

**THE SYMPTOMS OF ADULT CHRONIC AND ACUTE LEUKAEMIA BEFORE DIAGNOSIS: LARGE
PRIMARY CARE CASE-CONTROL STUDIES USING ELECTRONIC RECORDS.**

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ABSTRACT

Background: Leukaemia is the eleventh commonest UK cancer. The four main sub-types have different clinical profiles, particularly between chronic and acute types.

Aim: To identify the symptom profiles of chronic and acute leukaemia in adults in primary care.

Design and setting: Matched case-control studies using Clinical Practice Research Datalink records.

Methods: Putative symptoms of leukaemia were identified in the year before diagnosis. Conditional logistic regression was used for analysis; to estimate risk, positive predictive values (PPVs) were calculated, using Bayes' theorem

Results: 4,655 cases were available aged ≥ 40 years, diagnosed between 2000 and 2009, with 2,877 being chronic leukaemia (CL), 937 acute leukaemia (AL) and 841 of unreported subtype, with 20,719 age, sex and practice-matched controls. The two studies examined CL and AL separately.

Ten symptoms were independently associated with CL, the three strongest associations being for: lymphadenopathy, odds ratio 2.2 (95% confidence interval 1.3,3.6), weight loss 3.0 (2.1,4.2) and bruising 2.3 (1.6,3.2). Thirteen symptoms were independently associated with AL, the three strongest being: nosebleeds and/or bleeding gums 5.7 (3.1,10), fever 5.3 (2.7,10) and fatigue 4.4 (3.3,6.0). Infection was reported frequently in both AL and CL, but the associations were small. No individual symptom or combination of symptoms had a PPV $> 1\%$.

Conclusions: The symptom profiles of CL and AL have both overlapping and distinct features. This presents a dichotomy for GPs: diagnosis, by performing a full blood count, is easy; however, the

symptoms of leukaemia are non-specific and of relatively low risk. This explains why many leukaemia diagnoses are unexpected findings.

Keywords: Chronic leukaemia; acute leukaemia; Primary Health Care; diagnosis

HOW THIS FITS IN

What is already known on this subject?

- Leukaemia can be diagnosed in primary care through blood tests, either incidentally or once the disease is considered.
- The differences between the chronic (CL) and acute leukaemia (AL) prodromes are not clear.
- There are no previous studies from primary care.

What this study adds

- The symptom profiles overlap on general symptoms like infection, fatigue, malaise and weight loss but others are sub-type specific : lymphadenopathy, cough and hypertension are significant in CL, while nosebleeds and bleeding gums, fever, flu, abdominal pain, chest pain and vomiting and nausea are significant in AL.
- Individual and combined symptom risk estimates are all under 1%, making guidance for GPs as to when to take blood tests difficult.
- The lymphocyte count increases greatly in CLL cases in the 6 months before diagnosis, though some patients have raised counts for several years before diagnosis.

INTRODUCTION

Leukaemia is characterised by proliferation of abnormal leukocytes.¹ There are four main subtypes: chronic myeloid leukaemia (CML), chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL). The incidence, clinical presentation and survival all vary by subtype. Around 8,600 UK people are diagnosed with leukaemia with 4,800 deaths annually. It mainly a disease of adults, with 88% of new diagnoses occurring in the over 40s.¹⁻⁵

The latest leukaemia survival figures show a reduction in the percentage of 'avoidable UK deaths' from 4.5% (1985-89) to 1.3% (1995-99); however, a discrepancy in mortality between the rich and poor in England still exists.^{6,7} Updated UK guidance on the diagnosis of leukaemia gives several symptoms which GPs may consider investigating by a full blood count; however, none of these recommendations was based on primary care evidence.⁸

