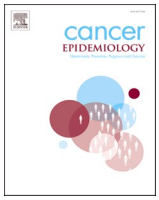
Cancer Epidemiology 88 (2024) 102513

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep



Lymphoid blood cancers, incidence and survival 2005-2023: A report from the UK's Haematological Malignancy Research Network

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ARTICLE INFO

Keywords:
Acute lymphoblastic leukaemia
Lymphoma
Myeloma
Incidence
Survival

ABSTRACT

Background: Population-based information on cancer incidence and outcome are required to inform clinical practice and research; but contemporary data are lacking for many lymphoid cancer subtypes.
Methods: Set within a socio-demographically representative UK population of ~4 million, data are from an established UK patient cohort (N = 22,414 diagnoses). Information on incidence (crude and age-standardised) and survival (overall and net) is presented for > 40 subtypes.
Results: The median diagnostic age was 69.9 years (interquartile range 59.1–78.3), but unlike many other cancers, lymphoid malignancies can be diagnosed at any age; different subtypes dominating at different ages. Males were more likely to be diagnosed than females (age-standardised sex rate ratio: 1.55 (95% Confidence Interval: 1.50,1.59)), and most subtypes had a male predominance, some more than three-fold (e.g. Burkitt lymphoma 3.26 (2.42, 4.40)). Five-year net survival estimates varied hugely, ranging from 97.4% (95% CI: 56.5, 99.9) in patients with hairy cell leukaemia to 31.6% (95% CI: 2.5, 69.8) in those with T-cell prolymphocytic leukaemia. No significant sex difference in survival were observed for the majority of diagnoses; one exception being classical Hodgkin lymphoma, where males had a higher mortality (Excess Mortality Ratio: 1.44 (95% CI: 1.11, 1.87)). An improvement in survival over time was observed for some, but not all, of the major diagnostic groups.
Conclusions: Marked incidence and survival variations by subtype, sex and age confirm the heterogeneity of lymphoid neoplasms and highlight the importance of accurately characterising disease entities. Despite recent improvements, routine cancer registration of lymphoid neoplasms remains challenging and new issues continue to emerge; including the lack of an international consensus on classification and the recording of progressions and transformations. Furthermore, the increasing need for additional molecular and genomic information required for accurate classification is likely to impact negatively on the quality of cancer registration data, especially in low income countries.

1. Introduction

Arising in blood forming and lymphoid tissue, haematological malignancies (blood cancers) are collectively the fifth most frequently diagnosed cancer worldwide [1,2]. With diverse causes, treatments and outcomes over 100 different myeloid and lymphoid subtypes are currently recognised by the World Health Organization (WHO) [3,4]. Defining cancers by their presumed cell of origin, genetic abnormalities and clinical features, WHO's first consensus classification was published in 2001 [5], and with each subsequent update [3,4,6,7] the number of entities has grown, reflecting the increased understanding of disease pathogenesis and the growing importance of genetic and other molecular features.

Critically for epidemiology the information required to implement WHO's classification (histology, cytology, immunophenotyping, cytogenetics, molecular genetics including next generation sequencing and clinical data) poses significant challenges for population-based cancer registries to access. Initially, when the 2001 classification was published

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https://doi.org/10.1016/j.canep.2023.102513
Received 18 October 2023; Received in revised form 29 November 2023; Accepted 4 December 2023
Available online 30 December 2023

Table 1
Number of lymphoid diagnoses and median ages, distributed by sex and subtype: Haematological Malignancy Research Network 2005–2019.

	Number (%)			Median age (IQR)			
Diagnosis	Total	Males	Females	Total	Males	Females	P-value[7]
Total	22414 (100.0)	12829 (100.0)	9585 (100.0)	69.9 (59.1-78.3)	68.9 (58.4-77.5)	71.1 (60.5-79.3)	< 0.001
Precursor lymphoid neoplasms							
Acute lymphoblastic leukaemia	**692 (3.1)**	**387 (3.0)**	**305 (3.2)**	**14.8 (4.5-46.4)**	**15.9 (4.8-46.0)**	**12.4 (4.3-47.9)**	**0.022**
B-lymphoblastic leukaemia (B-ALL)	550 (2.5)	289 (2.3)	261 (2.7)	12.6 (3.8-47.3)	15.1 (3.8-47.8)	9.3 (3.9-44.4)	0.088
B-ALL, NOS	*232 (1.0)*	*132 (1.0)*	*100 (1.0)*	*19.9 (8.9-54.7)*	*21.1 (8.7-53.4)*	*17.5 (9.0-60.6)*	*0.428*
with t(9,22)(q34.1;q11.2); BCR-ABL1	*69 (0.3)*	*39 (0.3)*	*30 (0.3)*	*52.4 (32.5-65.0)*	*52.4 (41.0-65.0)*	*48.7 (22.3-65.0)*	*0.891*
with t(12;21)(p13.2;q22.1); ETV-RUNX1	*63 (0.3)*	*26 (0.2)*	*37 (0.4)*	*4.2 (3.0-5.2)*	*4.0 (2.4-4.8)*	*4.3 (3.2-5.4)*	*0.508*
with hyperdiploidy	*131 (0.6)*	*63 (0.5)*	*68 (0.7)*	*4.0 (2.8-7.4)*	*3.7 (2.8-7.8)*	*4.2 (2.8-7.1)*	*0.791*
T-lymphoblastic leukaemia (T-ALL)	142 (0.6)	98 (0.8)	44 (0.5)	21.1 (10.9-40.1)	18.4 (10.2-34.4)	29.2 (11.3-56.2)	0.046
Mature B-cell neoplasms[1]	**19181 (85.6)**	**10965 (85.5)**	**8216 (85.7)**	**71.3 (62.2-79.1)**	**70.4 (61.3-78.3)**	**72.5 (63.4-80.2)**	**< 0.001**
Chronic lymphocytic leukaemia	3947 (17.6)	2484 (19.4)	1463 (15.3)	71.7 (63.3-79.3)	70.4 (62.5-78.3)	74.1 (65.8-81.2)	< 0.001
Hairy cell leukaemia	188 (0.8)	147 (1.1)	41 (0.4)	67.3 (56.4-74.9)	65.4 (56.3-73.5)	71.9 (64.9-76.8)	0.005
Lymphoproliferative disorders, NOS	1245 (5.6)	678 (5.3)	567 (5.9)	77.0 (68.3-83.6)	75.5 (66.9-82.6)	78.6 (70.2-84.8)	0.001
Marginal zone lymphoma	2148 (9.6)	1209 (9.4)	939 (9.8)	72.4 (64.3-79.4)	72.0 (64.3-79.2)	72.9 (64.2-79.6)	0.104
Follicular lymphoma	1943 (8.7)	923 (7.2)	1020 (10.6)	66.0 (56.8-74.2)	65.5 (55.9-74.3)	66.5 (57.4-74.1)	0.134
Follicular lymphoma, NOS	*1887 (8.4)*	*896 (7.0)*	*991 (10.3)*	*66.1 (56.9-74.3)*	*65.5 (56.2-74.3)*	*66.6 (57.5-74.3)*	*0.080*
Follicular lymphoma, large cell	*42 (0.2)*	*21 (0.2)*	*21 (0.2)*	*61.1 (50.0-71.3)*	*61.5 (50.0-72.9)*	*60.9 (52.2-69.6)*	*1.00*
Mantle cell lymphoma	501 (2.2)	340 (2.7)	161 (1.7)	73.1 (64.2-80.1)	71.7 (62.2-79.7)	75.6 (67.2-82.3)	0.001
Large B-cell lymphomas	4688 (20.9)	2497 (19.5)	2191 (22.9)	70.4 (60.2-78.5)	68.9 (58.6-77.5)	71.6 (61.9-79.8)	< 0.001
Diffuse large B-cell lymphoma, NOS	*4172 (18.6)*	*2218 (17.3)*	*1954 (20.4)*	*71.0 (61.2-79.0)*	*69.4 (59.6-77.8)*	*72.7 (63.3-80.3)*	*< 0.001*
High grade B-cell lymphoma[2]	*69 (0.3)*	*40 (0.3)*	*29 (0.3)*	*72.9 (64.4-78.5)*	*72.7 (64.3-78.3)*	*74.5 (66.4-79.7)*	*0.555*
T-cell/histiocyte-rich large B-cell lymphoma[3]	*98 (0.4)*	*61 (0.5)*	*37 (0.4)*	*62.7 (52.0-74.4)*	*58.8 (44.1-73.5)*	*69.5 (58.8-77.7)*	*0.096*
Primary DLBCL of the CNS	*144 (0.6)*	*77 (0.6)*	*67 (0.7)*	*66.2 (58.4-71.6)*	*68.2 (58.5-72.9)*	*65.2 (58.4-69.9)*	*0.112*
Primary mediastinal large B-cell lymphoma	*115 (0.5)*	*53 (0.4)*	*62 (0.6)*	*38.9 (28.4-52.5)*	*42.2 (30.3-53.2)*	*37.7 (27.9-46.1)*	*0.404*
Plasmablastic lymphoma	*44 (0.2)*	*28 (0.2)*	*16 (0.2)*	*65.8 (54.0-76.1)*	*65.8 (54.4-75.4)*	*66.7 (54.0-78.4)*	*0.754*
Burkitt lymphoma	218 (1.0)	165 (1.3)	53 (0.6)	55.7 (21.9-72.5)	53.0 (15.3-72.6)	60.6 (43.8-71.2)	0.207
Intermediate between DLBCL/CHL[4]	45 (0.2)	24 (0.2)	21 (0.2)	64.6 (37.8-73.1)	54.1 (29.2-66.1)	71.8 (55.8-76.5)	0.053
Plasma cell neoplasms	***4231 (18.9)***	***2484 (19.4)***	***1747 (18.2)***	***72.3 (64.0-79.5)***	***71.5 (63.5-78.9)***	***73.2 (65.3-80.4)***	***< 0.001***
Plasmacytoma	255 (1.1)	172 (1.3)	83 (0.9)	68.4 (58.7-77.1)	68.5 (60.0-76.8)	68.3 (54.7-77.7)	0.894
Solitary plasmacytoma of bone	*172 (0.8)*	*114 (0.9)*	*58 (0.6)*	*66.3 (58.5-76.6)*	*66.0 (59.4-76.3)*	*68.4 (56.7-77.3)*	*0.956*
Extraosseous plasmacytoma	*83 (0.4)*	*58 (0.5)*	*25 (0.3)*	*70.0 (59.9-78.7)*	*71.2 (64.0-77.5)*	*67.5 (52.0-78.7)*	*0.684*
Myeloma	3975 (17.7)	2312 (18.0)	1663 (17.4)	72.5 (64.3-79.7)	71.7 (63.7-79.1)	73.4 (65.6-80.5)	< 0.001
Mature T and NK-cell neoplasms[5]	**844 (3.8)**	**475 (3.7)**	**369 (3.8)**	**68.6 (55.7-77.0)**	**67.8 (54.0-76.5)**	**69.9 (58.7-77.8)**	**0.331**
Peripheral T-cell lymphomas	443 (2.0)	255 (2.0)	188 (2.0)	66.1 (53.3-76.2)	65.2 (51.9-74.3)	68.7 (55.8-77.5)	0.197
Enteropathy-associated T-cell lymphoma	*40 (0.2)*	*23 (0.2)*	*17 (0.2)*	*64.6 (60.6-73.2)*	*62.0 (58.0-72.6)*	*66.9 (63.4-73.8)*	*0.522*
Peripheral T-cell lymphoma, NOS	*136 (0.6)*	*90 (0.7)*	*46 (0.5)*	*69.1 (54.5-77.8)*	*68.2 (51.4-76.5)*	*71.6 (59.0-81.5)*	*0.587*
Angioimmunoblastic T-cell lymphoma	*113 (0.5)*	*48 (0.4)*	*65 (0.7)*	*70.4 (63.0-78.2)*	*68.5 (59.2-74.1)*	*73.1 (64.6-80.0)*	*0.103*
Anaplastic large cell lymphoma, ALK	*42 (0.2)*	*27 (0.2)*	*15 (0.2)*	*37.9 (25.4-52.3)*	*42.6 (28.8-54.0)*	*31.3 (21.7-44.9)*	*0.198*
Anaplastic large cell lymphoma, ALK-	*77 (0.3)*	*45 (0.4)*	*32 (0.3)*	*68.9 (54.0-76.6)*	*69.1 (58.9-76.7)*	*65.1 (52.1-75.8)*	*0.550*
Cutaneous T-cell lymphomas	145 (0.6)	98 (0.8)	47 (0.5)	65.8 (52.5-76.2)	66.4 (54.1-77.5)	64.9 (50.8-74.3)	0.514
Mycosis fungoides	*62 (0.3)*	*44 (0.3)*	*18 (0.2)*	*67.8 (56.4-76.4)*	*67.9 (54.7-79.1)*	*66.9 (61.8-75.9)*	*0.780*
Primary cutaneous CD30 + T-cell LPD	*63 (0.3)*	*42 (0.3)*	*21 (0.2)*	*61.5 (47.1-74.0)*	*65.1 (50.7-76.3)*	*51.9 (43.6-65.5)*	*0.130*
T-cell prolymphocytic leukaemia	56 (0.2)	27 (0.2)	29 (0.3)	76.5 (65.0-84.1)	75.0 (63.0-81.6)	76.5 (66.5-86.0)	1.00
T-cell large granular lymphocytic leukaemia	196 (0.9)	93 (0.7)	103 (1.1)	70.9 (63.5-77.7)	71.4 (63.1-77.2)	70.8 (64.0-77.7)	0.775
Hodgkin lymphomas	**1639 (7.3)**	**968 (7.5)**	**671 (7.0)**	**43.9 (26.8-65.4)**	**44.4 (28.6-64.2)**	**42.4 (25.3-67.0)**	**0.434**
Classical Hodgkin lymphoma	1450 (6.5)	826 (6.4)	624 (6.5)	42.8 (26.3-65.7)	44.6 (28.2-64.7)	40.8 (25.1-66.9)	0.002
Nodular lymphocyte predominant	189 (0.8)	142 (1.1)	47 (0.5)	46.4 (31.1-60.0)	44.1 (30.6-57.1)	55.7 (38.9-67.1)	0.790
Post-transplant lymphoproliferative disorders[6]	**58 (0.3)**	**34 (0.3)**	**24 (0.3)**	**52.3 (37.4-61.6)**	**52.3 (38.6-62.4)**	**50.8 (30.3-59.4)**	**0.790**

