Patients with new onset haematuria: assessing the discriminant value of clinical information in relation to urological malignancies

Nicholas Summerton, Sara Mann, Alan S Rigby, Julie Ashley, Sarah Palmer and John W Hetherington

SUMMARY

Background: *There is little information available to assist general practitioners (GPs) in deciding which patients with haematuria are likely to have a malignancy.*

Aim: *To derive discriminant functions for specific items or clusters of clinical history information in relation to the categorisation of patients presenting to the 'open access' haematuria clinic in Hull.*

Design of study: *Recruitment of patients via an 'open-access' haematuria clinic.*

Setting: *A consecutive series of 363 patients aged between 18 and 80 years who attended the clinic.*

Method: *Between February 1999 and October 1999 clinical history information derived from the participating patients was compared with the patients' diagnoses. Diagnoses were established by a combination of cystoscopy and radiological assessments and rechecked against the patient records and the hospital patient administration system two to three months later.*

Results: *A number of individual variables seemed to be particularly helpful in discriminating malignancies. However, when indicants were combined using regression shrinkage techniques, only the following variables were preserved: age, sex, type of haematuria, number of episodes of haematuria, hesitancy, poor urinary stream, smoking history, and history of urinary tract infections.*

Conclusion: *It is possible to generate helpful discriminant information to assist GPs in making more appropriate decisions in a difficult area of clinical practice. However, it remains a matter of judgement as to how representative the study population is likely to be compared with all haematuria patients encountered in primary care. We have reasonable confidence in the general applicability of the rules for macroscopic haematuria; however, it seems likely that the prediction rules outlined for microscopic haematuria have their greatest relevance once a patient has been referred by a GP. In developing the work further and testing out the discriminators identified in this study, we propose that a primary care-based project now needs to be undertaken focusing on microscopic haematuria, with a particular emphasis on addressing selection biases. In addition, there is a more general need to assess the reliability of all the suggested items of clinical discriminant information.*

Keywords: *haematuria; cancer; urology; diagnosis.*

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Introduction

ACCORDING to textbooks[1] and referral guidance,[2] haematuria is a key feature of the three commonest urological malignancies. For example, in relation to transitional cell carcinoma of the bladder, Mommsen *et al* state that 79% of patients present with haematuria.[3] Lee and Davis reported that, of those tumours detected as a result of patients experiencing macroscopic haematuria, 69% were bladder, 16% were renal, and 10% were prostatic tumours.[4]

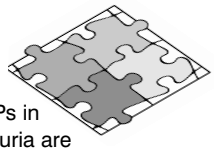
Within the United Kingdom the average general practitioner (GP) with a list size of 2000 patients will encounter one new patient with prostate cancer every 18 months, one new case of bladder cancer every two years, and one new case of renal cancer every five years.[5] The prevalence of microscopic haematuria has been demonstrated to be up to approximately 2.5% in population-based screening studies[6] and it is estimated that, on average, a GP will encounter fewer than one case of macroscopic haematuria per year (0.6 per year per GP in a 'standard practice' in the Netherlands[7]). Investigation of referred patients reveals a urological malignancy in between 14.7% and 21.8% of those with macroscopic haematuria, and between 2% and 11% of those with microscopic haematuria.[8]

The difficulty for the GP is in deciding which patients with haematuria are likely to have a urological malignancy (principally prostate, bladder, or renal) and which are likely to have a more benign cause. Unfortunately, education and training for GPs continues to focus on the symptom characteristics of patients with established urological malignancies as they present to urological surgeons. There is often little appreciation that such evidence is not the most appropriate with which to assist GPs in making a referral decision, as it represents information derived from a highly-selected group, often at an advanced stage of malignancy.

An extensive literature search using MEDLINE (between 1966 and 1999) and EMBASE (between 1982 and 1999), using a validated search strategy, identified two recent systematic reviews: one concerning asymptomatic microscopic haematuria[9] and another concerning macroscopic haematuria.[10] The conclusions were essentially the same for both reviews: that studies are needed to determine which findings GPs should use to select patients for referral. The most striking result of the review by Buntinx and Wauters[10] is that not a single study could be found that looked at the diagnostic value of macroscopic haematuria among medically unselected patients from general practice.

