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【 Original Article 】

Bimodal mixed normal distribution of cholinesterase and in-hospital mortality in patients with terminal colorectal cancer

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Abstract

OBJECTIVES: Malnutrition in cancer patients is associated with a poor prognosis. Nitrogen death occurs when lean body mass, a measure of muscle protein, falls below 70% of normal range.Cholinesterase (ChE) reflects protein concentration and has a shorter half-life than albumin (Alb); however, its utility as a biomarker has not been fully understood. To estimate ChE levels in colorectal cancer patients upon admission and prior to death, and to determine the cutoff value and usefulness of ChE as a biomarker for estimating in-hospital mortality.
METHODS: We measured ChE in 69 colorectal cancer patients hospitalized from April 2019 to March 2021. Changes in ChE levels were compared with those in Alb and other blood parameters. We also performed a multivariate analysis to assess the hazard ratio between the changes in ChE and in-hospital mortality.
RESULTS: In the blood draw prior to death, ChE exhibited a bimodal mixed normal distribution, with a hazard ratio of 2.52 for in-hospital mortality in the low ChE group (47%) with <100 IU/L as compared to the high ChE group (53%).
CONCLUSIONS: Our findings suggest that a cutoff ChE level of 100 IU/L could serve as a useful biomarker for estimating in-hospital mortality in colorectal cancer patients.

Key words: malnutrition, cholinesterase, colorectal cancer, complications, biomarker, in-hospital mortality, bimodal mixed normal distribution

Introduction

As cancer progresses, patients in a palliative care unit often experience malnutrition, particularly when protein levels drop to 70% of the lean body mass (LBM), which decreases visceral proteins, impairs the immune system, and ultimately results in organ dysfunction[1)]. Furthermore, there is a strong correlation between albumin (Alb) and cholinesterase (ChE)[2)]. Inadequate nutrition accompanied by decreased Alb and ChE levels, have been associated with a poor prognosis due to their detrimental effects on vital organs[1,3)]. There are two types of ChE found in human serum: acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). AChE

plays a role in nerve impulse transmission and can be found in erythrocyte membranes[4], while BChE is typically measured in clinical laboratory tests. This study collectively refers to them as ChE.

Typically, serum Alb (half-life of - 3 weeks)[5,6] is commonly used to assess protein levels in palliative care units. However, in such units where patients often have a short prognosis, ChE (half-life of - 10 days) may be more useful than Alb[7,8]. However, the clinical significance of ChE in this context remains unclear.

The objective of this paper was to demonstrate the utility of ChE as a biomarker for assessing nutritional status and predicting prognosis in terminally ill colorectal cancer patients in a palliative care unit.

Patients and Methods

This was a retrospective, observational study.The target patients were 69 patients with colorectal cancer who died between April 2019 and March 2021 in the Palliative Care Unit of Kagoshima Medical Association Hospital. The mean age (standard deviation) was 76.7 (10.6) years, with 31 males and 38 females. Consistent with previous studies[9-11], we gathered information such as age, sex, tumor location (colon or rectum), hospitalization days, presence of liver or lung metastasis, ChE and Alb levels, red blood cell count (RBC), white blood cell count (WBC), C-reactive protein (CRP), total cholesterol (T.Cho), triglycerides (TG) content, and loss of appetite. We also collected data on metastatic organs, including the presence of hydronephrosis using X-ray and computed tomography (CT) images. We conducted a retrospective analysis to explore the relationship between these parameters.

The primary endpoint of this study was to demonstrate the utility of ChE as a biomarker (cutoff value) for estimating in-hospital mortality among patients with colorectal cancer in a palliative care unit. Blood samples were collected upon admission and every 2 to 4 weeks, and the blood drawn closest to the patient's date of death was selected as the pre-death data. In the present analysis, patients were categorized into two groups based on their clinical empirical ChE values: Group A: ChE ≥ 100 IU/L and Group B: ChE < 100 IU/L.

Age and sex were treated as categorical variables and analyzed using the Pearson's chi-square test. Blood parameters were subjected to the Wilcoxon signed rank test as continuous variables. RBC results were classified into two groups based on the mean value, while WBC results were classified into two groups depending upon individual data (> 10,000/μL and < 10,000/μL). Pearson's chi-square test was performed to assess fatal complications during hospitalization and denoted as event D. Loss of appetite was compared between two groups of patients post-hospitalization: those who consumed less than 50% of the diet and those who consumed more than 50%. The McNemar test was