Subtypes with less than 40 diagnoses are not shown: [1]Burkitt-like lymphoma with 11q aberration, in situ follicular neoplasia and splenic B-cell lymphoma/leukaemia, unclassifiable. [5]Aggressive NK cell leukaemia, chronic lymphoproliferative disorder of NK-cells
[2]High grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements, cases classified 2016-2019; [3]Cases classified 2009-2019; [4]Large B-cell lymphoma with features intermediate between DLBCL/classical Hodgkin lymphoma, cases classified 2009-2019, [6]Cases classified 2007-2019.
[7]Median age: males vs. females
Abbreviations: ALK-anaplastic lymphoma kinase; CHL – classical Hodgkin lymphoma; CNS – central nervous system; DLBCL – diffuse large B-cell lymphoma; IQR – interquartile range; LPD – lymphoproliferative disorder; NK -natural killer; NOS – not otherwise specified.

alongside the associated International Classification of Disease for Oncology (ICD-O-3) [8], national cancer registries continued to report data by the broad diagnostic categories, leukaemia, myeloma, Hodgkin and non-Hodgkin lymphoma (NHL); this being particularly problematic for the heterogeneous NHLs and leukaemias, which contain a mixture of aggressive and indolent cancers of both myeloid and lymphoid origin [9].

A few specialist population-based registries have published additional statistics for some haematological cancer groups [9–18]; and more recently national registries, including the USA's National Cancer Institute's Surveillance, Epidemiology and End Results Program (SEER) and the English National Cancer Registration and Analysis Service, have started to do so [19–21]. Nonetheless, many of these registries still struggle to collect complete data on all entities and the "not otherwise specified" groups are often large. A further issue relates to the ability of many blood cancers to progress and transform into other, generally

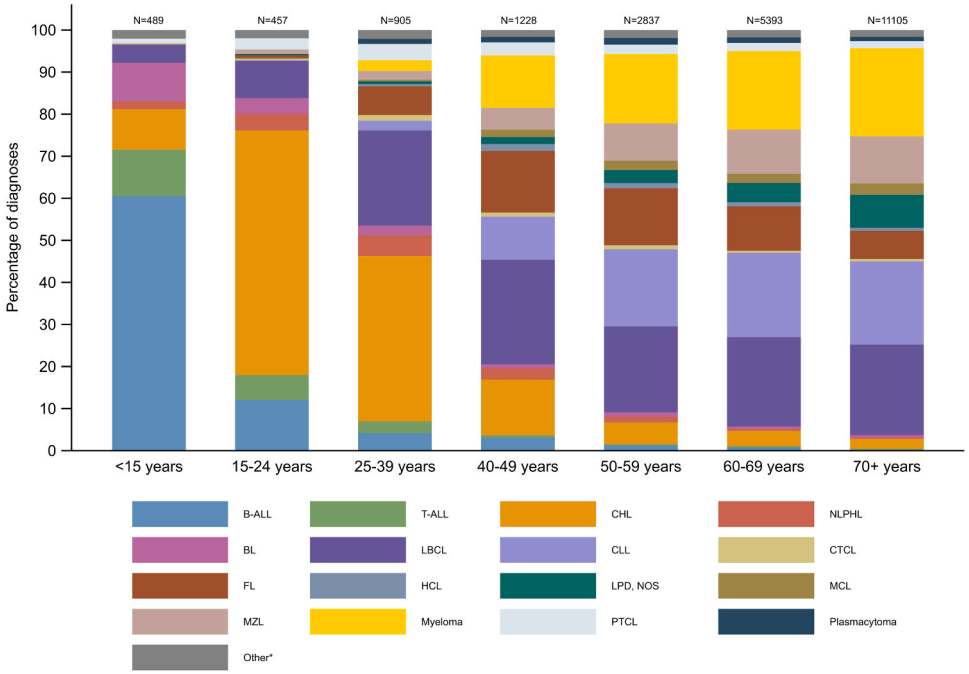

Fig. 1. Diagnostic frequency by age at diagnosis: Haematological Malignancy Research Network 2005–2019. *Other includes: aggressive NK-cell leukaemia, B-cell lymphoma intermediate between DLBCL & CHL, Burkitt-like lymphoma with 11q aberration, chronic lymphoproliferative disorder of NK-cells, in situ follicular neoplasia, post-transplant lymphoproliferative disorder, splenic B-cell lymphoma/leukaemia, unclassifiable, T-cell large granular lymphocytic leukaemia, T-pro-lymphocytic leukaemia.

more aggressive, subtypes; follicular lymphoma to diffuse large B-cell lymphoma (DLBCL) and myelodysplastic syndromes (MDS) to acute myeloid leukaemia (AML), for example. Such changes are challenging for non-specialist cancer registries to track and code correctly. Furthermore, the health infrastructure required to diagnose, and hence treat, these cancers is missing in many low income countries, and global statistics are still reported using traditional site-based topographic categories [1,2,22].

