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# Is Preoperative Low Serum Calcium Level a Poor Prognostic Factor of Gastric Cancer?

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## ABSTRACT

**Introduction:** Few reports evaluated the prognostic impact of hypocalcemia in patients with cancer. In this study, we evaluated the clinicopathological and prognostic significance of preoperative serum calcium level in patients with gastric cancer.

**Methods:** We analyzed preoperative serum calcium levels in 758 patients (514 men and 244 women) who underwent radical surgery for gastric cancer between 2004 and 2017. The cutoff value of calcium level was fixed to 8.7 mg/dL based on receiver operating characteristic curve analysis. We compared the patients' clinicopathological characteristics between the low- and high calcium groups based on this cutoff value. We employed univariate and multivariate analyses to evaluate the clinicopathological and prognostic significance of preoperative low serum calcium levels.

**Results:** The low serum calcium level was significantly associated with old age, deep tumor depth, positive nodal status, positive distant metastasis, low serum albumin, high C-reactive protein, and high white blood cell count. The low serum calcium group exhibited a significantly worse overall survival than the high serum calcium group ( $P < 0.001$ ). The survival difference was significant only in stage I cancer patients; however, young patients did not have this tendency. The low serum calcium level was an independent risk factor for poor overall survival in stage I cancer elderly patients.

**Conclusions:** Preoperative low serum calcium level was associated with poor overall survival in patients with gastric cancer. This prognostic impact was particularly evident in stage I cancer elderly patients.

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**KEYWORDS:** gastric cancer, hypocalcemia, preoperative serum calcium, prognosis

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## Introduction

Other than TNM staging<sup>1)</sup> and surgical curability,<sup>2)</sup> various serum biomarkers have been reported as prognostic indicators of gastrointestinal cancer.<sup>3,4)</sup> Among the routine laboratory data, electrolyte disorder in the blood test indicates the poor general condition of cancer patients.<sup>5)</sup> Although postoperative low serum calcium level has been considered as a poor prognostic factor in gastric cancer patients,<sup>6)</sup> a preoperative low serum calcium level has not been well analyzed. Two studies associated low serum calcium levels with disease progression and patient survival in nasopharyngeal cancer<sup>7)</sup> and non-small cell lung cancer.<sup>8)</sup> However, the clinicopathological and prognostic significance of preoperative serum calcium levels have not been well determined in gastric cancer.

Only a Chinese report indicated the clinical significance of preoperative low serum calcium level (less than the normal range) in Chinese patients with gastric cancer.<sup>9)</sup> They reported that low serum calcium level was a poor prognostic factor of survival only in elderly patients. However, the classification of “low serum calcium level” was not fixed so far based on receiver operating characteristic curve analysis. Moreover, they did not evaluate the impact of serum calcium levels in stage I cancer patients. The precise classification of “low serum calcium level” for predicting long-term survival in the Japanese population has not yet been evaluated.

Here, we evaluated the clinicopathological and prognostic significance of the preoperative low serum calcium level using appropriate cutoff values in Japanese patients with gastric cancer to address these research questions.

## Methods

### Patients and definition of low calcium

This retrospective study included 798 gastric cancer patients who were surgically treated at the Omori Medical Center, Toho University School of Medicine (Tokyo, Japan), between January 2004 and December 2017. After excluding the non-curative resection cases (n = 40), 758 patients were finally included in the present study (Fig. 1). The cohort consisted of 514 men (68%) and 244 women (32%) with a median age of 69 years (range, 32-96 years). The patients were categorized according to the tumor stage as follows: stage I (n = 439), stage II (n = 171), stage III (n = 139), and stage IV (n = 9; Fig. 2). Among those with stage IV cancer, five presented with liver metastases, two

with distant lymph node metastases, one with ovarian metastasis, and one with peritoneal metastasis; the tumors were simultaneously resected in these patients. The medical records were reviewed to evaluate the clinicopathological impact of a low preoperative serum calcium level. This study was approved by the ethics committee of Toho University Omori Medical Center (M20200 20196 19056 18002) and complied with the Declaration of Helsinki.

