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Semiquantitative, fully automated urine test strip analysis

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Objectives: Urinalysis is one of the most frequently ordered diagnostic laboratory tests. In order to reduce workload and costs, rapid screening tests such as urine test strip analyses are applied. The aim of this study was to evaluate the analytical performance of the UC-3500 as well as the diagnostic performance in comparison with reference methods.

Design and methods: We measured within-run and between-run imprecision based on quantitative reflectance values. 347 prospectively included urine specimens were investigated for the presence of glucose, protein, albumin, leukocyte esterase, and hemoglobin peroxidase activity, and ordinal scale results were compared to an automated urine particle analyzer (UF-5000, Sysmex, Kobe, Japan) and wet chemistry (Roche Cobas 8000, Mannheim, Germany).

Results: Within-run and between-run imprecision results based on reflectance data for both the 9 and 11 parameter test strips ranged from 0.07% to 1.36% for the low-level control and from 0.37% to 6.13% for the high-level control, depending on the parameter. Regarding diagnostic performance, the sensitivity/specificity for glucose, protein, albumin, leukocyte esterase, and hemoglobin peroxidase was 100/60%, 94.2/88.2%, 81.8/89.2%, 81.7/92.8%, and 85.1/88.6%, respectively; the negative predictive value was 100%, 83.3%, 89.1%, 94.6%, and 96.1%. The Spearman correlation coefficients of the UC-3500 vs reference methods ranged from 0.915 to 0.967, depending on the parameter.

Conclusion: This fully automated urine test strip analyzer overall shows a satisfying performance and can reliably screen out negative urine samples in order to focus on further characterization of positive samples in the following steps of the workflow.

KEYWORDS
dipstick, fully automated urine analyzer, test strip, urinalysis, urine chemistry analysis

1 | INTRODUCTION

Urinalysis is the third most requested analysis in clinical laboratories and can be used to identify patients with kidney diseases, urinary tract infections, or diabetes mellitus and can be part of their annual health checkup.[1,2] The high throughput of samples can create a significant workload, and a large proportion turns out to be negative.[3] Therefore, it is of importance that results from early diagnostic examinations accurately rule out urine samples from further analysis by urine sediment analysis and culture.

The European Confederation of Laboratory Medicine has proposed a stepwise procedural strategy describing different levels.[4]

Level 1 methods are applied as first step, often delivering results on an ordinal scale. Urine dipstick analysis is used as a fast, first-line screening method as part of a multistep workflow. As the reliability of visual inspection might be hampered by subjective color interpretation, instrumental reading is performed by automated analyzers.[5]

On most automated test strip readers, results are reported semiquantitatively. Due to the demand to analyze large sample volumes and in case a medical emergency situation implies the need for an instant urine status, semi-automated or fully automated urine strip readers have been well accepted for standardized, high-throughput screening. The obtained results should help to clearly separate samples without any indication for renal or genitourinary tract disorders from those samples with values exceeding the normal reference levels that need further examination. Positive samples might be subject for further microscopy, immunochemistry, or bacteriologic tests.

The recently introduced fully automated urine test strip reader UC-3500 (Sysmex, Kobe, Japan) is designed to screen for 11 urinary parameters. Recently, it was demonstrated that the instrument shows an outstanding performance in screening for albuminuria.[6] With an exceptionally low detection limit of 5.5 mg/L, this chemistry analyzer provides a very sensitive automated screening method. This is especially interesting as albumin levels between 20 and 200 mg/L act as an early indicator for vessel damage.[7-10] Also, the UC-3500 reflectance data of leukocyte esterase and hemoglobin peroxidase showed good agreement with red blood cell (RBC) and white blood cell (WBC) counts obtained on the urine particle analyzer UF-5000 (Sysmex, Kobe, Japan).[11]

In this study, we investigated the analytical and diagnostic performance of the UC-3500 compared to reference methods. Imprecision measurements were based on quantitative reflectance data. The diagnostic performance was determined using the semiquantitative result categories implied by the manufacturer.

2 | MATERIALS AND METHODS

2.1 | Patient samples

Three hundred forty-seven urine samples which were submitted to our laboratory between October 2016 and December 2016 were included. Routine diagnostic urinalysis and any additional study-related procedures were performed on fresh urine specimens within 2-4 hours after receipt.

