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Performance evaluation of Hipee S2 point-of-care testing urine dipstick analyser: a cross-sectional study

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ABSTRACT

Objective With advances in mobile technology, smartphone-based point-of-care testing (POCT) urinalysis hold great potential for disease screening and health management for clinicians and individual users. The purpose of this study is to evaluate the analytical performance of Hipee S2 POCT urine dipstick analyser.

Design A multicentre, hospital-based, cross-sectional study.

Setting Analytical performance of the POCT analyser was conducted at a clinical laboratory, and method comparison was performed at three clinical laboratories in China.

Participants Urine samples were collected from 1603 outpatients and inpatients at three hospitals, and 5 health check-up population at one of the hospitals.

Outcome measures All tests were performed by clinical laboratory technicians. Precision, drift, carry-over, interference and method comparison of Hipee S2 were evaluated. Diagnostic accuracy of semiquantitative albumin-to-creatinine ratio (ACR) for albuminuria was carried out using quantitative ACR as the standard.

Results The precision for each parameter, assessed by control materials, was acceptable. No sample carry-over or drift was observed. Ascorbate solution with 1 g/L had an inhibitory effect for the haemoglobin test. Agreement for specific gravity (SG) varied between moderate to substantial (κ values 0.496–0.687), for pH was moderate (κ values 0.423–0.569) and for other parameters varied between substantial to excellent (κ values 0.669–0.991), on comparing the Hipee S2 with laboratory analysers. The semiquantitative microalbumin and creatinine were highly correlated with the quantitative results. The sensitivity of semiquantitative ACR to detect albuminuria was 87.2%–90.7%, specificity was 70.7%–78.4%, negative predictive value was 85.3%–87.9% and positive predictive value was 73.9%–83%.

Conclusions Hipee S2 POCT urine analyser showed acceptable analytical performance as a semiquantitative method. It serves as a convenient alternate device for clinicians and individual users for urinalysis and health management. In addition, the POCT semiquantitative ACR would be useful in screening for albuminuria.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The analytical and clinical performance of the point-of-care testing urinalysis device is investigated by applying the same rigorous procedures used for routine instruments in the central laboratories.
⇒ Method comparison is assessed using patient samples from three clinical laboratories in three different settings.
⇒ Diagnostic accuracy of semiquantitative albumin-to-creatinine ratio (ACR) for albuminuria is evaluated in two clinical laboratories by using quantitative ACR as the standard.
⇒ Owing to the detection of urinary calcium is not performed in all of the three laboratories, this study does not evaluate urinary calcium testing.
⇒ The study took place by clinical laboratory technicians in tertiary care hospitals and did not explore the views of multidisciplinary and diverse group of participants in other settings.

INTRODUCTION

Urinalysis is one of the most prescribed laboratory tests that provides a lot of information to physicians. It has important significance in the screening, diagnosis and follow-up of nephritis, urinary tract infection, diabetes and other diseases.[1] At present, dry chemical strips are widely used in urinalysis. The colour changes of the corresponding items are read by urine analysers to obtain qualitative and semiquantitative results, including those of physical and biochemical analysis. Usually, urinalysis is carried out in the hospital or at a central laboratory. Although urine analysers in these facilities provide extremely high analytical performance, they have some limitations, such as high cost, tedious registration protocols and time-consuming process.[2]

Point-of-care testing (POCT) is defined as testing at or near the site of patient care whenever the medical care is needed.[3] POCT offers the advantages of widening accessibility to diagnosis, reduced costs, minimal sample volumes and rapid analysis times.[4] In recent years, POCT has become more and more popular in clinical diagnosis, health management and biological response to public health emergencies.[5] In today's digitised world, the mobile health technology is growing.[6] With the widespread use and

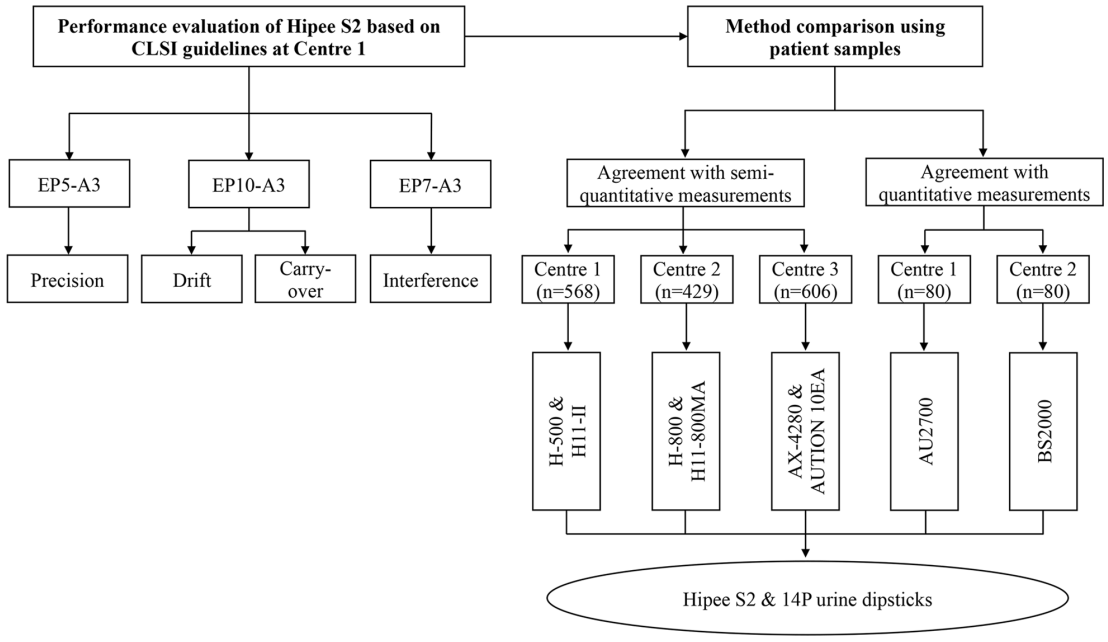

Figure 1 Flow diagram for the study. CLSI, Clinical and Laboratory Standards Institute.

advanced features of a smartphone, smartphone-based POCT devices are highly suitable for personalised and decentralised healthcare management as well as real-time monitoring and management of epidemics, particularly in remote areas and in private or public places with scarcity of resources.[7 8] However, the measurements of POCT devices are not necessarily qualitatively equivalent to those of central laboratory instruments. The POCT device, therefore, needs to have good analytical and clinical performance; however, data on these aspects are lacking.

