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Title Page

Full title

Disease-related factors affecting timely lymphoma diagnosis: a qualitative study exploring patient experiences

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Abstract

Background

Expediting cancer diagnosis is widely perceived as one of the keys to improving patient outcomes. Evidence indicates that lymphoma diagnosis is often delayed, yet understanding of the issues influencing this is incomplete.

Aim

To explore patients' perceptions of disease-related factors affecting time to diagnosis of Hodgkin and non-Hodgkin lymphoma.

Design and setting

Qualitative UK study involving patients with indolent and aggressive lymphomas, and their relatives.

Method

Semi-structured interviews with 35 patients recruited from an established population-based cohort and 15 of their relatives. Interviews were audio-recorded and transcribed, and qualitative descriptive analysis undertaken.

Results

Accounts suggest that certain features of lymphoma can impact on patients' and health care providers' (HCPs) responses to disease onset. Three characteristics stand out: disease occurrence (rare), manifestation (varied), and investigative options (often inconclusive). Interviewees described how they (and some HCPs) lacked familiarity with lymphoma, seldom considering it a likely explanation for their symptoms. Symptoms reported were highly variable, often non-specific and said to be initially associated with various benign, self-limiting causes. Blood tests and other investigations, while frequently able to detect abnormalities, did not reliably indicate malignancy. Interviewees reported the potential for improvements among HCPs in information-gathering, communication of uncertainty, and re-presentation advice for non-resolving/progressive health changes.

Conclusion

Our evidence demonstrates the complex characteristics of lymphoma, perceived by patients as prolonging time to diagnosis, often despite significant effort by themselves, their relatives and HCPs to expedite this process. The findings also illustrate why simple solutions to delayed diagnosis are lacking in this area.

Keywords

lymphoma; diagnosis; primary care; general practice; help-seeking; qualitative research

HOW THIS FITS IN

Prior research identifies significant consequences of delayed cancer diagnosis, yet little is known about the factors affecting time to identification of lymphoma, despite these diseases being associated with late recognition. Our study explores lymphoma patients' (and their relatives') perceptions of disease related issues impacting on time to diagnosis; it is one of few to use qualitative methods and to explore patient experiences before and after first help-seeking. It highlights three important factors: the rare occurrence of lymphoma, its varied manifestation, and the investigative options available, which may be inconclusive. This evidence furthers understanding of when and why lymphoma diagnosis may be delayed; how delay can occur despite significant efforts on the part of patients, their relatives and health care providers; and how simple solutions to this issue are lacking.

Introduction

Over a third of the 33,000 haematological malignancies diagnosed in the UK each year are lymphomas (1). These cancers comprise a heterogeneous group, with many distinct subtypes, which differ markedly in incidence, clinical pathways, and outcomes (2). For example, some subtypes are aggressive, progress rapidly, and are considered curable (such as diffuse large B-cell lymphoma and classical Hodgkin lymphoma); others are indolent, generally advance more gradually and are incurable (including follicular lymphoma and marginal zone lymphoma); and some may have both aggressive and indolent variants (e.g. mantle cell lymphoma). Definitive diagnosis generally requires examination of lymph node/extra-nodal and bone marrow tissue, along with a combination of specialist laboratory investigations (morphological, cytogenetic, immunocytochemistry and flow cytometry).

Early stage diagnosis of cancer is important, as this is one means of improving patients' survival (3) and quality of life (4). Despite this, the time leading to identification of lymphoma may be protracted and associated with avoidable delay (5,6). Unfortunately, although UK policy-based interventions (including referral guidance for GPs (7)), have resulted in improvements for several malignancies, these have had less impact for people with lymphoma (8). Patients with these cancers are still more likely to have multiple primary care appointments before hospital referral (9), and are less likely to be 'fast tracked' (two-week wait) by their GP (10). Furthermore, recent data also indicate that as many as two in five lymphoma diagnoses occur after emergency presentation, a route associated with late stage disease and poor survival (11).

Research on time to cancer diagnosis has grown significantly in recent years. For lymphoma, studies have calculated the duration of time between specific events prior to diagnosis (e.g. onset of symptoms, first help-seeking, hospital referral); often drawing on survey data, either examining individual or combinations of subtypes, frequently alongside other cancers (5,8,12,13). Theoretical models now exist to facilitate time to diagnosis research, and ensure consistency in definitions, methods and reporting. The 'Model of Pathways to Treatment' (MPT), is one example of this (14,15); it builds on earlier classification systems (16,17) and defines a linear series of intervals, events and processes, with several cross-cutting factors (Figure 1). These include; the 'appraisal' interval (detection of bodily changes to decision to consult a health care provider – HCP); the 'help-seeking' interval (decision to consult a HCP to first consultation); and the 'diagnostic' interval (first HCP consultation to diagnosis, including HCP appraisal, investigations, referrals and appointments).

