Identifying opportunities to enhance lymphoma diagnosis in primary care

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Abstract

BACKGROUND:

Lymphoma is the fifth most common cancer, classified into two subtypes: Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL). Unfortunately, evidence suggests that lymphoma diagnosis is often delayed leading to more than 40% of HL and over 50% of NHL patients being identified at an advanced disease stage (England, 2021). Late diagnosis is associated with poorer survival so efforts are required to identify lymphomas at the earliest opportunity. Selection of primary care patients referred for further investigation to secondary care services, however, remains a challenge. This is because the symptoms of lymphoma typically mimic those of benign conditions – such as fatigue, weight loss and shortness of breath. Moreover, there is a lack of reliable routine investigative tests for lymphoma and GPs have limited experience dealing with suspected lymphoma. A full-time GP is likely to diagnose approximately 1 person with NHL every 2-3 years; compared to approximately 1 person with HL during their career. This thesis sought, therefore, to review the available evidence to better determine the clinical signs, symptoms and test features observed and reported in primary care associated with a lymphoma diagnosis.

METHODS:

Studies were identified through MEDLINE, Embase and The Cochrane Database of Systematic Reviews that reported the clinical features of incident lymphoma within primary care. Data were extracted to estimate the diagnostic accuracy of clinical features for HL, NHL, and Lymphoma not otherwise specified (NOS). A narrative synthesis was conducted by outcome and clinical feature. The risk of bias was assessed using QUADAS-2. Variation in clinical features by outcome, age and study design was assessed using forest plots.

RESULTS:

Eight studies were eligible, published between 2013 to 2022. 4 investigated HL; 3 studies investigated NHL and 3 studies examined lymphoma NOS. 15 symptoms and 18 tests were identified. There was little consistency in reported features across studies and therefore meta-analysis could only be conducted for raised platelet count. The most frequently reported features included: head and neck swelling, lymphadenopathy, other lump swellings, serum cholesterol and any raised inflammatory marker test. The strongest association across all outcomes was for lymphadenopathy, with odds ratios of 184.5 (40.7,837.1) for lymphoma NOS; 263.0 (133.0, 519.0) for NHL, and 282.0 (25.0, 3123.0) for HL. Head and neck swellings and other lump swellings had lesser but considerable associations across subtypes. Raised CRP was the non-mass feature with the highest association, with an unadjusted OR, 50.0 (6.9, 364.2) for HL.

The highest sensitivities were for raised plasma viscosity at 81.3% (53.79, 95.0%) and 76.5% (62.2%, 86.8%) for lymphoma NOS and HL respectively. Most specificities were ≥ 80%, the highest being lymphadenopathy and head and neck swelling at nearly 100%.

Lymphadenopathy had the highest positive predictive values (PPVs), 5.6% and 13% for HL and NHL, respectively. The remaining PPVs were low, below the 3% NICE referral threshold. In studies reporting combined features, this often increased the PPVs. Combining lymphadenopathy with raised inflammatory markers or leucocytosis for NHL produced PPVs of 15%.

Across all types of lymphoma, head and neck swelling, lymphadenopathy and other lump swellings had strong evidence to rule in a lymphoma diagnosis, with LR+s > 5. No clinical feature had a negative likelihood ratio of < 0.3, sufficient to rule out lymphoma.

Age, sex and stage influenced risk for certain clinical features. For example, lymphadenopathy and other lump swellings were better diagnostic tools for NHL. Differing patient age impacted features including raised platelet count, raised ESR, raised CRP, raised PV. Moreover, the hazard and risk ratios for weight loss were higher for men and were found to be associated with increased late-stage lymphoma.

CONCLUSION:

Across all subtypes, lymphadenopathy and head and neck swelling are the best predictive features. Individually, the majority of features have a low predictive risk, < 3%. However, combining features often increased the predictive risk. This review has given evidence that sex, age and stage can influence the presentation of lymphoma and can help risk stratify referral decisions. Further primary care-based studies are needed, which should examine and report a broader range and combinations of features within primary care, accounting for age, sex and stage, to better stratify risk.

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Contents

Chapter 1: Background

The current lifetime risk of developing cancer in the UK is 50%(1). The best cancer outcomes are generally achieved when the disease is diagnosed at an early stage, so finding it promptly is imperative.

Within primary care, a cancer diagnosis is a relatively uncommon event(1). A primary care physician with 2000 patients typically finds 6–8 new cases per year, similar to the number of new cases of diabetes, and twice as frequent as new cases of stroke(1).

However, as cancer is a heterogeneous entity, the diagnosis of any single cancer type is a rare event, *as each is characterised by* different presenting signs and symptoms(1). Whilst a General Practitioner (GP) can anticipate to identify one case of each of the common cancers (colorectal, prostate, breast, and lung) in *any year, they* may only encounter one or two of the rarer cancers during their entire career(1). Lymphoma is a rarer cancer, with an average yearly incidence (UK) of 2.8 and 18.3 cases per 100 000 people per year for Hodgkin and non-Hodgkin lymphoma (NHL) respectively [Haematological Malignancy Research Network, HMRN diagnoses 2010-2019] (2)and it presents particular diagnostic challenges within the primary care setting.

Lymphoma

Lymphoma is the 5th most common cancer in the UK(3), constituting approximately 5% of new UK cancer diagnoses (2017)(4). The median age of diagnosis is 63 (United States) (5) . Lymphoma is not, however a single disease, but instead a heterogeneous group of haematological malignancies, arising from B, T and NK cells(6). There are over 80 different sub-types of lymphoma in the recent WHO classification (consensus and accepted global standard classification) of lymphoid neoplasms, 2022 (7)and their classification continues to

evolve with advancements in immunology, genetics and molecular pathology (8). An additional classification system is The International Consensus Classification (ICC) of mature lymphoid and histiocytic/dendritic cell neoplasms 2022 (9)

They can, however, be classified into two main groups, Hodgkin Lymphoma (HL) and Non-Hodgkin Lymphoma (NHL), the latter being more prevalent, accounting for approximately 80-90% of lymphomas (CRUK, 2017).

Among adolescents (aged 15-19 years), lymphoma is the most commonly diagnosed cancer, accounting for 21% of new diagnoses, almost two-thirds of which are HL(10).

The overall 5 year survival is estimated to be 72%; which is improving (6). In 2022, HL contributed 0.4% of new cases and 0.2% of new deaths of all cancers combined worldwide. NHL however, contributed 2.8% of new cases and 2.6% of new deaths of cancers combined worldwide, 2022(11).

There are both strong similarities and differences in pathology, incidence, presentation, disease course, treatment and survival between HL and NHL. Understanding these are essential to allow timely diagnosis and appropriate treatment.

In this thesis, the discussion will focus on lymphoma, that is, HL and NHL.

Hodgkin Lymphoma

HL can be termed as a B-cell lymphoma as the disease originates from only the B lymphocyte cells(4). It is diagnosed by the confirmed presence of Reed-Sternberg cells(4) within the right inflammatory background.

The two major variants of HL are: Classic HL (cHL) and nodular lymphocyte predominant HL (nLPHL)(12).

Classic HL

Over 90% of HL cases are of cHL(13). It is an aggressive lymphoma. cHL can be further subdivided based on morphology, the abundance of Hodgkin and Reed-Sternberg (HRS) cells, and the background infiltrate into: Nodular sclerosis, Mixed cellularity, Lymphocyte-rich and Lymphocyte-deplete subtypes(13). The subtypes have little difference in presentation or treatment plans, although the lymphocyte-deplete subtype has a poor prognosis(4).

Nodular lymphocyte predominant HL (nLPHL)

nLPHL is a rarer subtype, only seen in approximately 5% of HL cases(4). It is diagnosed with the presence of lymphocytic and histiocytic cells(14). nLPHL has a propensity to transform into diffuse large B cell lymphoma(15). It is generally treated differently to cHL, as it is regarded a low-grade condition(16). Treatment often involves ‘watch and wait’ and only localised radiotherapy(4). The ICC of mature lymphoid and histiocytic/dendritic cell neoplasms 2022 no longer terms nLPHL as HL - it is called 'nodular lymphocyte predominant B-cell lymphoma'. However, it is maintained as HL in the WHO.

Incidence, mortality and presentation:

Figure 1 Hodgkin lymphoma, European age-standardised incidence rates, persons population, 1993-2019 (17)

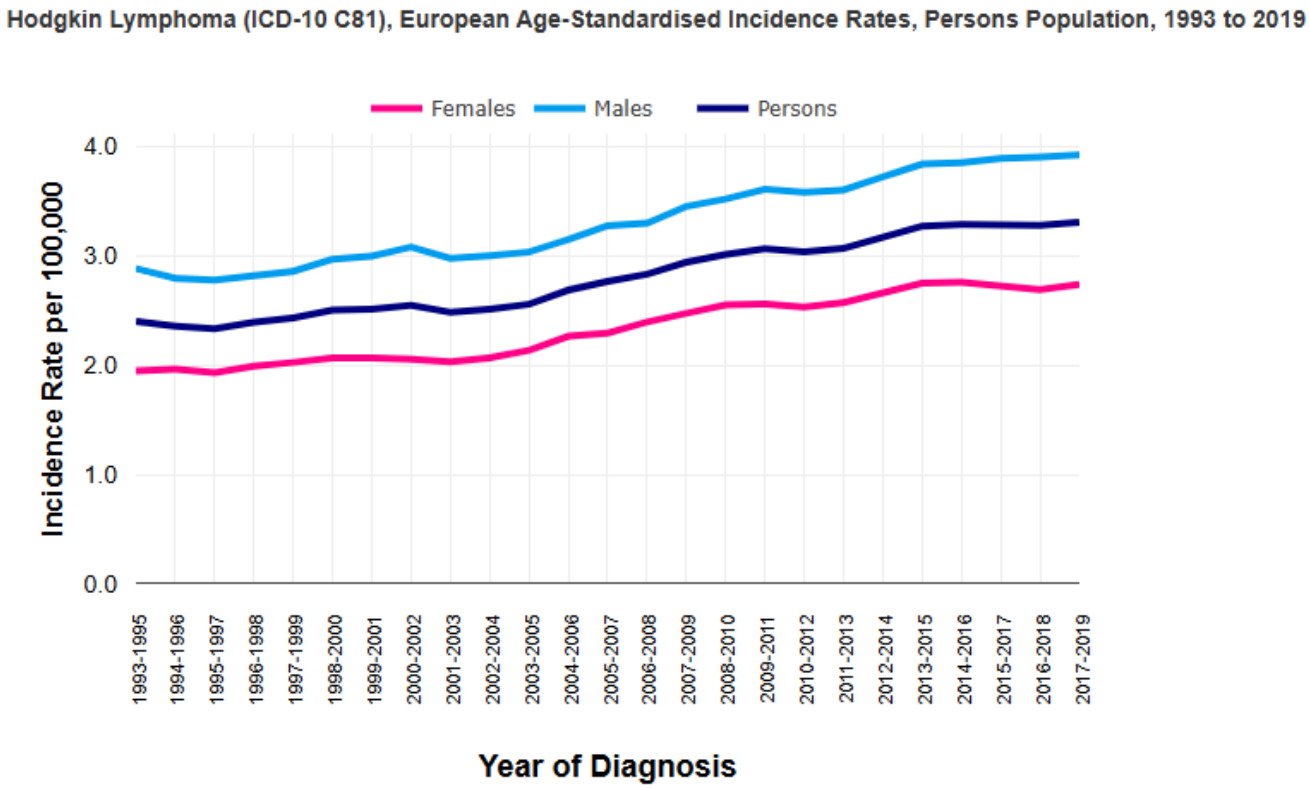


Figure 2 Hodgkin lymphoma, Average Number of New Cases per Year and Age-Specific Incidence Rates per 100,000 Females and Males, UK, 2017-2019 (17)

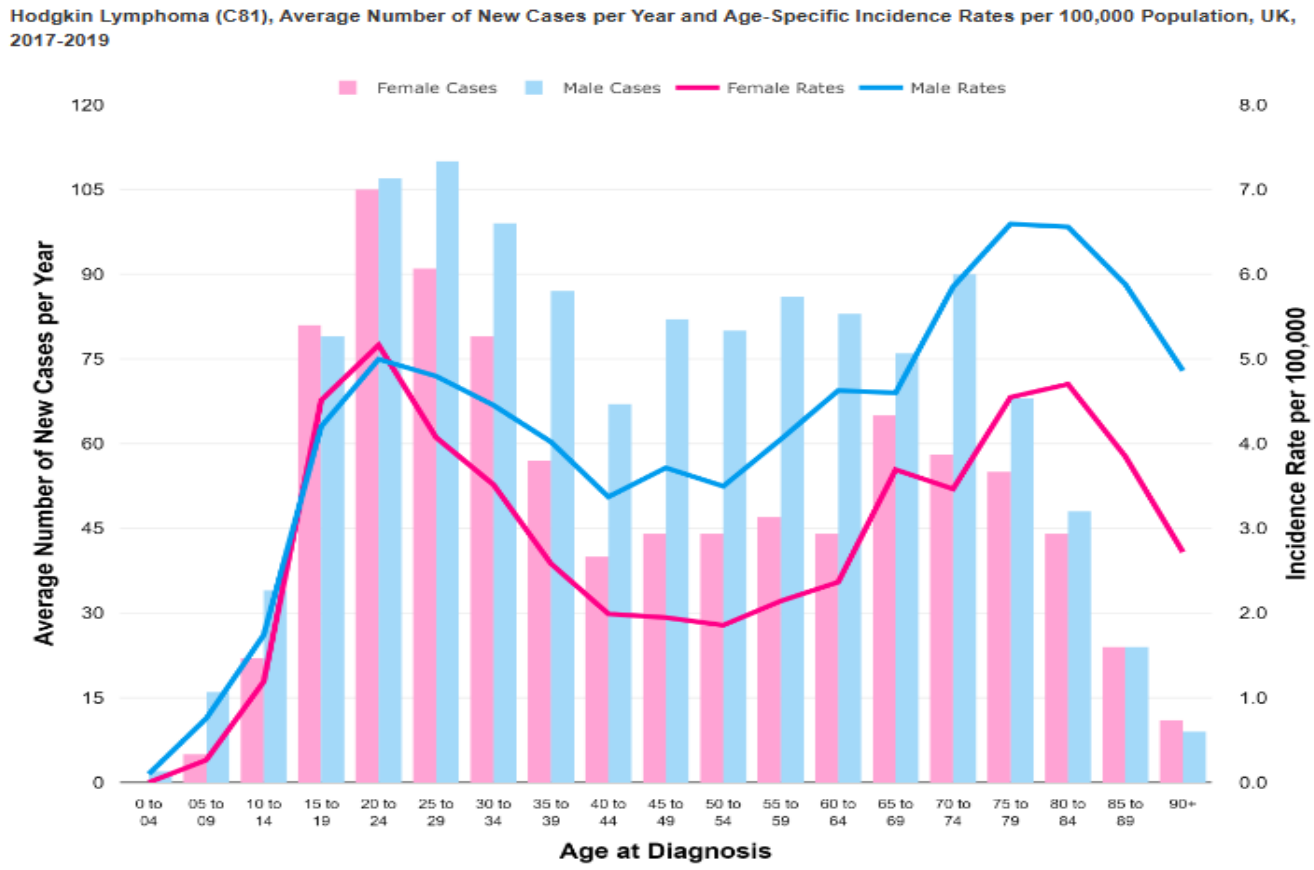
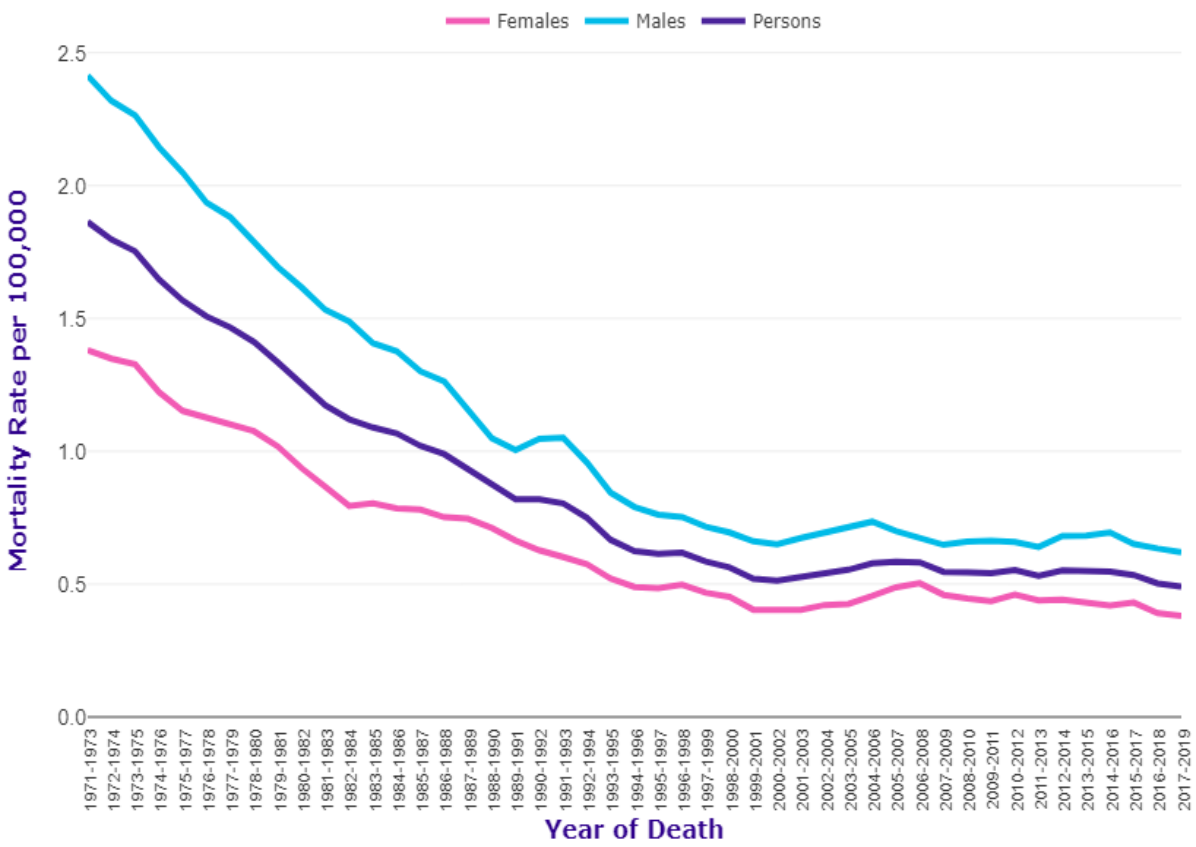


Figure 3 Hodgkin lymphoma, European age-standardised mortality rates per 100,000 persons population, UK, 1971-2019 (17)



Mortality rates have steadily declined from 1.3 cases per 100,000 in 1975 to 0.3 cases per 100,000 in 2014.

Painless lymphadenopathy enlarging over months is a common mode of presentation. The 3 most common sites of disease presentation are: mediastinal involvement, or left neck nodal enlargement, or right neck nodal enlargement. These are each seen in about 60% of patients(13). B symptoms (fever, > 10% weight loss in 6 months and night sweats) are frequent in patients with advanced-stage or bulky disease.

Non-Hodgkin Lymphoma

Approximately 85%-90% of NHLs originate from B cells, and the remaining from T or NK cells(18). NHL has over 60 classified subtypes, including diffuse large B-cell lymphoma

(DLBCL), and follicular lymphoma (FL) which account for approx. 65% of all NHLs. These subtypes are diagnosed on their morphology and by protein antigens present on the cell surface, including CD2, CD3, CD4, CD8 (T-cell cell surface markers) and CD10, CD19 and CD20 (B-cell cell surface markers)(4).

NHLs can be categorised into two groups: high-grade, aggressive (60%) and low-grade, indolent (40%). DLBCL is the most common type of aggressive NHL and FL the most common type of indolent lymphoma. All low grade or indolent lymphomas can undergo a high-grade transformation where they turn into high grade lymphoma(19).

The subtype of NHL is more influential on a patient's treatment and prognosis than HL(4).

Low grade lymphomas tend to grow relatively slowly and can be treated effectively, resulting in long remission although they are not usually cured and relapses are frequent and can occur late (20).

High grade lymphomas are typically faster growing and clinically more aggressive. Early deaths are more frequent, but most patients who achieve a complete remission are cured of their disease.(20)

Incidence, mortality and presentation:

Patients commonly present with lymphadenopathy or splenomegaly. A single lymph node or several nodes may be enlarged. Clustering of lymph nodes is common, and the disease can present above or below the diaphragm or both. The swelling develops over months or years in the case of low-grade lymphoma but is much faster with high grade lymphoma(21). Lymphoma can also occur in extra-nodal locations such as the brain, stomach, lung and bone(22) .

The most frequently quoted incidence of the different subtypes is taken from the International Non-Hodgkin's Lymphoma Classification Project (Anon 1997), based on submitted cases from selected hospitals (Table 1). (20)

Figure 4 Non-Hodgkin lymphoma, European age-standardised incidence rates, persons population, 1993-2019 (23)

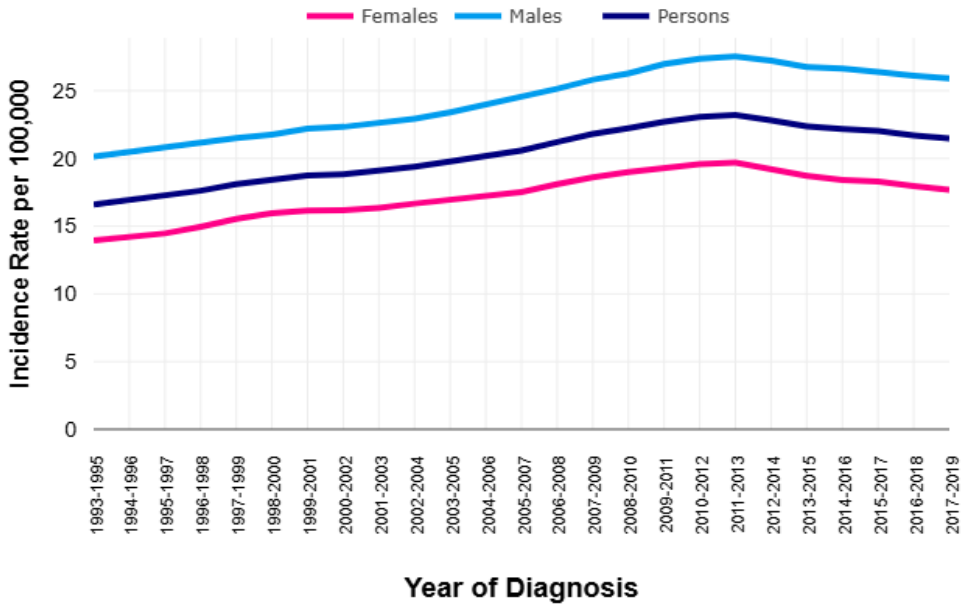


Table 1 Proportion of new NHL cases according to the main NHL subtypes

Subtype	Proportion of NHL %
Follicular lymphoma	22.0
Marginal zone lymphoma	9.0
Mantle cell lymphoma	6.0
Diffuse large B-cell lymphoma	35.0*
Burkitt lymphoma	1.0
T-cell lymphoma	7.0
All	

*includes primary mediastinal B-cell lymphoma and Burkitt-like lymphomas

The incidence of the most frequent lymphomas has also been determined by the Haematological Malignancies Research Network (HMRN) on a population basis (Table 2). The population of HMRN has a socio-demographic profile that is similar to UK/England.(20)

Table 2 Incidence of NHL in the UK based on extrapolation of the HMRN data

Subtype	Proportion of NHL	Expected cases per year in the UK
Follicular lymphoma	18.1	1860
Marginal cell lymphoma	19.9	2050
Mantle cell lymphoma	5.0	510
Diffuse large B-cell lymphoma	48.5	4990
Burkitt lymphoma	2.0	210
T-cell lymphoma	6.3	650
All		10,280

Figure 5: Non-Hodgkin lymphoma, average number of new cases per year and age-specific incidence rates per 100,000 population, UK, 2017-2019 (23)

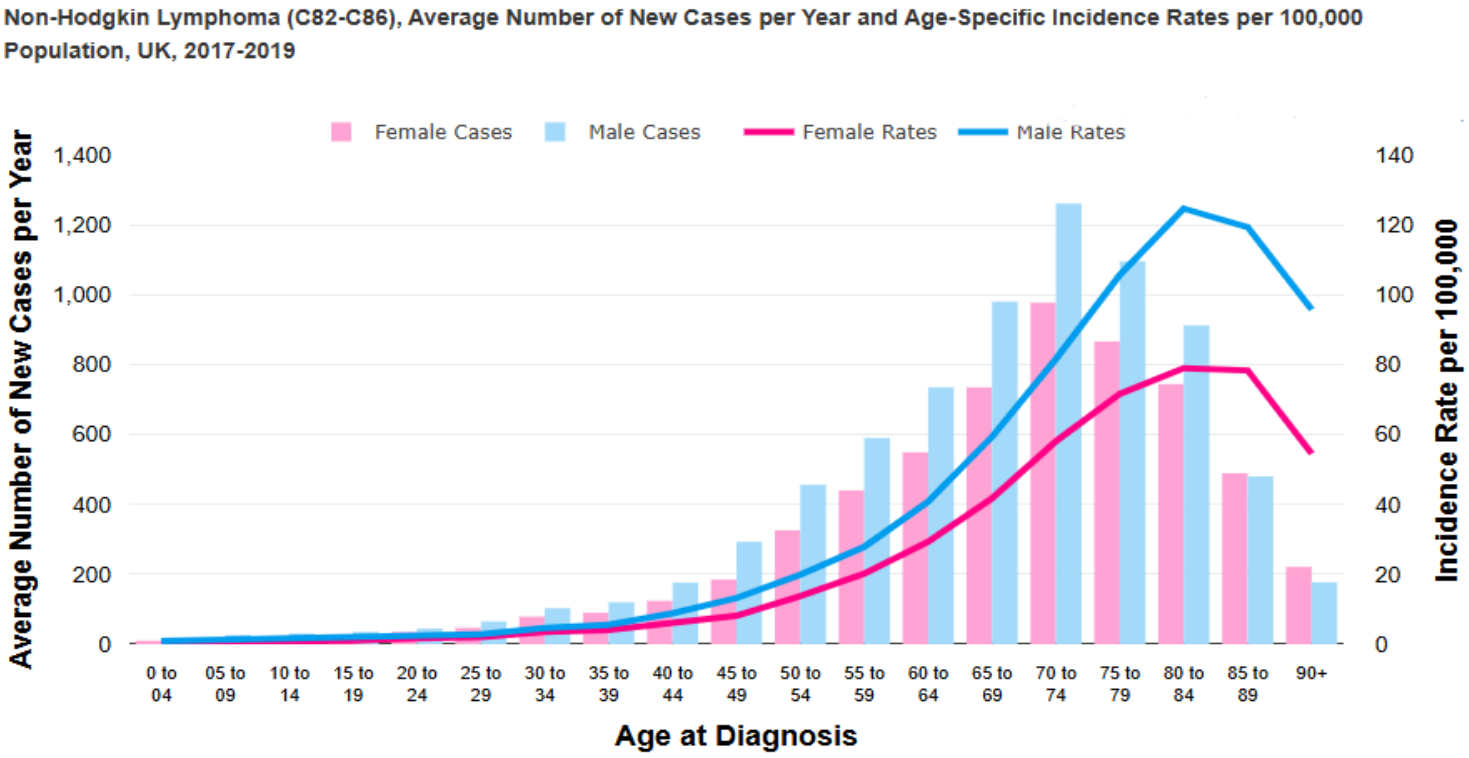
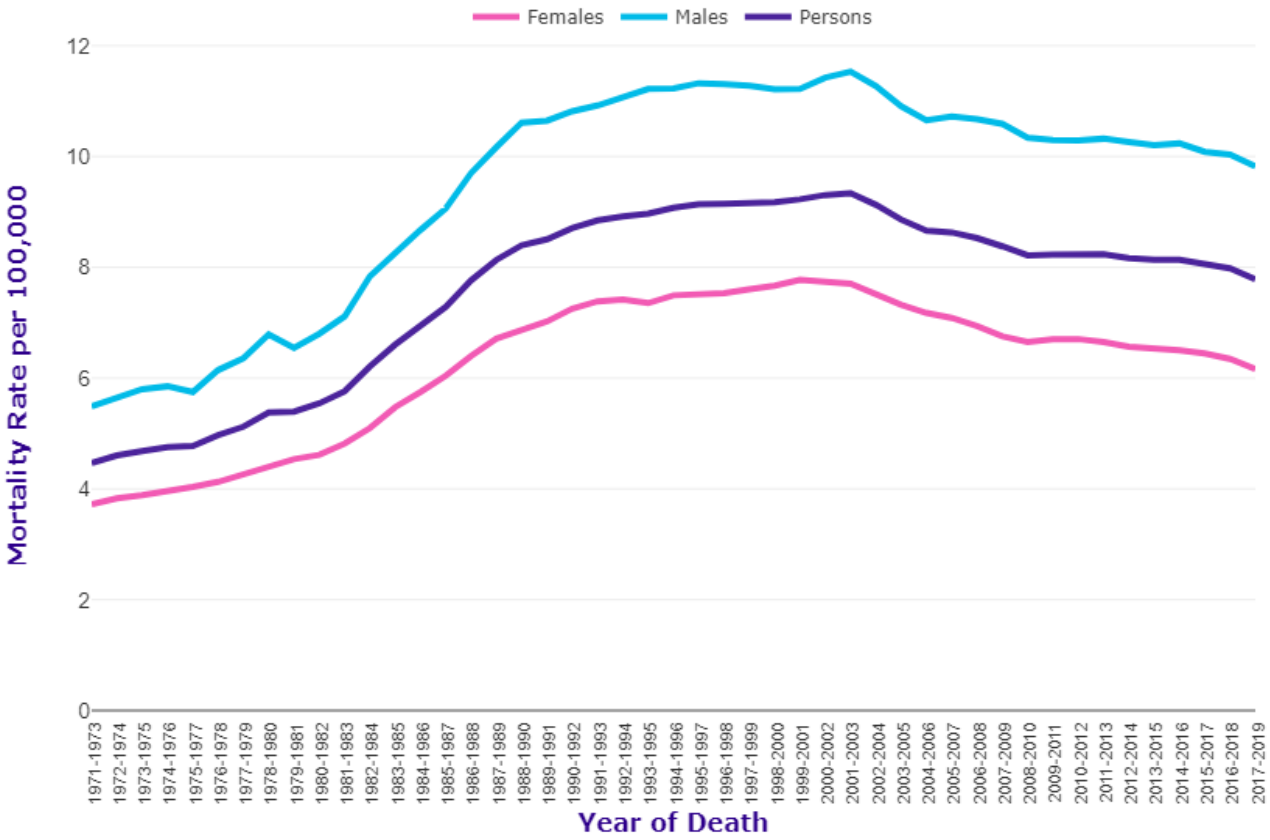


Figure 6 Non-Hodgkin lymphoma, European age-standardised mortality rates per 100,000 persons population, UK, 1971-2019 (23)



Epidemiology

Characteristic	Hodgkin lymphoma	Non-Hodgkin lymphoma
Diagnosis	• Presence of Reed Steinberg cells (4) • Few cell markers (4) • Upper body distribution (4)	• Absence of Reed Steinberg cells (4) • Specific cell markers, such as CD19 and CD20(4) • Disease sites above and below the diaphragm (4)
Incidence	Accounts for 10% of lymphomas, and for less than 1% of all new cancer diagnoses in the UK (2017-2019)(17).	Accounts for 80-90% of lymphomas, and for 4% of new cancer diagnoses in the UK (2017-2019) (23).
Over time	Age standardised (AS) incidence rates have increased between 1993-1995 and 2016-2018 for females and males combined by almost two-fifths (37%) in the UK – (Figure 1). The increase was similar for both females (38%) and males (35%). (17)	AS incidence rate for females and males combined increased by 38% between 1993-1995 and 2016-2018 in the UK (Figure 4) (23). The increase was similar in females and males. However, the rate of increase has slowed in recent years (23).
Subtypes	4 (4)	More than 60 (4).
Age	A bimodal pattern of incidence by age, with a peak at ages 20-34 years (young adults) and a second peak over 70 years(17). Incidence rates are highest in people aged 75 to 79 (2016-2018, UK) (17) (Figure 2).	Strongly associated with increasing age(8). Peak incidence in patients aged 80-89. Incidence rates in the UK are highest in people aged 80 to 84 (2017-2019) (23). Age-specific incidence rates increase from ages 20–24, with a steeper rise in males than females,

		and decline from age 80–84 (23). The highest rates for both sexes occur in the 80–84 age group (Figure 5)(23). Incidence rates are significantly lower in females than males across most age groups(23). The widest gap is at age 05 to 09, when the female age-specific incidence rate is 2.2 times lower than that of males(23).
Sex	Greater predominance in males (58%) than females (42%) UK(17). Incidence rates are significantly lower in females than males across several, primarily older age groups. The widest gap is at age 05-09, when the female age-specific incidence rate is 2.6 times lower than that of males(17).	Slightly more common in males (56%) than females (44%), UK (23).
Ethnicity	Incidence rates are higher among Asian and Black ethnic groups, and similar among people of mixed or multiple ethnicity, compared with the White ethnic group, in England (2013-2017) (17).	Incidence rates are lower among Asian, Black and mixed or multiple ethnic groups, compared with the White ethnic group, in England (2013-2017) (23).
Geographical variation	Incidence rates (European age-standardised (AS) rate) for	High income regions have a higher incidence of low-grade B-

	persons are similar to the UK average in all the UK constituent countries(17).	cell lymphomas compared with low and middle-income regions(23). In contrast, low and middle-income regions had a higher incidence of high-grade B-cell lymphomas as well as T-cell and natural killer (NK)-cell lymphomas, than high-income regions(23). Incidence rates (European age-standardised (AS) rate) are significantly lower than the UK average in Scotland and Wales and are similar to the UK average in all other UK constituent countries(23).
Deprivation	AS Incidence rates in females are similar in the most deprived quintile compared with the least, and in males are 19% higher in the most deprived quintile compared with the least (England, 2013-2017)(17).	AS incidence rates in England in females are similar in the most deprived quintile compared with the least, and in males are 10% lower in the most deprived quintile compared with the least (2013-2017)(23).
Disease site	Typically located in the lymph tissue of the upper body, neck, chest and axilla(24). Slightly more patients are diagnosed at an early stage than late stage. Over 40% of patients were diagnosed at an	Clustering of lymph nodes is common, and the disease can present above the diaphragm, below it, or in both regions(4). The later presentation is staged with more extensive disease, which is associated with a poor prognosis(26).

	advanced stage (stages III-IV), England 2021 (25).	The majority of patients (over 50%) are diagnosed at an advanced stage (Stages III-IV) , England 2021(25).
Survival and mortality	Accounts for less than 1% of all cancer deaths (2017-2019)(17). Since the early 1970s, mortality rates in the UK have fallen by approximately three-quarters (74%) (17). Over the past decade, mortality rates have remained stable for both females and males in the UK (2017-2019)(17) (Figure 3). Mortality rates in the UK are projected to decline by 9% between 2023-2025 and 2038-2040(17). Survival for HL patients diagnosed between 2013 and 2017 in the UK: at 1-year, 90.6% and 5-years, 82.2%. (17)	Accounts for 3% of all cancer deaths (2017-2019)(23). Over the last decade, mortality rates in the UK have decreased by more than a twentieth (7%) (23). Female mortality rates have declined by approximately a tenth (9%), while male fell by more than a twentieth (7%) (2017-2019) (Figure 6) (23). Mortality rates are projected to decrease by 12% in the UK between 2023-2025 and 2038-2040(23). Survival for NHL patients diagnosed between 2013 and 2017 in the UK: at 1-year, 79.4% and 5-years, 65.6%(23).

