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Review Article

Clinical characteristics, etiology, management and outcome of hematospermia: a systematic review

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Abstract: Introduction: Hematospermia is an uncommon symptom but can cause significant anxiety among the patient and his partner. The available data on the underlying etiology, management and outcome are variable and inconsistent. This systematic review was aimed to describe the clinical characteristics, etiology, treatment and outcomes of hematospermia. Methods: Keywords were searched in PubMed, Scopus, LILACS and Google Scholar. Relevant articles were manually added from the list of references of eligible articles. Studies with a considerable assessment of patients with hematospermia were included. Qualitative analysis was performed using the available data. Results: Twenty studies (Fifteen prospective and five retrospective, n=2079 patients, mean age =46.2 (range: 15-89) years) were eligible. Community screening reported a 0.5% prevalence of hematospermia (one study). Majority had hematospermia as the main/only symptom while dysuria (n=38/232, 16.4%), lower urinary tract symptoms (n=113/833, 13.6%), Hematuria (65/566, 11.5%) and testicular pain (n=68/631, 10.7%), were associated in some patients. Suspicious rectal examination (one study) and elevated PSA (Prostate Specific Antigen) levels (four studies) were indicative of sinister pathologies. Common etiologies were urogenital infections/inflammatory conditions followed by prostatic, seminal vesicular or urethral calculi. Malignancies were detected in 5.4% (n=74/1362, 11 studies) of patients >40 years old and the majority had prostate cancers (67/74, 90.5%). Etiology was unknown in 51.8% (n=603/1163). Definitive treatment of the underlying etiology (n=260/347, 74.9%) resolved the symptoms while spontaneous resolution occurred in the vast majority 88.9% (n=168/189) with unknown etiology. Conclusions: Hematospermia is relatively an innocent symptom. Malignancies are rare and occurred in men over 40 years. Clinical assessment including a rectal examination and a PSA level would be sufficient to identify most causes. Urogenital infections/inflammation and prostatic calculi are the commonly found etiologies. There was no identifiable cause in almost half of those with hematospermia. The majority has a benign course.

Keywords: Hematospermia, hemospermia, prostate specific antigen, urogenital infections, prostate cancer, outcome, systematic review

Introduction

Hematospermia or hemospermia is defined as the presence of blood in the ejaculate [1]. This is different from hematuria (which is blood in the urine) and bleeding or bloody discharge from the urethra. Hematospermia may present in isolation or in combination with other lower urinary tract symptoms or hematuria. The exact incidence or prevalence of hematospermia is difficult to determine. This is because many occurrences of hematospermia are likely to escapes without being noticed by the person, and therefore, are unrecognized and unreported. So much so, that some believe hematospermia became a significant clinical problem only after the use of condoms became prevalent. It is a relatively uncommon symptom but alarming to the patient and persuades them to seek medical advice due to fear of a malignancy or a potential threat to sexual function [1]. Commonly described causes of hematospermia are infections in the urogenital tract, prostatic and seminal vesicular calculi and tumors in a few cases [2-6]. However, a large disparity in the proportions of the reported etiologies have been noted across studies due to the variability in the diagnostic work up.

Although studies have reported that vast majority of cases of hematospermia do not have an identifiable cause, most clinicians still consider it as a serious symptomatic manifestation of a dangerous underlying illness and proceed with unnecessary invasive procedures [5, 6]. These additional investigations may lead to wastage of resources and unnecessary discomfort and anxiety to the patients. Different studies have evaluated the utility of a wide range of imaging techniques including the transrectal ultrasound scan (TRUS) and magnetic resonance imaging (MRI) scan in identifying underlying abnormalities. Although advanced imaging may identify certain abnormalities, establishing causality rather than mere association in those instances is challenging and difficult. Therefore, guidelines and protocols empowering judicious use of investigations is needed [5, 6].

Currently, there are no algorithms for investigation and treatment of hematospermia. Although National Institute for Health and Care Excellence (NICE) has a guideline for primary care physicians, there are no guidelines for urologists [7]. Therefore, the appropriate evidence-based management of the patient after referral to the urologist is unclear. The development of newer imaging techniques has changed the protocols of evaluation and treatment of hematospermia in recent times in individual units. The published studies show a large variability of the management policies of practicing urologists in investigation and treatment of hematospermia. Therefore, we aimed to analyze the pooled results of all published studies to formulate evidence-based recommendations for management of hematospermia.

Materials and methods

A systematic review of all studies on hematospermia including prospective and retrospective cohort analyses and experimental studies was performed. Inclusion criteria were defined as studies describing clinical characteristics, management and outcome of hematospermia/hemospermia. All types of interventions were included in the systematic review. The primary objective of this review was to describe the clinical characteristics, etiological factors, management and outcome of hematospermia. We also aimed to summarize the evidence to provide recommendations for clinical practice.

Search strategy

All publications in English language were searched electronically using PubMed/Medline, Scopus, LILACS and Google scholar without any restriction in the date or status of publication. Key words such as 'hematospermia' OR 'haematospermia' OR 'hemospermia' OR 'haemospermia' were searched in the title and abstract fields. Furthermore, an additional list of references of eligible articles were searched manually and incorporated to the review. The literature search, data extraction and analysis were performed according to the PRISMA guidelines [8]. Finally, qualitative analysis was performed with the available data. A meta-analysis could not be performed due to the heterogeneity in the study methodology, treatment options and description of outcomes. The risk of bias assessment of eligible studies was performed using the modified version of the Downs and Black checklist and the findings are shown in Table S1. The quality of each paper was graded as "excellent" (14-17 points), "good" (10-13 points), "fair" (5-9 points) or "poor" (<5 points) [9].

Results

Characteristics of selected studies

The initial search retrieved 705 records, of which 550 were duplicates. We short-listed 42 publications which met the inclusion criteria for full-text analysis (**Figure 1**). Finally, twenty studies were included in the systematic review. Of the selected studies, six were from the UK, three each from China and Hungary, two from the USA and the remaining six were from Germany, Israel, Japan, Iran, India and Sri Lanka. Five of them were retrospective studies and the rest were prospective. One study was conducted in two centers, another was a community based one while the others were hospital-based single-center studies. The studies described a cumulative number of 2079 patients with a mean age of 46.2 (range: 15-89) years. According to the Downs and Black scoring system, the quality of the studies were graded as "excellent" in 12 studies, "good" in 7 studies and "fair" in 1 study.

