Balkan Med J 2025;42:212-21

Etiology of Hematospermia in Turkish Men: Multicentric Study

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Background: Hematospermia is defined as the presence of blood in the semen. The data regarding its etiology and management is variable across the literature.

Aims: To investigate the etiology of hematospermia in Türkiye so as to contribute to the current management strategies for hematospermia.

Methods: An online study protocol was published through the Turkish Urology Association communication network, and the centers that met the criteria were included in the study. All patients who presented with hematospermia complaints in the past 1 year were subjected to detailed anamnesis, physical examination, and routine laboratory tests. Based on the results, the patients were assigned to Group 1 (patients aged < 40 years with only one episode of hematospermia in the past 6 months) or Group 2 (patients with concomitant symptoms or ≥ 40 years or ≥ 2 times in the past 6 months). Radiological imaging was performed for the patients in Group 2.

Results: A total of 199 patients (Group 1: 44, Group 2: 155; mean age: 43.07 ± 14.73 years; age range: 16-73 years) from across 42 cities and 22 different centers were enrolled in this study. In the etiological classification, inflammation was identified as the most common cause (n = 76, 38.1%). Idiopathic hematospermia was higher in Group 1 than in Group 2 (70.4% vs. 112.2%, respectively), and hematospermia was associated with malignancy in 9 (5.8%) Group 2 patients. Positivity was detected in urine or semen cultures in 20 (12.9%) patients, and hematospermia occurred after COVID-19 infection in 2 patients. A significant correlation was noted between patients showing no-concomitant symptoms and those showing idiopathic hematospermia, inflammation, malignancy, varicocele, and multiple etiological factors ($p = 0.004$, $p = 0.028$, $p = 0.002$, $p = 0.001$, $p = 0.026$, $p = 0.016$). The most common radiological findings were an increase in the prostate volume (n = 48, 30.9%) and changes in the signal intensities of the seminal vesicles (n = 29, 18.7%). Despite the use of different approaches to manage idiopathic hematospermia, the patients' survey results were generally similar.

Conclusion: Hematospermia in all age groups occurs generally due to self-limiting benign causes. Diagnostic imaging should therefore evaluate the elucidate etiology in patients with identified risk factors so as to avoid unnecessary treatments in idiopathic patients.

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Received: December 16, 2024 **Accepted:** March 13, 2025 **Available Online Date:** May 05, 2025 • **DOI:** 10.4274/balkanmedj.galenos.2025.2024-12-37

Available at www.balkanmedicaljournal.org

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Cite this article as: Gönültaş S, Baydilli N, Solakhan M, Güzel A, Kardaş S, Demirci A, Sulejman S, Yentür S, Ertaş K, Köse MG, Bulut B, Gelmiş M, Bozlu M, Kadıoğlu A. Etiology of Hematospermia in Turkish Men: Multicentric Study. Balkan Med J.; 2025; 42(3):212-21.

INTRODUCTION

Hematospermia (or hemospermia) is defined as the presence of blood in the semen. Depending on the timing of bleeding, it manifests as bright red blood or as brown or even black clots in the ejaculated semen. It is often detected macroscopically or incidentally during semen analysis. However, there is insufficient information available in the literature about the incidence of hematospermia, mainly because most men do not observe their ejaculate.[1] Hematospermia accounts for 1% of all urological symptoms, with a higher prevalence before the age of 40 years.[2,3] Historically, hematospermia is considered to occur from prolonged sexual abstinence or excessive sexual activity. The exact etiology in more than 70% of cases to date remains unknown, albeit advances in diagnostic methods in recent years have reduced these chances.[3,4]

Currently, urologists know no algorithm for the evaluation and treatment of hematospermia. The variability of data across the literature owing to the development of new imaging techniques has contributed to the differences in hematospermia-management policies. Therefore, evidence-based approaches continue to remain unclear. In this study, we investigated the etiology of hematospermia in Türkiye with the aim of contributing to the development of a consensus on the approach toward hematospermia management.

MATERIALS AND METHODS

After obtaining ethical approval (approval number: 27, date: 22.01.2020) from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Gaziosmanpasa Training and Research Hospital, a study protocol consisting of 31 questions under six headings was published online through the Turkish Urology Association communication network. Centers that met the protocol criteria were asked to include patients presenting with hematospermia during January 2020-2021 after obtaining signed informed consent from the participants. The patients were assigned to either Group 1 (included patients with hematospermia, aged < 40 years, and suffered from hematospermia only once in the past 6 months) or Group 2 (included patients with concomitant symptoms, or age ≥ 40 years, or hematospermia experience ≥ 2 times in the past 6 months). Patient management was performed according to the study protocol (Figure 1). After detailed anamnesis and physical examination (general and urogenital examination), urine and blood samples were collected from all patients. The semen samples were obtained by masturbation without using any lubricants after 2-5 days of sexual abstinence. Spot urine samples collected for direct microscopic examination were examined within 1 h of collection in biochemistry laboratories. The materials were also sent to microbiology laboratories for standard culture and differential culturing of *Mycobacterium tuberculosis*. In patients

