



Original Research

Prognosis of primary hepatic lymphoma: A US population-based analysis

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ABSTRACT

Objective: Primary hepatic lymphoma (PHL) is a rare malignancy with lesions confined to the liver. It is characterized by a large number of monomorphic, medium-sized lymphocytic infiltrates in the hepatic sinusoid. Due to the rarity of this malignancy, our current understanding of PHL is limited.

Methods: We collected incidence, mortality, and clinical data of PHL patients diagnosed between 1975 and 2016 using the Surveillance, Epidemiology, and End Results (SEER) database. The annual percentage changes (APCs) and prognoses were analyzed using the Joinpoint and R package.

Results: Among the 1,372 patients, white males were prevalent, and the most common histological subtype was diffuse large B-cell lymphoma (DLBCL). The incidence and mortality rate of PHL was 0.075/100,000 person-years and 0.055/100,000 person-years, respectively. The annual incidence rate of PHL increased significantly, with an APC of 2.74% ($P < 0.001$). The 3- and 5-year overall survival (OS) rates of patients with PHL were 43.553% and 39.242%, respectively. The 3- and 5-year relative survival (RS) rates were 46.925% and 45.300%, respectively. Multivariate Cox regression analysis revealed that older age, black, DLBCL, and advanced-stage disease were independent predictors of unfavorable OS and RS. The C-index and receiver operating characteristic (ROC) analysis confirmed the prognostic value of the nomograms established in this study.

Conclusion: The nomogram established in this study is a robust tool to predict the prognosis of PHL patients.

Introduction

Primary hepatic lymphoma (PHL) is a lymphoproliferative disease originating from intrahepatic lymphatic and residual hematopoietic tissues and is characterized by the absence of extrahepatic infiltration [1]. PHL is a rare disease, accounting for 0.1% of all liver malignancies, 0.4% of extranodal non-Hodgkin lymphomas (NHLs), and 0.016% of all NHLs [2,3].

PHL pathological features are similar to those of common liver tumors and can be broadly classified into three types: (1) unimodular, characterized by a single lesion > 3 cm in diameter; (2) multinodular, characterized by multiple lesions of varying size, usually < 3 cm in

diameter; (3) diffuse or hepatomegaly, characterized by the absence of distinct lesions. PHL often manifests as a solitary mass (42%) or as multiple lesions (50%) [4-6]. PHL patients present with various nonspecific symptoms, including fever, night sweats, abdominal pain, and hepatomegaly [4,7]. On ultrasonography, PHL lesions appear hypochoic relative to normal liver, while computed tomography (CT) scanning shows hypoattenuating lesions with uniform contrast enhancement [8]. Magnetic resonance imaging (MRI) in PHL patients often reveals hypointense lesions on T1-weighted images and hyperintense lesions on T2-weighted images; diffusion-weighted imaging (DWI) detects high-signal lesions, likely due to the high density of lymphoma cells, low interstitial component, and lack of blood supply in the lesions

Abbreviations: PHL, primary hepatic lymphoma; SEER, surveillance, epidemiology, and end results; APC, annual percentage changes; DLBCL, diffuse large B-cell lymphoma; OS, overall survival; RS, relative survival; ROC, receiver operating characteristic; NHLs, non-Hodgkin lymphomas; CT, computed tomography; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; PET, positron emission tomography; 18F-FDG, fluorine-18-2-fluoro-2-deoxy-d-glucose; AJCC, American joint committee on cancer; DSS, disease-specific survival; MZL, marginal zone lymphoma; CI, confidence interval.

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[9,10]. Diffuse PHL manifests as hepatomegaly without significant changes in density and signal; hence, diffuse PHL lesions are challenging to detect on MRI and CT. Positron emission tomography (PET) combined with CT in a single procedure (PET/CT) with fluorine-18-2-fluoro-2-deoxy-D-glucose (18F-FDG) is a whole-body imaging with high sensitivity and specificity for lymphoma, especially for Hodgkin lymphoma or aggressive NHL, which can clearly show the involvement of systemic lymph nodes and extra-nodal organs, and identify areas of lymphoma missed by CT alone, so it is widely used in the diagnosis, staging, and prognostic evaluation of lymphoma [11-13]. The application of FDG-PET/CT in the staging and re-staging of lymphoma is widely recognized and has been included in the American lymphoma treatment guidelines [14]. 18F-FDG PET/CT can distinguish primary liver lesions from metastatic disease. The degree of FDG uptake in PHL depends on the pathology of the lymphoma. The present results demonstrated that FDG uptake was lower in indolent lymphomas than in aggressive diseases like diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma, and T-cell lymphoma [15,16]. It should be noted that PET/CT may produce false positive for some non-malignant causes with moderate FDG avidity (e.g. granulomatous inflammation). Where the comprehensive evaluation seems unusual additional targeted biopsies should be considered. Liver biopsy remains the most valuable tool for the diagnosis of PHL [5].

Due to the rarity of this malignancy, our current understanding of PHL is predominantly derived from case reports or case series. In this retrospective study, we collected data from PHL patients through the Surveillance, Epidemiology, and End Results (SEER) database to assess the clinical characteristics, outcomes, and prognostic factors in PHL. We also developed a simple nomogram to refine PHL assessment and provide clinical guidance.

Materials and methods

Data collection

The SEER database is one of the most extensive and representative tumor registration databases in North America. We collected data from the SEER 18 (1975–2016, Nov2018 Sub) database released in April 2019 using the SEER* Stat software (Version 8.3.6) [17] and the following inclusion criteria: (1) diagnosis between 1975 and 2016; (2) C22.0 primary site code; (3) international classification of diseases for oncology, 3rd edition (ICD-O-3) codes of 9590–9591, 9650–9699, and 9702–9729. We collected information about age, gender, race, marital status, morphological subtype, surgery, radiation, chemotherapy, cancer stage, year of diagnosis, survival status, survival time, and the cause of death. Cancer stage was reported according to the Ann Arbor staging system of lymphoma. Data from patients with a prior cancer diagnosis and without microscopic confirmation were excluded. Patients whose diagnosis was based on autopsy or death certificate were also excluded [18].

