Platinum Priority – Review – Urothelial Cancer

Editorial by XXX on pp. x-y of this issue

Non-visible haematuria for the Detection of Bladder, Upper Tract, and Kidney Cancer: An Updated Systematic Review and Meta-analysis

Ibrahim Jubber a, Shahrokh F. Shariat k,c,d,e,f, Samantha Conroy a, Wei Shen Tan g,h, Patrick C. Gordon i, Yair Lotan d, Edward M. Messing j, Arnulf Stenzl k, Bas van Rhijn i, John D. Kelly g,m, James W.F. Catto a, Marcus G. Cumberbatch a,*

a Academic Urology Unit, University of Sheffield, Sheffield, UK; b Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; c Department of Urology, Weill Cornell Medical College, New York, NY, USA; d Department of Urology, University of Texas Southwestern, Dallas, TX, USA; e Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic; f Institute for Urology and Reproductive Health, IM Sechenov First Moscow State Medical University, Moscow, Russia; g Division of Surgery and Interventional Science, University College London, London, UK; h Department of Urology, Imperial College Healthcare NHS Trust, London, UK; i Department of Urology, Sheffield Teaching Hospital NHS Trust, Sheffield, UK; j Department of Urology, University College London, London, UK; k Department of Urology, University of Tübingen Medical School, Tübingen, Germany; l Department of Surgical Oncology (Urology), Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; m Department of Urology, University College London Hospitals, London, UK

Abstract

Context: Non-visible haematuria (NVH) is a common finding and may indicate undiagnosed urological cancer. The optimal investigation of NVH is unclear, given the incidence of cancer and the public health implications of testing all individuals with this finding.

Objective: We review contemporary literature to determine the association of NVH with the diagnosis of bladder cancer (BC), upper tract urothelial carcinoma (UTUC), and kidney cancer (KC).

Evidence acquisition: A systematic review of original articles in English was completed in May 2019. Meta-analyses for the diagnostic accuracy of NVH and urine cytology were performed.

Evidence synthesis: We screened 1529 articles and selected 78 manuscripts that fulfilled our inclusion criteria for narrative synthesis. Forty manuscripts were eligible for a meta-analysis (reporting 1919 persons). The likelihood of a urological cancer in patients with NVH increased with age (<1% in those aged <40 yr), male sex, and cigarette smoking. Less than 1% of patients are found to have a urological cancer after a negative NVH evaluation. Cancer detection rates in individuals evaluated for NVH ranged from 0% to 16% for BC in 37 studies, 0% to 3.5% for UTUC in 30 studies, and 0% to 9.7% for KC in 29 studies. Substantial statistical heterogeneity was present for the meta-analysis of detection rates.

Conclusions: We present an up-to-date review of the association of NVH with the diagnosis of BC, UTUC, and KC. Individuals with dipstick positive haematuria aged ≥40 yr, who have had potential precipitating causes excluded, should undergo an evaluation. Re-evaluation of patients with unremarkable initial investigations should be performed in high-risk patients or if new symptoms occur.

Patient summary: One in five people have microscopic traces of blood in their urine. This is an important indicator of urological cancer. Investigating all patients is uncomfortable and expensive. We evaluate the risk of cancer and estimate risks to groups of individuals.

© 2019 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Academic Unit of Urology, G Floor, The Medical School, University of Sheffield, Beech Hill Road, Sheffield S10 2RX, UK. Tel. +44 (0)114 226 1229, Fax: +44 (0)114 271 2268. E-mail address: m.g.cumberbatch@sheffield.ac.uk (M.G. Cumberbatch).

https://doi.org/10.1016/j.eururo.2019.10.010
0302-2838/© 2019 European Association of Urology. Published by Elsevier B.V. All rights reserved.

1. Introduction

Haematuria is a common indication for a referral to an urologist, as its presence may indicate urinary tract stones, an infection, or cancer [1]. Visible haematuria (VH; ie, gross haematuria or macrohaematuria) is accepted as an indication to investigate, given the risks of significant pathology [2–7]. In contrast, the need to investigate persons with non-visible haematuria (NVH; ie, microscopic haematuria) is contentious [8–10]. This reflects the high prevalence of NVH in the general population (estimated 20% in men over 60 yr) [11], contrasting definitions (eg, dipstick positive [and extent of positivity] or urine microscopy), and the low risk of underlying urological malignancies. Consequently, current guidelines differ regarding age thresholds and patient risk profiles that warrant investigation, and mode of evaluation [1,2,4,12]. For example, the American Urological Association (AUA) recommends investigating persons over the age of 35 yr with three or more red blood cells (RBCs) per high-power field (HPF) [2], the UK’s National Institute for Health and Care Excellence (NICE) advocates investigation of persons with NVH only in those over 60 yr with either dysuria or an elevated white cell count [4], and the National Board of Health and Welfare of Sweden does not recommend investigating patients with NVH at all [5].

Unconstrained investigation of patients with NVH carries significant individual and public health implications with associated clinical and financial risks and benefits [1,13]. Diagnostic tests such as cystoscopy and multidetector computed tomography with a urographic phase are costly, invasive, and uncomfortable, and carry risks of infection, contrast-medium–related toxicity, and radiation exposure. Up to 95% of urological evaluations of patients with NVH are negative for malignancy [14]. Conversely, many patients with urinary tract cancer are initially referred for NVH, and delays in diagnosis of these cancers lead to worse outcomes [13,15,16]. Two prospective studies found that haematuria screening in asymptomatic individuals is associated with lower-stage cancers at diagnosis (when compared with registry data) and so may improve survival [11,17,18]. Furthermore, a multicentre study of patients diagnosed with bladder cancer (BC) found that those who presented with NVH had a lower rate of muscle-invasive disease than those who presented with VH [19]. Of note, a contrasting multicentre study reported the opposite effect [20].

Given conflicts regarding the requirement and form of testing in individuals with NVH, we aimed to systematically review the literature for the most up-to-date evidence regarding the utility of NVH in the diagnosis of BC, upper tract urothelial carcinoma (UTUC), and kidney cancer (KC). We report the rate of cancers detected in individuals evaluated for NVH and the potential utility of cytology as an additional test in this setting, to provide an overview of the evidence to facilitate clinical decision making and help identify research necessary to advance this field.

2. Evidence acquisition

2.1. Systematic review

A systematic review of original articles was performed using PubMed/Medline in April 2018 and updated in May 2019. We used the following search terms: ((((((((((hematuria[Mesh Terms]) OR microscopic hematuria) OR haematuria) OR dipstick haematuria) OR dipstick hematuria) OR urine dip haematuria) OR urine dip hematuria) OR non-visible haematuria) OR non-visible hematuria) OR dipstick haematuria) OR microscopic haematuria) OR microscopic hematuria) OR haematuria) OR haematuria) AND ((((Urologic Neoplasms/diagnosis)[Mesh] OR "Urologic Neoplasms/diagnostic imaging"[Mesh])). Reference lists of identified manuscripts were also searched.

Articles were included in the systematic review if they met the following inclusion criteria: specified definition of NVH; reported detection rate of BC, UTUC, and KC in individuals evaluated for NVH; reported diagnostic utility/accuracy of upper tract imaging, cystoscopy, and urine cytology in those with NVH; reported factors that increase the likelihood of urological cancer diagnosis in NVH evaluations; and reported factors associated with delays to referral and diagnosis in NVH patients. Manuscripts were excluded if they were not in English, had fewer than 50 patients, and were not about humans. Systematic reviews and meta-analyses were excluded from this meta-analysis. Two reviewers (IJ. and P.C.) examined the abstracts using a priori exclusion/inclusion criteria and Covidence software (Cochrane library). Conflicts were resolved by consensus or with the involvement of a senior author (M.C.). Reference lists of included manuscripts were also searched.