Hipee S2, a recently introduced POCT urine dipstick analyser that can be connected to smartphone, can be conveniently performed qualitatively or semiquantitatively urinalysis. This study evaluated analytical and clinical performance of Hipee S2, its agreement with routine instruments used in different laboratories, and the accuracy of semiquantitative albumin-to-creatinine ratio (ACR) measured by Hipee S2 for the diagnosis of albuminuria through a multicentre study. The flow diagram for the study was shown in figure 1.

METHODS

Samples

A total of 1603 fresh, midstream spot urine samples were collected from inpatients and outpatients between May 2019 and December 2019. Among these urine samples, 568 cases were collected from a Branch of Tianjin Third Central Hospital (centre 1), 429 cases were collected from The Second Hospital of Tianjin Medical University (centre 2) and 606 cases were collected from Chinese PLA General Hospital (centre 3). Patients collected from different centres were selected with similar age and

Table 1 Clinical characteristics of patients

Variable	Centre 1 (n=568)	Centre 2 (n=429)	Centre 3 (n=606)	χ^2 value	P value
Age, n (%)				1.008	0.985
< 20 years	133 (23.4)	109 (25.4)	145 (23.9)		
20–40 years	141 (24.8)	108 (25.2)	155 (25.6)		
41–60 years	156 (27.5)	108 (25.2)	153 (25.2)		
>60 years	138 (24.3)	104 (24.2)	153 (25.2)		
Total	568 (100)	429 (100)	606 (100)		
Gender (male), n (%)				0.302	0.860
< 20 years	68 (51.1)	51 (46.8)	71 (49.0)		
20–40 years	71 (50.4)	53 (49.1)	80 (51.6)		
41–60 years	72 (46.2)	55 (50.9)	78 (51.0)		
>60 years	68 (49.3)	49 (47.1)	75 (49.0)		
Total	279 (49.1)	208 (48.5)	304 (50.2)		

gender characteristics, as shown in table 1. There were no additional inclusion or exclusion criteria on sampling in order to provide randomness. Five additional urine samples with negative results measured by urine dipstick were collected from adult health check-up population at Branch of Tianjin Third Central Hospital (centre 1), mixed well. The mixture was centrifuged at 400×g for 5 min, and the supernatant was collected as negative control urine. The commercial urine control material was used as positive quality control material (lot: 20190301, Dirui, Jilin, China). All measurements were performed by trained clinical laboratory technicians and completed within 2 hours of urine collection.

Equipment

The Hipee S2 (Fruitech, Tianjin, China) is 183×20×16 mm in size and 40 g in weight. It can be used independently as a traditional POCT urinalysis device to measure 14 parameters including urobilinogen, bilirubin, ketones, haemoglobin, proteins, nitrite, leucocytes, glucose, specific gravity (SG), pH, microalbumin, creatinine, calcium and ascorbate. The Hipee S2 system reads the colour change made by the reaction from chemically absorbed pads of the 14P urine dipsticks (Hongyi, Suzhou, China) using multiwavelength reflectance photometry. Each test-pad is irradiated by a light source generated by a light-emitting diode of the instrument and produces reflected light of different wavelengths. The instrument receives light signals at 620, 520 and 420 nm wavelengths through specific multiwavelength photoelectric receiver and converts them into the corresponding electrical signals. Then the change of reflectance rate (change %R) is calculated by the microprocessor, and assigns a qualitative or semiquantitative set point based on the value. The methods determinated by 14P dipsticks are as follows: urobilinogen (3–3'-di-methoxy-4–4'-diazo-biphenyl tetrafluoride borate), bilirubin (2-methyl-5-nitroaniline/sodium nitrite), ketones (sodium nitroprusside method), haemoglobin (cumene hydroperoxide), proteins (tetrabromophenol blue), nitrite (Griess method), leucocytes [3-(N-toluenesulphonyl-L-alanyloxy)-indole/2- Methoxy-4-(N-morpholino) benzenediazonium], glucose (glucose oxidase/peroxidase), SG (polyelectrolyteon ion dissociation method), pH (acid-base indicator method), microalbumin (tetrabromophenol blue), creatinine (metal complex method), calcium (o-cresolphthalein complexone) and ascorbate (2,6-dichlorophenol indigophenol). The concentration ranges corresponding to set points suggested by the manufacturer are listed in table 2.

The POCT urine dipstick analyser provides an additional ACR measurements to assess albuminuria by connecting to smartphone application or WeChat applet with Bluetooth. The dipstick uses a sensitive test-pad (proteins) and another less sensitive test-pad (microalbumin) to cover

Table 2 Concentration ranges corresponding to set points suggested by the Hipee S2 manufacturer

