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ORIGINAL ARTICLE

Prognostic significance of preoperative osteopenia on outcomes after gastrectomy for gastric cancer

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Abstract

Aim: Osteopenia, characterized by low bone mineral density, is a potential prognostic factor for patients with cancer. The aim of this study was to clarify the impact of preoperative osteopenia in patients with gastric cancer (GC) after gastrectomy.

Methods: We included 224 patients with GC who underwent gastrectomy between August 2013 and May 2022. Osteopenia was evaluated by measuring the pixel density in the mid-vertebral core of the 11th thoracic vertebra using computed tomography.

Results: Osteopenia was identified in 68 patients (30%). The osteopenia group had significantly worse overall survival (OS) and disease-free survival (DFS) than the non-osteopenia group ($P < .01$, $P < .01$, respectively). The postoperative hospital stay was significantly longer, and the occurrence of postoperative complications (Clavien-Dindo grade ≥ III) was significantly higher in the osteopenia group ($P = .04$, $P < .01$, respectively). In multivariate analysis, osteopenia ($P < .01$), stage ≥II ($P < .01$), and R1 or R2 curability ($P < .01$) were independent and significant predictors of DFS. Additionally, osteopenia ($P < .01$), intraoperative blood loss ($P = .04$), stage ≥II ($P < .01$), and R1 or R2 curability ($P < .01$) were independent and significant predictors of OS.

Conclusion: Preoperative osteopenia was independently associated with a poor prognosis and recurrence in patients who underwent gastrectomy for GC.

KEYWORDS
gastrectomy, gastric cancer, osteopenia, prognostic factor, sarcopenia

1 | INTRODUCTION

Gastric cancer (GC) is the fifth most common neoplasm worldwide. The mortality rate of GC has been decreasing in recent years owing to great progress in treatment. However, GC is the third most deadly cancer, with an estimated 768 793 deaths in 2020, worldwide.[1] The tumor-node-metastasis (TNM) stage is a reliable prognostic indicator. However, additional reliable prognostic factors are needed because of the heterogeneity of prognosis, even among patients with the same tumor stage. Therefore, early identification of high-risk patients with GC and provision of more active, comprehensive treatment will have a significant impact on the effectiveness of treatment. Increasing evidence shows that systemic inflammatory responses like Glasgow prognostic score (GPS), prognostic nutritional index (PNI), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) are important in the prognosis of GC.[2–5]

Osteopenia is a condition of low bone mineral density (BMD). It is a risk factor for fractures and falls, with negative financial, physical, and psychosocial effects on the patients and ultimately the prognosis. BMD assessment is generally performed using dual-energy X-ray absorptiometry (DEXA) as the standard method.[6] However, computed tomography (CT)-measured BMD by measuring the mean pixel density of the thoracic vertebral trabeculae on CT has recently been found to be correlated with DEXA.[7] Some studies have demonstrated that preoperative osteopenia in patients with digestive tract cancers, such as pancreatic, colon, and esophageal cancers, predicts poor prognosis.[8] However, the effect of preoperative osteopenia on the prognosis of patients with GC remains unclear. This study aimed to clarify the impact of preoperative osteopenia on the outcomes of patients who underwent gastrectomy for GC compared with other preoperative systemic inflammatory response markers and sarcopenia.

2 | METHODS

2.1 | Patients

A total of 224 consecutive patients with GC underwent initial gastrectomy between August 2013 and May 2022 at the Fuji City General Hospital, Shizuoka, Japan. The database of patients with GC was retrospectively reviewed. This study was approved by the Ethics Committee of Fuji City General Hospital (281).

2.2 | Treatment and patient management

Our GC treatment strategy, including surgical indications, surgical treatment, and chemotherapy selection, was based on the treatment guidelines edited by the Japanese GC Association.[9] For staging and pathological diagnosis, we used the Japanese classification of gastric carcinoma (3rd English Edition).[10] Total, distal, or proximal gastrectomy was performed depending on the location of the primary tumor. The selection between laparoscopic and open surgical approach was at the discretion of the attending surgeon. Postoperative complications were defined as Clavien-Dindo grade ≥III complications occurring within 30 days after surgery. Pathological stage II patients underwent adjuvant chemotherapy with TS-1 alone and pathological stage III patients underwent adjuvant chemotherapy with TS-1 alone or TS-1 in combination with cisplatin or oxaliplatin based on the patient preference. Basic surveillance was performed using tumor markers such as serum carcinoembryonic antigen (CEA) or carbohydrate antigen 19-9 (CA19-9) every 3 months. Chest and abdominal enhanced CT and endoscopy were performed every 6 months and every 1 or 2 years, respectively, for 5 years after surgery.[6] Recurrence was defined as the first newly detected local or distant metastatic tumor based on CT findings. For recurrence, systemic chemotherapy was selected based on the patient's performance status.

