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ORIGINAL ARTICLE

Retrospective Study

Characteristics and distinct prognostic determinants of individuals with hepatosplenic T-cell lymphoma over the past two decades

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Abstract

BACKGROUND

Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive peripheral T-cell lymphoma with historically dismal outcomes, representing less than one percent of non-Hodgkin lymphomas. Given its rarity, the true incidence of HSTCL is unknown and most data have been extrapolated through case reports. To the best of our knowledge, the largest and most up to date study addressing the epidemiology and outcomes of patients with HSTCL in the United States covered a period from 1996 to 2014, with a sample size of 122 patients.

AIM

To paint the most updated epidemiological picture of HSTCL.

METHODS
A total of 186 patients diagnosed with HSTCL, between 2000 and 2017, were ultimately enrolled in our study by retrieving data from the Surveillance, Epidemiology, and End Results database. We analyzed demographics, clinical characteristics, and overall mortality (OM) as well as cancer-specific mortality (CSM) of HSTCL. Variables with a *P* value < 0.01 in the univariate Cox regression were incorporated into the multivariate Cox model to determine the independent prognostic factors, with a hazard ratio of greater than 1 representing adverse prognostic factors.

RESULTS
Male gender was the most represented. HSTCL was most common in middle-aged patients (40-59) and less common in the elderly (80+). Non-Hispanic whites (60.75%) and non-Hispanic blacks (20.97%) were the most represented racial groups. Univariate Cox proportional hazard regression analysis of factors influencing all-cause mortality showed a higher OM among non-Hispanic black patients. CSM was also higher among non-Hispanic blacks and patients with distant metastasis. Multivariate Cox proportional hazard regression analysis of factors affecting CSM revealed higher mortality in patients aged 80 or older and non-Hispanic blacks.

CONCLUSION
Overall, the outlook for this rare malignancy is very grim. In this retrospective cohort study of the United States population, non-Hispanic blacks and the elderly had a higher CSM. This data highlights the need for larger prospective studies to investigate factors associated with worse prognosis in one ethnic group, such as treatment delays, which have been shown to increase mortality in this racial/ethnic group for other cancers.

Key Words: Extra nodal lymphoma; Mortality; Survival; Racial disparity; Age

Core Tip: Hepatosplenic T-cell lymphoma (HSTCL) is an uncommon and highly aggressive form of non-Hodgkin lymphoma that carries a very poor prognosis. Very little is known about the survival outcomes of patients with HSTCL given its rarity. This study will be the most updated and largest study on the survival outcomes of patients with HSTCL. We found that older age and Non-Hispanic black ethnicity are the single most important factors for poor prognosis.

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INTRODUCTION

Hepatosplenic T-cell lymphoma (HSTCL) is a malignancy derived from T cells expressing the gamma/delta T-cell antigen and more recently alpha/beta antigen that affects mainly the liver and fills the sinusoids, or the red pulp of the spleen[1-3]. The disease is often diagnosed in relatively younger patients with a history of immunodeficiency, autoimmune disease and or the use of immunosuppressive therapy[1]. However, the majority of cases of HSTCL occur de novo. Discontinuation of immunotherapy does not appear to affect tumor progression[1].

Systemic B symptoms (fever, weight loss, night sweats), abdominal discomfort due to hepatosplenomegaly, and clinical features of cytopenia are often present at diagnosis[4]. Hemophagocytic syndrome can be observed with a rapid disease progression[5,6]. Lymph nodes are not often involved, making it difficult to diagnose the malignancy which can mimic infectious etiologies or other malignant disorders. Diagnosis is made in most cases by liver and/or bone marrow biopsy, or splenectomy[7]. Given its rarity and paucity of clinical trials, the treatment is mostly extrapolated from clinical trials of other peripheral T-cell lymphomas[8]. A satisfactory response to induction chemotherapy has been observed, however, most patients tend to relapse[9,10].

Only a few studies have addressed the overall epidemiology of HSTCL[11-13]. However, there is still a paucity of conclusive data and a lack of adequately powered studies properly defining epidemiology characteristics, survival outcomes, and prognostic factors of patients with HSTCL over the past 2 decades. This is especially important with the more recent emergence of hematopoietic stem cell transplants in the management of this fatal malignancy[14,15].