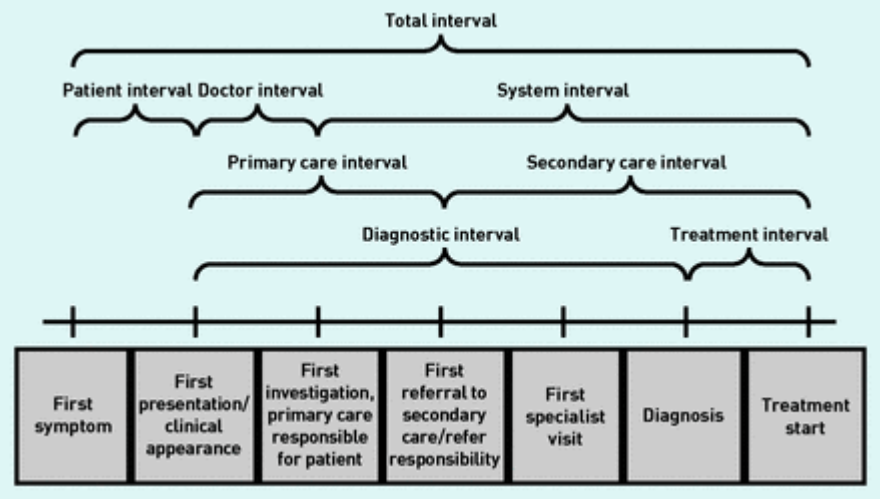
Diagnosis

The only definitive way to diagnose lymphoma is via lymph node, extra nodal and bone marrow biopsy, typically carried out in secondary care(27).

Diagnostic Pathway

The stages of cancer diagnosis can be illustrated using the Aarhus statement, (Figure 7)(28). The statement, published in 2012, provides methodological guidance on recording and reporting of time-point measurement to promote consistency in studies based on diagnostic intervals. Moreover, the statement recommends definitions of the key time-points for diagnostic and treatment pathways.

Figure 7 Cancer diagnostic intervals used in developing the Aarhus statement



The time interval from first symptom to start of treatment is often labelled as a delay even if parts of this delay are unavoidable(29).

The diagnostic pathway is broken down into three component intervals: the period from symptom recognition to first consultation with a health care professional, generally a GP (patient delay), the period from first consultation with a health care professional to initiation of investigations for cancer related symptoms (doctor delay) and the period from initiation of investigations to commencement of treatment (system delay).(28, 30)

The patient may fail to recognise suspicious cancer symptoms or act on them. This can be attributed to symptom misinterpretation (not recognising seriousness of symptom), fear (of a cancer diagnosis), concern on wasting GP time and prioritising other life events. Symptom misinterpretation is common, for example attribution of symptoms by patients to other factors such as minor ailments, physical exertion, ageing, and stress.(30, 31)

Primary care physicians are expected to identify patients with possible cancer at an early stage, but the diagnosis of cancer is relatively uncommon for individual primary care physician. Primary care physicians must differentiate the minority of patients who need urgent attention from the majority of patients who are likely to have self-limiting conditions. The primary care physician may not recognise patients with suspicious cancer symptoms and investigate them appropriately or refer on time. The National Institute for Health and Care Excellence (NICE)and other guidelines assist primary care providers assess whether a patient has suspected cancer based on their symptoms and requires a referral for further investigation(31). The decision is further shaped by GP-related factors, including their degree of risk aversion as well as both recent and career-long experience. Moreover, structural determinants—such as payment models and market competition—may also influence a GP's referral(32).

System-related factors include logistics, waits and administrative procedures(29). There may be a considerable wait for either non-urgent referrals (as is the case for the majority of patients) or GP-initiated diagnostic investigations.(33)

Delays are reported across the various intervals in the diagnostic pathway. An avoidable diagnostic delay of lymphoma was estimated to occur in 26.3% of patients, 11th highest(34),

NCDA 2014. There is no agreement in the diagnostic pathway intervals in reported literature.

The median patient interval (time from symptom onset to first consultation) is reported in 2 studies with 1 further study reporting the mean patient interval. The median patient interval is reported to be: 30 (IQR=2-77) days for HL(35) (1 study) and 14 (IQR =1-43) days for lymphoma NOS(36) (1 study). The mean patient interval for lymphoma NOS is reported to be 39 (IQR=1-44) days(37) (1 study).

The median primary care interval (time from first consultation to specialist referral) and mean primary care interval for lymphoma NOS are estimated to be 11 (IQR = 0-35) (34)and 33 (IQR = 0-31) days (37)respectively.

The overall median total interval (symptom onset to diagnosis): ranged between 158 (IQR = 84-288)(35) to 174 (range = 30-1041) days(38) for HL (2 studies) and 132 (range = 42-1396) days(38) for NHL (1 study).

The median treatment delay (diagnosis to treatment) is estimated to be 8 (range = 1-31) days for HL and 7 (range = 0-97) days for NHL(38).

According to the English National Audit of Cancer Diagnosis in Primary Care 2009–2010, the mean primary care interval for lymphoma is the 7th highest amongst the 28 cancers reported, (33 days)(37). The mean overall pre-referral interval for lymphoma (denoting the period from symptom onset to referral) by summing patient and primary care intervals is estimated to be (72 days), the 15th highest(37).

The data show that treatment starts very promptly once a diagnosis is made, but that diagnosis is often severely delayed. The delay in primary care of lymphoma is demonstrated

to be significant relative to other cancers and should be addressed. For breast cancer, most diagnosed cancer globally (2020) (39)the median and mean primary care intervals are 0 days (IQR = (0-0)) (34) and 6 days (IQR = 0-0 days) (37) respectively. An avoidable delay was in diagnosis was estimated in only 6.9% of breast cancer patients, NCDA 2014 (34).

Health inequalities to delays in diagnosis:

Within the NHS, health inequalities are a critical injustice, prompting the introduction of the Core20PLUS5 initiative. This strategy, introduced by NHS England, aims to reduce health inequalities, with a particular focus on the most deprived 20% of the population, the Core20(40). Cancer health inequalities, unequal access to and utilisation of cancer services, involves disparities in cancer incidence, outcomes, and healthcare access among different demographic groups(40, 41).

Disparities in health literacy can delay presentation to healthcare services, resulting in late-stage diagnoses.(40). Lower health literacy is more prevalent among ethnic minority groups and individuals from more deprived areas, impacting health care engagement(42, 43). Additionally, ethnic and cultural factors may further delay help-seeking, contributing to inequalities in cancer presentation through stigma and fear (40, 44). For instance, shame or stigma may be brought to an individual or family through the disclosing of certain health conditions, thus secrecy is maintained(40).

Routes to diagnosis

Routes (pathways) of diagnosis for lymphoma include: 2-week wait (urgent suspected cancer), GP referral (routine or urgent), emergency presentation, inpatient elective, other outpatient, death certificate only and Unknown. The proportion and outcomes of patients diagnosed by each route varies.

The majority of lymphoma cases are diagnosed through GP referrals or through emergency presentation, 65.7% (47% via two week wait; 7.7% via urgent and 11.0% via routine) and 19.4% respectively, NCDA 2014(34). Overall, 80.6% of cancer patients were diagnosed via GP referrals or emergency presentation (51.8% via two week wait; 4.4% via urgent; and 7.9% via routine) and 16.5% respectively, NCDA 2014(34). Emergency presentation is marginally higher for lymphoma patients. This route is associated with prolonged time to diagnosis, advanced disease stage and poorer survival (45).

Presenting features

There is no classic clinical presentation, standardized diagnostic pathway/workup, or single definitive test that can confirm or entirely rule out lymphoma.

Symptoms

Lymphomas have a wide range of presenting symptoms, dependent on the type and the involved sites(46) - commonly presents with fatigue, pain, palpable lymphadenopathy, and shortness of breath/cough, all of which are nonspecific findings with exceptionally broad differential diagnoses (47).

The most common manifestation is (painless) lymphadenopathy (swollen lymph nodes)(48), typically in the lymph nodes(49). It is detected incidentally by the patient or by imaging procedures performed in assessment for other conditions, or as part of investigation of

localized symptoms such as cough or pain(49). Even in clinical presentations with a more narrowly defined differential diagnosis, lymphoma remains an uncommon diagnosis. In patients presenting to primary care with lymphadenopathy, the overall incidence of any malignancy is 1.1%(50)

Symptoms may develop due to pressure effects of lymph nodes on surrounding structures or due to the involvement of extra nodal sites such as the gastrointestinal tract, central nervous system, liver or bone, leading to atypical presentations such as cough, pruritus and unexplained pain(51).

Systemic symptoms (B symptoms) occur in a subset of patients with more advanced disease(48). Their presence suggests the likelihood of a worse lymphoma prognosis(5). Alcohol induced lymph node pain is a rare symptom) that can present in <1%-2% of HL patients(49).

Primary care investigations

Once the diagnosis of lymphoma is suspected, further evaluation includes laboratory testing, imaging, and biopsy(47).

Before referral, to support decision making, GPs often order a range of primary care blood tests to be performed, (8, 47) including lactate dehydrogenase along with complete blood counts with differential, comprehensive metabolic panel, and uric acid(6).

Specific laboratory abnormalities are consistent with a lymphoma diagnosis and can raise concern for complications including bone marrow involvement, compressive adenopathy, or advanced disease(47). The absence of any of these abnormalities is not considered sufficient to exclude a diagnosis of lymphoma(47).

- Anaemia
- Thrombocytopenia
- Leukopenia/Leukocytosis
- Raised Lactate Dehydrogenase (LDH)
- Electrolyte abnormalities
- Elevated phosphorus (Hyperphosphatemia)
- Hyperuricemia (Raised uric acid)

Secondary care investigations

Once referred to secondary care, a patient undergoes further investigations in order to confirm a lymphoma diagnosis.

Biopsy:

Lymphoma diagnosis is confirmed by tissue biopsy(6). Core lymph node biopsyis the most common sampling method for suspected lymphomas as it allows for the assessment of whole lymph node architecture. If insufficient for diagnosis, then an excision biopsy is recommended.

Several benign causes of lymphadenopathy exhibit morphologic patterns that overlap with lymphoma, including reactive hyperplasia, (47). Expert histologic assessment of lymph node architecture remains essential for distinguishing between benign lymphadenopathy and the various subtypes of lymphoma(47).

Imaging techniques:

After the diagnosis is confirmed on biopsy, patients need to be staged which is determining where in the body the lymphoma is found (6).

The majority of lymphomas are metabolically active, therefore fluorodeoxyglucose (FDG) avid. They can often be differentiated from other causes of FDG uptake—such as physiologic processes, infection, or inflammation—based on the distribution of avid lymph nodes and/or their associated CT characteristics (47).

CT is widely adopted as the imaging modality of choice for both staging and monitoring treatment response in lymphoma (47).

Compared to CT alone, FDG PET-CT has superior accuracy for staging and greater specificity, particularly in the assessment for extranodal disease(47). However, it should be recognized that not all lymphomas are FDG avid; thus, lack of FDG uptake on PET-CT does not exclude the diagnosis of lymphoma(47).

Staging

Lymphoma is staged depending on the number and location of lymph nodes and other organs involved and the presence of B symptoms(52, 53). It can be classified as: limited/early-stage disease (stages I-II, non-bulky) and advanced stage disease (III-IV or II with bulky and B symptoms or II with extra-nodal sites)(13).

Lymphoma is staged routinely using the Lugano classification system, incorporating fluorodeoxyglucose positron emission tomography (FDG PET)/ CT to assess the extent of disease and treatment response (13). The lugano classification system is a modified version of the Ann Arbor system with Cotswolds modifications(54) .

The Ann Arbor system was originally designed for only HL in 1971 by the Committee on Hodgkin's Disease Staging Classification in Ann Arbor, Michigan, and then subsequently applied to NHL(55). The Cotswolds modification adds information regarding the prognostic significance of bulky disease and regions of lymph node involvement.

If lymphoma affects lymph nodes and organs inside the lymphatic system, these are called lymphatic sites, and include thymus, spleen and tonsils. However, if the disease affects areas outside the lymphatic system, these are called extra-nodal sites (extra lymphatic sites), which include the bone marrow, lungs, brain and kidneys(53).

Table 3: Staging system

Stage 1 (13, 54, 56)	Involvement of a single group of lymph nodes or an organ of the lymphatic system, lymphoid organ. *Extra-nodal:* One extra-nodal site involved.
Stage 2 (13, 54, 56)	Involvement of two or more lymph node groups on the same side of the diaphragm *Extra-nodal*: An extra-nodal site and one or more groups of lymph nodes are involved.
Stage 3 (13, 54, 56)	Involvement of lymph node groups on both sides of the diaphragm
Stage 4 (13, 54, 56)	Widespread disease. Means either: • Lymphoma in the lymph nodes and an extra-nodal site • Lymphoma in more than one extra-nodal site, for example the liver, bones or lungs Disseminated involvement of 1≥ extra lymphatic organ with or without any nodal involvement

For all stages, the assigning of the subscript: (13, 54, 56)

A indicates absence of B symptoms.

B indicates the presence of B symptoms (Fever (>38oC), drenching sweats, weight loss (UWL of >10% body weight over 6 months)).

For Stages I to III, the assigning of the subscript: (13, 54, 56)

E Indicates involvement of a single, extra-nodal site contiguous or proximal to known nodal site.

X Indicates bulky disease - nodal mass >1/3 of intrathoracic diameter or 10 cm in dimension.

Role of primary care

Primary care, where most patients present plays a significant role in the timely diagnosis of cancer(57, 58). Around 85% of cancers are diagnosed after symptomatic presentation to a primary care practitioner(1, 59).

Suspected lymphoma patients presenting in primary care are referred to specialist secondary care services by general practitioners, acting as gatekeepers(57, 58).

The most prevalent symptoms presented in primary care include: respiratory, musculoskeletal and gastrointestinal symptoms(1). The role of GPs is the timely (60) and accurate identification of patients deemed to be at risk of lymphoma for referral(61). GPs will assess the urgency of referral based on patient characteristics, medical history and their clinical presentation(57).

The development of urgent referral pathways (e.g. 2 week wait) has been to help in the assessment of symptomatic patients(1). Pathways have also been developed for patients presenting with non-alarm, non-specific symptoms(62).

NICE guidelines for diagnosis of lymphoma in the UK

Health-care systems are increasingly introducing guidance on urgent referral for the investigation of suspected cancer to promote early diagnosis(63). The UK NICE guidelines are used in general practice to help GPs with referral decisions(64).

The suspected cancer NICE referral guidelines were devised in 2005, and subsequently revised in 2015 (NG12), and reviewed in 2025 for investigation of lymphoma in primary care(64, 65). The guidelines are largely based on evidence obtained from published literature as well as clinical experience.

The current NICE guidelines recommend consideration for urgent (2 week wait) suspected cancer referral for lymphoma when patients present with unexplained lymphadenopathy or splenomegaly, taking into account associated symptoms such as fever, night sweats, shortness of breath, pruritus or weight loss(64). Alcohol induced lymph node pain, a rare symptom should also be taken into account for HL(64).

The guidelines use a cancer risk of 3% as a threshold risk to decide between urgent or routine investigation for cancer(66). Patients with atypical or low-risk symptoms will generally see a specialist routinely (with no guarantee of being seen rapidly)(66).

It is not mandatory to apply these recommendations. The guideline does not override the responsibility to make decisions appropriate to circumstances of the individual, in consultation with them and their families and carers or guardian(64).

Some patients undergo primary care investigations, such as imaging or blood testing, with those testing positive then offered a 2-week-wait referral(66).

Limitations of current NICE guidelines

The methods used to estimate the PPVs of features of lymphoma are likely to be inaccurate due to the limitations of the evidence. The quality of the evidence is low - only 4 published studies were utilised; not all studies were representative of UK primary care practice; there were a limited number of lymphoma cases in the studies and no distinction between subtypes of lymphoma(67).

The symptoms identified in the evidence all had positive predictive values < 3% (below recommended referral threshold). Moreover, there are no investigations are available in primary care for suspected lymphoma(67). Thus, despite low PPVs, the agreed appropriate action for patients presenting with signs and symptoms indicative of lymphoma would be a suspected cancer pathway referral(67).

Challenges in diagnosis

Lymphoma patients frequently experience delays in diagnosis.

Compared with many other cancers, the diagnostic pathway for haematological malignancies (including leukaemias, lymphomas, and myeloma) is notably complex, often characterized by prolonged intervals between symptom onset, help-seeking, and diagnosis; repeated primary care consultations prior to referral; and an increased likelihood of diagnosis following an emergency presentation(35).

Complex disease characteristics

As the occurrence of lymphoma is rare, healthcare professionals have a limited experience in dealing with suspected lymphoma cases (68). A full-time GP is likely to diagnose approximately 1 person with NHL every 2-3 years; compared to approximately 1 person with HL during their career(69).

Whereas certain cancers may have specific symptoms that are often associated with the disease and frequently present at diagnosis, such as breast lumps in breast cancer(63), lymphoma typically presents with a wide range of non-specific symptoms(70, 71), according to the type and site of disease, often associated with prevalent benign conditions, commonly initially attributed or 'normalised'(71). Many of the features exhibited in lymphoma patients are low-risk, and do not reach the NICE referral threshold or not included in the NICE referral guidelines(72). Patients may also present asymptomatically and be diagnosed incidentally(71).

There is also an absence of reliable, routine diagnostic tests within primary care for suspected lymphoma patients(68). No single test can diagnose or definitely rule out lymphoma diagnosis(47). It has been suggested that test combinations could have a greater potential to rule-in and rule-out patients for further cancer investigation(73).

Consequence of delayed diagnosis

Delays in diagnosis are associated with advanced-stage lymphoma at diagnosis, reduced disease-free survival, and poor patient-reported outcomes (71, 74, 75). Delay in diagnosis of lymphoma allows the cancer to remain undetected in the body for longer, increasing the opportunity for the cancer to spread around the body to progress to a more advanced stage, associated with poorer survival (74, 76, 77).

The majority of lymphoma patients are diagnosed at an advanced stage (stages 3-4), 44.2% and 51.1% for Hodgkin and Non-Hodgkin lymphoma respectively (25) (68) (England 2021).

Delayed diagnosis of lymphoma may be associated with more intensive treatments with greater adverse effects, including psychological consequences (78), reduced fertility, increased risk of second malignancies (79) and treatment induced cardiomyopathy(66, 74, 80, 81) – lower cure rates.

NHS waiting time targets:

As well as guidelines, targets have also been introduced to promote early diagnosis in the UK(63). The 2 Week Wait (2WW), which aims for people with suspected cancer to see a specialist within 14 days of being urgently referred by their GP or a cancer screening programme, is being replaced by the Faster Diagnosis Standard (FDS) (82) by NHS England.

The 28-day FDS – cancer should be ruled out or a diagnosis received within 28 days. **NHS target**: 75% of people should meet this standard. This is the only standard that has been met as of Jan 2025(83).

Nevertheless, delays in cancer diagnosis continue to be reported. An avoidable delay was found in 24% of cancer cases, with 49% of those occurring during GP assessment – including waiting for test results – 38% after referral to hospital and 13% before the patient saw their GP in England, 2014 (84). For lymphoma, an avoidable diagnostic delay of lymphoma was estimated to occur in 26.3% of patients, (34) NCDA 2014.

A large delay within primary care demonstrates the need to provide GPs with better guidance to help manage suspected cancer patients and reduce diagnostic delay.

Introduction

Rationale of thesis:

GPs must be equipped in managing suspected cancer patients to allow timely and accurate referrals. This thesis aims to provide evidence to improve the current National Institute for Health and Care Excellence (NICE) referral guidelines. The NICE referral guidelines for lymphoma are evidence-based recommendations to help clinicians in England and Wales manage suspected lymphoma patients(72, 85). Referral decisions are based on the estimated risk of lymphoma, which underpin the referral guidelines. The current guidelines are based on limited evidence, and the currently features identified struggle to meet the 3% NICE referral threshold (with the exception of swollen glands) are very low risk for lymphoma(13), thus does not incorporate the broad range of features experienced by lymphoma patients.

To allow timely referrals to secondary care, patients must determine when to seek help and, when they do, practitioners must be able to identify the symptoms of potential malignancy and to carry out appropriate investigative tests. Thus, further research is warranted to identify a broader range of predictive symptoms and tests to assist in referral decisions for further investigation for suspected lymphoma.

Considering the complex disease characteristics of lymphoma, limitations of current NICE guidelines and the significant role and delay (impact) of primary care on the diagnostic pathway, this review hopes to further understanding/awareness of which features may predict lymphoma earlier, to help trigger referral to secondary care services by reaching the NICE cancer referral threshold.

To reduce mortality and long-term consequences of treatment amongst lymphoma sufferers, early diagnosis is important(75, 86). Evidence indicates that lymphoma diagnosis is often delayed. Delayed diagnosis is associated with advanced stage disease and poor survival. Majority of patients are diagnosed at an advanced stage.

Most lymphoma patients present in primary care setting(87), where patients are likely to present at the earliest stages of their disease. The main source of delay in lymphoma occurs during diagnosis: over 40% and 30% of HL and NHL patients respectively consulted their GP three or more times before being referred(88).

This review is warranted, being the first systematic compilation of published literature on the clinical manifestations of lymphoma reported within primary care, with comparisons to healthy patients.

The review will provide evidence-informed description and evaluation of salient predictive symptoms and tests of lymphoma presented in primary care setting, pre-diagnosis to support early diagnosis. The findings will advance knowledge of clinical presentations of lymphoma, potentially guiding a revision of the current guidelines – last revised in 2015. The review aims to help practitioners to recognise and refer patients with signs and symptoms indicative of lymphoma in a timely manner.

Objectives:

The overarching objective in conducting this review is to determine the accuracy of the presenting signs, symptoms and tests of incident lymphoma in primary care with comparison to the general population of health-service users.

To achieve this I report the association and diagnostic value of symptoms and blood tests observed/detected in primary care.

The secondary objective is to determine via subgroup analysis if the association between symptoms and tests and lymphoma varies between lymphoma subtype, age, stage and sex. This could help further risk stratify referral guidelines.

Aging is indicated as a major determinant of lymphoma biology (89). There is a male predominance of lymphoma (18). Symptoms and test trajectories can differ according to disease stage. In most advanced stages of the disease, B symptoms may be present (27).

Subtypes of Lymphoma:

Hodgkin lymphoma (HL) and nonHodgkin lymphoma (NHL) were included as separate outcome as the pathologies, presentations and outcomes are different. NHL is more prevalent than HL(8). Alcohol induced pain is an uncommon (90)symptom of HL, included in the referral guidelines(91).

Clinical role of index test:

The anatomopathological examination, in conjunction with immunocytochemistry and molecular testing of the of lymph node biopsies, supervised by a certified pathologist is the only way to confirm a diagnosis of lymphoma(92), are an invasive, expensive procedure, carried out in secondary care. Selection of primary care patients for referral to secondary care is through minimally invasive tests.

Chapter 2: Methods

The Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) reporting guidelines (93)as well as the guidelines for diagnostic test accuracy studies (PRISMA-DTA) (94) were adhered to in conducting and writing this review. Here, clinical features are taken as the diagnostic (index) test.

Protocol and registration

In accordance with the PRISMA-P guidelines, this review protocol was written and registered with the International Prospective Register of Systematic Reviews (PROSPERO). The protocol can be found via the URL:

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=470986

(Registration number: CRD42023470986)

Eligibility Criteria

The eligibility criteria for studies selected for inclusion in the review were as follows:

Reference standard – lymphoma diagnosis (Outcome):

The reference standard test, a record of confirmed incidental diagnosis of lymphoma (any subtype) was captured. Mortality, prognosis, other disease diagnoses and quality of life were excluded.

Participants:

Inclusion

Studies examining the association between symptoms or tests and a first lymphoma diagnosis of patients presenting to primary care of all ages, genders and ethnicities. Pregnant women were also included. There were no sample size restrictions.

Exclusion

Studies where the population included past or relapsed lymphoma, or defined by other existing diseases (e.g. HIV) or symptoms were excluded as these findings may not be generalizable to the general population. Non-human studies were also excluded.

Study design:

Inclusion

The study designs: cohort, cross sectional, case-control, qualitative and diagnostic accuracy studies.

Exclusion

All other study designs, including randomised controlled trials (RCTs), reviews (including systematic reviews), and case studies/series.

Publication status:

Published literature in scientific journals was included. Unpublished material and specific types of records including commentaries, letters, conference abstracts, editorials, guidelines, clinical opinion pieces, book chapters, websites and all other grey literature were excluded.

Setting:

Studies were selected from the primary care setting only. This is usually the first point of contact for patients, primarily to general practitioners, but can also include emergency care settings.

Populations of patients in secondary or tertiary care, such as referred populations and patients receiving in-patient treatments or survivorship care were excluded. These

populations will have a higher risk of cancer and are not representative of the primary care setting.

Index test – clinical features (exposures):

Inclusion

Studies reporting the following clinical features within primary care, preceding a lymphoma diagnosis, were included: signs, symptomatology and tests.

To ensure the most common lymphoma features were captured, the following terms were incorporated into the search strategy:

Symptoms: (68, 95-99)

- Swollen/enlarged lymph nodes/lymphadenopathy
- Unexplained weight loss
- Night sweats/fever/hot flushes
- Itching/pruritus
- Repeated infections/immunosuppression/weak immunity
- Fatigue/weakness/lethargy

Tests: (47, 96, 97, 100)

- Full blood count
- Erythrocyte sedimentation rate (ESR)
- C-Reactive protein (CRP)
- Plasma viscosity (PV)

Additional features were extracted on a case-by-case basis, subject to what can be observed within primary care. Early manifestations such as Guillain-Barre syndrome (GBS) and markers such as hypercalcemia were included as signs of lymphoma.

If authors were not explicit about whether weight loss was unexpected or expected, we defaulted to classify weight loss as unexpected.

Exclusion

Studies reporting the complications following existing cancer diagnosis or on pre-dispositions or risk factors such as systemic lupus erythematosus (SLE) or hepatitis C were excluded.

Comparators:

Studies were only included if there was a comparator group without a lymphoma diagnosis. These patients were primary care patients, not specific disease cohorts, symptom cohorts or patients with a history of lymphoma.

Timing/Year of dissemination:

All studies reporting on the presenting symptoms and tests within the primary care interval (101) (beginning with date of first presentation and ending with date of referral), prior to lymphoma diagnosis were included. There was no restriction on the publication date.

Language:

There were no language restrictions. Literature published in non-English would not be accessible to the reviewers without linguistic aids, so translators or free online translation software were utilised.

Geography:

There were no geographical restrictions for study inclusion.

Information sources

The following electronic information sources were searched:

MEDLINE via Ovid (from inception, 1946 to 03/07/25), EMBASE via Ovid (from inception, 1947 to 03/07/25) and The Cochrane Database of Systematic Reviews (CDSR), from inception, 1996 to 03/07/2025.

Citation searching was updated to 03/07/25. The references of included studies and relevant excluded systematic reviews were reviewed for additional studies. The reference lists of any newly included studies were also reviewed.

Development process:

The search strategies were developed with the assistance of a librarian (NR) with expertise in systematic review searching. Candidate search terms were identified through developing a PECOS. The titles, abstracts, keywords, MESH terms and subject indexing of relevant literature on lymphoma diagnosis were also utilised.

The search was first developed in Medline (OvidSP) (Figure 8) and adapted to the syntax and subject headings of the other databases as required. The search strategy was validated and peer reviewed by a clinician (BN). The Embase search strategy can be found in Appendix 1. The CDSR search strategy was restricted to Cochrane reviews only.

Search strategy:

The search strategy combined subject headings and title/abstract keywords for the key concepts: Primary care, Lymphoma, Signs, Symptoms and Biomarkers.

Figure 8: Medline search strategy

Database: Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®)

Search Strategy:

1 Primary Health Care/
2 exp General Practice/
3 general practitioners/ or physicians, family/ or physicians, primary care/
4 exp Community Health Nursing/
5 Nurses, Community Health/
6 house calls/ or office visits/
7 Ambulatory Care Facilities/ or Community Health Centers/
8 Community Health Services/ or Community Pharmacy Services/
9 Emergency Service, Hospital/
10 Emergency Medicine/
11 (primary adj2 (health* or care)).ti,ab,kf.
12 (((general or family) adj2 (pract* or doctor* or physician*)) or (gp or gps)).ti,ab,kf.
13 family medicine.ti,ab,kf.
14 ((health* or medical or diagnos*) adj2 (center? or centre?)).ti,ab,kf.
15 ((emergency or urgent care) adj2 (service? or dept? or department? or unit? or ward? or centre? or center?)).ti,ab,kf.
16 (ambulatory adj2 (care or health* or centre? or center? or facilit*)).ti,ab,kf.
17 ((community adj2 nurs*) or health visitor? or district nurs*).ti,ab,kf.
18 (community adj2 (care or health* or service*)).ti,ab,kf.
19 (community adj2 pharmac*).ti,ab,kf.
20 ((home or house) adj (call? or visit?)).ti,ab,kf.
21 (primary care or primary health* or general practi* or family practi* or family medicine or family physician*).jw,in.
22 or/1-21
23 exp Lymphoma/
24 lymphoma*.ti,ab,kf.
25 ((hodgkin* or nonhodgkin) adj disease).ti,ab,kf.
26 lymphoid disease?.ti,ab,kf. not (chronic lymphatic leuk?emia? or cll).ti.
27 or/23-26
28 "signs and symptoms"/
29 (sign? or symptom? or feature? or manifestation? or flag? or alarm?).ti,ab,kf.
30 ((clinical or patient? or initial* or emergenc* or earl* or first or 1st) adj2 (presenting or presentation or contact?)).ab,kf.
31 "presenting with".ab,kf.
32 exp Lymphadenopathy/
33 lymphadenopath*.ti,ab,kf.
34 (((swollen or enlarge*) adj2 (lymph node? or gland?)) or swelling or lumps).ti,ab,kf.
35 fatigue/ or lethargy/ or Muscle Weakness/
36 (tiredness or fatigue or letharg* or exhaust* or weakness).ti,ab,kf.

37 medically unexplained symptoms/
38 weight loss/
39 (weight adj2 (loss or losing)).ti,ab,kf.
40 hot flashes/ or Sweating/
41 (sweat* or fever? or hot flash* or hot flush*).ti,ab,kf.
42 skin manifestations/ or pruritus/ or erythema/ or exanthema/
43 Epistaxis/ or hemorrhage/ or menorrhagia/ or purpura/ or Contusions/
44 (itching or itchiness or pruritus or rash or rashes).ti,ab,kf.
45 (nose bleed* or epistaxis or (heavy adj2 (period? or bleed* or menstru*)) or erythem* or petichia* or blood spot? or bruis* or contusion*).ti,ab,kf.
46 cough/ or dyspnea/
47 (dyspn?ea or ((short* or difficult*) adj2 breath*) or breathless*).ti,ab,kf.
48 Immunocompromised Host/
49 (immunosuppress* or immunocompromis*).ti,ab,kf.
50 ((repeat* or frequen* or unexplained or increas* or recur* or reoccur* or re-occur*) adj3 infection?).ti,ab,kf.
51 Arthralgia/
52 Alcohol Drinking/ and Pain/
53 (((joint or alcohol induced) adj2 pain) or arthralgia).ti,ab,kf.
54 constipation/ or diarrhea/
55 (constipat* or diarrhoea or diarrhea).ti,ab,kf.
56 or/28-55
57 22 and 27 and 56
58 hematologic tests/ or exp blood cell count/ or blood sedimentation/
59 Albumins/an [Analysis]
60 C-Reactive Protein/an, bl [Analysis, Blood]
61 Blood Viscosity/
62 exp Ferritins/an, bl [Analysis, Blood]
63 lactate dehydrogenases/an, bl or l-lactate dehydrogenase/an, bl
64 exp Immunoglobulins/an, bl
65 ((blood or h?ematologic*) adj2 test*).ti,ab,kf.
66 ((blood or leukocyte? or cell or platelet?) adj2 count).ti,ab,kf.
67 (((blood or erythrocyte?) adj sedimentation rate) or esr).ti,ab,kf.
68 (crp or c-reactive protein).ti,ab,kf.
69 albumin?.ti,ab,kf.
70 (ldh or lactae dehydrogenase).ti,ab,kf.
71 ((ferritin? or apoferritin?) adj2 (concentration or blood? or serum?)).ti,ab,kf.
72 ((immunoglobulin? or paraprotien?) adj2 (blood? or serum?)).ti,ab,kf.
73 ((antibody or anti-body) adj (level? or blood? or serum?)).ti,ab,kf.
74 ((blood or plasma) adj viscosity).ti,ab,kf.
75 ("Thymus and activation-regulated chemokine" or tarc or cll-17 or cll17).ti,ab,kf.
76 Biomarkers/
77 biomarker?.ti,ab,kf.
78 ((inflammatory or biological or molecular) adj2 marker?).ti,ab,kf.
79 or/58-78

80 22 and 27 and 79
81 57 or 80
82 exp animals/ not humans.sh.
83 (dogs or cats or mouse or mice or rat or rats or rodent?).ti.
84 82 or 83
85 81 not 84

Selection process:

Literature search results were uploaded to Covidence, which was used to record the study selection process. Duplicate studies were dealt with automatically by Covidence and manually.

