA (≥ 6.0 vs. < 6.0 ng/ml), serum CA19-9 (≥ 37 vs. < 37 U/ml) and postoperative complications (yes vs. no).A backward elimination was conducted with a threshold *P* of 0.05 to select variables for the final models

CAR C-reactive protein to albumin ratio, *CA19-9* carbohydrate antigen 19–9, *CEA* carcinoembryonic antigen, *NLR* neutrophil to lymphocyte ratio, *N.S.* not significant, *PNI* prognostic nutritional index

Table 4 Clinicopathological variables according to preoperative serum ChE levels in patients undergoing curative resection for CRC

Variables	High ChE (≥ 247 U/l) (*n* = 102)	Low ChE (< 247 U/l) (*n* = 72)	*P*-value[†]
Clinical/intraoperative			
Sex (male/female)	58/44	39/33	0.76
Age (year)	68 (23–92)	80 (45–98)	< 0.01
BMI (kg/m^2)	22.8 (17.3–32.0)	21.0 (12.1–30.2)	< 0.01
Diabetes mellitus	25 (24.5%)	19 (26.4%)	0.86
ASA-PS ≥ 3	13 (12.7%)	17 (23.6%)	0.069
Surgical approach (laparoscopic)	74 (72.5%)	34 (47.2%)	< 0.01
Serum albumin levels (g/dl)	4.2 (2.7–5.0)	3.5 (1.9–4.5)	< 0.01
NLR	2.60 (1.06–6.23)	2.96 (0.87–13.5)	0.021
PNI	49.8 (33.4–64.4)	43.2 (26.5–55.9)	< 0.01
CAR	0.024 (0.002–2.863)	0.166 (0.005–4.003)	< 0.01
Pathological			
Depth of invasion (T3-4)	63 (61.8%)	54 (75.0%)	0.073
Lymph node metastasis, positive	32 (31.3%)	33 (45.8%)	0.058
Postoperative			
Distant metastasis	7 (6.86%)	18 (25.0%)	< 0.01
Local recurrence	8 (7.84%)	7 (9.72%)	0.79

†To compare categorical data between the high-ChE or low-ChE groups, the chi-square test was performed.To compare continuous variables, Mann–Whitney *U*-test was performed

