Establishment and validation of an individualized nomogram for survival prediction of primary mediastinal germ cell tumors based on the SEER database

Longzhou Qi[1#^], Jiajun Han[1#], Yifan Shi[1], Ruizhi Wu[1], Bin Li[1], Weiqiang Shi[2], Shaomu Chen[1]

[1]Department of Thoracic Surgery, The First Affiliated Hospital of Soochow University, Suzhou, China; [2]Department of Pathology, The First Affiliated Hospital of Soochow University, Suzhou, China

Contributions: (I) Conception and design: L Qi; (II) Administrative support: S Chen, W Shi; (III) Provision of study materials or patients: R Wu, B Li; (IV) Collection and assembly of data: L Qi; (V) Data analysis and interpretation: L Qi, Y Shi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Weiqiang Shi. Department of Pathology, The First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou 215006, China. Email: twoliner@163.com; Shaomu Chen. Department of Thoracic Surgery, The First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou 215006, China. Email: michaelchensm@163.com.

Background: Primary mediastinal germ cell tumors (PMGCT) represent a rare but sometimes highly aggressive type of mediastinal tumors. The current prognostic models for PMGCT are insufficient. This study was undertaken to establish and validate an individualized nomogram for predicting the overall survival (OS) of patients with PMGCT.

Methods: We conducted a retrospective analysis of patients with PMGCT diagnosed between 2000 and 2018 in the Surveillance, Epidemiology, and End Results (SEER) database in the United States. Clinical variables included surgery subtype, gender, treatment regimens, age, histology, tumor size, stage, chemotherapy, radiation, race, and survival-related information. The main outcome measure was survival duration. The Kaplan-Meier method along with the log-rank test were utilized to estimate the OS. Independent prognostic factors were identified by performing the univariate and multivariate Cox proportional hazards regression analyses, from which an individualized nomogram was constructed to predict 3-, 5-, and 10-year OS of patients with PMGCT. The concordance index (C-index) and calibration curve were used to verify the discrimination and accuracy of the nomogram.

Results: A total of 845 patients with PMGCT were recruited from the SEER database and further randomly assigned to a training set (n=635) and a validation set (n=210) at a ratio of 7:3. The 3-, 5-, and 10-year OS for overall PMGCT was 70.0%, 67.1%, and 63.9%, respectively. Cox regression analysis indicated that age, tumor size, stage, chemotherapy, radiation, histology, and surgery type were as independent factors for OS in patients with PMGCT ($P<0.05$). An individualized nomogram for OS was constructed utilizing these variables, with the C-index of 0.714 [95% confidence interval (CI): 0.695 to 0.743] and 0.756 (95% CI: 0.735 to 0.787) in the training and validation groups. Moreover, good levels of agreement were observed according to the calibration curve between the predicted and actual 3-, 5-, and 10-year survival rates both in the training and validated cohorts, showing that the model could accurately predict patient prognosis.

Conclusions: This study documented the first attempt at establishing and validating a novel nomogram for predicting the 3-, 5-, and 10-year OS probabilities of PMGCT. The prognostic nomogram was demonstrated to have good performance for predicting individualized OS of patients with PMGCT.

^ ORCID: 0000-0001-7367-9024.

Keywords: Nomogram; primary mediastinal germ cell tumors (PMGCT); prognostic factor; SEER database; primary mediastinal non-seminomatous germ cell tumors (PMNGCT)

Submitted Aug 02, 2022. Accepted for publication Sep 06, 2022.
doi: 10.21037/atm-22-4181
View this article at: https://dx.doi.org/10.21037/atm-22-4181

Introduction

Germ cell tumors (GCTs) are a set of tumors that primarily arise from the gonads in adolescent and young boys. Extragonadal GCTs arise from the remnants of germ cells in extragonadal areas during embryologic development, such as the retroperitoneum and mediastinum (1,2). They are an uncommon group of tumors that account for just 2–5% of all GCTs. An increment of the short arm of chromosome (i12p) (3), which frequently results in the creation of an isochromosome, is a famous hallmark of malignant GCTs, both gonadal and extragonadal, and seminoma and non-seminoma. The primary mediastinal germ cell tumors (PMGCT) made up of non-seminomas and seminomas comprise 15% of adult mediastinal carcinomas (4). Primary mediastinal non-seminomatous germ cell tumor (PMNGCT) is considered a more malignant type whose major subtypes are choriocarcinoma, embryonal carcinoma, mixed GCT, teratoma, and yolk sac tumor (5). Like other mediastinal tumors, PMGCT has atypical clinical symptoms and no specificity, leaving it susceptible to misdiagnosis and mistreatment. The clinical features of primary mediastinal seminomas (PMS) and PMNGCT are slightly different. The clinical symptoms of PMS are usually related to tumor size and the compression or invasion of adjacent tissues, such as chest pain, dyspnea, cough, and loss of weight. Liver metastasis, brain metastasis, bone metastasis, PMNGCT, and elevation in logarithmic beta-human chorionic gonadotrophin (β-hCG) and alpha fetal protein (AFP) are associated with worse prognosis of PMGCT. GCTs are classified by the International Germ Cell Consensus Classification Group (IGCCCG), which was established in 1997, into good, intermediate, and poor risk based on data accumulated from 1975 to 1990. PMGCT was classified as "poor risk", which represented 14% of patients with a 5-year PFS of 41% and a 5-year OS of 48% (6). To date, there have been few large-scale investigations on the prognostic variables of PMGCT, and purported relationships have yet to be verified.

A nomogram is a plot that has been frequently utilized to predict the probability of clinical events. It is fairly valuable for clinical decision-making and risk stratification, especially for cancer patients. The wide application of nomogram for breast cancer, lung cancer, liver cancer, and other malignancies can help clinical doctors to predict the risks and benefits of treatment. Hence, there is currently no nomograph available for primary mediastinal germ cell malignancies. Our findings might help us better understand PMGCTs and improve individual treatment and prognosis. We present the following article in accordance with the TRIPOD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4181/rc).

