Non-Hodgkin Lymphoma of the Liver: 
A US Population-based Analysis

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Abstract

Background and Aims: Non-Hodgkin lymphoma (NHL) of the liver is a rare lymphoid malignancy, accounting for less than 1% of extranodal lymphomas. Methods: I conducted an analysis of the U.S Surveillance, Epidemiology, and End Results (SEER) database to evaluate the histological subtypes and the survival outcomes of 785 cases with hepatic NHL between 1973 and 2012. Results: There were 785 of 312 459 cases with NHL had a first primary hepatic NHL (0.25%). Of the total 785 cases, the median age at diagnosis was 61 years (range 3–95 years) and male-female ratio of 1.7:1. The most common subtype was diffuse large B cell lymphoma (63.2%). In all patients, the median overall survival (OS) was 33 months (95%CI, 22–48 months). The 5-year OS rate for indolent B-cell NHLs was 62%, compared with 44% for an aggressive B-cell NHLs and 42% for T-cell NHLs. The median OS improved from 19 months in patients diagnosed in a period 1996–2000 to 60 months when diagnosed between 2006 and 2012 (p < .001). In a multivariable Cox regression analysis, the age ≥80 years (adjusted hazard ratio [aHR] 3.21, p < .001), male gender (aHR 1.26, p = .02), Black race (aHR, 1.70, p < .001), and T-cell NHL variants (aHR 1.73, p = .03) were unfavourable prognostic factors. Conclusion: NHL of the liver comprises about 0.3% of all NHLs and survival was improved in the recent calendar period. Citation of this article: El-Fattah MA. Non-Hodgkin lymphoma of the liver: a US population-based analysis. J Clin Transl Hepatol 2017;5(2):1–9. doi: 10.14218/JCTH.2017.00015.

Introduction

Non-Hodgkin lymphoma (NHL) is the sixth leading cause of new cancer cases among men and the fifth among women, accounting for 3% to 4% of cancer-related deaths in the United States. Approximately 25% to 40% of NHL patients present with an extranodal lymphoma. Although liver contains lymphoid tissue, host factors seem to make the liver a poor environment for the development of malignant lymphomas. NHL is more likely than Hodgkin lymphoma to have hepatic involvement. The prevalence of liver involvement by NHL is reported to be 15% to 30%, and more than 50% in necropsy studies. Primary hepatic lymphoma (PHL) is a lymphoma limited to the liver or having major liver involvement without evidence of extrahepatic involvement (e.g., no spleen, lymph nodes, bone marrow, peripheral blood, or other lymphoid structures) for at least 6 months. PHL represents 0.4% of extranodal NHLs and 0.016% of all NHLs. Based on liver infiltration, PHL can be subdivided into uninnodal (39–42%), multinodular (50–55%), and diffuse (6–8%) types. Diffuse liver involvement of PHL is usually observed in immuno-compromised patients, such as human immunodeficiency virus (HIV) or liver diseases. Among 205 liver biopsies with lymphoma, 45% was diffuse large B cell lymphoma (DLBCL), and 12% was T cell lymphoma.

PHL most commonly affects men during their fifth decade of life, and has a male-to-female ratio of 2–3:1. Liver biopsy is the most valuable tool for diagnosis. Clinical presentation of PHL is nonspecific and includes such symptoms as fever, loss of weight, night sweats, abdominal pain, jaundice and hepatomegaly. Incidental identification has been documented in 10% of PHL cases. Acute liver failure reportedly accounts for 4.5% of PHL presentations, and about 3% of reported acute liver failure was related to hepatic lymphoma, notably of diffuse pattern. Most cases of acute liver failure from lymphoma are diagnosed on autopsy, with an average survival of 11 days from diagnosis. PHL patients have abnormal liver function tests, with elevation of lactate dehydrogenase and alkaline phosphatase. Alpha-fetoprotein and carcinoembryonic antigen are normal in almost all cases, and hypercalcemia was observed in 40% of cases, being related to release of calcitriol by malignant lymphoma cells.
Radiologically, PHL lesions on ultrasound are hypoechoic, and on computed tomography are hypodense. Approximately 80% of the reported cases with PHL have been of the B cell type (mainly DLBCL), whereas the remaining cases have been of the T cell type. T cell lymphoma of the liver accounted for 5–10% of PHL patients, and these patients have shown an aggressive clinical course, and are mainly of the Asian population.

