Original Article

Prediction of distant metastasis and survival prediction of gastric cancer patients with metastasis to the liver, lung, bone, and brain: research based on the SEER database

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Background: Gastric cancer (GC) is a globally important disease. It is the 5th most common malignancy and the 4th most common cause of death from cancer in the world. Patients with GC are often at an advanced stage when they are first diagnosed, and their overall prognosis is poor due to locally advanced and distant metastasis. This study sought to establish a predictive model of GC distant metastasis and survival that can be used to guide individualized treatment.

Methods: Patients diagnosed with GC from the Surveillance, Epidemiology, and End Results database were enrolled in the study. Univariate and multivariate logistic regression analyses were used to identify risk and prognostic factors for GC patients with distant metastasis. The factors were then used to construct nomograms to predict the probability of distant metastasis and the survival time of GC patients. Receiver operating characteristic (ROC) curve and decision curve analyses were used to verify the prediction ability of the nomograms.

Results: We established a comprehensive nomogram to predict the survival time of GC patients and 4 nomograms to predict distant metastasis. Nomograms could help oncologists to formulate treatment strategies and provide hospice care under an overall management model.

Conclusions: Establishing a prediction model for distant metastasis and the survival of GC patients is of great clinical significance. The prediction of distant metastasis could help clinicians to make individualized assessments of patients and formulate individualized examination measures. Survival prediction models could help oncologists to formulate good treatment strategies and provide hospice care.

Keywords: Gastric cancer (GC); nomogram; distant metastasis; overall survival (OS); decision curve analysis (DCA)

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Introduction

Gastric cancer (GC) is a globally important disease. It is the 5th most common malignancy, and the 4th most common cause of death from cancer in the world (1). In 2020, 769,000 people died of GC worldwide, and it has been estimated that there are >1 million new cases of GC each year (2,3). As patients with GC are often at an advanced stage when they are first diagnosed, the mortality rate of GC is extremely high, and the median survival rate of advanced stage GC patients is <12 months (4). Most newly diagnosed cases of GC involve locally advanced tumor growth or distant metastasis (5). According to a GC analysis in Sweden, >40% of GC patients had metastatic disease (6).

Some previous reports indicate that gender, age, race, TNM staging, lung metastasis, and tumor size are considered to be significantly related to the survival of elderly patients with gastric cancer (7). Tumor size and TMN stage are significantly related to the survival of young gastric cancer patients (8). Many studies have proposed that age, race, tumor size, and depth may be risk factors for distant metastasis of gastric cancer (9).

At present, the nomogram of distant metastasis and prognosis of GC has not been fully developed and verified. Compared with the previous prognostic analysis for different gastric cancer subtypes, we believed that GC patients need to establish a reliable clinical model with good performance.

The Surveillance, Epidemiology, and End Results (SEER) is the authoritative source of cancer statistics in the United States (US). In this study, we used data from SEER cancer registry of patients diagnosed with GC from 2010 to 2015 to establish a survival prediction model. On this basis, we had also established prediction models for distant metastasis in patients with GC.

We present the following article in accordance with the TRIPOD reporting checklist (available at https://dx.doi.org/10.21037/atm-21-6295).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

SEER database

The SEER program provides cancer statistics in an effort to reduce the cancer burden in the US population. SEER is supported by the Surveillance Research Program of the Division of Cancer Control and Population Sciences (DCCPS) of the National Cancer Institute. The SEER database released information on metastases in the liver, lungs, bones, and brain in 2010 (10). Public original data were obtained from the SEER database. The data were downloaded by SEER*Stat Software (version 8.3.9). The exact data used were extracted from the "Incidence–SEER Research Data, 18 Registries, Nov 2020 Sub (2000–2018)—Linked to County Attributes—Time Dependent (1990–2018) Income/Rurality, 1969–2019 Counties, National Cancer Institute, DCCPS, Surveillance Research Program", released April 2021, based on the November 2020 submission.

Patients

Histological types were defined by the following ICD-O-3 codes: 8140 to 8147, 8210 to 8211, 8220 to 8221, and 8260 to 8263 for adenocarcinoma, 8480 and 8481 for mucinous adenocarcinoma, and 8490 for Signet ring cell carcinoma.

The primary site was defined by the site recode ICD-O-3/WHO 2008: Stomach.

Patients were excluded if they met any of the following exclusion criteria: (I) it was unknown whether metastasis had occurred; (II) their survival time was "0" or unknown; (III) the patient did not have a tumor, node, metastasis (TMN) stage record; and/or (IV) information about collaborative stage (CS) extension or CS tumor size was missing or incomplete.

Statistical analysis

The categorized data are described as numbers and percentages (N, %). All the statistical analyses were performed using the R programming language and environment (http://www.r-project.org/). Univariate and multivariate logistic regression analysis were conducted to identify the risk and prognostic factors of GC patients with metastasis. A 2-tailed P value <0.05 was considered statistically significant (11). Factors that are statistically significant in univariate and multivariate analysis were included in the construction of nomograms. The "regplot" software package was used to construct nomograms to predict the probability of distant metastasis and the survival time of GC patients (12). The median overall survival (OS) time was determined using Kaplan-Meier survival curves, and differences were assessed using the log-rank test. The

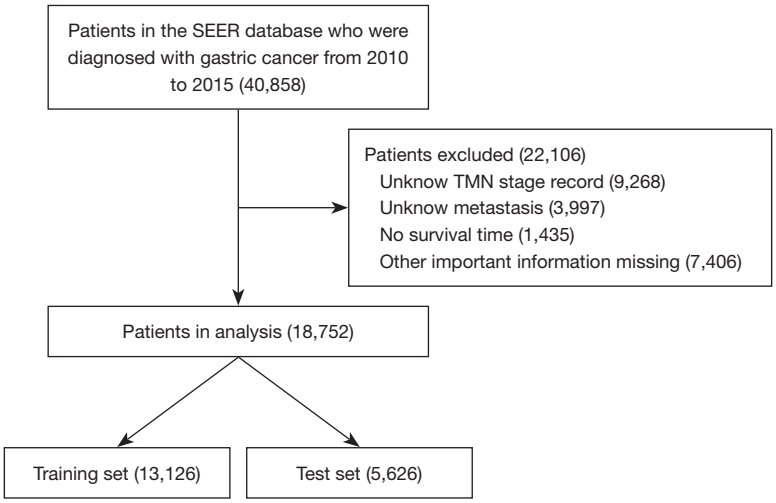


Figure 1 Flowchart of patients' enrollment in this study according to the inclusion and exclusion criteria.

outcomes of the prediction models include liver metastasis, lung metastasis, brain metastasis, bone metastasis and OS time of GC patients.