Factors affecting time to diagnosis remain relatively under-explored (18,19), however, and few studies have used qualitative methods to identify pertinent issues, including those addressing experiences after first help-seeking, either for lymphomas or other cancers (20–22). The aim of the current study was to improve understanding of experiences in the time leading to lymphoma

diagnosis, from the perspective of patients and family members, focusing on the impact of disease factors. To achieve this, we conducted a qualitative study, set within a large, ongoing patient cohort in the north of England (23), based on the intervals and events described in the MPT (14,15)

Methods

The study was carried out in accordance with the consolidated criteria for reporting qualitative studies (COREQ) (24) and guidance on standards for reporting qualitative research findings (25).

Context

The study is nested within the Haematological Malignancy Research Network (HMRN: www.hmrn.org), an ongoing population-based patient cohort established to generate evidence on haematological malignancies for research purposes and to inform clinical practice (2,26). Diagnoses (~2,400 annually, from a population of ~4 million in the Yorkshire & Humber region of the UK) are made by a single specialist laboratory and coded to the latest World Health Organization classification system (27). Core data are abstracted from medical records and patients are invited to complete a routine postal questionnaire soon after diagnosis, about their symptoms and help-seeking (including dates).

Participants

With appropriate ethical approval (REC 04/01205/69; REC 12/YH/0149), participants were identified from patients returning the routine postal questionnaire. Purposive sampling was used to ensure maximum variation in disease subtype, sex, age and time to diagnosis (Table 1). We approached 58 individuals, sending them information about the study and their potential involvement, and inviting them to participate; 35 expressed interest and were interviewed. Thirty patients had non-Hodgkin lymphoma (NHL; indolent and aggressive subtypes), and five Hodgkin lymphoma (HL); 18 were male; and median age at interview was 63 years (range 23-84). Patients were invited to ask a relative to take part in the interview if they wished, both to promote their own recall and so these family members could share their own perceptions; 15 agreed, all of whom invited their spouses/partners (Table 1).

Data collection

Potential participants were posted a study pack containing an introductory letter, information leaflet, response form, and prepaid return envelope. Those wishing to participate contacted the study team directly (via post or phone), and an interview was arranged. Two experienced qualitative researchers conducted the interviews (RH, DH), both of whom have significant track-records in health services research, one of which was a former registered nurse (DH, Principle Investigator), with two decades of academic experience with haematology patients, their relatives and clinicians. Neither researcher was known to participants.

All patients were assured of data confidentiality and gave written consent to take part in the study. Interviews were conducted face-to-face, largely within patients' homes (two in the hospital setting), and within a year of diagnosis. Several early pilot interviews were conducted, followed by an intensive period of fieldwork between November 2015 and May 2016. Data collection was semi-structured and guided by a schedule, which was informed by experience from within the research team and based on the appraisal, help-seeking and diagnostic intervals, as defined in Walter's MPT model (14,15). Issues included in the schedule are summarised in Table 2; precise questions were, however, adapted in situ to accommodate the full range of experiences and the manner in which patients chose to describe them. Interviews were digitally audio-recorded and, on average, completed in around 45 minutes.

Data analysis

Recordings were transcribed verbatim, field notes were used to confirm accuracy, and transcripts were checked and anonymised before import into the data management software, ATLAS-ti (Version 6.2.11). Our methodological orientation was qualitative description, a pragmatic approach producing minimally-theorized findings with practical applications (28,29). Analysis (RH and DH) was iterative, running alongside and informing data collection, which was discontinued once 'saturation' was achieved (30). After data familiarisation through reading/re-reading transcripts, several rounds of coding were undertaken, with constant comparison driving the refinement of codes. Memoing and mapping techniques (31) were used to explore patterns (i.e. similarities and differences between individuals) and relationships (between codes). The wider research team (ER and AS) had access to the data, analytical process and pathway maps which, along with codes and emerging themes, were regularly discussed and refined until consensus was reached.

Results

Based on the routine HMRN core postal questionnaire, in which patients document their symptoms and help-seeking activities, time from first symptom to diagnosis was found to vary markedly, the collective appraisal and help-seeking intervals having a median duration of 1 month (range 0.5-13), and the diagnostic interval 4 months (range 1-24). Accounts suggested that a combination of disease-related factors impacted on the behaviour of patients', their relatives and HCPs in primary care (GPs and nurses). Three significant themes emerged; the occurrence of lymphoma (rare); its manifestation (varied); and investigation (often inconclusive) (Figure 2). These issues impacted on the assessment, interpretation and response to symptoms across the appraisal, help-seeking and diagnostic intervals, with recurrent activities (e.g. patient appraisal before and after first help-seeking) preventing unilinear progression through each stage of the MPT before diagnosis. Each theme is described below with verbatim quotes.

Occurrence

Interviewees perceived lymphoma as a relatively rare disease (in contrast to other cancers they were aware of, such as breast cancer), typically affecting older adults.