Statistical analysis

The long-term incidence and mortality rates were age-adjusted as per the 2000 US standard population between 1975 and 2016. Annual percentage changes (APCs) were calculated using a log-linear model and Joinpoint software (Version 4.5.0). If no cases or deaths were recorded in a certain year, the incidence or mortality rate was recorded as a small positive constant (0.0001) for logarithmic transformation [19]. Statistical significance was determined using the Student's *t*-test [20]. We assessed the overall survival (OS), disease-specific survival (DSS), and relative survival (RS) using the actuarial method [21]. OS was defined as the survival rate for the respective time, regardless of the cause of death. DSS rate was defined as the survival rate for the respective

Table 1
Characteristics of patients with primary hepatic lymphoma (n = 1372).

Characteristics	No. of patient (%)
Age (years)	
< 60	581(42.35)
60–69	261 (19.02)
70–79	314 (22.89)
≥ 80	216 (15.74)
Gender	
Female	521 (37.97)
Male	851 (62.03)
Race	
White	1134 (82.66)
Black	140 (10.20)
Other	91 (6.63)
Unknown	7 (0.51)
Marital status	
Unmarried	673 (49.05)
Married	633 (46.14)
Unknown	66 (4.81)
Histology	
Hodgkin lymphoma	33 (2.41)
Non-Hodgkin lymphoma	1086 (79.15)
Lymphoma, NOS	253 (18.44)
NHL subtypes	
DLBCL	856 (78.82)
Follicular lymphoma	34 (3.13)
Marginal zone lymphoma	49 (4.51)
Small lymphatic lymphoma	27 (2.49)
Burkitt's lymphoma	47 (4.33)
Mixed diffuse B-cell lymphoma	14 (1.29)
Mantle cell lymphoma	5 (0.46)
T/NK-cell lymphoma	51 (4.69)
Lymphoblastic lymphoma	3 (0.28)
Surgery	
No surgery	1174 (85.57)
Surgery	157 (11.44)
Unknown	41 (2.99)
Radiation	
No radiation	1364 (99.42)
Radiation	8 (0.58)
Chemotherapy	
No/unknown	478 (34.84)
Chemotherapy	894 (65.16)
Stage	
I	530 (38.63)
II	140 (10.20)
III	34 (2.48)
IV	602 (43.88)
Unknown	66 (4.81)
Year	
1975–1985	25 (1.82)
1986–1999	276 (20.12)
2000–2016	1071 (78.06)

NOS: not otherwise specified; NHL: Non-Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma.

time for a specific cause of death (not from PHL). RS was defined as the survival rate for the respective time to exclude death from non-cancer causes. The Ederer method was used to calculate RS [22]. Cases with a recorded survival time of zero were excluded from the survival analysis. The Cox regression analysis, Kaplan–Meier survival analysis, nomogram drawing and correction, and competitive risk analysis were performed using R language software (Version 3.6.1).

Results

Demographic and clinical characteristics

According to our inclusion and exclusion criteria, 1372 patients were selected (Fig. 1), the demographic and clinical characteristics of whom are shown in Table 1. Male patients were approximately two times as

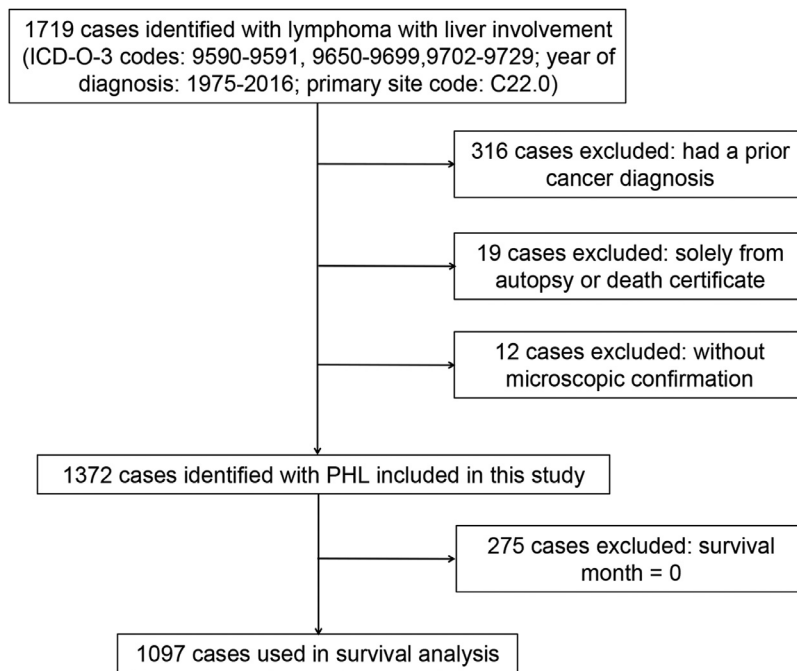


Fig. 1. Flow diagram of patient selection from the SEER database between 1975 and 2016.

many as female patients, and white individuals accounted for the majority (82.66%) of PHL cases. NHL was diagnosed in 79.15% of PHL patients, while Hodgkin lymphoma accounted for only 2.41% of PHL cases. The most common NHL subtype was DLBCL (78.82%), followed by T/NK-cell lymphoma (4.69%), marginal zone lymphoma (MZL; 4.51%), Burkitt's lymphoma (4.33%), follicular lymphoma (3.13%), and small lymphatic lymphoma (2.49%). Most patients did not receive surgery and radiotherapy; chemotherapy was administered to 65.16% of patients. The number of PHL cases increased significantly over time, especially since 2000.

