Incidence and survival of haemophagocytic lymphohistiocytosis: a population-based cohort study from England

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The data in this study are not able to be shared due to licensing constraints as described in detail here https://www.cprd.com/Data-access

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Abstract

Background: Haemophagocytic Lymphohistiocytosis (HLH) is a rare hyper-inflammatory condition with poor outcomes. Objectives: Few population based estimates of the incidence and survival in adults exist. We aimed to provide these data for England. Methods: We used population based linked data from primary care, secondary care, cancer registries and mortality databases in England to identify people diagnosed with HLH between 1st January 2000 and 31st December 2016. We calculated annual incidence rates by age and sex; modelled change in incidence over time with Poisson regression; calculated overall 1-year survival using Kaplan-Meier methods, and estimated adjusted hazard ratios (HR) of death using a Cox proportional hazards model. Results: We identified 214 patients with HLH. The reported age and sex-adjusted incidence increased 2-fold over the period, from around 1 to around 2 per million. Incidence was highest in those below 1-year (14.6 per million) and ≥75 years (2.2 per million), and lowest in those aged 15-44 years (0.8 per million). One year survival varied by age and sex from 77% (95% CI 63% to 86%) in those < 15 years to 30% (95% CI 14% to 49%) in those ≥75. In patients with hematological cancer, the adjusted HR for death was 2.60 (95% CI 1.45 to 4.66) compared to patients with no malignant or rheumatological disease. Conclusion**:** Reports of a HLH diagnosis in England has increased between 2000 and 2016 and occurs in all ages with varying underlying diseases. One year survival varies substantially being particularly poor in those aged over 75 years and those with hematological malignancy.

Keywords: HLH; epidemiology; incidence; survival

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a rare syndrome characterized by fever, hyper-inflammation, organ dysfunction, cytopenias and haemophagocytosis. The balance of the incidence and severity of a variety of constitutive, acquired and iatrogenic risk factors for any given patient influences their risk of developing of HLH. These risks vary markedly with age of presentation, and in general infants tend to have inherited T- and NK-cell defects impairing cytotoxic function, younger adults have underlying acute viral infections and autoimmunity/inflammation while older adults are those most likely to suffer from underlying cancer. [1, 2]. There is good evidence to suggest that the diagnosis of HLH remains under-recognized, frequently mistaken for severe sepsis and remains associated with high mortality rates in all age groups [3] particularly those with underlying malignancy[4]. The incidence of HLH on a population level has rarely been quantified despite many case series present in the literature. What incidence information is available is focused on children and primary HLH[5-7], whereas in adults there are no reported estimates of incidence. No previous study has included all ages and all types of HLH on a population basis. Mortality rates have been reported previously[3] , although, as with incidence studies, these reports have rarely been carried out on a population level.

It is crucial to understand the incidence and survival of a rare disease such as HLH at a population level in order to avoid the problems of selection bias and chance that inevitably occur in smaller studies from geographically restricted or specialty centered populations. Recent literature suggests some evidence of increasing awareness of this disease suggesting the possibility of either a true rise in diagnoses or improved ascertainment[8]. It remains unclear if

the increasing incidence and prevalence of lymphoma, autoimmune diseases or the documented rising age at acquisition of Epstein-Barr virus (EBV) are implicated [9, 10].

To assess incidence and survival of HLH, we have carried out a population based cohort study utilizing primary and secondary care electronic health care records in England that are linked to both cancer registry data and mortality statistics. With this approach we provide unique insights into the incidence and balance of the multiple underlying factors associated with HLH.

Materials and Methods

Data sources

Linked primary and secondary care electronic healthcare databases, which have been previously described in detail, were utilized in this study[11, 12]. In brief, the Clinical Practice Research Datalink (CPRD) is a UK government, not-for-profit research service utilizing primary care routinely collected diagnostic, testing and prescription data. For this study, primary care data were linked to Hospital Episodes Statistics data (HES)[13]; the National Cancer Registration Analysis Service (NCRAS) datasets[14], including: cancer registration, chemotherapy; and Office for National Statistics (ONS) death registration data. The patient records in HES, NCRAS and ONS are coded using a combination of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes for diagnoses and the Office of Population, Censuses and Surveys (OPCS) Classification of Surgical Operations and Procedures version 4 codes for any procedure. General practice data is coded with a combination of Read, SNOMED-CT and local (Egton Medical Information Systems) EMIS codes which use standardized core sets of clinical healthcare terminology for electronic health records. The source population

providing data for this project were extracted from the May 2020 version of the datasets (linkage set 17) and totaled 23,696,548 approved by the CPRD Independent Scientific Advisory Committee (ISAC) reference number: 19_165.

This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data are collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of Public Health England (PHE). Access to the data was facilitated by the PHE Office for Data Release. Link to ISAC Protocol

https://www.cprd.com/protocol/occurrence-and-consequences-langerhans-cell-histiocytosis-malignant-histiocytosis-erdheim

Study population

All patients within primary care, secondary care and cause of death data with a code for HLH (ICD10 D76.1 Haemophagocytic lymphohistiocytosis and D76.2 Haemophagocytic syndrome, infection-associated (primary care codes in supplementary table S1)) recorded within the period between 1st January 2000 and 31st December 2016 inclusive, were initially included. Any events that occurred within 1 month of the current registration date with the general practice of the individual were considered prevalent[15, 16], leaving only incident cases (including those identified via death certification only) as the study population. Person-time at risk for the purposes of survival analysis commenced on the day of diagnosis (therefore excluding those identified via death certification only). Patients were followed up for death until the end of 2019.