2.3 | Definition of osteopenia and sarcopenia

The BMD in the trabecular bone was measured by calculating the average pixel density within a circle of the mid-vertebral core at the bottom of the 11th thoracic vertebra (Th11) on preoperative plain CT. Osteopenia was defined as a decrease in BMD below the standard values, which was calculated, as previously reported, as follows: (men = [308.82–2.49 × age]; women = [311.84–2.41 × age]).[11] CT images at the Th11 level, with and without osteopenia, are shown in Figure 1. Preoperative treatment of osteoporosis included medication of calcium, vitamin D, and bisphosphonate.

Sarcopenia was defined as a psoas muscle mass area (PMA) at the third lumbar vertebra below the sex-specific median size, calculated as follows: length of the major axes × length of the minor axes × π (Figure 2).[12]

2.4 | Preoperative systemic inflammation response markers

Systemic inflammatory response markers based on preoperative laboratory tests, such as GPS,[3] PNI,[13] NLR,[4] and PLR,[14] were examined in this study. GPS scores were defined as a combination of C-reactive protein (CRP) and albumin levels. Patients with both elevated CRP (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were given a score of 2, those with only one of these abnormalities were given a score of 1, and those with neither of these abnormalities were given a score of 0. The PNI was calculated as 10 × albumin (g/dL) + 0.005 × lymphocyte count/μl. NLR was calculated as the number of neutrophils divided by the number of lymphocytes and PLR as the number of platelets divided by the number of lymphocytes.

2.5 | Analyses of risk factors for recurrence and overall survival

We investigated the association between clinicopathological variables and disease-free survival (DFS) or overall survival (OS) after initial gastrectomy using univariate and multivariate analyses. Variables included age, serum CEA level, osteopenia, sarcopenia, GPS, PNI, PLR, NLR, operative time, intraoperative blood loss, complications, neoadjuvant chemotherapy, stage, and curability. Continuous variables were classified into two groups based on the Cox proportional hazards regression model. The cutoff values for CEA were set at the upper normal limit, and the optimal cutoff values were determined by using a receiver operating characteristic analysis for age, PNI, PLR, NLR operative time, and intraoperative blood loss.

2.6 | Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22 (IBM Corp.). Continuous variables are