### Surgery, adjuvant chemotherapy, and follow-up

All patients underwent radical gastrectomy with standard lymphadenectomy according to the Gastric Cancer Treatment Guidelines (5<sup>th</sup> edition, 2018).<sup>10)</sup> After surgery, 219 out of 761 patients (29%) received adjuvant chemotherapy. All patients were regularly followed up with clinical examination and imaging until the end of December 2018 or till the death of the patient, whichever came first. The average follow-up period for the survivors was 53 months (range, 0-179 months); in the current study, 296 patients (39%) survived for more than 5 years. Postoperative cancer recurrence was defined as positive findings during the successive monthly clinical examinations, in the 6-12-month computed tomography scans, and during the monthly monitoring of the serum tumor markers (CEA and CA19-9).

### Study design and data collection

The cutoff value for the serum calcium level was 8.7 mg/dL based on the receiver operating characteristic analysis results used to predict the patients' overall survival. The patients were divided into two groups based on this cutoff value (low and high serum calcium groups) to compare the clinicopathological factors and prognoses. Univariate and multivariate analyses were employed to evaluate the prognostic impact of serum calcium. A standard flow sheet was used to collect data on the preoperative parameters, pathological parameters, and patient survival.

### Statistical analyses

Statistical analyses were conducted using the EZR software.<sup>11)</sup> Univariate and multivariate analyses were employed to evaluate the clinicopathological and prognostic significance of the serum calcium levels before surgery. Logistic regression analysis was employed to compare the two groups in this study, whereas the Kruskal-Wallis test was employed to compare multiple groups. The survival curves were calculated using the Kaplan-Meier product-limit estimate, and the survival differences between the groups were analyzed using the log-rank test. Significant

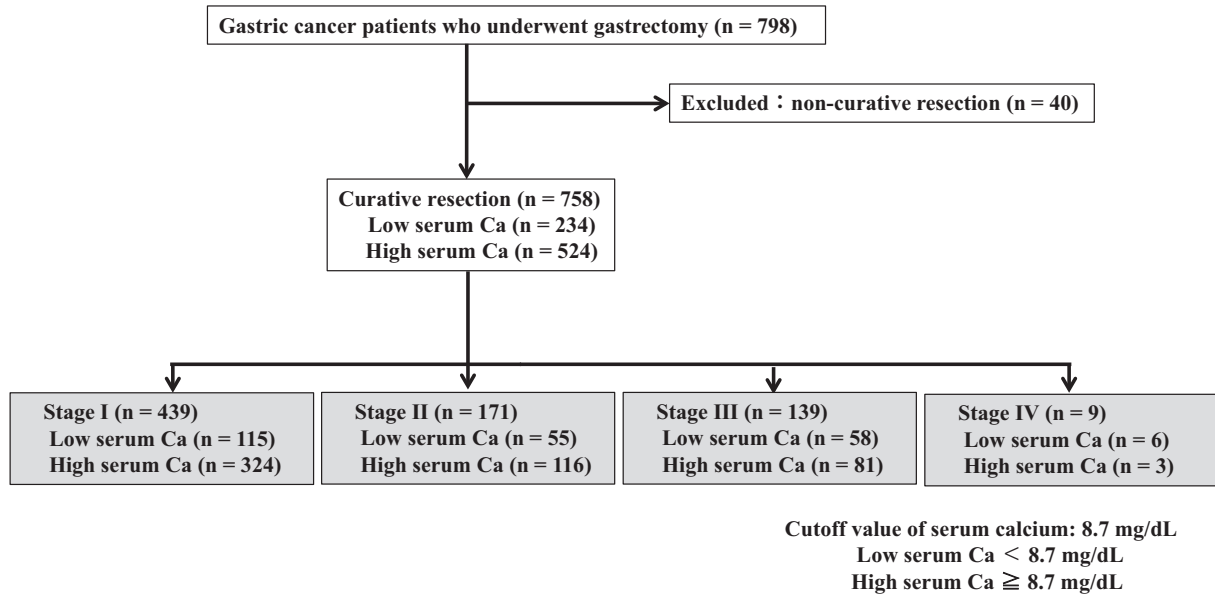


Fig. 1 A flowchart showing patient selection for this study.

