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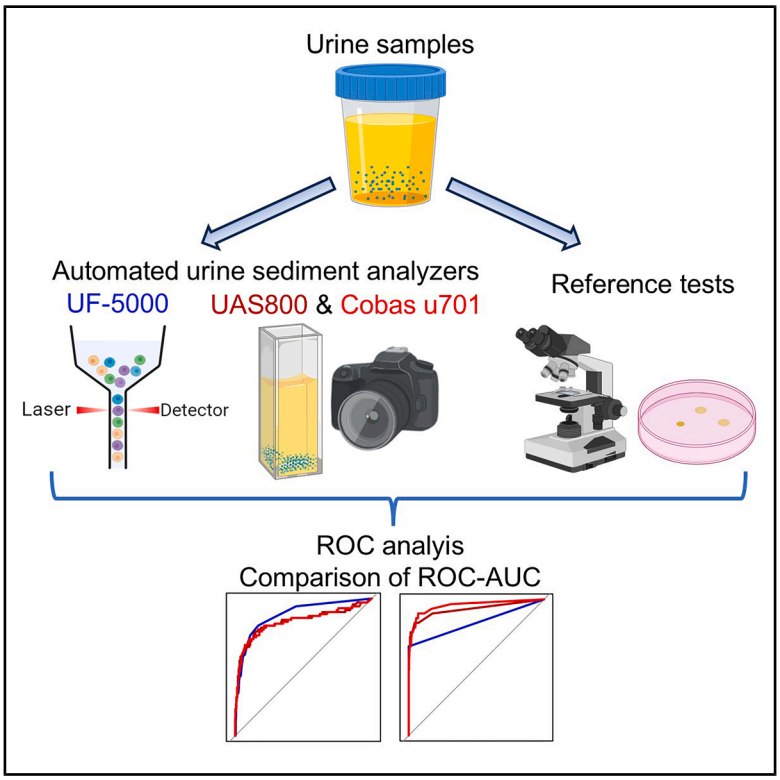
Comparative evaluation of three automated urine sediment analyzers excluding cutoff-related trade-offs

Graphical abstract



Highlights

- UF-5000 exhibited better performance for detecting bacteriuria or mucous thread
- However, UF-5000 demonstrated worse performance for detecting crystals
- UAS800 and Cobas u701 had generally similar but significantly different performance
- The operating mechanism is a key, but not sole, determinant of performance

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In brief

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Comparative evaluation of three automated urine sediment analyzers excluding cutoff-related trade-offs

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SUMMARY

Performance comparison of automated urine sediment analyzers is difficult due to cutoff-related trade-offs. In this study, we evaluated and compared UF-5000, UAS800, and Cobas u701 using receiver operating characteristic (ROC) analysis. A total of 774 urine samples were analyzed using manual microscopic examination and microbial culture as the reference test. The area under the ROC curve (ROC-AUC) was compared using DeLong's test. UF-5000, a flow cytometry analyzer, demonstrated significantly better performance than both the automated imaging analyzers UAS800 and Cobas u701 for detecting significant bacteriuria or mucous thread. However, its performance was significantly worse for detecting crystals. UAS800 and Cobas u701 showed generally similar performance, but with significant differences for detecting red blood cells, sperm, and significant bacteriuria. Our results highlight the operating mechanism as a key determinant of performance, and also show that analyzers with similar operating mechanisms can still have significant differences in their performance.

INTRODUCTION

As part of routine urinalysis, urine sediment analysis serves as the first screening tool for clinical investigation of the urogenital system.[1] For example, crystal in urine can be associated with various clinical conditions such as metabolic disorders and crystalline nephropathy.[1–5] The gold standard method for urine sediment analysis is manual microscopic examination.[1] However, this manual approach is time-consuming, labor-intensive, requires skilled technicians, and is subject to interobserver variations. Urine culture is the gold standard method for diagnosing urinary tract infection (UTI).[1] For microbial urine sediments such as bacteria and yeast, urine culture can give objective evidences without interobserver variations. Still, urine culture requires nearly 24 h which can be critical for intensely ill patients. The combined difficulties led to the development of automated urine sediment analyzers.

In general, automated urine sediment analyzers can be classified into two groups based on their operating principles.[1] Automated urinary flow cytometry analyzers recognize urine sediments based on flow cytometric signals such as forward-scattered light (FSC) and side-scattered light (SSC). UF-5000 (Sysmex Corporation, Kobe, Japan) belongs to this group. In contrast, automated imaging analyzers capture digital images of sediment grains and recognize them using graphical identification softwares. UAS800 (Siemens Healthineers, Erlangen, Germany) and Cobas u701 (Roche Diagnostics, Rotkreuz, Switzerland) belong to this latter group.

