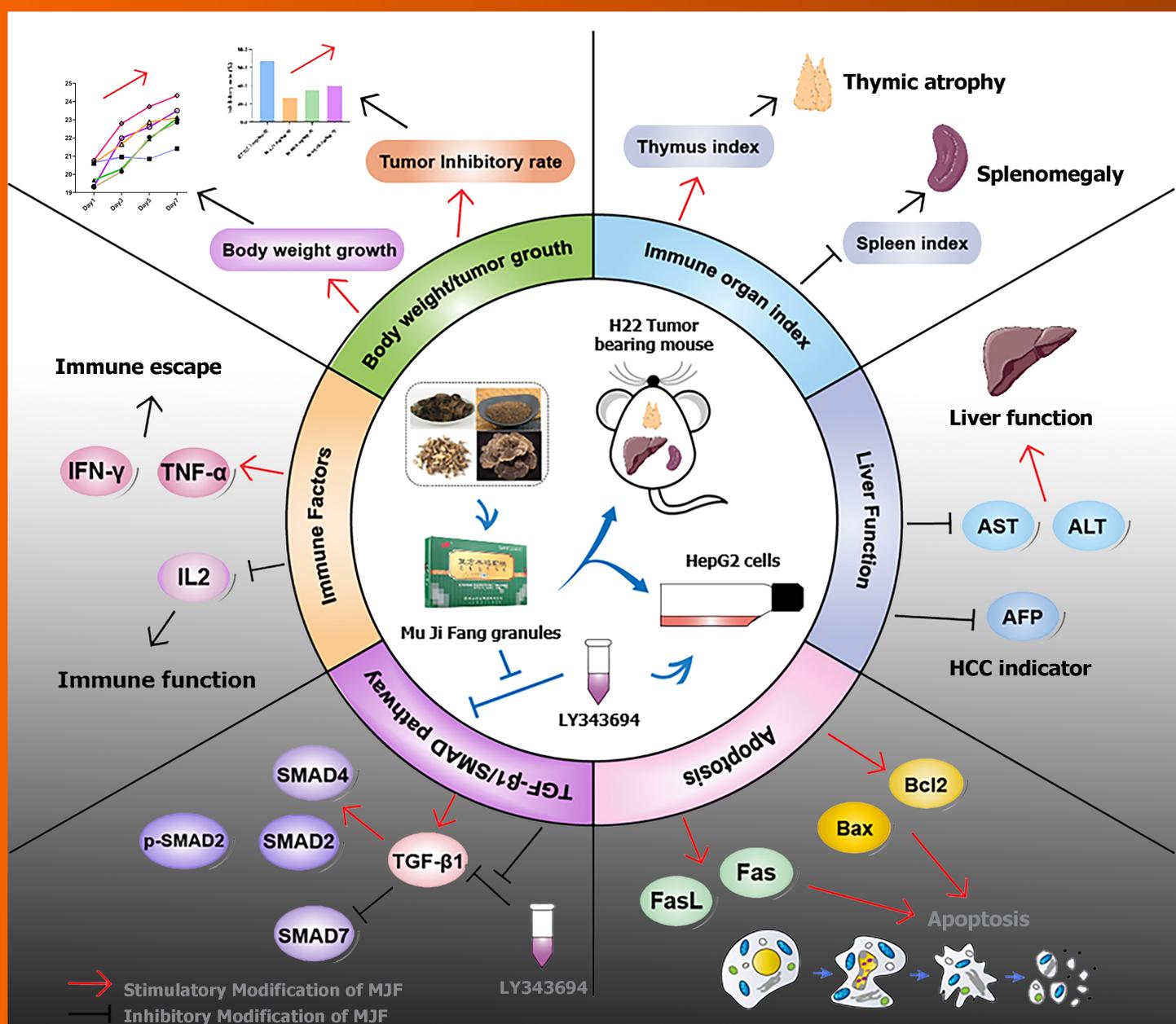


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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

INDEXING/ABSTRACTING

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Retrospective Study

Nomogram model predicting the overall survival for patients with primary gastric mucosa-associated lymphoid tissue lymphoma

Dan Wang, Xin-Lin Shi, Wei Xu, Rui-Hua Shi

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Abstract

BACKGROUND

Increasingly extranodal marginal B-cell lymphoma of mucosa-associated lymphoid tissue, known as mucosa-associated lymphoid tissue (MALT) lymphoma, is a type of non-Hodgkin's lymphoma. The prognosis of primary gastric MALT (GML) patients can be affected by many factors. Clinical risk factors, including age, type of therapy, sex, stage and family hematologic malignancy history, also have significant effects on the development of the disease. The available data are mainly focused on epidemiology; in contrast, few studies have investigated the prognostic variables for overall survival (OS) in patients with primary GML. Based on the realities above, we searched a large amount of data on patients diagnosed with primary GML in the Surveillance, Epidemiology and End Results (SEER) database. The aim was to develop and verify a survival nomogram model that can predict the overall survival prognosis of primary GML by combining prognostic and determinant variables.

AIM

To create an effective survival nomogram for patients with primary gastric GML.

METHODS

All data of patients with primary GML from 2004 to 2015 were collected from the SEER database. The primary endpoint was OS. Based on the LASSO and COX regression, we created and further verified the accuracy and effectiveness of the

survival nomogram model by the concordance index (C-index), calibration curve and time-dependent receiver operating characteristic (td-ROC) curves.

