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SHORT REPORT

Haematological Malignancy – Clinicals

Ethnicity and socio-economic status affects the incidence and survival of hepatosplenic T-cell lymphoma

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Summary

To address the lack of contemporary population-based epidemiological studies of hepatosplenic T-cell lymphoma (HSTCL), we undertook a population-based study of ICD-O-3-coded HSTCL in England. We used the National Cancer Registration Dataset and linked datasets on hospital admissions, Systemic Anti-Cancer Therapy, socio-demographics, comorbidities and death, identifying cases from 1 January 2013 to 31 December 2019 with survival data up to 5 January 2021. Crude and directly age-standardised incidence rates per million persons per year were calculated. Crude and adjusted incidence rate ratios compared incidence between groups using Poisson regression. A Cox proportional hazards model estimated mortality risks adjusted for age, sex, ethnicity, deprivation and allogenic stem cell transplant (allo-SCT; time varying). We identified 44 patients, mean age 42 years. Median survival was 11 months, and 1 and 5 year survivals were 48% (95% CI 29%–43%) and 22% (95% CI 12%–42%) respectively. The age-standardised incidence was 0.1 per million/year. Incidence was higher in areas with greater deprivation (0.15 per million/year), and more cases than expected were in non-White patients (39%). Non-Whites had a twofold increased risk of death (adjusted hazard ratio 2.21 [95% CI 1.03–4.78]) even after adjusting for deprivation, younger age and allo-SCT. In conclusion, ethnicity and socio-economic status affect both the incidence and survival of HSTCL.

KEYWORDS
deprivation, ethnicity, hepatosplenic lymphoma

INTRODUCTION

Hepatosplenic T-cell lymphoma (HSTCL) is a rare, aggressive disease, commonly presenting with hepatosplenomegaly and cytopenias, with alpha/beta and gamma-delta subtypes recognised.[1] Only a few hundred cases of HSTCL have been reported, with only one series of 12 patients diagnosed over 14 years reporting an incidence rate of 0.6 per million population per year.[2,3] The largest prior study comes from the International T-Cell project (ITCP), which recruited 31 patients from 22 centres worldwide between 2006–2016,[4] but otherwise data are limited to large cancer institutions, with cases accrued over multiple decades, largely prior to standardised ICD-O-3 coding.[5,6]

Most series describe a median age of 30–40 years at diagnosis, male predominance and a history of prior lymphoproliferative disorder, solid organ transplantation or inflammatory bowel disease (IBD) in ~20% of cases.[7] While half of the patients respond to chemotherapy, remissions are generally short lived with median overall survival (OS) around 1 year.[4,5,8,9] There is no established standard of care, but cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-based regimens appear associated with poor outcomes, resulting in a general consensus that intensive chemotherapy and/or consolidation with allogeneic stem cell transplantation (allo-SCT) are preferred.[4,5,8,9] To address the lack of contemporary and comprehensive population-based epidemiological estimates of HSTCL, we undertook

a nationwide population-based study of all ICD-O-3-coded HSTCL in England between 2013 and 2019.

METHODS

The National Cancer Registration Dataset (NCRD) holds the population-based national cancer registry for England, is linked to other datasets, including Hospital Episode Statistics,[10] the Systemic Anti-Cancer Therapy (SACT) dataset, and holds information on socio-demographics, Charlson score, socio-economic status (deprivation quintile), operations, procedures and death.[11] Cases were identified using ICD-O-3 morphology code 9716/3 for neoplasms diagnosed between 1 January 2013 and 31 December 2019. Comorbidities were defined using ICD-10 codes, available when patients were admitted to hospital or for a day case procedure. Ethnicity was characterised into White and non-White (non-White included in those without stated ethnicity). For Stem Cell Transplant (SCT), Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures version 4 (OPCS-4) codes were used, and included procedures occurring 90 days prior to and 730 days after diagnosis.