Methods

Study participants

The Surveillance, Epidemiology, and End Results (SEER)-18 dataset was adopted in the study, which comprises 18 tumor registries from around the US. The SEER*Stat software (version 8.3.9; https://seer.cancer.gov/seerstat/) was employed to retrieve the data. Patients with PMGCTs identified between 2000 and 2018 were chosen based on the related histological codes (9060-9065, 9070-9073, 9080-9085, 9090-9091, 9100-9102) and primary site (C37.9-C38.8). Clinical variables included surgery subtype, gender, treatment regimens, age, histology, tumor size, stage, chemotherapy, radiation, race, and survival-related information. Patients with more than one primary malignant tumor, as well as incomplete or unavailable survival data, less than three survival months, diagnosis only based on clinical evidence, and no prognostic data were excluded (*Figure 1*). Eligible patients were randomly assigned to a training group and a validation group in a 7:3 ratio, using the caret package in the R language software (The R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

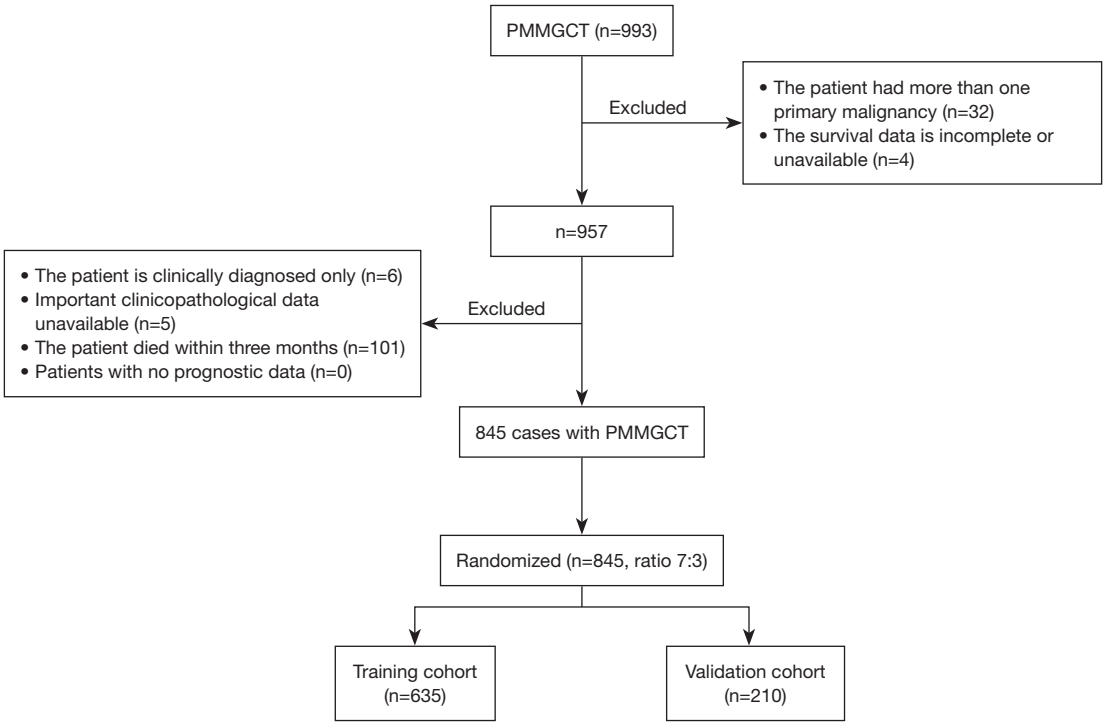

Figure 1 Schematic flow diagram for the process of study selection. PMMGCT, primary mediastinal malignant germ cell tumor.

Statistical analysis

In the study, we transformed continuous variables into categorical variables, which were later expressed in the form of quantity and proportion. Survival duration was defined as the date of diagnosis to the date of death or the end of the study. The Kaplan-Meier method was employed to calculate the overall survival (OS) of the study population, and the log-rank test was used to compare differences in OS. The relationship between clinicopathological characteristics and survival time was assessed utilizing Cox proportional hazards regression models. Hazard ratios (HRs) were expressed as numerical values and their 95% confidence intervals (CIs). For survival analyses, univariate Cox analysis was used to determine significant variables, defined as a P value of less than 0.05, from clinical data. Only a two-sided P value of <0.05 was considered statistically significant. Based on the Akaike information criterion (AIC), the variables with statistical significance in the univariate Cox regression analysis were subjected to multivariate Cox regression analysis. Statistically significant variables, which had a P value of less than 0.05, in multivariate Cox regression analysis were identified as independent prognostic factors affecting survival outcomes. All statistical analyses in this study were conducted with the software SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R language software (version 4.1.2).

Construction and validation of the nomogram

Using cph() function of the rms package in the R language software, a predictive model for predicting 3-, 5-, and 10-year OS of patients with PMGCT was constructed based on independent prognostic factors. At the same time, the nomogram() and plot() functions were used to draw the corresponding survival prediction nomogram to visualize the prediction model. To assign scores in the nomogram, we used regression coefficients to define linear predictor values. Indicators for evaluating the performance of clinical prediction models mainly included model discrimination and model calibration. Model discrimination referred to the ability of the model to correctly distinguish individuals at high risk from those at low risk for the occurrence of an outcome, which meant the ability of the model to distinguish whether an outcome event occurs or not. Model discrimination is mainly evaluated by Harrel's concordance index (C-index), which was calculated using the rcorrcens()

function in the R language. A C-index less than 0.60 indicated poor discrimination; 0.60 to 0.75 indicated a potentially helpful discrimination; and greater than 0.75 indicated a significantly useful discrimination (7). The closer the C-index is to 1, the better the model discrimination is. Model calibration was used to determine the degree of agreement between model predicted probabilities and actual observed probabilities, which was primarily assessed through a calibration curve. We used the calibrate() and plot() functions in R language to draw the calibration chart. The calibration chart took the model predicted probability as the x-axis, the actual observed probability as the y-axis, and the 45-degree diagonal line as the standard line. It was ideal when the calibration line and the standard line were completely coincident. A poorly calibrated model would underestimate or overestimate the probability of an outcome event occurring.

Results

Patient characteristics

As presented in *Figure 1*, 845 patients with PMGCT were enrolled in further research, and were randomly divided into a training group and a validation group at a 7:3 ratio. The basic characteristics of each cohort are listed in *Table 1*. The study included patients with PMGCTs diagnosed between 2000 and 2018. The mean age in the training cohort was 27±13 years, and 29 patients were female. Patients aged 20 to 39 years old comprised the main group, accounting for 63.5% of the training set. Approximately 27.2% of patients with PMGCT were diagnosed at the localized stage. The mean tumor size was 11.9±4.8 cm. In regard to treatment regimens, 90.4% of PMGCT patients underwent chemotherapy, and 47.1% underwent surgery; the rate for radiation was the lowest (11.5%). Chemotherapy alone and chemotherapy + surgery were common treatment regimens (40.6% and 39.1%). Hence, it was worth noting that variables to describe the sequence of surgery, radiation, and chemotherapy were unrecorded on SEER database, as well as elucidating the medications utilized in chemotherapy. There were 201 PMGCT patients who did not have their subtypes recorded. Seminoma accounted for the highest proportion (23.3%), followed by mixed GCT (19.8%), yolk sac tumors (12.9%), teratocarcinoma (6.0%), choriocarcinomas (3.6%), and embryonal carcinomas (2.7%).