Therapeutic management of PHL is based on surgery, chemotherapy, and radiotherapy. However, 14% of cases are inappropriate for therapy due to comorbidity or poor performance. With chemotherapy, the reported survival ranges from 3.7 to 30 months, and liver transplantation is favorable. The 5-year overall survival (OS) of treated patients with PHL is comparable to that of hepatocellular carcinoma patients who undergo liver transplantation. Prognosis of PHL depends on NHL subtype, type of liver involvement (nodular or diffuse), therapeutic modalities (chemotherapy, surgery or radiotherapy), HIV status, and liver disease. The aim of this retrospective study was to assess the clinical characteristics, subtypes and outcomes of NHL affecting the liver.

Methods

Data source

The Surveillance Epidemiology and End Results (SEER) program of the U.S National Cancer Institute collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 30% of the US population (www.seer.cancer.gov). The SEER database includes cancer registries in the following areas; Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, the Alaska Native Tumor Registry, Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia.

Study population

Hepatic NHL in the SEER cancer registry (1973 to 2012) was defined by cancer diagnosis in anatomic site of liver by International Classification of Diseases, 3rd edition codes (ICD-O-3 code, C22.0) and NHL morphologies (9590–9595 and 9670–9723). For this study, I used the same variable selection approach of O’Neill et al. for NHL of the central nervous system in the SEER database study. As shown in Fig. 1, I restricted analysis to the patients who had microscopic confirmation of their disease (tissue histology or cytology). In an attempt to assure that only first primary NHLs were included in the analysis, I excluded patients who had a prior, or a concurrent diagnosis of other cancers. I also excluded patients diagnosed by autopsy or death certificate, and who had a survival time of 0 months. The few patients who had incomplete data regarding radiation or surgery were not included in the analysis. The final cohort included 785 patients with hepatic lymphoma (HEL) grouped into categories according to cell origin and clinical aggressiveness as follows: (1) aggressive B cell NHLs (DLBCL and Burkitt’s lymphoma); (2) Indolent B cell NHLs (follicular lymphoma; small B cell lymphocytic lymphoma and marginal zone B cell lymphoma), (3) T cell NHLs (mature T cell lymphoma and anaplastic large cell lymphoma, T cell and null cell type); (4) NHL– not otherwise specified [NHL-NOS]; and (5) other rare subtypes. Race was categorized into 5 age groups of <50, 50–59, 60–69, 70–79, and ≥80 years. Race was categorized as White, Black, Asian and Others. The cohort was divided into 4 according to the year of diagnosis (1973–1995, 1996–2000, 2001–2005, and 2006–2012). HIV-related deaths were identified in the SEER by variable ‘cause of death to SEER site recode’ (code 50040).

Statistical analysis

The clinical and demographic characteristics were expressed as proportion (%) and frequency (n) for categorical variables, or as median and range for continuous variables. The primary endpoint of the study was OS, which was defined as the interval between the date of diagnosis of HEL to the date of death from any cause (follow-up to obtain vital status) or death from other causes. The clinical and demographic characteristics were compared by the chi-square test or Fisher’s exact test for categorical variables and by the Wilcoxon’s rank-sum test or the Kruskal-Wallis test for continuous variables. The survival distributions were estimated by the Kaplan-Meier method, and were compared by the log-rank test. The Cox proportional hazards regression model was used to identify the factors associated with OS.

Fig. 1. Flow diagram of patient selection within the SEER database during 1973–2012. Abbreviation: ICD, International Classification of Diseases for Oncology.
The estimated median follow-up was determined using the inverse Kaplan–Meier method. Kaplan–Meier curves and multivariable Cox model were built to analyze the OS and prognostic factors. I performed all statistical analyses by use of STATA, version 12 (STAT Corp, College Station, Texas, USA). All p values were two-sided, and p < 0.05 suggested statistical significance.