ASA-PS American Society of Anesthesiologists physical status, *BMI* body mass index, *CAR* C-reactive protein to albumin ratio, *ChE* cholinesterase, *CRC* colorectal cancer, *NLR* neutrophil to lymphocyte ratio, *PNI* prognostic nutritional index
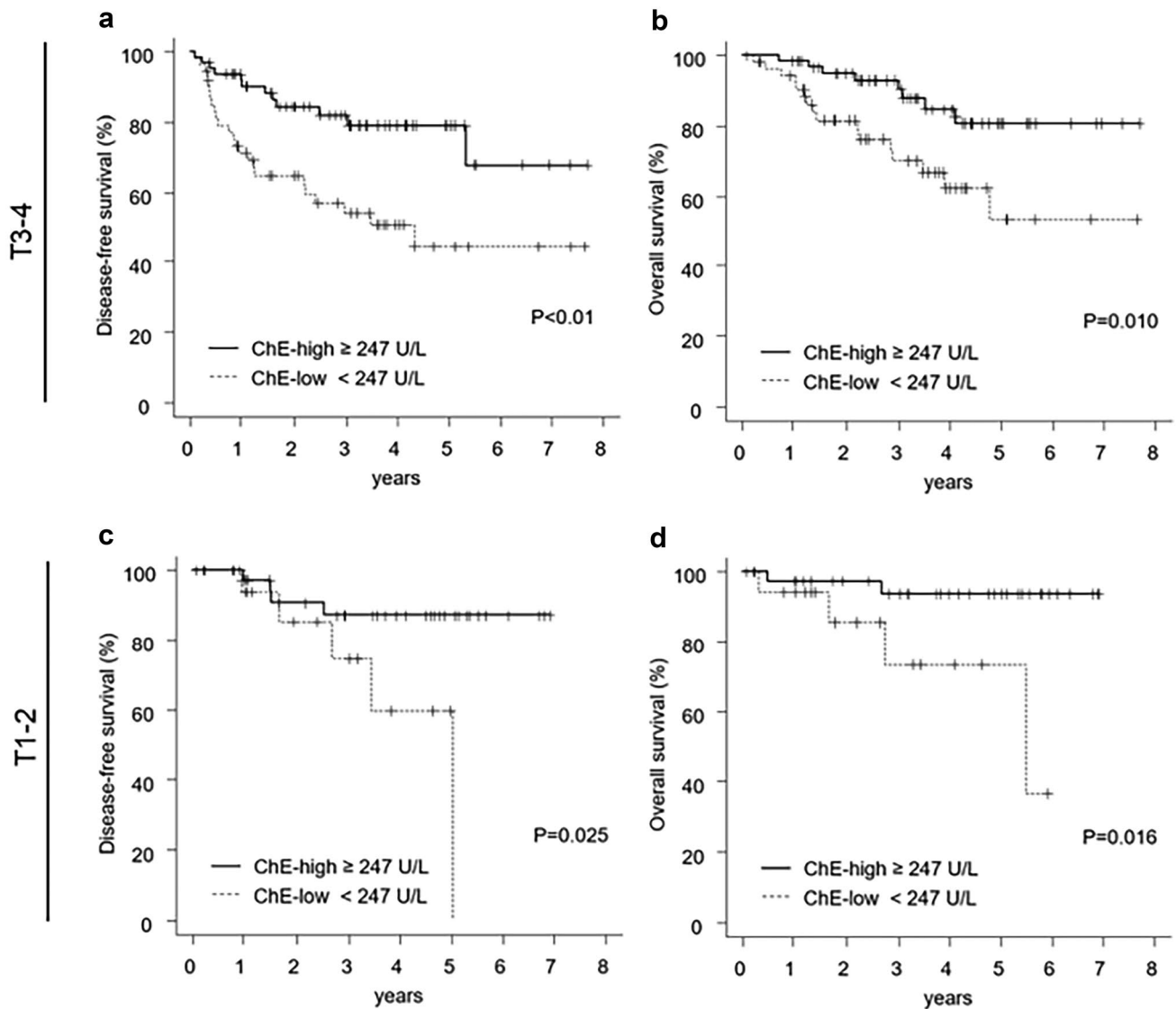
Fig. 2 Kaplan–Meier curves according to preoperative serum ChE levels