2.2 | Instrument and reagent strips

The fully automated urine test strip analyzer UC-3500 (Sysmex, Kobe, Japan) was used for semiquantitative measurement of specified analytes in human urine and commercially available control materials according to the manufacturer's instruction.

Test strips (Meditape UC-9A and UC-11A, Sysmex, Kobe, Japan; Lot number: AC5004) were used in this study. These strips include reagent pads for ordinal scale reporting of urobilinogen, glucose, protein, hemoglobin peroxidase, nitrite, bilirubin, ketone, leukocyte esterase, pH, creatinine (UC-11A), and albumin (UC-11A) (Table 1). All steps starting from sample aspiration to reporting of results were obtained automatically. A maximum number of 300 urine test strips can be installed in the instrument at one time and up to 276 samples can be analyzed per hour. The instrument is equipped with a reflective photometry unit and reagent strips are scanned with a color complementary metal oxide semiconductor detector (CMOS), taking reflectance readings from the reagent strip. The light reflected off the reagent pad is used to measure the concentration of a substance present in the urine. A high concentration of analyte corresponds to a low reflectance. The reflectance value, expressed as a percentage within a range from 100% (white) to 0% (black), is inversely related to the concentration of the analyte. To cover the whole measuring range with good linearity, two overlapping reflectance ranges are installed for the parameters pH, protein, glucose, bilirubin, and ketones.

TABLE 1 Diagnostic parameters and semiquantitative assessment

		Semiquantitative assessment categories					
Parameter	Unit	Normal	±	1+	2+	3+	4+
Urobilinogen	mg/dL			2.0	4.0	8.0	12.0
Glucose	mg/dL	-	50	100	250	500	2000
Protein	mg/dL	-	15	30	100	300	1000
Blood							
Red blood cells	cells/µL	-	10	20	50	250	
Hemoglobin	mg/dL	-	0.03	0.06	0.15	0.75	
Nitrite		-		+			
Bilirubin	mg/dL	-		0.5	1.0	2.0	
Ketone	mg/dL	-		10	30	80	
Leukocyte esterase	cells/µL	-		25	75	500	
Creatinine	mg/dL	10	50	100	200	300	
Albumin	mg/L	10	30	80	150	>150	
pH	NA		5.0 5.5	6.0 6.5	7.0 7.5	8.0 8.5	9.0

2.3 | Imprecision

Commercially available control material (UC-control low [LOT: 01601-L] and high [LOT: 01601-H]; Sysmex, Kobe, Japan) was used to assess within-run (n = 20) and between-run (n = 20) imprecision on both UC-9A and UC-11A urine test strips. Intra-run and between-run imprecision were determined during one run on one day and on 20 consecutive days with one analysis a day, respectively.

2.4 | Diagnostic accuracy

Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of the UC-3500 vs defined reference methods were calculated for glucose (n = 59), protein (n = 67), hemoglobin peroxidase (n = 347), leukocyte esterase (n = 347), and albumin (n = 177) using laboratory-specific reference intervals (RI) or predefined cutoffs.

2.5 | Reference methods

Urinary glucose (RI: 0.0-0.05 g/L), urinary creatinine (RI: 20-400 mg/dL), and urinary total protein concentrations (cutoff 0.2 g/L) were determined on the Roche Cobas 8000 (Roche Diagnostics, Mannheim, Germany) using the hexokinase, Jaffe,

and pyrogallol red-molybdate (Instruchemie BV, Delfzijl, The Netherlands) photometric immunochemistry reference methods, respectively. As a comparison method for hemoglobin peroxidase and leukocyte esterase, RBCs and WBCs were counted on the Sysmex UF-5000 fully automated urine particle analyzer (Sysmex Corporation, Kobe, Japan), respectively. The cutoff for both RBCs and WBCs was set at 25 cells/μL. The UF-5000 showed very good agreement when compared to phase-contrast microscopy using a Fuchs-Rosenthal chamber.[12] The Behring Nephelometer II analyzer (Siemens, Marburg, Germany) was used for assessment of urinary albumin concentration (cutoff 20 mg/L). The immunonephelometric assay was carried out using commercially available Siemens antibodies and the WHO/College of American Pathologists certified reference material 470.[13,14]

2.6 | Statistical analyses

All statistical analyses were performed by Excel 2013 (Microsoft, Seattle, WA, USA) and Analyse-it ™ software, version 3.90.5 (Analyse-it Software Ltd, Leeds, UK).

