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Published in:
European Journal of Internal Medicine

DOI:
10.1016/j.ejim.2021.03.010

Publication date:
2021

European Journal of Internal Medicine 87 (2021) 44–50

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Influence of gender on the performance of urine dipstick and automated urinalysis in the diagnosis of urinary tract infections at the emergency department

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ARTICLE INFO

Keywords:
Urinary tract infection
Emergency medicine
Automated urinalysis
Gender differences

ABSTRACT

Background: Urinary tract infections (UTIs) are frequently encountered at the Emergency Department (ED). Given the anatomical differences between men and women, we aimed to clarify differences in the diagnostic performance of urinary parameters at the ED.
Methods: A cohort study of adults presenting at the ED with fever and/or clinical suspected UTI. Performance of urine dipstick (UD) and automated urinalysis (UF-1000*i*) were analysed for the total study population and men and women separately. We focused on 1) UTI diagnosis and 2) positive urine culture (UC, $\geq 10^5$ CFU/ml) as outcome.
Results: In 360 of 917 cases (39.3%) UTI was established (men/women 35.1%/43.6%). Diagnostic accuracy of UD was around 10% lower in women compared to men. Median automated leucocyte and bacterial count were higher in women compared to men. Diagnostic performance by receiver operating analysis was 0.851 for leucocytes (men/women 0.879/0.817) and 0.850 for bacteria (men/women 0.898/0.791). At 90% sensitivity, cut-off values of leucocyte count (men 60/μL, women 43/μL), and bacterial count (men 75/μL, women 139/μL) showed performance differences in favour of men. In both men and women, diagnostic performance using specified cut-off values was not different between normal and non-normal bladder evacuation. UC was positive in 327 cases (men/women 149/178), as with UTI diagnosis, diagnostic values in men outperformed women.
Conclusions: Overall diagnostic accuracy of urinary parameters for diagnosing UTI is higher in men. The described differences in cut-off values for leukocyte and bacterial counts for diagnosing UTI necessitates gender-specific cut-off values, probably reflecting the influence of anatomical and urogenital differences.

Introduction

Urinary tract infections (UTIs) are generally more common in women compared to men [1-3]. Beside incidence, also differences in presentation and course of UTI exist between men and women. This is due to a variety of factors, like (pelvic) anatomic differences, voiding issues, and vaginal mucosa colonization [4-8]. In addition, differences in causing uropathogens exist between men and women [9].

A suspected UTI is a frequently encountered condition at the Emergency Department (ED). Patients presenting at the ED are hardly comparable with primary care patients. In an ED setting, the majority of the patients have a complicated UTI (based on functional or structural abnormalities of the genitourinary tract, instrumentation of the urinary tract or antibiotic use) which will influence the performance of diagnostic tests. The influence of gender on the performance of urinary diagnostics, like urine dipstick (UD) and automated urinalysis, is not

Abbreviations: AUC, area under the curve; CI, confidence interval; CFU, colony forming unit; ED, emergency department; LE, leucocyte esterase; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; UC, urine culture; UD, urine dipstick; UTI, urinary tract infection; ROC, receiver operating characteristic.

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https://doi.org/10.1016/j.ejim.2021.03.010
Received 12 January 2021; Received in revised form 23 February 2021; Accepted 8 March 2021
Available online 26 March 2021

adequately analysed in the ED setting. Most gender-related studies are situated in the primary care, patient populations are insufficiently described and comparison between genders is lacking [10-19]. In addition, in contrast to the ED, the majority of cases in the primary care setting are women [3,20].

The aim of this study was to clarify the gender-specific performance of urinary diagnostics in a large cohort of adults presenting with signs or symptoms possibly related to UTI at the ED. Therefore we studied the performance of UD and automated urinalysis by the UF-1000*i* in our total cohort and for men and women separately. Furthermore, we assessed the influence of the vaginal flora on diagnostic performance by differentiation in normal and non-normal bladder evacuation. In the ED stetting, a limited relationship exists between clinical UTI diagnosis and urine culture results [20,21]. Therefore primary analysis was focused on clinical UTI diagnosis.

Methods

Patients

A prospective cohort study at the ED for Internal Medicine at the University Medical Center Groningen, the Netherlands (tertiary care center) was conducted. Consecutive patients of ≥18 years were included if fever (≥38.0°C), potentially caused by a UTI, was present at admission or at the day of presentation, or if on other ground UTI suspicion existed. Patients were excluded if they were transferred to another hospital (n=9) or if automated urinalysis and/or UC were not performed (n=375). Inclusion period was between January 1st 2016 and February 28th 2017. The study was approved by the institutional review board of the University Medical Center Groningen.

Clinical assessment

Patient characteristics and medical history were obtained from the electronic patient file. Symptoms and signs were divided into specific and nonspecific characteristics for UTI. Specific characteristics were: dysuria, pollakisuria, urinary urgency, haematuria, back pain or lower abdominal pain, and costovertebral tenderness (including pain in kidney transplant area). The nonspecific characteristics were: fever, shivers, malaise, flank or perineal pain, delirium, newly developed urinary incontinence, smelly urine, and turbid urine.