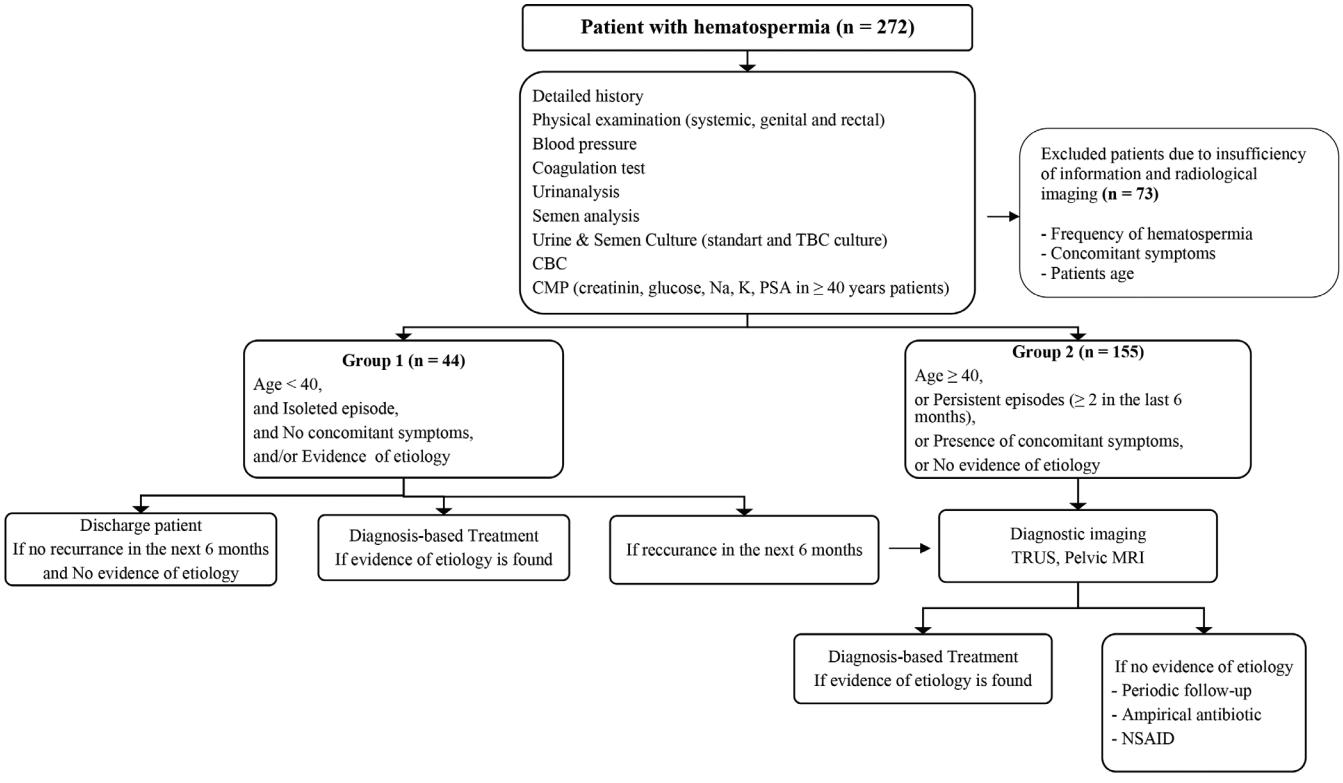

FIG. 1. Hematospermia algorithm for evaluating and managing.

MRI, magnetic resonance imaging; TRUS, transrectal Doppler ultrasonography; CBC, complete blood count; CMP, comprehensive metabolic panel; PSA, prostate-specific antigen; TBC, tuberculosis; NSAID: non-steroidal anti-inflamatuary drugs

with complaints of urethral discharge, swabs were collected from urethral discharge to investigate the presence of microorganisms such as *Ureoplasma* and *Mycoplasma*. Venous blood samples were analyzed for complete blood count, biochemical analysis (prostate-specific antigen, creatinine, glucose), and coagulation parameters (i.e., prothrombin time and activated partial thromboplastin time).

Patients in Group 2 underwent multi-sequence pelvic magnetic resonance imaging (MRI) and/or transrectal Doppler ultrasonography (TRUS) after 2-5 days of sexual abstinence for standardization purposes. The examination was performed by a radiologist and a total of 17 evaluation criteria [including benign prostate hyperplasia (BPH), prostatic cyst, seminal vesicle inflammation, seminal vesicle cyst, ejaculatory duct cyst, ejaculatory duct stone, and urethral stone] were established for imaging standardization. The obtained data were classified etiologically, anatomically, and radiologically.

Statistical analysis

Statistical analyses were performed using NCSS 2013 (Number Cruncher Statistical System, Utah, USA). Descriptive statistics were reported as the mean ± standard deviation for continuous variables and as frequency (percentage) for categorical variables. Comparisons of categorical variables were performed using Pearson's chi-square test when the minimum expected cell count was > 5; otherwise, Fisher's exact test was applied. A binary logistic regression was performed to analyze the predictors of hematospermia. The predictor variables were selected based on clinical factors identified in the literature and the study hypothesis. Initially, all potential predictor variables were included in the model by using a full-model approach. Following this, backward elimination was applied to iteratively remove the least significant variables based on the *p* values, retaining only those that contributed significantly to the model. This approach ensured a parsimonious model while minimizing the risk of overfitting). The agreement between MRI and TRUS findings was assessed by Cohen's kappa test, with agreement classified as poor (< 0.20), fair (0.21-0.40), moderate (0.41-0.60), good (0.61-0.80), and very good (0.81-1.00). All statistical tests were two-tailed, and significance was set at $p < 0.05$.

RESULTS

The data of 272 patients from across 42 cities and 22 different centers were uploaded to an online study protocol. Due to the lack of data on basic parameters (such as the frequency of hematospermia, presence of concomitant symptoms, etc.) required for inclusion in the study, 59 patients were excluded. In addition, 14 patients who met the inclusion criteria for Group 2 but did not perform radiological imaging were excluded from the study. A total of 199 patient data were evaluated, with 44 in Group 1 and 155 in Group 2. The mean age of the patients in Group 1 was 28.70 ± 7.17 years and that in Group 2 was 46.47.15 ± 13.9 years. Hematospermia appeared as fresh blood without any clots in 80 (Group 1: 27, Group 2: 53) patients, with clots in 62 (Group 1: 6, Group 2: 56) patients, and as old blood in 57 (Group 1: 11, Group 2: 46) patients. A concomitant symptom was present in 63 (40.6%) of Group 2 patients, which most commonly included dysuria (n = 30, 19.3%), scrotal-pelvic pain (n = 15, 9.6%), and hematuria (n = 13, 8.3%) (Table 1). No significant relationship was noted between the appearance of hematospermia and etiological parameters (Table 2).

