Systematic Review of the Incidence of and Risk Factors for Urothelial Cancers and Renal Cell Carcinoma Among Patients with Haematuria

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MAIN MANUSCRIPT:

1. INTRODUCTION

Haematuria is commonly the presenting symptom in patients with bladder, upper tract urothelial cancers and on occasions renal cell cancer (1). The estimated detection rates of genitourinary cancer in patients presenting with visible haematuria (VH) and non-visible haematuria (NVH) is 20% and 5% respectively (2). Smokers, male gender and older patients have higher predilection for these cancers (2). Patients presenting with haematuria are commonly investigated with a cystoscopy, upper tract imaging and on occasions with urine cytology and/or novel urinary biomarkers (1-3). The economic impact on healthcare organisations and potential harm of excessive haematuria investigations cannot be under-estimated, particularly for NVH wherein the prevalence is high with a relatively low cancer yield (4). The investigations involve subjecting patients to invasive investigations such as cystoscopy, and the risks of intravenous contrast and radiation exposure with upper tract imaging such as computed tomography urography (CTU), intravenous urography (IVU) (1-3). Despite these recognised issues, there remains discrepancy in consensus statements and guidelines amongst global advisory bodies (3). The National Institute for Health and Care Excellence (NICE) 2015 guidelines advocate an urgent 2-week referral for suspected cancer by primary care physicians for patients above the age of 45 with unexplained visible haematuria without a UTI or persistent/recurrent VH after UTI treatment (5). The guidelines do not consider any risk factors in their haematuria investigative models. Canadian Urological Association (CUA) guidelines recommend a more stringent criteria whereby a cystoscopy and upper tract imaging is recommended in all patients over 35 years asymptomatic NVH (≥3 RBCs/hpf) (3). The recently updated American Urological Association/ Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction guidelines (AUA/SUFU) have adopted a risk stratified approach (6). The aforementioned concerns underpin the need to develop pragmatic, yet individualised risk stratified models for haematuria investigations supported by high-quality evidence.

In this systematic review we have evaluated the incidence of bladder, upper tract urothelial (UTUC) and renal cancers in patients presenting with haematuria. The review has also explored any risk factors of bladder, UTUC and renal tract cancers (BUR) in haematuria.

2. EVIDENCE ACQUISITION

The review protocol was registered with PROSPERO (CRD42020214108)

2.1 Search Strategy

The systematic review was performed in accordance with The Cochrane Guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (5,6). The Medline, Embase and Cochrane controlled trials databases and clinicaltrials.gov were searched for all relevant publications from 01/01/2000 to 06/2021. The literature search was carried out based on the search strategy provided in Appendix 1. Four review authors (BR, JLDE, LV, TK) independently screened the titles and abstracts of identified records for eligibility. Four review authors independently extracted outcome data (BR, JLDE, LV, TK). Study characteristics were extracted by one review author (BR) and a second review author (JLDE) checked data extractions for accuracy. Any disagreements were resolved by discussion. Data extraction was informed by the reporting recommendations for tumour MARKER prognostic studies (REMARK)(7).

2.2 Inclusion Criteria

Participants:

- Age ≥16 years
- Patient investigated for haematuria with no previous history of genitourinary malignancy

Criteria for considering studies for this review

- Prospective, Retrospective and Cross-sectional studies
- Minimum patient population of 50 patients
- Studies in English
- Only articles published in journals. Conference abstracts were excluded

2.3 Outcomes measures

Primary outcome:

- Incidence of bladder cancer, UTUC and renal cell cancer in patients with VH and NVH (as defined by individual studies)

Secondary outcomes:

- Risk factors for BUR (Bladder, UTUC and RCC) with haematuria reported by individual studies