Model validation

Receiver operating characteristic (ROC) curves were used to verify the diagnostic accuracy and sensitivity of the nomograms, which are useful for organizing classifiers and visualizing their performance (13). The higher the area under the curve (AUC), the higher the accuracy of the nomogram (14). Calibration plots (graphical tools for investigating the reliability of prediction models) were used to verify the prediction ability of the survival nomogram (15). Decision curve analyses (DCAs) and clinical impact curves (CICs) were used to examine the discrimination and calibration of the model, and the clinical impact of the model was quantified using R package "rmda" (16,17).

Results

Clinical characteristics of GC patients in the SEER cohort

From 2010 to 2015, 18,752 GC patients in the SEER database met the inclusion criteria for this study (see *Figure 1*). Among them, 1,775 GC patients had liver metastasis, 594 had lung metastasis, 479 had bone metastasis, and 73 had brain metastasis.

The patients were randomly divided into training and validation sets according to the ratio of 7:3. *Table 1* sets out the demographic and clinicopathological characteristics of the patients in the training cohort (n=13,126) and the validation cohort (n=5,626). 60% of the patients were aged >60 years. We used the 8th edition of American Joint Committee on Cancer (AJCC) to classify the TMN stages of GC patients. Under the AJCC (8th ed.) 26%, 20%, 29%, and 25% of the patients had stage I, stage II, stage II and stage IV TNM GC, respectively. More than 70% of the patients had adenocarcinoma. The incidence of lung, liver, brain, and bone metastasis was 3%, 9%, 3%, and 0.4%, respectively. The incidence of patients with distant metastases to 1 of these 4 sites was 12.7%.

Prediction of distant metastasis in patients with GC

We analyzed the risk factors of distant metastasis in patients with GC. The univariate analysis and the multivariate analysis showed that tumor size, N stage, histological type, and extension were related to liver metastasis, tumor size, N stage, age, and extension were related to lung metastasis and bone metastasis, and tumor size, N stage, T stage, and extension were related to brain metastasis. Using the risk factors identified in the multivariate logistic regression analysis model, we constructed 4 nomograms for distant metastasis of the liver, lung, bone, and brain (see *Figure 2*). The total number of points can be attached to the probability of distant metastasis by calculating each variable point.

The ROC curves used to assess the nomogram of distant metastasis are shown in *Figure 3*. The area under the curve (AUC) of liver metastasis was 0.817 (see *Figure 3A*), the

Table 1 The demographic and clinicopathological characteristics of patients in the training cohort (n=13,126) and validation cohort (n=5,626)

Variable	All subjects, N=18,752		Training cohort, N=13,126		Validation cohort, N=5,626	
	N	%	N	%	N	%
Age						
<40	629	3	437	3	192	3
40–49	1,447	8	1,006	8	441	8
50–59	3,578	19	2,512	19	1,066	19
60–69	5,413	29	3,783	29	1,630	29
70–79	5,528	29	3,849	29	1,679	30
≥80	2,157	12	1,539	12	618	11
AJCC stage						
IA	3,337	18	2,332	18	1,005	18
IB	1,527	8	1,058	8	469	8
IIA	1,389	7	988	8	401	7
IIB	2,354	13	1,687	13	667	12
IIIA	2,847	15	1,963	15	884	16
IIIB	1,549	8	1,103	8	446	8
IIIC	1,034	6	725	6	309	5
IV	4,715	25	3,270	25	1,445	26
Histology						
Adenocarcinoma	14,423	77	10,109	77	4,314	77
Mucinous adenocarcinoma	394	2	255	2	139	2
Signet ring cell carcinoma	3,935	21	2,762	21	1,173	21
Tumor size						
0	1,969	11	1,346	10	623	11
1	5,923	32	4,177	32	1,746	31
3	7,926	42	5,570	42	2,356	42
5	1,538	8	1,061	8	477	8
6	1,396	7	972	7	424	8
Extension						
<300	5,485	29	3,856	29	1,629	29
300–600	11,244	60	7,841	60	3,403	60
>600	2,023	11	1,429	11	594	11
N stage						
N0	8,803	47	6,114	47	2,689	48
N1	5,353	29	3,785	29	1,568	28
N2	2,319	12	1,617	12	702	12
N3	2,277	12	1,610	12	667	12

Table 1 (*continued*)

Table 1 (*continued*)

Variable	All subjects, N=18,752		Training cohort, N=13,126		Validation cohort, N=5,626	
	N	%	N	%	N	%
Lung Met						
Yes	594	3	418	3	176	3
No	18,158	97	12,708	97	5,450	97
Liver Met						
Yes	1,775	9	1,227	9	548	10
No	16,977	91	11,899	91	5,078	90
Bone Met						
Yes	479	3	332	3	147	3
No	18,273	97	12,794	97	5,479	97
Brain Met						
Yes	73	0.4	49	0.4	24	0.4
No	18,679	99.6	13,077	99.6	5,602	99.6

AUC of lung metastasis was 0.811 (see *Figure 3B*), the AUC of bone metastasis was 0.818 (see *Figure 3C*), and the AUC of brain metastasis was 0.784 (see *Figure 3D*). The AUCs show that the nomograms had a good predictive performance. We also constructed forest plots of lung metastasis and liver metastasis (see *Figure 4*).

In this study, the median OS for patients was 20 months for the whole cohort. The median OS time of patients with liver metastasis was 7 months. The median OS time of patients with lung metastasis was 5 months. The median OS time of patients with brain metastasis was 5 months. The median OS time of patients with bone metastasis was 6 months. The median OS times of patients with different types of metastasis are shown in *Figure 5*. The decision curve and clinical impact curve analyses showed that within a large interval, the benefits of the 4 metastasis prediction models were higher than the extreme curve, which proves that the prediction models had good clinical utility (see *Figures 6*,*7*).

Construction and validation of the OS nomogram

The survival-related factors of the SEER cohort were determined based on the multivariate logistic regression analysis model. A forest plot was constructed to show the survival-related factors and their P value (see *Figure 8*). All of these factors were used to construct a survival prediction nomogram for GC patients at 12, 24, and 36 months (see *Figure 9*). By adding up the total scores shown in the bottom scale, the nomogram could predict the OS for individual patients at 12, 24, and 36 months. The C-index of the survival prediction nomogram was 0.701. In the test cohort, the C-index of the survival prediction nomogram was 0.703. The ROC curves were used to evaluate the survival prediction nomogram (see *Figure 10*). The calibration plots of the model showed that the 24-month survival time predicted was consistent with the actual value (see *Figure 11*).