Characteristics, comorbidities and prescription drug exposures

Sociodemographic, comorbidity and relevant prescription drug exposures were determined from the provided data for the entire study population. Risk factor diseases defined were those

known or previously reported to be often present in people who develop HLH i.e. hematological malignancy or rheumatological disease (see supplementary tables S2-4 for code lists and included conditions) or that would indicate treatment with immunosuppressant or immunomodulatory medications for example inflammatory bowel disease. Evidence of Epstein-Barr Virus (EBV)[10], Human Immunodeficiency Virus (HIV) or Acquired immunodeficiency syndrome (AIDS)[17], Cytomegalovirus (CMV) and Herpes Zoster virus[18] (HZV) infection was assessed similarly (code lists/process for identification in the cited references): in addition these diseases were included if any of those infections appeared on the death certificate as a cause of death. Evidence of diagnoses that occurred in primary care, secondary care or NCRAS records prior to and up to 3 months after the diagnosis of HLH, were included as being previously present or diagnosed around the time of HLH diagnosis. Prescription drug exposures were defined by evidence of a prescription (or record of administration) within 6 months and prior to diagnosis of HLH diagnosis in either primary care (supplementary tables S5, S6), secondary care or NCRAS data (for DMARDs, chemo or immunotherapy). This was classified as either current (within 2 months prior to diagnosis) or recent exposure (within 6 months prior to diagnosis). Peripheral blood stem cell transplantation at any time before HLH diagnosis was defined using OPCS4 coding (X334, X335, X336) of the procedure within HES.

Statistical analysis

Numbers and frequencies of the various characteristics were calculated for the whole cohort overall, with several then calculated within strata of age groups and sex. The reported incidence of HLH was calculated by summing the number of cases (including those diagnosed via death certificate only) within age group, sex and calendar year strata and dividing by the relevant summed person years at risk within each stratification variable. Overall rates were then presented by calendar year, age and sex with 95% confidence intervals around the estimates

derived via a Poisson distribution. A Poisson regression model was fitted to estimate the adjusted incidence rate ratios (IRR) associated with each age category, sex and calendar year. To estimate the annual % change in incidence a further model was fitted using calendar year as a linear term adjusted for age and sex. This model was compared to the model with calendar year as a categorical variable with a likelihood ratio test to assess evidence of departure from a linear trend. Survival analyses were carried out on the cohort of people alive on the day of diagnosis (i.e. excluding death certificate identified cases) and was estimated using Kaplan-Meier methods truncated at 1 year of follow up. A Cox proportional hazards model was fitted with the associated disease as the main explanatory variable, adjusted for age and sex, to estimate the hazard ratios of death given the presence of these risk factors, compared to patients that had none of them recorded. Finally, for comparison to our incidence analysis, as mortality is high in the condition, we calculated crude mortality rates using publicly available data on deaths recorded in England that had an underlying ICD10 cause of D76.1 and D76.2 combined with mid-year age-sex population estimates for each calendar year (2001-2016). These rates were directly age standardized to the European 2013 population.

Results

Study population

In the calendar period 2000 to 2016, we identified 214 patients with an incident diagnosis of HLH. The majority, 173 (81%), were identified through an admission to hospital coded with either ICD10 D76.1 or D76.2 in HES, while a further 16 (7.5%) were identified with the same codes used anywhere on their death certificates. The characteristics of the cases are described in table 1. 70% of the HLH cases were $\geq$15, just over half (52%) were male and the majority (74%) were of white ethnicity. Overall, approximately half of people had one of the risk factor

diseases recorded in their records (either prior to or up to 3 months following their HLH diagnosis) known to be associated with later development of HLH. This varied by age such that 27% (n=17) of those <15 years, 55% (n=27) of those aged 15-44 years and 48% (n=48) of those ≥45 years had one of these diseases recorded. The distribution of risk factor diseases varied by age such that there is most malignancy in the older age groups, most autoimmune disease in the 15-44 year old group and the highest proportion of no reported disease risk factor in the 0-14 year olds (table S1). Of these diseases, the commonest single disease entities were lymphoma, systemic lupus erythematosus (SLE) and systemic juvenile idiopathic arthritis (SJIA). There was evidence of clinically diagnosed HIV, EBV or CMV infection either in the health record or on the death of certificate in 2.3%, 8.9% and 3.3% respectively. Just under a third of patients had had recent or current exposure to a chemo- or immuno- therapy, systemic corticosteroid or disease modifying anti-rheumatic drug (DMARD). Fewer than 5 patients had a peripheral blood stem cell transplant prior to HLH diagnosis.

