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Identifying opportunities for timely diagnosis through patterns of primary care tests in patients with bladder and renal cancer: a longitudinal linked data study

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Abstract

Background:
Understanding pre-diagnostic test use could reveal diagnostic windows where more timely evaluation for cancer may be indicated.

Aim:
To examine pre-diagnostic patterns of results of abnormal blood tests in bladder and renal cancer patients.

Design and setting:
Retrospective cohort study using primary care and cancer registry data on bladder and renal cancer patients diagnosed between 2012-2015 in England.

Method:
We examined the rates of patients with a first abnormal result in the year before diagnosis, for "generic" (full blood count components, inflammatory markers, calcium) and "organ-specific" blood tests (creatinine, liver function test components) which may lead to subsequent detection of incidental cancers. We used Poisson regression, to detect the month during which the cohort's rate of each abnormal test started to increase from baseline, and examined the proportion of patients with a test found in the first half of the window, as these 'early' tests might represent opportunities where further evaluation could be initiated.

Results:
Data from 4,533 bladder and renal cancer patients were analysed. The monthly rate of patients with a first abnormal test increased towards the time of cancer diagnosis. Abnormalities of both generic and organ-specific tests started to increase from 6-8 months pre-diagnosis, with 25-40% of these patients having an abnormal test in the "early half" of the diagnostic window.

Conclusion:
Population-level signals of bladder and renal cancer can be observed in abnormalities in commonly performed primary care blood tests up to 8 months before diagnosis, indicating the potential for earlier diagnosis in some patients.

Keywords:
Renal cancer, bladder cancer, early detection of cancer, test utilisation

How this fits in:
Understanding which and when abnormal blood tests start to increase from a baseline rate in patients with bladder and renal cancer may highlight opportunities for more timely evaluation for cancer in some patients. We found that commonly performed generic and organ-specific abnormal blood tests for bladder and renal cancer started to increase around 6-8 months before diagnosis. Findings suggest that there are population-level signals of bladder and renal cancer in commonly performed primary care blood tests, indicating potential for earlier diagnosis for some patients.

Background

Early diagnosis of cancer is associated with improved survival and patient reported outcomes. However, timely detection of urinary tract cancers, in particular bladder and renal cancer, can be challenging in some patients [1]. In the United Kingdom (UK), clinical guidelines from the National Institute for Health and Care Excellence (NICE) exist to guide general practitioners (GPs) on when to refer symptomatic patients with suspected cancer [2]. However, these guidelines are often based on alarm symptoms. Early detection of cancer in patients without these symptoms can therefore be challenging [1 3]. In patients with bladder cancer, longer diagnostic intervals were found especially in those presenting without haematuria [4-6] and women [3 7-10]. Renal cancer is one of the cancers with rapidly rising incidence [11-15]. With up to 60% of renal cell carcinoma presenting asymptomatically and it commonly associated with incidental diagnosis in recent decades [16], understanding the clinical scenarios triggering incidental identification would be useful.

Population-based studies have documented that among some patients subsequently diagnosed with cancer, use of investigations starts to increase many months before the eventual diagnosis. This evidence highlights the presence of periods (or "diagnostic windows") during which earlier diagnosis could in principle be possible for at least some patients [17-20]. However, previous evidence mostly focused on the use of tests (regardless of results), as opposed to whether tests were abnormal. Furthermore, evidence from well-characterised case series studies indicate that abnormal test results were commonly not followed-up in patients subsequently found to have cancer [21-23]. Therefore, it is important to study patterns of abnormal tests before the diagnosis; when prolonged intervals between abnormal tests and diagnosis occur, they may reflect missed diagnostic opportunities.

Motivated by these realisations, we set out to find out:

- Patterns of non-specific ("generic") abnormal blood tests commonly performed in primary care in the 12 months before diagnosis of bladder and renal cancer. We focused on tests such as abnormal haemoglobin concentrations, high platelet count, raised inflammatory markers, and raised calcium, known to convey a predictive value for cancer above what is expected by the patients' age and sex in patients with non-specific symptoms [24-28]. The aim of this aspect of our inquiry is to document how often abnormalities in these commonly used blood tests could have triggered further investigations leading to shorter diagnostic intervals.
- The occurrence of abnormalities in "organ-specific" blood tests such as raised creatinine and abnormal liver function tests that could have triggered investigation by subsequent imaging, potentially leading to incidental identification of renal cancer.