Although the analytical performance of automated urine sediment analyzers has improved, it is still not considered equivalent to the gold standards in terms of accuracy. Evaluating performance of the automated analyzers is important not only to select the most accurate analyzer, but also to predict error-prone results for which manual double-check rules should be applied. Some studies have previously performed evaluations for these automated analyzers.[6–10] However, these studies focused mostly on sensitivity and specificity, which are determined not only by the analyzers' genuine performance but also by their default cutoff values. Manufacturers set their analyzers' cutoff values based on different standards, with cutoff-related trade-offs between sensitivity and specificity. For instance, in a previous study, UF-5000 showed a low sensitivity of 46.8% but a very high specificity of 99.8% for non-amorphous crystals, hampering straightforward conclusion about its performance.[6] Therefore, comparative evaluation requires a unified metric independent from the manufacturer-presented default cutoff values, which can be achieved through receiver operating characteristics (ROC) analysis.

In this study, we compared the analytical performance of UF-5000, UAS800, and Cobas u701 using a common sample set with reference test results (Figure 1). Manual microscopic examination was utilized as reference for non-microbial sediment types, and urine culture served as reference for bacteria and yeast. For all analyzers, we performed ROC analysis to uncover their genuine performance and statistically compared the results using DeLong's test.[11]

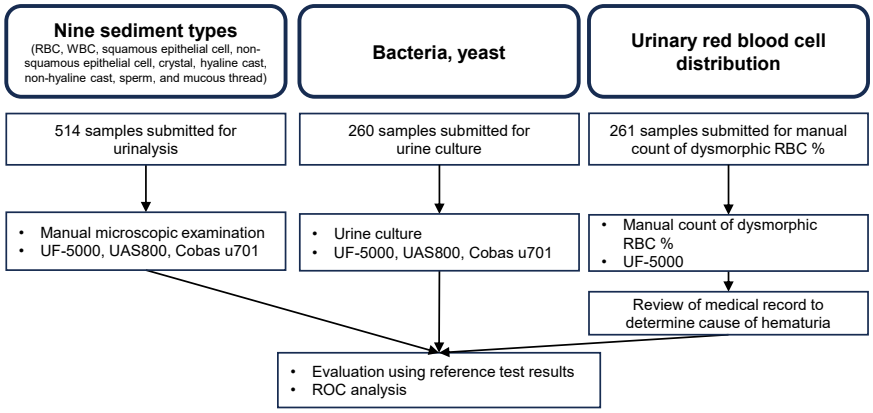

Figure 1. Workflow chart of the overall study design

RESULTS

Non-microbial sediment types

The results from manual microscopic examination of the 514 samples submitted for urinalysis are summarized in Table S1. At least 10 samples were positive for each sediment type except for hyaline cast and sperm. Hyaline casts were present in 76 samples, but were generally insufficient to be considered "positive" rather than normal variations.

Using this data as reference, sensitivity, specificity, and ROC-AUC of UF-5000, UAS800, and Cobas u701 were evaluated (Table 1). All the analyzers showed good performance for RBC and WBC with sensitivity and specificity near 90%, and ROC-AUC values near 0.950. However, comparing the ROC analysis results, Cobas u701 performed slightly better than UAS800 for RBC (ROC-AUC 0.960 vs. 0.941, $p = 0.043$), while it performed slightly worse than UF-5000 for WBC (ROC-AUC 0.967 vs. 0.985, $p = 0.039$). For squamous and non-squamous epithelial cells, UF-5000 showed skewed performance metrics with 36.6% sensitivity for squamous epithelial cells and 31.1% specificity for non-squamous epithelial cells. However, its ROC-AUC values were comparable with the other two analyzers, indicating a sensitivity-specificity trade-off rather than a true difference in performance. UF-5000 was significantly worse than the other analyzers for detecting crystals, even when amorphous crystals were excluded ($p = 0.037$ vs. UAS800, 0.011 vs. Cobas u701). Still, it was significantly better than the other analyzers for detecting mucous thread ($p = 0.046$ vs. UAS800, 0.043 vs. Cobas u701). For cast and sperm, all analyzers showed generally similar performance, although UAS800 showed significantly better performance than Cobas u701 for sperm (ROC-AUC 0.783 vs. 0.763, $p = 0.004$).

In the process, UAS800 did not report quantitative results for 10 samples, with flags indicating positivity for an unspecified sediment type. These samples were excluded from the statistical analyses in Table 1. The characteristics of these samples are summarized in Table S2 and specified in more detail in Table S3. Some of these samples were enriched with a sediment type.

Bacteria and yeast

The characteristics of the 260 samples utilized for UTI diagnostic evaluation in comparison with urine culture results are summarized in Table 2. Bacteria colonies were observed from 97 samples, but yeast colonies were observed from only 8 samples. UF-5000 generally reported less bacteria than UAS800 and Cobas u701, although this may be due to less false positivity. Indeed, the interquartile ranges (IQRs) of bacterial counts from UF-5000 showed less overlap between different colony-forming units (CFU)/mL categories, compared to those from UAS800 and Cobas u701.