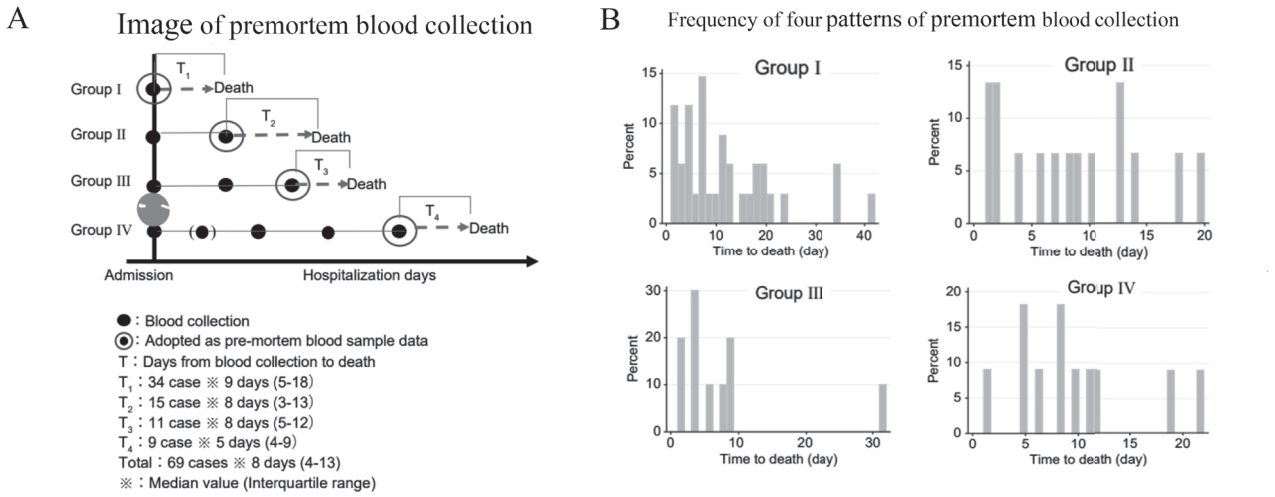
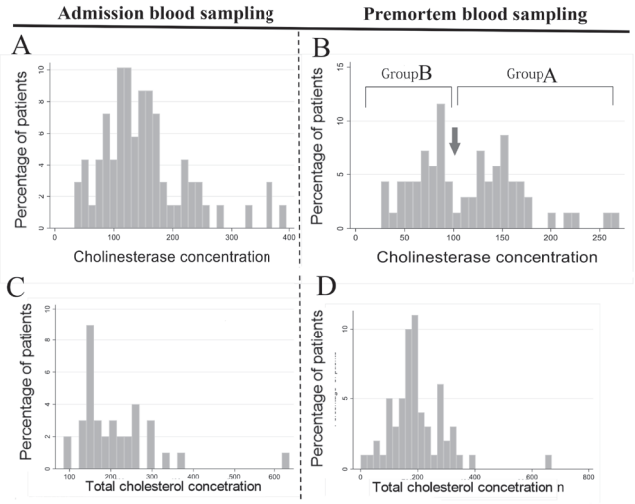


Figure 1

(A) Blood sampling was performed every 2–4 weeks after hospital admission. T shows the number of days from last blood sampling to death, and as shown in the figure, Group I: Group with one blood sampling at admission [T1: median of 9 days], Group II: Group that died after two blood samplings [T2: median of 8 days], Group III: Group that died after three blood samplings [T3: median of 8 days], and Group IV: Group that died after four to five blood samplings [T4: median of 5 days]. The overall T was a median of 8 days.

(B) Four patterns of histograms of the number of days from the last blood draw to death are shown. The number of days before death was shown in terms of median values (interquartile range) because all groups had non-normal distribution.



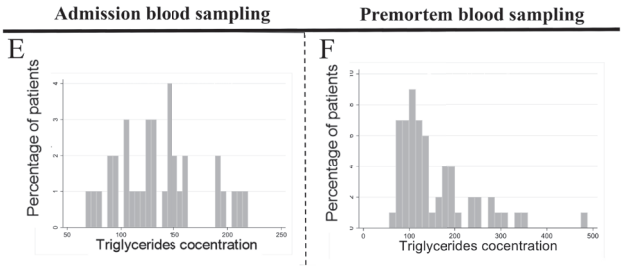


Figure 2
This is the histogram of cholinesterase. (A) The cholinesterase during admission to the palliative care unit was distributed at a median of 140 IU/L. (B) The median blood draw before death was 109 IU/L, with a bimodal mixed normal distribution based on an approximate level of 100 IU/L. Group A was defined as 100 IU/L or higher and Group B as 100 IU/L or lower. (C,D) Total cholesterol and (E,F) triglycerides did not exhibit a clear bimodal distribution even in the blood draw taken prior to death.

performed to evaluate changes in WBC count during the course of the disease, comparing the ratio of patients with WBC counts above and below 10,000/μL in the two groups at the time of admission and before death.

The relationship between ChE groups A and B and various factors including tumor location, hospitalization, liver metastasis, lung metastasis, performance status (PS), surgery and chemotherapy, and occurrence of event D were tested using Pearson's chi-square test as secondary endpoints. Survival during hospitalization was analyzed using log-rank test and Kaplan–Meier method, considering the impact of surgery, chemotherapy, event D, and the presence of liver or lung metastasis.

