Review

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What causes delays in diagnosing blood cancers? A rapid review of the evidence

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Abstract

Objective: We undertook a rapid review of literature relating to the diagnosis of blood cancers, to find out what factors contribute to delays in diagnosis, including symptom recognition, appraisal and help-seeking behaviours. *Methods:* We used rapid review methodology following Tricco *et al.* to synthesise current literature from two electronic databases. We searched for studies about symptom appraisal help-seeking for all blood cancers published between 2001 and 2021, written in English. *Results:* Fifteen studies were included in the review, of which 10 were published in the United Kingdom. We found a number of factors associated with delays in blood cancer diagnosis. These included patient factors such as gender, age and ethnicity, as well as health system factors such as poor communication and seeing a locum clinician in primary care. A narrative synthesis of the evidence produced four types of symptom interpretation by patients: (1) symptoms compatible with normal state of health, (2) event-linked problems, (3) mild or chronic illness and (4) non-specific unwell state. These four interpretations were linked to different help-seeking behaviours. After seeking help, patients often experienced delays due to healthcare professionals' (HCPs') non-serious interpretation of symptoms, misleading blood tests, discontinuity of care and other barriers in the diagnostic pathway. *Conclusion:* Blood cancers are difficult to diagnose due to non-specific heterogeneous symptoms, and this is reflected in how those symptoms are interpreted by patients and managed by HCPs. It is important to understand how different interpretations affect delays in help-seeking, and what HCPs can do to support timely follow-up for patients.

Introduction

Background

Blood cancer is often diagnosed late and claims more lives than breast or prostate cancer each year (*Blood Cancer UK*). Nearly a third of patients are diagnosed via emergency admission to hospital. Survival of patients diagnosed via an emergency route has worse outcomes than patients who presented via other routes (Kane *et al.*, 2017). For those diagnosed as an emergency, 40% will live for 3 years or more compared to 77% of those diagnosed via their GP (*Blood Cancer UK*, 2019). These patients also have fewer options in terms of treatment and are at greater risk of morbidity. Improving earlier diagnosis of blood cancer involves understanding where in the patient pathway there are opportunities to intervene. This approach has been applied across different cancer types (Cassim *et al.*, 2019; Grimley, Kato and Grunfeld, 2020; Lima *et al.*, 2021; Najor *et al.*, 2021; van Os *et al.*, 2021) or focused on socio-demographics (Fish *et al.*, 2015; McCutchan *et al.*, 2015) or regional (McCutchan *et al.*, 2021) influences on key patient behaviours, such as medical help-seeking. Findings suggest that factors such as low symptom awareness (Petrova *et al.*, 2020), perceived challenges around accessing primary care (Cassim *et al.*, 2019) and emotional barriers (e.g. fear and embarrassment) (Fish *et al.*, 2015) may influence help-seeking, but it is unclear whether these are relevant to blood cancer. This is because blood cancers (including leukaemia, lymphoma and multiple myeloma) have broad symptom signatures comprising symptoms with low predictive value, which means they are difficult to suspect and diagnose (Koo *et al.*, 2018).

Frameworks for help-seeking behaviours in other cancers suggest that specific heuristics influence symptom appraisal and help-seeking. For example, rate of change refers to symptoms that are worsening, increasing or have a sudden onset and this can trigger a help-seeking response (Kummer *et al.*, 2019). However, these heuristics may not be applicable to blood cancer due to the predominance of non-specific symptoms including fatigue and susceptibility to infections. Previous qualitative work has shown that concepts related to people's perceived eligibility for healthcare (e.g. candidacy) and confidence in reaching a

desired outcome (Renzi *et al.*, 2016; Howell *et al.*, 2019) impact on whether patients are likely to seek help promptly and also impact on whether they visit the doctor again following an "all-clear" diagnosis (Renzi *et al.*, 2016), but this research is not specific to experiences of blood cancer patients.

The challenge posed by blood cancer is evident across the diagnostic pathway; blood cancer patients have a high frequency of multiple consultations in primary care before specialist referral (Lyratzopoulos *et al.*, 2015), prolonged diagnostic intervals (Howell *et al.*, 2013) and are less likely to be fast-tracked for suspected cancer by GPs than patients with other cancer types (Zhou *et al.*, 2018). To date there has been no synthesis of factors influencing the blood cancer care pathway.

We undertook a rapid review of literature relating to the diagnosis of blood cancers, to find out what factors contribute to long diagnostic intervals, including symptom recognition, appraisal and help-seeking behaviours. Previous reviews have identified factors that cause diagnostic delays in all cancers (Smith *et al.*, 2005) or have attempted to quantify delays in one type of blood cancer (Koshiaris, Oke, *et al.*, 2018). This analysis is distinct in that it focuses on blood cancers as a group of diseases with non-specific and heterogeneous symptoms, (*Blood Cancer UK*, no date; Cerqua *et al.*, 2016) and how these affect patient cognition and behaviour.

Review methods

This review forms part of the *BLood cancer: understanding public Awareness, help-seeking behaviours and Diagnostic managEment* (BLADE study). We chose a rapid review methodology to synthesise current literature and provide timely findings that would inform subsequent strands of the BLADE study as well as blood cancer policy (Hartling *et al.*, 2016). The review follows the methods described by Tricco *et al.* (2017). The review was made rapid using the following modifications:

1. Targeted research questions
2. Limiting searches to two electronic databases
3. Reduced timeframe
4. Exclusion of grey literature
5. Limiting inclusion criteria by date (2001–2021) and in the English language.