The data included in the present report are from the UK's Haematological Malignancy Research Network (https://hmrn.org/), one of the first specialist registries to publish incidence, prevalence and survival figures [9,17,18] using WHO's ICD-O-3 classification [8]. Linking directly to centralised diagnostic haematopathology, HMRN was specifically designed to rapidly respond to changes in disease classification. The challenges outlined above, along with the recent increase in the number of recognised disease entities and continuing therapeutic advances, means that there is a lack of contemporary population-based data. Accordingly, this report focuses on the incidence and survival of the lymphoid neoplasms as classified to the 4th Edition of the WHO classification (WHO HAEM-4R) [7], which account for around two-thirds of all newly diagnosed bloods cancers.

2. Methods

Providing robust, generalisable data to inform contemporary clinical practice and research, the methods underpinning HMRN's ongoing population-based patient cohort are outlined on the study website (https://hmrn.org/) and fully described elsewhere [9,17,23]. Briefly, HMRN's catchment population of ~4 million people has a socio-demographic composition that broadly mirrors that of the UK as a whole, and clinical practice adheres to national guidelines. Patient care is provided by 14 hospitals, organised into five multidisciplinary teams (MDTs), and all initial and subsequent diagnoses are made and coded using the latest WHO ICD-O-3 by clinical specialists at the Haematological Malignancy Diagnostic Service (HMDS; https://hmds.info/). This is in line with national guidance mandating that all diagnoses need to be reviewed by specialists and discussed by an MDT [24]. Accordingly, all samples from patients from the 14 hospitals with a suspected haematological cancer are sent to HMDS; irrespective of age, assumed prognosis, treatment intent and whether originating from the NHS or private sector. HMRN has full ethical approval including Section 251 support under the NHS Act 2006 and all patients have prognostic, treatment, response and outcome data collected and all are 'flagged' via their NHS number and followed-up for death by NHS England (www.nhsdigital.nhs.uk), ensuring notification of all deaths within the UK even if the patient moves away from the HMRN region.

All lymphoid diagnoses between 1st January 2005 and 31st December 2019, with follow-up to July 2023, are included. As some haematological malignancies progress and transform to more aggressive subtypes, a small number of patients are included in these analyses more than once. Incidence rates and 95% confidence intervals (95% CI) were calculated using Poisson regression using population estimates from the Office of National Statistics [25]. Directly age-standardised estimates (European 2013 [26]) were generated using the Stata command dstdize and corresponding sex rate ratios were estimated. To enable comparison with other studies, age-standardised estimates using the US 2000 and World standards are provided in the supplementary information (Supplementary tables 2a-c).

Overall survival (OS) was calculated using standard time-to-event methods and cancer-specific survival using net survival (NS), which uses background population mortality rates to account for deaths from other causes rather than relying on the cause of death recorded on death certificates. Net survival was estimated by the program strs [27], implementing the Pohar Perme estimator [28], with age and sex-specific background mortality rates derived from national life tables [29]. The strs command was used as it was specifically designed to facilitate modelling, meaning comparisons in lymphoid-specific survival could be made by sex and diagnostic year. HMRN's population-based cohort has no age exclusions, enabling examination across the full age-range, and because some diagnoses are more common in children (e.g. acute lymphoblastic leukaemia) and/or young adults (e.g. Hodgkin lymphoma), 5-year net survival estimates were age-standardised, using an

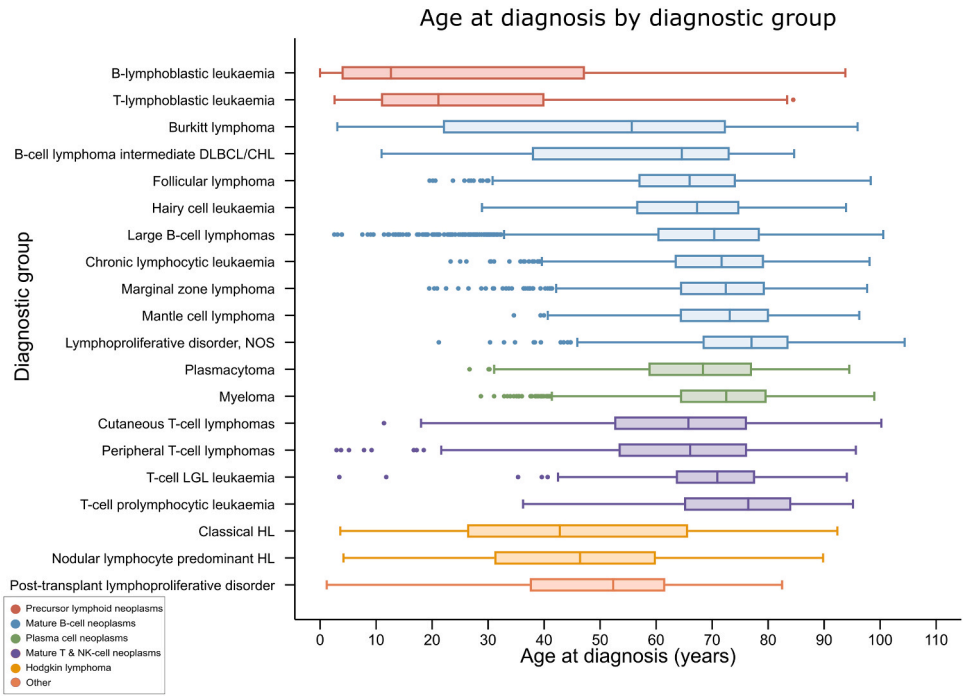

Fig. 2. Age at diagnosis box and whisker plots[1]: Haematological Malignancy Research Network 2005–2019. Abbreviations: DLBCL/CHL – diffuse large B-cell lymphoma/classical Hodgkin lymphoma; HL – Hodgkin lymphoma; LGL – large granular lymphocytic; NOS –not otherwise specified. [1]Boxes represent the inter-quartile range (IQR) with the median line drawn. Whiskers include all points within 1.5 IQR of the nearest quartile with outliers included as points.

adapted version of the International Cancer Survival Standard weights [30–32]. To examine for differences in outcome by sex and calendar year (2005–09, 2010–14, 2015–19), excess mortality ratios were estimated using Poisson regression [27]. All analyses were performed using Stata 18 [33].

3. Results

During the 15-year period 2005–2019, a total of 22,414 lymphoid cancers were diagnosed in 21,564 patients (Table 1). Providing information on sex and age for all subtypes with at least 40 diagnoses, Table 1 is ordered according to the WHO-HAEM4R hierarchy [7]; beginning with the precursor lymphoid neoplasms, followed by mature B-cell and T- & Natural Killer-cell (NK) neoplasms, Hodgkin lymphomas, and finally the post-transplant lymphoproliferative disorders. The subtypes included in each diagnostic category are listed in Supplementary Table 1 alongside corresponding ICD-O-3 codes. Mature B-cell neoplasms dominate (85.6%); the most common diagnostic category is large B-cell lymphoma (LBCL), comprising one in five of all lymphoid diagnoses (20.9%), closely followed by chronic lymphocytic leukaemia (17.6%) and multiple myeloma (17.7%). In contrast to B-cell forms, mature T and NK-cell neoplasms are rare, accounting for only 3.8% of the total.

With a median diagnostic age of 69.9 years (interquartile range (IQR) 59.1–78.3), like most other cancers, lymphoid malignancies are more likely to be diagnosed at older ages. However, unlike many other cancers, they can be diagnosed at any age with different subtypes dominating at different ages (Table 1, Figs. 1–2). For example, accounting for 70% of diagnosis in those under 14 years (Fig. 1), the precursor-cell conditions B-lymphoblastic leukaemia (B-ALL) and T-lymphoblastic leukaemia (T-ALL) dominate, and have the lowest median ages at 12.6 years and 21.1 years respectively (Table 1). Within these broad categories, age variations by subtype are, however, evident; for example, B-ALL patients with a translocation between the BCR gene on chromosome 22 and the ABL1 oncogene on chromosome 9, 't[9,22] (q34.1;q11.2); BCR-ABL1′, have a median diagnostic age of 52.4 years, whereas those with B-ALL with hyperdiploidy have a median of 4.0 years (Table 1).

Hodgkin lymphomas, which can also be diagnosed at any age (Fig. 1), are the most common blood cancer in individuals aged 15–24 years (62%) and 25–39-years (44%). Occurring less frequently at younger ages than Hodgkin lymphoma and ALL, some other lymphoid cancers also span the whole age range (Fig. 2), including Burkitt lymphoma (median age = 55.7 years) and the large B-cell lymphomas (median age = 70.4 years). Interestingly, distinct age differences are also evident for several large B-cell lymphomas, including high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (median diagnostic age = 72.9 years) and primary mediastinal large B-cell lymphoma (median diagnostic age = 38.9 years) (Table 1). Conversely, diagnoses such as chronic lymphocytic leukaemia and myeloma are rarely made under 40-years; indeed, these cancers, together with the large B-cell lymphomas, account for the majority of diagnoses over 50-years (Fig. 1).