We report our findings in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [21]. The review was registered with the PROSPERO database (registration: CRD42018099457) before initiation.

2.2. Data abstraction

From each study, we extracted the first author’s last name, publication year, country, study type, sex of study participants, number of patients with NVH, number of patients with BC or UTUC or KC, smoking status, presence or absence of symptoms, diagnostic tests used, definitions of NVH, and urine cytology thresholds if present.

2.3. Statistical methods

The statistical analysis was performed using Stata version 15 (Stata Corp, College Station, TX, USA) and Review Manager (RevMan [computer program], version 5.3; Copenhagen: the Nordic Cochrane Centre, the Cochrane Collaboration, 2014). The meta-analysis for detection rates was performed on the double arcsine transformation for each proportion, using the generic inverse-variance method [22]. The double arcsine transformation stabilizes the
variance and is particularly beneficial for proportions closer to 0 or 1, as is likely the case for BC, UTUC, and renal cell carcinoma (KC). Asymmetrical confidence intervals (CIs) are created, and therefore the use of funnel plots to assess publication bias would not be appropriate as the funnel plot shape relies on symmetry of CIs.

Heterogeneity was estimated using Cochran’s Q statistic and $I^2$. Cochran’s Q is calculated as the weighted sum of squared differences between the effects of individual studies and the pooled effect across studies. $I^2$ estimates the percentage of variation across studies, which is due to heterogeneity rather than chance [23]. The pooled detection rate was calculated using a random-effect model [24].

A meta-analysis of diagnostic test accuracy (sensitivity and specificity) for urine cytology was performed using a two-level mixed logistic regression model, with independent binomial distributions for the true positives and true negatives conditional on the sensitivity and specificity in each study, and a bivariate normal model for the logit transforms of sensitivity and specificity between studies. A p value of $<0.05$ was considered statistically significant. The QUADAS-2 risk of bias tool [25] was used for the studies that evaluated the diagnostic accuracy of urine cytology for the diagnosis of urothelial carcinoma (UC) in NVH patients. No studies were excluded from the meta-analysis based on risk of bias scores.

To investigate potential sources of heterogeneity, we performed a subgroup analysis according to study area (Europe, North America, Asia, and Africa), presence of symptoms (asymptomatic, symptomatic, and both), and sex, as well as exclusion of patients with an active urinary tract infection (UTI) from the study. Subanalysis for age and smoking status was not possible due to insufficient data in the included studies.

3. Evidence synthesis

We found 1529 articles, of which 78 full-text manuscripts were included in the systematic review and 40 in the meta-analysis (reporting on 19 193 persons; Tables 1 and 2, and Supplementary Fig. 1). The participants in the studies were predominantly patients with NVH who were referred from primary care to secondary care for evaluation.

In total, 11 studies enabled the calculation of sensitivity and specificity of urine cytology for UC in patients with NVH, of which seven (reporting on 2425 persons) were amenable to the meta-analysis.

3.1. Definition of NVH

There was significant variation in terminology and definitions used for NVH (Table 1), such as “microscopic haematuria”, “microhaematuria”, “dipstick haematuria”, and “non-visible haematuria”. Most studies used either a dipstick definition or a microscopy definition with differing thresholds as to what constitutes NVH. The minimum dipstick threshold used was trace and the minimum microscopy threshold was one RBC per HPF. There were differing approaches as to whether dipstick positive haematuria required confirmation with microscopy before proceeding to investigation.

A large prospective cohort with 982 NVH patients demonstrated a relatively large number of patients with urolological cancer at the lowest RBC per HPF on microscopy and suggested that any dipstick haematuria warranted a full evaluation [26]. Others agreed with this approach [27–29]. In contrast, a smaller retrospective cohort study of 368 NVH patients found no malignancy in those who tested positive for haematuria on dipstick but negative on microscopy [30].

The number of samples collected for the diagnosis of NVH also differed considerably. A retrospective cohort study of 85 NVH patients, which defined NVH as more than three RBCs per HPF, demonstrated that the first urinalysis detected 95% of patients with NVH. The addition of a second and a third urinalysis detected haematuria in the remaining patients, suggesting that a “one-off” test may be satisfactory. Of their BC diagnoses, 20% had a negative initial urinalysis with a subsequent positive urinalysis (one patient with a papillary neoplasm of low malignant potential on histology). The only renal tumour had a positive first urinalysis for NVH [31]. Large population screening studies of asymptomatic participants such as those reported by Britton et al [32] and Messing et al [33] evaluated their patients with urine dipstick tests on numerous occasions, with any participant with a single positive test being evaluated. The screening study by Britton et al [32] demonstrated that 29% of their BC diagnoses in NVH patients had a negative initial dipstick for haematuria, all of which were G1pTa tumours on histology. Furthermore, there is evidence that, overall, one positive sample is sufficient to prompt evaluation due to the intermittent nature of haematuria [32–34] in urolological malignancy, and a significant number of urolological malignancies and non-malignant conditions that require management and/or follow-up [35,36].

Most guidelines on NVH do not accept dipstick haematuria as sufficient to mandate an evaluation. The AUA [2], HTA [37], and Dutch [38] use more than three RBCs per HPF as their threshold. The Canadian guidelines use more than two RBCs per HPF [39], and the Japanese guidelines use more than five RBCs per HPF [6]. UK guidelines, however, use ≥1+ on dipstick as the cut-off for significant haematuria [40].

3.2. Diagnostic utility of imaging in patients with NVH

Multidetector computed tomography (CT) urography (CTU) is superior in clinical and practical utility to intravenous urography (IVU) for the diagnosis of urinary tract cancers, and has therefore by and large replaced it [41–43]. However, there is little consensus as to whether patients with NVH should have their upper tracts investigated with ultrasound (US) scan (US) or CTU as a first-line investigation. Whilst a technically satisfactory USS is a good diagnostic test for renal parenchymal tumours over 2 cm, there are concerns regarding its diagnostic ability for renal pelvic, ureteric, and smaller bladder tumours [44].

Table 1 – Characteristics of included studies.