Search methods

Two electronic databases (Medine and PsychINFO) were searched on 20th July 2021 on the Ovid platform, including results from 1st January 2001. The search strategy was developed based on a combination of keyword and expert search strings which was compiled by consulting similar published reviews and by exploring the relevant MeSH terms in the two databases. The search strategy for Medline was as follows:

1. **Leukaemia, Myeloid, Acute/**or **Hematologic Neoplasms/**or **Lymphoma/**or **Myelodysplastic Syndromes/**or **Leukaemia/** or **Multiple Myeloma/**or blood cancer
2. Symptom appraisal or appraisal or symptom awareness or help-seeking or seek help or early presentation or late presentation or healthcare-seeking or patient interval or help-seeking interval or diagnostic interval or diagnos$ delay or patient delay or experiences or symptomatic presentation
3. 1 and 2.

Table 1. Eligibility criteria

Inclusion	Exclusion
Qualitative or quantitative data, or mixed methods data	Systematic or other reviews, editorials, books, dissertations or grey literature
Published and peer-reviewed	Full text unavailable
Sample of patients diagnosed with blood cancers to include all individual types of the following sub-groups: leukaemia, lymphoma, myeloma	Undiagnosed or community sample
Focus on symptom appraisal, help-seeking or healthcare experiences	Explicit focus on experiences of treatment or survivorship only
Published in English	Published in any other language
Publication date 2001–2021	Published before 2001

The search strategy for PsychINFO is below:

1. blood cancer or haematological cancer or haematological neoplasms or haematological malignancies or lymphoma or leukaemia or myeloma or myelodysplastic syndromes or myeloproliferative neoplasms or multiple myeloma
2. Symptom appraisal or appraisal or symptom awareness or help-seeking or seek help or early presentation or late presentation or healthcare-seeking or patient interval or help-seeking interval or diagnostic interval or diagnos$ delay or patient delay or experiences or symptomatic presentation
3. 1 and 2.

MeSH terms are shown in bold. The search results were limited by language (English) and by date (2001–2021).

Eligibility criteria

Both qualitative and quantitative studies were included in the review provided they met the criteria displayed in Table 1. We included studies of adults and children, as we considered the help-seeking and appraisal processes to be broadly similar, even if some of these processes were experienced by parents or carers by proxy in the case of early childhood cancers.

Studies were screened by abstract and full text for eligibility by two reviewers (LB and GB) independently, with a minimum of 20% double coding to ensure the reliability of decision-making; disagreements regarding inclusion were resolved by discussion with the wider study team. We completed additional searches using key authors' names and relevant search terms in the web engine Google Scholar, and by searching reference lists. This resulted in no additional papers.

Quality appraisal

All articles were formally assessed for quality using the Mixed Methods Appraisal Tool (MMAT) Version 2018 (Appendix A) (Hong *et al.*, 2018). No papers were excluded as a consequence. The qualitative papers contained few poor quality items, and the issues were associated with deficiency of information in methods. The main limitations of the quantitative papers included a lack of information about the representativeness of the samples compared with the target population and risk of nonresponse bias.
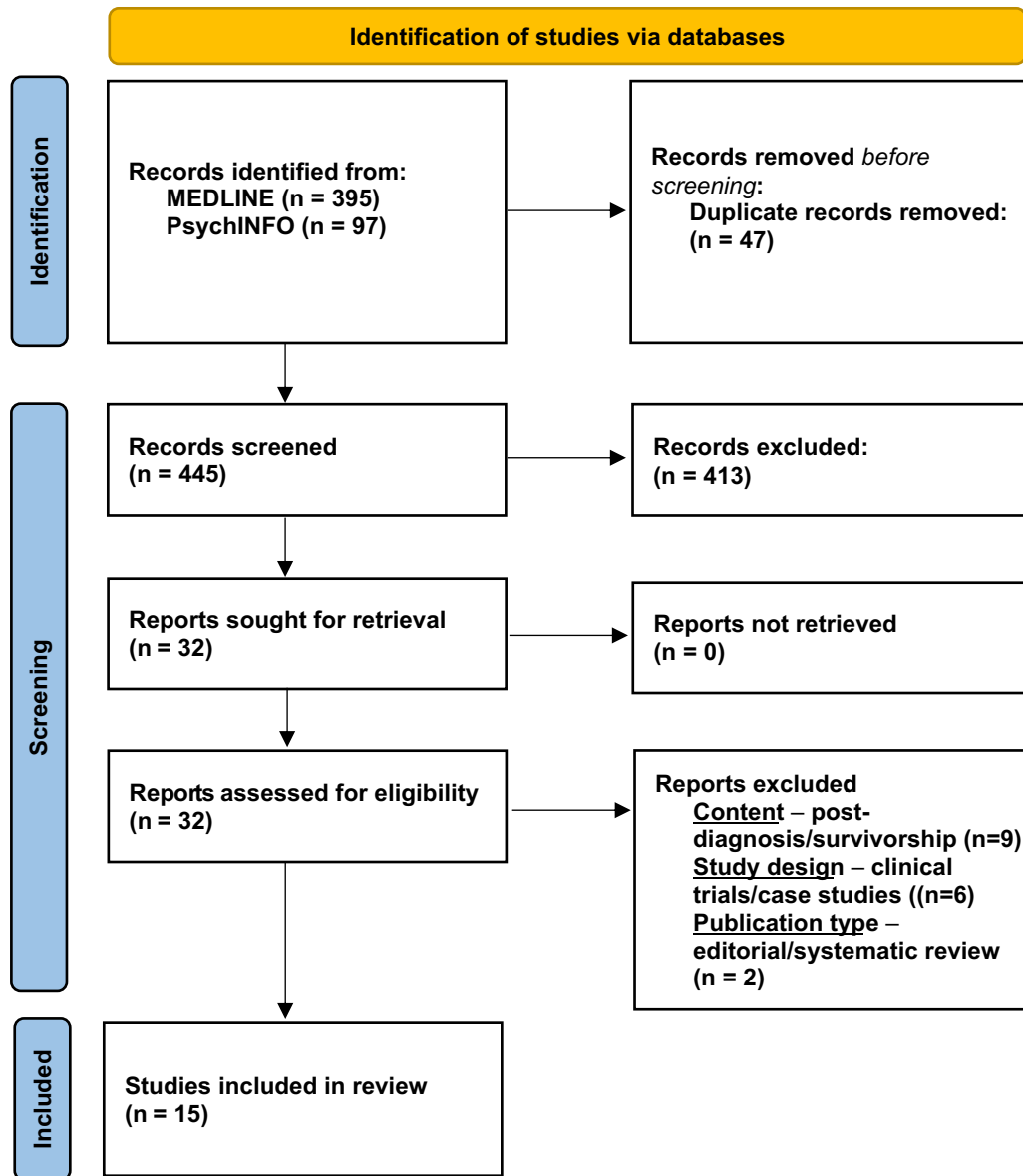
Figure 1. Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines flow diagram of study selection