Semiquantitative results obtained by the UC-3500 were compared to those of quantitative reference methods. The European Confederation of Laboratory Medicine provided guidance for the

TABLE 2 Imprecision of reflectance (R) values obtained on the UC-3500 using two control materials (UC-control low, UC-control high; R1 and R2 are values obtained at two different wavelengths) and two test strips (UC-9A and UC-11A)

| Parameter	UC-control material	Meditape UC-9A		Meditape UC-11A	
		Within-run CV, %	Between-run CV, %	Within-run CV, %	Between-run CV, %
Urobilinogen	Low	0.12	0.17	0.20	0.20
	High	1.81	6.08	2.66	5.22
Glucose	Low: R1/R2	0.56/0.56	0.65/0.62	0.45/0.45	0.60/0.57
	High: R1/R2	4.31/2.24	4.80/3.07	3.18/2.11	4.55/2.73
Protein	Low: R1/R2	0.23/0.77	0.29/1.00	0.29/0.71	0.23/0.74
	High: R1/R2	0.81/1.20	1.29/3.00	0.86/1.90	1.04/2.27
Blood	Low	0.84	0.82	1.09	0.92
	High	2.25	3.31	3.58	4.24
Nitrite	Low	0.14	0.27	0.19	0.27
	High	1.17	1.04	0.98	1.04
Bilirubin	Low: R1/R2	0.12/0.14	0.08/0.13	0.07/0.12	0.10/0.20
	High: R1/R2	1.04/1.00	2.26/2.30	1.13/1.21	2.33/2.37
Ketone	Low: R1/R2	0.10/1.04	0.16/1.36	0.17/1.15	0.11/1.04
	High: R1/R2	0.92/3.10	1.03/5.69	0.98/6.13	0.95/5.59
Leukocyte esterase	Low	0.35	0.34	0.41	0.39
	High	2.11	4.00	2.09	3.27
pH	Low: R1/R2	1.61/0.97	1.43/0.66	1.20/1.12	1.12/1.21
	High: R1/R2	1.15/3.38	1.12/3.65	1.04/3.81	1.25/4.76
Creatinine	Low	Not available		0.71	0.93
	High			3.97	5.13
Albumin	Low	Not available		0.21	0.24
	High			0.37	0.42
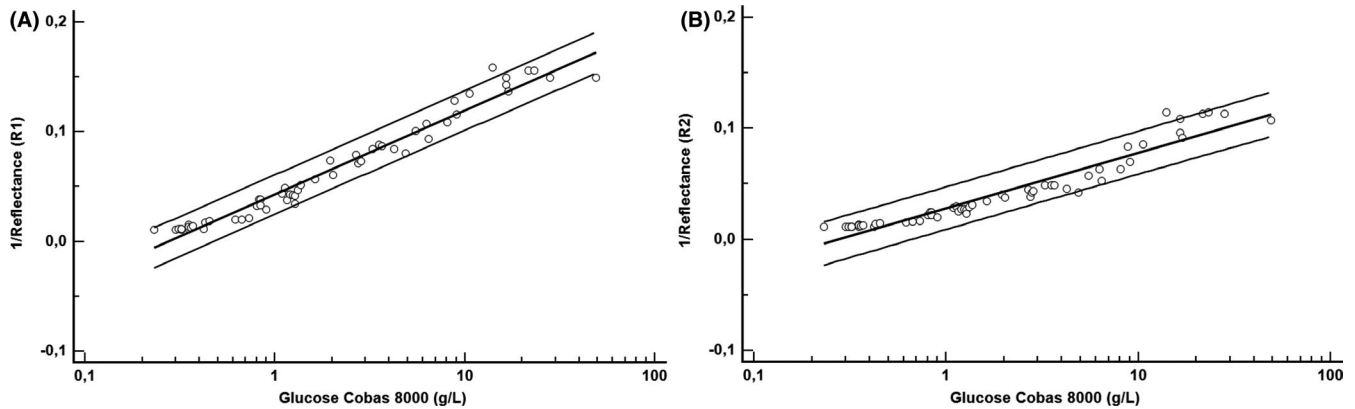
FIGURE 1 Correlation between glucose concentrations (x, hexokinase) and test strip glucose concentration (y, R1 (A) and R2 (B)) (n = 58). The two outer lines represent the 95% prediction interval around the regression line