for disease-free survival and overall survival in the subgroups of T3-4 or T1-2 patients. In the s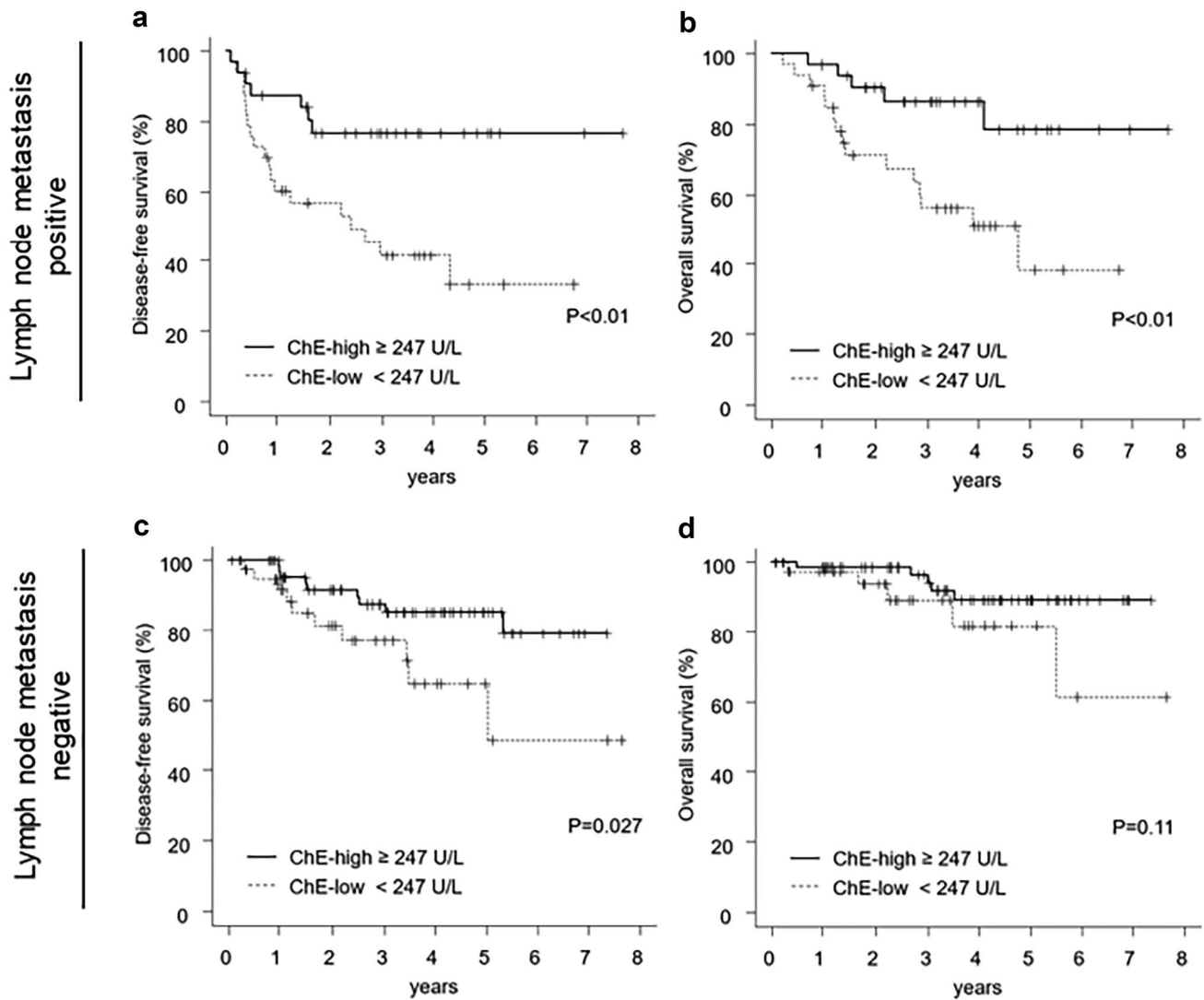ubgroup of T3-4 patients, the low-ChE group had worse disease-free survival (**a**) and overall survival (**b**) than the high-ChE group. Similar associations were observed in the subgroup of T1-2 patients (**c** and **d**)

