

Development and Validation of a Prognostic Nomogram to Predict Overall Survival of Elderly Patients with Gastric Cancer

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Abstract

Background

Gastric cancer (GC) is one of the most common malignant tumors of digestive tract origin in China. The proportion of elderly patients with gastric cancer (GC) gradually increases as the population ages. We aimed to develop a prognostic nomogram for prediction of elderly (≥ 75 years old) GC patients in overall survival (OS).

Patients and Methods

Patients with GC from 2005 to 2014 were selected from the Surveillance, Epidemiology, and End Result (SEER) database and randomly assigned to development and validation sets. The variables for establishing nomogram were confirmed by univariate and multivariate Cox proportional hazard analysis based on the development set. The predictive accuracy and discriminative ability of the model was evaluated using the receiver operating characteristic (ROC) curve, the concordance index (C-index) and calibration curves, while its clinical utility was assessed using decision curve analysis (DCA) and Kaplan-Meier curve.

Results

A total of 1445 patients were included in this study. The nomogram was developed including histologic grade, AJCC stage T, N, M and surgery according to the univariate and multivariate cox regression analysis, the area under the time-dependent receiver operating characteristic curve (AUC) and Occam's Law of Razor. The C-index of the nomogram was higher than the TNM system in the training cohort (0.710 vs 0.652, $p < 0.001$), which was also confirmed in the validation cohort (0.701 vs 0.643, $p < 0.001$); and high AUCs were noted in both development and validation sets. The nomogram showed good discrimination and calibration in both development and validation sets. The DCA curves showed that the nomogram had better clinical utility compared to the AJCC stage model. In addition, participants could be divided into three disparate risk groups (low, moderate, high) by the nomogram.

Conclusion

This study established a prognostic nomogram that improved the performance of the AJCC staging system with incorporation of risk factors to better predict the short-term survival in elderly GC patients.

Background

Gastric cancer (GC) has been ranked the second leading cause of cancer-related morbidity and mortality worldwide, resulting in approximately 1 million of newly diagnosed cases and 780,000 deaths in 2018 [1].

Due to its peak prevalence in the 7th decade, the proportion of aged patients with GC will increase with the progression of aging populations [2, 3]. Current treatment guidelines for GC are primarily based on evidence from randomized clinical trials (RCT) conducted in young patients, rather than in elderly patients, despite that these population have been corroborated to have poor prognosis [2].

The management of gastric cancer in elderly patients is undoubtedly very challenging for surgical oncologists. A wide range of progressive physiological changes appear with advancing age, including deterioration of physical function and body composition [4]; which lead to advanced aged patients commonly exhibit longer postoperative hospital stays, higher rates of wound infection, higher all-cause mortality, as well as higher all-cause mortality [5].

The American Joint Committee on Cancer (AJCC) built a staging standard for classification of GC by the depth of tumor invasion (T), number of metastatic lymph nodes (N), and presence or absence of distant metastases (M) [6]. This staging system has been generally applied to predict the clinical status and prognosis of patients with GC. However, it is common for patients of the same stage to present with very different survival outcomes. This may be caused by other clinical factors such as sex [7], tumor size [8], or inflammation-related factors [9]. Nomogram has been widely used in clinical tumor research to quantify risk through screening significant prognostic factors and models have also been set up based on these to calculate individual risk score to estimate the probability of a specific result for an individual. Compared with the traditional AJCC staging system, nomograms have better prediction accuracy and have been validated to predict the prognosis of young GC patients [10]. However, thus far there is no nomogram explicitly to predict the prognosis of elderly patients.

The main objective of this was to develop and validate a nomogram that can improve the performance of the AJCC staging system with incorporation of clinicopathological risk factors to predict the prognosis of elderly GC patients.

Patients And Method

Study Population

The research data is extracted from the Surveillance, Epidemiology, and End Results (SEER) using SEER*Stat software (version 8.3.5, National Center Institute). We have obtained permission to visit them for research only (Reference number: 18942-Nov2018). The inclusion criteria were as follow: over 75 years old at time of diagnosis; known diagnosis time between 2005 and 2014; diagnosis staged with American Joint Committee on Cancer (AJCC) 7th edition; classification of tumor sites into upper, middle and lower; histopathologic types were limited to adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma based on the International Classification of Oncology (Third Edition (ICD-O-3)) system. The exclusion criteria were incomplete clinical information, incomplete stage information, tumor site not included in classification, other histopathologic type and incomplete follow-up information (Figure.1).

After initial screening, a total of 1445 patients were included. American Indian/Alaskan Native and Asian/Pacific Islanders were recorded as 'others' under race. Tumor size was translated into categorical variables based on traditionally accepted cut-off values. For further analysis, all included patients were randomly divided into development and verification sets (split ratio: 7:3).

Statistical Analysis

Statistical analysis were performed with the statistical software package SPSS for Windows, version 24.0 (IBM, New York, US) and R software version 3.6.3 (<http://www.r-project.org>). The R packages "caret", "rms", "ggplot2", "survminer", "survival", "survivalROC", "rmda" were used. All p values were two-tailed with statistical significance set at 0.05.

Demographic Comparison between Development and Validation Set

Categorical variables expressed as percentages were analyzed by the chi-squared test. Univariate cox analysis was conducted to analyze the association between each variable with OS.

Development of a Prognostic Nomogram

Multivariate cox proportional hazard analysis was applied to evaluate the independent factor selected by univariate cox analysis. This is to determine which variables to be used to establish the nomogram. We used the area under the time-dependent receiver operating characteristic curve (AUC) to comprehensively assess the combined performance of filtered variables. Furthermore, we eliminated unnecessary variables in order to make the model more concise based on Occam's Law of Razor [11].

The prognostic nomogram was developed based on the five most significant factors to predict the short-term survival rate of elderly GC patients.

