Original Article

Prognostic significance of preoperative creatine kinase in resected thymic epithelial tumors

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Background: The preoperative serum creatine kinase (CK) concentration is a prognostic factor for malignant diseases. We investigated the significance of CK in surgically resected thymic epithelial tumors and the relationship between CK and clinicopathological factors.

Methods: We retrospectively evaluated the relationship between preoperative CK levels and prognosis in 120 patients with thymic epithelial tumors who underwent surgical resection at two centers. The cutoff for CK was determined by the standard value in our institution (<62 IU/L for men and <45 IU/L for women). The paravertebral muscle at the Th12 level was used to assess skeletal muscle area to investigate sarcopenia.

Results: Eighteen patients (15.0%) were categorized into the low CK group. The CK level was not associated with age, sex, performance status, myasthenia gravis, and pathological findings. Preoperative serum albumin and total cholesterol concentrations were significantly lower in the low CK group than in the normal CK group (both P<0.001). Moreover, the Th12 muscle index was lower in the low CK group (P=0.03), indicating that low CK was related to sarcopenia. Kaplan-Meier curve analysis illustrated that patients in the low CK group had significantly shorter disease-free survival (DFS) and overall survival (OS) than those in the normal CK group (P=0.03 and P=0.002, respectively). Multivariate analysis identified low CK as an independent prognostic factor for DFS (P=0.03) and OS (P=0.005).

Conclusions: Preoperative serum CK might reflect the host nutritional status in patients with resected thymic epithelial tumors; therefore, CK could be a biomarker of postoperative prognosis.

Keywords: Thymoma; thymic epithelial tumor; creatine kinase (CK); sarcopenia

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Introduction

Background

Thymomas are rare tumors, representing only 0.2–1.5% of all malignancies, arising from the thymus in the anterior mediastinum (1). Thymic epithelial tumors are associated with paraneoplastic syndromes and autoimmune disorders such as myasthenia gravis, aplastic anemia,

and hypogammaglobulinemia. The standard therapeutic approach for thymic epithelial tumors is surgical resection, and adjuvant radiotherapy is recommended for tumors at advanced stages (2). The prognosis of patients with thymomas has been reported to be favorable, including 5-year overall survival (OS) of 90–95% and 5-year disease-free survival (DFS) of 97% (3,4). However, 10–30% of surgically resected thymomas eventually recur, which can occur up to several decades after initial surgery because of the slowly progressive nature of the tumor (5,6). Therefore, it is conceivable that lifelong follow-up is necessary, and the discovery of prognostic factors for thymic epithelial tumors is important to select adjuvant treatments and appropriate follow-up durations.

The prognosis of thymic epithelial tumors is associated with age, Masaoka-Koga stage, World Health Organization (WHO) histological classification, tumor size, and the completeness of resection (3,4). Prognostic biomarkers have also been reported, such as serum lactate dehydrogenase, C-reactive protein (CRP), fibrinogen, and neutrophil-to-lymphocyte ratio (7-9). However, because of the rarity and slow progression of thymic epithelial tumors, there are few reports of useful biomarkers.

Serum creatine kinase (CK) is present in skeletal muscle, heart, and brain tissue (10). CK catalyzes the reversible conversion of a phosphoryl group from adenosine triphosphate to creatine, and it is associated with metabolism in cancer (11), in which CK has important roles in cancer cell viability and cell cycle progression. Moreover, CK is associated with the nutritional and immune status. Several studies assessed the relationship between prognosis and CK levels in patients with lung, gastric, esophageal, or gastric cancer (12-15). Therefore, we hypothesize that serum CK is a prognostic factor in thymic epithelial tumors. This study aimed to assess the significance of the preoperative serum CK concentration for prognostic prediction in patients with surgically resected thymic epithelial tumors. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1797/rc).

Highlight box

Key findings

- Low preoperative serum creatine kinase (CK) levels were associated with sarcopenia and poor prognosis in patients with resected thymic epithelial tumors.

What is known and what is new?

- Preoperative serum CK is a prognostic factor for various malignant diseases.
- In patients with resected thymic epithelial tumors, low preoperative serum CK levels were associated with host nutrition factors such as sarcopenia, low albumin, and low total cholesterol, and CK was an independent prognostic factor for disease-free survival and overall survival.

What is the implication, and what should change now?

- Preoperative serum CK might reflect the host nutritional status in patients with resected thymic epithelial tumors; therefore, CK could be a biomarker of postoperative prognosis.