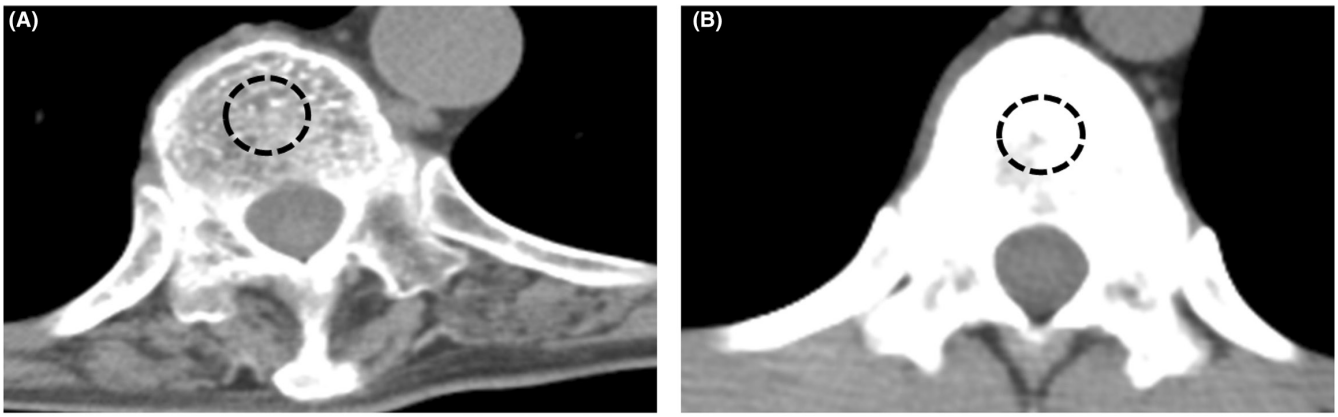

FIGURE 1 We measured in the trabecular bone by calculating the average pixel density within a circle of the mid-vertebral core at the bottom of 11th thoracic vertebra on preoperative plain computed tomography. A, Osteopenia and B, Non-osteopenia

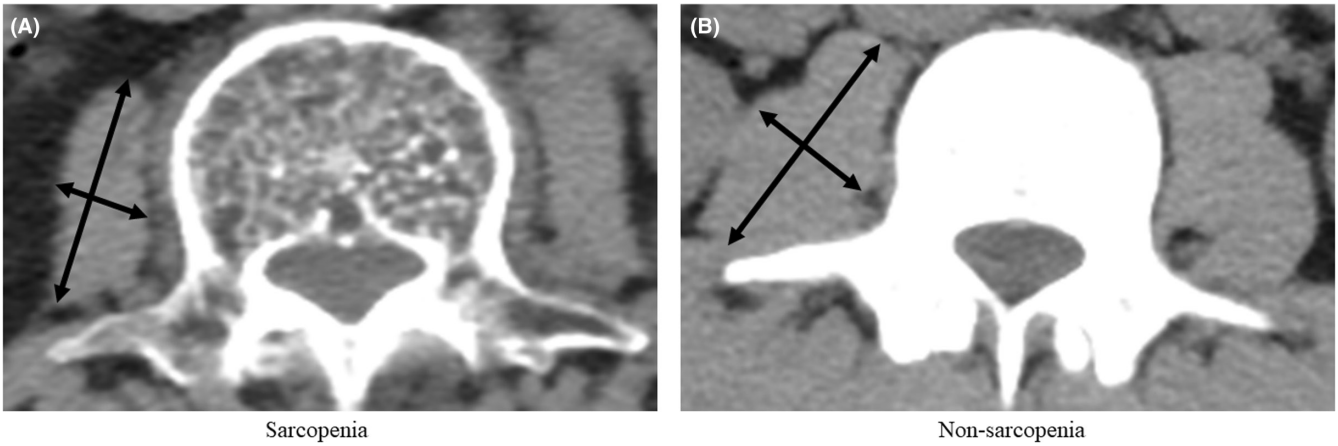

FIGURE 2 We measured psoas muscle mass area at the third lumbar vertebra as follows: length of the major axes × the length of the minor axes × π. A, Sarcopenia and B, Non-sarcopenia

expressed as medians with interquartile ranges. Categorical variables are expressed as numbers with percentages. Univariate analysis was performed using the Mann-Whitney U and chi-square tests. Univariate and multivariate analyses of the DFS and OS rates were performed using the Cox proportional hazards model. Variables identified as significant in the univariate analysis were considered candidates for multivariate Cox regression analysis. The Kaplan-Meier analysis was used to evaluate survival, and the log-rank test was used to compare the cumulative probability between the groups. Statistical significance was set at $P < .05$.

3 | RESULTS

3.1 | Patients' characteristics

The patient characteristics are shown in Table 1. The patients consisted of 174 men (78%) and 50 women (22%), with a median age of 73 years (range, 66-79 years). The median PMAs were 21.8 and 13.9 cm^2 for men and women, respectively. Sarcopenia was diagnosed in 111 (49%) patients. The median value of BMD was 147 Hounsfield units (HU), and osteopenia was diagnosed in 68 (30%) patients, according to the calculated standard BMD values. Laparoscopic surgery was performed in 119 (53%) and open surgery in 105 (47%) patients, with a postoperative complication (Clavien-Dindo grade III or higher) rate of 11% (25/224 patients). In the pathological diagnosis of GC, 39% (n = 87), 22% (n = 49), and 31% (n = 70), 8% (n = 18) of patients had stage I, II, III, and IV respectively.