Using a nationally representative and most up to date database available, we evaluated the independent prognostic factors amongst patients with HSTCL, to help fill in the existing gap of literature on the subject. Furthermore, we aimed to establish patient populations that are predisposed to have a poorer prognosis. In our examination of HSTCL, we have

identified a significantly higher cancer-specific mortality (CSM) among non-Hispanic blacks, a finding unprecedented in the existing literature on this disease. This calls for a comprehensive multidisciplinary approach to explore the underlying causes of this disparity in CSM. Our study not only sheds light on these urgent issues but also sets the stage for both retrospective and prospective research aimed at uncovering the mechanisms behind these prognostic differences.

MATERIALS AND METHODS

Study design

A population-based retrospective cohort study of patients with HSTCL was conducted using the Surveillance, Epidemiology, and End Results (SEER) research plus data, 18 registries, Nov 2020 submission database (http://www.seer.cancer.gov). The SEER Program is one of the largest and most authoritative sources of the cancer-related dataset in the United States, which is sponsored by the United States National Cancer Institute. The SEER 18 database collects cancer incidence, patients' clinicopathological features, and survival data from 18 population-based cancer registries and covers nearly 28% of the United States population[16].

Data selection

Inclusion criteria: All patients with HSTCL diagnosed from 2010 to 2017 were selected in our cohort from the SEER database based on: (1) Primary site [c42.2, c22.0]; and (2) histological type [ICD-O-3: 9716,9702). The above-mentioned ICD-9, ICD-10, and/or ICD-0–3 codes were used to extract data regarding these patients from the SEER database. This database is a critical resource for research, particularly for rare cancers like HSTCL, because it aggregates data from diverse demographics and geographical locations across the United States, enhancing the representativeness and generalizability of the findings. The database is updated regularly, ensuring that the data reflect recent diagnostic, treatment, and survival trends.

Exclusion criteria: We excluded patients with an unknown age at diagnosis, race, or stage of HSTCL.

Study variables

Main exposure: All the variables included in this cohort except year of diagnosis were used as main predictors of prognosis.

Outcomes: Overall mortality (OM): Patients who died of any causes at the end of the study were categorized as "yes", and those who did not were categorized as "no". Cancer-specific mortality: Patients who died of HSTCL at the end of the study were categorized as "yes", and those who died of other causes were classified as "no".

Survival months: For OM, survival time was calculated from the date of diagnosis to the date of death, or the date of last follow-up (December 31, 2017) as reported in the SEER registry. For the CSM, survival time was calculated from the date of diagnosis to the date of HSTCL related death, or the date of last follow-up as recorded in the SEER registry.

Sociodemographic and tumor characteristics: Variables such as age at diagnosis, gender, race (White, Black, and others), origin (Non-Hispanic and Hispanic), stage at diagnosis (localized, regional, and distant), geographic residential area, yearly income, marital status, year of diagnosis, surgery and radiation were extracted.

Statistical analysis

Cox proportional hazard regression model is based on the assumption that hazard rates are proportional over time. Variables with value < 0.1 in the univariate Cox regression model were incorporated into the multivariate Cox proportional analysis to determine the independent prognostic factors associated with OM and CSM, with a hazard ratio > 1 representing adverse prognostic factors. All tests were two-sided, with a confidence interval set as 95% and P value < 0.05 deemed statistically significant. All statistical tests were performed by using Software STATA 18.0.

RESULTS

Our study included a total of 186 patients with a primary diagnosis of HSTCL. Table 1 summarizes the baseline characteristics of patients included in our cohort. A male predominance (68.82%) was observed in our cohort. Most patients were diagnosed between the ages of 40- and 59-years-old (36.02%), while non-Hispanic whites (60.75%) and non-Hispanic blacks (20.97) comprised most of the cohort. The most commonly identified demographic features of diagnosed patients included being diagnosed at later stages (69.35%), coming from counties in metropolitan areas of 1 million persons (63.44%), having an annual income of $75000+ (46.24%), and being married (44.09%). Systemic B symptoms were reported by up to 34.41% of patients and cancer directed surgery was performed in up to 37.63% of patients.

A crude analysis of factors associated with OM and CSM among United States patients between 2000 and 2017 is demonstrated in Table 2. Non-Hispanic blacks had the highest OM. non-Hispanic blacks and those diagnosed at a later stage had the highest CSM. Advanced age, marital status, B symptoms or surgery did not affect the OM nor the CSM.