To determine the hazard ratios of mortality over time for ChE groups A and B, univariate analysis was performed using the Cox proportional hazards model. Additionally, multivariate analysis was performed by selecting age, sex, RBC, CRP, and chemotherapy as adjustment variables. Pleural effusion was classified as a broad-sense pulmonary metastasis, an intrathoracic condition that causes respiratory distress. The unit of ChE was IU/L at that time, although U/L is used in in-hospital examinations at the time of writing.

Statistical significance was defined as $p < 0.05$. All of the data were analyzed using Stata 17 BE-Basic Edition (StataCorp LP, College Station, TX, USA)

Results

As depicted in Figure 1A, the patients were divided into four groups: (1) those who passed away shortly after a single blood draw upon admission, (2) those who died after two blood draws, (3) those who died after three blood draws, and (4) those who died after four or more blood draws. Figure 1B presents the histograms of these four groups; however, due to the non-normal distributions observed in all groups, the median time to death was calculated. The overall median time was 8 days, with an interquartile range of 4–13 days.

Serum ChE at admission to the palliative care unit had a median value of 140 U/L as shown in Figure 2A, but this

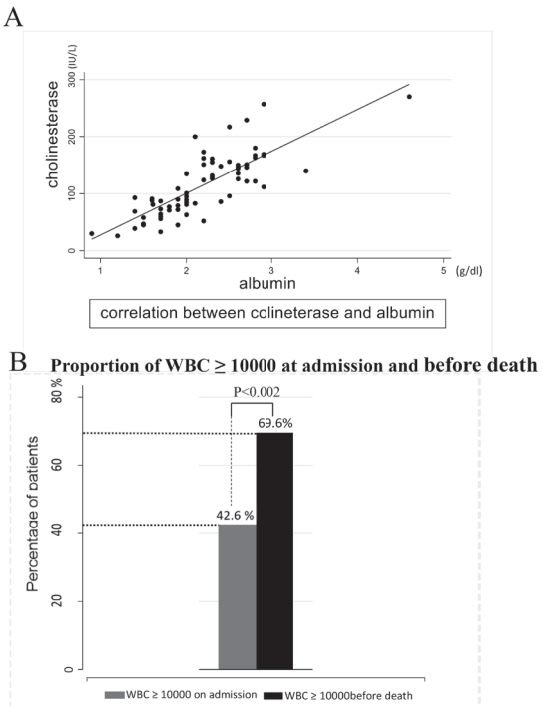


Figure 3A
Cholinesterase and albumin were strongly correlated with a coefficient of determination $R^2 = 0.69$, which was over 0.5, and considered to be collinear factors. This suggests that cholinesterase may indirectly reflect protein concentration instead of albumin.

Figure 3B
Percentage of patients with WBC ≥ 10,000/μL at admission and before death increased significantly from 42.6% to 69.6% ($P < 0.002$).

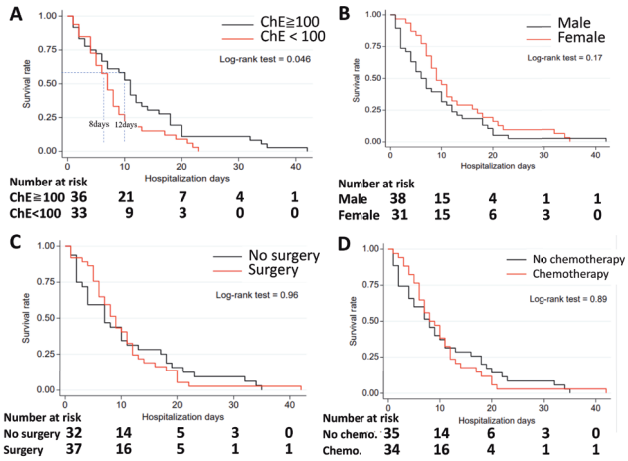


Figure 4
Kaplan–Meier survival curves were used to compare survival rates during hospitalization under various conditions. (A) Comparison of survival rates between high (A: Ch E ≥ 100 IU/L) and low (B: ChE < 100 IU/L) cholinesterase groups. The high group had a significantly higher survival rate than the low group. (B) Comparison of survival rates by gender. No significant difference was noted. (C) Comparison of survival rate by surgical procedure. No significant difference was noted. (D) Comparison of survival rate by presence or absence of chemotherapy. No significant difference was noted.