RESULTS

A total of 2604 patients diagnosed with primary GML were selected for this study. A total of 1823 and 781 people were randomly distributed into the training and testing sets at a ratio of 7:3. The median follow-up of all patients was 71 mo, and the 3- and 5-year OS rates were 87.2% and 79.8%, respectively. Age, sex, race, Ann Arbor stage and radiation were independent risk factors for OS of primary GML (all $P < 0.05$). The C-index values of the nomogram were 0.751 (95% CI: 0.729-0.773) and 0.718 (95% CI: 0.680-0.757) in the training and testing cohorts, respectively, showing the good discrimination ability of the nomogram model. Td-ROC curves and calibration plots also indicated satisfactory predictive power and good agreement of the model. Overall, the nomogram shows favorable performance in discriminating and predicting the OS of patients with primary GML.

CONCLUSION

A nomogram was developed and validated to have good survival predictive performance based on five clinical independent risk factors for OS for patients with primary GML. Nomograms are a low-cost and convenient clinical tool in assessing individualized prognosis and treatment for patients with primary GML.

Key Words: Primary gastric mucosa-associated lymphoid tissue lymphoma; Nomogram; Prognosis; Overall survival; SEER database

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Core Tip: Increasingly extranodal marginal B-cell lymphoma of mucosa-associated lymphoid tissue, known as mucosa-associated lymphoid tissue (MALT) lymphoma, is a type of non-Hodgkin's lymphoma. The prognosis of primary gastric MALT (GML) patients can be affected by many factors. The available data are mainly focused on epidemiology; in contrast, few studies have investigated the prognostic variables for overall survival (OS) in patients with primary GML. Based on the realities above, we searched a large amount of data on patients diagnosed with primary GML in the Surveillance, Epidemiology and End Results database. The aim was to develop and verify a survival nomogram model that can predict the OS prognosis of primary GML by combining prognostic and determinant variables. In this manuscript, our results demonstrated that Nomogram is developed and validated to have a good survival predictive performance, basing on five clinical independent risk factors of OS for primary GML patients. Nomogram will be a low cost and convenient clinical tool in assessing individualized prognosis and treatment for primary GML patients.

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INTRODUCTION

Increasingly extranodal marginal B-cell lymphoma of mucosa-associated lymphoid tissue, known as mucosa-associated lymphoid tissue (MALT) lymphoma, is a type of non-Hodgkin's lymphoma[1,2]. Approximately one-third of cases of MALT lymphoma and 85% of gastrointestinal MALT lymphomas present in the stomach as the affected site[3,4]. Primary gastric MALT lymphoma (GML) has a rare incidence and only accounts for approximately 5% of all primary gastric neoplasms[5].

This disease demands high attention. Researchers have observed that GML patients had significant risk of atrophic gastritis, intestinal metaplasia[6,7] and secondary tumors[8]. Compared to the healthy population, the incidence of gastric adenocarcinoma in GML patients was 6 times higher in the GML population[9,10].

The prognosis of primary GML patients can be affected by many factors. Clinical risk factors, including age, type of therapy, sex, stage and family hematologic malignancy history, also have significant effects on the development of the disease[11-14]. Meanwhile, previous studies demonstrated a good prognosis of the disease, with 5-year survival rates of up to 99%. However, more than 95% of studies were only based on stage I/II patients with a small sample size, and few of them even used

different staging standards[15-19]. Matysiak-Budnik *et al*[11] conducted a multicenter study in France, and 416 GML patients were retrospectively enrolled. They surprisingly found that 25% of subjects diagnosed at stage III/IV and 11% of patients obtained missed or false diagnoses, which was similar to other studies[20-22].

Furthermore, the available data are mainly focused on epidemiology; in contrast, few studies have investigated the prognostic variables for overall survival (OS) in patients with primary GML. Based on the realities above, we searched a large amount of data on patients diagnosed with primary GML in the Surveillance, Epidemiology and End Results (SEER) database. The aim was to develop and verify a survival nomogram model that can predict the OS prognosis of primary GML by combining prognostic and determinant variables.

MATERIALS AND METHODS

Patient selection and data extraction from the SEER database

The data for our study were extracted from the SEER database (username: 12262-November 2019, software version: SEER * Stat 8.3.6). Due to the openness of the database, our research was exempted from the need for approval by the Ethics Committee of Zhongda Hospital, the Affiliated Hospital of Southeast University.

All patients diagnosed with primary GML from 2004 to 2015 were ultimately included in this study. Subjects meeting the following conditions were excluded: (1) Hospitalized death and autopsy source patients; (2) patients with tumor history; (3) patients who were not followed up or who were lost follow-up; (4) age at diagnosis < 20; (5) unknown data (race, stage, and cause of death); and (6) survival months < 1.

A total of 2604 selected GML patients were randomly assigned to the training and validation sets with a ratio of 7:3. There were 1823 and 781 people in the two groups, respectively.

The clinical covariates included sex, age, race, primary site, Ann Arbor stage, surgery, chemotherapy, and radiation. Data on the survival month and vital status of patients were also analyzed. The primary endpoint was OS.

Establishment and verification of the survival nomogram

In the training set, the least absolute shrinkage and selection operator (LASSO) and multivariate Cox proportional hazard regression were combined to identify the significantly correlated prognostic factors that influenced OS. The nomogram model was established based on the above results. Meanwhile, primary GML patients were divided into low- and high-risk groups at the cutoff point of the risk score. Scatter plots, forest plots and Kaplan-Meier curves were generated to visually compare the OS times of patients in the two different risk groups.

Internal validation was performed on the patients in the validation set. The discriminatory performance of the model was measured by the concordance index (C-index) value[23]. We also adopted time-dependent receiver operating characteristic (td-ROC) curves to assess the 3- and 5-year OS predictive power of the nomogram. Additionally, calibration plots were applied to compare the agreement between actual and predicted probability.

Data analysis

Statistical analysis was performed by IBM SPSS version 22.0 (Chicago, IL, United States) and R version 4.0.2. Continuous variables were grouped and transformed into categorical variables and are expressed as frequency and percentage values, *n* (%). The chi-square test was used to compare categorical variables between groups. Two-sided *P* values < 0.05 were considered statistically significant.