Clinical characteristics of hematospermia

Hematospermia was the main/only symptom in almost all the study participants (n=2069,

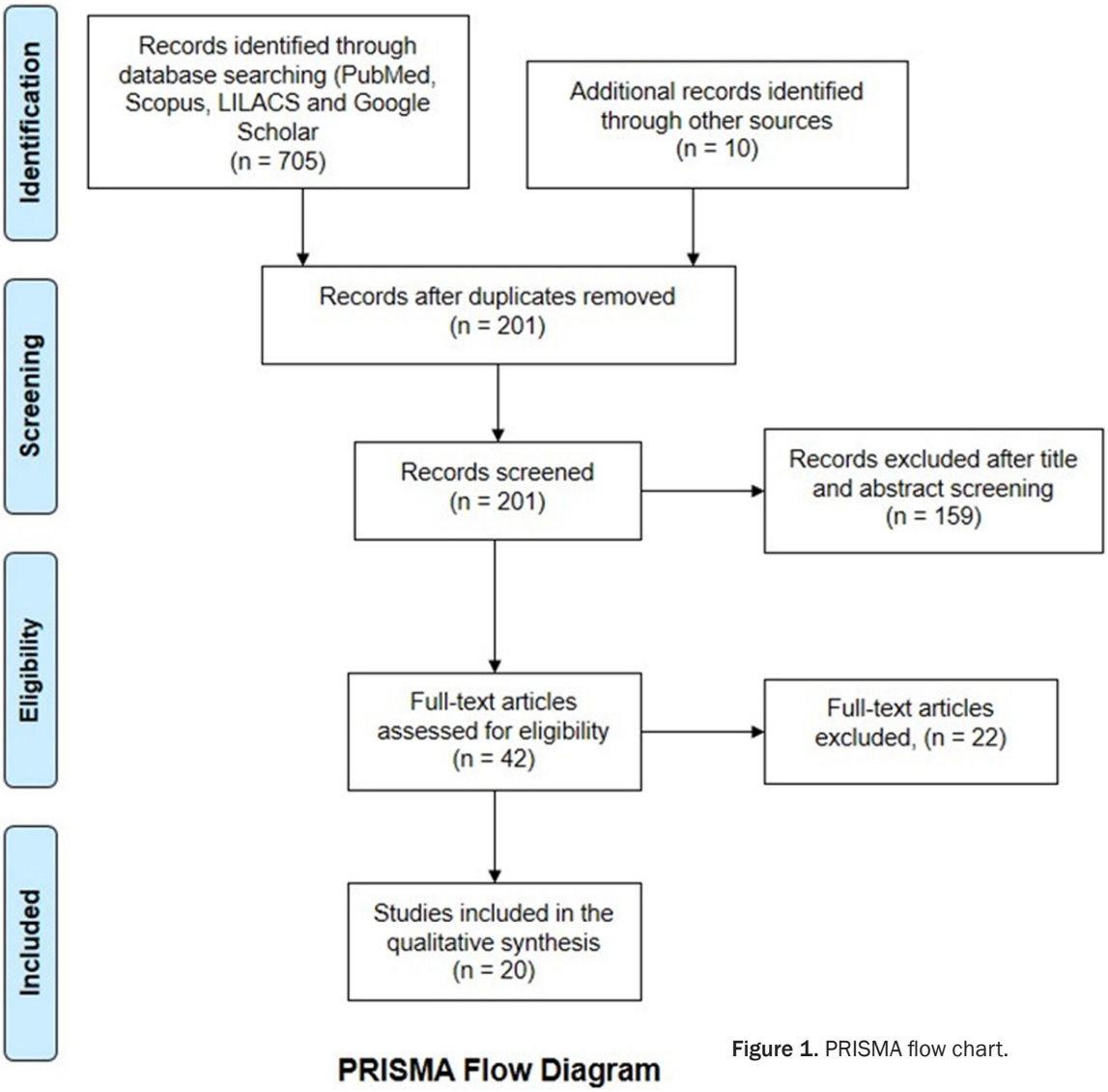

Figure 1. PRISMA flow chart.

99.5%). However, dysuria (n=38/232, 16.4%), non-specific lower urinary tract symptoms (n= 113/833, 13.6%) hematuria (65/566, 11.5%) and testicular pain (n=68/631, 10.7%) were associated symptoms in some patients. Abnormal or suspicious digital rectal examination (DRE) was reported in 42/463 (9.1%) and abnormal DRE and/or raised prostate specific antigen (PSA) levels were reported in 90/754 (11.3%) patients with hematospermia (**Table 1** [1-6, 10-23]).

In a community based screening study for prostate cancer among older men, the PSA levels were elevated in 30/139 (22%) in men with hematospermia compared to the rest with no hematospermia (n=4180/26126, 16%) [15]. In a study by Kumar and colleagues, the mean PSA was 0.2 ng/ml in those less than 40 years old with a mean prostate volume of 13.3 ml. However, abnormal DRE and/or raised PSA was found in 27/104 (26.0%) and raised PSA and normal DRE was reported in 10/104 (9.6%) among the patients older than 40 years [16]. Interestingly, 3 out of 10 patients with raised PSA and normal DRE had prostatic carcinoma. Wilson and colleagues reported elevated PSA levels in 5/41 study participants (12%) [5].

Etiology of hematospermia

Urogenital infections were diagnosed in 212/1055 (20.1%) [1-4, 6, 10-14] while tuberculosis (TB) was positive in 17/309 (5.5%) [2, 10,

Table 1. Demography and clinical features of patients with Hematospermia

	Author	Study type	N	Mean age (range)	Inclusion/Exclusion Criteria	Clinical symptoms	Risk factors/Associated symptoms	Examination
1	Tolley (1975) UK	Prospective	26	39 y (18-63)	Presence of Hematospermia	Hemospermia on one occasion only in 6/26 (23.1%) Recurrent episodes in 20/26 (76.9%) Only hematospermia in 18/26 (69.2%)	Had coitus in 24/26 (92.3%)-Frequent in 1 and less frequent in 1 Hematuria in 4/26 (15.4%), Dysuria in 2/26 (7.7%), Hesitancy in 1/26 (3.8%), outflow obstruction in 1/26 (3.8%), Trauma in 2/26 (7.7%), Hemophilia in 1/26 (3.8%)	Hemangioma on the glans in 1/26 (3.8%) Hydrocoeles in 3/26 (11.5%) BEP in 1 with tract obstruction Tender prostates in 2 complained of dysuria
2	Henry (1977) Hong Kong	Prospective	65	37.4 y (16-69)	Presence of Hematospermia	Hemospermia in 65/4333 (1.5%) of all referrals Multiple recurrent attacks of hemospermia in 32/65 (49.2%) One episode in 19/65 (29.2%) Two attacks in 11/65 (17%) Three attacks in 3/65 (4.6%)	Venereal disease in 9/65 (13.8%) Dysuria in 14/65 (21.5%) Hematuria in 8/65 (12.3%) Frequency in 5/65 (7.7%) Loin pain in 2/65 (3.0%) Epididymo-orchitis in 2/65 (3.0%) Nil 37 (56.9%)	Normal in 26/65 (40%) nodularity in the epididymis in 18/65 (27.7%) palpable seminal vesicles in 8/65 (12.3%)-(3 with nodular epididymis) Prostate-boggy and tender in 6/65 (9.2%), firm in 15/65 (23.1%), and hard in 2/65 (3.1%) All were normotensive
3	Fletcher (1981) UK	Prospective	81	40 y (15-73)	Presence of Hematospermia	Only hemospermia in 32/81 (39.5%)	Hematuria in 15/81 (18.5%)	N/A
4	GY. PAPP (1981) Hungary	Prospective	38	19-64 y	Presence of Hematospermia	Hematospermia only	N/A	N/A
5	DJ. Jones (1991) UK	Prospective	56/74 (76%)	29.6 y	Presence of Hematospermia	Only 1 or 2 episodes of hemospermia in 56/74 (76%)	Previous STD in 1/34 (2.9%) Sexual foreplay in 1/34 (2.9%) Intercourse x 8/24 h in 1/34 (2.9%) Occasional dysuria, pain on ejaculation and a tender prostate in 1/9 (11.1%)	oldest patient in this group (73 years) complained of a “wet dream” with blood-stained semen and found to have an obvious prostatic carcinoma on DRE
6	W. Weidner (1991) Germany	Prospective	72	38 y (19-72)	Complained of more than one bout of hemospermia before attending the prostatitis outpatient department	Recurrent bouts of hemospermia over periods ranging from 1 month to more than 2 years in 60/72 (90%) Hemospermia of <1 month in 12/72 (10%) Hemospermia was the main symptom in 62/72 patients (86%)	Dysuria in 17/72 (23.6%), testicular pain in 9/72 (12.5%), perineal pain in 17/72 (23.6%) and prostatism in 28/72 (38.9%)	N/A
7	GK. Papp (1994) Hungary	Retrospective	84	28-71 y (median 52 y)	Presence of Hematospermia	Hematospermia only	N/A	N/A
8	GK. Papp (2003) Hungary	Retrospective	205		Presence of Hematospermia	Hematospermia only	N/A	N/A
9	Misop Han (2004) USA	Prospective	139/26126	61 y (range 40 to 89)	Community based prostate cancer screening. Men with a history of prostate cancer, acute prostatitis or prostate biopsy was excluded from study	Hematospermia in 139/26126 (0.5%)	History of hematuria in 187/26126 (0.7%)	Suspicious DRE in patients with hematospermia in 21/139 (15%) & in the overall screening population 1984/26126 (7.6%)

