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Detection rates of urogenital cancers and benign pathology in men presenting with hematospermia

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Abstract

Background: Hematospermia, although often found to be a benign condition, can be an alarming sign. Consequently, patients can undergo multiple investigations with no current standardized pathway based on data from large series. The aim of this study was to evaluate the incidence of an underlying pathology and the value of diagnostic investigations performed in patients presenting with hematospermia.

Materials and methods: A retrospective review of 393 consecutive men who underwent investigations for hematospermia was performed in a single tertiary center. Patient demographics, radiological and microbiological results were recorded together with symptoms of concomitant hematuria and clinical outcomes.

Results: In this cohort, the overall prostate cancer detection rate was 5.3% and 7.2% in the ≥40 years group. One patient was diagnosed with testicular seminoma detected on scrotal ultrasound scan and one with G1pTa urothelial carcinoma of the bladder detected on flexible cystoscopy. In addition, 5.6% of patients were found to have a significant benign pathology for which intervention was proposed. A total of 288 patients underwent a transrectal ultrasound scan and 58.7% ($n = 169$) of these patients were found to have a positive finding. One hundred ten patients underwent a multiparametric magnetic resonance imaging and 73.6% ($n = 81$) had a positive finding.

Conclusions: Apart from transrectal ultrasound and multiparametric magnetic resonance imaging, the remaining investigations have a low diagnostic yield. Prostate cancer detection was 5.3%; 7.2% in the ≥40 years group, and two further patients were diagnosed with testicular and bladder malignancy. Based on our results, we propose an algorithm for the management of hematospermia to limit unnecessary investigations with the majority requiring reassurance.

Keywords: Differential diagnosis; Ejaculation; Hematospermia; Male; Prostatic neoplasm

1. Introduction

Hematospermia refers to the presence of blood in the semen which is often alarming for the patient and a sign warranting referral to secondary care. Although regarded as a benign condition, patients undergo multiple investigations to ensure that there is no underlying urogenital pathology, particularly malignancy. Recurrent episodes of hematospermia again prompt further investigations although there is currently no agreed consensus on the best imaging modality.

The current literature reassuringly shows that hematospermia is often a benign condition secondary to idiopathic, inflammatory, or infectious causes. It has been estimated to account for 1% of urological symptoms.[1] The reported prostate cancer detection rate varies from 1.1% to 13.7%. The latter however was conducted in a prostate cancer screening group in those who reported hematospermia.[2,3]

The aim of this study was to retrospectively review all patients presenting with hematospermia to a tertiary specialist center to report the diagnostic yield of all the investigations undertaken and the incidence of underlying pathology. Investigations were requested according to individual clinician preferences and therefore are a reflection of the varied practice of urologists investigating the condition.

2. Materials and methods

A single center retrospective study identifying all patients presenting to a tertiary referral center over a 17-year period with a single or recurrent episodes of hematospermia was performed. Patient demographics and the diagnostic investigations performed for each patient were recorded on an institutional database. This comprised radiological investigations including transrectal ultrasound of the prostate (TRUSS), multiparametric magnetic resonance imaging of the prostate (Mp-MRI), computed tomography of the urinary tract (CT) and ultrasonography of the urinary tract (USSKUB), and scrotum. Results of microbiological investigations of the urine and semen cultures and flexible cystoscopy were recorded. The serum prostate specific antigen (PSA) and digital rectal examination (DRE) was recorded for patients ≥40 years. Frequency of

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hematospermia was assessed as either a single episode or recurrent if >1 episode was reported. Associated symptoms of visible hematuria were also documented. Patients who had an existing diagnosis of prostate cancer at the time of the referral were excluded from the study.

All patients in the study were reviewed by a urological surgeon. The investigations were requested at the individual clinicians discretion as there was no standardized pathway for investigation of hematospermia. All follow-up visits were assessed up until the point of data collection with a minimum of 6-month follow-up period to ensure that the initial investigations were completed.

3. Results

In this cohort, the median age of presentation was 50 years (range 15–82 years). A total of 393 patients were included in the study, of which 292 (74.3%) were ≥40 years of age.

Of the 292 patients ≥40 years, 211 (72.3%, 211/292) underwent a PSA test. Of those who did not have a PSA, further 19 (6.5%, 19/292) patients had a DRE the findings of which were normal. Thirty one (14.7%, 31/211) of those who had a PSA test, had an abnormal reading according to the age specific range. Prostate imaging was performed using TRUSS or a Mp-MRI scan of the prostate. Fifty-eight patients underwent both prostate imaging modalities.

