Original Article

Preoperative Low Serum Calcium Levels Predict Poor Prognosis for Patients with Esophageal Cancer

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Purpose: Hypercalcemia has been reported as a poor prognostic factor in malignant tumors. However, no report has shown the clinical impact of serum calcium levels on patients with esophageal cancer. We evaluated the prognostic impact of preoperative serum calcium levels on patients with esophageal cancer.

Methods: We evaluated 240 patients (197 men, 43 women; mean age, 66 years; age range, 34–85 years) with esophageal cancer who underwent radical surgery between September 2008 and December 2017. After assigning the patients to two groups (high calcium group, 8.8 mg/dL or more and low calcium group, 8.7 mg/dL or less), we compared the groups' overall survival and the clinicopathological features. The clinicopathological and prognostic significance of preoperative serum calcium levels were evaluated in a univariate and multivariate analysis.

Results: The patients with deep tumors showed low serum calcium levels significantly more frequently (*P* <0.05). The low calcium group showed a significantly worse prognosis than the high calcium group (*P* <0.05). However, low serum calcium level was not an independent poor prognostic factor.

Conclusions: Preoperative low serum calcium levels were associated with advanced tumors. Low serum calcium might be associated with esophageal cancer progression.

Keywords: esophageal cancer, serum calcium level, prognosis

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Introduction

Recent improvements in the diagnosis[1] and in the chemotherapy[2,3] for esophageal cancer have improved patients' prognoses. Although TNM stage is the most important and simple golden standard, additional prognostic factors are needed to further personalize the treatment strategy. There have been various reports on prognostic factors in esophageal cancer using routine blood tests.[4,5] Several inflammatory parameters have been reported to be associated with patient prognoses.[6,7] Serum tumor markers have also been reported as prognostic indicators.[8,9] Among the routine laboratory data,

low electrolyte concentrations in blood tests have been noted as an indicator of the poor general condition of patients with cancer. Store-operated calcium entry is an essential intracellular calcium signaling pathway that plays an important role in tumor cell proliferation, migration, metastasis, invasion, and resistance to apoptosis.[10] There have been reports on patients with cancer showing that high serum calcium levels are a poor prognostic factor.[11–13] However, few reports have assessed the clinicopathological significance of low serum calcium levels and cancer. Elderly patients with cancer can develop low serum calcium levels due to low oral intake. Xu et al.[14] reported that low serum calcium levels were associated with a poor prognosis in patients over 60 years of age with gastric cancer. However, the authors did not correct for albumin levels. About 40% of calcium in blood binds to proteins mainly albumin, 10% forms a complex with anions such as phosphoric acid, and the remaining about 50% exists in the state of ionized calcium. Since the bound calcium concentration decreases in hypoalbuminemia, the correction formula is used when Alb (g/dL) is less than 4.[15] In this study, we corrected the serum calcium levels in patients with serum albumin levels <4.0 g/dL using the following formula: corrected calcium (mg/dL) = measured calcium (mg/dL) + 4-serum albumin (g/dL).[15] Gonçalves et al. reported that patients with cancer and low serum calcium levels had poor prognoses.[16] And more Huang et al.[17] reported that patients with

nasopharyngeal carcinoma with low serum calcium levels had worse survival than those with high serum calcium levels, and serum calcium levels can act as an independent prognostic indicator. However, they reported that a low serum calcium level is associated with several types of cancer and is more common in hematological, colorectal, lung, thyroid cancer, and nasopharyngeal carcinoma but not esophageal cancer. So far, no reports have examined the significance of low serum calcium levels in patients with esophageal cancer. The relationship between preoperative serum calcium levels and clinicopathological factors and prognoses in patients with esophageal cancer remains unclear. We therefore evaluated the clinicopathological and prognostic impact of preoperative serum calcium levels on patients with esophageal cancer.