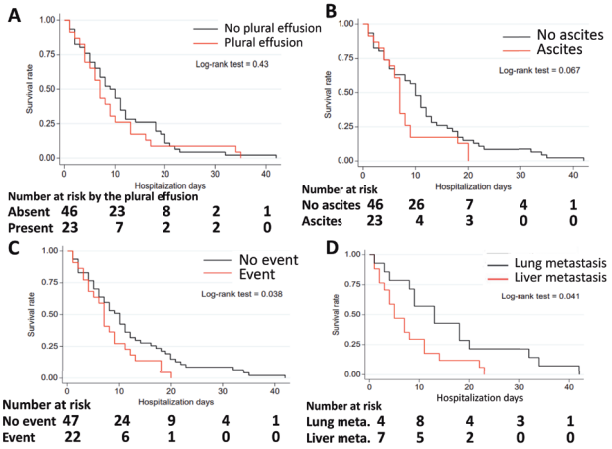


Figure 5
Kaplan–Meier survival curves were used to compare survival rates during hospitalization for various complications. (A) Comparison of survival rates and presence or absence of pleural effusion. No significant difference was noted. (B) Comparison of survival rates and presence or absence of ascites. No significant difference was noted. (C) Comparison of survival rates and severe complications (refer to Table 2). The survival rate was lower for severe complications. (D) Comparison of survival rates and lung metastasis. The survival rate was lower with lung metastasis.

decreased to a median value of 109 IU/L (73–150 IU/L) as shown in Figure 2B in the blood draw immediately before death, indicating a bimodal mixed normal distribution.

Figures 2D and 2F demonstrate that pre-death T.Cho and TG levels, which are associated with liver function, did not exhibit a clearly defined bimodal mixed normal distribution. ChE and Alb, both associated with protein metabolism, exhibited a strong correlation, indicating collinearity between the two factors, as shown in Figure 3A. The coefficient of determination (R^2) was 0.69, exceeding the threshold of 0.5.

Figure 3B reveals a significant increase in the ratio of patients with elevated WBC during the course of hospitalization, rising from 42.6% at admission to 69.6% before death (P = 0.002).

Table 1 presents a comparison between the two ChE groups, indicating no significant differences in age (< 70 and ≥ 70) (P = 0.83), sex (P = 0.57), tumor location (colon or rectum) (P = 0.14), hospitalization (P = 0.13), liver metastasis (P = 0.33), and lung metastasis (P = 0.77). However, significant differences were observed in Alb (p < 0.001), CRP (P = 0.02), RBC <346 (n = 32) and RBC ≥ 346 (n = 37) (P = 0.006), WBC categorized into < 10,000/μL or ≥ 10,000/μL groups (P = 0.008), PS (low: 2 and high: > 2) (P = 0.03), and T.Cho (P = 0.007). There was no significant difference in TG (P = 0.59). Surgery did not show a significant difference (P = 0.19), but chemotherapy did (P = 0.04). There were no significant differences in terms of event D (Table 2) (P = 0.27), loss of appetite (P = 0.68), and hydronephrosis (P = 0.42).

Figure 4A depicts a comparison of the in-hospital survival rates between ChE groups A and B using the Kaplan–Meier method. The log-rank test showed that group A had a significantly higher survival rate (P = 0.046). Although the median durations of hospitalization were 12 and 8 days for groups A and B, respectively, the difference was not statistically significant (Table 1). Figure 4B, 4C and 4D compare the survival rates of patients based on sex (P = 0.17), surgery (with or without; P = 0.96), and chemotherapy (with and without; P = 0.89), respectively. However, none of these factors significantly affected the in-hospital survival rate.

Figure 5A and 5B compare the in-hospital survival rates between patients with and without pleural effusion (P = 0.43) and those with and without ascites retention (P = 0.067); however, no significant differences were observed in either of them.

Table 2 categorizes event D, which led to patient death in the palliative care unit, into five categories. These include circulatory system events (such as massive bleeding and cardiac tamponade), respiratory system events (asphyxiation, aspiration pneumonia, metastatic lung tumor, massive pleural effusion, pulmonary embolism, and others), digestive system events (massive ascites, small bowel ileus, colon ileus, liver failure, short gut syndrome, intrahepatic tumor bleeding, and others), renal urinary system events (renal failure and

Table 1. Comparison of patient characteristics based on serum cholinesterase level