Two hundred eighty eight (73.3%, 288/393) patients underwent a TRUSS of which 169 (58.7%, 169/288) were deemed to have a positive finding (total number of findings: $n=187$). In those ≥ 40 years, 4 patients demonstrated a prostate nodule requiring further investigation which led to diagnosis of prostate cancer in 2 patients. No prostate nodules or suspicious lesions were reported in those <40 years. A total of 110 (28%, 110/393) patients underwent a Mp-MRI of the prostate of which 81 (73.6%, 81/110) had relevant findings detected (total number of findings: $n=89$). Thirty-three of these patients had significant PIRAD score prompting further investigation which led to a diagnosis of prostate cancer in 20 patients. No significant PIRAD lesions were reported in those <40 years. A summary of the findings for those who underwent prostate imaging are illustrated in Table 1 and have been separated in to 2 groups (<40 years and ≥40 years).

A bladder lesion seen on USSKUB was excluded during a normal flexible cystoscopy. Ureteric filling defects reported on CT of the urinary tract were excluded with a normal ureteroscopy. No other sinister findings were detected on an USSKUB or CT of the urinary tract. USS of the scrotum identified a 8 mm seminoma in 1 (0.25%, 1/393) patient who was under 40 years of age. Two (0.5%, 2/393) patients aged ≥40 years had benign lesions demonstrated that required no further intervention. Table 2 summarizes the investigations performed for this group.

Table 1

Summary of results of prostate imaging for the investigation of hematospermia in those <40 and ≥40 years.

Imaging modality	Total number of patients (n)	Number of patients with positive findings	Findings	Number of patients (n)	Percentage (%)
TRUSS < 40	74	41	Calcification within the prostate	13	17.6
			Midline prostatic cysts	11	14.9
			Ejaculatory duct stones	7	9.4
			Dilatation/debris within seminal vesicles	5	6.7
			Blood in the seminal vesicles	3	4.0
			Ejaculatory duct obstruction	2	2.7
			Prostatitis	2	2.7
			Stone in the seminal vesicles	1	1.4
TRUSS ≥ 40	214	128	Calcification within the prostate	59	27.6
			Midline prostatic cysts	18	8.4
			Ejaculatory duct stones	17	7.9
			Dilatation/debris within seminal vesicles	21	9.8
			Blood in the seminal vesicles	2	0.9
			Cystic adenomatous changes	14	6.5
			Prostate nodule	4	1.8
			Ejaculatory duct obstruction	3	1.4
			Prostatitis	3	1.4
			Stone in the seminal vesicles	1	0.5
Mp-MRI < 40	20	17	Blood in the seminal vesicles	6	30
			Midline prostatic cysts	3	15
			Zinner syndrome	2	10
			Ejaculatory duct stones	1	5
			Seminal vesicle stones	1	5
			Ejaculatory duct obstruction (due to stone/no clear cause seen)	1	5
			Urachal remnant	1	5
Mp-MRI ≥ 40	90	64	Prostate nodule/PIRAD score ≥3/ "suspicious region"	33	36.7
			Blood in the seminal vesicles	18	20
			Midline prostatic cysts	8	8.8
			Prostatitis	8	8.8
			Dilatation of the seminal vesicle	5	5.5
			Ejaculatory duct stones	1	1.1
			Seminal vesicle stones	1	1.1

Mp-MRI = multiparametric magnetic resonance imaging; TRUSS = transrectal ultrasound of the prostate.

Table 2

Summary of results of other investigations performed.

Investigation	Total number of patients (n)	Number of patients with positive findings	Findings	Number of patients with finding (n)	Percentage (%)
USS scrotum	130	40	Varicocoele	26	20.0
			Microlithiasis	7	5.3
			Orchitis	5	3.8
			Testis lesions:	1	0.8
			Wedge infarct	1	0.8
			Benign 2 mm lesion	1	0.8
			8 mm seminoma	1	0.8
USSKUB	144	8	Renal stone	6	4.2
			Chronic PUJO	1	0.7
			Bladder lesion	1	0.7
CT urinary tract	70	10	Renal stone/bladder stone	6	8.6
			Ureteric filling defect	2	2.9
			Bladder lesion	1	1.4
			Hepatic hemangioma	1	1.4
			Bosniak 2F cyst	1	1.4
Flexible cystoscopy	162	6	Benign bladder/urethral lesion	3	1.8
			G1pTa bladder TCC	1	0.6
			Prostatic stones	1	0.6
			Bladder stones	1	0.6

CT = computed tomography; PUJO = pelvoureteric junction obstruction; TCC = transitional cell carcinoma; USSKUB = ultrasonography of the urinary tract.