An unfamiliar disease

Few interviewees reported encountering anyone with lymphoma prior to diagnosis, and several had never heard of it before. Those who had, often described their knowledge as limited: *'I'd heard of non-Hodgkin's lymphoma. I didn't know quite what it meant'* (Patient 2: P2). Some said that at diagnosis, they had not initially known that lymphoma was a form of cancer. Awareness of Hodgkin lymphoma was somewhat greater, with several interviewees identifying this as life-threatening. However, prior knowledge of symptoms was consistently low. Some – often younger – patients reporting finding references to lymphoma when using the internet to facilitate symptom appraisal and the decision to seek help.

Several interviewees also perceived HCPs as having limited exposure to, and familiarity with, lymphoma: *'because it's quite rare, a doctor… might only see one case in their existence'* (P7). A few suggested HCPs were ill-equipped to recognise symptoms: *'the diagnosis was definitely late, no doubt about that… there's not enough known about the early symptoms'* (P24). This was said to prolong the diagnostic interval by holding up investigation and/or referral. Gaps in HCPs' knowledge seemed most problematic where symptoms were subtle and gradual in onset. Accounts suggest HCPs acted quickly and decisively (e.g. arranging emergency admission) when patients were acutely ill.

An improbable disease

Except for well-known common cancers associated with older age and gender, interviewees rarely perceived themselves as at risk of cancer as they appraised their symptoms: *'I had this stupid notion that if I, if I ate properly and looked after myself, I'd never go down with anything like that'* (P4). They drew attention to prior health, healthy lifestyles, and lack of a family history: *'cancer isn't something that runs in our family'* (P31). Where internet searches returned references to lymphoma, this could therefore seem an unlikely explanation for symptoms: *'I went on the internet and read up. Well, when I started reading about cancer I just switched it off, because I thought, "No, no, that's not right"'* (P5). Some interviewees suggested that perceptions of lymphoma as rare also inclined HCPs to judge it unlikely, and discount it as an explanation for symptoms during the diagnostic interval. One interviewee surmised age was also significant, with lymphoma dismissed due to their (relative) youth: *'I think the GPs knew the symptoms of, of lymphoma. I just don't think they were willing to, er, consider them, because of my age'* (P6).

<u>Manifestation</u>

Accounts revealed marked differences in symptom type and combinations, speed of onset, progression and intensity. Again, these characteristics affected the duration of the appraisal interval, the decision to seek help, and the length of the diagnostic interval.

Highly variable

Interviewees described a wide range of symptoms they had come to associate with onset of their lymphoma (Table 3). A few reported isolated changes, aside from which they felt well. In such instances help-seeking was often delayed, even where the symptom was widely associated with cancer (e.g. lumps, unexplained bleeding). The absence of pain seemed to provide reassurance: *'for some strange reason I'd always assumed there would be pain'* (P2). Sometimes medical attention arose from help-seeking for other concerns. One interviewee described consulting their GP about a groin swelling: *'she said it was a hernia, but she were more concerned about these* [other] *lumps, which I couldn't understand… I wa'n't having any problems with them'* (P19). Meanwhile interviewees experiencing multiple symptoms were often slow to connect these or appraise them collectively. Some suggested HCPs were similarly late in doing this: *'the… GPs… never pieced it together. Whilst we* [patient and relative] *were looking at the symptoms individually, they* [HCPs] *were too'* (P14).

Something or nothing?

Some interviewees, typically with seemingly aggressive disease, described rapid symptom development, with marked changes in their health. Severe and disruptive symptoms encouraged early help-seeking and – unless the sole symptom was pain – usually led to prompt investigation or referral to secondary care. However, many more described subtle symptoms, emerging insidiously or intermittently. These were often overlooked, or if appraised, judged unremarkable: *'on reflection, I had, possibly some sweating… these things are sort of so slow and imperceptible that you don't always… think much of it at the time'* (P13). Non-specific feelings of being generally unwell were also often described (*'vaguely off' P4; 'just didn't feel right' P18'*) (Table 3). Interviewees perceived HCPs as under strain and felt a responsibility to determine if symptoms were important before seeking help: *'you know, the NHS hasn't got unlimited resources, infinite resources, and I don't want to waste doctors' time'* (P13). As part of the appraisal process, they often consulted friends and family about their symptoms and whether they should seek help from an HCP. Usually they were encouraged to see a doctor – but not always: *'I showed the lump to my friends and they said, "You're just freaking out, it's nothing, we can't even see the lump"'* (P23). Intermittent symptoms were sometimes misconstrued as resolved, which could interrupt and extend the diagnostic interval (e.g. due to the cancellation of investigations).