"Positive culture" can be defined in many ways, since a minimal number of microbes may not actually lead to UTI. Therefore, we calculated the analyzers' performance with four different culture positivity criteria (Table 3). For bacteria, UF-5000 exhibited slightly lower sensitivity but much higher specificity, indicating fewer false-positive results. Indeed, ROC analysis revealed that UF-5000 performed significantly better than the others for detecting bacteria, regardless of culture positivity criteria. Comparing UAS800 and Cobas u701, UAS800 exhibited slightly but significantly better ROC-AUC, regardless of culture positivity criteria. For yeast, there were less differences between analyzers. Still, UF-5000 had the highest ROC-AUC for detecting yeast $\geq 10^3$ CFU/mL or significant yeasturia, which was significant compared to UAS800.

In the process, UAS800 did not report quantitative results for 5 samples but gave a positive flag for an unspecified sediment type (Table S4). These samples were excluded from the statistical analyses in Table 3. Meanwhile, UF-5000 reported "++++" without exact quantification for bacteria of 3 samples. Since this did convey the meaning "very large quantity," these 3 samples were not excluded from statistical analysis but were interpreted as positive results.

Urinary red blood cell distribution

UF-5000 outputs a novel index called urinary RBC distribution (URD) to discriminate glomerular and non-glomerular hematuria. As a supplementary analysis, the discriminative performance of URD was compared with manual microscopic count of dysmorphic RBC. The characteristics of the 261 samples submitted for manual count of dysmorphic RBC % are summarized in Table S5. UF-5000 successfully reported URD for all samples. Although cause of hematuria was not clear (indeterminate) for more than half of the samples, we were able to classify 76 samples as glomerular and 41 samples as non-glomerular. Density plots were visualized along with Passing-Bablok regression plot between dysmorphic RBC % and URD (Figures S1A–S1C). Pearson's correlation coefficient was 0.441.

After excluding indeterminate samples that could not be clearly classified as either glomerular or non-glomerular hematuria, 117 samples were used for evaluating the performance of the two parameters in discriminating glomerular hematuria. We performed ROC analysis and optimized the cutoffs (Figure S1D and

Table 1. Performance of the three automated analyzers per each sediment type

Sediment type	Default cutoff		ROC-AUC (CI)	DeLong's test, *p* value		
	Sensitivity	Specificity		vs. UF-5000	vs. UAS800	vs. Cobas u701
RBC						
UF-5000	87.0%	92.7%	0.951 (0.915–0.987)	–	0.688	0.629
UAS800	92.6%	81.8%	0.941 (0.891–0.991)	0.688	–	**0.043**
Cobas u701	92.6%	78.0%	0.960 (0.928–0.992)	0.629	**0.043**	–
WBC						
UF-5000	89.7%	95.4%	0.985 (0.977–0.994)	–	0.061	**0.039**
UAS800	96.6%	78.2%	0.972 (0.955–0.989)	0.061	–	0.360
Cobas u701	88.5%	92.8%	0.967 (0.947–0.987)	**0.039**	0.360	–
Squamous epithelial cell						
UF-5000	36.6%	99.4%	0.980 (0.969–0.991)	–	0.124	0.108
UAS800	95.1%	89.2%	0.969 (0.952–0.986)	0.124	–	0.462
Cobas u701	90.2%	85.7%	0.962 (0.940–0.985)	0.108	0.462	–
Non-squamous epithelial cell						
UF-5000	97.4%	31.1%	0.880 (0.830–0.930)	–	0.298	0.135
UAS800	52.6%	94.0%	0.830 (0.747–0.913)	0.298	–	0.283
Cobas u701	73.7%	76.8%	0.798 (0.704–0.892)	0.135	0.283	–
Crystal (excluding amorphous)						
UF-5000	65.5%	99.8%	0.827 (0.739–0.915)	–	**0.037**	**0.011**
UAS800	72.4%	98.8%	0.926 (0.860–0.992)	**0.037**	–	0.158
Cobas u701	75.9%	97.5%	0.954 (0.907–1.000)	**0.011**	0.158	–
Hyaline cast						
UF-5000	85.7%	87.7%	0.919 (0.780–1.000)	–	0.420	0.072
UAS800	85.7%	85.7%	0.956 (0.906–1.000)	0.420	–	0.090
Cobas u701	71.4%	79.9%	0.872 (0.729–1.000)	0.072	0.090	–
Non-hyaline cast						
UF-5000	76.9%	95.3%	0.913 (0.814–1.000)	–	0.942	0.335
UAS800	76.9%	84.7%	0.918 (0.853–0.982)	0.942	–	0.140
Cobas u701	100.0%	81.3%	0.963 (0.943–0.983)	0.335	0.140	–
Sperm						
UF-5000	57.1%	100.0%	0.786 (0.588–0.984)	–	0.985	0.886
UAS800	0.0%	100.0%	0.783 (0.583–0.982)	0.985	–	**0.004**
Cobas u701	42.9%	97.0%	0.763 (0.560–0.967)	0.886	**0.004**	–
Mucous thread						
UF-5000	59.2%	92.8%	0.880 (0.836–0.925)	–	**0.046**	**0.043**
UAS800	69.0%	88.9%	0.832 (0.766–0.898)	**0.046**	–	0.783
Cobas u701	85.9%	55.9%	0.831 (0.765–0.897)	**0.043**	0.783	–