10	Ellen Bamberger (2005) Israel	Prospective	16	33 y (17-66)	A recent history of hematospermia Non-infectious aetiologies were excluded	Hematospermia was the only current symptom in all 16/16 (100%) Recurrent Hematospermia lasted for 1-24 months in 12/16 (75%), <1 m-2/16 (12.5%), Not sure-2/16 (12.5%)	Two or less sexual partners in the last 6 months in 13/16 (81%), seldom use of condoms-2/16 (12.5%), never use condoms-14/16 (87.5%) Sex-organ lesions in 2/16 (12.5%) Prostatism and dysuria in 1/16 (6.25%)	N/A
11	Pal (2006) India	Prospective	35	22-64 y	Presence of Hematospermia	Single episode of hemospermia in 23/35 (65.7%) Recurrent episodes in 12/35 (34.3%)	N/A	N/A
12	M. Manoharan (2007) USA	Prospective observational	63	61.5 (78) y	Patients who underwent TRUS-PB were included. Men who were not able to ejaculate were excluded	No history of hemospermia within 6 months before the date of procedure-0/63 (0%) Hemospermia during the first week in 32/38 (84.2%) At 8 weeks, one man (2.6%) had persistently altered blood in the ejaculate, but this cleared in 10 weeks Mean duration of hemospermia was 3.5 (71.7) weeks	Past history of prostatitis in 4/38 (10.5%) No bleeding history in any patient 0/38	DRE was performed but results are not available
13	C. Wilson (2010) UK	Retrospective	41	54 y (range 26-77)	Patients with hematospermia were included. Patients with an elevated PSA were excluded from this study	N/A	N/A	None had an abnormal DRE
14	Ashish A. Kumar (2011) UK	Prospective	118 <40-14/118 (11.9%) ≥40-104/118 (88.1%)	53 y	Presence of hematospermia within six months and a clinician's decision to investigate	<40 y-Hematospermia was the only symptom in 14/14 (100%) ≥40 y-multiple episodes of hematospermia alone in 59/104 (56.7%)	Triad of hematospermia, a raised PSA and an abnormal DRE in 14/104 (13.5%)	<40-enlarged prostate on DRE in 1/14 (7.1%) ≥40-18/104 (17.3%) of men had BPE on DRE with a normal PSA. Abnormal DRE and/or raised PSA in 27/104 (26%)
15	Yeung H. Ng (2012) UK	Prospective	300/18987 (1.5%)	54 y-range 16-82 y	Patients whose hematospermia was a consequence of recent prostate biopsies was excluded	Hematospermia was the main symptom in all (100%)	LUTS in 39/300 (13%), Hematuria in 36/300 (12%), Testicular/penile pain in 26/300 (8.7%). Defaulted further review-26/300 (8.7%)	An Abnormal DRE or PSA>3.0 ng/dl in 33/300 (11%)
16	Hongwei Zhao (2012) China	Prospective	270	41.2 y (15 to 75)	Presenting with hematospermia	The duration of symptoms was 1 day to 8 years (Mean-3.4 months)	N/A	DRE was performed but results are not available
17	J. Zargooshi (2013) Iran	Retrospective	165	38 y (18-76)	Presenting with hematospermia to urology clinic with specialised sexual medicine	144 had hemospermia in 1 visit, 21 had in 2 or more visits	Urinary calculi: 41 (24.8%), flank pain: 21 (12.7%), testicular pain: 18 (10.9%), ejaculatory pain: 4 (2.4%), erectile dysfunction: 37 (22.4%), LUTS: 35 (21.2%), infertility: 15 (9.1%), epididymo-orchitis: 8 (4.8%), varicocele: 27 (16.3%)	PSA and DRE normal in all
18	Seiji Furuya (2016) Japan	Prospective	189	21-78 y <50 (52.4%) ≥50	Present with painless Hematospermia Excluded 10 due to underlying causes	Only the Hematospermia was considered	Prostatitis-like symptoms in 3/189 (1.6%) (e.g. pelvic pain and lower urinary tract symptoms). Abnormal lesions were found in the genitourinary tract in 122/189 (64.5%)	N/A

19	Long Tian (2018) China	Retrospective	22 SVC=7, PUH=15	SVC=34.1 ± 14.0 PUH=44.5 ± 10.8	Presence of seminal vesicle calculi (SVC) or posterior urethral hemangioma (PUH)	SVC-recurrent hematospermia. Dark red blood-semen mixture with ejaculation pain and no blood clots PUH-recurrent hematospermia and urethral opening bleeding after sexual arousal. No visible blood-semen mixture, bright red semen with blood clots, and no ejaculation pain	N/A	N/A
20	Sivanandan (2019) Sri Lanka	Prospective	94	43.7 y (23-67 y)	Hemospermia treated at the urology unit of CSTH Patients who had undergone any instrumentation or biopsy of the lower urinary immediately before the onset of hemospermia were excluded	Hemospermia ranged from a single episode to recurrent episodes over 6 months Anxiety about malignancy in 51/94 (55.4%)	Post-ejaculatory penile, testicular, perineal or groin pain in 15/94 (16%) Dysuria in 3/94 (3.2%) Hematuria in 2/94 (2.1%) Hemopyospermia in 1/94 (1.1%) Antiplatelet drugs in 7/94 (7.4%)	Abdomen-normal. Prostate-clinically malignant prostate in 1/94 (1.1%). Tender prostate in 3/94 (3.2%). Epididymis, cord structures-normal

UK-United Kingdom, USA-United States of America, DRE-Digital Rectal Examination, TRUS-PB-Trans Rectal Ultrasonography-Prostate biopsy, UAE-United Arab Emirates, PSA-Prostate Specific Antigen, BPE-Benign Prostatic Enlargement, SVC-Seminal Vesicle Calculi, PUH-Posterior Urethral Hemangioma, CSTH-Colombo South Teaching Hospital.