Data charting and analysis

We extracted information from each study to a spreadsheet, including the authors, title, year, journal and reference, country, sample size, gender split, age range, participant characteristics, clinical setting, data type, study design, analysis method and included blood cancer types. The Model of Pathways to Treatment (MPT) is a framework that can be used to direct research into early diagnosis of cancer (Scott *et al.*, 2013). In this study, we used parts of the framework to extract the findings from each included study into categories:

1. Appraisal
2. Help-seeking
3. Diagnostic interval
4. Other.

The fourth category was included to help capture any data which did not fit easily into the intervals of the MPT. For example,

findings that traversed more than one category or contextual information such as the availability of blood testing.

Our analysis proceeded using data synthesis techniques drawn from rapid methodologies such as summarising key findings, regular discussions between authors and iterative cycles of interpretation. This produced a narrative synthesis of the studies, as well as charts and tables summarising the quantifiable aspects.

Results

Search outcome

Figure 1 outlines the searching and identification of eligible studies for the review. The searches in Medline and PsychINFO produced 492 records. These articles were imported to Rayyan systematic review software where duplicates were removed. Initial screening of titles and abstracts excluded 413 articles, leaving 32 remaining.

Table 2. Characteristics of studies included in review

Number of studies in final results	15	
Countries included	10	UK
	2	USA
	1	Brazil
	1	Lithuania
	1	South Africa
Dates published	2008–2019	
Types of studies	7	Quantitative
	8	Qualitative
Data sources	● Clinical databases ● Interviews ● Questionnaires ● Databases ● Cancer registry data – surveillance ● Patient case reports	

A full-text review produced a final sample of 15 studies, after excluding 17 that were ineligible for the review.

Study selection and characteristics

Ten articles were from the UK, two from the United States, one from Brazil, one from Lithuania and one from South Africa. All studies were published between 2008 and 2019. Full study details including participant characteristics, data collection and findings can be found in Tables 2 and 3.

Narrative synthesis

Estimating delay

Seven studies aimed to estimate delays in diagnosing blood cancers using quantitative approaches. The reported delays ranged from 30 days to 7 months. These studies varied in their approach to measurement of delay, including self-report (n = 3), GP or patient records (n = 4). Four studies used a combination of both. Self-report methods included face-to-face interviews or postal surveys. The intervals themselves were defined from different time points. Additionally, some studies focused on several intervals, for example, Antel et al. (2019), whereas other studies attempted to measure one interval, for example, Howell et al. (2015). We noted that studies published after the Aarhus statement/MPT (Weller et al., 2012; Scott et al., 2013) which defined cancer delay intervals by discrete events such as time to first presentation, time to referral to secondary care and time to diagnosis, were more consistent in their reporting. There were exceptions however (e.g. Dapkevičiūtė et al., 2019) which did not report delay within the MPT intervals. This may reflect differences in health systems.

When several intervals are measured, there was interest in where there is greatest "delay" and this also varied between studies and blood cancer types. The most common analytical approach was to decide what would constitute "delay" and perform logistic regression, with correlates (e.g. demographics) included in the model and delayed/not delayed as the dependent variable. One study used linear regression and therefore continuous measure of delay (Dapkevičiūtė et al., 2019). One study used the interval from symptom onset to presentation at primary care, using

a 3-month threshold to define delay (Howell et al., 2015). Two studies used the interval between symptom onset and diagnosis to measure delay, but there was variation in its definition, for example, one study defined delay as >30 days (Lins et al., 2012) where another used the distribution of diagnosis times to identify patients experiencing greater delays greater than the median (Friese et al., 2009). One study used the interval from first presentation to diagnosis, with a threshold of 6 weeks to define delay (Antel et al., 2019).

We noted that some studies' samples were too small to use logistic regression optimally, and several studies did not justify their sample size. Those retrospective studies based on case note review had insufficient information about data quality and how they handled missing data. Overall, we appraised the quantitative sample to lack robust examples or methodological rigour.

Factors associated with delay

Our data analysis produced a number of factors associated with delayed diagnosis in terms of disease-related factors, patient characteristics and health system factors (Table 4). There was no consistent pattern of factors associated with delay across these quantitative studies, although explanations for how disease and patient-related characteristics contributed to delay often related to lower cancer suspicion in some groups over others (i.e. due to the way the disease presented or who was presenting with the disease). There was relatively little discussion of health system factors (being the focus of one study in younger people).

How do people make sense of vague/intermittent symptoms relevant to blood cancer and make decisions about seeing a healthcare professional (HCP)?