Incidence and mortality

The age-adjusted incidence and mortality rates during the study period were 0.075 per 100,000 person-years (95% confidence interval [CI], 0.070–0.081) and 0.055 per 100,000 person-years (95% CI, 0.051–0.060), respectively. Overall, the incidence of PHL increased from 0.021 per 100,000 person-years (95% CI, 0.006–0.055) in 1975 to 0.122 per 100,000 person-years (95% CI, 0.087–0.167) in 2016, leading to an APC of 2.74% (95% CI, 1.24–4.32; $P < 0.001$; Fig. 2A and Supplementary Table 1). PHL mortality increased from 0.005 per 100,000 person-years (95% CI, 0.000–0.031) in 1975 to 0.078 per 100,000 person-years (95% CI, 0.046–0.123) in 1993, resulting in an APC of 20.85% (95% CI, 11.03–31.62; $P < 0.001$); PHL mortality remained stable between 1993 and 2016 (APC, -0.17% ; 95% CI, -2.54 – 2.31 ; $P = 0.610$; Fig. 2B and Supplementary Table 2).

Patient prognosis analysis

The age-adjusted OS, RS, and DSS rates from 1975 to 2016 were calculated using the actuarial method. The 1, 3, 5, and 10-year OS rates of PHL patients were 49.684%, 43.553%, 39.242%, and 28.364%, respectively, while RS rates were 51.068%, 46.925%, 45.300%, and 38.723%, respectively. The 1, 3, 5, and 10-year DSS rates were 53.711%, 49.189%, 47.842%, and 43.464%, respectively (Fig. 3).

The results of univariate and multivariate analyses are shown in Fig. 4. Univariate analysis revealed that the following factors were associated with poor OS in PHL patients: older age (> 60 years old vs. < 60 years old), unmarried status (unmarried vs. married), advanced disease stage (stage III/IV vs. stage I), a histologic subtype of DLBCL (DLBCL vs. follicular lymphoma and MZL), a histologic subtype of mixed diffuse B-cell lymphoma (mixed diffuse B-cell lymphoma vs. DLBCL), and diagnosis between 1986 and 1999 (1986–1999 vs. 1975–1985). Multivariate analysis identified the following parameters as independent worse prognostic factors: older age (> 60 years old vs. < 60 years old), male (male vs. female), black (black vs. white), unmarried status (unmarried vs. married), no chemotherapy (no chemotherapy vs. chemotherapy), advanced stage (stage III/IV vs. stage I), a histologic subtype of DLBCL (DLBCL vs. follicular lymphoma, MZL, and small lymphatic lymphoma), a histologic subtype of mixed diffuse B-cell lymphoma (mixed diffuse B-cell lymphoma vs. DLBCL), and diagnosis between 1986 and 1999 (1986–1999 vs. 1975–1985) (Fig. 4A). For RS, univariate analysis revealed that the following factors were associated with unfavorable survival outcomes: older age (> 60 years old vs. < 60 years old), advanced stage (stage IV vs. stage I), a histologic subtype of DLBCL (DLBCL vs. MZL), a histologic subtype of mixed diffuse B-cell lymphoma (mixed diffuse B-cell lymphoma vs. DLBCL), and diagnosis between 1975 and 1985 (1975–1985 vs. 2000–2016). Older age (> 60 years old vs. < 60 years old), unmarried status (unmarried vs. married), advanced stage (stage III/IV vs. stage I), and a histologic subtype of DLBCL (DLBCL vs. follicular lymphoma and MZL) were identified as independent prognostic factors for poor RS (Fig. 4B).

The Kaplan–Meier survival analysis revealed that the patients who were younger, were white, were married, were diagnosed with follicular lymphoma, MZL, and Burkitt's lymphoma, had disease of early stage (stages I and II), and were diagnosed in 1975–1985 predicted longer OS (Fig. 5A). In contrast, the marital status did not associate significantly with RS, while diagnosis in 1975–1985 was associated with poor RS (Fig. 5B). To assess the role of baseline characteristics in OS, we classified deaths into cancer-related deaths and non-cancer-related deaths (e.g., chronic liver disease and heart disease). We found that older,

