

# Prediction of risk of osteoporosis after gastrectomy for gastric cancer

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## Abstract

**Introduction:** There are few guidelines for screening of osteoporosis in patients who have undergone gastrectomy. This study aimed to develop and validate a nomogram to predict the risk of osteoporosis after gastrectomy in patients with gastric cancer.

**Methods:** Bone densitometry results for 522 patients with gastric cancer and 2088 individuals from a health-promotion centre were compared using propensity score matching to develop a nomogram to predict osteoporosis after gastrectomy. External validation was performed using an independent data set.

**Results:** In the 10 years after gastrectomy 53.5 per cent of patients developed osteoporosis. In multivariable analysis, the odds ratios of subtotal gastrectomy and total gastrectomy were 5.46 and 8.69 ( $P < 0.001$  for both). Seven risk factors (type of gastrectomy, age, sex, BMI, and serum levels of albumin, creatinine and phosphorus) were incorporated into the nomogram. The prediction accuracy of the nomogram in the development set was 0.830 (area under the curve (AUC)); (95 per cent c.i. 0.812 to 0.848). In the validation set, the AUC was 0.807 (95 per cent c.i. 0.741 to 0.873).

**Conclusion:** Gastrectomy was a risk factor for osteoporosis, and its incidence in the first 10 years after surgery was high. This nomogram can help clinicians to identify patients with gastric cancer most at risk of developing osteoporosis after surgery.

## Introduction

Osteoporosis is characterized by compromised bone density and bone quality. It is a risk factor for fracture with negative financial, physical and psychosocial effects on the affected individual, family and community. Diagnosis before the occurrence of fragility fractures is generally made using dual-energy X-ray absorptiometry (DXA), which measures bone mineral density (BMD)<sup>1,2</sup>. Patients who have undergone gastrectomy for cancer, alone or in combination with chemotherapy, have various potential risk factors for osteoporosis. Improved survival for both early and locally advanced gastric cancer has resulted in a parallel increase in the incidence of postoperative osteoporosis after gastrectomy<sup>3</sup>. Bone loss after cancer therapy is more rapid and severe compared with postmenopausal bone loss in women or normal age-related osteoporosis in men<sup>4</sup>.

Few studies have determined which patients should undergo DXA for osteoporosis, when this should be instituted and whether there are differences from osteoporosis in the general population<sup>5,6</sup>. The aim of the study was to investigate clinicopathological factors associated with osteoporosis after gastrectomy, in order to develop and validate a nomogram for predicting the incidence of osteoporosis after surgery for gastric cancer.

## Methods

### Study population and data organization

Data of patients who underwent gastrectomy at two different gastric cancer centres and of subjects who underwent DXA at a health-promotion centre were reviewed. Data of patients from Seoul St. Mary's Hospital Gastric Cancer Centre and of subjects from the health-promotion centre of Seoul St. Mary's Hospital were used for development of the nomogram ('development set'). The data set from St. Vincent's Hospital Gastric Cancer Centre was used for its validation ('validation set').

Data of patients undergoing curative gastrectomy for primary gastric cancer (subtotal or total gastrectomy with D1 plus or D2 lymph node dissection according to the Korean guidelines for gastric cancer) between January 2009 and December 2018 at the St. Mary's Hospital Gastric Cancer Centre were examined<sup>7</sup>. Patients with pre-existing osteoporosis, a previous malignancy within the last 5 years, a history of steroid use, those receiving neoadjuvant chemotherapy or having a completion gastrectomy, and patients where no postoperative BMD information was available were excluded from the analysis.

Data from the health-promotion centre included individuals undergoing bone densitometry between January 2009 and December 2018. Individuals were excluded according to the

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following criteria: age less than 19 years, history of gastric or oesophageal cancer, history of steroid use, or incomplete data. A 1:4 propensity score-matching analysis was performed to minimize selection bias and configure a development set. Age and sex were used as matching factors.

The validation set from St. Vincent's Hospital Gastric Cancer Centre database for the period between January 2009 and December 2018 used the same criteria as the development set. Patient data were collected prospectively by upper gastrointestinal surgeons and researchers in each centre. General data of patients from the health-promotion centre were collected through a survey and data on BMD extracted from medical records. This study was approved by the ethics committee of the institutional review board (approval number: KC19RESI0695). The requirement for informed consent was waived because the nature of the study design.