TABLE 1. Clinical Characteristic of the 199 Hematospermia Patients After Anamnesis, Physicial Examination and Laboratory Tests.

	Group 1, (n=44)	Group 2, (n=155)	*p*
Age	28.70 ± 7.1	47.15 ± 13.9	**< 0.001**
Urological disease			0.992
BPH	-	29 (18.7%)	
Stone diseases	-	3 (1.93%)	
Infertility	-	6 (3.87%)	
ED	-	5 (3.22%)	
Prostate cancer	-	2 (1.29%)	
Bladder cancer	-	1 (0.64%)	
Sysemic disease			0.996
DM	-	12 (7.74%)	
HT	-	23 (14.83%)	
CVD	-	9 (5.80%)	
Others	-	15 (9.67%)	
Family history			
Prostate cancer	3 (6.81%)	3 (1.93%)	
Concomitance symptoms			
Urgency	-	6 (3.87%)	
Dysuria	-	30 (19.35%)	
Hematuria	-	13 (8.38%)	
Scrotal-pelvic pain	-	15 (9.67%)	
Urethral discharge	-	4 (2.58%)	
ED	-	8 (5.16%)	
Others	-	13 (8.38%)	
Frequency of sexual activity			0.903
< 1 times/week	2 (4.54%)	1 (0.64%)	
1-2 times/week	18 (40.90%)	122 (78.70%)	
3-5 times/week	19 (43.18%)	30 (19.35%)	
> 5 times/week	5 (11.36%)	2 (1.29%)	
Hematopsermia frequency			0.990
1 times/6 months	44 (100%)	42 (27.09%)	
2 times/6 months	-	53 (34.19%)	
3 times/6 months	-	26 (16.77%)	
> 3 times/6 months	-	34 (21.93%)	
Hematospermia appearence			0.622
Fresh bleeding	27 (61.36%)	53 (34.19%)	
Bright red with clots	6 (13.63%)	56 (36.12%)	
Old blood (brown)	11 (25%)	46 (29.67%)	

TABLE 1. Continued

	Group 1, (n=44)	Group II, (n=155)	*p*
Traumatic/iatrogenic			
Urogenital trauma	2 (4.54%)	10 (18.7%)	
Prostatic biopsy	-	3 (1.93%)	
Cystoscopy/URS	-	1 (0.64%)	
Prostatic surgery	-	1 (0.64%)	
Excessive sexual intercourse (masturbation,coitus interraptus)	2 (4.54%)	4 (2.58%)	
Physicial examination			
Gynecomastia	-	1 (0.64%)	
HT (MAP > 140/90 mmHg)	-	10 (6.45%)	
Genital examination			
Testicular mass	-	2 (1.29%)	
Hydocele	-	1 (0.64%)	
Orchitis/epididymitis	2 (4.54%)	12 (7.74%)	
Varicocele	3 (6.81%)	8 (5.16%)	
Penile plaque	-	1 (0.64%)	
Epididymal cyst	2 (4.54%)	5 (3.22%)	
Prostate rectal examination			
Enlargement	2 (4.54%)	37 (23.87%)	
Asimetry/nodule	-	9 (5.80%)	
Fluctuation	1 (2.27%)	1 (0.64%)	
Palpable vesicula seminalis (asimetry/ enlargement)	1 (2.27%)	10 (6.45%)	
CBC and CMP			
Kreatinin (mg/dl)	0.9 ± 0.3	1.28 ± 1.5	
Glucose (mg/dl)	94 ± 8.61	101.85 ± 19.6	
Na (mmol/l)	138.2 ± 3.3	138.8 ± 3.5	
K (mmol/l)	4.08 ± 1.27	4.2 ± 0.5	
PSA (nmol/ml)	-	1.3 (0.1-12.81)	
Coagulopathy (PTT > 20 sec, INR > 1.35)	-	3	
Anemia (Hgb < 12 g/dl)	-	2	
Thrombocytopenia (PLT < 10^5/mm^3)	-	1	
Urianalysis			
Hematuria	5 (11.36%)	28 (18.06%)	
Pyuria	5 (11.36%)	39 (25.16%)	
Bacteriuria	1 (2.27%)	2 (1.29%)	
Semen analysis			
Red blood cell	9 (20.45%)	51 (32.90%)	
White blood cell	7 (15.90%)	25 (16.12%)	
Urine culture			0.995
E. coli	-	10 (6.45%)	
S. aureus	-	4 (2.58%)	
C. pneumonia	-	1 (0.64%)	
E. faecalis	-	2 (1.29%)	
M. tuberculosis	-	1 (18.7%)	
Others	-	3 (1.93%)	
Semen culture			0.992
E. coli	-	4 (2.58%)	
S. aureus	-	4 (2.58%)	
C. pneumonia	-	1 (0.64%)	
E. faecalis	-	1 (0.64%)	
M. tuberculosis	-	1 (0.64%)	
Others	2 (4.54%)	3 (1.93%)	

The effectiveness of Urological Disease, Sysemic Disease, Frequency of Sexual Activity, Hematopsermia Frequency and Hematospermia Appearence was evaluated between the groups at a 95% confidence interval using the logistic regression analysis method. However, no statistical significance was found between the parameters other than age. BPH, benign prostate hyperplasia; ED, erectile dysfunction; DM, diabetes mellitus; HT, hypertension; CVD, cardiovascular diseases; URS, ureterorenoscophy; MAP, mean arterial pressure; CBC, complet blood count; CMP, compressive metabolic panel; PSA, prostate-specific antigen; PTT, partial thromboplastin time; INR, international normalized ratio; Hgb, hemoglobin; PLT, platelet.

