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Alarm symptoms and identification of non-cancer diagnoses in primary care: cohort study

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ABSTRACT

Objective To evaluate the predictive value of alarm symptoms for specified non-cancer diagnoses and cancer diagnoses in primary care.

Design Cohort study using the general practice research database.

Setting 128 general practices in the UK contributing data, 1994-2000.

Participants 762 325 patients aged 15 or older.

Main outcome measures Up to 15 pre-specified, non-cancer diagnoses associated with four alarm symptoms (haematuria, haemoptysis, dysphagia, rectal bleeding) at 90 days and three years after the first recorded alarm symptom. For each outcome analyses were implemented separately in a time to event framework. Data were censored if patients died, left the practice, or reached the end of the study period.

Results We analysed data on first episodes of haematuria (11 108), haemoptysis (4812), dysphagia (5999), or rectal bleeding (15 289). Non-cancer diagnoses were common in patients who presented with alarm symptoms. The proportion diagnosed with either cancer or non-cancer diagnoses generally increased with age. In patients presenting with haematuria, the proportions diagnosed with either cancer or non-cancer diagnoses within 90 days were 17.5% (95% confidence interval 16.4% to 18.6%) in women and 18.3% (17.4% to 19.3%) in men. For the other symptoms the proportions were 25.7% (23.8% to 27.8%) and 24% (22.5% to 25.6%) for haemoptysis, 17.2% (16% to 18.5%) and 22.6% (21% to 24.3%) for dysphagia, and 14.5% (13.7% to 15.3%) and 16.7% (15.8% to 17.5%) for rectal bleeding.

Conclusion Clinically relevant diagnoses are made in a high proportion of patients presenting with alarm symptoms. For every four to seven patients evaluated for haematuria, haemoptysis, dysphagia, or rectal bleeding, relevant diagnoses will be identified in one patient within 90 days.

INTRODUCTION

Most major and minor illnesses in the United Kingdom are managed by general practitioners and, in other countries, by generalist primary care physicians.[1] The number of new cases of serious illness seen each year by an individual general practitioner, however, is relatively small. For example, each of the 42 000 general practitioners in the UK will see about seven new cancers, three to four strokes, and five to six myocardial infarctions each year, assuming a notional list size of 1800-2000.[2] Many years ago, however, Thomas noted that up to 40% of patients presenting in primary care and observed over a two week period recover without specific treatment and often without a specific diagnosis being made.[3]

Operating in conditions of diagnostic uncertainty, general practitioners have the often difficult task of separating the minority of patients whose symptoms could indicate serious disease and who require urgent diagnostic attention from the majority with less serious, self limiting illness,[4] in whom time can often be used both as a "diagnostic and therapeutic tool."[5 6] To make these difficult judgments general practitioners use various personal "heuristics"—commonsense rules often involving the use of questions thought to have high negative or positive predictive values to rule out serious disease and often without a firm evidence base to support them.[7-9] This has led to continuing uncertainty about the optimum use and timing of invasive or costly investigations (such as endoscopy and imaging) and controversy about the content of clinical practice guidelines. For example, our limited knowledge of the epidemiology of common cancers has formed the basis of referral guidelines, including the two week rule in the UK, which provides rapid access to specialists for patients presenting in primary care with symptoms that might indicate cancer. There is uncertainty, however, about whether this approach has resulted in more rapid identification of cancers at a more treatable stage.[10] Another example of the need for more diagnostic research concerns the investigation of upper gastrointestinal symptoms and the relative roles of upper gastrointestinal endoscopy, *Helicobacter pylori* testing, and empirical acid suppression, which have been debated for many years without a firm conclusion being reached.[11-13]

There is a need for more "diagnostic research" to generate the evidence base on which to refine diagnostic criteria in primary care and to develop decision rules for the management of symptoms and symptom complexes. In his recent publication on evidence

based diagnosis in primary care, Polmear[14] found few studies in primary care that provide accurate information about the predictive value of common symptoms, emphasising the need for more research of this kind.

Previously we used the general practice research database to study the incidence of cancers in patients presenting in primary care with four "alarm symptoms"—haematuria, dysphagia, haemoptysis, and rectal bleeding.[15] We have now used the database to examine the identification of non-cancer diagnoses in patients presenting with alarm symptoms. The database is the world's largest primary care database, holding clinical and healthcare information on around 13 million patient years. Several hundred representative general practices in the UK contribute data, and the structure, utility, and validity of the database and the data extracted from it have been widely described and validated.[16 17] The risk of a cancer diagnosis in the three year period after presentation with alarm symptoms was 8.0% for haematuria in men and 3.7% in women, with corresponding figures of 8.0% and 4.5% for haemoptysis, 5.9% and 2.5% for dysphagia, and 2.7% and 2.1% for rectal bleeding. Additionally, individual alarm symptoms had surprisingly high predictive values in certain groups of patients—notably, those in older age groups—although of course most patients with these symptoms did not have cancer.

It can, however, be just as important to make an early accurate diagnosis of a serious non-malignant condition so that treatment can be instituted promptly. Clear guidance on the likely yield of early investigations (rather than using time as a diagnostic tool and waiting for diagnoses to emerge) is urgently needed. We report on the incidence of a range of pre-specified non-cancer diagnoses and provide predictive values for a range of diagnoses associated with alarm symptoms, defining the characteristics of patients presenting with alarm symptoms who turn out to have these diagnoses at 90 days and three years after presentation.