Table 1 Demographic and Clinicopathologic characteristics of United States patients with hepatosplenic T-cell lymphoma between 2000 and 2017

Characteristics	*n*	%
Total	186	100
Gender		
Female	58	31.18
Male	128	68.82
Age at diagnosis, yr		
0-39	63	33.87
40-59	67	36.02
60-79	44	23.66
80+	12	6.45
Race		
Non-Hispanic white	113	60.75
Non-Hispanic black	39	20.97
Hispanic	15	8.06
Other	19	10.22
Tumor stage		
Localized	44	23.66
Regional	13	6.99
Distant	129	69.35
Living area		
Counties in metropolitan areas of 1 million persons	118	63.44
Counties in metropolitan areas of 250000 to 1 million persons	38	20.43
Counties in metropolitan areas of 250000 persons	17	9.14
Nonmetropolitan counties	13	6.99
Income per year		
$ < $55000	22	11.83
$55000-64999	33	17.74
$65000-74999	45	24.19
$75000+	86	46.24
Marital status		
Married	82	44.09
Single/unknown	78	41.94
Divorced/separated	14	7.53
Widowed	12	6.45
Radiation		
No	173	93.01
Yes	13	6.99
Surgery		
No	116	62.37
Yes	70	37.63
B symptoms		

No	122	65.59
Yes	64	34.41
Year of diagnosis		
2000	1	0.54
2001	6	3.23
2002	5	2.69
2003	11	5.91
2004	10	5.38
2005	5	2.69
2006	11	5.91
2007	7	3.76
2008	8	4.30
2009	12	6.45
2010	11	5.91
2011	14	7.53
2012	10	5.38
2013	16	8.60
2014	12	6.45
2015	14	7.53
2016	14	7.53
2017	19	10.22

Table 3 summarizes the results of multivariate cox proportional hazard regression analyses of characteristics influencing OM and CSM of patients with HSTCL diagnosed between 2000 and 2017. Age 80+ and non–Hispanic blacks had the highest CSM. Once again, we found that advanced age, marital status, annual income, tumor stage, B symptoms or surgery did not affect either the OM or the CSM.

DISCUSSION

Non-Hispanic blacks were found to have a higher CSM. To the best of our knowledge, our cohort is the first to make this observation in HSTCL. HSTCL are extremely rare and there is a serious paucity of data in the epidemiologic profile of this malignancy. In this United States population-based study, we found a male and non-Hispanic Whites predominance. Elderly patients were also found to have a worse CSM. Advanced age, marital status, annual income, tumor stage, B symptoms or surgery did not affect the mortality.

Most patients in our cohort were diagnosed between the ages of 40 and 59; these findings are different from the series of Master *et al*[17] where most patients were diagnosed between 25-44 years of age. A male predominance was observed in our cohort which is congruent with the literature[18,19]. Our cohort was predominantly white, findings that also mirror the literature[13].

Splenomegaly is present in all patients with HSTCL[20,21]. The benefits of a splenectomy in the survival of patients with HSTCL remain controversial with conflicting data[21,22]. A single institution observation at mayo clinic did not find any survival benefits of the splenectomy[21], while the study by Gumbs *et al*[22] found substantial benefits of splenectomy especially in patients with severe thrombocytopenia as this intervention led to resolution of the thrombocytopenia and allowed patients to tolerate more aggressive therapies. Up to a third of patients in our cohort underwent a splenectomy. However, this intervention did not seem to affect either OM or CSM.

Most diagnoses of HSTCL were made in metropolitan areas where higher income seemed to correlate with increased incidence compared to lower income. Metropolitan areas tend to be better served with more advanced medical expertise, and given the rarity and nonspecific presentation of HSTCL, patients with higher income will be more likely to afford the extensive medical evaluation required to make the diagnosis.

Systemic B symptoms of fever, night sweats, or weight loss have been reported in 80% of patients with HSTCL[23]. The prognostic value of B symptoms in non-Hodgkin lymphomas remains unclear with opposing data. Studies by Coiffier *et al*[24], and Anderson *et al*[25], found worse prognosis in patients with systemic B symptoms, whereas studies by Portlock *et al*[26], and McLaughlin *et al*[27], were unable to confirm this prognostic value. Up to a third of patients in our cohort had documented systemic B symptoms. However, the systemic B symptoms did not appear to affect OM or CSM.