Crude and directly age-standardised incidence rates (ASR) per million persons per year were calculated. The total at-risk population were the English Office for National Statistics mid-year population estimates.[12] ASRs were age-adjusted to the 2013 European Standard Population.[13] Crude and adjusted incidence rate ratios (IRRs) were calculated to compare the incidence between groups using Poisson regression, and calendar time trends were assessed. Overall survival (OS) was calculated from the date of diagnosis to date of death from any cause up to 5 January 2021. To reduce survival bias, for those receiving SCT, survival was calculated from the date of SCT. Overall survival (OS) was estimated using Kaplan–Meier methods and we fitted a Cox proportional hazards regression model adjusted (where variables were available) for age, sex, ethnicity, deprivation and SCT (time varying). We computed survival curves for patients of White versus non-White ethnicity, adjusting for differences in age, sex, socio-economic status and SCT (time varying), allowing direct comparisons between groups visually. The resulting adjusted survival curves were survival estimates for White versus non-White patients of the same age, sex, socio-economic status and history of SCT (time varying). For this procedure, we used the function 'ggadjustedcurves' from the R package 'survminer', choosing the 'conditional' method following a stratified (by ethnicity) Cox model. Statistical analyses were performed using R (R Core Team 2022 https://www.R-project.org/).

RESULTS

A total of 44 patients were identified. The overall incidence when age standardised to the European 2013 population was 0.12 (95% confidence interval [CI]: 0.08–0.16) per million population per year, with no clear trend over calendar year. The mean age at diagnosis was 42 years, with 21 patients <40 years old (incidence 0.11 [95% CI 0.06–0.15] per million) and 23 patients ≥40 years (incidence 0.12 [95% CI 0.07–0.17] per million). There were 30 (68%) male patients (incidence 0.16 [95% CI 0.10–0.21] per million) and 14 (32%) female patients (incidence 0.07 [95% CI 0.03–0.11] per million). 27 patients (61%) were White and 17 (39%) were non-White. Over half of the patients diagnosed (23; 52%) were within the two most deprived population quintiles (incidence 0.15 [95% CI 0.09–0.21] per million), compared to 25% in the two least deprived quintiles (incidence 0.07 [95% CI 0.03–0.12] per million). In a mutually adjusted model including age, sex and deprivation as continuous variables, patients with the least deprivation had a statistically significantly reduced incidence of disease (incidence rate ratios 0.71 [95% CI 0.49–1.00] per million) compared to more deprived patients, but incidence rate ratios (IRR) for age and sex showed no differences between groups (Table 1; categorical data for deprivation shown). Denominator data for ethnicity were not available and so in the incidence model, we were not able to adjust for ethnicity. Fisher's exact testing (only on the case numbers) confirmed ethnicity and socio-economic status to have a statistically significant relationship ($p = 0.01$), suggesting residual confounding may exist in the model. Non-White patients had a younger mean age at diagnosis (35 years [95% CI 0–72]) compared to White patients (46 years [95% CI 6–85]). No prior diagnoses of solid organ transplant were noted, but five patients (11%) had a history of IBD and less than five patients had coeliac disease, diabetes or auto-immune disease. Less than five patients had a prior immuno-suppressant infusion (non-specified), none of whom had IBD. Twelve (27.2%) patients received CHOP/CHOP-like induction chemotherapy, 21 (47.7%) non-CHOP/intensive regimens (including multiple different ifosfamide, platinum and high-dose methotrexate-based regimens) and 11 (25%) had missing data. Eleven patients, six of whom were White and five non-White, with a mean age of 26 years had first-line therapy consolidated with allo-SCT, with no cases of auto-SCT recorded. For the whole cohort, with a median follow-up of 1 year (inter quartile range: 0–3), median survival was 11 months, and overall 1- and 5-year survivals were 48% (95% CI 29%–43%) and 22% (95% CI 12%–42%) respectively. Although females had a 3-year OS of 42% (95% CI 21%–81%) versus 23% (95% CI 11%–48%) for males, there was no difference on univariate analysis. Allo-SCT was not associated with improved unadjusted survival (allo-SCT 30% [95% CI 11%–85%] vs. no allo-SCT 28% [95% CI 16%–50%]), although numbers were small. Patients with least deprivation had a slightly better survival (quintiles 1 and 2, 25% [95% CI 12%–55%]; quintile 3, 20% [95% CI 6%–69%] 45% [95% CI 24%–87%]). Multivariate analysis showed no difference in survival for most of the factors assessed, except the mortality hazard was approximately twofold higher in non-White ethnicity compared to White (adjusted hazard ratio [aHR]: 2.21 [1.03–4.78]); they were similar for non-receipt of

TABLE 1 Baseline characteristics of patients with hepatosplenic T-cell lymphoma, incidence, incidence rate ratios and 3-year survival.