Survival analysis

The median OS utilizing Kaplan-Meier method was 152 months. Some 33.1% (210/635) of patients died in the training group, where 3-, 5-, and 10-year OS ratios were 70.0%, 67.1% and 63.9%, respectively. In the validation group, the median OS was 146 months and 3-, 5- and 10-year OS ratios were 67.4%, 64.0%, and 59.9%, respectively. Univariate analysis suggested that age, tumor size, treatment regimens, radiation, histology, stage, chemotherapy, surgery type, and metastasis were significant risk factor of OS (*Table 2*). To adjust for the interaction between various covariates, relevant clinicopathological factors with P values <0.05 in the univariate analyses were contained in the multivariate Cox proportional hazards model to identify independent prognostic factors. Multivariate analysis showed that age (P<0.001), tumor size (P<0.001), stage (P<0.001), chemotherapy (P=0.024), radiation (P=0.043), histology (P<0.001), and surgery type (P<0.001) remained as independent predictors of prognosis (*Table 2*). According to the Kaplan-Meier method, young age, tiny tumors, chemotherapy, radiation, seminoma, early-stage tumors, undiscovered metastasis, and radical surgery were factors of significantly better OS (*Figure 2*). Moreover, patients who underwent surgery demonstrated greatly higher survival ratios (P<0.001) than those who were surgery naïve. Local excision, total resection, and radical surgery exhibited a superior influence on prognosis compared to partial resection/debulking.

Nomogram validation

In this study, based on independent factors obtained by multivariate Cox regression analysis, a model for predicting 3-, 5-, and 10-year OS was constructed with the help of R language software and visualized in the form of a nomogram (*Figure 3*), indicating that histology showed the greatest influence on prognosis, followed by chemotherapy, surgery type, age, size, and radiation. For estimation of OS, grade scores for each factor were calculated with total scores summed up on the point scale, on which each level of each factor was assigned a grade score. The degree of calibration of the prediction model constructed in this study was assessed by the calibration curve plot. A poorly calibrated model will underestimate or overestimate the probability of an outcome event occurring. The calibration chart of this study took the model-predicted OS rate as x-axis, the

Table 1 Demographics and baseline characteristics of patients with PMGCT in each cohort

Characteristics	Validation cohort (n=210), n (%)	Training cohort (n=635), n (%)
Age, years		
<20	41 (19.5)	106 (16.7)
20–39	128 (61.0)	403 (63.5)
≥40	41 (19.5)	126 (19.8)
Gender		
Male	192 (91.4)	606 (95.4)
Female	18 (8.57)	29 (4.57)
Histological subtypes		
Seminoma	56 (26.7)	148 (23.3)
Teratocarcinoma	15 (7.1)	38 (6.0)
Dysgerminoma	0	0
Embryonal carcinoma	4 (1.9)	17(2.7)
Yolk sac tumor	27 (12.9)	82 (12.9)
Mixed germ cell tumor	49 (23.3)	126 (19.8)
Choriocarcinoma	7 (3.3)	23 (3.6)
NOS	52 (24.8)	201 (31.7)
Vital status		
Alive	139 (66.2)	425 (66.9)
Dead	71 (33.8)	210 (33.1)
Stage		
Unknown	52 (24.8)	144 (22.7)
Localized	56 (26.7)	173 (27.2)
Regional	51 (24.3)	151 (23.8)
Distant	51 (24.3)	167 (26.3)
Chemotherapy		
No	22 (10.5)	61 (9.61)
Yes	188 (89.5)	574 (90.4)
Surgery types		
No	110 (52.4)	336 (52.9)
Local excision	29 (13.8)	98 (15.4)
Partial removal/debulking	34 (16.2)	92 (14.5)
Radical surgery/total resection	32 (15.2)	98 (15.4)
Surgery, NOS	5 (2.4)	11 (1.7)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Validation cohort (n=210), n (%)	Training cohort (n=635), n (%)
Radiation		
No	180 (85.7)	562 (88.5)
Yes	30 (14.3)	73 (11.5)
Treatment regimens		
Unknown	9 (4.3)	19 (3.0)
Surgery alone	11 (5.2)	37 (5.8)
Chemotherapy alone	84 (40.0)	258 (40.6)
Radiotherapy alone	1 (0.5)	4 (0.6)
Chemotherapy + surgery	76 (36.2)	248 (39.1)
Surgery + radiotherapy	1 (0.5)	1 (0.2)
Chemotherapy + surgery + radiotherapy	10 (4.8)	16 (2.5)
Chemotherapy + radiotherapy	18 (8.6)	52 (8.2)
Metastasis		
No	117 (55.7)	336 (52.9)
Yes	46 (21.9)	151 (23.8)
Unknown	47 (22.4)	148 (23.3)
Cause of death		
Alive	139 (66.2)	425 (66.9)
Dead due to cancer	62 (29.5)	174 (27.4)
Dead of other cause	8 (3.81)	32 (5.04)
Unknown cod	1 (0.48)	4 (0.63)
Race		
Black	17 (8.10)	46 (7.24)
White	166 (79.0)	499 (78.6)
Other	27 (12.9)	90 (14.2)
Tumor size (cm)		
≤15	132 (62.9)	382 (60.2)
>15	25 (11.9)	96 (15.1)
Unknown	53 (25.2)	157 (24.7)

PMGCT, primary mediastinal germ cell tumor; NOS, not otherwise specified.

actually observed OS rate as the y-axis, and the 45-degree diagonal line as the standard line. No matter whether in the modeling group or the validation group, the calibration line was highly coincident with the standard line, and the deviation was very small (*Figure 4*). It showed that OS rates predicted by the nomogram was highly correspondent with the actual observed survival rate, with a good degree of calibration. Further, the calibration curve of the external validation set demonstrated a fairly good correspondence between the predicted and actual OS of patients with