estimation of trueness of ordinal scale test strip evaluations when compared to other methods.[2] Three analytical specifications zones and the allowance ranges of deviation were defined as follows: L_D = detection limit below which a sample should be negative (false positives: optimum/minimum: <10/<20%); L_c = confirmation limit above which a sample should be positive (false negatives: optimum/minimum: <5/<10%); and L_G = grey zone, between L_D and L_c (false negatives: optimum/minimum: <30/<50%). Agreement between reference methods and test strip data for glucose and protein was evaluated by Spearman rank regression analysis.

3 | RESULTS

3.1 | Imprecision

The within-run imprecision ranged from 0.12% to 4.31% and 0.07% to 6.13% for the 9A and 11A urine test strip parameters, respectively. The between-run imprecision ranged from 0.08% to 6.08% and 0.10 to 5.59% for the 9A and 11A urine test strip parameters, respectively. A summary of the imprecision results is presented in Table 2.
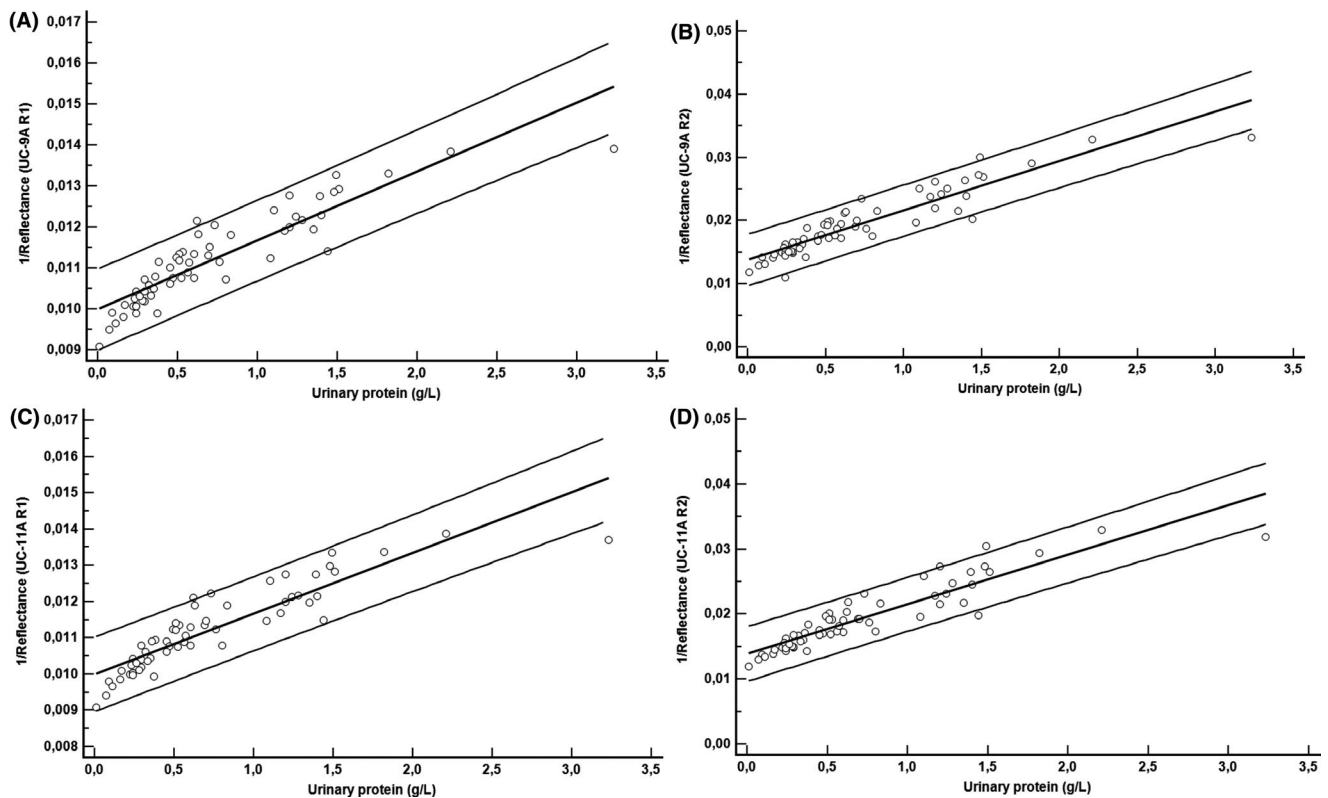
FIGURE 2 Correlation between urinary protein concentrations (x, pyrogallol red-molybdate) and test strip protein concentration (y, R1 (A and C) and R2 (B and D)) for the 9A (A and B) and 11A (C and D) urinary test strips. The two outer lines represent the 95% prediction interval around the regression line