The screening process was two-step. At each step, two independent reviewers (TS, CFS, KC, RB) independently and in duplicate screened the studies identified according to the search which satisfied the selection criteria. The first screening step was the title/abstract screening, followed by screening of the retrieved full texts for eligibility. Disagreements during the screening process were resolved through discussion between the reviewers in conflict, with involvement of a senior researcher (CB and BN).

4 principal investigators of studies were contacted to clarify methodological queries or full text. The maximum response time was one month.

Studies without access to full-text or extractable data on clinical features of lymphoma were excluded.

Data collection process:

Two authors independently and in duplicate extracted the data from eligible studies using piloted electronic spreadsheets. Consensus was reached through discussion, to resolve any potential discrepancies with the involvement of a senior researcher (CB and BN). 7 principal

investigators of studies were contacted to request access to unpublished data relevant to this review.

The baseline characteristics extracted per study included: title, authors, year of publication, study design and type, study location, setting, study period, and age range of patients.

Data items:

Outcomes

The primary outcome (reference standard test) extracted, namely a new diagnosis of lymphoma (any subtype), treated as a reference standard test could also be referred to as:

- Hodgkin/Non-Hodgkin disease
- Immunoproliferative disease
- Mycosis fungoides (form of cutaneous T-cell lymphoma)

Incident lymphoma diagnosis was defined using a coded entry from electronic health records (reference standard) - taken from GP records, cancer registry, Hospital Episode Statistics (HES), Office for National Statistics (ONS) records or another source judged to be reliable. Results were classified by subtype of lymphoma, HL, NHL and lymphoma not otherwise specified (NOS).

The stage at diagnosis if provided was recorded to find the association between severity and presenting characteristics. Stage was classified into early stage (I,II) or advanced stage (III,IV).

Patient characteristics:

Data on age, sex, ethnicity were extracted for eligible population – subdivided by lymphoma status were possible.

Clinical features:

Signs, symptoms and investigative tests, treated as index tests observed within primary care were extracted from eligible studies.

The index test was assumed to be the presence of a clinical feature. The index test was taken as binary, classified as abnormal if features were present. For symptoms, index test positivity was defined as the presence of the symptom, whereas for tests, test positivity was whether an abnormal result was detected. Otherwise, tests were defined by the test name, with no clear abnormality specific to lymphoma investigated.

All features were defined using a coded entry in the GP electronic health record.

Missing data

For studies with incomplete reporting of results, the desired statistics were estimated based on 2x2 tables (see below), where possible. If the missing data could not be obtained, the data items were marked “not reported” and assumed to be missing at random. No secondary analyses were applied to missing data.

Measures:

Effect and diagnostic accuracy measures (sensitivity, specificity, positive likelihood ratios (LR+s), negative likelihood ratios (LR-s), diagnostic odds ratios (DORs) and positive predictive values (PPVs) alongside 95% confidence intervals (CIs) and p values were extracted for each clinical feature. These measures were estimated from proportions (raw data) where necessary (and possible).

Effect measures:

Dichotomous measures included: proportions and estimates of effect (risk and odds measurements). To allow comparisons, effect measures such as odds ratios (ORs), risk ratios and risk differences were extracted.

Thresholds for a good test are: odds ratio (OR) > 1 or Hazard ratio (HR) >1 or Risk ratio (RR) > 1 (102)

Continuous measures included: summary statistics (means, medians, standard deviation and inter-quartile range).

Where reported, correlation measures were extracted.

Diagnostic accuracy measures:

Diagnostic accuracy statistics were estimated for binary index tests (where results could be categorised as abnormal or normal) by extracting data to allow the construction of 2 x 2 tables for individual features. Features with multiple thresholds were treated ordinally.

Diagnostic definitions:

To construct the 2 x 2 tables, the four possible outcomes were:

- True positive: a diagnosis of lymphoma with presence of symptom or abnormal test result.
- True negative: no diagnosis of lymphoma with absence of symptom or normal test result.
- False positive: no diagnosis of lymphoma with present of symptom or abnormal test result.
- False negative: a diagnosis of lymphoma with absence of symptom or normal test result.

Diagnostic odds ratios

The DOR measures the discriminative power of a diagnostic test - the ratio of the odds of a positive test result among the diseased to the odds of a positive test result among the non-diseased(103). The DOR is not prevalence dependent(103). It can be expressed in terms of sensitivity and specificity.

DOR = (TP/FN)/(FP/TN) = [sensitivity / (1–sensitivity)] / [(1–specificity) / specificity] (103).

The further the odds ratio is from 1, the more likely it is that those with the disease are exposed when compared with those without the disease (risk factor) (103). A value of 1 means that a test does not discriminate between patients with lymphoma and those without it(103). Values lower than 1 suggest a reduced risk of lymphoma associated with the clinical feature (protection factor) (103).

Thresholds for interpreting DORs were as follows:

- Uninformative test: DOR = 1
- Improper test: < 1
- Useful test: >1

DORs were estimated for all features as not all studies provided reported ORs. For features that had reported adjusted ORs, these were prioritised in the discussion of results over estimated DORs. However, as must reported ORs were adjusted, we did not compare these to estimated DORs.

Sensitivity and specificity

Sensitivity is the proportion of people with a disease who have a clinical feature present(104). A test with a 100% sensitivity will correctly identify all patients with

lymphoma with no false negative results. Specificity is the proportion of people without a disease who do not have a clinical feature present(104). A test with 100% specificity will correctly identify all patients without lymphoma with no false positive results. Thresholds for interpreting sensitivity and specificity are as follows(105):

- 100% perfect test

Estimating positive predictive values:

Positive predictive value is the proportion of patients with a positive test who have the disease of interest – that is the proportion of patients with a clinical feature present who have lymphoma. It is calculated as the prior odds multiplied by positive likelihood ratios (LR+s). As the prior odds of disease (prevalence) increases, so does the PPV (posterior odds).

The UK's NICE suspected cancer guidance is based its recommendations for cancer investigation on clinical situations where the PPV is ≥3%(64, 85).

Only a minority of studies reported PPVs. All studies did not report the prevalence of lymphoma in the included population, and the majority of studies were case-control in design, making it difficult to estimate PPVs. To allow comparisons to be made, PPVs were estimated for all studies via Bayes theorem(106) (Appendix 6) using the most up to date age specific national annual incidence rates from the cancer registration statistics compiled by National Disease Registration Service (NDRS) in England 2020(107). The CancerData dashboard tool allowed age groups to be combined. To capture patients 18+, we used the age group 20-24 as the starting group as the previous group 15-19 incorporated majority ≤18. The estimated PPVs were compared with those reported in studies. To obtain the incidence for lymphoma NOS, we combined HL and NHL incidence rates. Incidence rates

were used instead of prevalence as these are not reported in the existing lymphoma literature.

As all the estimated PPVs were close to 0 or 1, their 95% CIs were calculated using the normal approximation (logit transformation)(108).

Where possible, estimated PPVs were compared alongside reported PPVs for validity.

Likelihood ratios

To determine which clinical features could be used to rule in or rule out lymphoma(109), positive and negative likelihood ratios were extracted. Positive likelihood ratio (LR+) is the ratio between the proportion of those with lymphoma who have a clinical feature present and the proportion of people without lymphoma who have a clinical feature present(104). Negative likelihood ratio (LR-) is the ratio between the proportion of those with lymphoma who do not have a clinical feature present and the proportion of people without lymphoma who do not have a clinical feature present(104).

The discriminatory value of a test (or symptom) is its ability to distinguish the presence of disease from its absence(110). In this review, this the ability of a test abnormality or symptom to identify underlying lymphoma. A diagnostic test has no discriminative value when its likelihood ratio equals one. The higher a LR+, and the lower a LR-, the greater the discriminatory value of the test(110).

Likelihood ratios were estimated using the sensitivity and specificity values for each clinical feature: LR+= sensitivity/(1-specificity) and LR-=(1-sensitivity)/(specificity) (104).

A rule of thumb that will be used to interpret likelihood ratios are as follows: a test with a LR+ ≥ 5 is good for ruling in disease and a test with a LR- ≤ 0.2 is good for ruling our disease

(111, 112). These thresholds have been used in other diagnostic accuracy studies (113, 114) - they are usually considered moderate to strong evidence for ruling in or ruling out the disease.

Likelihood ratios allow for the estimation of the probability that a positive or negative test result reflects to the presence or absence of the disease, given a specified pre-test probability of disease presence(110, 115).

This pre-test probability represents the assumed probability that a given tested individual has the condition, based on the available information prior to the test(110). If an individual's risk of having the condition is not known or suspected to differ from that of other patients in the same population undergoing the diagnostic test, the pretest probability can be approximated by the condition's prevalence within that population(110, 116).

Dumbbell plots were constructed for all features with likelihood ratios by taking the prevalence as the same age-specific national annual incidence rates (2020) used to estimate PPVs as not all studies had extractable prevalences of lymphoma. See further details below.

Synthesis Methods

Preparing for synthesis

Synthesis was carried out by grouping similar clinical features together, under a common term. If multiple thresholds of index test positivity were stated for a given feature across studies, a common optimal threshold was taken within grouping, if possible.

Meta-analysis:

If sufficient papers allowed (at least 2), meta-analysis was conducted - see protocol for planned methods. Bivariate, random effect meta-analysis(117) (taking into account heterogeneity between studies) was carried out separately for studies reporting the same feature and outcome, using restricted maximum likelihood (REML) (118)as the between-study variance estimator and wald-type confidence interval to calculate pooled estimates (119)for adjusted odds ratios(120), sensitivity, specificity(121) and likelihood ratios (121) using the R packages, meta and mada (version 4.3.3). Meta-analysis was not performed if there was high statistical heterogeneity, if $I^2 > 50\%$ (122).

There was little consistency in the reported features across studies. Although many features were reported in more than one study, for example lymphadenopathy and weight loss they could not be meta-analysed as these were reported for different populations (subtypes of lymphoma).

Thus, meta-analysis was only possible for the feature raised platelet count for the outcome HL (2 studies).

Narrative synthesis

A narrative synthesis of the results of all eligible studies was conducted and summarised into descriptive tables.

Tabular presentation:

All descriptive tables were ordered by study identifier.

The **descriptive study characteristics table (Table 5)** for each study tabulated the: aim, setting, data source, patient characteristics, duration, type and definition of clinical features

(index test), definition of lymphoma (reference standard) and subgroups reported; missing data; results and conclusions.

The **descriptive results table (Table 6)** for each study captured: the summary, effect and diagnostic accuracy measures.

The **results table (Table 7)** present the features by the type of feature, ordered by age of study patients and labels the outcome of lymphoma and study design.

Graphical presentation:

Study results are presented graphically by plotting the estimates of reported odds ratios by feature type, sensitivity and specificity by outcome and feature type with 95% CIs in forest plots, ordered by age. In the absence of meta-analysis, plots were presented without the pooled effect estimate.

To further illustrate the ability of a test to either rule in or rule out lymphoma, dumbbell plots were constructed showing pre- and post-test probabilities for the clinical features in every study where LRs were obtained, ordered by age group. For each feature, we plotted the pre-test probability, the prevalence of the outcome of lymphoma examined in the study, (blue dot) - the same age specific national annual incidence rates from the cancer registration statistics compiled by National Disease Registration Service (NDRS) in England 2020 used to estimate PPVs were taken. The probability of having the outcome of lymphoma after testing (post-test probability) then depended on a positive test result (red dot) or a negative test result (green dot).

Exploring variation

To evaluate the differential impacts across studies examining the same feature with variation in statistical results, the following subgroups were explored as most likely sources of heterogeneity: age, sex (male/female), stage (early and advanced stage), subtype of lymphoma, year of publication (time frame), study design, location and risk of bias.

Informal investigation of heterogeneity was carried out by grouping similar features, and through presenting results tables by feature type and by visually inspecting plots ordered by outcome and age. Where meta-analysis was performed, heterogeneity was statistically described using Higgins I^2.

To account for possible overlap in populations between studies, baseline characteristics were examined and effect of potential overlap explored as a source of heterogeneity.

Sensitivity analysis

Sensitivity analysis could not be performed as we did not have sufficient included studies to allow for meaningful evaluation.

Study risk of bias assessment

To assess the methodological quality of the included studies, a risk of bias assessment was performed. Two researchers (from TS, RB, KC) independently and in duplicate applied the risk of bias tools to each study. Any disagreements were resolved through discussion between the two reviewers, with recourse to a third reviewer (CB, BN) where needed. All studies were included in the review regardless of the score. Various tools were considered to find the adequate tool.

The first tool trialled was the Newcastle-Ottawa Scale. The Newcastle-Ottawa Scale a quick and adaptable tool (123), applicable to both case control and cohort studies. It uses a 'star' scale system which covers three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest (123). Studies could score a maximum of four stars for the selection criteria, two stars for the comparability criteria, and three stars for the exposure or outcome criteria, totalling a maximum of nine stars. The Newcastle-Ottawa Scale ranks each domain and the overall a risk of bias as either low bias, high bias, or with some bias concerns (See Appendix 8c)

As this review aimed to also quantify the diagnostic value of the identified features, a second tool, the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) was trialled and subsequently selected to assess the risk of bias. The QUADAS-2 tool comprises four domains: patient selection, index test, reference standard, and flow and timing with each being assessed in terms of the risk of bias and the first three in terms of applicability concerns. Signalling questions are provided to guide the judgement of the risk of bias across the four domains. The tool judges a risk of bias and applicability to be: "low", "high" or "unclear"(124). Guidance on each question can be found in Appendix 8a).

QUADAS-2 assesses the index test by its ability to accurately define the clinical feature. The reference standard (confirmed lymphoma diagnosis in records) was considered to have a low a risk of bias if it included dataset linkage, through Office for National Statistics (ONS), Hospital Episode Statistics (HES) and Cancer Registries, as these would capture diagnoses potentially missing in primary care records(125-127). Patients were judged to have received the same reference standard, even when studies used multiple reference standards (due to

linkage) if the same consistent method was used to identify a lymphoma diagnosis. If not stated, blinding of the results of the index test and reference standard test results were assumed where there were a large number of patients.

To assess the timing between index and reference standard tests, an appropriate follow-up time interval of up to 2 years was selected using the findings of trajectories of clinical features for other blood cancers such as myeloma as a guide, as studies investigating lymphoma are scarce.

If there was insufficient information reported to answer a criterion, then the criterion was judged to be 'unclear'.

Reporting bias assessment

Studies with potential publication bias were identified and informally discussed. We identified studies that did not report all the clinical features investigated and commented on the features that we were aware had been excluded from the final results.

Chapter 3: Results

Literature search

Eligible studies:

The literature search identified 4801 citations. Removal of duplicates resulted in 3924 studies for Title/Abstract Screening. 3806 studies were excluded at Title/Abstract screening, leaving 118 studies for full text screening. Only 116 studies were assessed for full-text screening as full texts could not be retrieved for 2 studies. The main reasons for exclusion of literature at full text screening were due to wrong study design (n = 75), wrong setting (n = 19) and the wrong patient population (n = 8).

7 studies were identified, whose reference lists were manually screening alongside excluded relevant systematic reviews, identifying 1 additional study.

8 eligible studies were captured (Figure 9) according to the screening criteria, 5 case-control studies and 3 cohort studies. These studies are summarised in Table 4.

Figure 9: PRISMA Flow-Diagram

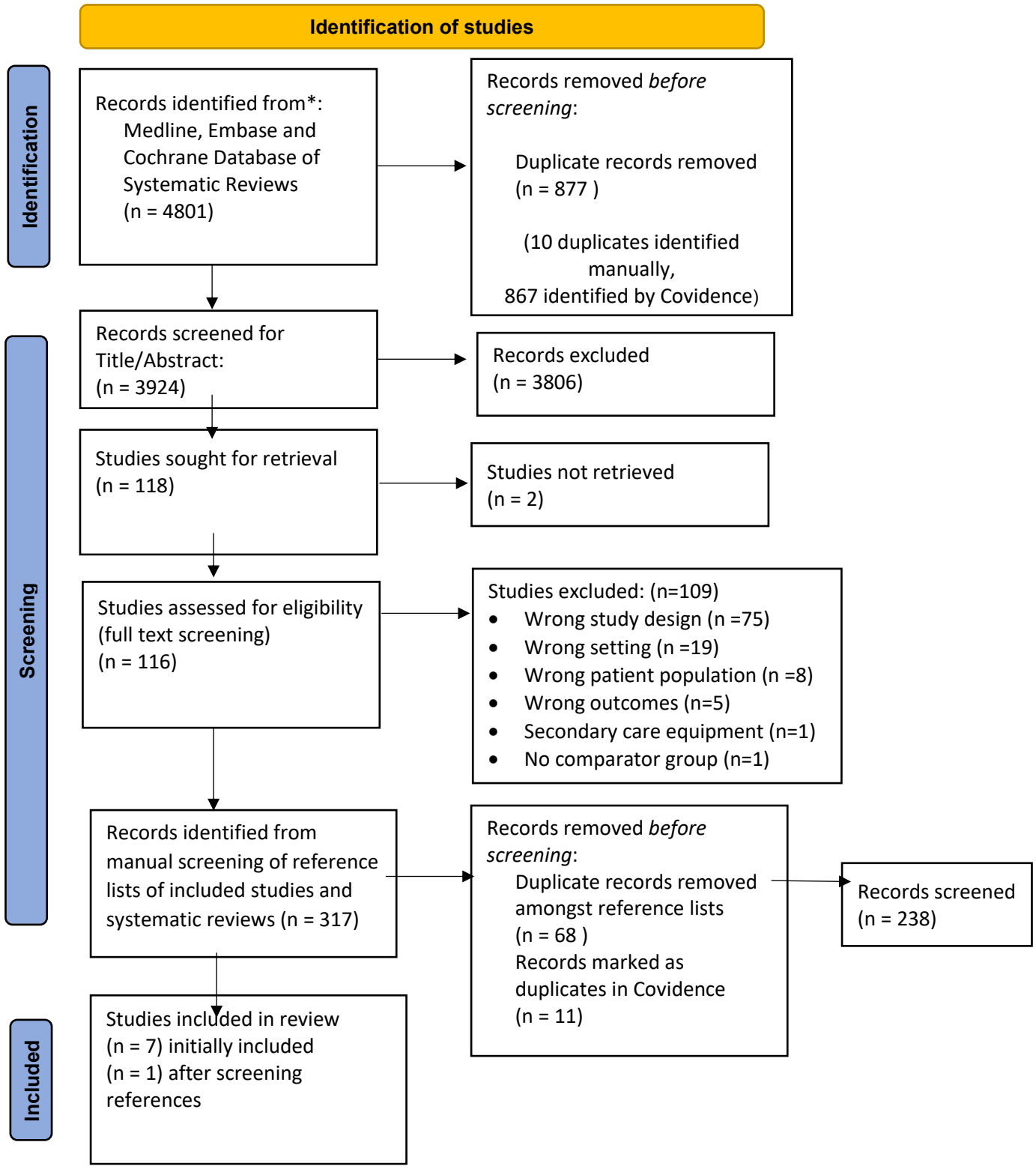


Figure 9 PRISMA flow-chart

Table 4: Baseline Characteristics Table

Study identifier	Study title	Year of publication	Location	Study design	Study type	Follow-up length	Study participants	Lymphoma Outcome focussed:	Study period
Anderson, 2013 (128)	Eosinophilia in routine blood samples and the subsequent risk of haematological malignancies and death	2013	Denmark	Cohort	Prospective design	3 years	Aged 18–80 years with at least one differential cell count (DIFF) in the period	HL and NHL	1st January 2001 to 31st December 2007
Dommett, 2013 (129)	Features of cancer in teenagers and young adults in primary care: a population-based nested case–control study	2013	UK	Nested case control study	Retrospective; and observational	1 year	Patients 15-24 years	Lymphoma NOS	1st January 1988 to 31st December 2010
Fortuny, 2022 (130)	Serum lipid trajectories in the years before a lymphoma diagnosis	2022	UK	Case-control	Observational, retrospective	Between 10.4-11.8 years	Aged ≥40 years	HL and NHL	1st January 2000 to 31st December 2017

Nicholson, 2020 (131)	The association between unexpected weight loss and cancer diagnosis in primary care: a matched cohort analysis of 65,000 presentations	2020	UK	Cohort	Matched, retrospective	2 years	Aged (>18 years)	Lymphoma NOS	1st January 2000 to 31st December 2012
Rafiq, 2022 (132)	Inflammatory marker testing in primary care in the year before Hodgkin lymphoma diagnosis: a UK population-based case–control study in patients aged ≤50 years	2022	UK	Case-control	Retrospective	1 year	Patients aged ≤50 years with linked data from CPRD	HL	1st January 2002 to 31st July 2016
Shephard, 2015a (96)	Quantifying the risk of Hodgkin lymphoma in symptomatic primary care patients aged ≥ 40 years: a case–control	2015	UK	Case-control	Matched, retrospective	1 year	Cases were selected if aged ≥40 years and diagnosed with HL	HL	January 2000 to December 2009

	study using electronic records								
Shephard, 2015b (97)	Quantifying the risk of non-Hodgkin lymphoma in symptomatic primary care patients aged ≥ 40 years: a large case–control study using electronic records	2015	UK	Case-control	Matched, retrospective	1 year	Cases selected if aged ≥40 years, diagnosed with NHL	NHL	January 2000 to December 2009
Watson, 2019 (133)	Predictive value of inflammatory markers for cancer diagnosis in primary care: a prospective cohort study using electronic health records	2019	UK	Cohort	Prospective design	1 year	Aged ≥18, of either sex, who had a primary care inflammatory marker blood test (CRP, ESR or PV) taken in 2014	Lymphoma NOS	2014

Table 4 Publication details of the 8 eligible papers following full-text screening

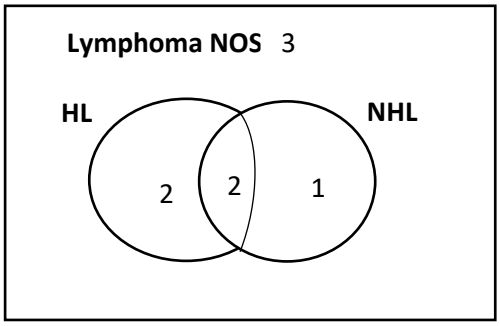
Outcomes:

The target condition in all studies was the first record of (incidental) lymphoma of the following types: lymphoma NOS, HL and NHL (Figure 10).

4/8 (50%) of studies investigated other cancer types, not just lymphoma.

Incident lymphoma diagnosis was defined using a coded entry from electronic health records (reference standard). The reference standard used varied between studies. 7/8 studies included the use of primary care health records; 2/8 studies the use of HES and 3/8 included cancer registries.

Figure 10: Number of studies reporting each category of lymphoma



Study characteristics

The 8 eligible studies were published between 2013 and 2022, with one study conducted in Denmark (128) and the rest in the UK. The sample size of eligible patients ranged between 1,520(96) to 356,196(128).

The longest follow-up (time between diagnosis and data collection) was almost 12 years (130). The most common follow up time was 1 year (n = 4).

6 studies were retrospective; and 2 studies prospective. However, all studies extracted data on clinical features experienced before lymphoma diagnosis from routinely collected patient

electronic health records, either from CRPD (n = 7) or The Copenhagen Primary Care Differential Count database (CopDiff) (n=1). More than half (n = 6) studies linked primary care data records to data sources including HES, ONS and Cancer Registries.

Clinical features

In total, 15 different symptoms and 18 tests (index tests) were reported singularly (Table 6-7). Similar features were grouped to create 16 different categories: lymphadenopathy, head and neck swelling, other lump swellings, weight loss, mild eosinophilia, severe eosinophilia, raised eosinophilia, lowered full blood count (FBC), raised platelet count, raised erythrocyte sedimentation rate (ESR), raised C-reactive protein (CRP), raised plasma viscosity (PV), any raised inflammatory marker test, abnormal liver function tests (LTFs), serum cholesterol (total cholesterol, LDL-C and HDL-C) and triglyceride tests. For example, abnormal LFTs consists of the tests, lowered albumin and raised LFTs (Table 7).

All these features were defined using coded entries in the GP electronic health record.

The prevalence of occurrence of symptoms and test abnormalities amongst lymphoma cases was greater than non-cases (Table 7).

The most frequently cited features were head and neck swellings, lymphadenopathy, other lump swellings, any raised inflammatory marker and serum cholesterol tests.

Selection of clinical features amongst the 8 eligible studies:

Anderson (2013)(128) investigated eosinophilia due to its reported link with lymphoma (134-136)and potential role as an early paraclinical marker of haematological malignancy. However, its predictive value remained unclear, prompting evaluation of its utility in supporting earlier diagnosis.

Dommett (2013) (129)derived clinical features from NICE guideline-defined alert symptoms(137), with inclusion and retention based on predefined frequency (≥2%) and statistical significance thresholds ($P \leq 0.1$ for inclusion; $P < 0.01$ for retention) to identify those most strongly associated with individual cancers, including lymphoma.

Fortuny (2022)(130) investigated serum lipid levels (cholesterol and triglycerides) based on prior evidence linking cholesterol to lymphoid malignancies, including observed declines in cholesterol preceding lymphoma diagnosis(138). To provide further insight into the relationship between lipid levels and lymphoma diagnosis, the study replicated and extended these findings by incorporating triglycerides, examining a longer pre-diagnostic period, and adjusting for additional confounders.

Nicholson (2020) (131)investigated unexpected weight loss as a non-specific symptom commonly seen in primary care that does not point to a specific cancer site(139, 140). Given limited and conflicting evidence (141, 142), the study aimed to clarify its association with cancer and the types of cancers diagnosed.

Rafiq (2022) (132)selected six common inflammatory markers (ESR, CRP, PV, ferritin, albumin, and platelet count) due to reported associations between elevated inflammatory markers and Hodgkin lymphoma(143), with uncertain timing of these changes. The study aimed to examine associations between inflammatory marker testing and results in primary

care and subsequent Hodgkin lymphoma diagnosis, including the timing of pre-diagnostic changes.

Shephard (2015a, 2015b)(143, 144) identified potential clinical features for Hodgkin and non-Hodgkin lymphoma (symptoms, signs, and abnormal investigations) from existing literature and online patient support group data, using searches of PubMed, EBSCO, and Google Scholar to capture known and emerging features. Features occurring in ≥2% of cases were retained, and those meeting predefined statistical thresholds ($P \leq 0.05$ for entry and $P \leq 0.01$ for retention) were carried forward into multivariable models.

Watson (2019) (145)selected ESR, CRP, and PV as commonly used inflammatory markers in primary care, where patients often present with non-specific low-risk symptoms (61, 146, 147), making cancer diagnosis challenging. Reported associations between raised inflammatory markers and lymphoma have been described(143, 144). Given limited evidence on their overall diagnostic utility, the study assessed their predictive value and accuracy for cancer detection.

Table 5: Descriptive Characteristics Table - Study methodology

Study identifier	Rationale	Data Source(s)	Patient Selection criteria	Clinical features (Exposures)	Relevant outcomes	Follow-up length	Model fitted:	Model development
Anderson, 2013(128)	To investigate eosinophilia in routine blood samples as a potential risk marker for the development of haematological malignant disease and death.	The Copenhagen Primary Care Differential Count database (CopDiff) CopDiff linkage to three nationwide registers as of April 2011: i) The Danish Civil	**Inclusion:** Patients identified from the CopDiff database during 2000-2007, aged between 18-80 years. Had at least one **differential cell count** (DIFF) in period 1.1.2001 to 31.12.2007, with one DIFF selected randomly. **Exclusion:**	Eosinophilia, according to: -No (< 0.5 x 10^9/L) -Mild (≥ 0.5–1.0 x 10^9/L) -Severe eosinophilia (≥ 1.0 x 10^9/L) C-reactive protein (CRP) categorised by: -Increased (≥ 10 mg/L) -Normal (< 10 mg/L) -No blood test <u>Previous Eosinophilia</u> Another DIFF made during 6 months before	Incidence of haematological malignancies following the DIFF: Including Hodgkin lymphoma (HL), and Non-Hodgkin lymphoma (NHL). *Identified from DCR*	3-year follow-up period	Multivariable logistic regression model fitted.	The model adjusted for: sex, age (quadratic), year, month, previous cancer, comorbidity, CRP and previous eosinophilia. P-values less than 0.0271 were regarded to be significant to control the false discovery rate at 5%. *To adjust for possible confounding, the Charlson's comorbidity*

		Registration System (CRS) ii) the Danish Cancer Registry (DCR) iii) The Danish National Patient Register (NPR)	Patients with previous cancer (before index DIFF) were omitted.	the request and whether eosinophilia present in this DIFF. Categories: -Only negative DIFF tests -At least one positive test -No blood test *Identified from CopDiff.*				*Index (CCI) was computed using The Danish National Patient Register (NPR) records within 3 years before the index DIFF.*
Dommett, 2013(148)	To investigate the risk of cancer in TYA presenting to primary care with symptoms and/or increased consultation frequency.	The General Practice Research Database (GPRD) records, now known as CPRD Gold.	**Inclusion:** Teenage and young adults (TYA), aged 15-24 from 1 January 1988 to 31 December 2010 with an up-to standard GP practice for at least 1 year before the date	• Lump mass swelling in head and neck • Lymphadenopathy • Lump mass swelling below neck excluding abdomen Libraries of codes used (Dommett et al, 2012, 2013)(149, 150)	Diagnosis of cancers including lymphoma NOS *Cancers identified from predefined malignancy medical codes in GPRD.*	3 months before diagnosis.	For each cancer type: Conditional logistic regression	Only variables occurring in ≥2% of either cases or controls and with a uni-variable p value ≤ 0.1, entered the multivariable analysis. Retention in final multivariable logistic

			of cancer diagnosis (index date). Up to 13 controls, never diagnosed with cancer were randomly selected per case, matched on age (within 1 year), sex, and practice (registered on index date of case).	*Identified from GPRD*				regression model was carried out using p value of < 0.01.
Fortuny, 2022(130)	To describe the trajectories of serum lipid in the years before a diagnosis of lymphoma, providing further insight into the	CPRD General Practitioner Online Database **(GOLD)** records and Hospital Episode	**Inclusion:** <u>Base population:</u> Patients in CPRD who had at least one 'valid' cholesterol measurement during the study period, 1 January 2000 to 31 December 2017.	Lipid measurements: •Total serum cholesterol [TSc] • Low-density lipoprotein cholesterol [LDLc] • High-density lipoprotein cholesterol [HDLc]	Diagnosis of lymphoma, categorized into: Classical Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL)	The average follow-back period for each lipid measurement amongst cases and	Random-intercept multilevel multivariate linear regression models	To estimate the values of cholesterol and triglycerides at each test in years before lymphoma diagnosis, the dependent variables were: i) time to index date ii) case-control status

	relationship between lipid levels and lymphoma diagnosis.	Statistics (HES) records.	No evidence of another cancer diagnosis (except non-melanoma skin cancer), HIV infection or organ transplant before or on the index date. <u>Cases:</u> Aged ≥40 years at the date of first lymphoma diagnosis (index date). <u>Controls:</u> Up to 5 controls per case were randomly selected, matched on practice, sex, calendar year at	•Triglycerides **Abnormal cholesterol** (TSc, LDLc and HDLc) levels were defined as follows: TSC > 240 mg/dL LDLc > 160 mg/dL HDLc < 45 mg/dL **High triglyceride levels** defined as: triglycerides >200mg/L *Identified using CPRD GOLD.*	Unspecified lymphoma cases were analysed separately. *Identified using CPRD GOLD and HES data.*	controls ranged between 10-12 years.		iii) time-varying potential confounders measured at each test (including age, hypertension, T-cell and B-cell activating diseases) vi) time-invariant variables measured at index date (including family history of cancer, index of multiple deprivations (IMD), and year of the index date). Best fit was assessed through log-likelihood ratio tests. The relationship between time and TSc,

			index date, and age at index date. **Exclusion:** If all matched controls selected for a case were non-eligible, the case was dropped from analyses.					HLDc, LDLc and triglycerides were modelled as a quartic polynomial with interaction with case-control status.
Nicholson, 2020(131)	To examine the association between unexpected weight loss (UWL) and a diagnosis of cancer and whether any association varies over time, for all	CPRD records, Office for National Statistics (ONS), Index of Multiple Deprivation (IMD) and Cancer registries.	**Inclusion criteria** <u>Entry into cohort:</u> NHS patients from England and Wales aged > 18 years registered with an up-to standard GP practice with acceptable CPRD records with eligibility for linkage to cancer registry,	UWL *Identified from CPRD, using codes from a previously conducted internal validation study(151).*	First cancer diagnosis following index date. ➔ Including lymphoma NOS. *Identified using CPRD and cancer registry data. The first cancer code following the index date was used to define cancer type.*	Records examined for a diagnosis of cancer for 2 years after the index date.	Univariable and multivariable Cox models fitted.	Cox models fitted for cancer for each 3-month and 6-month period of follow-up using CPRD data between 2000 to 2014 Potential confounders taken before index date adjusted for included: gender, age, IMD, BMI, smoking,

	cancers combined and separately by cancer site and stage.		ONS and IMD data between 1 January 2000 and 31 December 2012. Patients identified through first weight loss code. UWL patients were matched to those without UWL 1:5 by age, gender, GP practice and consulting within 3 months. **Exclusion criteria:** Patients with previous cancer, recent weight loss intervention in previous 6 months					alcohol status, comorbidity related to weight loss and family history of cancer.

