

Investigation of non-visible haematuria in a tertiary urology service

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Abstract

Aim

Non-visible haematuria (NVH) is a common reason for referral to urology services¹. There is contrasting guidelines internationally regarding its investigation^{1,2}. The aim of this study is to investigate the rate of detection and resource burden of NVH on a tertiary urology service.

Methods

A retrospective chart review was performed which identified patients who were investigated for NVH from July 2023 to July 2024. Data was collected on patient demographics, indication, findings, and radiological imaging. Information regarding cost of investigations were also obtained.

Results

A total of 1,868 flexible cystoscopies were reviewed, with 175 (9.4%) indicated for NVH. One clinical diagnosis of bladder tumour was identified, and two cystoscopies identified an erythematous area warranting biopsy, both of which were benign. Imaging identified three patients with findings requiring follow-up imaging. Cost of flexible cystoscopy is estimated at €609, ultrasound imaging €102, CT imaging €170, and outpatient clinic appointment €150. This equates to minimum cost of €861 for investigation of NVH.

Discussion

Non-visible haematuria has a detection rate of 6% for urological malignancy in recent large volume studies^{2,3}. Investigation contributes to a significant resource burden. Additionally, the risk to patients of these investigations must be considered. We welcome universal terminology and guidelines to be established.

Introduction

Non-visible haematuria (NVH) is a frequently encountered condition in clinical practice and constitutes a common reason for referral to urology outpatient services¹. NVH is defined as three or more red blood cells per high-power field (RBC/HPF) in the absence of infection or

proteinuria². While healthy people lose around a million red blood cells in their urine each day, this equates to approximately one cell per high-power field³. If persistent, it often prompts extensive diagnostic evaluations¹. This condition, although seemingly benign, can be indicative of underlying pathologies ranging from benign urological conditions to significant malignancies such as transitional cell carcinoma or renal cell carcinoma^{4,5}.

The background rate of asymptomatic NVH can be 2.5%, increasing to 22% in those >60 years⁶. Despite its common occurrence, there is considerable ambiguity in the current guidelines internationally. These guidelines vary widely in terms of definitions, age thresholds, and the consideration of patient factors, leading to inconsistencies in clinical practice⁷. Indeed, the terminology and definitions have not been standardised, and guidelines are currently based on consensus agreement and expert opinion due to the paucity of evidence⁶.

The aim of this study is to evaluate the rate of detection of significant urological conditions in patients referred for NVH and to assess the resource burden that these referrals place on a tertiary urology service. By analysing the outcomes of NVH referrals, this study seeks to contribute to the ongoing discourse on optimising the investigation protocols to balance the need for thorough diagnostic evaluation with the prudent use of limited healthcare resources.

Methods

Ethical approval was obtained from the audit department at Galway University Hospital. Inclusion criteria for the study were patients undergoing primary cystoscopy with isolated non-visible haematuria as their referring symptom. Any patient with multiple or overlapping symptoms including NVH or with another indication for cystoscopy were excluded.

A comprehensive retrospective chart review was conducted. All patients who had flexible cystoscopy from July 2023 to July 2024 were identified from the endoscopy room logbook. From this population, the inclusion criteria were applied to identify study subjects. Electronic patient records were then used to record additional information including patient demographics (age and gender), the date and specific indication for the investigation to ensure they met the inclusion criteria, and the outcomes of flexible cystoscopy procedures. Additionally, the type of radiological imaging utilised in these cases, along with the results obtained, were carefully recorded and documented.

Data regarding the cost of each radiological investigation was obtained from the HIPE (Hospital In-Patient Enquiry) department. Clinical practice and decision making was not impacted as a result of this process as the study. All data was maintained on a hospital issued and password protected desktop.

Results

A total of 1,868 flexible cystoscopies were reviewed for inclusion in this study. Of these, 192 investigations met the inclusion criteria. This subgroup of patients was carefully examined to determine the diagnostic utility of flexible cystoscopy in this context. 17 cases were subsequently excluded from the analysis because they presented with concurrent indications alongside NVH. These indications included recurrent urinary tract infections and lower urinary tract symptoms.

Of the 175 patients included in the study, 86 were male and 89 were female. The mean age of the patient group was 56.9 years (range 24-82). Nine patients were aged under 35 years, a total of 116 patients were aged between 35-65 years, and 50 patients were over 65 years of age.

