Original Article

Urine pH and imaging findings of prostate useful predictors of prolonged duration of hematospermia

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Background: Few investigations regarding hematospermia duration have been reported thus far. The aim of this study was to identify clinical factors associated with the duration of hematospermia.

Methods: Clinical data of 198 patients with hematospermia treated at Toho University Omori Medical Center from 2007 to 2022 were retrospectively evaluated. To identify independent predictors of hematospermia duration, uni- and multivariate Cox analyses were performed. Receiver operating characteristic analysis, Kaplan-Meier survival curves, and propensity score matching were applied for statistical evaluations.

Results: Multivariate analysis of all 198 patients showed urine pH (UpH) level and any abnormal imaging finding of the prostate to be independent predictors of hematospermia duration. Based on the receiver-operating curve of UpH level for hematospermia improvement, the patients were divided into two groups using a threshold of 6.0 (Low-UpH 5.0–6.0, n=128; High-UpH 7.0–9.0, n=70). Kaplan-Meier curves indicated that patients in the High-UpH group or with any abnormal imaging finding had a higher rate of hematospermia persistence (both P<0.05). Even after matching between the groups classified by UpH (n=60 each), multivariate analysis showed that UpH level (hazard ratio 0.75, 95% CI: 0.61–0.92; P=0.006) and any abnormal imaging finding (hazard ratio 1.55, 95% CI: 1.04–2.31; P=0.033) were independent predictors of hematospermia duration. In Kaplan-Meier analysis findings of matched cohorts, High-UpH and presence of any abnormal imaging findings remained significantly correlated with higher rate of hematospermia persistence, while further stratification using a combination of these two factors identified a stepwise reduction in that rate (P=0.019). In addition, the proportion of patients with these two factors present simultaneously was significantly higher in the group with hematospermia for two months or more, and especially with a duration of greater than six months, than in the group with a duration of less than two months.

Conclusions: Although further research is needed, both UpH level and imaging findings of the prostate are considered useful biomarkers for predicting prolonged hematospermia.

Keywords: Hematospermia; urine pH; imaging findings of prostate; propensity score matching; prolonged symptom

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Introduction

Hematospermia is defined as the presence of blood in seminal fluid. Although the exact rate of incidence or prevalence is unknown, it has been reported that this disease accounts for 1.5% of patients visiting a urology clinic, while it was also detected in 0.5% of a population that underwent prostate cancer screening (1,2), suggesting it to be relatively uncommon. Commonly described causes of hematospermia are benign conditions, such as infection, prostate and seminal vesicle stones, and abnormalities of the urogenital tract, as well as idiopathic disorders in about half of all cases (1,3-6).

Spontaneous resolution without treatment occurs in most patients, unless hematospermia is due to malignancy or an overt urinary tract infection (5,6). An investigation of the natural history of hematospermia showed spontaneous resolution of symptoms in 88.9% of patients without any treatment, with a median disease duration of 1.5 months (6). However, it should be noted that that there is a certain percentage of cases where symptoms persist for a long period or do not show improvement (1,6,7). Interestingly, a study presented in 2014 noted abnormal imaging findings in affected patients, such as seminal vesicle hemorrhage (SVH) and midline cyst (MLC) of the prostate, as a potential predictor of prolonged duration of hematospermia (6). However, to the best of our knowledge, no other studies have been conducted since that time to confirm those results or examine other factors associated with prolonged duration of hematospermia.

Highlight box

Key findings

- High UpH level (alkaline urine) and abnormal findings shown by prostate imaging are promising biomarkers for predicting prolonged hematospermia.

What is known and what is new?

- There is a certain percentage of patients with hematospermia, where symptoms persist for a long period or do not show improvement. However, there is no useful means of predicting such patients.
- Presence of urine alkalinization as well as abnormal imaging findings of the prostate were found to be associated with prolonged hematospermia.

What is the implication, and what should change now?

- The present results will provide useful information regarding findings that can be used to reassure patients with hematospermia and regarding the need for therapeutic intervention.

We believe that accurate information regarding the expected duration may be helpful for reassuring patients with hematospermia or determining the need for therapeutic intervention. Thus, this retrospective study of hematospermia patients treated at our institution was conducted to identify clinical factors associated with persistence. We present this article in accordance with the STARD reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-108/rc).

