



## Epidemiologic Profile of Microscopic Hematuria in Iran: A Systematic Review and Meta-Analysis

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### Abstract

**Background:** Hematuria is one of the most common symptoms in nephrology and urology. Due to the lack of extensive meta-analysis studies on the epidemiology of hematuria in Iran, this study was conducted to determine the epidemiological status of hematuria in Iran.

**Methods:** In Sep 2020, researchers studied six international databases such as PubMed, ISI/WOS, ProQuest, Embase, Scopus, and Google Scholar for English papers and Iranian databases (SID and MagIran) for Persian papers. Joanna Briggs Institute (JBI) checklist was used to review and control the quality of articles. Heterogeneity between studies was assessed by Cochran's test and its composition using I<sup>2</sup> statistics.

**Results:** After several screening phase, the number of 25 article included to the final analysis. The prevalence of hematuria in the general population and children, in Iran were estimated at 16.4% (95% CI, - 0.05-37.9) and 1.6% (95% CI, 0.9-2.3) respectively. The odds ratio (OR) of women to men in the prevalence of hematuria in the general population 1.74, 95% CI: 1.20-2.52,  $P=0.003$ , patients with beta-thalassemia major 2.02, 95% CI: 1.11-3.65,  $P=0.020$ , children 2.61, 95% CI: 1.19-5.71,  $P=0.016$ , the elderly 1.50, 95% CI: 1.15-1.94,  $P=0.002$ , and taxi drivers 3.73, 95% CI: 2.58-5.38,  $P<0.001$  was obtained.

**Conclusion:** The prevalence of hematuria in the general population is relatively high. Hematuria is a good predictor for detecting of bladder cancer and Idiopathic hypercalciuria and the physician should attention to microscopic hematuria.

**Keywords:** Epidemiology; Microscopic hematuria; Systematic review; Meta-analysis; Iran



## Introduction

Hematuria is one of the most common symptoms in nephrology and urology (1), observed to be self-limiting or chronic (2). According to the guidelines of the American Urological Association, published in 2012 and reviewed in 2016, hematuria refers to the presence of three or more red blood cells in a collected urine sample (without benign cause of the hematuria) (3), according to the severity of the disease, it is classified into two categories: microscopic and macroscopic (4, 5). Hematuria is seen in urinary tract sediment examination for a long time (6) and can be considered as an isolated finding associated with other renal abnormalities or as part of systemic disease (7). Hematuria can also be a sign of other diseases such as malignancies (8). For this reason, for accurate assessment of the individual, cross-sectional imaging using computed tomography and cystoscopy in patients aged 35 years and older, physical examination, urinalysis, and referral to an urologist are recommended (3, 9).

Hematuria is most often self-limiting, resolving with treatment of the underlying infection. Treatment of the underlying infectious etiology is paramount to preventing or attenuating the course of hematuria (10).

Numerous factors such as inflammation, bladder or prostate infection, urological malignancies, kidney stones, past or current smoking, old age, occupational exposure, and the use of anti-inflammatory drugs can play a role in causing hematuria (2, 11, 12).

The choice of a diagnostic protocol for patients with microscopic hematuria has wide clinical and economic implications, due to the high diagnostic costs, ultrasound with cystoscopy is more cost effective for diagnosis (13).

In Iran the prevalence of hematuria in general population is varies, as Bahrami et al reported 12.6% of hematuria and Mansour-Ghanaei et al reported 34.1% (14, 15). Moreover, the American Urological Association has recently reported that the prevalence of hematuria varies from 0% to 56% and is associated with factors such as age,

sex, estimated population, source of referral, and clinical status (16). Occasionally asymptomatic microscopic hematuria can be companion by macroscopic attacks, in addition can be cause of proteinuria, hypertension and chronic renal failure, and ordinarily leads to end-stage renal disease (ESRD)(1). These symptoms may occur at any time between the first and seventh decade of life (8). Approximately 3.6% of patients with hematuria will develop urinary tract malignancy in the future (16). In patients with advanced chronic renal disease who also have hematuria, the rate of renal function decline is more (6). Many studies have tested the prevalence of microscopic hematuria with varying percentages in a general screening population. In a similar study, out of 37 people with urological malignancies, 16 had to have a urine test again, of which 13 had hematuria (3). The prevalence of hematuria is significantly higher in elderly people who took regular doses of aspirin than in older people who did not take aspirin (17).