A wide variety of symptoms were reported in relation to multiple blood cancer types including fever, pallor/skin change, fatigue or tiredness, non-blanching rash, behavioural changes, bodily pain (particularly bones/joint and back), cough, lump, rectal bleeding, abdominal swelling, nausea, sweating, weakness, feeling 'sickly' or generally unwell, weight loss, respiratory problems, swollen lymph nodes, bleeding, itching, thirst, stomach tenderness and hoarseness (Howell et al., 2008; Gibson et al., 2013; Clarke et al., 2014; Howell et al., 2015, 2019, 2020).

These symptoms are not specific to blood cancers, and the studies reported a variety of alternative interpretations by patients. We have synthesised these findings to produce a four-part typology of symptom interpretation.

(1) **Nothing wrong at all – symptoms compatible with normal state of health**

In this interpretation, participants judged what they were experiencing to be a part of the normal functioning of their body. This could be just a particular feature of their body, "just me" (Gibson et al., 2013) or due to ageing (Howell et al., 2020). This could also be due to the long-lasting nature of the symptoms. For example, Gibson et al. reported a woman who had experienced the same symptoms for over 10 years (including rectal bleeding and abdominal swelling) and had therefore integrated these symptoms into her normal interpretation of health, saying "'The symptoms were just me' (Participant 1)" (Gibson et al., 2013). This typology also included participants who were not sure whether or not their symptoms existed because they were hard to see or to feel or were not sure whether they were normal:

Table 3. Summary of included studies

Citation	Country	Sample	Data source/type of data	Study design	Type/s of cancer	Aim of study
Antel *et al.* (2019)	South Africa	163 newly diagnosed lymphoma patients	Clinical database/ patient records and patient interviews	Descriptive study	Non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL)	To review the pathway to diagnosis of aggressive NHL and HL in a large tertiary hospital in Cape Town, South Africa. Secondary aims were to describe the determinants of diagnostic delay, and the impact of diagnostic delay on overall survival
Clarke *et al.* (2014)	UK	21 parents of children with leukaemia and their GPs (n = 9)	Semi-structured interviews cross referenced against databases	Case report	Leukaemia	To identify disease and non-disease-related factors which facilitate or impede the diagnosis of paediatric cancer, by exploring the patient and diagnostic intervals
Dapkevičiūtė *et al.* (2019)	Lithuania	100 patients with multiple myeloma	Face-to-face questionnaire and medical records	Case report	Multiple myeloma and lymphoma	To evaluate diagnostic delay, disease, patient and health-system-related influencing factors and the effects of longer times to diagnosis among multiple myeloma and lymphoma patients
Friese *et al.* (2009)	USA	5483 patients having survived 6 or more months after diagnosis	Cancer registry data	Case control study	Multiple myeloma	To identify the predictors of diagnostic delay and associated complications in patients with multiple myeloma
Gibson *et al.* (2013)	UK	24 patients 2–4 months from the diagnosis of a solid tumour	Semi-structured interviews followed by fact checking of medical databases	An interpretive qualitative research design using narrative inquiry	Multiple (non-blood) cancers including lymphomas	To explore how recently diagnosed young people experience the patient and diagnostic intervals
Howell, Smith & Roman (2008)	UK	32 newly diagnosed patients	Semi-structured interviews	Observational/ descriptive	Lymphoma	To ascertain the beliefs and actions of patients in terms of help seeking for lymphoma symptoms
Howell *et al.* (2018)	UK	20 newly diagnosed patients	Semi-structured interviews	Descriptive case report	Myeloma	To explore the experiences of patients' (and their relatives') in the time leading to diagnosis, their perceptions of whether delays occurred and why
Howell *et al.* (2019)	UK	35 patients (including some spouses/ partners)	Semi-structured interviews	Descriptive case report	Lymphoma	To improve understanding of experiences in the time leading to lymphoma diagnosis by exploring the perspective of patients and family members and focusing on the impact of disease factors
Howell *et al.* (2015)	UK	785 patients	Questionnaire	Case report	Leukaemia, lymphoma, and myeloma	To explore symptoms of haematological malignancies and examining associated barriers to diagnosis
Howell *et al.* (2020)	UK	83 (55 patients and 28 relatives)	Semi-structured interviews	Descriptive case report	Lymphoma and myeloma	To describe the diagnostic experiences of patients with lymphoma and myeloma and their relatives using the Model of Pathways to Treatment
Koshiaris *et al.* (2018)	UK	14 860 patients with multiple myeloma and matched controls	Clinical database	Case control study	Multiple myeloma	To identify the best inflammatory marker for initial investigation of possible myeloma, useful blood tests for ruling out symptomatic myeloma, and how to distinguish early and late features of the disease
LeBlanc *et al.* (2017)	USA	32 patients	Semi-structured interviews	Descriptive study	Acute myeloid leukaemia (AML)	To understand the experience of being diagnosed with AML, receiving information about it, and making a treatment decision
Lins *et al.* (2012)	Brazil	288 children with leukaemia	Patients case reports from hospital	Descriptive study	Leukaemia	To describe the interval between symptom onset and diagnosis of acute leukaemia; secondly, to assess the risk

(*Continued*)

Table 3. (Continued)

Citation	Country	Sample	Data source/type of data	Study design	Type/s of cancer	Aim of study
						factors for possible delayed diagnosis; and to investigate the effect of delayed diagnosis on early morbid-mortality
Molassiotis et al. (2010)	UK	75 patients	In-depth interviews	Descriptive study	Multiple cancers including lymphoma	To explore the pathway from initial persistent change in health to diagnosis of cancer in a sample of patients from seven diagnostic groups in the UK and the factors mediating this process
Saunders et al. (2015)	UK	69 086 patients	English Cancer Patient Experience Survey	Case report	Multiple cancers	To describe and summarise variation in patient experience by age, gender, deprivation, ethnicity and cancer diagnosis across all survey questions