12, 13, 18]. Inflammatory conditions of the urogenital tract where pus cells were present in urine analysis with a negative urine culture for bacteria were reported in 169/836 study participants (20.2%) [1-4, 10, 12, 16, 19]. The presumptive diagnoses were prostatitis in 112/836 (13.4%), epididymitis in 19/327 (5.8%), urethritis in 5/65 (7.8%) and non-specified in 33/836 (3.9%). Calculi (prostatic/seminal vesicular/urethral) were reported in a total of 89/938 patients (9.5%) [1, 3, 4, 6, 10, 19, 20] and systemic hypertension was reported as the probable etiology in 23/298 (7.7%) [1, 3, 4]. Malignancies were detected in 5.4% (n=74/1362, 11 studies) of patients more than 40 years old. The majority had prostatic carcinoma (67/74, 90.5%) [1, 3-6, 13-18]. Etiology was unknown in 51.8% (n=603/1163) (**Table 2** [1-6, 10-23]).

Treatment and outcome of hematospermia

As expected, treatment given was based on the diagnosis. Anti-infective treatments were given to patients who became culture positive or who had hemato-pyospermia. Benign prostatic enlargement (n=21) was either managed medically or surgically, but clear data were not available in most of the studies. Radical prostatectomy, radical radiotherapy, brachytherapy and androgen deprivation therapy were carried out for patients diagnosed with prostatic carcinoma where appropriate (n=67). Transurethral endoscopic surgery was performed for nine patients who had persistent hematospermia for more than 24 months [19]. Transurethral unroofing was carried out for six patients with midline cysts of the prostate. Transurethral resection of the ejaculatory duct was performed for three patients with ejaculatory duct obstruction [19]. A case of posterior urethral hemangioma was treated with transurethral resection and fulguration [20]. Definitive treatment of the underlying etiology resolved the symptoms in 260/347 (74.9%) while spontaneous resolution occurred in 88.9% (n=168/189) with an unknown etiology (**Table 3** [1-6, 10-23]).

Discussion

Our systematic review was aimed at analyzing the studies that described the clinical characteristics and outcome of hematospermia. According to our review, primary hematospermia was benign in almost all patients and concurrent symptoms like dysuria, hematuria, testicular or epididymal pain would merit further evaluation. Appropriate treatment for the underlying cause if found was adequate in the majority. In this systematic review, approximately 50% had no apparent etiology. This may be due to lack of high-quality studies and significant heterogeneity and variations in investigations due to lack of guidelines or standard of care.

Han and colleagues reported a higher percentage of suspicious DRE in patients with hematospermia compared to the overall screening population - 15% vs. 7.6% [15]. However, this study was conducted in a population undergoing screening for prostate cancer (age was more than 50 years or age over 40 years in the presence of a family history of prostate cancer). Therefore, the high rates were due to the sampling bias and such results cannot be extrapolated to hematospermia in the general population. In another study, the triad of hematospermia, abnormal DRE findings and elevated PSA was reported to be clinically significant as 57.1% of them were eventually diagnosed with prostate cancer [16]. Additionally, abnormal DRE and/or raised PSA level were seen among a considerable number of patients with hematospermia (19.3%) [6, 16]. Wilson and colleagues in his study of 41 patients (mean age-54 years, range 26-77 years), suggested to have a serum PSA level in all patients with hematospermia as 5-7% of them were found to have prostate cancer [5]. Variability in the proportion of prostate cancer as the cause for hematospermia in different studies may be related to the differences in the study population and the changing prevalence of prostate cancer in respective countries.

Following the initial workup, most patients are left with negative findings. Such patients can be reassured and do not require routine urological follow-up. Adequate reassurance is mandatory as the symptom may be associated with significant fear and anxiety. One study reported a positive correlation between anxiety scores and the duration of hematospermia with reduced sexual activity due to the condition [21]. Isolated episodes can safely be managed in the community level and patients should only be referred to a specialized uro-

Table 2. Investigations and Aetiology of hematospermia

	Author & Year	Investigations	Aetiology	Aetiology Unknown
1	Tolley (1975)	Urine microscopy and cultures normal in all (100%) AFB negative in checked 18/18 (100%) Signs of outflow obstruction on excretion urography in 1/24 (4.2%) Abnormal pan endoscopy in 2/20 (10%)	Trauma in 2/26 (7.7%) Hemophilia in 1/26 (3.8%) hemangioma of the glans penis in 1/26 (3.8%)	18/26 (69.2%)
2	Henry (1977)	Positive urine cultures in 4/65 (6.2%), Urine cultures for AFB positive in 3/40 (7.5%) Semen cultures positive in 6/12 (50%)-clinical evidence of prostatitis only in 1 IVU-Renal TB changes in 3/40 (5%)-calcifications in one of them and confirmed histologically Pan endoscopy-oedematous verumontanum in 15/23 (66.2%), Normal in 8/23 (34.8%)	Urinary TB in 7/65 (10.8%) UTI in 4/65 (6.2%) Prostatitis in 6/65 (9.2%)	
3	Fletcher (1981)	Seminal analysis positive in 22/41 (54%) Cystourethroscopy positive in 26/52 (50%) Vasography positive in 16/22 (73%) Prostatic biopsy showed BPH in 7/7 Urine analysis/cultures positive in 22/76 (29%) IVU 4/58 (6%)	Inflammatory cause in 54/81 (66.7%)-Prostatitis or seminal vesiculitis in 41, epididymo-ochitis in 12, extensive urethral condylomata in 1 TB in none Trauma in 3/81 (3.7%) Neoplastic cause in 6/81 (7.4%)-Prostate in 3, bladder in 2, urethra in 1 Miscellaneous in 7/81 (8.6%)-Urethral stricture in 1, BPH in or prominent veins in 4, amyloidosis in 2	11/81 (13.6%)
4	GY. PAPP (1981)	Hemato-pyospermia in 1/38 (2.6%) Prostate concrement (obtained together with the ejaculate) of microscopic size causing hematospermia was observed A cystic change causing hemato-pyospermia was detected in a 42 year old patient	Chronic prostatitis in 9/38 (23.7%) Prostatic calculi in 6/38 (15.8%) Chronic epididymitis in 5/38 (13.2%) Specific epididymitis in 2/38 (5.3%) Trichomoniasis in 2/38 (5.3%) Prostatic tuberculosis in 3/38 (7.9%) Testicular tuberculosis in 1/38 (2.6%) Seminal vesicle tuberculosis in 1/38 (2.6%) Intraurethral condyloma in 1/38 (2.6%)	7/38 (18.4%)
5	DJ. Jones (1991)	Pus cells seen on microscopy of seminal fluid in the patient with dysuria, pain on ejaculation and tender prostate One patient had calcified seminal vesicles also noted on plain X-ray However, early morning urine specimens were negative and no ova or cysts were seen on urine microscopy	Up to age 40 y (n=65) Prostatitis 21/65 (32.3%)-[Positive semen culture in 6/21 (28.6%) and Pus cells seen 13/21 (61.9%)] Urethritis 5/65 (7.7%) Urinary tract infection 1/65 (1.5%) Urethral stricture 1/65 (1.5%) Self-instrumentation 1/65 (1.5%) Posterior urethral vein 1/65 (1.5%) Sexual excess 1/65 (1.5%) Meatal papillomata 1/65 (1.5%) Urethral condylomata 1/65 (1.5%) Prostatic calculi 1/65 (1.5%) Above 40 y (n=9) BPH in 5/9 (55.5%) Friable veins in the prostatic urethra and bladder neck in 3/9 (33.3%) Hypertension in 3/9 (33.3%) Prostatic carcinoma in 1/9 (11.1%)	31/65 (47.7%)