RESULTS

Clinical characteristics of subjects

The specific clinical and pathological characteristics of all enrolled patients and the training and testing groups are presented in [Table 1](#).

Initially, 4475 GML patients were searched in the SEER database. The following populations were excluded: One primary tumor = NO (*n* = 1408), age < 20 (*n* = 9), unknown race (*n* = 74), unknown stage (*n* = 317), unknown COD (*n* = 16), and survival month < 1 (*n* = 47). In total, 2604 primary GML patients were included in our study. The median survival time was 71 mo.

All patients (median age: 65 years old) were divided into three subgroups (age < 45, 45-65, and > 65; [Table 1](#)). Compared to patients < 45 years old (8.98%), the 45-65 years (39.94%) group had a higher proportion (*P* = 0.001, HR 4.29, 95%CI: 1.881-9.815). The proportion of patients > 65 years old was 51.08%. In total, 1250 (48.00%) were male, and 2059 (79.07%) were white. In addition, primary GML could be located in all parts of the stomach and was mostly diagnosed at stage I (2088/80.18%)

Table 1 Clinical pathology characteristics of patients with primary gastric mucosa-associated lymphoid tissue in all subjects, the training and validation sets, *n* (%)

Variable	All cohort	Training cohort	Validation cohort	<i>P</i> value ^a
Total	2604	1823	781	
Age				0.423
<45	234(8.98)	168 (71.79)	66(28.21)	
45-65	1040(39.94)	739 (71.06)	301(28.94)	
≥65	1330(51.08)	916 (68.87)	414(31.13)	
Sex				0.262
Male	1250(48.00)	862 (68.96)	388(31.04)	
Female	1354(52.00)	961 (70.97)	393(29.03)	
Race				0.699
White	2059(79.07)	1434 (69.65)	625(30.35)	
Black	284(10.91)	201 (70.77)	83 (29.23)	
Other	261(10.02)	188 (72.03)	73 (27.97)	
Location				0.734
Upper third	314(12.06)	212 (67.52)	102(32.48)	
Middle third	642(24.65)	455 (70.87)	187(29.13)	
Low third	425(16.32)	291 (68.47)	134(31.53)	
Stomach, NOS	1020(39.17)	723 (70.88)	297(29.12)	
Overlapping lesion of stomach	203(7.80)	142 (69.95)	61 (30.05)	0.516
Stage (Ann Arbor)		1452 (69.54)	636(30.46)	
I	2088(80.18)	187 (73.91)	66 (26.09)	
II	253(9.71)	47 (72.31)	18 (27.69)	
III	65(2.50)	137 (69.19)	61 (30.81)	
IV	198(7.60)			0.332
Surgery		1700 (70.25)	720(29.75)	
No/unknown	2420(92.93)	123 (66.85)	61 (33.15)	
Yes	184(7.07)			0.82
Chemotherapy		1440 (69.90)	620(30.10)	
No/unknown	2060(79.11)	383 (70.40)	161(29.60)	
Yes	544(20.89)			0.36
Radiation		1231 (70.58)	513(29.42)	
No/unknown	1744(66.97)	592 (68.84)	268(31.16)	
Yes	860(33.03)			

^a χ^2 test.Categorical variables were represented by *n*(%).The *P* value result is the comparison result between the training and validation groups.

according to the Ann Arbor staging system[24]. The numbers of patients who received surgery, chemotherapy and radiation were 184 (7.07%), 544 (20.89%) and 860 (33.03%), respectively. The 3- and 5-year OS rates of primary GML were 87.2% and 79.8%, respectively.

To establish the nomogram model, 1823 subjects were randomly assigned to the training cohort, while 781 were assigned to the validation cohort. No significant difference in variables was observed between the two groups (all *P* > 0.05).

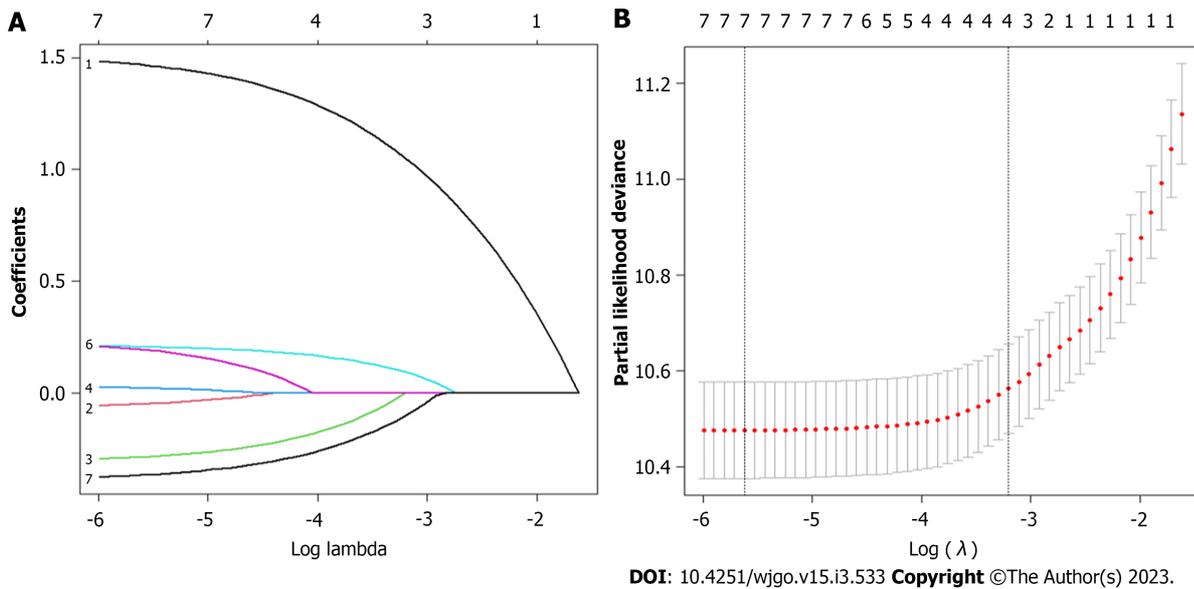


Figure 1 Identify the correlated prognostic factors by least absolute shrinkage and selection operator regression. A: Least absolute shrinkage and selection operator coefficient profiles of the 8 primary gastric mucosa-associated lymphoid tissue lymphoma-associated variables; B: The selection of optimal prognostic factors by cross-validation. GML: Gastric mucosa-associated lymphoid tissue lymphoma.