Methods

Patients and samples

We retrospectively identified and enrolled 158 patients with surgically resected thymic epithelial tumors between 1991 and 2019 at Kyushu University Hospital and the Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center between January 2007 and December 2016. We excluded 38 patients because we could not obtain preoperative laboratory data; thus, 120 patients were enrolled in this study, and we investigated the preoperative serum CK concentration measured within 1 month before surgery. Preoperative computed tomography (CT) images were available for 99 patients. The histological types of the thymomas were classified following the eighth edition of the WHO classification, and staging was performed using the Masaoka-Koga system (16,17). The analyzed variables were sex, age, histological findings, performance status (PS), and the surgical procedure. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board (IRB) of Kyushu University Hospital (IRB No. 2019-232). Written informed consent to access medical records was obtained from each patient.

Follow-up

After surgical resection, routine check-ups (including a physical examination, blood tests, and chest X-ray) were performed at 3-month intervals for the first 3 years and at 6-month intervals thereafter. CT was performed twice each year for the first 3 years and at 1-year intervals thereafter. The cutoff date was December 31, 2022. Recurrent thymic epithelial tumors were diagnosed on the basis of physical examination and diagnostic imaging consistent with

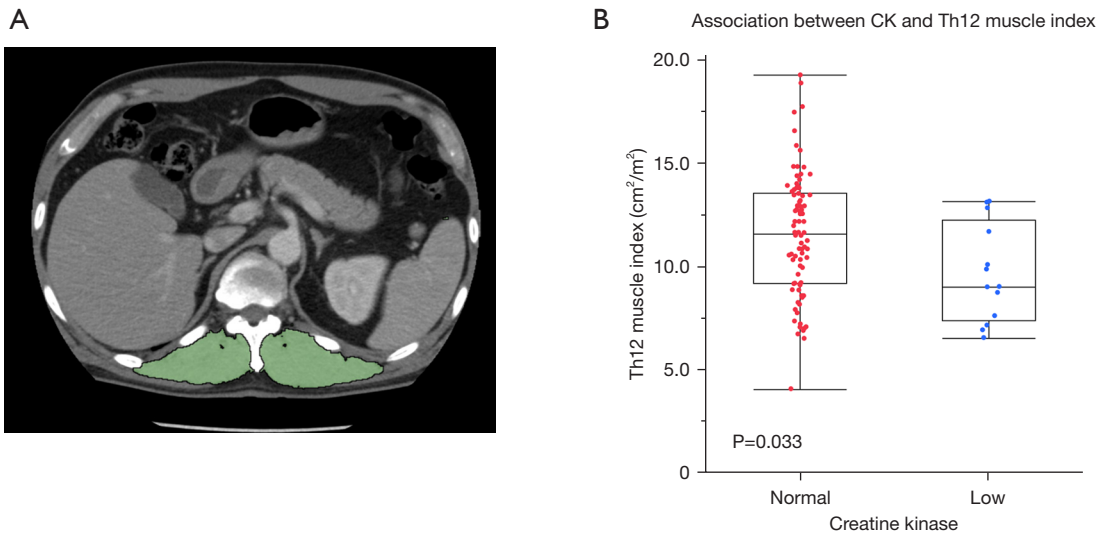

Figure 1 Relationship between sarcopenia and serum CK. (A) Computed tomography image illustrating areas (green) of the paravertebral muscle area at the Th12 level. (B) Association between the Th12 muscle index (cm^2/m^2) and serum CK level (normal *vs.* low). CK, creatine kinase.

recurrent disease. The date of recurrence was defined as the date on which recurrence was histologically proven or, in cases that were diagnosed by clinical evidence, when recurrent disease was recognized by the attending physician.

Cutoff serum CK concentration

The serum CK cutoff was defined in accordance with the standard values in Kyushu University Hospital as 62 IU/L for men and 48 IU/L for women.

Imaging and assessment of the skeletal muscle area (SMA) and cutoff of the Th12 muscle index

Preoperative CT was performed within 1 month before surgery. We investigated the paravertebral muscle area at the Th12 level using OsiriX software (32 bit, version 5.8; Geneva, Switzerland) with a threshold from −29 to +150 Hounsfield units (*Figure 1A*). The Th12 muscle index was standardized as the paravertebral SMA at the Th12 level divided by height squared.