2.4 Assessment of methodological quality

Risk of bias (ROB) was assessed by using the QUIPS tool (8) as recommended by the Cochrane Prognosis Methods Group (9). The following pre-specified confounders were selected: Study population which is predominantly men or women (≥ 60%), extremes of age (Median Age ≥65 years or ≤40 years), predominantly smokers (≥ 60%), in patients with established risk factor(s) for BUR, in a country where the incidence of GU malignancies is high. The overall quality of evidence for each outcome according to the GRADE approach (10)

2.5 Data synthesis

Weighted-pooled analysis of incidence data for all studies has been presented using a Random effects (DerSimonian-Laird) model. Sub-analysis of studies with low ROB was performed. Inclusion criteria for sub-analysis was: 1) Studies judged as low ROB for all domain of QUIPs and/or studies with one or no confounders. A composite crude incidence analysis integrating age deciles, gender and haematuria type was presented where data was available. Age deciles was used with a view to define threshold for investigative strategies

Meta-analyses were performed if valid data was available assessing the association of risk factors in patients with “BUR” and “non BUR ”. Meta-analysis was summarised with pooled estimates of the effect size and 95% CIs, estimates of Tau^2 (between study variance) and 95% prediction intervals for the risk effect in a single population (15). If meta-analysis was inappropriate, a narrative synthesis was presented (16). Sensitivity analysis was performed where appropriate. For Sensitivity analysis, studies were excluded if they had a high risk of bias for any of the standard domains of QUIPS. Additional criteria for study exclusion for

sensitivity analysis for individual risk factors have been described in the respective risk factor results section.

3. EVIDENCE SYNTHESIS

3.1 Description of Studies (Table-1)

The study selection process is described using a PRISMA flow diagram Figure-1 (11). We identified 2124 references. 107 references underwent comprehensive full text evaluation. 44 studies were included in the review (12-54) . One study had a control arm, and the remaining were single arm studies (21). Total number of participants in the included studies was 229,701. 14 (12,15,16,21-23,28,29,31,34,38,46,52,55) studies were prospective studies, of which 5 studies had a published protocol (21,23,25,46,55). Five studies were primary care studies (23,28,32,42,49), and 39 studies were secondary care studies. 17 studies were multicentre trials (17,20,22,23,25,28,29,31,32,34,38-40,46,52,53,55)and 2 were studies from national registries (37,42)

3.2 Primary Outcomes

3.2.1 Incidence analysis

VH

1. Bladder cancer

19 studies had data for incidence analysis (2,12-14,16,19,21-23,25-27,35,38,40,41,45,53,55). The cumulative number of participants was 18,750. The weighted pooled proportion was 18% (95% CI-15% to 20%) (Supplementary Figure 1a). 11 studies were judged as low ROB (2,12,13,16,21,26,27,38,41,53,55). The cumulative number of participants in these studies was 17,034. The weighted pooled proportion was 17% (95% CI-14% to 20%) (Figure-2).

2. RCC

13 studies had data for incidence analysis (2,12-14,16,19,26,27,35,40,41,53,55). The cumulative number of participants was 17,067. The weighted pooled proportion was 2% (95% CI-1% to 2%) (Supplementary Figure-1b). 9 studies were judged as low ROB (2,12,13,16,26,27,41,53,55). The cumulative number of participants was 16,300. The weighted pooled proportion was 2% (95% CI-1% to 2%) (Supplementary Figure-1c).

3. UTUC (Supplementary Figure-1)

13 studies had data for incidence analysis of UTUC (2,12-14,16,19,26,27,35,40,41,53,55). The cumulative number of participants was 17,067. The weighted pooled proportion was 0.8% (95% CI-0.5% to 1.3%) (Supplementary Figure-1d). 9 studies were judged as low ROB (2,12,13,16,26,27,41,53,55). The cumulative number of participants was 16,300. The weighted pooled proportion was 0.75% (95% CI-0.4 to% 1.2%) (Supplementary Figure-1e).