6	W. Weidner (1991)	Erythrocytes detected in 62/72 (86%) Non-bacterial prostatitis in 19/72 (26.4%) Elevated leucocytes in 9/19 (47.4%) C. trachomatis positive in 6/19 (31.6%) Ureaplasma positive in 4/19 (21%) Tuberculosis negative in all Local urethral bleeding in 6/72 (8.3%)-Prostatic CA in 1/6 (16.7%) Persistent asymmetry of seminal vesicles in 20/72 (27.8%) Transrectal prostatic ultrasonography demonstrated-Adenoma in 18/72 (25%) Prostatic calcification in 5/72 (6.9%) with chronic bacterial prostatitis Cystic lesions in 4/72 (5.5%)	Urogenital infections were found in 36/72 (50%) Symptomatic urethritis, epididymitis and prostatitis were diagnosed in 33/72 (45.8%) General and local disorders usually associated with hemospermia were found in 18/72 (25%)	3/72 (4.2%)
7	GK. Papp (1994)	N/A	Prostate calculi in 17/84 (20.2%) Chronic prostatitis in 11/84 (13.1%) Prostate cancer in 7/84 (8.3%) Posterior urethral vessels in 6/84 (7.1%) Chronic epididymitis in 6/84 (7.1%) Hypertension in 5/84 (6%) Trichomoniasis 4/84 (4.7%)	13/84 (15.4%)
8	GK. Papp (2003)	N/A	Prostate calculi 50/205 (24.4%) Chronic prostatitis 39/205 (19%) Prostate cancer 7/205 (3.4%) Tumour prostate 10/205 (4.9%) Posterior urethral vessels 11/205 (5.4%) Chronic epididymitis 6/205 (2.9%) Hypertension 15/205 (7.3%) Trichomoniasis 4/205 (1.9%)	31/205 (15.1%)
9	Misop Han (2004)	PSA between 2.6 and 10 ng/ml in 30/139 (22%) (16% of men in the overall screening population)	Prostate cancer was diagnosed in 13.7% (19 of 139). In overall screening population was 6.5% (1,708 of 26,126 cases, p=0.001). Half of the men were 60 to 69 years old	N/A
10	Ellen Bamberger (2005)	PCR was performed only in 1/16 (6.25%) and positive for HSV-2 N. gonorrhoeae was neither cultured nor detected by PCR or semen and urine specimens	Infectious agent in 12/16 (75%) HSV in 5/12 (42%) (HSV-2 in 4/5 (80%) & HSV-1 in 1/5 (20%)), C. trachomatis in 4/12 (33%), Enterococcus faecalis in 2/12 (17%) & U. urealyticum in 1/12 (8%)	NA
11	Pal (2006)	NA	Genitourinary infections in 14/35 (40%)-genitourinary TB in 5/35 (14.3%) Prostatic biopsy 2/35 (6%) Carcinoma prostate 2/35 (6%) Post hemorrhoidal injection 1/35 (3%) Prostatic calculi 1/35 (3%) Prostatic abscess 1/35 (3%)	NA
12	M. Manoharan (2007)	Mean PSA was 6.9 (± 9) ng/ml Mean estimated volume of the prostate was 52 (± 24) ml Previously done prostate biopsies in 5/38 (13.2%)	Positive biopsy for prostate cancer in 12/63 (19%)	9/35 (25.7%)
13	C. Wilson (2010)	PSA was elevated beyond age related reference range in 5/41 patients (12%)-all of whom had prostate biopsies Biopsies were performed for elevated PSA or abnormal DRE in 7/41 (17%) patients Abdominal ultrasound was performed in 21/41 (51%) Flexible cystoscopy was performed in 35/41 (85%)	Prostate cancer was demonstrated histologically in 2/41 (4.9%) patients (both Gleason 3 + 3). A prostate cancer incidence of 5%, rising to 7% if histologically unconfirmed cancer is included and 85% (35/41) of patients were discharged at review	90% of subjects

14	Ashish A. Kumar (2011)	<40-mean PSA 0.2 ng/dL TRUS for all 14/14 (100%). Mean prostate volume on TRUS was 13.3 ml. Abnormal findings on TRUS in 1/14 (7.1%)-Histologically normal. Non-specific calcification within the prostate in 2/14 (14.3%) ≥40-TRUS in 77/104 (74%) who were in two subgroups (59 + 18) Abnormal DRE and/or raised PSA 27/104 (26.0%) Raised PSA and normal DRE in 10/104 (9.6%)-3/10 prostatic cancers were diagnosed from biopsy (30%)	BPE (5.2%), calcification of seminal vesicles and/or ejaculatory ducts (20.8%), ejaculatory duct cysts (2.6%), and seminal vesicle stones (3.9%) Prostate cancers in 7/104 (6.6%) 4/7 (57.1%) in patients with triad of hematospermia, an abnormal DRE and raised serum PSA Prostatitis in 23/118 (20%)-The detection rate in the total population was 7/118 (5.9%)	NA
15	Yeung H. Ng (2012)	Flexible Cystoscopy in 206/469 (43.9%) Renal Ultrasound in 232/469 (49.5%) Scrotal ultrasound in 15/4693.2 (5%) Intravenous Urethrogram in 16/469 (3.4%) Overall diagnostic yield was 0.4% (2/469) 19 had prostate biopsies yielding 12 cases of prostate cancer-12/19 (63.2%)	Overall diagnostic yield was 0.4% (2/469) Infection in 34/300 (11.3%) Stone in 6/300 (2%) Prostate cancer in 13/300 (4.3%) Testicular cancer in 1/300 (0.3%) Polycystic kidney in 1/300 (0.3%) Penile urethral transitional cell carcinoma (1/300) (0.3%) Benign pathology not requiring intervention was picked up in 11/300 (3.7%) Additional presenting features alongside Hematospermia included 38/300 (17%) with LUTS. Of those patients, 8/38 (21.1%) subsequently found to have prostate cancer	240/300 (80%)
16	Hongwei Zhao (2012)	The 14 patients in which no abnormalities were found by TRUS underwent further magnetic resonance image (MRI) examination, and no causative evidence was discovered	One or more pathological conditions that could cause hematospermia in 256/270 (94.8%) TRUS revealed 2 or more abnormalities in 75/270 (27.8%). Malignant tumours in 8/270 (3.0%)-5 prostate cancers, 2 seminal vesicle cancers, and 1 bladder cancer All of the malignancies occurred in patients more than 40 years old and the percentage of malignant diseases was 6.3% in patients more than 40 years old Pathological conditions located in the seminal vesicles in 125/270 (46.3%), in the ejaculatory ducts in 80/270 (29.6%) in the prostate in 149/270 (55.2%) and in the bladder in 1/270 (0.4%). No Cowper gland abnormalities were found	NA
17	J. Zargooshi (2013)	Means of Alphafetoprotein (ng/ml): 2.41 ± SD 1.32, B-Human Chorionic Gonadotrophin (U/L): .16 ± SD 0.61, PSA (ng/ml): 0.9 ± SD, Prostate size (ml): 27.7 ± SD 11.83 All PSA were normal	Urinary tuberculosis: 1/165 Bladder tumor: 1/165 Biopsy-proven benign papillary lesions at verumontanum: 3/165 Bilateral partial ejaculatory duct obstruction by stones: 1/165 All pathologies were found in young patients <32 years	151/157 (96%)
18	Seiji Furuya (2016)	The Meares-Stamey four-glass test was carried out for three patients who complained of prostatitis-like symptoms 3/189 (1.6%) Urethrocystoscopy was carried out for nine patients with initial and/or terminal hematuria. In addition, MRI and TRUS-guided seminal vesicle puncture were carried out for selected patients After aspiration of seminal vesicular fluid, the fluid was subjected to cytological and microbiological examinations	SVH (Seminal vesicle hemorrhage) in 80/189 (42.3) MLC (Midline cyst of the prostate) in 55/189 (29.1) SVD (Seminal vesicle dilation) in 39/189 (20.6) Prostatic polyp in the posterior urethra in 9/189 (4.8) Ejaculatory duct obstruction in 7/189 (3.7) Chronic prostatitis/chronic pelvic pain syndrome in 3/189 (1.6) Benign prostatic hyperplasia in 2/189 (1.1) Seminal vesicle amyloidosis in 1/189 (0.5) Seminal vesicle calculi in 1/189 (0.5)	NA
19	Long Tian (2018)	Urine analysis was normal. transrectal ultrasound was normal or showed hyperechoic shadows in the seminal vesicles in SVC All cases of seminal vesicle calculi occurred in one side, especially in the right seminal vesicle Hemangioma samples were collected from 8 patients to confirm the presence of vessel components with CD31 and CD34 positive staining	Inclusion was made based on the aetiology (SVC or PUH)	NA