Diagnostic tests

All urine samples were collected and analysed according to our hospital guidelines. Urine collection method at the ED was patient dependent. The standard protocol was a clean midstream (the most used method), if this was impossible, patients used a chamber pot or a (one-time) catheterization was performed. If a catheter was already present the second portion of urine was used for urinalysis. Urine samples were collected with the BD Vacutainer™ urine collection system (Becton, Dickinson and Company, Franklin Lakes, USA) using the Vacutainer™ urine collection cup and Vacutainer™ urinalysis tubes. Urine samples were divided into two tubes, one for the laboratory department and one for the microbiology department. The tubes were immediately sent to the departments by a pneumatic tube system. At the laboratory department, urine samples were kept at room temperature and UD and automated urinalysis were analysed within an hour of arriving. At the microbiology department, during office hours urine samples were kept at room temperature and inoculation of plates for urine culture were finished within 2 hours of arriving and mostly within one hour. Outside office hours urine samples were refrigerated (± 7°C) until the next day. The maximum time urine samples stayed outside the refrigerator is estimated to be <4 hours. Bottles for blood culture were kept at room temperature and analysis was done within 20 hours after blood withdrawal.

For UD nitrite and leucocyte esterase (LE) the UD Combur10 test was used in combination with the automated stick reader c411 (Roche Diagnostics, Mannheim, Germany). Automated urinalysis, to determine bacterial and leucocyte count, was performed with the UF-1000*i* (Sysmex Corporation, Kobe, Japan); in a previous study the method has been described in detail [20]. For UC, 1 μL urine was inoculated on two agars (sheep blood agar and MacConkey3 agar) and incubated for 16-20 hours at 35°C. Isolated organisms were measured semi-quantitatively as colony-forming units per millilitre (CFU/ml). Possible diagnostic test results of the urinary parameters are shown in Table 1. Blood cultures were performed based on clinical suspicion of bacteraemia or sepsis (SIRS criteria, shivers) and analysed by BacT/ALERT FA Plus (aerobic) or the Bactec™ FX system (Becton, Dickinson and Company, Franklin Lakes, USA) using BD BACTEC™ Aerobic plus and BD BACTEC™ Lytic Anaerobic bottles.

Definition of UTI

Our primary outcome was diagnosis of UTI, which was based on one or more of the following criteria: 1) clinical presentation, based on the clinical assessment, 2) successful treatment without other focus, 3) UC result, and 4) final conclusion of the attending physician [20]. Diagnosis of UTI was subdivided in UTI with and without systemic symptoms. UTI with systemic symptoms was further subdivided in the presence of urosepsis based on clinical presentation (SIRS criteria and shivers), and bacteraemia/urosepsis confirmed by blood culture. UTI was considered absent despite a positive UC result when another focus for fever/inflammation was more likely. At least two independent sources, the attending physicians and the investigator team (S.J.M., C.A.), determined the UTI diagnosis. The medical records were analysed retrospectively and it was checked if the investigator team came to the same conclusion as the attending physicians. The conclusive judgment of UTI diagnosis was made by the investigator team.

Secondly, we used positive urine culture as outcome, the commonly used standard in the literature. A positive UC was defined as growth of $\geq 10^5$ CFU/ml for at least one uropathogen; cultures containing only aerobic mixed flora and yeast were considered negative. In men, a growth of $\geq 10^3$ CFU/ml is sometimes used as definition of a positive UC. Analyses of urinary parameters were therefore partly repeated with $\geq 10^3$ CFU/ml as cut-off value for positive UC in men.

Subgroup analysis

We subdivided the patients based on normal and non-normal bladder

Table 1
Possible diagnostic test results of urine dipstick, automated urinalysis, and urine culture.

Diagnostic test	Parameter	Count	Value
Urine dipstick	Nitrite	-	Negative
		-	Positive
	Leucocyte esterase	<10/μL	Negative
		~ 10-25/μL	+
		~ 75/μL	++
		~ 500/μL	+++
Automated urinalysis[a]	Bacterial count	Continuous variable	/μL
	Leucocyte count	Continuous variable	/μL
Urine culture		0 CFU	No growth
		1-5 CFU	10^3 CFU/ml
		6-50 CFU	10^4 CFU/ml
		51-500 CFU	10^5 CFU/ml
		>500 CFU	$>10^6$ CFU/ml

CFU = colony forming unit. [a] Performed by the UF-1000*i*.

[a] Performed by the UF-1000*i*.

evacuation to further analyse the influence of urogenital differences between men and women. Non-normal bladder evacuation was defined as bladder evacuation by catheter (catheter à demeure, suprapubic catheter, nephrostomy or clean intermittent self-catheterisation) or urostomy (e.g. Indiana pouch, Bricker conduit). Normal bladder evacuation was defined as bladder evacuation without catheter (with exception of double J catheter) or urostomy.

