Preoperative occult vertebral fracture is a stronger predictor than osteopenia of the clinical outcomes after gastrectomy for gastric cancer

NAOKO FUKUSHIMA[1,2], TAKAHIRO MASUDA[1], KENEI FURUKAWA[1], KAZUTO TSUBOI[1,2], KEITA TAKAHASHI[1], MASAMI YUDA[1], MASASHI TSUNEMATSU[1], TORU IKEGAMI[1], FUMIAKI YANO[1] and KEN ETO[1]

[1]Department of Surgery, The Jikei University School of Medicine, Tokyo 105-8461, Japan; [2]Department of Surgery, Fuji City General Hospital Fuji, Shizuoka 417-8567, Japan

Received August 17, 2024; Accepted November 27, 2024

DOI: 10.3892/ol.2025.14925

Abstract. Osteopenia is a potential prognostic factor in patients with cancer. Occult vertebral fracture, the most common complication of osteopenia, has recently been associated with cancer. The present study aimed to investigate the prognostic value of occult vertebral fracture after gastrectomy in patients with gastric cancer. The current retrospective study included 222 patients who underwent gastrectomy for gastric cancer between October 2013 and February 2023. Occult vertebral fracture was quantitatively evaluated using preoperative sagittal computed tomography images from the 11th thoracic to 5th lumbar vertebrae. Multivariate analysis showed that occult vertebral fracture (P<0.01, P=0.02, respectively), stage II or III (P<0.01, P<0.01, respectively), and R1 or R2 curability (P<0.01, P=0.03, respectively) were independent and significant predictors of disease-free and overall survival rates. Additionally, patients with both occult vertebral fracture and osteopenia had significantly lower disease-free and overall survival rates than those with either osteopenia or occult vertebral fracture (P<0.01, P<0.01, respectively). In conclusion, occult vertebral fracture may be considered a strong predictor of poor clinical outcomes in patients undergoing gastrectomy for gastric cancer.

Introduction

The mortality rate of cancer patients has been declining annually owing to advances in diagnostics, surgery, and medications. However, the estimated number of new cases of gastric cancer (GC) exceeds one million, ranking fifth among all newly diagnosed cancers, and many patients experience recurrence after gastrectomy for GC (1). Establishing an accurate prediction of its clinical outcomes is crucial for improving the quality of life of patients with GC and reducing mortality and medical burden.

Recent research has confirmed that sarcopenia or systemic inflammatory response markers such as the Glasgow Prognostic Score (GPS) or Prognostic Nutritional Index (PNI) can predict survival in patients with GC (2-4). Osteopenia, a condition of low bone mineral density (BMD), is associated with the progression of sarcopenia and is independently associated with poor prognosis in patients with various digestive tract cancers, including GC (5,6). Occult vertebral fracture (OVF) are the most common complications of osteopenia, and more than two-thirds of patients with this condition are incidentally diagnosed (7). Some reports have demonstrated the effectiveness of OVF in prognostic prediction in patients with colorectal liver metastasis and pancreatic cancer (8,9). However, no study has explored the correlation between OVF and the clinical outcomes of patients with GC. Therefore, the aim of this study was to investigate the prognostic impact of OVF in GC patients undergoing gastrectomy.

Materials and methods

Patients. This retrospective study included 242 patients who underwent primary gastrectomy for GC between October 2013 and February 2023 at the Fuji City General Hospital (Shizuoka, Japan). This study was approved by the Institutional Review Board of Fuji City General Hospital (approval no. 297: Approved February 15, 2023.). The requirement for acquisition of informed consent from patients was waived because of the retrospective design of this study and anonymized data. The inclusion criteria as follows: i) Patients underwent gastrectomy with Stage I, II, III GC, ii) not applicable for endoscopic submucosal dissection, and iii) computed tomography (CT) performed within 30 days before surgery. Patients who had stage IV disease (n=16), synchronous malignant neoplasms (n=3), and underwent emergency surgery (n=1) were excluded; the remaining 222 patients were enrolled in this study.

Correspondence to: Dr Naoko Fukushima, Department of Surgery, The Jikei University School of Medicine, 3-25-8 Nishishinbashi, Minato, Tokyo 105-8461, Japan
E-mail: naoko9037@gmail.com

Key words: gastric cancer, gastrectomy, occult vertebral fracture, osteopenia, predictor

Treatment and follow-up. The Japanese Gastric Cancer Treatment Guidelines, including surgical indications, treatment, and selection of chemotherapy, were used in our treatment strategy for GC (10). Staging and pathological diagnoses were based on the Japanese Classification of Gastric Carcinoma (11). Neoadjuvant chemotherapy with S-1 plus cisplatin was administered to patients with bulky lymph nodes. Depending the location of the tumor, distal, total, or proximal gastrectomy was performed. Laparoscopic gastrectomy is primarily performed in patients with stage I clinical disease. In patients with clinical stage II or III disease, the attending surgeon selected between the laparoscopic and open surgical approaches. Postoperative complications were defined as grade III-V based on the Clavien-Dindo classification, occurring within 30 postoperative days (12). Patients with pathological stage II were treated with S-1 alone, and stage III were treated with S-1 alone or S-1 in combination with oxaliplatin with adjuvant chemotherapy, if the general condition was judged to be tolerated based on patients' performance status. Basic surveillance was conducted until death or 5 years post-operatively. Patients with stage I disease were followed-up every 6 months, and those with stage II or III were every 3 months to check for recurrence by performing blood tests, including those for the screening of tumor markers. Enhanced CT was performed every 6 months, and upper gastrointestinal endoscopy was performed every 1-2 years. For recurrence, systemic chemotherapy was administered based on the patient's performance status.