Incidence

Reported crude incidence rates of HLH increased during the study period from around 1 per million person years in the first 5 years (estimates varying between 0.96 and 1.97 per million) to around 2 per million in the last 5 years (estimates varying between 1.67 and 3.53 per million), equating to approximately a 2-fold increase in the reported incidence of HLH over the whole study period (figure 1, table 2). Across the whole study period, the estimated year-on-year relative increase (calendar year fitted as a continuous variable), assuming a linear trend, of HLH incidence was 7.7% (95% CI 4.6% to 10.9%). When compared to the model with calendar year as a categorical variable, there was some evidence of departure from a linear trend (p=0.04). There was variation in reported incidence with age: the highest rates were seen in those <15

years of age and ≥75 years - both were between 2 and 3 per million person years whereas those aged 16- 75 had incidence rates lower than 1 per million (table 2). Reported incidence was lower among female patients compared to male patients (table 2). Overall reported incidence in those aged ≥15 years was 1.3 per million person years (95% CI 1.1 to 1.5).

Survival

Unadjusted survival analysis

Overall, there were 83 deaths among 195 patients with HLH who were alive at diagnosis and followed up for one year (figure 2). This equated to a 1-year survival estimate of 56% (95% CI 49% to 63%). Survival varied substantially by age (figure 3): those <15 years had a 1-year survival of 77% (95% CI 63% to 86%), those aged 15-24 60% (95% CI 35% to 77%), those aged 25-44 79% (95% CI 57% to 91%) and those >75 30% (95% CI 14% to 49%). One year survival also varied by sex: males 48% (95% CI 38% to 58%), females 66% (95% CI 55% to 75%) and by underlying disease (figure 4): rheumatological 74% (95% CI 56% to 85%), hematological malignancy 21% (95% CI 8% to 38%), other malignancy 45% (95% CI 24% to 64%) and none of these 61% (95% CI 51% to 69%). Of the 32 deaths that occurred among people with underlying hematological or other malignancy 20 of them, 62%, occurred within 1 month of the diagnosis of HLH and 28 (87%) within 3 months. The majority of these 32 deaths had an underlying cause of death coded as either HLH or their underlying malignancy.

Adjusted survival analysis

In the adjusted Cox proportional hazards model (table 3), patients with hematological malignancy had an age and sex adjusted 2-fold (aHR 2.60 (95% CI 1.45 to 4.66)) relative increase in risk of death compared to those with neither rheumatological disease nor other malignancy.

Those with either rheumatological disease or another malignancy had broadly similar age and sex adjusted relative risks of death to those with none of these etiologies identified.

European age standardized mortality rates (deaths due to HLH (as an underlying cause) in England)

Figure 5 shows the European age standardized mortality rates and 95% confidence intervals by calendar year for deaths with an underlying cause of HLH. These rates increased steadily over the study period from approximately 0.1 per million in 2001 to 0.6 per million in 2016.

Discussion and Conclusion

We report a population based cohort study that describes the incidence and survival of HLH in England between the calendar years 2000 and 2016. We found that among our cohort approximately 50% overall had a recognized underlying condition or were recently prescribed medication which previously has been reported to be associated with HLH. The most commonly recorded of these underlying conditions, either prior to or around diagnosis, were hematological malignancy, EBV, SLE and SJIA. We estimated that the reported incidence of HLH was approximately 1 per million person years in the year 2000 which over the course of the study doubled to around 2 per million person years, with on average a 7.6% increase year-on-year. We also show that reported incidence varied by age and sex with the highest incidence in those $\leq$1 year of age. In our study, patients with HLH had poor overall one year survival ranging from 77% in those $\leq$15 to 30% in those $\geq$75 years. Survival was worst in those patients with an underlying hematological malignancy such that after accounting for age and sex differences they had a 2-fold increased risk of death compared to other patients with HLH.

By using electronic health records to study a rare disease like HLH, we were able to get a large enough sample to estimate with reasonable precision the important epidemiological metrics of disease incidence and overall survival. These estimates are likely to be generalizable to similar areas of the world to England in terms of sociodemographic profile. We were reliant on the accurate use of electronic recording of HLH in primary and secondary care, and on death certificates. In a systematic review of validation studies, HES recording has been shown to be accurate for the purposes of research in this manner[19]. There are only two specific ICD 10 codes for HLH that are used in the coding of hospital records and death certificates in England (D76.1 and D76.2). These codes have been shown to be reasonably accurate for identifying HLH in France[20] and Chicago, USA[21]. In addition, we have carried out a validation exercise via National Congenital Anomaly and Rare Disease Registration Service and shown that the positive predictive value of D76.1 and D76.2 for a diagnosis of HLH in HES is 89.0% (95% CI 80.2-94.9%)[22] which is similar to the accuracy of coding in HES for rare rheumatic diseases that required admission to hospital[23]. Nonetheless we are reliant on the assumption that the diagnosis of HLH is is underpinned by the use of diagnostic scoring systems such as the "HScore"[24] or the "HLH-2004 diagnostic criteria"[25, 26]. Inevitably, however, there will have been under-ascertainment of HLH as it is recognized to be a difficult disease to diagnose[3] and it may well be that recognition, and therefore ascertainment, has improved over the period of our study. This will lead to two biases. The first is that overall our estimates of incidence are likely to be, in general, underestimates as cases of HLH that occurred but were not diagnosed as such in the hospital setting will not have been included in our study – however, as there are no previous baseline estimates of the incidence of secondary HLH in adults, it is difficult to accurately judge how much of an underestimate we will have made. Secondly, our observed increase in HLH incidence over the study period could partly be ascribed to improved

recognition and therefore subject to increased ascertainment rather than changes in underlying causal mechanisms, diseases or treatments.