Table 2 Univariable and multivariable analysis of the training cohort

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age, years						
<20	Reference			Reference		
20–39	3.022	1.645–5.552	<0.001*	2.487	1.317–4.696	<0.001*
≥40	4.013	2.09–7.703	<0.001*	3.406	1.733–6.695	<0.001*
Gender						
Male	Reference					
Female	0.738	0.391–1.392	0.348			
Histology[1]						
Seminoma	Reference			Reference		
Teratocarcinoma	5.551	2.597–11.866	<0.001*	7.693	3.446–17.173	<0.001*
Embryonal carcinoma	5.13	1.925–13.673	<0.001*	4.506	1.67–12.161	<0.001*
Yolk sac tumor	6.313	3.266–12.202	<0.001*	5.501	2.777–10.896	<0.001*
Mixed germ cell tumor	5.791	3.075–10.908	<0.001*	7.229	3.76–13.899	<0.001*
Choriocarcinoma	16.301	7.693–34.541	<0.001*	12.132	5.656–26.023	<0.001*
NOS	5.624	3.056–10.348	<0.001*	5.606	3.019–10.413	<0.001*
Histology[2]						
Seminoma	Reference			Reference		
Non-seminoma	6.075	3.389–10.889	<0.001*	6.034	3.33–10.932	<0.001*
Stage						
Localized	Reference			Reference		
Regional	1.457	0.889–2.388	0.135	1.218	0.739–2.009	0.439
Distant	5.135	3.357–7.854	<0.001*	3.355	2.161–5.207	<0.001*
Unknown	1.639	1.03–2.607	0.037	1.309	0.817–2.097	0.264
Chemotherapy						
Yes	Reference			Reference		
No	0.215	0.088–0.522	<0.001*	0.356	0.145–0.874	0.024*
Surgery types						
No	Reference			Reference		
Local excision	0.591	0.385–0.907	<0.01*	0.598	0.385–0.928	0.022*
Partial removal/debulking	0.818	0.549–1.219	0.324	0.724	0.481–1.09	0.122
Radical surgery/total resection	0.519	0.324–0.832	<0.001*	0.463	0.286–0.751	<0.001*
Surgery, NOS	0.919	0.376–2.247	0.853	0.897	0.358–2.245	0.816

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Radiation						
No	Reference			Reference		
Yes	1.386	0.955–2.011	0.026*	1.324	0.902–1.943	0.043*
Treatment regimens						
Chemotherapy alone	Reference			Reference		
Radiotherapy alone	0	0	0.951	0	0	0.961
Chemotherapy + surgery	0.689	0.507–0.937	0.017*	0.592	0.428–0.817	<0.001*
Surgery + radiotherapy	0	0	0.966	0	0	0.976
Chemotherapy + surgery + radiotherapy	1.286	0.65–2.546	0.47	1.003	0.489–2.054	0.994
Chemotherapy + radiotherapy	1.191	0.762–1.862	0.442	1.286	0.811–2.041	0.285
Surgery alone	0.063	0.009–0.454	<0.001*	0.058	0.008–0.424	<0.001*
Unknown	0.572	0.211–1.556	0.274	0.819	0.29–2.314	0.706
Metastasis						
No	Reference					
Yes	4.489	3.267–6.17	<0.001*			
Unknown	1.358	0.94–1.963	0.103			
Race						
Black	Reference					
White	0.906	0.549–1.494	0.698			
Other	0.924	0.507–1.681	0.795			
Tumor size (cm)						
≤15	Reference			Reference		
>15	2.035	0.908–4.557	0.084	2.699	1.163–6.26	0.021*
Unknown	1.432	0.65–3.152	0.373	1.864	0.825–4.211	0.134

[1], all pathologic types of PMGCT; [2], main pathologic types of PMGCT; *, P<0.05. HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified.

PMGCT (*Figure 5*). The C-index was 0.714 (95% CI: 0.695 to 0.733) and 0.756 (95% CI: 0.735 to 0.787) in the training and validation groups, indicating that the prediction model constructed in this study had a good degree of discrimination.

Discussion

Few prognostic models have been investigated due to the rarity of PMGCTs (8). In order to reach a consensus on GCTs, IGCCCG was formed, whose findings were published in 1997 (4). The IGCCCG now divides GCTs into 3 risk classifications: good, intermediate, and poor (9). There are no nomogram models for PMGCTs. As a result, we aimed to create a nomogram model that might be employed to predict and confirm long-term survival rates for customized treatments. We found that age, chemotherapy, radiation, histology, size, stage, and surgical