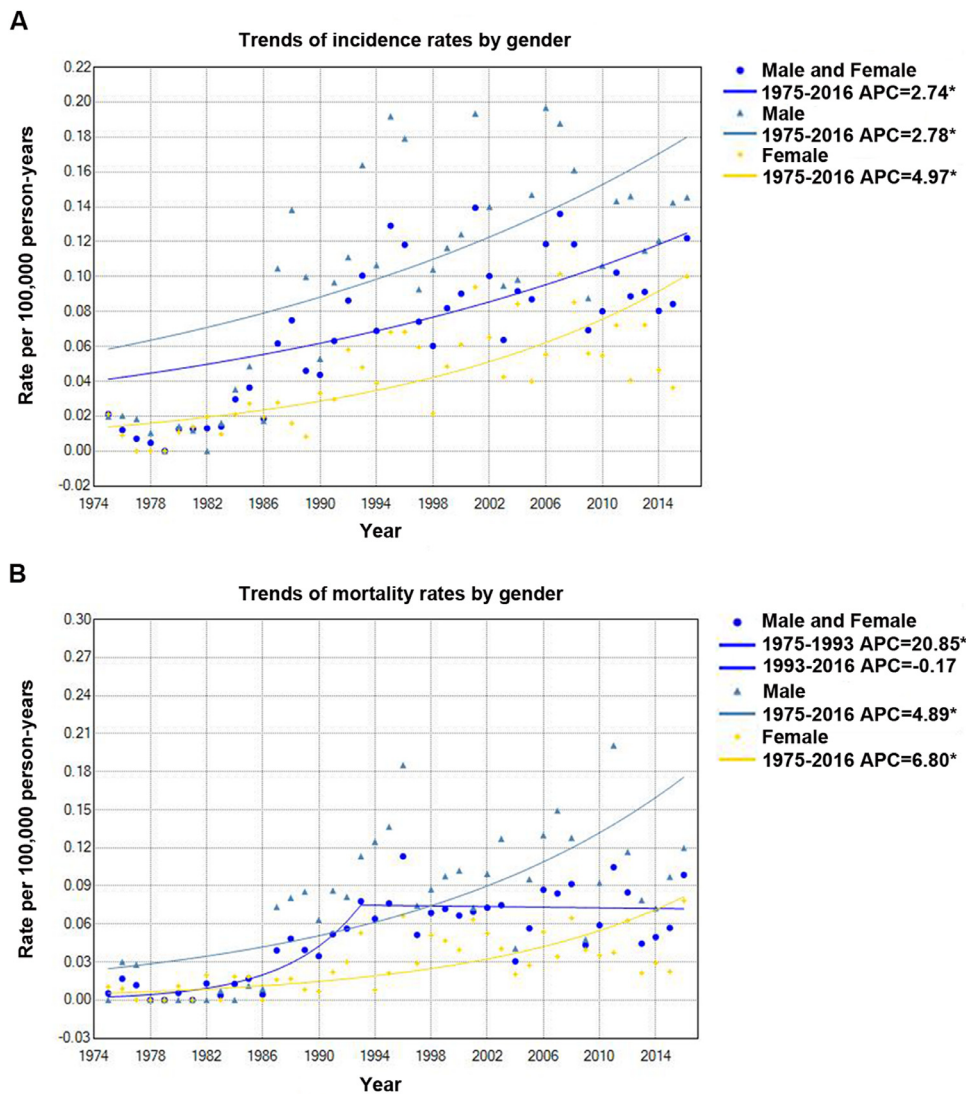


Fig. 2. Incidence and mortality rates of primary hepatic lymphoma (PHL) and annual percentage change (APCs) in PHL trends. (A) Incidence rates and relative APCs. (B) Mortality rates and relative APCs. Notes: incidence and mortality rates were age-adjusted as per the 2000 US standard population and expressed per 100,000 person-years.

black, unmarried PHL patients with DLBCL or T/NK-cell lymphoma had a significantly increased risk of cancer-related death, while older patients had an increased risk of non-cancer related death (Supplementary Fig. 1).

Clinical stage is important for the prognosis and treatment guidance of PHL. We analyzed the correlation between clinical stage and common variables (Supplementary Table 3). The results showed that clinical stage was associated with age and NHL subtypes, but not with gender, race, and marital status. We found that more patients in the early stage who were older than younger and the age composition ratio was not significantly different in the later stage. The most common diffuse large B-cell lymphoma was also not significantly different in clinical stage.

Nomograms predict PHL patient prognosis

To evaluate the prognostic value of different clinicopathological characteristics, we plotted nomograms of OS and RS and all clinicopathological variables except surgery and radiation (Fig. 6A and B). The prognostic accuracy of the nomograms was evaluated using the C-index and the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. The C-index for OS was 0.640 (95%

CI, 0.616–0.664), and the AUC values for the 1, 3, 5, and 10-year OS were 0.600, 0.647, 0.627, and 0.665, respectively (Fig. 7A). The C-index for RS was 0.697 (95% CI, 0.670–0.728), and the AUC values for the 1, 3, 5, and 10-year RS were 0.700, 0.703, 0.691, and 0.717, respectively (Fig. 7B).

Discussion

Although PHL is extremely rare, our understanding of PHL has increased over the last years. In this study, we collected data from 1372 PHL cases from the SEER database (1975 to 2016). To our best of knowledge, this is the largest evaluation of hepatic lymphoma to date. We found that the annual prevalence of PHL increased from 1975 to 2016, reaching a peak of 78.06% of the total number of patients after 2000. Over the 40-year period, the incidence rate of APC for male and female patients was 2.78% (95% CI, 1.24–4.26; $P < 0.001$) and 4.97% (95% CI, 2.58–7.43; $P < 0.001$), respectively. The overall mortality rate of PHL also gradually increased until 1993, but then stabilized between 1993 and 2016 with the mortality rate of APC of -0.17% (95% CI, -2.47 – 2.33 ; $P > 0.05$), likely due to the significant improvement in early screening and treatment of PHL.

