Low prealbumin level is a poor prognostic biomarker for surgically treated pancreatic cancer

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Abstract. The present study aimed to evaluate the clinicopathological and prognostic significance of preoperative prealbumin levels in patients with surgically treated pancreatic cancer. The present retrospective study included 95 patients with pancreatic cancer who underwent radical surgery between January 2011 and December 2021. Of the patients, 49 were male and 46 were female, with a median age of 73 years. According to the median preoperative prealbumin level of 21.1 mg/dl, the patients were divided into low (<21.1 mg/dl) and high (≥21.1 mg/dl) prealbumin groups. Univariate and multivariate analyses were performed to evaluate the prognostic significance of prealbumin levels. Notably, no clinicopathological factors were associated with low prealbumin levels. Overall (P=0.008) and recurrence-free (P=0.004) survival were significantly lower in the low prealbumin group than those in the high prealbumin group. In addition, multivariate analysis showed that low prealbumin levels were an independent risk factor for poor overall (P=0.024) and recurrence-free (P=0.013) survival. Furthermore, the liver (P=0.038) and peritoneal recurrence (P=0.012) rates were higher in the low prealbumin group than those in the high prealbumin group. In conclusion, low preoperative prealbumin levels may be a poor prognostic biomarker in patients with surgically treated pancreatic cancer.

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Abbreviations: BMI, body mass index; CRP, C-reactive protein; OS, overall survival; RFS, recurrence-free survival

Key words: prealbumin, pancreatic cancer, radical surgery, OS, RFS

Introduction

Pancreatic cancer is one of the solid cancers with the poorest prognoses, and its incidence has more than doubled in the past 25 years (1). Currently, the incidence and mortality of patients with pancreatic cancer are increasing worldwide (2). Although much of this increase is due to aging, there are other risk factors for pancreatic cancer, including smoking, obesity, diabetes, and alcohol consumption (3). Considering that pancreatic cancer is often diagnosed at an advanced stage, its 5-year survival rate is low, ranging from 2 to 9% (4). Only approximately 20% of patients are diagnosed at a stage where surgical resection is possible, and the 5-year survival rate of patients who undergo surgical resection is approximately 15-25% (3). CA19-9 is a valuable tumor marker for evaluating pancreatic cancer (5). However, because it may be affected by obstructive jaundice and cholangitis, CA19-9 levels alone may be insufficient and further biomarkers are needed.

Preoperative nutritional status has been shown to affect the survival of patients with pancreatic cancer (4,6,7). Prealbumin, a 55 kDa homotetrameric protein, is primarily synthesized in the liver, the primary site of its production, and is found in the blood. It is also known as transthyretin because of its role in transporting thyroid hormones, including thyroxine (T4) and triiodothyronine (T3), as well as holo-retinol-binding protein, a complex of retinol-binding protein and vitamin A. Prealbumin has a circulating half-life of approximately 2 days, which is shorter than that of albumin, which is approximately 20 days. Therefore, prealbumin is superior for assessing short-term changes in the body's nutritional status and may be a more sensitive nutritional indicator than albumin (8,9). Low prealbumin levels may be a risk factor for survival in patients with gastric cancer (10) and hepatocellular carcinoma (11). The C-reactive protein-to-prealbumin ratio (12), fibrinogen-to-prealbumin ratio (13), and prealbumin as a factor in prognostic scoring systems (14) have been reported in pancreatic cancer. However, reports evaluating the prognostic significance of prealbumin itself in pancreatic cancer are lacking.

Therefore, in the present study, we aimed to assess the clinicopathologic and prognostic significance of preoperative prealbumin level in patients with pancreatic cancer.

