Nomogram to Predict Overall and Cancer-Specific Survival in Patients with Primary Bone Diffuse Large B-Cell Lymphoma: A Population-Based Study

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Abstract

Background: Primary bone diffuse large B-cell lymphoma accounts for more than 80% of primary bone lymphoma, and as a rare disease, we created two nomogram to predict overall survival (OS) and cancer-specific survival (CSS) in patients with PD-DLBCL.

Methods: 891 patients diagnosed with PB-DLBCL between 2007 and 2016 were extracted from the Surveillance, Epidemiology and End Results (SEER) database. Univariate and multivariate Cox analyses were performed to explore independent prognostic factors and to create two separate nomogram for OS and CSS. The area under the curve (AUC), calibration curve, decision curve analysis (DCA), and Kaplan-Meier curve analysis were used to evaluate the nomogram.

Results: 4 variables were identified as independent prognostic factors for OS and 3 variables were identified as independent prognostic factors for CSS. the ROC curves demonstrated good discriminatory power of the nomogram. Calibration curves and DCA curves showed that nomogram had satisfactory ability to predict OS and CSS. k-M curves showed that age, gender, first location, chemotherapy, and tumor stage affected patient survival.

Conclusions: Age, race, primary site, and chemotherapy are variables that affect OS. And age, race, and chemotherapy are variables that affect CSS in patients with PD-DLBCL. Two nomogram were created based on the above variables to provide more accurate individual survival prediction for PD-DLBCL patients and to help physicians make appropriate clinical decisions.

Background

Primary bone lymphoma (PBL) was reported by Oberlin in 1928 as "primary reticulocytic sarcoma" and was only precisely defined by Shoji et al. in 1971[1]. With the advancement of medical technology, PBL is recognized as a malignant tumor of bone originating from the hematopoietic system. It is also a rare form of extranodal lymphoma, accounting for 3%-7% of extranodal lymphomas[2]. There are no specific manifestations of this disease in its early stages, and the first symptoms are fever, the appearance of lumps, and weight loss[3]. PBL can occur in all bones of the body, with the femur and pelvis being the most common [4]. The age of onset is mostly 45-60 years, with a slight excess of men over women, and the trend seems to have increased in recent years, but the factors leading to its occurrence are less clear[5]. More than 80% of the pathological types in PBL are Primary bone diffuse large B-cell lymphoma (PD-DLBCL)[2, 6]. Because of its heterogeneity, there is no standard treatment plan, and the treatment options are chemotherapy, radiotherapy and surgery. Surgery is only used for symptoms of compression, pathological fractures or to take biopsies. Currently, CHOP and CHOP-like regimens are commonly used for chemotherapy. Bruno Ventre et al showed that anthracycline-based regimens were more effective and that PD-DLBCL patients treated with chemotherapy were significantly better than those treated with radiotherapy [3]. The effectiveness of radiotherapy as a consolidation modality after chemotherapy is controversial [7, 8]. In a study on PB-DLBCL, Held et al demonstrated that radiotherapy helped improve

patient survival [9]. there are many factors that affect the survival rate of PB-DLBCL patients, and so far, to our knowledge, no study has been conducted to predict and analyze the clinical characteristics specifically for the survival rate of PB-DLBCL patients. In this study, we used the Surveillance, Epidemiology, and End Results (SEER) program database to predict survival and analyze clinical characteristics in patients with PB-DLBCL.

Methods

1.1 Patients

We selected the SEER data, which contains epidemiological information from 18 cancer registries in the United States. Most importantly it is a publicly available database covering 30% of the entire US population, reducing ethical conflicts to an overwhelming extent. We used SEER Stat [8.3.9.2], from which we selected a total of 891 patients from 2007-2016. Inclusion criteria [1] Histological type of PB-DLBCL was confirmed (histological code 9680/3 in the third edition of the International Album of Oncological Diseases) [2] Confirmed as primary tumor [3] Bone only (position code C40.0-C41.9 in the third edition of the International Album of Oncological Diseases) [4] Complete follow-up information Exclusion criteria [1] Incomplete information on age, gender, race, pathological type, radiotherapy, chemotherapy, tumor metastasis [2] Survival time ≤ 1 month [3] The onset of the disease is not in the bones. Patients meeting the above criteria were randomly divided into a training set (70%) and a test set (30%). In our study, column line graphs were built from the training set and validated in the test set. In this study, we mainly analyzed the overall survival (OS) and cancer-specific survival (CSS) of patients.