Methods

Data collection and ethics statement

The records of 273 patients with hematospermia, excluding iatrogenic cases, newly treated at Toho University Omori Medical Center between April 1, 2007 and March 31, 2022 were retrospectively reviewed. After exclusion of 75 (prostate cancer 9, symptomatic bacterial urinary tract infection 4, no imaging prostate assessment 41, no blood test or urinalysis 21), 198 patients were enrolled. Since the study was retrospective in nature, the process of obtaining patient consent was omitted. However, for those who did not wish to participate in the study, information was posted on the hospital website with instructions on how to contact to request exclusion. This study was approved by the Ethics Committee of Toho University Omori Medical Center (No. M22170) and conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Evaluation and definition of clinical characteristics

Hematospermia was defined as reddish or dark brown semen found to be contaminated with blood by macroscopic observation. All 198 patients underwent initial testing, including a physical examination of the genitourinary system, and blood and urinalysis, as well as assessments of age and comorbidities such as hypertension and diabetes mellitus (DM). Blood sampling and urinalysis were performed between 8:30 and 11:00 am for all. Blood and urine laboratory information obtained included a complete blood count, albumin, blood urea nitrogen, creatinine, aspartate transferase, alanine transferase, and urine pH (UpH) levels, and urinary red blood cell (RBC) and white blood cell (WBC) counts. UpH level was determined qualitatively with the dipstick method and expressed in a range of 5.0–9.0, with intervals of 1.0. Abnormal urinary RBC and WBC findings were determined when there were

five or more urinary RBCs or WBCs per high power field.

Subsequently, imaging studies for each patient were performed to assess prostate volume and abnormal findings, including SVH, MLC, seminal vesicle dilation (SVD), inflammation, and prostatic stones. Imaging modalities used for prostate assessment included abdominal or transrectal ultrasonography (US), pelvic magnetic resonance imaging (MRI), abdominal computed tomography (CT), or a combination of those. Cystoscopy was performed for nine patients judged to require further examination due to coexisting gross hematuria. SVH was diagnosed based on MRI findings, according to previous reports (8,9). SVD was defined as an anteroposterior dimension for seminal vesicle size greater than 1.5 cm shown in transverse views with transrectal US, MRI, or CT (10). Inflammatory findings were defined as those suggestive of inflammation in fat surrounding the prostate or seminal vesicles using MRI or CT imaging, with most cases of MLC diagnosed based on US or MRI results. Clinical data for each patient were compiled by two urologists blinded to the study endpoints (SH and MO).

Treatment and follow-up

Generally, the presence or absence of symptom improvement was determined from two to four weeks after the start of treatment. The need for medication during that period was decided by the attending physician. For temporary empirical treatment, some patients received antibiotics and/or hemostats for approximately two weeks, though none received a 5α-reductase inhibitor. No additional treatment other than such temporary measures was given during the observation period, even for patients who did not improve. The duration of hematospermia was defined as the period from when the patient first became aware of symptoms until improvement and follow-up was terminated when the symptoms were confirmed to be improved, though instruction was given to return if hematospermia recurred.

Statistical analyses

Measurement values are expressed as the mean ± standard deviation or number (percent of total). A receiver-operating characteristic (ROC) curve for UpH level related to improvement of hematospermia was analyzed to determine the optimum threshold. ANOVA or a Chi-square test was used to examine differences in characteristics between two patient groups, which were divided based on UpH level. Propensity score matching (PSM) at a 1:1 ratio, based on results obtained with a caliper width of 0.2, was employed to adjust for any imbalance in patient characteristics (age, prostate volume, blood and urine laboratory data, treatment) between the groups. To identify factors associated with duration of hematospermia until spontaneous resolution, univariate and multivariate analyses were performed using a Cox proportional hazards regression model both before and after PSM. Kaplan-Meier analysis with a log-rank test was performed to evaluate differences in persistence of hematospermia between the groups. A P-value less than 0.05 was considered to indicate statistical significance. All data were analyzed using the statistical software application EZR (Easy R) (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html) (11).

Results

Characteristics of entire cohort

The clinical characteristics of all 198 patients are summarized in *Table 1*. Mean age was 50.3±13.1 years and prostate volume was 19.0±8.0 mL. Imaging of the prostate confirmed SVH in 32 (16.2%), MLCs in 22 (11.1%), inflammation in 13 (6.6%), and SVD in nine (4.5%). Other abnormal imaging findings, such as urethral cysts or intraprostatic hematoma, were noted in seven (3.5%). Urinalysis revealed an average UpH level of 6.0±1.0. One hundred fourteen (57.6%) patients received empirical treatment with either an antibiotic or hemostatic agent. The median observation period was 2.1 months (range 0.1–68 months). Spontaneous improvement of hematospermia was noted in 176 (88.9%) patients, with a median disease duration of 1.8 months. On the other hand, hematospermia persisted in 22, while among those who showed improved symptoms, 20 (10.1%) had recurrence and returned to the hospital during the follow-up period.