20	Sivanandan (2019)	PSA level-<4 ng/ ml in 86 (92.5%), (range: 0.2-11.3 ng/ml; median: 0.98 ng/ml). malignant prostate-PSA level of 11.3 ng/ml-underwent a TRUS-guided core biopsy of the prostate Urine cultures-negative in all Seminal fluid culture-growth in 5/94 (5.3%) Diagnostic cystoscopy-normal in 5/6 (83.3%), urethral stricture in 1/6 (16.7%) Hypertensive patient-S.cr-1.94 mg/dl, Biopsy-mesangio proliferative glomerulonephritis	Prostatitis 27/94 (28.7%) Prostate carcinoma 1/94 (1.1%) Prostatic cyst 1/94 (1.1%) Uncontrolled hypertension 1/94 (1.1%) After sclerotherapy for hemorrhoids 1/94 (1.1%) Post-chemotherapy 1/94 (1.1%) After epididymectomy 1/94 (1.1%)	61/94 (64.9%)

BPH-Benign Prostatic Hyperplasia, HSV-Herpes Simplex Virus, PSA-Prostate Specific Antigen, DRE-Digital Rectal Examination, TRUS-Transrectal Ultrasonography, SVC-Seminal Vesicle Calculi, PUH-Posterior Urethral Hemangioma, S.cr-Serum Creatinine, SD-standard deviation.

Table 3. Interventions, outcome and other important facts

	Author & Year	Interventions	Outcome	Other facts
1	Tolley (1975)	Transurethral resection in 1/26 (3.8%) who had median lobe enlargement	N/A	Changes in sexual activity play no part in its causation Primary hemospermia as the only symptom need no further investigation, whereas, those with hemospermia and other urologic symptoms require further investigation
2	Henry (1977)	Anti-TB treatment for 7/65 (10.8%)	Spontaneous remission in 29/65 (44.7%) Intermittent attacks in 36/65 (55.4%)	Hemospermia is essentially a benign and self-limiting disease and detailed urologic investigation is seldom indicated unless tuberculous infection is strongly suspected
3	Fletcher (1981)	Antibiotics for patients with infections	Resolved hemospermia in all who were treated with antibiotics (dramatic response of condylomata patient was seen to 5-FU cream)	N/A
4	GY. PAPP (1981)	Transurethral resection, orchidectomy, epididymectomy. Antibacterial treatment for the patient with hemato-pyospermia	N/A	N/A
5	DJ. Jones (1991)	TURP in 1/9 (11.1%) Antibiotics for 1/9 (11.1%) TURP and hormonal therapy for the patient with prostatic carcinoma Treated with diathermy in a patient with condylomata Meatal papilloma was treated by cauterisation	Reduced levels of hematospermia in 9/65 (13.8%) and remaining cases were resolved at 3-month review	N/A
6	W. Weidner (1991)	N/A	N/A	N/A
7	GK. Papp (1994)	N/A	N/A	All patients should undergo a careful investigation to rule out the presence of malignancy or other significant disease
8	GK. Papp (2003)	N/A	N/A	Only 2.4% of the malignancies occurred in patients under 40 years of age. Hence a detailed diagnosis is advocated in hemospermia patients over 40 years
9	Misop Han (2004)	Two-thirds (66.7%) of the men elected radical prostatectomy	Hemospermia was a predictor of prostate cancer diagnosis after adjusting for age, PSA and DRE results (OR 1.73) The presence of hemospermia closely approached statistical significance (P=0.054) Interestingly hematuria was not significantly associated with prostate cancer in the multivariate logistic regression model (OR 0.75, P=0.32)	the observed frequencies of prostate cancer in men with and without hemospermia were significantly different from the expected frequencies of prostate cancer (P=0.035) based on age, DRE, PSA and the year of entering screening