Statistical analysis

The associations of CK levels with clinicopathological factors were analyzed using Student's *t*-test, Fisher's exact test, and Pearson's χ^2 test. DFS and OS were calculated by Kaplan-Meier estimation methods using the log-rank test. Univariate and multivariate analyses with the Cox proportional hazards regression model were performed to assess the relationships of OS and DFS with clinical variables. We used the backward elimination method for multivariate Cox proportional hazards regression analysis. The model was run with all variables and the variable with the highest P value. P<0.05 was considered statistically significant. All statistical analyses were performed using JMP version 16.0.

Results

Clinicopathological characteristics

Table 1 presents the clinicopathological characteristics of the 120 patients with surgically resected thymic epithelial tumors. The median age of the patients was 60 years (range, 20–86 years). In total, 51 patients (42.5%) were male, and 101 (84.2%) had PS 0. Myasthenia gravis was present in 10 patients (8.3%). Histological analysis revealed that 15 (12.5%), 28 (23.3%), 25 (20.8%), 32 (26.7%), and 10 (8.3%) had WHO type A, AB, B1, B2, and B3 thymoma, respectively, and 8 (6.7%) and 2 (1.7%) had thymic carcinoma (TC) and neuroendocrine thymic tumors (NETT), respectively. Regarding the Masaoka-Koga stage, 56 (46.7%), 36 (30.0%), 18 (15.0%), and 10 (8.3%) had stage I, II, III, and IV, respectively. The most frequently performed surgery was sternotomy (n=61, 50.8%), followed by video-assisted thoracoscopic surgery (n=44, 36.7%)

Table 1 Clinicopathological characteristics of patients with surgically resected thymic epithelial tumors (n=120)

Characteristic	Value
Age (years)	60 [20–86]
Body weight (kg)	57 [34–94]
BMI (kg/m^2)	22.4 [14.0–34.2]
Sex	
Male	51 (42.5)
Female	69 (57.5)
Performance status	
0	101 (84.2)
1	19 (15.8)
Myasthenia gravis	
Present	10 (8.3)
Absent	110 (91.7)
WHO histologic type	
A	15 (12.5)
AB	28 (23.3)
B1	25 (20.8)
B2	32 (26.7)
B3	10 (8.3)
TC	8 (6.7)
NETT	2 (1.7)
Masaoka-Koga	
I	56 (46.7)
II	36 (30.0)
III	18 (15.0)
IV	10 (8.3)
Operation method	
Sternotomy	61 (50.8)
Thoracotomy	15 (12.5)
VATS	44 (36.7)
Surgical procedure	
Tumor resection	56 (46.7)
Complete thymectomy	37 (30.8)
Extended thymectomy	19 (15.8)
Subtotal resection	8 (6.7)

Data are presented as median [range] or n (%). BMI, body mass index; WHO, World Health Organization; TC, thymic carcinoma; NETT, neuroendocrine thymic tumor; VATS, video-assisted thoracoscopic surgery.

Table 2 Associations of CK levels with clinicopathological factors in patients with surgically resected thymic epithelial tumors

Factors	Normal CK (n=102)	Low CK (n=18)	P value
Age			>0.99[a]
<70 years	84 (82.4)	15 (83.3)	
≥70 years	18 (17.6)	3 (16.7)	
Sex			0.74[b]
Male	58 (56.9)	11 (61.1)	
Female	44 (43.1)	7 (38.9)	
Performance status			0.16[a]
0	88 (86.3)	13 (72.2)	
≥1	14 (13.7)	5 (27.8)	
Myasthenia gravis			>0.99[a]
Present	9 (8.8)	1 (5.6)	
Absent	93 (91.2)	17 (94.4)	
WHO histologic type			0.053[a]
A, AB, B1	58 (56.9)	10 (55.6)	
B2, B3	38 (37.2)	4 (22.2)	
TC, NETT	6 (5.9)	4 (22.2)	
Masaoka-Koga			0.47[b]
I	49 (48.0)	7 (38.9)	
II–IV	53 (52.0)	11 (61.1)	
Surgical procedure			0.21[a]
Tumor resection and complete thymectomy	77 (75.5)	16 (88.9)	
Extended thymectomy and subtotal resection	25 (24.5)	2 (11.1)	

Data are presented as n (%). [a], Fisher's exact test; [b], χ^2 test. CK, creatine kinase; WHO, World Health Organization; TC, thymic carcinoma; NETT, neuroendocrine thymic tumor.

and thoracotomy (n=15, 12.5%). Tumor resection (n=56, 46.7%), complete thymectomy (n=37, 30.8%), extended thymectomy (n=19, 15.8%), and subtotal resection (n=8, 6.7%) were also performed. The median CK level was 79 IU/L (range, 14–320 IU/L).