When comparing the osteopenia and non-osteopenia groups, osteopenia was significantly more common in older and low PLR patients ($P = .03$, $P < .01$, respectively). Furthermore, the postoperative hospital stay was significantly longer and the occurrence of postoperative complications (Clavien-Dindo grade ≥ III) were significantly higher in the osteopenia group (15 vs 12 days, $P = .04$; 22 vs 6%, $P < .01$, respectively).

TABLE 1 Patients' characteristics

Variables	Total (n = 224)	Osteo		*P*-value
		Yes (n = 68)	No (n = 156)	
Age, yeas	73 (66-79)	75 (70-81)	72 (65-79)	**0.03**
Gender, male	174 (78%)	53 (78%)	121 (78%)	1.00
Body mass index, kg/m^2	21.8 (20.0-24.3)	22.1 (20.5-25.5)	21.5 (20.0-24.0)	0.23
Serum CEA, 5 ≥ ng/mL	74 (33%)	26 (38%)	48 (31%)	0.28
Preoperative medications	10 (5%)	3 (4%)	7 (4%)	1.00
BMD, HU	147 (113-177)	103 (85-113)	165 (140-189)	**<0.01**
PMA, cm^2	19.0 (13.6-24.9)	16.5 (11.7-23.2)	20.1 (14.7-25.7)	**0.03**
GPS, 1 or 2	68 (30%)	26 (38%)	42 (27%)	0.11
PNI	48 (42-52)	48 (41-53)	48 (42-52)	0.69
NLR	2.3 (1.6-3.2)	2.2 (1.7-3.3)	2.3 (1.6-3.1)	0.80
PLR	145.4 (98.5-203.4)	116.3 (94.0-176.7)	154.2 (108.3-238.4)	**<0.01**
Sarcopenia				
Yes	111 (49%)	42 (62%)	69 (44%)	**0.02**
No	113 (51%)	26 (38%)	87 (56%)	
Histological type				
tub1	74 (33%)	20 (30%)	54 (35%)	0.91
tub2	29 (13%)	11 (16%)	18 (12%)	
por	91 (40%)	27 (40%)	64 (41%)	
sig	20 (9%)	7 (10%)	13 (8%)	
pap	6 (3%)	2 (3%)	4 (2%)	
muc	4 (2%)	1 (1%)	3 (2%)	
Neoadjuvant chemotherapy, yes	4 (2%)	1 (2%)	3 (2%)	1.00
Operative approach				
Open	105 (47%)	35 (51%)	86 (55%)	0.39
Laparoscope	119 (53%)	33 (39%)	70 (45%)	
Operative procedure				
DG	138 (62%)	42 (62%)	96 (62%)	0.97
PG	4 (2%)	1 (1%)	3 (2%)	
TG	82 (36%)	25 (37%)	57 (36%)	
Lymph node dissection				
D1	65 (29%)	22 (32%)	43 (27%)	0.43
D1+	79 (35%)	25 (37%)	54 (35%)	
D2	80 (36%)	21 (31%)	59 (38%)	
Operative time, min	268 (228-331)	268 (227-350)	268 (231-325)	0.60
Blood loss, ml	230 (50-450)	290 (100-585)	200 (45-430)	**0.01**
Postoperative hospital stay, days	12 (10-20)	15 (11-30)	12 (10-16)	**0.04**
Postoperative complication (Clavien-Dindo grade III-V)	25 (11%)	15 (22%)	10 (6%)	**<0.01**
Reoperation	9 (4%)	5 (7%)	4 (3%)	0.14
T factor				
1	82 (37%)	23 (33%)	59 (38%)	0.45
2	23 (10%)	10 (15%)	13 (8%)	
3	56 (25%)	10 (15%)	46 (30%)	
4	63 (28%)	25 (37%)	38 (24%)	

TABLE 1 (Continued)