Definition of sarcopenia, osteopenia, and OVF. Sarcopenia, osteopenia, and OVF were preoperatively evaluated using CT. Sarcopenia was defined as psoas muscle mass area (PMA) at the third lumbar vertebra below the sex-specific median size. The PMA was calculated as follows: Length of the major axes x the length of the minor axes x π (13). Osteopenia was defined as a decrease in the BMD below the standard value. The BMD was measured by bone mineral density in the midvertebral core of the 11th thoracic vertebra. The cut-off values of BMD were evaluated based on the previous reports as follow: Men=308.82-2.49 x age in years, women=311.84-2.41 x age in years (Fig. 1A and B) (14). OVF was evaluated using the anterior (A), central (C), and posterior (P) heights of the vertebrae from the 11th thoracic vertebra to the 5th lumbar vertebra. The criteria for OVF were C/A <0.8 or C/P <0.8 in the any of the vertebrae regardless of fracture history (pathological fractures and symptomatic fractures were excluded) (Fig. 1C and D) (15).

Measurement of preoperative GPS and PNI. The GPS was defined as a combination of C-reactive protein (CRP) and albumin levels. In cases where both levels were abnormal (CRP >1.0 mg/dl and albumin <3.5 g/dl), the score was 2; if one level was abnormal, the score was 1; and if neither level was abnormal, the score was 0 (16). The PNI was calculated as 10x serum albumin level (g/dl) +0.005x lymphocyte count (17).

Statistical analysis. All statistical analyses were conducted using a statistical software program (SPSS Statistics for Windows, version 22; IBM Corp., Armonk, N.Y., USA). Quantitative variables are expressed as median and interquartile range, and differences were analyzed using the Mann-Whitney U test. Qualitative variables were compared using the Fisher's exact test. The Kaplan-Meier method was used to analyze the survival rates, and the log-rank test was used to compare the differences between the survival rates of the groups. A Cox proportional hazards regression model was used to identify the independent prognostic factors associated with disease-free survival (DFS) and overall survival (OS) rates. Variables identified as significant in univariate analysis were included in multivariate analysis. The continuous variables were classified into two groups. The cutoff value for CEA was set at the upper normal limit, and the cutoff values for age, PNI, operative time, and intraoperative blood loss were determined via a receiver operating characteristic curve using the survival status at the 3-year follow-up. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patients' characteristics. The patient characteristics and associations between clinical variables and OVF are summarized in Table I. The median patient age was 74 years (range: 68-80 years). This study included 170 (77%) men. Osteopenia, sarcopenia, and OVF were observed in 68 (31%), 110 (50%), and 64 (28%) patients, respectively. The pathological diagnosis of GC showed that 91 (41%), 55 (25%), and 76 (34%) patients had stage I, II, and III cancers, respectively.

In the univariate analysis, patients with OVF were significantly associated with older age ($P<0.01$), operative approach (open gastrectomy, $P=0.01$), T factor ($P<0.01$), lymph node metastases ($P<0.01$), advanced stage ($P<0.01$), and adjuvant chemotherapy ($P<0.01$). In terms of body composition, patients with OVF had higher GPS ($P=0.04$) and lower BMD ($P<0.01$), PMA ($P=0.02$), and PNI ($P=0.01$) than those without OVF. In addition, postoperative recurrence occurred in 28 (44%) patients in the OVF group and 25 (16%) patients in the non-OVF group. Of these, 11 (17%) patients in the OVF group and 12 (8%) patients in the non-OVF group were administered with postoperative chemotherapy for recurrence.

Univariate and multivariate DFS analyses of patients with GC. Table II shows the prognostic factors for the DFS rates according to Cox proportional hazard analysis. The univariate analysis of the DFS rates indicated that osteopenia ($P<0.01$), sarcopenia ($P<0.01$), OVF ($P<0.01$), GPS score of 1 or 2 ($P=0.02$), PNI <45 ($P=0.04$), intraoperative blood loss ≥227 ml ($P=0.01$), stage ≥II ($P<0.01$), and R1 or R2 ($P<0.01$) were significant prognostic factors. The multivariate analysis revealed that OVF [hazard ratio (HR): 2.35, 95% confidence interval (CI): 1.30-4.27; $P<0.01$], stage ≥II (HR, 6.15; 95% CI, 2.36-16.01; $P<0.01$), and R1 or R2 (HR, 2.35; 95% CI, 1.30-4.27; $P<0.01$) were independent and significant predictors of DFS.