Clinicopathological factors associated with CK

Table 2 presents the clinicopathological factors of patients in the normal (n=102, 85.0%) and low CK groups (n=18,

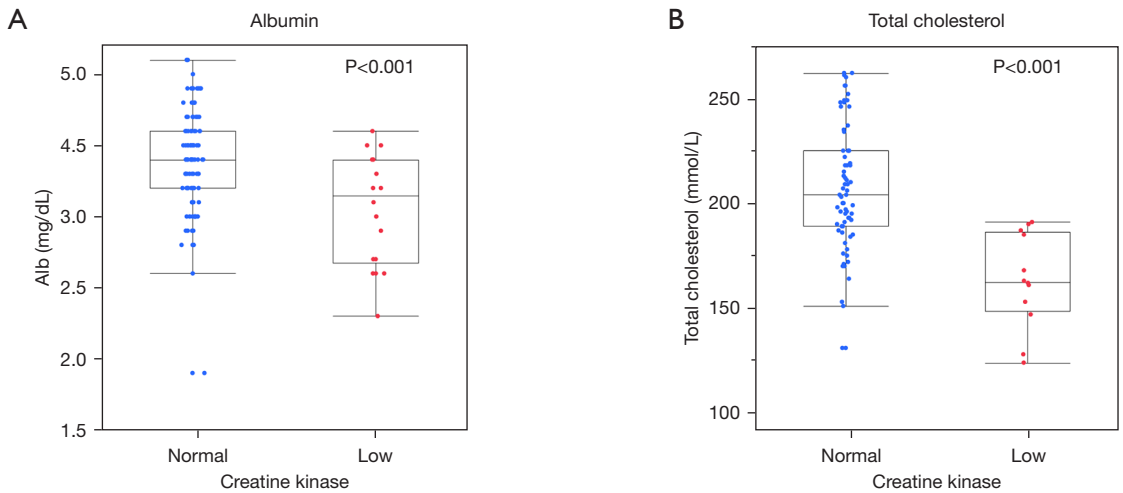

Figure 2 Association between serum CK and blood tests data related to nutrition. Associations of the serum CK levels (normal *vs.* low) with serum albumin (A) and serum total cholesterol (B). CK, creatine kinase.

15.0%). Age, sex, PS, myasthenia gravis, the WHO histological type, the Masaoka-Koga stage, the type of operation, and the surgical procedure were not associated with CK levels. *Figure 1B* illustrates that the Th12 muscle index was lower in the low CK group than in the CK normal group (P=0.03). Furthermore, we focused on serum albumin and total cholesterol levels to elucidate the relationship between CK levels and the nutrition status. We identified 14 patients with hyperlipidemia and three patients with liver diseases, and these patients were excluded from the analysis. Serum albumin and total cholesterol levels were significantly lower in the low CK group than in the normal CK group, as observed in the prior analysis (both P<0.001, *Figure 2A*,*2B*).

Relationships of DFS and OS with serum CK levels

The median follow-up period was 6.88 years. The numbers of recurrences and deaths were 17 and 12, respectively, and the recurrence and mortality rates were 14.2% and 10.0%, respectively. We described the clinical and pathological features and the prognosis of patients who experienced recurrence of thymic epithelial tumors in Table S1. In addition, the main causes of death were thymic epithelial tumors (n=4, 33.3%), other cancers (n=3, 25.0%) and pneumonia (n=2, 16.7%).

Figure 3 presents the DFS and OS curves for the normal and low CK groups. The log-rank test revealed that DFS was significantly shorter in the low CK group than in the normal CK group in patients who underwent complete resection of thymic epithelial tumor (5-year DFS: 91.0% *vs.* 73.7%, P=0.03, *Figure 3A*). OS was also significantly shorter in the low CK group than in the normal CK group in all patients cohort (10-year OS: 92.9% *vs.* 60.6%, P=0.002, *Figure 3B*). To distinguish thymomas from TC and NETT, survival in patients with thymoma was also investigated. In patients with thymoma, DFS did not differ between the low and normal CK groups (P=0.36, Figure S1). However, low CK levels were linked to significantly shorter OS (10-year OS: 68.4% *vs.* 92.7%, P=0.02, Figure S1B).