Traditionally the attempts to distinguish between underlying genetic defects compared to an acquired infectious or other cause for HLH lead to the terminology of 'primary' HLH when occurring in children and 'secondary' HLH was seen in adults. It has become clear that both gene mutations and infections or other events resulting in hyper-inflammation events, occur in individuals of any age and with any family history. Our study describes the pattern of the many acquired and iatrogenic risk factors for HLH and the age groups in which they occur. We have, through the available linked cancer registration data and access to the primary care record, excellent recording of comorbidities and many prescribed medications.

Many reports of HLH in children and adults are present in the literature. These have been well summarized in a recent review by Ramos-Casals et al[3] and our cohort is similar to the case series within that report, in terms of age, sex and risk factors, including more recently those reported from China[27, 28]. For adults, the most relevant reports for comparison are those recently reported from European countries i.e. France[20, 29] and Germany[30] where the age and sex distribution and underlying causes of disease are most likely to be similar. Riviere et al[20] reported a regional study from France. HLH cases were drawn from three tertiary referral centers where bone marrow aspirate requests for suspected HLH were reviewed[20], while the study from Germany is a nationwide registry based study[30] – although it primarily comprises contributions from haematology/oncology centers that have to proactively report cases. Underlying malignancy was present in 28% of our cohort (Germany 35%[30], France 60%[20]) and 15% had hematological malignancy (Germany 34%[30], France 57%[20]). We found

evidence of rheumatological or inflammatory bowel disease in 22% compared to 9.5% in the German cohort and 3.1% in the French. In the German cohort, 20% and had evidence of EBV, CMV or both infections, compared to 1% (EBV) and 3.7% (CMV) in the French cohort, and 9% (EBV) and 3.4% (CMV) in our study. The proportion with HIV varied substantially, from 38% in France, 1.5% in Germany and 2.4% in ours. The differences in risk factors are in part explained by the differences in the methods by which populations studied were assembled. Both the French[20, 29] and German[30] studies only reported cases in adult patients and are likely to have been influenced in terms of case mix by the specialization in haematology or oncology. What appears to be a lack of recording of known risk factors in a proportion of our cohort may be partially explained by the fact that our cohort is population based. As such the cases were diagnosed throughout England within the NHS which means that the majority of the cohort would not have been seen in specialist centers for haematology or rheumatology. As such there could have been some under-ascertainment of the previously reported risk factors for HLH. This is particularly true in those cases that died rapidly after diagnosis, or were diagnosed at post-mortem). Alternatively, our cohort represents the real world experience of HLH across England, and that, for a significant proportion of patients, underlying risk factors or disease present in HLH may not be identified.

For children the most relevant comparable work is from Sweden[5, 7] and the reports focus on primary HLH whereas we include both primary and secondary HLH. The overall incidence of primary HLH in children <15 years of age has remained the same in Sweden, at 1.2 per million, between 1971 and 2006 whereas our estimate was 2.9 per million. They report that the incidence was highest in the youngest age group (11 per million in the first year of life), which we also observed (14.6 per million (95% CI 7.0 to 26.8)). As our study included both primary and

secondary HLH, we cannot directly compare our rates. However, in children, if we assume that the incidence rate of primary HLH in Sweden in <15 year old is similar to England then the remainder would be a rough estimate of the incidence of secondary HLH in children <15 years. This calculation gives an estimate of 1.7 per million of secondary HLH among under 15 year old in England. For incidence, there are no studies, worldwide, that appear to have reported incidence of secondary HLH in adults that can be directly compared to our estimates.

Our survival estimates concur with much of the relevant HLH literature[20, 21, 30-35]. Younger patients in general fair better than older patients, men do worse than women and those with hematological malignancy have a 2-fold increased risk of death compared to those with other malignancies, rheumatological disease or neither of these. Our data do suggest that young people (aged 15-24) with HLH have worse survival compare to people under 15 and aged between 25 to 45 years. This could reflect that adolescents and especially young adults with acute and chronic diseases are recognized to have poorer health outcomes than either children or adults[36-38].

Our findings of an increasing incidence of HLH between 2000 and 2016 are likely to be explained by a combination of reasons, including improved ascertainment (diagnosis) of HLH as a syndrome, and a true increase in incidence perhaps driven by the increasing incidence and prevalence of the underlying medical conditions and prescriptions in England. Unsurprisingly given the high mortality of the condition, when we calculated age standardized mortality rates due to HLH using the same ICD 10 underlying cause of death codes as we used to identify incident cases, we found a similar pattern of increasing rates during the period of our study (figure 5).

Conclusion

In conclusion, we provide the first estimates of incidence of HLH on a population basis for children and adults, primary and secondary HLH. We show important trends over time, variation by demographic characteristics and the continuing poor survival that is associated with this disease.