Plausible competing explanations

Interviewees described how, as part of the appraisal process, they often initially identified alternative explanations for symptoms (Table 4); this was also common among HCPs in the

diagnostic interval. Expectations of age-related deterioration enabled patients to normalise many symptoms at this time, perceiving them as 'change', and not disease. Patients often attributed non-specific symptoms and localised pain to lifestyle (e.g. hectic), life stage (e.g. menopause) or other conditions (e.g. hernia). They did not always report such changes to HCPs: *'I wrongly assumed, at the time, that it* [night sweats] *was associated with this* [other] *problem… With hindsight, perhaps, I should have mentioned it'* (P30). HCPs too were recalled as proposing a range of explanations for symptoms in the diagnostic interval, including non-physical causes*:* '[the GP] *said, "Well what's probably happening is your body, you know, now that your mum's gone in the* [nursing] *home, your body is saying, 'Pffh, that's it, you know, just relax'…and this is why you're sleeping so much"'* (P31).

A few HCPs were described as attributing symptoms to psychological conditions including stress, anxiety and depression – these examples mostly came from patients aged under 40 years. Many HCPs initially diagnosed other physical but non-malignant conditions: *'the assumption* [was] *that it was, er, iron deficiency and the vitamin B12… they were, perhaps a little bit more complacent about the symptoms than they ought to have been'* (P11). These explanations often seemed plausible to patients (who had sometimes considered these explanations themselves), even in hindsight. HCPs' readiness to consider more serious explanations, including malignancy, appears to have varied. Accounts suggest some considered cancer from the first help-seeking episode: *'Honest to God this is how it happened, he turned and looked at me, and he went, "cancer clinic for you". He knew, straightaway'* (P22). Others, however, seem to have done so only after treatment failure excluded benign explanations*: 'he realised that it can't be that* [polymyalgia] *because the steroids should have altered it, and it ha'n't done'* (P16). In many instances, patients re-appraised their symptoms after first help-seeking and re-presented to their GP – sometimes on multiple occasions – before HCPs undertook re-appraisal, initiated investigations, and/or discussed referral.

Investigation

In the diagnostic interval, interviewees described undergoing blood tests, various imaging/scans, and one or more biopsies, and reflected on the timing, costs and/or invasiveness of these, as well as the uncertainty of findings.

Variation in access

Accounts suggest considerable variation in when tests were undertaken, and at whose instigation. For example, some recalled having blood tests after first help-seeking, others only after several visits. One interviewee remarked: *'there seems to be a reservation… about what bloods, you know, what bloods to take and what's done with the* [tests] *– I suppose it's money'* (P24). A few described efforts to negotiate investigations. These were not always successful: '[the Dr] *said, "Well, if we sent everybody for an x-ray who was complaining of a pain or something, there'd be queues outside miles long"'* (P21). Access to MRI scans was portrayed as constrained, even where HCPs

viewed this as appropriate. A related issue was that investigations were typically conducted in sequence, with the results of one determining the need for another. Some interviewees viewed staggering tests as sensible: *'there is no point putting somebody through surgery* [for a biopsy] *that they don't need'* (P19). Others, however, were more critical: *'You went for a biopsy later on… to find out what it was, what kind of cancer it was. But all these things, it drags on, and weeks go into months… it's agonising'* (Relative of P20).

Results not always reliable or clear

Participants commented on the reliability of available tests and the certainty with which they could detect disease. Some interviewees described getting decisive evidence of abnormality, suggestive of lymphoma or another serious condition. Many, however, reported receiving 'normal' or inconclusive results, in particular from blood tests and (to a lesser extent) imaging: *'nothing showed up in my blood, no abnormalities'* (P18). Accounts suggest patients often interpreted normal results as an 'all clear' and a disincentive to further appraisal and help-seeking: *'I think, looking back, that that scan was very reassuring… all blood tests were good, that radiologist said everything looked healthy… I felt quite reassured'* (P26). Others recalled inconclusive or ambiguous results, which could prove challenging for HCPs to interpret: '[the GP] *looked at the* [blood results]*… and he says, "I can't make head nor tail of this"'* (P24). A few interviewees inferred gaps in HCPs' knowledge and understanding of how lymphoma might manifest in tests. They reported receiving a range of explanations for irregular bloods (infection, benign conditions, contamination) and enlarged lymph nodes (infection and/or injury). Where the significance of results was unclear, tests were typically repeated, but not always promptly: *'You waited seven weeks for the* [second] *scan, which is too long. It had doubled, if not more, in size by that time'* (Relative of P32).

Discussion

Summary

This study aimed to improve understanding of disease-related factors affecting the time to diagnosis of lymphoma within the appraisal, help-seeking, and diagnostic intervals described in Walter's MPT (14,15). It is novel in that findings are derived from patients' self-reported experiences, and it examines activities before and after first help-seeking. Lymphoma occurrence was considered rare by interviewees, descriptions of its manifestation were varied, and patients often commented on the lack of specific investigations to clearly raise suspicion of cancer. These features resulted in a scenario whereby, with no (or very limited) knowledge, patients typically experienced the onset of subtle, non-specific symptoms or perceptions of ill-health, which during appraisal were often attributed to benign, mundane conditions, and/or non-physical, lifestyle and age-related factors. In the diagnostic interval, HCPs often faced an unfamiliar disease, with

symptoms similar to those of other common, non-malignant conditions, for which investigations did not reliably show abnormality or suggest malignancy; until symptoms progressed, the case for further tests/hospital referral was often unclear.