METHODS

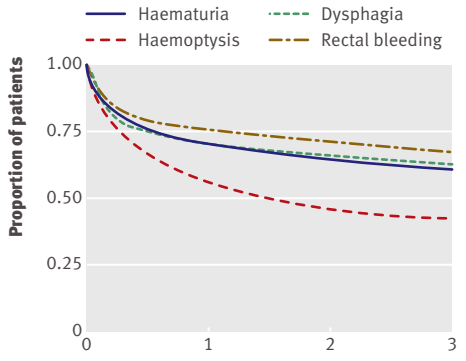
The methods have been described in our previous report.[15] We selected all 128 general practices that provided up to standard data from 1 January 1994 to 31 December 2000 and whose data were exclusively Read coded. We selected all 923 605 patients who were permanently registered with these practices between 1 January and 31 December 1994 and were aged 100 or less in 1994. There were few patients aged over 100 and data quality and approaches to diagnosis might differ in very old age. From these, we identified patients whose first ever recorded occurrence of each alarm symptom (macroscopic haematuria, haemoptysis, dysphagia, or rectal bleeding) was after 31 December 1995 or who were diagnosed with neoplasms of the urinary tract, respiratory tract, oesophagus, or colon and rectum.

To include only those patients who were previously free from cancer, we excluded all those with a diagnosis of any other cancer than the ones of interest before the date of the first recorded symptom, or before the date of diagnosis of the index cancer if the related symptom was not recorded. We excluded patients aged less than 15 at the time of the first symptom, patients with incomplete dates for diagnosis of either symptom or cancer, and patients whose first recorded date of symptom was later than the date of cancer diagnosis.

In this study we included only patients who had a first ever alarm symptom, with a complete date, recorded between 1 January 1995 and 31 December 2000, and whose data were up to standard at the date of the symptom.

We constructed a list of pre-specified, potentially important diagnoses (that is, conditions that generally require treatment or are likely to be progressive, or both) for each of the alarm symptoms by referring to recently published standard textbooks describing differential diagnoses in primary care and validated these lists by circulating and discussing them with general practitioner colleagues. For haematuria we included urinary tract cancer, kidney stone, benign prostatic hyperplasia, orchitis, urinary tract infection, menstrual disorders, glomerulonephritis, urethritis, bleeding disorders, renal tuberculosis, polycystic kidneys, infective endocarditis, schistosomiasis, and cancers of the uterus and prostate. For haemoptysis we included respiratory tract cancer, acute upper respiratory infection, acute lower respiratory infection, chronic obstructive pulmonary disease, bronchiectasis, asthma, influenza, pulmonary embolism, bleeding disorders, pulmonary oedema/left ventricular failure, mitral stenosis, polyarteris nodosa, pulmonary tuberculosis, aspergillosis, Goodpasture's syndrome, and pulmonary atrioventricular malformation. For dysphagia we included upper gastrointestinal cancers, oesophagitis, oesophageal stricture, hiatus hernia, gastritis, stomach disorders, peptic ulcer (including gastric and duodenal ulcer), globus hystericus, pharyngeal pouch, Chagas' disease, scleroderma, myasthenia gravis, achalasia, and gastric cancer. Finally, for rectal bleeding we included colorectal and anal cancer, diverticulitis, anal fissure, Crohn's disease, ulcerative colitis, infectious gastroenteritis, haemorrhoids, peptic ulcer, bleeding disorders, angiodysplasia, intussusception, and Meckel's diverticulum. Sets of Read codes were identified for each condition.

Analyses were implemented in a time to event framework. Separate analyses were conducted for each outcome. The start date was the date of the first consultation for the alarm symptom. The end date was the date of the first recorded outcome event. Data were censored if patients left the practice or died. We estimated the proportion in whom the outcome was recorded before 90 days and three years from the failure function using the "sts list" command in Stata version 10. Thus, the positive predictive value of an alarm symptom for cancer was estimated as the proportion diagnosed with the outcome by 90 days or three years after adjustment for deaths and censoring. We collected data at 90 days and three years because the former represents an upper limit of time in which a practitioner might aim to make a diagnosis after



No at risk				
Haematuria	11 106	6755	5156	3845
Haemoptysis	4812	2336	1627	1215
Dysphagia	5998	3596	2745	2010
Rectal bleeding	15 289	9604	7140	5059

Proportion of patients not diagnosed with any of the selected outcomes by time since first alarm symptom

presentation with an alarm symptom, while three years might represent an upper limit of time during which serious clinical diagnoses would become evident. We carried out a sensitivity analysis in which we included deaths before the outcome of interest in a competing risks analysis[18] using the "stcompet" command in Stata version 10. Results showed negligible differences from the initial analysis. An individual patient could have a diagnosis of more than one of the outcome events. Tests for trend by age group were implemented with the log rank test. Three patients, two with haematuria and one with dysphagia, were excluded from time to event analyses because of missing ages. A few patients with cancer diagnoses, up to three cases per site and sex, that were included previously[15] were excluded from these analyses because cancer diagnoses were at the same time or before presentation with the first symptom.