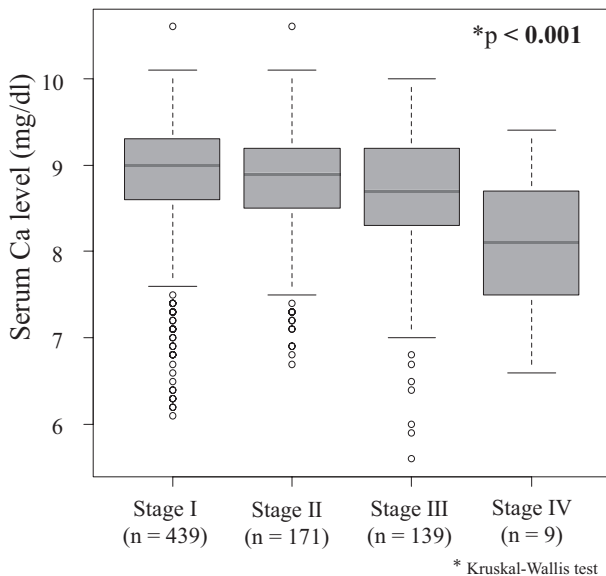


Fig. 2 Serum calcium levels according to the tumor stages.

prognostic indicators identified *via* univariate analysis were evaluated *via* multivariate analysis using the Cox proportional-hazards model. A two-tailed *P*-value of < 0.05 was considered statistically significant.

## Results

### Comparison of the clinicopathological factors between the high and low serum calcium groups

The serum calcium levels, based on the tumor stages, are presented in Fig. 2. The levels at stage IV were significantly

lower than those at the other stages. Comparisons of the clinicopathological variables between the high and low serum calcium groups are presented in Table 1. The serum calcium levels were low in patients with advanced cancer, low albumin level ( $P < 0.001$ ), high white blood cell (WBC) count ( $P < 0.001$ ), and high C-reactive protein level (CRP;  $P < 0.001$ ). Elderly patients presented with lower serum calcium levels than young ones ( $P = 0.006$ ). The other clinicopathological variables were not related to the serum calcium level. In the multivariate analysis, low albumin level, high CRP level, and high WBC count were independent factors for the low serum calcium levels (Table 1).

### Comparison of the clinicopathological factors between the high and low serum calcium groups in patients with stage I cancer

Comparisons of the clinicopathological variables between the high and low serum calcium groups in patients with stage I cancer are presented in Table 2. Low serum calcium level was significantly associated with lymph node metastasis ( $P = 0.011$ ), low albumin level ( $P < 0.001$ ), high WBC count ( $P < 0.001$ ), and high CRP level ( $P < 0.001$ ). The multivariate analysis revealed that lymph node metastasis, low albumin level, high CRP level, and high WBC count were independent factors for low serum calcium levels in patients with stage I cancer (Table 2).

### Prognostic impact of low serum calcium level on overall survival

Fig. 3 presents the comparison of the overall survival between patients in the two groups. The patients in the

Table 1 Univariate and multivariate analyses of clinicopathological characteristics associated with Ca level in all patients