Strengths and limitations

Utilising qualitative methods allowed us to engage with the complexity of patients' self-reported, pre-diagnostic experiences, something previously identified as an important challenge (32). We included patients diagnosed with both indolent and aggressive lymphoma subtypes, and covered a broad range of age-groups, both sexes and varying pre-diagnostic time-intervals, including the period of time before and after first help-seeking. Our study sample and in-depth interview techniques yielded rich data that provide new insights into an important but under-researched area. To promote accurate recall, we largely interviewed patients within a year of diagnosis, encouraging reference to letters, calendars and diaries, and the involvement of family members.

Accounts were not corroborated by review of medical records or HCP perspectives, as this was not the objective of the study. Compliant with ethical approvals, transcripts and findings were not returned to interviewees for verification. Transcripts were checked alongside interview recordings, however, and the study team was satisfied that the evidence generated largely reflected the experiences often reported by the patient population, both during clinical practice and at engagement events. We included patients who had previously returned a routine postal questionnaire, so did not capture the perspectives of those who either died soon after diagnosis, or who were not sent (or did not return) a questionnaire for other reasons (e.g. rapid health deterioration). Transferability' (i.e. consideration of findings in relation to their relevance for understanding similar issues and processes) is a key aspiration in qualitative research, rather than generalizability (33). Extrapolation should therefore take into account any study-specific contextual factors (e.g. different health-care systems; universal health-care coverage etc.), which may limit transferability (34).

Comparison with existing literature

Research into factors affecting time to lymphoma diagnosis specifically, and cancers more widely, has consistently identified patient tendencies to ascribe routine explanations to their symptoms (e.g. stress, normal ageing process/life phase), rather than recognising these as serious (20,22,35–37). Our results echo these findings; the broad range of symptoms described were often subtle, and did not always incorporate the common, or 'red-flag' (38) characteristics listed on public-targeted lymphoma-specific websites (e.g. swollen lymph nodes, fatigue, weight loss or sweats (39)). Intermittent symptoms, interpreted by patients in our study as potentially resolved, were also considered reassuring among patients with other malignancies, such as pancreatic cancer (40); as were negative investigation results, by both patients and GPs (41–43). A recent systematic review of factors impacting on cancer diagnosis reported patient difficulties in assessing

the significance of vague, non-specific symptoms, and also perceptions that HCPs had not taken their concerns seriously, had not taken a thorough history, and had not asked relevant questions; patients were also anxious that they themselves did not overburden or waste doctors' time (44).

Studies exploring factors after first help-seeking in primary care are perceived as limited, both with respect to lymphoma and other less familiar cancers (21,22). Available evidence suggests 'practitioner delay' is influenced by the nature of symptoms and how these are interpreted, as well as use of appropriate diagnostic testing and follow-up (42). Our study confirms that the relevance of these findings extends to lymphoma. Concurring with Walter's model (14,15), it also suggests patients' interpretations and actions (e.g. re-appraisal and re-presentation for ongoing symptoms) remain significant after first presentation, and that improved understanding of interactions between patients and HCPs is required.

Implications for practice and research

Although effective for some cancers (45,46), the characteristics of lymphoma may mean interventions such as education campaigns, aiming to facilitate appraisal, and encourage help-seeking and specialist referral, are ineffective. This is due to the myriad of symptoms that may be experienced, which vary with the site of disease origin and spread (nodal/extra-nodal; organs/locations in the body). The vague symptoms noted as a consequence of ineffective lymphatic and bone marrow functioning (e.g. non-specific/multiple infections, anaemia-related fatigue), further compound this obstacle; as do differences in the severity, resulting dysfunction and pace of symptom progression, which are contingent on the lymphoma variant. For relatively rare conditions such as lymphoma, campaigns encouraging people to take note of changes in their body that persist/worsen or diverge from what is 'normal' for them, may be a more effective approach to encouraging help-seeking.