There are a number of methodological difficulties that

HOW THIS FITS IN



What do we know?

There is little information to assist GPs in deciding which patients with haematuria are likely to have a urological malignancy. In evaluating patients, GPs often consider symptoms in combination and research into diagnosis needs to accommodate this.

What does this paper add?

This work demonstrates a method to derive adjusted estimates of clinical history information for the diagnosis of urological malignancy in patients presenting with macroscopic haematuria. However, this work illustrates the difficulties of seeking to assess the diagnostic significance of microscopic haematuria owing to selective biases.

must be addressed when looking at possible discriminant functions that can be applied with confidence within general practice settings. Primarily, there is a need to be clear about the spectrum of patients that is being studied and how this study population relates to the types and characteristics of patients encountered in day-to-day general practice. Ideally, a large number of general practice patients would have been recruited into a delayed-type cross-sectional study, in which all patients presenting with haematuria would have had their medical history taken, and then they would have been followed up for a predefined period to assess key outcomes. However, because of concerns about the practical feasibility, as well as the costs of such an approach, this study aimed to derive discriminant information for GPs by using an 'open-access' haematuria clinic as a proxy for primary care. The statistical methods used in this paper are complex and the statistical methodology is explained in detail in the next section.

The primary purpose of this study was to derive discriminant functions for specific items or clusters of clinical history information in relation to the categorisation of patients aged between 18 and 80 years with new onset haematuria presenting to the 'open access' haematuria clinic in Hull.

Method

In 1995 an 'open access' haematuria clinic was established in Hull. The clinic is now staffed by three nurse practitioners under the supervision of three consultant urologists and a staff grade doctor in urology. The only criteria for patient inclusion in the clinic is that the individual is over 18 years old and that the reason for referral is haematuria. Patients can be referred directly for inclusion in the clinic. Nurse practitioners can also scan all the urology outpatient referral letters to identify other patients whose primary problem is haematuria. These patients are also assessed in the clinic. Since its inception the clinic has been rigorously audited and it receives between 15 and 20 referrals per week.

In 1998 it was decided to redesign the clinic patient encounter forms and the scope of the audit data collection. This presented an opportunity to generate discriminant diagnostic information from the routinely collected patient information. The redesigned form was aimed at collecting a

Commentary

The patient's history and the physical examination provide complex and sophisticated data. In the consultation, the doctor will generate a number of clinical variables that need to be sifted, ranked, and weighted. This is the complex area of clinical judgement that is important in general practice, where overly fearful judgements may lead to high referral to technological medicine. Many consultations will not appear to have the level of order that allows the wise deduction that results in good quality clinical judgements.

In the 1970s and 1980s, there was lively interest in the area of clinical judgement and in using Bayes' probability approach to clinical variables. It was hoped that such an approach would lead to clinical support systems that perhaps could be used by both patients and doctors. Numerate and computer literate physician-scientists have been lured into other areas of medicine that are both rewarding and interesting and certainly not at all as difficult as the area of clinical judgement.

This paper on patients with new onset haematuria reintroduces us to clinical judgement and the authors make the point that most clinical probabilities are based on referred populations which are already filtered by general practitioners. The question posed in this paper is simple but compelling: 'What are the chances that a patient with microscopic haematuria presenting in general practice has a serious illness?' Unsurprisingly, one review (Buntinx and Wauters) could not find a single study about the diagnostic value of microscopic haematuria from patients referred from general practice. Based on current estimates, the best guess is that between one in ten and one in 50 referred patients with haematuria have a urological malignancy. The present study by Summerton moves us on from a simple likelihood approach to using logistic regression which adds weight to important clinical variables, thereby increasing their likelihood of predicting which patients will have serious illnesses. In this study, older men with a single report of haematuria occurring at the beginning of the stream increases the likelihood of urological malignancy.