Univariate and multivariate OS rate analyses of patients with GC. Table III shows the prognostic factors for the OS rates according to Cox proportional hazard analysis. Univariate analysis of the OS rates indicated that osteopenia ($P=0.01$), sarcopenia ($P<0.01$), OVF ($P<0.01$), GPS score of

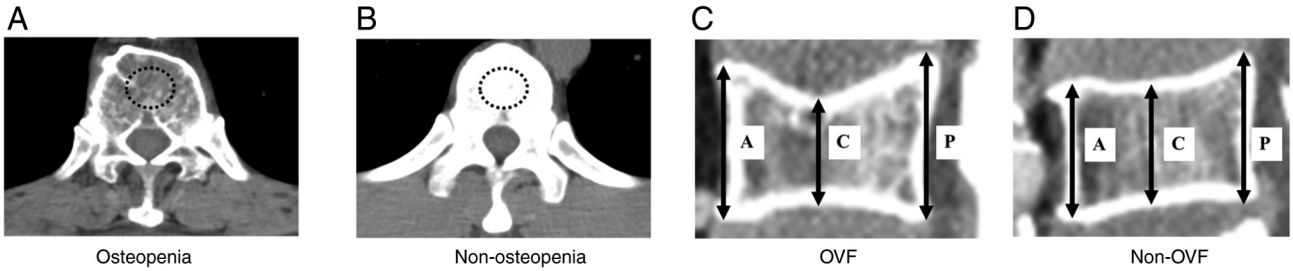

Figure 1. Bone mineral density was measured in the trabecular bone by calculating the average pixel density within a circle in the midvertebral core at the bottom of 11th thoracic vertebra on preoperative computed tomography. (A) Osteopenia and (B) non-osteopenia. We measured the A, C and P heights of vertebrae from the 11th thoracic vertebra to the 5th lumber vertebra. The criteria for OVF were C/A <0.8 or C/P <0.8 in the any of the vertebrae. (C) OVF and (D) non-OVF. A, anterior; C, central; OVF, occult vertebral fracture; P, posterior.

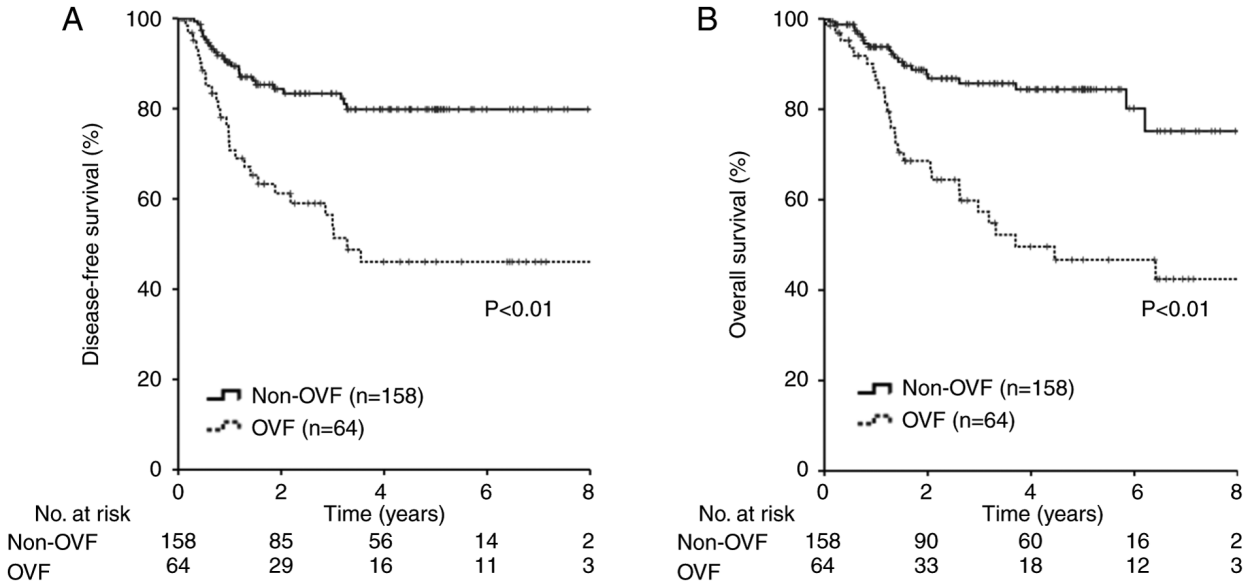

Figure 2. Kaplan-Meier curve for (A) disease free survival and (B) overall survival after gastrectomy in the patients with gastric cancer according to the status of OVF. OVF, occult vertebral fracture.

1 or 2 (P<0.01), PNI <45 (P<0.01), intraoperative blood loss ≥227 ml (P<0.01), stage ≥II (P<0.01), and R1 or R2 (P<0.01) were significant prognostic factors. The multivariate analysis revealed that OVF (HR, 2.16; 95% CI, 1.15-4.03; P=0.02), stage ≥II (HR, 5.31; 95% CI, 2.02-13.93; P<0.01), and R1 or R2 (HR, 5.95; 95% CI, 2.47-14.35; P<0.01) were independent and significant predictors of OS.