1.2 Data analysis

The variables we observed included age, race, gender, primary site, surgery, radiotherapy, chemotherapy, and tumor stage (Localized, Regional, Distant). In order to better determine the cut-off value of the continuous variable Age, we used the X-tile software [Yale University, New Haven, CT, USA] for analysis. The training cohort was screened for variables by univariate cox regression models ($P < 0.2$), and the screened variables were enrolled in multivariate Cox regression to clarify the independent risk factors for OS and CSS in PB-DLBCL patients ($P < 0.05$), which were finally plotted in nomogram. The effect of these independent risk factors on OS and CSS in PB-DLBCL patients was demonstrated using Kaplan-Meier curves and log-rank tests. Using ROC curves and calibration curves to confirm the accuracy of nomogram. The DCA curve was used to calculate the net benefit to determine the predictive effect of the nomogram in clinical outcomes. All data were analyzed using statistical software R (version 3.43, <http://www.r-project.org>).

Results

2.1 Demographic characteristics

We included 891 patients with PB-DLBCL in Seer database from 2007 to 2016table 1. It was divided into a training cohort (N=627) and a validation cohort (N=264). 500 (56.1%) were male and 391 (43.9%) were female. The primary tumors were located in the mandible, skull, pelvis, spine, ribs and other axial sites in 560 (62.9%) and in the extremities in 331 (37.1%). A total of 154 (17.3%) PB-DLBCL patients received surgery, 488 (54.8%) received radiotherapy, and 776 (87.1%) received chemotherapy. Most patients were localized stage (46151.7%), 129(14.5%) were regional stage, and 301 (33.8%) were distant stage.

2.2 Variable screening and creation of nomogram

First, we used X-tile to determine the optimal cutoff for age, dividing age into 7-62, 63-75, >75Fig.1. Before creating the nomogram, we performed univariate and multivariate regression analyses for age, race, sex, primary site, surgery, chemotherapy, radiotherapy, and tumor stage, respectively. In the analysis for OS, univariate analysis suggested that age, race, sex, primary site, and chemotherapy were independent risk factors. And in a further multivariate analysis, gender was no longer an independent risk factortable 2. In the analysis of CSS, age, race, sex, primary site, chemotherapy, and tumor stage were independent risk factors in the univariate analysis, and in the multivariate analysis, only age, race, and chemotherapy information were independent risk factorstable 3. The selected variables are used to construct a nomogram, and the patient's prognosis is predicted by calculating the total scoreFig.2. Subsequently, the accuracy of the nomogram was verified. The ROC curve shows that the nomogram has better discrimination abilityFig.3. The calibration curve also effectively demonstrated the accuracy of the nomogram prediction versus the actual probability of survival (Fig. 4). For the DCA curve, it was confirmed that the nomogram has a certain net benefit, and can effectively improve patient outcomes (Fig. 5).

2.3 Risk factor analysis

Patient survival was assessed using Kaplan-Meier curves. As shown, longer OS was associated with younger age ($P<0.001$), gender being male ($P=0.024$), first site in the extremities ($P<0.001$), choice of chemotherapy ($P<0.001$), and tumor stage being Regional ($P=0.05$). And race ($P=0.65$), surgery or not ($P=0.25$), and radiotherapy ($P=0.75$) did not have a significant effect on OS (Fig. 6).

table1Patient demographic characteristics

	Training cohort	Validation cohort	Total
	N(%)	N(%)	N(%)
n	627	264	891
Age(%)			
7-62	340 (54.2)	142 (53.8)	482 (54.1)
63-75	160 (25.5)	71 (26.9)	231 (25.9)
≥75	127 (20.3)	51 (19.3)	178 (20.0)
Race (%)			
White	536 (85.5)	228 (86.4)	764 (85.7)
Black	43 (6.9)	18 (6.8)	61 (6.8)
Other	48 (7.7)	18 (6.8)	66 (7.4)
Gender (%)			
Male	342 (54.5)	158 (59.8)	500 (56.1)
Female	285 (45.5)	106 (40.2)	391 (43.9)
Primary Site (%)			
Axial	404 (64.4)	156 (59.1)	560 (62.9)
Appendix	223 (35.6)	108 (40.9)	331 (37.1)
Surgery (%)			
Yes	104 (16.6)	50 (18.9)	154 (17.3)
No	523 (83.4)	214 (81.1)	737 (82.7)
Radiation (%)			
Yes	342 (54.5)	146 (55.3)	488 (54.8)
No	285 (45.5)	118 (44.7)	403 (45.2)
Chemotherapy (%)			
Yes	543 (86.6)	233 (88.3)	776 (87.1)
No	84 (13.4)	31 (11.7)	115 (12.9)
Stage (%)			
Localized	314 (50.1)	147 (55.7)	461 (51.7)
Regional	92 (14.7)	37 (14.0)	129 (14.5)