The median diagnostic age of all lymphoid subtypes combined was higher for females than males (median 71.1 versus 68.9 years respectively); which, in part reflects the fact that women tend to live longer than men. However, clear age differences are evident for some subtypes, with males tending to be diagnosed at significantly younger ages than females with T-ALL (18.4 versus 29.2 years respectively, $p = 0.046$), and large B-cell lymphoma with features intermediate between DLBCL/classical Hodgkin lymphoma (54.1 versus 71.8 years, $p = 0.053$). However, there are exceptions where females tend, on average, to be younger; including B-ALL (males 15.1 years, females 9.3 years, $p = 0.088$) and classical Hodgkin lymphoma (males 44.6 years, females 40.8 years, $p = 0.002$).

Age-standardised incidence rates and sex-rate ratios (SRR; European 2013 population) are shown in Table 2 (see Supplementary Table 2 for World and US standards) and Fig. 3. In general, with an overall male/female age-standardised sex rate ratio (SRR) of 1.55 (95% CI: 1.50–1.59), males were more likely than females to be diagnosed with a lymphoid malignancy. The majority of diagnostic groups show a male excess, most notably hairy cell leukaemia, Burkitt lymphoma and nodular lymphocyte predominant Hodgkin Lymphoma where males

Table 2
Age-standardised (European 2013) annual incidence rates (per 100,000 persons): Haematological Malignancy Research Network 2005–2019.

Diagnosis	Annual incidence rate (per 100,000 persons)			Sex rate ratio (95% CI)
	All	Males	Females	
Total	40.59 (40.06, 41.13)	50.15 (49.27, 51.02)	32.45 (31.79, 33.10)	1.55 (1.50, 1.59)
Precursor lymphoid neoplasms				
Acute Lymphoblastic Leukaemia	**1.10 (1.02, 1.19)**	**1.24 (1.11, 1.36)**	**0.97 (0.86, 1.08)**	**1.27 (1.09, 1.48)**
B-lymphoblastic leukaemia (B-ALL)	0.87 (0.80, 0.94)	0.92 (0.81, 1.02)	0.83 (0.72, 0.93)	1.11 (0.94, 1.31)
B-ALL, NOS	0.38 (0.33, 0.43)	0.43 (0.36, 0.51)	0.33 (0.26, 0.39)	1.33 (1.02, 1.72)
B-ALL with t(9,22)(q34.1;q11.2); BCR-ABL1	0.12 (0.09, 0.15)	0.14 (0.09, 0.18)	0.10 (0.07, 0.14)	1.35 (0.83-2.17)
B-ALL with t(12;21)(p13.2;q22.1); ETV-RUNX1	0.09 (0.07, 0.11)	0.07 (0.04, 0.10)	0.11 (0.07, 0.14)	0.65 (0.40-1.08)
B-ALL with hyperdiploidy	0.19 (0.16, 0.23)	0.18 (0.14, 0.23)	0.20 (0.15, 0.25)	0.89 (0.63-1.26)
T- lymphoblastic leukaemia (T-ALL)	0.23 (0.19, 0.27)	0.32 (0.26, 0.38)	0.15 (0.10, 0.19)	2.20 (1.55, 3.11)
Mature B-cell neoplasms[1]	**35.01 (34.51, 35.50)**	**43.47 (42.65, 44.29)**	**27.87 (27.26, 28.48)**	**1.56 (1.52, 1.61)**
Chronic lymphocytic leukaemia	7.23 (7.00, 7.45)	9.90 (9.51, 10.30)	4.95 (4.69, 5.20)	2.00 (1.87, 2.14)
Hairy cell leukaemia	0.34 (0.29, 0.39)	0.57 (0.47, 0.66)	0.14 (0.10, 0.18)	4.03 (2.88, 5.63)
Lymphoproliferative disorders, NOS	2.28 (2.15, 2.41)	2.83 (2.61, 3.04)	1.86 (1.70, 2.01)	1.52 (1.36, 1.71)
Marginal zone lymphoma	3.93 (3.76, 4.10)	4.82 (4.55, 5.09)	3.20 (2.99, 3.40)	1.51 (1.38, 1.65)
Follicular lymphoma	3.52 (3.37, 3.68)	3.56 (3.32, 3.79)	3.53 (3.31, 3.74)	1.01 (0.92, 1.10)
Follicular lymphoma, NOS	*3.42 (3.27, 3.58)*	*3.45 (3.22, 3.68)*	*3.43 (3.21, 3.64)*	*1.01 (0.92, 1.10)*
Follicular lymphoma, large cell	*0.08 (0.05, 0.10)*	*0.08 (0.05, 0.12)*	*0.07 (0.04, 0.11)*	*1.10 (0.60, 2.02)*
Mantle cell lymphoma	0.91 (0.83, 1.00)	1.35 (1.21, 1.50)	0.54 (0.46, 0.63)	2.49 (2.06, 3.01)
Large B-cell lymphomas	8.55 (8.30, 8.79)	9.80 (9.41, 10.19)	7.43 (7.12, 7.75)	1.32 (1.24, 1.40)
Diffuse large B-cell lymphoma, NOS	*7.61 (7.38, 7.85)*	*8.73 (8.37, 9.10)*	*6.62 (6.32, 6.91)*	*1.32 (1.24-1.40)*
High grade B-cell lymphoma[2]	*0.48 (0.37, 0.60)*	*0.61 (0.42, 0.80)*	*0.38 (0.24, 0.52)*	*1.61 (0.99, 2.63)*
T-cell/histiocyte-rich large B-cell lymphoma[3]	*0.24 (0.19, 0.29)*	*0.31 (0.23, 0.39)*	*0.17 (0.12, 0.23)*	*1.79 (1.19, 2.70)*
Primary DLBCL of the CNS	*0.26 (0.22, 0.30)*	*0.29 (0.23, 0.36)*	*0.23 (0.18, 0.29)*	*1.25 (0.90, 1.74)*
Primary mediastinal large B-cell lymphoma	*0.20 (0.16, 0.24)*	*0.19 (0.14, 0.24)*	*0.22 (0.16, 0.27)*	*0.87 (0.60, 1.26)*
Plasmablastic lymphoma	*0.08 (0.06, 0.10)*	*0.11 (0.07, 0.15)*	*0.05 (0.03, 0.08)*	*2.01 (1.08, 3.74)*
Burkitt lymphoma	0.38 (0.33, 0.43)	0.59 (0.50, 0.68)	0.18 (0.13, 0.23)	3.26 (2.42, 4.40)
Intermediate between DLBCL/CHL[4]	0.11 (0.08, 0.14)	0.12 (0.07, 0.16)	0.10 (0.06, 0.15)	1.13 (0.63, 2.04)
Plasma cell neoplasms	**7.73 (7.50, 7.97)**	**9.91 (9.52, 10.31)**	**5.92 (5.65, 6.20)**	**1.67 (1.57, 1.78)**
Plasmacytoma	0.47 (0.41, 0.52)	0.67 (0.57, 0.78)	0.28 (0.22, 0.34)	2.39 (1.83, 3.10)
Solitary plasmacytoma of bone	*0.31 (0.27, 0.36)*	*0.44 (0.36, 0.53)*	*0.20 (0.15, 0.25)*	*2.25 (1.64, 3.09)*
Extraosseous plasmacytoma	*0.15 (0.12, 0.18)*	*0.23 (0.17, 0.29)*	*0.09 (0.05, 0.12)*	*2.71 (1.69, 4.34)*
Myeloma	7.26 (7.04, 7.49)	9.24 (8.86, 9.62)	5.64 (5.37, 5.91)	1.64 (1.54, 1.75)
Mature T and NK-cell neoplasms[5]	**1.54 (1.43, 1.64)**	**1.86 (1.69, 2.03)**	**1.26 (1.13, 1.39)**	**1.48 (1.29, 1.69)**
Peripheral T-cell lymphomas	0.80 (0.73, 0.88)	0.99 (0.86, 1.11)	0.64 (0.55, 0.74)	1.53 (1.27, 1.86)
Enteropathy-associated T-cell lymphoma	*0.07 (0.05, 0.10)*	*0.09 (0.05, 0.12)*	*0.06 (0.03, 0.09)*	*1.47 (0.78, 2.75)*
Peripheral T-cell lymphoma, NOS	*0.25 (0.21, 0.29)*	*0.36 (0.28, 0.43)*	*0.16 (0.11, 0.20)*	*2.30 (1.60, 3.29)*
Angioimmunoblastic T-cell lymphoma	*0.21 (0.17, 0.24)*	*0.18 (0.13, 0.24)*	*0.22 (0.17, 0.28)*	*0.83 (0.57, 1.20)*
Anaplastic large cell lymphoma, ALK+	*0.07 (0.05, 0.09)*	*0.10 (0.06, 0.13)*	*0.05 (0.03, 0.08)*	*1.89 (1.00, 3.57)*
Anaplastic large cell lymphoma, ALK-	*0.14 (0.11, 0.17)*	*0.18 (0.12, 0.23)*	*0.11 (0.07, 0.15)*	*1.64 (1.03, 2.59)*
Cutaneous T-cell lymphomas	0.26 (0.22, 0.31)	0.39 (0.31, 0.46)	0.16 (0.12, 0.21)	2.36 (1.66, 3.35)
Mycosis fungoides	*0.11 (0.09, 0.14)*	*0.17 (0.12, 0.23)*	*0.06 (0.03, 0.09)*	*2.80 (1.62, 4.83)*
Primary cutaneous CD30 + T-cell LPD	*0.11 (0.09, 0.14)*	*0.16 (0.11, 0.21)*	*0.07 (0.04, 0.11)*	*2.15 (1.27, 3.61)*
T-cell prolymphocytic leukaemia	0.10 (0.08, 0.13)	0.11 (0.07, 0.15)	0.10 (0.06, 0.13)	1.16 (0.68, 1.98)
T-cell large granular lymphocytic leukaemia	0.36 (0.31, 0.41)	0.37 (0.29, 0.45)	0.35 (0.28, 0.42)	1.05 (0.79, 1.40)
Hodgkin lymphomas	**2.85 (2.71, 2.98)**	**3.46 (3.24, 3.68)**	**2.26 (2.09, 2.44)**	**1.53 (1.38, 1.69)**
Classical Hodgkin lymphoma	2.51 (2.38, 2.64)	2.95 (2.75, 3.16)	2.10 (1.93, 2.27)	1.41 (1.27, 1.56)
Nodular lymphocyte predominant Hodgkin lymphoma	0.33 (0.28, 0.38)	0.50 (0.42, 0.59)	0.16 (0.12, 0.21)	3.07 (2.24, 4.21)
Post-transplant lymphoproliferative disorder[6]	0.12 (0.09, 0.15)	0.14 (0.09, 0.19)	0.09 (0.06, 0.13)	1.47 (0.87, 2.48)