Impact of OVF on DFS and OS after gastrectomy for GC. Patients with OVF had significantly lower DFS and OS rates than those without OVF. (DFS: 5-year survival rate, 46.0 vs. 79.8%, respectively, P<0.01; OS: 5-year survival rate, 46.7 vs. 84.4%, respectively, P<0.01) (Fig. 2). In terms of bone status, 121 (55%) patients had healthy bones, 37 (17%) had osteopenia without OVF, 33 (15%) had non-osteopenic OVF, and 31 (14%) had osteopenia with OVFs. Patients with OVF had significantly lower DFS and OS rates than those without OVF, regardless of osteopenia (P<0.01, P<0.01, respectively) (Fig. 3). The 5-year mortality rates after gastrectomy were as follows: healthy bone (14.1%); osteopenia without OVF (10.8%); non-osteopenic OVF (36.4%); and osteopenia with OVF (51.6%) (Fig. 4).

Discussion

Our results showed that preoperative OVF was significantly associated with poor prognosis and recurrence in patients undergoing gastrectomy for GC. To the best of our knowledge, this is the first report to demonstrate the impact of OVF on mortality in patients with GC.

OVF is common and result in acute and chronic pain, reduced quality of life, and diminished lifespan (7). OVF is a public health problem, with approximately 750,000 cases occurring annually. The prevalence of OVF increased from 3% in women aged <60 years to 20% in those aged >70 years and from 7.5 to 20% in men in the same age group, increasing in prevalence with age (18). In the present study, the OVF rate was 26% in women and 29% in men, with a median age of 74. OVF is the hallmark of osteopenia, which is characterized by a low BMD and occurs at a higher incidence earlier in life than any other type of osteoporotic fractures (19). We have previously shown that osteopenia could be a prognostic factor in patients with GC (5). However, in the present study, we found that OVF, a complication of osteopenia, was a stronger predictor than osteopenia. In addition, the combination of

Table I. Patients' characteristics.

Variable	Total (n=222)	OVF		P-value
		Yes (n=64)	No (n=158)	
Age, years[b]	74 (68-80)	77 (71-81)	73 (64-79)	<0.01[a]
Sex, male[c]	170 (77%)	50 (78%)	120 (76%)	0.86
Body mass index, kg/m^2[b]	21.7 (19.9-24.4)	21.7 (19.3-24.2)	21.7 (20.4-24.5)	0.57
Serum CEA, ng/ml[b]	3.7 (2.5-5.8)	3.7 (2.8-5.9)	3.7 (2.5-5.6)	0.76
BMD, HU[b]	142 (113-176)	120 (98-145)	154 (120-187)	<0.01[a]
PMA, cm^2[b]	19.1 (13.6-24.6)	16.8 (12.1-22.9)	19.8 (14.3-25.1)	0.02[a]
GPS, 1 or 2[c]	64 (29%)	25 (39%)	39 (25%)	0.04[a]
PNI[b]	48 (42-52)	45 (39-51)	48 (43-52)	0.01[a]
Osteopenia, yes[c]	68 (31%)	31 (48%)	37 (23%)	<0.01[a]
Sarcopenia, yes[c]	110 (50%)	40 (63%)	70 (44%)	0.02[a]
Histological type[c]				0.12
tub1	75 (34%)	19 (30%)	56 (35%)	
tub2	35 (16%)	10 (15%)	25 (16%)	
por	84 (38%)	29 (45%)	55 (34%)	
sig	19 (8%)	2 (3%)	17 (11%)	
pap	5 (2%)	1 (2%)	4 (3%)	
muc	4 (2%)	3 (5%)	1 (1%)	
Neoadjuvant chemotherapy, yes[c]	4 (2%)	1 (2%)	3 (2%)	>0.99
Operative approach[c]				0.01[a]
Open	95 (43%)	36 (56%)	59 (37%)	
Laparoscope	127 (57%)	28 (44%)	99 (63%)	
Operative procedure[c]				0.03[a]
DG	139 (63%)	34 (53%)	105 (67%)	
PG	6 (3%)	0 (0%)	6 (4%)	
TG	77 (34%)	30 (47%)	47 (29%)	
Lymph node dissection[c]				0.16
D1	58 (26%)	18 (28%)	40 (25%)	
D1+	87 (39%)	19 (30%)	68 (43%)	
D2	77 (35%)	27 (42%)	50 (32%)	
Operative time, min[b]	270 (230-326)	271 (236-328)	265 (229-325)	0.69
Blood loss, ml[b]	154 (50-415)	223 (100-453)	150 (20-400)	0.10
Postoperative hospital stay, days[b]	12 (10-20)	14 (11-22)	12 (10-19)	0.06
Postoperative complication (Clavien-Dindo grade III-V)[c]	25 (11%)	6 (9%)	19 (12%)	0.65
Reoperation[c]	8 (3%)	2 (3%)	6 (4%)	>0.99
T factor[c]				<0.01[a]
1	84 (38%)	16 (25%)	68 (43%)	
2	27 (12%)	6 (9%)	21 (13%)	
3	58 (26%)	15 (24%)	43 (27%)	
4	53 (24%)	27 (42%)	26 (17%)	
Lymph node metastases, yes[c]	99 (45%)	39 (61%)	60 (38%)	<0.01[a]
Stage[c]				<0.01[a]
I	91 (41%)	17 (26%)	74 (47%)	
II	55 (25%)	14 (22%)	41 (26%)	
III	76 (34%)	33 (51%)	43 (27%)	
Adjuvant chemotherapy, yes[c]	52 (23%)	23 (36%)	29 (18%)	<0.01[a]
Curability[c]				>0.99
R0	209 (94%)	60 (94%)	149 (94%)	
R1 or R2	13 (6%)	4 (6%)	9 (6%)	