It has been reported that empirical treatment may not be necessary for improvement of hematospermia (7). In the present study, hematospermia improvement was confirmed in 89.5% (102/114 cases) of the empirically treated patients, which was not significantly different from the untreated patients (88.1%, 74/84 cases) (P=0.760).

Identification of predictors of hematospermia persistence

To identify patient factors associated with duration of hematospermia until spontaneous resolution, uni- and

Table 1 Characteristics of 198 patients with hematospermia

Characteristics	Value
Age, years	50.3±13.1
Comorbidities	
Hypertension	40 (20.2)
Diabetes mellitus	14 (7.1)
Prostate volume, mL	19.0±8.0
Prostate imaging findings	
Any	76 (38.4)
Seminal vesicle hemorrhage	32 (16.2)
Midline cyst of prostate	22 (11.1)
Inflammation	13 (6.6)
Seminal vesicle dilation	9 (4.5)
Others	7 (3.5)
Laboratory data	
Hemoglobin, g/dL	15.0±1.3
WBC, $\times 10^9$/L	6.1±1.7
Platelet, $\times 10^4$/μL	22.0±4.8
Albumin, g/dL	4.4±0.4
Blood urea nitrogen, mg/dL	15±5
Creatinine, mg/dL	0.9±0.5
Aspartate transferase, IU/L	24±13
Alanine transferase, IU/L	26±19
Urinalysis	
pH	6±1
RBC ≥5/HPF	30 (14.4)
WBC ≥5/HPF	19 (9.1)
Treatment	
Any	114 (57.6)
Antibiotics	82 (41.4)
Hemostatic agents	52 (26.3)
Improvement of hematospermia	176 (88.9)
Recurrence of hematospermia	20 (10.1)

Data are presented as mean ± standard deviation or number (percentage). RBC, red blood cells; WBC, white blood cells; HPF, high-power field.

multivariate Cox analyses incorporating age, comorbidities, prostate volume, imaging findings, blood and urine laboratory findings, and treatment were performed. As presented in *Table 2*, univariate analysis of all 198 patients showed that the presence of any abnormal imaging findings of the prostate (P=0.006) as well as UpH level (P=0.017) were related to the duration of hematospermia. In multivariate Cox analyses, these two prognostic factors, presence of any abnormal imaging findings of the prostate [(hazard ratio (HR) 1.49; 95% CI: 1.09–2.04; P=0.012] and UpH level (HR 0.85; 95% CI: 0.73–0.99; P=0.038), remained independently associated with hematospermia duration (*Table 2*).

Relationship of UpH level or prostate findings with hematospermia in full cohort

Analysis of the association of UpH level with symptomatic improvement showed that patients who did not show improved hematospermia had a mean level significantly greater as compared to those who demonstrated improvement (6.8 *vs.* 6.1, P=0.0038). Subsequently, the optimal threshold for UpH value associated with improvement of hematospermia was examined. The entire cohort was subjected to ROC analysis without dividing by treatment, as it was considered that the effects of treatment on improvement or persistence of hematospermia could be excluded. Results of ROC curve analysis with the Youden index showed that the optimal cutoff value of UpH to indicate hematospermia improvement was 6.0 (area under the curve 0.687, sensitivity 0.676, specificity 0.591) (*Figure 1*). Based on this optimal cutoff level, patients were divided into the Low-UpH (UpH 5 and 6, n=128) and High-UpH (UpH 7–9, n=70) groups. As shown in *Table 3*, there were significant differences between the groups in regard to age, prostate volume, and several blood data factors, while there was no such difference for recurrence rate of hematospermia between them (Low UpH 9.4%, High-UpH 11.4%). In Kaplan-Meier survival analysis, the High-UpH group had a longer median duration of hematospermia than the Low-UpH group (median 2.3 *vs.* 1.8 months) (*Figure 2A*, P=0.0325). Furthermore, the median duration of symptoms in patients without abnormal imaging findings of the prostate was 2.9 months,

Table 2 Uni- and multivariate Cox proportional hazards analysis findings for persistence of hematospermia before and after propensity score matching