Discussion

We showed the significant association between preoperative serum ChE levels and poor prognosis in patients who had underwent curative resection for CRC. Multivariable analysis revealed that low ChE levels were the independent risk factor for worse disease-free survival and overall survival. Furthermore, subgroup analyses revealed that the low-ChE group had worse disease-free survival and overall survival than the high-ChE group regardless of T and N stage. Also, the low-ChE group had more distant metastasis and higher systemically inflammatory response compared with the high-ChE group. These findings suggest that preoperative serum ChE levels, which is a classical nutrition marker, can

be one of the prognostic values compared with the other systemic inflammatory response in patients who underwent colorectal resection for CRC.

ChE has been reported as predictor of postoperative prognosis in various cancers, including gastric [23] and pancreatic cancer [24]. In consistent with the previous studies, our finding revealed that serum ChE levels can be a significant predictor in patients with CRC. The mechanism that preoperative serum ChE levels are sensitive for predicting poor prognosis in patients with CRC is unclear. However, there are some reasons for determining that ChE is a valuable factor compared with the other systemic inflammatory response. Preoperative serum ChE levels can reflect nutritional status more acutely than albumin,

Fig. 3 Kaplan–Meier curves according to preoperative serum ChE levels for disease-free survival and overall survival in the subgroup of lymph node metastasis-positive or -negative patients. In the subgroup of lymph node metastasis-positive patients, the low-ChE group had worse disease-free survival (**a**) and overall survival (**b**) than the high-ChE group. Similar associations were observed in the subgroup of lymph node metastasis negative patients (**c** and **d**)

because the half-life of ChE is shorter than albumin (3–11 vs. 12–21 days) to reflect preoperative general condition more sensitively [7, 25–27]. In fact, serum ChE levels were more accurately than albumin, PNI, and CAR for assessing poor prognosis in the present study. Furthermore, low serum ChE levels can reflect the elevation of inflammation status [15]. In patients with cancer or frailty, cytokine such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), which were negatively correlated with serum ChE levels, significantly increase to activate signal transducer and activator of transcription 3 (STAT3) and nuclear factor-kappa B (NF-kB) pathway in cancer [15, 16]. These inflammatory cascades have been reported to block the synthesis of ChE and albumin in favor of acute-phase protein

synthesis [15, 28], and promote cancer-related inflammation, epithelial-to-mesenchymal transition (EMT)-mediated invasion, and metastasis in CRC [29, 30]. These evidence support our findings that several systemic inflammatory responses and distant metastasis were negatively associated with serum ChE levels.

The present study has several limitations. The most important limitation was the retrospective observational study and the confounding factors cannot be completely ruled out. Serum ChE levels might be confounded by several factors such as inflammatory, nutritional status, and cancer stage, which may have influenced the results. Also, since the present study was conducted at a single institution with limited sample size. Further prospective studies with the

large sample size are needed to robustly assess the prognostic value of ChE and validate our findings.

Conclusion

Preoperative low serum ChE levels predicted worse disease-free survival and overall survival in patients with CRC. Routine preoperative measurement of preoperative serum ChE levels in patients undergoing curative resection for CRC would be useful for assessing their nutritional-inflammatory status and predicting postoperative outcome.

Declarations

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359–E386. https://doi.org/10.1002/ijc.29210

2. Dienstmann R, Vermeulen L, Guinney J, Kopetz S, Tejpar S, Tabernero J (2017) Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. Nat Rev Cancer 17:79–92. https://doi.org/10.1038/nrc.2016.126

3. Vallribera Valls F, Landi F, Espín Basany E, Sánchez García JL, Jiménez Gómez LM, Martí Gallostra M, Salgado Cruz L, Armengol Carrasco M (2014) Laparoscopy-assisted versus open colectomy for treatment of colon cancer in the elderly: morbidity and mortality outcomes in 545 patients. Surg Endosc 28:3373–3378. https://doi.org/10.1007/s00464-014-3597-4

4. Riihimaki M, Hemminki A, Sundquist J, Hemminki K (2016) Patterns of metastasis in colon and rectal cancer. Sci Rep 6:29765. https://doi.org/10.1038/srep29765

5. Neki K, Eto K, Kosuge M, Ohkuma M, Ito D, Takeda Y, Yatabe S, Sugano H, Yanaga K (2019) Identification of the risk factors for

6. van Gestel YR, de Hingh IH, van Herk-Sukel MP, van Erning FN, Beerepoot LV, Wijsman JH, Slooter GD, Rutten HJ, Creemers GJ, Lemmens VE (2014) Patterns of metachronous metastases after curative treatment of colorectal cancer. Cancer Epidemiol 38:448–454. https://doi.org/10.1016/j.canep.2014.04.004

7. Gamsjager T, Brenner L, Sitzwohl C, Weinstabl C (2008) Half-lives of albumin and cholinesterase in critically ill patients. Clin Chem Lab Med 46:1140–1142. https://doi.org/10.1515/CCLM.2008.220