Therefore, by examining patterns of abnormal blood tests commonly used in primary care, we aimed to elucidate both the potential for earlier diagnosis in symptomatic patients, and common clinical scenarios that may be leading to incidental identification**.**

Method

Data

We used linked data from a primary care dataset, Clinical Practice Research Datalink (CPRD), and the National Cancer Registration Analysis Service (NCRAS) to examine the patterns of abnormal test results in a cohort of bladder and renal cancer patients diagnosed between 2012-2015 in England. Details of data acquisition and cohort identification have been described in previous studies [17 29]. Patients aged 25 and above who were diagnosed with bladder and renal cancer between April 2012 and December 2015 were extracted from the CPRD. These data were linked at source to the Cancer Registry, from which additional cases were identified using ICD-10 cancer codes. We used the Cancer Registry diagnosis and date where available, and CPRD diagnosis and date in patients without linked data. Cancers were sub-divided into bladder, kidney or upper urinary tract urothelial cell cancer (UTUC). UTUC patients were separately analysed due to possible difference in presentation from other renal cancer patients, but we focused mainly on results of bladder and renal cancer patients due to their larger sample sizes.

Tests examined

The records of the patients included in the study were inspected for the use of primary care blood tests up to 12 months pre-diagnosis. Using the clinical experience of co-authors and existing knowledge of associations between primary care blood markers and cancer [14 16 27 28 30], we examined the pre-diagnostic patterns of the following abnormal tests (Table 1):

- generic blood tests
    - Full blood count (FBC) sub-components: low and high haemoglobin (Hb), high platelet (Plt) count, high white cell count (WCC),
    - Raised inflammatory markers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR),
    - Raised calcium;
- specific blood tests pointing to organ-specific abnormalities: abnormal liver function tests (LFTs) including high aspartate aminotransferase (AST) and alanine transaminase (ALT), high creatinine

Local laboratory reference ranges, as captured in the CPRD test file, were used to define whether individual blood tests were normal or abnormal (low or high). Ambiguous results (due to incomplete reference ranges in the CPRD test file), were regarded as missing. The overall percentages of missing test results were low (0 to 8%, with 6 of the 9 tests having 0-2% missing results), and therefore discarded (Supplementary Data – Table S1).

Analyses

For each test, we examined the number of patients with an index abnormal test in each month up to 12 months pre-diagnosis. We excluded the month immediately prior to diagnosis (i.e. excluding month 1 pre-diagnosis), due to the likelihood that these patients would have already entered the final stage of the diagnostic process for possible cancer [17 25 28]. Each patient's index abnormal test was defined as the first abnormal test within the 12 month period before diagnosis, concordant with prior literature [17 29].

Then, we estimated the inflection point at which the rate of abnormal tests increased above a baseline. To do so we employed Poisson regression, adjusting for age and sex, to model both the baseline rate of abnormal tests, and a departure from baseline occurring at the inflection point. 10 separate models were fitted, corresponding to 10 possible inflection points occurring at 2 to 11 months pre-diagnosis (months 1 and 12 omitted due to collinearity). All 10 models included data from all patients across the whole 12-month period with the outcome being the monthly count of

abnormal results. Each model included a term to account for any baseline trend, and a second 'inflection month' variable to capture deviation from the baseline trend at different inflection points (one at a time, 10 in total, see illustration in Supplementary Box 1). We took the inflection point associated with the best fitting model (i.e. that with the largest log likelihood) as the best point estimate for the month of departure from baseline. We used bootstrapping to provide a confidence interval around this point.