Validation of the Prognostic Nomogram

Nomogram performance was assessed in the development and verification sets by discrimination and calibration [12]. The C-index and the AUC-ROC were used to assess the discriminative ability of the nomogram. The calibration curves were used for comparison between the actual outcomes and the nomogram-predicted probabilities. Moreover, nomogram was subjected to bootstrapping with 1,000 resamples to evaluate prediction accuracy.

DCA Curve Analysis

Decision curve analyses (DCA) were conducted to the development set to determine the clinical benefits and usefulness of the prognostic nomogram by comparing the net benefits at various threshold probabilities with the traditional AJCC stage model.

Risk Stratification

Each included variable was assigned a corresponding risk score in the nomogram. By computing the total risk score through the nomogram and making a vertical line, we can know the short-term survival rate of each individual. In terms of the best cut-off value generated by the X-tile analysis, the total risk score was assigned into high, medium and low risk groups. The Kaplan–Meier method analysis further demonstrated the performance of nomogram in risk stratification

Result

Characteristics of Development and Validation sets

A total of 1,445 elderly GC patients were recruited in the study, of which 1013 were randomly assigned to development set and 432 were assigned to verification set (Figure.1). The sets were analogous in sex ratio, race, marital status, tumor site, histopathologic type, the AJCC TNM stage and surgery. Histologic grade and tumor size were different between the two sets. The median follow-up in the development set was 38 months (interquartile range, 24 to 54 months); 3-year OS was 37.5% (95% CI, 34.0–40.6%) and 5-year OS was 22.8% (95% CI, 17.3–28.3%). The median follow-up in the validation set was 45 months (interquartile range, 23 to 56 months); 3-year OS was 36.1% (95% CI, 31.0–41.2%) and 5-year OS was 22.8% (95% CI, 17.3–28.3%). Detailed clinical characteristics were list in Table 1.

Table 1
Patients' demographics and clinicopathological characteristics

	All patients	Training Cohort	Validation Cohort	
Characteristic	n = 1,445	n = 1,013	n = 432	<i>P</i>
Sex, no. (%)				0.170
Male	773 (53.5)	530 (52.3)	243 (56.3)	
Female	672 (46.5)	483 (47.7)	189 (43.8)	
Race, no. (%)				0.497
White	867 (60.0)	601 (59.3)	266 (61.6)	
Black	204 (14.1)	150 (14.8)	54 (12.5)	
Others	374 (25.9)	262 (25.9)	112 (25.9)	
Marital status, no. (%)				0.849
Married	743 (51.4)	528 (52.1)	215 (49.8)	
Divorced	84 (5.8)	59 (5.8)	25 (5.8)	
Single	123 (8.5)	86 (8.5)	37 (8.6)	
Others	495 (34.3)	340 (33.6)	155 (35.9)	
Tumor site, no. (%)				0.072
Upper	106 (7.3)	65 (6.4)	41 (9.5)	
Middle	309 (21.4)	226 (22.3)	83 (19.2)	
Lower	1,030 (71.3)	722 (71.3)	308 (71.3)	
Histopathologic type, no. (%)				0.938
Adenocarcinoma	1,207 (83.5)	844 (83.3)	363 (84.0)	
AM	47 (3.3)	33 (3.3)	14 (3.2)	
SRCC	191 (13.2)	136 (13.4)	55 (12.7)	
Histologic grade, no. (%)				0.030
I/II	620(42.9)	416 (41.1)	204 (47.2)	
III/IV	825 (57.1)	597 (58.9)	228 (52.8)	
Tumor size, mm, no. (%)				0.036
≤ 10	115 (8.0)	87 (8.6)	28 (6.5)	

	All patients	Training Cohort	Validation Cohort	
11–30	687 (26.8)	270 (26.7)	117 (27.1)	
31–50	456 (31.6)	299 (29.5)	157 (36.3)	
> 50	487 (33.7)	357 (35.2)	130 (30.1)	
T stage, no. (%)				0.818
T1	454 (31.4)	312 (30.8)	142 (32.9)	
T2	181 (12.5)	126 (12.4)	55 (12.7)	
T3	427 (29.6)	306 (30.2)	121 (28.0)	
T4	383 (26.5)	269 (26.6)	114 (26.4)	
N stage, no. (%)				0.997
N0	712 (49.3)	501 (49.5)	211 (48.8)	
N1	338 (23.4)	236 (23.3)	102 (23.6)	
N2	194 (13.4)	136 (13.4)	58 (13.4)	
N3	201 (13.9)	140 (13.8)	61 (14.1)	
M stage, no. (%)				0.574
M0	1,243 (86.0)	868 (85.7)	375 (86.8)	
M1	202 (14.0)	145 (14.3)	57 (13.2)	
Surgery, no. (%)				0.471
No	268 (18.5)	183 (18.1)	85 (19.7)	
Yes	1,177 (81.5)	830 (81.9)	347 (30.3)	

Factors Selection and Development of a Nomogram Depending on Development Set

Following univariable cox analysis, the variables of race, marital status, histopathologic type, histologic grade, tumor size, AJCC stage T, N, M and surgery were selected into the multivariate cox model (Table 2). The multivariate cox model showed that 8 characteristics were significant predictors with OS in Table 2: other races (HR = 0.799, $p = 0.026$), poor histologic grade (HR = 1.249, $p = 0.012$), stage T3 (HR = 1.593, $p < 0.001$), stage T4 (HR = 2.660, $p < 0.001$), stage N2 (HR = 1.399, $p = 0.009$), stage N3 (HR = 1.964, $p < 0.001$), stage M1 (HR = 1.666, $p < 0.001$), surgery (yes) (HR = 0.285, $P < 0.001$). To develop a best-fit nomogram, we used ROC curves to comprehensively assess the individual and combined performance of these factors. The individual AUC at 3 years of race, histologic grade, AJCC stage T, N, M and surgery of the development set was 0.502, 0.592, 0.658, 0.674, 0.577, 0.631, respectively. The individual AUC at 5 years

was 0.507, 0.578, 0.627, 0.621, 0.562, 0.627, respectively. As demonstrated in Figure.2, the AUC were similar between combination1 (race, histologic grade, AJCC stage T, N, M, and surgery) and combination2 (histologic grade, AJCC stage T, N, M, and surgery) and there were no statistical discrepancies (3-year AUC: 0.807 vs 0.806, $p = 0.157$; 5-year AUC: 0.826 vs 0.828, $p = 0.157$). By taking into account the importance and practicality of the nomogram, we removed race from the model due to its relatively small AUC.