Of the total 175 cases included, cystoscopy revealed three abnormal findings. One patient (0.57%) received a clinical diagnosis of bladder malignancy and was scheduled for transurethral resection of bladder tumour. Histology subsequently confirmed a pTa low grade transitional cell cancer in a seventy-three year old male. At time of publication, this patient remains under surveillance with no recurrences. Additionally, cystoscopy identified erythematous lesions in two patients (1.14%), which were deemed to warrant biopsy. The histopathological examination of these biopsy samples were both benign. Of note, while seventeen investigations were excluded from the study due to concurrent indications for investigation, two of these excluded cystoscopies identified a clinically diagnosed bladder tumour. Both cases were excluded due to concurrent indication of bothersome lower urinary tract symptoms.

A total of 94 patients had ultrasound kidneys (US) to assess their upper tract anatomy and assess for a pathological cause of NVH. 34 patients had a CT urogram, with the remainder 47 patients undergoing other imaging studies. These include CT Kidney Ureter Bladder (CT KUB) without contrast, CT urogram (CTU), CT Thorax, abdomen pelvis (CT TAP) and CT abdomen pelvis (CT AP). Of the 94 ultrasounds performed, no scans identified findings which necessitated additional follow up imaging. Of the 34 CTU's performed, three scans identified abnormalities, namely a bosniak 2F cyst, a pelvic-ureteric junction (PUJ) obstruction and bilateral hydronephrosis. A CT TAP identified a pulmonary nodule requiring re-imaging in 6 months. All of these findings occurred in patients aged between 35-65 years and can be considered incidental as they are not a primary cause of NVH. At time of publication, these three cases remain under surveillance.

Costing data from the HIPE department showed that a CTU is €170, US is €102, and diagnostic flexible cystoscopy costs €609. This equates to a minimum cost of €861 for investigation of

NVH. As almost all patients attended an outpatient clinic appointment, either before or after investigation, the €150 cost of each appointment must also be considered.

Discussion

The findings of this study are lower than that of existing literature, with one diagnosis of urological malignancy (0.57%). NVH has a detection rate of 6% for urological malignancy identification in recent large volume studies⁸⁻¹⁰. A systematic review by Jubber et al. reported a detection rate of 3.2% for bladder cancer in patients with NVH (95% CI 2.3–4.1%, $I^2 = 90\%$, $p < 0.001$)¹. Indeed, this reduces to 2.1% (95% CI 0.93–3.7%, $I^2 = 84\%$, $p < 0.001$) in the ten studies that specifically excluded persons with active urinary tract infection (UTI). This emphasises that while NVH can be an indicator of serious conditions, the occurrence of malignancies is relatively low¹. Similarly, Tan et al. conducted a prospective study involving 3,556 patients and found that extensive investigations with cystoscopy and radiological imaging often yield low rates of malignancy detection suggesting that a more targeted approach might be more appropriate for managing NVH¹¹.

These findings are significant when considering the resource burden associated with NVH investigations. The current study's cost analysis revealed that each investigation incurred a minimum cost of €861, a figure that includes the costs of flexible cystoscopy and upper tract imaging. This cost is consistent with other studies, such as the work by Yuan et al., who performed a cost analysis of NVH diagnostic protocols and concluded that the financial burden of extensive investigations might not be justified by the relatively low yield of significant findings¹². Previous cost analysis of NVH investigation was performed by Halpern et al., which records an average cost of \$208 for cystoscopy, increasing to \$373 in cystoscopy and biopsy. It also assigns a cost of \$115 for renal US and \$356 for CTU¹³.

Moreover, Edwards et al. highlighted the cost burden surrounding NVH investigations, arguing that alternative approaches, such as more selective use of cystoscopy and imaging, could reduce costs while maintaining diagnostic efficacy¹⁴. This comparison underscores the importance of balancing thorough diagnostic evaluation with the need to manage healthcare resources efficiently.