Factors	All patients (n=198)				Patients after matching (n=120)			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.00 (0.99–1.01)	0.997	–	–	1.01 (0.99–1.02)	0.483	–	–
Hypertension	1.02 (0.71–1.46)	0.919	–	–	0.97 (0.55–1.72)	0.921	–	–
Diabetes mellitus	0.93 (0.54–1.61)	0.790	–	–	0.90 (0.45–1.79)	0.762	–	–
Prostate volume	0.99 (0.98–1.01)	0.394	–	–	1.01 (0.98–1.04)	0.740	–	–
Prostate imaging findings, any	1.55 (1.14–2.11)	0.006	1.49 (1.09–2.04)	0.012	1.58 (1.09–2.28)	0.016	1.55 (1.04–2.31)	0.033
Prostate imaging findings, SVH	1.36 (0.91–2.04)	0.134	–	–	1.41 (0.84–2.38)	0.197	–	–
Prostate imaging findings, MLCs	1.47 (0.89–2.43)	0.136	–	–	1.57 (0.87–2.83)	0.135	–	–
Prostate imaging findings, inflammation	1.19 (0.66–2.16)	0.560	–	–	1.01 (0.49–2.01)	0.985	–	–
Prostate imaging findings, SVD	1.10 (0.54–2.25)	0.786	–	–	1.06 (0.39–2.89)	0.913	–	–
Prostate imaging findings, others	1.32 (0.58–2.98)	0.508	–	–	1.37 (0.60–3.13)	0.458	–	–
Hemoglobin	1.02 (0.92–1.14)	0.657	–	–	1.01 (0.86–1.17)	0.934	–	–
WBC	1.00 (1.00–1.00)	0.108	–	–	1.00 (1.00–1.00)	0.195	–	–
Platelets	1.00 (0.99–1.00)	0.499	–	–	1.00 (0.99–1.01)	0.206	–	–
Albumin	0.84 (0.55–1.28)	0.416	–	–	1.08 (0.61–1.91)	0.801	–	–
Blood urea nitrogen	0.99 (0.96–1.02)	0.418	–	–	1.00 (0.96–1.04)	0.790	–	–
Creatinine	0.99 (0.78–1.26)	0.950	–	–	1.22 (0.39–2.88)	0.734	–	–
Aspartate transferase	1.00 (0.99–1.01)	0.653	–	–	1.00 (0.98–1.01)	0.597	–	–
Alanine transferase	1.00 (0.99–1.01)	0.770	–	–	1.00 (0.99–1.01)	0.489	–	–
Urinalysis, pH	0.83 (0.71–0.97)	0.017	0.85 (0.73–0.99)	0.038	0.74 (0.60–0.91)	0.004	0.75 (0.61–0.92)	0.006
Urinalysis, RBC (≥5/HPF)	1.01 (0.66–1.55)	0.958	–	–	0.61 (0.32–1.14)	0.120	–	–
Urinalysis: WBC (≥5/HPF)	0.68 (0.41–1.13)	0.139	–	–	0.69 (0.35–1.37)	0.290	–	–
Treatment, any	1.00 (0.74–1.35)	0.998	–	–	1.16 (0.77–1.73)	0.481	–	–
Treatment, antibiotic	1.00 (0.74–1.35)	0.982	–	–	1.10 (0.72–1.55)	0.780	–	–
Treatment, hemostatic agent	1.25 (0.89–1.76)	0.199	–	–	1.26 (0.82–1.94)	0.295	–	–

HR, hazard ratio; CI, confidence interval; SVH, seminal vesicle hemorrhage; MLC, midline cysts; SVD, seminal vesicle dilation; RBC, red blood cells; WBC, white blood cells.

significantly shorter than for patients with such findings at 7.0 months (*Figure 2A*, P=0.0049).

Relationship of UpH level or prostate findings with hematospermia in PSM cohorts

PSM was performed to correct imbalances in patient baseline characteristics between the two groups classified by UpH level. After use of PSM of 1:1, the cohort included 120 patients, with 60 in each group. As shown in *Table 3*, no statistically significant differences in examined baseline covariates were identified in these PSM cohorts. Spontaneous improvement of hematospermia was seen in 105 (87.5%) of the 120 patients, with a median disease