[a]P<0.05. Data are presented as [b]median (interquartile range) or [c]number (%). BMD, bone mineral density; CEA, carcinoembryonic antigen; DG, distal gastrectomy; GPS, Glasgow prognostic score; muc, mucinous adenocarcinoma; OVF, occult vertebral fracture; pap, papillary adenocarcinoma; PG, proximal gastrectomy; 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.

Table II. Univariate and multivariate analyses of clinicopathological variables in relation to disease-free survival after gastrectomy for gastric cancer.

		DFS univariate analysis		DFS multivariate analysis	
Variable	n	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age, years					
≥72	123	1.04	0.88		
<72	99	(0.61-1.79)			
Sex					
Male	170	0.57	0.14		
Female	52	(0.27-1.20)			
Serum CEA, ng/ml					
≥5	72	1.43	0.21		
<5	150	(0.82-2.51)			
Neoadjuvant chemotherapy					
Yes	4	0.84	1.22		
No	218	(0.17-8.84)			
Osteopenia					
Yes	68	2.20	<0.01[a]	1.65	0.10
No	154	(1.27-3.80)		(0.91-2.98)	
Sarcopenia					
Yes	110	2.37	<0.01[a]	1.66	0.11
No	112	(1.34-4.18)		(0.89-3.06)	
OVF					
Yes	68	3.20	<0.01[a]	2.35	<0.01[a]
No	154	(1.87-5.50)		(1.30-4.27)	
GPS					
1 or 2	64	1.93	0.02[a]	1.36	0.48
0	158	(1.10-3.38)		(0.60-2.92)	
PNI					
≥45	142	1.74	0.04[a]	0.61	0.22
<45	80	(1.01-3.01)		(0.27-1.35)	
Operative time, min					
≥267	110	0.87	0.60		
<267	112	(0.51-1.49)			
Intraoperative blood loss, ml					
≥227	100	2.06	0.01	1.56	0.14
<227	122	(1.19-3.56)		(0.86-2.81)	
Postoperative complication (Clavien-Dindo grade III-V)					
Yes	25	1.47	0.38		
No	197	(0.63-3.44)			
Adjuvant chemotherapy					
Yes	52	1.69	0.07		
No	170	(0.97-2.97)			
Stage					
I	91	9.29	<0.01[a]	6.15	<0.01[a]
II or III	131	(3.69-23.37)		(2.36-16.01)	
Curability					
R1 or 2	13	8.47	<0.01[a]	2.35	<0.01[a]
R0	209	(3.97-18.05)		(1.30-4.27)	

[a]P<0.05. CEA, carcinoembryonic antigen; CI, confidence interval; DFS, disease-free survival; GPS, Glasgow prognostic score; OVF, occult vertebral fracture; PNI, prognostic nutrition index.

Table III. Univariate and multivariate analyses of clinicopathological variables in relation to overall survival after gastrectomy for gastric cancer.

		OS univariate analysis		OS multivariate analysis	
Variable	n	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age, years					
≥72	123	1.22	0.49		
<72	99	(0.69-2.14)			
Sex					
Male	170	0.64	0.24		
Female	52	(0.30-1.46)			
Serum CEA, ng/ml					
≥5	72	1.21	0.53		
<5	150	(0.67-2.20)			
Neoadjuvant chemotherapy					
Yes	4	1.43	0.72		
No	218	(0.20-10.44)			
Osteopenia					
Yes	68	2.04	0.01[a]	1.68	0.10
No	154	(1.15-3.61)		(0.91-3.12)	
Sarcopenia					
Yes	110	2.98	<0.01[a]	1.77	0.10
No	112	(1.60-5.55)		(0.90-3.46)	
OVF					
Yes	68	3.50	<0.01[a]	2.16	0.02[a]
No	154	(1.98-6.17)		(1.15-4.03)	
GPS					
1 or 2	64	2.56	<0.01[a]	1.19	0.66
0	158	(1.45-4.51)		(0.54-2.61)	
PNI					
≥45	142	2.69	<0.01[a]	0.98	0.97
<45	80	(1.53-4.72)		(0.45-2.16)	
Operative time, min					
≥267	110	0.75	0.32		
<267	112	(0.43-1.32)			
Intraoperative blood loss, ml					
≥227	100	2.48	<0.01[a]	1.84	0.06
<227	122	(1.38-4.46)		(0.97-3.47)	
Postoperative complication (Clavien-Dindo grade III-V)					
Yes	25	2.05	0.08		
No	197	(0.92-4.56)			
Adjuvant chemotherapy					
Yes	52	1.19	0.58		
No	170	(0.64-2.21)			
Stage					
I	91	8.89	<0.01[a]	5.31	<0.01[a]
II or III	131	(3.52-22.46)		(2.02-13.92)	
Curability					
R1 or 2	13	9.98	<0.01[a]	5.95	<0.01[a]
R0	209	(4.42-22.54)		(2.47-14.35)	

[a]P<0.05. CEA, carcinoembryonic antigen; CI, confidence interval; GPS, Glasgow prognostic score; OVF, occult vertebral fracture; OS, overall survival; PNI, prognostic nutrition index.

