Haemospermia in the Real- Life Setting: A New High-Risk Stratification

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OBJECTIVE To (i) identify a novel risk stratification for patients complaining of haemospermia; and, (ii) compare its predictive ability to select high-risk patients by retrospectively validating the EAU guidelines classification.

METHODS Data from 283 consecutive patients complaining of a single episode/recurrent haemospermia were retrospectively analyzed. Patients were stratified into low vs high-risk according to EAU guidelines, whose diagnostic performance was then validated. We identified a new risk stratification model based on clinical factors associated with (i) positive semen culture and (ii) prostate cancer (PCa) and bladder cancer (BC). Diagnostic accuracy of the two predictive models (EAU vs New) was assessed and decision curve analyses (DCA) tested their clinical benefit.

RESULTS Overall, 259 (91.5%) were high-risk and 24 (8.5%) low risk according to the EAU guidelines. Recurrent haemospermia was reported by 134 (47.4%) patients. 126 (44.5%) had baseline CCI score ≥ 1. At MVA logistic regression analysis, history of recurrent genito − urinary tract infections was identified as a predictor for positive semen culture (OR: 3.39, 95% CI: 1.77 - 6.57, P =.002). Likewise, baseline CCI ≥ 1 was identified as a predictor for PCa and BC (OR: 1.55, 95% CI: 1.17 - 2.04, P =.009). Sensitivity, specificity, and AUC of the EAU guidelines were 13.3%, 89.2% and 51% respectively, whereas the new model performed substantially better: 98.9%, 58% and 78% respectively.

CONCLUSION The application of the EAU guidelines risk stratification does not ensure proper identification of high-risk patients complaining of haemospermia. We propose a novel, better performing and easily implementable risk stratification tool. UROLOGY 171: 146–151, 2023. © 2022 Elsevier Inc.

The cause of haemospermia has mostly been ascribed to benign conditions.[1-3] Although this holds true, a non-negligible proportion of patients harbor more serious and harmful conditions, which surely deserve further diagnostic tests and investigations.[4] As such, haemospermia may also be regarded as an alarm bell of something that deserves a correct diagnostic interpretation and eventually appropriate treatment.[4-6] In this context, the identification of a proper high-risk category among these patients remains a matter of debate. According to the recently published Sexual and Reproductive Health guidelines of the European Association of Urology (EAU), patients over 40 years of age and patients complaining of recurrent episodes of haemospermia (regardless of their age) are considered "high-risk", thus having a higher likelihood to harbor medical conditions that need to be identified and treated (eg., ongoing semen infection, prostate cancer (PCa), bladder cancer (BC) and testicular cancer (TC)).[1] These men should undergo a series of diagnostic tests and/or empirical treatments including antibiotics, anti-inflammatory drugs, trans-rectal ultrasound (TRUS), pelvic magnetic resonance (MRI), PCa screening with prostate-specific antigen (PSA) dosage and digital rectal examination (DRE) (in men ≥ 40 years old), TC screening with testicular ultrasounds (in men <40 years old) and BC screening with cystourethroscopy and eventually biopsy.[7-9] Possibly, a high proportion of patients presenting with haemospermia would fall into

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the EAU high-risk category undergoing many unnecessary diagnostic and empirical treatments; this, not only translates into higher costs but also provides unneeded information over the patients' diagnostic work-up of these patients.[6,10-12] A proper identification of those who would truly benefit from second-level diagnostic investigations is still needed. We aimed to identify a novel risk stratification for patients complaining of haemospermia and to compare its predictive ability to select high-risk patients by retrospectively validating the EAU guidelines classification.