Table 2 Crude analysis of factors associated with all-cause mortality and hepatosplenic T-cell lymphoma mortality among patients between 2000 and 2017

Characteristics	Overall mortality crude proportional hazard ratio (95% confidence interval)	HSTCL crude proportional hazard ratio (95% confidence interval)
Gender		
Female	1 (reference)	1 (reference)
Male	0.96 (0.65-1.39)	0.99 (0.65-1.52)
Age at diagnosis, yr		
0-39	1 (reference)	1 (reference)
40-59	0.80 (0.53-1.22)	0.69 (0.44-1.11)
60-79	0.95 (0.59-1.54)	0.85 (0.50-1.45)
80+	1.60 (0.68-3.77)	1.44 (0.57-3.65)
Race		
Non-Hispanic white	1 (reference)	1 (reference)
Non-Hispanic black	1.97 (1.27-3.07)[b]	2.34 (1.47-3.72)[b]
Hispanic	1.44 (0.71-2.89)	1.41 (0.64-3.13)
Other	1.65 (0.96-2.86)	1.62 (0.86-3.04)
Tumor stage		
Localized	1 (reference)	1 (reference)
Regional	1.28 (0.57-2.86)	1.63 (0.62-4.30)
Distant	1.54 (0.97-2.43)	2.23 (1.24-4.02)[b]
Living area		
Counties in metropolitan areas of 1 million persons	1 (reference)	1 (reference)
Counties in metropolitan areas of 250000 to 1 million persons	0.73 (0.46-1.16)	0.69 (0.41-1.17)
Counties in metropolitan areas of 250000 persons	1.19 (0.63-2.24)	1.02 (0.49-2.12)
Nonmetropolitan counties	1.43 (0.76-2.70)	1.22 (0.59-2.56)
Income per year		
$ < $55000	1 (reference)	1 (reference)
$55000-64999	1.26 (0.65-2.45)	1.39 (0.65-2.99)
$65000-74999	1.18 (0.63-2.20)	1.25 (0.59-2.61)
$75000+	0.82 (0.45-1.49)	1.02 (0.51-2.03)
Marital status		
Married	1 (reference)	1 (reference)
Single/unknown	1.12 (0.76-1.64)	1.32 (0.86-2.04)
Divorced/separated	1.49 (0.8-2.85)	1.77 (0.88-3.56)
Widowed	1.98 (0.89-4.38)	1.82 (0.72-4.65)
Radiation		
No	1 (reference)	1 (reference)
Yes	0.77 (0.37-1.58)	0.81 (0.38-1.75)
Surgery		
No	1 (reference)	1 (reference)

Yes	0.76 (0.53-1.09)	0.72 (0.48-1.09)
B symptoms		
No	1 (reference)	1 (reference)
Yes	1.23 (0.85-1.80)	1.14 (0.75-1.75)

[b]$P < 0.01$.
HSTCL: Hepatosplenic T-cell lymphoma.

Table 3 Multivariate cox proportional hazard regression analyses of factors affecting all-cause mortality and hepatosplenic T-cell lymphoma related mortality among patients between 2000 and 2017

Characteristics	Overall mortality adjusted proportional hazard ratio (95% confidence interval)	HSTCL adjusted proportional hazard ratio (95% confidence interval)
Gender		
Female	1 (reference)	1 (reference)
Male	0.79 (0.48-1.29)	0.83 (0.49-1.41)
Age at diagnosis, yr		
0-39	1 (reference)	1 (reference)
40-59	0.60 (0.32-1.13)	0.62 (0.30-1.26)
60-79	1.32 (0.67-2.58)	1.65 (0.78-3.49)
80+	2.98 (0.88-10.09)	4.72 (1.14-19.54)[a]
Race		
Non-Hispanic white	1 (reference)	1 (reference)
Non-Hispanic black	1.61 (0.89-2.89)	2.02 (1.08-3.79)[a]
Hispanic	1.87 (0.73-4.78)	1.90 (0.69-5.28)
Other	1.59 (0.79-3.19)	1.49 (0.67-3.37)
Tumor stage		
Localized	1 (reference)	1 (reference)
Regional	0.69 (0.24-2.01)	1.17 (0.33-4.19)
Distant	1.03 (0.57-1.87)	1.85 (0.87-3.89)
Living area		
Counties in metropolitan areas of 1 million persons	1 (reference)	1 (reference)
Counties in metropolitan areas of 250,000 to 1 million persons	1.19 (0.69-2.07)	1.05 (0.55-2.02)
Counties in metropolitan areas of 250000 persons	1.07 (0.44-2.60)	0.68 (0.24-1.94)
Nonmetropolitan counties	2.71 (0.78-9.39)	2.36 (0.50-11.09)
Income per year		
$ < $55000	1 (reference)	1 (reference)
$55000-64999	2.72 (0.82-9.07)	2.54 (0.58-11.08)
$65000-74999	1.75 (0.53-5.85)	1.04 (0.23-4.63)
$75000+	1.46 (0.43-4.96)	1.23 (0.28-5.53)
Marital status		
Married	1 (reference)	1 (reference)
Single/unknown	0.83 (0.48-1.44)	0.94 (0.51-1.75)