TABLE 3 Diagnostic accuracy of UC-3500 vs reference methods for clinically most relevant parameters of urinalysis

Parameter	Test strip	No. of Samples	Sensitivity (%)	Specificity (%)	NPV[a] (%)	PPV[b] (%)
Glucose	UC-11A	59	100	60	100	88
Protein	UC-9A	67	94.2	82.4	82.4	94.2
	UC-11A	67	94.2	88.2	83.3	96.1
Hemoglobin peroxidase	UC-9A	347	85.1	89.3	96.2	65.5
	UC-11A	347	85.1	88.6	96.1	64.0
Leukocyte esterase	UC-9A	347	80.5	91.7	93.8	75.0
	UC-11A	347	81.7	92.8	94.6	77.9
Albumin	UC-11A	177	81.8	89.2	89.1	81.8

[a]Negative predictive value.
[b]Positive predictive value.

3.2 | Comparison of biochemical reference method with test strip results

The correlation between urinary glucose concentrations and glucose oxidase on the test strip is presented in Figure 1. The following regression equations were obtained: y (1/reflectance (R1)) = 0.0433 + 0.0764 $\log_{gluC}$ (g/L); Spearman r = 0.967; P < 0.001 (Figure 1A) and y (1/reflectance (R2)) = 0.0285 + 0.0500 $\log_{gluc}$ (g/L); Spearman r = 0.915; P < 0.001 (Figure 1B).

The correlation between urinary protein concentrations and protein quantification on the urinary test strip is presented in Figure 2. The following regression equations were obtained for the UC-9A test strips: y (1/reflectance (R1)) = 0.0099 + 0.0017 $\log_{prot}$ (g/L); Spearman r = 0.939; P < 0.001 (Figure 2A) and y (1/reflectance (R2)) = 0.0138 + 0.0078 $\log_{prot}$ (g/L); Spearman r = 0.944; P < 0.001 (Figure 2B) and the UC-11A test strips: y (1/reflectance (R1)) = 0.0100 + 0.0017 $\log_{prot}$ (g/L); Spearman r = 0.945; P < 0.001 (Figure 2C) and y (1/reflectance (R2)) = 0.0139 + 0.0076 $\log_{prot}$ (g/L); Spearman r = 0.943; P < 0.001 (Figure 2D).

3.3 | Diagnostic performance

The diagnostic accuracy of the UC-3500 for urinary hemoglobin peroxidase, leukocyte esterase, glucose, protein, and albumin is presented in Table 3.

An excellent NPV of 96.2% for RBCs and just below 95% for WBCs in comparison with flow cytometry was obtained. Both test strips provided similar results. For hemoglobin peroxidase and leukocyte esterase, we found a sensitivity of 85.1% (both test strips) and 80.5/81.7% (UC-9A/UC-11A), respectively (Table 3).

For glucose analysis, we determined a specificity of 60%. On the other hand, we found no negative results compared to the hexokinase method, yielding a sensitivity and NPV of 100%.