Diagnosis generally follows symptomatic presentation to a health professional, usually in primary care, prompting blood testing or through an incidental blood test result when leukaemia had not been considered. No primary care symptomatic papers have been published. One secondary care paper reported the percentage of patients with symptomatic presentations: these were least frequent in CLL (47%) compared with 71% in CML, 77% in AML and 78% in ALL. Tiredness and pain were common to all leukaemias but some symptoms were more specific: chest pain in AL; bruising/bleeding and shortness of breath/cough in AML, masses in ALL and CLL and abnormal sweating in CL.⁹ Another study of over 5,000 CLL patients reported infection in 32%, fatigue in 17% and lymphadenopathy in 7%, with splenomegaly and excessive sweating much rarer.¹⁰ For CML, fatigue has been reported in nearly 34%, with bleeding and weight loss in 21% and 20% respectively.¹¹ Infection, headache, cough, malaise and nausea were rarer, reported in 7% of cases. For the acute leukaemias, fatigue, haemorrhage, fever and infection are common in AML, whilst fatigue, infection, bone pain, fever, bruising/bleeding and petechiae have been reported in ALL.^{12 13}

Haematological abnormalities in CLL have been reported up to ten years before diagnosis, with monoclonal B-cell lymphocytosis (MBL) believed to be a precursor condition in almost all CLL patients¹⁴. Declining haemoglobin values have been reported in lymphatic leukaemias beginning five years before diagnosis.¹⁵

This study aimed to identify and quantify the separate primary care *symptom-only* profiles of chronic and acute leukaemias, to guide GPs when to initiate blood tests for possible leukaemia. We also took the opportunity to assess how the lymphocyte count changes in the five years before a diagnosis of CLL.

METHODS

This was a matched case-control study using electronic patient record data from the UK's Clinical Practice Research Datalink (CPRD). The methods follow those of our other primary care cancer papers.^{16 17} The CPRD contains anonymised primary care medical records from around 680 UK general practices, representing 8.8% of the population. Personal information is collected, as well as clinical events such as symptom reporting, diagnoses, prescriptions and investigation results.

Cases and controls

A list of 96 leukaemia diagnostic codes (available from the authors) was used to identify cases in the CPRD. Cases were aged ≥ 40 years, diagnosed with leukaemia between 2000-2009 inclusive. For each case, up to five, age, sex and general practice matched controls were chosen. The first leukaemia code was taken as the date of diagnosis, or 'index date'. Controls matched their cases' index date. Cases were categorised to 'chronic leukaemia' (CL), 'acute leukaemia' (AL) or 'undetermined' based on their first code sub-type. 40 cases (33 CL and 7 AL) had additional multiple codes for leukaemia, including five with codes for both AL and CL on their index date: all five were assigned to CL, after examining subsequent disease codes. Exclusion criteria were: cases with reticulo-endothelial cancer or thrombocytic leukaemia and their matched controls; any case or control with less than one year of records before the index date; cases without controls; controls with leukaemia; and controls who had not sought medical care after registration.

Selection of putative clinical variables

A list of reported clinical features of leukaemia from research literature and cancer websites was compiled and supplemented with self-reported symptoms from online patient support group. PubMed, EBSCO and Google Scholar were used with the search terms 'acute/chronic leukaemia symptoms', 'chronic/acute leukaemia reported to GP', and 'early signs/indications/symptoms of acute/chronic leukaemia.' The CPRD contains many codes associated with each feature. A symptom

library was therefore compiled for each clinical feature, and their occurrences identified in the year before the index date. Only those features present in $\geq 2\%$ of cases entered analysis.

Blood test results were not included in the primary analysis as most patients having blood tests will have a full blood count, which in almost always reveal any leukaemia. Secondary analyses included adding the white cell count to the final multivariable model, and examined pre-diagnostic lymphocyte counts over five years. Recording bias was tested using a feature thought to have no association with leukaemia – fracture.

Analysis and statistical methods

The main analytical method was conditional logistic regression. Variables with a p-value of ≤ 0.1 from univariable analysis entered multivariable analysis. Features were grouped according to similarity – such as abdominal pain, back pain, chest pain. All features from the group stage attaining a p-value threshold of ≤ 0.05 entered final modelling, which used a $p \leq 0.01$ threshold for retention. Clinically plausible interaction terms and lymphoid/myeloid interactions were tested against the final model and retained if their p-value was ≤ 0.01 .

Positive predictive values (PPVs) for the risk of CL or AL was calculated separately using Bayes' theorem (prior odds x likelihood ratio = posterior odds). Prior odds were calculated from the age-specific national incidence of CL and AL for 2008, expressed as odds. PPVs were estimated for consulting patients only: thus, the posterior odds for CL were divided by 0.910 as 1,272 (9%) of 14,103 eligible controls were non-consulters. The conversion factor for AL was 0.915 respectively. A separate analysis of the lymphocyte count (selected in preference to the WCC, as it is more specific for CLL) was conducted in CLL, and values in the five years before diagnosis plotted as a monthly moving average.