In the etiological classification, inflammation (i.e., the presence of pyuria without positive urine/semen cultures, leucospermia and/or radiological density changes in the urogenital organs) was the most common cause (n = 76, 38.1%) (Table 2). Positivity was detected in urine or semen cultures in 10% (n = 20) of patients. The most commonly isolated bacteria in these cultures were *Escherichia coli* (n = 7, 35%) and *Staphylococcus aureus* (n = 4, 20%). Multiple bacterial positivity was observed in 20% (n = 4) of culture-positive patients. Hematospermia developed after COVID-19 infection in 2 patients, while *Corynebacterium bacilli* growth was detected in the semen culture of 2 patients (Table 1). Idiopathic hematospermia was higher in Group 1 than in Group 2 (70.4% vs. 12.2%, respectively). In the history of 6 patients evaluated as idiopathic hematospermia (Group 1: 2, Group 2: 4), coitus interruptus and excessive sexual behavior were noted. Hematospermia was associated with malignancy in 9 (5.8%) Group 2 patients, all of whom also had hematuria. More than one etiological factor was detected in 56 (25.1%) patients (Table 2). In the anatomical classification, the most common pathologies reported were prostate-related (such as BPH, prostatitis, cysts, calcifications, and cancer) in 81 (40.7%) and seminal vesicle pathologies in 13 (6%). A correlation was noted between the BPH and with frequency of hematospermia (p = 0.021) (Table 3).

TABLE 2. The Relationship of the Etiological Parameters with the Hematospermia Appearance.

		Hematospermia appearance							
		Group 1			Group 2				
	n	Fresh bleeding	Bright red with clots	Old blood (brown)	Fresh bleeding	Bright red with clots	Old blood (brown)	p_1	p_2
Idiopathic	50	19 (61.3%)	5 (16.1%)	7 (22.6%)	4 (21.1%)	10 (52.6%)	5 (26.3%)	0.696	0.246
Inflamation	76	5 (62.5%)	1 (12.5%)	2 (25%)	22 (32.4%)	23 (33.8%)	23 (33.8%)	0.994	0.607
Infection	20	1 (100%)	0 (0%)	0 (0%)	6 (31.6%)	6 (31.6%)	7 (36.8%)	-	0.763
Seminal or ductal lithiasis	6	0 (0%)	0 (0%)	0 (0%)	3 (50%)	2 (33.3%)	1 (16.7%)	-	0.662
Prostatic or seminal cysts	13	0 (0%)	0 (0%)	0 (0%)	8 (61.5%)	5 (38.5%)	0 (0%)	-	0.260
Epidiymal cyst or hydrocele	7	1 (100%)	0 (0%)	0 (0%)	3 (50%)	0 (0%)	3 (50%)	-	0.164
Benign prostate hyperplasia	38	0 (0%)	0 (0%)	0 (0%)	12 (31.6%)	12 (31.6%)	14 (36.8%)	-	0.533
Malignancy	9	0 (0%)	0 (0%)	0 (0%)	2 (22.2%)	2 (22.2%)	5 (55.6%)	-	0.216
Hemangiom	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	-	-
Iatrogenic/traumatic	12	0 (0%)	1 (100%)	0 (0%)	4 (36.4%)	2 (18.2%)	5 (45.5%)	-	0.356
Varicocele	11	1 (33.3%)	0 (0%)	2 (66.7%)	4 (50%)	2 (25%)	2 (25%)	-	0.616
Systemic diseases	23	0 (0%)	0 (0%)	0 (0%)	11 (47.8%)	7 (30.4%)	5 (21.7%)	-	0.319
Others	2	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)	-	-
Multiple etiologic factors	56	1 (50%)	1 (50%)	0 (0%)	20 (37%)	15 (27.8%)	19 (35.2%)	-	0.267

Statistical evaluation (chi-square analysis) was performed for each parameter separately. For group analyses where the minimum expected count more than 5, Pearson's chi-square test was used, while Fisher's exact test *p* values were considered for groups with a minimum expected count of 5 or below. "-": The test was not performed due to insufficient sample size rather. There was no significant correlation between etiological parameters with hematospermia appearance. p_1: Group 1 *p* value, p_2: Group 2 *p* value.

TABLE 3. The Relationship of the Etiological Parameters with the Frequency of the Hematospermia.

		Frequency of hematospermia (x/6 months)					
		Group 1		Group 2			
	n	1	> 1	1	> 1	p_1	p_2
Idiopathic	50	31 (100%)	0 (0%)	5 (26.3%)	14 (73.7%)	-	0.935
Inflamation	76	8 (100%)	0 (0%)	20 (29.4%)	48 (70.6%)	-	0.566
Infection	20	1 (100%)	0 (0%)	4 (21.1%)	15 (78.9%)	-	0.527
Seminal or ductal lithiasis	6	0 (0%)	0 (0%)	1 (16.7%)	5 (83.3%)	-	0.558
Prostatic or seminal cysts	13	0 (0%)	0 (0%)	3 (23.1%)	10 (76.9%)	-	0.516
Epidiymal cyst or hydrocele	7	1 (100%)	0 (0%)	1 (16.7%)	5 (83.3%)	-	0.558
Benign prostate hyperplasia	38	0 (0%)	0 (0%)	16 (42.1%)	22 (57.9%)	-	**0.021**
Malignancy	9	0 (0%)	0 (0%)	0 (0%)	9 (100%)	-	0.059
Hemangiom	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	-	-
Iatrogenic/traumatic	12	1 (100%)	0 (0%)	2 (18.2%)	9 (81.8%)	-	0.728
Varicocele	11	3 (100%)	0 (0%)	2 (25%)	6 (753%)	-	0.891
Systemic diseases	23	0 (0%)	0 (0%)	8 (34.8%)	15 (65.2%)	-	0.369
Others	2	0 (0%)	0 (0%)	0 (0%)	2 (100%)	-	-
Multiple etiologic factors	56	2 (100%)	0 (0%)	15 (27.8%)	39 (72.2%)	-	0.889