Regarding the determination of total protein, a sensitivity and specificity of 94.2% (both test strips) and 82.4/88.2% (UC-9A/UC-11A) were obtained, respectively.

For albumin measurement, a sensitivity of 81.8%, a specificity of 89.2%, a NPV of 89.1%, and a PPV of 81.8% were found for UC-11A test strip analysis compared to the reference immunonephelometric method.

3.4 | Agreement and evaluation of trueness

For the five parameters evaluated, an L_D and L_C were defined as follows: For RBC and WBCs, the L_D and L_C were set at 25 and 125 cells/μL, respectively; for glucose, the L_D and L_C were defined as 50 and 250 mg/dL, respectively; for albumin, the L_D and L_C were defined as 20 and 100 mg/dL, respectively; and for creatinine, the L_D and L_C were defined as 150 and 250 mg/dL. The agreement between the reference method and test strip analysis is presented in Table 4.

The calculated FP_D was well within the optimum criterion (<10%) for leukocyte esterase and within the minimum criterion (<20%) for the albumin, creatinine, and hemoglobin peroxidase. For protein and glucose, the FP_D was not within the predefined criterion (Table 5).

The calculated FN_G was well within the optimum criterion (<30%) for albumin, creatinine, glucose, and hemoglobin peroxidase and within the minimum criterion (<50%) for protein and leukocyte esterase (Table 5).

Finally, the calculated FN_C was well within the optimum criterion for hemoglobin peroxidase and leukocyte esterase (UC-11A) and within the minimum criterion for leukocyte esterase (UC-9A). For protein and creatinine, the FN_C was not within the criterion (Table 5).

4 | DISCUSSION

In the European Urinalysis Guidelines,[2] four sequential diagnostic procedure levels with increasing accuracy were recommended for urinalysis. Level 1 methodologies represent fast screening tests often placed in primary care laboratories and at points-of-care. They should have a clinically acceptable performance to act as a sieving system in order to reduce the workload for higher levels. A good analytical and diagnostic accuracy in the lower range around the cutoff is especially important for primary screening technologies as they should reliably distinguish normal from positive samples. Only positive or suspicious samples would be subject for further investigation.

TABLE 4 Agreement (%) between UC-3500 and reference methods

Parameter	Test strip	Perfect agreement (%), same category	Agreement ±1 category (%)
Glucose	UC-11A	78.0	98.3
Protein	UC-9A	63.8	97.1
	UC-11A	65.2	98.6
Hemoglobin peroxidase	UC-9A	64.8	86.2
	UC-11A	65.1	86.5
Leukocyte esterase	UC-9A	77.2	96.5
	UC-11A	78.1	97.1
Albumin	UC-11A	79.1	100.0
Creatinine	UC-11A	53.9	95.7

TABLE 5 Calculation of the trueness according to the European Urinalysis Guidelines[2]

Parameter	Test strip	FP at L_D	FN in L_G	FN at L_C
Glucose		50mg /dL	50-250mg /dL	>250mg /dL
	UC-11A	40.0% (6/15)	0.0% (0/20)	ND
Protein		<30mg /dL	30-150mg /dL	>150mg/dL
	UC-9A	37.5% (6/16)	44.7% (17/38)	23.1% (3/13)
	UC-11A	43.8% (7/16)	44.7% (17/38)	38.5% (5/13)
Hemoglobin peroxidase		<25 cells/µL	25-125 cells/µL	>125 cells/µL
	UC-9A	10.7% (30/280)	28.1% (9/32)	2.9% (1/35)
	UC-11A	11.4% (32/280)	28.1% (9/32)	2.9% (1/35)
Leukocyte esterase		<25 cells/µL	25-125 cells/µL	>125 cells/µL
	UC-9A	8.3% (22/265)	31.8% (14/44)	5.3% (2/38)
	UC-11A	7.2% (19/265)	31.8% (14/44)	2.6% (1/38)
Albumin		<20mg /dL	20-100mg /dL	>100mg /dL
	UC-11A	10.0% (11/110)	25.5% (12/47)	ND
Creatinine		<150mg /dL	150-250mg /dL	>250mg /dL
	UC-11A	10.8% (10/93)	8.3% (1/12)	33.3 (1/3)

In brackets, the absolute numbers of samples are displayed.
FP, false positive; FN, false negative, L_D, detection limit; L_G, limit grey zone; L_C, confirmation limit; ND, not determined.