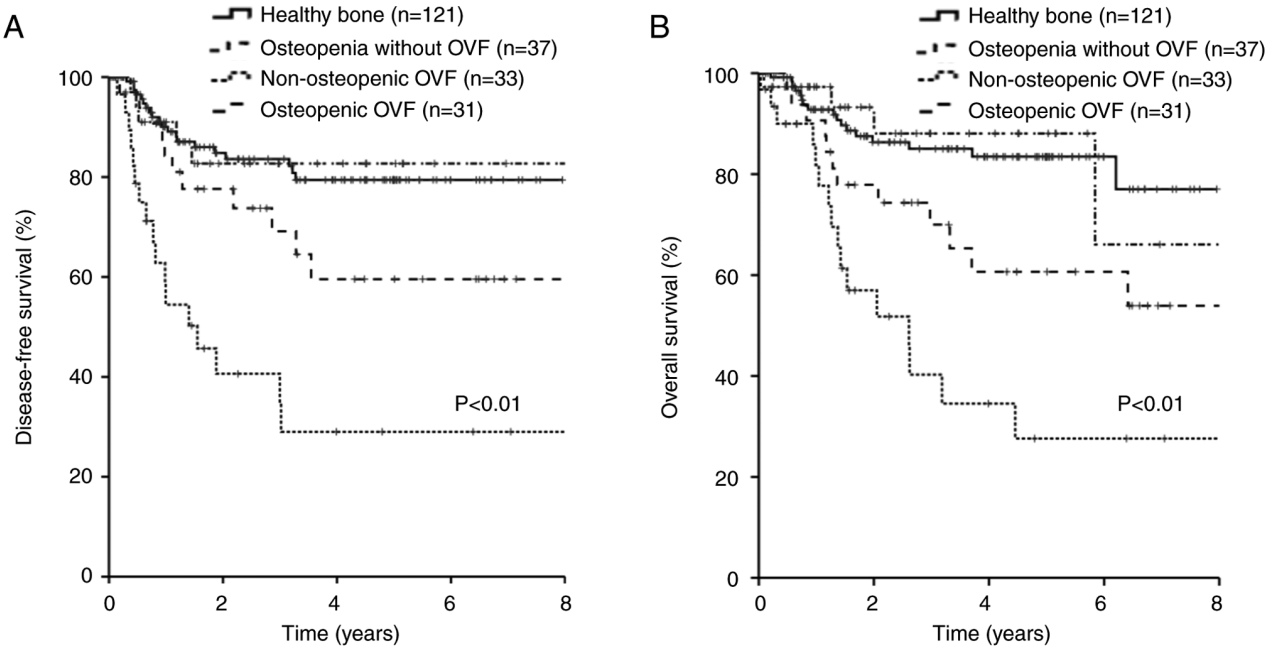

Figure 3. Kaplan-Meier curve for (A) disease free survival and (B) overall survival after gastrectomy in the patients with gastric cancer according to the bone status. OVF, occult vertebral fracture.

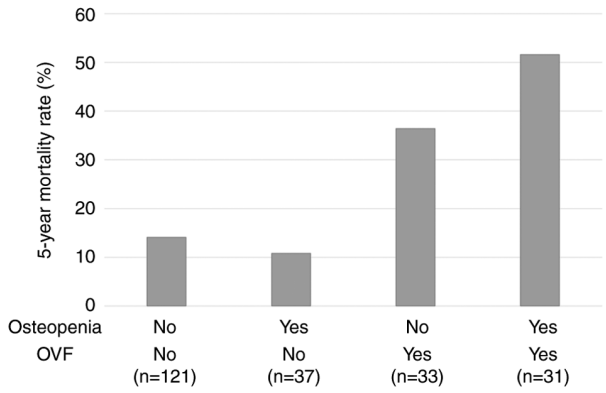

Figure 4. The rate of 5-year mortality rate according to the bone status. OVF, occult vertebral fracture.

OVF and osteopenia is associated with worse prognosis. Thus, this study identified a strong prognostic factor and is a valuable finding.

The presence of one or more OVF was estimated to increase the risk of fractures by approximately 5-10 fold. Furthermore, mortality is reported to increase by approximately 10%, 5 years after OVF (20,21). If the presence of OVF alone increases mortality, even in the absence of cancer, it can be inferred that the prognosis of patients with GC with preoperative OVF is even worse. In the current study, patients with OVF had significantly worse OS and DFS rates than those without OVF.