			(for example weight loss medication or bariatric surgery) and < 1 year registration. <u>Exit from cohort:</u> Earliest date of: first cancer diagnosis (any site), death, transfer out of CPRD, or 2 years following entry. If a patient with UWL was excluded, their matched comparators were excluded.					
Rafiq, 2022(132)	To examine associations between	CPRD records and linked data	<u>Eligible:</u> Patients aged ≤50 years actively	• Erythrocyte sedimentation rate (ESR), mm/h	1. Diagnosis of HL 2. Co-occurrence of inflammatory	1 year follow-back	Conditional logistic regression	**Conditional logistic regression conducted** to compare baseline

	primary care inflammatory marker blood test use/findings and subsequent Hodgkin lymphoma (HL) diagnosis, and timing of changes in inflammatory markers pre-diagnosis.	from Hospital Episode Statistics (HES) and Index of Multiple Deprivation (IMD).	registered with a CPRD practice for more than a year with 'up-to-standard' data during the study period, 1 January 2002 and 31 July 2016. **Cases:** The earliest recorded date of lymphoma diagnosis taken as the index date (ranging between January 2003 and 31 July 2016). **Controls:** Six controls were randomly matched to each patient in	• C-reactive protein (CRP). mg/l • Plasma viscosity (PV), mPa/s • Platelet count, x 10^9 / l • Ferritin concentration, ug/l Abnormalities: raised levels. • Albumin, g / l Abnormality: decreased levels of albumin. *Identified using CPRD.*	marker test result with red flag symptoms (lymphadenopathy/ lumps, night sweats and weight loss) by test timing: early (3-12 months before diagnosis) or late (<3 months before diagnosis) *CPRD and HES data used for identification of HL*.	from index date.		characteristics (sex, year of index date, IMD quintile and region) of study population and examine associations between both inflammatory marker test use (any test versus none) and abnormal results (any versus none) with HL diagnosis in the following year. These analyses were carried out separately for individual and combined inflammatory markers.

			the case group based on sex and age at index date (plus or minus 1 year of age). **Exclusion:** Patients were excluded if they had a previous diagnosis of HL, or if the diagnosis was made within 1 year of practice registration.					
Shephard, 2015a(96)	To identify and quantify the early clinical features (symptoms, signs, and abnormal investigations) of Hodgkin	CPRD electronic health records	**Inclusion:** Cases: aged ≥ 40 years and diagnosed with HL between January 2000 and December 2009. Up to 5 controls were matched by	• Lymphadenopathy (incorporating generalised lymphadenopathy and lymphadenopathy with no site mentioned)	Diagnosis of HL. *Identified using CPRD.*	1 year follow-back	Univariable and multivariable conditional logistic regression.	Non-parametric methods were used as the data was not normally distributed. 43 symptoms and 22 abnormal test results were considered as features to

	lymphoma (HL) in primary care, with the aim of expediting selection of patients for definitive investigation.		age, sex, practice and index date (their cases' diagnosis date). For analysis purposes, one control was added to lymphadenopathy and head and neck mass. **Exclusion:** • Cases and their matched controls with non-Hodgkin lymphoma (NHL), mycosis fungoides, or Sezary syndrome. • Case or control with < 1 year of	• Head and neck mass (incorporating cervical lymphadenopathy) • 'Other' Mass/Lump (present elsewhere in the body) • Raised inflammatory markers (any of abnormal Erythrocyte sedimentation rate, Plasma viscosity, or C-reactive protein) • Low full blood count (any of: low haemoglobin, low white cell count, or low platelets)				incorporate in model fitting All features present in at least 2% of either cases of controls were used. P-value thresholds and likelihood ratio tests were used for variable selection. Those features associated with HL at $p \leq 0.1$ were grouped into small clinically coherent groups (such as back pain and chest pain) for multivariable analysis.

			records before index date • Cases without controls • Controls with HL • Controls not sought medical care after registration (non-consulter).	• Raised platelet count (Thrombocytosis) • Abnormal liver function tests (a raised value of any of the hepatic enzymes) <u>Abnormality in test results</u>: falls outside the patient's local laboratory's normal range. <u>Normal test results:</u> grouped with untested patients. *Identified using CPRD.*				Features entered the final stage of modelling with association at p ≤0.05. Retention into final model for those variables with a p value threshold of 0.01. Omitted variables were checked against final model and restored if a likelihood ratio test comparing the models had p ≤ 0.01. Clinically plausible interaction terms were added to final

								model and retained if p value ≤ 0.01.
Shephard, 2015b(97)	To identify and quantify the clinical features of NHL in primary care, to guide GPs when to consider referral for investigation, and to inform health policy regarding referral and investigation pathways.	CPRD records	**Inclusion:** Cases: aged ≥ 40 years and diagnosed with NHL between January 2000 and December 2009. Up to 5 controls were matched by age, sex, practice and index date (their cases' diagnosis date). **Exclusion:** • Cases and their matched controls with Hodgkin	**Symptoms:** • Infection (UTI/URTI/Skin/ Chest) • Lymphadenopathy (incorporating generalised lymphadenopathy and lymphadenopathy with no site mentioned) • Abdominal pain • Mass (present elsewhere in the body) • Shortness of breath • Head and neck mass (incorporating	Diagnosis of NHL *Identified using CPRD.*	1 year follow-back (before diagnosis):	Univariable and multivariable conditional logistic regression models.	43 symptoms and 22 abnormal investigation results were considered as features to incorporate in model fitting. Only those features present in at least 2% of cases retained. Those features associated with HL at p ≤0.1 were grouped into small clinically coherent groups (such as malaise and nausea) for multivariable analyses.

			lymphoma (HL), mycosis fungoides, or Sezary syndrome • Case or control with < 1 year of records before index date • Cases without controls • Controls with non-Hodgkin lymphoma (NHL) • Controls not sought medical care after registration (non-consulter)	cervical lymphadenopathy) • Fatigue • Constipation • Vomiting and nausea • Indigestion • Weight loss • Back pain: second occurrence • Malaise **Investigations:** • Low full blood count (any of low haemoglobin, low white cell count, or thrombocytopenia) • Raised inflammatory markers (a composite of any of abnormal				Retention in multivariate analysis was for those variables with a p value threshold of ≤0.05 and entered the final modelling stage. The final model used a p-value threshold of 0.01. Omitted variables were checked against final model and restored if a likelihood ratio test comparing the models had p ≤0.01 Clinically plausible interaction terms

				Erythrocyte sedimentation rate, Plasma viscosity, or C-reactive protein) • Raised liver function tests (reflected a raised value of any of the hepatic enzymes reported by each laboratory) • Leucocytosis • Microcytosis • Raised gamma globulin Abnormal investigation results: test value outside the patient's local laboratory's normal range.				were added to the final model and retained if p value ≤0.01.

				Normal laboratory results: grouped with untested patients. *Identified using CPRD.*				
Watson, 2019(145)	To measure the overall clinical utility of inflammatory markers (ESR, CRP and PV) for cancer diagnosis in primary care: determining the diagnostic accuracy of inflammatory markers.	CPRD linked with Cancer Registry data. Linked data from the English Cancer Registry was able to be obtained from CPRD for 110,245 patients.	**Inclusion:** Patients (n=160,000) aged ≥18, of either sex, who had a primary care inflammatory marker blood test (CRP, ESR or PV) taken in 2014, randomly selected from CPRD. Index date: the first date of inflammatory marker blood testing in 2014; controls were allocated the	Three inflammatory marker tests: CRP, ESR and PV. The mean upper limit of normal from laboratories within the study defined a raised inflammatory marker. • CRP mean was 6.8mg/l, giving a threshold of 7mg/l. • PV the upper limit of normal was 1.72mPa.s. • ESR, above mean upper limit of normal, stratified by	1. Primary outcome: one-year cancer (including lymphoma NOS) incidence for patients with raised vs. normal inflammatory markers, and vs. untested patients. For those with raised inflammatory markers, this is equivalent to the PPV.	1 year follow-up period.	Logistic regression model	Logistic regression to examine the dose-response relationship between CRP, ESR and PV test results as continuous variables, and cancer diagnosis as a binary variable. Generating diagnostic odds ratios (DOR), which were adjusted for age and gender. Several sensitivity analyses in subgroups were performed; excluding those with <1 year follow-up in

			same index date as their matched case. A comparison sample of 40,000 patients with no inflammatory markers taken (untested) during 2014 was matched by age (within 5-year bands), sex and practice to a random subset of 40,000 patients from the inflammatory marker test group. **Exclusion:** Pre-existing cancer (in 2-year period	gender/age, which varied from 11mm/h for women under 40, to 23mm/h for men over 80. For patients with more than one type of inflammatory marker on the same day a binary variable was generated for **'any raised inflammatory marker'**, which was positive if any of CRP, PV or ESR were raised. *Identified using CPRD.*	Also examined two-year incidence. *Identified using CPRD CPRD or the cancer registry, with the earliest record of cancer assigned as the date of diagnosis.* 2. To identify the main symptoms associated with inflammatory marker testing in the 28 days prior to and including the index date. Cancer incidence in patients with normal and raised			CPRD (for example patients moving practice), excluding those with pre-existing autoimmune disease and recent infections (who might be expected to have tests for monitoring purposes) and excluding those with myeloma (as this is already known to have a strong association with raised inflammatory markers).

			before the index date). Only for tested cohort - Missing index test results Spurious test results		inflammatory markers with these symptoms calculated.			

Table 6: Descriptive Characteristics Table - Statistics reported, baseline characteristics, results and conclusions

Study identifier	Relevant statistics reported	Baseline Characteristics	Eligible patients	*Relevant* results[a]	Conclusions[a]
Anderson, 2013(128)	Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and p values for 3-year incidence for lymphoma following index differential cell count (DIFF).	Male = 180,578 (50.2 %) Female = 179,372 (49.8%) A balanced sex-distribution and a mean age of 48.3 years **Eosinophilia:** No: 341,790 (96.0%) Mild: 13,118 (3.7%) Severe 1,288 (0.3%)	356196 patients	In the subsequent 3-year period, 956 patients developed a haematological malignancy, of which 71 exhibited eosinophilia in the index differential count. **Incident lymphoma cases:** 39 exhibited eosinophilia Amongst 82 Hodgkin lymphoma (HL) cases; 5 mild eosinophilia and 3 severe eosinophilia. Amongst 555 non-Hodgkin lymphoma (NHL) cases; 28 mild eosinophilia and 3 severe eosinophilia. ORs for developing HL was significantly increased in patients exhibiting severe eosinophilia, 9.09 (2.77,29.84, P =	The results confirm that there is an association between blood eosinophilia and HL. Only patients demonstrating severe eosinophilia are at risk, indicating the existence of a specific reaction where pronounced eosinophilia is produced by signalling during the development of HL. Unexplained eosinophilia should prompt clinicians to consider conditions where early diagnosis may improve prognosis.

				0.0003), but not in cases with mild eosinophilia, 1.71 (0.68,4.27), p = 0.25. No association was found with NHL. ORs and p values were 1.29 (0.88,1.90), p = 0.17 and 1.23 (0.39,3.86), p = 0.72 for mild and severe eosinophilia respectively.	
Dommett, 2013(148)	Adjusted odds ratios (ORs), likelihood ratios (LRs), positive predictive values (PPVs) with 95% confidence intervals (CIs) for multivariable analysis of features of lymphoma NOS and diagnosis. PPVs calculated using national incidence figures from 2007.	In 12 months before diagnosis, cancer cases had a median of 5 consultations (IQR: 3-9) compared with two (IQR: 0-4) in controls. In the 3 months before diagnosis, 64.81% of lymphoma patients had 3 or more consultations compared to 8.73% controls.	14270 patients: 1064 cancer cases matched to 13206 controls **For lymphoma**: Cases = 270 (25.38%) Matched Controls = 3350 (25.37%)	Four features remained in the final lymphoma model. **Positive Predictive values:** Lump/mass/swelling of the head and neck had the highest PPV of 50.34 per 10 000 (6.96,367.86). The second highest PPV was for lymphadenopathy (27.75 per 10000, (10.26,75.44) followed by lump mass swelling below neck excluding abdomen (2.79 per 10000, (1.52, 5.15).	TYAs with **lymphoma** consulted more frequently than controls in the 3 months before diagnosis. Primary care features of cancer match secondary care reports, but were of very low risk; nonetheless, some features increased the likelihood of cancer substantially and should be seriously taken when assessing TYA.

				Head and neck swelling, lymphadenopathy and lump mass swelling below neck excluding abdomen combined gives PPV of 9.03 per 10 000 (5.73,14.25). **LRs and ORs with 95% CIs:** • Head/neck mass: LR = 434 (60, 3158), and OR = 71.85 (8.98,575.07) • Lymphadenopathy: LR = 238.84 (88.09,647.59) and OR = 184.46 (40.65,837.06) • Lump mass swelling: LR = 23.99 (13.02,44.19) and OR = 14.08 (5.33,37.19) • 3 or more consultations: LR = 7.39 (6.42,8.50) and OR = 7.67 (4.92,11.95).	
Fortuny, 2022(130)	<u>Summary statistics:</u> Mean test result and number of abnormal cholesterol and triglyceride levels per patient per test.	**NHL:** Median age at index date: 70-72 years Female: 40.6%-45%	81784 patients: 11,969 NHL patients 473 HL patients	<u>Cholesterol vs triglyceride measurements:</u> Mean cholesterol levels (Total serum cholesterol [TSc], low-density lipoprotein cholesterol [LDLc], high-density	A decrease in the levels of serum cholesterol in the years before a diagnosis of lymphoma, not seen in a group of non-cancer controls was shown.

	Adjusted trajectory levels of the studied lipids amongst cases and controls plotted per test over time with 95% confidence intervals (CIs) separately by type of lymphoma, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).	**HL:** Median age at index date: 63-69 years Female: 32.9%-42.4% For each type of cholesterol measurement, demographic (e.g. age, ethnicity and IMD), lifestyle variables (e.g. alcohol consumption and smoking history), and comorbidities had similar distributions among cases and controls, both for NHL and HL. *The number of cholesterol measurements was similar between cases*	68,099 matched controls 1243 unspecified lymphoma cases	lipoprotein cholesterol [HDLc]) in the years before the index date showed a more pronounced decrease in the 4 years before lymphoma diagnosis than in controls. The decrease in mean cholesterol levels were more marked for HL than NHL. Triglyceride levels were unrelated to case status – they did not show a decrease amongst cases or controls in the years before index date. No association of triglyceride levels and risk of lymphoma was observed. The unspecified lymphoma cases provided similar results to known NHL cases. **Weight:** Consistent downward trajectory for both weight and lipids starting about 4 years	No decrease in triglycerides serum levels was seen. Overall, the lower levels of cholesterol among lymphoma cases compared to non-lymphoma controls were seen to exist up to 12 years before diagnosis, and this pattern was observed for TSc, LDLc, and HDLc. At about 14–15 years before diagnosis, cholesterol trajectories appeared to be similar between cases and controls. No major differences were seen by subtype of lymphoma. There is a potential role of cholesterol as a biomarker for lymphoma development in the years prior to its diagnosis.

		and controls for both NHL and HL patients.		before diagnosis of lymphoma for cases; this decrease not found amongst the controls.	
Nicholson, 2020 (131)	Hazard ratios (HRs) for each 6-month period of follow-up: Adjusted or cumulative. Adjusted risk ratios for lymphoma in patients with unexpected weight loss (UWL) in men and women in the 6 months following presentation.	63,973 patients in cohort with <u>at least one record of UWL</u> in eligible population (19.36%) Mean age (years) = 58.66 (SD 20.98) Male = 41.83% Female = 58.17% 266,471 <u>without UWL</u> (80.64%) Mean age (years) = 59.01 (SD 20.56) Male = 42.5% Female = 57.5% **<u>Lymphoma cases</u>**: 407 cases (0.12% of cancer cases); 94 with	330,444 patients	<u>Summary:</u> 63,973 patients had UWL recorded, of whom 1375 (2.2%) were diagnosed with cancer within 2 years. Lymphoma is amongst the commonest cancers (those associated with increased likelihood). **407 lymphoma cases** of whom: 94 with UWL; 0.15% of UWL patients (days-to diagnosis: mean 146; median 80) Expressed as the cumulative hazard of lymphoma, 0.08% of patients with UWL and 0.02% without UWL had been diagnosed with lymphoma in the first three months after the index consultation, a difference that remains constant over time, 0.12% and 0.06% by 9	UWL was associated with an increased risk of lymphoma compared with controls. Patients with a record of UWL are at increased risk within the **next 3 and 6 months of lymphoma**. Men with UWL had a higher likelihood of being diagnosed with lymphoma compared to comparators within 3- and 6-months periods than women. After the initial 12-month period, the risk of a lymphoma diagnosis for patients with UWL became similar to those patients without UWL.

		UWL and 313 without UWL. Amongst 94 UWL patients: Men = 55 Women = 39		months and then to 0.13% and 0.08% by 12 months. By 18 months the difference narrows to, 0.14% and 0.11%, and by 24 months it is almost equivalent, 0.15% and 0.14%. **In 6 months following presentation with UWL, adjusted risk ratios for lymphoma**: Men: 4.7 (2.9,7.6), p <0.001 Women: 2.5 (1.4,4.2), p =0.001 **Adjusted hazard ratios:** In the first 3 months men with UWL had more than a 6-fold likelihood of being diagnosed with lymphoma compared to comparators (HR 6.69 (3.82,11.73)) in the Cox models, whereas for women it was less (3.21 (1.75,5.88)). Similar differences between sexes were seen across the first 6 months, but with smaller HRs. *-Men have higher adjusted HRs and adjusted RRs compared to women.*	Future analyses must establish the role of risk factors and accompanying symptoms, signs and simple primary care tests to safely select patients with UWL for further intensive investigation.

Rafiq, 2022(132)	Odds ratios (ORs), 95% confidence intervals (CIs) and p values calculated for combined and individual inflammatory markers for abnormal results (any versus none).	453 (54.0%) male Hodgkin lymphoma (HL) patients; matched controls 2719 (54.0%) males **Tested in last year n(%)** •Platelet: HL = 578 (68.9); Controls = 742 (14.7) •Albumin: HL = 452 (53.9); Controls = 542 (10.8) •Erythrocyte Sedimentation Rate (ESR): HL = 361 (43.0); Controls = 213 (4.2) •C-reactive protein (CRP): HL = 320 (38.1); Controls = 191 (3.8)	5874 patients: (839 HL patients; 5035 matched controls)	<u>Summary:</u> Among tested patients, inflammatory markers were more often abnormal in the year preceding diagnosis or index date in patients with HL (69.5%, 413/594) compared with controls (17.9%, 146/816) (P<0.001). **Abnormal results for HL and controls n(%) and ORs with 95% CIs and p values**: • Platelet: HL = 198 (34.3), Controls 59 (8.0), 8.07 (5.02 to 12.99), p <0.001 • Albumin: HL = 95 (21.0), Controls = 36 (6.6), 3.16 (1.79 to 5.59), p <0.001 • ESR: HL = 266 (73.7), Controls = 78 (36.6), 6.37 (2.85 to 14.27), p <0.001 • CRP: HL = 217 (67.8), Controls = 32 (16.8), 50.0 (6.9 to 364.2), p <0.001	Increases in abnormal results occur in many patients with HL several months pre-diagnosis, suggesting that a diagnostic time window of appreciable length exists in many patients with HL, many of whom have no other red-flag features. In the year preceding diagnosis: The mean levels of HL cases were greater than controls for platelet, ESR, CRP, PV and ferritin. But, the mean levels of HL cases were lower than controls for albumin. All abnormal inflammatory marker tests are found to be significantly positively associated with a diagnosis of HL except for Ferritin. An inflammatory response also occurs in patients with HL with non-specific

		•Plasma viscosity (PV): HL = 51 (6.1); Controls = 28 (0.6) •Ferritin: HL = 113 (13.5); Controls = 160 (3.2) •Any inflammatory marker test: HL patients = 594 (70.8%) Controls = 816 (16.2%)		• PV: HL = 39 (76.5) and controls = 10 (35.7) • Ferritin: HL = 30 (26.5), Controls = 5 (3.1), 3.00 (0.31 to 28.84), p= 0.34 **Mean(SD) of result values for HL and controls:** • Platelet: 354.2 (143.2); 267.6 (74.8) • Albumin: 39.8 (6.0); 43.3 (4.5) • ESR: 39.0 (32.0); 11.4 (13.0) • CRP: 49.9 (57.7) 7.9 (16.9) • PV: 1.9 (0.2) 1.7 (0.1) • Ferritin: 230.5 (296.4); 64.9 (95.4) **Red-flag features:** Close to half of all patients with HL with an abnormal result had no other 'red-flag' features recorded (see Appendix 2).	symptoms. Abnormal inflammatory marker levels can represent early detectable signs of HL in this group.

Shephard, 2015a(96)	Likelihood ratios (LRs) and adjusted odds ratios (ORs) reported with corresponding 95% confidence intervals (CIs) from multivariable analysis. Risk estimates calculated as positive predictive values (PPVs), ≥ 40 years and 60 years, for individual and combined clinical features for consulting patients. à Using the age-specific national incidence of Hodgkin lymphoma (HL) for 2008.	<u>Cases:</u> [Inter-quartile range, IQR] **Male:** n = 158; **Female:** n= 125 **Overall:** n = 283; Median age at diagnosis = 63 [55-72] Median no. of consultations = 15[9-24] <u>Controls:</u> [IQR] **Male:** n = 657; **Female:** n = 580 **Overall:** n = 1237; Median age at diagnosis = 64 [56-73] Median no. of consultations = 7 [3-13] Cases consulted significantly more frequently than controls	1520 patients: (283 HL; 1237 controls)	**Final model** 6 features remained significant, which were independently associated with HL, with **ORs**: • Lymphadenopathy = 280(25,3100) • Head and neck mass = 260 (21, 3200) • Other mass = 2 (4.4,35) • Thrombocytosis = 6.0 (2.6,14) • Raised inflammatory markers = 5.2 (3.0, 9.0) • Low full blood count (FBC) = 2.8 (1.6, 4.8). The **highest LRs** were for lymphadenopathy, head and neck mass and thrombocytosis: 223(31,1606), 131(18,958) and 14(8.2,24). **PPVs (aged ≥60 years):** • Lymphadenopathy, head and neck mass and other mass had PPV of 5.6%, 2.3% and 0.03% respectively for HL.	Three symptoms and three abnormal investigations were associated with HL. The main finding is the importance of lymphadenopathy and head and neck masses. Results are consistent with secondary care findings; lymphadenopathy is the clinical feature with the highest risk of HL in primary care and warrants urgent investigation. No association found with B symptoms may reflect the relatively small sample size or exclusion of younger patients. Predictive risk of features tends to increase with age – comparing PPVs for ≥40 years to ≥60 years.

		in the year before diagnosis		• Lymphadenopathy combined with a low FBC or raised inflammatory markers produced PPVs of 2.5% and 2.2%, respectively. • Thrombocytosis as a single feature produced a small PPV of 0.04% (0.02%, 0.07%). Appendix 3 shows the **PPVs for single and paired features for patients aged ≥40 years**: • Lymphadenopathy, head and neck mass, other mass and thrombocytosis had PPV of 0.7%, 0.4%, 0.02% (0.01, 0.04%) and 0.05% (0.03, 0.08%) respectively for HL. • Low FBC and raised inflammatory markers have PPVs of 0.02%. • Lymphadenopathy combined with low FBC or raised	Results combined with associated non-Hodgkin lymphoma (NHL) show that lymphadenopathy and head and neck masses are strong predictors of both HL and NHL in adults aged ≥ 60 years, warranting further investigation, particularly if present for ≥ 6 weeks. No blood test or other symptoms change this.

				inflammatory markers produced PPVs of 2.5% and 2.8%.	
Shephard, 2015b(97)	Likelihood ratios (LRs) and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) reported for patients aged ≥ 40 years. Positive predictive values (PPVs) reported for consulting patients only, aged ≥ 60 years. The age specific national incidence of non-Hodgkin lymphoma (NHL) for 2008 was used to help estimate the PPVs. PPVs were not calculated if <5 cases had the feature. Where <10 cases or controls had the combined	Cases: [Inter-quartile range, IQR] **Male:** n = 2300; **Female**: n= 2062 **Overall:** n = 4362; Median age at diagnosis = 70[61-78];Median no. of consultations = 16[10-24] Controls: [IQR] **Male:** n = 9932; **Female**: n = 9536 **Overall:** n = 19468; Median age at diagnosis = 71[61-78];Median no. of consultations = 8[4-14] Cases consulted significantly more	23830 patients (4362 NHL; 19468 controls)	**Final model**: Twenty features (13 symptoms and 7 abnormal investigations) remained significant and were independently associated with NHL. The five **highest risk** symptoms were lymphadenopathy, ORs 263 (133,519), head and neck mass ORs 49 (32, 74), other mass ORs 12 (10, 16), weight loss ORs 3.2 (2.3, 4.4), and abdominal pain ORs 2.5 (2.1, 2.9). Recording bias was minimal – the proportion of patients with varicose veins did not differ between cases and controls (p =0.68). The **highest LRs** were for lymphadenopathy, head and neck mass	Unexplained lymphadenopathy in patients aged ≥60 years produces a very high risk of NHL in primary care. These patients warrant urgent investigation, potentially sooner than 6 weeks from initial presentation if the GP is particularly concerned. No blood test or other symptoms change this. Masses elsewhere in the body also had high PPVs but were lower than lymphadenopathy. This remained the case, even when combined with abnormal blood test results or symptoms. Weight loss was the only other symptom to have a moderately high PPV, yet this was only when additional features were present, such as recurrent back pain, or with abnormalities in blood tests.

	features, CIs were omitted for PPVs.	frequently than controls in the year before diagnosis.		and weight loss – 217(125,375), 44(31,62) and 6.4(5.0,8.1) respectively. **PPVs:** <u>Appendix 4 shows the PPVs for single and paired features for patients aged ≥60 years</u> • Lymphadenopathy, PPV = 13% for NHL • <u>All three mass variables produced risk estimates of between 0.6% and over 10% when combined with other symptoms</u> • The PPV for two mass codes at least 42 days apart was 6.4% (3.1%, 13%). • Weight loss in conjunction with repeated back pain or raised gamma globulin had PPVs >2%. <u>Patients aged 40–59 years</u> • Lymphadenopathy, head and neck mass, and masses elsewhere were	

				3.7% (1.4%, 10%), 3.7% (0.9%, 14%), and 0.1% (0.1%, 0.2%), respectively. • The PPV for two mass codes at least 42 days apart was 1.8% (0.6%, 5.7%).	
Watson, 2019(145)	*Diagnostic accuracy statistics are not available for lymphoma. 2x2 tables obtained from author can be found in Appendix 7 that are used to estimate the diagnostic accuracy measures.*	<u>Raised inflammatory markers (one or more raised inflammatory markers)</u> Number of patients (n)= 46092 <u>Normal inflammatory markers (all inflammatory markers normal)</u> Number of patients (n)= 109554 Frequency of lymphoma patients tested for: ESR = 54 CRP = 56 PV = 16	**Total tested cohort:** 155,646 patients • Cohort only = 116,708 • Matched tested = 38,868 **Untested (matched) cohort:** 39,131 patients	5360 cancers diagnosed; 103 lymphomas (93 lymphomas in tested cohort; 10 in untested) **Amongst total tested cohort of lymphoma patients (n = 93):** Raised ESR = 28 (51.85%) Raised CRP = 33 (58.93%) Raised PV = 13 (81.25%) Any raised inflammatory marker= 57 (61.29%) **Lymphoma patients with raised inflammatory markers (one-year lymphoma incidence) compared to national 2014 England diagnosed incidence:** Male = 2.29% (n=24)	Raised inflammatory markers are associated with cancer and may predate the diagnosis by several months, especially in older patients, male patients, and those with very high or persistent abnormalities. The majority of lymphoma patients had a raised inflammatory marker test result when tested. However, inflammatory markers generally have a poor sensitivity for cancer and are therefore not useful as 'rule-out' test.

		Any of ESR, CRP, PV = 93		National male incidence = 4.94% Female = 3.08% (n=33) National female incidence = 4.07% Broadly reflects overall lymphoma incidence in 2014 from National Cancer Registry figures. <u>Symptoms:</u> None of the symptoms identified were high-risk under current NICE guidelines.	

[a] *Focussing on results and conclusions relevant to the outcome of lymphoma*

Result table:

For each extracted clinical feature, the results can be found in Table 7, alongside information on adjustments of estimates by covariates, such as age, sex, general practice, smoking status, previous cancer and family history of cancer. All studies adjusted for at least age and sex except for Rafiq 2022, where no adjustments were made. See the footnote of Table 7 for detail on covariates adjusted for each study.

Fortuny 2022 reported on the mean serum lipid levels over time, pre-index date using thresholds for abnormality based on cardiovascular disease and not lymphoma. Given this, their results based on thresholds of abnormality were difficult to interpret and hence the tests were referred to as the test names rather than the abnormality. To compare the test levels between cases and controls, summary measures, adjusted trajectories and plotted CIs were discussed.

Anderson 2013 reported eosinophilia in an ordinal scale, of severe, mild and no eosinophilia. Diagnostic accuracy statistics were estimated using severe vs non-severe eosinophilia and raised, which combines both mild and severe eosinophilia, $\geq 0.5 \times 10^9$/L, vs non-raised, $< 0.5 \times 10^9$/L.

The studies Shephard 2015a and Shephard 2015b were part of a project looking at the clinical profile of 13 common cancers among primary care patients aged ≥40 years as for most cancers, the median age of cancer diagnosis was found to be in the early 70s. PPVs figures were reported for those aged ≥40 years for each feature for HL. However, PPV figures for NHL were calculated for those aged ≥60 years to target patients near to the average age of NHL diagnosis; this accounted for 78.5% of overall cases. By estimating figures for the same age group for HL (≥ 60 years), the PPV values could be added together

to give overall estimated risks for each symptom. Thus, for HL, PPVs are reported for two age cut offs, ≥ 40 and ≥ 60 years for lymphadenopathy, head and neck swelling and other lump swellings. Reported PPVs can be found in Table 7. All estimated PPVs can be found in Appendix 6.