Table 2
Univariate and multivariate Cox hazards analysis of the development set

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Sex				
Male	Reference		NI	
Female	0.977(0.834–1.144)	0.774		
Race				
White	Reference		Reference	
Black	1.030(0.822–1.290)	0.797	1.083(0.863–1.359)	0.492
Others	0.778(0.642–0.943)	0.010	0.799(0.657–0.973)	0.026
Marital status				
Married	Reference		NI	
Divorced	1.303(0.930–1.826)	0.124		
Single	1.255(0.944–1.669)	0.118		
Others	1.278(1.074–1.520)	0.006		
Tumor site				
Upper	Reference		NI	
Middle	0.825(0.590–1.155)	0.262		
Lower	0.776(0.571–1.055)	0.105		
Histopathologic type				
Adenocarcinoma	Reference		NI	
AM	1.352(0.890–2.055)	0.158		
SRCC	1.272(1.024–1.581)	0.030		
Histologic grade				
Ⅰ/Ⅰ	Reference		Reference	
Ⅱ/Ⅱ	1.602(1.356–1.894)	< 0.001	1.249(1.051–1.485)	0.012
Tumor size, mm				
≤ 10	Reference		NI	
11–30	2.110(1.390–3.203)	< 0.001		

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
31–50	3.024(2.009–4.553)	< 0.001		
> 50	3.238(2.161–4.852)	< 0.001		
T stage				
T1	Reference		Reference	
T2	1.106(0.823–1.487)	0.503	1.333(0.984–1.805)	0.063
T3	1.597(1.286–1.983)	< 0.001	1.593(1.261–2.013)	< 0.001
T4	2.615(2.193–3.118)	< 0.001	2.660(2.078–3.405)	< 0.001
N stage				
N0	Reference		Reference	
N1	1.456(1.191–1.780)	< 0.001	1.071(0.863–1.330)	0.531
N2	1.725(1.366–2.179)	< 0.001	1.399(1.088–1.799)	0.009
N3	2.383(1.910–2.972)	< 0.001	1.964(1.519–2.539)	< 0.001
M stage				
M0	Reference		Reference	
M1	2.753(2.261–3.353)	< 0.001	1.666(1.348–2.060)	< 0.001
Surgery				
No	Reference		Reference	
Yes	0.344(0.286–0.413)	< 0.001	0.285(0.232–0.350)	< 0.001

Eventually, a nomogram incorporated the above independent predictors from the development set was developed for the prediction of survival of elderly GC patients at 3 and 5 years (Figure.3). The total risk scores were classified into three risk groups by the X-tile analysis: low-risk (< 68), moderate-risk (68 ~ 105), high-risk (> 105) (Figure.6).

Validation of the Prognostic Nomogram

To confirm the validity of the nomogram in predicting prognosis of elderly GC patients, we conducted exhaustive validations of the nomogram between the development and validation sets. We verified from the following three heading: Firstly, the C-index for the nomogram of development set was 0.710 (95% CI, 0.689 to 0.732) and of the validation set was 0.701(95% CI, 0.668 to 0.734) which performed better than those from the AJCC stage model: development set was 0.652 (95% CI, 0.628 to 0.676), verification set

was 0.643 (95% CI, 0.608 to 0.678), there was a significant difference in two sets ($p < 0.01$); Secondly, high AUCs were noted in both development and validation sets (Figure.2); Thirdly, the nomogram calibration plot demonstrated high consistency between nomogram-predicted probabilities and actual outcomes for 3- and 5-year survival both in the development and validation sets (Fig. 4).

Clinical Benefits

The results of DCA for the prognostic nomogram and that for the traditional AJCC stage model were presented in Figure.5. The nomogram's 3- and 5-year DCA curves showed larger net benefits at all threshold probabilities in the development set compared to the AJCC stage model.

Performance in Risk Stratification of Patients

The total risk scores which were computed by the nomogram in the development set were classified into three risk groups based on the cut-off value reckoned by the X-tile analysis: low-risk (< 68), moderate-risk ($68 \sim 105$), high-risk (> 105), in which the distribution of patients were also shown in Figure.6. The validation set was also divided into three risk groups through the same classification criteria. The Kaplan-Meier curves explicitly manifested that the low-risk group has a better prognosis than the moderate- and high-risk group in both the development and the validation sets.

Discussion

The morbidity of GC was shown to increase with age and older age in GC patients often means a poor prognosis [13]. Accurately predicting the survival of elderly GC patients is still imperative and a grand challenge for clinicians because it could effectively improve elderly patients' prognosis. Chinese average life span in 2019 was 76.1 years showed in the data released by the World Health Organization (WHO); therefore, we define patients older than 75 years as elderly patients which is more representative to predict their short-term survival. In the study, we developed and validated a prognostic nomogram to predict survival of elderly GC patients based on the SEER database. The nomogram involving five variables of histologic grade, AJCC stage T, N, M and surgery showed excellent discrimination and calibration in both internal and external validation, which manifested the nomogram could assist with the clinical prognostic prediction.