8. Wang Y, Wang H, Chen HZ (2016) AChE Inhibition-based multi-target-directed ligands, a novel pharmacological approach for the symptomatic and disease-modifying therapy of Alzheimer's disease. Curr Neuropharmacol 14:364–375. https://doi.org/10.2174/1570159x14666160119094820

9. Ramachandran J, Sajith KG, Priya S, Dutta AK, Balasubramanian KA (2014) Serum cholinesterase is an excellent biomarker of liver cirrhosis. Trop Gastroenterol 35:15–20. https://doi.org/10.7869/tg.158

10. Seo M, Yamada T, Tamaki S, Hikoso S, Yasumura Y, Higuchi Y, Nakagawa Y, Uematsu M, Abe H, Fuji H, Mano T, Nakatani D, Fukunami M, Sakata Y (2020) Prognostic significance of serum cholinesterase level in patients with acute decompensated heart failure with preserved ejection fraction: insights from the PURSUIT-HFpEF registry. J Am Heart Assoc 9:e014100. https://doi.org/10.1161/JAHA.119.014100

11. Khalil SN, Dudrick SJ, Mathieu A, Rigor BMS, Fody EP (1980) Low level of pseudocholinesterase in patient with Crohn's disease. Lancet 2:267–268. https://doi.org/10.1016/s0140-6736(80)90160-9

12. Santarpia L, Grandone I, Contaldo F, Pasanisi F (2013) Butyryl-cholinesterase as a prognostic marker: a review of the literature. J Cachexia Sarcopenia Muscle 2:267–268. https://doi.org/10.1007/s13539-012-0083-5

13. Cheng BN, Jin YL, Chen BQ, Zhu LY, Xu ZC, Shen T (2016) Serum cholinesterase: a potential assistant biomarker for hand, foot, and mouth disease caused by enterovirus 71 infection. Infect Dis Poverty 5:27-y. https://doi.org/10.1186/s40249-016-0124-y

14. Gu SZ, Zhao XH, Quan P, Li SB, Pan BR (2005) Alterations of serum cholinesterase in patients with gastric cancer. World J Gastroenterol 11:4604–4606. https://doi.org/10.3748/wjg.v11.i29.4604

15. Camarero Gonzalez E, Munoz Leira V, Iglesias Guerrero M, Fernandez Alvarez JA, Cabezas-Cerrato J (1995) Protein-energy malnutrition: its effects on 4 metabolic parameters. Nutr Hosp 10:158–160

16. De Simone V, Franzè E, Ronchetti G, Colantoni A, Fantini MC, Di Fusco D, Sica GS, Sileri P, MacDonald TT, Pallone F, Monteleone G, Stolfi C (2015) Th17-type cytokines, IL-6 and TNF-alpha synergistically activate STAT3 and NF-kB to promote colorectal cancer cell growth. Oncogene 34:3493–3503. https://doi.org/10.1038/onc.2014.286

17. Takano Y, Haruki K, Tsukihara S, Ito D, Kanno H, Son K, Eto K, Hanyu N, Ikegami T (2021) Preoperative serum cholinesterase levels as a risk factor of postoperative complications for the elderly undergoing emergency surgery. Surg Today 51:1828–1834. https://doi.org/10.1007/s00595-021-02288-4

18. Hayama T, Hashiguchi Y, Okada Y, Ono K, Nemoto K, Shimada R, Ozawa T, Toyoda T, Tsuchiya T, Iinuma H, Nozawa K, Matsuda K (2020) Significance of the 7th postoperative day neutrophil-to-lymphocyte ratio in colorectal cancer. Int J Colorectal Dis 35:119–124. https://doi.org/10.1007/s00384-019-03463-3