Our knowledge about global and regional burden of hematuria is very limited, but in a recent study of the Global Burden of Disease (GBD) published on chronic kidney disease (CKD), valuable information has been obtained. Globally, in 2017, 1.2 million people worldwide died of CKD. The prevalence of CKD worldwide has increased by 29.3% since 1990. In Iran, the age-standardized prevalence of CKD was 10924 per 100000 in 2017 and the age-standardized death rate was 16.6 per 100000 (18).

In Taiwan, hematuria was significantly associated with sex, age, BMI, and urbanization (19). In Chronic Renal Insufficiency Cohort (CRIC) Study, hematuria was associated with a significantly higher risk of CKD progression and death in the first 2 years of follow-up. Individuals with hematuria were more likely to be Hispanic (22% vs. 9.5%, respectively), lower mean eGFR (40.2 vs. 45.3 ml/min/1.73 m<sup>2</sup>), higher levels of urinary albumin >1.0 g/day (36% vs. 10%), and have diabetes (56% vs. 48%) (20).

Hematuria has a major effect on global health, both as a direct cause of morbidity and death and as an important risk factor for CKD. Studies on the epidemiology of hematuria in Iran are limited and there is not accurate information about the epidemiology of hematuria. Otherwise, the results of other studies have shown different estimates in the general population, children and other groups. Due to the lack of extensive meta-analysis studies on the epidemiology of hematuria in Iran, this study was conducted to determine the epidemiological status of hematuria in Iran.

## **Methods**

### ***Study protocol***

The present study was a systematic review of the microscopic hematuria and its risk factors in Iran. The reporting method of the present study is based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) checklist (21). PRISMA is an evidence-based minimum set of items aimed at helping authors to report a wide array of systematic reviews and meta-analyses. PRISMA focuses on ways in which authors can ensure a transparent and complete reporting of this type of research.

### ***Search strategy***

In Sep 2020, researchers studied six international databases such as PubMed, Embase, ProQuest, ISI/WOS, Scopus, and Embase for English papers and Iranian databases (MagIran and SID) for Persian papers. The selected keywords for databases included "Hematuria", "Epidemiology", "Prevalence", "Frequency", "occurrence", "Incidence", "Risk factor" and "Iran". Two researchers examined the articles separately. The collected articles was entered into EndNote, X7 software and duplicate articles were automatically deleted.

### ***Inclusion and exclusion criteria***

#### ***Inclusion criteria***

All articles done on the prevalence and risk factors related to microscopic hematuria without time and language restrictions in Iran.

#### ***Exclusion criteria***

Articles whose full text was not available, also, conferences paper, seminars, and dissertations.

#### ***Quality assessment***

The Joanna Briggs Institute (JBI) checklist was used to assess the quality of the articles (22). The purpose of this appraisal was to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its conduct, design, and analysis. The checklist has nine questions that are marked with the answer "Yes", "No", "Not applicable" and "Not clear". If the score was more than 7, the article was of high quality, if it was between 4 and 6, it was of medium quality; and if it was less than 4, it was of low quality. The results of the quality assessment presented in Table 1.

#### ***Screening studies***

The initial search for the articles was performed independently by two people (S.H and M.K). Screening of the studies, extracting results, and assessing the quality control of studies was done separately by two people (M.K and F.H). If there were no agreement between the two, the team leader (S.H) would give the final opinion on the article.

#### ***Data extraction from***

All final papers submitted to the study process were prepared for data extraction by a pre-prepared checklist. This checklist included the author's first name, year of publication, study period, place of study, and point estimate.

#### ***Statistical analysis***

Heterogeneity between studies was assessed by Cochran's test (with a significance level of less than 0.1) and its composition using  $I^2$  statistics. If the  $I^2$  was higher than 50%, it indicates high heterogeneity. In the case of heterogeneity, the random-effects model was used with the inverse variance method. The prevalence of hematuria was calculated based on the percentage or the amount reported in the studies. The results of prevalence

were reported as the pooled estimates and the 95% confidence intervals (CIs). Meta-regression was used to examine the impact of moderator variables on prevalence of hematuria using regression-based techniques. Meta-regression was done to explore the sources of potential hetero-

geneity using the following variables: publication year and sample size. The odds ratio (OR) index was used to compare prevalence of hematuria in groups. Publication bias was investigated using Egger test. All analyzes were performed using CMA version 2 statistical software.