Lastly, we estimated a diagnostic window for each abnormal test during which potential further investigations could be initiated. This was calculated as the interval from the month at which the inflection point occurred, to the month immediately prior to diagnosis. We examined the number of patients who had an early test, defined as a test which was performed in the first half of this diagnostic window, furthest back from diagnosis. We postulated that probable opportunities existed for a more timely diagnosis especially during this early half of the diagnostic window. Where a diagnostic window included an odd number of months, the number of patients with an early test was calculated for the duration from the inflection point to the month immediately prior to the midpoint of the diagnostic window (e.g.. for inflection point at 7 months pre-diagnosis, the first 'half' of the window was defined as 5-7 months inclusive; for inflection point at 6 months, first half of the window was defined as 5-6 months inclusive).

All analyses were performed using STATA v15.

Results

5,322 patients, consisting of 3,398 (63.9%), 1,715 (32.2%) and 209 (3.9%) bladder, renal cancer and upper urinary tract urothelial cell cancer (UTUC) patients respectively were initially identified from our dataset. 141 patients (2.6%) had no tests at all recorded in CPRD and 648 patients (12.2%) had tests but not the studied tests in the 12 months prior to cancer diagnosis. Therefore 4,533 patients, consisting of 2,890 (63.8%) bladder cancer, 1,465 (32.3%) renal cancer and 178 (3.9%) UTUC patients with at least one of the ten abnormal blood tests were further analysed. 3,133 male and 1,400 female patients ageing between 25 and 101 years old (median age 74, IQR 66-82) were included.

The most common blood tests performed in bladder and renal cancer patients in the year before diagnosis were creatinine and FBC subcomponents (haemoglobin, white cell count and platelet count), in about 83% and 74% of patients respectively. The highest proportion of abnormal results recorded were for raised inflammatory markers (CRP or ESR) (43-45%), low haemoglobin (35%) and high creatinine (32%) (Supplementary Table 1). In general, there were no appreciable and consistent pattern of variation in abnormal tests by age and sex (Supplementary Figure 1 and Supplementary Table 2).

Rate of abnormal tests by month

There was an increasing rate of abnormal tests for all tests towards diagnosis except high AST (likely due to small number of tests performed) (Figure 1).

We found evidence of inflection points for 8 of the 10 blood tests examined: low haemoglobin, high WCC, high platelet count, high CRP and ESR, high ALT and AST, and high creatinine ($p<0.05$; Figure 1 and Table 2). The earliest rate of increase was for high ESR and AST at 8 months pre-diagnosis, while the rate of increase was the closest to diagnosis for high ALT (4 months pre-diagnosis).

Proportion of early test during diagnostic windows

Between one-quarter to two-fifths of all patients who had an abnormal result on one or more of the examined tests during the diagnostic window (from inflection point to the month immediately prior to diagnosis) had an early test, that is, one which was performed in the first half of the diagnostic

window (Table 2). In particular, the highest proportion of patients who had an early test were patients with a high AST and raised creatinine (42% for each), with this pattern also being consistent for individual cancer sites for raised creatinine (43% and 41% for bladder and renal cancer). Lower proportion of patients with an abnormal generic test had the test early (eg. high platelets, high WCC and high ESR - about 25% for each).

Discussion

Summary

We found that abnormalities in common primary care blood tests started to appear from 6 to 8 months before patients were diagnosed with bladder or renal cancer. Between 25-40% of patients with an abnormal test had the test performed in the early half of the diagnostic window, suggesting that opportunities might exist to initiate further investigations or referrals, and potentially expedite subsequent bladder or renal cancer diagnosis in at least some patients.

Strengths and limitations

To our knowledge, this is the first paper to examine the pre-diagnostic pattern of abnormal blood tests in patients with bladder and renal cancer and when the abnormalities might appear before diagnosis. Our study benefits from having a large sample size, with reliable coded information on test results. A major strength is that blood test results are automatically transferred to CPRD, therefore minimising any bias in recordings due to manual handling of the results. Lastly, our method can also be used to examine patterns of pre-diagnostic tests and related abnormalities in other cancers.

Our study assumes implicitly that inflection points in abnormal test findings occurred within a 12-month period. While earlier inflection points are theoretically possible, this can be deemed unlikely from the observed findings. Furthermore, previous case-control studies looking at pre-diagnostic test patterns found that the majority of cancers were diagnosed in the year after the index test, and that cancer incidence returned to baseline in the second year after the index abnormal test [25].