In our study, we discovered that the proportion of elderly GC patients with poor histologic grade, T4, N3, M1 were higher than the reported proportion of early cases [14], and elderly GC patients had a lower OS than early-onset gastric cancer (EOGC) [15]. In addition, we confirmed five variables associated with the OS of elderly GC patients. A foregoing study by Li et al. showed that BMI, tumor site, T stage and N stage were connected with the OS of GC patients who received neoadjuvant chemotherapy [16]. Roberto et al. reported that age, T stage, N stage, tumor residual after surgery, and pre-operative ECOG-PS (performance status of Eastern Cooperative Oncology Group) were risk factors for prognosis of elderly GC patients after surgery; in addition, GC patients undergoing surgery performed better survival results [17]. Most studies

indicated that elderly GC patients had worse survival outcomes than younger GC patients. These studies were consistent with our findings.

Taking the influence of the risk factors mentioned above into account, the traditional AJCC staging system may not predict the survival of elderly GC patients well. Due to this reason, we developed a prognostic nomogram incorporating clinicopathological risk factors to predict survival of the elderly GC patients. Notably, Yu et al. [18] published a nomogram to evaluate the prognosis of EOGC, by including tumor size and tumor site as significant risk factors of survival of EOGC; however, in our study, they did not show sufficient predictive performance in the multivariate Cox model related to the prognosis of elderly GC patients. This may be due to the collinearity with other variables or the potential influencing factors different from EOGC in elderly GC patients.

As can be found in our nomogram, surgery emerged as the most significant predictor which could be expressed by the length of the axis standing for this. Despite several related research have reported that surgical resection could control elderly patients' condition and improve their prognosis [19–21], there remains controversial [22, 23]. In view of its high surgical risk, poor prognosis, low quality of life and low survival rate, many clinicians are reluctant to offer surgery to advanced aged patients [24, 25]. Currently there is no strong evidence to draw robust conclusions in this population. There was a report that age alone should not preclude gastrectomy in elderly patients [26]. They think that elderly patients should undergo operation because the benefit is the same as for young patients from short-term and long-term prognosis. On the other hand, Choo et al. [27] found elderly patients aged 80–85 years could have a large benefit from the surgical resection and for elderly patients aged over 86 years, especially those with cardiovascular and renal system diseases, the risks and benefits of the procedure should be weighed before surgery. Surgery and chemotherapy should be the recommended treatment strategy in elderly patients which can effectively improve patients' survival compared with conservative treatment [28]. Consistent with previous reports, our study suggested that surgery could improve the prognosis of elderly GC patients. The patients older than 74 years who underwent surgery had a good outcome, 96% of which improve quality of life and resume daily activities [29]. Therefore, we should adapt active treatment strategies including surgery or chemotherapy to improve patients' quality of life. For patients with poor physical conditions or comorbidities, we need to weigh their surgical risk and survival benefit.

The validation of the nomogram including C-index, the ROC curves and calibration curves all showed good results, which means that the nomogram was discriminative and reliable in predicting 3- and 5-year survival of elderly GC patients. However, the discrimination and calibration could not response the clinical consequences of extent of miscalibration that could affect a model's clinical utility [30]. To evaluate its clinical effectiveness, the DCA curves was applied in our study by comparing the net benefits with the traditional AJCC stage model. The DCA curves showed that using the nomogram in this study for predicting the short-term survival of elderly GC patients is more beneficial than the AJCC staging system. In order to get a better performance in the clinical prediction, we used the nomogram to calculate the patients' total risk score for death. Elderly patients were divided into different classification through X-tile analysis, which could facilitate the personal health management of elderly patients. In addition, the

clinicopathological variables building the nomogram were relatively accessible, hence, the nomogram can be applied universally to clinical work. This system also can give clinicians and patients an approximate range of survival at the time of diagnosis. Prognostication is not a targeted result during disease development, as it might change with the adjustment of the patients' treatment plan and subsequent treatment response. We believe that our nomogram could assist clinicians quantify the risk factors associated with cancer death, so as to develop a suitable personalized treatment plan for elderly GC patients.

There are some potential limitations that need to be acknowledged in our study. Firstly, this was a retrospective analysis based on the SEER database, among which the recruited patients were predominantly white race. There may be potential racial heterogeneity. Secondly, several factors that are closely related to prognosis are not available in the SEER database, such as tumor markers (CEA, CA 199), surgery details (surgical approach, lymphadenectomy extent, digestive tract reconstruction) and follow-up treatment (radiotherapy, and chemotherapy). Thirdly, we did not build a nomogram to predict cancer-specific survival (CSS) of elderly GC patients. It is important to note that gastric cancer is not the only factor affecting prognosis in this population group. Deaths due to other comorbidities account for 34%-37% of the total deaths in GC patients over eighty years [31]. Fourthly, some patients with missing data were excluded from the development and the validation sets, which may lead to selection bias.

In conclusion, we developed and validated a nomogram to predict 3- and 5-year survival rate of elderly GC patients based on a large sample cohort, which could improve the performance of the AJCC staging system. This might be extremely beneficial in assisting the prediction of survival and formulating individualized treatment protocols for elderly GC patients.

Abbreviations

GC: Gastric cancer; OS:Overall survival; SEER:Surveillance, Epidemiology, and End Results; ROC:Receiver operating characteristic curve; C-index:Concordance index; DCA:Decision curve analysis; AUC:Area under the time-dependent receiver operating characteristic curve; RCT:Randomized clinical trials; AJCC:American Joint Committee on Cancer; ICD-O-3:International Classification of Oncology (Third Edition); WHO:World Health Organization; EOGC:Early-onset gastric cancer; ECOG-PS:performance status of Eastern Cooperative Oncology Group; CSS:Cancer-specific survival.

Declarations

Acknowledgement

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Authors' contributions

XZ and YD conceived the study. YW and YX collected and analyzed the data; XZ and YZ wrote the manuscript; CD and WZ reviewed and modified the paper. All authors approved the final manuscript.