**Table 1:** JBI critical appraisal checklist applied for included studies

<i>Author Name/Year</i>	<i>Q1</i>	<i>Q2</i>	<i>Q3</i>	<i>Q4</i>	<i>Q5</i>	<i>Q6</i>	<i>Q7</i>	<i>Q8</i>	<i>Q9</i>	<i>Quality points</i>	<i>Quality</i>
Mansour-Ghanaei, 2019(15)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	7/9	High
Motamed, 2018(23)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	6/9	Medium
Akhavan Sepahi, 2017(24)	Yes	Yes	Yes	Yes	Yes	Not clear	No	No	Not clear	5/9	Medium
Esteghamati, 2017(25)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Not clear	4/9	Medium
Moghtaderi, 2013(26)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	5/9	Medium
Safaei, 2013(27)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Not clear	7/9	Medium
Shafi, 2013(28)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	8/9	High
Madani, 2012(29)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9/9	High
Ahmadi, 2012(9)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8/9	High
Barahimi, 2011(14)	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	No	Not clear	6/9	Medium
Salehi,2011(30)	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	No	No	6/9	Medium
Mahdavi-Mazdeh, 2010(31)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not clear	8/9	High
Emamghorashi, 2010(32)	Yes	Yes	Yes	Yes	Yes	No	No	No	Not clear	5/9	Medium
Akhavan Sepahi, 2010(33)	Yes	Yes	Yes	Not clear	Yes	Not clear	No	No	Not clear	4/9	Medium
Fallahzadeh, 2010(34)	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	No	No	6/9	Medium
Shajari, 2009(35)	Yes	Yes	Yes	Yes	Yes	No	No	No	No	5/9	Medium
Badeli, 2009(36)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Not clear	6/9	Medium
Derakhshan, 2008(37)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7/9	High
Ahmadzadeh, 2008(38)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Not clear	6/9	Medium
Sadeghi, 2008(39)	Yes	Yes	Yes	Yes	No	No	Yes	No	Not clear	4/9	Medium
Esfahani, 2007(40)	Yes	Yes	Yes	Not clear	No	Yes	No	No	Not clear	4/9	Medium
Safary, 2005(41)	Yes	Yes	Yes	Yes	Yes	Not clear	No	No	Not clear	5/9	Medium
Ghasemi, 2004(42)	Yes	Yes	Yes	Yes	No	No	No	No	Not clear	4/9	Medium
Vazirian, 2004(43)	Yes	Yes	Yes	Yes	No	No	Yes	No	Not clear	4/9	Medium
Shahidi, 2001(44)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	7/9	High