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Tables

Table 1. Characteristics, risk factors and drug exposures in 214 patients with HLH

Characteristic	**Frequency**	**Percent**
Age categories (years)		
0-<1	10	4.7
1-4	25	12.0
5-14	29	13.6
15-24	20	9.4
25-34	13	6.1
35-44	16	7.5
45-54	19	8.9
55-64	18	8.4
65-74	39	18.2
75-	25	11.7
Sex		
Male	112	52.3
Female	102	47.7
Ethnicity		
White	159	74.3
Asian	16	7.5
Black	15	6.1

Mixed or other	11	5.1
Unknown	13	6.1
Hematological cancer	32	15.0
Lymphoma	24	11.2
Other hematological malignancy	8	3.7
Other malignancy	30	14.0
Inflammatory bowel disease	9	4.2
Rheumatological disease	41	19.2
Systemic Lupus Erythematosus	12	5.6
Systemic juvenile idiopathic arthritis	12	5.6
Rheumatoid arthritis	6	2.8
Viruses		
Human immunodeficiency virus/Acquired immunodeficiency syndrome (HIV)	5	2.3
Epstein-Barr Virus infection (EBV)	19	8.9
Cytomegalovirus (CMV)	7	3.3
Herpes Zoster Virus (HZV)	<5	
Prescription medications		
Chemo or immunotherapy within 2 months of diagnosis	48	22.4
Systemic corticosteroids (community prescribed) within 2 months of diagnosis	8	3.7
DMARDs (community prescribed) within 6 months of diagnosis	<5	
Peripheral blood stem cell transplantation	<5	

*DMARDS: disease modifying anti-rheumatic drugs

Table 2. Incidence rates per million person years, adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) for HLH

Covariate	**Incidence rate**	**95% CI**	**IRR****	**95% CI**
Age groups (years)				
0-<1*	14.56	6.98 to 26.78	1	
1-4	3.82	2.48 to 5.65	0.26	0.12 to 0.54
5-14	1.92	1.28 to 2.76	0.13	0.06 to 0.27
15-44	0.86	0.63 to 1.13	0.06	0.03 to 0.12
45-74	1.61	1.27 to 2.02	0.11	0.06 to 0.21
75-	2.20	1.43 to 3.25	0.15	0.07 to 0.32
Calendar year				
2000*	0.96	0.39 to 1.98	1	
2001	0.80	0.30 to 1.75	0.84	0.28 to 2.49
2002	1.97	1.10 to 3.25	2.05	0.84 to 5.04
2003	0.90	0.36 to 1.85	0.94	0.33 to 2.67
2004	1.14	0.52 to 2.16	1.18	0.44 to 3.18
2005	0.62	0.20 to 1.45	0.65	0.20 to 2.03
2006	0.49	0.13 to 1.25	0.51	0.15 to 1.73
2007	0.84	0.34 to 1.73	0.87	0.30 to 2.47
2008	1.07	0.49 to 2.03	1.10	0.41 to 2.95
2009	1.76	0.99 to 2.91	1.81	0.74 to 4.45
2010	1.41	0.73 to 2.46	1.44	0.57 to 3.66
2011	2.12	1.25 to 3.35	2.16	0.90 to 5.17
2012	2.35	1.44 to 3.63	2.39	1.01 to 5.66
2013	1.67	0.92 to 2.81	1.70	0.69 to 4.22
2014	3.53	2.36 to 5.06	3.59	1.57 to 8.18
2015	2.57	1.59 to 3.94	2.62	1.11 to 6.17
2016	1.98	1.13 to 3.21	2.01	0.83 to 4.90

Sex					
Male*	1.62		1		
Female	1.48	1.21 to 1.80	0.90	0.69 to 1.18	

* Baseline category

** Mutually adjusted for all covariates

Table 3. Unadjusted one year mortality rates per 1000 person years, adjusted hazard ratios (HR) and 95% confidence intervals (CI) for one-year all-cause mortality

Covariate	**N**	**Mortality rate**	**HR****	**95% CI**
Risk factors				
No rheumatological disease or malignancy*	107	50	1	
Rheumatological	40	30	0.71	(0.35 to 1.42)
Other malignancy	26	96	1.37	(0.67 to 2.80)
Hematological malignancy	26	204	2.60	(1.45 to 4.66)
Age groups (years)				
0-14	57	24	1	
15-24	20	60	2.50	(1.01 to 6.18)
25-44	27	20	0.66	(0.23 to 1.90)
45-64	34	117	3.44	(1.81 to 7.49)
65-74	34	119	3.28	(1.69 to 7.00)
75-	23	159	3.61	(1.63 to 8.00)
Sex				
Male*	102	82	1	
Female	93	41	0.65	(0.41 to 1.04)

* Baseline category

** Mutually adjusted for all covariates

Figures

Figure 1. Incidence rate (95% Confidence interval) of HLH per million person years by calendar year

rate = incidence rate of HLH per million person years

lb = lower 95% confidence interval

ub = upper 95% confidence interval

Figure 2. Overall 1 year survival in 195 HLH cases

Figure 3. Overall 1 year survival by age groups

Figure 4. Overall 1 year survival by risk factor groups

Figure 5. European age-standardized mortality rates due to HLH per million population*

This figure includes deaths recorded in England as having an underlying cause of D76.1 and D76.2 (ICD10 coding) by the Office for National Statistics (ONS) 2001 to 2016. Mid-year populations for each calendar year were used from ONS and rates calculated as deaths/population. These crude rates were directly age-standardized to the European 2013 Population to create rates and 95% confidence intervals.