Materials and Methods

Patients and healthy controls

Based on their medical records, we retrospectively analyzed 329 consecutive patients who underwent radical esophagectomy with D2 lymphadenectomy[18] between September 2008 and December 2017 at the Toho University School of Medicine (Tokyo, Japan). The study excluded double cancers, non-standard operations, neuroendocrine cancer, angiosarcoma, stromal mucosal cancer, and noncurative operation ultimately analyzing 240 patients (**Fig. 1**) consisting of 197 men
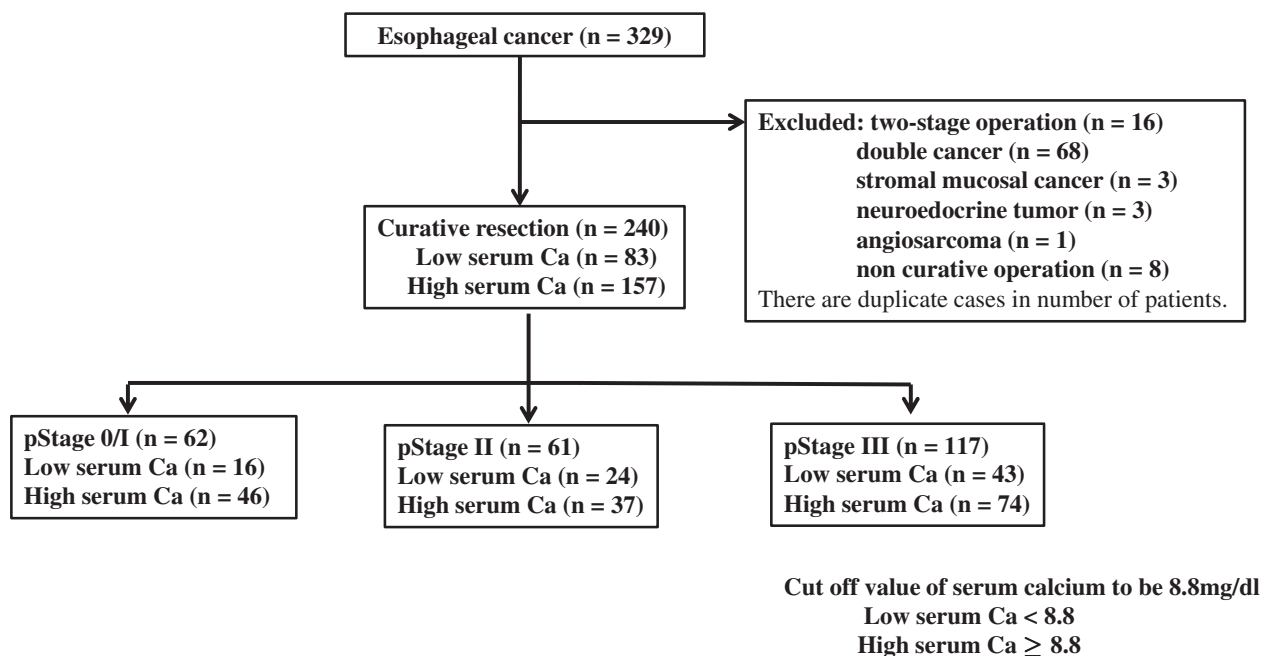

Fig. 1 Flowchart showing selection of patients for this study.

and 43 women, with a median age of 66 years (range 34–85 years). The tumor stages of resected specimens were classified based on the Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus (11th Edition)[19] as follows: pathological stage 0/I, 62 patients; pathological stage II, 61 patients; and pathological stage III, 117 patients. We evaluated postoperative complications using Clavien-Dindo classification.[20] According to the Clavien-Dindo classification, all patients with complications were identified as having the following grades of disease: 93 (39%), grade IIIa or lesser disease; 15 (6.3%), grade IIIb or higher disease.

The median follow-up period was 40.5 months (range, 0–92 months). The Ethics Committee of Toho University School of Medicine approved this retrospective study (no. M20200 20196 19056 18002). In this study, serum calcium levels were evaluated at the time of first visit in our hospital. Serum samples were taken before neoadjuvant chemotherapy. We corrected the serum calcium levels in patients with serum albumin levels <4.0 g/dL using the following formula: corrected calcium (mg/dL) = measured calcium (mg/dL) + 4 × serum albumin (g/dL).

We assigned the patients to two groups according to preoperative serum calcium level (high calcium group, 8.8 mg/dL or more; low calcium group, 8.7 mg/dL or less) using a cut-off of 8.8 mg/dL which is the minimum value that is the facility standard of our hospital. We compared the groups' overall survival and the clinicopathological features between the low calcium group and the high calcium group.