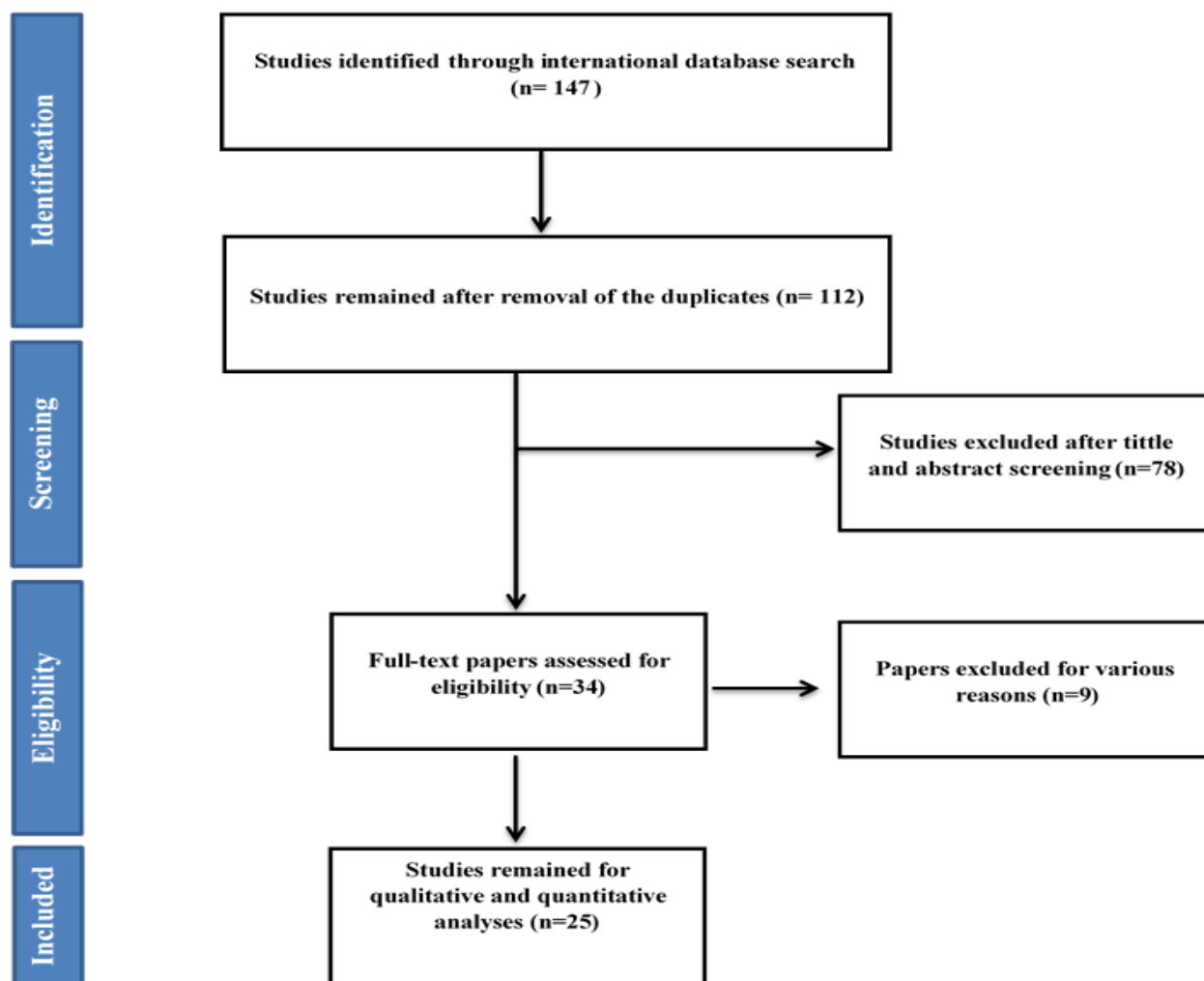
Q1. Sample was representative? Q2. Participants appropriately recruited? Q3. Sample size was adequate? Q4. Study subjects and the setting described?  
 Q5. Data analysis conducted? Q6. Objective, standard criteria, reliably used? Q7. Appropriate statistical analysis used? Q8. Confounding factors/subgroups/ differences identified and accounted? Q9. Subpopulations identified using objective criteria?

## Results

### *Description of the study search*

After searching all international databases, 147 articles were found, which after removing 35 duplicate articles, the 112 article entered the review stage in terms of title and abstract. After reviewing the titles and abstracts of the articles, 34 articles entered the next stage, in which the full text

of the articles was reviewed and 25 articles entered the final analysis. References to imported articles were also reviewed to add relevant studies. Articles were excluded from the study for a variety of reasons, including insufficient information (15), irrelevant population (71), and duplication of results (n=1). The flowchart of the included studies is shown in Fig. 1.



**Fig. 1:** Flowchart of the included studies in systematic review

### *Description of the entered studies*

The characteristics of the included studies (9, 14, 15, 23-44) presented in Table 2. Based on the results obtained from the geographical explanation, 6 studies in Fars Province(23, 30, 32, 34, 35, 37), 3 studies in Tehran Province(29, 31, 40), 3 studies in Guilan Province(15, 27, 36), 2 studies

in Isfahan Province(14, 44), 2 studies in Qom Province(24, 33), 2 studies in Mazandaran Province(9, 28), and one study in the Hormozgan(25), Bushehr(42), Gorgan (Golestan Province)(26), Khuzestan(38), Zahedan (Sistan & Baluchestan Province)(39), Hamedan(41), and Kermanshah(43).