RESULTS

The study population consisted of 762 325 eligible patients aged 15 and older registered with 128 practices in 1994. We examined diagnoses made after the first occurrence of alarm symptoms in patients with no previous diagnosis of our specified conditions. We identified 11 108 first occurrences of haematuria, 4812 of haemoptysis, 5999 of dysphagia, and 15 289 of rectal bleeding between 1 January 1995 and 31 December 2000. Full details of the age and sex standardised rates for alarm symptoms and their age specific incidence rates are available elsewhere.[15] The mean age at first symptom was 58.5 (SD 18.9) for haematuria, 61.6 (18.0) for dysphagia, 54.5 (19.4) for haemoptysis, and 52.5 (18.8) for rectal bleeding. The figure shows the proportion of patients free of any of the selected outcomes by time since their first alarm symptom. Patients ceased to be at risk if they were diagnosed with one or more of the outcomes, died, left the practice, or reached the end of the study. Although a high proportion of cases were censored by three years, this had limited impact on estimates as diagnoses of interest were most commonly recorded soon after symptom onset.

We have presented our main findings for men and women separately because healthcare use by men and women is often different and also because some of the outcomes are sex specific. In patients presenting with macroscopic haematuria, 17.5% of women and 18.3% of men had one of the pre-specified diagnoses at 90 days (table 1). At three years these figures rose to 42.0% and 36.6%, respectively, with cystitis and urinary tract infection being the commonest diagnosis in men and women at three years, followed by urinary tract cancers (8.0% in men) and benign prostatic hypertrophy (7.3%) in men and menstrual disorders (8.5%) in women. Urinary tract cancers were less common in women at three years (3.7%), with a further 0.4% being diagnosed with uterine cancer. Orchitis was reported in 2.6% of men. Renal calculi were reported in 3.8% of men and 1.5% of women. Although the event rates were similar across the three age ranges studied in women, there was a clear age gradient in men, with significantly higher event rates in men over the age of 64 (χ^2 test for trend: P=0.022 for women, P<0.001 for men).

Acute lower respiratory infection was the most common diagnosis in men with haemoptysis (10.2% at 90 days and 30.3% at three years). In women with haemoptysis the most common diagnosis was acute upper respiratory infection (10.6% and 47.4%, respectively) (table 2). At 90 days the prevalence of a diagnosis of chronic obstructive pulmonary disease (COPD) was 2.7% in women and 2.5% in men, with corresponding rates for asthma of 4.5% and 2.5%. Severe acute disorders were relatively rare at 90 days, with pulmonary embolism being diagnosed in only 0.6% of women and 0.9% of men. Tuberculosis was also rare, with rates of only 0.3% in women and 0.5% in men at three years. Cardiac causes of haemoptysis, including pulmonary oedema and mitral stenosis, were also rare, even at three years. The event rates were clearly related to age at 90 days in both men and women, and in men at three years, although event rates were fairly evenly distributed across age groups in women at this time (χ^2 test for trend: P=0.103 for women, P<0.001 for men)

In the patients with dysphagia, 22.6% of men and 17.2% of women had received a definite diagnosis at 90 days (table 3). The commonest diagnosis in both men and women was oesophagitis (7.1% and 5.4%, respectively), followed by hiatus hernia (4.6% and 4.8%), followed by disorders of the stomach and duodenum. Oesophageal stricture was diagnosed in only 2.9% of men and 1.7% of women. At three years the rate of important diagnoses had risen to 39.4% in men and 33.6% in women, with similar rank ordering, although disorders of the stomach were diagnosed in 11.4% of men and 11.9% of women. The diagnosis of oesophageal stricture was still relatively rare (4.5% in

Table 1 | Diagnoses 90 days and three years after presentation with haematuria in general practice. Percentages represent positive predictive value