## Data collection

Clinical variables included age, sex and BMI. Subjects were categorized into four groups according to BMI based on the WHO guidelines for the Asia-Pacific region: underweight, BMI less than 18.5; normal, 18.5–22.9; overweight, 23.0–24.9; and obese, 25.0 or greater<sup>8</sup>. In gastric cancer patients, age and BMI at the time of gastrectomy were recorded. Blood samples were collected within a month before surgery after an overnight fast for evaluation of serum haemoglobin, creatinine, calcium, phosphorus, alkaline phosphatase (ALP), albumin and blood urea nitrogen (BUN). The standard for dividing normal and abnormal was based on the blood test standards of the Korean Society for Laboratory Medicine<sup>9</sup>.

## Bone densitometry

DXA was performed to determine the BMD of the lumbar spine (lumbar vertebrae L1–L4), total hip, femoral neck and trochanter (Hologic Delphi W<sup>®</sup>; Hologic Inc., Bedford, Massachusetts, USA). The T-scores of the BMD, that is the standard deviation from the mean BMD of young normal adults, were analysed. Osteoporosis was defined as T-score less than –2.5 based on the criteria of the WHO<sup>10</sup>.

## Statistical analysis

The collected data were analysed using R<sup>®</sup>, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) with the following packages: moonBook, rms, ResourceSelection. Continuous variables were analysed using Student's t test or the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test. The baseline characteristics were summarized as mean and standard deviation for continuous variables and as frequency and proportion for categorical variables. All tests were two-sided unless otherwise indicated, and  $P < 0.050$  was taken to indicate statistical significance. The associations of relevant clinical variables with the risk of osteoporosis were assessed by logistic regression analysis. Backward stepwise selection was used to identify variables for multivariable logistic regression analyses. Variables with  $P < 0.100$  in univariable analysis were included in multivariable analysis. Odds ratios were presented with their 95 per cent confidence intervals. Selected variables were incorporated in the nomogram to predict the risk of osteoporosis after curative gastrectomy for gastric cancer. The nomogram obtained from the development set was applied to the validation set for external validation. The predictive accuracy of the model was evaluated using receiver operating characteristic (ROC) curves. The

nomogram was subjected to 1000 bootstrap resampling for internal and external validation to assess calibration.

## Results

Of 715 patients examined by DXA between January 2009 and December 2018 at Seoul St. Mary's Hospital Gastric Cancer Centre who underwent curative gastrectomy for primary gastric cancer, 193 were excluded from analysis according to the following criteria: diagnosis of osteoporosis before gastrectomy (35 patients); no post-operative bone densitometry data available (100); patients who received neoadjuvant chemotherapy or completion total gastrectomy (18); and patients with a history of other malignancies within 5 years before gastrectomy or steroid use (40).

Of 31 440 individuals with data from the health-promotion centre, 1518 individuals were excluded according to the following criteria: age less than 19 years (25 individuals); history of gastric or oesophageal cancer (109); history of steroid use (3); incomplete data (1381).

Following propensity matching, data from both databases resulted in 2610 subjects being included in the development set, consisting of 522 from the gastric cancer centre and 2088 from the health-promotion centre (Fig. 1). For the validation set, 109 out of 300 patients were excluded, leaving 191 subjects for analysis (Fig. S1).

## Characteristics of the study population

Differences in clinical characteristics according to the presence or absence of osteoporosis in the development set are summarized in Table 1. Patients with osteoporosis were more frequently females, were older, had lower BMI and more frequently had a history of gastrectomy compared with patients without osteoporosis. With regard to laboratory findings, patients with osteoporosis showed lower haemoglobin and albumin levels and higher creatinine, phosphorus and alkaline phosphatase levels. The baseline characteristics of the development and validation set are shown in Table S1.

## Incidence of osteoporosis after gastrectomy

In the development set, osteoporosis was diagnosed in 262 (50.2 per cent) patients who underwent gastrectomy and in 403 (19.3 per cent) subjects evaluated at the health-promotion centre. In the validation set, osteoporosis was diagnosed in 116 (60.7 per cent) patients (Table S2). The incidence of osteoporosis according to the duration after gastrectomy in the development and validation sets is shown in Fig. 2.