Statistical evaluation (chi-square analysis) was performed for each parameter separately, and those with significant correlations ($p < 0.05$) were marked in "bold*". "-": The test was not performed due to insufficient sample size rather. For group analyses where the minimum expected count more than 5, Pearson's chi-square test was used, while Fisher's exact test *p* values were considered for groups with a minimum expected count of 5 or below. p_1: Group 1 *p* value, p_2: Group 2 *p* value.

There was a significant correlation between the frequency of sexual activity with the infection, BPH, and varicocele (Table 4). In Group 2, a significant correlation was noted between the no-concomitant symptoms and the idiopathic hematospermia, inflammation, malignancy, varicocele, and multiple etiological factors in patients. A significant correlation was noted between the hematuria and the seminal or ductal lithiasis, malignancy, iatrogenic, and multiple etiological factor patients. A significant correlation was noted between infection and multiple etiological factors in patients with dysuria. A significant correlation was observed between the scrotal or pelvic pain with the inflammation and varicocele patients. Moreover, there was a significant correlation between infection and multiple etiological factors in patients with multiple concomitant symptoms. A reverse correlation was detected between the presence of concomitant symptoms and idiopathic patients, while a significant association was observed with infectious disease patients (Table 5). Statistical analysis of potential factors contributing to symptomatology was performed. During group formation, the factor "age", which determines the risk classification, showed a significant relationship with the frequency of hematospermia ($p < 0.001$). The presence of multiple factors in the etiology also showed a significant relationship with the frequency of hematospermia ($p = 0.007$) (Table 6).

In Group 2, radiological imaging data was missing for 14 patients, while 14 patients underwent imaging (MRI: 4, TRUS: 10) despite being in Group 1. In Group 2, 76 patients underwent TRUS, 7 underwent MRI, and 72 underwent both imaging methods. No pathology was detected in any of the Group 1 patients who underwent imaging, while the most common findings in Group 2 patients were an increase in the prostate volume (n = 51/155, 32.9%) and changes in seminal vesicle-signal intensities (n = 29/155, 18.7%). The findings in terms of the evaluated parameters were statistically significantly correlated in patients who underwent both imaging methods ($p < 0.001$). The frequencies of findings in patients who underwent only TRUS were similar to those of patients who underwent both imaging methods (Table 7).

Therapeutic approaches applied to patients with identified etiology were similar. The management of patients with idiopathic hematospermia or inflammation was left to the clinician's discretion, with two different options: follow-up without treatment or use of empirical drugs (such as anti-inflammatory, antibiotics, α-blockers, 5-alpha reductase inhibitor). Despite different approaches, the surveys of these patients were similar in terms of hematospermia recurrence (Table 8).

DISCUSSION

In non-recurrent monosymptomatic young patients with hematospermia, advanced etiological investigations are generally not preferred. However, serious underlying pathologies can be present in patients with recurrent hematospermia or concomitant symptoms.[5,6] In our study, we found that the frequency of hematospermia showed an inverse correlation with idiopathic hematospermia ($p < 0.001$). We also demonstrated that the appearance of hematospermia had no clinical significance.

TABLE 4. The Relationship of the Etiological Parameters with the Frequency of Sexual Activity.

	Frequency of sexual activity (x/week)								
		Group 1			Group 2				
	n	1-2	3-4	≥ 5	1-2	3-4	≥ 5	p_1	p_2
Idiopathic	50	15 (48.4%)	13 (41.9%)	3 (9.7%)	14 (73.7%)	5 (26.3%)	0 (0%)	0.861	0.349
Inflamation	76	3 (37.5%)	3 (37.5%)	2 (25%)	55 (80.9%)	12 (17.6%)	1 (1.5%)	0.398	0.678
Infection	20	1 (100%)	0 (0%)	0 (0%)	12 (63.2%)	6 (31.6%)	1 (5.3%)	-	**0.063**
Seminal or ductal lithiasis	6	0 (0%)	0 (0%)	0 (0%)	5 (83.3%)	1 (16.7%)	0 (0%)	-	0.806
Prostatic or seminal cysts	13	0 (0%)	0 (0%)	0 (0%)	9 (69.2%)	4 (30.8%)	0 (0%)	-	0.144
Epidiymal cyst or hydrocele	7	0 (0%)	0 (0%)	1 (100%)	4 (66.7%)	2 (33.3%)	0 (0%)	-	0.806
Benign prostate hyperplasia	38	0 (0%)	0 (0%)	0 (0%)	37 (97.4%)	1 (2.6%)	0 (0%)	-	**< 0.001**
Malignancy	9	0 (0%)	0 (0%)	0 (0%)	9 (0%)	0 (0%)	0 (0%)	-	0.115
Hemangiom	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	-	-
Iatrogenic/traumatic	12	1 (100%)	0 (0%)	0 (0%)	9 (81.8%)	2 (18.2%)	0 (0%)	-	0.834
Varicocele	11	0 (0%)	3 (100%)	0 (0%)	3 (37.5%)	4 (50%)	1 (12.5%)	-	**0.003**
Systemic diseases	23	0 (0%)	0 (0%)	0 (0%)	20 (87%)	3 (13%)	0 (0%)	-	0.413
Others	2	0 (0%)	0 (0%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)	-	-
Multiple etiologic factors	56	1 (50%)	0 (0%)	1 (50%)	44 (81.5%)	9 (16.7%)	1 (1.9%)	-	0.632

Statistical evaluation (chi-square analysis) was performed for each parameter separately, and those with significant correlations ($p < 0.05$) were marked in "bold*". "-": The test was not performed due to insufficient sample size rather. There was significant correlation between the etiological parameters and the frequency of sexual activity (infection, benign prostate hyperplasia, varicocele). p_1: Group 1 p value, p_2: Group 2 p value.