Figure 1. Reported incidence rate of HLH per million person years by calendar year

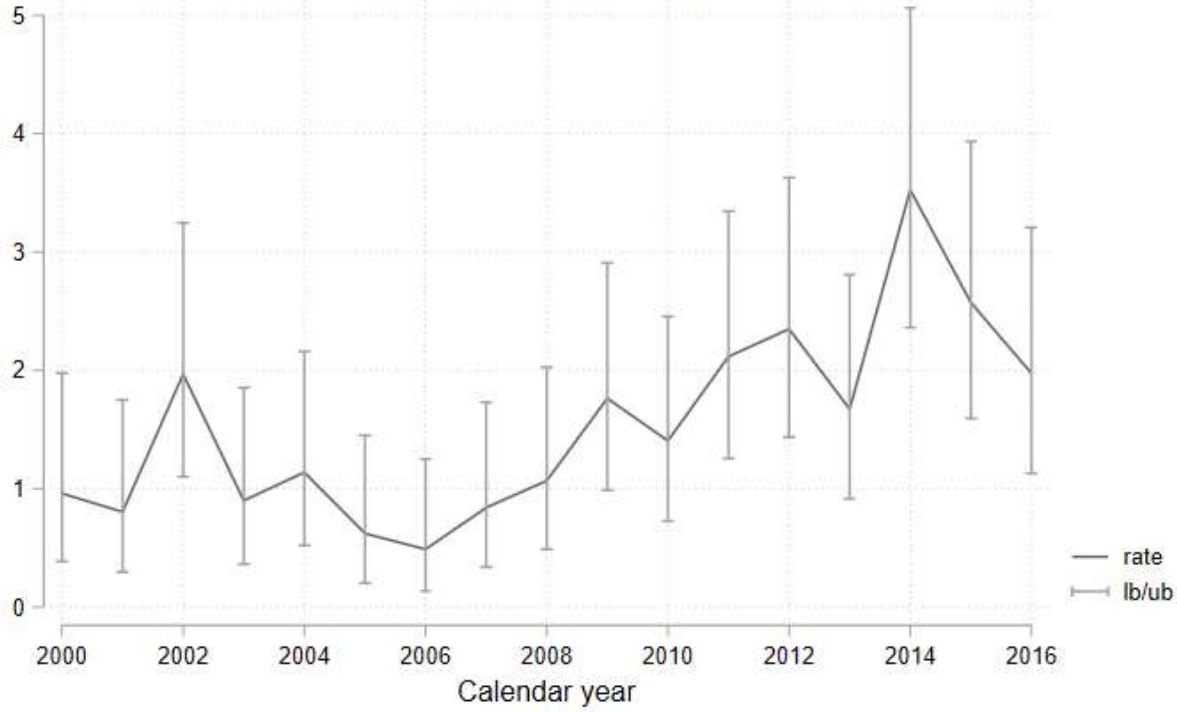
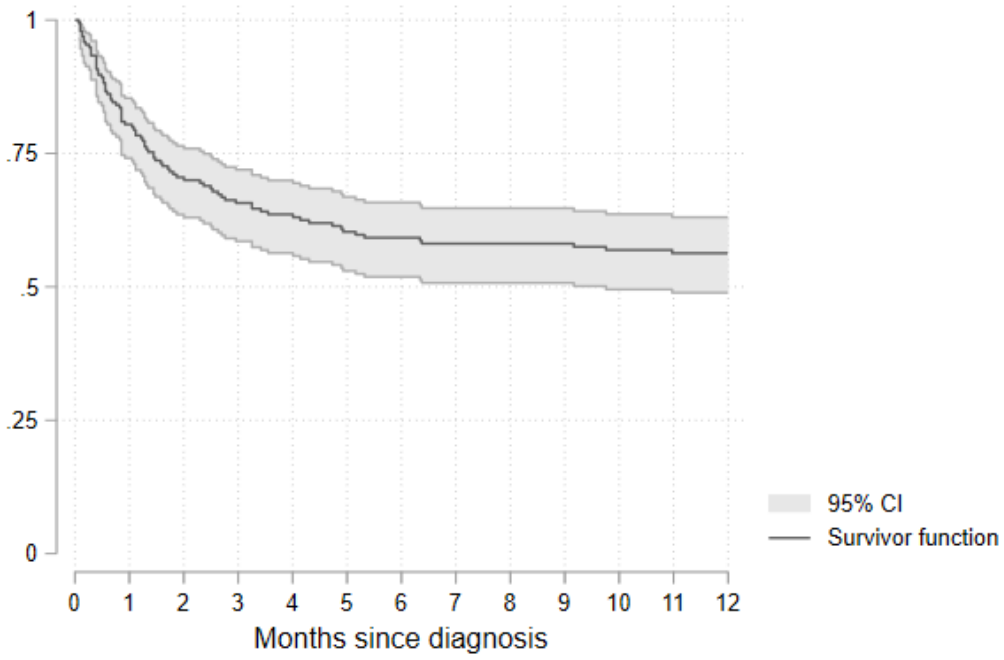