	90 days				Three years			
	Women (n=4723)		Men (n=6385)		Women (n=4723)		Men (n=6385)	
Diagnosis	No of patients	% (95% CI)	No of patients	% (95% CI)	No of patients	% (95% CI)	No of patients	% (95% CI)
Urinary tract cancer	77	1.7 (1.3 to 2.1)	235	3.8 (3.3 to 4.3)	161	3.7 (3.2 to 4.3)	469	8.0 (7.3 to 8.7)
Renal calculi	28	0.6 (0.4 to 0.9)	121	1.9 (1.6 to 2.3)	64	1.5 (1.2 to 1.9)	227	3.8 (3.4 to 4.4)
Urinary tract infection	670	14.3 (13.3 to 15.3)	587	9.3 (8.6 to 10.0)	1475	34.7 (33.2 to 36.2)	1178	20.6 (19.5 to 21.7)
Benign prostatic hypertrophy	—	—	158	2.5 (2.2 to 2.9)	—	—	409	7.3 (6.7 to 8.1)
Orchitis	—	—	51	0.8 (0.6 to 1.1)	—	—	140	2.6 (2.2 to 3.0)
Menstrual disorders	76	1.6 (1.3 to 2.0)	—	—	342	8.5 (7.7 to 9.5)	—	—
Glomerulonephritis	1	0.0 (0.0 to 0.2)	8	0.1 (0.1 to 0.3)	6	0.1 (0.1 to 0.3)	14	0.2 (0.1 to 0.4)
Urethritis	2	0.0 (0.0 to 0.2)	10	0.2 (0.1 to 0.3)	6	0.1 (0.1 to 0.3)	21	0.4 (0.2 to 0.6)
Bleeding disorders	3	0.1 (0.0 to 0.2)	9	0.1 (0.1 to 0.3)	12	0.3 (0.2 to 0.5)	23	0.5 (0.3 to 0.7)
Renal tuberculosis	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)
Polycystic kidneys	1	0.0 (0.0 to 0.2)	5	0.1 (0.0 to 0.2)	3	0.1 (0.0 to 0.2)	5	0.1 (0.0 to 0.2)
Infective endocarditis	0	0.0 (0.0 to 0.0)	2	0.0 (0.0 to 0.1)	2	0.1 (0.0 to 0.2)	2	0.0 (0.0 to 0.1)
Schistosomiasis	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)
Prostate cancer	—	—	73	1.2 (0.9 to 1.5)	—	—	178	3.1 (2.7 to 3.6)
Uterine cancer	4	0.1 (0.0 to 0.2)	—	—	19	0.4 (0.3 to 0.7)	—	—
Any diagnosis* by age (years):								
<45	237	17.5 (15.6 to 19.6)	153	11.8 (10.1 to 13.6)	568	46.1 (43.3 to 49.0)	233	19.1 (17.0 to 21.4)
45-64	187	12.3 (10.7 to 14.0)	313	15.8 (14.3 to 17.5)	473	34.3 (31.8 to 37.0)	577	31.5 (29.4 to 33.7)
>64	395	21.8 (20.0 to 23.8)	690	22.7 (21.3 to 24.2)	759	45.4 (42.9 to 47.8)	1329	47.3 (45.4 to 49.3)
All ages	819	17.5 (16.4 to 18.6)	1156	18.3 (17.4 to 19.3)	1800	42.0 (40.5 to 43.5)	2139	36.6 (35.3 to 37.8)

*Some patients received more than one diagnosis.

men and 2.7% in women). No cases of achalasia were recorded in this group of patients. A small proportion of patients were diagnosed with globus hystericus, pharyngeal pouch, scleroderma, and myasthenia gravis. Most important diagnoses were more commonly identified in older men and women (χ^2 test for trend: P<0.001 for men and women)

Finally, in patients with rectal bleeding 16.7% of men and 14.5% of women had received a diagnosis at 90 days, and at three years 32.3% of men and 32.4% of women had a clear diagnosis (table 4). The most common diagnosis made at both times was haemorrhoids (10.0% in men and 7.8% in women at 90 days and 19.0% and 16.8% at three years), followed by anal fissure and diverticulitis. New diagnoses of Crohn's disease and ulcerative colitis were made in less than 1% of women at 90 days, with these figures rising to around 1% for Crohn's disease and 2% for ulcerative colitis in both men and women at three years. Small numbers of patients were found to have bleeding disorders, angiodysplasia, intussusception, and Meckel's diverticulum.

Taking these results together, the "number needed to evaluate"—that is, the number of patients in whom clinically relevant diagnoses would be made as a result of investigation, calculated as the reciprocal of the positive predictive value—is between four and seven for the four alarm symptoms studied.

Table 5 shows the incidence of non-cancer diagnoses in patients who were later diagnosed with cancer. Interval diagnoses were most common for haemoptysis and included respiratory tract infections and chronic obstructive pulmonary disease. For the other alarm symptoms, common interval diagnoses included urinary tract infection, oesophagitis and oesophageal stricture, haemorrhoids, and diverticulitis.

DISCUSSION

We investigated the incidence rates of non-cancer diagnoses in primary care in patients who presented with four important alarm symptoms. Within 90 days of presentation, an associated diagnosis had been made in around 15.3% with rectal bleeding, 19.3% with dysphagia, 17.8% with haematuria, and 24.4% with haemoptysis. Most of these diagnoses could have been made clinically or confirmed by performing simple investigations such as urine culture, chest radiology, and upper or lower gastrointestinal endoscopy. Over the three year follow-up these figures rose to about 28.9%, 33.0%, 35.5%, and 53.9%, respectively. The diagnostic rates for most of the outcomes that were not sex specific were similar in men and women. After three years' follow up, over three quarters of patients presenting with rectal bleeding did not have a definite diagnosis, with comparable figures of about 67% for dysphagia, 64% for haematuria, and 46% for haemoptysis.

Strengths and limitations

The strengths of this study include the large representative population of patients studied, the accuracy of

Table 2 | Diagnoses 90 days and three years after presentation with haemoptysis in general practice. Percentages represent positive predictive value