The sample size relating to patients with UTUC precludes precise estimations of associations. Therefore, we focused on results from patients with bladder and renal cancer, in whom we can make more reliable inferences due to their large sample sizes. Although a statistically significant inflection point was found for abnormal AST, the confidence intervals on this estimate are wide, reflecting the small sample size and the exact estimate should be interpreted with caution.

Our study did not examine presenting symptoms or other indications for the tests performed. Nevertheless, new abnormalities in either generic or organ-specific blood tests might represent situations where additional clinical explanations might be required, and further investigations or referrals are recommended.

Comparison with existing literature

Building on prior evidence, we found that the monthly rate of abnormal primary care blood tests that are associated with increased risks for all cancers increased in patients with bladder and renal cancer in the months before diagnosis [4 5 24 25 27 28]. Additionally, we were able to examine organ-specific tests which could be associated with incidental detection of bladder or renal cancer, and identify when these abnormalities started to appear.

Implications

This study suggests that some patients with bladder or renal cancer could have their diagnosis expedited if abnormal tests led to definitive cancer investigation. We found similar diagnostic windows (about 6-8 months pre-diagnosis) for both abnormal generic and organ-specific tests,

suggesting that there may be opportunities to initiate earlier investigations for both types of abnormal tests depending on the clinical context. For the 8 blood tests which demonstrated a rise in their baseline rates before diagnosis, at least one-quarter of the patients had the abnormality first detected in the early diagnostic window and prior to 3 months before diagnosis, a diagnostic interval threshold which could negatively affect survival in some bladder and renal cancer patients [31 32].

Our findings suggest that there may be greater propensity to improve evaluation of abnormal organ-specific than generic tests. We found 33-42% of patients with abnormal LFTs and creatinine having an abnormality early in the diagnostic window, a relatively high proportion of patients with an early abnormal test, suggesting that opportunities for more rigorous evaluation of abnormal organ-specific tests might exist in some patients, especially in the presence of other risk factors such as age and smoking status. Symptomatic presentation of renal cancer has been associated with advanced disease, whereas incidental diagnosis have been reported during investigations for pre-existing or non-urological cancer clinical features, including for hepatobiliary causes or urinary tract obstruction [16 33]. It is possible that with improved direct access in primary care to imaging such as ultrasound, further investigations of abnormal LFTs and creatinine can result in continued increase in incidental, and therefore early stage diagnosis of renal cancer [34].

When considering the generic tests, earlier investigations could nevertheless be triggered in at least some patients, given that about one-quarter of patients with an abnormal generic blood test also had the abnormality first detected in the early half of the diagnostic window. It is possible that the generic tests representing markers of inflammation might be associated with more symptomatic disease, and are more likely to result in further active monitoring or investigations which subsequently led to a cancer diagnosis.

Lastly, it is important to note that although our study found diagnostic windows during which further investigations for abnormal results could potentially be initiated, it does not illuminate whether this clinical behaviour should happen. Many of the abnormal tests have low positive predictive values (PPV) for cancer and would not qualify for urgent investigation under current UK clinical guidance, which currently suggests investigations for clinical features with PPVs above 3% [2]. They should be considered in combination with other patient and clinical risk factors and clues, including age of patient, duration and severity, and presence of other symptoms and signs. Although we were unable to examine the indications leading to the performance of each abnormal test, our findings suggest that changes in the level of abnormal tests from background rate exist in patients subsequently diagnosed with bladder and renal cancer, either in response to symptomatic disease or through routine blood monitoring carried out for other reasons. Should the current NICE guidance be liberalised and referral threshold reduced, this study suggests there is considerable potential for earlier diagnosis of bladder and renal cancer. Further studies that examine positive predictive values of the examined tests for bladder and kidney cancer are also necessary to guide clinicians on the most appropriate subsequent management plans following abnormalities in these tests.