	Concentration					
Variable	**–**	**+/–***	**1+**	**2+**	**3+**	**4+**
Urobilinogen (µmol/L)	3.3	NA†	33	66	131	200
Bilirubin (µmol/L)	0	NA	17	50	100	NA
Ketone (mmol/L)	0	NA	1.5	4.0	8.0	NA
Haemoglobin (g/L)	0	0.0003	0.001	0.003	0.006	NA
Protein (g/L)	0	0.15	0.3	1.0	3.0	10
Nitrite (mg/dL)	0	NA	0.125	NA	NA	NA
Leucocyte (cells/µL)	0	15	70	125	500	NA
Glucose (mmol/L)	0	2.8	5.5	14	28	55
Microalbumin (mg/L)‡	0	30	80	150	NA	NA
Creatinine (mmol/L)§	0	4.4	8.8	17.7	26.5	NA
Calcium (mmol/L)¶	0	1.25	3.7	12.5	NA	NA
Ascorbate (g/L)	0	0.1	0.25	0.5	1	NA
SG**	1.005	1.010	1.015	1.020	1.025	1.030
pH††	5.0	6.0	7.0	8.0	9.0	NA

*The set point of '**+/–**' represents weak positive.
†NA represents the set point is not available.
‡The set points of microalbumin are reported as 10, 30, 80 and 150 mg/L.
§The set points of creatinine are reported as 0.9, 4.4, 8.8, 17.7 and 26.5 mmol/L.
¶The set points of calcium are reported as 0, 1.25, 3.7 and 12.5 mmol/L.
**The set points of SG are reported as 1.005, 1.010, 1.015, 1.020, 1.025 and 1.030.
††The set points of pH are reported as 5.0, 6.0, 7.0, 8.0 and 9.0.
SG, specific gravity.

the linearity of albumin in the range of 10 mg/L to 10 g/L. The ACR is calculated using the following formula: ACR (mg/mmol) = albumin (mg/L) / creatinine (mmol/L), which can be reported as a calculated value or set point depending on individual setting of the smartphone application or WeChat applet. In this study, the semiquantitative ACR is reported as 'dilute' (albumin 10 mg/L and creatinine 0.9 mmol/L), 'normal' (< 3.4 mg/mmol), '1+' (3.4–34 mg/mmol, microalbuminuria) or '2+' (> 34 mg/mmol, macroalbuminuria). In addition, some extended functions can also be performed through Bluetooth connection with smartphone application or WeChat applet, such as querying historical results, personalised health monitoring by setting up different users, and real-time analysis of urine results for early disease risk warning using preset cut-off values.

Precision study

Within-run and between-run precision were assessed on Hipee S2 for the following parameters based on Clinical and Laboratory Standards Institute (CLSI) EP5-A3 guideline: urobilinogen, bilirubin, ketones, haemoglobin, proteins, nitrite, leucocytes, glucose, SG, pH, microalbumin and creatinine.[9] The within-run precision of Hipee S2 was assessed by analysing 20 aliquots of positive and negative controls during the same day. The between-run precision was obtained by analysing the controls for the following 20 days consecutively.

Drift and carry-over study

A preliminary evaluation for drift and carry-over was conducted using CLSI EP10-A3 guideline where 10 urine samples with low, medium or high concentration collected from patients were measured in following specific sequence on five consecutive working days: medium, high, low, medium, medium, low, low, high, high and medium.[10] The low, medium and high concentrations of each parameter were as listed in table 3.

Interference study

The CLSI EP7-A3 guideline was followed for studying analytical interference of ascorbate on glucose, haemoglobin and nitrite.[11] An ascorbate solution (L-ascorbic acid, 99%, Sigma-Aldrich, St. Louis, Missouri, USA) was added to the positive urine samples in steps of 0.2–1 g/L, and compared with the measurement obtained on a different aliquot of the same urine sample, where only matrix urine was added.

Method comparison

The comparison analysers for urinary dipstick analysis were H-500 and H11-II dipsticks (Dirui, Jilin, China) in Centre 1, H-800 and H11-800MA dipsticks (Dirui, Jilin, China) in Centre 2, AX-4280 and AUTION Sticks 10EA (Arkray, Kyoto, Japan) in centre 3, respectively. The set points and test concentrations suggested by the manufacturers for different urinary dipstick analysis systems were listed in online supplemental table S1. The agreement of the following parameters was assessed by comparing the results measured by Hipee S2 with those detected by the comparison analysers: urobilinogen, bilirubin, ketones, haemoglobin, proteins, nitrite, leucocytes, glucose, SG and pH.

Considering that urine dipstick measurements of microalbumin and creatinine were carried out in none of the three centres, the agreement of microalbumin and creatinine was evaluated by comparing the semiquantitative results measured by Hipee S2 with the quantitative results obtained by biochemical analyser. In centre 1 and centre 2, 80 samples were selected for quantitative urinalysis, respectively. Microalbumin was measured quantitatively by immunoturbidimetric method and creatinine

Table 3 Drift and carry-over study with urine samples (n=50)

	Expected levels			Agreement, n (%)	
Variable	Low	Medium	High	Same level	±1 level
Urobilinogen	–	1+	3+	49 (98)	50 (100)
Bilirubin	–	1+	3+	50 (100)	50 (100)
Ketone	–	1+	3+	48 (96)	50 (100)
Haemoglobin	–	1+	3+	44 (88)	50 (100)
Protein	–	1+	3+	46 (92)	50 (100)
Nitrite	–	NA	1+	50 (100)	50 (100)
Leucocyte	–	1+	3+	46 (92)	50 (100)
Glucose	–	1+	3+	47 (94)	50 (100)
Microalbumin	10	80	150	49 (98)	50 (100)
Creatinine	0.9	8.8	26.5	50 (100)	50 (100)
SG	1.005	1.015	1.030	44 (88)	50 (100)
pH	5.0	7.0	9.0	41 (82)	50 (100)

NA, not available; SG, specific gravity.

by kinetic Jaffé method on AU2700 biochemical analyser (reagents were purchased from BSBE, Bejing, China, and analyser was purchased from Beckman Coulter, California, USA) in centre 1 and BS2000 analyser (reagents and analyser were purchased from Mindray, Shenzhen, China) in centre 2. According to the quantitative measurements, urine samples with ACR less than 3.4 mg/mmol were defined as non-albuminuria, while those with ACR greater than 3.4 mg/mmol were defined as albuminuria. In addition, albuminuria was divided into microalbuminuria and macroalbuminuria, and the quantitative ACR was 3.4–34 mg/mmol and greater than 34 mg/mmol, respectively. In semiquantitative methodology, 'dilute' or 'normal' was considered ACR negative, while '1+' or '2+' was considered positive.