<table>
<thead>
<tr>
<th>Study author</th>
<th>Year</th>
<th>Study design</th>
<th>Definition used</th>
<th>Number of NVH patients</th>
<th>Investigation(s)</th>
<th>% with BC</th>
<th>% with UTUC</th>
<th>% with KC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aguilar-Davidov et al [76]</td>
<td>2013</td>
<td>Retrospective cohort</td>
<td>&gt;3 RBCs/HPF in 2 consecutive urine samples</td>
<td>112</td>
<td>CT urography, cystoscopy</td>
<td>3.6</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ahmed et al [77]</td>
<td>2015</td>
<td>Prospective cohort</td>
<td>NS</td>
<td>55</td>
<td>USS, cystoscopy</td>
<td>7.3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Aslaksen et al [78]</td>
<td>1990</td>
<td>Cohort</td>
<td>NS</td>
<td>193</td>
<td>IVU and USS</td>
<td>NS</td>
<td>NS</td>
<td>0.5</td>
</tr>
<tr>
<td>Breitau et al [48]</td>
<td>2015</td>
<td>Retrospective cohort</td>
<td>Screening study, dipstick haematuria, initial test followed by home testing once per week for 10 wk or once per day for 10 d</td>
<td>376</td>
<td>CT urography, cystoscopy</td>
<td>NS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Britton et al [32]</td>
<td>1992</td>
<td>Prospective cohort (screening)</td>
<td>&gt;3 RBCs/HPF from two of three properly collected urine specimens</td>
<td>265</td>
<td>IVU and/or USS, cystoscopy, cytology</td>
<td>6.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carson et al [79]</td>
<td>1979</td>
<td>Retrospective cohort</td>
<td>4 grades: grade 1, 1–8 RBCs/HPF; grade 2 8–30 RBCs; grade 3, 30 to 3/4 of the field; grade 4, the entire field is packed with RBCs</td>
<td>200</td>
<td>IVU, cystoscopy, “usually” urine cytology</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cha et al [56]</td>
<td>2012</td>
<td>Cohort</td>
<td>&gt;3 RBCs/HPF</td>
<td>804</td>
<td>Upper tract imaging (not specified), cytoscopy, cytology</td>
<td>15.7</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Dikranian et al [35]</td>
<td>2005</td>
<td>Prospective cohort</td>
<td>2 RBCs/HPF</td>
<td>247</td>
<td>IVU and USS, cytology, cystoscopy and CT in selected cases</td>
<td>0</td>
<td>0</td>
<td>0.8</td>
</tr>
<tr>
<td>Edwards et al [80]</td>
<td>2006</td>
<td>Prospective cohort</td>
<td>Dipstick testing</td>
<td>1950</td>
<td>AXR and US; IVU in BC, and CT or IVU in suspected upper tract cancer; cystoscopy</td>
<td>3.7</td>
<td>0.2</td>
<td>1</td>
</tr>
<tr>
<td>Feifer et al [50]</td>
<td>2010</td>
<td>Retrospective cohort</td>
<td>3 RBCs/HPF</td>
<td>200</td>
<td>US or CT or IVU or different combinations of the 3 (full numbers in paper), cytoscopy, cytology</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Goldberg et al [81]</td>
<td>2008</td>
<td>Retrospective cohort</td>
<td>Dipstick of a clean catch midstream specimen</td>
<td>235</td>
<td>Cystoscopy, cytology</td>
<td>1.7</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Gray Sears et al [82]</td>
<td>2002</td>
<td>Prospective cohort</td>
<td>2 specimens of at least 3 RBCs per HPF on urine microscopy and was confirmed once in the office of the treating urologist</td>
<td>115</td>
<td>IVU and CTU, cytoscopy</td>
<td>NS</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Hedelin et al [83]</td>
<td>2006</td>
<td>Prospective cohort</td>
<td>Dipstick testing of sample that had been retained in the bladder for &gt;3 h; &gt;1+ considered positive</td>
<td>174</td>
<td>Cystoscopy</td>
<td>2.9</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Jaffe et al [46]</td>
<td>2001</td>
<td>Prospective cohort</td>
<td>&gt;2 RBCs/HPF</td>
<td>372</td>
<td>USS, IVU in persistent NVH and no apparent aetiology on initial assessment, cytoscopy</td>
<td>5.4</td>
<td>0.8</td>
<td>3</td>
</tr>
<tr>
<td>Khadra et al [26]</td>
<td>2000</td>
<td>Prospective cohort</td>
<td>No single definition</td>
<td>982</td>
<td>AXR and USS and IVU, cystoscopy, cytology</td>
<td>4.8</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Khan et al [30]</td>
<td>2002</td>
<td>Retrospective and prospective cohort</td>
<td>Dipstick testing</td>
<td>368</td>
<td>USS and IVU, cystoscopy, cytology</td>
<td>1.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lang et al [47]</td>
<td>2002</td>
<td>Prospective cohort</td>
<td>Defined at 1 institution as a positive dipstick test and at the other 3 as &gt;5 RBCs/HPF</td>
<td>350</td>
<td>CT urogram, cystoscopy, cytology</td>
<td>1.4</td>
<td>1.4</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 1 (Continued)