However, biological mechanisms underlying bone metabolism and malignancy remain unclear. Recently, it was suggested that the RANK/RANKL system may be associated with bone metabolism and cancer development. RANKL is a member of the tumor necrosis factor family that binds to its receptor RANK to control osteoclast differentiation, activation, and survival. Proinflammatory and pro-osteolytic cytokines derived from cancer cells such as tumor necrosis factor-alpha, parathyroid hormone-related protein, interleukin (IL)-1, IL-6, and IL-8 activates RANK/RANKL signaling mechanism, causing bone loss (22). Furthermore, the RANK/RANKL pathway promotes epithelial-mesenchymal transition and metastasis (23). In the current study, the OVF group had more advanced disease stage (T-factor; P<0.01; lymph node metastases; P<0.01; stage, P<0.01).

Various systemic diseases, including metabolic, genetic, immune, inflammatory, and endocrine diseases, are associated with an increased risk of OVF; besides, deficiencies of vitamin D and estrogen are also one of the causes (20). Vitamin D and estrogen have been reported to be involved in the development of GC. Du *et al* have shown that vitamin D and its metabolites inhibit the viability, growth, and metastasis of GC cells. In addition, vitamin D metabolites may inhibit *Helicobacter pylori* infection and *H. pylori*-associated GC (24). According to recent reports, vitamin D may be involved in the anti-cancer mechanism of GC by affecting the expression of microRNAs, promoting the effects of cisplatin, and regulating intracellular signal transduction (25). Ge *et al* reported that estrogen receptors might be related to the progression and deterioration of GC (26). Thus, vitamin D and estrogen may be associated with the occurrence of GC and OVF; however, further research is needed to assess the relationship between GC and OVF.

The risk of bone loss after gastrectomy in patients with GC increases owing to malabsorption and malnutrition. The absorption of calcium and vitamin D is impaired because most of the stomach has been removed (27). Postoperative BMD in patients with GC after gastrectomy is decreased, and a knowledge of the presence of OVF preoperatively in patients with GC is more important than in other cancers because the conditions of patients with lower preoperative BMD are expected to be worse after gastrectomy (28). Calcium, vitamin D, and weight-bearing exercises are important for patients

with osteopenia, and bisphosphonates, raloxifene, and nasal calcitonin have been shown to reduce the incidence of new OVF by 30-50% (29). OVF is often asymptomatic or underdiagnosed and under-treated (7). However, the diagnosis of OVF during routine medical care and appropriate intervention may improve the prognosis of patients with GC and OVF.

This study has several limitations. First, it was retrospective and conducted at a single institution with a small number of patients. Second, the effect of chemotherapy on recurrent cases is not reflected in the OS, which may lead to bias. Third, the definitions of sarcopenia, osteopenia, and OVF are controversial, and the cut-off values vary among studies. Fourth, we did not consider the diets rich in calcium, patients' medical histories and medications, such as vitamin D supplements and bisphosphonates. People with symptomatic fractures are excluded in the current study, however, those people have interventions such as vitamin D or bisphosphonate, and may have a good prognosis. Similarly, people with osteopenia or racial differences who have bisphosphonates or a high calcium diet may have a better prognosis. Therefore, we believe that further analysis by these factors will help to elucidate the mechanism of OVF and GC. Taken together, our findings need to be validated in large-scale prospective studies. Furthermore, evaluation in different racial groups is also needed in the future.

In conclusion, we demonstrated that preoperative OVF was significantly associated with worse DFS and OS rates in patients who underwent gastrectomy for GC. In addition, we showed that the combination of osteopenia and OVF could be a stronger prognostic indicator than osteopenia and OVF alone.

Acknowledgements

Not applicable.

Funding

This research was supported by JPSP KAKENHI (grant no. 23K16454).