Multivariate risk factor analysis and establishment of the nomogram. In the training set, the LASSO Cox regression model was adopted to filter risk factors for OS. The results revealed that 5 out of 8 factors were significantly associated with 3- and 5-year OS, and the specific information is listed in [Figure 1](#) and [Table 2](#). Increased age, male sex, black race and higher disease stage were inversely correlated with survival, while radiation treatment showed a positive correlation with survival (all $P < 0.05$). Based on the five variables above, we established an efficient survival nomogram to precisely calculate the probability of 3- and 5-year OS in primary GML patients ([Figure 2](#)). In the nomogram, the C-index value was 0.751 (95% CI: 0.729-0.773) and demonstrated satisfactory discrimination ability. Patients were separated into high- and low-risk groups according to the median risk score (cutoff: 0.28; [Figure 3A](#)). A scatter plot ([Figure 3B](#)) visually showed a shorter survival time and a higher mortality rate of high-risk patients. The Kaplan-Meier curve ([Figure 4A](#) and [B](#)) clearly revealed that, compared to the high-risk population, more low-risk patients had a better OS (all $P < 0.0001$, HR 0.190, 95% CI: 0.153-0.236), which is consistent with the results shown in [Figure 5](#) (all HR > 2). Td-ROC curves also showed good predictive power of the nomogram assessing the 3- and 5-year OS. The areas under the curve (AUCs) were 0.727 ([Figure 6A](#)) and 0.734 ([Figure 6B](#)), respectively. Moreover, another analysis, the calibration curves of the model, shown in [Figure 7A](#) and [B](#), confirmed a high agreement between actual and predictive survival proportions. All the above results indicate the good discrimination and predictive capacities of the model.

Internal validation in the validation set

To better validate the nomogram model, we carried out the relevant analysis in the validation set. The C-index of validation patients was 0.718 (95% CI: 0.680-0.757), indicating good predictive accuracy of the nomogram model. There were significant survival differences between the low- and high-risk groups on Kaplan-Meier curves (HR 0.233, 95% CI: 0.174-0.312, $P < 0.0001$; [Figure 4C](#)). As shown in [Figure 6C](#) and [D](#), the AUC values of the 3- and 5-year OS td-ROC curves were 0.689 and 0.715, respectively, which were similar to the results in the training set, further confirming the reliable predictive ability of the model. The same phenomenon was also observed between the calibration plots in the training and validation groups ([Figure 7C](#) and [D](#)). In conclusion, the survival nomogram model displayed a favorable performance to discriminate and predict the OS of primary GML patients in 2 sets.

DISCUSSION

Primary GML is confirmed as a low-grade, rare incidence rate lesion, and the main risk for the disease is a histological transformation to diffuse large B-cell lymphoma[19,25]. Studies mostly focus on epidemiology[26,27] and the prognosis affected by different treatment methods of the disease[14,22,28,29]. Few large studies have reported the relationship between clinical variables and prognostic survival in primary GML. Until now, no available survival model has been established for predicting the prognosis of patients with primary GML. Our study successfully constructed and validated an effective

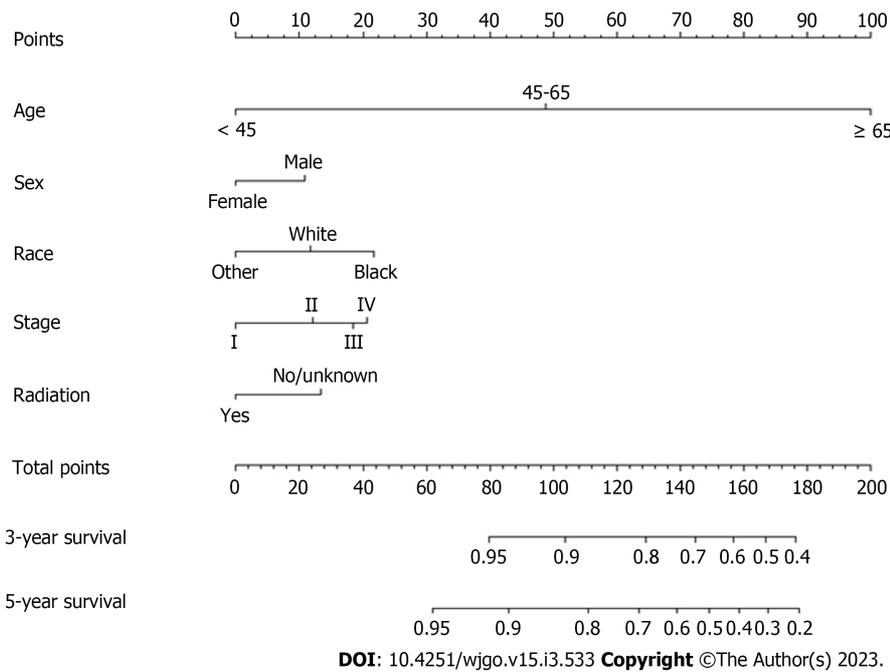


Figure 2 Survival nomogram for primary gastric mucosa-associated lymphoid tissue lymphoma in 3- and 5-year overall survival.