- NVH

1. Bladder cancer

25 studies had data for incidence analysis (2,12,16,17,21,23,25-29,34,37,39-41,43-45,47,48,50,51,53,55). The cumulative number of participants was 201,158. The weighted pooled proportion was 2.3% (95% CI-1.57% to 3.1%) (Supplementary Figure-2). 9 studies were judged as low ROB (2,12,16,21,26,27,41,53,55). The cumulative number of participants was 10,046. The weighted pooled proportion was 3.3% (95% CI-2.45% to 4.3%) (Figure 3).

2. RCC (Supplementary Figure-3)

17 studies had data available for incidence analysis (2,12,16,26-29,37,39-41,43,44,47,49,53,55). The cumulative number of participants was 39,098. The weighted pooled proportion was 0.41% (95% CI-0.24% to 0.63%). Nine studies were judged as low ROB (2,12,16,26,27,41,49,53,55). The cumulative number of participants was 12,089. The weighted pooled proportion was 0.58% (95% CI-0.42% to 0.77%)

3. UTUC (Supplementary Figure-3)

Sixteen studies had data available for incidence analysis (2,12,16,26-28,34,39-41,43,44,47,49,53,55). The cumulative number of participants 33,813. The weighted pooled proportion was 0.13% (95% CI-0.065% to 0.23%). Nine studies were judged as low ROB (2,12,16,26,27,41,49,53,55). The cumulative number of participants was 12,089. The weighted pooled proportion was 0.17% (95% CI-0.081% to 0.299%)

3.2.2 Composite Incidence Analysis using Age (Decile), Gender and Haematuria type stratification (Table-2)

Three prospective studies with low risk of bias had data available on age (deciles) and gender stratification for VH and NVH (2,12,16). Edwards et al presented distribution of BUR in VH

and NVH cohort, however, they did not present distribution of VH and NVH in the entire population evaluated (16). Tan and Khadra et al presented both BUR distribution in VH and NVH cohorts as well as distribution of VH and NVH in the entire population evaluated (2,12) Therefore, overall incidence was calculated for haematuria types from the three studies (Number of BUR in patients with VH or NVH/All haematuria) for individual age decile threshold. (2,12,16) Proportion of BUR for individual haematuria type (BUR in VH/All VH and BUR in NVH/All NVH) were calculated from 2 studies which had this data available (2,12)

- VH:

Males:

No BUR was detected below the age of 20. A pooled analysis of 2 studies suggested 4.6% of males between 20-29 yrs. presenting with VH have a BUR (2,12).

Females:

No BUR was detected below the age of 30. A pooled analysis of 2 studies suggested 0% of females between 30-39 presenting with VH have a BUR (2,12). A pooled analysis of 2 studies suggested 6.3% of females between 40-49 presenting with VH have a BUR (2,12).

- NVH:

Males:

No BUR was detected below the age of 30. A pooled analysis of 2 studies suggested 1.5% of males between 30-39 presenting with NVH have a BUR (2,12). A pooled analysis of 2 studies suggested 1.5% of males between 30-49 presenting with NVH have a BUR (2,12). A pooled analysis of 2 studies suggested 1.6% of males between 30-59 presenting with NVH have a BUR (2,12). A pooled analysis of 2 studies suggested 3.3% of males between 30-69 presenting with NVH have a BUR (2,12). A pooled analysis of 2 studies suggested 5.8% of males between 60-69 presenting with NVH have a BUR (2,12).

- Females:

No BUR was detected below the age of 30. A pooled analysis of 2 studies suggested BUR detection was less than 3% for all deciles under the age of 80 in females with NVH (2,12).

3.3 Secondary Outcomes-Risk factor analysis:

There was data available on 9 risk factors for BUR from the included studies: male gender, advancing age, smoking history (Ex-smokers and current smoker included), presence of symptoms, presence of urinary tract infections, mean RBCs/HPF, occupational history, obesity and pelvic radiotherapy.

3.3.1 Male Gender

For Sensitivity analysis, studies were also excluded, if the study population had a significantly high male or female population (>=65%).