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Availability of data and materials

The research data is extracted from the Surveillance, Epidemiology, and End Results (SEER) using SEER*Stat software. We have obtained permission to visit them for research only (Reference number: 18942-Nov2018). The data can be used publicly.

Ethics approval and consent to participate

The SEER program database is publicly available and we signed the data usage agreement. So this study did not require the informed consent.

Consent of publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

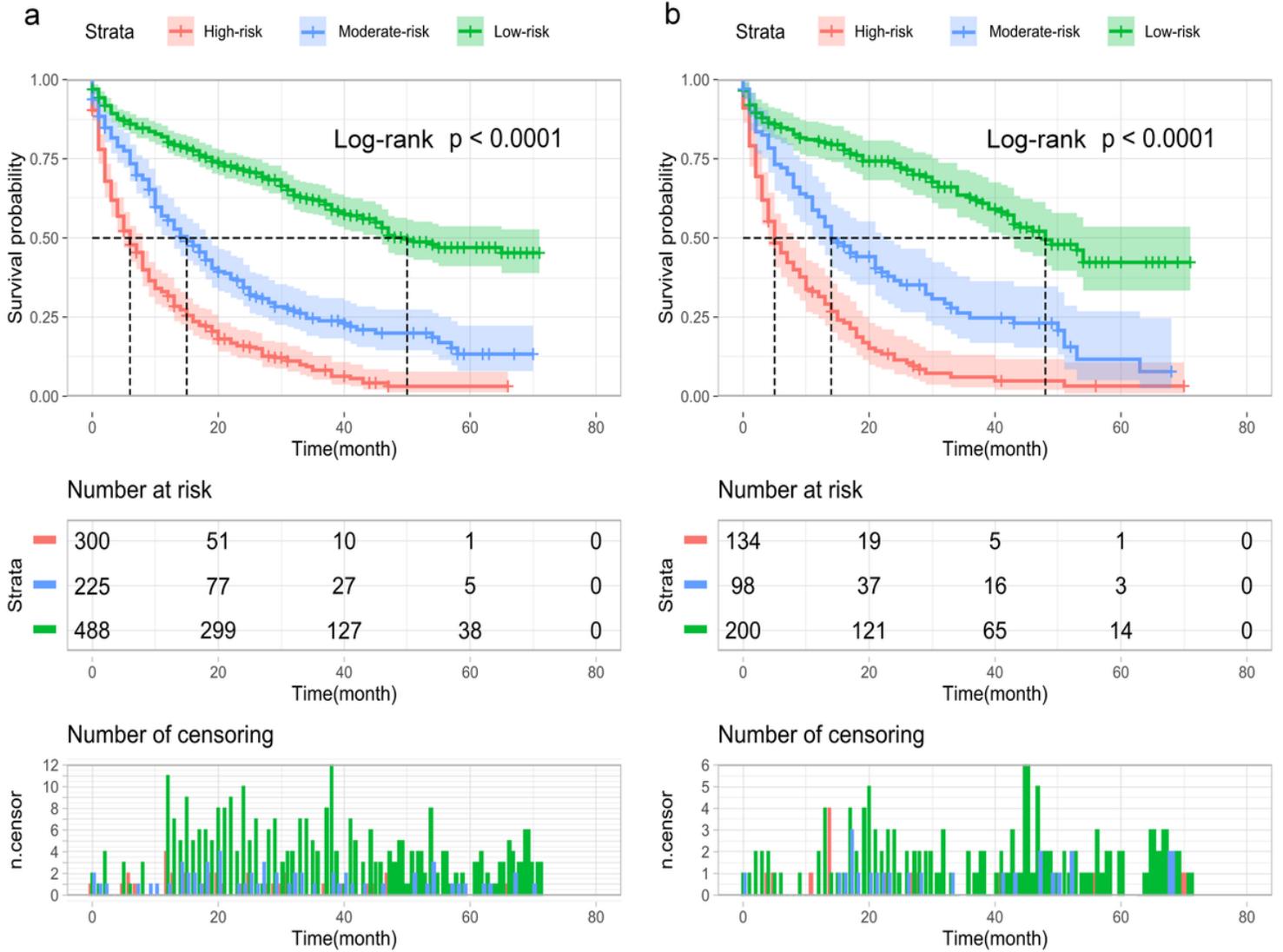


Figure 1

The Kaplan-Meier curves stratified by the total risk scores computed by the nomogram in the development (a) and validation sets (b): low-risk (<68), moderate-risk (68~105), high-risk (>105). Distribution of patients in the training set and validation set in each risk group.