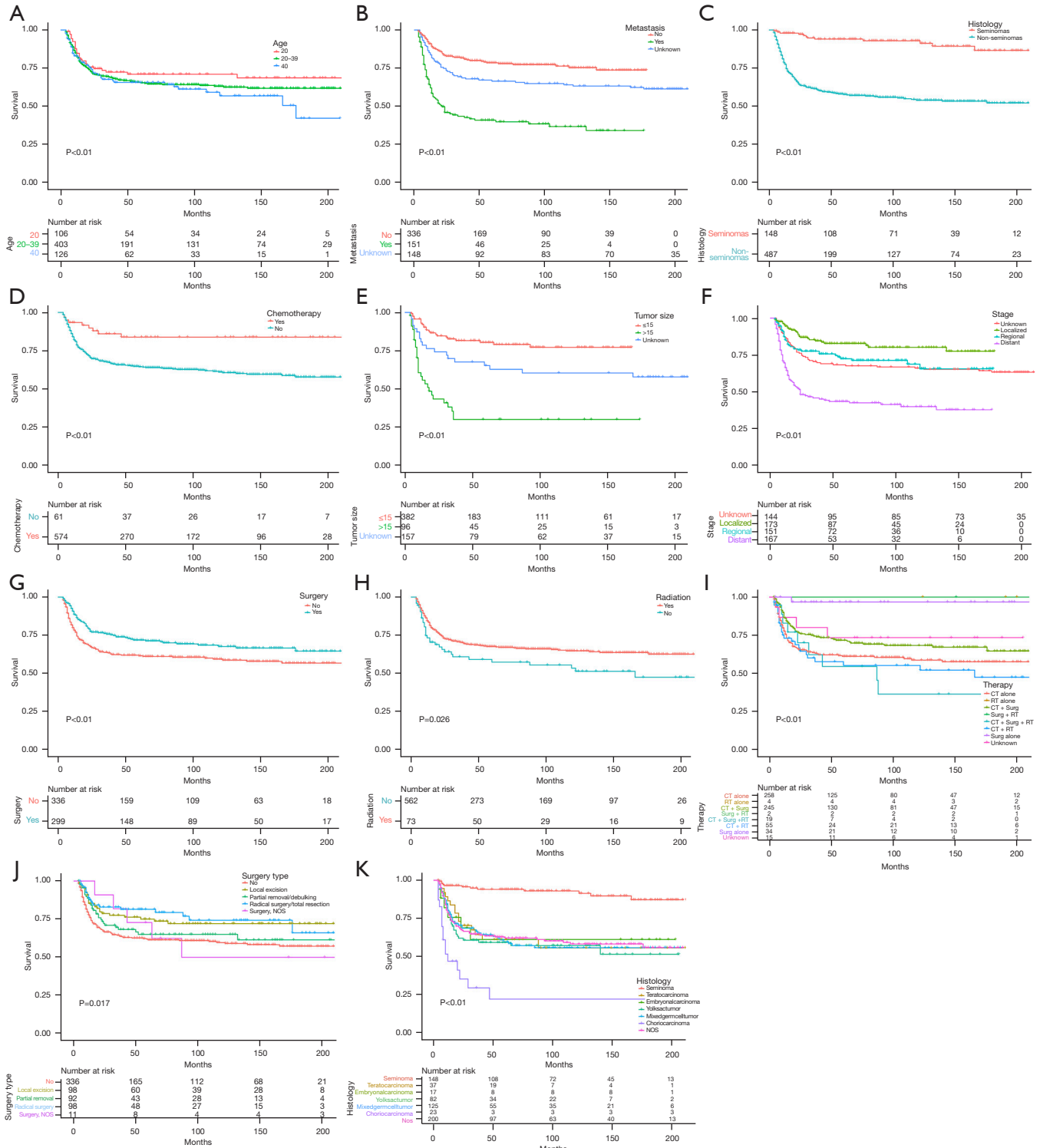

Figure 2 KM methods were conducted to predict the OS of patients with PMGCT according to (A) age, (B) metastasis, (C) histology, (D) chemotherapy, (E) tumor size, (F) stage, (G) surgery, (H) radiation, (I) therapy, (J) surgery type, (K) histology. CT, chemotherapy; RT, radiotherapy; Surg, surgery; NOS, not otherwise specified; KM, Kaplan-Meier; OS, overall survival; PMGCT, primary mediastinal germ cell tumor.

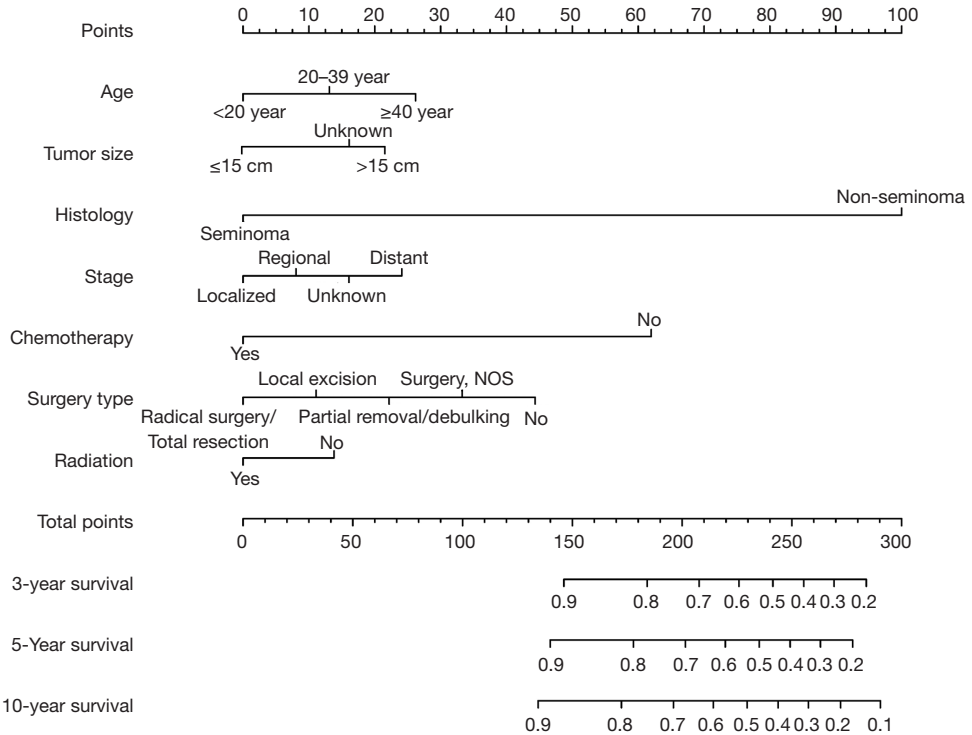

Figure 3 Prognostic nomogram for predicting OS in patients with PMGCT. NOS, not otherwise specified; OS, overall survival; PMGCT, primary mediastinal germ cell tumor.

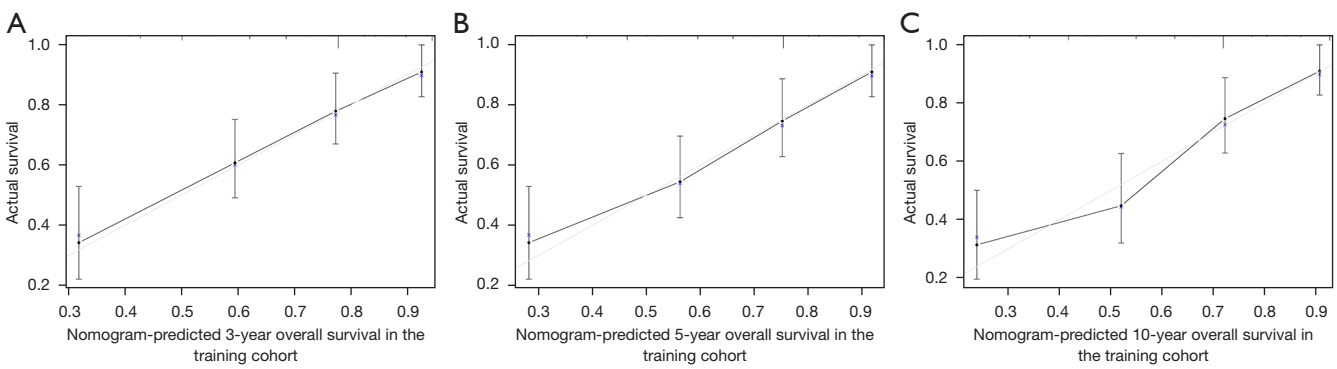

Figure 4 The calibration curves for predicting OS of patients with PMGCT in the training cohort. (A) 3-year, (B) 5-year, and (C) 10-year. OS, overall survival; PMGCT, primary mediastinal germ cell tumor.

type were all independent predictive markers for OS in our analysis, which extracted the information of 845 patients from the SEER database.