Discussion

At present, due to the early diagnosis and standardized treatment of GC, the survival time of patients is significantly longer than it was previously; however, overall it is still relatively poor (18). Distant organ metastasis is a sign of poor prognosis in patients with GC. Thus, a prediction model for distant organ metastasis in patients with GC could help to identify patients who are prone to distant metastasis based on clinical characteristics. Following the in-depth study of GC in recent years, many clinical molecular markers had been identified that can be used in the prediction of distant metastasis and the survival time of GC patients. Further, such molecular markers may help in the early diagnosis of metastasis and the development of

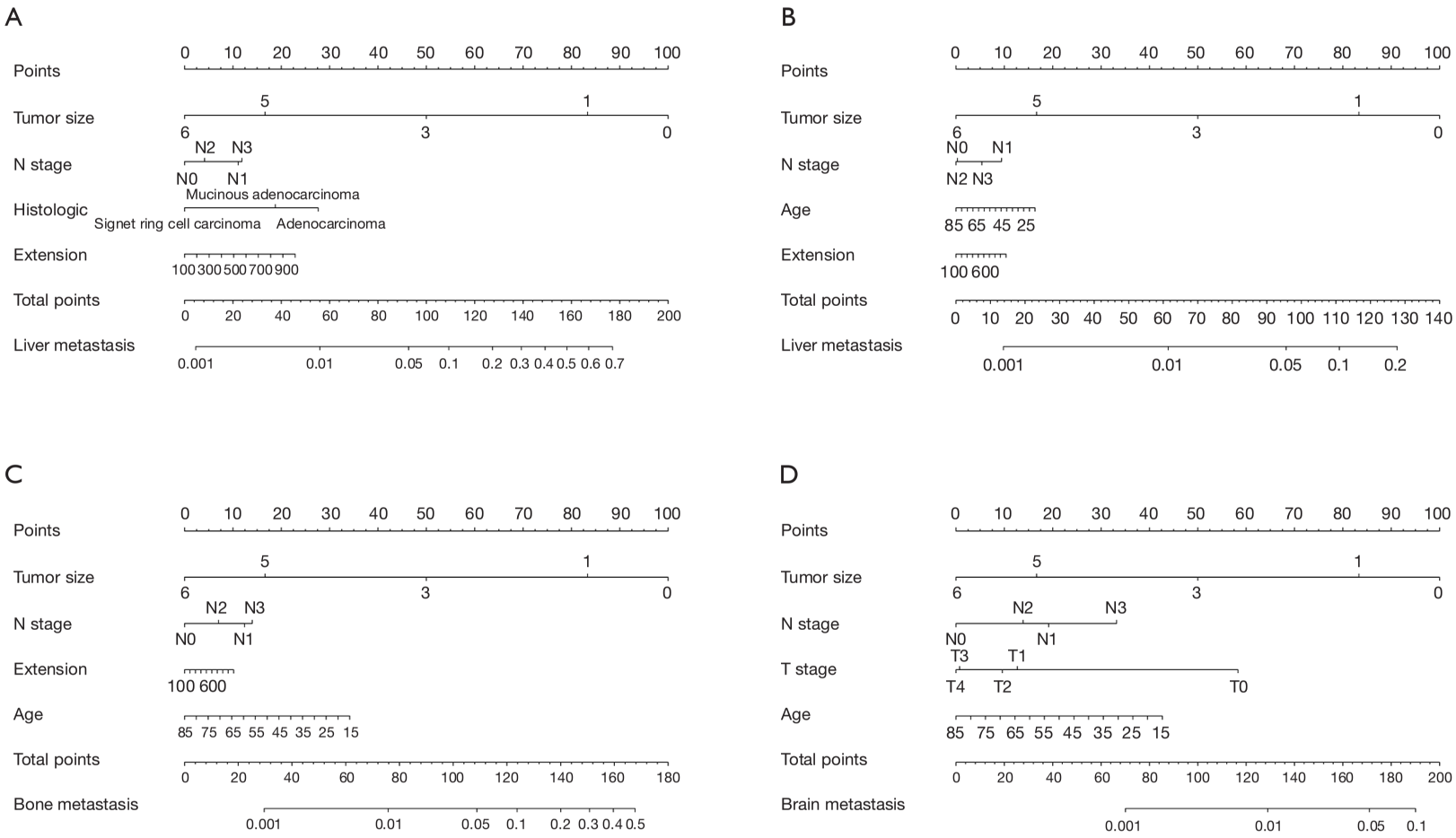


Figure 2 Nomograms for predicting the risk of metastasis in patients with gastric cancer (GC). (A) Nomogram for predicting the risk of liver metastasis in patients with GC. (B) Nomogram for predicting the risk of lung metastasis in patients with GC. (C) Nomogram for predicting the risk of bone metastasis in patients with GC. (D) Nomogram for predicting the risk of brain metastasis in patients with GC.