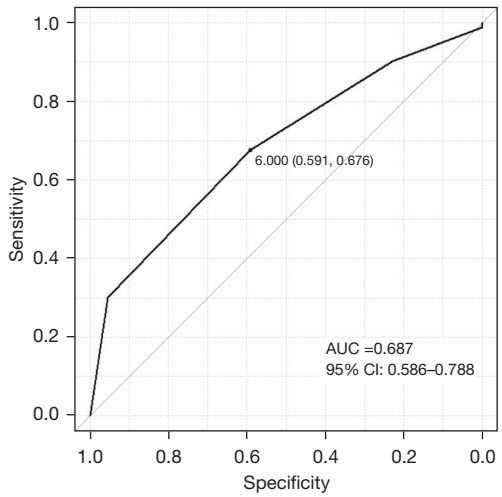

Figure 1 ROC curve analysis for determination of optimal cutoff value of urine pH to indicate hematospermia improvement. The optimal cutoff value for urine pH level was determined to be 6.0 (area under the curve 0.687, sensitivity 0.676, specificity 0.591). ROC, receiver-operating characteristic; AUC, area under the curve.

duration of 1.8 months. In this cohort, the duration of hematospermia was less than two months in 63 (52.5%), two to six months in 35 (29.2%), and greater than six months in 22 (18.3%). For all 120 patients, UpH level 5 was noted in 20, level 6 in 40, level 7 in 41, level 8 in 18, and level 9 in one.

The High-UpH group had significantly inferior outcomes in terms of persistence rate of hematospermia after dividing into the PSM cohorts (P=0.0223), which was also confirmed in the group without any abnormal imaging findings of the prostate (P=0.0433) (*Figure 2B*). In comparisons of the five groups divided by UpH level (UpH 5–9), it was also noted that the persistence of hematospermia tended to be prolonged as the level increased (*Figure 3A*). Furthermore, uni- and multivariate Cox proportional analyses showed that both UpH level and abnormal image findings of the prostate remained independent predictors of hematospermia duration (UpH: HR 0.75, 95% CI: 0.61–0.92; P=0.006, abnormal imaging findings: HR 1.55, 95% CI: 1.04–2.31; P=0.033) (*Table 2*). As shown in *Figure 3B*, further stratification with the combination of UpH level and imaging findings of the prostate identified a stepwise reduction in persistence rate of hematospermia, with the shortest persistence of symptoms found in the Low-UpH group patients without abnormal imaging findings of the prostate (0 factors), while the longest was in the High UpH group with abnormal imaging findings (two factors). In addition, the proportion of patients with these two factors was found to be significantly greater in the group with hematospermia for two months or more, and especially with a duration greater than six months, as compared to the group with a duration of less than two months (*Figure 4*).

Discussion

To the best of our knowledge, the present study is the first to show an association of UpH level with duration of hematospermia. Patients with hematospermia and a high level of alkaline in urine were found to have longer prolongation of symptoms as compared to those with acidic urine. Also, the presence of abnormal imaging findings of the prostate was indicated to be a significant factor in prevention of symptomatic recovery in these patients. It is thus speculated that the combination of these two candidate predictors may be useful for stratification of risk of symptom persistence rate in hematospermia cases.

A variety of studies have examined the relationship of UpH level with different types of disease. For example, acidic urine has been found to be common in patients with sarcopenia (12), coronary artery disease (13), DM (14), and metabolic syndrome (15). In investigations related to nephro-urology, acidic urine was reported to increase the risk of chronic renal failure and urolithiasis (16,17), and may also be associated with poor prognosis in urothelial carcinoma patients (18). On the other hand, alkaline urine is commonly found in urinary tract infection cases and often promotes formation of infected urolithiasis. Interestingly, a UpH level of 7 or higher, identified as a predictor of hematospermia duration in the present study, has been incorporated as one of the important factors in a nomogram prepared by Wang *et al.* for predicting the risk of urinary tract infection development in patients with a neurogenic bladder (19). Furthermore, it is noteworthy that prostatic fluid has been reported to change from acidic (pH 6.6) to alkaline (pH 7–8) in the presence of inflammation (20). Those findings led us to consider that a putative mechanism exists to explain the present results showing that patients with idiopathic hematospermia may actually have an infection or inflammation in the prostate and surrounding area, thus inducing elevated urinary pH and delaying healing.