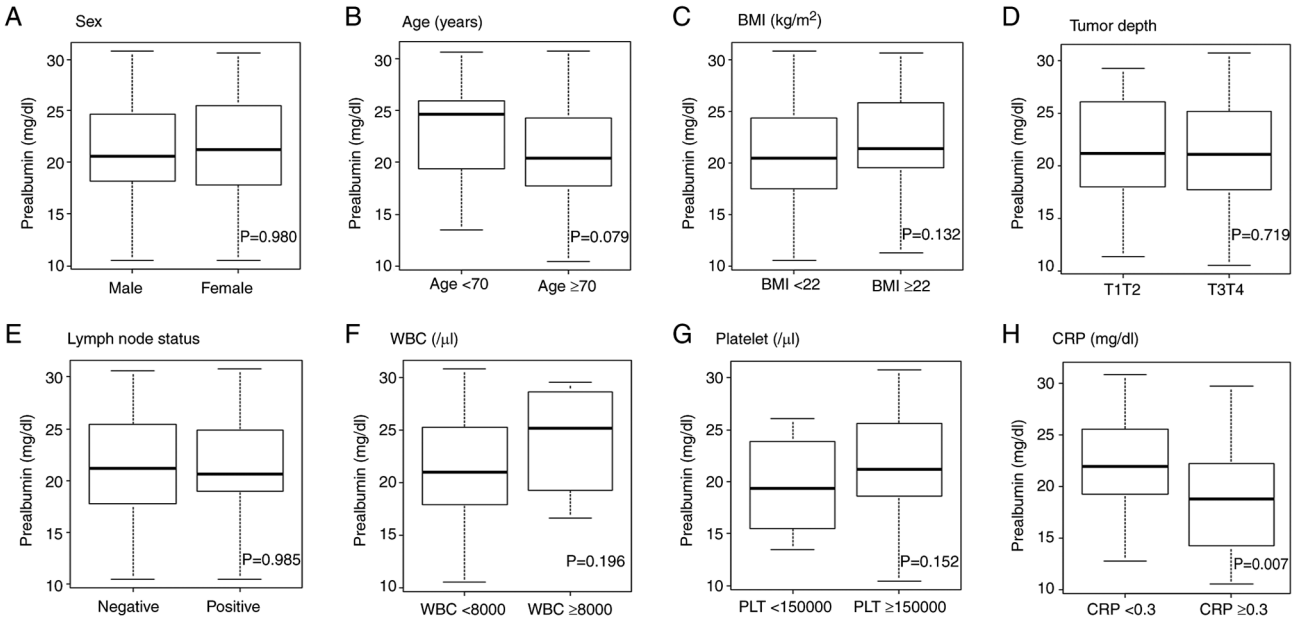

Figure 1. Comparison of prealbumin levels in patients split according to clinicopathological factors. (A) Sex, (B) age, (C) BMI, (D) tumor depth, (E) lymph node status, (F) WBC, (G) platelet, (H) CRP. Data were analyzed using unpaired Student's t-test. BMI, body mass index; CRP, C-reactive protein; WBC, white blood cell.

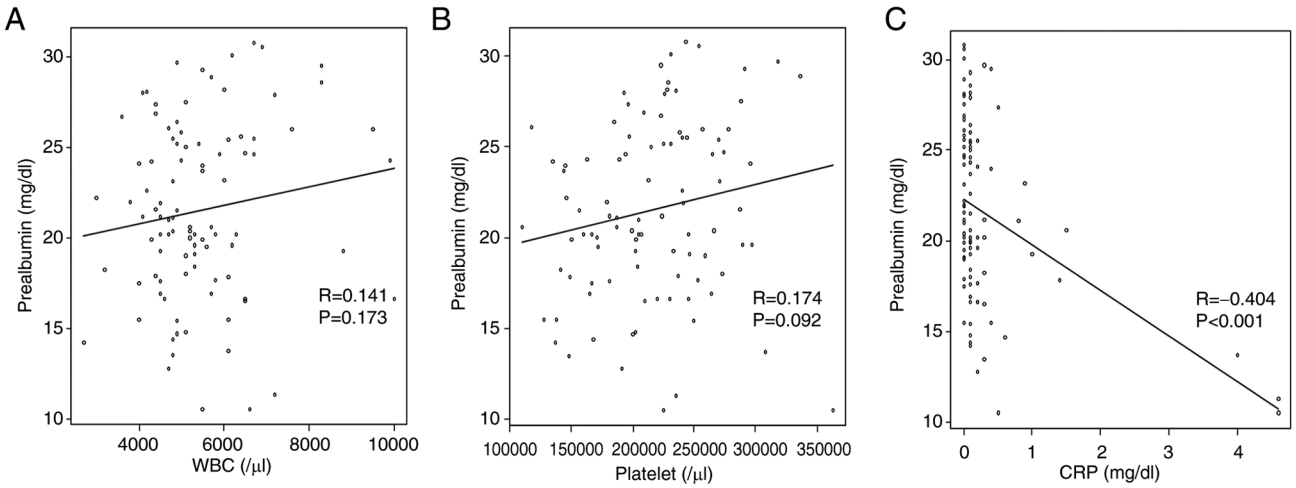

Figure 2. Scatter diagram showing the correlation between prealbumin and (A) WBC counts, (B) platelet counts and (C) CRP levels. Data were analyzed using Pearson's correlation coefficient. CRP, C-reactive protein; WBC, white blood cell.