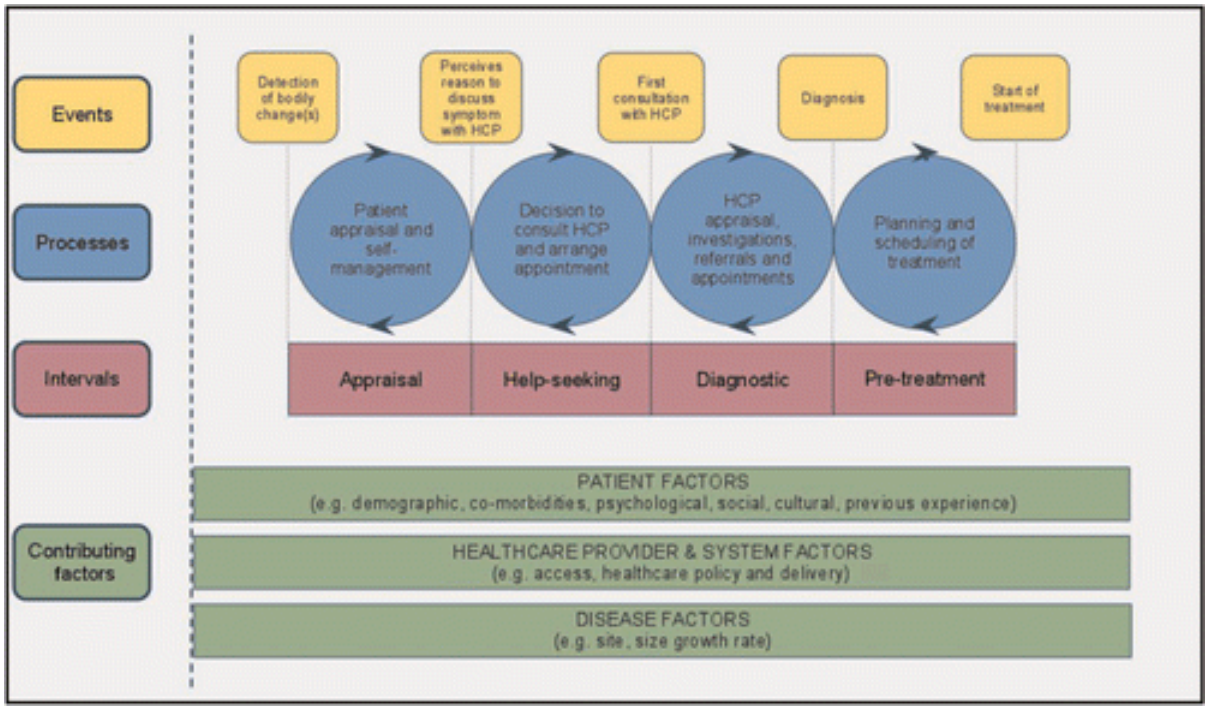
Most people consult a GP in the diagnostic interval, preceding cancer diagnosis, even if the malignancy is identified following emergency presentation (41,47,48). Consequently, for both insidious and acute manifestations, GPs are faced with the complex task of differentiating benign symptoms from those that may indicate cancer. These decisions are made more difficult because the only high-risk factors indicative of lymphoma are unexplained lymphadenopathy (if present) in people aged 60 years and over, and an increase in consultation frequency to a doubling from normal in the year before diagnosis (49,50). Furthermore, the signs and symptoms of lymphoma cited in UK referral guidance, aiming to support GPs' clinical evaluation and decision-making (7), present only the most common symptoms, so are not ideal where clinical presentation deviates from this, a situation that the current study highlights as being common. The lack of investigations available to clearly identify or exclude lymphoma, as well as the propensity for normal inflammatory markers until late in the trajectory contributes a further complication (49,50). Unsurprisingly, a study with UK GPs reported the early detection of malignancy as particular burdensome, due to the

challenges in identifying potential cancer symptoms, managing cancer anxiety among patients and their families and making appropriate referrals (51).

Certain aspects of the diagnostic interval are modifiable by HCPs, however, and may address some of the challenges raised by patients in our study. 'Safety netting' has been suggested as a means of managing diagnostic uncertainty, ensuring timely and appropriate follow-up, and avoiding emergency presentation, particularly where symptoms are non-specific or associated with 'low' cancer-risk, but not 'no' cancer-risk (7,21,41,44,52). Strategies encouraged include effective and precise GP communication (to the patient/family) and documentation of issues such as uncertainty, potential signs of deterioration and/or complications, what to expect over time, and when, how and where to seek further help (e.g. for ongoing or worsening health-issues) and access test results (38,53). This approach would facilitate appropriate patient re-appraisal of symptoms and provide reassurance that repeated help-seeking was justified, and indeed may be required. In the diagnostic interval, it would provide HCPs with a useful summary of events, and highlight that uncertainty had been recognised. Furthermore, research into vague and/or non-site specific symptoms (e.g. weight loss) has led to recommendations for ways in which such manifestations should be managed, including the development of 'vague symptoms' pathways (7,54).