Statistical analysis

Data were analysed using MedCalc software, V.18.2 (Mariakerke, Belgium). Categorical variables were described as frequency and analysed by χ^2 test. Urine dipsticks are characterised by the presence of set points of analytes that result in qualitative or semiquantitative data.[12] Therefore, the precision cannot be evaluated as coefficient of variance but as a percentage of reproducibility of set points.[12 13] Agreement of semiquantitative data was assessed by the weighted kappa coefficient (κ). The level of agreement was defined by κ as excellent (0.81–1.00), substantial (0.61–0.80), moderate (0.41–0.60), fair (0.21–0.40) and poor (0.00–0.20).[14] Spearman correlation and scatter dot plots were used to evaluate the correlation between semiquantitative and quantitative assays. The diagnostic accuracy of semiquantitative ACR for albuminuria was evaluated using quantitative ACR as the standard. The sensitivity, specificity, positive (PPV) and negative predictive value (NPV) were calculated. Statistical significance was defined as $p<0.05$. In addition, two-sided 95% CIs were calculated.

Patient and public involvement

No patients or members of the public were involved in the design of this study.

RESULTS

Precision study

The results of within-run and between-run precision for each parameter measured on negative and positive controls demonstrated good repeatability. As shown in table 4, all data were placed within one set point or distributed between two contiguous set points.

Drift and carry-over study

As shown in table 3, the percentage of exact agreement on comparing measurement with its expected level ranged from 82% to 100%, especially within±1 level, where the accuracy rate was 100% for any of the parameters.

Interference study

As shown in table 5, ascorbate solutions in a range of 0.2–1 g/L did not show any significant interference effect

Table 4 Precision study with positive and negative controls

	Within-run precision (n=20), %						Between-run precision (n=20), %					
Variable	**–**	**+/–***	**1+**	**2+**	**3+**	**4+**	**–**	**+/–**	**1+**	**2+**	**3+**	**4+**
Urobilinogen	100†	NA‡	0	100	0	0	100	NA	0	95	5	0
Bilirubin	100	NA	0	0	100	NA	100	NA	0	0	100	NA
Ketone	100	NA	0	95	5	NA	100	NA	0	90	10	NA
Haemoglobin	100	0	0	15	85	NA	100	0	0	65	35	NA
Protein	100	0	0	5	95	0	100	0	0	15	85	0
Nitrite	100	NA	100	NA	NA	NA	100	NA	100	NA	NA	NA
Leucocyte	100	0	0	90	10	NA	100	0	0	75	25	NA
Glucose	100	0	0	10	90	0	100	0	0	15	85	0
Microalbumin§	100	0	100	0	NA	NA	100	0	100	0	NA	NA
Creatinine¶	100	0	0	100	0	NA	100	0	5	95	0	NA
SG**	0	0	100	0	0	100	0	0	100	0	0	100
pH††	0	95/35	5/65	0	0	NA	0	100/30	70	0	0	NA

*The set point of '**+/–**' represents weak positive.
†Numbers with underlines are reported data corresponding to the negative urine controls, and those without underlines corresponding to the positive urine controls.
‡NA represents the set point is not available.
§The set points of microalbumin are reported as 10, 30, 80 and 150 mg/L.
¶The set points of creatinine are reported as 0.9, 4.4, 8.8, 17.7 and 26.5 mmol/L.
**The set points of SG are reported as 1.005, 1.010, 1.015, 1.020, 1.025 and 1.030.
††The set points of pH are reported as 5.0, 6.0, 7.0, 8.0 and 9.0.
SG, specific gravity.

Table 5 Interference of ascorbic acid effect on tested haemoglobin, glucose and nitrite

	Haemoglobin			Glucose				Nitrite
Ascorbate (g/L)	1+	2+	3+	1+	2+	3+	4+	1+
0.2	N (1+)*†	N (2+)	N (3+)	N (1+)	N (2+)	N (3+)	N (4+)	N (1+)
0.4	N (1+)	N (2+)	N (3+)	N (1+)	N (2+)	N (3+)	N (4+)	N (1+)
0.6	N (1+)	N (2+)	N (3+)	N (1+)	N (2+)	N (3+)	N (4+)	N (1+)
0.8	N (1+)	N (2+)	N (3+)	N (1+)	N (2+)	N (3+)	N (4+)	N (1+)
1.0	Y‡ (–)	Y (–)	N (3+)	N (1+)	N (2+)	N (3+)	N (4+)	N (1+)

*N indicates that the results were within the same set point with addition of the interferences.
†The set points in the parentheses represent the concentration levels according to the change of reflectance rate.
‡Y means that the results were not within the same set point with addition of the interferences.

on semiquantitative results of urine samples characterised by '3+' of haemoglobin. When the same concentrations of ascorbate solutions were added to urine samples containing '1+' or '2+' of haemoglobin, we found that an ascorbate solution concentration of 1 g/L had significant inhibitory effect on urine dipstick analysis in haemoglobin test.

The addition of ascorbate solution in a range of 0.2–1 g/L to urine samples characterised by initial glucose levels of '1+', '2+', '3+' and '4+' did not result in glucose level reduction. When the same concentrations of ascorbate solutions were added to nitrite-positive urine samples, ascorbate did not show any effect on nitrite levels (table 5).