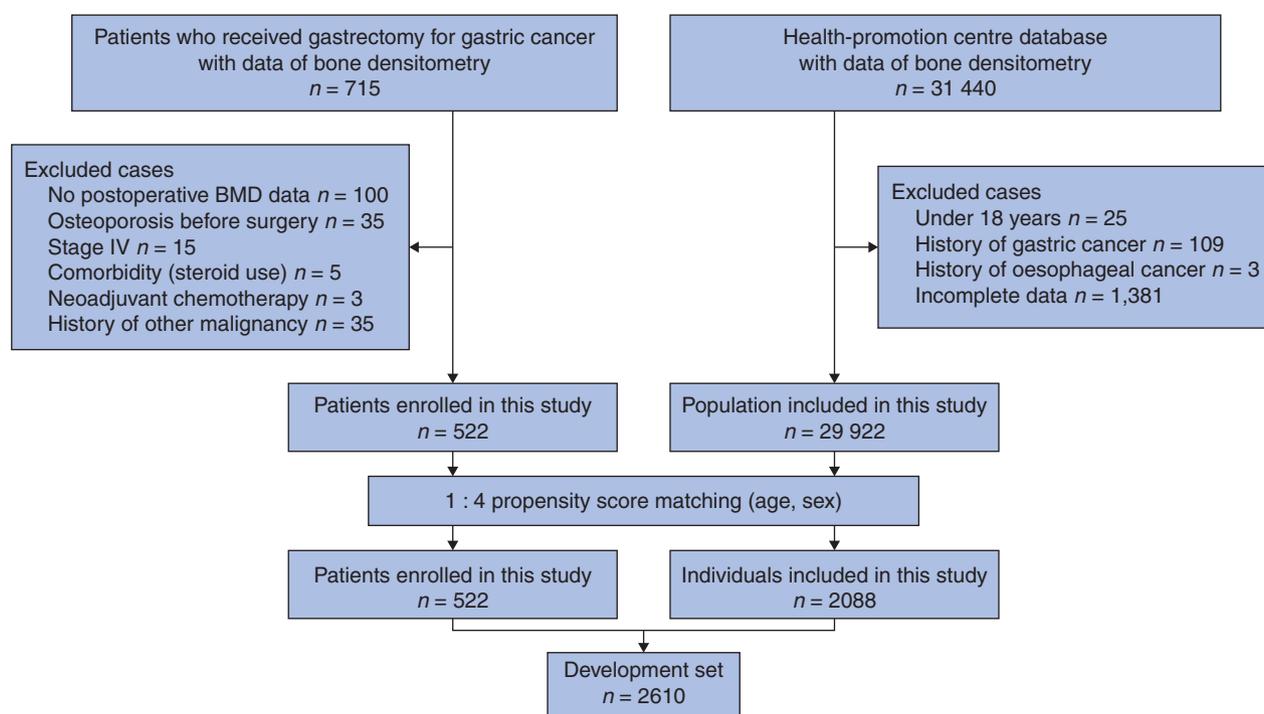
## Development of a nomogram for risk of osteoporosis

In uni- and multivariable logistic regression analysis, type of gastrectomy, female sex, older age, obesity, higher creatinine level and higher phosphorus level were associated with osteoporosis (Tables 2 and 3). The odds ratio of subtotal gastrectomy was 5.35 (95 per cent c.i., 4.06 to 7.05;  $P < 0.001$ ) and that of total gastrectomy was 8.67 (95 per cent c.i. 5.63 to 13.35,  $P < 0.001$ ).

The nomogram for the risk of osteoporosis is shown in Fig. 3. Seven risk factors (type of gastrectomy, age, sex, BMI, and levels of serum albumin, creatinine and phosphorus) were incorporated into the nomogram. Scores assigned to each variable are shown in Table S3.

## Validation of the nomogram

Internal validation demonstrated an AUC of 0.830 (range 0.812–0.848) (Fig. 4a). The calibration plot showed that the risk of



**Fig. 1** Flow chart of development set

BMD, bone mineral density.