CI, confidence interval; RBC, red blood cell; ROC-AUC, area under the receiver operating characteristic curve; WBC, white blood cell. Bold numbers indicate *p* values with statistical significance.

Table S6). Default cutoff was set as >0% for dysmorphic RBC % and >20.1% for URD, which were reported as optimal cutoffs in a previous study.[12]

DISCUSSION

In this study, we evaluated and compared the performance of UF-5000, UAS800, and Cobas u701. Varying degrees of sensitivity-specificity trade-offs were recapitulated in this study. For instance, a previous study of UF-5000 showed a low sensitivity of 46.8% but a high specificity of 99.8% for detecting non-amorphous crystals.[6] A similar trend was observed in our study, as UF-5000 showed the lowest sensitivity of 65.5% and the highest specificity of 99.8% among all the three analyzers. It is true that caution is needed when using cutoffs different from those presented by the manufacturer.[13] Nevertheless, our study result confirms that different manufacturers set their default cutoffs with different target goals, and supports the need for ROC analysis to compare the performance.

Comparing the ROC analysis results of the three analyzers, UF-5000 was significantly better than both UAS800 and Cobas u701 for detecting bacteria and mucous thread, but

Table 2. Characteristics of 260 samples submitted for urine culture

Culture result, CFU/mL	Number of samples (%)	UF-5000 count,/μL, median [IQR]	UAS800 count,/μL, median [IQR]	Cobas u701 count,/μL, median [IQR]
Bacteria				
No growth (<10^3)	163 (62.7%)	8.9 [3.3–27.5]	106.5 [64.2–200.6]	65.6 [42.2–143.7]
Growth (≥10^3)				
≥10^3 and <10^4	46 (17.7%)	17.35 [6.7–39.2]	73.3 [46.5–141.1]	49.1 [27.9–89.0]
≥10^4 and <10^5	32 (12.3%)	138.15 [43.7–293.2]	117.3 [62.3–196.9]	60.1 [32.1–121.4]
≥10^5	19 (7.3%)	4579.1 [818.2–27063.8]	493.2 [133.3–1259.3]	233.2 [49.1–435.4]
Significant bacteriuria[a]	70 (26.9%)	151.05 [36.1–1332.1]	129.2 [64.0–366.5]	77.9 [33.9–174.8]
Yeast				
No growth (<10^3)	252 (96.9%)	0.2 [0.1–0.5]	0.0 [0.0–0.0]	0.0 [0.0–0.0]
Growth (≥10^3)				
≥10^3 and <10^4	5 (1.9%)	1.4 [1.4–1.9]	0.0 [0.0–0.9]	0.0 [0.0–1.3]
≥10^4 and <10^5	3 (1.2%)	80.2 [41.5–272.3]	6.6 [3.3–11.0]	43.6 [23.3–46.6]
≥10^5	0 (0.0%)	–	–	–
Significant yeasturia[a]	5 (1.9%)	30.3 [2.8–80.2]	0.0 [0.0–6.6]	3.1 [0.0–43.6]

CFU, colony-forming units; IQR, interquartile range.
[a]Significant bacteriuria (or yeasturia) was defined as either ≥10^4 CFU/mL regardless of clinical status, or ≥10^3 CFU/mL from patients with urinary symptoms (e.g., fever, chill, dysuria, and urinary frequency) or with an indwelling urinary catheter.

was significantly worse than both for detecting crystals. UAS800 and Cobas u701 showed mostly similar performance for these sediment types, with a significant difference only for detecting bacteria. UF-5000 is the only urinary flow cytometry analyzer in this study, while UAS800 and Cobas u701 are both automated imaging analyzers. Therefore, it is likely that the operating mechanism was the key factor of these differences. Indeed, a similar trend was observed in a previous study of other automated analyzers; compared with the automated imaging analyzer UriSed 3, the flow cytometry analyzer UX-2000 showed higher sensitivity for detecting bacteria, but lower sensitivity for detecting crystals, with similar specificities.[14]