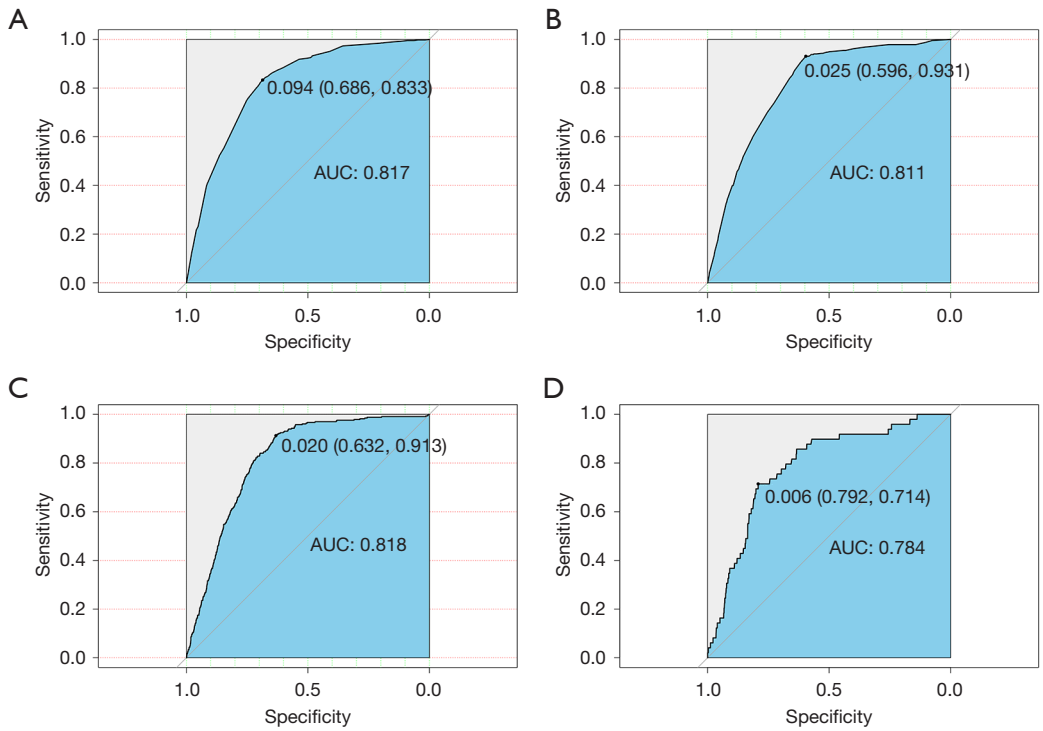


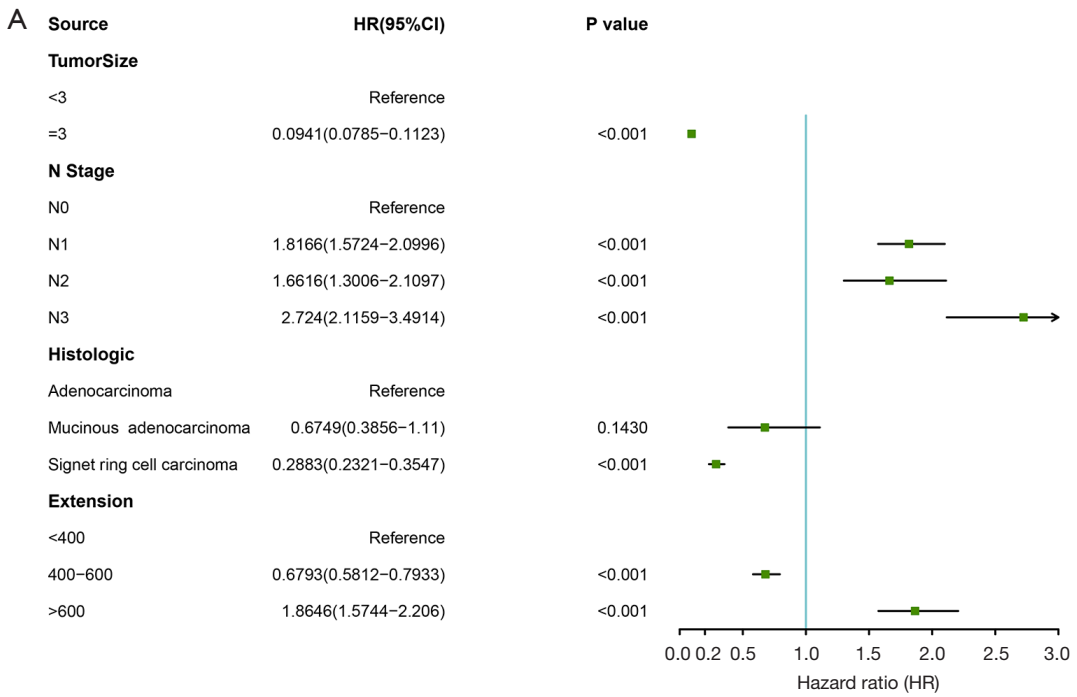
Figure 3 ROC curves of distant metastasis prediction nomograms in patients with gastric cancer (GC). (A) ROC curve of liver metastasis prediction nomogram in patients with GC. (B) ROC curve of lung metastasis prediction nomogram in patients with GC. (C) ROC curve of bone metastasis prediction nomogram in patients with GC. (D) ROC curve of brain metastasis prediction nomogram in patients with GC.

individualized treatment strategies.

In the distant metastasis data of GC patients, we found that the probability of liver metastasis was 9%, which was the highest among the 4 organs. The probability of liver metastasis was the highest among the 4 organs may be due to differences in the metastasis pathways and the popularity of the inspection measures. The common ways for patients with GC to develop distant metastasis are lymph node metastasis and abdominal cavity metastasis (19,20). Conversely, the common ways of liver metastasis are direct infiltration, blood metastasis, lymphatic metastasis, and planting metastasis (19). The liver is connected to digestive organs, such as the stomach, through the hepatic portal vein, which is conducive to the blood metastasis of GC (21). Studies have shown that GC cells spread to various organs through the portal vein, and the liver becomes the first filter for GC cells (22). This may be why the liver is the first organ of distant metastasis in patients with GC (6). Due to advancements in medical technologies and the continuous improvement of detection methods, cases of liver metastasis can be detected in early or even asymptomatic stages (23).

We found that patients with GC have a low rate of bone metastasis (the incidence of bone metastasis was 3%). The occurrence of GC bone metastasis may be underestimated because GC bone metastasis is rare, and bone metastasis is usually not included in routine examinations (24). Using the prediction model for GC bone metastasis, patients at high risk of bone metastasis could be detected in advance. It would be unreasonable to suggest that all parts of their body be checked in all GC patients. However, those at high risk of metastasis could be identified using the metastasis prediction model, and targeted inspection measures and feasible medical solutions could be formulated.

In this study, the incidence of brain metastases was 0.4%. In stage-IV patients, the probability of brain metastasis was 1.5%. As many patients with brain metastasis have a short survival time and rapid disease progression, there is a lack of clinical information about these patients, and these patients could not be included in our model. Thus, the incidence of brain metastasis in this study may be



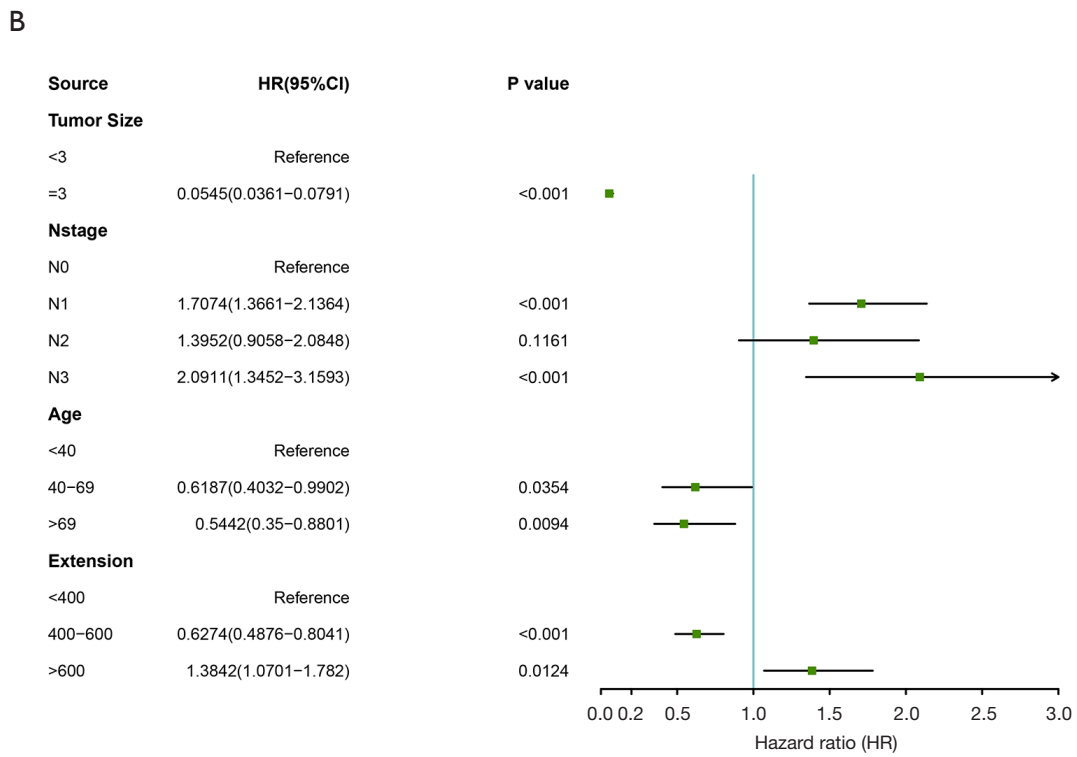


Figure 4 Forest plot (A) Forest map of liver metastasis and the P value for each factor. (B) Forest map of lung metastasis and the P value of each factor.