Fedyanin *et al.* (8,10) found that clinicopathologic traits of larger tumor size (≥19 cm), bleomycin, etoposide, and cisplatin (BEP) regimen, and age ≥24 years old were independent negative prognostic factors, which matched our findings of older adult and tumor size >15 cm having poorer OS. Laflamme *et al.* reported that postpubertal PMNGCT had the poorer prognosis among GCTs, with a 5-year survival ratio of 45–50% (11). According to El-Zaatari *et al.*'s research (3), the median age at PMS onset was 33 years (range, 18 to 65 years) and the median age at PMNGCT onset was 28 years (range, 12 to 42 years). The occurrence of PMGCT showed a bimodal age distribution, with a first apex at 0–4 years of age, a decline in childhood,

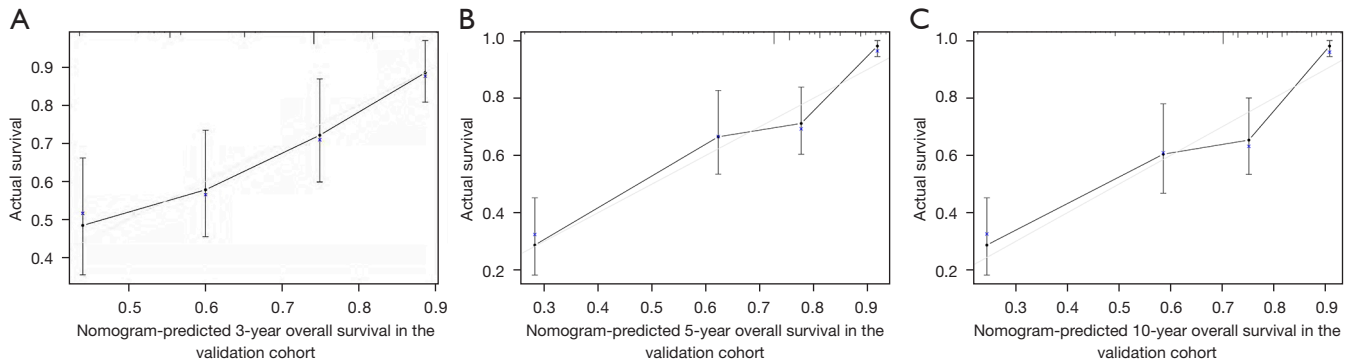

Figure 5 The calibration curves for predicting OS of patients with PMGCT in the validation cohort. (A) 3-year, (B) 5-year, and (C) 10-year. OS, overall survival; PMGCT, primary mediastinal germ cell tumor.

and then a second peak at 10–20 years of age. Hartmann *et al.* (12) verified that metastasis of liver or brain, PMNGCT, and a rise in logarithmic β-hCG were enumerated as negative factors for OS in patients with PMGCT, keeping agreement with our study that metastasis was an independent risk factor for PMGCTs. It was worth noting that stage was identified as an important factor in PMGCT. The definition of stage contained localized, regional, and distant in the SEER stage group, which was in accordance with stages I, II, and III in the clinical staging for primary mediastinal non-seminomas (PMNS) (13). As previously reported (14-16), patients with extra-mediastinal metastases had a worse OS than patients with tumors restricted to the mediastinum.

Currently, the clinical treatment of PMGCT is mainly based on comprehensive chemotherapy, supplemented by radiotherapy and surgical treatment. Stram *et al.* (17,18) showed that PMS was greatly chemosensitive, resulting in a superior cure ratio with cisplatin-based treatment (BEP ×4). No surgical removal was required post-chemotherapy. Hence, PMNGCT, which accounted for the majority of GCTs in mediastinum, was typically aggressive with a poor-risk prognosis and an overall 5-year survival rate of about 45%. This was consistent with our data that histology presented an independent risk factor. The PMNSGCTs were the most complicated type of malignant GCT to treat and categorized as poor risk by the IGCCCG. Multimodal therapy with BEP chemotherapy as initial treatment followed by surgical excision of residual tumor was the conventional treatment regimen for PMNGCT. Some 10–20% of patients with PMNGCT still had residual malignant tumor components after chemotherapy, for whom a multimodality approach containing chemotherapy combined with surgery of residual disease was of certain significance (19). The PMNGCT required substantial post-chemotherapy surgery, which carried a high risk of pulmonary toxicity, including respiratory complications (pneumonia or acute respiratory distress syndrome (ARDS)]. Bleomycin was well-known for causing pulmonary damage. Etoposide, ifosfamide, and cisplatin (VIP) combination chemotherapy may be recommended as similarly efficacious but with less post-surgical respiratory complications (20). Surgery was found to be a protective factor in our research. At present, the selection of the timing of surgery is quite controversial. Kesler *et al.* (21) showed that the treatment of PMNGCT could be preceded by radiotherapy and chemotherapy, combined with surgical resection of the residual tumor, which can significantly improve the long-term survival rate of PMNGCT. Lee *et al.* (22) reported that if the tumor was localized, radical resection of the tumor should be performed first, followed by postoperative chemoradiotherapy. Necchi *et al.* (14) reported that surgery, regardless of modalities, resulted in a better OS than no surgery. Upgrades on surgical skills plus early diagnosis employing superior imaging instrument ameliorated the rates of local excision, total resection, and radical surgery. In recent years, increased rates of local excision, total resection, and radical surgery rate have contributed to a longer survival time. Complete surgical resection was found to be a positive prognostic factor of PMNGCT. If the tumor was small and did not invade adjacent tissues at the initial diagnosis, surgery could be performed for radical tumor resection first, followed by radiotherapy and chemotherapy; if the tumor invaded other tissues in the mediastinum such as pleura, pericardium, and great blood vessels, which increases the difficulty of performing