Microbiological investigations of the urine and semen were also performed. Of the 76 patients who underwent a semen culture, 5 (6.6%, 5/76) patients were found to have a positive culture. Two hundred sixteen patients underwent a urine culture of which 9 (4.2%, 9/216) had a positive culture. Table 3 illustrates the results of each.

Data regarding the frequency of hematuria experienced as a single episode or recurrent symptom was obtained for 320 patients. Eighty-nine (27.8%, 89/320) patients experienced a single episode of hematospermia whilst 231 (72.2%, 231/320) reported >1 episode.

The overall prostate cancer detection rate in this study was 5.3% (21/393). The median age of these patients was 63 years (range 49–80 years). Two hundred ninety-two patients were ≥40 years, increasing the prostate cancer detection rate in this age group to 7.2% (21/292).

Fourteen of the 21 patients with prostate cancer had an elevated age specific PSA and 7 had an abnormal DRE and underwent prostate imaging and biopsy as per our hospital protocol which led to the diagnosis of prostate cancer in this group. One further patient had a diagnosis of high grade prostatic intraepithelial neoplasia and was kept under PSA surveillance. Table 4 illustrates the histological diagnosis of the 21 patients diagnosed with adenocarcinoma of the prostate and the treatment received.

One hundred sixty-eight patients underwent a flexible cystoscopy of which only 74 (44%, 74/168)) had a concomitant history of visible hematuria. Three bladder lesions were detected in patients with concomitant visible hematuria, one of which was confirmed as a G1pTa urothelial carcinoma of the bladder in a patient ≥40 years.

The detection rate of testicular cancer in this cohort was 0.25%. USS of the scrotum detected one seminoma confirmed on histology after an orchidectomy was performed for an indeterminate testis lesion.

Table 3

Microbiological results of urine and semen tests.

Samples	Microbiological results
Urine culture	*Citrobacter freundi*
	Enterobacter
	Enterococcus
	Escherichia coli (n = 2)
	Streptococcus Agalactiae
	Klebsiella pneumoniae (n = 2)
	Mixed growth
Semen culture	*Klebsiella pneumonia*
	Enterococcus faecalis
	Gram positive cocci
	Mixed growth of *coliforms* and *enterococcus*
	Mixed growth

Table 4

Histological diagnosis and treatment of patients with adenocarcinoma of the prostate.

Histology		First line treatment
Gleason 3+3	10	- Active surveillance (n = 8)
		- RALP (n = 1)
		- HIFU (n = 1)
Gleason 3+4	6	- HIFU (n = 4)
		- RALP (n = 1)
		- ADT (n = 1)
Gleason 4+3	1	- EBRT
Gleason 3+5	1	- ADT + docetaxel
Gleason 4+4	1	- HDR brachytherapy + EBRT
No biopsy	2	- Radiological T3aN0M0 disease. Kept on watchful waiting
		- PI RAD 3/5 lesion on MRI. Transferred to private sector for biopsy; underwent RALP

ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; HDR = high dose-rate; HIFU = high-intensity focused ultrasound; RALP = robotic-assisted laparoscopic prostatectomy.

Table 5
Surgical and radiological interventions performed.

Unilateral/bilateral seminal vesicle washout	n = 6
Ureteroscopy/cystolitholapaxy	n = 4
Bladder biopsy	n = 3
Transurethral deroofing of midline cyst	n = 2
Transurethral resection of ejaculatory ducts	n = 2
Radical orchidectomy	n = 1
Robotic excision of mesonephric duct abnormality (Zinner syndrome)	n = 1
Seminal vesiculogram	n = 1
Transrectal aspiration of 4 cm midline prostatic cyst	n = 1
Prostate artery embolization	n = 1

Twenty-two (5.6%, 22/393) patients in this group were offered some form of intervention based on initial investigations of conditions other than prostate cancer (Table 5).