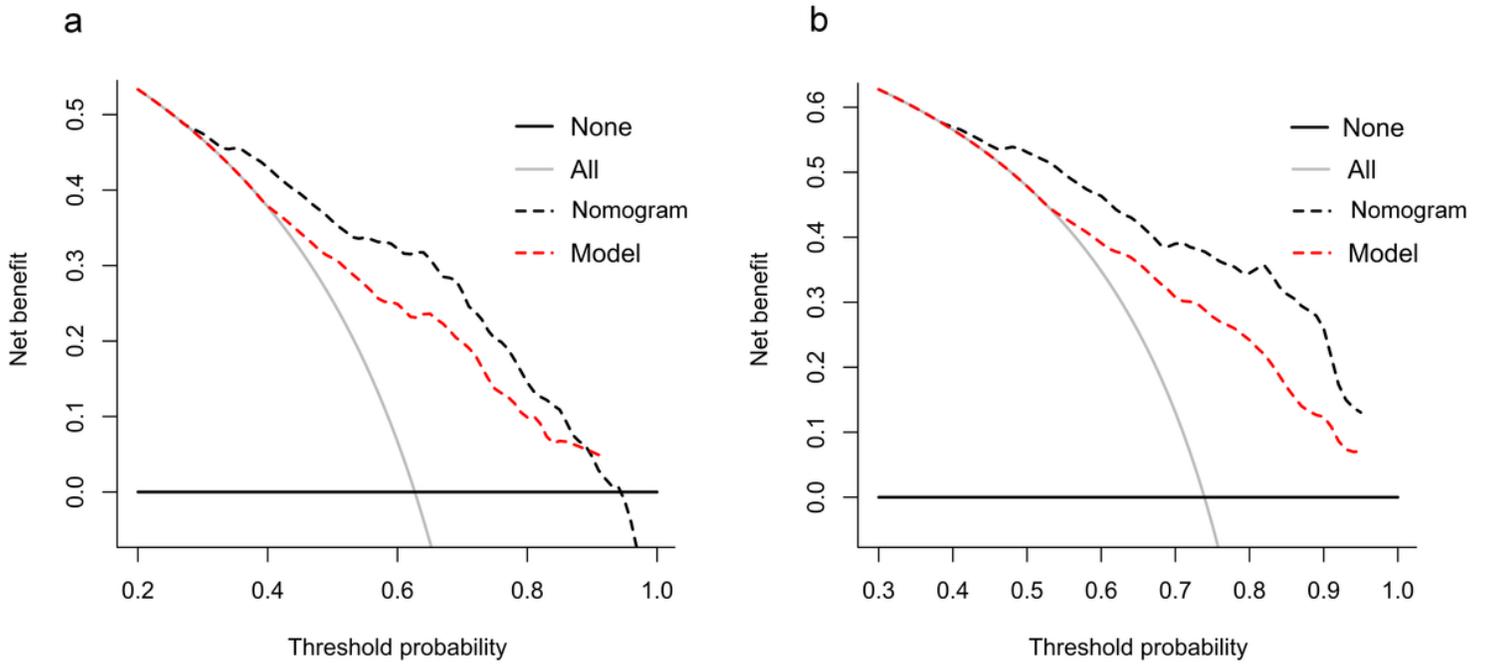


Figure 2

DCA for the nomogram and the model with AJCC stage TNM. (a) DCA for the nomogram and the model in the development set. (b) DCA for the nomogram and the model in the validation set.

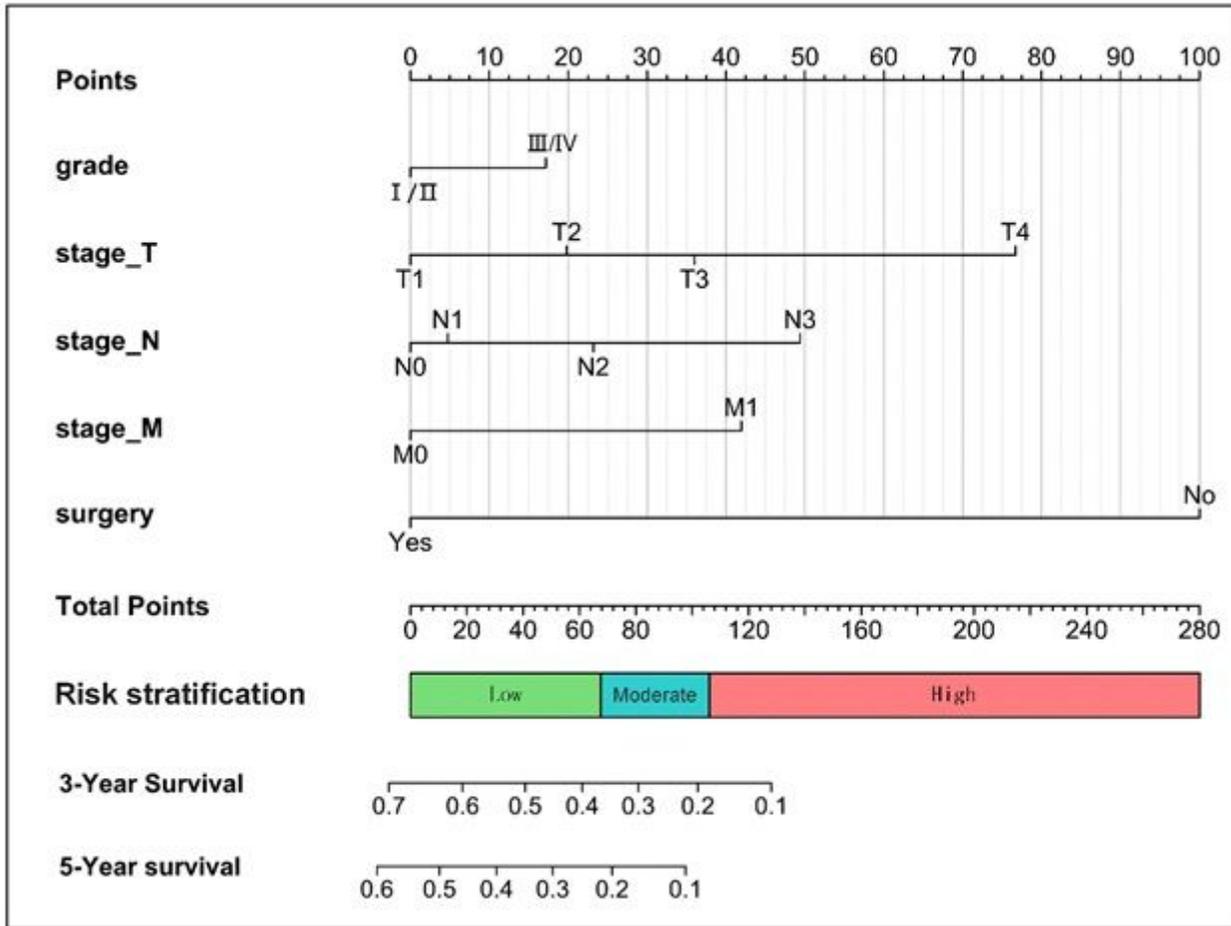


Figure 3

Developed prognostic nomogram predicted 3- and 5-year overall survival (OS) for elderly gastric cancer (GC) patients. The nomogram was developed in development set including histologic grade, AJCC stage T, N, M and surgery.