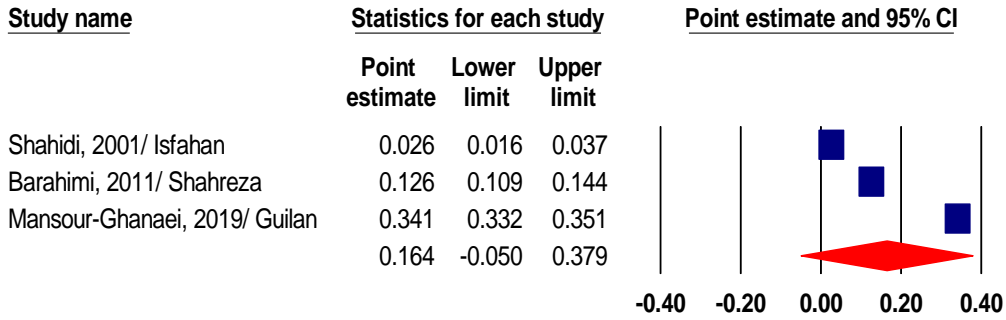
**Table 2:** Basic characteristics of the studies included in the review

Order	Author, year	Location	Sample size	Population	Age (mean or range)	Prevalence of hematuria			Age category
						Gender Male	Gender Female	Total	
1	Shahidi 2001(44)	Isfahan	1000	Adult	-	-	-	2.6 %	
2	Vazirian 2004(43)	Kermansh	6831	Children	Primary school	-	-	0.25%	
3	Ghasemi 2004(42)	Boushehr	2047	Children	6-13 y	(18/1035) 1.74 %	(28/1012) 2.77 %	(43/2047) 2.1%	-
4	Safary 2005(41)	Hamad	800	Children	10-11 y	-	-	4.1%	
5	Esfahani 2007(40)	Tehran	28	Idiopathic Hypercalciuria	6-11	(2/16) 12.5%	(1/12) 8.33%	(3/28) 10.71%	
6	Sadeghi 2008(39)	Zahedan	1169	Children	7-15 y	1	2.1		7-9 = 1.59 10-12= 1.48 13-15= 1.54
7	Ahmadzadeh 2008(38)	Khuzestan	15	Idiopathic Hypercalciuria	6-12 y	-	-	(10/15) 66%	
8	Derakhshan 2008(37)	Fars	108	Beta-Thalassemia	4-24 y for thalassemia intermediate 3-24 y for thalassemia major	-	-	(17/50) 34%	In all thalassemia: (19/108) 17.6%
9	Badeli 2009(36)	Guilan	1520	Children	4-6 y	-	-	0.85%	
10	Shajari 2009(35)	Fars	1601	Children	6-7	-	-	1%	
11	Fallahzadeh 2010(34)	Fars	500	Beta-Thalassemia Major	6m – 32y	19/256	34/244	(53/500) 10.6%	< 20= 9.8 >20= 20

12	Akhavan Sepahi 2010(33)	Qom	100	Urolithiasis (renal stone)	<14 y	-	-	(70/100) 70%	
13	Emamghorashi 2010(32)	Fars	1068	Children	7-11 y	-	-	3.3 %	
14	Mahdavi-Mazdeh 2010(31)	Tehran	30747	Taxi Drivers	18-86	(546/30254) 1.8%	(32/502) 6.4%	(578/30747) 1.87%	
15	Salehi 2011(30)	Fars	216	Bladder Cancer	-	-	-	(183/216) 84.7%	
16	Barahimi 2011(14)	Isfahan	1400	General population >30	>30	7.2 %	14.6 %	12.6%	
17	Ahmadi 2012(9)	Mazandaran	112	Bladder Cancer	-	-	-	49.1%	
18	Madani 2012(29)	Tehran		Hypercalciuria				40.7%	
19	Shafi 2013(28)	Mazandaran	175	Bladder Cancer	-	-	-	(111/175) 63.4%	>40 63.4% (99/156) <40 = 63.1% (12/19)
20	Safaei 2013(27)	Guilan	19	Idiopathic Hypercalciuria	-	(2/11) 18.1%	(1/8) 12.5%	(3/19) 15.78%	
21	Moghtaderi 2013(26)	Gorgan	3000	Children	6-14	(8/1800) 0.44 %	(27/1200) 2.25 %	(35/3000) 1.16%	
22	Esteghamati 2017(25)	Hormozgan	153	Idiopathic Hypercalciuria	2m-14y	-	-	(28/153) 18.3%	
23	Akhavan Sepahi 2017(24)	Qom	199	Children with Nephrolithiasis	< 14 y	-	-	38.7%	
24	Motamed 2018(23)	Fars	756	Bladder Cancer	-	79.3 %	78.9 %	(598/756) 79.1%	
25	Mansour-Ghanaei 2019(15)	Guilan	10520	General population >35	35-70	(1431/4887) 29.3%	(2151/5633) 38.1	(3585/10520) 34.1%	

**Prevalence of hematuria in Iran in different groups**  
**General population**

Based on the results of 3 studies (14, 15, 44), the overall prevalence of hematuria in the general population was estimated at 16.4% (95 % CI, -0.05-37.9, I<sup>2</sup>=99.8%, P<0.001) (Fig. 2).