	90 days				Three years			
	Women (n=1882)		Men (n=2930)		Women (n=1882)		Men (n=2930)	
	No of patients	% (95% CI)	No of patients	% (95% CI)	No of patients	% (95% CI)	No of patients	% (95% CI)
Lung cancer	52	2.8 (2.1 to 3.7)	140	4.9 (4.1 to 5.7)	80	4.5 (3.7 to 5.6)	217	8.0 (7.0 to 9.1)
Acute upper RTI	197	10.6 (9.3 to 12.1)	218	7.5 (6.6 to 8.6)	786	47.4 (44.9 to 49.9)	879	35.0 (33.1 to 37.0)
Acute lower RTI	188	10.1 (8.8 to 11.5)	297	10.2 (9.2 to 11.4)	626	38.0 (35.6 to 40.5)	775	30.3 (28.5 to 32.1)
Chronic obstructive pulmonary disease	51	2.7 (2.1 to 3.6)	71	2.5 (2.0 to 3.1)	166	10.3 (8.9 to 11.9)	219	8.8 (7.7 to 10.0)
Asthma	84	4.5 (3.7 to 5.6)	72	2.5 (2.0 to 3.1)	254	15.2 (13.5 to 17.1)	242	9.6 (8.5 to 10.9)
Pulmonary embolism	12	0.6 (0.4 to 1.1)	27	0.9 (0.6 to 1.4)	20	1.2 (0.8 to 1.8)	32	1.1 (0.8 to 1.6)
Bleeding disorders	0	0.0 (0.0 to 0.0)	2	0.1 (0.0 to 0.3)	4	0.3 (0.1 to 0.7)	10	0.4 (0.2 to 0.8)
Pulmonary oedema	3	0.2 (0.1 to 0.5)	5	0.2 (0.1 to 0.4)	3	0.2 (0.1 to 0.5)	7	0.2 (0.1 to 0.5)
Mitral stenosis	1	0.1 (0.0 to 0.4)	0	0.0 (0.0 to 0.0)	3	0.2 (0.1 to 0.5)	3	0.1 (0.0 to 0.4)
Polyarteris nodosa	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)
Tuberculosis	4	0.2 (0.1 to 0.6)	7	0.2 (0.1 to 0.5)	6	0.3 (0.2 to 0.7)	12	0.5 (0.3 to 0.8)
Aspergillosis	0	0.0 (0.0 to 0.0)	1	0.0 (0.0 to 0.3)	0	0.0 (0.0 to 0.0)	2	0.1 (0.0 to 0.3)
Goodpasture's syndrome	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)
Pulmonary arterio-venous malformation	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)
Bronchiectasis	18	1.0 (0.6 to 1.5)	28	1.0 (0.7 to 1.4)	41	2.4 (1.7 to 3.2)	44	1.6 (1.2 to 2.2)
Any diagnosis* by age (years):								
<45	124	22.6 (19.3 to 26.3)	144	15.2 (13.1 to 17.7)	313	60.6 (56.3 to 64.9)	392	45.3 (42.0 to 48.8)
45-64	160	25.4 (22.2 to 29.0)	212	22.9 (20.3 to 25.7)	379	64.0 (60.0 to 68.0)	474	56.3 (52.8 to 59.8)
>64	196	28.5 (25.2 to 32.0)	340	33.0 (30.3 to 36.0)	402	62.1 (58.3 to 66.0)	636	66.2 (63.0 to 69.3)
All ages	480	25.7 (23.8 to 27.8)	696	24.0 (22.5 to 25.6)	1094	62.3 (60.0 to 64.7)	1502	56.2 (54.2 to 58.1)

*Some patients received more than one diagnosis.

the data contained in the database, and the ability to identify enough patients to draw valid conclusions about the incidence of diagnoses after the presentation of alarm symptoms. Several studies have evaluated the validity of diagnoses recorded in the general practice research database with generally satisfactory results.[19-21] All symptoms we evaluated are well defined and are characterised by only a small number of Read and Oxmis codes, with little scope for varying definitions. We have noted previously that our results show some sensitivity to the scope of case definitions. Thus the predictive value of dysphagia for cancer depends on whether stomach cancers as well as oesophageal cancers are included; the predictive value of haematuria for urinary tract neoplasms depends on whether prostate cancer is included. Limitations, however, include the lack of clinical contextual detail concerning the individual alarm symptoms and, in particular, the fact that we do not know about the other symptoms that patients might have been experiencing when the alarm symptom was recorded in the general practice record. We rely, of course, on symptom recording rather than symptom reporting and these might differ. This might be particularly relevant, for example, for dysphagia, which might represent several problems such as pain on swallowing or difficulty in swallowing. We had to rely on the accuracy of recorded diagnoses and did not have sufficient information to know whether these diagnoses were made on the basis of investigations or not. It might also be worth considering whether analysis of a more recent dataset, collected after the introduction of the Quality and Outcomes Framework (QOF), might have changed our results. We think this is unlikely because the framework will tend to encourage more accurate documentation of chronic disease management rather than acute disease presentation, and there are no targets directly related to our alarm symptoms. Although the 90 day follow-up is likely to reflect diagnostic outcomes of single episodes of the presentation and investigation of alarm symptoms, we do not have information about clinical events and relevant interventions taking place during the three year follow-up and, while we accounted for patients from analysis who have died and left the practice, we do not have information on the extent or severity of disease or its treatment during this time. We concede, of course, that three year follow-up is not relevant to the natural course of acute infectious conditions.