The application of test strips with multiple reagent pads belongs to the group of primary screening procedures. In 2016, the urine chemistry analyzer UC-3500 was introduced in our laboratory. As the instrument is fully automated, interobserver variability associated with visual reading of test strips is overcome.

The within-run and between-run imprecision for the low-level quality control, covering the negative and 1+ semiquantitative categories, were excellent. CVs for nine out of eleven parameters were below 1% and for ketones and pH just above 1%. A good analytical accuracy in the lower level range is especially important to distinguish normal or negative samples from positive samples. These results are comparable to other urinary test strip analyzers.[15] CVs for within-run and between-run imprecision of high-level control, covering 1+, 2+, 3+, and 4+ categories, ranged from below 1% (albumin) to 6% (ketones). This can be regarded as sufficient as the exact value in pathological samples will be determined by workflow level 2-4 procedures.

The Spearman r-values for glucose (0.96) and protein (0.90 and 0.92) were excellent and indicate a strong correlation with quantitative results. Earlier reports[15] comparing hexokinase-based glucose analyses and test strip reflectance readings on the URISYS 2400 (Roche Diagnostics, IN, USA) indicated a Spearman r of −0.85. In a recent publication, good correlation was found for flow cytometric WBC and UC-3500 leukocyte esterase results (r = 0.82) as well as RBC and peroxidase (r = 0.84).[11] Regression analysis of albumin measured on Meditape UC-11A UC test strip versus immunonephelometry showed a strong correlation (r = 0.92), similar for creatinine (r = 0.90).[6]

Whereas the reference instrument UF-5000 counts RBC and WBC via flow cytometry, the UC-3500 measures the enzymatic activity of hemoglobin peroxidase and leukocyte esterase, respectively. It has been reported that due to low sensitivity and NPV, screening for urinary infections by test strips alone might not be sufficient.[16] Despite these findings, in our study, the NPV was just below 95% for WBCs, and values for trueness of ordinal scale measurements

fulfilled optimum criteria for the detection and confirmation limit. With 31.8% FN for the grey zone, the value was slightly above the optimum of 30%. In conclusion, the absence of urinary tract infections based on leukocytes can be reliably ruled out by test strip analysis using the UC-3500. Results for the diagnostic accuracy for the detection of hematuria were also excellent: A NPV and sensitivity of 96.1% and 85.1% were obtained, respectively, and optimum criteria for evaluation of trueness were fully reached for L_c and L_G; for L_D, the value was slightly above the optimum 10% FP.

Screening for glycosuria by urine dipstick analysis may identify patients with undetected diabetes mellitus. Sensitivity and NPV of UC-3500 vs Cobas 8000 glucose measurement were 100%, and there were no false-negative cases above the detection limit. Below the L_D, 40% FP were found and the minimum criterion of <50% FP was met. Detection of undiagnosed diabetes by urinary glucose screening happens only by chance and is therefore of minor relevance. Both the detection of diabetes and monitoring of a respective therapy are superior in blood testing.

Proteinuria is defined as the excretion of more than 150 mg of protein per day, a hallmark of renal disease, and an indicator for hypertension in pregnant women. Repeatability for total protein was acceptable with ≤1% CV for low-level and ≤3% CV for high-level control material, along with an excellent sensitivity (94.2%) and PPV (94.2/96.1). The NPV was well above 80% for the two test strips. In a previous publication, a correlation coefficient of 0.97 for a range of 15-1000 mg/dL was described, reflecting a nearly perfect positive relationship between UC-3500 reflectance data and Cobas 8000 immunochemistry results for proteinuria.[6]

Regarding albumin measurement, all optimum criteria for trueness were fulfilled and the performance for ordinal scale measurements confirmed the ones recently published for nominal scale measurements.[9]

In conclusion, the fully automated test strip analyzer UC-3500 provides a high-throughput first-level screening method for urinalysis which acts as a reliable sieving system to reduce the workload for further validation methods.

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