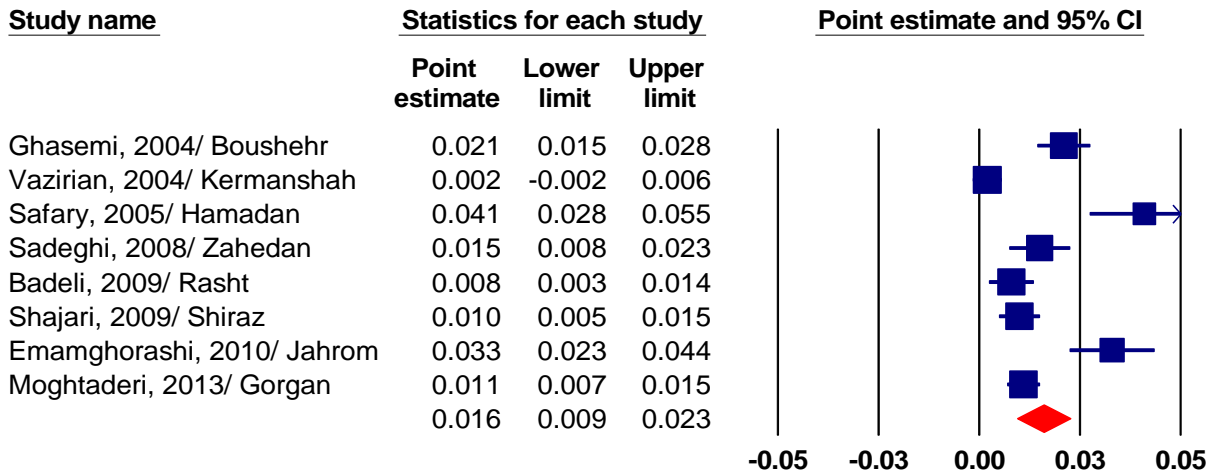


**Fig. 2:** The prevalence of hematuria in Iranian general population

**Children**

According to the results of eight studies(26, 32, 35, 36, 39, 41-43) that reported the prevalence of

hematuria in children, the prevalence in Iran was 1.6% (95 % CI, 0.9-2.3,  $I^2=90.2$  %,  $P<0.001$ ) (Fig. 3).

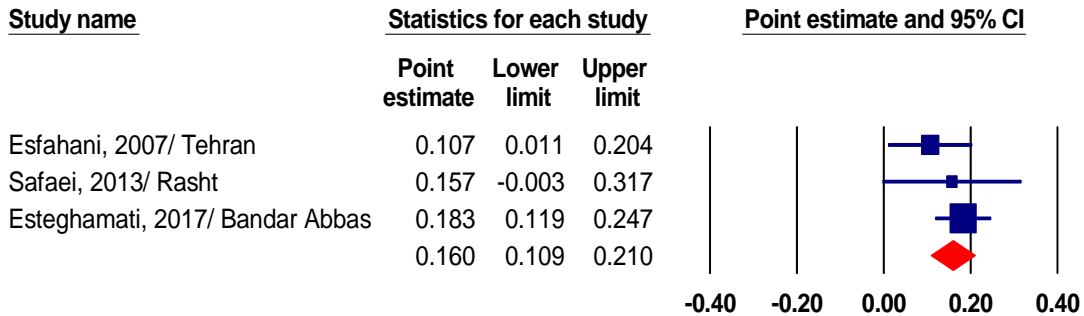


**Fig. 3:** The prevalence of hematuria in Iranian children

**Idiopathic Hypercalciuria**

Based on three studies in the population (25, 27, 29), the prevalence of hematuria was estimated at

16% (95% CI, 10.9-21.0,  $I^2=82.1$  %,  $P<0.001$ ). (Fig. 4).