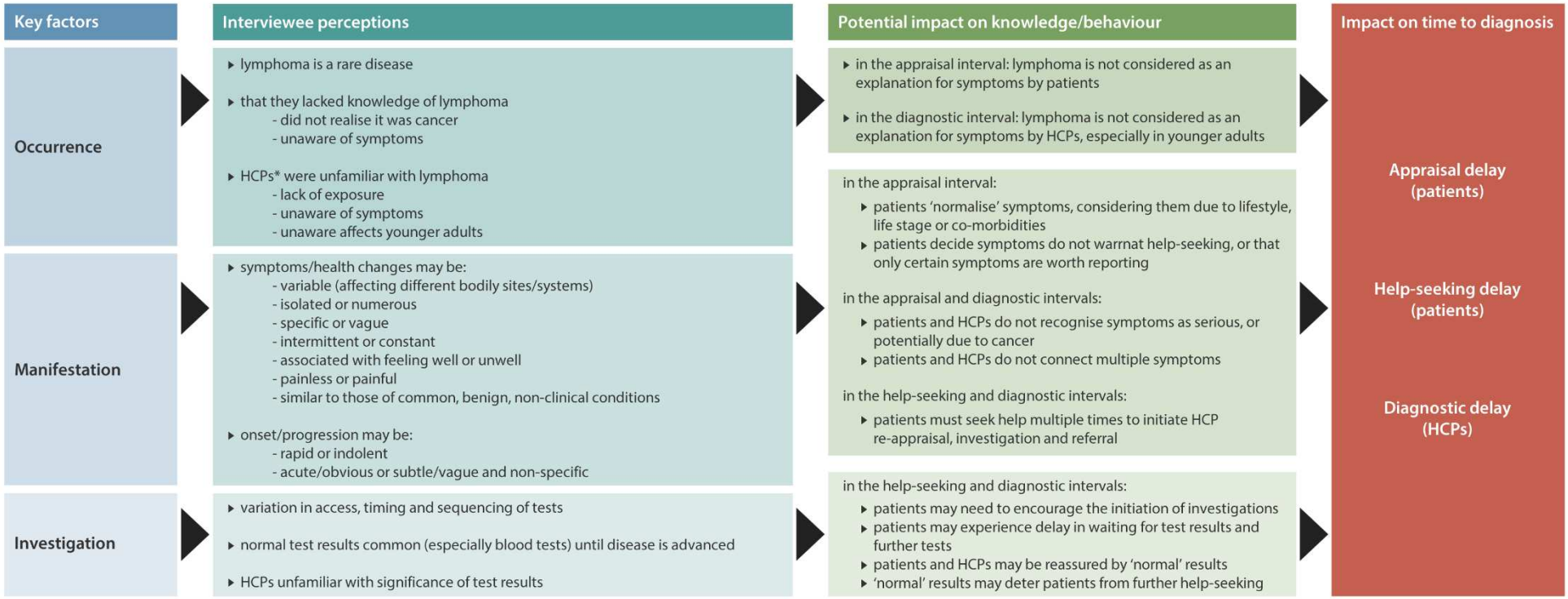
Unfortunately, evidence from HCPs is absent for lymphoma, yet research with this group is crucial if the barriers and facilitators to timely diagnosis are to be wholly comprehended and relevant remedial strategies identified.

Figure 1 Model of Pathways to Treatment (14)



HCP: Health Care Provider

Figure 2 Summary of interviewee perceptions about disease-related factors and their impact on time to lymphoma diagnosis



*HCP: Health Care Provider

Additional information

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Ethical approval

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Competing interests

The authors have declared no competing interests.

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Table 1 Participant characteristics (n=35)

Diagnosis (Patient Identification)	Patients (Relatives[1])	Females	Males	Age (years)	Duration of appraisal and help-seeking intervals[2, 3] (months)	Duration of diagnostic interval[3,4] (months)
				Median (range)	Median (range)	Median (range)
Non-Hodgkin lymphoma						
Diffuse large B-cell (P2,4,8,9,20,21,24,27,29,31,32,35)	12 (7)	5	7	64 (48-81)	1 (0.5-13)	2.5 (1-14)
Follicular (P1,3,6,10,12,13,18,22,26)	9 (2)	4	5	63 (39-84)	1 (0.5-12)	3 (1.5-15)
Marginal zone (P5,16,25,28,30,33)	6 (1)	4	2	62 (57-76)	1 (0.5-10)	12 (3-25)
Mantle cell (P11,15,34)	3 (3)	2	1	71 (70-75)	1 (1-6)	2 (2-10)
Hodgkin lymphoma (P7,14,17,19,23)	5 (2)	2	3	36 (23-56)	0.5 (0.5-2)	5 (3-24)
Total	**35 (15)**	**17**	**18**	**63 (23-84)**	**1 (0.5-13)**	**4 (1-24)**

[1]All were spouses/partners of the interviewee with lymphoma; [2]First symptom to first help-seeking; [3]Estimate based on information provided by patients in the routine HMRN core questionnaire about symptoms and help-seeking; [4]First help-seeking to diagnosis.