complete surgical resection with a low long-term survival rate, radiotherapy and chemotherapy were recommended to perform first, followed by complete surgical resection of the residual tumor. To allow for patient recovery, surgery to remove the residual tumor was usually scheduled 4–6 weeks after chemotherapy. As previously reported (12,16,17,23), a regimen of removing residual tumor if deemed feasible was recommended in spite of serum tumor marker (STM) status, which mainly built on the fact that surgical salvage appears to provide superior overall results in individuals with residual malignancy following first-line chemotherapy than second-line chemotherapy response rates. In other words, in the treatment of PMNGCT, the timing of surgical intervention should be determined according to the specific situation of different patients. Customized chemotherapy and excellent thoracic surgeons were both required for a good prognosis. Radiotherapy was found to be an effective clinical intervention and a positive factor for OS in the largest reported study of PMNGCT treated with radiotherapy, which was consistent with our findings (24). The radiosensitivity of PMNGCT was found to be excellent. Sterotactic body radiation therapy (SBRT), a popular radiotherapy segmentation method gradually emerging in radiotherapy of solid tumors, is characterized by large fractional irradiation. The number of radiotherapy fractions could be effectively reduced by increasing the fractional dose of a single radiotherapy, which could provide a sufficient radiation dose to effectively kill tumor cells. The reduction in the number of fractions was shown to be easy for patients and their families to accept, which was also the advantage of SBRT compared with traditional radiotherapy. Laflamme *et al.* (11) also showed that SBRT, which allowed for the precise delivery of ablative doses of radiation, had become a more popular alternative to surgery for PMGCT.

With comprehensive treatment, the prognosis for PMGCT has been ameliorated considerably. Hence, a tiny percentage of individuals experience relapses. Patients who relapse after undergoing initial chemotherapy have a terrible prognosis, with an OS of 10% (25). When compared to patients with extra-mediastinal GCTs, these patients experience significantly worse outcomes of salvage chemotherapy (12). Einhorn *et al.* (19,26) showed that high-dose chemotherapy (HDCT) can obtain a cure rate of 70% when administered as initial salvage chemotherapy, as well as peripheral stem cell transplant (PBSCT). Rodney *et al.* (27) reported that surgery is a powerful salvage method for relapsed mediastinal NSGCT.

In addition, PMNGCT can be complicated by hematologic malignancy (HM), considered as a unique propensity, which predominantly affects adolescent and young adult males. There are many types of HM which can complicate PMNGCT, including acute myeloid leukemia (AML), histiocytosis, hemophagocytic syndrome, lymphoma, granulocytic sarcoma, myelodysplastic syndromes (MDS), essential thrombocytosis, mastocytosis, and acute lymphoblastic leukemia (ALL). As previously reported (28), AML remains the predominant type, for which occurrence of HM involving the megakaryocyte lineage was an important feature. Alteration of i(12p) was a characteristic and common genetic alteration of GCT, which occurred in up to 80% of GCTs of testicular origin. Chaganti *et al.* (29) reported a patient who developed AML 1 month after their diagnosis of PMNGCT, with i(12p) karyotype in both GCTs and leukemia bone marrow. The study by Lu *et al.* (30) revealed by exome sequencing of patients with PMNGCT and AML, that both tumor specimens contained PTEN and TP53 mutations. Woodruff *et al.* (31) reported a patient with PMNGCT who was not complicated by leukemia at the early stage, but developed leukemia 1 year later and had a 49, XY, +X, +8, +i(12p) karyotype of bone marrow, the same as karyotype of chromosomes on the tumor specimen of PMNGCT. This indicated a common clonal origin of the 2 tumors, and that leukemia had originated from a malignant germ cell clone. Multiple cytogenetic information revealed that they shared a common clonal origin. Patients with PMGCT and HM have a worse prognosis than those without HM, and they often die from direct effects or complications of HM. Nichols *et al.* (32) reported that the median OS for patients with PMNGCT diagnosis of HM was 1 month.

There were a few flaws in this research. Foremost, retrospective investigations are regarded as inferior to large randomized controlled trials, due to unavoidable potential selection bias. Secondly, the SEER database, as the main clinical tumor database in the United States, involves a variety of ethnic groups, but mainly Caucasians and Blacks, and Asians have fewer clinical data records. The SEER database's limitations prohibited us from obtaining a more precise conclusion, as the database lacks factors to verify the sequence of surgery, radiation, and chemotherapy, as well as variables to elucidate chemotherapy medicines and comprehensive STMs. Thirdly, additional parameters, such as surgical margin status, may influence prognosis; therefore, more research is needed to uncover the prognostic markers and enhance the prediction accuracy of nomogram. In addition, the clinical prediction model

that we constructed incorporated many variables; its practical application requires a high degree of completeness of relevant information, which limits the scope of use. The drawn nomogram was a little tedious, leading to a certain impact on the calculation efficiency. As some of the included variables are not uniform in measurement and evaluation methods, the accuracy of prediction would also have been affected to a certain extent. Predictive models cannot provide a real-time prognosis. With the implementation of treatment plans or changes in the course of disease, the accuracy will be significantly affected, and the same predictive model will no longer be fully applicable. Age, size, stage, chemotherapy, surgery types, histology, and radiation are all independent prognostic variables for OS in patients with PMGCT, according to our findings. Furthermore, we created a nomogram that can accurately predict 3-, 5-, and 10-year OS in patients with PMGCT.

In conclusion, age, size, stage, chemotherapy, surgery types, histology, and radiation are prognostic factors for patients with PMGCT. The accuracy and clinical applicability of the risk prediction model established based on these indicators were acceptable, which had certain reference value for medical workers to conduct intuitive and individualized risk analysis in clinical work. However, lack of STM and concrete chemotherapy medicines had a significant impact on tumor incidence and survival prognostication. Caution should be exercised when applying the nomogram for guidance of patients with PMGCT in clinical work. In the future, it is still necessary to increase investment in the research of PMGCT and establish a large-sample, multi-center study to provide better guidance for prognosis and treatment.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4181/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4181/coif). 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).

References

1. Fukui N, Kohno Y, Ishioka J, et al. Treatment outcome of patients with extragonadal nonseminomatous germ cell tumors: the Saitama Cancer Center experience. Int J Clin Oncol 2013;18:731-4.
2. Kang CH, Kim YT, Jheon SH, et al. Surgical treatment of malignant mediastinal nonseminomatous germ cell tumor. Ann Thorac Surg 2008;85:379-84.
3. El-Zaatari ZM, Ro JY. Mediastinal Germ Cell Tumors: A Review and Update on Pathologic, Clinical, and Molecular Features. Adv Anat Pathol 2021;28:335-50.
4. Adra N, Althouse SK, Liu H, et al. Prognostic factors in patients with poor-risk germ-cell tumors: a retrospective analysis of the Indiana University experience from 1990 to 2014. Ann Oncol 2016;27:875-9.
5. Fizazi K, Pagliaro L, Laplanche A, et al. Personalised chemotherapy based on tumour marker decline in poor prognosis germ-cell tumours (GETUG 13): a phase 3, multicentre, randomised trial. Lancet Oncol 2014;15:1442-50.
6. Urbini M, Schepisi G, Bleve S, et al. Primary Mediastinal and Testicular Germ Cell Tumors in Adolescents and Adults: A Comparison of Genomic Alterations and Clinical Implications. Cancers (Basel) 2021;13:5223.
7. Alba AC, Agoritsas T, Walsh M, et al. Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. JAMA 2017;318:1377-84.
8. Yang X, Zhao K, Mei J, et al. Primary Mediastinal Nonseminomas: A Population-Based Surveillance,