TABLE 5. The Relationship Between Etiology and Symptomatology was Evaluated in Patients of Group 2.

		Concomitant symptoms														
	n	N	*p*	H	*p*	D	*p*	U	*p*	*p*	*p*	UD	*p*	M	*p*	Total
Idiopathic	19	**17 (89.5%)**	**0.004**	0 (0%)	-	1 (5.3%)	0.126	1 (5.3%)	0.867	2 (10.5%)	0.948	0 (0%)	-	1 (5.3%)	0.473	**0.040**
Inflamation	68	**36 (52.9%)**	**0.028**	6 (8.8%)	0.536	16 (23.5%)	0.174	2 (2.9%)	0.696	**11 (16.2%)**	**0.06**	1 (1.5%)	0.710	12 (17.6%)	0.119	0.164
Infection	19	**5 (26.3%)**	**0.002**	2 (10.5%)	0.682	**8 (42.1%)**	**0.013**	2 (10.5%)	0.114	2 (10.5.5%)	0.894	**3 (15.8%)**	**0.006**	**5 (26.3%)**	**0.049**	**0.035**
Seminal or ductal lithiasis	6	2 (33.3%)	0.225	**5 (83.3%)**	**< 0.001**	0 (0%)	-	0 (0%)	-	0 (0%)	-	0 (0%)	-	0 (0%)	-	0.566
Prostatic or seminal cysts	13	10 (76.9%)	0.178	0 (0%)	-	2 (15.4%)	0.705	1 (7.7%)	0.414	1 (7.7%)	0.745	0 (0%)	-	2 (15.4%)	0.662	0.300
Epidiymal cyst or hydrocele	5	2 (40%)	0.397	0 (0%)	-	2 (40%)	0.248	0 (0%)	-	1 (20%)	0.424	0 (0%)	-	1 (20%)	0.485	0.884
Benign prostate hyperplasia	38	24 (63.2%)	0.583	4 (10.5%)	0.712	7 (18.4%)	0.867	1 (2.6%)	0.811	2 (5.3%)	0.362	3 (7.9%)	0.046	5 (13.2%)	0.783	0.338
Malignancy	9	**0 (0%)**	**0.001**	**9 (100%)**	**< 0.001**	2 (22.2%)	0.686	0 (0%)	0.535	0 (0%)	0.601	0 (0%)	-	2 (22.2%)	0.351	0.230
Hemangiom	1	1 (100%)	-	0 (0%)	-	0 (0%)	-	0 (0%)	-	0 (0%)	-	0 (0%)	-	0 (0%)	-	-
Iatrogenic/ traumatic	11	4 (36.4%)	0.123	**4 (36.4%)**	**0.01**	2 (18.2%)	0.919	0 (0%)	-	2 (18.2%)	0.317	0 (0%)	-	1 (9.1%)	0.655	0.256
Varicocele	8	**7 (87.5%)**	**0.026**	0 (0%)	-	0 (0%)	-	0 (0%)	-	**1 (12.5%)**	**0.044**	0 (0%)	-	0 (0%)	-	0.778
Systemic diseases	23	13 (56.5%)	0.764	4 (17.4%)	0.105	4 (17.4%)	0.796	2 (8.7%)	0.278	1 (4.3%)	0.469	1 (4.3%)	0.384	3 (13%)	0.983	0.978
Others	2	2 (100%)	-	0 (0%)	-	0 (0%)	-	0 (0%)	-	0 (0%)	-	0 (0%)	-	0 (0%)	-	-
Multiple etiologic factors	54	**25 (46.3%)**	**0.016**	**9 (16.7%)**	**0.031**	13 (24.1%)	0.277	4 (7.4%)	0.184	6 (11.1%)	0.659	3 (5.6%)	0.122	**12 (22.2%)**	**0.011**	0.454

To minimize the effect of potential confounding factors such as the absence of concomitant symptoms and age, patients from Group 1 were excluded. Statistical evaluation (chi-square analysis) was performed for each parameter separately, and those with significant correlations ($p < 0.05$) were marked in "bold*". "-": The test was not performed due to insufficient sample size rather. There was significant correlation between the no concomitant symptoms and the idiopathic hematospermia, inflamation, malignancy, varicocele and multiple etiologic factors patients. There was significant correlation between the hematuria with the Seminal or ductal lithiasis, malignancy, iatrogenic and multiple etiologic factors patients. There was significant correlation between infection and multiple etiologic factors patient with dysuria. There was significant correlation between the pain with the inflamation and varicocele patients. There was significant correlation between infection and multiple etiologic factors patient with multiple concomitant symptoms. Total: p values for the overall statistical evaluation (95% confidence interval binary logistic regression analiysis) of etiological parameters and concomitant symptoms. A reverse correlation was found between the presence of concomitant symptoms and idiopathic patients, while a significant association was observed with infectious disease patients. N, none; H, hematuria; D, dysuria; U, urgency; P, pain (scrotal/pelvic), UD, urethral discharge; M, multiple concomitant symptoms, p, p value.