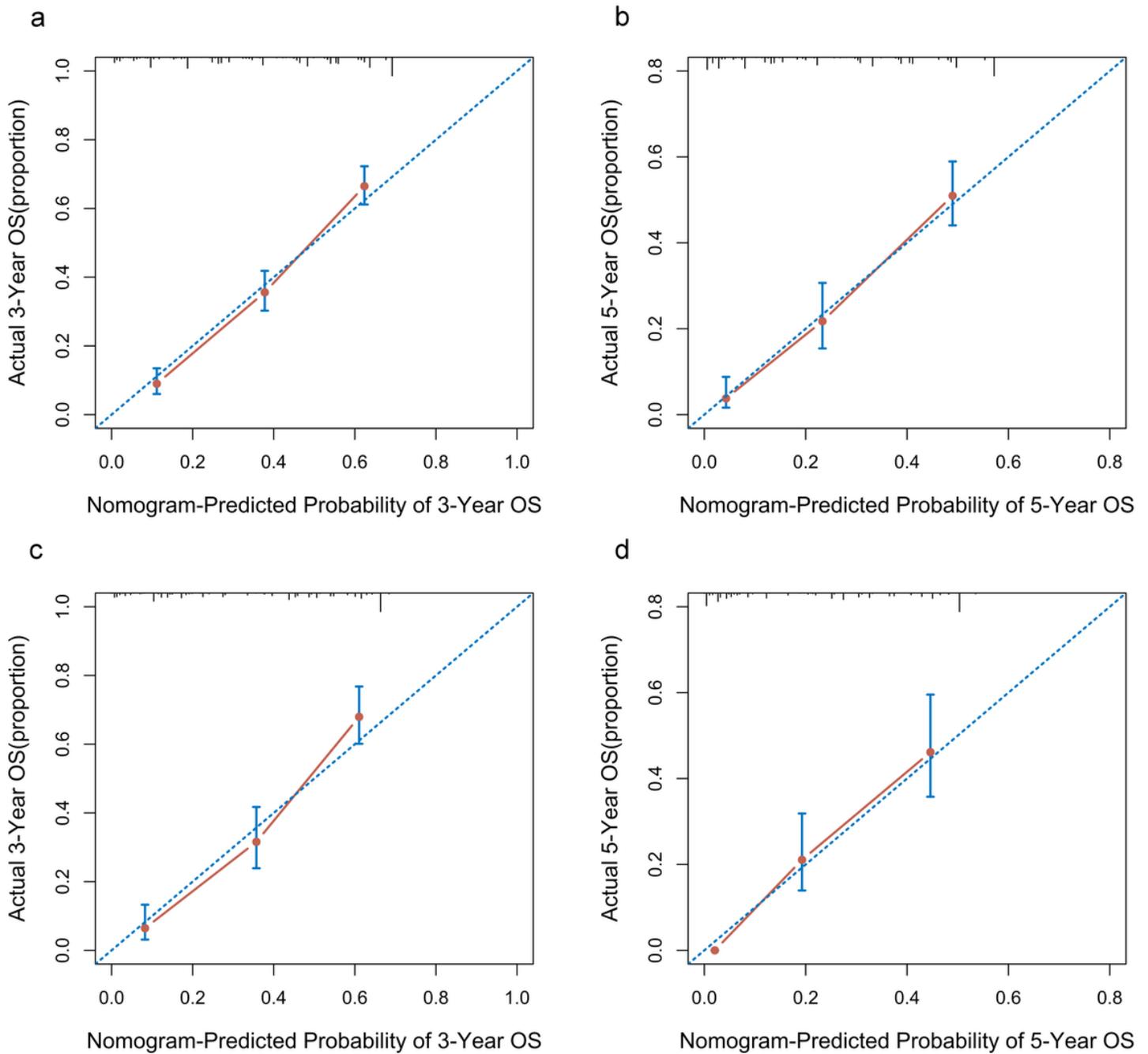


Figure 4

Calibration curves for predicting patient survival. (a) Calibration curve of the prognostic nomogram at 3-year in the development set. (b) Calibration curve of the prognostic nomogram at 5-year in the development set. (c) Calibration curve of the prognostic nomogram at 3-year in the validation set. (d) Calibration curve of the prognostic nomogram at 5-year in the validation set.