Method comparison

As shown in table 6, the results of urobilinogen, bilirubin, ketones, haemoglobin, proteins, nitrite, leucocytes and glucose detected by Hipee S2 had excellent or substantial agreement (κ values 0.669–0.991) with those detected by H-500, H-800 and AX-4280, and the agreement of pH was moderate (κ values 0.423–0.569). For the SG test, the agreement showed substantial on comparing Hipee S2 with H-500 (κ value 0.613) or H-800 (κ value 0.687), but moderate on comparing with AX-4280 (κ value 0.496).

A strong correlation was found on comparing the levels of microalbumin detected by the semiquantitative assay (Hipee S2) with those obtained by quantitative methods (AU-2700 (Spearman's correlation coefficient 0.904, 95% CI 0.854 to 0.937) and BS2000 (Spearman's correlation coefficient 0.871, 95% CI 0.806 to 0.916)). The scatter dot plots showed good agreement between the semiquantitative and quantitative microalbumin results through the measurement range from normal to highly pathological levels in the two laboratories (figure 2A,B). A similarly strong correlation in terms of the creatinine level was found between semiquantitative and quantitative measurements (AU2700 (Spearman's correlation coefficient 0.87, 95% CI 0.804 to 0.915) and BS2000 (Spearman's correlation coefficient 0.884, 95% CI 0.816 to 0.928)). As shown in figure 2C,D, the two data groups also showed a good agreement in the two laboratories.

As shown in figure 3A, semiquantitative ACR measured by Hipee S2 in centre 1 correctly classified 60 (75%) of the urine samples into the correct albuminuria stages of non-albuminuria (<3.4 mg/mmol), microalbuminuria (3.4–34 mg/mmol) and macroalbuminuria (> 34 mg/mmol). Accuracy was 85% (29/34), 69% (27/39) and 57% (4/7). Twelve false positive results (FPs) were identified in 41 urines without albuminuria (quantitative ACR <3.4 mg/mmol), while 5 false negative results (FNs) were identified in 39 urines with albuminuria (quantitative ACR ≥3.4 mg/mmol, contained microalbuminuria and macroalbuminuria) (table 7). The sensitivity of semiquantitative ACR to detect albuminuria was 87.2%, specificity was 70.7%, PPV was 73.9% and NPV was 85.3%.

A similarly results were observed in centre 2 (figure 3B). Semiquantitative assay correctly classified 64 (80%) of the samples into non-albuminuria, microalbuminuria and macroalbuminuria. Accuracy was 88% (29/33), 73% (30/41) and 83% (5/6), respectively. Eight FPs were identified in 37 urines without albuminuria, while 4 FNs were identified in 43 urines with albuminuria (table 7). The sensitivity of semiquantitative ACR to detect albuminuria was 90.7%, specificity was 78.4%, PPV was 83.0% and NPV was 87.9%.

DISCUSSION

In recent years, several previous papers have evaluated the analytical and clinical performance of the urine dipstick analysers.[12 15 16] However, to our knowledge, this is the first report wherein the performance of a POCT urinalysis device that can be connected to a smartphone has been investigated by applying the same rigorous performance measures used by the central laboratory.

As mentioned previously, a set point on the parameter scale of the urine dipstick represents a range of concentrations. At the borderline of two adjacent set points, the corresponding concentrations may partially overlap. In addition, different urinalysis systems from different manufacturers are not exactly the same in their set points and corresponding concentration ranges. Therefore,

Table 6 Agreement between Hipee S2 and the instruments used in the three centres

Variable	H-500 (n=568)			H-800 (n=429)			AX-4280 (n=606)		
	±1 level, n (%)	Same level, n (%)	κ value, κ (95% CI)	±1 level, n (%)	Same level, n (%)	κ value, κ (95% CI)	±1 level, n (%)	Same level, n (%)	κ value, κ (95% CI)
Urobilinogen	560 (98.6)	527 (92.8)	0.853 (0.825 to 0.882)	428 (99.8)	377 (87.9)	0.750 (0.692 to 0.808)	600 (99.0)	555 (91.6)	0.770 (0.705 to 0.843)
Bilirubin	544 (95.8)	538 (94.7)	0.815 (0.723 to 0.907)	422 (98.4)	413 (96.3)	0.889 (0.845 to 0.932)	592 (97.7)	571 (94.2)	0.834 (0.786 to 0.882)
Ketone	531 (93.5)	458 (80.6)	0.669 (0.584 to 0.754)	405 (94.4)	343 (79.9)	0.719 (0.673 to 0.765)	597 (98.5)	503 (83.0)	0.806 (0.772 to 0.839)
Haemoglobin	560 (98.6)	464 (81.7)	0.871 (0.836 to 0.905)	425 (99.1)	367 (85.6)	0.837 (0.803 to 0.870)	599 (98.9)	472 (77.9)	0.755 (0.717 to 0.794)
Protein	565 (99.5)	432 (76.1)	0.783 (0.731 to 0.835)	418 (97.5)	352 (82.0)	0.769 (0.730 to 0.808)	571 (94.2)	485 (80.0)	0.727 (0.692 to 0.763)
Nitrite	568 (100)	552 (97.2)	0.888 (0.813 to 0.964)	429 (100)	428 (99.8)	0.991 (0.975 to 1.000)	606 (100)	588 (97.0)	0.916 (0.881 to 0.952)
Leucocyte	528 (93.0)	458 (80.6)	0.731 (0.668 to 0.794)	385 (89.7)	308 (71.8)	0.674 (0.629 to 0.718)	556 (91.7)	489 (80.7)	0.731 (0.683 to 0.778)
Glucose	536 (94.4)	450 (79.2)	0.789 (0.738 to 0.841)	425 (99.1)	373 (86.9)	0.776 (0.722 to 0.829)	606 (100)	546 (90.1)	0.845 (0.813 to 0.877)
SG	538 (94.7)	324 (57.0)	0.613 (0.551 to 0.674)	405 (94.4)	269 (62.7)	0.687 (0.650 to 0.724)	533 (88.0)	299 (49.3)	0.496 (0.457 to 0.535)
pH	496 (87.3)	264 (46.5)	0.569 (0.515 to 0.622)	371 (86.5)	270 (62.9)	0.505 (0.459 to 0.551)	528 (87.1)	328 (54.1)	0.423 (0.380 to 0.466)

SG, specific gravity.

variation of one level higher or lower than the expected level is acceptable.[17]

In the precision evaluation test, Hipee S2 yielded good precision for both within-run and between-run study measured with control materials for the following parameters: urobilinogen, bilirubin, ketones, haemoglobin, proteins, nitrite, leucocytes, glucose, SG, pH, microalbumin and creatinine. No significant drift and carry-over were observed in any parameter evaluated by urine samples collected from patients, considering that all measurements were placed within the same level or ±1 level relative to the expected concentration.