<table>
<thead>
<tr>
<th>Study author</th>
<th>Year</th>
<th>Study design</th>
<th>Definition used</th>
<th>Number of NVH patients</th>
<th>Investigation(s)</th>
<th>% with BC</th>
<th>% with UTUC</th>
<th>% with KC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisanti et al [49]</td>
<td>2014</td>
<td>Retrospective cohort</td>
<td>&gt;1 urinalysis with 3–50 RBCs/HPF</td>
<td>442</td>
<td>CT urogram, cystoscopy</td>
<td>0.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Loo et al [55]</td>
<td>2013</td>
<td>Prospective cohort</td>
<td>Urinalysis definition—details NS</td>
<td>4414</td>
<td>CT urogram or USS or IVU or combinations, cystoscopy</td>
<td>2.3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Lotan et al [84]</td>
<td>2014</td>
<td>Prospective cohort</td>
<td>&gt;3 RBCs/HPF</td>
<td>200</td>
<td>Upper tract imaging (not specified), cystoscopy, cytology</td>
<td>2.5</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Lynch et al [85]</td>
<td>1994</td>
<td>Cohort</td>
<td>NS</td>
<td>181</td>
<td>IVU (and USS “if indicated”), cystoscopy, cytology</td>
<td>2.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Messing et al [33]</td>
<td>1989</td>
<td>Prospective cohort (screening)</td>
<td>Screening study: dipstick testing; &gt;trace considered positive; patients tested urine daily for 5 d and weekly thereafter for 1 yr; instructed not to test first void of day or urinations after sexual or extreme physical activity; &gt;1 positive result led to evaluation</td>
<td>31</td>
<td>IVU, cystoscopy, cytology, other tests if appropriate</td>
<td>16.1</td>
<td>0</td>
<td>9.7</td>
</tr>
<tr>
<td>Messing et al [34]</td>
<td>1992</td>
<td>Prospective cohort (screening)</td>
<td>Screening study: dipstick testing; &gt;trace considered positive; patients tested urine daily for 14 consecutive days; instructed not to test first void of day or urinations after sexual or extreme physical activity; &gt;1 positive result led to evaluation</td>
<td>192</td>
<td>IVU (USS and retrograde in contrast allergy or creatinine &gt;2 mg/dl, cystoscopy, cytology</td>
<td>4.7</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Mishra et al [86]</td>
<td>2004</td>
<td>Retrospective cohort</td>
<td>NS</td>
<td>451</td>
<td>USS and IVU, cystoscopy, cytology</td>
<td>2.9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mishrki et al [53]</td>
<td>2008</td>
<td>Prospective cohort</td>
<td>&gt;1+ on &gt;2 occasions 1 wk apart</td>
<td>292</td>
<td>IVU ± USS, cystoscopy, cytology</td>
<td>4.1</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>Miyanaga et al [87]</td>
<td>1999</td>
<td>Prospective cohort</td>
<td>NS</td>
<td>309</td>
<td>USS or IVU (numbers not specified and unclear how many had both), cystoscopy, cytology</td>
<td>4.9</td>
<td>1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Murakami et al [36]</td>
<td>1990</td>
<td>Prospective cohort</td>
<td>&gt;5 RBCs/HPF on &gt;1 of 3 urinalyses and urine protein &lt;1+ on dipstick and no history of urological disorders</td>
<td>1034</td>
<td>USS and IVU (excluded when glomerulopathic condition suspected from urinalysis), CT in selected cases, cystoscopy, cytology</td>
<td>1.3</td>
<td>0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Ng et al [88]</td>
<td>2012</td>
<td>Cohort</td>
<td>&gt;3 RBCs/HPF</td>
<td>245</td>
<td>USS or IVU (numbers not specified), cystoscopy</td>
<td>1.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ooi et al [89]</td>
<td>2011</td>
<td>Prospective cohort</td>
<td>NS</td>
<td>204</td>
<td>CT urogram preferred method in NVH with risk factors, preferred method for without risk factors not specified (numbers not specified), cystoscopy</td>
<td>2.9</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Study author</td>
<td>Year</td>
<td>Study design</td>
<td>Definition used</td>
<td>Number of NVH patients</td>
<td>Investigation(s)</td>
<td>% with BC</td>
<td>% with UTUC</td>
<td>% with KC</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------</td>
<td>--------------</td>
<td>-----------------------------------------------------</td>
<td>------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Rosser et al [90]</td>
<td>2011</td>
<td>Retrospective cohort</td>
<td>&gt;3 RBCs/HPF</td>
<td>85</td>
<td>CT urogram (76%) or IVU or in patients contraindicated in MRI or USS with retrograde cystoscopy, cytology</td>
<td>5.8</td>
<td>0</td>
<td>1.2</td>
</tr>
<tr>
<td>Sagnak et al [57]</td>
<td>2011</td>
<td>Prospective cohort</td>
<td>&gt;3 RBCs/HPF on &gt;2 different occasions, with at least 2 wk in between</td>
<td>164</td>
<td>USS (and IVU or CTU in patients with positive NMP22BC and atypical cytology with absence of lesion and negative biopsy), cystoscopy, cytology</td>
<td>1.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Steiner et al [91]</td>
<td>2008</td>
<td>Prospective cohort</td>
<td>Dipstick testing of midstream urine from 2nd void of the day</td>
<td>57</td>
<td>CT, cystoscopy, cytology</td>
<td>1.8</td>
<td>3.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Sudakoff et al [92]</td>
<td>2008</td>
<td>Retrospective cohort</td>
<td>&gt;2 RBCs/HPF</td>
<td>180</td>
<td>CT urogram, cystoscopy, cytology (not in all patients)</td>
<td>2.2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sugimura et al [93]</td>
<td>2001</td>
<td>Retrospective cohort</td>
<td>&gt;2 RBCs/HPF on &gt;1 of &gt;2 urine specimens collected 1–2 wk apart</td>
<td>823</td>
<td>IVU (754/823) or USS (359/823) or CT (105/823) or combinations (not specified), cystoscopy, cytology (738/823)</td>
<td>1.7</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Sultana et al [28]</td>
<td>1996</td>
<td>Prospective cohort</td>
<td>Any dipstick positive for blood where blood was not visible to the naked eye</td>
<td>381</td>
<td>IVU (in those with bladder tumours on cystoscopy) or AXR and USS (in those with no bladder tumour), cystoscopy, cytology</td>
<td>2.9</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Suzuki et al [29]</td>
<td>2000</td>
<td>Retrospective cohort</td>
<td>Positive reaction on a dipstick for blood</td>
<td>263</td>
<td>IVU and USS (CT “in cases of necessity”), cystoscopy, cytology</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tan et al [73,74]</td>
<td>2018</td>
<td>Prospective cohort</td>
<td>&gt;1 RBC on urine dipstick on &gt;2 occasions</td>
<td>1249</td>
<td>Upper tract imaging (USS, CTKUB, or CTU) and cystoscopy</td>
<td>2.6</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Turkeri et al [51]</td>
<td>2014</td>
<td>Prospective cohort</td>
<td>NS</td>
<td>303</td>
<td>USS or CT or MRI (or combinations—not specified) or other (not specified), cystoscopy, cytology</td>
<td>5.0</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Viswanath et al [94]</td>
<td>2008</td>
<td>Prospective cohort</td>
<td>NS</td>
<td>340</td>
<td>USS, cystoscopy, cytology</td>
<td>5</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>Yasumasu et al [95]</td>
<td>1994</td>
<td>Retrospective cohort</td>
<td>Threshold not shown; midstream urine samples examined for haematuria; cases in which haematuria not detectable after repeated urinalysis were excluded</td>
<td>355</td>
<td>IVU (310/355) or USS (288/355) or both (numbers not specified), cystoscopy, cytology</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AXR = abdominal x-ray; BC = bladder cancer; CT = computed tomography; CTKUB = CT of kidneys, ureters, and bladder; CTU = CT urography; HPF = high-power field; IVU = intravenous urography; KC = kidney cancer; NS = not significant; NVH = non-visible haematuria; RBC = red blood cell; US = ultrasound; USS = ultrasound scan; UTUC = upper tract urothelial carcinoma.
Table 2 – Included studies with follow-up.

<table>
<thead>
<tr>
<th>Study author</th>
<th>Year</th>
<th>Study design</th>
<th>Number of NVH patients</th>
<th>Investigation(s)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carson et al [79]</td>
<td>1979</td>
<td>Retrospective cohort</td>
<td>200</td>
<td>IVU, cystoscopy, “usually” urine cytology</td>
<td>&gt;24 mo</td>
</tr>
<tr>
<td>Khadra et al [26]</td>
<td>2000</td>
<td>Prospective cohort</td>
<td>982</td>
<td>AXR and USS and IVU, cystoscopy, cytology</td>
<td>&gt;2.5 yr</td>
</tr>
<tr>
<td>Mishraki et al [53]</td>
<td>2008</td>
<td>Prospective cohort</td>
<td>292</td>
<td>IVU = USS, cystoscopy, cytology</td>
<td>13 yr</td>
</tr>
<tr>
<td>Murakami et al [36]</td>
<td>1950</td>
<td>Prospective cohort</td>
<td>1034</td>
<td>USS and IVU (excluded when glomerulopathic condition suspected from urinalysis), CT in selected cases, cystoscopy, cytology</td>
<td>&gt;1 yr</td>
</tr>
<tr>
<td>Suzuki et al [29]</td>
<td>2000</td>
<td>Retrospective cohort</td>
<td>263</td>
<td>IVU and USS (CT “in cases of necessity”), cystoscopy, cytology</td>
<td>&gt;2 yr</td>
</tr>
<tr>
<td>Yasumasu et al [95]</td>
<td>1994</td>
<td>Retrospective cohort</td>
<td>355</td>
<td>IVU (310/355) or USS (288/355) or both (numbers not specified), cystoscopy, cytology</td>
<td>&gt;1 yr</td>
</tr>
</tbody>
</table>

AXR = abdominal x-ray; CT = computed tomography; IVU = intravenous urography; NVH = non-visible haematuria; USS = ultrasound scan.

A recent report (from the DETECT I evaluation of the novel UroMark) detailed superior diagnostic accuracy for CTU compared with USS in patients with NVH and VU [45]. The positive predictive values (PPVs) for CTU versus USS were 72% versus 50% for UTUC, and 94.6% versus 41.4% for KC. The sensitivity of USS for UTUC was only 14.3% (vs 85.7% for KC). The specificity for CT versus USS was 99.6% versus 100% for UTUC and 99.9% versus 99.2% for KC. The authors were unable to determine the sensitivities and negative predictive values for CTU, as patients with a normal CTU result were discharged back to primary care.

In a prospective cohort study of 372 NVH patients, 21% of the upper tract tumours were diagnosed using IVU and not seen on US. It is worth noting that tumours diagnosed with IVU but missed by USS were low-grade tumours that did not produce any collecting system dilatation [46]. Similarly, in a prospective cohort study with 982 patients with NVH, a quarter of upper tract cancers were diagnosed using IVU but not detected on USS [26]. In contrast, a large prospective cohort of 1034 NVH patients demonstrated that USS was able to diagnose all upper tract cancers, with no further tumours found during follow-up of >3 yr [36].