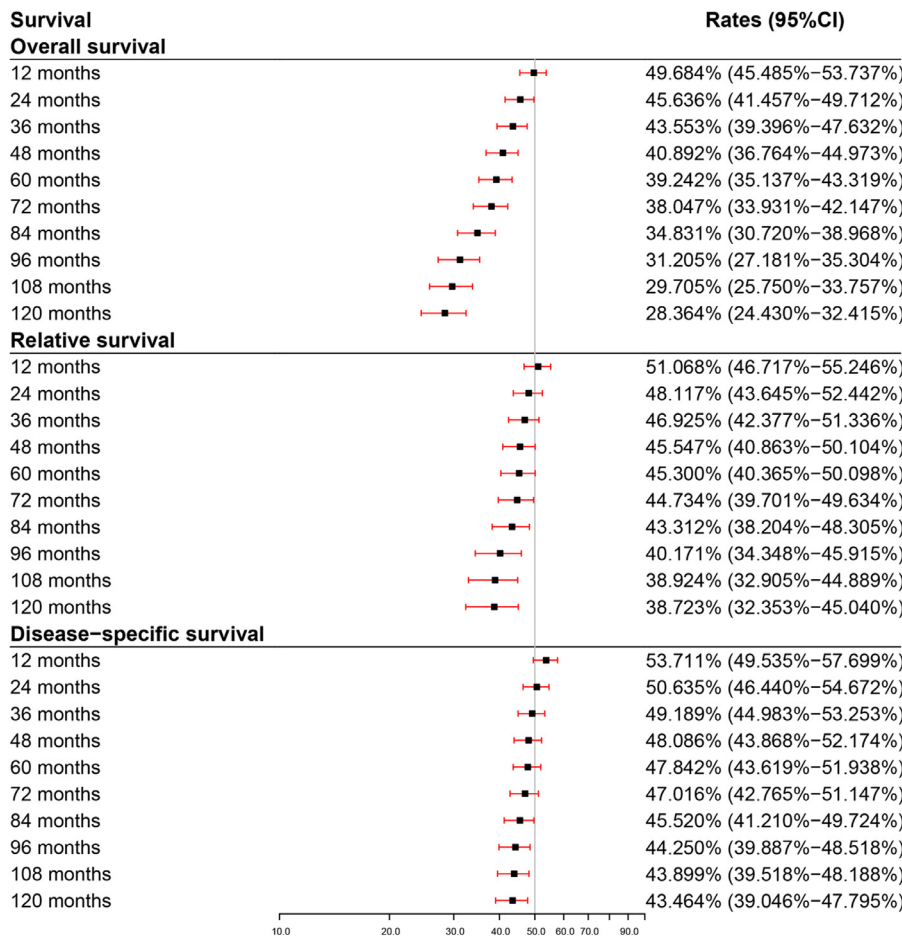


Fig. 3. Overall survival, relative survival, and disease-specific survival rates in patients with primary hepatic lymphoma were estimated using the actuarial method.

At present, PHL etiology remains largely unclear. In recent years, studies have indicated that the increased incidence of PHL may be related to the human immunodeficiency virus (HIV) and hepatitis B/C virus epidemic, which may stimulate B lymphocytes chronic proliferation and chronic antigenic stimulation, leading to liver lymphoma [23–26]. In addition, PHL was usually seen in organ transplant recipients, in patients receiving immunosuppressive therapy, etc. Since the virus is not integrated into the host cell genome, it is more likely for the virus to disrupt the immune environment, leading to immune escape of malignant cells for proliferation and invasion. These all indicate that the host’s immune environment plays an important role in the onset and progression of PHL. Of course, the increased incidence of PHL may also be related to modern imaging techniques, especially the use of PET/CT. Only when the detection technique is higher, people are more aware of it and it is easier to consider the disease. Although PHL can occur at any age, it is common in men aged 50–60 with a male-to-female ratio of 2–3:1 [5,27,28]. In this study, the median age at diagnosis was 65 years (range, 3–95 years), similar to what previous studies have reported. The male-to-female ratio was 1.63 (62.03% vs. 37.97%). DLBCL is the most frequent PHL, especially with often unimodular [2,26,29]. Notably, hepatic DLBCL accounted for approximately 6% of all primary extranodal DLBCL [30]. In this study, we found a considerably lower frequency of Hodgkin lymphoma (2.41%) compared to that reported previously [31]. B-cell NHL accounted for approximately 80.11% of all hepatic NHLs, and the most common histological subtype was DLBCL, which was observed in 856 (78.82%) cases. T/NK-cell NHL accounted for 4.69%, and the most observed

subtypes were peripheral T-cell lymphoma-NOS (33 cases) and anaplastic large cell lymphoma (13 cases), consistent with previous reports [32].

Surgery, chemotherapy, radiation therapy, or combination therapies are used for PHL [5,33]. Liver transplantation has also been used in PHL patients [7]. In our data, most patients (65.16%) received chemotherapy, while the proportion of patients that underwent surgery or radiation was low. Although surgery and radiation therapy were included in the Cox proportional hazards model and Kaplan–Meier survival analyses, we excluded these treatment modalities from the nomograms, to avoid sampling bias. The median OS for patients with PHL was 56.02 months, and 661 patients (60.26%) died during the study period. PHL was the cause of death in 43.58% cases. Other major causes of death included cardiovascular diseases (4.16%), other malignant cancers (3.51%), infectious diseases (1.02%), cerebrovascular diseases (0.92%), and chronic obstructive pulmonary diseases (0.3%). We identified older age, unfavorable histologic subtypes, and advanced disease stage as independent factors predicting poor OS and RS, which may partly reflect the increased malignancy of PHL and the impact of poor physical performance. Kaplan–Meier survival curve revealed that black patients aged over 60 years with unfavorable histologic subtypes and advanced-stage disease had shorter OS and RS. However, between 1975 and 1985, patients had shorter RS, suggesting that patients may have a significantly increased risk of death due to untimely diagnosis and treatment of the disease during this time. The RS of PHL patients was significantly longer between 2000 and 2016, likely due to the development of new drugs, such as rituximab [34]. Cur-