**Results**

**Clinical characteristics of all patients**

In the SEER database, between 1973 and 2012, there were 362,697 cases with lymphoma (NHL = 312,459; Hodgkin lymphoma = 50,238). Of the total 312,459 NHL cases, there were 215,072 cases (68.8%) with nodal NHL, and 97,387 cases with extranodal NHL (31.2%). Out of 97,387 cases with extranodal NHL, there were 1,325 cases (1.3%) with hepatic NHL. The final cohort included 785 cases with a first primary NHL of the liver (HEL) after applying my exclusion criteria (Fig. 1), that represented 0.25% of all NHLs. The clinical features of the 785 patients with HEL are presented in Table 1. Of the 785 eligible cases, the median age at diagnosis was 61 years (range, 3–95 years) and 33.5% were equal or older than 70 years. Most of the patients were male (64.2%) and Whites (82.3%).

**Histologic subtypes**

The clinical characteristics of the various subtypes of HEL are presented in Tables 1 and 2. According to lymphoma cell origin and clinical aggressiveness, there were 521 (66.4%) cases of aggressive B cell NHLs, 59 (7.5%) indolent B cell NHLs and 27 (3.4%) T cell NHLs. The most common subtypes identified were DLBCL (n = 496, 63.2%) and NHL-NOS (n = 155, 19.7%). The next most common subtypes were T cell lymphomas (3.4%), Burkitt’s lymphoma (3.2%), follicular lymphoma (2.8%), marginal zone B cell lymphoma (MZL) (2.9%) and small B cell lymphocytic lymphoma (SLL) (1.8%).

**Outcomes**

With a median follow-up of 87 months (95%CI: 79 to 100 months), 474 (60.4%) patients had died by the end of
study. Of which, 256 patients (54%) died due to NHL, and 80 patients (16.9%) due to HIV-related complications. HIV-related deaths accounted for 16.2% of deaths of DLBCL, and 40% of deaths of Burkitt’s lymphoma (data not shown).

Survival and prognostic variables

For the entire cohort, with a median OS of 33 months (95% confidence interval [CI]: 22–48 months), the estimated 1-, 3-, 5-, 10- and 20-year OS rates were 59% (95%CI: 56–62%), 49% (95%CI: 46–53%), 44% (95%CI: 41–48), 35% (95%CI: 32–39%) and 21% (95%CI: 15–27%), respectively. Compared to patients aged <50 years, the hazards of mortality of 60–69 years age group, 70–79 years age group and ≥80 years age group were 1.61-fold (p < 0.001), 1.8-fold (p < 0.001) and 3.2-fold (p < 0.001), respectively (Fig. 2).

Males had a shorter 5-year OS than females (41% vs. 50%), and risk of death in males was 26% higher than in females (adjusted hazard ratio [aHR]: 1.26, 95%CI: 1.03–1.54, p = 0.02). The OS was lower in Blacks (aHR: 1.70, 95%CI: 1.26–2.29, p < 0.001) and Asians (aHR: 1.57, 95% CI: 1.10–2.25, p = 0.01) compared with White patients (Table 3, Fig. 3).

The estimated 5-year OS rates during the periods of 1973–1995, 1996–2000, 2001–2005 and 2006–2012 were 33% (95%CI: 26–41%), 35% (95%CI: 26–44%), 50% (95%CI: 43–57%) and 50% (95%CI: 44–56%), respectively (p < 0.001). The median OS of patients with HEL improved from 19 months when diagnosed in the period of 1996–2000 to 60 months when diagnosed between 2006 and 2012 (p < 0.001) (Table 3, Fig. 4).

The OS rates for the various subtypes of HEL are shown in Table 1 and Fig. 5. The 5-year OS for indolent B cell NHLs was 62% (95%CI: 47–74%), as compared with 44% (95%CI: 39–48%) for aggressive B cell NHLs and 42% (95%CI: 23–60%) for T cell NHLs. The best 5-year OS rates were observed for follicular lymphoma (84%), MZL (50%) and Burkitt’s lymphoma (46%). The 5-year OS of DLBCL was 43%, which was comparable to SLL (42%) and T cell NHL (42%).

Table 3 details the multivariable Cox regression analysis of the 785 HEL patients in which age of ≥80 years (aHR: 3.21, p < 0.001), male sex (aHR: 1.26, p = 0.02), Black race (aHR: 1.70, p < 0.001), and T cell NHL histologic subtype (aHR: 1.73, p = 0.03) were unfavorable prognostic factors.