Epidemiology, and End Results Analysis. J Surg Res 2021;267:25-36.
9. Marx A, Chan JKC, Chalabreysse L, et al. The 2021 WHO Classification of Tumors of the Thymus and Mediastinum: What Is New in Thymic Epithelial, Germ Cell, and Mesenchymal Tumors? J Thorac Oncol 2022;17:200-13.
10. Fedyanin M, Tryakin A, Mosyakova Y, et al. Prognostic factors and efficacy of different chemotherapeutic regimens in patients with mediastinal nonseminomatous germ cell tumors. J Cancer Res Clin Oncol 2014;140:311-8.
11. Laflamme P, Doucet C, Sirois C, et al. Stereotactic radiation therapy for residual chemorefractory primary mediastinal non-seminomatous germ cell tumor after surgical thoracotomy. Pract Radiat Oncol 2017;7:260-3.
12. Hartmann JT, Einhorn L, Nichols CR, et al. Second-line chemotherapy in patients with relapsed extragonadal nonseminomatous germ cell tumors: results of an international multicenter analysis. J Clin Oncol 2001;19:1641-8.
13. Kesler KA, Rieger KM, Ganjoo KN, et al. Primary mediastinal nonseminomatous germ cell tumors: the influence of postchemotherapy pathology on long-term survival after surgery. J Thorac Cardiovasc Surg 1999;118:692-700.
14. Necchi A, Giannatempo P, Lo Vullo S, et al. A prognostic model including pre- and postsurgical variables to enhance risk stratification of primary mediastinal nonseminomatous germ cell tumors: the 27-year experience of a referral center. Clin Genitourin Cancer 2015;13:87-93.e1.
15. Kim E, Thomas CR Jr. Conditional survival of malignant thymoma using national population-based surveillance, epidemiology, and end results (SEER) registry (1973-2011). J Thorac Oncol 2015;10:701-7.
16. De Latour B, Fadel E, Mercier O, et al. Surgical outcomes in patients with primary mediastinal non-seminomatous germ cell tumours and elevated post-chemotherapy serum tumour markers. Eur J Cardiothorac Surg 2012;42:66-71; discussion 71.
17. Stram AR, Kesler KA. Mediastinal Germ Cell Tumors: Updates in Diagnosis and Management. Surg Oncol Clin N Am 2020;29:571-9.
18. Rosti G, Secondino S, Necchi A, et al. Primary mediastinal germ cell tumors. Semin Oncol 2019;46:107-11.
19. Suleiman Y, Siddiqui BK, Brames MJ, et al. Salvage therapy with high-dose chemotherapy and peripheral blood stem cell transplant in patients with primary mediastinal nonseminomatous germ cell tumors. Biol Blood Marrow Transplant 2013;19:161-3.
20. Ranganath P, Kesler KA, Einhorn LH. Perioperative Morbidity and Mortality Associated With Bleomycin in Primary Mediastinal Nonseminomatous Germ Cell Tumor. J Clin Oncol 2016;34:4445-6.
21. Kesler KA, Stram AR, Timsina LR, et al. Outcomes following surgery for primary mediastinal nonseminomatous germ cell tumors in the cisplatin era. J Thorac Cardiovasc Surg 2021;161:1947-1959.e1.
22. Lee KS, Im JG, Han CH, et al. Malignant primary germ cell tumors of the mediastinum: CT features. AJR Am J Roentgenol 1989;153:947-51.
23. Schneider BP, Kesler KA, Brooks JA, et al. Outcome of patients with residual germ cell or non-germ cell malignancy after resection of primary mediastinal nonseminomatous germ cell cancer. J Clin Oncol 2004;22:1195-200.
24. Wang J, Bi N, Wang X, et al. Role of radiotherapy in treating patients with primary malignant mediastinal non-seminomatous germ cell tumor: A 21-year experience at a single institution. Thorac Cancer 2015;6:399-406.
25. Einhorn LH, Abonour R, Kesler KA. Paclitaxel plus ifosfamide followed by high-dose carboplatin plus etoposide for patients with relapsed primary mediastinal nonseminomatous germ cell tumors: benefit from chemotherapy, surgery, or both? J Clin Oncol 2010;28:e739; author reply e740.
26. Einhorn LH, Williams SD, Chamness A, et al. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med 2007;357:340-8.
27. Rodney AJ, Tannir NM, Siefker-Radtke AO, et al. Survival outcomes for men with mediastinal germ-cell tumors: the University of Texas M. D. Anderson Cancer Center experience. Urol Oncol 2012;30:879-85.
28. Sowithayasakul P, Sinlapamongkolkul P, Treetipsatit J, et al. Hematologic Malignancies Associated With Mediastinal Germ Cell Tumors: 10 Years' Experience at Thailand's National Pediatric Tertiary Referral Center. J Pediatr Hematol Oncol 2018;40:450-5.
29. Chaganti RS, Ladanyi M, Samaniego F, et al. Leukemic differentiation of a mediastinal germ cell tumor. Genes Chromosomes Cancer 1989;1:83-7.
30. Lu C, Riedell P, Miller CA, et al. A common founding clone with TP53 and PTEN mutations gives rise to a concurrent germ cell tumor and acute megakaryoblastic leukemia. Cold Spring Harb Mol Case Stud

2016;2:a000687.
31. Woodruff K, Wang N, May W, et al. The clonal nature of mediastinal germ cell tumors and acute myelogenous leukemia. A case report and review of the literature. Cancer Genet Cytogenet 1995;79:25-31.
32. Nichols CR, Roth BJ, Heerema N, et al. Hematologic neoplasia associated with primary mediastinal germ-cell tumors. N Engl J Med 1990;322:1425-9.

Cite this article as: Qi L, Han J, Shi Y, Wu R, Li B, Shi W, Chen S. Establishment and validation of an individualized nomogram for survival prediction of primary mediastinal germ cell tumors based on the SEER database. Ann Transl Med 2022;10(18):988. doi: 10.21037/atm-22-4181