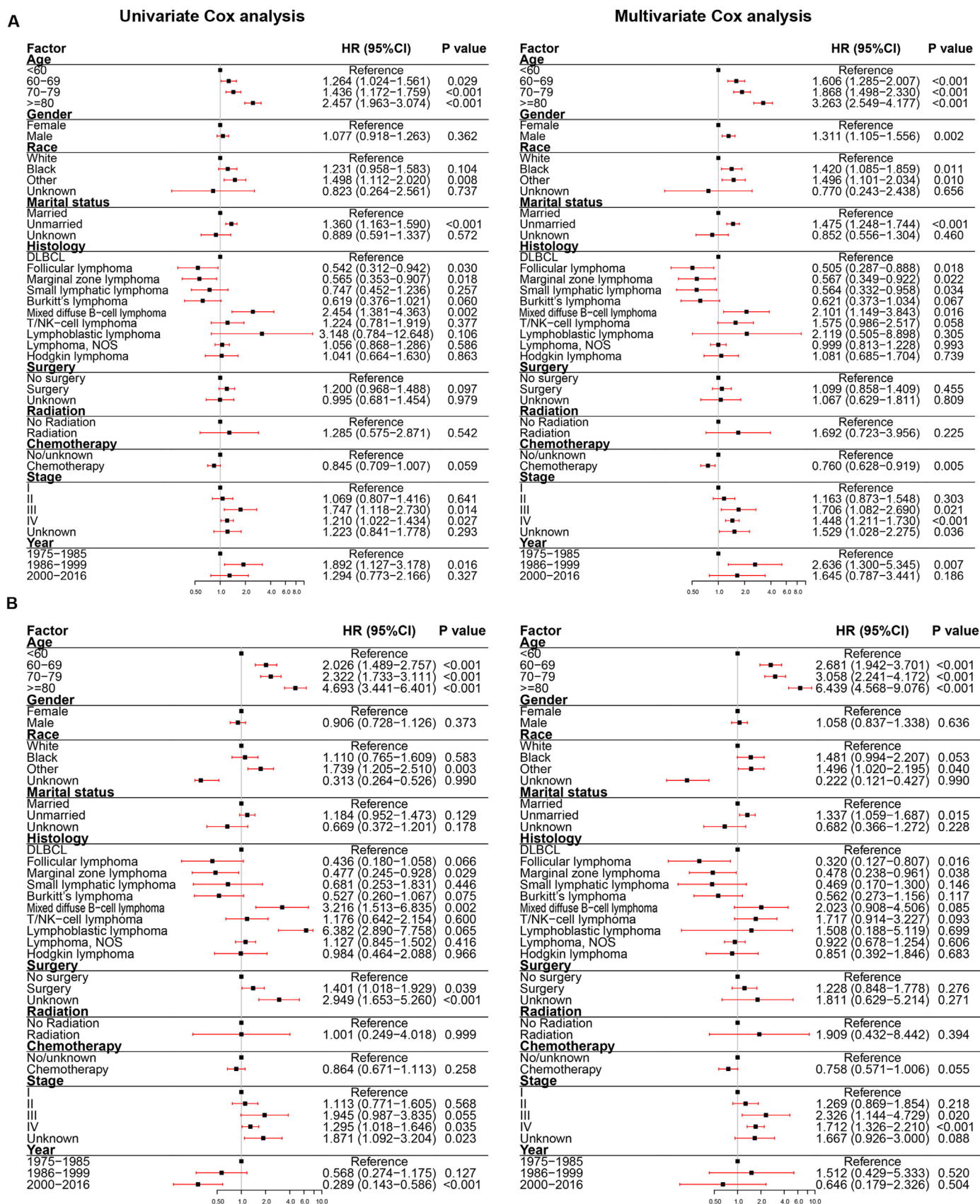


Fig. 4. Forest plot showing the univariable and multivariate analyses results for patients with primary hepatic lymphoma using the Cox proportional hazards model. (A) Cox regression for overall survival analysis. (B) Cox regression for relative survival analysis.