Another possible explanation is the association of genetic

Table 3 Patient characteristics according to urine pH in all 198 cases and in 138 cases after propensity score matching

Characteristics	All 198 patients			120 patients after propensity score matching		
	Low UpH, n=128	High UpH, n=70	P value	Low UpH, n=60	High UpH, n=60	P value
Age, years	52.0±13.0	47.2±12.8	0.0132	49.0±13.8	48.6±13.0	0.8760
Comorbidities						
Hypertension	30 (23.4)	10 (14.3)	0.1252	5 (8.3)	9 (15.0)	0.2553
Diabetes mellitus	9 (7.0)	5 (7.1)	0.9766	4 (6.7)	5 (8.3)	0.7289
Prostate volume, mL	19.8±8.4	17.1±5.4	0.0171	17.9±5.7	17.3±5.8	0.5739
Prostate imaging findings (any)	44 (34.4)	32 (45.7)	0.1168	22 (36.7)	29 (48.3)	0.1961
Laboratory data						
Hemoglobin, g/dL	15.1±1.2	14.7±2.5	0.0457	15.0±1.2	15.0±1.1	0.9186
WBC, $\times 10^9$/L	6.2±1.7	5.8±1.6	0.1192	6.2±1.7	5.9±1.7	0.3626
Platelet, $\times 10^4$/μL	21.6±4.9	22.7±4.4	0.1515	22.6±5.3	22.8±4.1	0.8134
Albumin, g/dL	4.4±0.4	4.4±0.3	0.6615	4.4±0.4	4.5±0.3	0.3954
Blood urea nitrogen, mg/dL	15.1±4.6	13.7±6.0	0.0584	13.6±3.4	13.8±6.0	0.8223
Creatinine, mg/dL	0.9±0.2	0.9±0.8	0.7703	0.9±0.1	0.8±0.2	0.7955
Aspartate transferase, IU/L	25±14	22±11	0.1253	24±15	23±11	0.7307
Alanine transferase, IU/L	28±21	22±15	0.0447	24±21	24±15	0.9605
Urinalysis						
RBC ≥5/HPF	20 (19.1)	8 (11.4)	0.4179	6 (10.0)	6 (10.0)	1.0000
WBC ≥5/HPF	13 (10.2)	4 (5.7)	0.2862	5 (8.3)	4 (6.7)	0.7289
Treatment						
Any	73 (57.0)	46 (65.7)	0.2136	41 (68.3)	35 (58.3)	0.2557
Antibiotics	49 (38.3)	36 (51.4)	0.0683	29 (48.3)	27 (45.0)	0.7144
Hemostatic agents	36 (28.1)	19 (27.1)	0.9205	17 (28.3)	15 (25.0)	0.6797
Improvement of hematospermia	125 (97.7)	59 (84.3)	0.0112	56 (93.3)	49 (81.7)	0.0533
Recurrence of hematospermia	12 (9.4)	8 (11.4)	0.6289	3 (5.0)	6 (10.0)	0.2985

Data are presented as mean ± standard deviation or number (percentage). UpH, urine pH; RBC, red blood cell; WBC, white blood cell; HPF, high power filed.

factors that contribute to UpH regulation. Canales *et al.* (21) recently found relationships of single nucleotide polymorphisms in several genes, including insulin-like growth factor binding protein 7 (*IGFBP7*), with basal UpH regulation. Factors known to delay tissue healing include systemic factors such as age and malnutrition, as well as local factors such as the presence of inflammation and poor blood supply. Of note, IGFBP7 is expressed in an extensive variety of tissues, including testes, prostate, and seminal vesicles (male genitourinary organs) (22), and has been found to be one of the factors regulating angiogenesis and collagen production associated with tissue repair (23,24). Thus, specific genetic factors, such as *IGFBP7* mutation, may contribute to the association of higher UpH level with delayed healing in hematospermia cases, though further investigation is needed.

Abnormal findings obtained with prostate imaging was also an important factor associated with prolonged duration of symptoms in the present patients. Although both SVH and MLCs were significant predictive factors in