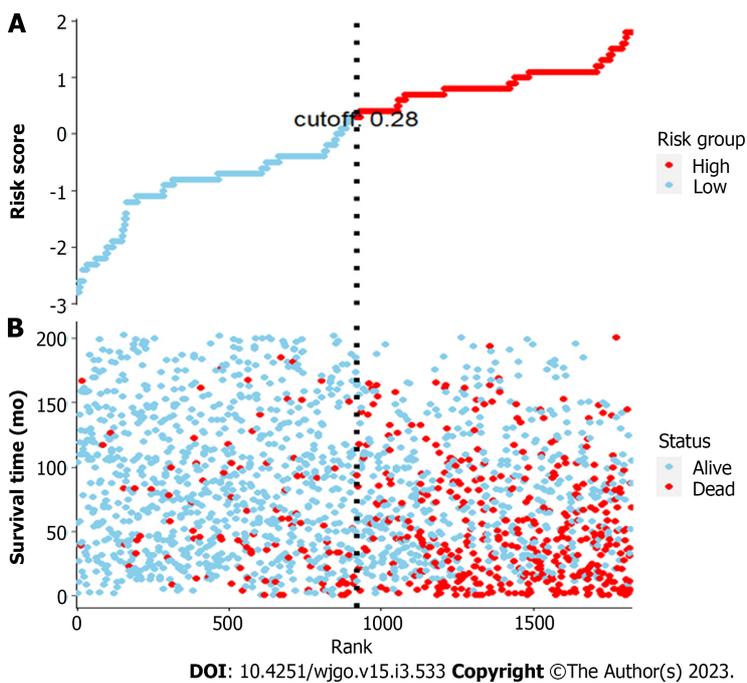


Figure 3 Patients in the training set were separated into high- and low-risk groups. A: The Cox regression risk score (cutoff point: 0.28); B: Scatter plot showing that patient survival time was sorted by risk score; high-risk patients had shorter survival times and higher mortality rates.

nomogram model to predict the overall survival of the disease based on clinical and pathological risk factor analysis. We demonstrated that age, gender, race, Ann Arbor stage and radiation therapy (RT) were independent risk factors for OS of primary GML. The nomogram was proven to have good predictive ability for disease prognosis.

Considering the indolent natural development of the disease, long-term and very large follow-up clinical datasets are needed. In our study, all of the data were obtained from the SEER database. This is a national cancer database gathering a large amount of data from different hospitals in the United States, and patient information is strictly managed and reliable[30]. Meanwhile, we developed and validated a survival nomogram. In recent years, nomograms have been widely used as an effective tool for cancer prognosis[31-33]. Tailored to the specific information of every patient, the nomogram can visually