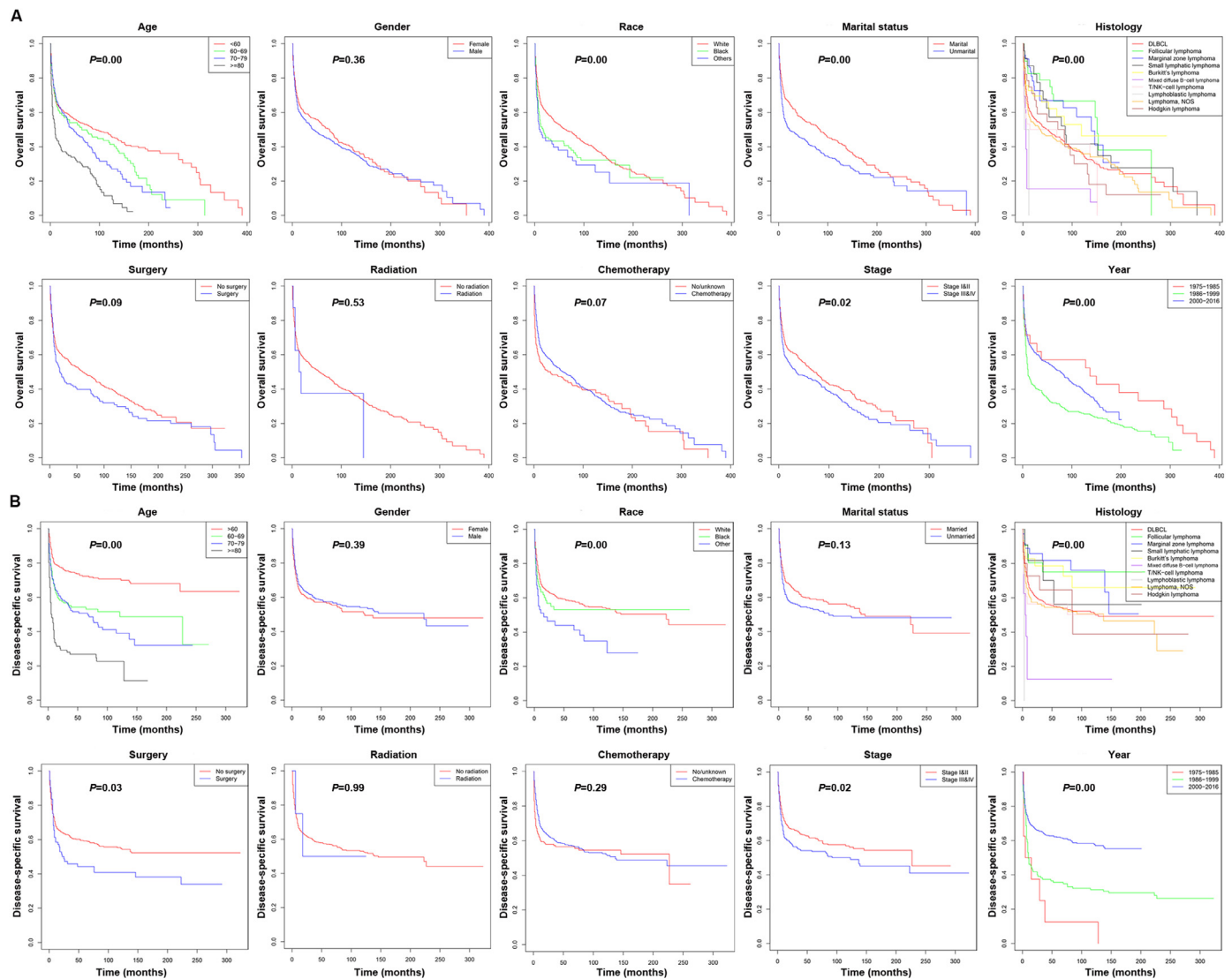


Fig. 5. Kaplan–Meier survival analyses for overall survival (OS) and relative survival (RS) in patients with primary hepatic lymphoma (PHL). (A) OS analyses of PHL patients. (B) RS analyses of PHL patients.

rently, most PHL patients with early disease are treated with vincristine, cyclophosphamide, doxorubicin, and prednisone-based chemotherapy; the combination of rituximab with conventional chemotherapeutics is also being used [5,35–38]. Thus, the better survival of PHL observed in our study since 2000 may reflect the more frequent use of new drugs.

Nomograms are used to predict the patient outcome using scores from different indicators [39]. Approximately 50% and 30% of PHL patients had a score > 100 for the 3-year and 10-year OS, respectively, while the rates for RS were 55% and 45%, respectively. Additionally, the C-index and AUC values confirmed that our nomograms are a feasible and accurate prognostic tool in PHL.

Our study has several limitations. First, the prognosis treated with non-surgical and non-radiation approaches were better, likely due to the high disproportionation of these patients in the study cohort. Hence, the clinical usefulness of surgery and radiation therapy in PHL patients remains unclear. Second, information on chemotherapy was inaccurate or absent for some patients. 34.84% of all PHL

patients had no information regarding chemotherapy, which might have impacted our findings in the clinical value of chemotherapy in improving patient survival. In recent years, tumor immunotherapy has been recognized as the most promising method for curing malignant tumors. More and more immune checkpoint inhibitors have been applied to the rare cancers like PHL that have no specific treatment. In recent years, targeted immunotherapy for CD20-positive B lymphoma represented by rituximab has further improved the prognosis [40–43]. However, the SEER database lacks data records for these variables, and we were unable to analyze the prognostic impact of chemo-immunotherapy on patients with PHL. Third, studies have shown that laboratory parameters, including abnormal lactate dehydrogenase, abnormal aminotransferases, and alkaline phosphatase, have prognostic value in PHL [5,33]. However, this information, as well as information on liver infections, was not available in the SEER database. Despite these limitations, the SEER database remains a valuable resource for the study of PHL and other rare cancers based on a large population.