10	Ellen Bamberger (2005)	Appropriate antibiotics in case where a pathogen was identified. The treatmet protocol was valacyclovir for HSV, Doxycycline for C. trachomatis and U. urealyticum, amoxicillin for Enterococcus faecalis The 5 patients for whom no pathogen was identified were referred to a urologist for further evaluation	Symptoms resolved for each patient following therapy All 12 patients remained free of disease during the 1-year follow-up. The 5/16 (31.25%) whom no pathogen was identified were referred to a urologist for further evaluation	N/A
11	Pal (2006)	Milin's prostatectomy for the patient with prostatic enlargement TURP for CA prostate + ochidectomy and hormone therapy TURP for BPH TURP and antibiotics for prostatic abscess	Symptoms resolved in prostatic abscess	N/A
12	M. Manoharan (2007)	Men were instructed not to take aspirin or non-steroidal anti-inflammatory agents for at least 5 days before the procedure All patients were started on 3-day course of a fluroquinolone antibiotic before the procedure No pre-biopsy bowel preparation or cleansing enema was used	Anxiety scores and the number of ejaculations had positive correlation with the duration of hemospermia (P=0.04, P=0.047)	None of the clinical and pathological factors was a significant predictor of the duration of hemospermia
13	C. Wilson (2010)	N/A	In follow up of these patients, one had subsequently developed a renal tumour 9 years after the initial diagnosis and is being assessed for surgery One patient developed a superficial (TaG2) bladder transitional cell carcinoma near the left ureteric orifice. This patient previously had a normal flexible cystoscopy during hematospermia evaluation 8 years before No specific diagnosis was made in 90%, and 85% of patients were discharged at review	Flexible cystoscopy and abdominal ultrasound appear always to be normal in patients who have hematospermia and a normal physical examination and should not be used routinely. Prostate specific antigen testing is mandatory in view of the 5-7% detection rate for prostate cancer. The pickup of testis malignancy is 2%. Isolated self-limiting episodes of hematospermia can safely be managed in general practice and only referred in the presence of abnormal examination, elevated PSA or recurrent episodes unresponsive to 5-alpha reductase therapy
14	Ashish A. Kumar (2011)	<40 y-Given the negative clinical findings patients received reassurance and advice regarding the changes to their semen and discharged back to their general practitioner	<40 y-Re-presentations within at least 3 years 0/14 (0%)	N/A
15	Yeung H. Ng (2012)	Radical prostatectomy in 7/12 (58.3%), radical radiotherapy in 1/12 (8.3%) and brachytherapy in 2/12 (16.7%). Metastatic disease in 0/12 (0%)	469 investigative episodes, only 2 (0.4%) resulted in findings of significant new pathology which required surgical intervention	An abnormal DRE or a PSA of greater than 3.0 ng/dl would seem a reasonable level to offer prostate biopsies Investigation for hematospermia such as routine cystoscopy, ultrasound and IVU are questionable unless merited by concomitant presenting features or for reassurance in persistent cases
16	Hongwei Zhao (2012)	N/A	N/A	N/A
17	J. Zargooshi	Empiric treatment with a fluoroquinolone (Ciprofloxacin) plus an nonsteroidal anti-inflammatory drug (Celecoxib) for all. Definitive treatment for underlying causes: NA	Hemospermia was absent in the second visit and never recurred in 149/157 patients Lost to follow up: 8/157 patients Persistent mild symptoms: 2/157 Definitive aetiology: 6/157-outcome not mentioned	No difference in outcome among patients with more than one symptom besides hemospermia, including ejaculatory pain or infertility. None had life threatening causes

18	Seiji Furuya (2016)	Transurethral endoscopic surgery was carried out for nine patients after their hematospermia persisted for 24 months Transurethral unroofing was carried out for six patients with MLCs TURED for three patients with EDO	Hematospermia resolved spontaneously in 168/189 (88.9%) Mean disease duration was 1.5 months The duration was 22 months in 15/189 (7.9%) Unclear of the disappearance in 6/189 (3.2%) Hematospermia duration was significantly longer in those with SVH, those with MLCs, and those aged 50 years or older Persistent symptoms >1 year in 23/189 (12.2%)-All 23/23 (100%) had abnormal lesions Recurrence of hematospermia was found in 20/189 (13.5%) The time until recurrence after spontaneous resolution was 12 months Recurrence-free rates were 96.6% at 3 months, 89.0% at 1 year, 84.8% at 5 years and 78.2% at 10 years	Specific underlying diseases were not strongly involved in the recurrence of hematospermia
19	Long Tian (2018)	SVC-anti-infective treatment and holmium laser lithotripsy and basket extraction under a transurethral seminal vesiculoscopy PUH did not respond to anti-infective treatment and was treated with transurethral resection and fulguration	SVC-could improve after anti-infective treatment For both groups, clinical symptoms gradually disappeared during follow-up, with no complications of urinary incontinence, urethral bleeding, urethral stricture, urination pain, retrograde ejaculation, ejaculation pain, orchitis, or epididymitis	N/A
20	Sivanandan (2019)	Prostate CA-Radical radiotherapy and androgen deprivation therapy Prostatitis-levofloxacin (500 mg daily) for 28 days Patients with bladder outflow obstruction and those with continued hemospermia (44 patients) were given finasteride Prostate cyst-deroofed endoscopically	Recurrences in 11/94 (11.7%)-self-limiting in 10/11 Deroofed cyst-Continuous hemospermia and prostatitis. Settled after several months and many courses of antibiotics	N/A

TURP-Transurethral Resection of the Prostate, PSA-Prostate Specific Antigen, DRE-Digital Rectal Examination, OR-Odds ratio, IVU-Intravenous Urogram, MLC-Midline cyst of the prostate, TURED-transurethral resection of the ejaculatory duct, EDO-ejaculatory duct obstruction, SVH-Seminal vesicle hemorrhage, SVC-Seminal Vesical Calculi, PUH-Posterior Urethral Hemangioma.

logical service in the presence of abnormal examination findings, elevated serum PSA, or recurrent episodes [5, 24].

Microbiological analysis of semen including cultures may be required in selected patients as infections of the urogenital tract were responsible for approximately 20% of patients. However, only five studies have assessed patients for genito-urinary TB, It seems that the available data is inadequate to comment on the prevalence of genito-urinary TB among patients with hematospermia, as the prevalence of genitourinary TB is highly variable in different countries [12]. Malignant etiologies were rare in patients with hematospermia particularly in patients less than 40 years. Nevertheless, few studies have demonstrated a high incidence of malignancies among patients more than 40 years group [4, 16, 17].

Clinical practice recommendations

In a patient complaining of hematospermia, a spot semen sample may be needed for confirmation of the symptom in selected doubtful circumstances as semen can get contaminated with blood originating from other parts of the urogenital tract and/or female genital tract after coitus. A detailed history including sexual history, frequency of intercourse and other associated symptoms particularly dysuria, testicular pain, perineal pain, hematuria, lower urinary tract symptoms and previous history of sexually transmitted infections is important to narrow down the most probable diagnosis [1, 6, 11]. In a study among sexually active patients with hematospermia, 12 out of 16 (75%) patients were culture positive for sexually transmitted infections and most were having risk factors such as past history of sexually transmitted diseases or partners with sexually transmitted diseases [11]. Uncontrolled hypertension should not be missed in any patient presenting with hematospermia as treatment may be required urgently [25]. Attention to antiplatelet drugs is important as clopidogrel has been reported to be associated with hematospermia [26]. Careful examination of external genitalia should be performed with the aim of finding any associated lesions and to exclude micro lesions of the frenulum that may have occurred during coitus. Palpation of the testes and epididymis for tenderness and for suspicious lesions, including inguinal lymph nodes is necessary. DRE of the prostate is a key assessment in these patients to identify any abnormalities raising suspicion. Microscopic analysis and culture of semen/urine in sexually active men seemed valuable as a short course of anti-infective treatment was shown to be effective. In men over 40 years, a serum PSA level is important to supplement the clinical assessment. Yeung H Ng and colleagues suggested to proceed with a prostate biopsy in men over 40 years with an abnormal DRE or a PSA of greater than 3.0 ng/ml [6].