Statistical analysis

Statistical analysis was performed using SPSS version 23 (IBM corp., Armonk, NY, USA) and GraphPad prism version 8 (GraphPad Software, La Jolla, California, USA). Analyses were performed for the total study population and for men and women separately. Categorical data were presented as number and percentages and continuous data as median and interquartile range (IQR) (due to skewed distribution). Distribution of UF-1000*i* bacterial count was depicted as box and whisker plots. By means of receiver operating characteristic (ROC) curves the performance of the UF-1000*i* bacterial and leucocyte count were analysed. For determination of diagnostic values, 2 × 2 tables for true-positive, false-positive, true-negative, and false-negative were constructed. From these tables, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), the accuracy, the false-positive-rate, and their 95% confidence intervals (CI) were calculated. To primarily exclude UTI, the cut-off values were determined based on 90% sensitivity. Furthermore, curves representing the accuracy for both UF-1000*i* bacterial and leucocyte count were established, cut-off values were based on the highest accuracy. Depending on data type, Chi-square test, Fisher's exact test or Mann-Whitney U test were used for comparison between men and women. A two-tailed p-value <0.05 indicated statistical significance. Concerning UTI diagnosis, the inter-rater-agreement between the attending physician and the investigators was calculated with the Cohen's Kappa value.

Results

Case characteristics

During the inclusion period 917 consecutive cases were included, consisting of 786 patients of which 97 visited the ED on multiple occasions. The median age at presentation was 65 years, 49.1% were women. No significant gender differences existed in CRP levels, leucocyte levels were marginally higher in men. Bladder evacuation was normal in 765 cases (men 359/ women 406), non-normal bladder evacuation was present in 152 cases (men 108/ women 44), [Table 2]. Women had more frequently specific UTI characteristics compared to men (p=0.007), while the frequency of nonspecific characteristics did not differ (p=0.100), (supplemental table 1).

Diagnosis of UTI was established in 360 cases (39.3%), 164 men and 196 women. A good inter-rater agreement existed between UTI diagnosis established by the physician and the investigators (Cohen's Kappa 0.96); with only 17 discrepant cases (in 10 cases UTI diagnosis was withdrawn, in 7 cases UTI diagnosis was established). In 305 (84.7%) cases with a diagnosis of UTI, the UC contained at least 1 uropathogen with $\geq 10^3$ CFU/ml, in 262 (72.8%) cases UC was positive ($\geq 10^5$ CFU/ml). In 98 cases (27.2%) UC was negative, of these 10 had a urosepsis based on a positive blood culture. In 57 UC negative cases antibiotics were used prior to presentation (no growth: 23, mixed flora & yeast: 15, $<10^5$ CFU/ml: 19). A UTI without systemic symptoms was present in 234 cases of which the majority were women (p=0.065). A UTI with systemic symptoms was present in 126 cases (equally distributed between genders; p=0.169). Diagnosis of urosepsis confirmed by blood culture was equally distributed between genders (p=0.504), while urosepsis based on clinical presentation tended to be more diagnosed in women (p=0.055), (supplemental table 2).

Table 2
Case characteristics (n=917).

	Men (n=467)	Women (n=450)	p-value
Age at presentation (in years)	67 (56.0-75.0)	63 (51.0-74.0)	0.001*
Urologic history	194 (41.5)	167 (37.1)	0.170
CRP (mg/L)	63.5 (22.8-128.0)	54 (17.0-142.8)	0.485
Leucocytes blood sample (10^9/L)	11.5 (7.6-15.9)	10.5 (6.9-14.8)	0.036*
Antibiotic therapy before presentation at the ED[a]	161 (34.5)	144 (32.0)	0.426
Treatment with immunosuppressive medication[a]	146 (31.3)	150 (33.3)	0.503
Normal bladder evacuation	359 (76.9)	406 (90.2)	<0.001*
Non-normal bladder evacuation	108 (23.1)	44 (9.8)	<0.001*
UTI risk factors			
No UTI risk factors	200 (42.8)	252 (56.0)	<0.001*
Anatomical malformation[b]	13 (2.8)	8 (1.8)	0.309
Evacuation disorder[b,c]	39 (8.4)	17 (3.8)	0.004*
Polycystic kidney[b]	14 (3.0)	20 (4.4)	0.246
Congenital disorder of the urinary tract[b]	10 (2.1)	20 (4.4)	0.050
Nephrolithiasis/ urolithiasis[b]	21 (4.5)	16 (3.6)	0.469
Kidney transplantation[b]	83 (17.8)	65 (14.4)	0.171
Leucocytopenia (<4.0 × 10^9 cells/L)[b]	40 (8.6)	45 (10.0)	0.454
- Chemotherapy/ radiotherapy induced[d]	24 (5.1)	22 (4.9)	0.862
- Not chemotherapy/ radiotherapy induced	16 (3.4)	23 (5.1)	0.206
Chemotherapy/ radiotherapy without leucocytopenia[b,d]	24 (5.2)	39 (8.7)	0.035*
Catheter[b]	112 (24.0)	43 (9.6)	<0.001*
- Catheter à demeure	33 (7.1)	19 (4.2)	0.063
- Suprapubic catheter	15 (3.2)	4 (0.9)	0.014*
- Double J catheter	14 (3.0)	7 (1.6)	0.144
- Nephrostomy	9 (1.9	0 (0.0)	0.004*
- Clean intermittent self-catheterisation	43 (9.2)	14 (3.1)	<0.001*
Urostomy[b]	9 (1.9)	8 (1.8)	0.867

Case characteristics for men and women, data presented as number (%) or median (IQR); UTI = urinary tract infection; ED = emergency department.
[a] Defined positive if antibiotic/ immunosuppressive medication was used within 48 hours before presentation
[b] Cases could be part of more than one group.
[c] Including neurogenic bladder dysfunction.
[d] Defined positive when chemotherapy/radiotherapy was ≤3 months ago. *P-value <0.05, statistical significant.