With regard to the diagnostic utility of CT, in a multicentre prospective cohort of 350 NVH patients with undetermined cause, all upper tract renal masses were diagnosed by CTU (one RCC was interpreted as being an oncocytoma on CTU) with no further masses diagnosed on at least 6-mo follow-up [47]. In a retrospective analysis of 376 NVH patients who had CTU, there were no new upper tract cancer diagnoses and no false negative occurrences within 3 yr of follow-up in case of negative primary CTU [48].

Unenhanced CT in patients with asymptomatic NVH younger than 50 yr has been proposed as an imaging option to reduce the risks associated with CTU. A retrospective cohort of 442 NVH patients demonstrated no further diagnostic benefit of CTU over unenhanced CT [49].

3.3. Detection of bladder and upper tract cancer

Authors predominantly evaluated NVH using cystoscopy and US, IVU, or CTU. There were differences with regard to their study populations, patient risk factors, type of NVH (asymptomatic vs symptomatic), whether the cancers were reported to have been confirmed with histology in the paper, region of the world, and whether studies excluded patients with UTI or not. A subgroup analysis was performed primarily by gender (Fig. 1–3). Subgroup analysis was also performed for: the type of NVH i.e. presence of symptoms, whether studies excluded patients with UTI, whether cancers were reported to have been confirmed by histology and by region of the world (Supplementary Fig. 2–4).

The detection rate of BC ranged from 0% to 16% in 37 studies. The pooled detection rate of BC in patients referred for NVH evaluations was 3.2% (95% CI 2.3–4.1%, I² = 90%, p < 0.001; Fig. 1). The pooled detection rate was higher in studies evaluating males only (5.3%, 95% CI 2.6–8.8%, I² = 61%, p = 0.054) with markedly reduced heterogeneity. The pooled detection rate in asymptomatic patients was 3.1% (95% CI 1.7–4.9%, I² = 94%, p < 0.001; Supplementary Fig. 2A). In total, 10 studies specifically stated that they excluded persons with active UTI. The pooled BC detection rate in these studies alone was 2.1% (95% CI 0.93–3.7%, I² = 84%, p < 0.001; Supplementary Fig. 2B).

The detection rate of UTUC ranged from 0% to 3.5% in 30 studies. The pooled UTUC detection rate in NVH evaluations was 0.042% (95% CI 0.0–0.15%, I² = 39%, p = 0.02; Fig. 2). There were no UTUCs in the studies with male patients only (0%, 95% CI 0–0.15). The pooled detection rate in studies that evaluated asymptomatic NVH patients only was 0.054% (95% CI 0–0.23%, I² = 35%, p = 0.080; Supplementary Fig. 3A). In total, eight studies specifically stated that they excluded persons with active UTI. The pooled UTUC detection rate in these studies alone was 0.053% (95% CI 0–0.32%, I² = 38%, p = 0.13; Supplementary Fig. 3B).

The detection rate of KC ranged from 0% to 9.7% in 29 studies. The pooled KC detection rate in NVH evaluation was 0.28% (95% CI 0.10–0.52%, I² = 62%, p < 0.001; Fig. 3). The pooled KC detection rate in studies that evaluated males only (three studies) was 0.86% (95% CI 0–5.0%). The pooled detection rate in studies evaluating asymptomatic patients only was 0.35% (95% CI 0.057–0.81%, I² = 69%, p < 0.001; Supplementary Fig. 4A). In total, seven studies specifically stated that they excluded persons with active UTI. The pooled KC detection rate in
these studies alone was 0.52% (95% CI 0.026–1.41%, $I^2 = 76\%$, $p < 0.001$; Supplementary Fig. 4B).

It is important to note that the substantial heterogeneity present in the above meta-analyses limits the conclusions that can be drawn.

### 3.4. The role of urine cytology

Whilst urine cytology has been recommended and is widely used in BC surveillance, there is no consensus among guideline bodies regarding the inclusion of urine cytology for the diagnosis of new UC during NVH workup. In total, 12 studies included data on the sensitivity and/or specificity of urine cytology for UC diagnosis in individuals evaluated for NVH, and nine studies had data enabling calculation of both sensitivity and specificity. In studies that had data on the number of patients with cellular atypia or inconclusive cytology, for the purposes of consistency, atypia was considered negative and inconclusive cytology was excluded. One study [50] evaluated low risk patients only, and one study only included BCs and so were excluded from the meta-analysis [51].

The sensitivity of urine cytology for UC in an NVH patient cohort that had undergone evaluation ranged from 0% to 59%, and specificity ranged from 97% to 100%. The pooled sensitivity in seven studies was 20% (95% CI 2.5–72%). The pooled specificity in seven studies was 99.8% (95% CI 94–100%; Fig. 4). When including only studies that reported on histologically confirmed tumours, the pooled sensitivity and specificity were, respectively, 16% (95% CI 0.9–79%) and 99.6% (95% CI 95–100%) in five studies. The large CIs for sensitivity, however, make these results difficult to interpret.

In a large prospective cohort screening study including 265 NVH patients, 59% of the UC diagnoses had a positive urine cytology result all of which were G2 tumours. Furthermore, of patients with abnormal urine cytology who did not have a cancer diagnoses in their initial workup, 10% (one patient) were found to have a UTUC on follow-up [32].
With the widespread adoption of CTU, the role of urine cytology in the primary evaluation of haematuria including NVH has diminished. However, urine cytology or urothelial urine markers may have a role in the future before cystoscopy or prior to referral to a haematuria clinic.

### 3.5. Long-term follow-up

Three studies included long-term follow-up data on NVH patients with a negative initial evaluation. There were differences in the evaluation protocols that the patients underwent for their NVH.

The follow-up time ranged from 1 to 14 yr. A subsequent diagnosis of cancer occurred in <1% of NVH patients with a negative initial evaluation. The longest follow-up of 14 yr [52] was reported by a large prospective screening study following up 234 NVH patients, who were negative for urological cancer on their initial evaluation and demonstrated 0.85% (2/234) incidence of BC at 6.7 and 11.4 yr, respectively. Another prospective cohort study of 213 NVH patients with initially negative haematuria investigations had no diagnosis of cancer during 13 yr of follow-up. One patient re-presented 2 yr after discharge from clinic with visible haematuria, and the re-evaluation revealed BC emphasising the importance of re-evaluation of patients who develop new concerning signs or symptoms associated with a risk of urinary tract cancers such as VH [53]. In clinical practice, it is not uncommon to investigate persons who re-present after 12 mo with recurrent signs. The recent International Bladder Cancer Network consensus on asymptomatic NVH advised that re-evaluation of patients with unremarkable initial investigations should be performed only in high-risk patients or if new symptoms occur (eg, VH, lower urinary tract symptoms [LUTS], flank pain, and worsening of renal function) [12].