19. Sato R, Oikawa M, Kakita T, Okada T, Abe T, Yazawa T, Tsuchiya H, Akazawa N, Sato M, Ohira T, Harada Y, Okano H, Ito K, Tsuchiya T (2020) The prognostic value of the prognostic

nutritional index and inflammation-based markers in obstructive colorectal cancer. Surg Today 50:1272–1281. https://doi.org/10.1007/s00595-020-02007-5

20. Matsuoka H, Ando K, Hu Q, Zaitsu Y, Tsuda Y, Hisamatsu Y, Nakashima Y, Kimura Y, Oki E, Mori M (2020) Postoperative C-reactive protein/albumin ratio is a biomarker of risk of recurrence and need for adjuvant chemotherapy for stage III colorectal cancer. Int J Clin Oncol 25:1318–1326. https://doi.org/10.1007/s10147-020-01672-3

21. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D et al (2009) The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 250:187–196. https://doi.org/10.1097/SLA.0b013e3181b13ca2

22. Benson AB 3rd, Choti MA, Cohen AM, Doroshow JH, Fuchs C, Kiel K, Martin EW Jr, McGinn C, Petrelli NJ, Posey JA, Skibber JM, Venook A, Yeatman TJ, Network NCC (2000) NCCN practice guidelines for colorectal cancer. Oncology (Williston Park) 14:203–212

23. Bi Y, Zhang J, Zeng D, Chen L, Ye W, Yang Q, Ling Y (2021) Cholinesterase is associated with prognosis and response to chemotherapy in advanced gastric cancer. Pathol Oncol Res 27:580800. https://doi.org/10.3389/pore.2021.580800

24. Mitsunaga S, Kinoshita T, Hasebe T, Nakagohri T, Konishi M, Takahashi S, Gotohda N, Ochiai A (2008) Low serum level of cholinesterase at recurrence of pancreatic cancer is a poor prognostic factor and relates to systemic disorder and nerve plexus invasion. Pancreas 36:241–248. https://doi.org/10.1097/MPA.0b013e31815b6b2b

25. Robinson MK, Trujillo EB, Mogensen KM, Rounds J, McManus K, Jacobs DO (2003) Improving nutritional screening of hospitalized patients: the role of prealbumin. JPEN J Parenter Enteral Nutr 27:389–395; quiz 439. https://doi.org/10.1177/0148607103027006389

26. Ostergaard D, Viby-Mogensen J, Hanel HK, Skovgaard LT (1988) Half-life of plasma cholinesterase. Acta Anaesthesiol Scand 32:266–269. https://doi.org/10.1111/j.1399-6576.1988.tb02727.x

27. Spiess A, Mikalunas V, Carlson S, Zimmer M, Craig RM (1996) Albumin kinetics in hypoalbuminemic patients receiving total parenteral nutrition. JPEN J Parenter Enteral Nutr 20:424–428. https://doi.org/10.1177/0148607196020006424

28. Santarpia L, Marra M, Montagnese C, Alfonsi L, Pasanisi F, Contaldo F (2009) Prognostic significance of bioelectrical impedance phase angle in advanced cancer: preliminary observations. Nutrition 25:930–931. https://doi.org/10.1016/j.nut.2009.01.015

29. Rokavec M, Öner MG, Li H, Jackstadt R, Jiang L, Lodygin D, Kaller M, Horst D, Ziegler PK, Schwitalla S, Slotta-Huspenina J, Bader FG, Greten FR, Hermeking H (2014) IL-6R/STAT3/miR-34a feedback loop promotes EMT-mediated colorectal cancer invasion and metastasis. J Clin Invest 124:1853–1867. https://doi.org/10.1172/JCI73531

30. Ye X, Wu H, Sheng L, Liu YX, Ye F, Wang M, Zhou H, Su Y, Zhang XK (2019) Oncogenic potential of truncated RXRalpha during colitis-associated colorectal tumorigenesis by promoting IL-6-STAT3 signaling. Nat Commun 10:1463–1468. https://doi.org/10.1038/s41467-019-09375-8

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.