Variables	Number of patients	Low serum Ca n = 234 (%)	High serum Ca n = 524 (%)	Univariate analysis P value †	Multivariate analysis		
					O.R ‡ (95%CI§)	P value †	
Age	<65	255	62 (24)	193 (76)	0.006	1.05 (0.71-1.56)	0.812
	≥65	503	172 (34)	331 (66)			
Gender	Female	244	69 (28)	175 (72)	0.287	1.12 (0.76-1.63)	0.568
	Male	514	165 (32)	349 (68)			
Tumor depth	T1T2	487	122 (25)	365 (75)	<0.001	1.36 (0.91-2.03)	0.140
	T3T4	271	112 (41)	159 (59)			
Nodal status	Negative	498	135 (27)	363 (73)	0.002	0.99 (0.66-1.48)	0.948
	Positive	260	99 (38)	161 (62)			
Distant metastasis	Negative	749	228 (30)	521 (70)	0.033	3.21 (0.65-15.80)	0.152
	Positive	9	6 (67)	3 (23)			
Histological type	Differentiated	440	136 (31)	304 (69)	0.98	1.32 (0.92-1.91)	0.132
	Poor	318	98 (31)	220 (69)			
Serum ALB (g/dl)	≥4.1	289	27 (9)	262 (91)	<0.001	5.89 (3.70-9.37)	<0.001
	<4.1	469	207 (44)	262 (56)			
CRP (mg/dl)	≤0.2	529	124 (23)	405 (77)	<0.001	1.63 (1.12-2.38)	0.011
	>0.2	228	109 (48)	119 (52)			
WBC (/μL)	<8600	637	166 (26)	471 (74)	<0.001	2.55 (1.64-3.97)	<0.001
	≥8600	121	68 (56)	53 (44)			

CRP: C-reactive protein

WBC: white blood cell count

†: Logistic regression analysis

‡: Adjusted odds ratio

§: Adjusted 95% confidence interval

low serum calcium group had significantly worse survival than those in the high serum calcium group (Fig. 3a); further analysis revealed that this significant difference was observed only among patients with stage I cancer (Fig. 3b-e).

#### Univariate and multivariate analyses of overall survival

Based on the univariate analysis, old age ( $P < 0.001$ ), T3 T4 tumors ( $P < 0.001$ ), lymph node metastasis ( $P < 0.001$ ), distant metastasis ( $P < 0.001$ ), low serum calcium level ( $P < 0.001$ ), low serum albumin level ( $P < 0.001$ ), and high CRP level ( $P < 0.001$ ) were the significant prognostic factors of poor overall survival. Conversely, based on the multivariate analysis, old age ( $P = 0.003$ ), T3T4 tumors ( $P = 0.006$ ), lymph node metastasis ( $P < 0.001$ ), and low serum albumin level ( $P = 0.020$ ) were the independent prognostic factors. A low serum calcium level ( $P = 0.075$ ) and high CRP level ( $P = 0.068$ ) tended to be associated with poor prognosis (Table 3 left panel).

Based on the univariate analysis of patients with stage I cancer, old age ( $P < 0.001$ ), sex (men;  $P = 0.038$ ), low serum

calcium level ( $P < 0.001$ ), low serum albumin level ( $P < 0.001$ ), and high CRP level ( $P < 0.001$ ) were significant poor prognostic factors of overall survival. Based on the multivariate analysis of these patients, old age ( $P = 0.007$ ) and low serum calcium level ( $P = 0.006$ ) were the independent poor prognostic factors of overall survival (Table 3 right panel).

#### Comparison of the overall survival among patients with stage I cancer based on their age

Among the stage I cancer patients, no significant difference was observed in the overall survival between young patients (below 65 years old) in the two groups in this study (Fig. 4a). However, there was a significant difference between the elderly patients (above 65 years old) in the two groups (Fig. 4b). Table 4 presents the results of the univariate and multivariate analyses of the clinicopathological factors for overall survival in elderly patients with stage I cancer. Low serum calcium level was an independent poor prognostic factor of overall survival.

Table 2 Univariate and multivariate analyses of clinicopathological characteristics associated with Ca level in stage I patients