Multivariate analysis identified low CK and Masaoka-Koga stage (stage II/III/IV) as independent prognostic factors for shorter DFS (P=0.03 and P=0.02, respectively, *Table 3*). Multivariate analysis also revealed that a low CK level was an independent prognostic factor for shorter OS (P=0.005, *Table 4*).

Discussion

We examined the prognostic significance of preoperative serum CK in patients with resected thymic epithelial tumors. Kaplan-Meier curve analysis for DFS and OS revealed that low CK was associated with poor prognosis in patients with thymic epithelial tumors. Multivariate analysis identified low CK as an independent prognostic factor for shorter OS and DFS. In addition, low CK was significantly associated with a low Th12 muscle index and low serum albumin and total cholesterol levels, suggesting that the preoperative

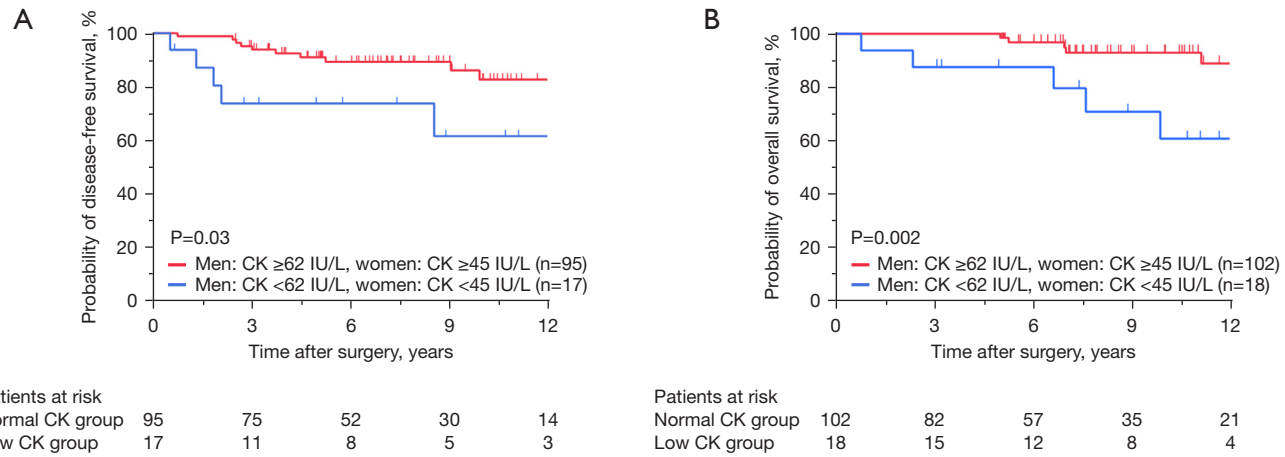

Figure 3 The prognosis according to serum CK level in patients with thymic epithelial tumors. Kaplan-Meier curves presenting DFS (A) and OS (B) according to the CK level for patients with thymic epithelial tumors who underwent surgery. CK, creatine kinase; DFS, disease-free survival; OS, overall survival.

Table 3 Univariate and multivariate analyses of disease-free survival in patients with completely resected thymic epithelial tumors

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age: ≥70 *vs.* <70 years	1.44 (0.33–6.35)	0.63		
Sex: male *vs.* female	1.36 (0.52–3.53)	0.53		
WHO histologic type: *vs.* A, AB, B1				
B2, B3	2.02 (0.73–5.62)	0.18		
TC, NETT	6.78 (1.36–33.66)	0.02		
Masaoka-Koga stage: II–IV *vs.* I	3.65 (1.19–11.21)	0.02	3.80 (1.23–11.71)	0.02
Procedure: extended thymectomy *vs.* tumor resection and complete thymectomy	2.12 (0.75–6.03)	0.16		
CK: low *vs.* normal	2.99 (1.04–8.60)	0.04	3.18 (1.10–9.22)	0.03

HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; TC, thymic carcinoma; NETT, neuroendocrine thymic tumor; CK, creatine kinase.

serum CK level reflects the host nutritional status in patients with thymic epithelial tumors. This might explain why preoperative serum CK is a useful prognostic factor for thymic epithelial tumors. Furthermore, CK levels might be useful in determining appropriate follow-up durations and intervals in patients with thymic epithelial tumors. To the best of our knowledge, this is the first report of the relationship between preoperative CK levels and outcomes in patients with surgically resected thymic epithelial tumors.