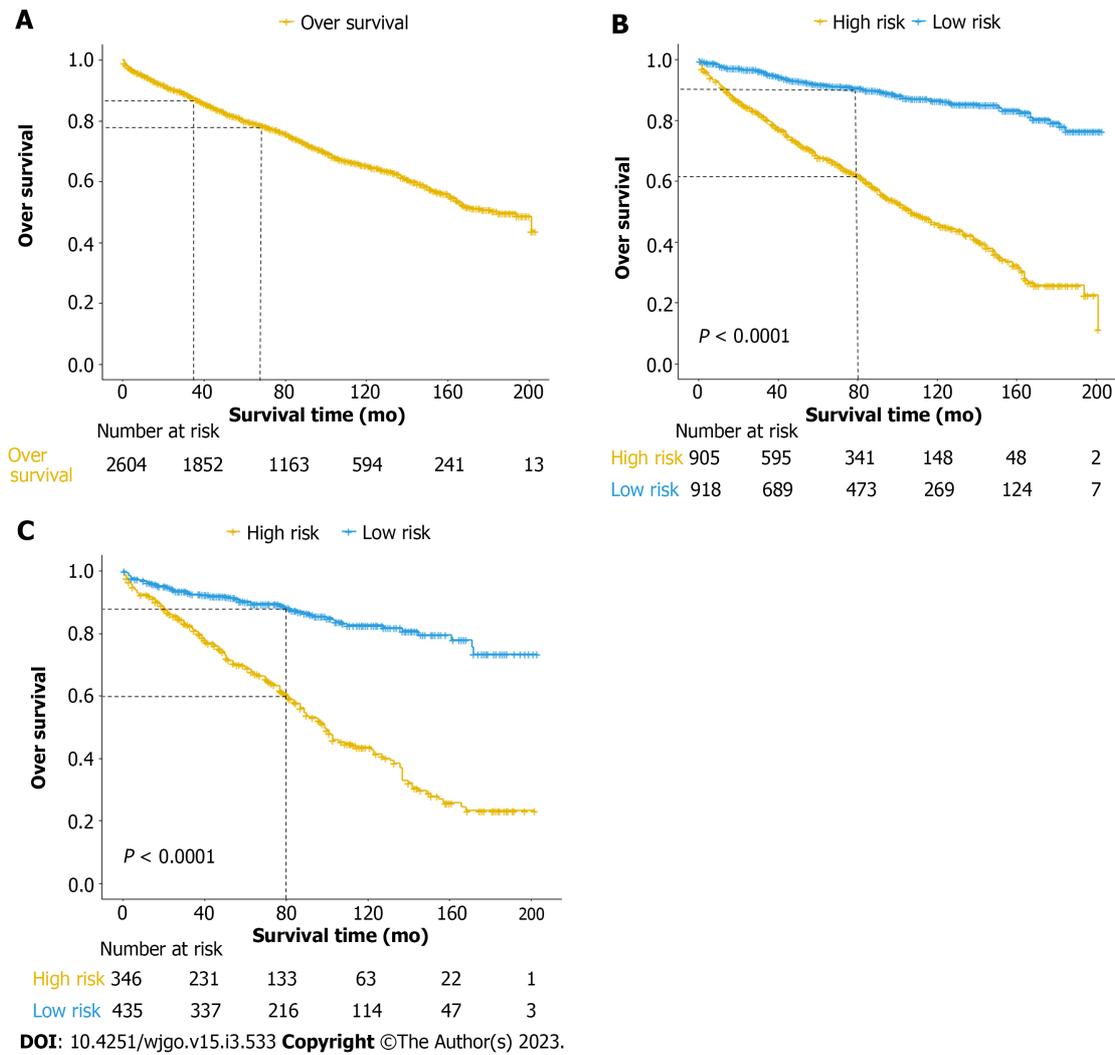


Figure 4 Kaplan–Meier curves of overall survival for patients in the high- and low-risk groups. A-C: Analysis results of all patients (A), the training set (B), and the testing set (C). OS: Overall survival.

analyze and present the disease event (such as OS) with a single numerical probability[34]. In summary, on the basis of high-quality data and validation analysis methods, our model has good clinical prediction ability and can be applied to clinical work.

The 3- and 5-year OS rates calculated in our study were 87.2% and 79.8%, respectively. In 2019, the first national study was conducted on the general population in France. They confirmed that the 5-year OS of all populations was 79% (95%CI: 75-83)[11]. This rate is similar to published studies and may reflect a better prognostic outcome of GML disease than other gastric malignancies.

In 2017, Thieblemont *et al*[35] generated a novel MALT lymphoma prognostic index (MALT-IPI), including age ≥ 70 years, elevated LDH levels and Ann Arbor stage III or IV. They concluded that this index would be an effective method to predict poor outcome for MALT lymphoma. A similar conclusion was found in other studies[11,14,19,29]. Matysiak-Budnik *et al*[11] conducted a multiple retrospective study in French, including 416 cases of GML. They found that 5-year OS was better for patients < 67 years old (93.6%) than for those with an older age (93.6% vs 68.5%, $P < 0.0001$). Another multicenter cohort follow-up study of 420 patients found that age (each incremental year) was an independent prognostic factor for OS ($P = 0.024$)[14]. In our study, age had the highest risk and showed a significant correlation with the prognosis of primary GML ($P < 0.0001$, HR 19.843). The nomogram obviously indicated that increased age, especially > 65 years old, had a negative impact on the OS of the disease. Although several researchers found no association between them[20,29], an insufficient number of subjects in these studies need to be considered. Therefore, we still insist that age and prognosis are closely related. Regardless of the specific cutoff point of age, it is recognized that advanced age means an increased risk of primary GML[13]. Multiple analyses also indicated that Ann Arbor stage was a significant independent prognostic factor for the disease. In our study, most patients presented with stage I-II disease (89.9%), and as the severity of the disease increased, the prognosis of the disease worsened (all $P < 0.05$). The proportion of patients with localized and advanced disease at diagnosis varies among reported series[11,14,36], and we have a consensus that the prognosis of these patients is

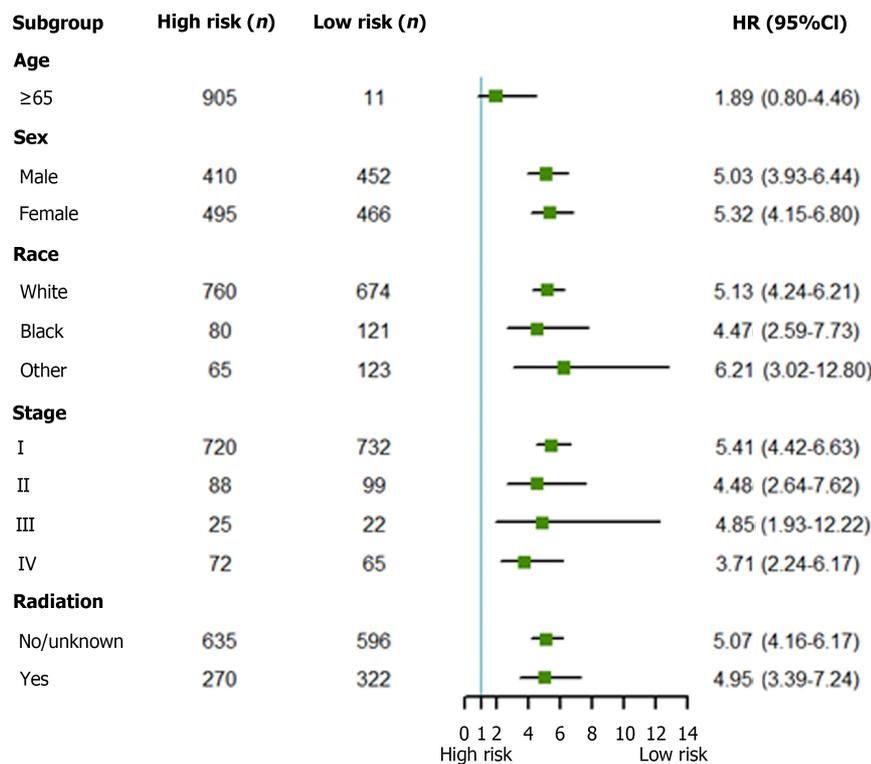


Figure 5 Subgroup analysis results of associations between independent factors and overall survival time between high- and low-risk patients in the training set. 95%CI: 95% confidence interval; HR: Hazard ratio.