PATIENTS AND METHODS

After institutional review board approval, we retrospectively analyzed data from 283 consecutive patients seeking first medical help for single/recurrent episode of haemospermia at a single outpatient clinic between January 2006 and September 2020. Sociodemographic characteristics, including age and relationship status, were collected for every patient. All subjects were assessed via a detailed medical history and all drugs have been comprehensively collected. Health significant comorbidities were scored using the Charlson comorbidity index (CCI).[13] The CCI was categorized as 0 or ≥1. Arterial hypertension (HTN) was defined as office systolic blood pressure values ≥ 130 mmHg and/or diastolic blood pressure values ≥ 90 mmHg. Data on recreational habits including physical activity (defined as at least 2 self-reported physical exercise sessions per week per individual), cigarette smoking history, and alcohol use were also collected. Recurrent haemospermia was defined as ≥ 2 episodes reported at baseline. The entire cohort of patients has been longitudinally followed up with outpatient clinical assessments to detect the aetiology of haemospermia. Patients lost to first follow − up evaluation were eventually excluded from the analysis (n = 32). Venous blood samples were drawn from each patient between 7 AM and 11 AM after overnight fasting. In all cases, fasting glucose levels were measured via a glucose oxidase method (Aeroset Abbott). Patients were invited to complete the International Prostate Symptom Score (IPSS), Becks Inventory for Depression (BDI), Overactive bladder (OABq) and the International Index of Erectile Function (IIEF) questionnaires at first clinical evaluation.[13-15] As for our internal protocol, after first assessment, each man was asked to undergo semen and urine culture tests to identify potential common urogenital pathogens. Prostate specific antigen (PSA) dosage was offered to all patients ≥ 40 years. Real − time polymerase chain reaction (rt − PCR) platform was used to detect infections by Mycoplasma, Ureaplasma, and Chlamydia spp. PCR was performed by the same laboratory for every individual. A concentration of ≥ 10^3 CFU/mL of urinary tract pathogens in the ejaculate was considered indicative of positive bacteriospermia as suggested by the WHO.[16] Likewise, a concentration ≥ 100,000 CFU/mL of urinary tract pathogens in the urine was considered indicative of a positive urine culture. The same laboratory was used for the analyses of all parameters. Standardized protocols on how to collect semen and urine samples have been explained to every patient. Data regarding history of sexually transmitted diseases (STD) (past confirmed infections of Neisseria Gonorrhea, Chlamydia Trachomatis, Herpes simplex 1 and 2 and Syphilis), history of symptomatic recurrent urinary tract infections (rUTI), and past episodes of symptomatic acute prostatitis were collected for each participant. PCa and BC diagnostic workup was performed in accordance with EAU guidelines.[17-19] More in details, all patients who eventually have had a PCa diagnosis, underwent prostate biopsy over the initial period and subsequently multiparametric magnetic resonance imaging of the prostate followed by fusion trans-perineal prostate biopsy. Likewise, those patients with a final BC diagnosis had been submitted to urine cytology test, flexible cystoscopy, and trans-urethral resection of the bladder for definitive diagnosis. Lastly, diagnosis of PCa and BC was achieved after expert histopathological review of prostate and bladder tissue specimens.

Data collection followed the principles outlined in the Declaration of Helsinki. All patients signed an informed consent agreeing to share their own anonymous information for future studies. The study was approved by the IRCCS San Raffaele Hospital Ethical Committee (Prot. 2014 — Pazienti Ambulatoriali).

Statistical Analysis

Data are presented as medians (interquartile range; IQR) or frequencies (proportions). The analyses consisted of several statistical steps. First, patients were segregated into two groups according to the low vs high-risk classification proposed by the recently revised Sexual and Reproductive Health EAU guidelines.[7] EAU high-risk patients were those with ≥ 1 of these characteristics at first clinical assessment:(i) age ≥ 40 years; (ii) recurrent or persistent haemospermia (any age); (iii) actual risk for PCa (eg., positive family history); and, (iv) concurrent haematuria. The remaining cohort was classified as low risk. Second, we tested the diagnostic accuracy (sensitivity, specificity, and discrimination) of EAU guidelines. Third, in order to improve the diagnostic accuracy of the EAU guidelines, we sought for clinical factors associated to (i) positive semen culture, and (ii) PCa and BC, since these factors represent the most frequent unfavourable clinical outcomes in men complaining of haemospermia. The newly identified factors were grouped in order to provide an updated risk stratification. The diagnostic accuracy (sensitivity, specificity, and discrimination) of the updated risk stratification was assessed and compared with the EAU guidelines using a DeLong test. Lastly, decision curve analysis (DCA) tested their clinical benefit. All statistical tests were two − sided with a significance value set at 0.05. The analyses were conducted using R (2019), a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