### 3.6. Factors associated with increased likelihood with BC and upper tract cancers

The predominant factors discussed in the included papers were age, sex, and smoking status. Overall, 16 papers specifically stated the age range of the NVH patients,
### Table 1

<table>
<thead>
<tr>
<th>Study author</th>
<th>Year</th>
<th>Symptoms</th>
<th>Country</th>
<th>Weight</th>
<th>ES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aslaksen</td>
<td>1990</td>
<td>Not specified</td>
<td>Norway</td>
<td>2.82</td>
<td>0.005 (0.001, 0.029)</td>
</tr>
<tr>
<td>Bretlau</td>
<td>2015</td>
<td>Mixed</td>
<td>Denmark</td>
<td>3.87</td>
<td>0.000 (0.000, 0.010)</td>
</tr>
<tr>
<td>Carson</td>
<td>1979</td>
<td>Asymptomatic only</td>
<td>USA</td>
<td>2.87</td>
<td>0.000 (0.000, 0.019)</td>
</tr>
<tr>
<td>Dikranian</td>
<td>2005</td>
<td>Asymptomatic only</td>
<td>USA</td>
<td>3.21</td>
<td>0.008 (0.002, 0.029)</td>
</tr>
<tr>
<td>Edwards</td>
<td>2006</td>
<td>Not specified</td>
<td>UK</td>
<td>5.69</td>
<td>0.010 (0.006, 0.015)</td>
</tr>
<tr>
<td>Feiler</td>
<td>2010</td>
<td>Asymptomatic only</td>
<td>Canada</td>
<td>2.87</td>
<td>0.000 (0.000, 0.019)</td>
</tr>
<tr>
<td>Gray Sears</td>
<td>2002</td>
<td>Asymptomatic only</td>
<td>USA &amp; Canada</td>
<td>2.04</td>
<td>0.009 (0.002, 0.048)</td>
</tr>
<tr>
<td>Jaffe</td>
<td>2001</td>
<td>Asymptomatic only</td>
<td>USA</td>
<td>3.85</td>
<td>0.030 (0.017, 0.052)</td>
</tr>
<tr>
<td>Khadra</td>
<td>2000</td>
<td>Mixed</td>
<td>UK</td>
<td>5.12</td>
<td>0.003 (0.001, 0.009)</td>
</tr>
<tr>
<td>Khan</td>
<td>2002</td>
<td>Not specified</td>
<td>UK</td>
<td>3.76</td>
<td>0.002 (0.000, 0.010)</td>
</tr>
<tr>
<td>Lang</td>
<td>2002</td>
<td>Asymptomatic only</td>
<td>USA and Austria</td>
<td>3.76</td>
<td>0.020 (0.010, 0.041)</td>
</tr>
<tr>
<td>Lisanti</td>
<td>2014</td>
<td>Asymptomatic only</td>
<td>USA</td>
<td>4.11</td>
<td>0.000 (0.000, 0.009)</td>
</tr>
<tr>
<td>Lynch</td>
<td>1994</td>
<td>Mixed</td>
<td>UK</td>
<td>2.72</td>
<td>0.000 (0.000, 0.021)</td>
</tr>
<tr>
<td>Mishra</td>
<td>2009</td>
<td>Not specified</td>
<td>UK</td>
<td>4.14</td>
<td>0.000 (0.000, 0.008)</td>
</tr>
<tr>
<td>Mishriki</td>
<td>2008</td>
<td>Asymptomatic only</td>
<td>UK</td>
<td>3.48</td>
<td>0.007 (0.002, 0.025)</td>
</tr>
<tr>
<td>Murakami</td>
<td>1990</td>
<td>Asymptomatic only</td>
<td>Japan</td>
<td>5.17</td>
<td>0.007 (0.003, 0.014)</td>
</tr>
<tr>
<td>Ng</td>
<td>2012</td>
<td>Mixed</td>
<td>Malaysia</td>
<td>3.20</td>
<td>0.000 (0.000, 0.015)</td>
</tr>
<tr>
<td>Rosser</td>
<td>2011</td>
<td>Not specified</td>
<td>USA</td>
<td>1.65</td>
<td>0.012 (0.002, 0.064)</td>
</tr>
<tr>
<td>Sagnak</td>
<td>2011</td>
<td>Asymptomatic only</td>
<td>Turkey</td>
<td>2.56</td>
<td>0.000 (0.000, 0.023)</td>
</tr>
<tr>
<td>Steiner</td>
<td>2008</td>
<td>Asymptomatic only</td>
<td>Austria</td>
<td>2.56</td>
<td>0.018 (0.003, 0.093)</td>
</tr>
<tr>
<td>Sugimura</td>
<td>2001</td>
<td>Asymptomatic only</td>
<td>Japan</td>
<td>4.93</td>
<td>0.002 (0.001, 0.009)</td>
</tr>
<tr>
<td>Sultana</td>
<td>1996</td>
<td>Mixed</td>
<td>UK</td>
<td>3.89</td>
<td>0.008 (0.003, 0.023)</td>
</tr>
<tr>
<td>Suzuki</td>
<td>2000</td>
<td>Asymptomatic only</td>
<td>Japan</td>
<td>3.11</td>
<td>0.000 (0.000, 0.014)</td>
</tr>
<tr>
<td>Tan</td>
<td>2018</td>
<td>Not specified</td>
<td>UK</td>
<td>5.35</td>
<td>0.005 (0.002, 0.010)</td>
</tr>
<tr>
<td>Viswanath</td>
<td>2008</td>
<td>Not specified</td>
<td>UK</td>
<td>3.71</td>
<td>0.006 (0.002, 0.021)</td>
</tr>
<tr>
<td>Yasumatsu</td>
<td>1994</td>
<td>Asymptomatic only</td>
<td>Japan</td>
<td>3.78</td>
<td>0.000 (0.000, 0.011)</td>
</tr>
<tr>
<td>Subtotal (I² = 60.605%, p = 0.000)</td>
<td></td>
<td></td>
<td></td>
<td>93.15</td>
<td>0.003 (0.001, 0.005)</td>
</tr>
</tbody>
</table>

#### Subtotal (Males only)

<table>
<thead>
<tr>
<th>Study author</th>
<th>Year</th>
<th>Symptoms</th>
<th>Country</th>
<th>Weight</th>
<th>ES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Britton</td>
<td>1992</td>
<td>Asymptomatic only</td>
<td>UK</td>
<td>3.32</td>
<td>0.000 (0.000, 0.014)</td>
</tr>
<tr>
<td>Messing</td>
<td>1989</td>
<td>Asymptomatic only</td>
<td>USA</td>
<td>0.73</td>
<td>0.097 (0.033, 0.249)</td>
</tr>
<tr>
<td>Messing</td>
<td>1992</td>
<td>Asymptomatic only</td>
<td>USA</td>
<td>2.81</td>
<td>0.005 (0.001, 0.029)</td>
</tr>
<tr>
<td>Subtotal (I² = 6.85%, p = .)</td>
<td></td>
<td></td>
<td></td>
<td>6.85</td>
<td>0.009 (0.000, 0.050)</td>
</tr>
</tbody>
</table>

#### Overall (I² = 62.288%, p = 0.000)

<table>
<thead>
<tr>
<th>Study author</th>
<th>Year</th>
<th>Symptoms</th>
<th>Country</th>
<th>Weight</th>
<th>ES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Notes

- **ES** = effect size; **KC** = kidney cancer; **NVH** = non-visible haematuria.

---

**Fig. 3** – Forest plot of study-specific and pooled KC detection (%) with 95% confidence interval (CI) in patients evaluated for NVH (stratified by gender). The studies are listed in Table 1. ES = effect size; KC = kidney cancer; NVH = non-visible haematuria.
specifically of those in whom malignancies were diagnosed. Increasing age, male gender, and smoking are well-established risk factors for BC [54], and therefore a higher pretest probability in these populations increases the PPV of NVH.

3.6.1. Age
With regard to haematuria cohorts, age ≥50 yr was independently associated with a higher odds of urinary tract cancer diagnosis on multivariable analysis in a large prospective cohort including a total of 4414 patients (80% with NVH; odds ratio [OR] 16.3, 95% CI 2.22–119, and OR 13.7, 95% CI 1.86–101 in the test and validation cohorts, respectively) [55]. A multicentre study evaluating 1182 consecutive patients with asymptomatic haematuria (68% with NVH and 32% with VH) demonstrated increased risks associated with age (OR 1.03, p < 0.0001) [56].