Distant	221 (35.2)	80 (30.3)	301 (33.8)

table2 Univariate and Multivariate Analysis of OS in a Training Cohort

Characteristics	Univariate analysis HR (95% CI)	P	Multivariate analysis HR (95% CI)	P
Age	3.2 (2.61-3.91)	0	2.97 (2.4 - 3.66)	0
7-62				
63-75				
≥75				
Race	1.19 (0.92-1.53)	0.179	1.25 (0.98 - 1.59)	0.0726
White				
Black				
Other				
Gender	1.35 (0.98-1.85)	0.066	0.88 (0.64 - 1.22)	0.4513
Male				
Female				
Primary Site	0.53 (0.36-0.76)	0.001	0.67 (0.46 - 0.97)	0.0337
Axial				
Appendix				
Surgery	1.07 (0.69-1.64)	0.772	NA	NA
Yes				
No				
Radiation	0.85 (0.62-1.18)	0.339	NA	NA
Yes				
No				
Chemotherapy	4.05 (2.88-5.7)	0	3.08 (2.17 - 4.37)	0
Yes				
No				
Stage	1.09 (0.92-1.3)	0.321	NA	NA
Localized				
Regional				
Distant				

table3 Univariate and multivariate analysis of CSS in a training cohort

Characteristics	Univariate analysis HR (95% CI)	P	Multivariate analysis HR (95% CI)	P
Age	3.14 (2.13-4.63)	0	2.56 (1.68 - 3.9)	0
7-62				
63-75				
≥75				
Race	5.57 (2.92-10.66)	0	4.44 (2.08 - 9.48)	0.001
White				
Black				
Other				
Gender	1.7 (0.92-3.14)	0.089	1.1 (0.56 - 2.17)	0.7749
Male				
Female				
Primary Site	0.43 (0.21-0.87)	0.019	0.71 (0.33 - 1.5)	0.3701
Axial				
Appendix				
Surgery	0.71 (0.34-1.47)	0.36	NA	NA
Yes				
No				
Radiation	0.67 (0.35-1.27)	0.219	NA	NA
Yes				
No				
Chemotherapy	1.35 (0.97-1.87)	0.079	1.63 (1.11 - 2.39)	0.0128

Yes				
No				
Stage	2.28 (0.81-6.39)	0.118	2.28 (0.78 - 6.69)	0.1338
Localized				
Regional				
Distant				

Discussion

As an independent and rare disease, PB-DLBCL was limited to some case reports and small-sample retrospective studies in the past. It is crucial to summarize the pathological features of PB-DLBCL, to effectively predict the prognosis, and to deepen physicians' understanding of the disease. Nomogram is a statistical tool that can integrate multiple prognostic risk factors in clinic, neutralize various factors of patients and incorporate them into prognostic evaluation, and finally display them visually[10]. Correct use of nomograms can effectively improve patient outcomes and assist clinicians in making accurate survival assessments and treatment decisions [11].

In this study, based on the Seer database, we used the Cox proportional hazards model to screen out risk factors and constructed a nomogram, and then used Kaplan-Meier curve to evaluate the survival of patients. The good predictive and clinical net benefit of nomogram was demonstrated by ROC curve, calibration curve, and DCA curve. As far as we know so far, this study is the first to construct a nomogram for PB-DLBCL and analyze prognostic factors.

Through Cox multivariate analysis, we learned that age, race, gender, primary site, chemotherapy, and tumor stage were risk factors associated with survival. The nomogram this study shows that PB-DLBCL is a disease with a good prognosis, and although it is highly malignant, even some elderly people can survive for a long time after the disease[12]. This is in line with the results of some previous studies, where the 5-year survival rate of PB-DLBCL was able to exceed 70%[3, 13]. At the same time, some retrospective studies with small samples mentioned that the incidence rate of males is higher than that of females[14, 15], which is the same as our research results. In the K-M curves, we also found that OS was higher in men than in women. Age has always been an important factor affecting many malignancies, and in the study by Wang et al, it was found that patients with primary bone malignant lymphoma had a higher risk of death from OS and CSS in patients over 61 years old, up to 7 times [6]. Although our findings also show that older patients have a higher risk of death for OS and CSS, we think this question should be analyzed comprehensively, as many older patients have poor physical condition and also

contribute to increased mortality. The same is true for race. Due to the limitations of the Seer database, we included more patients who were white, which may cause data bias.

PB-DLBCL can occur in all bones of the body, with long bones and the spine being the most common[16]. On imaging, approximately 70% show osteolytic destruction [17]. In our study, we found that the primary site of the tumor also affected patient OS, CSS. tumor survival was significantly lower in the spine primary than in the extremity bones. In our analysis, this may be related to the compression of nerves by spinal lesions thus leading to more severe complications and reduced survival. For example: paralysis[18].