Conclusion

The findings demonstrate that abnormalities in commonly performed primary care blood tests represent population-level signals of bladder and renal cancer that can be observed up to 8 months before diagnosis suggesting that there may be opportunities to expedite the diagnosis in some patients. There is a need to further evaluate associations between abnormal tests and bladder and renal cancers for individual patients, and consider the clinical context in which these tests are performed, to better understand the clinical utility of these common tests in the early identification of symptomatic cancer.

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Ethical approval
A research protocol (17_107R) was submitted to and approved by the CPRD Independent Scientific Advisory Committee before the study was conducted. This study is a secondary analysis of anonymised patient data.

Competing interests
GDS has received educational grants from Pfizer, AstraZeneca and Intuitive Surgical; consultancy fees from Pfizer, Merck, EUSA Pharma and CMR Surgical; Travel expenses from Pfizer and Speaker fees from Pfizer. None of the other authors have competing interests.

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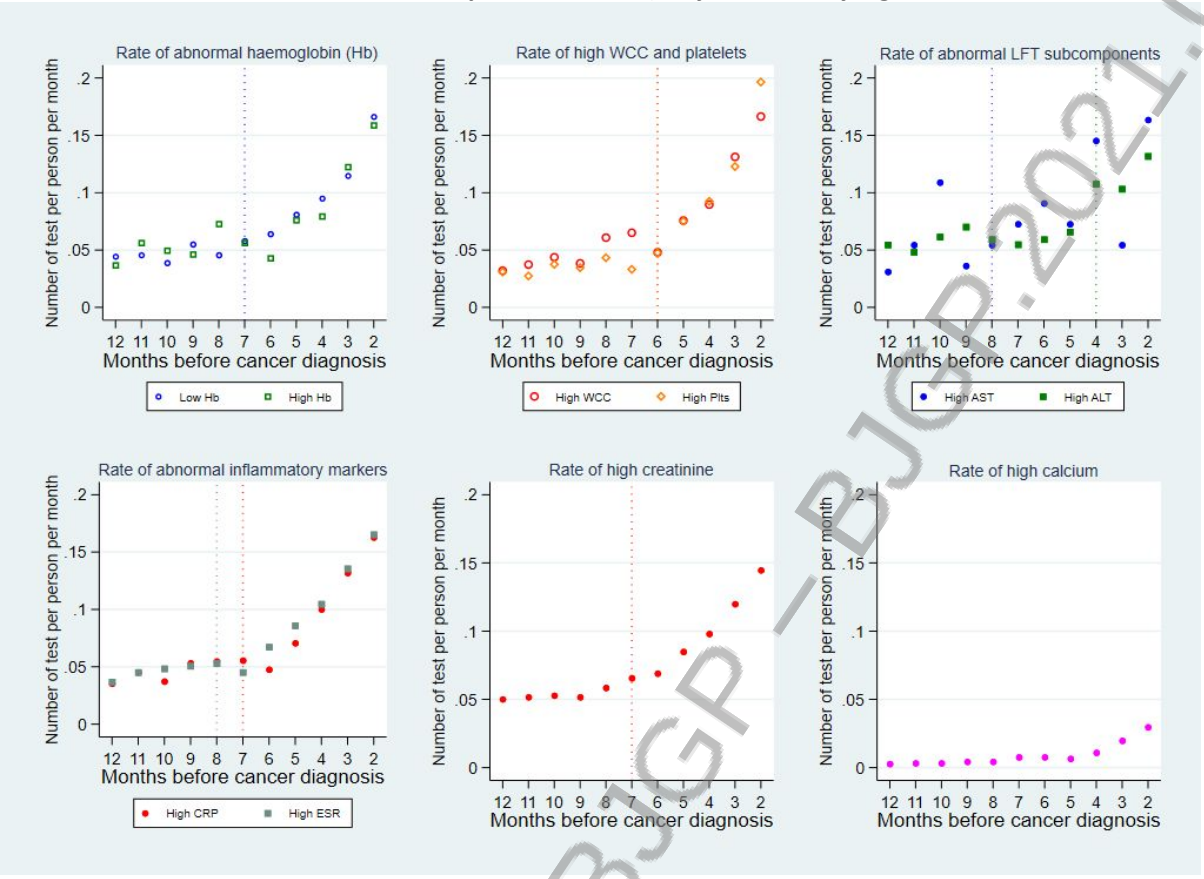
Table 1: Rationale for blood tests examined