Figure 2. Overall 1 year survival in 195 HLH cases



Number at risk

195 155 132 123 118 110 106 101 99 99 95 94 93

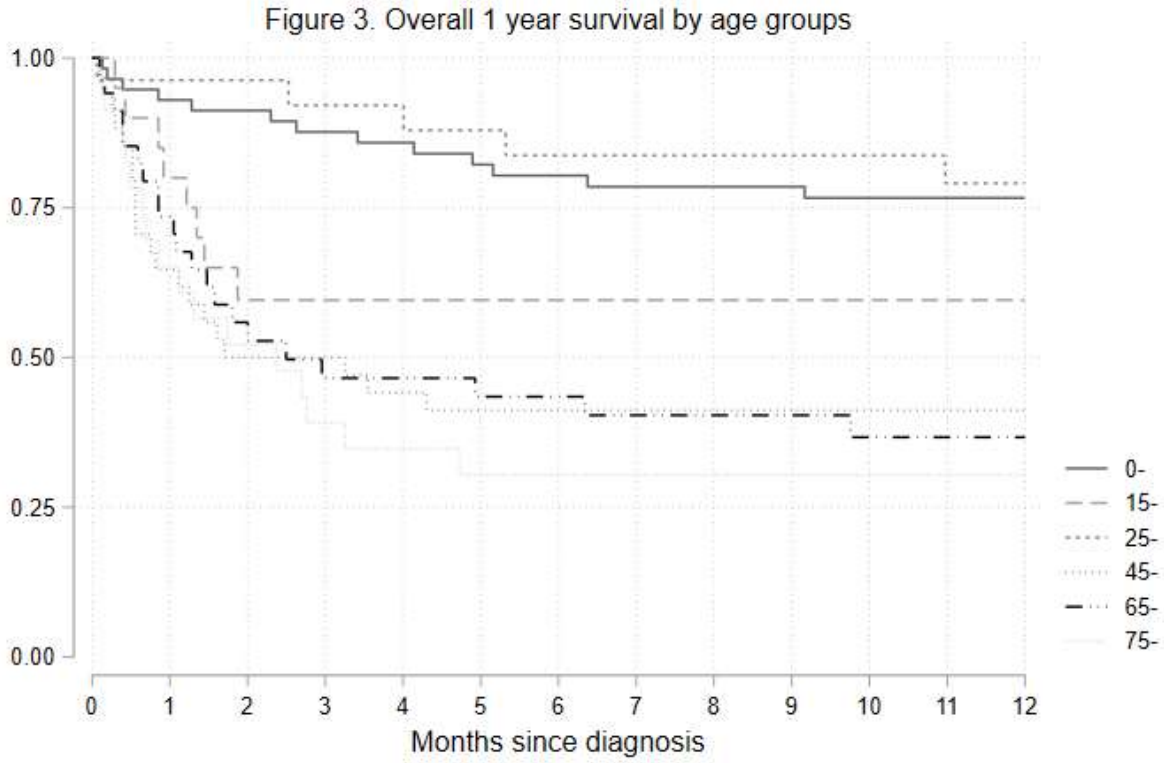
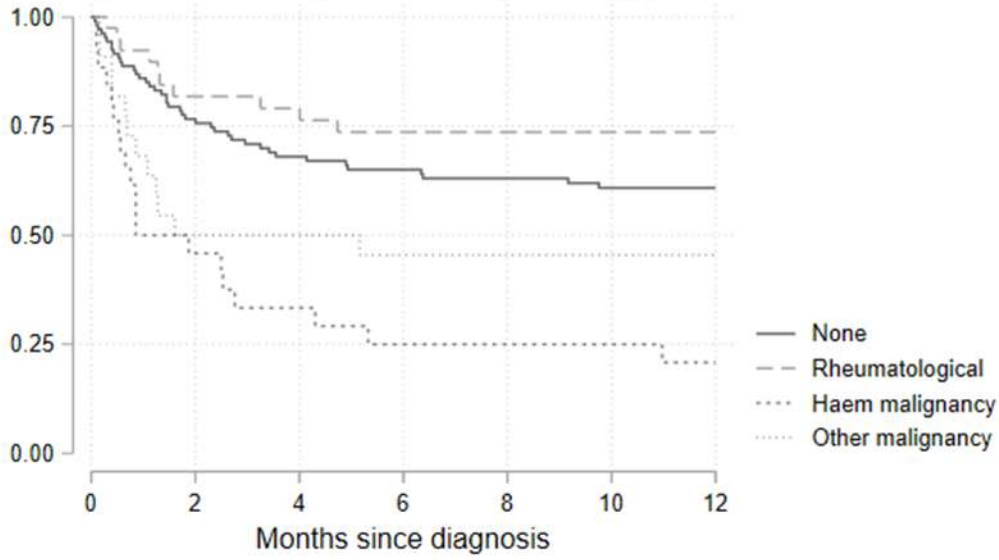