Subtypes with less than 40 diagnoses are not shown: [1]Burkitt-like lymphoma with 11q aberration, in situ follicular neoplasia and splenic B-cell lymphoma/leukaemia, unclassifiable. [5]aggressive NK cell leukaemia, chronic lymphoproliferative disorder of NK-cells
[2]High grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements, cases classified 2016-2019; [3]Cases classified 2009-2019; [4]Large B-cell lymphoma with features intermediate between DLBCL/classical Hodgkin lymphoma, cases classified 2009-2019; [6]Cases classified 2007-2019.
Abbreviations: ALK-anaplastic lymphoma kinase; CHL – classical Hodgkin lymphoma; CI – confidence interval; CNS – central nervous system; DLBCL – diffuse large B-cell lymphoma; LPD – lymphoproliferative disorder; NK - natural killer; NOS – not otherwise specified

were over three-times more likely to be diagnosed than females. However, there are exceptions; for example, the SRR for follicular lymphoma was 1.01 (95% CI: 0.92–1.10), and interestingly, while males were two times more likely to be diagnosed with T-ALL, B-ALL showed no significant excess (SRR: 1.11 95% CI: 0.94–1.31). Differences are also evident within the main diagnostic categories; among large B-cell lymphomas, for example, plasmablastic lymphoma exhibits a large male excess (SRR: 2.01 95% CI: 1.08–3.74).

Overall survival (OS) and age-standardised net survival (NS) estimates are in Table 3 (non age-standardised NS estimates are in Supplementary Table 3). As expected, survival varied widely within and between diagnostic groups, with 5-year net survival ranging from 97.4% (95% CI: 56.5, 99.9) in patients with hairy cell leukaemia to 31.6% (95% CI: 2.5, 69.8) in patients with T-cell prolymphocytic leukaemia (Table 3, Fig. 4). For the majority of aggressive lymphoid diagnoses, there is little difference between OS and NS estimates, suggesting that patients were generally dying as a consequence of their disease. In contrast, the discrepancy between overall and net survival for more indolent disorders, such as chronic lymphocytic leukaemia, hairy cell leukaemia, marginal zone lymphoma, and follicular lymphoma, is much larger; for chronic lymphocytic leukaemia, for example, the 5-year OS and NS estimates are 68.4% and 86.6% respectively, suggesting that many patients are dying from competing causes.

The importance of looking at the subtypes that contribute to the main diagnostic groups is also evident in Table 3: amongst the large B-cell lymphomas, for example, 5-year net survival was lowest for patients with primary diffuse large B-cell of the CNS (5-year NS 21.7% (95% CI: 3.3, 50.5)) and highest for patients with primary mediastinal B-cell lymphoma (5-year NS 83.3% (95% CI: 68.1,91.7)). Likewise, with a 5-year NS of 35.6% (95% CI 22.0, 49.5) survival was generally poor across the peripheral T-cell lymphomas, although ALK-positive anaplastic large cell lymphoma had a far better 5-year NS (75.7% (95% CI: 48.0, 90.0)).

No statistically significant differences in outcome were detected by sex for most diagnoses (Table 3). However, excess mortality was raised in men with classical Hodgkin lymphoma (Excess Mortality Ratio (EMR): 1.44 (95% CI: 1.11, 1.87)); primary mediastinal B-cell lymphoma (EMR: 7.70 (95% CI: 2.01, 29.55)) and anaplastic large cell lymphoma, ALK-positive (EMR: 10.97 (95% CI: 1.36, 88.7)). Interestingly, these are the conditions that often onset at a comparatively young age (Table 1).

Finally, Table 4 presents 5-year net survival and EMRs by calendar year of diagnosis (2005–2009, 2010–2014 and 2015–2019). Predominantly showing increases in survival between 2005–2009 and 2010–2014, improvements are evident for most groups: the largest being for mantle cell lymphoma and myeloma, with EMRs of 0.69 (95% CI: 0.51, 0.94) and 0.67 (95% CI: 0.59, 0.75) respectively. Improvements for chronic lymphocytic leukaemia, marginal zone lymphoma, follicular lymphoma and Burkitt lymphoma are, however, more recent (2015–2019). No statistically significant differences were observed for B-lymphoblastic leukaemia and peripheral T-cell lymphoma.

4. Discussion

Our findings on over 40 different subtypes provide important information on incidence and survival, and illustrate the heterogeneity of the lymphoid neoplasms; not only with respect to sex and age of onset, but also survival. The similarities and differences in overall and net survival within and between diagnostic groups demonstrate the divergent nature of the lymphoid neoplasms; with some patients having a near normal life expectancy and others dying rapidly from their disease. As far as we are aware, this is the most comprehensive report on the descriptive epidemiology of these cancers; demonstrating, for the first time, an improvement in survival over time for some of the major diagnostic groups. Our results further confirm the importance of characterising disease entities correctly, and underscore the importance that real-world population-based data have in informing aetiological hypotheses, planning health-care services, and providing baseline measures against which to monitor therapeutic changes.

Where comparisons can be made with other published studies and national cancer registries, both our incidence and survival estimates are generally concordant (see Supplementary Table 2 for standardised rates). For myeloma, however, while the incidence rates reported by specialist registries are broadly similar to those reported here [14,34], those from most national cancer registries tend to be higher [35,36]. The application of different coding rules for disease transformations is one factor affecting the validity of such comparisons. For example, follicular lymphoma may transform to large B-cell lymphoma, and 7% of the large

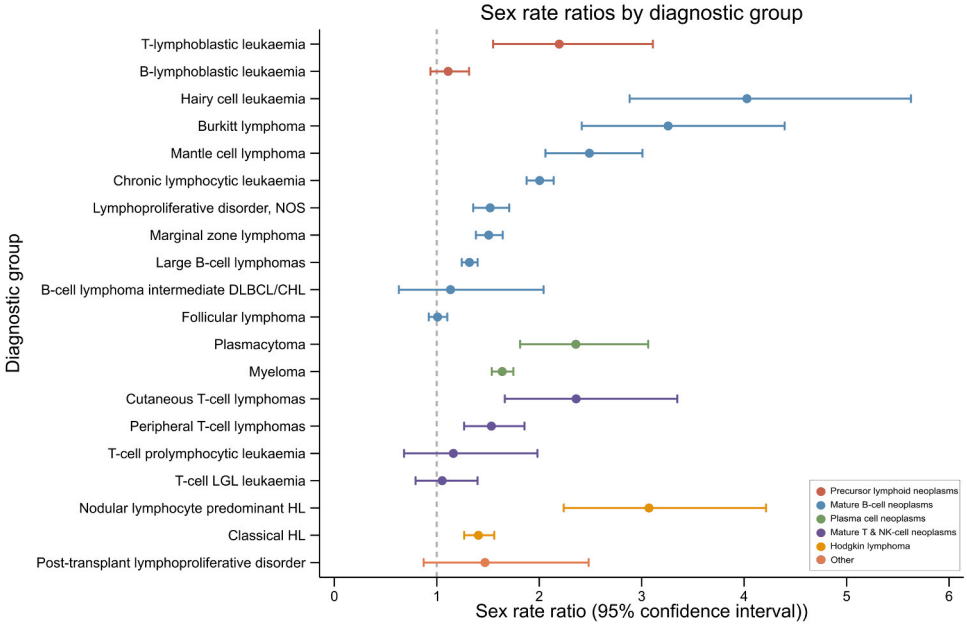

Fig. 3. Sex rate ratios (age-standardised) by diagnostic group: Haematological Malignancy Research Network 2005–2019. Abbreviations: DLBCL/CHL – diffuse large B-cell lymphoma/classical Hodgkin lymphoma; HL – Hodgkin lymphoma; LGL – large granular lymphocytic; NK – natural killer; NOS –not otherwise specified.