Table 7: Results by clinical feature and outcome investigated

Clinical feature/Outcome	**n, % reporting each feature**		**Association measure (95% CI)**	**Sensitivity (%) (95% CI)**	**Specificity (%) (95% CI)**	**Diagnostic odds ratio (DOR)**	**Positive predictive value (%) (95% CI)**	**LR+ (95% CI)**	**LR- (95% CI)**
	Cases	**Non-cases**							
Head and neck swelling									
Lymphoma NOS (129)	**n/N (%)** 35/270 (12.96)	**n/N (%)** 1/3350 (0.03)	Odd Ratio: 71.85 [a] (8.98,575.07), P value = 0.0001	12.96 * (9.31, 17.70)	99.97 * (99.81,100.00)	498.79 * (68.03, 3656.79)	0.5 ** (0.07,3.68)	434.26 (59.72, 3157.62)	0.87 * (0.83, 0.91)
Hodgkin lymphoma (96) [1]	**n/N (%)** 30/283 (11)	**n/N (%)** 0/1237 (0)	Odd Ratio: 261 [b] (21, 3171)	10.60 * (7.38,14.93)	99.92 * (99.48, 100.00)	146.56 * (19.90,1079.65)	Patients ≥ 40 years 0.4 Patients ≥ 60 years 2.3%	131 (18, 958)	0.89 * (0.86, 0.93)
Non-Hodgkin lymphoma (97)	**n/N (%)** 355/4362 (8)	**n/N (%)** 36/19468 (0.2)	Odd Ratio: 49 [c] (32, 74)	8.14 * (7.35, 9.00)	99.82 * (99.74, 99.87)	47.82 * (33.88, 67.49)	2.3 (1.6, 3.2)	44 (31, 62)	0.92 * (0.91, 0.93)
Lymphadenopathy									
Lymphoma NOS (129)	**n/N (%)** 77/270 (28.52)	**n/N (%)** 4/3350 (0.12)	Odd Ratio: 184.46 [a] (40.65,837.06), P value < 0.0001	28.52 * (23.29, 34.37)	99.88 * (99.67,99.96)	333.73 * (120.88, 921.38)	0.28 ** (0.10, 0.75)	238.84 (88.09, 647.59)	0.72 * (0.66, 0.77)
Hodgkin lymphoma (96) [1]	**n/N (%)** 51/283 (18)	**n/N (%)** 0/1237 (0)	Odd Ratio: 282 [b] (25, 3123)	18.02 * (13.82, 23.11)	99.92 * (99.48, 100.00)	271.71 * (37.36,1975.89)	Patients ≥ 40 years 0.7	223 (31, 1606)	0.82 * (0.78, 0.87)

							Patients ≥ 60 years 5.6		
Non-Hodgkin lymphoma (97)	**n/N (%)** 632/4362 (14)	**n/N (%)** 13/19468 (0.1)	Odd Ratio: 263 [c] (133, 519)	14.49 * (13.46, 15.58)	99.93 * (99.88, 99.96)	253.57 * (146.26 ,439.62)	13 (7.1, 22)	217 (125 ,375)	0.86 * (0.85, 0.87)
Other lump swellings									
Lymphoma NOS (129)	**n/N (%)** 29/270 (10.74)	**n/N (%)** 15/3350 (0.45)	Odd Ratio: 14.08 [a] (5.33, 37.19), P value < 0.0001	10.74 * (7.43, 15.21)	99.55 * (99.24, 99.74)	26.75 * (14.15, 50.58)	0.03 ** (0.02, 0.05)	23.99 (13.02, 44.19)	0.90 * (0.86, 0.93)
Hodgkin lymphoma (96) [1]	**n/N (%)** 19/283 (7)	**n/N (%)** 15/1237 (1)	Odd Ratio: 12 [b] (4.4, 35)	6.71 * (4.20, 10.46)	98.79 * (97.96, 99.29)	5.86 * (2.94, 11.69)	Patients ≥ 40 years 0.02 (0.01, 0.04) Patients ≥ 60 years 0.03	5.5 (2.9, 11)	0.94 * (0.91, 0.97)
Non-Hodgkin lymphoma (97)	**n/N (%)** 473/4362 (11)	**n/N (%)** 199/19468 (1)	Odd Ratio: 12 [c] (10, 16)	10.84 * (9.94, 11.81)	98.98 * (98.82, 99.11)	11.78 * (9.94, 13.95)	0.8 (0.7, 1.0)	11 (9,12)	0.90 * (0.89, 0.91)
Weight loss									
Lymphoma NOS (131) [α]	**n/N (%)** 94/407 (23.10*)	**n*/N* (%)** 63879/ 330037 (19.36*)	Hazard Ratios: *0-3 months* **Men:** 6.69 [d] (3.82, 11.73)	23.10 * (19.15, 27.56)	80.64 * (80.51, 80.78)	1.25 * (0.99, 1.58)	-	1.19 * (1.00, 1.42)	0.95 * (0.90, 1.01)

			Women: 3.21 [d] (1.75, 5.88) *0-6 months* **Men:** 4.22 [d] (2.72, 6.55) **Women:** 1.75 [d] (1.06, 2.91) <u>Risk Ratios:</u> **Men:** 4.7 [e] (2.9, 7.6), P value <0.001 **Women:** 2.5 [e] (1.4, 4.2), P value = 0.001						
Non-Hodgkin lymphoma (97)	**n/N (%)** 164/4362 (4)	**n/N (%)** 115/19468 (1)	<u>Odds Ratio:</u> 3.2 [c] (2.3, 4.4)	3.76 * (3.22, 4.38)	99.41 * (99.29, 99.51)	6.57 * (5.17, 8.36)	0.4 (0.3, 0.5)	6.4 (5.0, 8.1)	0.97 * (0.96, 0.97)

Mild eosinophilia									
Hodgkin lymphoma (128) [α]	**n/N* (%)** 5/82 (6.10*)	**n/N* (%)** 13113/ 356114 (3.68*)	Odd Ratio : 1.71 [f] (0.68,4.27), p value [g] = 0.25						
Non-Hodgkin lymphoma (128) [α]	**n/N* (%)** 28/555 (5.05*)	**n/N* (%)** 13090/ 355641 (3.68*)	Odd Ratio: 1.29 [f] (0.88,1.90), P value [g] = 0.17						
Severe eosinophilia									
Hodgkin lymphoma (128) [α]	**n/N* (%)** 3/82 (3.66*)	**n/N* (%)** 1285/ 356114 (0.36*)	Odd Ratio: 9.09 [f] (2.77, 29.84), p value [g] = 0.0003	3.66* (0.95, 11.06)	99.64* (99.62, 99.66)	10.49* (3.31, 33.26**)**	-	10.14* (3.33, 30.83)	0.97* (0.93, 1.01)
Non-Hodgkin lymphoma (128) [α]	**n/N* (%)** 3/555 (0.54*)	**n/N* (%)** 1285/ 355641 (0.36*)	Odd Ratio: 1.23 [f] (0.39,3.86), P value [g] = 0.72	0.54* (0.14, 1.71)	99.64* (99.62, 99.66)	1.50* (0.48, 4.67)	-	1.50* (0.48, 4.63)	1.00* (0.99, 1.00)
Raised eosinophilia [2]									
Hodgkin lymphoma (128) [α]	**n/N* (%)** 8/82 (9.76*)	**n/N* (%)** 14398/ 356114 (4.04*)	-	9.76* (4.61, 18.83)	95.96* (95.89, 96.02)	2.57* (1.24, 5.32)	-	2.41 * (1.25, 4.66)	0.94* (0.88, 1.01)
Non-Hodgkin lymphoma (128) [α]	**n/N* (%)** 31/555 (5.59*)	**n/N* (%)** 14375/ 355641 (4.04*)	-	5.59* (3.89, 7.92)	95.96* (95.89, 96.02)	1.40* (0.98, 2.02)	-	1.38* (0.98, 1.95)	0.98* (0.96, 1.00)

Abnormal liver function tests (LFTs)									
Hodgkin lymphoma (132)	**Abnormal result n/N(%) and Mean result (SD)** [h] 95/452, (21.0), 39.8 (6.0)	**Abnormal result n/N(%) and Mean result (SD)** [h] 36/542 (6.6), 43.3 (4.5)	Odd Ratio: 3.16 [i] (1.79, 5.59), P value < 0.001	21.02 * (17.41, 25.13)	93.36 * (90.84, 95.24)	3.74 * (2.49, 5.62)	-	3.16 * (2.20, 4.55)	0.85 * (0.80, 0.89)
Non-Hodgkin lymphoma (97)	**n/N (%)** 863/4362 (20)	**n/N (%)** 1878 /19468 (10)	Odd Ratio: 1.3 [c] (1.1, 1.5)	19.78 * (18.62, 21.00)	90.35 * (89.93, 90.76**)**	2.31 * (2.11, 2.52)	-	2.1 (1.9, 2.2)	0.89 * (0.87, 0.90)
Any raised inflammatory marker									
Lymphoma NOS (133) [α]	**n/N (%)** [j] 57/93 (61.29*)	**n/N (%)** [j] 46035/155553 (29.59*)	-	61.29 * (50.59, 71.05)	70.41 * (70.18, 70.63)	3.77 * (2.48, 5.72)	-	2.07* (1.76, 2.43)	0.55* (0.43, 0.71)
Hodgkin lymphoma (96)	**n/N (%)** 105/283 (37)	**n/N (%)** 66/1237 (5)	Odd Ratios: 5.2 [b] (3.0, 9.0)	37.10 * (31.51, 43.05)	94.66 * (93.22, 95.82)	10.47 * (7.41,14.79**)**	0.02 (0.02,0.03)	7.0 (5.3, 9.2)	0.66 * (0.61, 0.73)
Non-Hodgkin lymphoma (97)	**n/N (%)** 1184/4362 (27)	**n/N (%)** 1202/19468 (6)	Odd Ratios: 2.5 [c] (2.2, 2.9)	27.14 * (25.83, 28.49)	93.83 * (93.48, 94.16)	5.66 * (5.18, 6.19)	-	4.4 (4.1, 4.7)	0.78 * (0.76, 0.79)

Raised erythrocyte sedimentation rate (ESR)									
Hodgkin lymphoma (132)	**Abnormal result n/N(%) and Mean result (SD)** [h] 266/361 (73.7), 39.0 (32.0)	**Abnormal result n/N(%) and Mean result (SD)** [h] 78/213 (36.6), 11.4 (13.0)	Odd Ratio: 6.37 [i] (2.85, 14.27), P value < 0.001	73.68 * (68.76, 78.09)	63.38 * (56.49, 69.78)	4.85 * (3.37, 6.97)	-	2.01 * (1.67, 2.43)	0.42 * (0.34, 0.51)
Lymphoma NOS (133) [α]	**n/N (%)** [j] 28/54 (51.85*)	**n/N (%)** [j] 22410/90424 (24.78*)	-	51.85 * (37.98, 65.46)	75.22 * (74.93, 75.50)	3.27 * (1.92, 5.58)	-	2.09* (1.62, 2.71)	0.64* (0.49, 0.84)
Raised C-reactive protein (CRP)									
Hodgkin lymphoma (132)	**Abnormal result n/N(%) and Mean result (SD)** [h] 217/320 (67.8), 49.9 (57.7)	**Abnormal result n/N(%) and Mean result (SD)** [h] 32/191 (16.8), 7.9 (16.9)	Odd Ratio 50.0 [i] (6.9, 364.2), P value < 0.001	67.81 * (62.35, 72.84)	83.25 * (77.02, 88.10)	10.47 * (6.70, 16.36)	-	4.05 * (2.92, 5.60)	0.39 * (0.33, 0.46)
Lymphoma NOS (133) [α]	**n/N (%)** [j] 33/56 (58.93*)	**n/N (%)** [j] 27927/111384 (25.07*)	-	58.93 * (45.01, 71.63)	74.93 * (74.67, 75.18)	4.29 * (2.52, 7.30)	-	2.35* (1.89, 2.93)	0.55* (0.40, 0.75)

Raised plasma viscosity (PV)									
Hodgkin lymphoma (132)	**Abnormal result n/N(%) and Mean result (SD)** [h] 39/51 (76.5), 1.9 (0.2)	**Abnormal result n/N(%) and Mean result (SD)** [h] 10/28 (35.7) ,1.7 (0.1)	-	76.47 * **(**62.18, 86.75**)**	64.29 * (44.11, 80.69)	5.85 * (2.13, 16.03)	-	2.14 * (1.27, 3.60)	0.37 * (0.21, 0.65)
Lymphoma NOS (133) [α]	**n/N (%)** [j] 13/16 (81.25*)	**n/N (%)** [j] 4429/15654 (28.29*)	-	81.25 * (53.69, 95.03)	71.71 * (70.99, 72.41)	10.98 * (3.13, 38.56)	-	2.87* (2.27, 3.64)	0.26* (0.09, 0.73)
Lowered full blood count									
Hodgkin lymphoma (96)	**n/N (%)** 98/283 (35)	**n/N (%)** 88/1237 (7)	Odd Ratio 2.8 [b] (1.6, 4.8)	34.63 * (29.16, 40.53)	92.89 * (91.27, 94.23)	6.92 * (4.99, 9.59)	0.02 (0.01, 0.02)	4.9 (3.8, 6.3)	0.70 * (0.65, 0.77)
Non-Hodgkin lymphoma (97)	**n/N (%)** 1369/4362 (32)	**n/N (%)** 1645/19468 (8)	Odd Ratio 3.3 [c] (2.9, 3.7)	31.38 * (30.01, 32.79)	91.55 * (91.15, 91.94)	4.96 * (4.57, 5.38)	-	3.7 (3.5, 4.0)	0.75 * (0.73, 0.77)

Raised platelet count									
Hodgkin lymphoma (132)	**Abnormal result n/N(%) and Mean result (SD)** [h] 198/578 (34.3), 354.2 (143.2)	**Abnormal result n/N(%) and Mean result (SD)** [h] 59/742 (8.0), 267.6 (74.8)	Odd Ratio 8.07 [i] (5.02, 12.99), P value < 0.001	34.26 * (30.42, 38.31)	92.05 * (89.80, 93.85**)**	6.03 * (4.39,8.28)	-	4.31 * (3.29, 5.64)	0.71 * (0.67, 0.76)
Hodgkin lymphoma (96)	**n/N (%)** 54/283 (19)	**n/N (%)** 17/1237 (1)	Odd Ratio 6.0 [b] (2.6, 14)	19.08 * (14.77, 24.25)	98.63 * (97.76, 99.17)	16.92 * (9.64,29.72**)**	0.05 (0.03, 0.08)	14 (8.2, 24)	0.82 * (0.78, 0.87)
POOLED META-ANALYSIS			Odd Ratio: 7.51 (4.97, 11.36) p value < 0.0001	26.0 (13.8, 43.6)	96.6 (82.6, 99.4)			9.17 (2.46, 24.50)	0.77 (0.67, 0.87)
Total cholesterol ***									
Hodgkin lymphoma (130)	Mean of cholesterol/ triglyceride levels **Mean(SD)** 206.1(37.0) **Median(IQR)** 206 [182-232]	Mean of cholesterol/ triglyceride levels **Mean(SD)** 217.5(37.8) **Median(IQR)** 217 [191-244]							

Non-Hodgkin lymphoma (130)	Mean of cholesterol/ triglyceride levels **Mean(SD)** 212.1(39.4) **Median(IQR)** 212[186-239]	Mean of cholesterol /triglyceride levels **Mean(SD)** 219.1(37.1) **Median(IQR)** 218[193-244]							
Low-density lipoprotein cholesterol (LDL-C) ***									
Hodgkin lymphoma (130)	Mean of cholesterol/ triglyceride levels **Mean(SD)** 128.9(30.8) **Median(IQR)** 131 [106-150]	Mean of cholesterol/ triglyceride levels **Mean(SD)** 135.1(33.6) **Median(IQR)** 135 [112-158]							

Non-Hodgkin lymphoma (130)	Mean of cholesterol/ triglyceride levels **Mean(SD)** 136.0(32.7) **Median(IQR)** 135 [113-159]	Mean of cholesterol/ triglyceride levels **Mean(SD)** 136.0(32.7) **Median(IQR)** 135 [113-159]							
High-density lipoprotein cholesterol (HDL-C) ***									
Hodgkin lymphoma (130)	Mean of cholesterol/ triglyceride levels **Mean(SD)** 50.1(13.3) **Median(IQR)** 47 [41-58]	Mean of cholesterol/ triglyceride levels **Mean(SD)** 55.4(14.4) **Median(IQR)** 54 [45-64]							
Non-Hodgkin lymphoma (130)	Mean of cholesterol/ triglyceride levels **Mean(SD)** 53.4(14.6) **Median(IQR)** 51[43-62]	Mean of cholesterol/ triglyceride levels **Mean(SD)** 56.3(14.9) **Median(IQR)** 54[45-66]							

Triglycerides ***									
Hodgkin lymphoma (130)	Mean of cholesterol/ triglyceride levels **Mean(SD)** 167.6(77.0) **Median(IQR)** 151 [106-207]	Mean of cholesterol/ triglyceride levels **Mean(SD)** 161.1(79.7) **Median(IQR)** 141 [101-200]							
Non-Hodgkin lymphoma (130)	Mean of cholesterol/ triglyceride levels **Mean(SD)** 158.4(74.1) **Median(IQR)** 142[103-195]	Mean of cholesterol/ triglyceride levels **Mean(SD)** 158.0(73.2) **Median(IQR)** 142[105-195]							
Raised ferritin									
Hodgkin lymphoma (132)	**Abnormal result n/N(%) and Mean result (SD)** [h] 30/113 (26.5), 230.5 (296.4)	**Abnormal result n/N(%) and Mean result (SD)** [h] 5/160 (3.1), 64.9 (95.4)	Odd Ratio: 3.00 [i] (0.31 , 28.84), P value = 0.34	26.55 * (18.89, 35.83)	96.88 * (92.48, 98.84)	11.20 * (4.19, 29.96)	-	8.50 * (3.40, 21.22)	0.76 * (0.68, 0.85)

Abdominal pain									
Non-Hodgkin lymphoma (97)	**n/N (%)** 610/4362 (14)	**n/N (%)** 833/19468 (4)	Odd Ratio: 2.5 [c] (2.1, 2.9)	13.98* (12.98, 15.06)	95.72 * (95.43, 96.00)	3.64 * (3.26, 4.06)	0.2 (0.18, 0.22)	3.3 (3.0, 3.6)	0.90 * (0.89, 0.91)
Constipation									
Non-Hodgkin lymphoma (97)	**n/N (%)** 261/4362 (6)	**n/N (%)** 526/19468 (3)	Odd Ratio: 1.4 [c] (1.2, 1.8)	5.98* (5.31, 6.74)	97.30 * (97.06, 97.52)	2.29 * (1.97, 2.67)	0.1 (0.1, 0.2)	2.2 (1.9, 2.6)	0.97 * (0.96, 0.97)
Fatigue									
Non-Hodgkin lymphoma (97)	**n/N (%)** 300/4362 (7)	**n/N (%)** 547/19468 (3)	Odd Ratio: 1.4 [c] (1.2, 1.7)	6.88* (6.15, 7.68)	97.19 * (96.95, 97.42)	2.55 * (2.21, 2.95)	0.2 (0.15, 0.20)	2.5 (2.1, 2.8)	0.96 * (0.95 ,0.97)
Infection									
Non-Hodgkin lymphoma (97)	**n/N (%)** 902/4362 (21)	**n/N (%)** 2897/19468 (15)	Odd Ratio: 1.3 [c] (1.1, 1.4)	20.68 * (19.49 ,21.92)	85.12 * (84.61, 85.61)	1.49 * (1.37, 1.62)	0.1 (0.08, 0.10)	1.4 (1.3, 1.5)	0.93 * (0.92, 0.95)
Indigestion									
Non-Hodgkin lymphoma (97)	**n/N (%)** 203 /4362 (5)	**n/N (%)** 491/19468 (3)	Odd Ratio: 1.5 [c] (1.2 ,1.9)	4.65 * (4.06, 5.33)	97.48 * (97.25, 97.69)	1.89 * (1.60, 2.23)	0.1 (0.10, 0.14)	1.9 (1.6, 2.2)	0.98 * (0.97, 0.98)
Malaise									
Non-Hodgkin lymphoma (97)	**n/N (%)** 159/4362 (4)	**n/N (%)** 240/19468 (1)	Odd Ratio: 1.7 [c] (1.2, 2.3)	3.65 * (3.12, 4.26)	98.77 * (98.60, 98.92)	3.03 * (2.47, 3.71)	0.2 (0.16, 0.24)	3.0 (2.4, 3.6)	0.98 * (0.97, 0.98)
Shortness of breath									
Non-Hodgkin lymphoma (97)	**n/N (%)** 413/4362 (9)	**n/N (%)** 976/19468 (5)	Odd Ratio: 1.5 [c] (1.3, 1.8)	9.47 * (8.62, 10.38)	94.99 * (94.67, 95.29)	1.98 * (1.76, 2.23)	0.1 (0.10 ,0.13)	1.9 (1.7, 2.1)	0.95 * (0.94, 0.96)

Vomiting and nausea									
Non-Hodgkin lymphoma (97)	**n/N (%)** 247/4362 (6)	**n/N (%)** 391 /19468 (2)	Odd Ratio: 1.4 [c] (1.1, 1.7)	5.66 * (5.00, 6.40)	97.99 * (97.78, 98.18)	2.93 * (2.49 ,3.45)	0.2 (0.15, 0.21)	2.8 (2.4, 3.3)	0.96 * (0.96, 0.97)
Recurrent back pain									
Non-Hodgkin lymphoma (97)	**n/N (%)** 163/4362 (4)	**n/N (%)** 308/19468 (2)	Odd Ratio: 1.7 [c] (1.3, 2.3)	3.74* (3.20, 4.35)	98.42 * (98.23, 98.59)	2.41 * (1.99, 2.93)	-	2.4 (2.0, 2.9)	0.98 * (0.97, 0.98)
Leucocytosis									
Non-Hodgkin lymphoma (97)	**n/N (%)** 521/4362 (12)	**n/N (%)** 478/19468 (2)	Odd Ratio: 3.0 [c] (2.5, 3.6)	11.94 * (11.00 12.95)	97.54 * (97.32, 97.76)	5.39 * (4.74, 6.13)	-	4.9 (4.3, 5.5)	0.90 * (0.89, 0.91)
Microcytosis									
Non-Hodgkin lymphoma (97)	**n/N (%)** 227/4362 (5)	**n/N (%)** 246/19468 (1)	Odd Ratio: 1.5 [c] (1.1, 1.9)	5.20 * (4.57, 5.92)	98.74 * (98.57, 98.89)	4.29 * (3.57, 5.15)	-	4.1 (3.5 to 4.9)	0.96 * (0.95, 0.97)
Macrocytosis									
Non-Hodgkin lymphoma (97)	**n/N (%)** 207/4362 (5)	**n/N (%)** 405/19468 (2)	Odd Ratio: 1.4 [c] (1.1, 1.8)	4.75 * (4.14, 5.43)	97.92 * (97.71, 98.11)	2.34 * (1.98, 2.78)	-	2.3 (1.9 to 2.7)	0.97 * (0.97, 0.98)
Raised gamma globulin									
Non-Hodgkin lymphoma (97)	**n/N (%)** 174/4362 (4)	**n/N (%)** 228/19468 (1)	Odd Ratio: 1.8 [c] (1.3, 2.4)	3.99 * (3.44 ,4.62)	98.83 * (98.67, 98.97)	3.51 * (2.87, 4.28)	-	3.4 (2.8, 4.1)	0.97 * (0.97, 0.98)

95% Confidence intervals (CIs) for all the statistics where reported or estimated.

**Indicates diagnostic accuracy measures estimated using data from the study. These are rounded to 2 decimal places.*

*** Indicates converted statistic from per 10,000.*

**** Serum lipid tests will not be referred to as abnormalities. The test results will instead be compared between cases and controls. The thresholds for abnormality can be found in Table 5.*

[a] *Matched by age (within 1 year), sex, and practice. ORs are estimated from final model through multivariable analysis modelling, thus are adjusted for.*

[b] *Matched for age, sex, practice and index date (their cases' diagnosis date). For analysis purposes, one control was added to lymphadenopathy and head and neck swelling. ORs are estimated from final model through multivariable analysis modelling, thus are adjusted for.*

[c] *Matched by sex and age at index date (plus or minus 1 year of age). ORs are estimated from final model through multivariable analysis modelling, thus are adjusted for.*

[d] *Adjusted for potential confounders taken before index date: gender, age, Indices of Multiple Deprivation (IMD), Body mass index (BMI), smoking, alcohol status, comorbidity related to weight loss and family history of cancer.*

[e] *Adjusted before index date: Gender, age, smoking status, alcohol status. IMD, BMI, comorbidity related weight loss and family history of cancer.*

[f] *Adjusted for sex, age (quadratic), year, month, previous cancer, comorbidity, CRP and previous eosinophilia.*

[g] *P-values less than 0.0271 were regarded to be significant*

[h] *Estimated amongst patients who received the test. Differs between tests and amongst cases and controls.*

[i] *Matched by sex and age at index date (plus or minus 1 year of age)*

[j] *Estimated amongst tested cohort. Differs between tests and amongst cases and controls.*

[1] *PPV values calculated for ≥ 40 years, but for lymphadenopathy, head and neck swelling and lump swelling, PPV's are also reported for patients ≥ 60 years, however without CIs.*

[2] *Raised eosinophilia combines mild and severe eosinophilia. Negative raised eosinophilia is represented by the result 'no eosinophilia'*

[α] *Indicates cohort study design.*

Estimating positive predictive values

Comparing the estimated PPVs to those reported, the estimated PPVs were generally higher (Appendix 6). This is the effect of prevalence of lymphoma being higher over time. The incidence of HL has increased over time; NHL has risen marginally (England, 2008-2020) (152, 153).

Dommett 2013 reports PPVs using an incidence of lymphoma within 3 months (annual incidence reported as 0.47 per 10,000; thus a 3-month incidence of 0.47/4 per 10,000 is taken as prevalence), hence the estimated PPVs differ more substantially to those reported.

The PPVs estimated for studies which did not report PPVs (128, 131-133) produced very small PPVs, ranging between 0.01% to 0.08% (Appendix 6).

Dumbbell plot for likelihood ratios

Figure 14 shows that the presence of lymphadenopathy and head and neck swelling increased the probability of lymphoma in all studies, across all outcomes. The presence of other lump swellings had a marginal increase in the probability of NHL, but was not notable for HL and lymphoma NOS. For the remaining features, there was not much difference between pre and post-test probabilities.

The absence of any of the features did not affect the probability of lymphoma.

No major patterns emerged based on differences in the age range of patients.

Meta-analysis:

The review only identified a small number of studies (n = 8) which investigated a diverse range of symptoms and tests. Therefore, meta-analysis could only be conducted for raised platelet count, with 2 studies investigating HL(96, 132). As the I^2s (≈0%) were below 50%, the pooled estimated (adjusted) OR, sensitivity, specificity and likelihood ratios are presented in Table 7.

Narrative synthesis:

Each clinical feature identified in this review, except for raised ferritin for HL (p = 0.34) (132), mild and severe eosinophilia for NHL (p values 0.17 and 0.72 respectively) , mild eosinophilia for HL (p = 0.25) (128), serum cholesterol and triglyceride tests for both HL and NHL (130)and raised inflammatory marker tests(133) for lymphoma NOS, were confirmed to be positively associated with lymphoma based on reported effect measures (Table 7).

All features were found to be useful, with the estimated DORs and reported ORs greater than 1. Adjusted ORs of features were lower than the estimated DORs (Table 7).

In general, tests had a higher sensitivity compared to symptoms (Figure 13). The tests with the highest sensitivity were raised PV, 81.25% (53.69%, 95.03%) and raised ESR, 73.68% (68.76%,78.09%)

Raised inflammatory marker tests include the following features: raised ESR, raised CRP, raised PV and any raised inflammatory marker.

Lymphoma NOS

The following features were reported individually for the outcome of lymphoma NOS: head and neck swelling, lymphadenopathy, other lump swellings, weight loss and raised ESR, raised CRP, raised PV and any raised inflammatory marker test.

The highest reported ORs were for lymphadenopathy, 184.46 (40.65, 837.06) and head and neck swelling, 71.85 (8.98, 575.07).

All sensitivities were low, below 65% except for raised PV, with a strong sensitivity of 81.25% (53.69%, 95.03%). The specificities were higher, > 70%. Lymphadenopathy, head and neck swelling and other lump swellings had high specificities, > 90%. This implies almost 100% of patients without lymphoma NOS will not have these features.

Strong evidence to rule in a diagnosis of lymphoma NOS was found for lymphadenopathy, head and neck swelling and other lump swellings. The highest LR+ was 434.26 (59.72, 3157.62) for head and neck swelling. However, all LR-s were > 0.7, implying these features had weak evidence to rule out lymphoma NOS. The reported PPVs were all < 1%, implying a low predictive risk for lymphoma NOS.

Hodgkin lymphoma

16 tests and 3 symptoms were individually reported amongst the four studies investigating HL (96, 128, 130, 132). The most frequently reported features were serum cholesterol tests, any raised inflammatory marker and raised platelet count.

The highest reported ORs were for lymphadenopathy, 282 (25, 3123); head and neck swelling, 261 (21, 3171); other lump swellings, 12 (4.4, 35) and raised CRP, 50.0 (6.9, 364.2).

The majority of features had low sensitivities ≤ 37.10%. The highest sensitivities were for raised inflammatory marker tests, ranging between 67.81% (62.35%, 72.84%) for raised CRP to 76.47% (62.18%, 86.75%) for raised PV. In contrast, the majority of features had a high specificity, > 80%.

Only lymphadenopathy, head and neck swelling, other lump swellings, raised ferritin, any raised inflammatory marker, severe eosinophilia and raised platelet count had LR+s > 5. Lymphadenopathy had the highest LR+, 223 (31, 1606). There was weak evidence to rule out a diagnosis of HL amongst all features. The majority of PPVs were < 1%, implying a low predictive risk (Table 7 and Appendix 6). The highest PPVs were for lymphadenopathy and head and neck swelling, 5.6% and 2.3% respectively.

Non-Hodgkin lymphoma

14 tests and 13 symptoms were individually reported amongst the three studies investigating NHL(97, 128, 130). The most frequently reported feature was serum cholesterol tests.

The highest reported ORs were for lymphadenopathy, 263 (133, 519); head and neck swelling 49(32, 74); and other lump swellings, 12 (10, 16). Non-mass features with highest ORs were lowered FBC and weight loss, 3.3 (2.9, 3.7) and 3.2 (2.3, 4.4) respectively.

All sensitivities were low, < 32%. All specificities were high, > 85%. The highest specificity was for lymphadenopathy, 99.93% (99.88%, 99.96%), implying that almost 100% of patients without NHL will not have lymphadenopathy.

Lymphadenopathy, head and neck swelling, other lump swellings and weight loss had LR+s >5 which suggests these features have strong evidence to rule in NHL. Weak evidence was found to rule out NHL amongst all the features, with LR-s ≥ 0.75. The majority of features had low PPVs, < 1%, implying a low predictive risk of NHL. Lymphadenopathy had the highest PPV of 13%.

Exploring variation in clinical features:

Variations in results of clinical features across outcomes, age, sex, stage and study designs are discussed below. The forest plots (Figures 11-13) are irrespective of study design as there are a small number of these studies and not big differences as a result of differing study design.

Head and neck swelling

The symptom was examined in 3 case-control studies for the subtypes HL, 11%(96), NHL, 8%(97) and lymphoma NOS, 12.96%(129). The reported ORs ranged between 49 (32, 74) for NHL to 261 (21, 3171) for HL (Figure 11). The sensitivities were all poor, between 8.14% (7.35%, 9.00%) for NHL to 12.96% (9.31%, 17.70%) for lymphoma NOS. But the specificities were all very strong, between 99.82% (99.74%, 99.87%) for NHL and 99.97% (99.81%,100.00%) for lymphoma NOS. There was strong evidence to rule in, LR+s > 5 and weak evidence to rule out, LR-s > 0.3 a lymphoma diagnosis across all subtypes examined. The reported PPVs were all below 3%, lowest for lymphoma NOS. Head and neck swelling was a better diagnostic tool for HL compared to NHL, which both examined patients of the same age range. With younger patients examined for lymphoma NOS, sensitivities were found to be largest (Figure 13) and PPV lowest, 0.5% (0.07%,3.68%). The PPVs for HL were found to be raised for older patients - 0.4% and 2.3% for patients ≥ 40 years and ≥ 60 years respectively(96).

Lymphadenopathy

The symptom was reported in 3 case-control studies for the subtypes HL, 18%(96), NHL, 14%(97) and lymphoma NOS, 28.52%(129). All the reported ORs were very high, ranging between 184.46 (40.65, 837.06) for lymphoma NOS and 282 (25, 3123) for HL (Figure 11). The sensitivities were low, ranging between 14.49% (13.46%, 15.58%) for NHL to 28.52%

(23.29%, 34.37%) for lymphoma NOS. The specificities were all very strong, 99.88 % (99.67%,99.96%) for lymphoma NOS and 99.93% (99.88%, 99.96%) for NHL. There was strong evidence to rule in, LR+s > 5 and weak evidence to rule out a lymphoma diagnosis, LR-s > 0.2 across all subtypes. The reported PPVs for NHL and HL were > 5%. Lymphadenopathy seems to perform the best as a diagnostic tool for NHL compared to HL, both examined patients of the same age range. Variation in results was found in differing ages. Lymphoma NOS had the lowest PPV, 0.28% (0.10%, 0.75%) and sensitivity – likely due to a younger age range of patients examined (129). The reported PPVs for HL were found to be raised for older patients - 0.7% and 5.6% for patients ≥ 40 years and ≥ 60 years respectively(96).

Other lump swellings

The symptom was reported in 3 case-control studies for the subtypes HL, 7%(96), NHL, 11%(97) and lymphoma NOS, 10.74%(129). The reported ORs ranged from 12 for HL and NHL to 14.08 (5.33,37.19) for lymphoma NOS (Figure 11). The sensitivities were all poor, 6.71% (4.20%,10.46%) for HL and 10.84% (9.94% ,11.81%) for NHL. However, the specificities were very strong, 99.88% (99.67%,99.96%) for lymphoma NOS to 99.93% (99.88%, 99.96%) for NHL. All reported PPVs were below 1%. Moreover, there was strong evidence to rule in all subtypes of lymphoma, LR+s > 5. Lymphadenopathy seems to perform the best as a diagnostic tool for NHL compared to HL - both studies examined patients of the same age range.

Variation in results was found in differing ages. Lymphoma NOS had the lowest PPV, 0.03% (0.02%, 0.05%) and sensitivity - likely due to a younger age range of patients examined (129)

(Figure 13). Moreover, the reported PPVs for HL were raised for older patients - 0.02% and 0.03% for patients ≥ 40 years and ≥ 60 years respectively(96).

Weight loss

Weight loss was reported in 2 studies for lymphoma NOS, 23.10%(131), a cohort study and NHL, 4%(97), a case-control study. There was a non-significant association between weight loss and HL (96)so these results were not reported.

An increase in the risk of lymphoma NOS was found amongst patients presenting within 6 months with weight loss, greater amongst men than woman, with adjusted risk ratios ranging between 2.5 for women and 4.7 for men. In addition, adjusted HRs were higher for men than women within 3 and 6 months of presenting with weight loss (Table 7). The adjusted HR showed that, within 6 months of presenting with weight loss, men are 4.22 and women 1.75 times as likely to be diagnosed with lymphoma NOS (within 3 months of presenting with weight loss, men are 6.69 and women 3.21 times as likely). The presence of weight loss increased the probability of lymphoma marginally greater for older patients (Figure 14). Weight loss was found to be associated with increased late-stage cancer diagnoses (131).

The estimated DORs ranged between 1.25(0.99, 1.58) for lymphoma NOS to 6.57(5.17, 8.36) for NHL – highest for the case control study (97). The lower end of the CI for weight loss in cohort (131), (0.99,1.58) was less than 1, showing it to be potentially less useful as a test. However, the sensitivities were all poor, between 3.76% (3.22%, 4.38%) for NHL and 23.10% (19.15%, 27.56%) for lymphoma NOS - largest for the cohort study which examines younger patients (Figure 13). However, specificities were strong, 80.64% (80.51%,80.78%) for lymphoma NOS and 99.41% (99.29%, 99.51%) for NHL – highest from the case-control study,

which examines older patients (97). Weight loss only had strong evidence to rule in NHL, with a LR+ of 6.4. The estimated PPVs were both low, 0.37% and 0.03% for NHL and lymphoma NOS respectively – an older patient population was examined for NHL. Overall, despite differences in ages of patients examined, NHL appears to have a better diagnostic value than lymphoma NOS. Differing study design may explain the higher specificity and DOR for NHL, a case-control study design.

Eosinophilia

Eosinophilia (128) was reported in 1 cohort study for both HL (6.10%, 3.66% and 9.76% for mild, severe and raised eosinophilia respectively) and NHL (5.05%. 0.54% and 5.59% for mild, severe and raised eosinophilia respectively). An association was only found between mild eosinophilia and HL, OR, 1.71 (0.68,4.27)(128). All sensitivities were poor, < 10% (Figure 13). Specificities however were strong, close to 100%. Specificities for raised eosinophilia and severe eosinophilia were 95.96% (95.89%, 96.02%) and 99.64% (99.62%, 99.66%) respectively for both HL and NHL (Figure 13). Only severe eosinophilia had strong evidence to rule in HL, LR+ > 5. The estimated PPVs were all very low, ≤ 0.04% (Appendix 6). Hodgkin lymphoma appears to the best outcome for mild, severe and raised eosinophilia.