Materials and methods

Patients. This retrospective study included 95 patients (49 male and 46 female patients) with a median age of 73 years (range: 33-87 years) who were diagnosed with pancreatic cancer and underwent radical resection between 2011 and 2021 in Toho University Omori Medical Center. The present study was approved by the Ethics Committee of Toho University Omori Medical Center (approval nos. M23174, 21320, 21039, 20200, 20196, 19056 and 18002) and conducted following the guidelines stipulated in the Declaration of Helsinki. Information about the study was disclosed on the institutional website, and potential participants were free to opt out; those who did not opt out were included and those who did opt out were excluded. We accessed the medical records of the patients for the purpose of this specific study in August 2024. The following clinicopathologic factors were included to evaluate their association with preoperative prealbumin levels: sex, age, body mass index (BMI), tumor depth, lymph node status, white blood cell counts, platelet counts, and C-reactive protein (CRP) levels. Pathological findings were determined using the Japanese Classification of Pancreatic Cancer, 8th edition, based on the tumor-node-metastasis classification (15). This study examined cutoff values based on median, mean, and quartiles. We chose the median as the cutoff value because it is more stable and easier to interpret. The median preoperative prealbumin level of 21.1 mg/dl was considered the cutoff value for all patients. Based on the cutoff value, the patients were categorized into low and high prealbumin groups to evaluate the association of preoperative prealbumin levels with clinicopathologic factors,

Table I. Clinicopathologic factors of patients with pancreatic cancer.

Variable	Number of patients (n=95)	Low prealbumin group <21.1 mg/dl (n=47)	High prealbumin group ≥21.1 mg/dl (n=48)	P-value[a]
Sex				0.838
Male	49	25	24	
Female	46	22	24	
Age, years				0.079
<70	31	11	20	
≥70	64	36	28	
BMI, kg/m^2				0.307
<22	49	27	22	
≥22	46	20	26	
Tumor depth				>0.999
T1T2	21	10	11	
T3T4	74	37	37	
Lymph node status				0.516
Negative	64	30	34	
Positive	31	17	14	
White blood cell, /μl				0.677
<8,000	89	45	44	
≥8,000	6	2	4	
Platelet, /μl				0.552
<150,000	12	7	5	
≥150,000	83	40	43	
CRP, mg/dl				0.137
<0.3	75	34	41	
≥0.3	20	13	7	

[a]Fisher's exact probability test. BMI, body mass index; CRP, C-reactive protein.

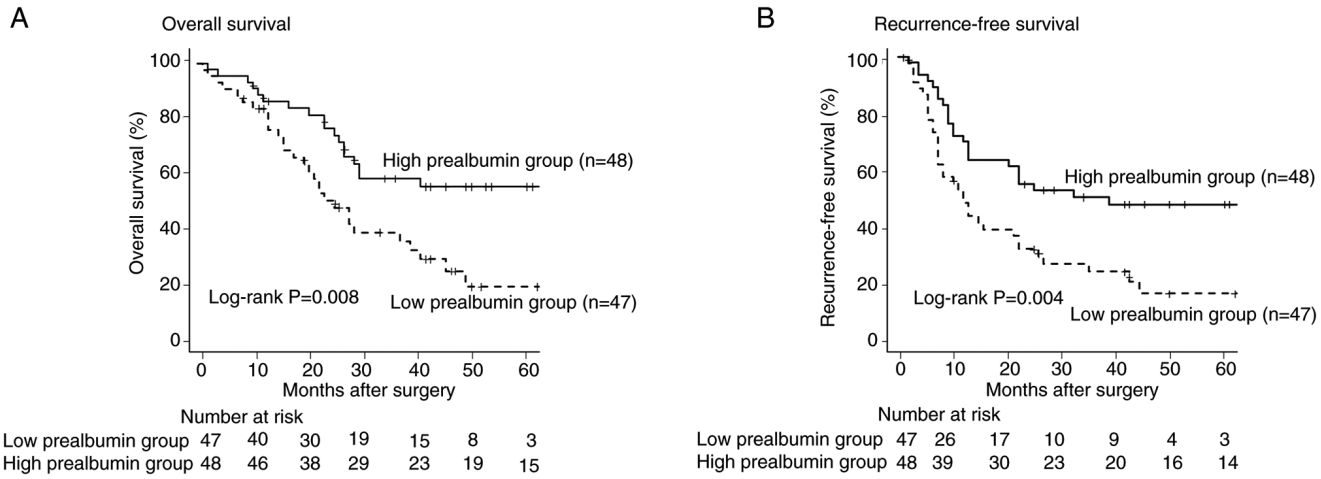

Figure 3. Comparisons of (A) overall survival and (B) recurrence-free survival curves between the low and high prealbumin groups.