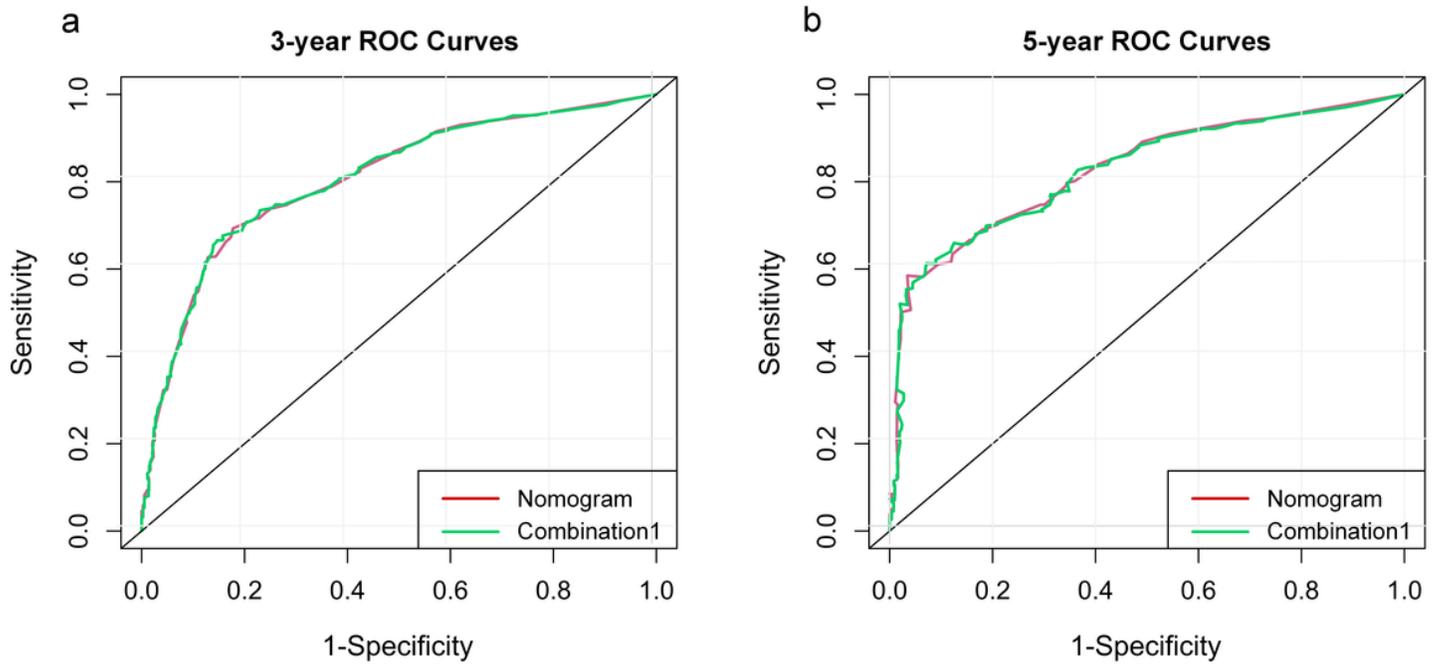


Figure 5

ROC curves of the nomogram and the combination1. (a) ROC curve of the nomogram (AUC: 0.806) and the combination1 (AUC: 0.807) at 3-year in the development set. (b) ROC curve of the nomogram (AUC: 0.828) and the combination1 (AUC: 0.826) at 5-year in the development set.

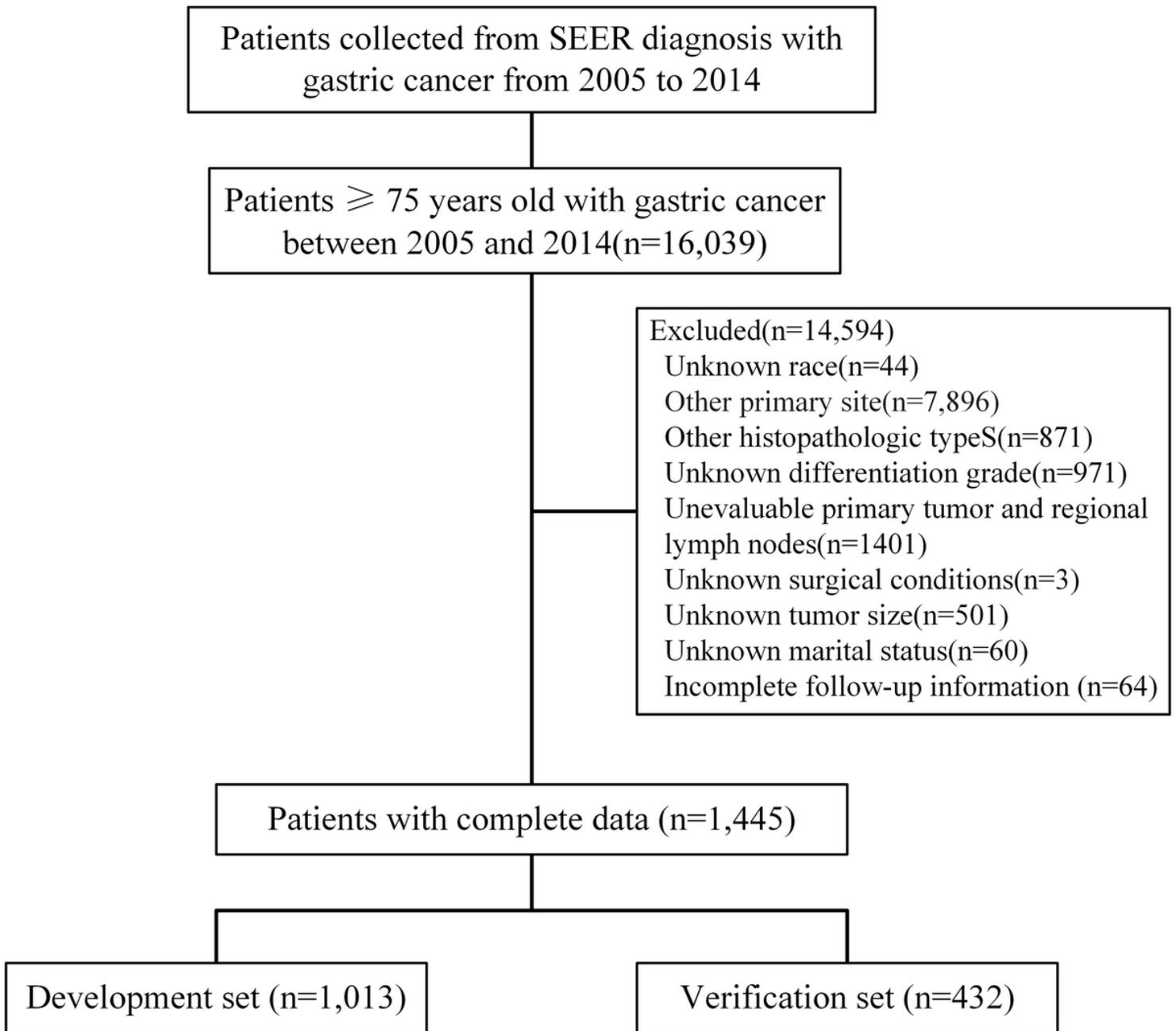


Figure 6

Flow diagram of the patients