Variables	Total (n = 224)	Osteo		P-value
		Yes (n = 68)	No (n = 156)	
Lymph node metastases				
Yes	119 (53%)	38 (56%)	81 (52%)	0.66
No	105 (47%)	30 (44%)	75 (48%)	
Stage				
IA	71 (32%)	19 (28%)	52 (33%)	0.66
IB	16 (7%)	7 (10%)	9 (6%)	
IIA	22 (10%)	5 (7%)	17 (11%)	
IIB	27 (12%)	6 (9%)	21 (14%)	
IIIA	18 (8%)	6 (9%)	12 (8%)	
IIIB	17 (8%)	7 (10%)	10 (6%)	
IIIC	35 (15%)	13 (19%)	22 (14%)	
IV	18 (8%)	5 (8%)	13 (8%)	
Adjuvant chemotherapy, yes	46 (22%)	11 (17%)	35 (25%)	0.28
Curability				
R0	194 (87%)	58 (85%)	136 (87%)	0.83
R1 or R2	30 (13%)	10 (15%)	20 (13%)	

Abbreviations: BMD, bone mineral density; CEA, carcinoembryonic antigen; DG, distal gastrectomy; GPS, Glasgow prognostic score; muc, mucinous adenocarcinoma; NLR, neutrophil-lymphocyte ratio; pap, papillary adenocarcinoma; PG, proximal gastrectomy; PLR, platelet-lymphocyte ratio; PMA, psoas muscle mass area; PNI, prognostic nutrition index; por, poorly differentiated adenocarcinoma; sig, signet ring cell adenocarcinoma; TG, total gastrectomy; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma.

3.2 | Impact of osteopenia on DFS and OS after gastrectomy for GC

The DFS of patients with osteopenia was significantly lower than that of patients without osteopenia (3-year survival: 49.2% vs 73.1%; $P < .01$) (Figure 3A). Additionally, the OS of patients with osteopenia was significantly lower than that of patients without osteopenia (3-year survival: 54.1% vs 77.5%; $P < .01$) (Figure 3B).

3.3 | Univariate and multivariate DFS analyses of patients with GC

Table 2 lists the prognostic factors for DFS according to Cox proportional hazard analysis. In univariate analysis, DFS was significantly worse in patients with osteopenia ($P < .01$), sarcopenia ($P < .01$), GPS 1 or 2 ($P < .01$), PNI <45 ($P = .01$), intraoperative blood loss ≥137 mL ($P < .01$), Stage ≥II ($P < .01$), and R1 or R2 curability ($P < .01$). The significant factors in multivariate analysis were osteopenia (hazard ratio [HR]: 2.18; 95% confidence interval [CI]: 1.30-3.67; $P < .01$), Stage ≥II (HR: 7.77; 95% CI: 3.02-19.86; $P < .01$), and R1 or R2 curability (HR: 4.62; 95% CI: 2.63-8.10; $P < .01$).

3.4 | Univariate and multivariate OS analyses in patients with GC

Table 3 lists the prognostic factors for OS according to the Cox proportional hazard analysis. In univariate analysis, OS was significantly worse in patients with osteopenia ($P < .01$), sarcopenia ($P < .01$), GPS 1 or 2 ($P < .01$), PNI <45 ($P < .01$), intraoperative blood loss ≥137 mL ($P < .01$), Stage ≥II ($P < .01$), and R1 or R2 curability ($P < .01$). The significant factors in multivariate analysis were osteopenia (HR: 2.42; 95% CI: 1.37-4.29; $P < .01$), intraoperative blood loss ≥137 mL (HR: 2.07; 95% CI: 1.04-4.11; $P = .04$), Stage ≥II (HR: 6.70; 95% CI: 2.57-17.43; $P < .01$), and R1 or R2 curability (HR: 4.72; 95% CI: 2.51-8.88; $P < .01$).

4 | DISCUSSION

Our study demonstrated that preoperative osteopenia was an independent risk factor for poor OS and DFS. To the best of our knowledge, this is the first report to show the impact of preoperative osteopenia on the prognosis of GC and to compare this risk factor with other preoperative systemic inflammatory response markers or sarcopenia.