Table 4. Factors associated with delay identified in reviewed studies

Finding	Reference
Disease-related factors	
Multiple myeloma may incur longer delays than non-Hodgkin's lymphoma or Hodgkin's lymphoma	Dapkevičiūtė et al. (2019))
Hodgkin's lymphoma can also be a predictor for delay compared to non-Hodgkin's lymphoma	Antel et al. (2019)
Patients with chronic myeloid leukaemia may wait longer than patients with other blood cancer types to visit a doctor	Howell et al. (2015)
Patient characteristics	
Patients who experienced delayed diagnosis of multiple myeloma were on average 1 year older	Friese et al. (2009)
Black patients are more likely to have delayed diagnosis than white patients in multiple myeloma	Friese et al. (2009)
Women are more likely to have a delayed diagnosis than men in multiple myeloma	Friese et al. (2009)
Patients with co-morbidities are more likely to have a delayed diagnosis than patients without co-morbidities in multiple myeloma	Friese et al. (2009)
Having three or more children is associated with greater diagnostic delay in leukaemia	Lins et al. (2012)
Having a birth order of third or greater is associated with diagnostic delay in leukaemia	Lins et al. (2012)
Health system factors	
Locum GP visit associated with delay	Gibson et al. (2013)
Patients who are acutely ill are more likely to be referred	Gibson et al. (2013); Howell et al. (2015)
Plasma viscosity and erythrocyte sedimentation rate are the most indicative tests for myeloma	Koshiaris et al. (2018a); Koshiaris et al. (2018b)
Delays associated with lack of communication between different services, e.g., GP, 'walk in' clinic, accident and emergency	Gibson et al. (2013)
Delays associated with prolonged waiting times for consultant appointment	Gibson et al. (2013)

"Patient appraisal of symptoms and health changes was described as ongoing by participants, with observation and monitoring occurring periodically or continuously from first symptom to diagnosis. When 'normal' health was not regained, appraisal was said to become more deliberate and rigorous. It involved, for example, checking and comparing affected and non-affected sites: 'My mind was going, "If you can feel (a lump)...both sides, then it's normal. If you can feel it on one side, then that's something to worry about". So I tried, I felt the other side, and again...' [Lymphoma patient 06: L06]. This was said to take place repeatedly over time: 'I couldn't decide whether my skin was a different colour...I'd look at it and think, "It looks strange", and then I'd look again, and it didn't' [L03]."(Howell et al., 2020)*

This typology also included isolated changes (even cancer-related e.g. lumps or unexplained bleeding) apart from which the participant felt well. This meant that they continued to consider themselves to be well (Howell et al., 2019). In one isolated example, a participant was reassured by friends despite noticing a significant bodily change (lump):

'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) (Howell et al., 2019)

Studies suggested that individuals falling into this part of the typology needed extra influence or active measures from friends or family members in order to seek help, as they themselves did not have a sense of being unwell.

My wife was more worried than me and made me an appointment at the doctors. Because we were going away on holiday, the following week. [My wife] insisted that I went down. I'd have waited longer before going to see the doctor

if it hadn't already gone. I was expecting it to go in a couple of days. I thought well okay, see how it goes. I didn't feel any effect you see. It wasn't making me ill or anything like that. The point was we were going overseas. I think that that's what annoyed me, affected me. The wife was a little bit 'you're not going if you're not well'. (P037) (Howell, Smith and Roman, 2008)

However, friends could also delay help-seeking by offering reassurance and normalising symptoms, or reinforcing the idea that the symptom did not exist:

'I had these lumps on my neck and I, I didn't take any notice of them … I said to a friend and she said … "Oh it's nothing, everybody gets lumps".' [L15]. (Howell *et al.*, 2020)

(2) Event-linked problem

Patients often plausibly related their symptoms to an event such as an accident or difficult time in their lives. This was particularly relevant to pain, which could be explained as a consequence of injury (e.g. twisted ankle) (Gibson *et al.*, 2013). Two studies identified social/psychological causes for symptoms, such as stress (Howell *et al.*, 2018, 2019).

Another common explanation was life changes or stress: 'we'd got my daughter, son-in-law and three year old living here … so it was very, very hectic here, and stressed' [P02]. (Howell et al., 2018)

Lack of pain was reassuring and caused participants to maintain their attribution or diminish likelihood of alternative diagnosis (Howell *et al.*, 2019) and they responded by, for example, reducing physical activity rather than seeing help (Howell *et al.*, 2018).

(3) Mild or chronic illness

Patients and/or their parents often explained symptoms by relating them to a known mild illness or non-serious condition such as viruses or bad back. Around half of the blood cancer patients assumed that their initial symptoms would resolve on their own (Dapkevičiūtė *et al.*, 2019). One of the key challenges with symptoms of blood cancer is that there were multiple plausible explanations depending on the individual's circumstances (Molassiotis *et al.*, 2010).

For example, a patient with hoarseness of voice blamed smoking for this change in health; back or rib pains were interpreted as pulled muscles; cough and breathlessness were associated with a cold or chest infection; fatigue was attributed to stress; night sweats were linked to menopause; and itching to an allergy, thus leading to misinterpretations of their implications for changed health. (Molassiotis et al., 2010)

This meant that the same symptom could be normalised differently to fit each individual, for example, fever and fatigue could be explained by self-limiting illness in children (Clarke *et al.*, 2014) and explained as part of the ageing process for older adults (Howell *et al.*, 2018).

Patients particularly associated their symptoms – at least initially – with any co-existing chronic conditions, for example, a change in bowel habit was attributed to pre-existing irritable bowel syndrome in the Molassiotis *et al.*'s (2010) study. Intermittent symptoms were sometimes misconstrued as resolved, which could interrupt and extend the diagnostic interval, for example, because of the cancellation of investigations (Howell *et al.*, 2019). Symptom type was important, as study of multiple cancer types noted that *"It seemed that patients who had a lump as the presenting symptom sought medical advice with minimal delay, whereas patients with other symptoms delayed presentation to health service"* (Molassiotis *et al.*, 2010).