**Table 1** Comparison of clinical characteristics between patients without and with osteoporosis in the development set

Characteristics	No osteoporosis (n = 1945)	Osteoporosis (n = 665)	P
<b>Sex</b>			<0.001
Male	1360 (69.9)	215 (32.3)	
Female	585 (30.1)	450 (67.7)	
<b>Age (years)*</b>	65.4(10.1)	69.1(7.5)	<0.001
<b>Obesity</b>			<0.001
Underweight	46 (2.4)	38 (5.7)	
Normal	643 (33.1)	304 (45.7)	
Overweight	516 (26.5)	163 (24.5)	
Obese	740 (38.0)	160 (24.1)	
<b>Gastrectomy</b>			<0.001
No gastrectomy	1685 (86.6)	403 (60.6)	
Subtotal gastrectomy	198 (10.2)	190 (28.6)	
Total gastrectomy	62 (3.2)	72 (10.8)	
<b>Haemoglobin (g/l)</b>			<0.001
<120.0	101 (5.2)	84 (12.6)	
≥120.0	1844 (94.8)	581 (87.4)	
<b>BUN (mmol/l)</b>			0.362
>0.71	277 (14.2)	105 (15.8)	
≤0.71	1668 (85.8)	560 (84.2)	
<b>Creatinine (μmol/l)</b>			<0.001
>97.2	353 (18.1)	40 (6.0)	
≤97.2	1592 (81.9)	625 (94.0)	
<b>Calcium (mmol/l)</b>			0.413
<2.0	10 (0.5)	6 (0.9)	
≥2.0	1935 (99.5)	659 (99.1)	
<b>Phosphorus (mmol/l)</b>			<0.001
<0.83	61 (3.1)	2 (0.3)	
≥0.83	1884 (96.9)	663 (99.7)	
<b>Albumin (g/l)</b>			<0.001
<35.0	25 (1.3)	32 (4.8)	
≥35.0	1920 (98.7)	633 (95.2)	
<b>ALP (U/L)</b>			0.029
>120.0	7 (0.4)	8 (1.2)	
≤120.0	1938 (99.6)	657 (98.8)	

Values in parentheses are percentages unless indicated otherwise; values are mean(s.d.). BUN, blood urea nitrogen; ALP, alkaline phosphatase.

osteoporosis predicted by the nomogram agreed well with the actual probabilities in the development set (Fig. 4c). The Hosmer-Lemeshow test was not significant ( $P=0.947$ ), indicating that the model was well calibrated with no departure from perfect fit. In the external validation set, the AUC for predicting the risk of osteoporosis was 0.807 (range 0.741–0.873) (Fig. 4b). The Hosmer-Lemeshow test for validation set was not significant ( $P>0.999$ ) and good calibration was also observed in the validation set (Fig. 4d).

## Discussion

Osteoporosis can lead to serious complications, including fractures, chronic pain, reduced quality of life and increased mortality rate. In patients undergoing gastric cancer surgery, the incidence and severity of osteoporosis are higher compared with those of the general population due to impaired calcium absorption<sup>11</sup>. There are few guidelines for osteoporosis screening in patients undergoing gastrectomy for gastric cancer, although the American Gastroenterological Association Guidelines recommend DXA within the first 10 years<sup>5</sup>. The WHO Fracture Risk-Assessment Tool, FRAX, has no checkbox for gastrectomy<sup>6</sup>. In the present study, a nomogram to predict the risk of osteoporosis after gastrectomy for gastric cancer was developed. In the present study, 53.5 per cent of patients who underwent bone densitometry within 10 years after gastrectomy were diagnosed with osteoporosis, suggesting that the risk of osteoporosis persists for a long time after gastrectomy, consistent with previous studies<sup>12,13</sup>.

A previous study demonstrated that bone resorption increased as early as 1 month and bone formation began to increase about 6 months after gastrectomy<sup>11</sup>. Due to this imbalance between bone resorption and formation, cumulative bone loss during the first year was reported to be 5.7 per cent in the lumbar spine and 5.4 per cent in the total hip compared with basal levels<sup>11</sup>. In another study, the prevalence of