In investigating the denominator of clinical medicine, which is general practice, this study provides a methodology that can be used for other common conditions that lead to general practice referral. Advances in information technology, coupled with some knowledge of statistics and epidemiology, will make this area of medicine both interesting and rewarding, and also important in attributing risk to common symptoms and signs.

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broader range of clinical information that would be defined and more clearly categorised. In addition, more detailed information was obtained on comorbidities to provide some additional information on the patient spectrum. The form was piloted in a 'run-in' phase to clarify meaning and content prior to formal adoption.

Between February 1999 and October 1999, clinical history information derived from a consecutive series of 363 patients was examined. In accordance with routine practice, a patient attending the haematuria clinic was assessed by a nurse practitioner, with the clinical history information being recorded on the redesigned audit form. The final diagnosis was arrived at by using a combination of cystoscopy and radiological assessments. The diagnosis recorded in the clinic was then checked by the lead author two to three months later, using patient records together with the hospital patient administration system. This served to address uncertainties at the time of the clinic and also to act as a check for misclassification at the time of the original clinic assessment.

All the data was entered onto an SPSS database with double data entry checks.

Statistical methods

Individual indicants. The discrimination between two groups of patients was the statistical problem which was addressed. Of particular interest was how knowledge of the presence or absence of certain clinical signs and symptoms (also referred to as indicants) could allow inferences to be made about membership of a disease group. The analysis focused on the two comparisons of most clinical relevance: non-urological cancer versus urological cancer, and normal/non-cancerous conditions versus urological cancer. Non-cancerous conditions included benign prostatic disorders, strictures or stenoses, and calculi. Urological cancer incorporated prostate, renal or bladder cancer.

There are several methods for evaluating diagnostic information and the method selected was based on the one-variable Bayes' discriminant. This approach has already been successfully applied in other diagnostic situations, such as those encountered in gastroenterology[11-13] and rheumatology.[14] Bayes' discriminant is equivalent to multiplying the likelihood ratio (the ratio of the proportion of those with the disease who show the symptom, to the proportion of those without the disease but who also show the symptom), by the prior probability to give the posterior probability of disease. In other words, posterior odds = likelihood ratio x prior odds.

In our analysis the likelihood ratio was converted to a 'weight of evidence' based on Good's method.[15] This involved converting the Bayes' discriminant to natural logarithms, multiplying this weight of evidence by a factor of 10, and then rounding off to the nearest whole number.[14] Where there were zeros in cells, a correction factor suggested by Cox was used.[16] Standard errors were calculated using methods outlined by Spiegelhalter and Knill-Jones.[11]

Indicants in combination. In general medical practice it is usual to consider symptoms and signs in combination. The naïve Bayes' approach (whereby individual indicants are simply added together) is a popular choice for many.[17-19] Proponents of naïve Bayes' argue for its simplicity and ease of interpretation; however, others consider that the independence assumption is misleading, giving rise to over-optimistic probabilistic statements.[20,21] We agreed with the latter view and, to allow for the co-dependence of the various indicants, we adopted a 'regression shrinkage' method on the individual weights of evidence. Logistic regression was used to derive 'shrinkage coefficients', which scaled down the individual weights of evidence by varying amounts to reflect the degree of dependency in the data. A backwards elimination method was followed, in which an indicant was removed from the logistic regression if the ratio between the parameter estimate and its standard error was less than 1.96 (although we accept that this is an arbitrary level of significance). The standard errors of the adjusted weights of evidence were calculated according to methods outlined by Spiegelhalter.[12]

Results

Of the 363 patients recruited into the study, 212 were male and 151 female. One hundred and seventy-two patients reported macroscopic haematuria and 186 microscopic haematuria. The final diagnoses of the 363 patients were as follows: 260 had no abnormality detected, 42 had benign prostatic disorders, 12 had strictures or stenoses, 13 had calculi, and 36 had urological cancers. Of the cancers, the vast majority (n = 28) were bladder tumours, two were prostate cancers, five were renal cancers, and one patient had both renal and bladder tumours. The mea and median ages for the patients (by group) are as outlined in Table 1.