Power calculation

Initial estimates from the CPRD indicated approximately 3,000 CL and 1,000 AL cases were available; these transpired to be minor overestimates. A power calculation showed that for CL, there was >98% power to detect a difference in a rare variable present in 2% cases and 1% of controls. For a commoner variable, there was >99% power to detect a difference in prevalence of 20% in cases to 15% in controls. For AL, power was >98% for detecting a difference from 3% in cases to 1% in controls and >96% power 20% in cases and 15% in controls. All analysis was conducted using Stata software, version 13.1.¹⁸

RESULTS

The CPRD supplied 27,619 patients (4,673 cases and 22,946 controls). After applying the exclusion criteria (Figure 1) 4,655 cases and 22,852 controls remained. There were 2,877 CL cases and 12,811 controls and 937 AL cases and 4,214 controls. The remainder were undetermined leukaemia subtypes, and omitted.

Figure 1 here

Patient demographic and consultation information is given in Table 1. CL and AL cases consulted significantly more frequently than controls in the year before diagnosis ($p < 0.001$; ranksum test).

Table 1 here

Symptoms

Fifty symptoms were considered initially. Ten remained significant in the CL final model; thirteen in AL. Their frequencies, univariable likelihood ratios and multivariable odds ratios are shown in Table 2. From the 2,877 CL cases, 1,400 (49%) had either no symptoms or symptoms not present in the

final model, compared with 351 (37%) of the 937 AL cases. Some previously reported symptoms were too infrequent for reliable analysis: bone pain, 1.7% in CL, 1.5% in AL; splenomegaly, 0.9% CL, 0.5% AL; excessive sweating, 0.8% CL, 0.7% AL, and petechiae, 0.6% CL, 0.7% AL. Within CL, there was a significant interaction of lymphoid versus myeloid leukaemia and lymphadenopathy (general and site specific), with lymphadenopathy being reported more in CLL cases, interaction odds ratio 0.014 ($p < 0.001$). For AL, there was a significant gender interaction for chest pain, with more males reporting the symptom OR 0.403 ($p < 0.005$). The proportion of patients with a fracture in both CL and AL did not differ between cases and controls ($p < 0.33$ and $p < 0.62$, respectively).

The secondary analysis of the CL dataset incorporating raised white cell counts (WCC) was very different, containing only five variables, and dominated by the very high odds-ratio of the raised white cell count: raised WCC OR 81 (95 % confidence interval 64,102), lymphadenopathy, 21 (11,41), bruising/haematoma/contusion 1.9 (1.3,3.0), fatigue 1.6 (1.3,2.1) and infection 1.4 (1.2,1.6).

Table 2 here

Positive predictive values

PPVs were calculated for the over 60s, targeting patients around the average age of leukaemia diagnosis - accounting for 83% of CL cases, and 82% of AL cases. For CL, the highest PPV was 0.34% for lymphadenopathy; weight loss, bruising and fatigue were all under 0.01%. Lymphadenopathy with cough had the highest combined PPV of 0.27%; many combinations were too rare to allow a PPV calculation. For AL, all single symptoms had PPVs $< 0.01\%$. Fever with infection produced the highest combined PPV of 0.13%.

Lymphocyte counts in the years before diagnosis of CLL

The lymphocyte counts in 1,751 out of 2379 (74%) CLL cases in the five years before the index date are shown in figure 2. The graph indicates a steady increase in lymphocyte count in cases, becoming

greater in the 6 months before a CLL diagnosis. Many abnormally high values were present up to five years before diagnosis.

Figure 2 here

DISCUSSION

Summary

This is the first study to investigate separate CL and AL symptoms from primary care. Ten were independently associated with CL; thirteen with AL. Non-specific symptoms such as fatigue, infection, malaise, weight loss, diarrhoea, bruising and shortness of breath were common to both CL and AL. The remaining symptoms were unique to the sub-type: lymphadenopathy, cough and hypertension were significant in CL, while nosebleeds and bleeding gums, fever, flu, abdominal pain, chest pain and vomiting and nausea were significant in AL. No single symptom or symptom pair had a PPV of over 1%. The raised lymphocyte count in CLL cases up to five years before diagnosis suggests the diagnosis could be advanced considerably, though the clinical advantages of this are debatable.