A particularly large difference in performance was observed for detecting bacteria, regardless of the positivity criteria applied to the urine culture. This was in line with previous studies which reported UF-5000 to be highly accurate for detecting bacteria.[10,15] The performance of UAS800 and Cobas u701 in detecting bacteria appears to have diminished primarily due to false-positive recognition. This is indicated not only by their low specificities, but also by their IQRs of quantification that substantially overlapped across different CFU/mL categories. This suggests that UAS800 and Cobas u701 may require in-depth double-checking and frequent manual correction for accurate UTI detection, which would be less effective for labor-saving. A previous study pointed that both the automated imaging analyzers U-SCANNER II and UAS800 misidentified amorphous crystals and artifacts as bacteria more often than UF-5000.[16] Considering the operating mechanisms, it is possible that small non-cellular objects are prone to be misrecognized as bacteria by automated imaging analyzers, while flow cytometry analyzers readily distinguish them from cellular objects.

UF-5000 is not capable of detecting amorphous crystals, since its standard operating protocol requires dissolving them using a special reagent.[17] This is not a clinically critical flaw since amorphous crystals are mostly non-pathologic.[18] However, UF-5000 exhibited low sensitivity even for non-amorphous crystals in previous studies.[6,7] Although non-amorphous crystals are not always pathologic, they are associated with various clinical conditions such as metabolic disorders, nephrolithiasis, and crystalline nephropathy.[1–5] In this study, UF-5000 demonstrated significantly lower ROC-AUC for non-amorphous crystals, confirming that the low sensitivity is not simply a result of sensitivity-specificity trade-off. Detection of crystals has been a weakness for urinary flow cytometry analyzers, as the scattergram of crystals can partially overlap with that of erythrocytes.[17,19,20] Although DSS has been introduced in UF-5000 as a metric to overcome this weakness, it seems that flow cytometry analyzers still have a room for improvement for detecting crystals.

Although mucous threads are often present in normal urine, they are not only associated with inflammation or irritation of the urinary tract, but also prone to interfere with the detection of other sediments on automated urinalysis.[21,22] The detection performance for mucous thread has been discussed in a previous study, which only focused on the low sensitivity of UF-5000.[6] In our study, while UF-5000 had the lowest sensitivity, it exhibited not only the highest specificity but also the highest ROC-AUC. To distinguish hyaline casts and pathologic casts from mucous threads, UF-5000 disperses mucous threads using surfactants and analyzes not only the scattergram but also the individual shapes of the SF signal waveforms.[17] Our study reveals that this was an effective method, comparable to or even slightly better than automated imaging analyzers.

Comparing UAS800 and Cobas u701, both showed generally similar performance as can be expected from their similar operating mechanisms. Still, UAS800 showed significantly higher ROC-AUCs for sperm and bacteria, while Cobas u701 exhibited significantly higher ROC-AUC for RBC. Although several previous studies have compared UF-5000 with UAS800 or Cobas

Table 3. Performance of the three automated analyzers per different culture positivity criteria

Culture positivity criteria, CFU/mL	Default cutoff			DeLong's test, *p* value		
	Sensitivity	Specificity	ROC-AUC (CI)	vs. UF-5000	vs. UAS800	vs. Cobas u701
Bacteria, $\geq 10^3$						
UF-5000	18.1%	99.4%	0.763 (0.702–0.825)	–	**<0.001 (7.38×10^{-11})**	**<0.001 (2.89×10^{-12})**
UAS800	40.4%	59.6%	0.493 (0.416–0.569)	**<0.001 (7.38×10^{-11})**	–	**0.016**
Cobas u701	41.5%	56.5%	0.454 (0.378–0.529)	**<0.001 (2.89×10^{-12})**	**0.016**	–
Bacteria, $\geq 10^4$						
UF-5000	33.3%	99.0%	0.899 (0.854–0.943)	–	**<0.001 (1.48×10^{-10})**	**<0.001 (9.41×10^{-12})**
UAS800	52.1%	62.3%	0.606 (0.509–0.703)	**<0.001 (1.48×10^{-10})**	–	**0.016**
Cobas u701	52.1%	59.4%	0.560 (0.460–0.660)	**<0.001 (9.41×10^{-12})**	**0.016**	–
Bacteria, $\geq 10^5$						
UF-5000	70.6%	97.5%	0.969 (0.942–0.997)	–	**0.012**	**0.005**
UAS800	76.5%	62.2%	0.777 (0.626–0.928)	**0.012**	–	**0.006**
Cobas u701	76.5%	59.7%	0.725 (0.554–0.895)	**0.005**	**0.006**	–
Significant bacteriuria[a]						
UF-5000	25.37%	99.5%	0.844 (0.788–0.899)	–	**<0.001 (2.38×10^{-10})**	**<0.001 (5.03×10^{-12})**
UAS800	47.76%	62.2%	0.572 (0.489–0.656)	**<0.001 (2.38×10^{-10})**	–	**0.018**
Cobas u701	49.25%	59.6%	0.527 (0.441–0.612)	**<0.001 (5.03×10^{-12})**	**0.018**	–
Yeast, $\geq 10^3$						
UF-5000	87.5%	85.4%	0.907 (0.826–0.988)	–	**0.036**	0.103
UAS800	25.0%	96.4%	0.701 (0.504–0.897)	**0.036**	–	0.438
Cobas u701	62.5%	92.7%	0.757 (0.553–0.961)	0.103	0.438	–
Yeast, $\geq 10^4$						
UF-5000	100.0%	84.1%	0.974 (0.936–1.000)	–	0.373	0.255
UAS800	66.7%	96.4%	0.801 (0.442–1.000)	0.373	–	0.318
Cobas u701	100.0%	92.1%	0.988 (0.970–1.000)	0.255	0.318	–
Significant yeasturia[a]						
UF-5000	80.0%	84.4%	0.907 (0.773–1.000)	–	**0.049**	0.182
UAS800	40.0%	96.4%	0.654 (0.390–0.919)	**0.049**	–	0.395
Cobas u701	60.0%	92.0%	0.753 (0.470–1.000)	0.182	0.395	–