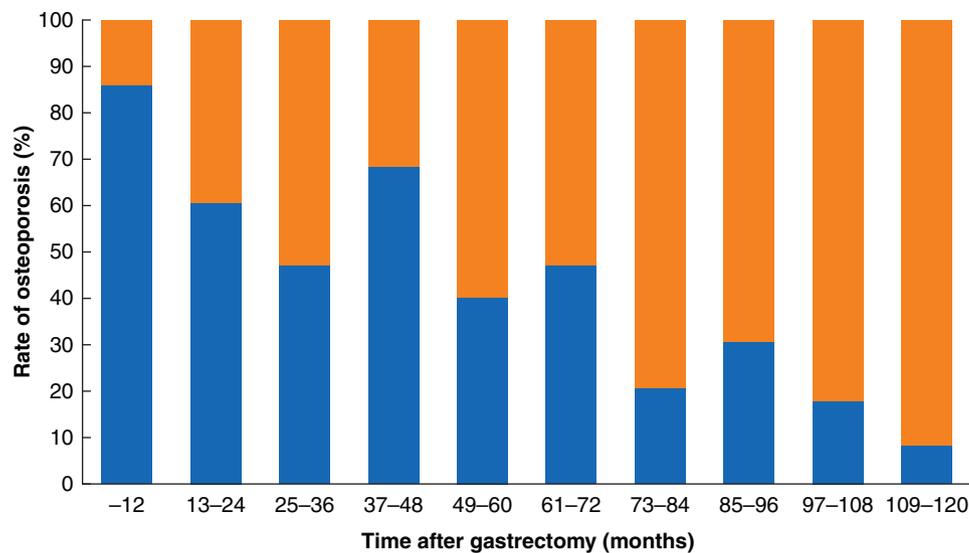


Fig. 2 Incidence of osteoporosis in patients who underwent surgery for gastric cancer according to time after gastrectomy

Table 2 Univariable analysis for the risk of osteoporosis in the development set

Risk factor	Unadjusted odds ratio	P
<b>Gastrectomy</b>		
Subtotal gastrectomy	5.31 (4.02, 7.00)	<0.001
Total gastrectomy	8.64 (5.58, 13.36)	<0.001
<b>Sex</b>		
Male	Reference value	
Female	7.60 (5.96, 9.68)	<0.001
<b>Age (years)</b>		
<50	Reference value	
50-59	8.98 (3.79, 21.29)	<0.001
60-69	19.01 (8.39, 43.08)	<0.001
70-79	36.02 (15.78, 82.21)	<0.001
≥80	52.20 (20.30, 134.19)	<0.001
<b>Obesity</b>		
Underweight	1.80 (1.05, 3.08)	0.031
Normal	Reference value	
Overweight	0.64 (0.49, 0.84)	<0.001
Obese	0.42 (0.32, 0.54)	<0.001
<b>Haemoglobin (g/l)</b>		
<120.0	1.07 (0.72, 1.58)	0.736
≥120.0	Reference value	
<b>BUN (mmol/l)</b>		
>0.71	1.14 (0.83, 1.56)	0.410
≤0.71	Reference value	
<b>Creatinine (μmol/l)</b>		
>97.2	0.53 (0.35, 0.81)	0.003
≤97.2	Reference value	
<b>Calcium (mmol/l)</b>		
<2.0	0.49 (0.12, 2.02)	0.330
≥2.0	Reference value	
<b>Phosphorus (mmol/l)</b>		
<0.83	0.13 (0.03, 0.62)	0.010
≥0.83	Reference value	
<b>Albumin (g/l)</b>		
<35.0	1.89 (0.91, 3.89)	0.084
≥35.0	Reference value	
<b>ALP (U/L)</b>		
>120.0	2.38 (0.66, 8.63)	0.184
≤120.0	Reference value	

Values in parentheses are 95 per cent confidence intervals. BUN, blood urea nitrogen; ALP, alkaline phosphatase.

osteoporosis after gastrectomy in long-term survivors at least 5 years after gastrectomy was higher than in the general population<sup>12</sup>. These data indicate that efforts to diagnose or prevent