Discussion

A number of individual variables appear to be helpful in discriminating urological malignancies from non-malignant conditions in patients with haematuria. These are: increasing age, male sex, macroscopic-type haematuria, and whether the haematuria was noticed at the beginning or throughout the stream rather than just at the end (Table 2). Interestingly, a single episode of haematuria seems to be as important as multiple episodes, and this accords with Connelly's view that excretion of red blood cells in the urine of patients with urothelial malignancies may be intermittent and that any further evaluation should be dependent on its initial discovery.[22] Multiple UTIs are less helpful than a single documented episode or no episodes of UTI in suggesting malignant disease.

There appears to be a dose-response effect between the number of episodes of nocturia and the weight of evidence. However, in general it seems that obstructive symptoms, such as hesitancy or poor stream, provide greater individual weights of evidence in favour of urological malignancy than do the irritative symptoms of nocturia or urgency.

When indicants are combined only the following variables are preserved: age, sex, type of haematuria, number of episodes of haematuria, hesitancy, poor stream (Table 3), smoking history (Table 4) and history of UTI (Table 4). The initial weights of evidence have been scaled down by amounts ranging from between 9% to 17%, and in both

Table 1. Age distribution (by group) of participating patients.

	Diagnosis		
	Normal conditions (*n* = 253)	Cancer (*n* = 36)	Non-cancerous abnormalities (*n* = 67)
Mean age (years)	58.1	69.4	64.3
Median	60.0	73.0	68.0

*Table 2. Log-likelihood ratios for haematuria data for normal conditions (*n *= 260) versus urological cancer (*n *= 36). Weight of evidence = Log-likelihood ratio multiplied by 10 and rounded to nearest whole number.[14] For missing data, the weight of evidence scores zero as recommended by Spiegelhalter and Knill-Jones.[11] Details of the weights of evidence for other individual variables are available from the lead author on request, as are the unadjusted comparisons between 'normal conditions versus urological cancer'. (The unadjusted comparisons 'normal/non-cancer versus urological cancer' were of the same order and magnitude as those between 'normal versus urological cancer').*

Variable	Frequency of normal condition (%)	Frequency of cancer (%)	Weight of evidence (standard error)
Age in years			
45	56 (22.1)	1 (2.8)	-21 (10)
46–59	69 (27.3)	6 (16.7)	-5 (4)
60–74	90 (35.6)	15 (41.7)	+2 (3)
75+	38 (15.0)	14 (38.9)	+10 (3)
Sex			
Male	126(48.5)	28 (77.8)	+5 (2)
Female	134(51.5)	8 (22.2)	-8 (4)
Type of haematuria			
Microscopic	159 (61.9)	3 (86)	-20 (6)
Macroscopic	98 (38.1)	32 (91.4)	+9 (2)
Timing of blood (macroscopic) in urinary stream			
Beginning	12 (13.0)	7 (21.9)	+5 (5)
Throughout	25 (27.2)	13 (40.6)	+4 (3)
End	14 (15.2)	3 (9.4)	-5 (6)
Unsure	41 (44.6)	9 (28.1)	-5 (4)
Number of episodes of haematuria			
0	61 (23.5)	2 (5.6)	-14 (7)
1	59 (22.7)	15 (41.7)	+6 (3)
2	65 (25.0)	5 (13.9)	-6 (5)
3+	75 (28.8)	14 (38.9)	+3 (3)
History of urinary tract infections (UTIs)			
0	195 (75.0)	29 (80.6)	+1 (2)
1	28 (10.8)	7 (19.4)	+6 (4)
2+	37 (14.2)	0 (0.0)	-24 (14)
Nocturia (number of episodes per night)			
0–1	157(60.4)	18 (50.0)	-2 (3)
2–4	88 (33.8)	15 (41.7)	+2 (3)
5+	15 (5.8)	3 (8.3)	+4 (6)
Hesitancy			
No	231(88.8)	24 (68.6)	-3 (2)
Yes	29 (11.2)	11 (31.4)	+10 (4)
Poor stream			
No	221(85.0)	25 (71.4)	-2 (2)
Yes	39 (15.0)	10 (28.6)	+7 (4)
Urgency			
No	171(65.8)	21 (60.0)	-1 (2)
Yes	89 (34.2)	14 (40.0)	+2 (3)