RESULTS

Table 1 shows patients' characteristics of the whole cohort of 283 patients and according to the low vs high-risk classification proposed by the EAU Sexual and Reproductive Health guidelines. Overall, the median (IQR) age at first presentation was 49 (37 - 48) years. Recurrent haemospermia was reported by 134 (47.4%) patients. Of all, 126 (44.5%) had a baseline CCI score ≥ 1, 67 (23.7%) had arterial hypertension, 30 (10.6%) were active smokers, 38 (13.4%) and 15 (5.3%) had a positive history for rUTI and STD at first clinical assessment, respectively. Median (IQR) PSA at first presentation was 1.1 (0.6 - 2.4) ng/mL. Of all, 31 (11%) patients had a positive semen culture at follow − up, 16 (5.7%) a positive urine culture and 15 were found to harbor genitourinary (GU) cancers (ie, 12 (4.2%) PCa and 3 (1.1%) BC), respectively.

According to EAU guidelines, 259 (91.5%) men were classified as high-risk patients, whilst 24 (8.5%) low risk. High-risk patients reported higher PSA levels than low risk ones (P

<.0008). Moreover, high-risk patients were more likely to suffer of arterial hypertension (P <.0001). On the contrary, patients in the high-risk category were similar in terms of reporting history of rUTI, history of STD, positive urine, and semen cultures after first clinical assessment, compared to low-risk men (Table 1).

Table 2.1 depicts the logistic regression analyses of clinical factors associated to a positive semen culture; history of recurrent genito-urinary infections was an independent predictor (OR: 3.39, 95%CI: 1.77 - 6.57, P =.002), after adjusting for being high-risk according to the EAU guidelines, baseline CCI ≥ 1 and BMI.

Table 2.2 depicts the logistic regression analyses of clinical factors associated to PCa or BC diagnosis. Baseline CCI ≥1 was identified as a predictor (OR:1.55, 95%CI: 1.17 - 2.04, P =.009) after adjusting for being high-risk according to the EAU guidelines, smoking (previous and current smoking) and BMI. Supplementary Table 1 details the characteristics of the entire cohort of patients according to the new risk stratification.

Table 3 reports the diagnostic accuracy (sensitivity, specificity, and discrimination) of the EAU guidelines compared with the updated risk stratification. The calculated sensitivity and specificity of the EAU guidelines were 13.3% and 89.2%,

Table 1. Characteristics of the entire cohort of patients (n = 283), EAU low risk category (n= 24) and EAU high risk category (n= 259)