Comparison with other studies

Our analyses were implemented in a time to event framework, allowing for deaths and censoring before three years. Compared with our earlier paper,[15] predictive values were estimated to be slightly higher by this method, with the largest difference being 0.6% at three years for urinary tract cancer after haematuria in men. In general, censoring had limited impact on the estimates of

Table 3 | Diagnoses 90 days and three years after presentation with dysphagia in general practice. Percentages represent positive predictive value

	90 days				Three years			
	Women (n=3371)		Men (n=2628)		Women (n=3371)		Men (n=2628)	
	No of patients	% (95% CI)	No of patients	% (95% CI)	No of patients	% (95% CI)	No of patients	% (95% CI)
Oesophageal cancer	59	1.8 (1.4 to 2.3)	114	4.4 (3.7 to 5.3)	80	2.5 (2.0 to 3.1)	149	5.9 (5.0 to 6.9)
Oesophagitis	180	5.4 (4.7 to 6.2)	184	7.1 (6.2 to 8.2)	354	11.8 (10.7 to 13.1)	348	14.7 (13.3 to 16.2)
Oesophageal stricture	56	1.7 (1.3 to 2.2)	76	2.9 (2.4 to 3.7)	85	2.7 (2.2 to 3.4)	110	4.5 (3.7 to 5.4)
Hiatus hernia	159	4.8 (4.1 to 5.6)	119	4.6 (3.9 to 5.5)	277	9.1 (8.1 to 10.2)	203	8.5 (7.5 to 9.7)
Gastritis	57	1.7 (1.3 to 2.2)	64	2.5 (1.9 to 3.2)	133	4.5 (3.8 to 5.4)	131	5.6 (4.8 to 6.7)
Stomach disorders	90	2.7 (2.2 to 3.3)	86	3.3 (2.7 to 4.1)	333	11.9 (10.8 to 13.2)	252	11.4 (10.1 to 12.8)
Peptic ulcer	39	1.2 (0.9 to 1.6)	63	2.4 (1.9 to 3.1)	72	2.4 (1.9 to 3.1)	112	4.8 (4.0 to 5.7)
Globus hystericus	12	0.4 (0.2 to 0.6)	6	0.2 (0.1 to 0.5)	32	1.1 (0.8 to 1.6)	9	0.4 (0.2 to 0.7)
Pharyngeal pouch	10	0.3 (0.2 to 0.6)	13	0.5 (0.3 to 0.9)	16	0.5 (0.3 to 0.8)	22	0.9 (0.6 to 1.4)
Chagas' disease	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)
Scleroderma	2	0.1 (0.0 to 0.2)	0	0.0 (0.0 to 0.0)	11	0.4 (0.2 to 0.7)	1	0.0 (0.0 to 0.3)
Myasthenia gravis	2	0.1 (0.0 to 0.2)	0	0.0 (0.0 to 0.0)	2	0.1 (0.0 to 0.2)	0	0.0 (0.0 to 0.0)
Gastric cancer	16	0.5 (0.3 to 0.8)	23	0.9 (0.6 to 1.3)	25	0.8 (0.5 to 1.2)	36	1.5 (1.1 to 2.1)
Achalasia	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)
Any diagnosis* by age (years):								
<45	45	7.1 (5.4 to 9.4)	47	9.9 (7.5 to 12.9)	110	20.2 (17.0 to 24.0)	106	24.7 (20.8 to 29.2)
45-64	167	16.3 (14.1 to 18.7)	239	25.7 (23.1 to 28.7)	321	34.2 (31.2 to 37.5)	389	44.9 (41.5 to 48.4)
>64	360	21.6 (19.7 to 23.6)	301	25.2 (22.8 to 27.8)	594	38.2 (35.8 to 40.8)	458	41.1 (38.1 to 44.1)
All ages	572	17.2 (16.0 to 18.5)	587	22.6 (21.0 to 24.3)	1,025	33.6 (31.9 to 35.3)	953	39.4 (37.4 to 41.5)

*Some patients received more than one diagnosis.

positive predictive value because the incidence of diagnoses was highest soon after the onset of symptoms.

Our figures for diagnostic rates in patients with haematuria are similar to those reported by Bruyninckx and colleagues in a study from Belgium[22] but are slightly lower than those reported by Summerton and colleagues,[23] who analysed patients referred to an open access haematuria clinic. In that study the population was "enriched" because urinary tract infections had previously been treated or excluded. Both haematuria and haemoptysis were strong indicators of the presence or subsequent development of acute infection, with high rates of diagnosis of urinary tract infection and cystitis in both men and women with haematuria and of acute and chronic respiratory infection in men and women with haemoptysis. Given the rates of diagnosis of urinary tract cancer and lung cancer, both at 8% for men at three years, it is clear that it is important to pursue an infective or neoplastic cause in patients presenting in primary care with these symptoms. The incidence of tuberculosis (<0.5% at three years) was low in this population, as were diagnoses of potential cardiac causes of haemoptysis. The diagnostic rates in our patients with haemoptysis are much lower than those commonly emerging from studies in secondary care,[24,25] but no primary care based studies of the causes of haemoptysis in the general population have been published.