Strengths and limitations

The use of the CPRD ensured good data quality, a large sample size, and a representative spread of patients across the UK. Analysis by sub-type, gender and age was possible, allowing the identification of relevant symptoms, though even this large dataset was insufficient for some symptom combinations, which were simply too rare in controls. The selection of putative symptoms was inclusive and derived from our literature review, supplemented by self-reported symptoms. It is unlikely that pertinent symptoms were excluded.

Nearly a fifth of the total leukaemia cases had a generic leukaemia code which could not be categorised to either AL or CL: we omitted them from study. This is unlikely to have introduced bias, though it will have reduced power a little.

Recording of duration and severity of symptoms is generally poor in GP notes, and GPs appear to preferentially record diagnoses over symptoms. Information on cancer staging is also poor, preventing sub-analyses of, for example, early stage cancers. GPs can choose to record information in a free text ('uncoded') section which is generally not available to researchers: this can influence the results if such differential recording occurs preferentially in either cases or controls – though this affect appears to be minor.¹⁹ Cases have a higher attendance rate, thereby increasing the chance of reporting a symptom. However, our test for this bias, of the fracture rate, did not support this potential concern.

Comparison with existing literature

Tiredness has been reported in the secondary care literature: both malaise and fatigue were present, but with a higher prevalence in AL.⁹⁻¹¹ Similarly, we only found chest pain to be associated with AL.⁹ Bruising, previously reported in AML patients, was found in both CL and AL but twice as commonly in AL. Shortness of breath, also previously reported in AML patients, was significant in both CL and AL; cough was only found in CL, as has been reported for CML previously.¹¹ The symptom with the highest odds ratio, lymphadenopathy, which was previously reported in ALL and CLL, was only found in CLL patients in this study.⁹ Hypertension was significantly associated with CL, but with such a small odds ratio as to be of little value clinically. Finally, raised lymphocytes long before a CLL diagnosis has been reported in the secondary care literature before.¹⁴

Implications for practice

In theory, primary care diagnosis of leukaemia should be easy, as nearly all leukaemias have abnormal full blood counts. Indeed, many leukaemias – especially CLL, are identified serendipitously, with possible leukaemia not considered likely – or at all – at the time of testing.⁹ Ideally we would have separated the truly asymptomatic group of patients from those with a symptom which did not reach the final model; however this was not possible, as our methods only included putative leukaemia symptoms, and omitted symptoms deemed irrelevant. It is likely most patients having a full blood count were symptomatic, even if the symptoms were not those of leukaemia. Only 51% of our CL patients had a symptom appearing in the final model; this suggests roughly half are serendipitously discovered. Thus our results should be seen as symptoms which should prompt consideration of a blood count. The symptoms largely match those in the revised NICE guidance – which combined all forms of leukaemia. However, shortness of breath, chest and abdominal pain and diarrhoea are not included in the guidance.

It was not clear what events had triggered full blood counts in our cases, particularly those who were apparently asymptomatic. Blood testing is remarkably common in primary care, with approximately a quarter of those over thirty having a full blood count in any one year.²⁰

The clinical problem is that all PPVs are tiny. All the symptoms reported here have much more likely benign alternative explanations, though some of the alternative diagnoses – such as anaemia – would require a blood count to be taken for diagnosis. In truth, however, the small possibility of leukaemia will only add marginally to the decision to investigate by a blood count. Some symptoms, such as fatigue, are frequently investigated, particularly when persistent.²¹ A second group of symptoms often suggests important underlying disease, such as weight loss, bruising, nose bleeds, bleeding gums or lymphadenopathy, especially in the over 60s: our results suggest that a blood count should be included in investigation of these. The graph of lymphocyte counts before diagnosis of CLL suggests there is a considerable opportunity to expedite the diagnosis; this could include software in the primary care clinical systems or in the reporting laboratory which could alert the GP

to a raised white cell count, mentioning the possibility of CLL. This is supported by the analysis retaining WCCs in the chronic leukaemia model, showing a very high odds-ratio with only lymphadenopathy adding much to the predictive power of the model. Indeed, it is plausible other haematological measures are changing in the years before CLL is diagnosed: this is an avenue for further study. Although treatment of early CLL is sometimes considered, many patients are observed without active treatment initially, so the imperative to diagnose early is arguably much less in CLL than in most other cancers.