CFU, colony-forming units; CI, confidence interval; ROC-AUC, area under the receiver operating characteristic curve.
[a]Significant bacteriuria (or yeasturia) was defined as either $\geq 10^4$ CFU/mL regardless of clinical status, or $\geq 10^3$ CFU/mL from patients with urinary symptoms (e.g., fever, chill, dysuria, and urinary frequency) or with an indwelling urinary catheter. Bold numbers indicate p values with statistical significance.

u701, only few studies have compared UAS800 and Cobas u701.[6,10] For RBCs, a correlation study with manual microscopy showed that Cobas u701 was more accurate than UAS800. This was consistent with our finding, although this study did not test whether the difference was significant.[6] For sperm and bacteria, the previous studies could not effectively compare UAS800 and Cobas u701; the analyzer with higher sensitivity also exhibited lower specificity, hampering straightforward comparisons.[6,10] Our study indicates that analytical efforts can effectively reveal significant differences, even for analyzers with similar operating mechanisms.

When examined for test failures, UAS800 raised positive flag without quantification for about 2% of samples, which was not rigorously evaluated in the previous study.[23] Some of these samples were discovered to be saturated with some kind of sediments, which could lead to inaccurate image recognition. Therefore, it is possible that these failures were more of an intentional safeguard, rather than a sign of actual limitation.

URD is an index generated by UF-5000 to discriminate glomerular from non-glomerular hematuria. As a supplementary analysis, we compared the discriminative performance of URD with that of the conventional index, dysmorphic RBC %. Although URD did not show a good correlation with dysmorphic RBC %, it demonstrated comparable ROC-AUC for discriminating glomerular hematuria, consistent with previous studies.[12,24] Interestingly, in our ROC analysis, URD showed lower specificity in the low-sensitivity region but maintained superior specificity in the high-sensitivity region compared to dysmorphic RBC %, which can be explained by the density plot analysis. The density plot showed that dysmorphic RBC % values in glomerular hematuria samples were often not markedly elevated, with a median value of 17%, overlapping with the values observed in some non-glomerular hematuria samples. This pattern aligns with a previous study, which reported 0% of dysmorphic RBC in 38.5% of glomerular hematuria samples.[12] This overlapping distribution likely contributed to the weak discriminative

performance of dysmorphic RBC % at lower cutoffs, whereas URD maintained reliable discrimination even when the cutoff was lowered.

In conclusion, ROC analysis enabled systematic head-to-head comparison, with each analyzer having superior performance in distinct sediment types. Our results highlight the operating mechanism as a key determinant of performance, but also show that analyzers with similar operating mechanisms can still have significant differences in their performance.

Limitations of the study

Limitations of the study include the following. First, some sediment types had a small number of positive samples, especially hyaline cast, sperm, and yeast. Although this was due to the random selection of samples to better reflect the real clinical setting, it may have resulted in insufficient statistical power for some sediment types. Second, since this study was conducted in a single laboratory, the performance of the analyzers may vary in other laboratory settings due to contextual factors such as the reference ranges and the specific composition of each sediment type. Third, manual microscopic examination was performed on each sample after centrifugation rather than in its original state. Although this approach aimed to minimize false negatives in samples containing only a small concentration of sediments, the centrifugation process may have introduced some imprecision in the quantitation of the sediments. Fourth, URD was evaluable by only UF-5000. Therefore, the diagnostic value of URD could not be compared among the automated analyzers but was compared with the manual microscopic count of dysmorphic RBC. Further development of hematuria-related parameter from other automated analyzers is expected to be compared with URD in the upcoming future.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, John Hoon Rim (johnhoon1@yuhs.ac).