Data analysis methods

The statistical analysis was performed using Fisher's exact test for categorical data and the Kaplan–Meier method for estimating the overall survival rate, which we analyzed using the log-rank test. We performed a univariate and multivariate analysis to evaluate the prognostic impact of serum calcium levels. For patients who remained alive, the data was censored at the date of the last contact. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, http://jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html), a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). More precisely, EZR is a modified version of R commander (version 1.6.3) designed to facilitate the use of statistical functions frequently employed in biostatistics. Probability values <0.05 indicated a statistically significant difference.

Results

The relationship between serum calcium levels and clinicopathological factors

Each of the clinicopathological features was compared between the low calcium group and the high calcium group using a cut-off value of 8.8 mg/dL (**Table 1**). The patients with deep tumors and adenocarcinoma showed low serum calcium levels significantly more frequently (*P* <0.05). The other clinicopathological factors were not related to calcium levels. Also, serum calcium levels before and after neoadjuvant chemotherapy were compared, but no significant difference was observed (*P* = 0.43). **Figure 2** shows the results of the comparison by serum calcium level and tumor stage. There were no significant differences in serum calcium levels between each stage (**Fig. 2**).

Comparison of overall survivals and recurrence-free survivals between high calcium group and low calcium group

The overall survival of the low calcium group (n = 83) was significantly worse than that of the high calcium group (n = 157) (*P* <0.01, **Fig. 3A**). The recurrence-free survival of the low calcium group was also significantly worse than that of the high calcium group (*P* <0.01, **Fig. 3B**).

The impact of low serum calcium levels on overall survival and recurrence-free survival

The univariate analysis for overall survival showed that male sex, deep tumors, lymph node metastasis, low serum calcium levels, and enforcement of neoadjuvant chemotherapy were poor prognostic factors (**Table 2**). The multivariate analysis for overall survival showed that deep tumors (*P* <0.01), lymph node metastasis (*P* <0.01), and postoperative complication (*P* <0.01) were independent poor prognostic factors. The overall survival and recurrence-free survival of low calcium group were significantly worse than those of high calcium group (*P* <0.01) (**Fig. 3A** and **3B**). The median recurrence-free survival was 34 months in the low calcium group and 79 months in the high calcium group. However, low serum calcium level was not an independent poor prognostic factor based on the multivariate analysis. Recurrence was confirmed in 97 cases by endoscopy, computed tomography, and/or positron emission-computed tomography. Recurrence patterns and the number of patients were as follows: lymph node recurrence (n = 69), lung and pleura metastasis (n = 13), liver metastasis (n = 6), local recurrence (n = 8), and bone metastasis (n = 2).

Table 1 Comparison of clinicopathological characteristics between low calcium and high calcium groups

Variables		Number of patients	Low serum Ca group (n = 83)	High serum Ca group (n = 157)	*P* value[a]	H.R (95% CI)	*P* value[b]
Age (year)	<65	102	33	69	0.58		
	≥65	138	50	88			
Gender	Female	43	13	30	0.6		
	Male	197	70	127			
Tumor depth	T0T1	85	21	64	<0.05	0.51 (0.27–0.95)	<0.05
	T2T3T4	155	62	93			
Nodal status	Negative	96	31	65	0.58		
	Positive	144	52	92			
Histological type	Squamous carcinoma	229	77	152	0.2	0.43 (0.12–1.54)	0.19
	Adenocarcinoma	11	6	5			
Neoadjuvant chemotherapy	Absent	109	34	75	0.34	0.87 (0.48–1.58)	0.65
	Present	131	49	82			
Postoperative complications	C–D classification ≤IIIa	225	75	150	0.16	0.43 (0.15–1.28)	0.13
	C–D classification ≥IIIb	78	8	70			
Serum Albumin level	<4.0	150	72	78	<0.001	5.91 (2.81–12.5)	<0.001
	≥4.0	90	11	79			
Body mass index	<17	24	10	14	0.5		
	≥17	216	73	143			

[a]Fisher's exact probability test

[b]Logistic regression analysis

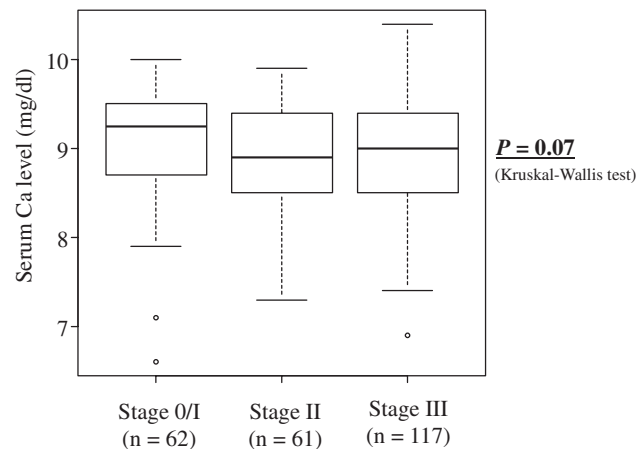C–D classification: Clavien–Dindo classification; HR: hazard ratio; CI: confidence interval

Fig. 2 Serum calcium level according to the tumor stages.