Variables	Number of patients	Low serum Ca		Univariate analysis P value †	Multivariate analysis	
		n = 115 (%)	High serum Ca n = 324 (%)		O.R ‡ (95%CI §)	P value †
Age	<65	170	38 (22)	0.146	0.74 (0.42-1.31)	0.298
	≥65	269	77 (29)			
Gender	Female	139	32 (23)	0.304	1.14 (0.65-2.02)	0.643
	Male	300	83 (28)			
Tumor depth	T1a	149	36 (24)	0.471	0.83 (0.48-1.43)	0.492
	T1b	244	67 (27)			
Nodal status	Negative	407	100 (25)	0.008	2.73 (1.17-6.36)	0.020
	Positive	32	15 (47)			
Histological type	Differentiated	258	74 (29)	0.158	0.96 (0.55-1.67)	0.889
	Poor	181	41 (23)			
Serum ALB (g/dl)	≥4.1	212	21 (10)	<0.001	5.26 (2.88-9.61)	<0.001
	<4.1	227	94 (41)			
CRP (mg/dl)	≤0.2	346	73 (21)	<0.001	1.88 (1.04-3.42)	0.038
	>0.2	92	41 (45)			
WBC (/μL)	<8600	372	77 (21)	<0.001	3.73 (1.99-7.01)	<0.001
	≥8600	67	38 (57)			

CRP: C-reactive protein

WBC: white blood cell count

†: Logistic regression analysis

‡: Adjusted odds ratio

§: Adjusted 95% confidence interval

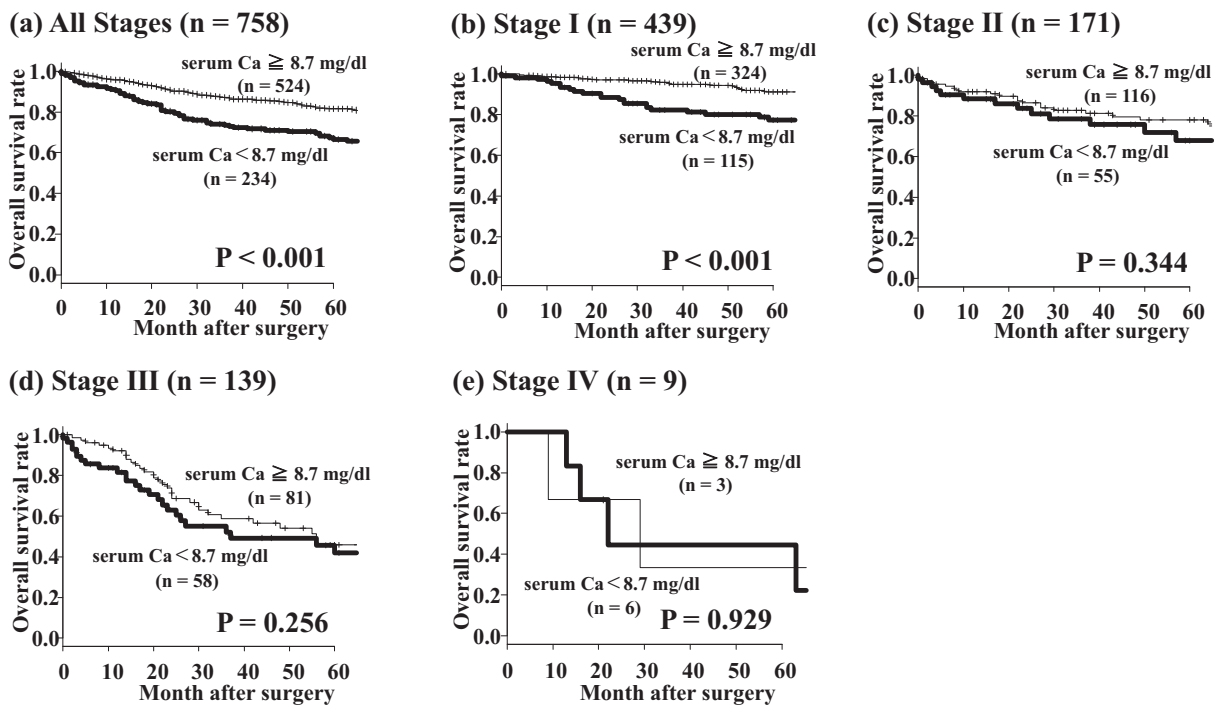


Fig. 3 Comparison of overall survival according to the serum calcium levels at each tumor stage. (a) All stages, (b) stage I, (c) stage II, (d) stage III, and (e) stage IV.