Availability of data and materials

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

Authors' contributions

NF, KF, TI, FY and KE conceptualized the study. NF, KF and FY analysed the data. NF wrote the original draft, and FY, KE and TI revised and edited the draft. TM and KF performed statistical analyses. KaT, KeT, MY and MT collected the data and analyzed the results. NF and KaT confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Fuji City General Hospital (297). The requirement for acquisition of informed consent from patients was waived because of the retrospective design of this study and the use of anonymized data.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Kawamura T, Makuuchi R, Tokunaga M, Tanizawa Y, Bando E, Yasui H, Aoyama T, Inano T and Terashima M: Long-term outcomes of gastric cancer patients with preoperative sarcopenia. Ann Surg Oncol 25: 1625-1632, 2018.
3. Wang DS, Ren C, Qiu MZ, Luo HY, Wang ZQ, Zhang DS, Wang FH, Li YH and Xu RH: Comparison of the prognostic value of various preoperative inflammation-based factors in patients with stage III gastric cancer. Tumor Biol 33: 749-756, 2012.
4. Li Q, Huang LY and Xue HP: Comparison of prognostic factors in different age groups and prognostic significance of neutrophil-lymphocyte ratio in patients with gastric cancer. World J Gastrointest Oncol 12: 1146-1166, 2020.
5. Fukushima N, Tsuboi K, Nyumura Y, Hoshino M, Masuda T, Suzuki T, Kajimoto T, Yano F and Eto K: Prognostic significance of preoperative osteopenia on outcomes after gastrectomy for gastric cancer. Ann Gastroenterol Surg 10: 255-264, 2022.
6. Watanabe J, Saitsu A, Miki A, Kotani K and Sata N: Prognostic value of preoperative low bone mineral density in patients with digestive cancers: A systematic review and meta-analysis. Arch Osteoporos 17: 33, 2022.
7. McCarthy J and Davis A: Diagnosis and management of vertebral compression fractures. Am Fam Physician 94: 44-50, 2016.
8. Furukawa K, Haruki K, Taniai T, Yanagaki M, Tsunematsu M, Tanji Y, Ishizaki S, Shirai Y, Onda S and Ikegami T: Occult vertebral fracture (OVF) in patients who underwent hepatectomy for colorectal liver metastasis: Strong association with oncological outcomes. Cancers (Basel) 15: 5513, 2023.
9. Ishizaki S, Furukawa K, Haruki K, Tsunematsu M, Shirai Y, Matsumoto M, Okui N, Onda S, Taniai T and Ikegami T: Prognostic significance of occult vertebral fracture in patients undergoing pancreatic resection for pancreatic cancer. Pancreatology 24: 249-254, 2024.
10. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 14: 101-112, 2011.
11. Ochiai A: The 15th Edition of Japanese Classification of Gastric carcinoma. Japanese Gastric Cancer Association, Volume 89, Tokyo, Japan pp , 2017 (In Japanese).
12. Dindo D, Demartines N and Clavien PA: Classification of surgical complications: A new proposal with evaluation in a cohort of 6,336 patients and results of a survey. Ann Surg 240: 205-213, 2004.
13. Masuda T, Shirabe K, Ikegami T, Harimoto N, Yoshizumi T, Soejima Y, Uchiyama H, Ikeda T, Baba H and Maehara Y: Sarcopenia is a prognostic factor in living donor liver transplantation. Liver Transpl 20: 401-407, 2014.
14. Toshima T, Yoshizumi T, Ikegami T, Harada N, Itoh S, Mano Y, Motomura T, Soejima Y and Maehara Y: Impact of osteopenia in liver cirrhosis: Special reference to standard bone mineral density with age. Anticancer Res 38: 6465-6471, 2018.
15. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, Kushida K, Miyamoto S, Soen S, Nishimura J, *et al*: Diagnostic criteria for primary osteoporosis: Year 1996 revision. J Bone Miner Metab 14: 219-233, 1997.
16. Forrest LM, McMillan DC, McArdle CS, Angerson WJ and Dunlop DJ: Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer 89: 1028-1030, 2003.
17. Onodera T, Goseki N and Kosaki G: Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai Zasshi 85: 1001-1005, 1984 (In Japanese).

18. Li Y, Yan L, Cai S, Wang P, Zhuang H and Yu H: The prevalence and under-diagnosis of vertebral fractures on chest radiograph. BMC Musculoskelet Disord 19: 235, 2018.
19. Grigoryan M, Guermazi A, Roemer FW, Delmas PD and Genant HK: Recognizing and reporting osteoporotic vertebral fractures. Eur Spine J 12: S104-S112, 2003.
20. Bazzocchi A and Guglielmi G: Vertebral fracture identification. Semin Musculoskelet Radiol 20: 317-329, 2016.
21. Watts NB: Osteoporotic vertebral fractures. Neurosurg Focus 10: E12, 2001.
22. Jones DH, Nakashima T, Sanchez OH, Kozieradzki I, Komarova SV, Sarosi I, Morony S, Rubin E, Sarao R, Hojilla CV, *et al*: Regulation of cancer cell migration and bone metastasis by RANKL. Nature 440: 692-626, 2006.
23. Rokavec M, Öner MG, Li H, Jackstadt R, Jiang L, Lodygin D, Kaller M, Horst D, Ziegler PK, Schwitalla S, *et al*: IL-6R/STAT3/miR-34a feedback loop promotes EMT-mediated colorectal cancer invasion and metastasis. J Clin Invest 124: 1853-1867, 2016.
24. Du C, Yang S, Zhao X and Dong H: Pathogenic roles of alterations in vitamin D and vitamin D receptor in gastric tumorigenesis. Oncotarget 8: 29474-29486, 2017.
25. Shah S, Iqbal Z, Alharbi MG, Kalra HS, Suri M, Soni N, Okpaleke N, Yadav S and Hamid P: Vitamin D and gastric cancer: A ray of sunshine? Cureus 13: e18275, 2021.
26. Ge H, Yan Y, Tian F, Wu D and Huang Y: Prognostic value of estrogen receptor alpha and estrogen receptor beta in gastric cancer based on a meta-analysis and the cancer genome atlas (TCGA) datasets. Int J Surg 53: 24-31, 2018.
27. Yoo SH, Lee JA, Kang SY, Kim YS, Sunwoo S, Kim BS and Yook JH: Risk of osteoporosis after gastrectomy in long-term gastric cancer survivors. Gastric Cancer 21: 720-727, 2018.
28. Muszyński T, Polak K, Frątczak A, Miziołek B, Bergler-Czop B and Szczepanik A: Vitamin D-the nutritional status of post-gastrectomy gastric cancer patients-systematic review. Nutrients 14: 2712, 2022.
29. Watts NB: Focus on primary care postmenopausal osteoporosis: An update. Obstet Gynecol Surv 55: S49-S55, 2000.