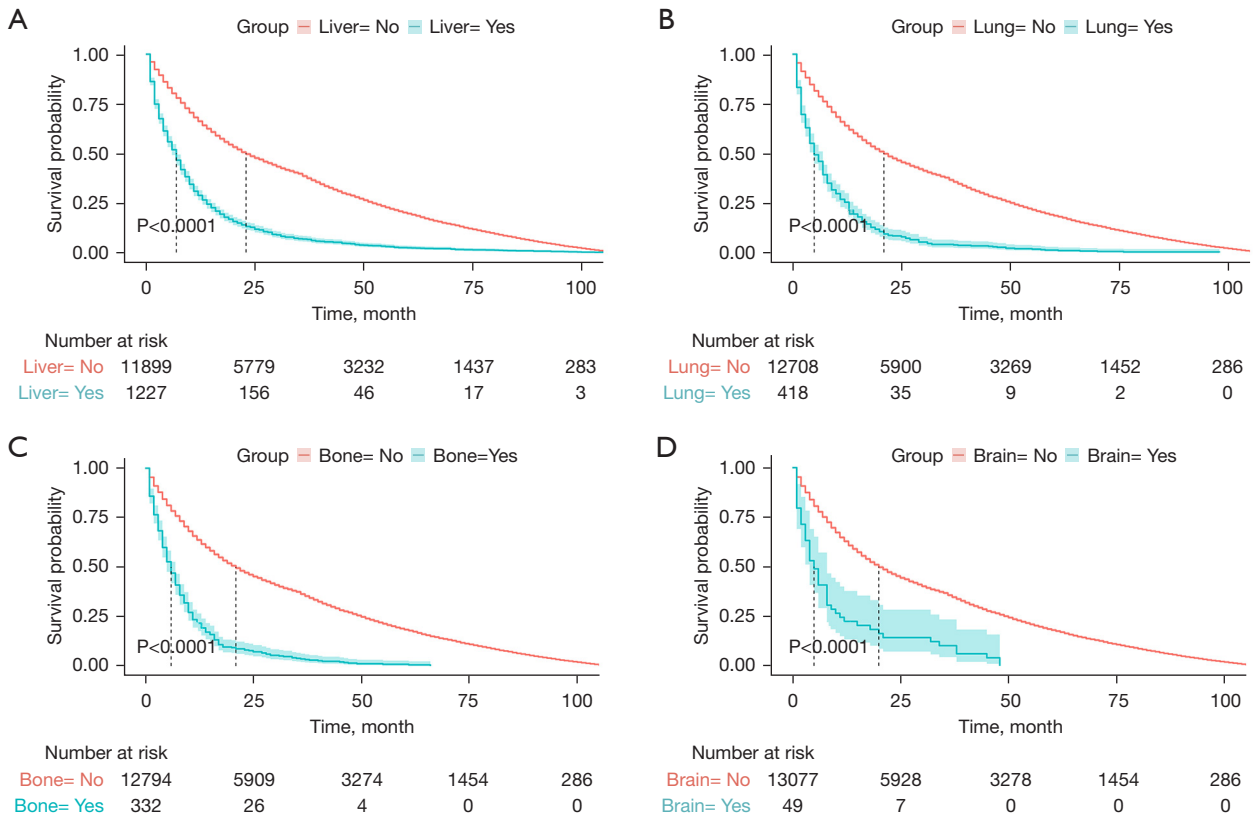


Figure 5 Kaplan-Meier analyses of OS in GC patients with distant metastasis stratified by liver metastasis, lung metastasis, bone metastasis, and brain metastasis.

underestimated. The actual incidence of brain metastasis from GC is not low. Indeed, about 10% of cancer patients will develop brain metastasis during advanced disease progression (25). When brain metastasis occurs, the patient's survival period is significantly shortened (11,25). Even if more and more targeted drugs or chemotherapeutic drugs are developed to prolong the survival time of patients, the existence of the blood-brain barrier makes it difficult to increase the concentration of drugs in the brain, resulting in poor therapeutic effects (26). Through this prediction model, we can identify patients at high risk of brain metastasis early and implement corresponding measures as early as possible to reduce or even block the occurrence of brain metastasis.

In our study, the younger the age, the higher the probability of bone metastasis and brain metastasis. This may be due to differences in lymph node involvement in different age groups. Among GC patients, the proportion of patients with >15 lymph node metastases decreases significantly with age (27). Many studies have also shown that a younger age is positively correlated with distant metastasis in GC patients (28). Palliative chemotherapy has been reported to improve the survival rate of GC patients with bone metastasis (29).

In this study, we first downloaded data from the SEER public database on GC patients. Studies have shown that a number of factors, including histological type, TMN staging, and age, may be signs of distant metastasis (10,11,30). Through single-factor and multi-factor analyses, we selected factors, such as N stage, tumor invasion, and tumor size, and established a predictive model for distant metastasis. Many studies have evaluated the survival rate and related factors of patients with GC metastasis, and found that age, tumor stage, and tumor histological type, are independent factors related to the survival of GC patients (28,31,32). Our prediction model included tumor stage, tumor histology type, tumor invasion depth, tumor size and age. However, many other factors, such as marital status, sex and insurance, are also considered independent factors for the survival of GC