The relationship between serum calcium levels and postoperative complications

We analyzed the postoperative complications. There were no significant differences between the low calcium group and the high calcium group (**Supplemental Figure 1**, available Online).

Discussion

In total, 83 (34.6%) of the 240 patients had low serum calcium level. Preoperative low serum calcium levels were associated with advanced tumors. The low calcium levels were significantly associated with deep tumors. The low calcium group showed significantly worse prognosis than high calcium group; however, the multivariate analysis showed that low serum calcium level was not an independent risk factor for a poor prognosis.

There are numerous causes for the development of low serum calcium levels in patients with cancer. In esophageal cancer, one of the major causes is passage disturbance and poor oral intake. However, we could not find correlation between body mass index and serum calcium levels in this study. Body mass index, calculated as weight divided by height squared (kg/m^2), is a measure of body fat based on height and weight. We therefore considered that the cancer itself was a cause of the low serum calcium levels, along with poor nutritional condition. Drugs such as bisphosphonates that are frequently
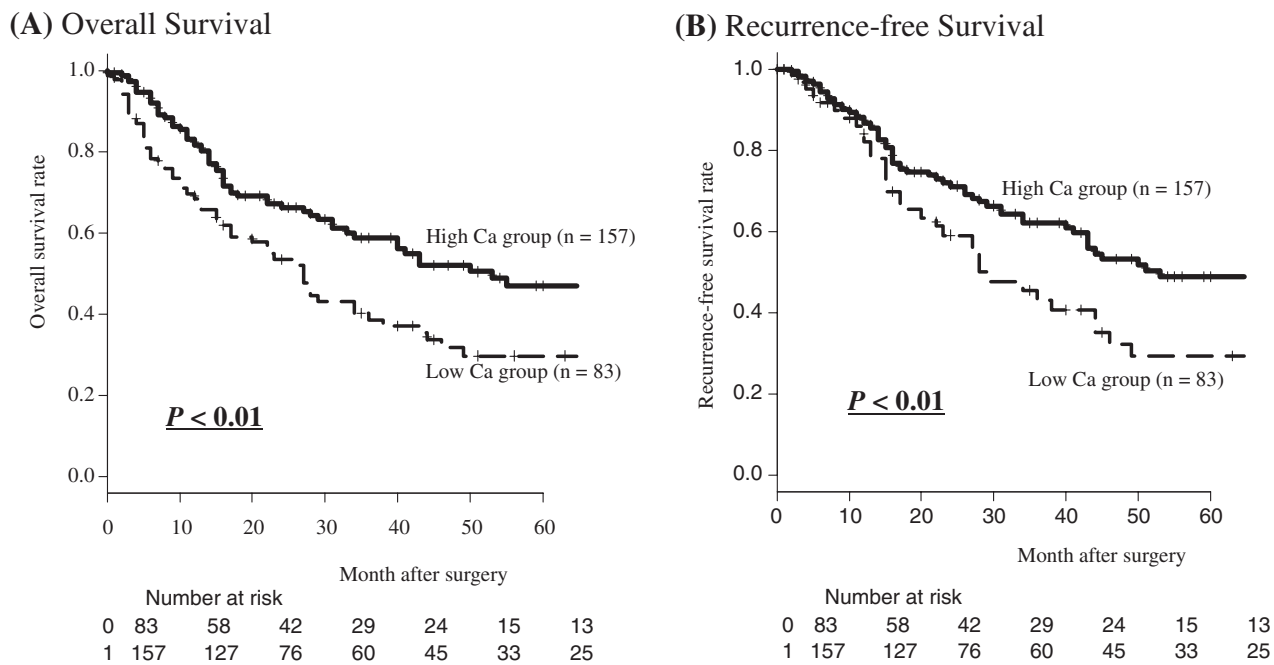
(A) Overall Survival

(B) Recurrence-free Survival

Number at risk (A)

	0	10	20	30	40	50	60
0	83	58	42	29	24	15	13
1	157	127	76	60	45	33	25

Number at risk (B)

	0	10	20	30	40	50	60
0	83	58	42	29	24	15	13
1	157	127	76	60	45	33	25

Fig. 3 Comparison of overall survivals and recurrence-free survivals according to the low calcium group and high calcium group.