	Whole Cohort	Low Risk EAU	High Risk EAU	P-Value
No. of participants [no. (%)]	283 (100)	24 (8.5)	259 (91.5)	
Age (years) Median (IQR)	49 (37 - 48)	27 (26 - 29)	51 (40 -61)	<.0001
BMI (kg/m^2) Median (IQR)	25.1 (23.1 - 27.3)	24.09 (21.8 - 25.8)	25.1 (23.1-27.3)	.2
Recurrent Haemospermia [n. (%)]	134 (47.4)	0 (0.0)	134 (51.7)	<.0001
CCI [n. (%)]				
0	156 (55.5)	19 (79.2)	137 (52.9)	
≥1	126 (44.5)	5 (20.8)	121 (47.1)	.02
Arterial hypertension [n. (%)]	67 (23.7)	0 (0.0)	67 (25.8)	<.0001
Cigarette smoking [n. (%)]				
Yes	30 (10.6)	6 (25)	24 (9.3)	.1
No	209 (73.9)	15 (62.5)	194 (74.9)	
Ex-smoker	44 (15.6)	12.5)	41 (15.8)	
Diabetes mellitus* [n. (%)]	8 (2.8)	0 (0.0)	8 (3.1)	.8
PSA (ng/mL) Median (IQR)	1.1 (0.6 – 2.4)	0.7 (0.2 – 0.9)	1.1 (0.6 – 2.4)	.0008
Epididymal Cysts [n. (%)]	14 (4.9)	1 (4.2)	13 (5)	.7
BDI Questionnaire Median (IQR)	6 (2.5 – 8.5)	6 (3 – 8.3)	5 (2 – 8.3)	.5
IPSS questionnaire Median (IQR)	11 (5 – 15)	11 (3.3 – 13)	10 (5 – 15)	.8
IPSS–QoL single question Median (IQR)	3 (2 – 4)	4 (4 – 4.8)	3 (2 – 6)	.2
IIEF–Tot questionnaire Median (IQR)	26 (18 – 29)	25 (25 – 28)	26 (15 – 29)	.9
BPH [n. (%)]	45 (15.9)	1 (4.2)	44 (16.9)	.2
History of rUTI [n. (%)]	38 (13.4)	5 (20.8)	33 (12.7)	.9
History of STD † [n. (%)]	15 (5.3)	13 (5)	2 (0.8)	.9
Current anti–coagulation therapy [n. (%)]	9 (3.2)	1 (4.2)	8 (3.1)	.9
Urinary tract infection‡ [n. (%)]	16 (5.7)	1 (0.0)	15 (5.8)	.7
Escherichia Coli	8 (2.8)	1 (4.2)	7 (2.7)	
Enterococcus Faecalis	2 (0.7)	1 (4.2)	1 (0.4)	
Klebsiella Pneumoniae	2 (0.7)	0 (0.0)	2 (0.8)	
Streptococcus Agalactiae	1 (0.4)	0 (0.0)	1 (0.4)	
Staphylococcus Aureus	2 (0.7)	1 (4.2)	1 (0.4)	
Viridans Streptococci	1 (0.4)	0 (0.0)	1 (0.4)	
Prostatitis [n. (%)]	13 (4.6)			
Acute	5 (1.8)	2 (8.3)	3 (8.3)	.7
Chronic	8 (2.8)	0 (0.0)	8 (3.1)	.8
Positive semen culture	31 (11)	3 (12.5)	28 (10.8)	.9
Intracellular pathogens [n. (%)]	10 (3.5)	2 (8.3)	8 (3.1)	.7
Chlamydia	1 (0.4)	1 (4.2)	0 (0.0)	
Mycoplasma	2 (0.7)	1 (4.2)	1 (0.4)	
Ureaplasma Urealyticum	7 (2.5)	0 (0.0)	7 (2.7)	
Extracellular pathogens	21 (7.4)	1 (4.2)	20 (7.7)	.5
Escherichia Coli	9 (2.5)	1 (4.2)	8 (3.1)	
Enterococcus Faecalis	10 (3.5)	0 (0.0)	10 (3.9)	
Pseudomonas Aeruginosa	1 (0.4)	0 (0.0)	1 (0.4)	
Streptococcus Agalactiae	1 (0.4)	0 (0.0)	1 (0.4)	
Diagnosis of Prostate Cancer [n. (%)]	12 (4.2)	0 (0.0)	12 (4.6)	.6
Diagnosis of Bladder Cancer [n. (%)]	3 (1.1)	0 (0.0)	3 (1.6)	.9

Abbreviations: BDI, becksiInventory depression;BMI, body mass index, BPH, benign prostatic hyperplasia; CCI, charlson comorbidity index (includes ages' cut-off); IIEF, international index erectile function; IPSS, International Prostate Symptom Score; PSA, Prostate Specific Antigen; rUTI, recurrent urinary tract Infection;STD, sexually transmitted disease.

* All patients reported type 2 diabetes mellitus.

† STD history includes past confirmed infections of Neisseria Gonorrhea, Chlamydia Trachomatis, Herpes simplex 1 and 2.