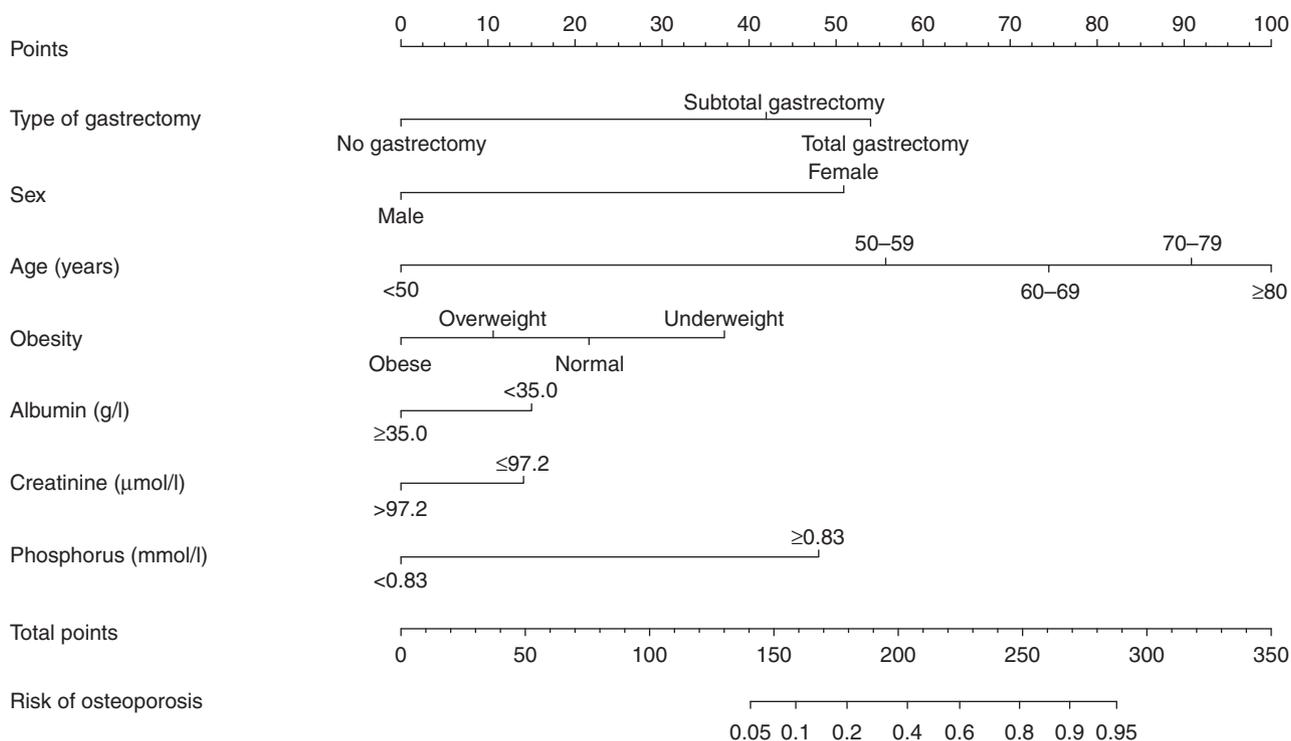
Table 3 Multivariable logistic regression analysis for the risk factors of osteoporosis in the development set

Risk factor	Adjusted odds ratio	P
<b>Gastrectomy</b>		
No gastrectomy	Reference value	
Subtotal gastrectomy	5.35 (4.06, 7.05)	<0.001
Total gastrectomy	8.67 (5.63, 13.35)	<0.001
<b>Sex</b>		
Male	Reference value	
Female	7.66 (6.02, 9.74)	<0.001
<b>Age (years)</b>		
<50	Reference value	
50-59	9.24 (3.89, 21.94)	<0.001
60-69	19.61 (8.63, 44.53)	<0.001
70-79	37.85 (16.56, 86.50)	<0.001
≥80	54.38 (21.11, 140.06)	<0.001
<b>Obesity</b>		
Underweight	1.87 (1.10, 3.17)	0.021
Normal	Reference value	
Overweight	0.65 (0.50, 0.84)	0.001
Obese	0.42 (0.33, 0.55)	<0.001
<b>Creatinine (μmol/l)</b>		
>97.2	0.57 (0.38, 0.84)	0.005
≤97.2	Reference value	
<b>Phosphorus (mmol/l)</b>		
<0.83	0.15 (0.03, 0.66)	0.012
≥0.83	Reference value	
<b>Albumin (g/l)</b>		
<35.0	1.82 (0.93, 3.55)	0.078
≥35.0	Reference value	