- VH:

Non-Sensitivity Analysis:

8 studies with 12,308 participants were included (2,12,13,22,34,35,38,55). The proportion of male gender in the BUR cohort is higher than the non-BUR cohort (risk ratio (RR) 1.14, 95% CI-1.12 to 1.17, I^2=0%); low-certainty evidence (p< 0.00001) (Supplementary Figure 4)

Sensitivity Analysis:

4 studies with 10,865 participants were included (2,12,38,55). The proportion of male gender in the BUR cohort is higher than the non-BUR cohort (risk ratio (RR) 1.14, 95% CI-1.10 to 1.17, I^2=12%); Moderate-certainty evidence (p< 0.00001) (Figure-4)

- NVH

Non-Sensitivity Analysis:

12 studies with 340658 participants were included (2,12,17,19,39,44,47-51,55). The proportion of male gender in the BUR cohort is moderately higher than the non-BUR cohort (risk ratio (RR) 1.62, 95% CI-1.41 to 1.87, I^2=91%); very low-certainty evidence (p< 0.00001) (Supplementary Figure 4)

Sensitivity Analysis:

4 studies with 7523 participants were included (2,12,49,55). The proportion of male gender in the BUR cohort is higher than the non-BUR cohort (risk ratio (RR) 1.54, 95% CI-1.34 to 1.78, I^2=45%); moderate-certainty evidence (p< 0.00001) (Figure-4)

Visual inspection of the funnel plots did not obviously suggest publication bias (Supplementary Figure-5)

3.3.2 Smoking history (Supplementary Figure-6)

For Sensitivity Analysis, studies were also excluded if the study population had a significantly higher proportions of patients with a smoking history (≥60%)

- VH:

3 studies with 8202 participants reported on smoking history (22,34,55).The proportion of patients with smoking history in the BUR cohort is higher than the non-BUR cohort (risk ratio (RR) 1.39, 95% CI 1.26 to 1.54, I^2=55%); very low-certainty evidence (p< 0.00001)

Sensitivity Analysis:
2 studies with 7615 participants were included (22,55). The proportion of patients with smoking history in the BUR cohort is higher than the non-BUR cohort (risk ratio (RR) 1.41, 95% CI-1.24 to 1.61, I^2=63%); moderate evidence (p< 0.00001)

- NVH:

9 studies with 30392 reported on smoking history (29,39,44,47-51,55). The proportion of patients with smoking history in the BUR cohort is higher than the non-BUR cohort (risk ratio (RR) 1.75, 95% CI-1.47 to 2.09, I^2=76%); very low-certainty evidence (p< 0.00001)

Sensitivity Analysis:
2 studies with 5290 participants were included (49,55) . The proportion of patients with smoking history in the BUR cohort is higher than the non-BUR cohort (risk ratio (RR) 1.53, 95% CI-1.36 to 1.71, I^2=0%); moderate-certainty evidence (p< 0.00001)

Visual inspection of the funnel plots did not obviously suggest publication bias (Supplementary Figure 6c)

3.3.3 Age

10 studies with 19,885 participants reported comparative data for mean age (including imputed data) between BUR and non-BUR cohorts (2,15,23-25,38,44,48,51,55). Pooled analysis was not performed as studies reporting on VH and NVH had a high risk of bias for age (mean age ≥65 or ≤ 40) as a confounder (2,23-25,38,44,48,51). Descriptive forest plots have been presented (Supplementary Figure 7). The mean age was higher in all studies for the BUR cohort when compared to non-BUR cohort (Very low-certainty evidence)

3.3.4 The analysis of the remaining risk factors has been presented in Supplementary Main manuscript

3.4 Quality assessment

We have summarised the risk of bias for individual studies in Supplementary Figure-14. The GRADE evaluation is summarised in Supplementary Table-3. We downgraded the certainty of evidence for study limitations, imprecision and inconsistency