adjustments certain individual variables seem to lose their discriminatory effectiveness. It is interesting that this further analysis again indicates the importance of two of the obstructive symptoms but none of the irritative symptoms. It is also important to appreciate that, although multiple episodes of haematuria are significant, the single episode still provides the greatest weight of evidence. In relation to the past medical history it seems that a past history of smoking (Table 4) is of greater significance than current smoking and is perhaps a reflection of the longer-term risks of smoking in relation to bladder cancer.

The use of the information generated can easily be illustrated. For example, based on Table 4 (urological cancer versus normal conditions/non-cancerous abnormality), and taking the prevalence (prior probability) of urological malignancy to be 9.9% (36/363), it can be calculated that the 'starting score' is -22. Consider a male patient (+2.6) aged 76 (+7.0) presenting with macroscopic haematuria (+7.3)

Table 3. Adjusted weights of evidence: urological cancer versus normal conditions.

Variable	Shrinkage coefficient (standard error)	Adjusted weight of evidence (standard error)
Age in years	0.85 (0.26)	
45		-17.9 (4.6)
46–59		-4.3 (1.1)
60–74		+ 1.7 (0.4)
75+		+ 8.5 (2.2)
Type of haematuria	0.91 (0.22)	
Microscopic		-18.2 (4.4)
Macroscopic		+ 8.2 (2.0)
Number of episodes	0.90 (0.27)	
0		-12.6 (3.5)
1		+ 5.4 (1.6)
2		-5.4 (1.6)
3+		+ 2.7 (0.8)
Hesitancy	0.86 (0.32)	
No		-2.6 (1.0)
Yes		+ 8.6 (3.2)
Poor stream	0.83 (0.37)	
No		-1.7 (0.7)
Yes		+5.8 (2.6)
Sex	0.84 (0.20)	
Female		-6.7 (1.6)
Male		+ 4.2 (1.0)

Table 4. Adjusted weights of evidence: urological cancer versus normal conditions/non-cancer.

Variable	Shrinkage coefficient (standard error)	Adjusted weight of evidence (standard error)
Age in years	0.88(0.19)	
45		-17.6 (3.8)
46–59		- 3.5 (0.8)
60–74		+ 0.9 (0.2)
75+		+ 7.0 (1.5)
Type of haematuria	0.91 (0.14)	
Microscopic		-17.3 (2.7)
Macroscopic		+ 7.3 (1.1)
Number of episodes	0.90 (0.19)	
0		-12.6 (2.7)
1		+ 5.4 (1.1)
2		-5.4 (1.1)
3+		+ 2.7 (0.6)
Hesitancy	0.84 (0.21)	
No		-1.7 (0.4)
Yes		+ 5.9 (1.5)
History of UTIs	0.89 (0.38)	
0		+ 0.9 (0.4)
1		+ 5.3 (2.3)
2+		-19.7 (8.4)
Smoking history	0.89 (0.33)	
Never		0.0 (0.0)
Former		+ 3.6 (1.3)
Current		-4.5 (1.7)
Sex	0.86 (0.17)	
Female		-6.0 (1.2)
Male		+2.6 (0.5)

on at least three occasions (+2.7). He also has hesitancy (+5.9), no history of UTIs (+0.9) and he is a former smoker (+3.6). This gives a total weight of evidence of +8.0, which corresponds to a high risk for urological malignancy (posterior probability = 69%). A female presenting with the same symptoms would have a posterior probability for urological malignancy of 47%.