Divorced/separated	1.33 (0.61-2.90)	1.79 (0.77-4.19)
Widowed	1.19 (0.39-3.62)	1.01 (0.26-3.87)
Radiation		
No	1 (reference)	1 (reference)
Yes	0.86 (0.35-2.10)	1.07 (0.38-3.01)
Surgery		
No	1 (reference)	1 (reference)
Yes	0.83 (0.49-1.40)	0.97 (0.54-1.76)
B symptoms		
No	1 (reference)	1 (reference)
Yes	1.66 (0.85-3.24)	2.21 (0.99-4.89)

[a]$P < 0.05$.
HSTCL: Hepatosplenic T-cell lymphoma.

Non-Hispanic blacks were found to have a higher CSM. Since the lack of documentation of outcomes in non-Hispanic blacks and given the growth of the Hispanic population in the United States, it is imperative to understand the difference for personalized medicine. Extrapolating data from other cancer areas, several factors have explained higher CSM in non-Hispanic black patients. The study by Fwelo *et al*[28] in breast cancer found that non-Hispanic black women were more likely to undergo treatment delays compared their non-Hispanic White counterparts, and the variations in treatment, socioeconomic status, and clinicopathological factors significantly explained 70% of the excess Breast cancer specific mortality among non-Hispanic Blacks compared to their non-Hispanic White counterparts[29]. A study by Yabe *et al*[6], supported the novel suggestions that HSTCL patients can be stratified into 2 prognostic groups, with an elevated serum bilirubin level, αβ T-cell receptor (TCR) expression, and trisomy 8 correlating with a poorer prognosis. Perhaps most non-Hispanic black patients belong to the group classified by Yabe *et al*[6] as the poorer prognostic group. A multidisciplinary team effort is needed to better understand the reason for this poorer CSM in non-Hispanic Blacks. This study paves the way for future retrospective and prospective studies focusing in part on factors that can potentially explain this variation.

Certain limitations must be considered when interpreting the results of this study. Information gathered on patients that underwent chemotherapy was not complete as the information available was reported as either "yes" or "no/unknown". As a result, that information could not be used in our cohort. Furthermore, the SEER database publicly available does not provide information on comorbidities. However, this study has the merit of collecting data from the largest cancer database in the USA. Furthermore, we were also able to enroll an adequate sample size despite the rarity of the pathology.

CONCLUSION

The elevated CSM rates observed among non-Hispanic Black individuals and older populations over 80 years highlighted in our study bring to the forefront significant disparities in health outcomes. This discrepancy necessitates a deeper investigation into potential causative factors, which may include socioeconomic constraints, unequal access to medical resources, and inherent differences in disease biology. Socioeconomic issues, such as delays in treatment coupled with lower income levels and limited access to high-quality healthcare, can significantly influence survival outcomes across racial lines. Additionally, the accessibility and quality of healthcare services, which vary dramatically with race and age, can affect the timeliness and efficacy of treatment options available to patients. Moreover, biological factors, like distinctive genetic markers and TCR expressions, may also contribute to prognostic differences. These complexities demand a multidisciplinary approach for a fuller understanding and addressing these health inequities. Our study emphasizes the critical need for extensive, targeted research to dissect these multifaceted causes of health disparities, advocating for future studies that not only validate these findings but also examine potential interventions aimed at reducing these disparities. Through such efforts, we can move closer to achieving personalized medicine that caters effectively to the diverse needs of all population segments, thereby improving overall health outcomes.

FOOTNOTES

Author contributions: Bangolo A designed research; Bangolo A, Fwelo P performed research; Bangolo A, Fwelo P, Lo A, Weissman S, Cho C analyzed data; Bangolo A, Fwelo P, Dey S, Sethi T, Sagireddy S, Chatta J, Goel A, Nagpaul S, Chen EPS, Saravanan C, Gangan S, Thomas J, Potiguara S, Nagesh VK, Elias D, Mansour C, Ratnaparkhi PH, Jain P, Mathew M, Porter T, Shadiya Sultan, Abbisetty S, Tran L, Chawla M, Lo A, Weissman S, Cho C wrote the paper.

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