Two patients with the finding of a thick wall midline prostate cyst and blood seen within a seminal vesicle on MRI underwent a transurethral resection of ejaculatory ducts (TURED). Six patients underwent a unilateral or bilateral seminal vesicle washout. Resolution of hematospermia was seen in 2 patients and recurrence in 6 of which 1 patient requested a redo procedure in view of the initial benefit.

One patient underwent a seminal vesiculogram for stones seen in the seminal vesicles and ejaculatory ducts which demonstrated patent ejaculatory ducts, however calculi and debris remained. He was advised against a TURED procedure in view of his age and to avoid the risks of surgery to his fertility status. A further patient had dilated seminal vesicles with suspected ejaculatory duct obstruction. In view of the symptoms of bladder outflow obstruction, he was offered a transurethral resection of the prostate with TURED and seminal vesicle washout, however the patient requested a prostate artery embolization which he received.

Another patient was found to have a distended/lobulated seminal vesicle which was further evaluated using MRI which showed a dilated seminal vesicle attached to a vestigial ureter. This was in keeping with Zinner syndrome, and following excision of the vestigial ureter and seminal vesicles, his symptoms resolved.

4. Discussion

4.1. Causes of hematospermia

The current literature reassures us that hematospermia is most often a benign condition and largely of an idiopathic, inflammatory or infectious origin. In addition to these recognized causes various case reports have been published highlighting rare diagnoses as the causative factor. The initial history is important in formulating a differential diagnosis. Blood in the ejaculate can arise from any pathological condition within the testis, epididymis, vas deferens, seminal vesicles, prostate, urethra, and bladder. Although the detection rate of malignancy in these organs is low, the inability of being able to provide patients with a clear explanation can be frustrating and prompt further investigations. Table 6 illustrates the differential diagnoses that should be considered during the initial assessment and investigations.[4–6]

4.2. Literature review

The most frequently quoted study by Han et al. conducted in a prostate cancer screening group demonstrates that in a population of men ≥50 years or with risk factors for prostate cancer, men who reported hematospermia at the start of the study (n = 139), 13.7% were diagnosed with prostate cancer.[2] The median age in this sub group was 61 years (range 40–89 years).[2] This study was conducted in a prostate cancer screening group with men over the age of 50 years or in those over 40 years with risk factors for prostate cancer and this may account for the higher prostate cancer detection rate in comparison to our findings.

Table 6
Reported causes of hematospermia.

Idiopathic	
Inflammatory	Prostatitis
	Seminal vesiculitis
	Epididymo-orchitis
Infectious	Sexually transmitted infections
	Mycobacterium tuberculosis
	Urethral condylomata acuminate (associated with HPV 6 and 11)
	Ureaplasma urealyticum
	Urinary tract infections (gram-positive or gram-negative bacteria)
	Schistosomiasis
Congenital	Midline prostatic cysts (likely originating from utricle or Mullerian duct)
	Coagulation disorder (Von Willebrand)
Obstructive	Seminal vesicle stones
	Ejaculatory duct stones
	Ejaculatory duct obstruction secondary to stones/midline cysts/infections
Malignant	Prostate cancer
	Testis cancer
	Seminal vesicle adenocarcinoma
Traumatic	Prostate biopsy
	Prostate surgery
	Radiation to prostate
	Trauma to external male genitalia + perineum
	Hemorrhoid injections
Other	Urethral hemangioma
	Bladder neck/prostate varices
	Excessive ejaculation
	Prolonged abstinence

A case series of 165 patients in Iran reporting long-term outcomes of patients with persistent hematospermia found no cases of prostate cancer in their patient cohort (age range 18–76 years). All of their patients had a normal PSA, DRE and transabdominal USS. However no prostate imaging was performed in this group.[7]

A further case series in Scotland demonstrated similar results to those found in our study. Prostate cancer was detected in 13 out of 223 (5.8%) patients over the age of 40, testicular cancer was detected in one patient and G1pTa of the bladder in one patient out of a total of 296 patients.[8]

A Sri Lankan study comprising 94 patients reported a clinical diagnosis of prostatitis as the commonest diagnosis in 29% with a prostate cancer detection rate of only 1.1%.[3]

In our series, the overall prostate cancer detection rate was 5.3% in the overall cohort and a detection rate of 7.2% in the ≥40 years group. One patient had a finding of an incidental 8 mm testicular lesion found to be a seminoma detected in a patient under 40 years. It is difficult to ascertain the true significance of this relationship and although rare, has been reported in other case reports.[9,10] One patient with concomitant hematuria had a diagnosis of G1pTa urothelial carcinoma of the bladder.