The IDENTIFY study¹⁵ evaluated the prevalence of urinary tract cancer in patients referred to secondary care and represents the largest international prospective observational study on the topic. It reports a prevalence of 6.38% of urinary tract cancer in patients with NVH, with no cancers recorded in patients <35 years of age ($n = 117$) and no upper tract urothelial cancer in patients <60 years of age ($n = 1,313$). Our study is consistent with a low prevalence of urothelial tract cancer, particularly in these age groups. Data from the IDENTIFY study has become the new reference standard and can inform international guidelines for investigation.

In our study, the tertiary institution protocol for investigation of persistent NVH in this study sets flexible cystoscopy and upper tract US as a minimum investigation protocol. This is broadly in line with current international guidelines. At present, this data has not changed our minimum investigation protocol, however, it is hoped this work will contribute to a national consensus or guideline to standardise management of these patients.

Current guidelines vary, notably guidelines published by the American Urological Association (AUA)⁷ and National Institute for Health and Care Excellence (NICE)¹⁶. The AUA uses the term 'microhaematuria' and defines it as three or more RBC/HPF in an evaluation of a single, properly collected urine specimen⁷. As such, comprehensive guidelines for the evaluation of patients presenting with NVH have been developed⁷. These guidelines advise that all patients over the age of 35 with confirmed NVH should undergo a thorough evaluation that includes cystoscopy and upper tract imaging⁷. This recommendation is based on the increased risk of urological malignancies, particularly bladder cancer, in this age group¹⁷. The AUA emphasises a risk-based approach, recommending that patients with low risk for bladder cancer (women age <50 years; men age <40 years, never smoker, 3-10 RBC/HPF on single urinalysis no additional risks for bladder cancer)⁷ and no significant findings on initial evaluation (comprehensive history and exam, with properly collected urinalysis) may be managed with less invasive follow-up strategies.

In contrast, the UK National Institute for Health and Care Excellence (NICE) adopts the term non-visible haematuria and defines it as the presence of red blood cells in urine¹⁶. It recommends a more conservative approach to the investigation of NVH, particularly in younger populations¹⁶. The NICE guidelines state that only patients over the age of 60 with NVH or those under 60 with other risk factors such as persistent NVH, recurrent urinary tract infections, or known risk factors for bladder cancer, should be referred for urological assessment, including cystoscopy¹⁶. NICE suggests that in the absence of these risk factors, extensive investigations may not be necessary, as the likelihood of malignancy is low, with a large multicentre observational study (IDENTIFY) reporting no cancers in the NVH group in patients <35 years ($n=117$)¹⁸. This approach reflects a broader trend within the UK healthcare system to prioritise cost-effectiveness and patient-centred care in clinical decision-making¹⁸.

The divergent guidelines reflect the underlying uncertainty in the risk stratification and management of patients with NVH. Some studies have suggested that extensive investigations, including cystoscopy and imaging, may lead to significant healthcare resource utilization without proportional benefits in patient outcomes^{12, 14}.

Numerous studies have also investigated the psychological 'cost' and impact of flexible cystoscopy. Some report a prevalence of significant anxiety of 15% and depression of 3.5% associated with the cystoscopy procedure¹⁹⁻²¹. This was highest in younger, female and unmarried patients¹⁹. This was found to be higher than similar cohorts of patients undergoing TRUS-guided biopsy of prostate^{21,22}.

The authors acknowledge that the retrospective nature of the study introduces potential biases, including selection bias. The analysis was conducted at a single tertiary centre, which may limit the generalisability of the findings to other settings with different patient demographics or healthcare resources. One must also acknowledge that the cost analysis focused on direct costs associated with diagnostic procedures and did not account for indirect costs, such as patient anxiety, time off work, or the long-term costs of follow-up investigations²².

In conclusion, the findings from this study are even more conservative than those of other recent research, confirming the low detection rate of significant urological conditions in patients with NVH. The resource burden of these investigations is substantial, raising important questions about the cost-effectiveness of current diagnostic protocols. Moreover, these investigations may be better allocated to patients with visible haematuria which has significant detection rate of up to 25%¹⁸. The results support the need for more standardised guidelines that balance thorough investigation and the prudent use of healthcare resources. Future research should focus on prospective studies with larger cohorts and longer follow-up periods to provide more definitive data on the optimal management strategies for NVH, with the goal of optimizing patient outcomes and cancer detection, while minimising unnecessary interventions.

Declarations of Conflicts of Interest:

None declared.

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