In recent years, many studies have been conducted on the best treatment options for PB-DLBCL. CHOP and CHOP-like regimens are commonly used for chemotherapy, and there are no clear guidelines for combination regimens. In the study by Bruno Ventre et al, patients with PB-DLBCL showed a good prognosis when receiving anthracycline-based chemotherapy regimens with or without the administration of radiotherapy regimens. In patients receiving radiotherapy, the use of larger radiation fields and doses was not associated with better outcomes[3]. In a further combination regimen Pfreundschuh M et al. suggest that rituximab in combination with CHOP-like chemotherapy regimens improves the long-term prognosis of young patients with diffuse large B-cell lymphoma [18]. In the Bhagavathi S et al study, the addition of rituximab increased 3-year PFS (progression-free survival) from 52% to 88%[19]. Radiotherapy used the usual doses for non-Hodgkin's lymphoma (35-45 Gy in 1.8-2 Gy fractions)[20], In numerous scholarly studies, it is also suggested that radiotherapy should only be used as a consolidation option for treatment [8]. However, in the present study, we conclude that surgical treatment is not a factor affecting patient survival. It is also mentioned in some studies that surgery does not seem to be a necessary option for patients with PB-DLBCL [12, 21]. With the progress of chemotherapy and radiotherapy, most surgical operations are used to clarify the nature of lesions.

Of course, there are some limitations in our current study. First, we only used the Seer database and did not apply information from other databases for external validation. Finally, the SEER database lacks some important information, such as disease progression, comorbidities, and complications, as well as specific information on radiotherapy and chemotherapy. This lack of information is also the direction of our future research. However, these defects did not affect the results obtained in this study. Although these factors made the study imperfect, we evaluated the impact of various factors on the survival of patients with PB-DLBCL, and the line graphs were able to help clinicians predict the prognosis of their patients.

Conclusion

The current study identified age, race, primary site, and chemotherapy as variables affecting OS in PD-DLBCL patients; age, race, and chemotherapy as variables affecting CSS. These factors were incorporated into the construction of the nomogram, and the nomogram we constructed were able to

provide more accurate individual survival predictions for PD-DLBCL patients to some extent and help physicians make appropriate clinical decisions.

Abbreviations

Primary bone diffuse large B-cell lymphoma (PD-DLBCL); Surveillance, Epidemiology, and End Results (SEER); overall survival (OS); cancer-specific survival (CSS); Primary bone lymphoma (PBL); PFS (progression-free survival)

Declarations

Acknowledgments

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Authors' contributions

All authors were responsible for experimental design. XY is mainly responsible for data analysis and article writing. HX is involved in data analysis, ZY is responsible for experimental design guidance.

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Availability of data and materials

Our data is available from the Surveillance, Epidemiology, and End Results (SEER) research database. This is a public research database.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no potential conflicts of interest.

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Figures

Figure 1

Optimal age cutoff by X-tile analysis. (A) black spot indicates that the optimal cut-off for age has been determined. (B) histograms and (C) Kaplan-Meier curves were constructed based on determined cutoff values.

Figure 2

Nomogram for the prediction of 3 and 5 year OS CSS in patients with PB-DLBCL. OS, overall survival. CSS,Cancer-Specific Survival. PB-DLBCL,Primary bone diffuse large B-cell lymphoma.

Figure 3

ROC curves of 3-year and 5-year OS, CSS in PB-DLBCL patients. (A) ROC curves for the training cohort for 3 and 5 years OS. (B) ROC curves for the training cohort for 3 and 5 years CSS. (C) ROC curves for the validation cohort for 3 and 5 years OS. (C) ROC curves for the validation cohort for 3 and 5 years CSS. OS, overall survival. CSS,Cancer-Specific Survival. PB-DLBCL,Primary bone diffuse large B-cell lymphoma.

Figure 4

Calibration curves for predicting 3- and 5-year OS, CSS nomogram in patients with PB-DLBCL. (A) Calibration curves for 3- and 5-year OS for the training cohort. (B) Calibration curves for 3- and 5-year OS of the validation cohort. (C) Calibration curves for the 3- and 5-year CSS for the training cohort. (D) Validation cohort 3-year and 5-year CSS calibration curves. OS, overall survival. CSS, Cancer-Specific Survival. PB-DLBCL, Primary bone diffuse large B-cell lymphoma.

A

B

Figure 5

Nomogram of the decision curves, A (OS, 5-years) and B (CSS,5-years).The x-axis represents the threshold probability and the y-axis represents the net benefit.

Figure 6

Survival curves for factors associated with healing in 891 patients.