overall survival (OS), and recurrence-free survival (RFS). OS was defined as the interval from the date of surgery to the date of death or last follow-up, and RFS was defined as the interval from the date of surgery to the date of known recurrence.

Statistical analysis. Unpaired Student's t-test and Fisher's exact probability test were used for two-group comparisons. Pearson's correlation coefficient was used to evaluate the correlation between the two groups. OS and RFS were calculated

Table II. Univariate and multivariate analysis of clinicopathological factors for predicting overall survival of patients with pancreatic cancer.

Variable	Number of patients (n=95)	P-value[a]	Multivariate analysis Hazard ratio (95% confidence interval)	P-value[b]
Sex		0.424		
Male	49			
Female	46			
Age, years		0.059		
≥70	64			
<70	31			
BMI, kg/m^2		0.668		
≥22	46			
<22	49			
Tumor depth		0.632		
T3T4	74			
T1T2	21			
Lymph node status		0.026	1.800 (1.011-3.205)	0.046
Positive	31			
Negative	64			
White blood cell, /μl		0.789		
≥8,000	6			
<8,000	89			
Platelet, /μl		0.308		
<150,000	12			
≥150,000	83			
CRP, mg/dl		0.001	2.588 (1.377-4.864)	0.003
≥0.3	20			
<0.3	75			
Prealbumin, mg/dl		0.008	1.974 (1.095-3.559)	0.024
<21.1	47			
≥21.1	48			

[a]Log-rank test. [b]Cox proportional hazard regression analysis. BMI, body mass index; CRP, C-reactive protein.

using the Kaplan-Meier method, and differences between groups were evaluated using the log-rank test. Multivariate analyses were performed using Cox proportional hazards regression. All statistical analyses were performed using EZR version 1.68 (16). Two-sided P<0.05 was considered to indicate a statistically significant difference.

Results

Association between preoperative prealbumin levels and clinicopathologic factors. The prealbumin levels according to clinicopathologic factors are shown in Fig. 1. Among the clinicopathologic factors, patients with high CRP levels had significantly lower prealbumin levels than those with low CRP levels (P=0.007).

Association between preoperative prealbumin levels and blood collection items. The prealbumin levels based on white blood cell counts, platelet counts, and CRP levels are shown in Fig. 2. There was a moderate negative correlation between preoperative prealbumin and CRP levels (R=-0.404, P<0.001).

Association of clinicopathologic factors between low and high prealbumin groups. The patients were divided into the following two groups based on the median preoperative prealbumin levels: low (<21.1 mg/dl, n=47) and high (≥21.1 mg/dl, n=48) groups. Table I shows the association between clinicopathologic factors and prealbumin levels. No clinicopathologic factors were associated with low prealbumin levels.

Comparison of overall survival between low and high prealbumin groups. The OS of the low prealbumin group was significantly lower than that of the high prealbumin group (P=0.008, Fig. 3A). Univariate analysis revealed that OS was significantly lower in patients with low prealbumin levels, positive lymph node status, and high CRP levels than that in patients with high prealbumin levels, negative lymph node status, and low CRP levels (P<0.05, Table II left panel).

Table III. Univariate and multivariate analysis of clinicopathological factors for predicting recurrence-free survival of patients with pancreatic cancer.

Variable	Number of patients (n=95)	P-value[a]	Multivariate analysis Hazard ratio (95% confidence interval)	P-value[b]
Sex		0.412		
Male	49			
Female	46			
Age, years		0.203		
≥70	64			
<70	31			
BMI, kg/m^2		0.169		
≥22	46			
<22	49			
Tumor depth		0.091		
T3T4	74			
T1T2	21			
Lymph node status		0.028	1.922 (1.144-3.231)	0.014
Positive	31			
Negative	64			
White blood cell, /μl		0.618		
≥8,000	6			
<8,000	89			
Platelet, /μl		0.686		
<150,000	12			
≥150,000	83			
CRP, mg/dl		0.003	2.251 (1.254-4.041)	0.007
≥0.3	20			
<0.3	75			
Prealbumin, mg/dl		0.004	1.931 (1.146-3.255)	0.013
<21.1	47			
≥21.1	48			

[a]Log-rank test. [b]Cox proportional hazard regression analysis. BMI, body mass index; CRP, C-reactive protein.