4 DISCUSSION

Summary of Main Results

This review suggests that bladder urothelial cancer incidence rates for VH and NVH (studies with low ROB) is 17% and 3.3% respectively. RCC incidence rates for VH and NVH is 2% and 0.58% respectively. UTUC incidence rates for VH and NVH is 0.75 and 0.17% respectively. The included studies in the review reported on nine potential risk factors for BUR. The proportion of male gender and smoking history appeared to be higher in BUR cohorts when compared to non-BUR cohorts in a majority of the included studies. Following a sensitivity analysis, the certainty of evidence for all haematuria sub-groups for these 2 risk factors was judged as moderate on GRADE evaluation. The review was unable to demonstrate an association between the remaining seven studied risk factors and BUR detection rates in patients presenting with haematuria on pooled analysis. The GRADE evaluation suggested either low or very low certainty of evidence for the remaining seven risk factor even where sensitivity analysis was possible. The mean age was higher in all studies for the cancer cohort when compared to non-cancer cohort, however a pooled analysis wasn't performed due to high risk of bias in individual studies.

Three prospective studies with low risk of bias had data available on age and gender stratification for VH and NVH. A pooled analysis suggested 4.6% of males between 20-29 yrs. with VH have a BUR. A pooled analysis suggested 0% of females between 30-39 yrs. with VH have a BUR. A pooled analysis suggested 6.3% of females between 40-49 yrs. with VH have a BUR. The cumulative data did not identify any BUR under the age of 30 yrs. with NVH. A pooled analysis of suggested 1.6% and 3.3% of males under 60yrs and 70yrs respectively with NVH have a BUR. A pooled analysis suggested BUR detection was less than 3% for all deciles under the age of 80 yrs. in females with NVH

Implications on clinical practise

The review serves as a reference standard for clinicians and global organisations in developing risk stratified investigative models for patients presenting with haematuria. Based on the evidence from this review the integration of age thresholds, gender and smoking history into investigative algorithms are likely to offer an individualised approach. There is currently no universal consensus on how haematuria should be investigated with significant variation in contemporary guidelines (1,2). (5) The evidence from this review suggests that 4.6% of males presenting with VH between the ages of 20-40 will have a cancer and would be considered unsuitable for an urgent 2 week wait referral under the NICE criteria. Canadian Urological Association (CUA) guidelines recommend a more stringent criteria whereby a cystoscopy and upper tract imaging is recommended in all patients over 35 years asymptomatic NVH (≥3 RBCs/hpf) (3). The evidence from this review suggests that 1% and 0% of males and females respectively presenting with NVH between the ages of 20-40 will have a cancer if a threshold of 35 years is adopted. Acceptable thresholds for investigations will take into account investigation related harms, patient expectations and economic impact. The NICE guidelines have adopted a threshold 3% positive predictive value of cancer detection prompting urgent 2-week wait referral for subsequent investigations (5). Based on the aforementioned threshold, all men regardless of age presenting with VH must be investigated based on the evidence from this review. Interestingly, the existing NICE guidelines recommend urgent referral for VH in patients above the age of 45yrs. Aggressive diagnostic strategies, however, have to be balanced against the harm of over investigation. This is particularly pertinent in NVH, where ambiguity in the definition of its significance can lead to relatively high prevalence in the general population. Despite these uncertainties, the cancer yields with NVH as observed in this review is extremely low. In a recent micro-simulation model, it was reported that previous American