The risk of all-cause mortality for patients diagnosed in the periods of 2001–2005 and 2006–2012 were 40% and 43% lower than those diagnosed in the period of 1973–1995 (all, p < 0.001).

Discussion

PHL is defined according to Caccamo’s criteria34 as lymphoma with only liver involvement at presentation. Although, some have accepted cases as being primary, describing predominant liver involvement, even with the presence of extra-hepatic disease.3,29,31

Over a long period of time, I found 785 cases with a first primary NHL of the liver were recorded in the US National Cancer Institute database (1973 to 2012), without a history of prior or concurrent cancer diagnosis. This study represents the largest evaluation of hepatic lymphoma to date. I observed that HEL accounted for 0.25% of all NHLs, which accords with
The median age at diagnosis was 61 years (range, 3–95 years), which was slightly older than the literature (50 to 56 years), with a male-to-female ratio of 1.8:1.

DLBCL comprises 33% of all NHL, and 46% to 96% of PHL cases. Hepatic DLBCL accounted for approximately 6% of all primary extranodal DLBCL. My analysis revealed that B cell NHL accounted for approximately 74% all hepatic NHLs, and the most common histopathological diagnosis was DLBCL, which was observed in 496 (63.2%) cases. In a retrospective review of 31 patients with PHL collected from 55 French hospitals, 22 cases (71%) had DLBCL. Immunophenotyping analysis of 59 PHL cases; most were of B cell lineage (37 cases, 63%) and 15 were T cell (25%).

In the current study, the frequency of T-cell NHL is low (3.4%) compared to previous reports (5–10%). The most observed hepatic T cell NHLs were mature T cell lymphoma-NOS (59.3%) and anaplastic large cell lymphoma T cell/null cell type (33.3%). In literature, the described subtypes of T cell lymphoma of the liver include peripheral T cell lymphoma, anaplastic T cell lymphoma and hepatosplenic T cell lymphoma. The frequency of aggressive T cell NHLs increased in Asians (8.7%) and Blacks (6.0%), as compared to Whites (2.8%). This may, in part, reflect increased exposure to pathogenic factors, such as human T cell leukemia virus-1 (HTLV-1) and EBV in Asian and African nations.

I observed that the 5-year OS of hepatic DLBCL was 44%, which was comparable to the Japanese report (43%). In addition, the risk of mortality for hepatic T cell NHL cases was 73% higher than those with an aggressive B cell NHL of the liver (HR: 1.73, p = 0.03). Notably, many patients with primary hepatic T cell lymphoma present with aggressive diffuse liver infiltration.

Hepatic marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT) lymphomas are reported to occur in 2–4% of cases of hepatic malignant lymphoma.