Type of test	Test group	Specific test or component test examined	Rationale
Generic	Full blood Count	Haemoglobin (Hb)	Low Hb (anaemia) is a non-specific sign of renal and bladder cancer [14]. High Hb (polycythaemia) may be associated with renal cancer as part of a paraneoplastic syndrome [14].
		White Cell Count (WCC)	Raised WCC especially with lower urinary tract symptoms may be a clinical feature of bladder cancer [27].
		Platelet (Plt)	High plt (thrombocytosis) may be a non-specific marker for cancer [27].
	Inflammatory markers	C-reactive protein (CRP)	Raised CRP may be a non-specific marker for cancer [27].
		Erythrocyte Sedimentation Rate (ESR)	Raised ESR may be a non-specific marker for cancer [27].
	Others	Calcium	Raised calcium has been associated with increased risk of bladder cancer, as well as renal cancer by manifesting as a paraneoplastic syndrome [14].
Organ-specific	Liver Function Test (LFTs)	Aspartate aminotransferase (AST)	Abnormal liver function tests can lead to subsequent imaging tests which reveal incidental renal cancers [16], and less commonly presenting as a paraneoplastic syndrome of renal cancer [14]
		Alanine transaminase (ALT)	
	Renal function	Creatinine	Raised creatinine may be related to upper tract obstruction secondary to malignancy.

Figure 1: Rate of abnormal blood tests in the year pre-diagnosis, with dotted line signifying increase in rate from baseline for that particular test (only statistically significant results shown)



ALT: alanine transaminase; AST: aspartate aminotransferase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: haemoglobin; LFT: liver function test; Plt: platelets; WCC: white cell count
Note: Inflection line for High WCC and High Plts both occur (and therefore overlap) at 6 months pre-diagnosis.
Y-axis refers to number of abnormal tests per person per month

Table 2: Estimated inflection point for increase in rate of abnormal blood tests and proportion of patients with an early test

Test type (number of patients with that abnormal test)	Number of patients with a test during the diagnostic window[ᵗ]	Any cancer type*		Number of patients with an abnormal early test^	
		Month of increase (95% CI)	P value	N	%
Low Hb (n=1,253)	659	7 (4.56, 9.44)	<0.001	232	35.2
High Hb (n=192)	123	5 (-0.27, 10.27)	0.063†		
High Platelets (n=391)	208	6 (4.65, 7.35)	<0.001	51	24.5
High WCC (n=573)	292	6 (4.65, 7.35)	<0.001	75	25.7
High ALT (n=302)	91	4 (0.58, 7.42)	0.022	30	33.0
High AST (n=39)	26	8 (2.25, 13.75)	0.006	11	42.3
High CRP (n=747)	426	7 (4.72, 9.28)	<0.001	120	28.2
High ESR (n=506)	321	8 (4.54, 11.46)	<0.001	82	25.5
High creatinine (n=1,364)	686	7 (3.92, 10.08)	<0.001	289	42.1
High calcium (n=84)	39	5 (-0.38, 10.38)	0.069†		

ALT: alanine transaminase; AST: aspartate aminotransferase; CI: confidence interval; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: haemoglobin; WCC: white cell count

**Number of analysed patients = 4,533 for all models. Highlighted cells denote results whereby p-value<0.05*

^Calculated for results where a statistically significant inflection point (p<0.05) is present.

[ᵗ]A diagnostic window is calculated from the inflection point to the month immediately prior to diagnosis. Where a diagnostic window included an odd number of months, the number of patients with an early abnormal test was calculated for the duration from the inflection point to the month immediately prior to the midpoint of the diagnostic window (eg. for inflection point at 7 months pre-diagnosis, the first 'half' of the window was defined as 5-7 months inclusive; for inflection point at 6 months, first half of the window was defined as 5-6 months inclusive).

†The lack of evidence for an inflection point may arise because of an absence of an inflection point, a lack of power or an inflection point occurring more than 11 months before diagnosis.