Conclusion

Leukaemia is relatively rare. We have identified a number of symptoms related to either chronic or acute leukaemia – or both. No symptom stands out as a high risk marker of the disease, though many of the symptoms would lead to testing which would then reveal the underlying leukaemia. This probably explains why most diagnoses are serendipitous – and are likely to remain so, especially as the number of patients having blood counts increases.

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Ethical approval: Independent Scientific Advisory Committee – protocol 09-110

Competing interests: WH is clinical lead on the ongoing revision of the NICE guidance on investigation of suspected cancer. His contribution to this article is in a personal capacity, and is not to be interpreted as representing the view of the Guideline Development Group, or of NICE itself. PR reports personal fees from GP Update Ltd, outside the submitted work. Other than this, no competing interests.

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Figure 1. Leukaemia exclusions

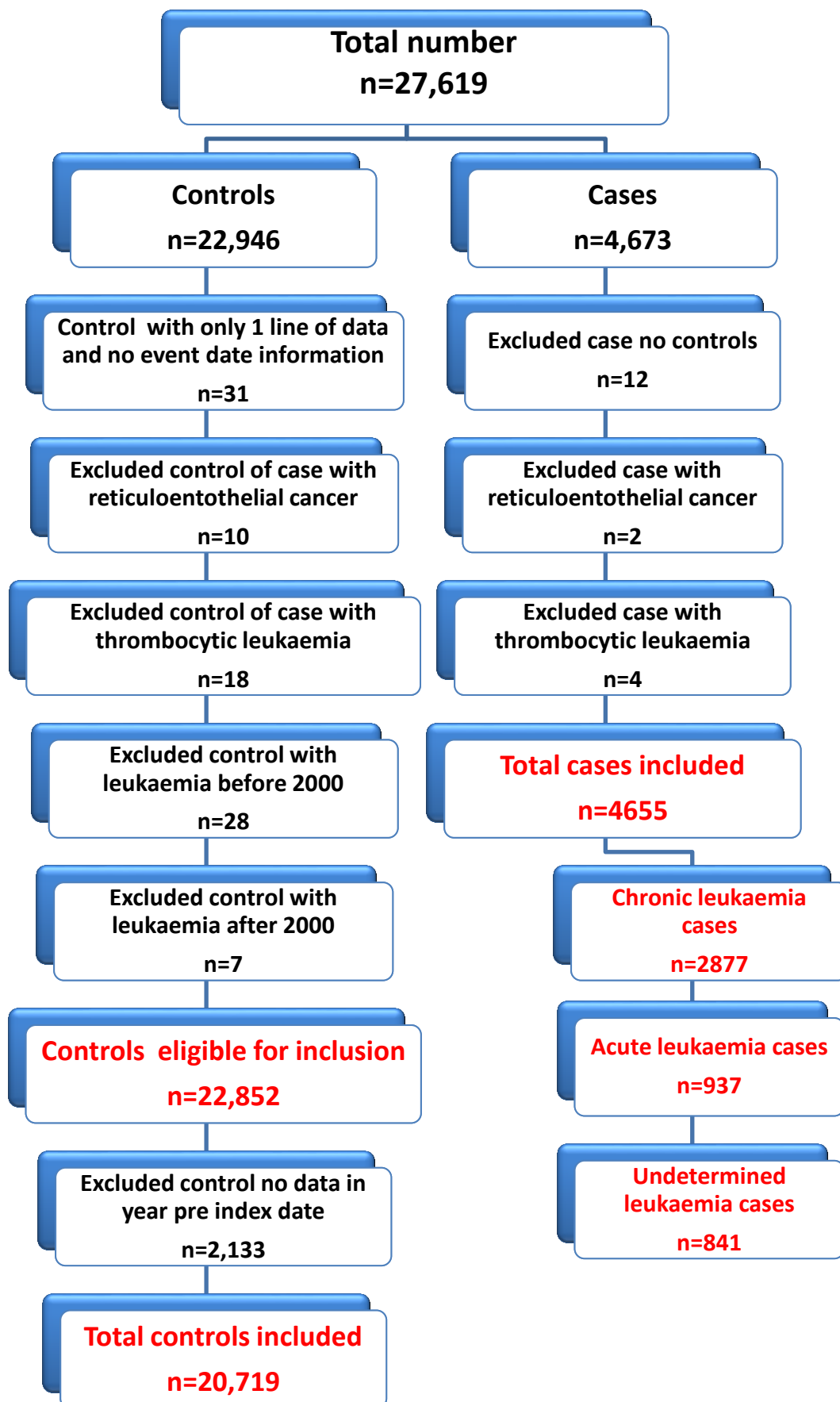


Table 1. Patient demographics and consultation rates in the year before diagnosis

CHRONIC LEUKAEMIA						
	Cases			Controls		
	Male (n=1679)	Female (n=1198)	Total (n=2877)	Male (n=7281)	Female (n=5530)	Total (n=12811)
Median (IQR) age in years at diagnosis	71 (62-79)	74 (64-81)	72 (63-80)	71 (63-79)	73 (65-81)	72 (64-80)
Median (IQR) number of consultations	12 (7-20)	13 (8-20)	13* (8-20)	8 (4-14)	9 (4-15)	8* (4-15)
ACUTE LEUKAEMIA						
	Cases			Controls		
	Male (n=541)	Female (n=3962)	Total (n=937)	Male (n=2377)	Female (n=1837)	Total (n=4214)
Median (IQR) age in years at diagnosis	72 (63-78)	73 (64-81)	72 (63-80)	72 (65-78)	73 (64-81)	73 (64-80)
Median (IQR) number of consultations	16 (9-24)	16 (9-25)	16* (9-25)	8 (4-15)	9 (4-16)	8* (4-16)

* Cases consulted significantly more frequently than controls in the year before diagnosis ($p < 0.001$).

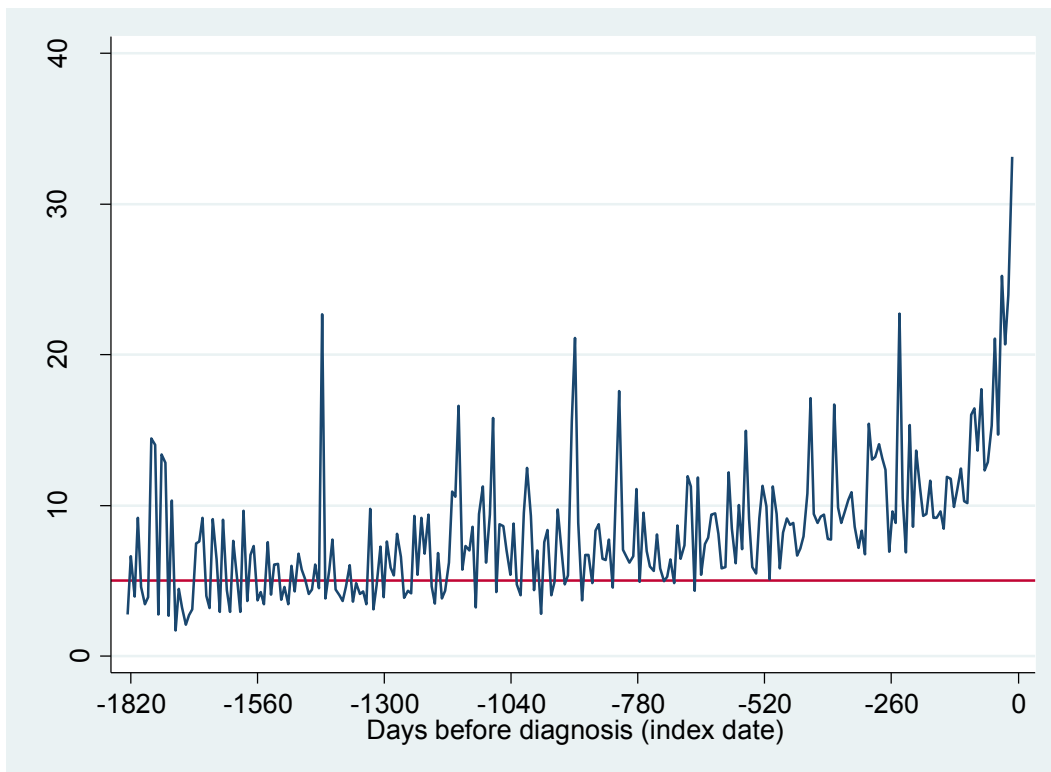
Table 2. Symptoms of acute and chronic leukaemia