### Table 3. Clinical features, outcomes and prognostic factors of non-Hodgkin lymphoma of the liver

<table>
<thead>
<tr>
<th>Variables</th>
<th>n (%)</th>
<th>Median OS in months</th>
<th>Multivariate analysis</th>
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<tr>
<td></td>
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<td>Hazard ratio (95%CI)</td>
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<tr>
<td>All patients</td>
<td>785 (100.0)</td>
<td>33.0</td>
<td>Ref</td>
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<tr>
<td>Age in years</td>
<td></td>
<td></td>
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<tr>
<td>&lt;50</td>
<td>240 (30.6)</td>
<td>58.0</td>
<td>Ref</td>
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<tr>
<td>50–59</td>
<td>137 (17.5)</td>
<td>119.3</td>
<td>1.10 (0.81–1.50)</td>
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<tr>
<td>60–69</td>
<td>145 (18.5)</td>
<td>28.3</td>
<td>1.61 (1.22–2.13)</td>
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<tr>
<td>70–79</td>
<td>158 (20.1)</td>
<td>28.3</td>
<td>1.88 (1.43–2.48)</td>
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<td>+80</td>
<td>105 (13.4)</td>
<td>9.02</td>
<td>3.21 (2.37–4.35)</td>
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<td>Sex</td>
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<tr>
<td>Female</td>
<td>281 (35.8)</td>
<td>60.1</td>
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<tr>
<td>Male</td>
<td>504 (64.2)</td>
<td>24.4</td>
<td>1.26 (1.03–1.54)</td>
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<td>Race</td>
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<tr>
<td>White</td>
<td>646 (82.3)</td>
<td>39.3</td>
<td>Ref</td>
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<td>Black</td>
<td>83 (10.6)</td>
<td>11.9</td>
<td>1.70 (1.26–2.29)</td>
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<td>Asian</td>
<td>46 (5.9)</td>
<td>6.9</td>
<td>1.57 (1.10–2.25)</td>
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<tr>
<td>Others</td>
<td>10 (1.3)</td>
<td>66.1</td>
<td>0.97 (0.43–2.19)</td>
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<td>NHL subtypes</td>
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<td>Aggressive B cell NHL</td>
<td>521 (66.4)</td>
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<td>Ref</td>
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<td>Indolent B cell NHL</td>
<td>59 (7.5)</td>
<td>152.4</td>
<td>0.50 (0.32–0.77)</td>
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<td>T cell NHL</td>
<td>27 (3.4)</td>
<td>8.3</td>
<td>1.73 (1.04–2.89)</td>
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<td>NHL-NOS</td>
<td>155 (19.7)</td>
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<td>Others</td>
<td>23 (2.9)</td>
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<td>1.25 (0.76–2.06)</td>
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<td>Calendar period</td>
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<tr>
<td>1973–1995</td>
<td>145 (18.5)</td>
<td>10.1</td>
<td>Ref</td>
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<tr>
<td>1996–2000</td>
<td>108 (13.8)</td>
<td>19.0</td>
<td>0.90 (0.67–1.21)</td>
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<td>2001–2005</td>
<td>196 (25.0)</td>
<td>48.9</td>
<td>0.60 (0.46–0.80)</td>
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<td>2006–2012</td>
<td>336 (42.8)</td>
<td>60.0</td>
<td>0.57 (0.44–0.75)</td>
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</table>

**Abbreviations:** n, number of cases; NOS, not otherwise specified; OS, overall survival; CI, confidence interval.

1American Indian/Alaska Native, unknown.

2Included diffuse large B-cell lymphoma and Burkitt’s lymphoma.

3Included follicular lymphoma, small B cell lymphocytic lymphoma and marginal zone B cell lymphoma.
as a result of chronic antigenic simulation. Most PHL in patients with primary biliary cirrhosis is low-grade MALT lymphoma. A quarter of primary hepatic MALT lymphomas are HCV sero-positive, and spontaneous remission has been reported. To date, only 46 cases with primary hepatic MALT lymphoma have been reported and 35.5% had a pre-existing...
liver disease. In the present study, hepatic MZL accounted for about 3% of all cases, with a long 5-year OS (60%) and median OS (82.9 months), comparable to the 84 months reported in 8 primary hepatic MALT lymphoma cases in Japan. In a review of 18 hepatic MALT lymphoma cases, median OS was 65 months.

Follicular lymphoma accounted for less than 4% of PHL. In our study, the 5-year OS rate of hepatic follicular lymphoma was 84%, which was comparable to the 5-year OS for population of follicular lymphoma (52% to 90%). I observed that the hepatic Burkitt's lymphoma has a slight predominance in females, with 5-year OS of 55% compared to 23% to 71% in a previous report. In addition, 40% of deaths in hepatic Burkitt's lymphoma were related to HIV-related complications. Of note, primary hepatic Burkitt's lymphoma had been reported in concurrent viral infection, such as HIV, HCV and HBV. Anti-HIV therapy has no significant impact on outcomes of HIV-Burkitt's lymphoma compared to some HIV-related lymphomas, such as primary effusion lymphoma. In addition, direct-acting antivirals could be promising in HCV-associated indolent B cell NHL.