TABLE 6. Evaluation of the Relationship Between Groups and Hematospermia Frequency with Etiopathological Factors Using Binary Logistic Regression Analysis.

		OR	OR Lower-Upper	*p*
Groups	Age	1.157	1.086-1.232	**< 0.001**
	Frequency of sexual activity	0.297	0.136-0.649	**0.002**
Frequency of hematospermia	Age	1.020	1.000-1.040	**0.046**
	Systemic diseases	0.774	0.442-2.401	0.774
	Multiple etiologic factors	2.692	1.316-5.507	**0.007**
	Frequency of sexual activity	0.946	0.466-1.921	0.878
	Hematospermia appearence	1.681	0.807-3.502	0.165

The results revealed a significant association between age and sexual activity frequency with the group classification. Additionally, a significant relationship was found between hematospermia frequency and both age and the presence of multiple etiologic factors. However, no significant relationship was observed between hematospermia frequency and other factors such as systemic disease presence, sexual activity frequency, or hematospermia appearance. The analysis was performed using a full model approach followed by backward elimination to ensure the most significant predictors were retained in the final model. OR, odds ratio.

TABLE 7. The Findings in Patients who Underwent both Imaging Methods.

	A: TRUS + MRI patients (n=72)						B: Only TRUS or TRUS + MRI patients		
Radiological parameters	MR: no TRUS: yes	MR: yes TRUS: no	MR: yes TRUS: yes	MR: no TRUS: no	Kappa	*p* value	TRUS (n=76)	MR + TRUS (n=72)	*p* value
None	8	8	27	29	0.55	< 0.01	23	43	< 0.01
BPH	11	2	11	48	0.52	< 0.01	27	24	0.762
Prostatic cyst	1	2	5	64	0.80	< 0.01	4	8	0.113
Prostatic calcification (> 3 mm)	2	1	6	63	0.81	< 0.01	10	9	0.831
Seminal vesicle inflammation	3	4	7	58	0.70	< 0.01	15	14	0.862
Seminal vesicle cyst	0	0	0	72	1	< 0.01	0	0	-
Ejaculatory duct cyst	0	0	0	72	1	< 0.01	1	0	-
Utricle cyst	0	1	2	69	0.88	< 0.01	4	3	0.753
Ejaculatory duct stone	0	0	1	71	1	< 0.01	1	1	0.962
Urethra stone	0	0	0	72	1	< 0.01	0	0	-
Arteriovenous malformation	0	0	0	72	1	< 0.01	0	0	-
Vasovenous fistula	0	0	0	72	1	< 0.01	0	0	-
Hemangioma	0	0	1	71	1	< 0.01	0	1	-
Bladder ca	0	2	0	70	-	-	0	2	-
Testicular mass	-	1	-	-	-	-	-	1	-
Epididymis cyst	-	1	-	-	-	-	-	1	-
Pelvic lymphadenopathy	-	-	-	72	-	-	-	0	-
Others	0	0	2	70	1	< 0.01	1	2	0.520

A: Cohen's kappa test was used to assess agreement between MRI and TRUS findings in Groups 2. Agreement was classified as poor (< 0.20), fair (0.21-0.40), moderate (0.41-0.60), good (0.61-0.80), and very good (0.81-1.00). B: Chi-square analysis of the detection rates of radiological parameters in only TRUS or TRUS + MRI patients. Radiological parameters: The parameters to be absolutely assessed for radiological imaging standardization. Yes: presence of findings, No: absence of findings. BPH: prostate volume ≥ 30 cc (prostatic axial length x coronal length x sagittal length x 0.52), Seminal vesicle inflammation: asymmetric seminal vesicle volume changes and/or signal intensity abnormalities on TRUS or MRI. BPH, benign prostatic hyperplasia; TRUS, transrectal ultrasound Imaging; MRI, magnetic resonance imaging.

TABLE 8. Treatment Options in Hematospermia Patient Management and Recurrence Rates within 6 Months.

	Patient		Recurrence (within 12 months)	
Management options	Group 1	Group 2	Group 1	Group 2
Untreated follow-up	32	42	-	3
Empirical antibiotic therapy	5	36	-	2
NSAI drug therapy	4	4	-	1
Specific antibiotic therapy	1	13	-	7
5α-RI therapy (3 months)	-	19	-	1
Cystoscopy	-	7	-	-
Vesiculoscopy	-	-	-	-
TUR-ED	-	6	-	-
TRUS guided prostate biopsy	-	7	-	-
TRUS guided cyst aspiration	-	4	-	-
Angio-embolization	-	-	-	-
Others	5	22	-	-

In some patients, multiple options were applied together. NSAI, non-steroidal anti-inflammatory; 5α-RI, 5-alpha reductase inhibitör; TUR-ED, transurethral resection of the ejaculatory ducts; TRUS, trans rectal ultrasound.

Several factors are involved in the etiology of hematospermia, most of which are benign (such as inflammatory, infectious, lithiasis, cystic, obstructive, vascular, traumatic, iatrogenic, and systemic factors).[7,8] Iatrogenic causes are the most commonly reported ones in the literature; however, in our series, the most common factors were inflammatory and infectious. This may be due to the postponement or non-performance of diagnostic procedures during the pandemic period. The frequencies of other etiological causes were similar to those of global parameters.[9] Although the presence of the virus in semen after COVID-19 infection has been demonstrated previously, this study is the first to report two patients who presented with hematospermia and who tested positive for COVID-19 polymerase chain reaction. The pathophysiology of hematospermia in these patients, who had no-concomitant symptoms other than widespread joint pain, could not be elucidated.