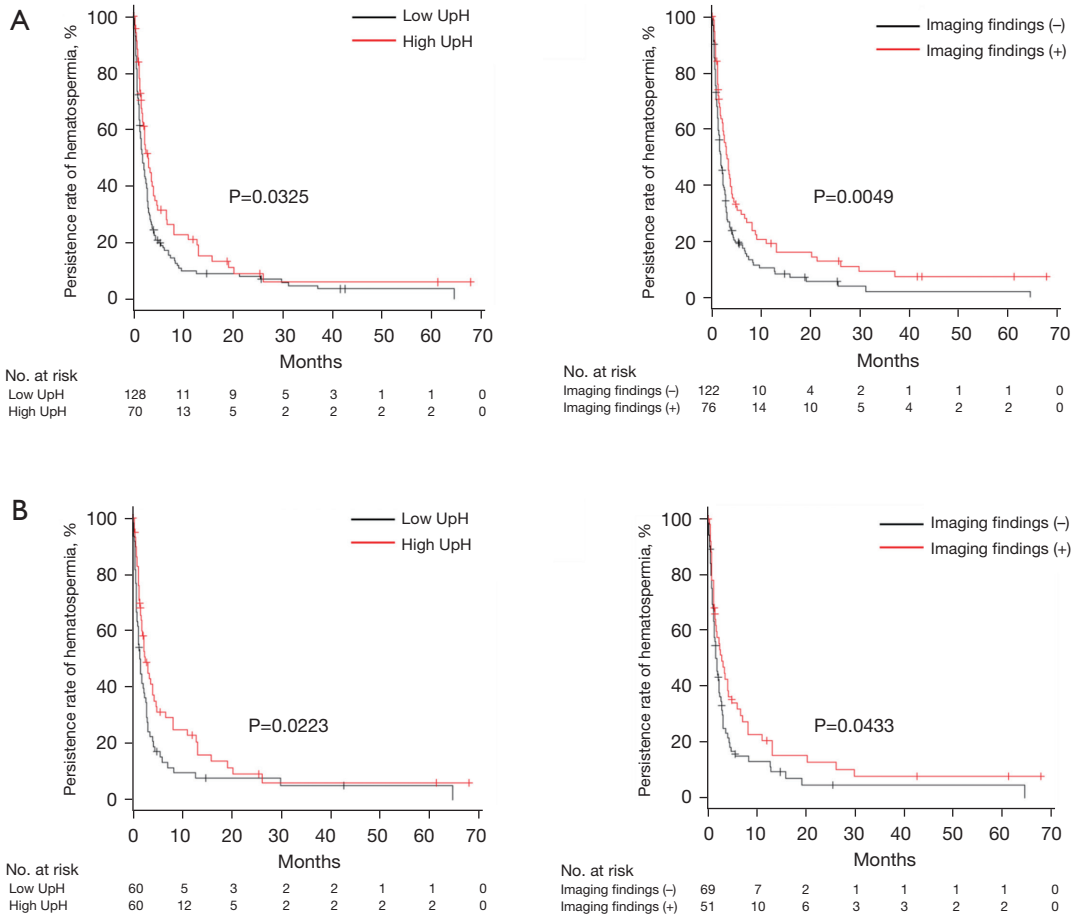

Figure 2 Kaplan-Meier analysis for rate of persistence of hematospermia according to urine pH or imaging findings in pre- and after propensity score matching cohort. (A) In the entire cohort (n=198), the High-UpH group had a higher persistence rate of hematospermia than the Low-UpH group (P=0.0325). A similar difference was also observed between patients with and without abnormal prostate imaging findings (P=0.049). (B) After propensity score matching, both high UpH level and abnormal prostate imaging findings were factors associated with significantly increased time before improvement of hematospermia (P=0.0223, P=0.0433, respectively). UpH, urine pH.

a previous investigation (9), the present findings indicated that the presence of any abnormal findings, including those as well as others, result in persistent hematospermia. Another study reported that more than 80% of patients with hematospermia had some prostate or seminal vesicle abnormality, while those comprised 38.4% in the present study (25). For example, the incidence of SVH in patients with hematospermia has been reported to range from 20% to 50% (9,25,26). Since many related abnormalities can be easily diagnosed by use of a minimally invasive method such as MRI and US, it is suggested that imaging studies be considered whenever possible for patients with hematospermia. Regarding treatment, transurethral endoscopic treatment has been reported to be effective for hematospermia accompanied with MLCs persisting for more than one year (9). Although observation is commonly employed for affected patients, it is important to consider surgical treatment when abnormal findings are noted in those with persisting symptoms.