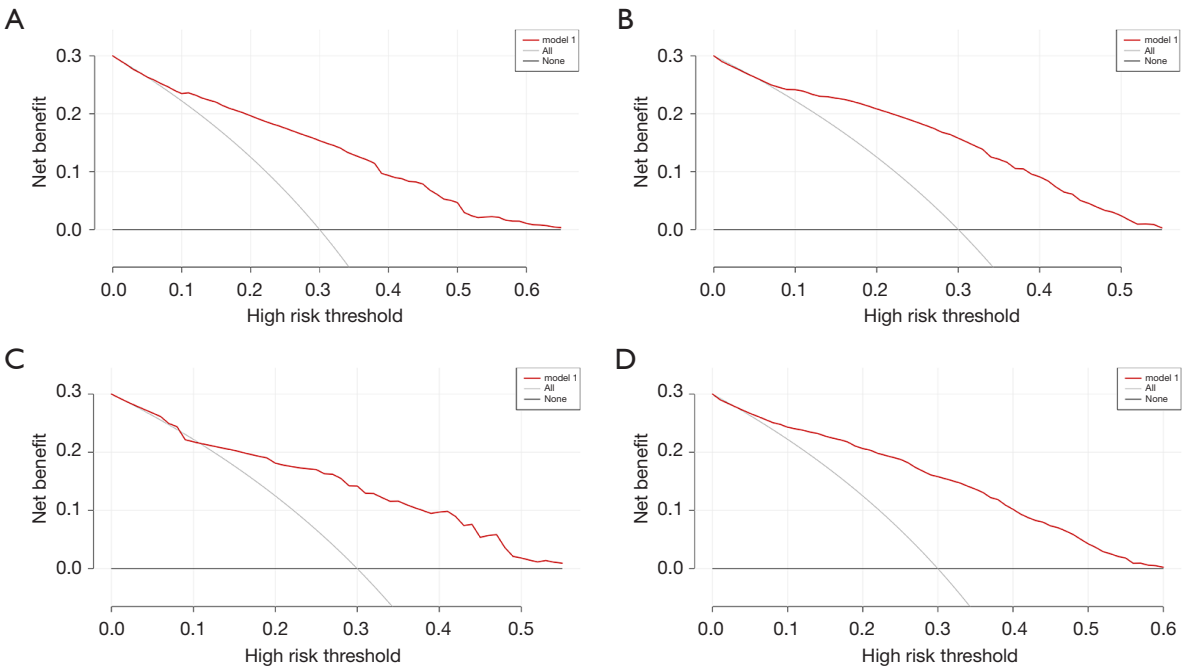


Figure 6 Decision curve analysis (DCA) for the nomograms of (A) liver metastasis (B) lung metastasis (C) brain metastasis, and (D) bone metastasis.

patients (28,33,34). We did not include all such factors in our prediction model, as including too many variables may lead to the over-fitting of models, which in turn may lead to falsely high ROC results. The results of the present study have been detailed above. We made individualized predictions based on the different clinical characteristics of each patient, which is somewhat better than previous studies that have only compared the possible metastasis of different types of GC patients.

In our study, we conducted a quantitative evaluation of the incidence of distant metastasis in patients with different clinical characteristics, established 4 prediction models for distant metastasis in the liver, lung, brain, and bone, and established ROC curves to evaluate their predictive efficacy. Among them, the predictive performance of bone metastasis model was the best, and had an AUC was as high as 0.818. This may be because bone metastasis patients has good homogeneity.

We also established a survival prediction nomogram to establish a prediction model for the survival of different types of patients. We used ROC curves to evaluate the predictive efficacy of the survival prediction model, and found that the 36-month prediction model performed the best, and had an AUC as high as 0.819 and 0.812 in train set and test set. Yu *et al.* also constructed a nomogram for young GC patients, and their 3-year OS AUC was 0.763 (8). Similarly, Zhang *et al.* constructed a nomogram for the survival rate of elderly GC patients after surgery (7), and their 3-year OS had a c-index of 0.765. Our c-index was 0.811. We drew a calibration curve to prove that its performance was very good, and that the prediction model has good clinical value. Survival prediction models could be used to effectively prevent excessive treatment, prevent the wastage of medical resources, and provide a scientific basis for medical staff and patients and their families to make medical decisions.

In our survival prediction model, the median OS time was 20 months, and the median OS time of patients with liver, lung, bone, and brain metastasis was 7, 5, 6, and 5 months, respectively. In our data, the 1-year survival rate of patients with liver metastasis was 29%. Some reports have indicated that the median survival time after diagnosis of liver metastasis is 4–34 months; however, if there are other distant metastases at the same time, the survival time is shorter (10,22,31,35). The median survival time of patients diagnosed with bone metastasis is approximately 4–7 months (10,36). In general, our findings did not differ greatly from the findings of other studies.