Table 3
Five-year overall and net survival estimates (95% Confidence Intervals): Haematological Malignancy Research Network 2005–2019, followed up to 2023.

Diagnosis	5-year overall survival % (95% Confidence Intervals)			5-year net survival % (95% Confidence Intervals)[1]			Excess mortality ratio (95% CI)[3] male:female
	All	Male	Female	All	Male	Female	
Precursor lymphoid neoplasms							
Acute lymphoblastic leukaemia[2]	64.0 (60.3, 67.5)	65.4 (60.4, 69.9)	62.3 (56.6, 67.5)	46.8 (29.7, 62.2)	50.0 (35.4, 63.1)	43.0 (18.8, 65.3)	0.89 (0.68, 1.15)
B-lymphoblastic leukaemia (B-ALL)	64.3 (60.1, 68.2)	64.5 (58.6, 69.7)	64.1 (57.9, 69.6)	46.1 (28.0, 62.4)	50.1 (33.3, 64.7)	41.7 (16.7, 65.3)	0.87 (0.65, 1.17)
B-ALL, NOS	*58.6 (51.9, 64.7)*	*58.6 (49.7, 66.5)*	*58.6 (48.2, 67.6)*	*46.3 (24.4, 65.7)*	*49.0 (25.8, 68.6)*	*44.3 (14.0, 71.5)*	*1.08 (0.69, 1.68)*
B-ALL with t(9,22)(q34.1;q11.2); BCR-ABL1	*36.1 (25.0, 47.3)*	*41.0 (25.7, 55.8)*	*30.0 (15.0, 46.6)*	*42.9 (19.1, 64.9)*	*48.6 (17.7, 74.0)*	*34.0 (4.4, 68.8)*	*0.59 (0.31, 1.12)*
B-ALL with t(12;21)(p13.2;q22.1); ETV-RUNX1	*91.9 (81.6, 96.5)*	*92.3 (72.6, 98.0)*	*91.5 (76.0, 97.2)*	*91.9 (82.0, 96.5)*	*92.4 (73.8, 97.9)*	*91.6 (76.6, 97.2)*	*0.85 (0.15, 4.82)*
B-ALL with hyperdiploidy	*85.5 (78.1, 90.5)*	*87.3 (76.2, 93.4)*	*83.8 (72.6, 90.7)*	*49.9 (10.3, 80.8)*	*69.7 (17.3, 92.8)*	*42.4 (1.4, 84.2)*	-
T-lymphoblastic leukaemia (T-ALL)	63.1 (54.6, 70.5)	68.2 (57.9, 76.4)	51.9 (36.2, 65.4)	48.7 (20.9, 71.9)	50.7 (21.0, 74.4)	47.8 (3.0, 85.7)	0.74 (0.41, 1.34)
Mature B-cell neoplasms							
Chronic lymphocytic leukaemia	68.4 (66.9, 69.8)	68.3 (66.4, 70.1)	68.5 (66.0, 70.8)	86.6 (84.4, 88.5)	86.8 (83.7, 89.3)	87.0 (83.7, 89.7)	1.17 (0.94, 1.46)
Hairy cell leukaemia	82.2 (75.9, 87.0)	82.7 (75.5, 88.0)	80.5 (64.8, 89.7)	97.4 (56.5, 99.9)	96.9 (48.1, 99.9)	98.4 (0.0, 100.0)	-
Lymphoproliferative disorder, NOS	55.0 (52.1, 57.7)	54.5 (50.5, 58.2)	55.6 (51.4, 59.7)	80.4 (75.8, 84.1)	78.6 (71.6, 84.0)	82.9 (76.8, 87.5)	1.16 (0.88, 1.53)
Marginal zone lymphoma	63.9 (61.8, 65.9)	62.1 (59.3, 64.8)	66.2 (63.1, 69.2)	80.4 (77.3, 83.2)	79.9 (75.5, 83.6)	81.2 (76.5, 85.0)	1.15 (0.91, 1.46)
Follicular lymphoma	75.4 (73.4, 77.2)	74.9 (71.9, 77.6)	75.8 (73.0, 78.4)	84.3 (80.2, 87.5)	86.2 (80.0, 90.5)	82.6 (76.8, 87.0)	1.02 (0.76, 1.38)
Follicular lymphoma, NOS	*75.3 (73.2, 77.2)*	*74.6 (71.6, 77.3)*	*75.9 (73.1, 78.5)*	*84.2 (80.1, 87.5)*	*85.7 (79.4, 90.2)*	*82.8 (77.0, 87.3)*	*1.07 (0.80, 1.45)*
Follicular lymphoma; large cell	*76.1 (60.1, 86.4)*	*85.7 (62.0, 95.2)*	*66.7 (42.5, 82.5)*	*86.5 (43.2, 97.5)*	-	*71.5 (16.4, 94.0)*	-
Mantle cell lymphoma	35.5 (31.2, 39.7)	35.6 (30.5, 40.8)	35.3 (27.8, 42.8)	47.3 (35.5, 58.2)	46.4 (31.6, 60.0)	50.5 (30.5, 67.5)	1.27 (0.96, 1.68)
Large B-cell lymphomas	50.3 (48.8, 51.7)	50.5 (48.5, 52.4)	50.1 (47.9, 52.1)	60.8 (58.0, 63.4)	60.5 (56.4, 64.3)	61.4 (57.5, 65.1)	1.04 (0.94, 1.14)
Diffuse large B-cell lymphoma, NOS	*50.5 (48.9, 52.0)*	*51.5 (49.3, 53.5)*	*49.4 (47.1, 51.6)*	*62.1 (59.2, 64.9)*	*62.5 (58.3, 66.3)*	*62.0 (57.9, 65.8)*	*0.98 (0.88, 1.08)*
High grade B-cell lymphoma	*38.7 (27.2, 50.0)*	*32.1 (18.4, 46.7)*	*47.8 (28.9, 64.5)*	*53.0 (27.1, 73.5)*	*52.9 (15.2, 80.6)*	-	-
T-cell/histiocyte-rich large B-cell lymphoma	*68.0 (57.7, 76.3)*	*67.0 (53.6, 77.3)*	*69.8 (52.1, 82.0)*	*71.2 (48.1, 85.4)*	*64.2 (20.9, 88.2)*	*79.7 (45.6, 93.6)*	*2.60 (0.82, 7.34)*
Primary DLBCL of the CNS	*20.6 (14.4, 27.6)*	*16.3 (9.0, 25.6)*	*25.4 (15.7, 36.2)*	*21.7 (3.3, 50.5)*	*18.8 (0.4, 60.2)*	-	-
Primary mediastinal B-cell lymphoma[2]	*85.0 (77.0, 90.4)*	*75.3 (61.3, 84.9)*	*93.4 (83.5, 97.5)*	*83.3 (68.1, 91.7)*	*72.7 (43.1, 88.6)*	*96.8 (83.4, 99.4)*	*7.70 (2.01, 29.55)*
Plasmablastic lymphoma	*25.0 (13.5, 38.4)*	*21.4 (8.7, 37.8)*	*31.2 (11.4, 53.6)*	*24.3 (0.2, 72.7)*	*22.8 (0.3, 68.5)*	-	-
Burkitt lymphoma	50.6 (43.8, 57.1)	54.5 (46.6, 61.7)	38.1 (25.1, 51.1)	39.5 (18.3, 60.2)	41.4 (21.0, 60.8)	34.6 (3.0, 72.5)	0.87 (0.56, 1.35)
Intermediate between DLBCL/CHL	66.5 (50.7, 78.3)	66.7 (44.3, 81.7)	66.3 (42.0, 82.3)	59.9 (17.0, 86.2)	-	62.9 (9.9, 91.1)	-
Plasma cell neoplasms							
Plasmacytoma	52.7 (46.3, 58.7)	52.9 (45.1, 60.1)	52.3 (40.8, 62.6)	61.0 (47.0, 72.4)	60.9 (40.9, 75.9)	58.5 (34.8, 76.2)	1.06 (0.66, 1.70)
Solitary plasmacytoma of bone	*51.8 (43.9, 59.1)*	*55.5 (45.8, 64.1)*	*44.1 (30.7, 56.7)*	*57.4 (36.3, 73.8)*	*62.0 (37.5, 79.2)*	*46.9 (12.0, 76.3)*	*0.68 (0.40, 1.15)*
Extraosseous plasmacytoma	*54.7 (43.2, 64.7)*	*47.6 (34.3, 59.9)*	*71.0 (48.5, 85.0)*	*66.2 (44.4, 81.1)*	*58.6 (29.0, 79.4)*	*83.1 (40.8, 96.2)*	*3.01 (0.95, 9.57)*
Myeloma	39.3 (37.7, 40.8)	39.4 (37.4, 41.4)	39.1 (36.7, 41.5)	52.2 (48.6, 55.8)	52.4 (47.5, 57.1)	51.9 (46.4, 57.2)	1.02 (0.92, 1.12)
Mature T and NK-cell neoplasms							
Peripheral T-cell lymphomas	31.1 (26.9, 35.5)	31.2 (25.5, 36.9)	31.1 (24.6, 37.8)	35.6 (22.0, 49.5)	37.8 (20.1, 55.3)	34.0 (13.9, 55.5)	1.00 (0.79, 1.28)
Enteropathy-associated T-cell lymphoma	*15.0 (6.1, 27.6)*	*13.0 (3.3, 29.7)*	*17.7 (4.4, 38.3)*	*12.1 (0.0, 82.3)*	-	-	-
Peripheral T-cell lymphoma, NOS	*22.9 (16.2, 30.4)*	*28.1 (19.2, 37.7)*	*13.0 (5.3, 24.4)*	*32.2 (9.4, 58.1)*	*41.6 (14.2, 67.5)*	*15.8 (0.0, 78.9)*	*0.58 (0.38, 0.99)*
Angioimmunoblastic T-cell lymphoma	*26.4 (18.6, 34.8)*	*25.0 (13.9, 37.8)*	*27.4 (17.2, 38.6)*	*32.1 (8.2, 59.6)*	*28.8 (1.6, 68.7)*	*36.5 (6.8, 68.5)*	*1.51 (0.93, 2.46)*
Anaplastic large cell lymphoma, ALK+[2]	*76.2 (60.3, 86.4)*	*66.7 (45.7, 81.1)*	*93.3 (61.3, 99.0)*	*75.7 (48.0, 90.0)*	*62.1 (20.9, 86.5)*	*98.0 (3.33, 100.0)*	*10.97 (1.36, 88.7)*
Anaplastic large cell lymphoma, ALK-	*37.1 (26.4, 47.9)*	*35.1 (21.6, 49.0)*	*40.6 (23.8, 56.8)*	*43.8 (15.1, 69.7)*	*45.3 (12.1, 74.3)*	*40.7 (4.6, 77.0)*	*0.70 (0.35, 1.38)*