In 327 (35.7%) cases the UC was positive ($\geq 10^5$ CFU/ml), of which 149 (45.6%) were men and 178 (54.4%) were women, p=0.016. In the positive UCs, 401 uropathogens had a density of $\geq 10^5$ CFU/ml. In men a total of 188 uropathogen were identified, 139 (73.9%) were gram negative and 49 (26.1%) were gram positive. In women a total of 213 uropathogens were identified, 175 (82.2%) were gram negative and 38 (17.8%) were gram positive. *Escherichia coli* was the most frequent identified uropathogen (50.1%) and was more common in women (supplemental table 3). In 203 men the UC result was $\geq 10^3$ CFU/ml; a total of 268 uropathogens with a density of $\geq 10^3$ CFU/ml were identified of which 189 (70.5%) were gram negative and 79 (29.5%) were gram positive. The presence of gram-positive bacteria in positive UC results was equally distributed between men and women (data not shown). In 173 cases an aerobe gram positive mixflora was present in the UC and was more frequently present in women (113 (23.8%)) compared to men (60 (16.9%)), p=0.017.

Performance of urine dipstick

In 168 (18.3%) cases the UD nitrite was positive, men 78 (16.7%)

and women 90 (20%), p=0.197. Diagnostic performance of UD nitrite was slightly better in men compared to women [Table 3]. The false positive rate was somewhat higher in women compared to men (women 8.7%, men 5.6 %). In 383 (41.8%) cases UD LE result was 3+, 173 (37.0%) men and 210 (46.7%) women (significant trend with increasing LE quantification). In general, performance of leucocyte esterase was better for men compared to women [Table 3]. The false positive rate for LE clearly differed between men and women (LE 3+: men 15.2%, women 28.0%).

Performance of UF-1000i

Distribution of the UF-1000i leucocyte and bacterial count

The median (IQR) leucocyte count detected by the UF-1000*i* was 77.0/μL (16.0-530.5) and was lower in men (57.0/μL (12.0-595.0)) compared to women (96.0/μL (24.8-495.4)), p=0.015. The median (IQR) bacterial count was 241.0/μL (17.0-6269.0) and was clearly lower in men (59.0/μL (8.0-2852.0)) compared to women (874.5/μL (72.5-10418.8)), p<0.001. As expected the UF-1000*i* bacterial count correlated with increasing UC density [figure 1]. It is noticeable that the UF-1000*i* bacterial counts in women were higher compared to men with the same urine culture density [figure 1]. In UC's with a density of $\geq 10^5$ CFU/ml and the presence of gram-negative bacteria, the UF-1000*i* leucocyte count was significantly higher in men compared to women and bacterial count was slightly higher in women compared to men. In UC with gram-positive bacteria, the leucocyte and bacterial count were not substantially different between men and women (supplemental table 4).

Determining relevant cut-off values

ROC analysis for diagnosis of UTI showed an area under the curve (AUC) of 0.851 (95% CI: 0.825-0.877) for leucocyte count and 0.850 (0.825-0.875) for bacterial count. Performance of both leucocyte and bacterial count were clearly better in men compared to women [figure 2].

The 90% sensitivity cut-off value for leucocyte count was 58/μL; cut-off value was higher for men (60 leucocytes/μL) compared to women (43 leucocytes/μL). Accuracy was clearly higher in men (78.6%) compared to women (69.8%). The 90% sensitivity cut-off value for bacterial count was 104/μL; cut-off value was lower for men (75 bacteria/μL) compared to women (139 bacteria/μL). Difference in accuracy was even more obvious; men 80.5% and women 66.7% [table 4].

Curves focusing on accuracy showed that for leucocyte count the highest accuracy was 80.3% for the total cohort with a corresponding

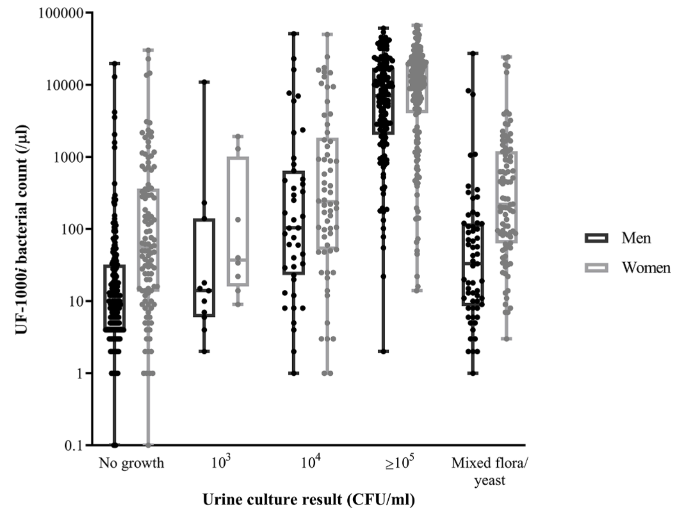

Fig. 1. Distribution of UF-1000*i* bacterial count according to the urine culture result among the total study population (n=917), depicted as box and whisker plots. Cases are categorized based on their highest density.

cut-off of 151/μL. For bacterial count, the highest accuracy for the total cohort was 79.1% with a corresponding cut-off of 774/μL. Clear differences existed between men and women [figure 3].