‡ Positive urine culture at time of first clinical assessment.

Table 2.1. Logistic regression analyzes to identify potential predictive factors for positive semen culture in the whole cohort of patients (n = 283)

	UVA			MVA		
	OR	95% CI	*P*-Value	OR	95% CI	*P*-Value
High Risk (EAU)	1.26	0.48, 4.18	.7	1.52	0.57, 5.11	.5
History of GU infection	3.09	1.64, 5.90	.003	3.39	1.77, 6.57	.002
CCI ≥ 1	0.64	0.33, 1.22	.3	0.58	0.29, 1.14	.2
BMI	1.39	0.41, 3.73	.6	2.07	0.58, 5.98	.3

†High risk category (EAU): men ≥ 40 years old of any age with persistent haemospermia, or haemospermia associated with symptoms or signs of disease.

respectively. The calculated sensitivity and specificity of the updated risk stratification were 98.9% and 58%, respectively. DeLong's test confirmed that the new model [AUC (0.78, 95%CI: 0.72 - 0.84)] performed better than the EAU guidelines [AUC (0.51, 95%CI: 0.44 - 0.68], P <.0001. Figure 1 displays the superior net benefit of using the new risk stratification in terms of diagnosing positive semen cultures, PCa and BC compared to the EAU guidelines stratification. Lastly, Supplementary Figure 1 displays the diagnostic work-up flowchart based upon the newly identified predictive model.

DISCUSSION

We applied the EAU guidelines risk stratification in a cohort of patients seeking first medical help for single/recurrent episodes of haemospermia at a single tertiary academic centre. Almost nine out of ten patients were classified as high-risk of harboring a treatable and identifiable aetiology according to the most recent EAU guidelines.[1] At first clinical evaluation, we did not find relevant clinical differences between high and low risk men apart from a higher prevalence of arterial hypertension and PSA levels in the high-risk group, without any difference in terms of past genitourinary tract infections. Against this background, we aimed at improving the selection of high-risk patients by identifying clinical factors mainly associated with positive semen culture, PCa and BC among patients seeking first medical help for haemospermia. We identified that those patients reporting past recurrent genitourinary tract infections and those with a baseline CCI ≥ 1 were the ones that should have received a focused diagnostic work-up for bacteriospermia, PCa and BC, respectively. In this context, the wording "high-risk" does not underlie the severity of a specific diagnosis (eg., high risk tumor), rather a condition that eventually warrants medical attention (eg., second level diagnostic tests and/or treatments). Lastly, the new risk stratification based on these associated factors was then compared to the EAU Guidelines on Sexual and Reproductive Health. AUC, sensitivity, and specificity confirmed the superiority of the new risk stratification as compared with the EAU guidelines in identifying high-risk patients (Table 3).

As a matter of fact, our results partially confirm the findings of previously published studies. Efesoy et al. investigated the aetiological factors among 342 patients complaining of haemospermia: the most frequent cause of haemospermia was inflammation/infection in 169 patients (49.4%), whereas genitourinary (GU) cancers were detected in only 11 patients (3.2%).[4] Although these findings reflect similar GU cancers prevalence to those of our cohort, we could not conclude the same regarding inflammation/infections; this difference may be due to the different and aggregate definition/assessment of both inflammation and infection. A prospective study by Furuya et al. confirmed the overall benign aetiology of haemospermia; among the analyzed cohort of 189 patients, the authors concluded that men with haemospermia without signs of infection, inflammation, or malignancy, had spontaneous resolution of their condition in more than 88% of cases.[20] Lastly, Ng YH et al. aimed to investigate the prevalence of significant underlying pathologies among 300 consecutive patients with haemospermia and simultaneously assess the diagnostic value of routine urological investigations. In the cohort analyzed, authors found 13 PCa cases (5.7%), all in men ≥ 40 years, confirming our findings. GU infection's rates were similar to ours, with 15% and 10.3% in men under 40 years and above 40 years, respectively.[3]