Patients characteristics	A ChE ≥ 100	B ChE < 100	p-value
Age			0.83[b]
<70 (n=18)	9 (25.0%)	9 (22.3%)	
≥70 (n=51)	27 (75.0%)	24(72.7%)	
Sex			0.57[b]
Male (n=31)	15 (41.7%)	16 (48.5%)	
Female (n=38)	21 (58.3%)	17 (51.5%)	
Tumor location			0.14[b]
Colon (n=44)	20 (55.6%)	24 (72.7%)	
Rectum (n=25)	16 (44.4%)	9 (29.3 %)	
Hospitalization days (mean±SD)	12.42±10.29	8.36±5.99	0.13[c]
Liver metastasis			0.33b
Absent (n=25)	15 (41.7%)	10 (30.3%)	
Present (n=41)	21 (58.3%)	23 (69.7%)	
Lung metastasis			0.77[b]
Absent (n=28)	14 (36.9%)	14 (42.4%)	
Present (n=41)	22 (61.1%)	19 (57.6%)	
Blood collection (premortem)			
Alb (mean±SD)	2.57± 8.3	1.76 ±0.32	<0.001[c]
RBC <346[a] (n= 32)	11 (30.6%)	21 (63.6%)	0.006[b]
RBC ≥346[a] (n=37)	25 (69.4%)	12 (36.4%)	
WBC<10000 (n=21)	16 (44.5 %)	5 (15.2%)	0.008 [b]
WBC≥10000 (n=48)	20 (54.5%)	28 (84.8%)	
CRP (mean±SD)	9.50±6.90	13.78±6.90	0.02[c]
T.cho (mean±SD)	227±110	168±80	0.007 [c]
T.G (mean±SD)	164±84	148±83	0.59 [c]
Performance status			0.03[b]
<2 (n=5)	5 (13.9%)	0 (0.0%)	
≥2 (n=64)	31 (86.1%)	33 (100.0%)	
Surgical therapy			0.19[b]
No (n=32)	14 (38.9%)	18 (54.6%)	
Yes (n= 37)	22 (61.1%)	15 (45.5%)	
Chemotherapy			0.04[b]
No (n=35)	14 (38.9%)	21 (63.6%)	
Yes (n=34)	22 (61.1%)	12 (36.4%)	
Event D			0.27 [b]
Absent (n=57)	28 (77.8%)	29 (87.9%)	
Present (n=12)	8 (22.2%)	4 (12.1%)	
Loss of appetite			0.68[b]
Absent (n=57)	18 (58.7%)	18 (52.9%)	
Present (n=12)	13 (41.9%)	16 (47.1%)	
Hydronephrosis			0.42[b]
Absent (n=57)	31 (86.1%)	26 (78.8%)	
Present (n=12)	5 (13.9%)	7(21.2%)	

[a] mean, [b] Pearson's chi-square test,[c] Wilcoxon rank-sum test, SD:standerd deviation,ChE:cholinesterase, Alb:albumin,RBC:red blood cell,WBC:white blood cell,CRP:C-reactiveprotain,T.cho:totalchoresterol, T.G:triglycerides,PS:performance status,Event D:contents of serious complications (refer to Table 2)

Table 2. EventD:Contents of serious complications (23cases)

	pathological condition
Circulatory system	massive bleeding(1cases)
	cardiac tamponade(1cases)
Respiratory system	asphyxiation (1cases)
	aspiration pneumonia (1cases)
	metastatic lung tumor (1cases)
	massive pleural effusion (2cases)
	pulmonary embolism (1cases)
Digestive system (metabolism/nutrition)	massive ascites (1cases)
	small bowel ileus (1cases)
	colon ileus (2cases)
	liver failure (5 cases)
	short gut syndrome (1cases)
	intrahepatic tumor bleeding (1cases)
Renal urinary system	renal failure (2 cases)
	bilateral hydronephrosis (1cases)
Cranial nervous system	metastatic brain tumor (1cases)

bilateral hydronephrosis), and cranial nervous system events (metastatic brain tumor with cerebral hypertension). A significant difference was observed between the in-hospital survival rates of patients with and without event D (P = 0.038), as shown in Figure 5C.

Additionally, a significant difference was observed on comparing the in-hospital survival rates between the liver metastasis group without lung metastasis and the lung metastasis group without liver metastasis (P = 0.026). Figure 5D illustrates that the liver metastasis group had a lower in-hospital survival rate compared to the lung metastasis group.

The results of the multivariate analysis, as shown in Table 3, indicated that the hazard ratio for unit time in group B was significantly higher [2.52 (95% confidence interval: 1.35–5.06, P = 0.004)] than that in the univariate analysis [1.61 (95% confidence interval: 0.983–2.643, P = 0.058)] for age, sex (male), RBC, CRP, and chemotherapy using Cox regression analysis.

Discussion

In the present study, ChE values, which serve as indicators of protein metabolism before death in colorectal cancer patients, showed a decrease in the two groups, namely the group with ChE above 100 IU/L (group A) and those below 100 IU/L (group B), displaying a bimodal mixed normal distribution. A previous study conducted by Takano *et al*. on preoperative patients with colorectal cancer found that high ChE levels were associated with a lower occurrence of distant metastasis, and low ChE was a determining factor for postoperative survival[11]. Conversely, Hamamoto *et al*., in their multivariate analysis of survival rates among patients with hepatocellular carcinoma, intrahepatic cholangiocellular carcinoma, and hilar cholangiocellular carcinoma treated with radiation therapy, found that the 2-year survival rates for the high and low ChE groups were 43% and 0%, respectively[12]. Another study by Mitsunaga investigated prognostic factors following radical surgery for advanced pancreatic cancer and reported that patients with low ChE exhibited systemic disorders such as general weakness[13].

In this study, for colorectal cancer patients in the palliative care unit, factors such as age, sex, tumor location, hospitalization, and PS did not show any correlation between the two ChE groups. However, blood parameters that are affected by inflammation,

Table 3. Univariate and multivariate survival analyses by the Cox model in patients with colorectal cancer.