Subgroup analysis

Normal bladder evacuation

In the 765 cases (men/women: 359/406) with normal bladder evacuation, diagnosis of UTI was established in 261 cases (34.1%). Both UD nitrite and LE were clearly more often positive in women compared to men (both p<0.001). Diagnostic performance of UD nitrite and LE were quite comparable with the total study population. Differences between men and women were similar as well, accuracy differed around 10% in favour of men (supplemental table 5).

Median (IQR) UF-1000*i* leucocyte count was quite comparable between men and women (men 33.0/μL (9.0-276.0), women 83.0/μL (22.0-404.3)). The median (IQR) UF-1000*i* bacterial count was clearly higher in women (men 28.0/μL (7.0-382.0), women 683.5/μL (62.0-9516.8)). ROC analysis showed higher overall performance in men compared to women for both UF-1000*i* leucocyte and bacterial count

Table 3
Diagnostic values of urine dipstick for the total study population with UTI as outcome.

	Parameter	Cut-off value	Sensitivity[a]	Specificity[a]	PPV[a]	NPV[a]	LR+	LR-	Accuracy[a]
Men	Nitrite	pos	37.2 (29.8-44.6)	94.4 (91.8-97.0)	78.2 (69.0-87.4)	73.5 (69.1-77.9)	6.63 (4.01-10.96)	0.67 (0.59-0.75)	74.3 (70.3-78.3)
	LE	+	92.7 (88.7-96.7)	61.4 (55.9-66.9)	56.5 (50.6-63.4)	93.9 (90.6-97.3)	2.40 (2.07-2.78)	0.12 (0.07-0.21)	72.4 (68.3-76.4)
		++	87.8 (82.8-92.8)	79.9 (75.4-84.4)	70.2 (64.0-76.5)	92.4 (89.2-95.6)	4.36 (3.46-5.50)	0.15 (0.10-0.23)	82.7 (79.2-86.1)
		+++	77.4 (71.0-83.8)	84.8 (80.8-88.9)	73.4 (66.8-80.0)	87.4 (83.6-91.2)	5.10 (3.86-6.74)	0.27 (0.20-0.36)	82.3 (78.8-85.7)
Women	Nitrite	pos	34.7 (28.0-41.4)	91.3 (87.9-94.8)	75.6 (66.7-84.4)	64.4 (59.5-69.4)	4.01 (2.57-6.24)	0.72 (0.64-0.80)	66.7 (62.3-71.0)
	LE	+	94.4 (91.2-97.6)	42.5 (36.4-48.6)	55.9 (50.5-61.2)	90.8 (85.6-96.0)	1.64 (1.47-1.84)	0.13 (0.07-0.24)	65.1 (60.7-69.5)
		++	87.8 (83.2-92.3)	61.0 (55.0-67.0)	63.5 (57.7-69.2)	86.6 (81.6-91.6)	2.25 (1.91-2.65)	0.20 (0.14-0.30)	72.7 (68.5-76.8)
		+++	70.9 (64.6-77.3)	72.0 (66.5-77.6)	66.2 (59.8-72.6)	76.3 (70.9-81.6)	2.54 (2.04-3.15)	0.40 (0.32-0.51)	71.6 (67.4-75.7)

Diagnostic values calculated from 2 × 2 tables; men n=467, women n=450; LE = leucocyte esterase; PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio.
[a] Data presented as % (95% CI).