(4) Non-specific unwell state

A significant minority of patients in the study attributed their symptoms to a general state of being unwell. This was particularly associated with systemic symptoms such as fatigue. Participants described feeling, for example, *"Vaguely off"* [or] *"Just didn't feel right."* (Howell et al., 2019); *"'off it', 'out of whammy', 'run down', 'deteriorated', 'worn', 'awful' and 'gone downhill'."* (Howell, Smith and Roman, 2008). The interpretation of this seemed more serious, but it was not related to cancer:

You felt you are no use to you or to anybody else, you felt so weak. and then the effects also were you felt sickly all the time, but not actually being sick, just sickly. (Howell, Smith and Roman, 2008)

Without a specific explanation, participants described being unsure about what to do. Some participants sought help from a HCP, asking for "broad health checks" which may have diminished urgency in the consultation:

Initial help seeking could include requests for broad health checks: 'I just felt, okay I'll go to the doctor's and … (say), "Well, I want an MOT … I seem a bit tired" (Howell et al., 2020)

Having a non-specific explanation for the symptoms also meant that individuals lacked appropriate language to communicate their fears to HCPs.

*"I knew there was **something that wasn't right**. I wasn't myself, and I couldn't explain it so well to the doctor."* (Howell, Smith and Roman, 2008)

Difficulty communicating with HCPs was also experienced by relatives who felt the need to communicate that their relative was "not right" to reinforce the urgency of the presentation (Howell *et al.*, 2020).

Alarming symptoms that precipitated help-seeking

Participants in multiple studies reported that they started with an interpretation of symptoms within the typology above, but that their thinking changed over time and eventually acknowledged that they required help from a HCP (Howell *et al.*, 2018). We found that this was often precipitated by particular symptoms or signs that provoked alarm. These symptoms (particularly pain) were a stronger indicator to the individual of a more serious illness. For example, one participant in Howell *et al.* (2018) described "alarm bells" when they experienced severe pain during physical activity:

"I just couldn't do anything. I mean I'm used to a fairly active (life), even though I'm retired, I've an exercise bike in there …, which I used to go on every day and do 10 to 12 mile. When I started that I couldn't do one mile … I knew–alarm bells there was something wrong [P10]." (Howell et al., 2018)

Other participants described a more formal appraisal process that led to feeling of alarm, such as tracking their weight or how much medication they were taking (Howell *et al.*, 2020). Participants were particularly alarmed by rapid changes, or those that were suddenly severe or disruptive (Molassiotis *et al.*, 2010; Howell *et al.*, 2019).

What happens once someone presents to primary care with symptoms relevant to blood cancer?

Our synthesis showed that delays in the diagnostic interval were caused by a number of factors including low recognition of blood cancer symptoms, misleading clinical tests, HCP reassurance of the patient and subsequent slow reconsultation by the patient.

HCP interpretation of blood cancer symptoms is similar to that of patients. HCP interpretation of symptoms directly maps onto the patient typology of symptom interpretation outlined above. HCP recognition and knowledge of symptoms also seemed particularly problematic where symptoms were subtle and gradual in onset (Clarke *et al.*, 2014; Howell *et al.*, 2019). Young people reported in the study by Gibson *et al.* reported delays and a lack of seriousness about their concerns, as well as slow decision-making by the HCP (Gibson *et al.*, 2013). For example, some studies reported that patients experienced normalisation of their symptoms from a doctor, with some being told that they definitely did not have cancer:

> "'I'd been in pain for a long time, and I actually said, "I think I've got cancer" and (Dr) said to me, "You don't look like somebody who's got cancer"' [M14]; '(GP) said, "No, no, you haven't...lymphoma, old people get lymphoma. You're (under 40)...don't even think about that"' [L06]." (Howell et al., 2020)

In other studies, it was reported that this caused diagnostic delays due to fear of conflict and patient over-reassurance (Molassiotis *et al.*, 2010). Some HCPs suggested alternative diagnoses (mild or chronic illness) which also caused delays if these alternatives were investigated and reassured the patient that the causes were not serious:

> 'I noticed, like, a little pea-sized lump in my leg...my right calf...I thought... "Probably me varicose veins". I didn't rush, I went to see the doctor, regarding something else, and I just happened to mention to him about it... he had a feel of it, and he says "right, we'll send you off to have and ultrasound", you know, get it checked out. I asked (radiographer)... "Is it a varicose vein?" She says "yes". 'I got on with my life, I just carried on. I thought well fair enough, you know, its varicose veins...I never bothered when I started getting other lumps in my leg, I thought, "well it's all just part of it". (Howell et al., 2020)

Some participants were being investigated for other conditions when their blood cancer was diagnosed, which meant that they were ill-prepared for the diagnosis:

> "I was completely shocked ... because they'd been treating me for a virus for two months. So that was ... kind of a shock. And uh ... Got a little ... hazy after that. I just felt numb because I didn't know that...it had progressed... into leukemia." (LeBlanc et al., 2017)

Howell *et al.* (2019) also found that HCPs proposed a range of explanations for symptoms, including psychological conditions (stress, anxiety, depression):

> "'They thought it was anxiety, because I'd got myself in a state, and I was in a tearful mess at the doctor's, because of feeling ill and they're not getting anywhere...So she just thought it was an anxiety issue. It was like turned from one thing to something else' [L17]." [...] "'[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) (Howell et al., 2019)

In contrast, a number of studies described effective symptom knowledge by HCPs and swift referrals for specialist consultation (Gibson *et al.*, 2013; Howell *et al.*, 2020). This included explicit admission of uncertainty and effective use of gut feeling reported by GPs in Clarke *et al.* (2014):

> This was one of those ones where I opened the door and thought, 'I ought to telephone, to get the hospital on the line, yeah.'... I just remember that lurch of your stomach, you know, when you think 'oh'... She wasn't bouncy, she was very quiet, she seemed to be in pain actually, she was moaning, and she looked slightly swollen, her face was rounder than it should have been. (GP1) (Clarke et al., 2014)

In the same study, GPs shared the view that their role was not to diagnose cancer but to discriminate between unwell and healthy patients (children in this case) and to refer quickly (Clarke *et al.*, 2014).