Category	Result *n* (%)	Incidence rate/million (95% CI)	Incidence rate ratios (95% CI)[a]	3-year overall survival % (95% CI)	Adjusted hazard ratios[b] (95% CI)
Male (%)	30 (68%)	0.16 (0.1–0.21)	Ref	23 (11–48)	Ref
Female (%)	14 (32%)	0.07 (0.03–0.11)	0.45 (0.23–0.84)	42 (21–81)	0.70 (0.30–1.60)
Age group 0–39	21 (48%)	0.11 (0.06–0.15)		21 (9–52)	Ref
Age group ≥40	23 (52%)	0.12 (0.07–0.17)	1.11 (0.61–2.01)	37 (21–65)	0.65 (0.29–1.46)
Ethnicity, White (%)	27 (61%)	N/A	N/A	36 (22–60)	Ref
Ethnicity, other (%)	17 (39%)	N/A	N/A	15 (4–55)	2.06 (0.88–4.83)
Most deprived quintiles 1, 2 (%)	23 (52%)	0.15 (0.09–0.15)	Ref	25 (12–55)	Ref
Deprivation quintile 3 (%)	10 (23%)	0.13 (0.05–0.21)	0.87 (0.4–1.78)	20 (6–69)	1.51 (0.55–4.15)
Least deprived quintiles 4, 5 (%)	11 (25%)	0.07 (0.03–0.12)	0.49 (0.23–0.99)	45 (24–87)	0.92 (0.31–2.77)
Allo-SCT (%)	11 (25%)	N/A	N/A	30 (11–85)	Ref
No allo-SCT	33 (75%)	N/A	N/A	28 (16–50)	2.52 (0.97–6.52)

Abbreviations: Allo-SCT, allogeneic stem cell transplant; N/A, not applicable.

[a]Mutually adjusted for age group, sex and deprivation.

[b]Mutually adjusted for all variables in the table.