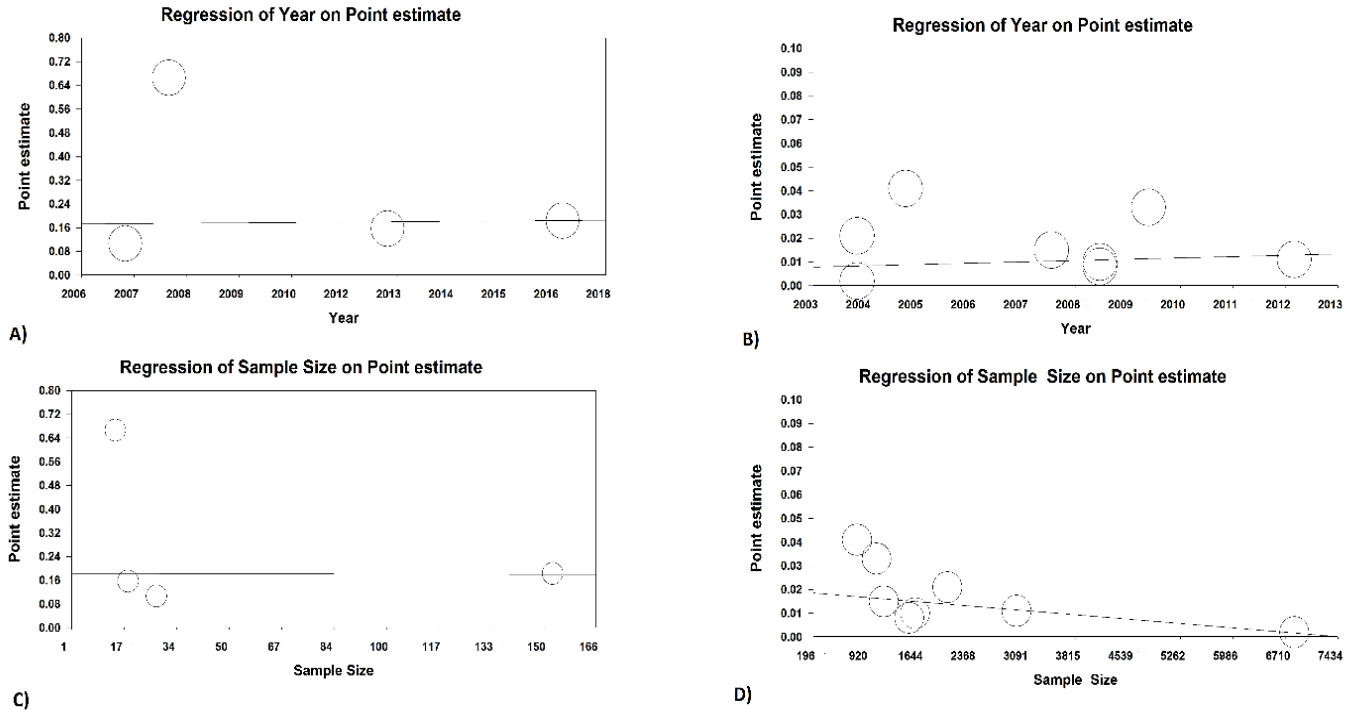
**Fig. 4:** The prevalence of hematuria in Idiopathic hypercalciuria



**Meta- regression**

The results of meta-regression for sample size showed that there was a negative significant association between sample size and prevalence of hematuria in children (Reg coef= -0.0001,  $P<0.001$ ). There was no significant association between year of publication and prevalence of

hematuria in children (Reg coef= 0.0001,  $P=0.061$ ). Moreover, no significant association between sample size (Reg coef= 0.0001,  $P=0.856$ ).and year of publication (Reg coef= -0.0002,  $P=0.964$ ) was observed in prevalence of hematuria in Idiopathic Hypercalciuria group (Fig. 5).



**Fig. 5:** Result of meta-regression for based on sample size and year of study  
 A: Year of study and prevalence of hematuria in Idiopathic Hypercalciuria group.  
 B: Year of study and prevalence of hematuria in children.  
 C: Sample size and prevalence of hematuria in Idiopathic Hypercalciuria group.  
 D: Sample size and prevalence of hematuria in children.

**Risk factors**

**Gender**

In most of the studied groups, women had a higher chance of hematuria, except for idiopathic hypercalciuria and bladder cancer patients, which was more common in men, but this relationship was not statistically significant ( $P>0.05$ ).