Mixed role of blood tests and other investigations in progressing diagnosis. The synthesis of our findings revealed that blood tests had a particularly important role in diagnosis. It was reported that over half of patients had urine or serum tests, around a third had bone scans or bone marrow biopsies (Friese *et al.*, 2009). Some blood tests were more helpful than others; Koshiaris *et al.* found that 55% of patients with multiple myeloma had at least one blood test in the year before diagnosis; however, some blood tests were unhelpful at detecting myeloma: *"plasma viscosity and erythrocyte sedimentation rate, while C-reactive protein is unhelpful. In addition, the combination of a normal haemoglobin and plasma viscosity can be used to rule out the disease on patients currently being tested in primary care"* (Koshiaris, Van den Bruel, et al., 2018). Howell *et al.* (2020) found that referral was delayed by blood tests with negative results in the lead up to diagnosis:

> "I think I'd three lots of blood tests done as well, to try and find out, you know, and yet none of 'em showed anything to do with the lymphoma' [L31]; 'The blood test revealed nothing, did it, and neither did the camera in the stomach' [L20]. Where abnormal blood tests were noted, rapid hospital referral was described: 'I'd had about four or five different blood tests, and it were all coming back negative' [M15] ... 'til these blood tests did come back abnormal, all of a sudden, so that's when they sent him up to haematology [Relative: M15]; '(GP) immediately, more or less said, I'm sending you into hospital. You're anaemic' [L24]." (Howell et al., 2020)

Many patients had investigations for other conditions/diseases, for example, vitamin B12 deficiency (LeBlanc *et al.*, 2017) and varicose veins (Howell *et al.*, 2020).

Varying effects of discontinuity of care. Three studies reported different effects of seeing multiple HCPs. Two studies reported that this could be helpful, for example, that seeing a different HCP from normal could precipitate a referral after a long delay as they interpreted symptoms differently (Gibson *et al.*, 2013). Similarly, Molassiotis *et al.* (2010) reported that other HCPs expedited referral, citing dentists in the case of symptoms around the head or neck area. In contrast, one study reported that the lack of continuity of GP between consultations was identified as a cause of delay by both patient (or their parents) and GPs themselves (Clarke *et al.*, 2014).

Overcoming barriers in the diagnostic pathway. Howell *et al.* (2020) were the only study to report detailed information about how patients had to advocate or actively direct steps in the diagnostic phase (Howell *et al.*, 2020). For example, patients reported multiple behaviours reported by patients to convince HCPs of the need for further investigative action, such as having to request specific input or be more directive in their requests for further investigation:

> I weren't going to take "no" for an answer... because I knew there was something' [L34]. Doubt about an earlier explanation was often key: 'I was convinced there was something wrong with me, other than osteoporosis, because I thought "I shouldn't feel, this unwell, with osteoporosis."' [M14]. (Howell et al., 2020)

One patient reported that they kept track of their weight loss in a diary in order to convince their GP to refer them for tests. Other

patients used other HCPs' opinions to try and persuade the GP or did their own research about cancer.

Discussion

This rapid review illustrates the complexity of blood cancer symptoms, and how patients appraise them, leading to distinct help-seeking patterns in primary care. The importance of patient appraisal and help-seeking in the timely diagnosis has been established in other cancers (Liu, n.d.; Oberoi *et al.*, 2016; O'mahony, 2016; Mills *et al.*, 2017; Scott *et al.*, 2019; van Os *et al.*, 2021); this review adds to this body of evidence about the specific qualities of blood cancer symptoms, and how these create distinct patterns of appraisal and behaviour.

We found that studies have measured diagnostic delay differently, although there has been more homogeneity since the introduction of the MPT (Scott *et al.*, 2013). We found a range of factors that contribute to delay including disease factors, patient characteristics and health system factors. There was a lack of consistency in the quantitative studies (in terms of sampling, approach, definitions and findings), making cross-study comparisons difficult. However, one unifying interpretation was that the overall reason for delay was due to lower cancer suspicion in particular disease types (because symptoms were more likely to be interpreted as non-significant) or demographic (e.g. younger) groups.

In a narrative synthesis of the included studies, we produced a four part typology of patient interpretation of symptoms and found that this was mirrored by HCPs. The typology includes (1) nothing being wrong, (2) an event-linked problem (e.g. injury), (3) mild or chronic illness and (4) a non-specific unwell feeling.

The problem of symptom normalisation and mild illness attribution in cancer diagnosis is well established (Andersen and Cacioppo, 1995; Smith *et al.*, 2005; Koo *et al.*, 2021), alongside the influence of sudden changes/worsening of symptoms referred to as the *rate of change rule* (Kummer *et al.*, 2019). However, of particular novelty in our review is the interpretation that nothing is wrong at all, due to the ambiguous nature of some blood cancer symptoms (e.g. pallor, swollen lymph nodes) where patients are not sure whether or not their symptom even exists. The fourth typology of a "non-specific unwell feeling" is also unusual and may be a target for interventions in primary care. Similar findings were found in a qualitative study of head and neck cancers, where the results highlighted the subtlety of symptoms (Scott *et al.*, 2019).