Urological Association (AUA) NVH guidelines (3), with a relatively low age-threshold and aggressive upper tract imaging policy, was least likely to miss a cancer. However, the previous AUA NVH guidelines had the highest probability of radiation induced related cancer deaths (575-95% CI, 184-1069 per 100 000 patients) and harms related to false positive results (22, 189-95% CI, 17 520-27 370) (56). The most up to date AUA/SUFU micro haematuria guidelines have adopted a risk stratified approach (6). Patient values and preferences is an important aspect of policy making within organisations. In a vignette-based study 87% of patients were willing to undergo investigation if there was a 1% risk of cancer diagnosis (57). The vignettes included symptoms, risk factors, diagnostic test, treatment, alternative diagnoses, and prognosis (57). The vignettes did not appear to include the harms of over-investigation and it remains unclear how this would have influenced patient decision making. The economic impact of haematuria investigations on healthcare organizations is significant. In addition to developing risk stratified models on whom to investigate, it is also vital to ascertain within cohorts of investigated patients who requires upper tract imaging and the type of imaging they should have. A recent decision-analytic model-based cost-effectiveness analysis reported a cystoscopy and renal USS to be most effective strategy of investigating asymptomatic NVH with an incremental cost per cancer detected to be 53,810 US Dollars (4). The model reported savings of up to US $6,480,484 by performing a USS in place of a CT (4). This came at the expense of missing one additional cancer for every 100,000 patients investigated (4). The evidence from this review would suggest that the incidence of upper tract cancers in patients with NVH is extremely low and perhaps females with no risk factors in acceptable age thresholds could avoid upper tract imaging altogether. In cohorts where upper tract imaging is deemed required an initial USS strategy would appear safe.

Limitations

The review has a few limitations.

There is variability in the diagnostic strategy employed by individual studies, which has been reflected in the wide range of incidence rates in patients without correction for bias. Therefore, we have performed a sub-analysis of incidence rates in studies following exclusion of studies with high risk of bias or more than one pre-decided confounders.

There is potentially a difference in referral patterns, screening strategies employed by individual studies which will impact on the demographic that is being evaluated. This is likely

to influence risk factor assessment. The authors have therefore performed a sensitivity analysis excluding studies with high risk of bias for any of the domains of QUIPS and/or if the risk factors evaluated is confounder.

The authors have deviated from the protocol in the MA of male gender in cancer and non-cancer cohorts wherein a sensitivity analysis studies with male population up to 65% was included. This was following consensus opinion amongst the authors. We also included the IDENTIFY trial in this review which had an age threshold of 16 years for inclusion (55). In our protocol the agreed age threshold for inclusion was 18 years and above. It is the authors view that the aforementioned study had very robust analysis with vital data on the review question and therefore a consensus opinion was taken to include the study.

The definitions of significant NVH remain a subject of debate i.e., dipstick haematuria vs. threshold of number of RBCs/hpf vs. number of samples that are positive. The review was unable to collate adequate data to make any robust conclusions on this parameter. Two studies with continuous data had divergent results.

Smoking history evaluation included current and ex-smokers. The review was unable to evaluate these two entities independently. Additionally, the impacts of pack years and years following smoking cessation on cancer detection in patients presenting with haematuria remains unclear.

The review was unable to demonstrate an obvious association between some of the risk factors and cancer detection. However, this does not exclude them from having causal relationship with cancer. Multiple factors such as limitations of study methodology, small number of studies and governance such as health and safety in individual countries may have influenced outcomes. The authors would therefore exercise caution in interpreting these results and give established risk factors due consideration while investigating patients with haematuria.

The GRADE evaluation for seven risk factor analysis was either “low” or “very low” due to study limitations, imprecision, and inconsistency. We attempted to mitigate these limitations with a sensitivity analysis.

There was some data that was imputed consistent with advice on the Cochrane Handbook.

5 CONCLUSION

Male gender and smoking history are risk factors for cancer detection in patients presenting with haematuria with bladder cancer being commonest detected cancer. The incidence of upper tract cancer in NVH is extremely low. The review serves as a reference standard for future policy making by global organisations for investing haematuria. Acceptable thresholds for investigations will have to take into consideration patient preferences and values, economic impact and harms of over-investigations. It would be advisable that risk factors are incorporated in developing individualised models. This data will allow development of individualized risk stratified investigative models for patients presenting with haematuria. A risk stratified approach is likely to be the most cost-effective method to investigate patients with haematuria.

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