In the current study, 474 patients (60.4%) had died by end of study. Of which, 256 patients (54%) died due to NHL, and 80 patients (16.9%) due to HIV-related complications. HIV was reported in 40% to 75% of PHL cases. In a single centre study, after a median follow-up of 19 months for 22 hepatic lymphoma cases, 12 patients (54.5%) had died. Most patients with PHL present with poor prognostic features, such as advanced age, constitutional symptoms, bulky disease, unfavorable histologic subtypes, elevated lactate dehydrogenase, and co-morbidities (cirrhosis, chronic active hepatitis, HIV, immunosuppression, etc.). Patients with PHL have a favorable survival compared to those with hepatic involvement of systemic lymphoma, but this issue is controversial. In the entire cohort, the median OS was 33 months (95%CI: 21–48 months) and the 5-year OS rate was 44% (95%CI: 41–48%). In the literature, the median survival of PHL cases ranged from 4 to 30 months rising to 60 months in patients who received combined triple-modalities (surgical resection and chemo-radiotherapy). The poorest 5-year OS rates were observed for aggressive B cell NHLs (44%, 95%CI: 39–48%) and T cell NHLs (42%, 95%CI: 32–60%). In the Japanese series of 10 PHL cases treated with combined chemotherapy (5 who received rituximab), the median OS was 27 months, and the 5-year OS rate was 44%. The 20-year experience with PHL at the MD Anderson Cancer Center (1974–1995) showed a 5-year OS of 83%. The pattern of tumor infiltration had an impact on clinical outcomes. In a review of 62 cases, the 3-year OS in nodular PHL was 57%, and in diffuse PHL was 18%, versus 49% (95%CI: 46–53%) in our analysis.

In the current study, the mortality risk increased remarkably with advancing age. In addition, the risk of deaths in males was 26% higher than in females (aHR: 1.26, 95%CI: 1.03–1.54). It seems that the poor performance status, rather than advanced age, has negative impact on the outcome of NHL, and lymphoma presenting as acute liver failure was seen twice as often in men as it was in women. Furthermore, the male predominance is striking in lymphomas of T cell origin.

I noted that the survival rates were lower in Blacks (aHR: 1.70, p < 0.001) and Asians (aHR: 1.57, p = 0.01) compared with White patients. Notably, Asian patients tended to have aggressive PHL subtypes (i.e. T cell NHL) with diffuse tumor burden, similar to that seen in advanced-stage systemic lymphoma, which could partly explain the worse outcomes in Asian patients. In addition, the survival rates were lower in Blacks (aHR: 1.70, p < 0.001) and Asians (aHR: 1.57, p = 0.01) compared with White patients. Notably, Asian patients tended to have aggressive PHL subtypes (i.e. T cell NHL) with diffuse tumor burden, similar to that seen in advanced-stage systemic lymphoma, which could partly explain the worse outcomes in Asian patients.

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infiltration. Furthermore, chronic liver disease before the onset of hepatic lymphoma was reported in 44% of Japanese cases compared to only 9.6% of Western cases.\(^1,2\) Regarding the year of diagnosis, the survival improved in the most recent calendar period (2001–2012), and new drugs such as Rituximab may have played a major role.\(^3\) Rituximab is an anti-CD20 monoclonal antibody, FDA approved in 1997 for the treatment of relapsed or refractory indolent B cell lymphomas, and then in 2006 approved as a frontline therapy for patients with diffuse large B cell or follicular B cell NHL.

There are several limitations to the present study. The SEER database provides no information regarding whether chemo-immunotherapy was administered. In addition, no data regarding the pattern of liver infiltration and viral status are provided. Although this analysis was restricted, the extranodal NHL affects liver diagnosed by pathology, with no history of prior, or a concurrent cancer diagnosis. Actually, I could not meet the strict criteria for NHL suggested by Caccamo et al.,\(^4\) and some cases were not actually PHL, and were cases of secondary liver involvement with extrahepatic disease. However, no standard diagnostic criteria of PHL exist, and have some accepted cases as being primary, describing predominant liver involvement, even with the presence of extrahepatic disease.\(^3,4\)

**Conclusions**

In the USA, over a long period of time, first primary NHL of the liver has accounted for about 0.3% of all NHLs. The most common histological variant was DLBCL (63.2%). It appears that the survival of patients with hepatic NHL has improved since 2000. This could reflect the more frequent use of novel agents, such as with rituximab as upfront management of NHLs. Asian and Black patients had more frequent aggressive T cell NHL with poor outcomes, which could be related to an endemic viral infection, such as with HTLV-1 or EBV.

**Conflict of interest**

The author has no conflict of interest related to this publication.

**Author contributions**

Designed the study, performed the data analysis and interpretations, and wrote the manuscript (MAE).

**References**

El-Fattah M.A.: Outcomes of hepatic non-Hodgkin lymphoma