Another finding of note is the fact that blood cancer symptoms could be interpreted differently for individuals according to age and co-morbidities, for example, fatigue was attributed to stress in younger people and ageing effects in older people. This is similar to the findings of a systematic review into delays in gynaecological cancer diagnosis, where bleeding was interpreted differentially by women according to their age (Williams *et al.*, 2019).

In line with other studies of primary care consultations, we found that diagnosis could be delayed by HCP interpretation of symptoms, either by misalignment between HCP and patient interpretation (Amelung *et al.*, 2020) or direct denial of any cancer risk (van Os *et al.*, 2021). Blood tests and their interpretation were also highlighted as a risk for delay, particularly if the wrong test was chosen or negative results were reported.

Finally, we found that there was a relative paucity of evidence about the burden on patients to overcome barriers in the blood cancer diagnostic pathway, with only one recent qualitative study reporting on this (Howell *et al.*, 2020). Most evidence to date has focused on the earlier part of the diagnostic pathway (e.g. symptom appraisal), with little discussion around other concepts relevant to how people with potential blood cancer symptoms navigated the healthcare system and influences on this. For example, it is important to understand perceived eligibility for healthcare (candidacy) (Dixon-Woods *et al.*, 2006; Tookey *et al.*, 2018), particularly given the vague nature of symptoms, or the ability to understand and cope with symptoms following primary care consultations (Howie *et al.*, 1997). This is surprising, particularly given the higher frequency of multiple consultations in primary care in this group and complex, often protracted pathways to diagnosis. Interestingly, social networks could have a detrimental impact on prompt help-seeking for blood cancer patients (e.g. by supporting the normalisation of symptoms), despite previous research demonstrating that lay conversations were considered important in the decision to seek medical help for new symptoms (e.g. Scambler *et al.*, 1981).

Study limitations

This review is the first to examine the factors influencing patient and health system factors in diagnosis delay for all blood cancers. It has been conducted rigorously according to a rapid review protocol and provides a summary of the available evidence to inform future research and complex interventions to reduce diagnostic delay.

There are some limitations. Despite a systematic search strategy, some studies may have been missed due to the limited database search entailed by the rapid design. The studies were heterogeneous with different methodologies, blood cancer types and populations, making it challenging to synthesise findings; however, our four-part typology aids their interpretation. Variations in methodology – including the definition of delay – prevented aggregation or meta-analysis. This methodological heterogeneity limits definitive conclusions about the primary causes of delay.

Clinical implications

HCPs are under increasing pressure in primary care, particularly in response to the COVID-19 pandemic, as well as lack of investment in the cancer workforce (Dacre *et al.*, 2022). Blood cancer symptoms are rarely presented and hard to interpret; we cannot expect all HCPs to retain this knowledge constantly. Our typology also suggests that patients relating to our Typologies 2 and 3 may initially present with symptoms that they interpret as mild illness or an event-linked problem. Solutions may be found in systems that reduce the burden on HCPs and patients to support effective decision-making and appropriate reconsultation, such as electronic safety netting software and risk calculation tools, as well as specialist referral to non-specific symptom pathways (Black *et al.*, 2022). Blood tests and investigations are crucial to blood cancer diagnosis, and access to these (as well as specialist advice) must be made available. Additionally, our Typologies 1 and 4 indicate that patients would not seek help at all initially as they have difficulty recognising a disease state. Greater public awareness of blood cancer signs and symptoms through educational campaigns and other types of public messaging may improve this, supported by accessible primary care services.

Conclusions

Blood cancers are difficult to diagnose due to non-specific heterogeneous symptoms, and this is reflected in how those symptoms are interpreted by patients, their family and friends, and subsequently managed by HCPs. It is important to understand how different interpretations affect delays in help-seeking, and what HCPs can do to support timely follow-up for patients presenting with non-specific symptoms such as these. Research relating to patient empowerment in progressing investigations for blood cancer symptoms would be beneficial.

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Appendix A

Quantitative studies

Research article	Is the sampling strategy relevant to address the research question?	Is the sample representative of the target population?	Are the measurements appropriate?	Is the risk of nonresponse bias low?	Is the statistical analysis appropriate to answer the research question?
Antel et al. (2019)	Yes	No	Yes	No	Yes
Dapkeviciute et al. (2019)	Yes	No	Yes	No	Yes
Friese et al. (2009)	Yes	No	Yes	Yes	Yes
Howell et al. (2015)	Yes	Yes	Yes	Yes	Yes
Koshiaris et al. (2018)	Yes	Yes	Yes	Yes	Yes
Lins et al. (2012)	Yes	Can't tell	Yes	Yes	Yes
Saunders et al. (2015)	Yes	No	Yes	No	Yes

Qualitative studies

Research Article	Is the qualitative approach appropriate to answer the research question?	Are the qualitative data collection methods adequate to address the research question?	Are the findings adequately derived from the data?	Is the interpretation of results sufficiently substantiated by data?	Is there coherence between qualitative data sources, collection, analysis and interpretation?
Clarke et al. (2014)	Yes	Yes	Can't tell	Yes	Yes
Gibson et al. (2013)	Yes	Yes	Yes	Yes	Yes
Howell, Smith & Roman (2008)	Yes	Yes	Can't tell	Yes	Yes
Howell et al. (2018)	Yes	Yes	Yes	Yes	Yes
Howell et al. (2019)	Yes	Yes	Yes	Yes	Yes
Howell et al. (2020)	Yes	Yes	Yes	Yes	Yes
LeBlanc et al. (2017)	Yes	Yes	Yes	Yes	Yes
Molassiotis et al. (2010)	Yes	Yes	Yes	Yes	Yes