Lowered full blood count

Lowered FBC was reported in 2 case-control studies for HL, 35% (96)and NHL, 32%(97), examining patients ≥40 years. The reported ORs ranged from 2.8 (1.6 ,4.8) for HL to NHL, 3.3(2.9, 3.7) (Figure 11). The sensitivities were low, 31.38% (30.01%, 32.79%) for NHL to 34.63% (29.16%, 40.53%) for HL. In contrast, the specificities were very strong, 91.55% (91.15%, 91.94%) for NHL to 92.89% (91.27%, 94.23%) for HL (Figure 13). All studies provided weak evidence to rule in, LR+ < 5 and rule out a diagnosis, LR- > 0.2 of HL and NHL. Moreover, all the PPVs were low, < 1% (Appendix 6), but greater for NHL as an older patient

age range was examined. Overall, diagnostic value appears to be very similar between HL and NHL.

Raised platelet count

Raised platelet counts were investigated in 3 case-control studies for HL(96, 132) and NHL(97). A non-significant association was found for NHL, so results were only reported from 2 studies for HL, 34.3%(132) and 19%(143). The mean levels of platelet count were found to be greater in cases than controls(132).

The overall pooled effect OR was 7.51(4.97, 11.36), implying the OR for raised platelet count among HL cases approximately 7.5 times higher than OR among controls; the test of overall effect p value was very small (< 0.0001). The pooled OR and 95% CI did not cross the line of no effect (Figure 12). The hypothesis of no heterogeneity has p value of 0.5479, thus failing to reject the null hypothesis, implying no heterogeneity. This is corroborated from the $I^2 \approx 0\%$.

The pooled sensitivity was poor, 26.0% (13.8%, 43.6%), with sensitivities appearing to be larger for younger patients (Figure 13). On the other hand, the pooled specificity was very strong, 96.6% (82.6%, 99.4%), with specificities appearing to be larger for older patients (Figure 13). There was strong evidence to rule in HL, with a pooled LR+, 9.17 (2.46, 24.50) but weak evidence to rule out HL, with a pooled LR- > 0.2. The estimated PPVs were very low, ranging between 0.01% to 0.04% (Appendix 6)– highest for the older patient population(96)

Any raised inflammatory marker

The test was reported in 3 studies for HL, (37%) (132), a case-control study, lymphoma NOS (61.29%)(133), a cohort study and for NHL, a case-control study (27%)(97). The estimated

DORs ranged between 3.77 (2.48, 5.72) for lymphoma NOS to 10.47 (7.41,14.79) for HL– highest for the case-control studies (97, 132) (Table 7). The sensitivities ranged between 27.14% (25.83%, 28.49%) for NHL to 61.29% (50.59%, 71.05%) for lymphoma NOS – largest for younger patients, a cohort study (Figure 13). The specificities ranged between 70.41% (70.18%, 70.63%) for lymphoma NOS to 94.66% (93.22%, 95.82%) for HL – highest for older patients, the case-control studies (Figure 13). There was strong evidence to rule in HL, LR+, 7.0(5.3, 9.2). The estimated PPVs were all low, < 0.3% (Appendix 6), but greatest for NHL as an older patient age range was examined. Overall, HL is generally stronger in diagnostic value compared to NHL. Differing study design may explain the higher specificity and DORs for NHL and HL, a case-control study design.

Raised ESR

The test was reported in 2 studies for the outcomes, HL (73.7%), a case-control study (132) and lymphoma NOS (51.85%), a cohort study (133). The mean levels of ESR were found to be greater in cases than controls(132).

The estimated DORs ranged between 3.27 (1.92, 5.58) for lymphoma NOS and 4.85 (3.37, 6.97) for HL (Table 7) – highest for the case-control study(132). Sensitivities ranged between 51.85% (37.98%, 65.46%) for lymphoma NOS to 73.68% (68.76%,78.09%) for HL – highest for younger patients (Figure 13). The specificities ranged between 63.38% (56.49%, 69.78%) for HL to 75.22% (74.93%, 75.50%) for lymphoma NOS - highest for older patients (Figure 13). The estimated PPVs were all low, < 0.3% (Appendix 6), but highest for lymphoma NOS which examined older patients. Differences observed are likely due to differences in the age range of patients investigated rather than the outcome examined.

Raised CRP

The test was reported in 2 studies for the outcomes HL (67.8%), a case-control study (132) and lymphoma NOS (58.93%), a cohort study (133). The mean levels of CRP were found to be greater in cases than controls(132).

The estimated DORs ranged between 4.29 (2.52, 7.30) for lymphoma NOS and 10.47(6.70, 16.36) for HL (Table 7)– highest for the case-control study(132). Sensitivities ranged between 58.93% (45.01%, 71.63%) for lymphoma NOS to 67.81% (62.35%, 72.84%) for HL – highest for younger patients (case-control) (Figure 13). The specificities ranged between 74.93% (74.67%, 75.18%) for lymphoma NOS to 83.25% (77.02%, 88.10%) for HL - highest for younger patients, a case-control study (Figure 13). The estimated PPVs were all low, < 0.3% (Appendix 6), but highest for lymphoma NOS which examined older patients. Overall, HL appears have the best diagnostic value for raised CRP. Differing study design may explain the higher sensitivity, specificity and DOR for HL, a case-control study design.

Raised PV

The test was reported in 2 studies for the outcomes, HL (76.5%), a case-control study (132) and lymphoma NOS (81.25%), a cohort study (133). The mean levels of PV were found to be greater in cases than controls(132).

The estimated DORs ranged between 5.85(2.13,16.03) for HL and lymphoma NOS, 10.98 (3.13, 38.56) (Table 7). The sensitivities ranged between 76.47% (62.18%, 86.75%) for HL to 81.25% (53.69%, 95.03%) for lymphoma NOS – largest for older patients (Figure 13). The specificities ranged between 64.29% (44.11%, 80.69%) for HL to 71.71% (70.99%, 72.41%) for lymphoma NOS - highest for older patients (Figure 13). The estimated PPVs were all low,

< 0.3% (Appendix 6), but highest for lymphoma NOS which examined older patients. Overall, lymphoma NOS seems to have the best diagnostic value for the test, raised PV.

Abnormal liver function tests

Abnormal LFTs consist of raised LFTs, investigated in 2 case-control studies for the outcomes HL and NHL (96, 97), and lowered albumin, investigated in a case-control study for HL, 21% (132). The test, raised LFTs were found to have a non-significant association with HL(96), so is only reported for NHL, 20% (97)

The mean levels of lowered albumin of HL cases were lower than controls (132). The reported ORs ranged between 1.3(1.1, 1.5) for NHL to 3.16 (1.79, 5.59) for HL - largest for younger patients (Figure 11). The sensitivities were poor, 19.78% (18.62%, 21.00%) for NHL and 21.02% (17.41%, 25.13%) for HL (Figure 13). In contrast, the specificities were very strong, 93.36% (90.84%, 95.24%) for HL and 90.35% (89.93%, 90.76%) for NHL (Figure 13). The estimated PPVs were low, but higher for NHL, 0.12% compared to HL, 0.01% (Appendix 6), which examined older patients. Overall, results are very similar for both HL and NHL – any differences observed are likely due to age.

Serum cholesterol tests

Serum cholesterol tests (total cholesterol, LDLc, and HDLc) were examined in 1 case-control study for both HL and NHL(130). HL and NHL cases had lower mean cholesterol levels compared to their controls prior to index date (130). The decrease in mean cholesterol levels in the years before diagnosis was more marked for HL patients compared to NHL patients.

When comparing cases with typically aggressive lymphomas (i.e. diffuse large B-cell lymphoma, DLBCL) to those with a more indolent nature (i.e. follicular lymphoma, FL and

chronic lymphocytic leukaemia/small lymphocytic leukaemia, CLL/SLL), the cholesterol trajectories were found to be similar. Thus, cholesterol levels were suggested to not be strongly associated with the aggressiveness of the lymphoma(130). It was found that sex does not modify the relationship between serum cholesterol levels and lymphoma(130).

Triglycerides

Triglyceride tests were examined in 1 case-control study for both HL and NHL(130).

HL and NHL cases had similar mean triglyceride levels compared to their controls prior to index date (130). Triglycerides however had higher mean levels prior to index date in HL cases compared to NHL cases. Triglyceride levels were found to be unrelated to HL diagnosis, with trajectories not showing a decrease in triglyceride mean levels among cases or controls(130). It was found that sex does not modify the relationship between triglyceride levels and lymphoma(130).

Combining clinical features

4 studies examined combinations of clinical features, estimating PPVs (96, 97, 129, 133). However, Watson 2019 reported for all cancers combined, not lymphoma separately, so is not discussed here. Shephard 2015a and Shephard 2015b examined combinations of symptoms and test abnormalities, for HL and NHL diagnosis respectively (Appendices 3-5).

Lymphoma NOS

Head and neck swelling, lymphadenopathy and other lump swellings combined as a single symptom gave a PPV of 0.09% (0.06%, 0.14%) (148).

Hodgkin lymphoma

10 combinations of symptoms and test abnormalities were reported for patients ≥ 40 years (Appendix 3) and 3 combinations amongst patients ≥ 60 years (143) (Table 7).

Lymphadenopathy in conjunction with lowered FBC or any raised inflammatory marker produced the highest PPVs of 2.5% and 2.2% respectively, for patients ≥ 60 years.

Non-Hodgkin lymphoma

77 combinations of symptoms, and 91 combinations of symptoms and test abnormalities were reported for patients ≥ 60 years (Appendix 4-5) (144). High PPVs were reported when lymphadenopathy was combined with every feature, with PPVs ≥ 5%. The highest PPV was when lymphadenopathy was combined with any raised inflammatory marker or leucocytosis, 15%. In this review, other tests measuring white blood cell abnormalities, such as neutrophilia or lymphocytosis, were not reported alongside leucocytosis and eosinophilia.

Head and neck swelling in conjunction with every test abnormality and the symptoms, shortness of breath, recurrent back pain, fatigue, nausea and abdominal pain gave PPVs ≥ 4%.

The predictive risk of NHL was lessened when lymphadenopathy was taken in conjunction with every other feature except vomiting and nausea, any raised inflammatory marker and leucocytosis.

Other relevant study results

Duration of features

The duration of features can be important and are discussed across some studies. The duration is not consistent across all of these features.

Weight loss

After the initial 12-month period of presenting with weight loss, the risk of a lymphoma diagnosis for patients with weight loss becomes similar to those patients without weight loss(131).

The diagnostic window for being diagnosed with lymphoma following presentation with weight loss was reported in days with a median 80, IQR: 23-205; mean 146, SD: 166.

Raised inflammatory markers

Increases in abnormal inflammatory marker results reportedly occur several months pre-diagnosis in many HL patients. CRP, ESR and platelet count levels – 12, 11 and 7 months pre-diagnosis increase respectively in HL but are stable in controls (132).

Lymphadenopathy and head and necks swelling

Combining results showed that for patients ≥ 60 years, lymphadenopathy and head and neck swelling should warrant urgent further investigation, particularly if present for ≥ 6 weeks. This is not changed by the presence of other symptoms or blood tests (96, 97).

Serum cholesterol levels

Up to 12 years before diagnosis, lower levels amongst lymphoma cases compared to non-lymphoma controls for cholesterol measures, TSc, LDLc and HDLc were observed(130).

Consultation frequency

Consultation frequency was discussed in 3 studies amongst lymphoma and non-lymphoma patients.

Shephard 2015a and Shephard 2015b:

Cases consulted GPs significantly more frequently than controls in the year before diagnosis (P≤0.001; rank-sum test). Cases have more opportunities to report symptoms because of their higher consultation pattern; *however, the test for recording bias did not support this.*

Dommett 2013:

Teenagers and young adults (TYAs) with lymphoma consulted more frequently than controls in the 3 months pre-diagnosis. In the 3 months before diagnosis, 64.81% of lymphoma patients had 3 or more consultations compared to 8.73% controls (OR: 7.67; 95% CI: 4.92-11.95; $p < 0.0001$).

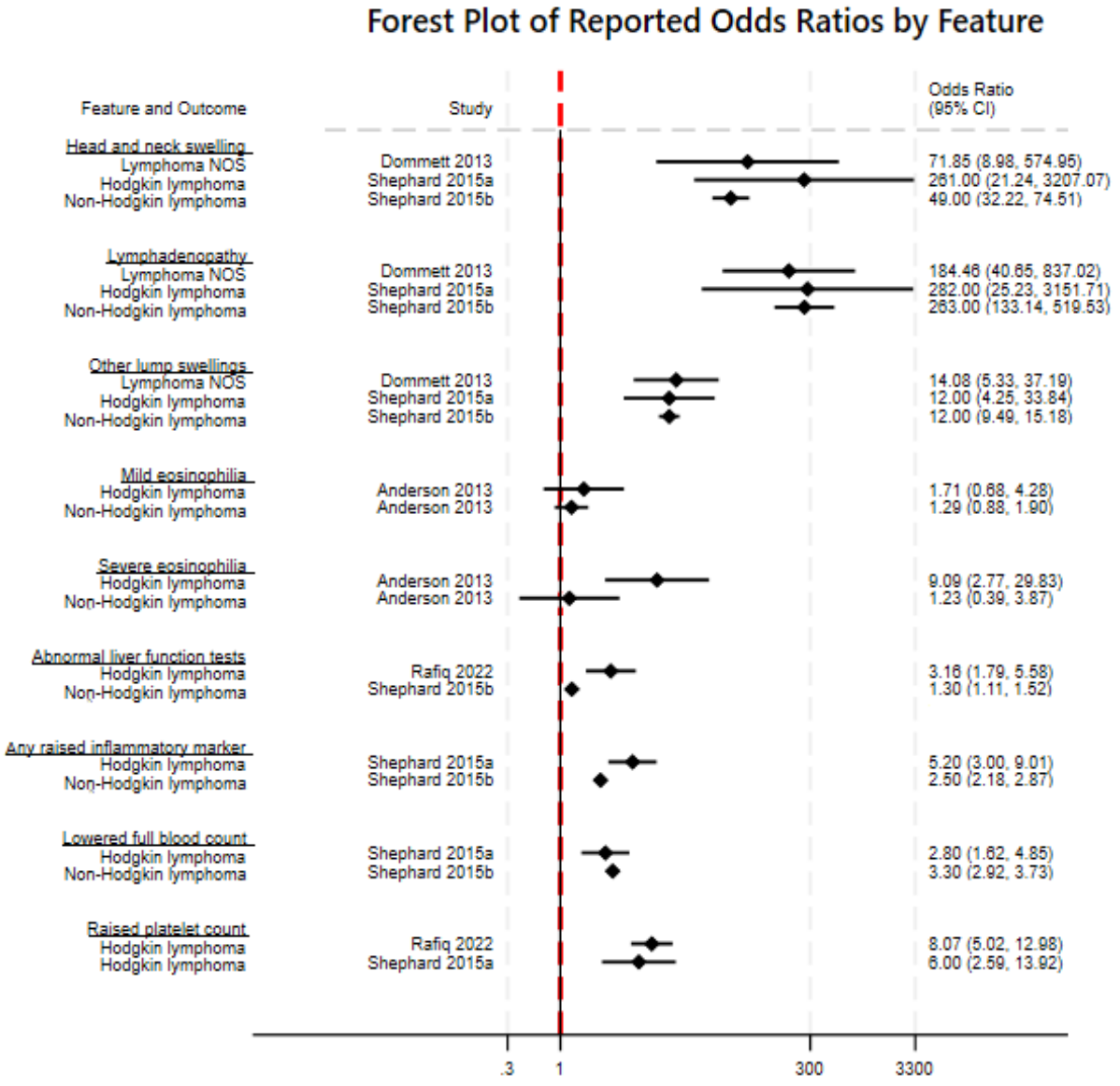
Comorbidities

These were only adjusted for in Anderson 2013 (128) (Charlson's comorbidity Index), Nicholson 2020 (131) (including Adrenal insufficiency, atrial fibrillation, alcohol dependence, anxiety and asthma) and Fortuny 2022 (130) (hypertension).

Odds ratios: Forest plots

Reported ORs for grouped features are displayed to allow comparisons to be made (Figure 11). This excludes Fortuny 2022, Nicholson 2020 and Watson 2019. Estimated DORs are not plotted. The *ORs are adjusted for in all features plotted, except those features reported from Rafiq 2022. A random effects forest plot for raised platelet count for HL can be found in Figure 12.* The vertical dotted line through 1 indicates line of null effect i.e. OR = 1 (Figures 11-12).

Figure 11: Forest plot of reported odds ratios by feature type:



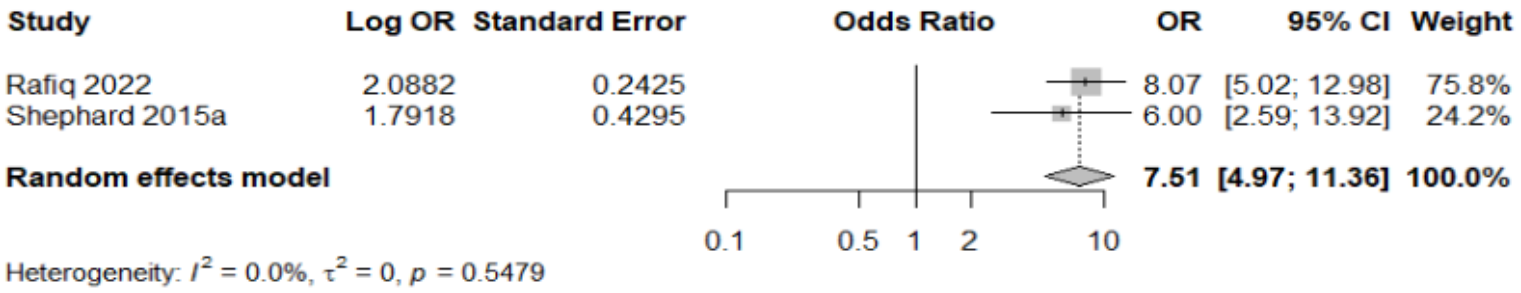
**Dommett 2013, Rafiq 2022, Shephard 2015a and Shephard 2015b are case-control studies. Anderson 2013 is a cohort study.*

HL = Hodgkin lymphoma; NHL = non-Hodgkin lymphoma; NOS = not otherwise specified Only ORs reported in studies are plotted here. Estimated ORs (DORs) are not shown here. Odds ratios have all been adjusted except for Rafiq 2022.
The only raised inflammatory marker test where a grouped OR forest plot could be created was for 'any raised inflammatory markers' test. Eosinophilia could only be separated into mild and severe eosinophilia. Figure 11 is ordered by age group (youngest to oldest) examined.

Figure 11 shows only reported ORs; not estimated ORs as these differ substantially.

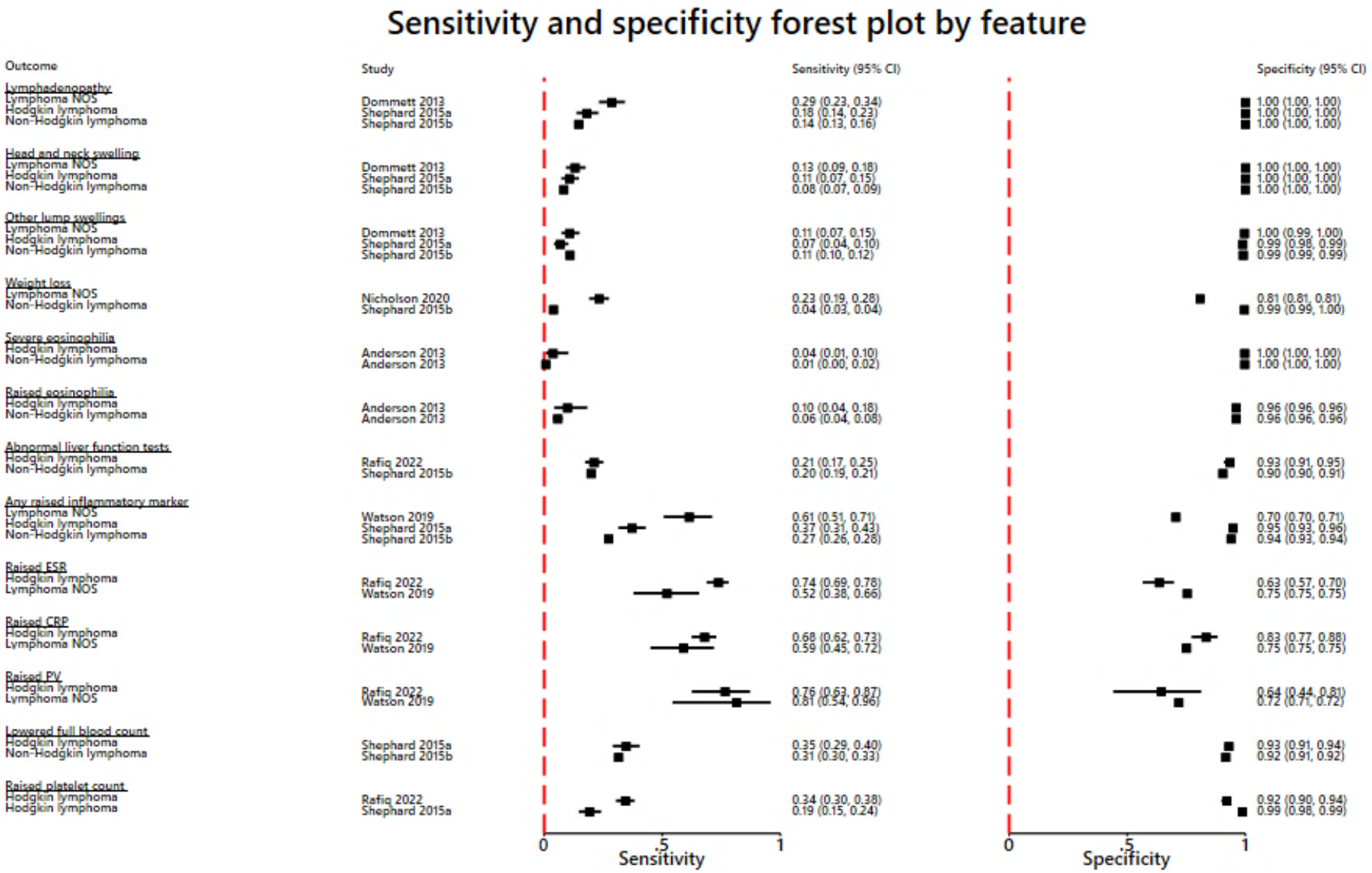
Odds ratios were not reported for Fortuny 2022, Nicholson 2020 and Watson 2019, thus these studies are omitted from this figure.

Figure 12: Random effects ORs forest plot



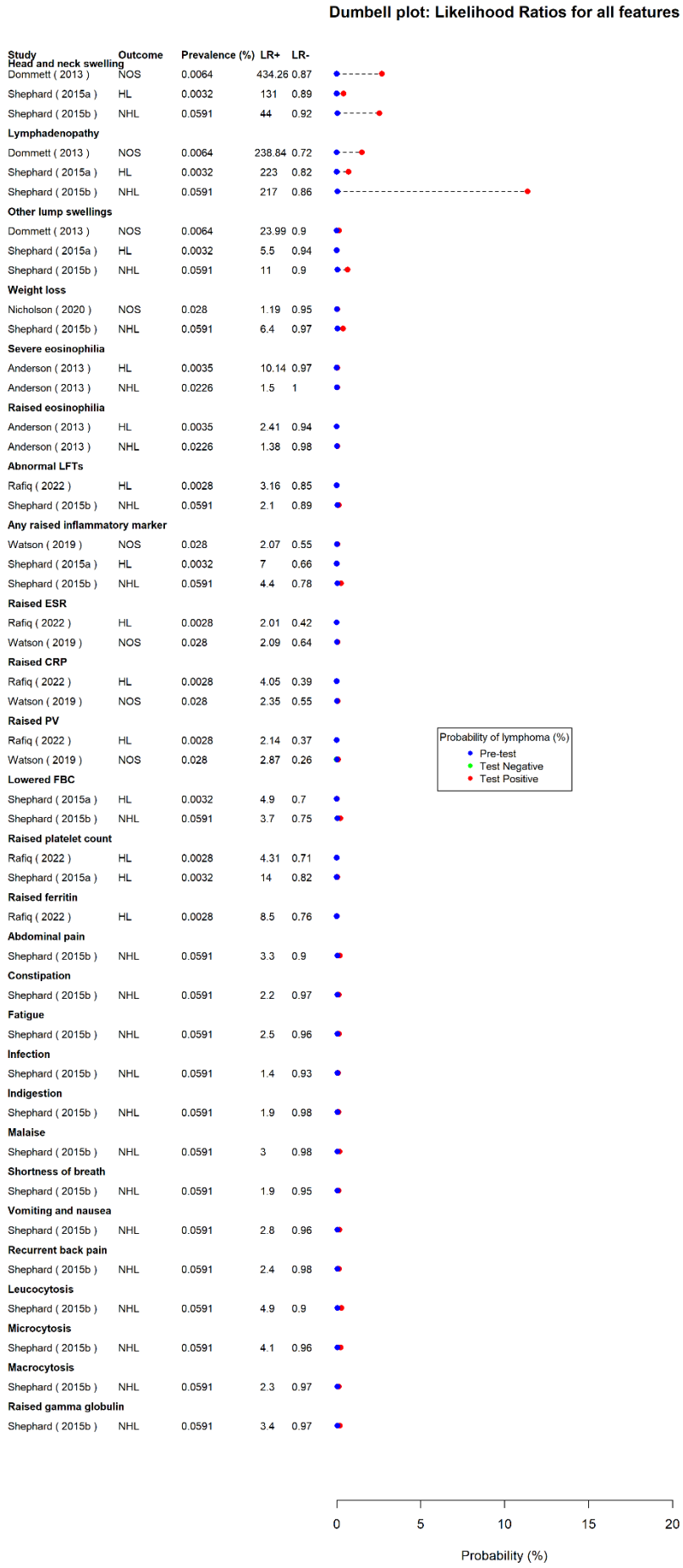
The reported ORs found in Table 7 are plotted here. The ORs for Rafiq 2022 have not been adjusted for.

Figure 13: Sensitivity and specificity forest plot by feature



Eosinophilia could only be separated into raised and severe eosinophilia. Figure 13 is ordered by age group (youngest to oldest).

Figure 14: Dumbbell plot



NOS = not otherwise specified;

HL = Hodgkin lymphoma;

NHL = Non-Hodgkin lymphoma;

FBC = Full blood count;

CRP = C-reactive protein;

ESR = erythrocyte sedimentation rate;

PV = plasma viscosity

Figure 14 is plotted by age (youngest to oldest)

Risk of bias assessment

Quality Assessment of Diagnostic Accuracy Studies 2

The QUADAS-2 risk of bias assessment was carried out on all studies to evaluate the risk of bias.

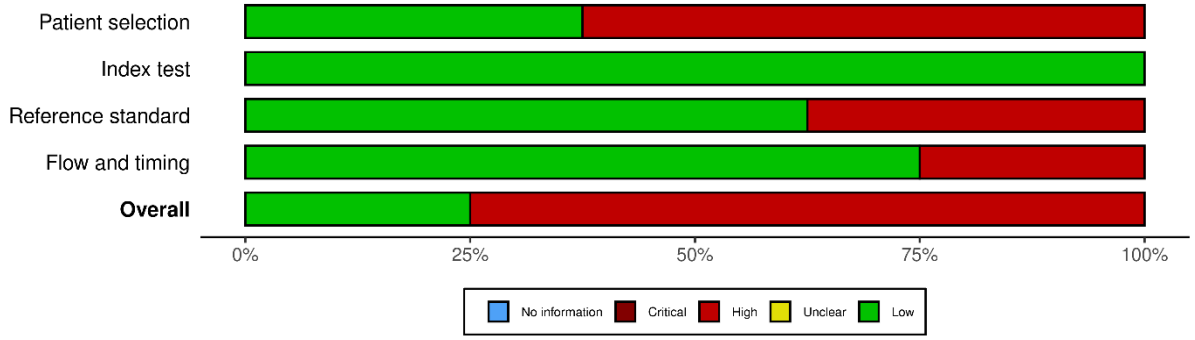
Table 8 presents the risk of bias results across all domains and the applicability concerns for the first three domains. The tool, its domains, criteria, scoring and justification of risk of bias assessment of studies can be found in Appendix 8a and 8b.

Table 8: Tabular representation of QUADAS-2 assessment

Study	**Risk of bias**				**Applicability concerns**		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Anderson 2013	Low	Low	Low	High	Low	Low	Low
Dommett 2013	High	Low	High	Low	High	Low	Low
Fortuny 2022	High	Low	Low	High	High	Low	Low
Nicholson 2020	Low	Low	Low	Low	Low	Low	Low
Rafiq 2022	High	Low	Low	Low	High	Low	Low
Shephard 2015a	High	Low	High	Low	High	Low	Low
Shephard 2015b	High	Low	High	Low	High	Low	Low
Watson 2019	Low	Low	Low	Low	Low	Low	Low

Figure 15: QUADAS-2 traffic light plot

Figure 16: QUADAS-2 summary plot



The tool improves on the Newcastle-Ottawa scale, Appendix 8c), by assessing the likelihood of the reference standard to correctly classify the target condition.

The majority of studies had a high overall risk of bias (6/8); only 2 studies had a low bias (Figure 16).

3/8 studies in the patient selection domain (D1) ranked low risk of bias. The remaining 5/8 (approx. 60%) studies ranked high risk of bias (selection bias). Despite appropriate patient selection criteria, only 3 studies were not case-control designs. On the other hand, adequate

defining and interpretation of the index test resulted in a low risk of bias for all studies in the index test domain (D2) (Figure 15).

3/8 studies scored a high risk of bias in the reference standard domain (D3) due to poor quality of the reference standard tests. These studies did not have record linkage to identify lymphoma diagnosis, increasing the risk of bias (125) (Figure 15).

The majority of studies, 6/8 had a low bias in the Flow and timing domain (D4). Only 2 studies ranked a high risk of bias as they (128, 130) did not meet the adequate follow-up time of up to 2 years. In all studies, all eligible patients were included in the analysis and all patients received a reference standard.

This review is interested in capturing features of lymphoma identified within primary care population with comparator group of healthy patients. In the assessment of applicability, the patient selection was deemed to be at a low risk of bias for all studies as no inappropriate exclusions were applied. In addition, the index tests and reference standard tests for all studies were applicable to this review.

Studies which examined the same feature, but differed in the risk of bias results in D3 included: Nicholson 2020 and Shephard 2015b for weight loss; Rafiq 2022, Watson 2019, Shephard 2015a and 2015b for raised inflammatory markers; and Rafiq 2022 and Shephard 2015a for raised platelet count. It is unlikely that differences in results are due to differences in the risk of bias.

Patient over-lap

The studies in this review have similar baseline characteristics (Table 4), including study location and study periods. Table 9 outlines the possible patient overlap between the studies.

Table 9: Potential patient overlap

Study	Anderson 2013	Dommett 2013	Fortuny 2022	Nicholson 2020	Rafiq 2022	Shephard 2015a	Shephard 2015b	Watson 2019
Anderson 2013								
Dommett 2013			✓	✓		✓	✓	
Fortuny 2022		✓			✓	✓	✓	
Nicholson 2020		✓			✓	✓	✓	
Rafiq 2022		✓	✓	✓		✓	✓	✓
Shephard 2015a		✓	✓	✓	✓			✓
Shephard 2015b		✓	✓	✓				✓
Watson 2019					✓	✓	✓	

A problem with patient overlap arises if the studies also have the same follow-up length and clinical feature recorded. This occurs between Dommett 2013 and Shephard 2015a & Shephard 2015b for lymphadenopathy, head and neck swelling and other lump swellings. This also occurs between Rafiq 2022, Watson 2019, Shephard 2015b and Shephard 2015a for raised inflammatory markers and raised platelet count.

Publication Bias:

No funnel plots for publication bias could be carried as the review identified insufficient studies.

Publication bias was found in 3 studies (96, 97, 129), which only reported the clinical features found to be significantly associated in univariate analysis at $p \leq 0.1$ with a lymphoma NOS, HL and NHL diagnosis respectively.

Chapter 4: Discussion/conclusion:

Summary of findings

Eight studies examining clinical features presenting in primary care that were associated with a diagnosis of lymphoma were identified and included in the review. They were all published between 2013 to 2022, indicating that research in this area has increased over the past decade. Amongst these studies, 4 investigated HL; 3 studies investigated NHL and 3 studies examined lymphoma NOS.

All symptoms and test abnormalities investigated were more prevalent amongst incident lymphoma cases than non-cases. However, serum cholesterol levels were lower in lymphoma patients but triglycerides levels were found to be similar. The symptoms with the strongest association with all types of lymphoma (HL, NHL and NOS) were lymphadenopathy, other lump swellings, head and neck swelling and raised inflammatory marker tests. These clinical features were amongst the most frequently reported in this review.

The majority of features in this review were confirmed to be positively associated with a lymphoma diagnosis when reported to primary care, exceptions included for raised ferritin for HL, mild/severe eosinophilia for NHL, mild eosinophilia for HL and serum lipid tests for both HL and NHL. The strength of association varied across clinical features and subtypes. The strongest association across all outcomes was for lymphadenopathy, with adjusted ORs of 184.5 (40.7,837.1) for lymphoma NOS; 263.0 (133.0, 519.0) for NHL, and 282.0 (25.0, 3123.0) for HL. Head and neck swellings and other lump swellings had lesser but considerable associations across subtypes. Raised CRP was also highly associated, with an unadjusted OR, 50.0 (6.9, 364.2) for HL.

The majority of features had low sensitivities, below 40%. On the contrary, the majority of specificities were strong, above 80%. The highest specificities across all subtypes were for lymphadenopathy and head and neck swelling, being close to 100%.

Across all outcomes of lymphoma, head and neck swelling, lymphadenopathy and other lump swellings had strong evidence to rule in a lymphoma diagnosis, with LR+s > 5. The presence of lymphadenopathy and head and neck swelling notably increased the probability of lymphoma in all studies, across all outcomes. The presence of other lump swellings had a marginal increase in the probability of NHL, but was not notable for HL and lymphoma NOS.