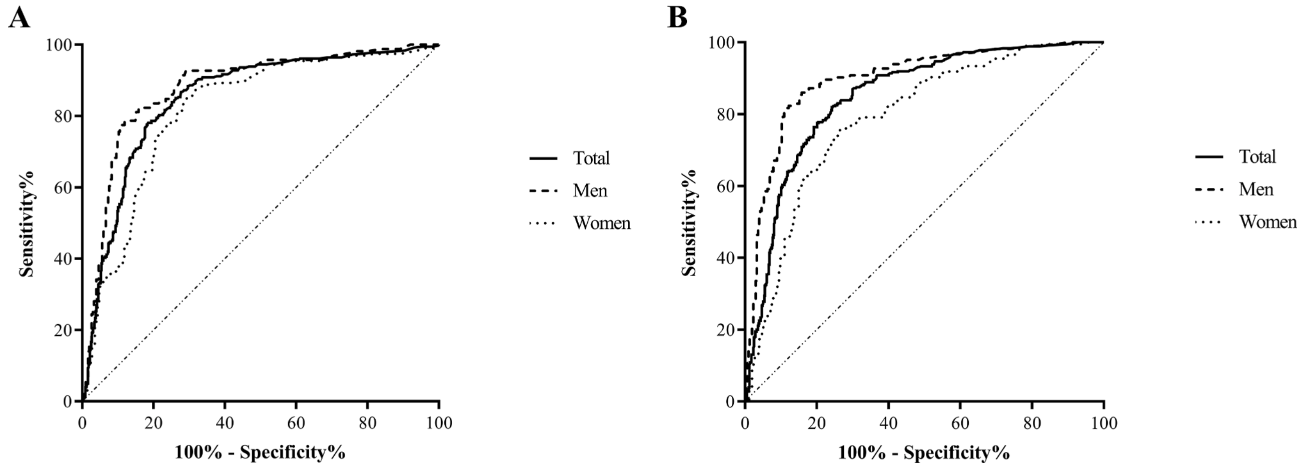

Fig. 2. ROC curves of UF-1000*i* leucocyte count (A) and bacterial count (B) for the total population and men and women separately with UTI diagnosis as outcome. AUC values (95% CI) UF-1000*i* leucocyte count: total group 0.851 (0.825-0.877), men 0.879 (0.845-0.913), women 0.817 (0.777-0.857). AUC values (95% CI) UF-1000*i* bacterial count: total group 0.850 (0.825-0.875), men 0.898 (0.867-0.928), women 0.791 (0.749-0.833).

Table 4
Diagnostic values of automated urinalysis by the UF-1000*i* for the total study population with UTI as outcome.

Automated urinalysis	Cut-off value	Sensitivity[a]	Specificity[a]	PPV[a]	NPV[a]	LR+	LR-	Accuracy[a]
UF-1000i Leucocyte count								
Total group	≥58/μL	90.0 (86.9-93.1)	67.9 (64.0-71.7)	64.4 (60.2-68.6)	91.3 (88.6-94.0)	2.80 (2.47-3.18)	0.15 (0.11-0.20)	76.6 (73.8-79.3)
Men	≥60/μL	89.6 (85.0-94.3)	72.6 (67.6-77.6)	63.9 (57.7-70.1)	92.8 (89.5-96.1)	3.27 (2.70-3.96)	0.14 (0.09-0.23)	78.6 (74.9-82.3)
Women	≥43/μL	89.8 (85.6-94.0)	54.3 (48.2-60.5)	60.3 (54.7-65.9)	87.3 (82.2-92.5)	1.97 (1.71-2.27)	0.19 (0.12-0.29)	69.8 (65.5-74.0)
UF-1000i Bacterial count								
Total group	≥104/μL	92.6 (89.8-95.3)	63.6 (59.6-67.6)	61.5 (57.3-65.6)	93.2 (90.6-95.7)	2.47 (2.20-2.77)	0.16 (0.11-0.22)	74.8 (71.9-77.6)
Men	≥75/μL	90.2 (85.7-94.8)	75.2 (70.4-80.1)	66.4 (60.2-72.6)	93.4 (90.3-96.5)	3.65 (2.98-4.47)	0.13 (0.08-0.21)	80.5 (76.9-84.1)
Women	≥139/μL	89.8 (85.6-94.0)	48.8 (42.7-55.0)	57.5 (52.0-63.1)	86.1 (80.5-91.8)	1.75 (1.54-2.00)	0.21 (0.14-0.32)	66.7 (62.3-71.0)

Diagnostic values calculated from 2 × 2 tables; total group n=917, men n=467, women n=450; PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio.
[a] Data presented as % (95% CI).

(supplemental figure 1). The leucocyte 90% sensitivity cut-off was slightly higher in women compared to men (41/μL vs. 25/μL). The bacterial 90% sensitivity cut-off was numerically higher in women compared to men (141/μL vs. 34/μL). For automated urinalysis, the overall performance was slightly lower compared to the total study population. However, differences in performance between men and women were quite similar compared to the total study population (supplemental table 6).

Non-normal bladder evacuation

In the 152 cases (men/women: 108/44) with non-normal bladder evacuation, diagnosis of UTI was established in 99 cases (65.1%). Positive UD nitrite and LE results did not differ between men and women (p=0.356 and p=0.640). Diagnostic values of UD nitrite were, for both men and women, lower compared to the total study population. For UD LE, specificity and NPV were clearly lower compared to the total study population. In contrast to normal bladder evacuation, the difference in the accuracy of UD LE between genders was smaller (supplemental table 7).

Median UF-1000*i* leucocyte and bacterial count were clearly higher compared to the total study population and normal bladder evacuation. Median (IQR) UF-1000*i* leucocyte count was quite comparable between men and women (men 504.0/μL (78.0-1580.0), women 473.0/μL (121.3-3478.3)) The median (IQR) UF-1000*i* bacterial count was higher in women (women 4959.5/μL (383.3-13327.8), men 4116.0/μL (106.5-11154.8)). ROC analysis showed higher overall performance in men compared to women for both UF-1000*i* leucocyte and bacterial count (supplemental figure 2). The 90% sensitivity cut-offs for both leucocyte and bacterial count were lower in women compared to men (leucocyte count men 122/μL; women 72/μL, bacterial count men 142/μL; women 97/μL). For automated urinalysis, the overall performance was slightly better compared to the total study population, mainly for women. Differences in performance between men and women were, as with normal bladder evacuation, quite comparable with the total study population (supplemental table 8).