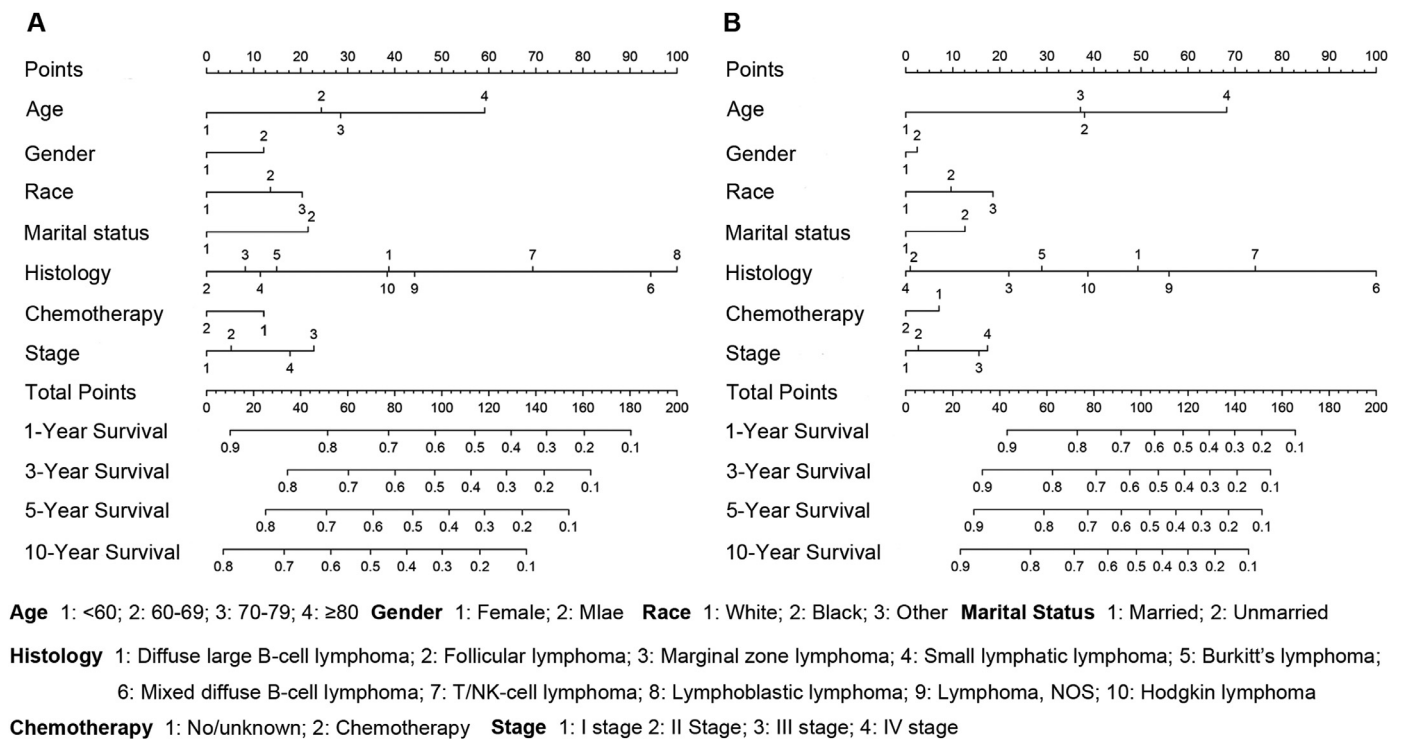


Fig. 6. (A, B) Nomograms for predicting overall survival (A) and relative survival (B) of patients with primary hepatic lymphoma (PHL).

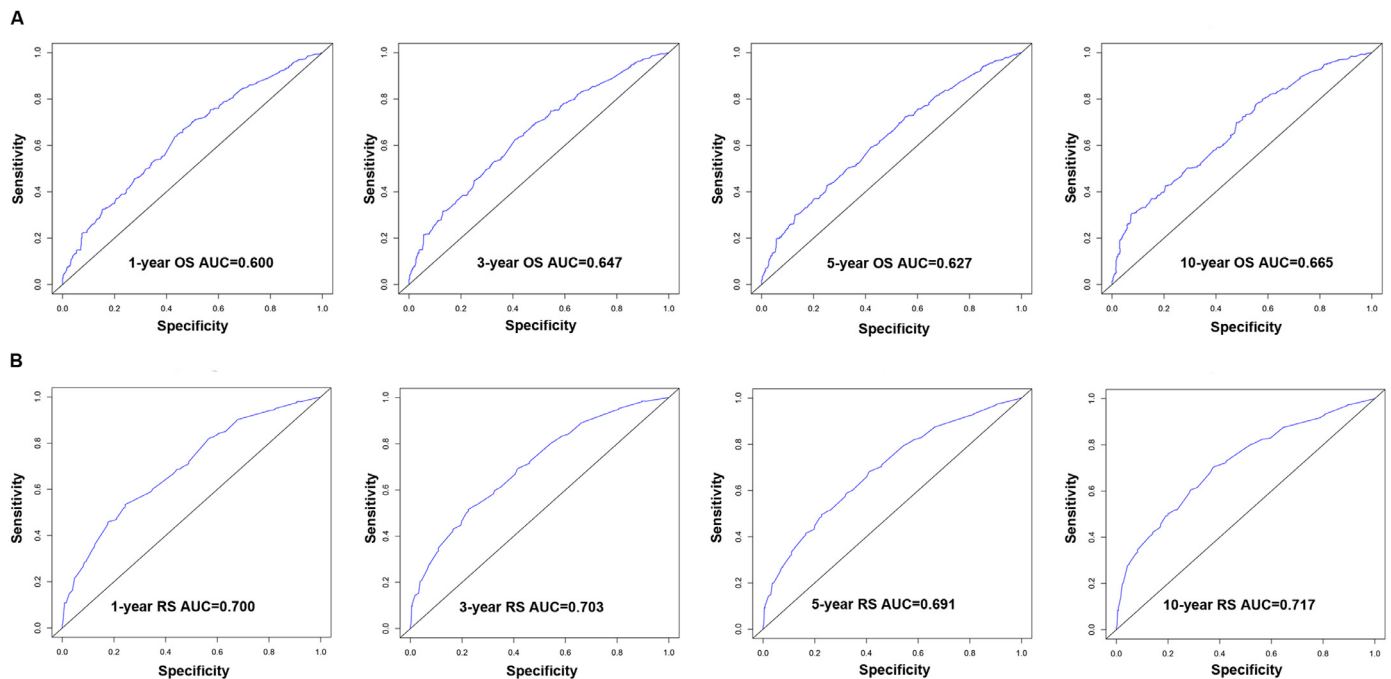


Fig. 7. (A, B) Receiver operating characteristic (ROC) curves and area under the curve (AUC) values for overall survival (A) and relative survival (B).

Conclusion

Although the primary extranodal lymphoma of the liver is rare, the incidence of PHL is rising. NHL is the most dominant PHL subtype. Unfavorable histologic subtypes, and advanced-stage disease were associated with poor survival outcomes. The nomogram established in this study may be a robust prediction model for PHL that can

forecast patients' dynamic survival rates at different time points during follow-up.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Meng-jun Qiu: Resources, Investigation, Validation, Writing - original draft, Writing - review & editing. **Xie-fan Fang:** Resources, Investigation, Validation. **Zao-zao Huang:** Resources, Investigation, Validation. **Qiu-ting Li:** Data curation, Formal analysis. **Meng-meng Wang:** Data curation, Formal analysis. **Xin Jiang:** Data curation, Formal analysis. **Zhi-fan Xiong:** Conceptualization, Methodology, Software. **Sheng-li Yang:** Conceptualization, Methodology, Software.

Ethics approval and consent to participate

Patient consent for this retrospective study was not required.

Consent for publication

The manuscript is approved by all authors for publication.

Availability of data and material

The data is available on the Surveillance, Epidemiology, and End Results (SEER, <http://seer.cancer.gov>) database.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2020.100931.

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