Table 2 Univariate and multivariate analysis of clinicopathological factors to predict overall survival

Variables		Univariate analysis P value[a]	Multivariate analysis H.R (95% CI)	P value[b]
Age	<65/≥65	0.78		
Gender	Female/Male	<0.05	1.50 (0.84–2.68)	0.17
Tumor depth	T0T1/T2T3T4	<0.001	3.28 (1.86–5.79)	<0.01
Nodal status	N(-)/N(+)	<0.001	2.51 (1.55–4.08)	<0.01
Histological type	SCC/Adeno	0.34		
Serum Ca level	Low/High	<0.01	1.23 (0.81–1.86)	0.33
Neoadjuvant chemotherapy	No/Yes	<0.001	1.00 (0.66–1.52)	0.96
Postoperative complications	C–D classification ≤IIIa/≥IIIb	<0.05	3.17 (1.51–6.64)	<0.01
Serum Alb level	<4.0/≥4.0	<0.001	1.58 (0.98–2.56)	0.06
Body mass index	<17/≥17	0.18		

[a]Log-rank analysis
[b]Cox proportional hazards regression analysis
C–D classification: Clavien–Dindo classification; HR: hazard ratio; CI: confidence interval

employed to treat patients with cancer and bone metastases can cause low serum calcium levels.[21–24] However, our present study focused on surgically treated patients without bone metastases. Therefore, the low serum calcium levels in our study population were not induced by bisphosphonates. Mirrakhimov et al. reported that another cause of low calcium levels[25] is tumor lysis syndrome; however, this syndrome rarely occurs in solid tumors. It is unlikely that tumor lysis syndrome occurred in our present series because all patients in our study had resectable tumors treated with radical intent.

And more Huang et al.[17] reported that in patients with nasopharyngeal carcinoma, it might be increased calcium and phosphate deposition in bone by osteoblastic metastases, resulting in a decrease in serum calcium levels. In other words, bone metastases are involved in low calcium levels. However, all patients in our study did not include cases of bone metastasis.

Xu et al. reported a relationship between postoperative complications and hyponatremia or hypocalcemia in patients with gastric cancer.[14] They reported that low serum calcium levels were a risk factor for postoperative complications and a poor prognosis and stated that treatment of low serum calcium levels might improve patients' general condition for further treatment. Moreover, low serum calcium levels were considered to be associated with myocardial damage, hemorrhage, and/or pulmonary embolism.[26–29] In our study, there was no significant difference between low calcium group and high calcium group in the ratio of postoperative complications. Therefore, we consider that correction of low serum calcium levels before surgery may improve general conditions and improve surgical outcomes.

This study had several limitations, the first of which is that it only investigated low serum calcium levels and did not examine other electrolytes. Although serum hyponatremia was not a prognostic factor in the previous report of gastric cancer,[14] no information was reported in esophageal cancer. In future studies, we plan to consider other electrolyte disorders. Second, a population selection bias in our study might be unavoidable due to its single-center design. A large-scale multicenter trial is therefore needed to confirm our findings. The mechanisms of prognostic impact of low serum calcium levels in esophageal cancer remain unclear. Our study only suggests that hypocalcemia is a poor prognostic factor, and it is unclear whether low serum calcium levels are the result of multiple pathophysiological effects or independent biological factors. Therefore, low serum calcium levels in patients with esophageal cancer may be corrected before surgery.

In conclusion, this is the first study to focus on low serum calcium levels in patients with esophageal cancer. Our study showed that preoperative low serum calcium levels were associated with advanced tumors. Low serum calcium might be associated with esophageal cancer progression. Clinical impact of the correction of low serum calcium levels before surgery should be assessed in further studies.

Compliance with Ethical Standards

The present study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Toho University Hospital (no. M20200 20196 19056 18002). We obtained informed consent from all the participants.

Disclosure Statement

All the authors declared that they have no conflict of interest.

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