Table 3 Univariate and multivariate analyses of clinicopathological characteristics associated with overall survival in all patients

Variables		All patients			Stage I patients		
		Univariate analysis P value †	Multivariate analysis		Univariate analysis P value †	Multivariate analysis	
			H.R ‡ (95%CI§)	P value ¶		H.R ‡ (95%CI§)	P value ¶
Age	≥65/<65	<0.001	1.79 (1.22-2.63)	0.003	<0.001	2.87 (1.34-6.14)	0.007
Gender	Male/Female	0.262	1.15 (0.81-1.62)	0.436	0.038	1.66 (0.81-3.42)	0.170
Tumor depth	T3T4/T1T2	<0.001	1.68 (1.16-2.43)	0.006	0.297	1.10 (0.58-2.11)	0.772
Nodal status	N (+)/N (-)	<0.001	2.33 (1.62-3.35)	<0.001	0.210	1.22 (0.52-2.84)	0.648
Distant metastasis	M1/M0	<0.001	1.60 (0.69-3.74)	0.275	—	—	—
Serum Ca level	Low Ca/High Ca	<0.001	1.36 (0.97-1.91)	0.075	<0.001	2.70 (1.33-5.48)	0.006
Serum ALB (g/dl)	<4.1/≥4.1	<0.001	1.65 (1.08-2.53)	0.020	<0.001	1.15 (0.53-2.50)	0.733
CRP (mg/dl)	>0.2/≤0.2	<0.001	1.38 (0.98-1.96)	0.068	<0.001	1.81 (0.97-3.39)	0.064
WBC (μL)	≥8600/<8600	0.269	0.91 (0.59-1.38)	0.649	0.230	0.94 (0.45-1.94)	0.862

CRP: C-reactive protein

WBC: white blood cell count

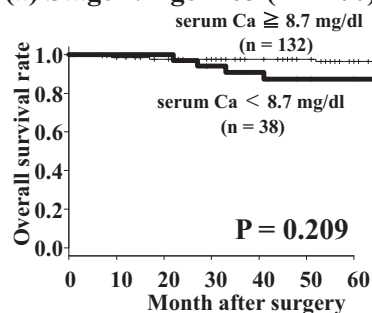
†: Log-rank test analysis

‡: Adjusted hazards ratio

§: Adjusted 95% confidence interval

¶: Cox proportional hazards regression analysis

(a) Stage I: Age &lt; 65 (n = 170)



(b) Stage I: Age ≥ 65 (n = 269)

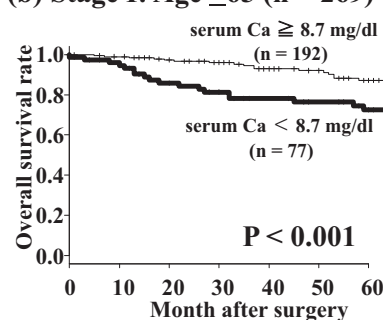


Fig. 4 Comparison of the overall survival of stage I cancer patients according to age group: (a) young patients, (b) elderly patients.

## Discussion

Previous studies have not clearly indicated the cutoff values for serum calcium during the prognostic evaluation of gastric cancer. The present study determined an appropriate cutoff value of 8.7 mg/dL based on the analysis results of the receiver operating characteristic curve. The clinicopathological and prognostic significance of low pre-

operative serum calcium levels was then evaluated among surgically treated gastric cancer patients. A low serum calcium level was significantly associated with old age, increased tumor depth, positive nodal status, distant metastasis, low serum albumin level, high CRP level, and high WBC count. The patients in the low serum calcium group had a significantly worse overall survival than those in the high calcium group; this difference was significant only



Table 4 Univariate and multivariate analyses of overall survival of stage I elderly patients