	Univariate			Multivariate		
Variable	HR	95 %CI	p-value	HR	95 %CI	p-value
ChE2G	1.61	0.98-2.64	0.06	2.53	1.37-4.67	<0.01
Age	0.99	0.96-1.01	0.18	0.98	0.96-1.02	0.55
Sex	1.38	0.85-2.23	0.19	1.22	0.56-1.65	0.89
RBC	1.01	1.00-1.01	0.02	1.01	1.00-1.01	<0.01
CRP	1.03	0.99-1.06	0.13	1.02	0.98-1.06	0.28
Chemotherapy	1.38	0.72-2.63	0.89	1.34	0.69-2.60	0.40

ChE2G: cholinesterase 2 group (ChE≥100, ChE<100), RBC:red blood cell, CRP: C-reactive protain, Chemotherapy (Absent, Present)

such as Alb, RBC, and CRP, exhibited significant correlation with these two groups. There correlation may be attributed to the presence of AChE in the RBC membranes[4]. The contrasting results for the significant difference in T.Cho and none in TG may be explained by the liver acinus model proposed by Rappaport. Based on their experiments involving T.Cho injection into the liver vasculature, it was found that amino acid metabolism and T.Cho synthesis occur in zone 1, while TG is synthesized in zone 3[14]. This distinct functional distribution in the liver might explain the correlation between T.Cho and the two ChE groups, although further detailed studies are warranted.

Histopathologic examination of resected nonneoplastic liver tissue from patients with colorestal cancer and liver metastases who received preoperative chemotherapy revealed chemotherapy-related liver damage, according to Krieger *et al*.[15] It has been reported that chemotherapy-induced damage to liver parenchyma can affect protein metabolism[16], and Reissfelder *et al*. developed a risk score for liver injury associated with various chemotherapy regimens[17]. In our study, chemotherapy showed a correlation with the two ChE groups; however, there was no significant clinical difference in in-hospital survival. Event D, an incidental complication, did not exhibit a significant difference compared to ChE fluctuations.

Analyzing factors in cases exhibiting a bimodal mixed normal distribution as observed in the present study, can be challenging from a statistical point of view[18]. First, renal impairment is a pathological condition that causes high ChE levels[19]. In our study, hydronephrosis occurred in 17.4% of the patients; however, there were no significant differences in hydronephrosis in the two ChE groups.

Another potential cause of low ChE is liver tumor[20]. However, despite liver metastases occurring in 63.8% of cases in our study, there were no significant differences in the two ChE groups.

Elevated WBC resulting due to infection is also known to contribute to low ChE[19], and it was significantly different between the two ChE groups. In this study, 69% of patients had elevated WBC (> 10,000/μl) and CRP levels in the pre-death blood draw, suggesting a state of high inflammation. According to Nagy-A *et al*., 25–65% of patients with terminal cancer have concurrent infections[21]. Additionally, Argiles et al. reported that 50% of colorectal cancer patients develop cachexia[22], which closely aligns with the 47% of patients in group B with decreased ChE and concomitant infection. Since cachexia involves a variety of mediators[23-26], the development of infection may be contributing to the bimodal mixed normal distribution of ChE. However, further research is needed to fully understand this relationship.

While a decrease in ChE does not predict incidental death, a ChE level below 100 IU/L at admission has a hazard ratio 2.52-fold higher for the outcome of death in unit time compared to a ChE level above 100 IU/L, suggesting its potential as a biomarker for mortality estimation. Thus, 100 IU/L was considered useful as the cutoff value.

As a secondary endpoint, low ChE levels are associated with an increased risk for complications[27]. However, in this study, death-causing event D did not show a significant difference between ChE A and B groups.

In a comparison between metastatic liver tumors and metastatic lung tumors, mortality from metastatic liver tumors was higher. Respiratory disorders from lung metastases can be managed by oxygen administration, but the extensive metabolic disorders caused by liver metastases, including protein synthesis and glycogen storage, is difficult to compensate for. Liver metastases occur more frequently than do lung metastases because the venous return from the colon passes through the liver to the lungs.Approximately 50% of colorectal cancers develop liver metastases[28, 29], which are considered one of the main causes of death in patients with colon cancer [30].

The following were the limitations of this study: 1) Since the results are from a single-center study with a limited patient population, there was a problem of generalizability; therefore, large-scale data collection by other centers is required. 2) Due to the poor condition of patients upon admission to the palliative care unit, we were unable to measure their body weight or have blood draws for cytokine measurement. This prevented further discussion of cachexia, which is important for nutritional

assessment. 3) Owing to ethical considerations, frequent blood draws are not permitted in the palliative care unit. Therefore, we utilized the blood data obtained closest to the date of death from the regular blood draws as the pre-death data. It is important to note that the median time of 8 days before death may not represent the data immediately preceding death accurately. 4) Comparisons with prognostic tools, such as the Palliative Prognostic Index, were not performed. 5) The study was not blinded because the main investigator analyzed the data with results collected from his own patients. Based on the aforementioned points, this study can be considered a preliminary study.