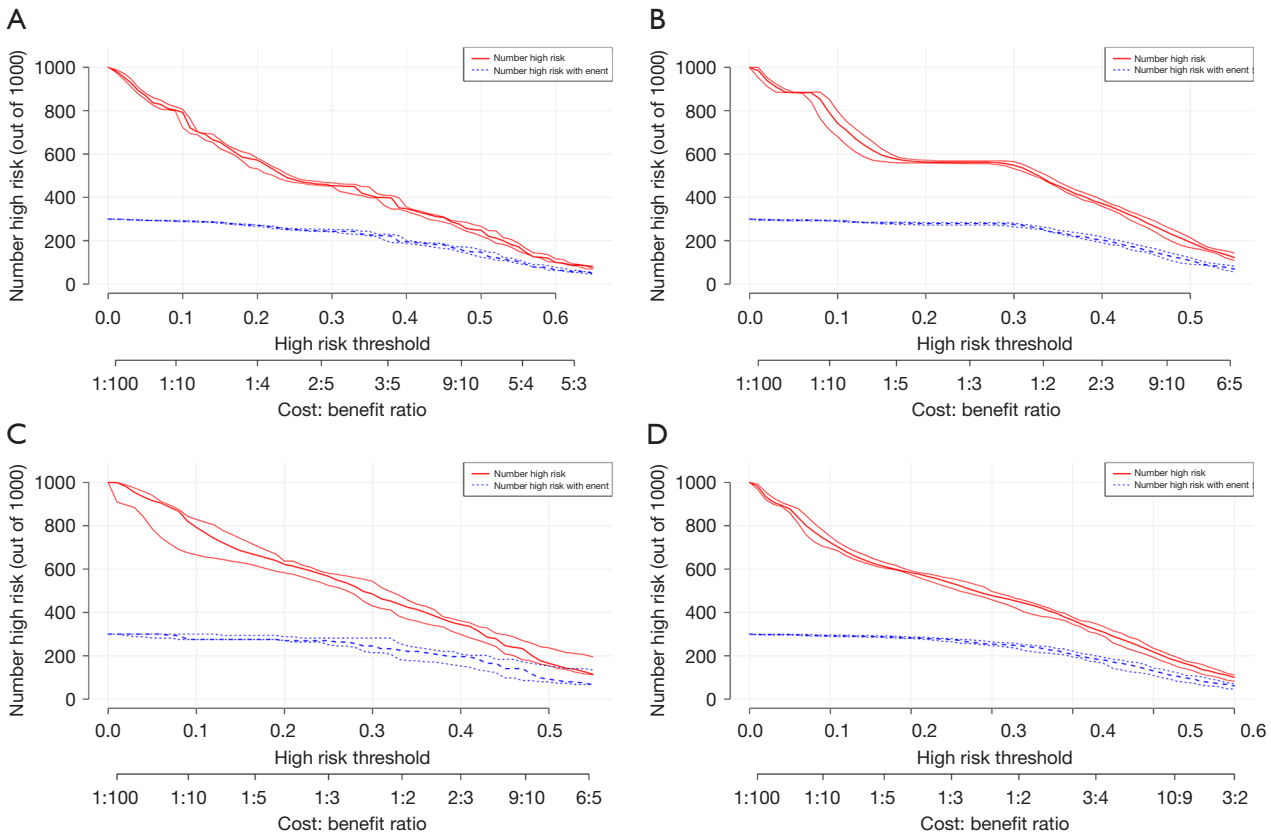


Figure 7 Clinical impact curve (CIC) for the distant metastasis prediction nomogram in patients with gastric cancer (GC). The red (number high risk) curve represents the number of people classified as positive (high risk) by the simple model at each threshold probability; the blue (number high risk with event) curve represents the number of people who are truly positive at each threshold probability. (A) CIC of the liver metastasis prediction nomogram. (B) CIC of the lung metastasis prediction nomogram. (C) CIC of the brain metastasis prediction nomogram. (D) CIC of the bone metastasis prediction nomogram.

According to previous studies, surgery is the only possible cure for GC (37). D2 lymphadenectomy with spleen and pancreas preservation may reduce the possibility of recurrence and distant metastasis after surgery, so that GC patients can obtain better survival benefits (38). Compared with chemotherapy alone, adding trastuzumab to the treatment of patients with HER2 receptor overexpression can improve overall survival and progression-free survival (37).

Many studies had shown that biomarkers play a key mechanism in angiogenesis and cancer metastasis (39). miR-375 partially inhibits the migration and invasion of GC cells by targeting JAK2 oncogene (40), and miR-10b activates RhoC-AKT signaling by targeting HOXD10 Conduction to promote the invasion of gastric cells (41). Targeted therapies for these potential molecular targets may have important implications for the distant metastasis of gastric cancer.

Our models have certain limitations, which we hope to resolve in our future work. First, we only selected the SEER database for GC patients from 2010–2015; thus, we had a small sample size, and we did not compare the data with data from other databases. Second, we only had information about the transfer of the liver, lung, bone and brain, and no information about other body parts. Third, the question of whether our models are reliable requires further verification by prospective cohort studies or case-control studies. Fourth, the data in this study came from American patients, and there are differences between Eastern and Western populations. Whether the model can be used for patients in other regions requires further research. In the future, we hope to conduct research on data in other regions to

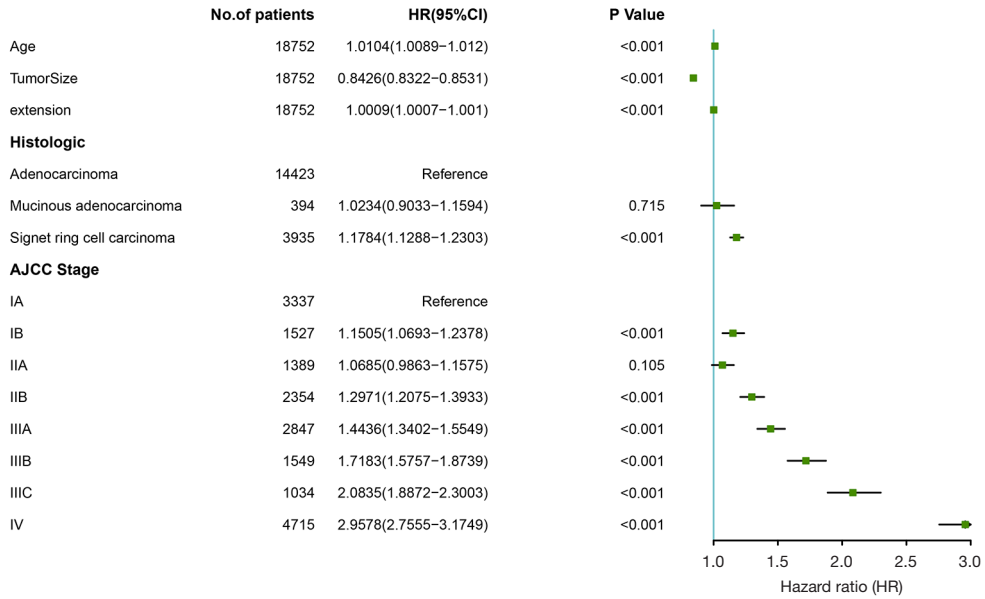


Figure 8 The forest plot of the survival prediction nomogram for gastric cancer (GC) patients, and the P value of each factor.

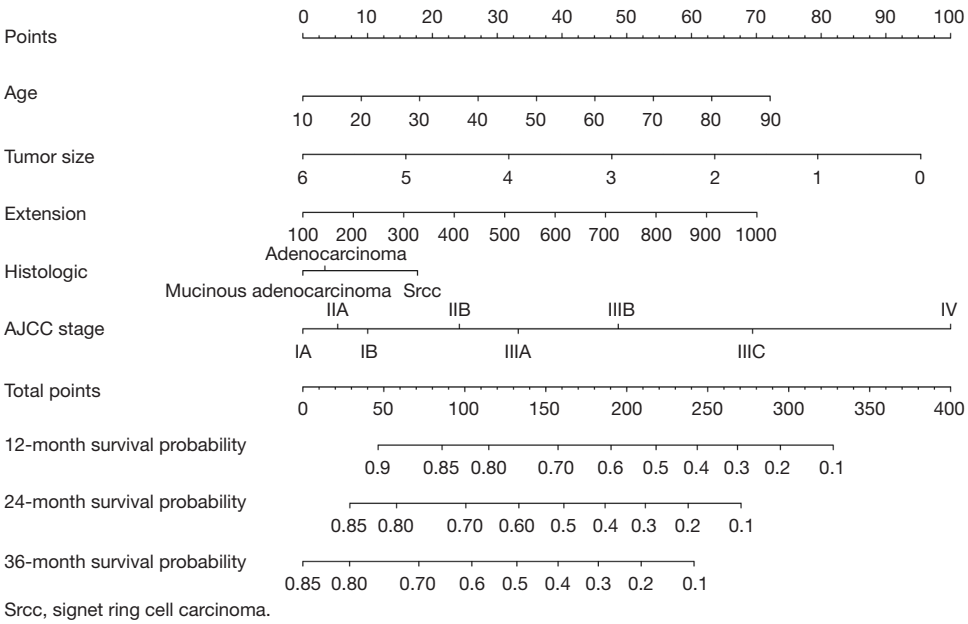


Figure 9 The survival prediction nomogram for gastric cancer (GC) patients at 12, 24, and 36 months.

further improve the models. In addition, the question of how to more scientifically screen for a lack of information is a problem that limited our accuracy when constructing the models for patients.