Urine culture as outcome. Urine culture was positive (≥10^5 CFU/ml) in 327 cases (men/women: 149/178). Diagnostic values for UD nitrite and LE were in general comparable with UTI diagnosis (supplemental table 9). ROC analysis showed an overall performance of the UF-1000*i* leucocyte count of 0.804 (men/women 0.845/0.754). For UF-1000*i* bacterial count the overall performance was 0.921 (men/women 0.952/0.887), (supplemental figure 3). The 90% sensitivity cut-off for leucocyte count was 35/μL for the total population, with a higher cut-off for men compared to women (59/μL vs. 29/μL). The bacterial 90% sensitivity cut-off was 491/μL for the total population, with a clearly higher

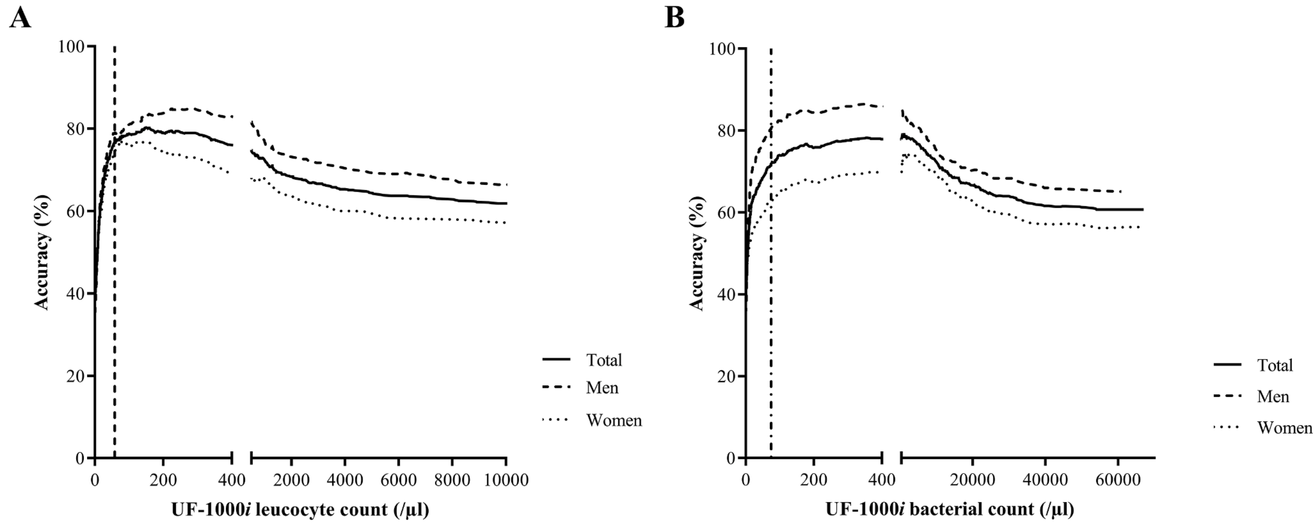

Fig. 3. Accuracy curves of UF-1000*i* leucocyte count (A) and bacterial count (B) for the total population (n=917) and men (n=467) and women (n=450) separately with UTI diagnosis as outcome. Highest accuracy (cut-off value) UF-1000*i* leucocyte count: total cohort 80.3% (≥151/µL), men 84.8% (≥293/µL), women 76.9% (≥157/µL). Highest accuracy (cut-off value) UF-1000*i* bacterial count: total cohort 79.1% (≥774/µL), men 86.5% (≥353/µL), women 74.4% (≥1220/µL). The vertical dotted line indicates the 90% sensitivity cut-off value of the total group for leucocyte and bacterial count, respectively.

cut-off for women compared to men (500/µL vs. 389/µL). Diagnostic values in men outperformed women for both leucocyte and bacterial counts (supplemental table 10). Using $\geq 10^3$ CFU/ml as cut-off for a positive UC in men did not numerically change the difference in performance compared with women (supplemental table 11, supplemental figure 4).

Discussion

Clear anatomical and genitourinary differences exist between men and women, however interpretation of urinary test results are lacking gender-specific attention. In addition, at the emergency department fast and accurate UTI diagnosis is important for a good clinical outcome. Therefore, we assessed gender-specific performance of UTI diagnostics in patients presenting at the ED.

In our cohort of 917 cases, diagnosis of UTI was established in 360 (39.3%) cases and was more frequently encountered in women. Positive UD nitrite was almost equally distributed between genders, while positive UD LE was significantly higher women. Noteworthy is the difference in overall accuracy which is around 10% lower in women compared to men for both UD nitrite and LE. Compared to general practice or primary care setting, UD nitrite performed worse for both men and women, while UD LE performed quite comparable [10,11]. Focusing on the ED and gender, we only found studies concerning women, in which UD nitrite and LE performed quite comparable [12,13]. The false positive rate of UD LE was clearly higher in women (around 13% for LE 3+), which might be due to urine contamination with vaginal flora [22]. Our finding suggests that gender has more influence on performance of UD LE compared to UD nitrite.