Sarcopenia is a syndrome characterized by the progressive and generalized loss of skeletal muscle and strength, and it is caused by aging, insufficient nutrition, low physical activity, and cancer cachexia (18). Sarcopenia has prognostic significance for various cancers, such as lung, hepatocellular, and pancreatic cancers (19-21). Several reports revealed that serum CK might be associated with sarcopenia (12,22). In addition, serum albumin is a well-established biomarker of the nutritional state and an indicator for various cancers (23,24), and serum total cholesterol levels reflect fat metabolism and nutrition status (25,26). This study found that low CK levels were significantly correlated with sarcopenia and low albumin and total cholesterol levels.

Table 4 Univariate and multivariate analyses of overall survival in patients with surgically resected thymic epithelial tumors

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age: ≥70 *vs.* <70 years	2.15 (0.57–8.19)	0.26		
Sex: male *vs.* female	1.46 (0.47–4.56)	0.52		
WHO histologic type: *vs.* A, AB, B1				
B2, B3	1.30 (0.36–4.67)	0.68		
TC, NETT	5.20 (0.99–27.38)	0.052		
Masaoka-Koga stage: II–IV *vs.* I	4.06 (0.88–18.69)	0.07		
Procedure: tumor resection and complete thymectomy *vs.* extended thymectomy and subtotal resection	1.08 (0.23–5.07)	0.92		
CK: low *vs.* normal	5.18 (1.67–16.11)	0.005	5.18 (1.67–16.11)	0.005

HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; TC, thymic carcinoma; NETT, neuroendocrine thymic tumor; CK, creatine kinase.

Therefore, CK might be a biomarker of the host nutritional status in thymic epithelial tumors.

CK activity appeared to decrease because of tumor progression in some research. Decreased CK levels are more commonly detected in tumor cells than in normal tissues in various human cancers (27). Previous reports revealed that low CK levels were related to tumor progression in gastric and esophageal cancers (13,14). However, our result indicated that CK levels were not significantly associated with factors of tumor malignancy, such as the WHO histological type and Masaoka-Koga stage. In addition, low CK levels were not associated with poor DFS in patients with thymoma (Figure S1A), although low CK levels were associated with poor DFS in patients with thymic epithelial tumors including TC and NETT (*Figure 3A*). The reason for the discrepancy between CK and tumor malignancy could be the slow progressive nature of thymomas. CK levels could reflect tumor malignancy in patients with TC and NETT but not in those with thymoma. Further studies investigating the relationship between CK level and malignancy are needed.

Conversely, low CK levels were associated with poor OS in both thymic epithelial tumors and thymomas (*Figure 3B* and Figure S1B). To elucidate the relationship between low CK levels and poor OS in thymic epithelial tumors, we focused on thymic immunological functions. The thymus is the primary organ responsible for generating immunocompetent T cells, and it decreases in size with aging (28). However, thymic immunological function persists even late in life, and age-related thymic involution contributes to the reduction of thymopoiesis, which precedes T-cell-related immunocompetence (29). Thymectomy leads to decreases in naive T helper and memory lymphocyte counts, which result in immunodeficiency (30). Furthermore, sarcopenia and malnutrition increase the risk of various infections or cancer-related death (12,31). Therefore, the potential immunocompetence caused by thymectomy could affect patients with low CK levels, which could explain the poor OS in such patients.

This study had several limitations. First, this was a retrospective study conducted at two institutions. We believe that a prospective study with a larger sample size is necessary to evaluate the prognostic significance of preoperative CK levels. Second, CK content is influenced by exercise and some diseases such as cardiovascular diseases and dermatomyositis (32). Third, we were unable to access the CT data of patients who underwent surgery before 2003; thus, we could not evaluate SMA for every patient. Fourth, although past studies usually used SMA at the L3 level to assess sarcopenia (18), we investigated the paravertebral muscle area at the Th12 level because CT scans for thymoma often were not performed at the lumbar level. In previous research, we revealed a significant correlation between SMA at the Th12 and L3 levels (12). In addition, the association between sarcopenia and prognosis in patients with idiopathic pulmonary fibrosis was demonstrated by measuring SMA at the Th12 level (33). Therefore, it was reasonable to assess sarcopenia at the Th12 level.

Conclusions

CK might be a prognostic biomarker of thymic epithelial tumors. However, given that sarcopenia and malnutrition are also poor prognostic factors in all cancers, further detailed analysis including the relationship between CK levels and the nutritional status is necessary.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1797/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1797/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1797/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the IRB of Kyushu University Hospital (IRB No. 2019-232). Written informed consent to access medical records was obtained from each patient.

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