Materials availability

This study did not generate any new unique reagents or materials.

Data and code availability

- The clinical data reported in this paper will be shared by the lead contact upon request.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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All tested analyzers and reagents were provided by three companies; Sysmex Corporation (Kobe, Japan); Roche Diagnostics International (Rotkreuz, Switzerland); and Siemens Healthineers (Erlangen, Germany). The manufacturers played no role in designing the study, collection, analysis and interpretation of data, writing of the report, or in the decision to submit the findings for publication. This research was supported by a grant of the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant no. HI22C103500). The graphical abstract and Figure S2 were created with BioRender.com.

AUTHOR CONTRIBUTIONS

Study concept and design, H.J., J.H.R., and J.-B.L.; data acquisition/analysis, J.L., H.C., and H.J.; data interpretation, J.L., H.J., J.H.R., S.-G.L., and J.-B.L. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

DECLARATION OF INTERESTS

There are no potential conflicts of interest relevant to this article to report.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Biological samples		
Urine samples	Severance Hospital, Seoul, Korea	N/A
Software and algorithms		
R Project for Statistical Computing (version 4.4.3)	R Project	SCR_001905
pROC	Robin et al.[25]	SCR_024286
Mcr	Potapov et al.[26]	SCR_027594
ggplot2	Wickham, H.[27]	SCR_014601
Other		
UF-5000	Sysmex Corporation (Kobe, Japan)	SCR_027592
UAS800	Siemens Healthineers (Erlangen, Germany)	SCR_027593
Cobas u701	Roche Diagnostics (Rotkreuz, Switzerland)	SCR_027607
Olympus BX43 clinical microscope	Olympus Life Science (Tokyo, Japan)	SCR_027598
KOVA™ Glasstic™ Slide 10	KOVA International Inc. (Garden Grove, CA, USA)	Catalog No. 22–749743

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

This study was conducted using urine samples submitted to the clinical laboratory of Severance Hospital, a tertiary-level hospital in Seoul, Korea. Sample collection period was from October to December 2023. The Institutional Review Board (IRB) of Severance Hospital approved this study (IRB no. 4-2023-1199) and waived the need for informed consent, as this study involved no patient intervention and used remnant samples without additional sample acquisition.

Three groups of samples were collected, corresponding to the evaluation of non-microbial sediment types, bacteria and yeast, and URD, respectively. Each sample was randomly selected without prior information about the originating patients. After collection, overall demographics were as follows. All patients were of Korean ethnicity. The first group was 56% male and 44% female, with a median age of 62.5 years (interquartile range [IQR] 43.3–74). The second group was 71% male and 29% female, with a median age of 63 years (IQR 44–73). The third group was 41% male and 59% female, with a median age of 58 years (IQR 40–69).

METHOD DETAILS

Overall study design and sample collection

This study was conducted using urine samples submitted for urinalysis or urine culture from October to December 2023. We collected three independent groups of urine samples based on the reference test to be utilized. All samples were randomly selected among those submitted for the reference test, without prior knowledge of the reference test result or the patients' clinical characteristics. This was to reflect the real-world performance of the automated analyzers. Only the samples with enough volume were selected. The required volume was 2 mL per each automated analyzer; 12 mL was additionally required for the first and third group for microscopic examination.

The first group consisted of 514 samples randomly selected from those submitted for urinalysis. This group of samples was used to test the following non-microbial sediment types: red blood cell (RBC), white blood cell (WBC), squamous epithelial cell, non-squamous epithelial cell, crystal, hyaline cast, non-hyaline cast, sperm, and mucous thread. Each sample was first aliquoted for manual microscopic examination, which was utilized as the reference test. Remnant volume was used to run the automated analyzers.

The second group consisted of 260 samples randomly selected from those submitted for urine culture. This group of samples was used to test for bacteria and yeast. Each sample was first inoculated to culture media for urine culture, which was utilized as the reference test. Remnant volume was used to run the automated analyzers.

As supplementary analysis, a third group consisted of 261 samples randomly selected from those submitted for manual microscopic count of dysmorphic RBC. These samples were first aliquoted to count the % of dysmorphic RBC, and the remaining volume was used to run UF-5000.

Manual microscopic examination

Considering recommendations from CLSI GP16-A3, manual microscopic examination was finished within 2 h of receipt of each sample.[28] The microscope used was the BX43 microscope manufactured by Olympus Life Science (Tokyo, Japan) with eyepiece field number 22. 12 mL of each sample was aliquoted and centrifuged at 400 g for 5 min. Supernatant 11 mL was discarded and the precipitant was resuspended with the remaining 1 mL, eventually concentrating the sample 12-fold. For each sample, 15 μL of the resuspension was smeared into the KOVA Glasstic Slide 10 (KOVA International Inc., Garden Grove, CA, USA). Two proficient laboratory technicians independently reviewed each type of sediments in 5 high power fields (HPFs) with ×400 magnification. Mucous thread, sperm, and amorphous crystal were qualitatively checked for presence. Other sediments were quantified as the average count of the two technicians and this average count was used to assign positivity according to cutoffs in Table S7.