Although the latter mentioned findings are comparable to ours, it is uncertain whether these conditions are causative or coincidental with the presentation of haemospermia. Moreover, most of the published literature have been

Table 2.2. Logistic regression analyses to identify potential predictive factors for PCa and BC in the whole cohort of patients (n. =283)

	UVA			MVA		
	OR	95% CI	*P*-Value	OR	95% CI	*P*-Value
High Risk (EAU)	0.79	0.42, 1.50	.5	0.47	0.39, 2.38	.9
Active or past smoking	1.44	0.53, 3.55	.5	1.15	0.41, 2.95	.8
CCI ≥ 1	1.61	1.22, 2.09	.002	1.55	1.17, 2.04	.009
BMI	2.01	0.43, 6.54	.4	1.33	0.27, 4.64	.7

†High risk category (EAU): men ≥ 40 years old of any age with persistent haemospermia, or haemospermia associated with symptoms or signs of disease.

Table 3. Sensitivity, specificity, and area under the curve (AUC) of the EAU and the new risk stratification models

High-Risk (EAU)	N (%)	95% CI
Sensitivity	13.3	\
Specificity	89.2	\
Area under the curve (AUC)	0.5	0.4, 0.7
High-Risk (New)	N (%)	95% CI
Sensitivity	98.9	\
Specificity	58	\
Area under the curve (AUC)	0.8	0.7, 0.8

focusing in establishing the true prevalence of serious underlying diseases rather than focusing on the selection of patients that deserve adequate screening for those conditions.[5,21,22] Albeit many diagnostic tests are routinely asked in the everyday medical practice for patients with haemospermia, more testing might not always bring benefit to patient care and could lead to patient dissatisfaction along with resource misallocation. Our findings confirm how the rigorous application of EAU guidelines may result in poor diagnostic accuracy, since virtually the entire cohort of patients should have been empirically treated and/or screened. This would have led asking for unnecessary diagnostic tests to patients that could have been treated conservatively (eg, observation). As such, the cost effectiveness of identifying a narrower spectrum of patients that deserve needless second-level diagnostic tests indirectly increases the cost-effectiveness of the proposed model (compared to EAU guidelines). To our knowledge, this is the first study to establish a new risk stratification for the selection of high-risk patients complaining of haemospermia (single episode and/or recurrent). On the other hand, our study is certainly not devoid of limitations. First, even though we analyzed a single homogeneous, same-ethnicity cohort of men presenting with haemospermia as their primary compliant, this was a single-centre cross-sectional study, thus raising the possibility of selection biases. Second, although having homogeneous data from white-Caucasian patients may only represent a further strength of the analyses, on the other hand, different geographical areas and ethnicity groups might have shown different and possibly more homogenous results. Third, not all patients in our cohort underwent TRUS and/or prostate MRI thus leading to the possibility of misdiagnosing seminal vesicle stones, Mullerian duct cysts or ejaculatory duct obstructions. Fourth, not all patients underwent PCa and/or BC diagnostic work-up nor were asked about family history thus potentially leading to the underdiagnosis of these malignancies. On the other hand, this study suggests that the way EAU guidelines currently recommend us to stratify patients with haemospermia is not satisfactory. In the light of this, we propose here a better and more accurate risk stratification of these men.