In past studies that stratified patients with hematospermia into risk groups, the frequency of hematospermia, patient age, and comorbidities were highlighted as important factors, although there are insufficient data on the importance of the diversity of concomitant symptoms.[5,6,10] In this study, we did not find any significant association between the presence of a systemic disease alone and the frequency of hematospermia. However, we found that the factors of age and the presence of multiple etiological factors were consistent with the literature. The increasing prevalence of systemic diseases in older age complicates the identification of their potential effects on the pathophysiology. Nevertheless, based on the present results, we concluded that the presence of a single systemic disease is not associated with an increased frequency of hematospermia. In addition, we found that patients with hematospermia and dysuria had more frequent infectious and inflammatory pathologies, while those with concurrent hematuria had a higher incidence of malignancy. Therefore, we concluded that the presence and variety of concomitant symptoms should be considered as a criterion when stratifying the hematospermia risk.

The European Association of Urology guidelines recommend the evaluation of the testes, prostate, bladder, and seminal vesicles in high-risk patients who are defined to have older age and recurrent hematospermia.[11] However, there is no consensus on which radiological method should be used to elucidate the etiology of hematospermia. In our study, we found that the etiological evaluation results were correlated in patients who underwent both MRI and TRUS and that the frequencies of etiological factors were similar in patients who underwent only TRUS. Therefore, we concluded that a single radiological imaging method would be sufficient for the management of hematospermia. Although TRUS appears to be cost-effective, its use frequency in radiological clinical practice is decreasing. Owing to the ability to evaluate the entire urogenital system simultaneously, its non-invasive nature, and its easy accessibility, the preference for MRI among clinicians is becoming more common. Our study results support that this preference may be radiologically sufficient.

The outcomes of therapeutic approaches applied to patients with identified etiology in the management of hematospermia are consistent across the literature. However, different approaches used in the management of patients recognized to have idiopathic hematospermia and those with inflammation, such as a follow-up without treatment, the use of anti-inflammatory drugs, and empirical antibiotic use, did not affect the clinical outcomes. Similar to a past study conducted on Japanese men, we concluded that informative measures to alleviate anxiety and preventive measures may be adequate for this patient group.[12]

Due to the participation of multiple centers in our study, efforts were made to eliminate the risk of bias in the collected data. To achieve this, the study protocol included 31 questions under six main headings, and the parameters to be evaluated, particularly those related to radiological assessments, were listed with their definitions to ensure data standardization. During the study, we intended to include every patient presenting with hematospermia. However, the presence of incomplete data not conforming to the study protocol due to unknown reasons was identified. Patients lacking the primary data used to determine their inclusion group (i.e., the frequency of hematospermia and/or the presence of concomitant symptoms) were naturally excluded from the study. However, it was concluded that the inclusion of patients with only missing radiological imaging could not significantly impact the non-radiological data. In addition, the inability to perform advanced investigations such as vesiculoscopy and seminal content microbiota analysis, which have recently gained popularity, and the short follow-up durations may be considered as some of the limitations of the study. Nevertheless, our present findings make a positive contribution to the literature by associating concomitant symptoms with etiological parameters, thereby helping achieve consensus in radiological evaluations and

the management of idiopathic hematospermia. The widespread participation of centers has provided comprehensive information on the etiology of hematospermia in Türkiye.

The etiology of hematospermia in Türkiye is similar to global scales. Hematospermia in all age groups generally arises due to self-limiting benign causes. Diagnostic imaging should therefore be evaluated to elucidate etiology in patients with identified risk factors, and unnecessary treatments should be avoided by providing reassuring information to idiopathic patients. With increasing age, the effects of systemic diseases should be considered in cases of recurrent hematospermia attacks and the risk of malignancy should be excluded.

Ethics Committee Approval: The study was approved by the Ethics Committee of the University of Health Sciences Türkiye, Gaziosmanpasa Training and Research Hospital (approval number: 27, date: 22.01.2020).

Informed Consent: The obtained signed informed consent from the participants.

Data Sharing Statement: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept- S.G., N.B., M.S., A.G., S.K., A.D., S.S., S.Y., K.E., M.G.K., B.B., M.G., M.B., A.K.; Design- S.G., N.B., M.S., A.G., S.K., A.D., S.S., S.Y., K.E., M.G.K., B.B., M.G., M.B., A.K.; Supervision- S.G., N.B., M.S., A.G., S.K., A.D., S.S., S.Y., K.E., M.G.K., B.B., M.G., M.B., A.K.; Fundings- S.G., N.B., M.S., A.G., S.K., A.D., S.S., S.Y., K.E., M.G.K., B.B., M.G., M.B., A.K.; Materials- S.G., N.B., M.S., A.G., S.K., A.D., S.S., S.Y., K.E., M.G.K., B.B., M.G., M.B., A.K.; Data Collection or Processing- S.G., N.B., M.S., A.G., S.K., A.D., S.S., S.Y., K.E., M.G.K., B.B., M.G., M.B., A.K.; Analysis or Interpretation- S.G., N.B., M.S., A.G., S.K., A.D., S.S., S.Y., K.E., M.G.K., B.B., M.G., M.B., A.K.; Literature Review- S.G., N.B., M.S., A.G., S.K., A.D., S.S., S.Y., K.E., M.G.K., B.B., M.G., M.B., A.K.; Writing- S.G., N.B., M.S., A.G., S.K., A.D., S.S., S.Y., K.E., M.G.K., B.B., M.G., M.B., A.K.; Critical Review- S.G., N.B., M.S., A.G., S.K., A.D., S.S., S.Y., K.E., M.G.K., B.B., M.G., M.B., A.K.

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: The authors declared that this study received no financial support.

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