Previous studies have shown that systemic inflammatory response markers and sarcopenia are associated with survival outcomes in patients with GC. Kawamura et al conducted an observational study with 951 patients who had GC and found that sarcopenia was associated with poor survival.[2] Wang et al reported that in 324 patients with GC, an elevated preoperative GPS was associated with a shorter OS and DFS.[3] Higher PLR and NLR have been associated with poor survival in GC.[4,5] However, only a few studies have compared the effectiveness of multiple inflammatory response markers for predicting survival outcomes. In the current

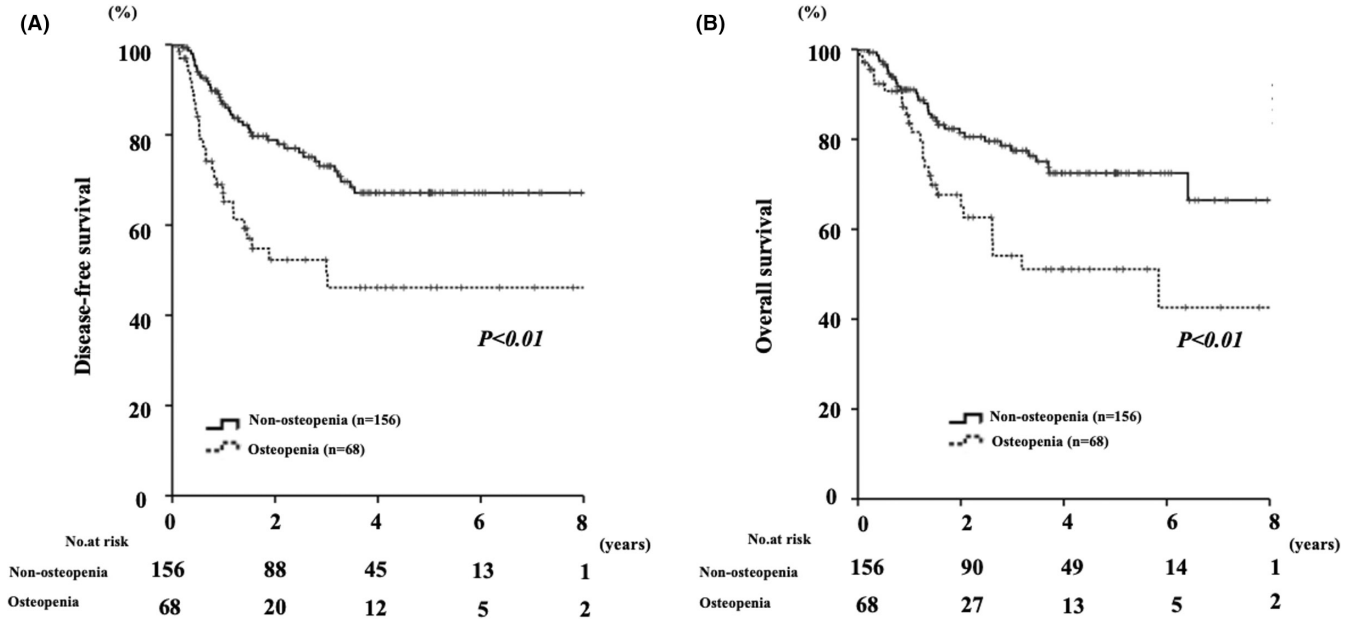

FIGURE 3 The prognostic analyses were based on osteopenia after gastrectomy in the patients with gastric cancer. Kaplan-Meier curve for (A) disease free survival and (B) overall survival after gastrectomy

study, we identified the most suitable predictor and demonstrated that preoperative osteopenia was an independent risk factor for poor OS and DFS. A review by Watanabe et al reported that low BMD in colorectal cancer, colorectal liver metastases, esophageal cancer, and extrahepatic cholangiocarcinoma was a significant risk factor for OS and DFS.[8] The same result was obtained in the current study; however, no prior studies have reported a prognostic association between osteopenia and GC; thus, these results are valuable.

The mechanism underlying the effect of osteopenia on a poor prognosis remains unclear. One possible explanation is that cytokines (e.g. PTHrP, Interleukin [IL]-1, IL-6, and IL-8) derived from cancer cells stimulate osteoclasts and activate the RANK/RANKL (receptor activator of NF-κB ligand) signaling mechanism, which results in osteopenia.[15] Systemic inflammatory response markers is also associated with proinflammatory cyokines such as IL-1, IL-6.[16] In the current study, OS and DFS was significantly worse in patients with osteopenia, sarcopenia, systemic inflammatory response markers such as GPS and PNI in univariate analysis. However, the significant factors in multivariate analysis were only osteopenia. There are other factors involved in osteopenia, and cytokines were a confounding factor in the multivariate analysis, as a result, systemic inflammatory response markers were not selected as independent prognostic factor. In addition, Pereira et al reported that osteopenia-related bone loss begins before sarcopenia-related muscle loss, suggesting that osteopenia may be an early indicator of deconditioning that precedes sarcopenia.[17] In the current study, 62% (42/68 patients) of the osteopenia patients had sarcopenia, and sarcopenia was significantly more common in patients with osteopenia ($P = .02$).