Severe eosinophilia, raised ferritin, any raised inflammatory marker and raised platelet count had strong evidence to rule in a HL diagnosis. Weight loss had strong evidence to rule in a NHL diagnosis. No clinical feature had a LR- <0.3, sufficient to rule out lymphoma. The absence of any of the clinical features did not affect the probability of lymphoma.

Amongst the PPVs for individual features, lymphadenopathy had the highest PPVs, 5.6% and 13% for HL and NHL, respectively. With the exception of lymphadenopathy and head and neck swellings, the remaining individual PPVs (Table 7 and Appendix 6) alongside their 95% CIs were very low, < 2%. Where combined features were reported, this often increased the PPVs. Combining lymphadenopathy with raised inflammatory markers or leucocytosis for NHL produced PPVs of 15%. Lymphadenopathy and head and neck swelling combined with other features substantially raised the PPVs of NHL, ≥ 4%(97).

Variation in results amongst similar clinical features were found due to the differing age range of patients, study design and the outcome of lymphoma under study. Head and neck swelling, eosinophilia, any raised inflammatory test, raised CRP test and serum cholesterol tests appeared to be a better diagnostic tool for HL; whereas lymphadenopathy and other

lump swellings for NHL. Raised PV seemed to be the best diagnostic tool for lymphoma NOS. Age may have played a role in differences in results for weight loss, raised platelet count, raised ESR, raised CRP, raised PV and abnormal liver function tests. Differing study design may have explained higher specificities and DORs in weight loss, raised CRP and any raised inflammatory marker test.

Six of the eight studies had a high overall risk of bias. The main sources were concerns on the defining and applicability of the reference standard and an inadequate follow-up interval.

Patient overlap across studies may explain the high similarity in the statistical results for lymphadenopathy, head and neck swelling and other lump swellings.

Table 10 provides a summary, showing the most informative features by outcome based on the association and diagnostic accuracy measures reported in this review.

Table 10: Most informative features by outcome

Lymphoma NOS	**HL**	**NHL**
Lymphadenopathy	Lymphadenopathy	Lymphadenopathy
Head and neck swelling	Other lump swellings	Other lump swellings
Raised PV	Head and neck swelling	Head and neck swelling
Other lump swellings	Raised ferritin	Weight loss
	Any inflammatory marker	
	Severe eosinophilia	
	Raised platelet count	
	Raised CRP	

The most informative features for each outcome of lymphoma are listed in Table 10. This is based on the association and diagnostic accuracy measures reported in this review.

Strengths and limitations

This review aims to improve the decision making for referral for suspected lymphoma patients through evidence-informed description of the salient predictive clinical manifestations of lymphoma observed within primary care.

Strengths

This is the first systematic compilation of published literature on the clinical manifestations of lymphoma reported within primary care. A strength is the restriction to the primary care population as the decision to refer patients to secondary care is based on the estimated risk of an underlying lymphoma within primary care. This cannot be done with secondary care data as the predictive values would be much higher, for example in referred populations or those presenting as an emergency. This is because GPs, for the former, would have already identified patients perceived to be at higher risk of cancer which could distort predictive values. Thus, the results of this review can better guide primary care in referral decisions (154), aiding earlier diagnosis, as findings will be more reflective of earlier presentations of disease onset.

Another strength is that a broad selection of clinical features were incorporated into the search criteria to ensure that all relevant studies were identified and the rigorous methodology used to ensure robust synthesise of all available evidence in this area.

The QUADAS-2 tool, designed for diagnostic accuracy studies, was applied to assess the risk of bias. The majority of included studies were found to have a low risk of bias when considering applicability in the patient selection, index test and reference standard domains.

By estimating the PPVs for all studies, using the age-specific incidence rates from CRUK (high quality national cancer incidence data), the reported PPVs were verified and comparisons of PPVs could be made between features (Appendix 6).

Limitations

All studies in this review relied solely on the accurate recording of symptoms and tests in medical records, hence are subject to recording bias (155). Clinicians tend to record characteristics deemed salient, resulting in a potential under-representation of the clinical manifestations of patients (156). An indication that this occurs can be demonstrated in studies using interviews to record self-reported symptoms, identifying a broader range of symptoms (68). This bias can result in inflated PPVs. Free-text amplifies clinical narrative after coding salient features, thus complete details of clinical features remain hidden, invisible to analyses solely using codes (157). Research which included free-text data reduced the PPV of jaundice for pancreatic cancer from 12.8% to 6.4% (157). That being said, three studies(97, 143, 148) in this review found minimal or little evidence for recording bias.

Moreover, additional data such as on severity and duration of these clinical features are unlikely to be recorded in medical records. This lack of high-quality data did not allow for a formal subgroup analysis. This remains to be addressed in future research.

A second limitation of this review is the small number of studies identified, which meant meta-analysis could only be conducted for raised platelet count in HL. Thus, this review cannot demonstrate precise statistical conclusions. However, this demonstrates the need for more primary care-based studies investigating the clinical feature of lymphoma.

A potential methodological limitation is that a majority of studies (5/8) are case control. Selection bias can falsely elevate sensitivity and specificity estimates. Moreover, odds ratios can be overestimated in case control studies (158). For example, with weight loss, the case control study, Shephard 2015b (97) had a higher specificity and unadjusted OR, 99.41% and 6.57 respectively compared to the cohort study, Nicholson 2020 (131), 80.64% and 1.25 respectively.

A further limitation was the presence of unadjusted confounding factors which may explain any observed associations(159). Where possible, we tried to obtain adjusted effect size measurements, however these were only reported in 5 of the studies reporting effect measures (128, 131, 143, 144, 148). As not every study reported ORs as an association measure, DORs were estimated, however these were unadjusted. The influence of potential confounders, for example the subtype of lymphoma and age were assessed in an informal heterogeneity analysis (160). Moreover, comorbidities were adjusted for in 3/8 studies (128, 130, 131).

QUADAS-2 ranked 3/8 studies with an unclear risk of bias in D4. These studies did not have record linkage to identify a lymphoma diagnosis, increasing the chance of misclassification bias, such as an under-recording of lymphomas (161). However, the majority of studies in this review (7/8) utilised CPRD records which has relatively high correctness (162, 163).

All studies except one were based in the UK. This is likely as a result of a sustained focus from major cancer funders in England on earlier cancer diagnosis in symptomatic patients attending primary care to improve national cancer outcomes (164-166). In conclusion, a limitation in the method in estimating PPVs is that the national incidence may not represent the incidence in the consulting primary care population who are symptomatic and therefore

anticipated to have higher cancer incidence. We used the most recent, 2020 age-specific prevalence to estimate the PPVs, which were marginally lower than previous years, due to the COVID-19 pandemic ,which resulted in a decrease in incidence for most cancers (2020) (167)due to disruptions in screening and diagnostic services, inevitably causing delays(167)Cancer incidence recovered to different extents in 2021–2022(167), however these prevalences could not be obtained for lymphoma. As the drop in incidence was only marginal (0.2 difference), the validity of our results will not be affected by using the 2020 prevalence for lymphoma.

Comparison of findings with existing literature

Consistent with previous research on cancer, this review has shown that lymphoma cases consulted their GP significantly more than controls in the year before diagnosis(96, 97, 129, 168).

This review demonstrates strong association with well-known clinical features of lymphoma. For example, lymphoma commonly presents with painless adenopathy(27). Consistent with secondary care literature, lymphadenopathy was strongly associated with lymphoma, conferring the highest risk for lymphoma NOS, HL and NHL(35, 169, 170). Research reports that approximately 30% patients report B symptoms (fever, drenching night sweats and unintentional weight loss)(5), associated with more advanced disease (27) – thus these patients should warrant further investigation if persistent and unexplained. However, within B symptoms, only weight loss was reported in this review, found to be associated with lymphoma NOS and NHL, with the highest predictive risk for a non-swelling feature of 0.4% (0.3%, 0.5%). No association was found between B symptoms and HL.

A broad range of non-red flag features was also identified that may play a central role in earlier detection of lymphoma, corroborating existing secondary care research including: shortness of breath, fatigue, indigestion, constipation and repeat infections, (68, 72). Low risk estimates of these features was likely due to their non-specific nature which can span several possible cancer sites. At a single cancer site level the risk may be small, but across cancer as a whole it may be important(171).

Absence of features identified from this review could be partially attributed to their low prevalence amongst lymphoma patients. Evidence from the English 2018 National Cancer Diagnosis Audit (NCDA) illustrates the prevalence of presenting symptoms of newly

diagnosed lymphoma patients (39), by subtype. For example, the prevalence of constipation, indigestion and shortness of breath is higher for NHL compared to HL, which may explain their absence in this review for HL (172).

Lymphadenopathy, weight loss and shortness of breath are the only features reported in the NICE referral guidelines for lymphoma identified from this review. Alcohol induced pain and splenomegaly, part of the NICE referral guidelines for lymphoma are both absent from this review. Alcohol induced pain is a very rare occurrence (173), reportedly in ≤ 0.5% of HL and NHL patients(90). Splenomegaly is an atypical presenting feature of NHL, not usually seen at initial presentation, although it may develop later (174). Moreover, splenomegaly is challenging to detect in primary care unless very enlarged or if the GP is suspicious of a diagnosis.

Consistent with previous research, this review finds that no single feature can definitively rule out a diagnosis of lymphoma, confirmed by the low estimated LR-s. However, strong evidence was found to rule in a lymphoma diagnosis amongst some clinical features identified in this review, contradicting previous research (47). Existing literature also reports on the majority of the test abnormalities identified in this review (27, 175-181). However, literature also reports lowered gamma globulin levels in patients with diffuse large B cell lymphoma (the most common NHL type) (182), contradicting the raised gamma globulin levels identified in this review.Amongst the most frequently reported tests in this review, the FBC has the highest use in primary care of 4272.1 per 10 000 person years (2015) (183), with 54% of NHL patients, the most common subtype of lymphoma reportedly tested in 2018 (184). The FBC test was not found to be very informative – diagnostic value was low. However, urea and electrolytes, not identified in this review has a test use of 3987

per 10 000 person years(185) [2009], with 47% of NHL reportedly tested in 2018(184).Several viral infections such as Epstein-Barr Virus (EBV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus **(**HIV) have been found to be associated with an increased risk of lymphomas(186). EBV is associated causally to Burkitt lymphoma, Hodgkin lymphoma, and various non-Hodgkin lymphomas (NHL) (187). HBV, HCV and HIV are associated with an increased risk of NHL(188-190).Despite these associations, viral tests have not formed part of the NICE guidelines. These tests are not cost effective as a mechanism for diagnosing lymphoma. Further evidence is needed to justify using these tests for risk stratification in diagnosis of lymphoma in primary care.

Plasma viscosity, drawn from 2 studies was identified as having the highest sensitivity for lymphoma NOS and HL. However, this test is not commonly ordered by GPs; it has a much lower test use in primary care per 10 000 person years (2005-2009) relative to CRP and ESR(191). More significantly, there are limitations to PV as a test. It is less accessible and technically more demanding(192) and its clinical utility is limited as it lacks specificity(193), reflecting only a general inflammatory response without identifying the underlying cause. It is often requested alongside ESR and CRP(194), but its diagnostic performance is broadly similar and low, creating redundancy. Simultaneous testing of multiple inflammatory markers does not improve the ability to rule out disease and leads to higher rates of discordant results and raises costs without tangible benefits(194).

However, relative to ESR and PV, CRP is more sensitive and specific for monitoring acute phase inflammation(195, 196) and is cheaper and more widely available (≈£1.19 vs ≈£3.18 for ESR/PV), (Bristol North Somerset and South Gloucester CCG laboratory costings). (194) As CRP is equivalent for autoimmune conditions and cancers, it is generally recommended

as the first-line test, which may explain why much fewer patients were tested amongst the two studies (132, 145)reporting PV in this review(194). Exceptions to this might include the use of ESR or PV rather than CRP for blood disorders such as myeloma(194).

Implications for future research and clinical practice

The review identified several features associated with lymphoma in patients presenting to primary care. Evidence of the important associations with lymphoma has been beneficial in the development of referral guidelines (67). Amongst these features, any raised inflammatory marker, raised platelet count, unexplained weight loss, lymphadenopathy, other lump swellings and head and neck swelling are strong indicators of a lymphoma diagnosis, based on LR+s warranting further investigation. Across all subtypes, lymphadenopathy and head and neck swelling are the best predictive features for lymphoma, with high PPVs and very strong specificities.

The majority of clinical features had a low sensitivity but very high specificities. Clinicians are likely to record symptoms believed to be important, yet many of these features are found in a range of clinical conditions. High specificity may reflect patients only attending primary care once the clinical feature is marked or may represent clinicians only coding the feature after conducting simple investigations to rule out other causes of the feature. In general, tests had higher sensitivities when compared with symptoms (Figure 13). Rafiq 2022, a study in this review has demonstrated that tests support earlier diagnosis in patients presenting with non-specific symptoms (132), which found that close to half of all HL patients with an abnormal inflammatory marker result had no other 'red-flag' features recorded (Appendix 2).

The estimated specificities were very high, close to or equal to 100% for the clinical features, lymphadenopathy, head and neck swelling, other lump swellings and severe eosinophilia. A potential explanation is that these features are very uncommon, especially in healthy individuals. For case control studies, the selection criteria emphasises that those that are

healthy become the controls. In a large population cohort, only a handful of patients will have the features. For example, in primary care practice, the annual incidence of unexplained lymphadenopathy is 0.6% (197). Only 1.1% of these cases are related to malignancy(197).

The early recognition of lymphoma remains a challenge. This review has highlighted the paucity of primary care research on the clinical features of lymphoma, based on the small number of studies identified. The existing NICE referral guidelines are largely based on evidence obtained from published literature (85) which is likely why the guidelines consist of a limited range of features(72). The guidelines thus are often based on alarm symptoms, identifying high-risk symptomatic patients, but may miss 'low-risk, but not no-risk' symptomatic patients(198). However, lymphoma presents with a broad range of symptoms (18). Nearly 87% of HL patients have reported symptoms before their diagnosis, rarely studied in primary care, where most patients initially present(35). Moreover, this review has found that ruling out lymphoma is difficult based on the absence of any of the clinical features identified. Thus, subsequent research should investigate and report a larger range of features, to more likely identify potential lymphoma. Additional presenting features that should be investigated, include: night sweats, pruritus, fever, alcohol induced pain(72), unexplained bleeding and bruising(68), unexplained splenomegaly(72), and genitourinary symptoms(68).

The PPVs of symptoms, signs, and non-diagnostic test results for cancer in primary care are generally low, making referrals challenging (199). The majority of PPVs reported in this review were very low. Only lymphadenopathy had a PPV exceeding the 3% referral threshold - 5.6% for HL and 13% for NHL patients (for patients≥ 60 years). Despite evidence

of low PPVs, the NICE referral guidelines are also based on clinical experience, thus includes commonly associated features of lymphoma such as fever, night sweats and weight loss, raising awareness amongst practitioners.

However, combining features generally increased the predictive risk. Lymphadenopathy combined with other features substantially raised PPVs for NHL(97). Combining lymphadenopathy with raised inflammatory markers or leucocytosis produced the highest PPVs of 15% for NHL (97). The guideline development group consider PPVs to be the most important outcome in identifying signs and symptoms to predict lymphoma(67). Thus, combinations of features should be explored further in future research.Future research should be stratified by subtypes of lymphoma. Table 10 shows a difference in the most informative features for each outcome of lymphoma. Moreover, there is evidence of different associations and diagnostic values amongst subtypes of lymphoma, for example for clinical features such as lymphadenopathy, weight loss and serum cholesterol tests. Referral guidelines should consider the value of separate triggers for referral versus simpler guidelines that are more likely to be followed. However, whether this is practical in primary care remains a question.

This review has given evidence that sex, age and stage can influence the presentation of lymphoma and can help risk stratify referral decisions, and should be considered in future analyses. Differing age has been shown to affect the diagnostic value for features including lymphadenopathy, head and neck swelling. The predictive risk for HL was shown to increase with age(96), comparing PPVs estimated for patients ≥40 years to ≥60 years(96). For weight loss, the hazard and risk ratios were reportedly higher for men and was found to be associated with increased late-stage cancer diagnoses.

Furthermore, the duration of a clinical feature can be a relevant factor. For example, an urgent investigation is warranted for persistent lymphadenopathy and head and neck swellings for over 6 weeks (96, 97); whereas after the initial 12-month period of presenting with weight loss, the risk of lymphoma becomes similar to those without weight loss (131). This is presumably due to the fact that if a malignant cause were underlying the weight loss it would have presented itself with other symptoms leading to investigation, within the 12-month period.

A diagnostic interval of up to a year was sufficient to capture the majority of abnormal results. However, as serum cholesterol (TSC, LDL-C and HDL-c) had a longer diagnostic interval of up to 12 years(130), it is beneficial to investigate longer intervals in further research.

As all studies in this review except one were based in the UK, the findings of this review are most applicable to countries with similar GP-led referral systems. As discussed earlier, the PPVs reported in this review may be lower due to the primary care population examined, in which cancer is a relatively rare occurrence(200). In contrast, in systems that allow direct specialist access or self-referral, patients typically present with higher-risk or alarm symptoms, increasing disease prevalence and therefore PPVs. In addition, several studies have shown that a test's sensitivity and specificity may vary with disease prevalence(201-204).

Therefore, the statistical results of this review are most applicable to countries with comparable referral pathways and diagnostic thresholds to the UK, including countries within the International Cancer Benchmarking Partnership, such as Denmark, Norway, Sweden, Australia and Canada(205).

However, the identified features from this review appear globally relevant, as lymphoma shows no evidence of regional variation in presentation. International literature consistently reports similar core symptoms, such as lymphadenopathy and B symptoms (87, 206-208), indicating broadly consistent worldwide symptom presentation.

To help guide a revision of the NICE guidelines, more research examining a broader range of clinical features of lymphoma within primary care is required. This review suggests that, to better support GPs in decision making for suspected lymphoma, particularly for patients presenting with non-specific symptoms, a common presentation, guidelines should include combinations of features, including test abnormalities in addition to symptoms to increase the predictive risk of lymphoma, helping to reach the 3% referral threshold. Predicted probabilities based on age, sex and stage may allow further risk stratification of patients.

Future research building on this review should investigate the features identified in this review to have an association with lymphoma or high predictive risk, as well as those features cited in literature to be linked to lymphoma, such as alcohol induced pain and splenomegaly. These features can be assessed on their ability to rule in or rule out a lymphoma diagnosis (individually and combined), calculating the change in the likelihood of lymphoma based on the presence or absence of the features. This can help guide the derivation of a clinical prediction tool to determine the risk of developing lymphoma for patients attending primary care based on combinations of presenting features (signs, symptoms and test results). A specialised clinical diagnostic prediction tool to calculate risk of lymphoma in general practice can assist clinicals in decision making, particularly under conditions of uncertainty, where patients are not presenting with alarm symptoms.

Conclusion

This thesis provides a comprehensive summary of the presentation of lymphoma within primary care, reporting the clinical features identified in existing literature by subtype. Across all subtypes, lymphadenopathy and head and neck swelling are the most predictive features. Age, sex and stage influenced risk for certain clinical features.

The challenges of recognising suspected lymphoma patients in primary care are highlighted. Heterogenous presentations of lymphoma are displayed; ruling out a diagnosis is difficult based on the absence of clinical features; and the majority of features have a low predictive risk, < 3%. However, combining features often increases the predictive risk. The review shows the duration of features is also important, art least for some features. Therefore, more primary care-based studies are needed to better explore the complex relationships that exist between the presence of symptoms, the characteristics of those experiencing them and the timelines under which they occur. Subsequent research, including a cohort study design, should investigate a wider range and combinations of clinical features, including tests, stratifying analysis by subtype, age, sex, and stage.

Appendix

APPENDIX 1: EMBASE Search Strategy

Database: Embase
Search Strategy:

1 primary medical care/ or primary health care/
2 general practice/ or family medicine/
3 general practitioner/
4 community medicine/
5 community care/ or community health nursing/
6 home visit/
7 ambulatory care/ or health center/
8 "pharmacy (shop)"/
9 emergency ward/
10 Emergency Medicine/
11 (primary adj2 (health* or care)).ti,ab,kf.
12 (((general or family) adj2 (pract* or doctor* or physician*)) or (gp or gps)).ti,ab,kf.
13 family medicine.ti,ab,kf.
14 ((health* or medical or diagnos*) adj2 (center? or centre?)).ti,ab,kf.
15 ((community adj2 nurs*) or health visitor? or district nurs*).ti,ab,kf.
16 (community adj2 (care or health* or service*)).ti,ab,kf.
17 (community adj2 pharmac*).ti,ab,kf.
18 ((home or house) adj (call? or visit?)).ti,ab,kf.
19 (primary care or primary health* or general practi* or family practi* or family medicine or family physician*).jw,in.
20 or/1-19
21 exp *Lymphoma/
22 lymphoma*.ti,ab,kf.
23 ((hodgkin* or nonhodgkin) adj disease).ti,ab,kf.
24 lymphoid disease?.ti,ab,kf. not (chronic lymphatic leuk?emia? or cll).ti.
25 or/21-24
26 exp *symptom/ or *symptomatology/ or *clinical feature/
27 (sign? or symptom? or feature? or manifestation? or flag? or alarm?).ti,ab,kf.
28 ((clinical or patient? or initial* or emergenc* or earl* or first or 1st) adj2 (presenting or presentation or contact?)).ab,kf.
29 "presenting with".ab,kf.
30 lymphadenopathy/
31 lymphadenopath*.ti,ab,kf.
32 (((swollen or enlarge*) adj2 (lymph node? or gland?)) or swelling or lumps).ti,ab,kf.
33 fatigue/ or lethargy/ or muscle fatigue/ or Muscle Weakness/
34 (tiredness or fatigue or letharg* or exhaust* or weakness).ti,ab,kf.
35 body weight loss/
36 (weight adj2 (loss or losing)).ti,ab,kf.

37 cold sweat/ or hot flush/ or night sweat/ or Sweating/
38 (sweat* or fever? or hot flash* or hot flush*).ti,ab,kf.
39 clinical skin reaction/ or exanthema subitum/ or exp rash/ or skin redness/ or pruritus/ or skin pruritus/
40 purpura/ or skin bleeding/ or *bleeding/ or epistaxis/ or menorrhagia/
41 (itching or itchiness or pruritus or rash or rashes).ti,ab,kf.
42 (nose bleed* or epistaxis or (heavy adj2 (period? or bleed* or menstru*)) or erythem* or petichia* or blood spot? or bruis* or contusion*).ti,ab,kf.
43 coughing/ or chronic cough/ or dyspnea/
44 (dyspn?ea or ((short* or difficult*) adj2 breath*) or breathless*).ti,ab,kf.
45 immunocompromised patient/ or recurrent infection/
46 (immunosuppress* or immunocompromis*).ti,ab,kf.
47 ((repeat* or frequen* or unexplained or increas* or recur* or reoccur* or re-occur*) adj3 infection?).ti,ab,kf.
48 Arthralgia/
49 (((joint or alcohol induced) adj2 pain) or arthralgia).ti,ab,kf.
50 constipation/ or diarrhea/
51 (constipat* or diarrhoea or diarrhea).ti,ab,kf.
52 or/26-51
53 20 and 25 and 52
54 hematological parameters/ or exp blood cell count/ or exp blood cell/an or erythrocyte sedimentation rate/ or exp erythrocyte parameters/
55 albumin blood level/
56 C reactive protein/an
57 Blood Viscosity/
58 ferritin/an or ferritin blood level/
59 lactate dehydrogenase/an [Drug Analysis]
60 exp immunoglobulin/an [Drug Analysis]
61 "thymus and activation regulated chemokine"/
62 ((blood or h?ematologic*) adj2 test*).ti,ab,kf.
63 ((blood or leukocyte? or cell or platelet?) adj2 count).ti,ab,kf.
64 (((blood or erythrocyte?) adj sedimentation rate) or esr).ti,ab,kf.
65 (crp or c-reactive protein).ti,ab,kf.
66 albumin?.ti,ab,kf.
67 (ldh or lactae dehydrogenase).ti,ab,kf.
68 ((ferritin? or apoferritin?) adj2 (concentration or blood? or serum?)).ti,ab,kf.
69 ((immunoglobulin? or paraprotien?) adj2 (blood? or serum?)).ti,ab,kf.
70 ((antibody or anti-body) adj (level? or blood? or serum?)).ti,ab,kf.
71 ((blood or plasma) adj viscosity).ti,ab,kf.
72 ("Thymus and activation-regulated chemokine" or tarc or cll-17 or cll17).ti,ab,kf.
73 *disease marker/ or *marker/ or *biological marker/ or exp *tumor marker/
74 biomarker?.ti,ab,kf.
75 ((inflammatory or biological or molecular) adj2 marker?).ti,ab,kf.
76 or/54-75
77 20 and 25 and 76

78 53 or 77
79 (exp animals/ or nonhuman/) not human/
80 (dogs or cats or mouse or mice or rat or rats or rodent?).ti.
81 79 or 80
82 78 not 81
83 conference*.pt.
84 82 not 83
85 82 and 83

APPENDIX 2: Rafiq 2022 supplementary table

Table S6: Proportion of tested Hodgkin lymphoma patients who had an abnormal inflammatory marker test stratified by presence of red-flag symptoms in the 12 months pre-diagnosis (n=594)

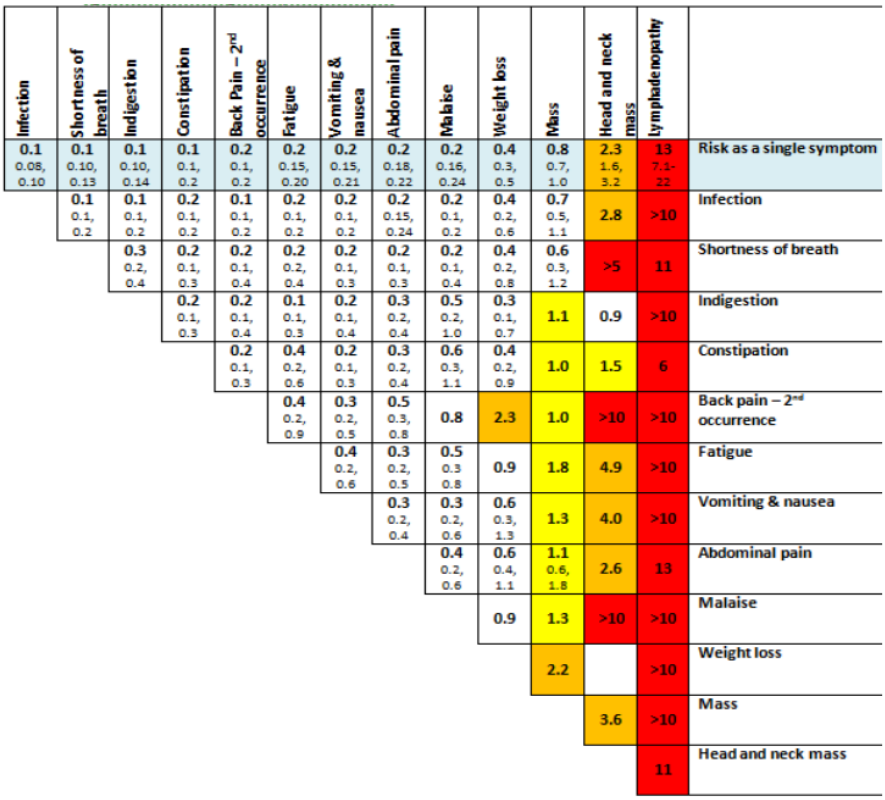
		Abnormal inflammatory marker test		
		No	Yes	Total
Red Flag	No	58 (32.0%)	176 (42.6%)	234 (39.4%)
	Yes	123 (68.0%)	237 (57.4%)	360 (60.1%)
	Total	181 (100%)	413 (100%)	594 (100%)

APPENDIX 3: Positive predictive values (PPVs) for HL from Shephard 2015a in patients aged ≥40 years for single and paired features:

Low full blood count	Raised inflammatory markers	Thrombocytosis	Lump	Head and neck lump	Lymphadenopathy	
0.02 0.01, 0.02	**0.02** 0.02, 0.03	**0.05** 0.03, 0.08	**0.02** 0.01,0.04	**0.4**	**0.7**	**Risk as a single symptom**
	0.04 0.02, 0.06	**0.05** 0.03,0.09		**0.9**	**2.5**	**Low full blood count**
		0.08	**0.9**	**1.1**	**2.8**	**Raised inflammatory markers**
					0.9	**Thrombocytosis**
						Lump/mass
					0.7	**Head and neck lump**

- PPVs not calculated if < 5 cases had the feature
- Confidence intervals are omitted if < 10 cases or controls had the combined features

APPENDIX 4: Positive predictive values (PPVs) for NHL from Shephard 2015b in patients aged ≥60 years for single and paired features



Infection	Shortness of breath	Indigestion	Constipation	Back Pain – 2nd occurrence	Fatigue	Vomiting & nausea	Abdominal pain	Malaise	Weight loss	Mass	Head and neck mass	lymphadenopathy	
0.1 (0.08, 0.10	0.1 (0.10, 0.13	0.1 (0.10, 0.14	0.1 (0.1, 0.2	0.2 (0.1, 0.2	0.2 (0.15, 0.20	0.2 (0.15, 0.21	0.2 (0.18, 0.22	0.2 (0.16, 0.24	0.4 (0.3, 0.5	0.8 (0.7, 1.0	2.3 (1.6, 3.2	13 (7.1-22	Risk as a single symptom
	0.1 (0.1, 0.2	0.1 (0.1, 0.2	0.2 (0.1, 0.2	0.1 (0.1, 0.2	0.2 (0.1, 0.2	0.2 (0.1, 0.2	0.2 (0.15, 0.24	0.2 (0.1, 0.2	0.4 (0.2, 0.6	0.7 (0.5, 1.1	2.8	>10	Infection
		0.3 (0.2, 0.4	0.2 (0.1, 0.3	0.2 (0.1, 0.4	0.2 (0.2, 0.4	0.2 (0.1, 0.3	0.2 (0.1, 0.3	0.2 (0.1, 0.4	0.4 (0.2, 0.8	0.6 (0.3, 1.2	>5	11	Shortness of breath
			0.2 (0.1, 0.3	0.2 (0.1, 0.4	0.1 (0.1, 0.3	0.2 (0.1, 0.4	0.3 (0.2, 0.4	0.5 (0.2, 1.0	0.3 (0.1, 0.7	1.1	0.9	>10	Indigestion
				0.2 (0.1, 0.3	0.4 (0.2, 0.6	0.2 (0.1, 0.3	0.3 (0.2, 0.4	0.6 (0.3, 1.1	0.4 (0.2, 0.9	1.0	1.5	6	Constipation
					0.4 (0.2, 0.9	0.3 (0.2, 0.5	0.5 (0.3, 0.8	0.8	2.3	1.0	>10	>10	Back pain – 2nd occurrence
						0.4 (0.2, 0.6	0.3 (0.2, 0.5	0.5 (0.3 0.8	0.9	1.8	4.9	>10	Fatigue
							0.3 (0.2, 0.4	0.3 (0.2, 0.6	0.6 (0.3, 1.3	1.3	4.0	>10	Vomiting & nausea
								0.4 (0.2, 0.6	0.6 (0.4, 1.1	1.1 (0.6, 1.8	2.6	13	Abdominal pain
									0.9	1.3	>10	>10	Malaise
										2.2		>10	Weight loss
											3.6	>10	Mass
												11	Head and neck mass

- PPVs not calculated if < 5 cases had the feature
- Confidence intervals are omitted if < 10 cases or controls had the combined features

APPENDIX 5: Positive predictive values for NHL from Shephard 2015b in patients aged ≥60 years for blood tests with symptoms:

Raised liver function tests	Macrocytosis	Raised gamma globulin	Low full blood count	Raised inflammatory markers	Microcytosis	Leucocytosis	
0.1 0.12to0.14	0.2 0.1to0.2	0.2 0.2to0.3	0.2 0.22to0.25	0.3 0.25to0.30	0.3 0.2to0.3	0.3 0.26to0.34	Risk of lymphoma as a single feature
>10	>10	>10	>10	15	>10	15	Lymphadenopathy
5.0	>10	>10	6	7	>10	6	Head and neck mass
1.1 0.7to1.9	1.1	1.0	1.5 0.9to2.4	2.3 1.3to4.2	0.9	2.1	Mass
1.5 0.8to2.8	0.2	3.5	0.9 0.6to1.3	0.8 0.6to1.3	1.4	1.0 0.5to2.0	Weight loss
0.4 0.3to0.6	0.1	0.8	0.4 0.3to0.6	0.5 0.3to0.7	0.6	0.5 0.3to0.9	Malaise
0.4 0.3to0.5	0.3 0.2to0.6	0.7 0.3to1.4	0.5 0.4to0.7	0.5 0.4to0.7	0.8 0.4to1.4	0.5 0.3to0.7	Abdominal pain
0.4 0.2to0.5	0.2 0.1to0.5	0.5	0.3 0.3to0.4	0.5 0.3to0.6	0.3 0.1to0.6	0.5 0.3to0.8	Vomiting and nausea
0.4 0.3to0.5	0.4 0.2to0.8	0.6 0.3to1.3	0.4 0.3to0.5	0.4 0.4to0.6	0.7 0.4to1.3	0.6 0.4to0.9	Fatigue
0.3 0.2to0.5	1.0	0.3	0.4 0.3to0.6	0.4 0.3to0.6	0.9	0.3 0.2to0.6	Back pain: 2nd occurrence
0.2 0.2to0.3	0.2 0.1to0.3	0.3 0.1to0.6	0.3 0.2to0.3	0.4 0.3to0.5	0.3 0.1to0.6	0.3 0.2to0.5	Constipation
0.2 0.1to0.3	0.2 0.1to0.5	0.2 0.1to0.5	0.3 0.2to0.4	0.3 0.2to0.4	0.7	0.4 0.2to0.8	Indigestion
0.2 0.2to0.3	0.2 0.1to0.3	0.3 0.2to0.5	0.3 0.2to0.3	0.3 0.2to0.3	0.3 0.2to0.4	0.3 0.2to0.5	Shortness of breath
0.2 0.1to0.2	0.2 0.1to0.3	0.3 0.2to0.4	0.3 0.2to0.3	0.3 0.2to0.3	0.4 0.2to0.5	0.3 0.2to0.4	Infection