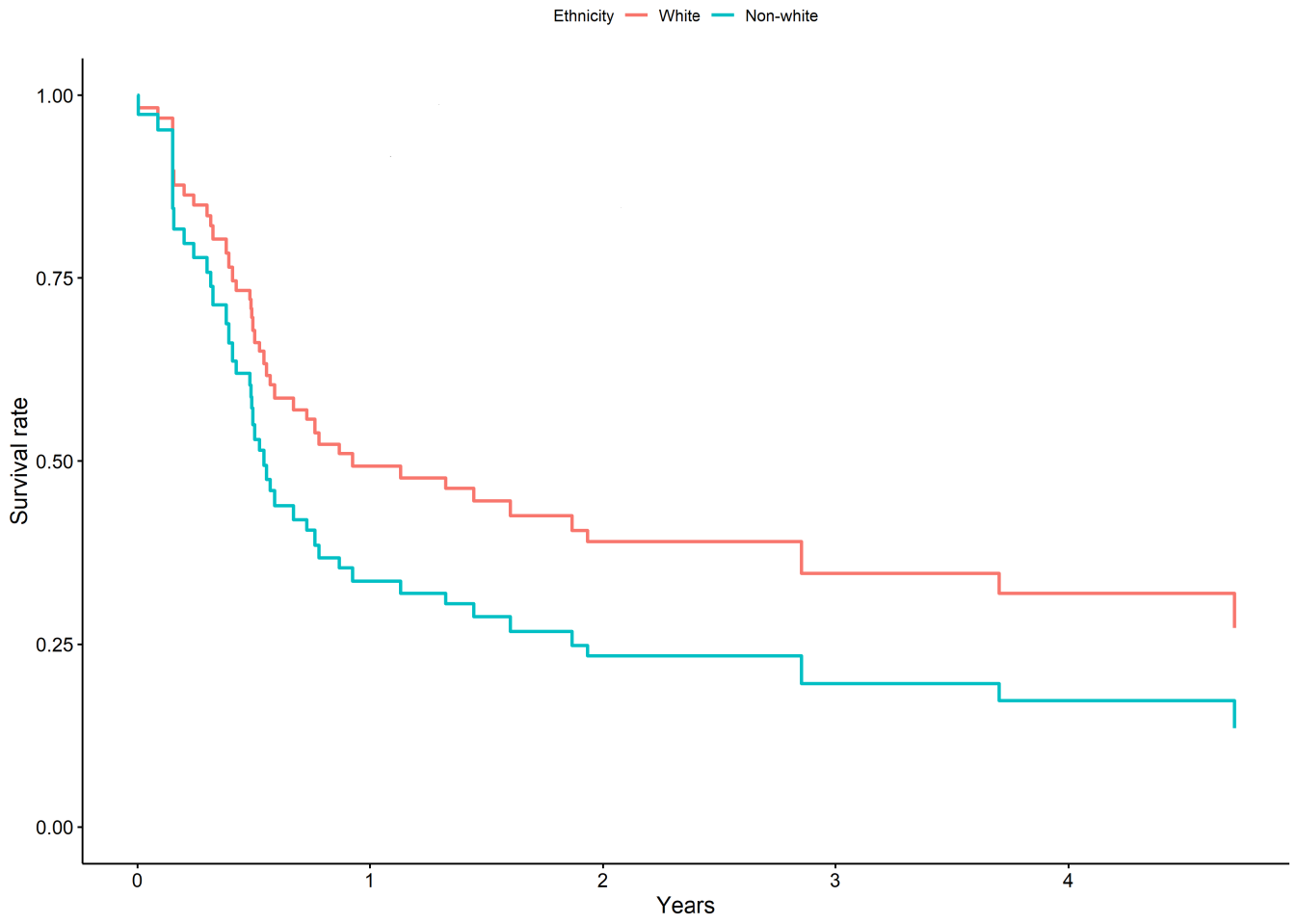

FIGURE 1 Adjusted overall survival by the ethnicity of patients with hepatosplenic T-cell lymphoma.

allo-SCT (aHR: 0.51 [0.20–1.33]). Age (aHR ≥40 compared to <40 0.66 [95% CI 0.30–1.45]), sex (aHR female compared to male: 0.65 [95% CI 0.29–1.48]) or deprivation (aHR for deprivation quintile 3: 1.53, [95% CI 0.60–3.91] and quintiles 4 and 5: 0.98 [95% CI 0.36–2.66]) compared to quintiles 1 and 2 showed no statistically significant differences for mortality. Adjusted survival curves stratified by ethnicity are shown in Figure 1.

CONCLUSIONS

Our national cohort data provide the first population-based age-standardised incidence of HSTCL over a contemporary timeframe, reducing bias in reporting socio-economic factors in comparison with prior series. The ITCP reported anthracycline-based induction in 60%, with five patients undergoing SCT in first remission, four allogeneic and one autologous with a median OS of 13 months.[3] Several of our findings are consistent with the ITCP and previously reported small studies of HSTCL, again describing diagnosis in the fifth decade, a male predilection, a clear association with IBD and the majority of patients dying within 1 year of diagnosis. Thanks to larger numbers, our series describes for the first time a higher incidence in areas with greater deprivation, and more cases than would be expected occurring in patients with non-White ethnicity.[12] Due to the need to suppress small numbers (<5), we were unable to report on all five deprivation quintiles, while a lack of denominator data for ethnicity means the possibility of residual confounding between ethnicity and deprivation could not be excluded, as there was a significant relationship between the two factors. Our data suggest an increased risk of death in non-White patients, even after adjusting for deprivation, the younger age of diagnosis of non-Whites, and receipt of allo-SCT. Careful biological and longitudinal clinical studies are needed to understand what are the predisposing factors which lead to this variation in incidence and survival by ethnicity as well as attempting to mitigate poor outcomes for all patients.

AUTHOR CONTRIBUTIONS

JW and MB wrote the application for permission to access the data. JW and CJC carried out the analysis. MB wrote the first draft, and all authors were involved in writing, reviewing and editing drafts of the paper, and approving the manuscript for submission.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

This work used data provided by the patients and collected by the NHS as part of their care and support. The data were collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of the Health and Social Care Information Centre (NHS-England). Access to the data was facilitated by the UK Health Security Agency (UKHSA) Office for Data Release. We do not own these data and hence are not permitted to share them in the original form. https://www.ndrs.nhs.uk/odr/.

ETHICS STATEMENT

The study protocol was reviewed by an NHS Research Ethics Committee (REC reference: 21/YH/0128) and was approved by the Health Research Authority Approval, which is the process for research in the NHS in England.

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