The odds ratio (OR) of women to men in the prevalence of hematuria in the general population (1.74, 95 % CI: 1.20-2.52,  $P=0.003$ ), patients with beta-thalassemia major (2.02, 95 % CI: 1.11-3.65,

$P=0.020$ ), children (2.61, 95 % CI: 1.19-5.71,  $P=0.016$ ), the elderly (1.50, 95 % CI: 1.15-1.94,  $P=0.002$ ), and taxi drivers (3.73, 95 %CI: 2.58-5.38,  $P<0.001$ ) was obtained.

**Publication Bias**

Publication bias was not observed amongst the included studies according to the results of the Egger test ( $P=0.452$ ).

## Discussion

Microscopic hematuria is often asymptomatic and generally has a clinical prevalence of 4% to 5% (45). This percentage may be due to underlying kidney or urinary tract disease, so extensive urological and nephrological differential diagnosis should be considered for hematuria.

Microscopic hematuria can have many reasons. According to our results, the prevalence of hematuria in patients with beta-thalassemia major is 7.1%, patients with bladder cancer 69.8%, in children 1.6%, patients with idiopathic hypercalciuria equal to 16%, and finally in the general population was equal to 16.4%.

“Urinary bladder cancer is usually associated with asymptomatic hematuria; the percentage of hematuria in patients with bladder cancer is very high (up to 5% of patients with microscopic hematuria and approximately 10% of patients with gross hematuria have urinary tract cancer” (46). This condition is important because it can be a warning sign for the initial detection of bladder cancers. Other studies have also shown that the percentage of hematuria in patients with bladder cancer is high (3).

Older age, being a man, and greater hematuria increase the risk of having urinary tract cancer in individuals (47).

The prevalence of hematuria in children in this study was 1.6%, which is lower than the percentage of hematuria in a review study (10), which was equal to 4%. This could be due to the measurement of hematuria in RBCs above five in each microscopic field. Being a girl increases the probability of having microscopic hematuria by 2.61 times.

Moreover, the percentage of hematuria in the general population in this study was much higher than in other studies and was equal to 16.4%. This is due to the high percentage of lyrical (15), the percentage of hematuria was equal to 34.1%. One of the reasons for this high percentage is the high age of the people studying lyrics, colleagues, and factors such as kidney stones and so on. The

percentage of hematuria in the general population in women was 1.74 times higher than men were.

This study also showed that the percentage of hematuria in patients with idiopathic hypercalciuria was high and was equal to 16%. This issue has also been seen in another study (25).

On the other hand, the prevalence of hematuria in idiopathic hypercalciuria patients was much higher and was equal to 31%. This indicates an increase in hematuria in idiopathic hypercalciuria patients, so these numbers may vary based on differences in the design environment of the model and the data collection.

According to the data obtained in different groups, women generally have more hematuria than men (except in idiopathic hypercalciuria groups) do. According to this chart, being a woman in the two groups of bladder cancer and idiopathic hypercalciuria were 2.5% and 36% protective in causing hematuria, respectively, but from a statistical point of view, this ratio was not significant and it can be practically concluded that being a woman is the cause. There is a risk of developing hematuria in kidney disease. An increase in the number of deliveries and the use of vaginal estrogen was associated with an increase in hematuria in women (48).

Whereas hematuria is a usual disease, there is no evidence-based algorithm for diagnostic evaluation. Therefore, to detect or deny underlying disease that needs treatment all the causes of hematuria should be investigated and each individual risk factor must be considered (45).

### *Study Limitations*

Our study was limited. One limitation of this study was the small number of studies performed on hematuria patients in Iran, which made our estimates difficult. Another limitation of this study was how hematuria-related factors were reported so that ultimately the only comparable factor for us was gender, and other factors such as hematuria-related risk factors could not be measured in Iran.

## Conclusion

The prevalence of hematuria in the general population is relatively high. Hematuria is one of the most important risk factors of bladder cancer and CKD, so the presence of hematuria can be an appropriate predictor of bladder cancer. Therefore, the physician should emphasize the hematuria in all age groups.

## Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

## Acknowledgements

None.

## Data availability

Resources of data and statistical analysis outputs of this study can be provided by the author of correspondence.

## Conflict of interest

The authors declare that there is no conflict of interest.

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