In general, we established a model for predicting distant metastasis and the survival of GC patients using a GC patient data set on the SEER database. The models were verified to have a good predictive performance and can provide some references for formulating treatment plans for patients with GC.

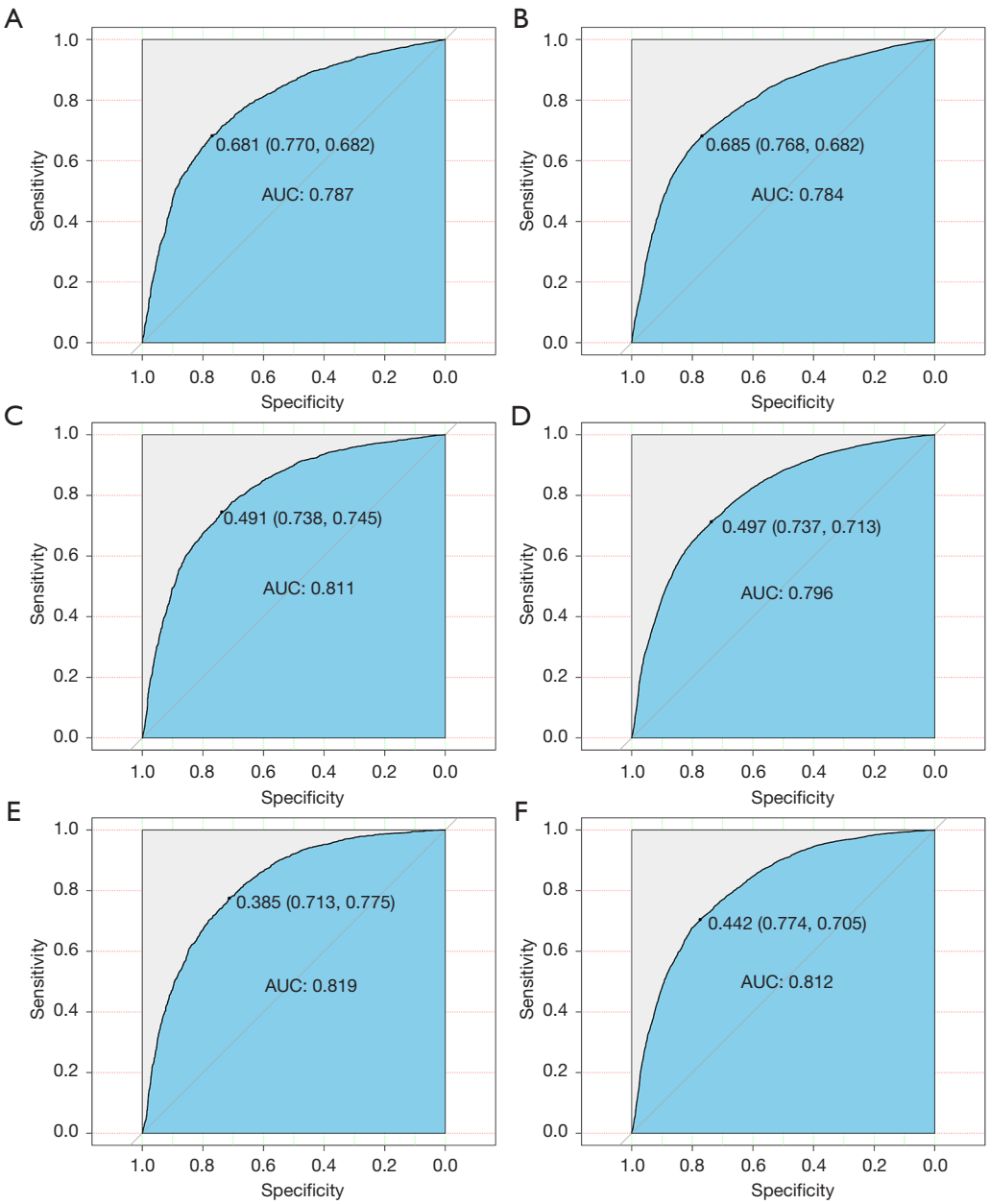


Figure 10 The ROC curves for the survival nomograms. (A) The ROC curve for the 12-month survival prediction nomogram in the training set. (B) The ROC curve for the 12-month survival prediction nomogram in the test set. (C) The ROC curve for the 24-month survival prediction nomogram in the training set. (D) The ROC curve for the 24-month survival prediction nomogram in the test set. (E) The ROC curve for the 36-month survival prediction nomogram in the training set. (F) The ROC curve for the 36-month survival prediction nomogram in the test set.

Conclusions

Establishing a prediction model for distant metastasis and the survival of GC patients is of great clinical significance. The prediction of distant metastasis could help clinicians to conduct individualized assessments of patients and formulate individualized examination measures. Survival prediction models could also help oncologists formulate good treatment strategies and provide hospice care.

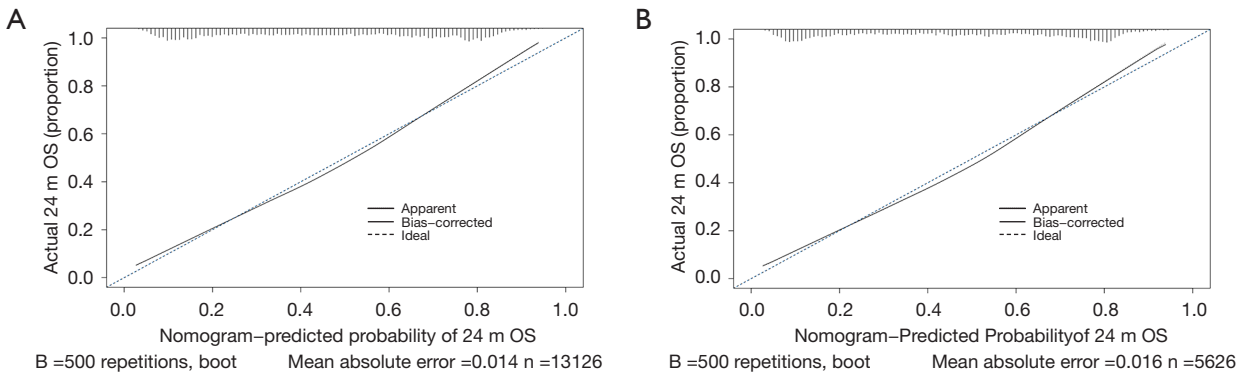


Figure 11 Calibration curve of the 24-month survival prediction nomogram. (A) Calibration curve of the 24-month survival prediction nomogram in the training set. (B) Calibration curve of the 24-month survival prediction nomogram in the test set.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-6295). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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