Low BMD is usually caused by a combination of physical, endocrine, and metabolic factors, including vitamin D and estrogen.[18] In regard to other factors, vitamin D and estrogen play an important role in the development of GC as well as osteopenia. Ren et al reported that vitamin D levels were an independent prognostic factor in patients with GC.[19] A review by Du et al reported that vitamin D may inhibit GC cell viability, proliferation, and metastasis and may inhibit *Helicobacter pylori* infection and Helicobacter-associated GC.[20] Lee suggested that estrogen aggravates tumor progression in females with GC.[21] Thus, vitamin D and estrogen are suggested to be associated with GC prevalence and mortality, and further investigation is needed in relation to osteopenia.

The postoperative complication rate after gastrectomy has not decreased, and recent studies reported that the rate was 11.5%-17.4%.[22,23] Some studies have shown that systemic inflammatory response or sarcopenia is associated with postoperative complications.[22,24] In the current study, the occurrence of postoperative complications was significantly higher in the patients with osteopenia ($P < .01$). In future studies, univariate and multivariate analyses of risk factors are required to determine whether osteopenia is a real risk factor for complications.

Currently several medications and exercises can play an important role in improving patients with osteopenia.[25] Preoperative nutritional support, especially calcium intake and vitamin D supplementation, may help prevent osteopenia because vitamin D deficiency is a significant risk factor for low BMD.[26] Even though it takes time for these interventions to increase BMD, maintaining preoperative BMD levels may contribute to a better prognosis after gastrectomy.[27] Also, previous studies have reported a high prevalence of low BMD after gastrectomy in patients with GC, regardless of operation type.[28,29] Calcium malabsorption, secondary hyperparathyroidism, and dominant bone resorption appear to contribute to the bone loss in these patients.[28] Bisphosphonate therapy with calcium and vitamin D supplementation or maintenance of adequate body

TABLE 2 Univariate and multivariate analyses of clinicopathological variables in relation to disease-free survival after gastrectomy for gastric cancer

		DFS univariate analysis		DFS multivariate analysis	
Variables	**N**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Age					
≥70	144	1.09	0.74		
<70	80	(0.67-1.77)			
Gender					
Female	174	0.58	0.12		
Male	50	(0.30-1.14)			
Serum CEA, ng/mL					
≥5	74	1.31	0.28		
<5	150	(0.81-2.14)			
Osteopenia					
Yes	68	2.30	**<0.01**	2.18	**0.01**
No	156	(1.41-3.70)		(1.30-3.67)	
Sarcopenia					
Yes	111	1.96	**<0.01**	1.55	0.09
No	113	(1.20-3.19)		(0.93-2.59)	
GPS					
1 or 2	68	1.97	**<0.01**	1.12	0.73
0	156	(1.21-3.20)		(0.58-2.16)	
PNI					
<45	124	1.85	**0.01**	0.84	0.59
≥45	100	(1.15-2.97)		(0.44-1.61)	
PLR					
≥127.4	133	1.03	0.90		
<127.4	91	(0.64-1.66)			
NLR					
≥2.12	127	0.69	0.13		
<2.12	97	(0.42-1.12)			
Operative time, min					
≥255	129	0.72	0.18		
<255	95	(0.50-1.16)			
Intraoperative blood loss, mL					
≥137	129	2.30	**<0.01**	1.45	0.23
<137	95	(1.34-3.93)		(0.80-2.63)	
Postoperative complication (Clavien-Dindo grade III-V)					
Yes	25	1.78	0.11		
No	199	(0.88-3.56)			
Adjuvant chemotherapy					
Yes	46	1.50	0.17		
No	178	(0.84-2.68)			
Stage					
II or III or IV	87	11.39	**<0.01**	7.77	**<0.01**
I	137	(4.58-28.36)		(3.02-19.86)	

(Continues)

TABLE 2 (Continued)

Variables	N	DFS univariate analysis		DFS multivariate analysis	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Lymph node dissection					
D1 or D1+	144	0.80	0.37		
D2	80	(0.48-1.31)			
Curability					
R1 or 2	30	8.48	**<0.01**	4.62	**<0.01**
R0	194	(5.10-14.10)		(2.63-8.10)	

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; DFS, disease-free survival; GPS, Glasgow prognostic score; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PNI, prognostic nutrition index.