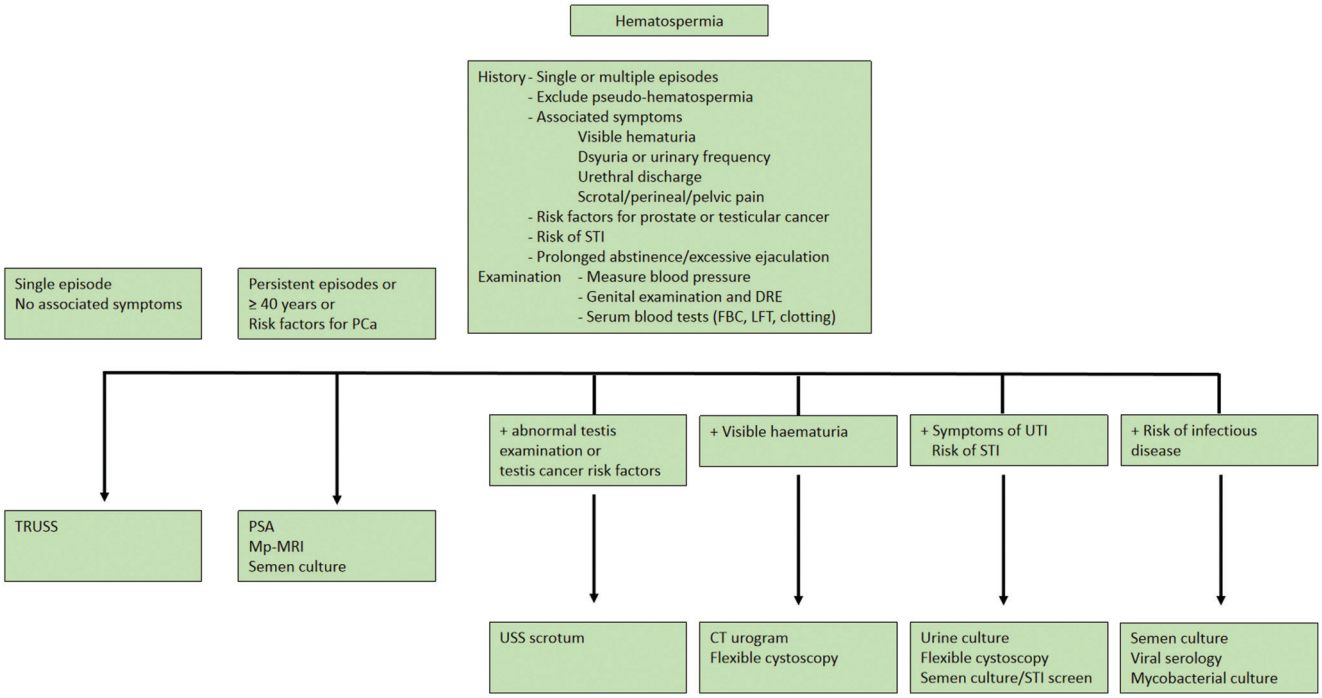

Figure 1. Algorithm for investigation of patients with a single episode or persistent hematospermia. CT = computed tomography; DRE = digital rectal examination; FBC = full blood count; LFT = liver function tests; MP-MRI = multiparametric MRI; PSA = prostate specific antigen; STI = sexually transmitted infections; TRUSS = transrectal ultrasound; USS = ultrasound.

4.3. Investigation of hematospermia

Although there is no formally accepted investigation algorithm for hematospermia in either UK or European guidelines, few articles have proposed algorithms for evaluation and management of these patients.[5,11,12] Based on the findings from our extensive cohort and the current literature we have proposed a risk stratified algorithm for the investigation of patients with hematospermia (Fig. 1).

A detailed history during the initial consultation is essential to work through the differential diagnoses. A condom test has been described to ensure the blood is not originating from the partner although this is rarely undertaken.[6,13] Blood pressure should be measured as hematospermia can be associated with uncontrolled hypertension. Blood tests including full blood count, renal function tests, and a clotting screen should be performed to exclude systemic causes such as coagulation disorders. A PSA should be offered to those ≥40 years after appropriate counselling.