(*continued on next page*)

Table 3 (*continued*)

Diagnosis	5-year overall survival % (95% Confidence Intervals)			5-year net survival % (95% Confidence Intervals)[1]			Excess mortality ratio (95% CI)[3] male:female
	All	Male	Female	All	Male	Female	
Cutaneous T-cell lymphomas	64.8 (56.1, 72.2)	62.8 (52.1, 71.8)	69.0 (53.2, 80.3)	74.7 (54.3, 87.0)	74.7 (48.7, 88.8)	75.2 (38.6, 91.9)	1.03 (0.43, 2.50)
Mycosis fungoides	*70.5 (57.4, 80.3)*	*72.2 (56.3, 83.2)*	*66.7 (40.4, 83.4)*	*85.6 (57.9, 95.7)*	*89.2 (52.6, 98.0)*	*84.1 (28.9, 97.6)*	*0.68 (0.11, 4.04)*
Primary cutaneous CD30 + T-cell LPD	*71.5 (58.1, 81.2)*	*64.4 (47.3, 77.2)*	*85.2 (60.6, 95.0)*	*71.5 (20.4, 93.2)*	*69.5 (18.4, 92.5)*	*74.2 (20.3, 94.6)*	*1.64 (0.23, 11.93)*
T-cell prolymphocytic leukaemia	15.7 (7.6, 26.5)	21.2 (8.1, 38.3)	10.3 (2.6, 24.3)	31.6 (2.5, 69.8)	35.3 (0.5, 81.4)	28.6 (0.1, 79.9)	0.81 (0.41, 1.61)
T-cell large granular lymphocytic leukaemia	75.5 (68.7, 81.0)	69.5 (58.9, 77.8)	80.9 (71.7, 87.4)	91.6 (77.5, 97.0)	87.0 (59.2, 96.4)	95.1 (68.2, 99.4)	3.56 (0.80, 15.92)
Hodgkin lymphomas[2]	78.6 (76.5, 80.5)	77.2 (74.4, 79.7)	80.6 (77.3, 83.4)	84.0 (81.1, 86.4)	82.4 (78.3, 85.6)	86.2 (82.2, 89.4)	1.41 (1.09, 1.83)
Classical Hodgkin lymphoma	77.1 (74.8, 79.2)	75.1 (72.0, 78.0)	79.6 (76.2, 82.6)	82.5 (79.4, 85.2)	80.8 (76.3, 84.5)	84.9 (80.4, 88.4)	1.44 (1.11, 1.87)
Nodular lymphocyte predominant HL	90.2 (84.9, 93.7)	89.1 (82.6, 93.3)	93.6 (81.4, 97.9)	94.8 (86.3, 98.1)	91.9 (79.7, 96.9)	-	-
Post-transplant lymphoproliferative disorder[2]	51.1 (37.5, 63.2)	43.9 (27.0, 59.6)	61.7 (39.1, 78.0)	63.2 (40.9, 79.1)	59.4 (31.8, 78.9)	79.1 (45.6, 93.2)	2.69 (1.04, 6.95)

Abbreviations: ALK-anaplastic lymphoma kinase; CI – confidence interval; CNS – central nervous system; DLBCL – diffuse large B-cell lymphoma; HL – Hodgkin lymphoma; LPD – lymphoproliferative disorder; NK – natural killer; NOS – not otherwise specified;
[1]Age standardised according to the Adjusted International Cancer Survival Standards (ICSS) https://github.com/CancerRegistryOfNorway/NORDCAN/wiki/nordcansurvival. The standard ICSS 1 Elderly was used or [2]ICSS 3 Young adults for the subtypes marked.
[3]Excess Mortality Ratio calculated using Poisson regression from net survival estimates adjusted for age and calendar year at diagnosis.

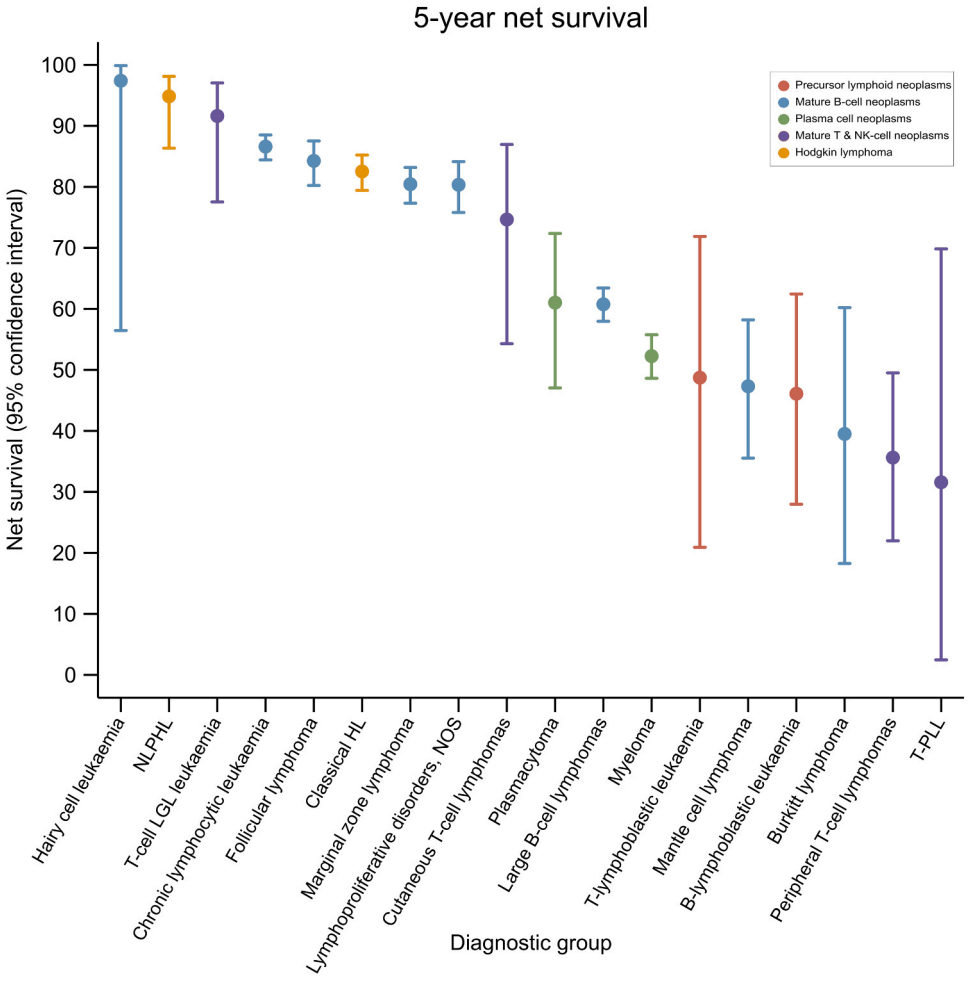

Fig. 4. 5-year net survival by diagnostic group: Haematological Malignancy Research Network 2005–2019, followed up to 2023. Abbreviations: HL – Hodgkin lymphoma; LGL – large granular lymphocytic; NK – natural killer; NLPHL – nodular lymphocyte predominant Hodgkin lymphoma; NOS – not otherwise specified; T-PLL – T-cell prolymphocytic leukaemia.

Table 4
5-year net survival by calendar year of diagnosis[1]: Haematological Malignancy Research Network 2005–2019, followed up to 2023.