This work also demonstrates that it is feasible to generate useful and usable discriminant information to assist GPs in making more appropriate decisions in a difficult area of clinical practice. However, it remains a matter of judgement as to how representative the study population is likely to be compared with all haematuria patients encountered within primary care. Some reassurance might be drawn from the observation that the proportion of patients represented in the study population with key co-morbidities, such as hypertension or diabetes, is comparable to general practice (data available from lead author on request). On the other hand, it could also be argued that, in a population of patients with haematuria, one would expect a greater proportion of patients with hypertension and diabetes than among unselected patients within general practice. Such comparability may therefore simply indicate the unrepresentative nature of patients being recruited into the haematuria clinic. However, using the macroscopic haematuria data from the Netherlands 'standard practice',[7] it can be estimated that the 299 GPs referring the majority of their patients to the Hull service would encounter approximately 135 cases of macroscopic haematuria over the course of the nine-month study period. It is therefore reassuring that we recruited 172 patients with macroscopic haematuria, a figure of a similar order of magnitude. However, we only picked up 186 patients with microscopic haematuria, and yet even the most conservative estimate of the incidence (0.1%) would lead us to expect a minimum of 600 cases.[8]

Our conclusions are that, for macroscopic haematuria, we have reasonable confidence in the similarity of our results to those that we would have derived from a direct survey of macroscopic haematuria cases in general practice settings. However, the issue for microscopic haematuria is somewhat different; in view of the suggestion of significant selection bias we feel that these results must be handled with care when dealing with first encounters. It seems likely that the prediction rules for microscopic haematuria have their greatest applicability once a patient has attended a GP and he has made a decision to refer. The information generated in this study may help the GP to assess what would be the most likely outcome from the clinic visit should the patient with microscopic haematuria attend. In addition, if a patient continues to have problems after a negative assessment in the 'open access' clinic, then the discriminant information might also provide some assistance to the GP in judging whether further investigation of the microscopic haematuria is warranted.

There are also statistical considerations, as there has been much discussion on determining good predictive models.[12,21,23] Some are of the opinion that the naïve Bayes' method is the ideal,[17-19] while others guard against the over-optimistic probabilistic statements arrived at using the naïve Bayes' approach.[20,21] Since we agreed with the latter, we adopted a 'regression shrinkage' method, whereby the initial weights of evidence were scaled down by varying amounts. The adjusted weights of evidence arrived at on our data (Tables 3 and 4) do not appear to have given us over-

optimistic statements of probability and, moreover, they appear to be in concordance with our clinical experience. However, it is important to appreciate that even this approach is not without its critics.[23]

Within this study we have deliberately grouped the urological cancers together as we believe that this accords more closely with the reality of GP decision-making when confronted with a patient with a symptom of possible oncological significance. There are clearly symptom similarities between the urological cancers, as there also are between the upper gastrointestinal cancers. For the GP the decision is more dichotomous and functional, i.e. referral versus non-referral, serious versus less serious, rather than pathological. However, a refinement in a much larger study could involve a separation out of the cancers into specific cancer groupings.

When confronted with a patient with a new piece of clinical information (e.g. symptom, sign or investigation), GPs must have confidence in the information generated by diagnostic research if they are going to apply it to their clinical practice. Although we are reasonably comfortable that the 'open access' clinic has provided useful and usable discriminant information for patients presenting with macroscopic haematuria, there is a need to replicate these results in other areas of the country and among different groups of patients and GPs. Furthermore, we also need to assess the reliability of the clinical discriminant information generated.[24] However, for microscopic haematuria it is clear that the open access clinic is not an adequate proxy for primary care in view of the tendency towards selection bias. This problem has also been noted by others[25-27] and any future work on microscopic haematuria will need to address this key bias. One possible solution would be to conduct a primary care-based study of microscopic haematuria but with more intensive monitoring of a representative proportion of the practices; such an approach seems both feasible and has already shown great promise in relation to rectal bleeding and colorectal cancer.[28]

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