In our series, of the 21 patients who were diagnosed with prostate cancer, 17 had an abnormal PSA or DRE or both. Four patients with normal PSA values were ≥50 years and had experienced recurrent hematospermia and therefore underwent an Mp-MRI which prompted a biopsy and subsequent diagnosis.

Most of the current literature has defined persistent hematospermia as ≥4 episodes or lasting >6 months. A small UK series of 125 patients also supported the use of Mp-MRI in patients with hematospermia at risk of prostate cancer and found no correlation between symptom duration and prostate cancer detection.[14] Following the results of the PROMIS trial, Mp-MRI was accepted as the gold standard imaging modality for the investigation of suspected prostate cancer providing information on prostate anatomy and characteristics.[15] We therefore recommend Mp-MRI as the prostate imaging modality of choice for those patients over the age of 40 years presenting with hematospermia and risk factors for prostate cancer.

Previous reviews of the literature have identified hematospermia as a condition affecting young men with a mean age of 37 years.[16] A literature review in 2007 identified that inflammatory or infectious causes accounted for up to 39% of hematospermia cases and mainly affected younger patients.[17] In our study, 74% of patients were ≥40 years. A limitation of this study is that these patients have not been captured in our series, and we assume the majority of those under 40 years may have either presented to primary care or sexual health clinics. However, our results are representative of a patient population presenting to tertiary care with the condition.

Of the investigations performed, 4 of the 162 (2.5%) flexible cystoscopies had a positive relevant finding that required biopsy. Seventy-five percent of these findings were in patients who had concomitant hematuria. Therefore, in the absence of hematuria or urinary symptoms, a flexible cystoscopy has a poor diagnostic yield when investigating isolated hematospermia.

Testicular examination must be performed in all patients. Three of 130 (2.3%) scrotal USS had positive findings that prompted further investigation of which one was confirmed as seminoma. However, in view of the low diagnostic yield, scrotal USS may not be necessary in the absence of positive examination findings or risk factors. The risk stratified diagnostic algorithm (Fig. 1) is proposed to reduce unnecessary investigations and costs associated with this.

Of the patients diagnosed with prostate cancer, 17 of the 21 patients had an abnormal PSA or DRE prompting investigation down the prostate cancer pathway. In order to evaluate an accurate association between prostate cancer and hematospermia, all patients should have undergone prostate imaging and

biopsy which may be considered another limitation of the study when reporting the incidence of underlying pathology.

Our retrospective study demonstrates the variability in investigations performed by urologists and emphasizes the need for the standardized diagnostic pathway and a prospective study to evaluate the true diagnostic yield of the conducted investigations.

To the best of our knowledge, this is the largest reported case series of patients presenting with hematospermia to a single center. Using our data and the literature to date, we propose an algorithm to help in the investigation of hematospermia, to limit the use of unnecessary investigations.

5. Conclusion

Hematospermia is often found to be a benign and often self-limiting condition. Our study reports an overall prostate cancer detection rate of 5.3% increasing up to 7.2% in those ≥40 years. The literature reports that hematospermia is associated with prostate cancer and consequently patients at risk should be investigated appropriately. For those under the age of 40, rare cases of testicular cancer have been reported and in our study only one patient was found to have a nonpalpable seminoma from the 130 scrotal USS performed (0.8%, 1/130 risk). These findings are reflected in the algorithm proposed for investigating patients presenting with hematospermia. When benign conditions such as ejaculatory duct stones, midline prostatic cysts or dilated seminal vesicles are diagnosed, treatment options can be proposed to patients who find the condition distressing and want an attempt at cure. Of the imaging performed, TRUSS and Mp-MRI were found to have the highest diagnostic yield. TRUSS is easy to perform, cheaper and is recommended as the imaging modality of choice in patients with a single episode of hematospermia. In those with persistent hematospermia, abnormal PSA or DRE or risk factors for prostate cancer, Mp-MRI is the investigation of choice.

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None.

Statement of ethics

This is a retrospective analysis with anonymized data. Our institution does not require ethics approval for studies with retrospective analysis and written consent from participants is not required as data has been anonymized. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interest statement

The authors declare no conflicts of interest.

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Author contributions

All authors contributed equally in this study.

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