It appears that extensive investigations of all patients with hematospermia would lead to wastage of resources and time, and would be harmful by causing more anxiety among patients. Yeung H Ng and colleagues had only managed to obtain a diagnostic yield of 0.4% following multiple investigations while Hongwei and colleagues could not find any abnormality even with transrectal ultrasound scan (TRUS) and magnetic resonance imaging (MRI) scans [6, 17]. Even if abnormalities were detected with TRUS or MRI, it would be difficult to conclude whether these abnormalities were mere associations or causative of hematospermia. Therefore, further endoscopic assessment or advanced imaging should be performed only if the patient is having additional symptoms such as dysuria, hematuria and lower urinary tract symptoms which require evaluation on their own merit [22]. Therefore, cystoscopy, intravenous urogram (IVU) and abdominal ultrasonography are discouraged unless merited by concomitant presenting features or for reassurance in persistent cases [5, 6, 14]. Advanced imaging such as TRUS or MRI may be of value in older patients with persistent symptoms for a prolonged period or frequently recurring episodes disturbing the quality of life [27].

Among patients with a detectable underlying cause, appropriate treatment resolved the symptoms in a majority (75%). Transurethral surgeries for benign etiologies were beneficial only in the presence of persistent symptoms [19]. Hematospermia can occur commonly following TRUS guided core biopsies of the prostate. Resolution of the symptom is complete in almost all patients within a month according to a study done in the USA. However, it has been shown to cause a considerable impact on

Table 4. Availability of information in the studies included in relation to the objective of the systematic review

Study	Author	Study Type	Single/Multicentre	Selection criteria defined	Comparison group involved	PSA levels	Microbiological studies	Aetiological diagnosis	Interventions mentioned	Outcome mentioned	Steps taken to minimise bias
1	Tolley (1975)	Prospective	Single-centred	Yes	No	No	Yes	Yes	Yes	Yes	No
2	Henry (1977)	Prospective	Single-centred	Yes	No	No	Yes	Yes	Yes	Yes	No
3	Fletcher (1981)	Prospective	Single-centred	Yes	No	No	Yes	Yes	Yes	Yes	No
4	GY. PAPP (1981)	Prospective	Single-centred	No	No	No	No	Yes	Yes	No	No
5	DJ. Jones (1991)	Prospective	Single-centred	Yes	No	No	No	Yes	Yes	No	No
6	W. Weidner (1991)	Prospective	Single-centred	Yes	No	No	Yes	Yes	No	No	No
7	GK. Papp (1994)	Retrospective	Multicentred (2)	Yes	No	No	No	Yes	No	No	No
8	GK. Papp (2003)	Retrospective	Single-centred	Yes	No	No	No	Yes	No	No	No
9	Misop Han (2004)	Prospective	Community-based screening	Yes	No	Yes	No	Yes	Yes	Yes	No
10	Ellen Bamberger (2005)	Prospective	Single-centred	Yes	No	No	No	Yes	Yes	Yes	No
11	Pal (2006)	Prospective	Single-centred	Yes	No	No	Yes	Yes	Yes	Yes	No
12	M. Manoharan (2007)	Prospective observational	Single-centred	Yes	No	Yes	No	Yes	Yes	Yes	No
13	C. Wilson (2010)	Retrospective	Single-centred	Yes	No	Yes	No	Yes	No	Yes	No
14	Ashish A. Kumar (2011)	Prospective	Single-centred	Yes	No	Yes	No	Yes	No	Yes	No
15	Yeung H. Ng (2012)	Prospective	Single-centred	Yes	No	No	No	Yes	Yes	Yes	No
16	Hongwei Zhao (2012)	Prospective	Single-centred	Yes	No	No	No	Yes	No	No	No
17	Zargooshi (2013)	Retrospective	Single-centred	Yes	No	Yes	No	Yes	No	Yes	No
18	Seiji Furuya (2016)	Prospective	Single-centred	Yes	No	No	No	Yes	Yes	Yes	No
19	Long Tian (2018)	Retrospective	Single-centred	Yes	No	No	Yes	Yes	Yes	Yes	No
20	Sivanandan (2019)	Prospective	Single-centred	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

patients' lives and proper counselling is needed to avoid undue anxiety and alterations in sexual activity [21].

Limitations

Only one study was a multicenter study and the rest were single-center studies. Detailed histories were lacking in most studies to identify probable risk factors and rectal examination results were not properly reported. Main interventions and their outcome with long term follow up were lacking in a large proportion of studies. Availability of information in the included studies as per objective of the systematic review is given in **Table 4** [1-6, 10-23]. A meta-analysis could not be performed due to the heterogeneity in the reporting of clinical characteristics and outcomes.

Conclusions

Hematospermia is generally a benign symptom. Urogenital infections/inflammation and prostatic/seminal vesicular calculi are commonly found etiologies. Malignancies are rare and occurred mainly in men over 40 years of age. Clinical assessment focusing on known etiologies including a DRE and serum PSA level are sufficient to identify most proven causes of hematospermia. Urine and seminal fluid microscopy and culture are useful in sexually active men. There was no identifiable pathology in half of those with hematospermia and adequate reassurance is therefore important to avoid undue anxiety among them. Spontaneous resolution of symptoms occurs in the vast majority and chances of recurrences are low. Further evaluation with or without intervention is justifiable in patients with persistent symptoms and associated impaired quality of life.

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Disclosure of conflict of interest

None.

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Table S1. Risk of bias assessment of included studies

	Tolley (1975)	Henry (1977)	Fletcher (1981)	Papp (1981)	Jones (1991)	Weidner (1991)	Papp (1994)	Papp (2003)	Han (2004)	Ellen (2005)	Pal (2006)	Manoharan (2007)	Wilson (2010)	Kumar (2011)	Yeung (2012)	Zhao (2012)	Zargoorshi (2013)	Seiji (2016)	Tian (2018)	Sivanandan (2019)
1. Is the hypothesis/aim/objective of the study clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3. Are the characteristics of the patients included in the study clearly described?	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4. Are the interventions of interest clearly described?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
6. Are the main findings of the study clearly described?	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1
7. Does the study provide estimates of the random variability in the data for the main outcomes?	0	0	0	0	1	0	0	0	1	1	1	1	1	1	1	0	0	1	1	1
8. Have all important adverse events that may be a consequence of the intervention been reported?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
9. Have the characteristics of patients lost to follow-up been described?	0	0	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
10. Have actual probability values been reported	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	1	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
14. Was an attempt made to blind study subjects to the intervention they have received?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
16. If any of the results of the study were based on “data dredging”, was this made clear?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	0	0	0	0	1	0	0	0	1	1	1	1	1	1	1	1	0	1	1	1
18. Were the statistical tests used to assess the main outcomes appropriate?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
19. Was compliance with the intervention/s reliable?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
20. Were the main outcome measures used accurate (valid and reliable)?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
23. Were study subjects randomised to intervention groups?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	1	1	1	0	1	0	0	0	1	1	1	1	1	1	1	0	0	1	1	1
26. Were losses of patients to follow-up taken into account?	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total score	12	11	13	9	14	12	12	12	17	15	15	14	15	15	15	13	14	15	15	15

NA: not applicable.