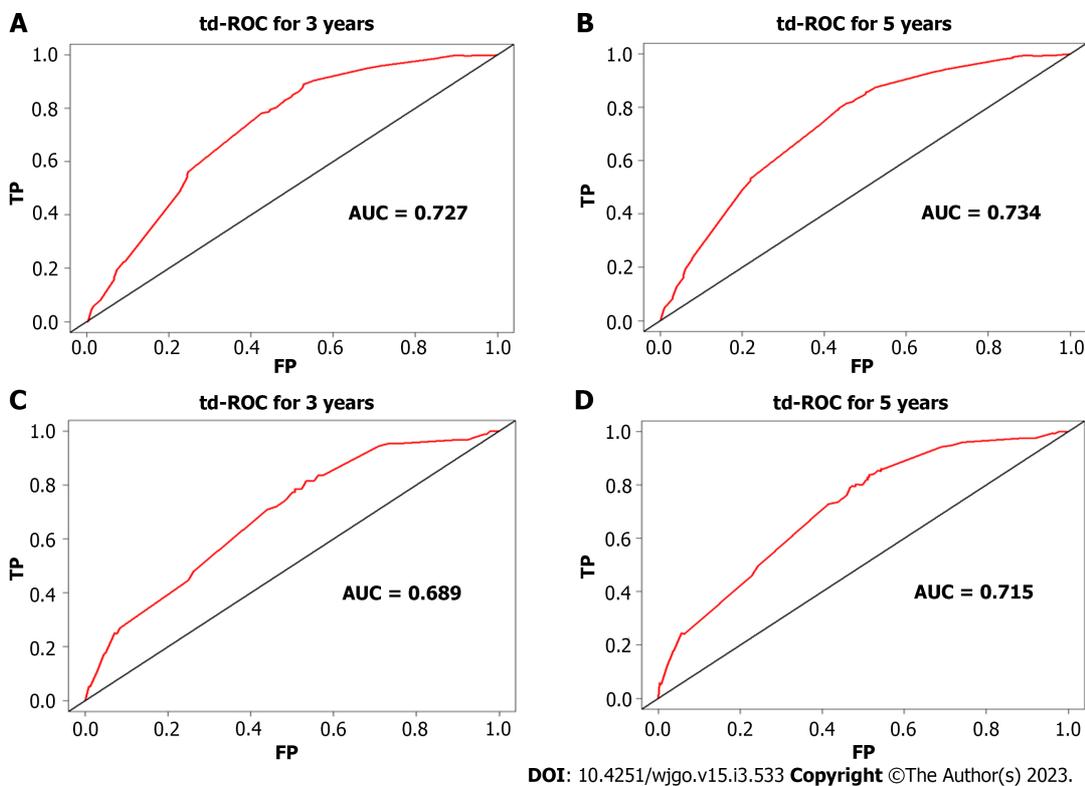
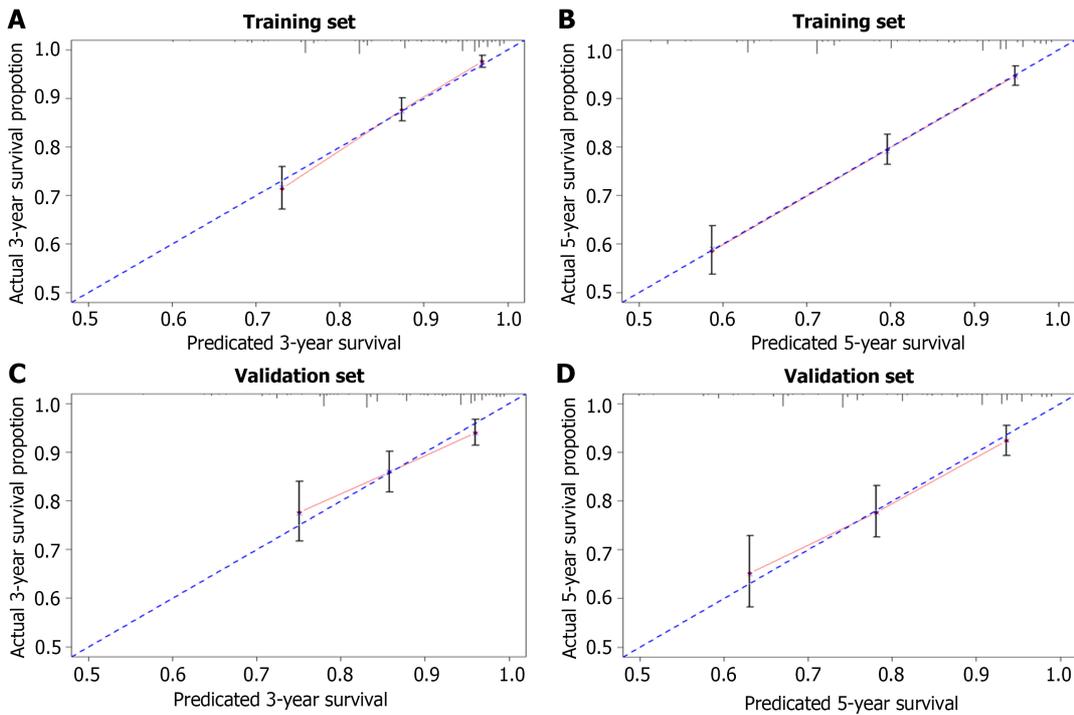


Figure 6 Time-dependent receiver operating characteristic curves to assess the predictive power of the nomogram. A-D: Curves of 3- and 5-year overall survival in the training set (A and B) and in the validation set (C and D). td-ROC: Time-dependent receiver operating characteristic; OS: Overall survival; AUC: Areas under the curve.



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Figure 7 The calibration plot. A-D: The calibration plot was applied to compare the agreement between actual and predicted probability of 3, 5 years overall survival in training (A and B) and testing set (C and D), respectively. OS: Overall survival.

different[13].