In contrast, a prospective cohort specifically evaluated a low-risk population of 164 NVH patients under the age of 40 yr, and identified two G1pTa (12%) bladder tumours and no upper tract tumours [57].

The DETECT 1 study demonstrated the absence of any urinary tract cancers below the age of 40 yr in individuals evaluated for NVH. However, 4/38 (11%) urinary tract cancers were found in patients under the age of 60 yr. Therefore, the application of the NICE-defined age threshold would have failed to detect 11% of cancers in NVH patients, but the application of the AUA threshold would detect all cancers. Three-fourths (75%) of the urinary tract cancers under the age of 60 yr were high- or intermediate-risk cancers, one of which was a G3pT1 cancer [20].

3.6.2. Gender
The worldwide age-standardised incidence rates (per 100,000 person/yr) for BC are 9.0 for men and 2.2 for women, and for KC are 6.0 for men and 3.1 for women [58]. Male sex was shown to be a significant predictor of urological cancer in a cohort of 4414 individuals (80% with NVH) in a multivariable analysis (OR 2.50, 95% CI 1.22–5.10 and OR 2.93, 95% CI 1.41–6.09, in the test and the validation cohort, respectively) [55].

3.6.3. Smoking
A large meta-analysis including 83 studies reported a pooled relative risk of 2.58 (95% CI 2.37–2.80) for all smokers, 3.47 (95% CI 3.07–3.91) for current smokers, and 2.04 (95% CI 1.85–2.25) for former smokers [59]. A multicentre study evaluating 1182 consecutive patients with asymptomatic haematuria (68% with NVH and 32% with VH) demonstrated increased risks associated with past/current smoking history (3.72, p < 0.001) [56]. A multivariable analysis in a study evaluating 4414 individuals (80% with NVH) demonstrated ever use of tobacco to be an independent predictor of cancer detection, and this did not differ by cohort (OR 1.88, 95% CI 1.01–3.53 in the validation cohort, and OR 1.48, 95% CI 0.78–2.81 in the test cohort) [55].

3.7. Factors affecting referral for investigation
There is concern regarding equity of evaluation for individuals with NVH. A primary care questionnaire survey study including 786 American practitioners demonstrated that only 36% would refer patients with NVH for further evaluation compared with 69% with VH [60]. Variations in referral and evaluation are demonstrated in a variety of studies. Loo et al. [55] reported 3,222,699 urinalyses performed in 1,117,542 patients in the Kaiser Permanente Organization. Of these patients, 456,674 had NVH and 389,207 had two positive urinalysis results meeting the threshold for evaluation. During this period, only 7,778 patients were seen by a urologist for evaluation of NVH and 4,721 underwent cystoscopy. A study using electronic medical records of patients with more than five RBCs per HPF identified 449 patients, of whom 85% had NVH. Evaluation for the source of haematuria was limited and included imaging (35.6%), cystoscopy (9%), and cytology (7.3%) [61]. Only 36% of men and 8% of women were referred to a urologist. Male gender, ethnicity, and VH (vs NVH) haematuria were associated with a higher rate of urological referral. Advanced age, smoking, provider practice type, and presence of urinary symptoms were not associated with an increased rate of urological referral [61]. Only 12.8% of high-risk males with >10 yr of smoking or environmental exposure who presented with NVH were referred for further evaluation in a study by Elias et al [62].

A retrospective population-based study demonstrated delays from the onset of NVH to the diagnosis in both sexes, but this delay was longer in females. Approximately one in six women experienced a delay of over 6 mo from the onset of haematuria (NVH and VH) to diagnosis compared with...
one in seven men [63]. Moreover, in a large cohort (34,000) of older BC patients (≥66 yr), it was shown that woman were more likely to have a delay in the time to referral and were less likely to undergo haematuria investigations [64]. This was thought to be due to a higher likelihood of exploring other diagnoses prior to referral of such UTI or potential gynaecological causes of bleeding. A smaller cohort of 305 patients did not demonstrate these sex disparities, but suggested that anticoagulated patients were more likely to undergo faster imaging [65].

3.8. Discussion

We present the largest contemporary systematic review evaluating NVH for the diagnosis of BC and upper tract cancers. There are many important findings in this review. First, the risk of urological malignancies is low among patients with NVH. The strongest risk factors for these malignancies are increasing age, male sex, and smoking status. Second, most patients with NVH are not adequately evaluated. Third, there is a large variation in the criteria for NVH used in the literature and subsequently adopted by guidelines. This leads to uncertainty regarding the need for evaluation of different populations. Moreover, this makes comparisons difficult.

There is a lack of consensus regarding the need to confirm haematuria seen on urine dipstick test with microscopy. Urine dipstick is known to be prone to false positives for cancer due to ejaculation, dehydration, exercise, menstrual blood, and UTI among others. However, it is evident from the literature that urological cancers can produce very small volumes of haematuria seen on dipstick and microscopy. Cancer-related haematuria can also be intermittent. Furthermore, urine microscopy has false negative tests due to RBC lysis caused by delays in processing urine. It has been demonstrated that RBCs degrade by 35% at 72 h. This is particularly relevant in primary care where samples sent for microscopy may not be processed for days. Requirement of confirmation of positive dipstick haematuria with microscopy prior to urological evaluation, therefore, risks missing clinically significant urological cancers.

Advancing age is associated with a higher likelihood of diagnosing BC and upper tract cancers in patients with NVH. This is related to the higher incidence of cancers in these populations and hence a higher pretest probability that increases the PPV of NVH. It is important to use this to aid in the decision of investigation for the presence of urological malignancy, particularly the use of the lower age threshold of 40 yr, below which the risk of finding a urinary tract cancer is 1.2% in a prospective cohort of 164 NVH patients [57] and 0% in a prospective study of 1249 NVH patients [20]. It is worth noting that the latter study also demonstrated that 10.5% of cancers diagnosed in NVH patients were found in those under the age of 60 yr and three-quarters of these cancers were of intermediate or high risk.

Interestingly, most guidelines do not take into consideration other risk factors such as sex and smoking status, as well as intensity, into their recommendations. It is well known that male sex, age, and tobacco exposure are significant risk factors for urological malignancies, specifically for BC and UTUC [54,66]. Based on the lower rates in low-risk women, the American College of Obstetricians and Gynecologists and the American Urogynecologic Society recommend that asymptomatic, low-risk, never-smoking women aged 35–50 yr undergo evaluation only if they have >25 RBCs per HPF [67]. Other guidelines use ages between 35 and 50 yr as a cut-off, but this is much lower than the mean age for BC diagnosis [12].

This review presents a contemporary systematic review on the use of NVH for the diagnosis of BC and upper tract cancers in individuals undergoing urological evaluation, and stratified by sex and the presence of symptoms, amongst other factors. A summary of recommendations is presented in Fig. 5. NICE recommends using a 3% PPV threshold value for symptoms that warrant investigation or referral. A UK-based study recently showed that 85% of patients would want referral for the evaluation of a symptom associated with a 1% risk of cancer, even if invasive testing such as colonoscopy for bowel cancer is required [68]. It is evident that NVH is an important indicator of urological cancers. This study is important for future screening studies evaluating the potential improvement in outcomes of patients with BC and upper tract cancers. The widespread adoption of screening has suffered from low prevalence rates despite convincing evidence from earlier screening studies [69]. Identification of high-risk groups such as smokers, older age groups, and males may increase yield and cost effectiveness.