Overall performance of automated urinalysis by the UF-1000*i*, based on AUC values, was better for men compared to women for both leucocyte and bacterial count. The few other studies focusing on gender-specific performance of the UF-1000*i* reported this as well [17-19]. Compared to these studies, our leucocyte AUC values were similar (reported range: men 0.876-0.950, women 0.798-0.937), while our bacterial AUC values were somewhat lower (reported range: men 0.956-0.990, women 0.930-0.946).

At the same urine culture density, the UF-1000*i* bacterial count was higher in women compared to men. Aerobe gram positive mixflora was clearly more present in women compared to men. This suggests possible contamination of the vaginal flora in at least a part of the women and could therefore be an explanation of the higher bacterial count in women. However, there is no gender difference in the frequency of identified gram-positive bacteria. In addition, there is no relevant gender difference in automated bacterial and leucocyte count in cases with gram-positive bacteria in a positive UC. Indicating there is no gender difference in non-contaminated urine with gram-positive bacteria.

In general, our gender-specific leucocyte cut-off values were somewhat higher (men 60/µL, women 43/µL) compared to other studies (men 3.9-52.1/µL, women 3.8-31.5/µL). The bacterial cut-offs (men 75/µL, women 139/µL) were within the reported range (men 31.3-240.5/µL, women 95-689.0/µL) [17-19]. It is important to realize that these studies used positive UC as definition of UTI, were not situated in an ED setting, and used different sensitivities to determine the cut-off values. In addition, in our study a relatively large proportion of men had a non-normal bladder evacuation (and therefore potential bacterial colonization) compared to women. Our bacterial cut-off value with positive UC outcome was clearly higher for men (389/µL), while the cut-off value for women (500/µL) was within the reported range of these other studies [17-19]. Diagnostic performance of bacterial and leucocyte count reported by others was better for men compared to women and was quite comparable with our findings [17,18]. This underlines the superior performance of automated urinalysis in men compared to women. Therefore, gender-specific bacterial and leucocyte cut-offs are needed to mainly improve the diagnostic performance in men. This view is also supported by other studies concerning the UF-1000*i* and its precursor, the UF-500 [15-17]. In addition, focusing on cut-off values based on the highest possible accuracy also showed that in men a higher overall accuracy existed at lower cut-off values for both UF-1000*i* leucocyte and bacterial count, reflecting better specificity in men compared to women for both parameters.

In patients with normal bladder evacuation (n=765), the diagnostic performance of the UD did not differ substantially from the total study population. After eliminating the possible influence of the vaginal flora by focusing on non-normal bladder evacuation (n=152), differences in diagnostic performance between genders faded for UD LE. On the other hand, the accuracy of UD nitrite was numerically lower in non-normal bladder evacuation for both men and women and gender differences did not change. This could be a reflection of catheter-related bacterial colonization in patients with non-normal bladder evacuation. Furthermore, these results indicate again that the influence of gender is more clear for UD LE compared to UD nitrite. The 90% sensitivity cut-off of the automated leucocyte count was lower in normal bladder evacuation compared to non-normal bladder evacuation for both men and women. Compared to normal bladder evacuation, the bacterial cut-off increased for men and decreased for women in non-normal bladder evacuation. As consequence, the difference in bacterial cut-off between genders was clearly smaller compared to normal bladder evacuation (107/μL vs. 45/μL). This could be a reflection of eliminating the influence of the vaginal flora. In general, the diagnostic performance of both leucocyte and bacterial count did not differ substantially between normal and non-normal bladder evacuation. This suggests that not only gender-specific cut-off values are needed, but cut-off values specified for bladder evacuation methods might be helpful as well, resulting in comparable diagnostic performance. It should be noted that the non-normal bladder evacuation group mainly consisted of men, only 44 were women.

We also examined the urine screening tests using UC ($\geq 10^5$ CFU/ml) as outcome. In 327 (35.7%) cases, the UC was positive and the distribution of uropathogens between men and women was consistent with previous studies [9,23]. Diagnostic performance of UD was quite comparable between UTI diagnosis and UC as outcome. Overall performance, based on ROC analysis, of automated leucocyte count showed only small differences between the two outcomes. ROC analysis of the automated bacterial count performed better in UC as outcome, mainly for women. In addition, bacterial cut-off values were higher in both men and women. Diagnostic values in men outperformed women for both leucocyte and bacterial count. UC outcome is focused on bacteria and it is therefore not surprising that automated bacterial count performed better compared to UTI outcome. Furthermore, a part of the positive UC outcomes, mainly in non-normal bladder evacuation, do not relate to a clinical relevant UTI. Changing the cut-off value for a positive UC in men to $\geq 10^3$ CFU/ml instead of $\geq 10^5$ CFU/ml did not change these findings.

In conclusion, we showed that in an unselected ED population the overall diagnostic accuracy of fast urinary parameters for diagnosing UTI is higher in men. The described differences in cut-off values for automated leucocyte and bacterial counts for diagnosing UTI necessitates gender-specific cut-off values, probably reflecting the influence of anatomical and urogenital differences. Differentiation between normal and non-normal bladder evacuation will result in specified cut-off values for automated urinalysis without substantial change of diagnostic values and should, therefore, be considered.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2021.03.010.

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