The predictive value of dysphagia for a serious organic lesion in the oesophagus has recently been called into question, not least because dysphagia is a common symptom in gastro-oesophageal reflux disease. A recent systematic review of 83 studies identified wide variation in the sensitivity and specificity of several alarm symptoms for upper gastrointestinal malignancies,[26] and the recently published Montreal consensus guidelines on gastro-oesophageal reflux disease[27] have suggested that only progressive dysphagia should be regarded as an alarm symptom, pointing out that dysphagia often improves with anti-secretory treatment in many reflux patients. Our data, however, do not entirely support this view. The diagnostic rates for cancer and oesophageal stricture at 90 days were 4.4% and 2.9%, respectively, in men and 1.8% and 1.7% in women, and at three years were 5.9% and 4.5%, respectively, in men and 2.5% and 2.7% in women. The highest detection rates were found in older men and women. Corresponding figures for a diagnosis of oesophagitis in men were 7.1% at 90 days and 14.7% at three years, suggesting that dysphagia should be taken seriously as a warning of an organic oesophageal lesion, particularly in older patients. The importance of hiatus hernia as a diagnosis is uncertain. At three years, between one in three and one in five patients presenting with dysphagia received a diagnosis of gastrointestinal disorders, including gastritis, gastric ulcer, and duodenal ulcer, adding further weight to the importance of dysphagia as a warning sign for important upper gastrointestinal pathology.

Given the current focus on screening for colorectal cancer, the importance of rectal bleeding is of

Table 4 | Diagnoses 90 days and three years after presentation with rectal bleeding in general practice. Percentages represent positive predictive value

	90 days				Three years			
	Women (n=7766)		Men (n=7523)		Women (n=7766)		Men (n=7523)	
	No of patients	% (95% CI)	No of patients	% (95% CI)	No of patients	% (95% CI)	No of patients	% (95% CI)
Colorectal cancer	78	1.0 (0.8 to 1.3)	98	1.3 (1.1 to 1.6)	151	2.1 (1.8 to 2.5)	181	2.7 (2.3 to 3.1)
Peptic ulcer	25	0.3 (0.2 to 0.5)	38	0.5 (0.4 to 0.7)	79	1.3 (1.0 to 1.6)	110	1.8 (1.5 to 2.2)
Diverticulitis	231	3.0 (2.7 to 3.4)	195	2.6 (2.3 to 3.0)	497	7.1 (6.5 to 7.7)	375	5.6 (5.0 to 6.1)
Anal fissure	92	1.2 (1.0 to 1.5)	95	1.3 (1.1 to 1.6)	226	3.4 (3.0 to 3.9)	187	2.8 (2.5 to 3.3)
Crohn's disease	38	0.5 (0.4 to 0.7)	19	0.3 (0.2 to 0.4)	68	1.0 (0.8 to 1.2)	47	0.8 (0.6 to 1.0)
Ulcerative colitis	60	0.8 (0.6 to 1.0)	64	0.9 (0.7 to 1.1)	129	1.9 (1.6 to 2.3)	146	2.2 (1.9 to 2.6)
Infective colitis	47	0.6 (0.5 to 0.8)	38	0.5 (0.4 to 0.7)	257	4.2 (3.7 to 4.8)	178	3.1 (2.6 to 3.5)
Haemorrhoids	596	7.8 (7.2 to 8.4)	738	10.0 (9.3 to 10.7)	1143	16.8 (15.9 to 17.7)	1282	19.0 (18.0 to 19.9)
Bleeding disorders	4	0.1 (0.0 to 0.1)	7	0.1 (0.1 to 0.2)	26	0.4 (0.3 to 0.6)	14	0.2 (0.1 to 0.4)
Angiodysplasia	0	0.0 (0.0 to 0.0)	2	0.0 (0.0 to 0.1)	1	0.0 (0.0 to 0.1)	6	0.1 (0.0 to 0.2)
Intussusception	1	0.0 (0.0 to 0.1)	0	0.0 (0.0 to 0.0)	1	0.0 (0.0 to 0.1)	0	0.0 (0.0 to 0.0)
Meckel's diverticulum	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	0	0.0 (0.0 to 0.0)	1	0.0 (0.0 to 0.1)
Any diagnosis* by age (years):								
<45	282	10.3 (9.2 to 11.5)	323	12.1 (11.0 to 13.4)	672	28.0 (26.1 to 29.9)	646	26.9 (25.1 to 28.8)
45-64	364	14.9 (13.6 to 16.4)	513	18.3 (16.9 to 19.8)	715	32.8 (30.8 to 34.9)	894	34.7 (32.9 to 36.7)
>64	461	18.6 (17.2 to 20.2)	400	20.5 (18.8 to 22.3)	840	36.8 (34.8 to 38.9)	654	36.3 (34.1 to 38.7)
All ages	1107	14.5 (13.7 to 15.3)	1236	16.7 (15.8 to 17.5)	2227	32.4 (31.2 to 33.5)	2194	32.3 (31.2 to 33.5)

*Some patients received more than one diagnosis.

particular interest. In our previous study the predictive value of rectal bleeding for a cancer diagnosis at 90 days was a little over 1%, rising to between 2% and 3% in men and women at three years, with higher rates in older age groups. These figures are broadly consistent with another study from the general practice research database[28] and also with a prospective study conducted in primary care in southern England. Diagnosis rates after presentation with rectal bleeding were the lowest of the four alarm symptoms that we studied, and most patients turned out to have haemorrhoids or an anal fissure. Rates of diagnosis of inflammatory bowel disease (Crohn's disease and ulcerative colitis) were surprisingly low in this population, with diagnostic rates for both of less than 1% at 90 days and around 1% for Crohn's disease and 2% for ulcerative colitis at three years. The diagnosis of a bleeding disorder was extremely rare in all four conditions, but occurred most often in patients with rectal bleeding. While we recognise that rectal bleeding is an alarm symptom, likely to trigger concern about a serious diagnosis, it is clearly important to consider the pattern of bleeding and accompanying symptoms, which, as Robertson and colleagues point out,[29] might considerably increase the likelihood of cancer.