Interference of ascorbic acid on urine dipstick analysis has been well-known for many years.[18] Ascorbic acid, a strong antioxidant, can consume peroxide. This explains the false underestimation of glucose and haemoglobin when they are detected by peroxidase reactions in the presence of ascorbic acid.[19] Ascorbic acid can also react with diazonium salts to yield a colourless complex, which subsequently leads to a false-negative result for nitrite. Presently, most urine dipstick are made to resist the interference of ascorbic acid in a concentration range. However, a previous report demonstrated that the interference of ascorbic acid at high concentrations was still a major issue in urine dipstick tests, and the intensity of how much the test was affected differed among different manufacturers.[20] In this study, we observed the interference of ascorbate solution in a range of 0.2–1 g/L. The results showed that 1 g/L ascorbate solution had a significant inhibitory effect on urine dipstick analysis in the haemoglobin test. These interferences may be associated with some potential risk for patients. Hipee S2 provides an additional ascorbic acid detection module in dipstick. When the concentration of ascorbic acid reaches 1 g/L ('3+'), the haemoglobin test should be further investigated and evaluated.

In a study of method comparison, a test method can be performed by comparing with not only a reference method but also a current routine method in a medical laboratory.[21] H-500, H-800 and AX-4280 are automatic urine dipstick analysers that have been used for a long time and have showed good performance in the three laboratories included in this study. Our multicentre study assessed a representative amount (n=1603) of urine samples collected from patients to gain deeper and more robust insight into the concordance between the POCT urine dipstick analyser and the automatic analysers used in laboratories. The results demonstrated that Hipee S2 showed good agreement with the three urinalysis instruments, considering agreement as the same level or±1 level; however, the level of agreement differed per parameter and per analyser. For the parameters of urobilinogen, bilirubin, ketones, haemoglobin, proteins, nitrite, leucocytes and glucose, the agreement varied between substantial to excellent. However, the pH test always showed moderate agreement. This may be attributed to the fact that the urine dipstick used by H-500, H-800 and AX-4280 had more set points in the pH detection range.

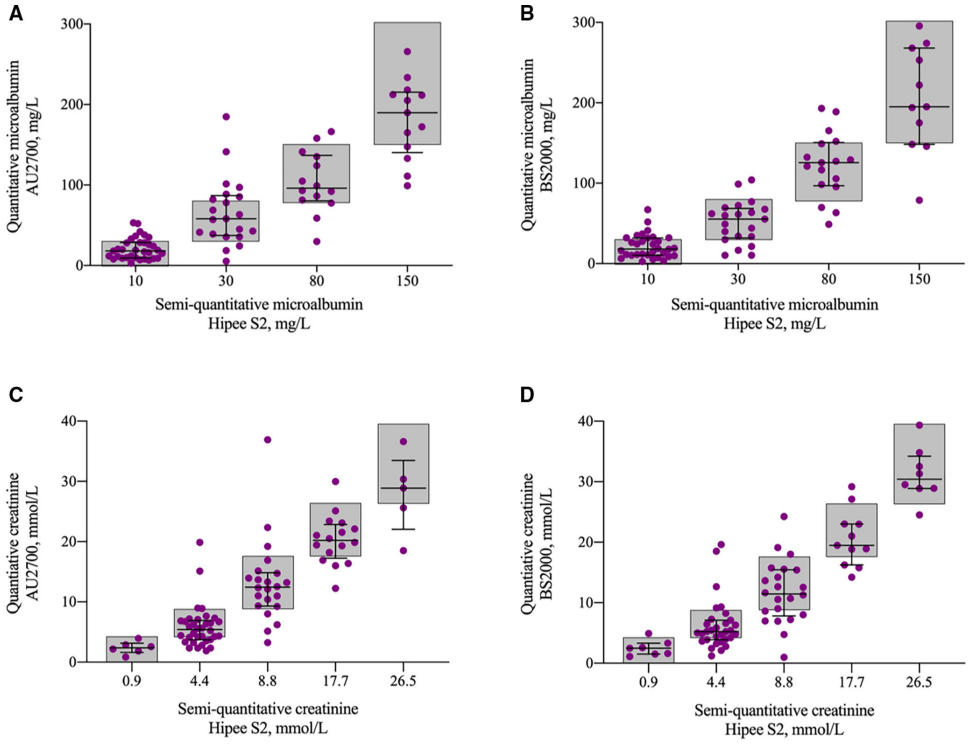

Figure 2 Comparison of urinary parameter determination between semiquantitative and quantitative assays. The purple circle shows the quantitative measurement. The black line represents median with IQR. The grey area represents the semiquantitative measurement range. (A) Comparison of microalbumin between Hipee S2 and AU2700; (B) Comparison of microalbumin between Hipee S2 and BS2000; (C) Comparison of creatinine between Hipee S2 and AU2700; (D) Comparison of creatinine between Hipee S2 and BS2000.

The three analysers increased 0.5 pH unit per set point in the range of 5.0 to 9.0 pH unit. Conversely, Hipee S2 increased 1.0 pH unit per set point in the same pH range. Consequently, the agreement between the pH obtained by Hipee S2 and those measured by the other three analysers was not always corresponding.