The percentage of female patients was higher than that of male patients (52.0% *vs* 48.0%), and more people were white (79.07%). Statistically significant correlations were found between male sex ($P < 0.001$), black race ($P = 0.036$) and primary GML overall survival. Whether sex is related to the disease remains controversial. Some studies have reported that males have a 2-3 times higher incidence rate of development and a worse prognosis than females[37,38], while other studies have not[11,35]. Until now, no study has focused on the relationship between race and primary GML. SEER provided us with detailed race data and indicated that black individuals are more likely to develop primary GML (HR: 1.374, 95%CI: 1.020-1.779). We still need more studies to further investigate prognostic factors in primary GML.

Management and treatment guidelines for MALT lymphomas have been extremely heterogeneous until the last few years. Over the past 2-3 decades, eradication of *Helicobacter pylori* (*H. pylori*) has been the preferred choice for GML regardless of the histological status of *H. pylori*[21,39]. Chemotherapy and RT were only suggested to be second-line therapies for nonresponders or advanced patients[39]. In contrast, ESMO guidelines suggested that RT might be the first option for GML patients with localized stages, and chemotherapy was an effective method in patients with all stages[40]. RT alone was also reported to have excellent treatment effects on GML with a total dose of 24-30 Gy[29,41]. Compared with other therapy methods, surgery showed no advantage over treatments in other trials[42]. In our study, no survival difference was found between patients with medication and surgical treatment. Multivariate analysis showed that only RT was significantly associated with better disease prognosis ($P < 0.001$). These data are consistent with previous studies of RT for gastric MALT lymphoma. In total, radiotherapy is a good choice for primary GML disease.

The limitations of this study are very obvious. First, this is a retrospective analysis. All information is from 2004-2015, and part of the data was recorded before the publication of guidelines for primary GML. This may cause heterogeneity in the clinical management of patients, resulting in data bias. Second, SEER cannot provide us with specific details of helicobacter pylori treatment and this is very important for primary GML. Some data even show unknown labels. Third, we have no external verification data. We collected a few cases of primary GML, but they are not worth analyzing considering analysis errors. More multiple, prospective datasets of primary GML are still necessary for further investigation.

CONCLUSION

In conclusion, a nomogram was developed and validated to have good survival predictive performance based on five clinical independent risk factors for OS for primary GML patients. Nomograms are a low-cost and convenient clinical tool in assessing individualized prognosis and treatment for patients with primary GML.

Table 2 Multivariate analysis of overall survival for patients with primary gastric mucosa-associated lymphoid based on least absolute shrinkage and selection operator regression in the training set ($n = 1823$)

Variable	Multivariate		Analysis
	HR	95%CI of HR	P value
Age			
< 45	Reference		
45-65	4.290	1.881-9.815	0.001 ^b
≥ 65	19.843	8.843-44.528	< 0.001 ^c
Sex			
Male			
Female	0.722	0.606-0.860	< 0.001 ^c
Race			
White	Reference		
Black	1.374	1.020-1.779	0.036 ^a
Other	0.704	0.493-1.003	0.052
Stage (Ann Arbor)			
I	Reference	1.084-1.904	0.012 ^a
II	1.732	1.076-2.786	0.024 ^a
III	1.844	1.401-2.428	< 0.001 ^c
IV			
Radiation	Reference		
No/unknown			
Yes	0.670	0.542-0.829	

^a $P < 0.05$.

^b $P < 0.01$.

^c $P < 0.001$.

OS: Overall survival; HR: Hazard ratio; CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background

Extranodal marginal B-cell lymphoma of mucosa-associated lymphoid tissue, known as MALT lymphoma, is a type of non-Hodgkin's lymphoma. The prognosis of primary gastric MALT (GML) patients can be affected by many factors. Few studies have investigated the prognostic variables for overall survival (OS) in patients with primary GML. We searched a large amount of data on patients diagnosed with primary GML in the Surveillance, Epidemiology and End Results (SEER) database.

Research motivation

In this study, we investigated the significant risk factors of primary GML and build an effective survival nomogram model for primary GML patients.

Research objectives

To develop and verify a survival nomogram model that can predict the OS prognosis of primary GML by combining prognostic and determinant variables.

Research methods

All data of patients with primary GML were collected from the SEER database. Based on the LASSO and COX regression, we created and further verified the accuracy and effectiveness of the survival nomogram model by the concordance index (C-index), calibration curve and time-dependent receiver operating characteristic (td-ROC) curves.

Research results

A total of 2604 patients diagnosed with primary GML were selected for this study. A total of 1823 and 781 people were randomly distributed into the training and testing sets at a ratio of 7:3. The median follow-up of all patients was 71 mo, and the 3- and 5-year OS rates were 87.2% and 79.8%, respectively. Age, sex, race, Ann Arbor stage and radiation were independent risk factors for OS of primary GML (all $P < 0.05$). The C-index values of the nomogram were 0.751 (95%CI: 0.729-0.773) and 0.718 (95%CI: 0.680-0.757) in the training and testing cohorts, respectively, showing the good discrimination ability of the nomogram model. Td-ROC curves and calibration plots also indicated satisfactory predictive power and good agreement of the model. Overall, the nomogram shows favorable performance in discriminating and predicting the OS of patients with primary GML.

Research conclusions

A nomogram was developed and validated to have good survival predictive performance based on five clinical independent risk factors for OS for primary GML patients.

Research perspectives

Nomograms are a low-cost and convenient clinical tool in assessing individualized prognosis and treatment for patients with primary GML.

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FOOTNOTES

Author contributions: Shi RH contributed to conceptualization and supervision; Wang D contributed to conceptualization, data curation, formal analysis, and writing-original draft preparation; Shi XL contributed to data curation and formal analysis; Xu W contributed to supervision and editing; all authors approved the manuscript.

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