	Year of Diagnosis – 5-year net survival (95% Confidence Intervals)			Excess mortality ratio (95% Confidence Intervals)[2]		
Diagnosis	2005-2009	2010-2014	2015-2019	2005-2009	2010-2014	2015-2019
Precursor lymphoid neoplasms						
B-lymphoblastic leukaemia	40.5 (10.7, 69.3)	45.1 (17.8, 69.2)	52.6 (29.7, 71.2)	1 (reference)	0.97 (0.68, 1.40)	0.83 (0.59, 1.17)
Mature B-cell neoplasms						
Chronic lymphocytic leukaemia	82.8 (78.3, 86.4)	85.6 (81.8, 88.7)	90.7 (86.9, 93.5)	1 (reference)	0.76 (0.60, 0.97)	0.51 (0.38, 0.67)
Marginal zone lymphoma	75.8 (68.6, 81.6)	78.3 (72.7, 82.9)	86.0 (81.3, 89.6)	1 (reference)	0.84 (0.64, 1.09)	0.53 (0.39, 0.72)
Follicular lymphoma	82.5 (74.0, 88.4)	82.5 (73.0, 89.0)	86.9 (81.2, 91.0)	1 (reference)	0.82 (0.57, 1.17)	0.69 (0.48, 0.99)
Mantle cell lymphoma	34.3 (7.7, 64.0)	52.0 (34.2, 67.1)	52.9 (31.8, 70.2)	1 (reference)	0.69 (0.51, 0.94)	0.62 (0.45, 0.84)
Large B-cell lymphomas	54.8 (49.1, 60.2)	63.6 (59.0, 67.8)	63.2 (58.6, 67.5)	1 (reference)	0.73 (0.65, 0.82)	0.71 (0.63, 0.79)
Burkitt lymphoma	35.1 (8.4, 64.2)	34.7 (8.2, 63.8)	45.0 (15.7, 70.8)	1 (reference)	0.84 (0.51, 1.37)	0.47 (0.28, 0.78)
Plasma cell neoplasms						
Myeloma	44.0 (36.4, 51.4)	55.6 (49.6, 61.3)	55.9 (50.1, 61.2)	1 (reference)	0.67 (0.59, 0.75)	0.65 (0.58, 0.73)
Mature T and NK-cell neoplasms						
Peripheral T-cell lymphomas	32.2 (7.9, 60.4)	35.0 (14.8, 56.3)	38.7 (16.7, 60.4)	1 (reference)	0.92 (0.69, 1.23)	0.88 (0.64, 1.20)
Hodgkin lymphomas						
Classical Hodgkin lymphoma	78.0 (72.0, 82.8)	83.5 (77.0, 88.4)	86.1 (81.2, 89.8)	1 (reference)	0.76 (0.56, 1.03)	0.51 (0.37, 0.69)

[1]including diagnostic groups with ≥ 30 events per stratum 5-years after diagnosis; [2]adjusted for age at diagnosis and sex

B-cell lymphomas included in this report were transformations; and for some patients this occurred more than 15 years after their original diagnosis. While SEER [37] and other registries [16] include such diagnoses as primaries (as we have done here), registries that follow the rules provided by the European Network of Cancer Registries, only count the first lymphoid diagnosis as incident, no matter how much time has elapsed [38]. This issue may, however, be resolved in the future with the recent publication of the latest WHO classification where, for the first-time, a description of high-grade transformation of indolent B-cell lymphomas that includes a summary of driver genes is detailed [3].

For rarer subtypes, such as the mature T and NK-cell, population-based data are sparse [14,19,39]. However, the information that does exist confirms the importance of examining the contributory subtypes. Many of our findings are novel; within the peripheral T-cell lymphomas (PTCL), for example, ALK-positive anaplastic large cell lymphoma (ALK-positive ALCL), stands apart from the rest; tending to be diagnosed at a younger age and having substantially better survival. Furthermore, ALK-positive ALCL is one of the few subtypes with a sex-difference in survival, along with classical Hodgkin lymphoma and primary mediastinal B-cell lymphoma. In this regard, while age is a well-recognised prognostic factor and is included in the majority of lymphoid international prognostic scores [40–42], the role of sex in predicting survival is less clear [16,34,43,44].

Not only do descriptive patterns have important implications for aetiological hypotheses, they are also essential for disease monitoring, and the maturity of HMRN's cohort means we are now able to examine temporal outcome patterns for some of the larger diagnostic categories. Haemato-oncology is one of the fastest moving fields in cancer research, and many of the lymphoid malignancy classification refinements have been mirrored by corresponding developments in new treatments and novel agents [45–47]; the temporal improvements in survival reported here corresponding with the introduction of these agents. While this has previously been observed by others for myeloma [48–51], and by us for mantle cell lymphoma [52], to our knowledge this is the first time it has been shown at the population-based level for chronic lymphocytic leukaemia and classical Hodgkin lymphoma.

While, we observed an improvement in survival over time, no evidence to support the suggestion that NHL, CLL and myeloma incidence was increasing in the UK was found [53–55]. Intriguingly, in contrast to the UK, SEER reported that CLL and FL incidence was decreasing over time [56,57], noting no change for ALL, DLBCL, and myeloma [58–60]. On balance, it seems likely that increases and decreases of this type are unlikely to be real, potentially illustrating the difficulties national cancer registries face implementing changes in disease classification over time, as well as managing the transition from bridge coding from ICD-O-3, utilised in the clinical setting, to ICD-10 (which is still mandated by many registries). The publication of the latest WHO classification also highlights a future challenge for cancer registries, since after 22 years of agreement, there is no longer an international standard for the diagnosis and classification of haematological cancers following the publication of two competing classifications systems in 2023; the WHO-HAEM5 and the International Consensus Classification (ICC) [3,61]. Fortunately, for the lymphoid neoplasms reported here there is general consistency between WHO and ICC; however, for the myeloid malignancies important differences have now been introduced.

Major strengths of HMRN include its large well-defined population-based catchment area, completeness of case ascertainment, active follow-up via tracking through national systems, world-class diagnostics and generalisability to the national population; which combine to ensure HMRN's patient cohort is not affected by the data quality issues commonly faced by many population-based cancer registries. Furthermore, as HMRN's population has a socio-demographic profile that is broadly representative of the UK as a whole and patients within the region are treated according to NHS/national guidelines, the incidence and survival figures reported here can be extrapolated to the UK as a whole. Moreover, the use of net survival to estimate cancer-specific mortality removes the need to rely on the cause of death specified at death certification, where misclassification may have occurred. Facilitating comparison with a wide-range studies, a further strength is the provision of age-standardised incidence rates using several standard populations. However, the number of statistical tests conducted could lead to some statistically significant results occurring by chance.

Importantly, with respect to HMRN's diagnostic and follow-up processes, as one of the largest integrated haematopathology laboratories in Europe the Haematological Malignancy Diagnostic Service (HMDS), which lies at the centre of HMRN, has a strong track-record of national/international research, and diagnostic policy adheres to European guidelines (http://hmds.info/). Nonetheless, for subtypes that require additional clinical information, HMDS is subject to some of the same limitations as other routine diagnostic laboratories. One such example relates to the classification of marginal zone lymphoma (MZL) where the presence of splenomegaly and level of IgM protein is required for some subtypes, such as splenic MZL and lymphoplasmacytic lymphoma. Fortunately within HMRN procedures have now been updated; paraproteins have been routinely collected since 2014 and the mutation MYD88 L265P [62], a diagnostic biomarker of lymphoplasmacytic lymphoma, is now routinely tested for.

Providing valuable information for researchers, clinicians, patients and policy makers, our contemporary analysis of population-based lymphoid cancers provides important insights into how incidence and survival estimates vary by subtype, age and sex. Furthermore, as descriptive studies often do, our findings have raised as many questions

Box 1
Abbreviations.

B-ALL – B-lymphoblastic leukaemia; BL – Burkitt lymphoma; CHL – classical Hodgkin lymphoma; CLL – chronic lymphocytic leukaemia; CTCL – cutaneous T-cell lymphoma; FL – follicular lymphoma; HCL – hairy cell leukaemia; LBCL – large B-cell lymphoma; LPD, NOS – lymphoproliferative disorder, not otherwise specified; MCL – mantle cell lymphoma; MZL – marginal zone lymphoma; NLPHL – nodular lymphocyte predominant Hodgkin lymphoma; PTCL – peripheral T-cell lymphoma T-ALL – T-lymphoblastic leukaemia.

as answers, notably in terms of age and sex differences in incidence and outcome; such associations requiring further in-depth study. However, despite recent improvements, it is clear that the routine cancer registration of lymphoid neoplasms remains challenging, and new issues are continuing to emerge. Indeed, the rapidly increasing knowledge about these cancers means that additional molecular and genomic information is becoming a routine requirement for accurate classification, which could serve to exacerbate the disparity in availability of cancer registration data, especially in low-income countries. .

Authorship contribution

AS, ER, and RP were responsible for the conception and design of the study. ML, DP and AS carried out the analyses. DH, SB, RdT, CC, RT, CB and RP provided clinical input regarding disease classification, data collection and the analysis, as well as interpretation of the findings. ER and AS are the study guarantors and take responsibility for the integrity of the data. All authors contributed to the final draft of the paper; and have had full access to all of the data in the study.

Funding

This work was supported by Cancer Research UK and Blood Cancer UK [Grant Number 29685]. ER and AS are supported in part by the National Institute for Health and Care Research (NIHR) Leeds Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the UK's National Health Service (NHS), the NIHR, or the Department of Health and Social Care.

Declaration of Competing Interest

None of the authors have any conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2023.102513.

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