The agreement of Hipee S2 in terms of SG was substantial when compared with H-500 and H-800, but was only moderate when compared with AX-4280. This could be due to differences in the SG measurement principles among different analysers. To detect the SG of urine samples, AX-4280 used refractometry, which is a method based on light refraction. Here, the refractivity of a solution was an indirect measurement of the total solute concentration.[16] In contrast, the other analysers relied on the correlation between the ionic solute concentration and urine SG to provide an indirect measurement. The principle was that the electrolyte in urine samples reacted with the carboxyl of polymethylvinylacetaldehyde or maleic acid in the dipstick to release hydrogen ions. Hydrogen ions turned the indicator of the dipstick to blue, and the SG value was inferred according to the extent of discolouration.[22] In previous studies that compared ionic environmental alteration and refractometry for the detection of urine SG, low correlations were reported, which is in agreement with our findings.[23] Urine SG measurements by the ionic

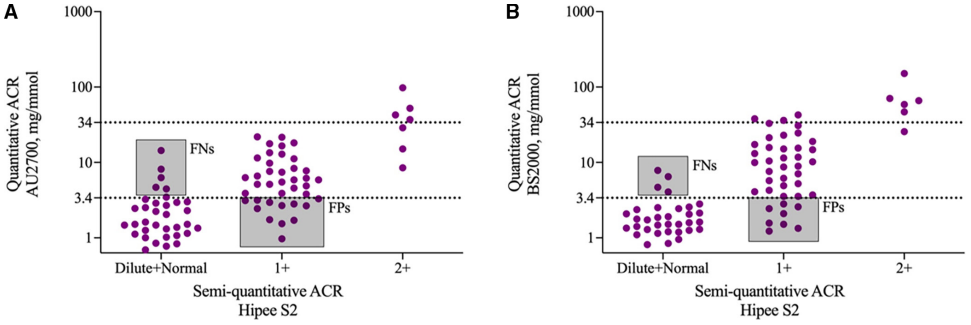

Figure 3 Comparison of ACR between semiquantitative and quantitative assays. The purple circle shows the quantitative measurement. The dot-dashed lines represent the threshold of microalbuminuria (3.4 mg/mmol) and macroalbuminuria (34 mg/mmol), respectively. FNs represent false negative results while FPs represent false positive results obtained by Hipee S2 system. (A) Comparison of ACR between Hipee S2 and AU2700; (B) Comparison of ACR between Hipee S2 and BS2000. ACR, albumin-to-creatinine ratio; FNs, false negative; FPs, false positive.

Table 7 Diagnostic accuracy of semiquantitative ACR for albuminuria

	Quantitative ACR		
Semiquantitative ACR	Non-albuminuria	Albuminuria	Total
Centre 1			
Negative, n (%)	29 (36.3)	5 (6.3)	34 (42.5)
Positive, n (%)	12 (15)	34 (42.5)	46 (57.5)
Total, n (%)	41 (51.3)	39 (48.8)	80 (100)
Sensitivity, % (95% CI)	87.2 (72.6 to 95.7)		
Specificity, % (95% CI)	70.7 (54.5 to 83.9)		
PPV, % (95% CI)	73.9 (63.4 to 85.3)		
NPV, % (95% CI)	85.3 (71.4 to 93.1)		
Centre 2			
Negative, n (%)	29 (36.3)	4 (5)	33 (41.3)
Positive, n (%)	8 (10)	39 (48.8)	47 (58.8)
Total, n (%)	37 (46.3)	43 (53.8)	80 (100)
Sensitivity, % (95% CI)	90.7 (77.9 to 97.4)		
Specificity, % (95% CI)	78.4 (61.8 to 90.2)		
PPV, % (95% CI)	83.0 (72.4 to 90.1)		
NPV, % (95% CI)	87.9 (73.7 to 94.9)		

ACR, albumin-to-creatinine ratio; NPV, negative predictive value; PPV, positive predictive value.

environmental alteration principle have been used as an easy, rapid, non-invasive and inexpensive way to interpret a patient's hydration status.[16] However, these results should be carefully interpreted, considering the differences in comparison with the refractometry. In addition, AX4280 had a wider range of 1.000–1.050 to measure SG, as contrasted with 1.005–1.030 for other urinalysis systems. This may also be one of the contributing factors to moderate agreement.

Agreements of microalbumin and creatinine were evaluated by comparing the semiquantitative results obtained by Hipee S2 with the quantitative results obtained using automatic biochemical analysers because the urine dipstick measurements of microalbumin and creatinine were carried out in none of the three centres. A comparison between the semiquantitative measurements and those obtained by quantitative methods showed strong correlation for microalbumin or creatinine. Representation of data as scatter dot plots also demonstrated good agreement between the semiquantitative and quantitative data groups obtained by the two laboratories (centre 1 and centre 2) through all measurement ranges for both microalbumin and creatinine. These results suggest that using the semiquantitative assay with Hipee S2 to detect microalbumin and creatinine can also provide good inspection quality comparing to quantitative assays.

The ACR is a well-established marker of albuminuria and now can be conveniently performed using a POCT urine dipstick analyser with on-site results available within several minutes. Our study showed that the sensitivity of semiquantitative ACR to detect albuminuria was higher than specificity, and the NPV was higher than PPV. This was in keeping with other previous studies in that PPV ranged from 46% to 82%, while NPV was higher than PPV ranging from 71% to 99% in all studies.[24–31] These findings suggest that a negative result measured by the POCT urinalysis device would be useful for excluding albuminuria, but any positive result would need to be confirmed with a quantitative ACR test. It seems to offer an opportunity to early screen for kidney disease.