Table 2 Interview schedule

Interviewees were asked to describe:

1. The symptoms and health changes they experienced and how (in the appraisal, help-seeking and diagnostic intervals) these:
    - changed
    - were appraised and interpreted (by themselves, relatives and HCPs[1])
    - were managed (by themselves, relatives and HCPs)
2. Factors promoting and preventing timely appraisal, help-seeking and diagnosis
3. Their knowledge and experience of lymphoma before diagnosis

[1]Health Care provider

Table 3 Pre-diagnostic symptoms considered due to lymphoma, as described by interviewees

General feelings of ill health

'can't put finger on it', 'couldn't do anything', 'generally looked ill', 'generally unwell', 'grotty', 'immunity whacked', 'just didn't feel right', 'just felt rotten', 'lousy', 'something wrong', 'thinking "this isn't right"', 'under par' 'not feeling well', 'not quite right', 'one thing after another', 'rough', 'something wasn't right', 'terrible', 'under the weather', 'unwell', 'vaguely off'

Specific symptoms

***Bleeding**: bruising, nosebleeds ('pumping out'), vaginal bleeding*

***Cognitive**: confusion, loss of concentration, memory loss, mistakes at work*

***Eating/drinking**: appetite loss, heartburn, indigestion, nausea, reacting to alcohol/food, unable to eat, unable to keep food/water down, weight loss*

***Faint/dizzy**: blacking out, dizziness, lightheaded, near collapse, passing out, 'weird turn'*

***Gastro-intestinal:** bloated, bulges/change in shape of stomach, constipation, diarrhoea/loose stool, feeling like something lodged in stomach, flatulence, jaundice, pancreatitis, passing 'white mass', 'pulsing' of stomach, stomach upset*

***Genito-urinary**: increased urination ('at night'), loss of bladder control*

***Lack of energy**: fatigue, lethargy, tiredness, weakness. Characteristics - 'abnormal', 'debilitating', 'desperate', 'extreme', 'immense', 'prolonged', 'really', 'very'. Impact (general): 'depleted', 'flattened', 'reserves disappearing', 'no reserve', 'running on empty', 'sleeping more' ('a lot', '12 hours'), 'shattered', 'exhaustion', 'worn out', 'honestly could drop'. Impact (on work/hobbies): 'fluctuating capacity for work', 'unable to do as much at gym', 'losing fitness', 'deteriorating fitness'*

***Mobility**: difficulty walking, falls, tripping*

***Mouth/taste:** altered taste in mouth ('metallic', 'nasty', 'taste buds changed), mouth ulcers*

***Infections:** Characteristics – fungal, recurrent, viral; Types - colds, cold sores, flu, flu-like symptoms, peri-anal abscess, pneumonia, sore throats, thrush, upper respiratory, urinary*

***Pain**: Characteristics – 'as bad as toothache', 'bent double', 'cramp', 'in agony', 'nagging', 'sciatic-like', 'stabbing', 'terrific', '7-8 out of 10'. Areas – abdomen, arms, back, chest, feet, groin, head ('pounding', 'pulsating'), knee, legs, lower back, ovary, shins, shoulder, stomach, thigh, rectal*

***Respiratory**: breathing difficulties at night, breathlessness, cough ('dry', 'bad'), hoarse voice, post-nasal drip, vocal changes*

***Neuro-sensory**: abnormal sensations (back: 'something rubbing', feet burning: 'as if I'd been scalded'), loss of feeling in legs, numbness (legs), visual disturbances ('black spots' in front of eyes)*

***Skin**: change in colour of skin and whites of eyes (yellow, green/yellow), itchiness, itchy rash, not healing properly, 'swollen spongy scalp'*

***Swellings/lumps:** Areas (specific): groin, neck, armpit, abdomen/stomach, mouth, jawline, over collarbone, 'glands', calf, 'on waist'. Areas (general): leg/thigh/foot ('ballooning'). Changes: 'started to hurt', 'started to go a 'bluey-purple' colour', 'growing… bigger than a grapefruit'*

***Temperature/sweats**: high temperature, hot flushes, 'really cold', running a temperature, sweats ('day', 'night', 'horrendous', 'hot')*

Table 4 Appraisal and interpretation of symptoms by patients and their relatives
Illnesses, comorbidities*: allergy, back trouble, bad cold, cancer, crohns disease, cyst, dengue fever, depression, diverticulitis, effects of surgery, existing musculo-skeletal problems, grumbling appendix, haemorrhoids, hernia, hypochondria, irritable bowel, lupus, lymphoma, ME, picked something up, prostate cancer, slipped a disc, some strange fungal thing, stomach cancer, testicular cancer, tumour, parathyroid problems, ulcer, varicose veins, vertigo, vitamin D deficiency weakening muscles and bones* ***Lifestyle, life-stage****: age/ageing, bored, busy life, driving, family problems, fasting, heavy work, hectic, hormonal changes, injury (gym), lifting weights, 'one-off', overdone things, 'man change', menopause, 'middle-age spread', responsibilities and worries, retirement, rushing around, stress, too much cycling, work,* ***Other****: altitude, antibiotics, duvet too thick, season*