Variables		Univariate analysis P value †	Multivariate analysis	
			H.R ‡ (95%CI §)	P value ¶
Gender	Male/Female	0.081	1.62 (0.72-3.66)	0.246
Tumor depth	T1b/T1a	0.099	1.48 (0.68-3.23)	0.320
Nodal status	positive/negative	0.350	1.29 (0.54-3.10)	0.572
Serum Ca level	Low Ca/High Ca	<0.001	3.19 (1.36-7.50)	0.008
Serum ALB (g/dl)	<4.1/≥4.1	0.078	0.86 (0.34-2.21)	0.760
CRP (mg/dl)	>0.2/≤0.2	<0.001	2.23 (1.14-4.37)	0.019
WBC (μL)	≥8600/<8600	0.390	0.94 (0.42-2.12)	0.887

CRP: C-reactive protein

WBC: white blood cell count

†: Log-rank test analysis

‡: Adjusted hazards ratio

§: Adjusted 95% confidence interval

¶: Cox proportional hazards regression analysis

among elderly patients with stage I cancer.

In our study, a low serum calcium level was an independent prognostic factor in stage I cancer patients, but albumin nor CRP was not an independent prognostic factor. Low preoperative serum calcium might significantly affect the prognoses of patients with early gastric cancer following gastrectomy. Therefore, it might be important to consider a preoperative serum calcium correction in such cases.

Hypocalcemia is likely to occur after gastrectomy, and patients with preoperative hypocalcemia are more likely to develop postoperative hypocalcemia, which could result in cognitive decline, osteoporosis, and trauma, such as a femoral neck fracture.<sup>12,13</sup> Regarding gastric sleeve surgery in obese patients, Carlin et al. reported that the addition of vitamin D supplementation for Roux-en-Y gastric bypass patients immediately after surgery was useful for osteoporosis and hypertension improvement.<sup>14</sup> Schmitz et al. reported that low serum calcium level was significantly associated with high acute myocardial infarction mortality. In the paper, the serum calcium level was analyzed, not the albumin correction value.<sup>15</sup> Furthermore, in our study, the prognostic significance of calcium was observed when serum calcium was used. However, a prognostic significance was not observed when albumin-corrected values were used (data not shown).

In patients with advanced cancer, the serum calcium level may be superficially corrected due to local osteolytic hypercalcemia caused by the cancer.<sup>16</sup> Therefore, the prognostic effect of hypocalcemia may be low in patients with stage II/III/IV cancer. These findings indicate that

preoperative serum calcium levels might prove useful as a prognostic indicator for those with gastric cancer; however, the reason for this is unclear. In the current study, a low serum calcium level was a significant prognostic factor in patients with stage I cancer but not stage II/III/IV cancer. Thus, it is important to evaluate the link between low serum calcium levels and other diseases to better understand this phenomenon.

In the prognostic analysis of stage I cancer cases, low calcium level was a poor prognostic factor only in elderly patients, not in young patients. The reason for this may be that the cardiovascular events associated with hypocalcemia were more fatal in elderly patients, which may have increased other causes of deaths, recurrence, and deaths from other cancers. The causes of death in 55 of stage I cancer patients were as follows: primary gastric cancer in 8; other types of cancer, 8; suicide, 1; other causes of death, 30; and unknown cause of death, 8. Among the 55 stage I cancer patients who died, 45 were elderly patients; 6 died of primary gastric cancer; 1, other types of cancer; 1, suicide; 32, causes other than cancer; and 5, unknown cause. Unfortunately, no particular trend was found cause of death in the elderly patients with low calcium levels.

This study had three limitations. First, no other electrolyte data was analyzed; second, there was shortage of data on the cause of death; third, data on postoperative serum calcium levels was lacking. Thus, further studies are needed.

In conclusion, low preoperative serum calcium levels were associated with poor overall survival in patients with gastric cancer. This prognostic impact was evident, par-



ticularly among elderly patients with stage I cancer. This tendency might be associated with other causes of death.

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**Authors' contribution:** R.K., Y.O., N.W., K.F., and H.S. designed the study; Y.O., T.S., S.Y., T.N., M.I., and F.S.; performed the experiments and analyzed the data; R.K., and H.S. wrote the manuscript.

**Ethics statement:** Approval of the research protocol. The ethics committee of Toho University Omori Medical Center approved this study (M20200 20196 19056 18002).

**Conflicts of interest:** None declared.

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