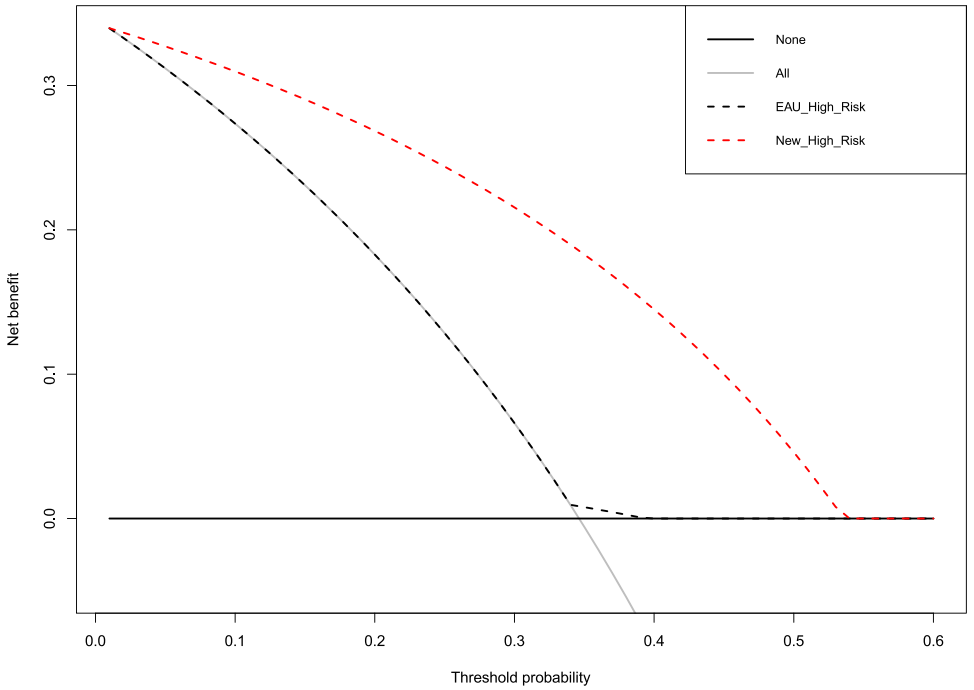

Figure 1. Decision curve analysis (DCA) showing the net benefit of using the novel high-risk predictive model to identify high-risk patients presenting with single episode/recurrent haemospermia who should be screened for (A) positive semen culture or (B) PCa and BC. The grey solid line represents the strategy of screening all patients; the black dashed line represents the strategy of screening high-risk patients according to the EAU guidelines; the black solid line represents the strategy of screening none of the patients. (Color version available online.)

CONCLUSION

The application of the EAU risk stratification does not adequately ensure the identification of high-risk patients complaining of haemospermia. In our cohort, nine out of ten patients were identified as high-risk according to EAU guidelines. Thus, we propose a novel and better performing risk stratification to identify those patients at higher risk of having unfavorable associated clinical conditions.

AUTHOR CONTRIBUTION

Conceptualization: Edoardo Pozzi, Eugenio Ventimiglia, Andrea Salonia. Data curation: Edoardo Pozzi, Eugenio Ventimiglia, Giuseppe Fallara, Paolo Capogrosso, Federico Belladelli, Luigi Candela, Massimiliano Raffo, Antonio Costa, Daniele Cignoli, Christian Corsini, Walter Cazzaniga, Luca Boeri, Rayan Matloob, Umberto Capitanio. Formal analysis: Edoardo Pozzi, Eugenio Ventimiglia. Funding acquisition: None. Investigation: Edoardo Pozzi, Eugenio Ventimiglia, Andrea Salonia. Methodology: Edoardo Pozzi, Eugenio Ventimiglia, Andrea Salonia. Project administration: Edoardo Pozzi, Eugenio Ventimiglia, Andrea Salonia, Francesco Montorsi. Supervision: Andrea Salonia, Francesco Montorsi. Validation: Andrea Salonia, Francesco Montorsi. Visualization: Edoardo Pozzi, Eugenio Ventimiglia, Giuseppe Fallara, Paolo Capogrosso, Federico Belladelli, Luigi Candela, Massimiliano Raffo, Antonio Costa, Daniele Cignoli, Christian Corsini, Walter Cazzaniga, Luca Boeri, Rayan Matloob, Umberto Capitanio, Francesco Montorsi, Andrea Salonia. Writing – original draft: Edoardo Pozzi, Eugenio Ventimiglia. Writing – review & editing: Edoardo Pozzi, Eugenio Ventimiglia.

CONFLICTS OF INTEREST

The authors have declared that no conflict of interest exists.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2022.09.018.

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