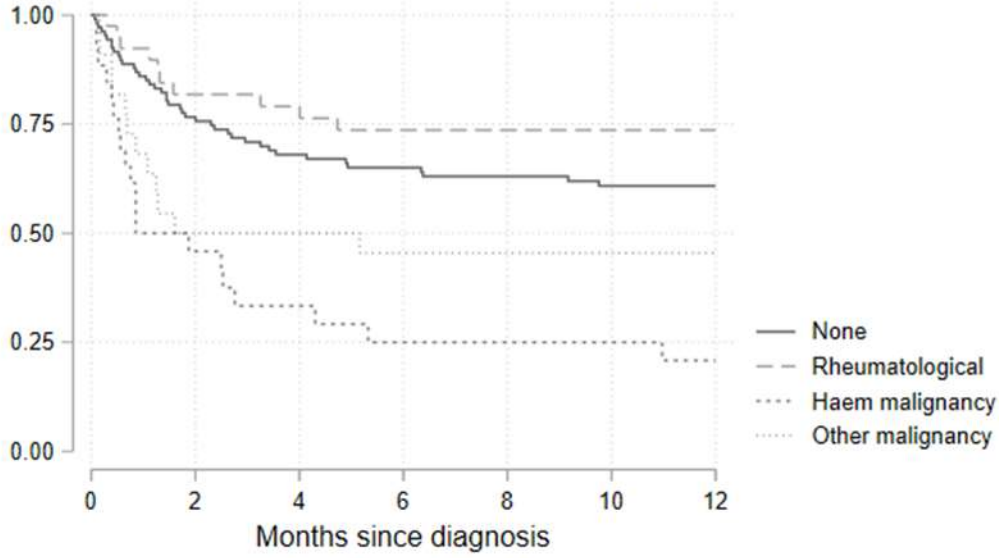
Figure 3. Overall 1 year survival by age groups
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
8
9
10
11
12
Months since diagnosis
0-
15-
25-
45-
65-
75-

Figure 4. Overall 1 year survival by aetiology groups



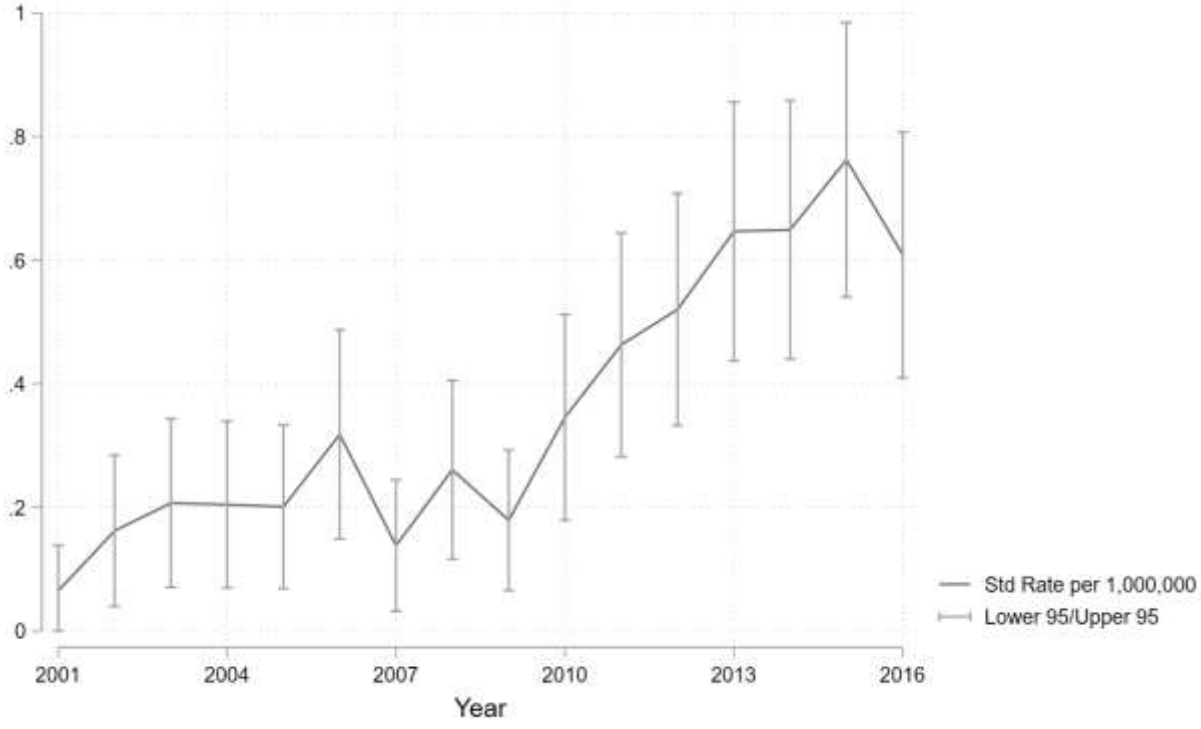
Number at risk							
None	107	80	70	65	59	56	55
Rheumatological	40	30	29	26	25	25	25
Haem malignancy	26	11	8	6	6	6	5
Other malignancy	22	11	11	9	9	8	8

Figure 4. Overall 1 year survival by aetiology groups



Number at risk							
None	107	80	70	65	59	56	55
Rheumatological	40	30	29	26	25	25	25
Haem malignancy	26	11	8	6	6	6	5
Other malignancy	22	11	11	9	9	8	8

Figure 5. European age-standardised mortality rates due to HLH per million population



Supplementary table

Table S1. Distribution of risk factors by age group among 214 people with HLH

	Risk factors			
Age group	None reported	Rheumatology	Malignancy	Total
	---	---	---	---
0-14	47	11	6	64
%	73.4	17.2	9.4	100
15-44	22	18	9	49
%	44.9	36.7	18.4	100
45-	49	12	40	101
%	48.5	11.9	39.6	100
Total	118	41	55	214
%	55.1	19.2	25.7	100