Conclusion

In 47% of patients with terminal colorectal cancer admitted to our palliative care unit, the ChE level was below 100 IU/L, and they experienced early deaths (group B), which was significantly different from cases involving infection exacerbation during hospitalization. Conversely, 53% of patients who died without infection showed a gradual decline in ChE as their cancer progressed. The ratio of these two groups was almost identical to the 50% incidence of cachexia in colorectal cancer patients. In the late stages of colorectal cancer, the mortality rate of the low ChE group (group B) was 2.52 times higher than that of the high ChE group (group A) at the time of admission, considering a ChE cutoff value of 100 IU/L.

Serum ChE is believed to be a useful biomarker for simple mortality estimation in patients with colorectal cancer admitted in palliative care units.

COI declaration

The authors have no conflicts of interest to declare .

Ethical approval and consent to participate

The clinical ethics committee of our hospital reviewed and approved the research. (Approval number: Kagoshima City Medical Association Hospital Clinical Ethics Committee: 2022-2) Patient consent for publication is not applicable for this study.

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References

1) Ooyanagi H. Parenteral and enteral nutrition guidelines for co-medicals. Nankodo, Tokyo, 2005; 5-8.
2) Brock A. Immunoreactive plasma cholinesterase (EC 3.1.1.8) substance concentration, compared with cholinesterase activity concentration and albumin: inter- and intra-individual variations in a healthy population group. J Clin Chem Clin Biochem. 1990; 28: 851-6.
3) Gu Y, Chow MJ, Kapoor A, et al. Biphasic Alteration of Butyrylcholinesterase (BChE) During Prostate Cancer Development. Transl Oncol. 2018; 11: 1012-22.
4) Gupta S, Belle VS, Kumbarakeri Rajashekhar R, et al. Correlation of Red Blood Cell Acetylcholinesterase Enzyme Activity with Various RBC Indices. Indian J Clin Biochem. 2018; 33: 445-9.
5) Brenner DA, Buck M, Feitelberg SP, et al. Tumor necrosis factor-alpha inhibits albumin gene expression in a murine model of cachexia. J Clin Invest. 1990; 85: 248-55.
6) Liu XY, Zhang X, Ruan GT, et al. One-Year Mortality in Patients with Cancer Cachexia: Association with Albumin and Total Protein. Cancer Manag Res. 2021; 13: 6775-83.
7) Mester S, Evers M, Meyer S, et al. Extended plasma half-life of albumin-binding domain fused human IgA upon pH-dependent albumin engagement of human FcRn in vitro and in vivo. MAbs. 2021; 13: 1893888.
8) Nilsen J, Trabjerg E, Grevys A, et al. An intact C-terminal end of albumin is required for its long half-life in humans. Commun Biol. 2020; 3: 181.
9) Gianotti L, Braga M, Radaelli G, et al. Lack of improvement of prognostic performance of weight loss when combined with other parameters. Nutrition. 1995; 11: 12-6.
10) Li Y, Chen Y, Zeng Y, et al. Enteral Nutrition Combined with Improved-Sijunzi Decoction Shows Positive Effect in Precachexia Cancer Patients: A Retrospective Analysis. Evid Based Complement Alternat Med. 2021; 2021: 7357521.