- PPVs not calculated if < 5 cases had the feature
- CIs omitted if < 10 cases or controls had the combined features

APPENDIX 6: Reported and estimated positive predictive values

Feature	Outcome	Study	Prevalence used to obtain the reported PPVs	Reported PPV and 95% CI (%)	Prevalence used to estimate the PPVs***	Estimated PPV and 95% CI (%)
Raised eosinophilia	HL	Anderson 2013	-	-	0.000035	0.01 (0.00, 0.02)
Severe eosinophilia	HL	Anderson 2013	-	-	0.000035	0.04 (0.01, 0.11)
Raised eosinophilia	NHL	Anderson 2013	-	-	0.000226	0.03 (0.02, 0.04)
Severe eosinophilia	NHL	Anderson 2013	-	-	0.000226	0.03 (0.01, 0.10)
Lymphadenopathy	Lymphoma NOS	Dommett 2013	0.00001175*	0.28 (0.10,0.75)	0.000064	1.51 (0.56, 3.98)
Head and neck swelling	Lymphoma NOS	Dommett 2013	0.00001175*	0.5 (0.07,3.68)	0.000064	2.70 (0.38, 16.81)
Other lump swellings	Lymphoma NOS	Dommett 2013	0.00001175*	0.03 (0.02,0.05)	0.000064	0.15 (0.08, 0.28)
Weight loss	Lymphoma NOS	Nicholson 2020	-	-	0.00028	0.03 (0.03, 0.04)
Raised ESR	HL	Rafiq 2022	-	-	0.000028	0.01 (0.00,0.01)
Raised CRP	HL	Rafiq 2022	-	-	0.000028	0.01 (0.01, 0.02)
Raised PV	HL	Rafiq 2022	-	-	0.000028	0.01 (0.00, 0.01)
Raised platelet count	HL	Rafiq 2022	-	-	0.000028	0.01 (0.01, 0.02)
Raised ferritin	HL	Rafiq 2022	-	-	0.000028	0.02 (0.01, 0.06)
Lowered albumin	HL	Rafiq 2022	-	-	0.000028	0.01 (0.01, 0.01)
Lymphadenopathy	HL	Shephard 2015a	**Patients ≥ 40 years **** 0.00002857142	**Patients ≥ 40 years** 0.7 **Patients ≥ 60 years** 5.6	0.000032	0.71 (0.10, 4.89)
Head and neck swelling	HL	Shephard 2015a	**Patients ≥ 40 years **** 0.00002857142	**Patients ≥ 40 years** 0.4 **Patients ≥ 60 years** 2.3	0.000032	0.42 (0.06, 2.97)
Other lump swellings	HL	Shephard 2015a	**Patients ≥ 40 years **** 0.00002857142	**Patients ≥ 40 years** 0.02	0.000032	0.02 (0.01, 0.03)

				(0.01,0.04) **Patients ≥ 60 years** 0.03		
Any raised inflammatory markers	HL	Shephard 2015a	0.00002857142	0.02 (0.02,0.03)	0.000032	0.02 (0.02, 0.03)
Lowered full blood count	HL	Shephard 2015a	0.00002857142	0.02 (0.01,0.02)	0.000032	0.02 (0.01, 0.02)
Raised platelet count	HL	Shephard 2015a	0.00002857142	0.05 (0.03,0.08)	0.000032	0.04 (0.03, 0.08)
Lymphadenopathy	NHL	Shephard 2015b	0.00055793991	13 (7.1, 22)	0.000591	11.37 (6.90, 18.17)
Head and neck swelling	NHL	Shephard 2015b	0.00055793991	2.3 (1.6, 3.2)	0.000591	2.54 (1.82, 3.53)
Other lump swellings	NHL	Shephard 2015b	0.00055793991	0.8 (0.7, 1.0)	0.000591	0.62 (0.53, 0.73)
Weight loss	NHL	Shephard 2015b	0.00055793991	0.4 (0.3, 0.5)	0.000591	0.37 (0.30, 0.47)
Abdominal pain	NHL	Shephard 2015b	0.00055793991	0.2 (0.18 , 0.22)	0.000591	0.19 (0.17, 0.21)
Constipation	NHL	Shephard 2015b	0.00055793991	0.1 (0.1 , 0.2)	0.000591	0.13 (0.11, 0.15)
Fatigue	NHL	Shephard 2015b	0.00055793991	0.2 (0.15 , 0.20)	0.000591	0.14 (0.13, 0.17)
Infection	NHL	Shephard 2015b	0.00055793991	0.1 (0.08, 0.10)	0.000591	0.08 (0.08, 0.09)
Indigestion	NHL	Shephard 2015b	0.00055793991	0.1 (0.10 , 0.14)	0.000591	0.11 (0.09, 0.13)
Malaise	NHL	Shephard 2015b	0.00055793991	0.2 (0.16, 0.24)	0.000591	0.17 (0.14, 0.21)
Shortness of breath	NHL	Shephard 2015b	0.00055793991	0.1 (0.10 ,0.13)	0.000591	0.11 (0.10,0.12)
Vomiting and nausea	NHL	Shephard 2015b	0.00055793991	0.2 (0.15 , 0.21)	0.000591	0.17 (0.14,0.19)
Recurrent back pain	NHL	Shephard 2015b	0.00055793991	-	0.000591	0.14 (0.12,0.17)
Lowered full blood count	NHL	Shephard 2015b	0.00055793991	-	0.000591	0.22 (0.21,0.23)
Any raised inflammatory markers	NHL	Shephard 2015b	0.00055793991	-	0.000591	0.26 (0.24, 0.28)
Raised liver function tests	NHL	Shephard 2015b	0.00055793991	-	0.000591	0.12 (0.11, 0.13)
Leucocytosis	NHL	Shephard 2015b	0.00055793991	-	0.000591	0.29 (0.25, 0.32)
Microcytosis	NHL	Shephard 2015b	0.00055793991	-	0.000591	0.19 (0.16, 0.23)
Macrocytosis	NHL	Shephard 2015b	0.00055793991	-	0.000591	0.11 (0.09, 0.13)
Raised gamma globulin	NHL	Shephard 2015b	0.00055793991	-	0.000591	0.15 (0.12, 0.19)

Raised ESR	Lymphoma NOS	Watson 2019	-	-	0.00028	0.06 (0.05, 0.08)
Raised CRP	Lymphoma NOS	Watson 2019	-	-	0.00028	0.07 (0.05, 0.08)
Raised PV	Lymphoma NOS	Watson 2019	-	-	0.00028	0.08 (0.06, 0.10)
Any raised inflammatory markers	Lymphoma NOS	Watson 2019	-	-	0.00028	0.06 (0.05, 0.07)

**a 3-month incidence is taken as prevalence, derived from 2007 lymphoma annual national incidence for teenagers and young adults, 0.47 per 10,000.*

Thus, the reported PPVs from Dommett 2013 are 3-monthly.

Shephard 2015a and Shephard 2015b use age-specific annual national incidences from 2008 for HL and NHL respectively.

***Prevalence could not be obtained for patients ≥ 60 years.*

**** All estimated PPVs use an annual prevalence. Derived using the most up to date age specific national annual incidence rates from the cancer registration statistics from the National Disease Registration Service (NDRS), England 2020 (107)*

Lowered albumin and raised liver function tests are also referred to as abnormal liver function tests.

PPVs for Shephard 2015a and Shephard 2015b are estimated using an age prevalence of ≥40 years and ≥60 years respectively.

APPENDIX 7: Watson 2019 results tables

Tested cohort, type of inflammatory marker test done:

Type of inflammatory marker test done	Freq.	Percent	Cum.
CRP	50,027	32.14	32.14
ESR	39,427	25.33	57.47
PV	4,647	2.99	60.46
CRP + ESR	50,522	32.46	92.92
CRP + PV	10,494	6.74	99.66
PV + ESR	132	0.08	99.74
CRP + ESR + PV	397	0.26	100.00
Total	155,646	100.00	

2x2 tables for lymphoma:

CRP tested cohort

CRP above 7	lymphoma 0	1	Total
0	83,457	23	83,480
1	27,927	33	27,960
Total	111,384	56	111,440

ESR tested cohort:

ESR above mean ULN for gender/age	lymphoma 0	1	Total
0	68,014	26	68,040
1	22,410	28	22,438
Total	90,424	54	90,478

PV tested cohort:

PV above | 1.72 |	lymphoma 0	1	Total
0	11,225	3	11,228
1	4,429	13	4,442
Total	15,654	16	15,670

Combined data for any raised inflammatory marker:

any RIM on index date | above | specified cutoffs |	lymphoma 0	1	Total
0	109,518	36	109,554
1	46,035	57	46,092
Total	155,553	93	155,646

APPENDIX 8: Supporting Material for Risk of bias assessment: tool guidance

a) Supporting Material for QUADAS-2 Risk of bias assessment

Algorithm for Domain-level judgements:

- If all signalling questions are marked as “Low”, then overall RISK OF BIAS => “Low”
- If any signalling question is marked as “High/Unclear”, then overall RISK OF BIAS => “High”
- If all signalling questions are marked as “Unclear”, then overall RISK OF BIAS=> “Unclear”

Signalling Question Guidance

A) **STUDY DESIGN & PARTICIPANT SELECTION**

1) Was a case-control design avoided?

   Bias assessed: Selection bias

   Low: A case-control study design with regards to the outcome of interest was not employed. **This refers to a participant selection method that is dependent on true outcome status.**

   High: A case-control design for the outcome of interest was employed.

   Unclear: There is insufficient information provided to make a judgement.

2) Was a consecutive or random sample of participants enrolled?

   Bias assessed: Selection bias

Low: A consecutive/random sample of participants, or all eligible participants, were included.

High: A non-random sub-sample of participants were included.

Unclear: There is insufficient information provided to make a judgement.

3) Did the study avoid inappropriate exclusions?

Bias assessed: Limited challenge bias

Low: Inappropriate exclusions were avoided.

High: Inappropriate exclusions were not avoided.

Unclear: There is insufficient information provided to make a judgement.

B) **INDEX TEST**

1) Were the index test(s) results interpreted without knowledge of the results of the reference standard?

Bias assessed: Information bias

Low: The results of the index test(s) were interpreted without knowledge of the reference test result. This may include studies where blinding of the index test(s) is not explicitly stated but is implied due to the large volume of data - the researchers are not likely to use knowledge of the participants disease status to help to interpret whether the index test is positive or negative.

High: The results of the index test(s) were interpreted with knowledge of the reference test result.

Unclear: There is insufficient information provided to make a judgement.

2) If a threshold was used, was it pre-specified?

If not explicitly stated, it was assumed a threshold was pre-specified if the study utilised CPRD data, as access to the data requires pre-specification of data items, including preparation of code lists.

C) **REFERENCE STANDARD**

1) Is the reference standard likely to correctly classify the target condition?

Bias assessed: Verification bias

Low: If the reference standard is identified through record linkage, e.g. HES, ONS or cancer registries.

High: The reference standard is unlikely to accurately classify the target condition, due to using only primary care records to identify a lymphoma diagnosis.

Unclear: There is insufficient information provided to make a judgement.

2) Were the reference standard results interpreted without knowledge of the results of the index test?

Bias assessed: Information bias

Low: The results of the reference standard were interpreted without knowledge of the index test result. This may include studies where blinding of the index test(s) is not explicitly stated but is implied due to the large volume of data - the researchers are not likely to use knowledge of the index test status to help interpret whether participants disease (lymphoma) status from the reference standard.

High: The results of the reference standard were interpreted with knowledge of the index test result.

Unclear: There is insufficient information provided to make a judgement.

D) **FLOW AND TIMING**

1) Was there an appropriate interval between index test(s) and reference standard?

   Bias assessed: Delayed verification bias

   Low: Data for index test(s) were selected up to 2 years prior to date of identification of reference standard test result.

   High: Data for index test(s) were selected for more than 2 years prior to date of identification of reference standard test result.

   Unclear: There is insufficient information provided to make a judgement.

2) Did all participants receive a reference standard?

   Bias assessed: Partial verification bias

Low: The reference standard was performed for all of the eligible patients who received index tests.

High: The reference test was performed only on a non-random sample of the patients who received the index test(s).

Unclear: There is insufficient information provided to make a judgement.

3) Did all participants receive the same reference standard?

Bias assessed: Differential verification bias

Low: All participants received the same reference standard – the same datasets were used to identify presence of lymphoma diagnosis.

High: Patients received different reference standard tests. A consistent method not employed to identify presence of lymphoma diagnosis.

Unclear: There is insufficient information provided to make a judgement.

4) Response rate: were all participants included in the analysis?

Bias assessed: Participation bias

Low: The number of eligible patients were included in the final analysis

High: The number of patients included in the final analysis did not match the number of eligible patients.

Unclear: There is insufficient information provided to make a judgement.

b) Supplementary Table 1 – Justification of QUADAS-2 signalling question judgements by study.

Study	Domain	Prompt	Justification	Decision
Anderson 2013	Study Design & Patient Selection	1) Was a consecutive or random sample of patients enrolled?	Random selection of patients with at least one DIFF requested by primary care physicians in period 1.1.2001 to 31.12.2007 encompassing the eosinophil count, aged 18-80 years in Copenhagen.	Yes
		2) Was a case-control design avoided?	A cohort study design was used.	Yes
		3) Did the study avoid inappropriate exclusions?	Patients were omitted from the analysis only if they had previous cancer before their index DIFF.	Yes
	Index Test	1) Were the index test results interpreted without knowledge of the results of the reference standard?	Cohort study design was used, thus patients were assigned to status of eosinophilia prior to obtaining lymphoma status.	Yes
		2) If a threshold was used, was it pre-specified?	The study states the thresholds for mild, severe and no eosinophilia.	Yes
	Reference standard	1) Is the reference standard likely to correctly classify the target condition?	CopDiff database linked to Danish Cancer Registry (DCR) used to identify lymphoma diagnoses.	Yes

		2)Were the reference standard results interpreted without knowledge of the results of the index test?	Large dataset study, thus the researchers unlikely to use the knowledge of the participants index test status to help to interpret the lymphoma status.	Yes
	Flow & Timing	1) Was there an appropriate interval between index test(s) and reference standard?	3-year follow-up of patients from index test DIFF.	No
		2)Did all participants receive a reference standard?	All 356,196 in the total cohort of patients irrespective of their eosinophil status (no, mild or severe eosinophilia) received a reference standard test.	Yes
		3) Did all participants receive the same reference standard?	The 2 reference standard datasets used to identify lymphoma diagnosis for all patients were CopDiff and DCR.	Yes
		4) Were all patients included in the analysis?	All 356,196 patients identified with one DIFF encompassing the eosinophil count were included in the analyses.	Yes

Study	Domain	Prompt	Justification	Decision
Dommett 2013	Study Design & Patient Selection	1) Was a consecutive or random sample of patients enrolled?	Cases are recruited via General Practice Research Database (GPRD).	Yes
		2) Was a case-control design avoided?	A case-control study design was used.	No
		3) Did the study avoid inappropriate exclusions?	Only GP practices contributing research-standard data for at least 1 year before the child's date of cancer diagnosis were included. All cases and controls were included in the analysis, irrespective of whether or not they had consulted.	Yes
	Index test	1) Were the index test results interpreted without knowledge of the results of the reference standard?	As study uses large healthcare databases, the researchers are unlikely to use knowledge of the participants lymphoma status to help to interpret whether the index test is positive or negative.	Yes
		2) If a threshold was used, was it pre-specified?	Study mentions the construction of code lists using established methodology from earlier conducted study. Moreover, as this is a GPRD study, thresholds will have it to have been pre-specified beforehand.	Yes
	Reference Standard	1) Is the reference standard likely to correctly classify the target condition?	Only the GPRD primary care dataset is used to identify a lymphoma diagnosis.	No

		2) Were the reference standard results interpreted without knowledge of the results of the index test?	A case-control study design was used, thus patients are assigned to cases and controls prior to obtaining the index test status.	Yes
	Flow & Timing	1) Was there an appropriate interval between index test(s) and reference standard?	The follow-back period was 3 months.	Yes
		2) Did all participants receive a reference standard?	GPRD records were used to assign eligible patients to case and control status.	Yes
		3) Did all participants receive the same reference standard?	Only GPRD records were used to identify the lymphoma status of all patients.	Yes
		4) Were all participants included in the analysis?	All 270 eligible lymphoma cases and 3350 matched controls entered the multivariable analysis for lymphoma.	Yes

Study	Domain	Prompt	Justification	Decision
Fortuny 2022	Study Design & Patient Selection	1) Was a consecutive or random sample of patients enrolled?	Cases identified using clinical records (CRPD Gold and HES data). Controls selected from same base population as cases, at random with the same exclusion criteria.	Yes
		2) Was a case-control design avoided?	A case-control study design was used.	No
		3) Did the study avoid inappropriate exclusions?	Selection criteria for both cases and controls: No evidence of another cancer diagnosis (except non-melanoma skin cancer) before or on the index date (the date of first lymphoma diagnosis).	Yes
	Index Test	1) Were the index test results interpreted without knowledge of the results of the reference standard?	As study uses large healthcare databases, the researchers are unlikely to use knowledge of the participants lymphoma status to help to interpret whether the index test is positive or negative.	Yes
		2) If a threshold was used, was it pre-specified?	CRPD study, therefore pre-specification of thresholds for cholesterol and triglycerides levels were required. The study reports the thresholds used for total serum cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides. See Table 5 for the thresholds used.	Yes

	Reference Standard	1)Is the reference standard likely to correctly classify the target condition?	Lymphoma status was identified using both CRPD GOLD and HES data (secondary care linkage).	Yes
		2)Were the reference standard results interpreted without knowledge of the results of the index test?	Case-control study design was used, thus patients assigned to cases and controls prior to obtaining the index test status.	Yes
	Flow & Timing	1) Was there an appropriate interval between index test(s) and reference standard?	The average follow-back period for each lipid measurement amongst cases and controls ranged between 10-12 years.	No
		2) Did all participants receive a reference standard?	CPRD Gold and HES data used to identify the eligible cases and controls.	Yes
		3) Did all participants receive the same reference standard?	CPRD GOLD and HES data records used as reference standards for all patients.	Yes
		4) Were all participants included in the analysis?	Patients with HL, NHL and unspecified lymphoma were analysed separately, but the results for unspecified lymphoma patients were not reported in the paper.	Yes

Study	Domain	Prompt	Justification	Risk of bias

Nicholson 2020	Study Design & Patient Selection	1) Was a consecutive or random sample of patients enrolled?	Base population, entry into cohort: NHS patients from England and Wales aged > 18 years registered with an up to standard GP practice with acceptable CPRD records b/w 2000 and 2014	Yes
		2) Was a case-control design avoided?	A cohort study design used.	Yes
		3) Did the study avoid inappropriate exclusions?	Exclusion criteria for patients with: previous cancer, recent weight loss intervention in previous 6 months (e.g. weight loss medication or bariatric surgery) and < 1 year registration *If a patient with unexpected weight loss (UWL) was excluded, their matched comparators were excluded. If a comparator patient without unexpected weight loss was excluded, only that one comparator was excluded.*	Yes
	Index Test	1) Were the index test results interpreted without knowledge of the results of the reference standard?	Cohort study design was used, thus patients with UWL and without UWL identified before obtaining lymphoma status.	Yes

		2) If a threshold was used, was it pre-specified?	CPRD study, therefore thresholds would have to have been pre-specified. Codes defining UWL can be found in the paper's supplementary Information 1. Previously conducted Nicholson study references Read codes for UWL representing a mean loss of ≥5% in a 6-month period.	Yes
	Reference Standard	1)Is the reference standard likely to correctly classify the target condition?	First lymphoma code following index date taken via CPRD, ONS and Cancer registry codes used to identify diagnosis of lymphoma	Yes
		2) Were the reference standard results interpreted without knowledge of the results of the index test?	Large dataset study, thus the researchers unlikely to use the knowledge of the participants index test status to help to interpret the lymphoma status.	Yes
	Flow and Timing	1) Was there an appropriate interval between index test(s) and reference standard?	2 years follow-up after the index date.	Yes
		2) Did all patients receive a reference standard?	All eligible patients with and without UWL had reference standard tests applied.	Yes
		3) Did patients receive the same reference standard?	CPRD, ONS and Cancer registry records used as reference standard tests for all patients.	Yes

		4) Were all patients included in the analysis?	Amongst the eligible population, N = 330444, 63973 UWL patients and 266,471 without UWL patients were followed up.	Yes

Study	Domain	Prompt	Justification	Risk of bias
Rafiq 2022		1)Was a consecutive or random sample of patients enrolled?	Patients in the case group were individuals defined as having a new diagnosis of Hodgkin lymphoma (HL) in	Yes

	Study Design & Patient Selection		either CPRD or HES between 1 January 2003 and 31 July 2016, with the earliest recorded date of diagnosis taken as the index date. 6 controls were individually matched randomly to each person in the case group based on sex and age at index date (plus or minus 1 year of age).	
		2) Was a case-control design avoided?	A case-control study design was used.	No
		3) Did the study avoid inappropriate exclusions?	Patients were excluded if they had a previous diagnosis of HL or if the diagnosis was made within 1 year of registering with their practice.	Yes
	Index Test	1) Were the index test results interpreted without knowledge of the results of the reference standard?	As study uses large healthcare databases, the researchers are unlikely to use knowledge of the participants lymphoma status to help to interpret whether the index test is positive or negative.	Yes
		2) If a threshold was used, was it pre-specified?	A CRPD study, therefore pre-specification of thresholds for inflammatory marker tests were required.	Yes

	Reference Standard	1)Is the reference standard likely to correctly classify the target condition?	Diagnosis of HL obtained from CPRD with linkage to HES records. Codes are available by requesting access from the authors to supplementary table 1.	Yes
		2)Were the reference standard results interpreted without knowledge of the results of the index test?	A case-control study design, thus patients assigned to cases and controls prior to obtaining the index test status.	Yes
	Flow & Timing	1)Was there an appropriate interval between index test(s) and reference standard?	12 months follow-back from the index date.	Yes
		2)Did all participants receive a reference standard?	Identification of eligible HL cases and controls using CPRD with linkage to HES records	Yes
		3)Did all participants receive the same reference standard?	CPRD and HES data records used as reference standard tests for all patients.	Yes
		4)Were all participants included in the analysis?	Analysis carried out for all 5035 eligible controls and 839 eligible cases.	Yes

Study	Domain	Prompt	Justification	Risk of bias
Shephard 2015a	Study Design & Patient Selection	1) Was a consecutive or random sample of patients enrolled?	Patients identified from Clinical Practice Research Datalink patient records (CPRD). Cases selected if: aged ≥ 40 years Diagnosed between January 2000-December 2009 The first HL code was taken as the date of diagnosis (index date)	Yes
		2) Was a case-control design avoided?	A case-control study design was used.	No
		3) Did the study avoid inappropriate exclusions?	Exclusion criteria: Cases and matched controls with non-Hodgkin lymphoma (NHL), mycosis fungoides or Sezary syndrome. Case or control with < 1 year of records before index date. Cases without controls Controls with HL. Controls not sought medical care after registration (non-consulter).	Yes
		1) Were the index test results interpreted without knowledge of the results of the reference standard?	As study uses large healthcare databases, the researchers are unlikely to use knowledge of the participants lymphoma status to help to interpret whether the index test is positive or negative	Yes

	Index Test	2) If a threshold was used, was it pre-specified?	CRPD study, therefore pre-specification of thresholds for symptoms and test abnormalities were required.	Yes
	Reference Standard	1) Is the reference standard likely to correctly classify the target condition?	Only primary care CPRD data records are used to identify HL diagnosis. Code list of 29 HL codes assembled and available upon request from authors.	No
		2)Were the reference standard results interpreted without the results of the index test?	Case-control study design, thus patients assigned to cases and controls prior to obtaining the index test status.	Yes
	Flow & Timing	1) Was there an appropriate interval between index test(s) and reference standard?	1 year follow-back period.	Yes
		2) Did all participants receive a reference standard?	CRPD records were used to assign patients to either case or control status using records of a HL diagnosis.	Yes
		3) Did all participants receive the same reference standard?	Only CPRD records were used to identify HL diagnosis for all patients	Yes
		4) Were all participants included in the analysis?	All eligible controls, 1237 and eligible cases, 283 entered the analysis.	Yes

Study	Domain	Prompt	Justification	Decision
Shephard 2015b	Study Design & Patient Selection	1) Was a consecutive or random sample of patients enrolled?	Cases selected from CPRD if aged ≥ 40 years and diagnosed b/w Jan 2000-December 2009. The first NHL code was taken as the date of diagnosis (index date).	Yes

		2) Was a case-control design avoided?	A case-control study design used	No
		3) Did the study avoid inappropriate exclusions?	Exclusion criteria: Cases and their matched controls with HL, mycosis fungoides, or Sezary syndrome Patients with < 1 year of records before index date. Cases without controls Controls with NHL Controls not sought medical care after registration (non-consulter)	Yes
	Index Test	1) Were the index test results interpreted without knowledge of the results of the reference standard?	As study uses large healthcare databases, the researchers are unlikely to use knowledge of the participants lymphoma status to help to interpret whether the index test is positive or negative	Yes
		2) If a threshold was used, was it pre-specified?	CRPD study, therefore pre-specification of thresholds for symptoms and test abnormalities were required.	Yes
	Reference Standard	1) Is the reference standard likely to correctly classify the target condition?	Only primary care CPRD records are used to identify NHL disease status. A list of 106 NHL codes used available from authors.	No
		2) Were the reference standard results interpreted without knowledge of the results of the index test?	Case-control study design, patients assigned to cases and controls prior to obtaining the index test status.	Yes

	Flow & Timing	1) Was there an appropriate interval between index test(s) and reference standard?	1 year follow-back period.	Yes
		2) Did all participants receive a reference standard?	CRPD records used to assign patients to either case or control status using records of a NHL diagnosis.	Yes
		3) Did all participants receive the same reference standard?	CPRD records used to identify NHL diagnosis for all patients.	Yes
		4) Were all participants included in the analysis?	All eligible controls, 19468 and eligible cases, 4362 were included in the analysis.	Yes

Study	Domain	Prompt	Justification	Decision
Watson 2019	Study Design & Patient Selection	1) Was a consecutive or random sample of patients enrolled?	Patients (n=160,000) aged ≥18, of either sex, who had a primary care inflammatory marker blood test (CRP, ESR or PV) taken in 2014, selected **at random** in CPRD.	Yes

	2) Was a case-control design avoided?	A cohort study design was used.	Yes
	3) Did the study avoid inappropriate exclusions?	Patients were omitted from the analysis if: Pre-existing cancer (in 2-year period before the index date). Index date was defined as the first date of inflammatory marker blood testing in 2014. Only for the tested cohort - Missing index test results Spurious test results	Yes
Index Test	1) Were the index test results interpreted without knowledge of the results of the reference standard?	Cohort study design, thus patients were assigned to status of prior to obtaining lymphoma status.	Yes
	2) If a threshold was used, was it pre-specified?	The study states the thresholds: • CRP, threshold of 7mg/l. • PV, threshold of 1.72mPa.s. •ESR, above mean upper limit of normal, stratified by gender/age, which varied from 11mm/h for women under 40, to 23mm/h for men over 80.	Yes
Reference standard	1) Is the reference standard likely to correctly classify the target condition?	The reference standard uses record linkage: CPRD with linked Cancer registry	Yes
	2)Were the reference standard results interpreted without knowledge of the results of the index test?	This is a large dataset study, thus the researchers are unlikely to use the knowledge of the participants index test status to help to interpret the lymphoma status.	Yes

	Flow & Timing	1) Was there an appropriate interval between index test(s) and reference standard?	1 year follow-up period.	Yes
		2)Did all participants receive a reference standard?	CRPD and/or cancer registry data were used as reference standard tests for both the tested and untested cohorts.	Yes
		3) Did all participants receive the same reference standard?	The same reference standard datasets (CPRD and cancer registry) were used to identify a lymphoma diagnosis for all patients.	Yes
		4) Were all patients included in the analysis?	We were only interested in the tested cohort (n = 155,646), all of which were used in the analysis.	Yes

c) Newcastle Ottawa Scale

The maximum score to be obtained for the Newcastle Ottawa Scale was nine stars.

The Scoring system used per domain:

Selection (D1): 0-1 (High bias); 2 (Some Concerns with bias); 3+ (Low bias)

Comparability (D2): 0 (High bias); 1 (Some Concerns with bias); 2+ (Low bias)

Exposure/Outcome (D3): 0 (High bias); 1 (Some Concerns with bias); 2+ (Low bias)

An overall score of 7 or higher was considered a low RISK OF BIAS, those with a score of 5 to 6 were considered with some bias concerns, and studies with a score below 5 were considered to have a high risk of bias.

For the cohort study assessment, an appropriate follow-up threshold of up to 2 years and an adequate follow-up of 80% were taken.

Table 2: Tabular representation of Newcastle Ottawa Scale results for case-control studies

	Selection				**Comparability**	**Exposure**			
Study	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	Overall
Dommett, 2013	1	1	1	1	2	1	1	1	9
Fortuny, 2022	1	1	1	1	2	1	1	1	9
Rafiq, 2022	1	1	1	1	2	1	1	1	9
Shephard, 2015a	1	1	1	1	2	1	1	1	9
Shephard, 2015b	1	1	1	1	2	1	1	1	9

Table 3: Tabular representation of Newcastle Ottawa Scale results for cohort studies

	Selection				Comparability	Outcome			
Study	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur[a]	Adequacy of follow up of cohorts[b]	Overall
Anderson, 2013	1	1	1	1	2	1	0	0	7
Nicholson, 2020	1	1	1	1	2	1	1	0	8
Watson 2019	1	1	1	1	2	1	1	0	8

[a] Up to 2 year follow-up threshold taken, [b] 80% follow-up threshold taken

The overall risk of bias was found to be low (good quality) for all studies, across all domains (Tables 2-3).

All the case-control studies received full points using the Newcastle Ottawa Scale, whereas the cohort studies lost only one point each in the "Adequacy of follow up of cohorts" criteria as no statement was given on the follow-up rate of patients.

Figure 1: Traffic light plots of Newcastle Ottawa Scale for case control and cohort studies

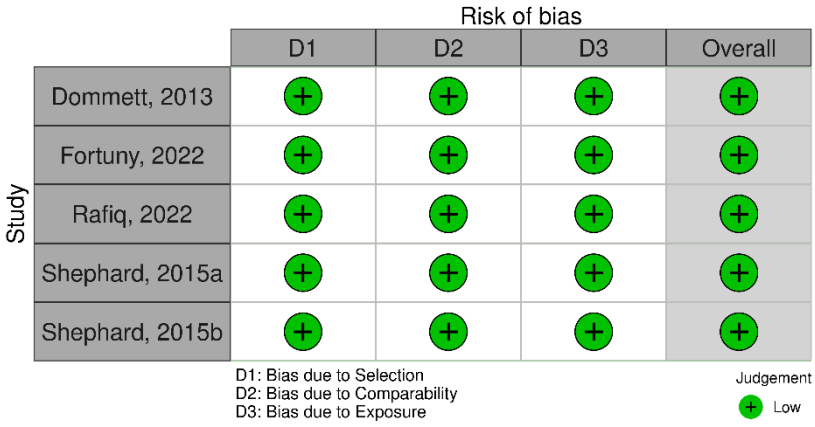


Figure 1a) Traffic light plot for case-control studies

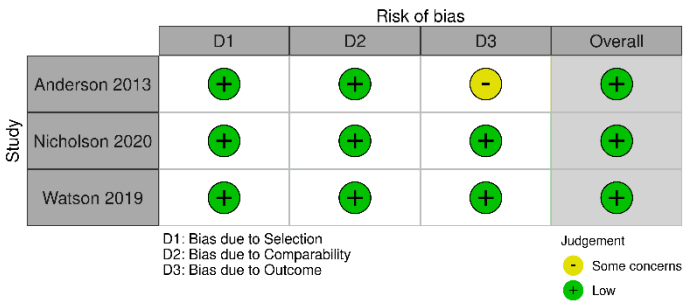


Figure 1b) Traffic light plot for cohort studies

Figure 2: Summary plots for case-control and *cohort studies*

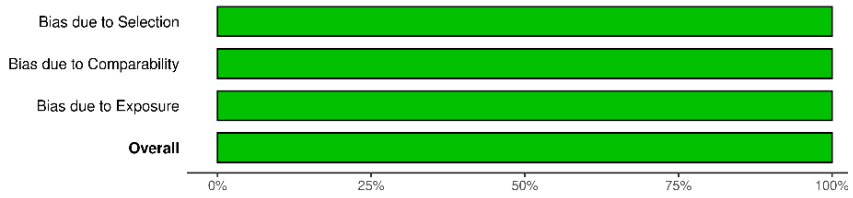


Figure 2a) Summary plot for case-control studies

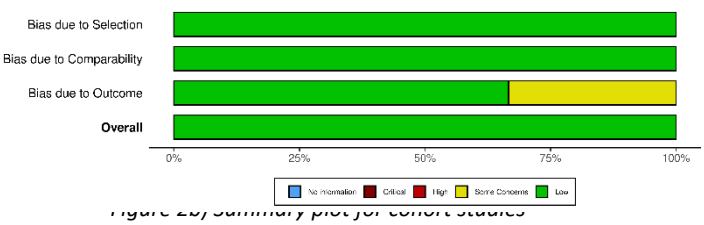


Figure 2b) Summary plot for cohort studies

The Newcastle Ottwa Scale shows little distinction in the risk of bias across domains (Figures 1-2). The tool is not appropriate for this systematic review, missing appropriate criteria for assessment. For example, the tool does not incorporate the diagnostic accuracy component of this review, such as the assessment of the interpretation of the index test and reference standard test results. Thus, other tools were explored.

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