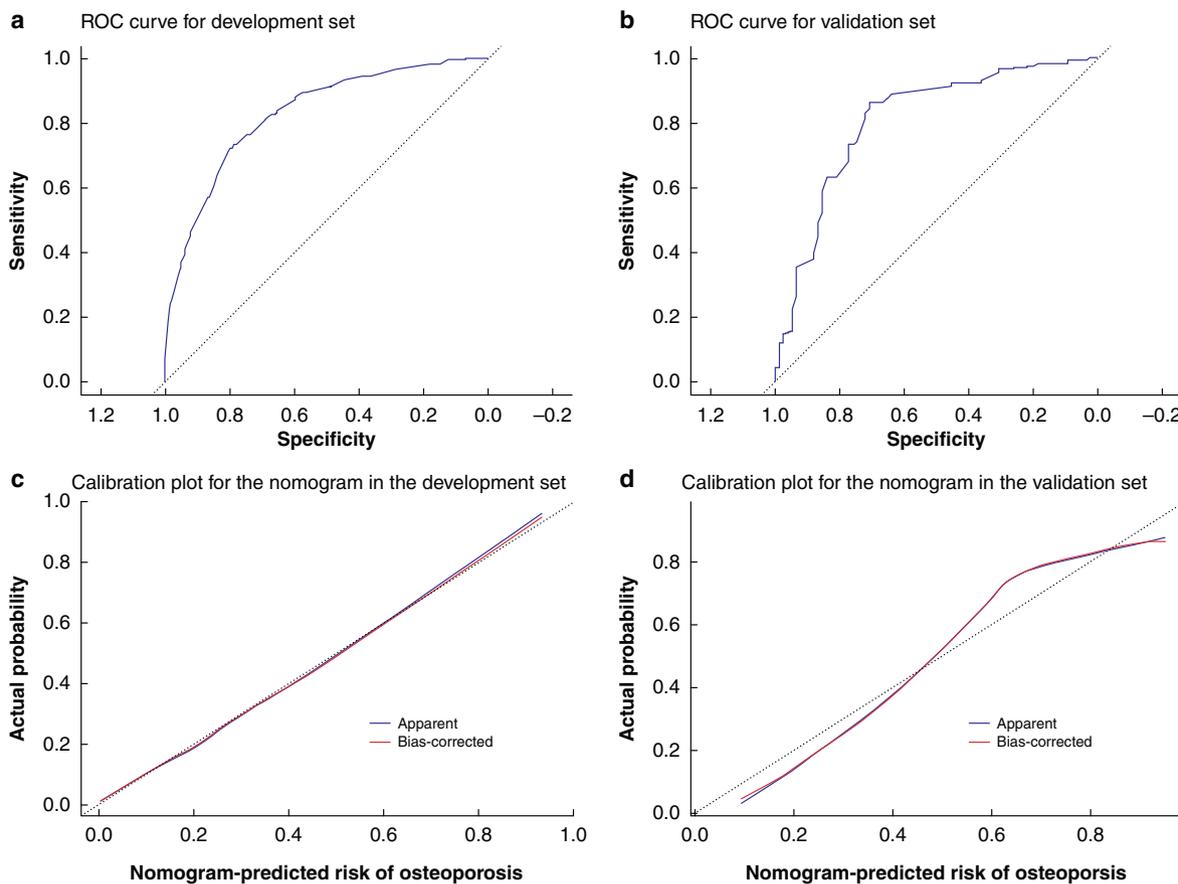
osteoporosis should be initiated soon after surgery and sustained for a long period after gastrectomy.

Considering all the above results, high-risk patients based on the nomogram should receive DXA within 6 months or 1 year after surgery. Given that the nomogram in the present study consists of preoperative and intraoperative factors, it enables clinicians to identify early high-risk patients, to plan a DXA for them within 6 months or 1 year after surgery and, potentially, to implement early treatment of osteoporosis.

This study had several limitations. Due to the retrospective design, not all patients with gastric cancer and gastrectomy underwent bone densitometry. However, this study had a relatively large cohort of 522 patients, and therefore the results



**Fig. 3** Nomogram for risk of osteoporosis after gastrectomy



**Fig. 4** Receiver operating characteristic and calibration curves

**a** Receiver operating characteristic (ROC) curve, development set. Area under the ROC curve 0.830 (95 per cent c.i. 0.812 to 0.848). **b** Receiver operating characteristic (ROC) curve, validation set. Area under the ROC curve 0.807 (95 per cent c.i. 0.741 to 0.873). Calibration curves for the nomogram in **c** the development set and **d** validation set. The blue line represents the entire cohort, and the red dashed line is the result after bias correction with 1000 bootstrap resampling, indicating nomogram performance.

would be representative to some degree. Exclusion criteria were different between the gastric cancer centre and health-promotion centre. This was an inevitable difference that appears because the characteristics of the data of the two centres are different. Time of bone densitometry after surgery was not standardized but varied according to patient's clinical status. The use of chemotherapy after gastrectomy was not evaluated. Some factors that have been shown to increase risk of osteoporosis in other studies, including diabetes mellitus and smoking history, were not evaluated as data from the health-promotion centre included information on co-morbidities based on a survey. It is acknowledged that this nomogram was developed and validated using data from South Korean patients. Different aspects of obesity and gastric cancer indicate that further validation for the nomogram in Western patients is required.

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Disclosure. The authors declare no conflict of interests.

## Supplementary material

Supplementary material is available at BJS Open online.

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