11) Takano Y, Haruki K, Tsukihara S, et al. The impact of low serum cholinesterase levels on survival in patients with colorectal cancer. Int J Colorectal Dis. 2022; 37: 869-77.
12) Hamamoto Y, Niino K, Ishiyama H, et al. Impact of pretreatment cholinesterase level on survival of inoperable intrahepatic or hepatic-hilar carcinomas treated with three-dimensional conformal radiotherapy. Radiat Med. 2004; 22: 316-23.
13) Mitsunaga S, Kinoshita T, Hasebe T, et al. 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. 2008; 36: 241-8.
14) Nakanuma Y. Histopathology Atlas. Bunkodo, Tokyo, 2005; 172.
15) Krieger PM, Tamandl D, Herberger B, et al. Evaluation of chemotherapy-associated liver injury in patients with colorectal cancer liver metastases using indocyanine green clearance testing. Ann Surg Oncol. 2011; 18: 1644-50.
16) Gangi A, Lu SC. Chemotherapy-associated liver injury in colorectal cancer. Therap Adv Gastroenterol. 2020; 13: 1756284820924194.
17) Reissfelder C, Brand K, Sobiegalla J, et al. Chemotherapy-associated liver injury and its influence on outcome after resection of colorectal liver metastases. Surgery. 2014; 155: 245-54.
18) Sugiyama S. An introduction to the analysis model for data analysis that captures the essence. Sosim Co., Ltd., Tokyo, 2022; 352-71.
19) Yoneyama A. Blood/urine chemical test/ immunological test in the second half-How to read the numbers - 7th edition(1). Nippon Rinsho 2009; 67: 241-399.
20) Nakamura Sea. Blood/urine chemical test/ immunological test in the second half-How to read the numbers - 7th edition(2). Nippon Rinsho 2009; 67: 15 -607
21) Nagy-Agren. Managemnt of infections in palliative care patients with advanced cancer. J Pain Symptom Manage 24:. 2002: 64-70.
22) Argiles JM, Busquets S, Stemmler B, et al. Cancer cachexia: understanding the molecular basis. Nat Rev Cancer. 2014; 14: 754-62.
23) Yoon SL, Grundmann O, Williams JJ, et al. Body composition changes differ by gender in stomach, colorectal, and biliary cancer patients with cachexia: Results from a pilot study. Cancer Med. 2018; 7: 3695-703.
24) Morera Ocon FJ, Ripoll Orts F, Garcia-Granero Ximenez M, et al. [Decrease of serum cholinesterase in colorectal cancer]. Med Clin (Barc). 2007; 129: 729-30.
25) Kasprzak A. The Role of Tumor Microenvironment Cells in Colorectal Cancer (CRC) Cachexia. Int J Mol Sci. 2021; 22.
26) Ahmad SS, Ahmad K, Shaikh S, et al. Molecular Mechanisms and Current Treatment Options for Cancer Cachexia. Cancers (Basel). 2022; 14.
27) Matsuo M, Yamagami T. Low serum cholinesterase predicts complication risk after orthopedic surgery in elderly patients: an observational pilot study. JA Clin Rep. 2019; 5: 39.
28) Cui X, Geng XP, Zhou DC, et al. Advances in liver transplantation for unresectable colon cancer liver metastasis. World J Gastrointest Surg. 2021; 13: 1615-27.
29) Ahmad R, Kumar B, Tamang RL, et al. Colonoscopy-based intramucosal transplantation of cancer cells for mouse modeling of colon cancer and lung metastasis. Biotechniques. 2021; 71: 456-64.
30) Jin H, Gao S, Song D, et al. Intratumorally CpG immunotherapy with carbon nanotubes inhibits local tumor growth and liver metastasis by suppressing the epithelial-mesenchymal transition of colon cancer cells. Anticancer Drugs. 2021; 32: 278-85.

終末期大腸癌患者のコリンエステラーゼの 2峰性混合正規分布と在院死亡率

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和文要約

【背景】癌患者の栄養不良は生存期間に影響があり，筋蛋白量を示す除脂肪体重が健常時の70％になると窒素死が生じる．筋蛋白量と相関を持つコリンエステラーゼ (ChE) はアルブミン (Alb)より半減期が約1/2と短くAlbと強く相関して蛋白質濃度を間接的に反映する為，緩和ケア病棟では栄養評価に有用と思われるが，これまでChEの有用性が明らかにされていない．

【目的】当院緩和ケア病棟における大腸癌患者の死亡前ChE値がどのような変化を呈しているかを検討し，在院死亡率推定のバイオマーカーとしての有用性とカットオフ値を示すことである．

【方法】2019年4月から2021年3月までに鹿児島市医師会病院緩和ケア病棟を退院した大腸癌患者69 名を後ろ向きに抽出した．入院時と死亡前の採血でChEを測定し，その変化とChE，Alb，赤血球，白血球, 総コレステロール，中性脂肪，C反応性タンパク質の値，水腎症との相関はピアソンのカイ二乗検定 を用いた．入院時と死亡前のWBC≥10,000/μLの値の割合の変化をマクネマーテストで比較検定し感染症の増加を評価した．

主要評価項目としてコリンエステラーゼの結果で在院生存率をカプラン・マイヤー法，在院死亡率のハザード比を コックス比例ハザードモデルを用いて多変量解析した．また二次的評価項目として重症合併症の関係はピアソンのカイ二乗検定を用いて評価した．

【結果】死亡前採血（中央値8日）ではChE値が100 IU/L以上のA群とChE値が100 IU/L以下となったB群の２峰性混合正規分布を示した．A群で有意に在院生存率が高く，ChEの低値群は高値群より経時的な在院死亡率のハザード比が2.52と上昇していた．また死亡前は白血球が10,000/μL以上になった割合が増加していた．

【結論】２峰性混合正規分布となった因子分析として，大腸癌患者では感染症を併発してChEが早々に減少して死亡する群(47％)と，癌が進行してChEが緩徐に低下して死亡する群(53％)の2群があり，悪液質の発生割合（50％）とほぼ一致した．

ChEのカットオフ値を100 IU/Lとすると低値群は高値群に比較して在院死亡率が2.52倍高く，ChEは100 IU/Lをカットオフ値として大腸癌患者の在院死亡率推定のバイマーカーとして有用と考えられた．