The present study has several limitations, including its retrospective nature, relatively small number of patients, and short observation period. Although overt urinary tract infection, DM, cardiovascular disorders, and renal dysfunction were included in the analysis as confounding factors affecting UpH level, other factors such as medication, dietary intake or gastrointestinal ailments, including vomiting and diarrhea, were not considered. A litmus strip method was used to provide integer values

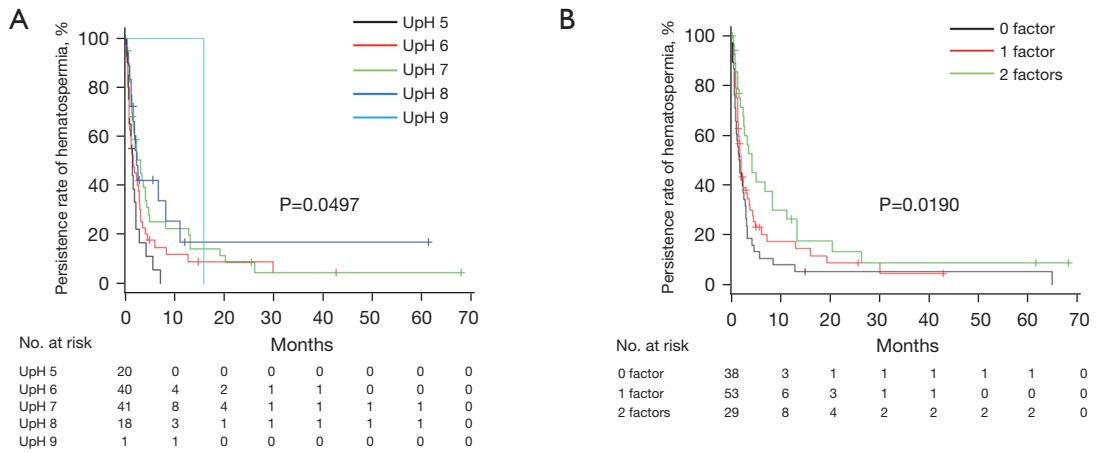

Figure 3 Kaplan-Meier analysis of hematospermia persistence using urine pH and that in combination with imaging findings in 120 patients stratified by propensity score matching. (A) Comparisons among five groups (UpH 5–9). The rate of persistence tended to increase along with increased UpH (P=0.0497). (B) Stratification using combination of UpH level and imaging findings. The longest term of hematospermia persistence was found in patients with both high UpH level and abnormal imaging findings, followed by those with one of those factors, while the shortest was in patients without either factor. UpH, urine pH.

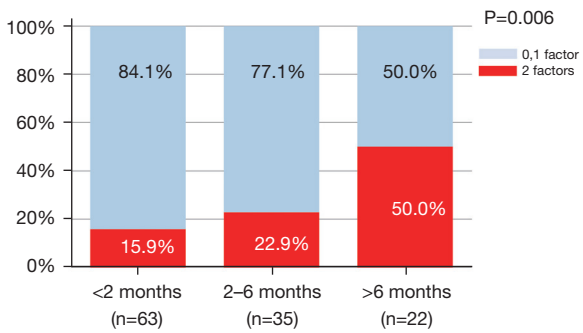

Figure 4 Persistent duration of hematospermia in patients with two factors. For patients with two factors present (high urine pH and imaging findings), a duration of blood in sperm for <2 months was noted in 15.9% (10/63), for 2–6 months was noted in 22.9% (8/35), and for >6 months was noted in 50% (11/22) (P=0.006).

for UpH levels to be used in analyses, though those may differ greatly from the actual value in some cases (27). In addition, UpH level was measured in spot urine rather than 24-hour urine samples, as it has been reported that the pH value of a spot urine sample may correlate well with that of a 24-hour sample (14,28), though the latter is considered to possibly provide more accurate values. Additionally, the effects of dynamic UpH value on clinical outcome were not evaluated. Although the effects of UpH level on recurrent and persistent urinary tract infections have been investigated, how pH level changes over time during a urinary tract infection remains unclear (29,30). We consider that UpH level may change over the course of treatment when infection or inflammation in the prostate and surrounding area are factors related to elevated UpH level and delayed healing of hematospermia. Even when using an optimal cut-off value for UpH value, it may be better to compare various patient groups, such as those with and without treatment. It will be important to conduct further studies that overcome these limitations to verify the results presented here.

Conclusions

This the first study to demonstrate that presence of urine alkalinization as well as abnormal imaging findings of the prostate are associated with prolonged hematospermia. By combining these two factors in analyses of affected patients, more accurate prediction of hematospermia duration was found to be possible. Blood in semen is unsettling for most patients, thus even when hematospermia is cured within a short period, those affected may continue to experience anxiety during that time. The present results provide useful

information to reassure patients with hematospermia and also determine the need for therapeutic intervention.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-108/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-108/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-108/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of Toho University Omori Medical Center (No. M22170) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). Since the study was retrospective in nature, the process of obtaining patient consent was omitted.

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