The interpretation of our findings will depend, to a large extent, on the clinical context in which the alarm symptom is presented and, in particular, on the presence of other symptoms or signs that may or may not add to the diagnostic probability of a serious organic problem. Patients with haemoptysis who are febrile and coughing up infected sputum are, clearly, more likely to have an infective cause for their symptoms than someone with haemoptysis experienced in the context of acute onset of pleuritic chest pain. When accompanied by dysuria and urinary frequency, haematuria is clearly more likely to be related to a urinary tract infection than the same symptom occurring without pain and without disturbance of bladder function. Dysphagia in the absence of symptoms suggestive of gastro-oesophageal reflux disease, particularly when progressive, should clearly be taken seriously, and our data suggest that dysphagia is an important alarm symptom for the diagnosis of cancer or oesophageal stricture. Rectal bleeding remains problematic, and it is a difficult matter of clinical judgment as to whether

Table 5 | Proportion of patients diagnosed with cancer who also had non-cancer diagnosis recorded after onset of symptoms and before diagnosis of cancer

	Haematuria: urinary tract cancer	Haemoptysis: lung cancer	Dysphagia: oesophageal cancer	Rectal bleeding: colorectal cancer
No with diagnosis of cancer	630	297	229	332
No (%) with preceding non-cancer diagnosis	135 (21)	155 (52)	71 (31)	49 (15)
Most common diagnoses	Urinary tract infection (112)	Upper respiratory tract infection (35); lower respiratory tract infection (71); chronic obstructive pulmonary disease (25); asthma (18)	Oesophageal stricture (29); oesophagitis (18)	Haemorrhoids (21); diverticulitis (13)

WHAT IS ALREADY KNOWN ON THIS TOPIC

Certain symptoms, such as haematuria, haemoptysis, dysphagia, and rectal bleeding, are generally regarded as "red flags" because of their association with serious disease

The predictive value of these red flag or alarm symptoms for a diagnosis of cancer have now been established, but little is known about their predictive value for non-cancer diagnoses, which might also have considerable implications for patients' health

WHAT THIS STUDY ADDS

In patients with haemoptysis, haematuria, dysphagia, and rectal bleeding around one in five have an associated diagnosis at 90 days and approaching half of all patients at three years

The "number needed to evaluate" to identify an associated diagnosis in this group of patients is between four and seven

Patients presenting with these symptoms merit timely investigation for non-cancer diagnoses and potential cancer diagnoses, rather than a policy of watchful waiting

the rather lower diagnostic rates at 90 days and at three years indicate investigation. Because of the frequent co-existence of perianal and more serious large bowel lesions, the presence of perianal pain or local bleeding should not be taken to exclude colon cancer, and it is probable that persistent, otherwise unexplained rectal bleeding merits urgent investigation. It is not clear from our data whether rectal bleeding is a valuable alarm symptom for the presence of inflammatory bowel disease, which is more likely to present as bleeding in combination with altered bowel habit, diarrhoea, abdominal pain, and other related symptoms.

Even in our analysis of outcomes in single alarm symptoms, without additional information on coexisting symptoms and signs, up to one in five patients had a diagnosis at 90 days, and this proportion would almost certainly have been higher in patients with multiple symptoms as described above. We argue that in patients with these, and perhaps other, "red flag" symptoms, particularly when accompanied by other features supportive of specific important diagnoses, the use of the "test of time" might be inappropriate and that early investigation should be recommended.

Conclusions

We believe that these data provide additional information to help clinicians manage patients presenting with symptoms suggestive of serious disease. In general terms they support the notion of alarm symptoms, which, because they possess reasonable predictive value for serious disease, should stimulate urgent intervention, notwithstanding the fact that the diagnoses made most often tend to be the least serious. We have, in conducting the study, extended the concept of "alarm symptoms" to include important non-cancer diagnoses, emphasising that these symptoms are not only red flags for malignancy but also "yellow flags" that should prompt clinicians to conduct investigations or intervene therapeutically in these benign but potentially serious disorders. For many of these patients the test of time should probably be replaced by a "timely test," although the interpretation of our data, in terms of the need for exhaustive investigation, is likely to vary according to the resources available in different healthcare systems. Further research in the primary care setting, using both large databases and prospective clinical cohorts, is required to better define symptom combinations and other clinical features that represent the most important targets for investigation and treatment to optimise the use of scarce resources and to minimise overinvestigation and unnecessary treatment. Because some of the conditions, such as respiratory and urinary tract infections and haemorrhoids, are common in the general population, further research is required to evaluate the occurrence of these diagnoses in controls with alarm symptoms. This research could then be followed by trials to evaluate the costs and outcomes of different strategies for the investigation of patients with alarm symptoms.

Data for this study were provided by EPIC, UK, a licence holder of an historical part of the general practice research database dataset.
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