Multivariate analysis revealed that low prealbumin levels, positive lymph node status, and high CRP levels were independent poor prognostic factors for OS (P<0.05, Table II right panel).

Comparison of recurrence-free survival between low and high prealbumin groups. The RFS of the low prealbumin group was significantly lower than that of the high prealbumin group (P=0.004, Fig. 3B). Univariate analysis revealed that RFS was significantly lower in patients with low preoperative prealbumin levels, positive lymph node status, and high CRP levels than that in patients with high prealbumin levels, negative lymph node status, and low CRP levels (P<0.05, Table III left panel). Multivariate analysis revealed that low preoperative prealbumin levels, positive lymph node status, and high CRP levels were independent poor prognostic factors for RFS (P<0.05, Table III right panel).

Comparison of clinicopathologic factors between patients with and without recurrence. The comparison of clinicopathologic factors between patients with and without recurrence during the postoperative observation period showed that those with recurrence had significantly lower prealbumin levels (P=0.033) and were more likely to have a positive lymph node status (P=0.022) (Table IV).

Comparison of recurrence sites between low and high prealbumin groups. Recurrence rates in the liver (P=0.038) and peritoneum (P=0.012) were higher in the low prealbumin group than those in the high prealbumin group (Table V).

Discussion

The OS and RFS were significantly lower in the low prealbumin group than in the high prealbumin group. Low prealbumin levels were an independent risk factor for poor OS and RFS.

There is no consensus on the cutoff value of prealbumin levels in patients with pancreatic cancer. In the present study,

Table IV. Comparison of the clinicopathological factors between the patients with and without recurrence.

Variable	Number of patients (n=95)	Recurrence group (n=60)	Non-recurrence group (n=35)	P-value[a]
Sex				0.209
Male	49	34	15	
Female	46	26	20	
Age, years				0.264
≥70	64	43	21	
<70	31	17	14	
BMI, kg/m^2				0.209
≥22	46	26	20	
<22	49	34	15	
Tumor depth				0.125
T3T4	74	50	24	
T1T2	21	10	11	
Lymph node status				0.022
Positive	31	25	6	
Negative	64	35	29	
White blood cell, /μl				>0.999
≥8,000	6	4	2	
<8,000	89	56	33	
Platelet, /μl				>0.999
<150,000	12	8	4	
≥150,000	83	52	31	
CRP, mg/dl				0.117
≥0.3	20	16	4	
<0.3	75	44	31	
Prealbumin, mg/dl				0.033
<21.1	47	35	12	
≥21.1	48	25	23	

[a]Fisher's exact probability test. BMI, body mass index; CRP, C-reactive protein.

Table V. Comparison of the recurrence site between the low and high prealbumin groups; all cases (n=95).

Recurrence site	Number	Low prealbumin group (<21.1 mg/dl) (n=47)	High prealbumin group (≥21.1 mg/dl) (n=48)	P-value[a]
Lung	12	6	6	>0.999
Liver	25	17	8	0.038
Local site	24	16	8	0.062
Lymph node	10	7	3	0.199
Peritoneal	20	15	5	0.012
Bone	5	2	3	>0.999

[a]Fisher's exact probability test.

because the median (21.1 mg/dl) and mean (21.4 mg/dl) values were highly similar, we chose the median as the cutoff value. The normal prealbumin levels range from 22.0 to 40.0 mg/dl. The cutoff values for gastric cancer and hepatocellular carcinoma are 20 (10) and 17 (11) mg/dl, respectively, and the cutoff value in the prognostic scoring system for pancreatic cancer is 23 (14) mg/dl. Therefore, the cutoff value used in the present study was reasonable.

No clinicopathologic factors were associated with low prealbumin levels. However, low prealbumin levels were weakly associated with old age and high CRP levels. Prealbumin is a marker of nutritional status, and malnutrition is closely associated with old age (17). A low prealbumin level is also a marker reflecting acute inflammation (9). Park *et al* (18) reported that acute inflammation increases CRP levels and decreases prealbumin synthesis in the liver.