USS and CTU are two commonly used modalities to image the upper tracts in NVH patients. Whilst USS has been shown to be an efficient upper tract imaging modality tool,

- Patients with dipstick positive haematuria aged ≥40 yr, who have had potential precipitating causes excluded (e.g., UTI), should undergo an evaluation.
- Evaluation should include cystoscopy and upper tract imaging in the form of ultrasound or CT urogram.
- Ultrasound is the most cost-effective and widely available imaging modality. CT urogram does however have a superior diagnostic accuracy for detecting upper tract tumours.
- At present, urine cytology adds limited benefit to evaluation of patients with NVH.
- Re-evaluation of patients with unremarkable initial investigations should be performed in high-risk patients or if new symptoms occur (e.g, visible haematuria, LUTS, flank pain and worsening of renal function).

Fig. 5 – Summary of recommendations. CT = computed tomography; LUTS = lower urinary tract symptoms; NVH = non-visible haematuria; UTI = urinary tract infection.
there is a risk of missing upper tract tumours, particularly small urothelial and renal tumours that do not produce collecting system dilatation. Therefore, USS is to be considered inferior in diagnostic performance to CTU for the diagnosis of urinary tract tumours. However, the risk of UTUC is low in patients with NVH, which is reflected in the result of this meta-analysis. A recent decision-analytic, model-based, cost-effectiveness analysis using inputs from the medical literature demonstrated that the combination of renal US with cystoscopy is the most cost-effective strategy for the initial evaluation of asymptomatic NVH. Replacement of US with CT led to the detection of just one additional cancer at an incremental cost per cancer detected of €6 480 484 [13]. In addition, the radiation risk from CTU in the evaluation of asymptomatic NVH patients was highlighted in a recent study that utilised a risk model. The study reported that CT for asymptomatic NVH may be associated with a small but significant risk of secondary malignancy relative to the additional diagnostic benefit offered. Furthermore, US has undoubted added advantages in terms of its widespread availability.

The majority of studies utilised urine cytology as an adjunct to cystoscopy and CTU in the evaluation of NVH patients. The sensitivities and specificities in the included studies show poor sensitivity and high specificity, particularly for higher-grade tumours [70,71]. However, the CIs for the meta-analytic pooled estimate for sensitivity were wide, limiting the conclusions that can be drawn from the low pooled meta-analytic estimate of 20%. Furthermore, biomarkers (urine and serum) have been evaluated to bridge the gap, but none has EAU/NICE approval outside of trials to date [72]. Recent data from the DETECT 1 study (mixed VH and NVH cohort of patients) showed that most positive cytology results were false positives, resulting in unnecessary investigations [73].

We have shown, from the limited number of studies with long-term follow-up data, that the risk of subsequently developing BC or upper tract cancers in patients who had negative evaluations for NVH and are asymptomatic is very low (<1%). However, it is imperative that patients are advised to re-present to health services should they develop concerning symptoms and signs such as VH.

There is increasing interest in using a nomogram approach to guide the selection of patients with haematuria for evaluation. A recent study incorporated patient age, gender, type of haematuria, and smoking history into a haematuria cancer risk score to improve selection for the investigation of haematuria. The study demonstrated that a risk score approach identified significantly more urinary tract cancers (11.4%), which would otherwise have been missed if NICE guidelines were applied, and reduced the number of patients subjected to investigations compared with AUA guidelines [74].

Comparable data on definitions of NVH and diagnostic accuracy of imaging modalities in NVH were limited. Therefore, a qualitative synthesis and narrative review was performed, but a meta-analysis of these domains was not performed.

There was variability in the diagnostic protocols that different centres used to evaluate patients with NVH in terms of different thresholds for warranting evaluation including whether patients with UTIs were excluded and choice of imaging (ie, CTU vs USS/IVU). This was reflected in the substantial levels of heterogeneity in the meta-analysis. The reported maximum detection rates of BC, UTUC, and KC reached 16%, 3.5%, and 9.7%, respectively, which were substantially higher than the pooled detection rates of 3.2%, 0.042%, and 0.28%, respectively. This likely reflects the variability in methodology and patient cohorts between studies. Screening studies by Britton et al [11,32] and Messing et al [17,33,34] evaluated male patients based on an initial dipstick haematuria test followed by regular testing, and investigated those with a single positive result thereafter, which may explain the higher BC detection rates of 6.4% for Britton et al’s and 16% and 4.7% for the Messing et al’s studies. The substantial levels of heterogeneity severely limit the potential utility of the meta-analytic pooled estimates of detection rates of BC, UTUC, and KC in NVH patients.

To evaluate other potential sources of bias, we stratified the analysis by gender, presence of symptoms, exclusion of patients with active UTI, reported histological confirmation of tumours, and region of the world. However, we were not able to stratify by ethnicity due to absence of data. The heterogeneity was markedly reduced for BC detection rates in NVH patients when stratifying by gender.

The QUADAS-2 risk of bias assessment for studies evaluating the diagnostic accuracy of urine cytology for UC in NVH patients demonstrated unclear and/or high risks of bias for the included studies with respect to the various parameters. There were unclear risks of bias for most studies with respect to the use of an index test and a reference standard, and for all studies with respect to flow and timing. Five studies demonstrated high risks of bias with respect to applicability concerns (Supplementary Fig. 5). In addition, the CIs for the meta-analytic pooled estimate for sensitivity ranged substantially from 2.5% to 72%, limiting any potential conclusions that can be drawn from the pooled meta-analytic estimate of 20%.

Furthermore, the participants in the studies were predominantly patients with NVH who were referred from primary care to secondary care for evaluation. Not all patients with NVH in primary care would have been referred. Therefore, the included studies are likely to reflect higher-risk patients with NVH.

4 Conclusions

We provide a large contemporary systematic review and meta-analysis on NVH for the diagnosis of bladder and upper tract cancers. NVH can be small volume and intermittent in nature in urological cancers. Confirmation of
NVH on repeated samples before more extensive evaluation risks missing clinically significant cancers. Patients with dipstick positive haematuria aged ≥40 yr, who have had potential precipitating causes excluded (eg, treatment for UTI), should undergo an evaluation. Evaluation should include cystoscopy and upper tract imaging in the form of US or CT urogram. US is the most cost-effective and widely available imaging modality. CT urogram, however, has superior diagnostic accuracy for detecting upper tract tumours. Re-evaluation of patients with unrewarding initial investigations should be performed in high-risk patients or if new symptoms occur (eg, VH, LUTS, flank pain, and worsening of renal function).

Further prospective screening data are required in high-risk populations to further evaluate the potential for NVH as a screening tool in reducing morbidity and mortality from bladder and upper tract cancers.

Author contributions: Ibrahim Jubber had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Jubber, Shariat, Cumberbatch.

Acquisition of data: Jubber, Gordon, Cumberbatch.

Analysis and interpretation of data: Jubber, Gordon, Cumberbatch, Shariat.

Drafting of the manuscript: Jubber, Shariat, Conroy, Tan, Gordon, Lotan, Messing, Stenzl, van Rhijn, Kelly, Catto, Cumberbatch.

Critical revision of the manuscript for important intellectual content: Jubber, Shariat, Conroy, Tan, Gordon, Lotan, Messing, Stenzl, van Rhijn, Kelly, Catto, Cumberbatch.

Statistical analysis: Jubber, Cumberbatch.

Obtaining funding: None.

Administrative, technical, or material support: None.

Supervision: Shariat, Cumberbatch.

Other: None.

Financial disclosures: Ibrahim Jubber certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Acknowledgements: The authors would like to acknowledge Beate Pesch at Ruhr-University Bochum, Germany, and Peter Sasieni at King’s College London for their support towards producing this work.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.eururo.2019.10.010.

References