Bold indicates statistical significant value ($p < 0.05$).

TABLE 3 Univariate and multivariate analyses of clinicopathological variables in relation to overall survival after gastrectomy for gastric cancer

Variables	N	OS univariate analysis		OS multivariate analysis	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age					
≥72	144	1.42	0.21		
<72	80	(0.82-2.45)			
Gender					
Female	174	0.73	0.36		
Male	50	(0.37-1.44)			
Serum CEA, ng/mL					
≥5	74	1.32	0.31		
<5	150	(0.78-2.24)			
Osteopenia					
Yes	68	2.14	**<0.01**	2.42	**<0.01**
No	156	(1.28-3.60)		(1.37-4.29)	
Sarcopenia					
Yes	111	2.24	**<0.01**	1.66	0.08
No	113	(1.31-3.85)		(0.94-2.93)	
GPS					
1 or 2	68	2.16	**<0.01**	0.99	0.99
0	156	(1.29-3.64)		(0.51-1.96)	
PNI					
<45	124	2.18	**<0.01**	1.01	0.97
≥45	100	(1.30-3.65)		(0.51-2.01)	
PLR					
≥127.4	133	0.95	0.84		
<127.4	91	(0.56-1.59)			
NLR					
≥2.12	127	0.74	0.27		
<2.12	97	(0.44-1.26)			
Operative time, min					
≥255	129	0.62	0.07		
<255	95	(0.37-1.04)			

TABLE 3 (Continued)

Variables	N	OS univariate analysis		OS multivariate analysis	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Intraoperative blood loss, ml					
≥137	129	3.13	**<0.01**	2.07	**0.04**
<137	95	(1.66-5.90)		(1.04-4.11)	
Postoperative complication (Clavien-Dindo grade III-V)					
Yes	25	1.90	0.09		
No	199	(0.90-4.01)			
Adjuvant chemotherapy					
Yes	46	1.10	0.77		
No	178	(0.58-2.09)			
Stage					
II or III or IV	87	9.96	**<0.01**	6.70	**<0.01**
I	137	(3.84-24.08)		(2.57-17.43)	
Lymph node dissection					
D1 or D1+	87	0.65	0.13		
D2	137	(0.38-1.14)			
Curability					
R1 or 2	30	8.42	**<0.01**	4.72	**<0.01**
R0	194	(4.75-14.92)		(2.51-8.88)	

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; GPS, Glasgow prognostic score; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PLR, platelet-lymphocyte ratio; PNI, prognostic nutrition index.
Bold indicates statistical significant value ($p < 0.05$).

weight has been reported to be effective in preventing osteopenia in patients with GC after gastrectomy[29,30]; surveillance and intervention of nutritional and bone health play an important role in patients after gastrectomy.

Several limitations of this study must be considered when interpreting these findings. This was a retrospective single-center cohort study with a limited number of patients and a short follow-up period. The surgical approach was performed at the discretion of the attending surgeon, resulting in a potential selection bias. However, there was no difference in the surgical approach between the osteopenia and non-osteopenia groups, which may have avoided bias. The cutoff value for defining osteopenia and sarcopenia is not well-established. However, we used the cutoff value based on a previous report; therefore, it is necessary to verify whether the values are appropriate, in the future.

In conclusion, we demonstrated that preoperative osteopenia was significantly correlated with poor prognosis and recurrence in patients who underwent gastrectomy for GC. Osteopenia may be an alternative prognostic factor to other systemic inflammatory response markers and sarcopenia.

DISCLOSURE

Conflict of Interest: The authors have no conflicts of interest and funding to declare.

Ethics Approval: This study was approved by the Ethics Committee of Fuji City General Hospital (281).

Informed Consent: The requirement for acquisition of informed consent from patients was waived because of the retrospective design of this study and anonymized data.

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