UF-5000 is unable to detect amorphous crystals, whereas the other two analyzers include them in their crystal counts. For equitable comparison, we aimed to exclude the effect of amorphous crystals from the study. A particular concern was the samples true negative for non-amorphous crystals but true positive for amorphous crystals; UAS800 and Cobas u701 (but not UF-5000) could interpret these samples as positive for crystals not due to test error, but due to the actual presence of amorphous crystals. Therefore, these samples were excluded from the statistical analysis of crystals, but were retained for analyses of other sediment types.

Urine culture

Each urine sample was collected in 50 mL sterile specimen cups. For patients with an indwelling urinary catheter, the catheter was used to obtained the samples; for patients without an indwelling urinary catheter, the midstream clean-catch technique was used. Each sample was refrigerated upon receipt and inoculated within 2 h, satisfying general recommendations.[28] Each sample was inoculated onto 5% blood agar and MacConkey agar plates using a 1 μL standard loop. The agar plates were incubated in a 5% CO_2 incubator at 37°C for 18–24 h. If no colonies were observed after incubation, the result was marked as $<10^3$ colony-forming units (CFU)/mL. If colonies were present, they were quantified and then observed with Gram stain, which was not only a routine process but also distinguished bacteria and yeasts in this study.

Culture positivity was defined with four different criteria: $\geq 10^3$ CFU/mL, $\geq 10^4$ CFU/mL, $\geq 10^5$ CFU/mL, and "significant bacteriuria" (or yeasturia). "Significant bacteriuria" (or yeasturia) was defined as either $\geq 10^4$ CFU/mL regardless of clinical status, or $\geq 10^3$ CFU/mL from patients with urinary symptoms (e.g., fever, chill, dysuria, urinary frequency) or with an indwelling urinary catheter. Each of all the four criteria was used for performance calculations.

Urinary RBC distribution

As a supplementary analysis, the discriminative performance of URD was compared with manual microscopic count of dysmorphic RBC. To minimize deformation of RBCs with time after sample acquisition, both dysmorphic RBC count and automated URD analysis were performed as soon as possible and within 1 h of receipt.[12,29] Slides were prepared and examined with the same protocol forementioned for manual microscopic examination.

In addition, the cause of hematuria was determined by review of electronic medical record (EMR) of the patient of each sample to provide the reference classification. Each sample was classified into glomerular, non-glomerular, and indeterminate according to the criteria in Table S8.

Automated urine sediment analyzers

The operating mechanisms of the three analyzers are briefly illustrated in Figure S2.

UF-5000 is a urinary flow cytometry analyzer manufactured by Sysmex Corporation (Kobe, Japan). The device uses FSC, SSC, side fluorescence (SF) and depolarized side-scattered light (DSS) to distinguish each sediment.[17] It can be used along with urine particles digital imaging device UD-10, which was not used in the present study.

UAS800 is a digital imaging-based urine sediment analyzer manufactured by Siemens Healthineers (Erlangen, Germany). The device first takes microscopic digital images of a sample smear via camera, and then differentiates each sediment using an image-recognition software. Cobas u701 is a digital imaging-based urine sediment analyzer manufactured by Roche Diagnostics (Rotkreuz, Switzerland), with operating mechanisms similar to that of UAS800.

All analyzers were operated and maintained according to the manufacturers' instructions. Run of the analyzers was completed within 2 h of receipt of each sample to comply with the conditions recommended for routine urinalysis.[28] If an analyzer failed to report result for a sample, analysis was repeated once. If this failed again, the sample was excluded from statistical analysis for all analyzers and was separately recorded.

QUANTIFICATION AND STATISTICAL ANALYSIS

Sensitivity and specificity were calculated based on the analyzers' default cutoffs using Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA) (Table S9). ROC analysis was performed and area under the ROC curve (ROC-AUC) was calculated per each analyzer and per each sediment type using the pROC package version 1.18.5 on R version 4.4.3.[25] Statistical differences between

the analyzers were tested per each sediment type with DeLong's method using the same pROC package.[11] *p* value less than 0.05 was considered statistically significant. Passing-Bablok regression analysis between dysmorphic RBC % and URD and the calculation of Pearson's correlation coefficient was conducted using the mcr package version 1.3.3.1 on R version 4.4.3.[26] The density plots, Passing-Bablok regression plot, and ROC curve for dysmorphic RBC % and URD were visualized using the ggplot2 package version 3.5.2 on R version 4.4.3.[27]