Consequently, low prealbumin levels may correlate with high CRP levels.

In this study, we minimized the effects of preoperative inflammation, liver dysfunction, and malnutrition by waiting until the patient was ready to undergo surgery. In addition, only a few patients had diseases that could potentially affect prealbumin levels, such as amyloid transthyretin amyloidosis, viral hepatitis, and autoimmune diseases. However, since prealbumin is a negative acute-phase protein, the possibility of a potential bias due to a decrease in its concentration due to inflammatory changes cannot be denied. In past reports, including other cancers, the effects of these conditions have not been examined, so further research is needed.

Low prealbumin level was an independent risk factor for poor OS and RFS. There are two main reasons for this association. First, prealbumin levels are linked to tumor progression. Cancer cells require more energy than normal cells to proliferate, and they actively absorb nutrients such as sugar and amino acids. Thus, nutrients in the body are preferentially consumed by cancer cells, resulting a deterioration in the nutritional status and a decrease in prealbumin levels (19). Second, low prealbumin levels are associated with decreased anti-tumor immunity. A decline in nutritional status causes a decrease in the function of immune cells, such as T cells, lymphocytes, macrophages, and natural killer cells, weakening the immune surveillance mechanism against cancer cells and making it easier for cancer cells to proliferate further (9). Therefore, patients with low prealbumin levels are at risk of deteriorating health conditions that can lead to tumor recurrence and metastasis after surgery.

In the present study, the hazard ratios for OS and RFS were similar, indicating that low prealbumin levels mainly affect the risk of recurrence and poor treatment response after recurrence. Chemotherapy in malnourished patients decreases treatment continuity and efficacy (20). Mękal *et al* (21) reported the importance of early nutritional intervention for improving the treatment outcomes in patients with pancreatic cancer. The short half-life of prealbumin (2-3 days) facilitates the early assessment of the effects of nutritional supplementation and changes in nutritional status. Therefore, monitoring prealbumin levels may help assess patients' nutritional status and improvement in OS and RFS.

This study excluded CRP, albumin, and CA19-9 from the multivariate analysis because they were confounding factors with prealbumin. However, in the report by Liang *et al* (14), the multivariate analysis included prealbumin and clinical pathological factors such as CRP, albumin, and CA19-9 in creating the prognostic nutritional score for pancreatic cancer patients. As a result, low prealbumin levels were an independent poor prognostic factor for OS and RFS (14). The population in this study comprised 95 patients, while the population in the study by Liang *et al* included 621 patients, indicating a significant difference in sample size. We think this is one reason for the differences in results. It is possible that the same results could have been obtained in this study if the population was the same as in the study by Liang *et al*. The limitation of this study is that it involved a small group. Therefore, we aim to increase the number of cases and re-examine the results in the future through a multi-center study.

Low prealbumin levels may be associated with liver metastasis recurrence and peritoneal dissemination. Liver metastasis and peritoneal dissemination are the most common types of pancreatic cancer recurrence and are considered poor prognostic factors (22). Therefore, it is important to monitor the patients, and attention should be paid to distant metastases, particularly liver metastases and peritoneal dissemination, in patients with low prealbumin levels before surgery.

The present study has several limitations. First, since it is a new finding that low prealbumin levels are a poor prognostic factor for pancreatic cancer, there is a lack of mechanistic insight, a lack of generalizability, and a lack of a validation cohort. Second, to understand the importance of changes in prealbumin levels over time, it is essential to consider postoperative prealbumin levels. Unfortunately, our study only measured preoperative prealbumin levels and did not include postoperative prealbumin levels. Finally, the sample size for this single-center study was relatively small. Other research institutions need to verify our results, and further large-scale multicenter prospective studies are required. We aim to resolve these limitations through future multicenter research.

In conclusion, low prealbumin levels may serve as a biomarker of poor prognosis in patients with surgically treated pancreatic cancer. Identifying patients with low prealbumin levels may help determine cases with poor nutritional status. Enhancing the nutritional status by monitoring prealbumin levels may improve OS and RFS in patients with pancreatic cancer.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YM and HS designed this study. YM, YO, HH, YK, RO, YI, KK, TM and MT were involved in the study conception, design and data collection. YM and HS wrote the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Toho University Omori Medical Center (approval nos. M23174, 21320, 21039, 20200, 20196, 19056 and 18002), and we provided a means of opting out for patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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