ACUTE LEUKAEMIA				
Symptom	Cases <i>n</i> (%) <i>n</i>=937	Controls <i>n</i> (%) <i>n</i>=4214	Likelihood ratio (95% CI)	Odds ratio in multivariable analysis (95% CI)
Infection ₁	237 (25)	651 (15)	1.6 (1.4-1.9)	1.5 (1.3 to 1.8)
Shortness of breath	136 (15)	248 (6)	2.5 (2.0-3.0)	2.5 (1.9 to 3.2)
Fatigue	109 (12)	128 (3)	3.8 (3.0-4.9)	4.4 (3.3 to 6.0)
Chest pain	90 (10)	202 (5)	2.0 (1.6-2.5)	1.5 (1.1 to 2.1)
Abdominal pain	89 (10)	202 (5)	2.0 (1.6-2.5)	1.7 (1.2 to 2.2)
Diarrhoea	64 (7)	118 (3)	2.4 (1.8-3.3)	2.2 (1.5 to 3.1)
Malaise	57 (6)	58 (1)	4.4 (3.1-6.3)	3.4 (2.2 to 5.2)
Vomiting and nausea	56 (6)	98 (2)	2.6 (1.9-3.5)	1.8 (1.2 to 2.6)
Bruising ₂	41 (4)	52 (1)	3.6 (2.4-5.3)	3.7 (2.3 to 5.8)
Fever	28 (3)	19 (0.5)	6.6 (3.7-12)	5.3 (2.7 to 10)
Nosebleeds and bleeding gums	26 (3)	30 (0.7)	3.9 (2.3-6.6)	5.7 (3.1 to 10)
Flu	20 (2)	24 (0.6)	3.8 (2.1-6.8)	3.9 (2.0 to 7.5)
Weight loss	18 (2)	33 (1)	2.5 (1.4-4.3)	3.0 (1.5 to 5.8)
CHRONIC LEUKAEMIA				
Symptom	Cases <i>n</i> (%) <i>n</i>=2877	Controls <i>n</i> (%) <i>n</i>=12811	Likelihood ratio (95% CI)	Odds ratio in multivariable analysis (95% CI)
Infection ₁	608 (21)	1887 (15)	1.4 (1.3-1.6)	1.5 (1.3 to 1.6)
Cough	415 (14)	1394 (11)	1.3 (1.2-1.5)	1.2 (1.1 to 1.4)
Hypertension	403 (14)	1619 (13)	1.1 (1.0-1.2)	1.2 (1.1 to 1.4)
Shortness of breath	214 (7)	666 (5)	1.4 (1.2-1.7)	1.3 (1.1 to 1.5)
Fatigue	196 (7)	409 (3)	2.1 (1.8-2.5)	2.1 (1.8 to 2.6)
Diarrhoea	138 (5)	381 (3)	1.6 (1.3-2.0)	1.4 (1.1 to 1.7)
Lymphadenopathy	90 (3)	18 (0.1)	22 (13-37)	22 (13 to 36)
Malaise	70 (2)	170 (1)	1.8 (1.4-2.4)	1.7 (1.3 to 2.3)
Weight loss	65 (2)	93 (1)	3.1 (2.3-4.3)	3.0 (2.1 to 4.2)
Bruising ₂	58 (2)	115 (1)	2.3 (1.6-3.1)	2.3 (1.6 to 3.2)

1 Infection consists of urinary tract infection, upper respiratory tract infection, skin infection and chest infection symptoms.

2 Bruising consists of bruising, haematoma and contusion symptoms

Figure 2. The **lymphocyte count** in patients with chronic lymphocytic leukaemia up to five years before their diagnosis presented as a monthly-moving average.



Note: the horizontal line represents a lymphocyte count of 5,000 (per cubic millimetre), the threshold value where CLL is diagnosed (Rawstron et al, 2008).

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