This study had several limitations. The first was the lack of evaluation of urinary calcium testing. Because the detection of urinary calcium was not performed in all of the three laboratories selected in this study. Another limitation was a small urine sample size on comparing the agreement between semiquantitative and quantitative results. A larger sample size study on early screening for albuminuria with the POCT semiquantitative ACR is currently conducting in one of the three clinical laboratories. The third limitation was that this study took place by professional technicians in clinical laboratories of tertiary care hospitals and did not explore the views of multidisciplinary and diverse group of participants in other settings. Considering the application of POCT devices in different scenarios, further research involving other key stakeholders, such as clinicians, nurses and individual users, would be very informative.

In conclusion, Hipee S2 POCT urine analyser showed acceptable analytical performance as a semiquantitative method. It serves as a convenient alternate device for clinicians and individual users for urinalysis and health management. In addition, the POCT semiquantitative

ACR would be useful in screening for albuminuria. However, we also observed significant interference of the haemoglobin test when the ascorbate levels exceeded 1 g/L in urine samples; therefore, caution is warranted while interpreting the results.

Contributors QZ designed and participated in all stages of the study. GW participated in study design, data analysis and writing of the manuscript. XZ participated in sample collection, data analysis and review of the manuscript. JS participated in sample collection, data analysis. All authors read and approved the final manuscript. QZ is responsible for the overall content as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Branch of Tianjin Third Central Hospital Ethics Committee (2019001). Residual specimens after routine clinical testing without any specific sampling were used in the study. An anonymised database provided analytical support. Therefore, informed consent was waived by Branch of Tianjin Third Central Hospital Ethics Committee.

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REFERENCES

1 Suzuki Y, Katayama K, Ishikawa E, *et al*. Granulomatous interstitial nephritis due to chronic lymphocytic leukemia: a case report. *BMC Nephrol* 2017;18:348.
2 Yang R, Cheng W, Chen X, *et al*. Color space transformation-based smartphone algorithm for colorimetric urinalysis. *ACS Omega* 2018;3:12141–6.
3 Vashist SK, Luppa PB, Yeo LY, *et al*. Emerging technologies for next-generation point-of-care testing. *Trends Biotechnol* 2015;33:692–705.
4 Luppa PB, Müller C, Schlichtiger A, *et al*. Point-Of-Care testing (POCT): current techniques and future perspectives. *Trends Analyt Chem* 2011;30:887–98.
5 Schot MJC, van Delft S, Kooijman-Buiting AMJ, *et al*. Analytical performance, agreement and user-friendliness of six point-of-care testing urine analysers for urinary tract infection in general practice. *BMJ Open* 2015;5:e006857.
6 Hunt M, Miguez S, Dukas B, *et al*. Efficacy of Zemedy, a mobile digital therapeutic for the self-management of irritable bowel syndrome: crossover randomized controlled trial. *JMIR Mhealth Uhealth* 2021;9:e26152.
7 Ozcan A. Mobile phones democratize and cultivate next-generation imaging, diagnostics and measurement tools. *Lab Chip* 2014;14:3187–94.
8 Vashist SK, Mudanyali O, Schneider EM, *et al*. Cellphone-based devices for bioanalytical sciences. *Anal Bioanal Chem* 2014;406:3263–77.
9 Clinical and Laboratory Standards Institute. Evaluation of precision of quantitative measurement procedures; Approved guideline-third edition, EP5-A3. Wayne, PA CLSI; 2014. https://clsi.org/media/3396/ep05a3e_sample.pdf
10 Clinical and Laboratory Standards Institute. Preliminary evaluation of quantitative clinical laboratory measurement procedures; Approved guideline-third edition, EP10-A3. Wayne, PA CLSI; 2014. https://clsi.org/media/1434/ep10a3amd_sample.pdf
11 Clinical and Laboratory Standards Institute. Interference testing in clinical chemistry; Approved guideline-third edition, EP7-A3. Wayne, PA CLSI; 2018. https://clsi.org/media/2235/ep07ed3_sample.pdf
12 Rota C, Biondi M, Trenti T. Evaluation of Aution max AX-4030 and 9UB Uriflet, 10PA Aution sticks urine dipsticks in the automated urine test strip analysis. *Clin Chem Lab Med* 2011;50:139–46.
13 Gambke B, Kouri T, Kutter D, *et al*. Multicentre evaluation of the urine analyser Miditron Junior. *Scand J Clin Lab Invest* 1997;57:605–11.
14 Shen C, Jiang B, Yang Q, *et al*. Mobile Apps for Drug–Drug interaction checks in Chinese app stores: systematic review and content analysis. *JMIR Mhealth Uhealth* 2021;9:e26262.
15 Hoffmann P, Hoffmann C, Ziebig R, *et al*. Evaluation of the iChem® Velocity™ urine chemistry analyzer in a hospital routine laboratory. *Clin Chem Lab Med* 2011;49:509–13.
16 Ko K, Kwon M-J, Ryu S, *et al*. Performance evaluation of three URiSCAN devices for routine urinalysis. *J Clin Lab Anal* 2016;30:424–30.
17 Sánchez-Mora C, Acevedo D, Porres MA, *et al*. Comparison of automated devices UX-2000 and SediMAX/AutionMax for urine samples screening: a multicenter Spanish study. *Clin Biochem* 2017;50:714–8.
18 Zweig MH, Jackson A. Ascorbic acid interference in reagent-strip reactions for assay of urinary glucose and hemoglobin. *Clin Chem* 1986;32:674–7.
19 Nikolac Gabaj N, Miler M, Unic A, *et al*. Ascorbic acid in urine still compromises urinalysis results. *Ann Clin Biochem* 2020;57:64–8.
20 Unic A, Nikolac Gabaj N, Miler M, *et al*. Ascorbic acid-A black hole of urine chemistry screening. *J Clin Lab Anal* 2018;32:e22390.
21 Clinical and Laboratory Standards Institute. Measurement procedure comparison and bias estimation using patient samples; Approved duideline—third edition, EP9-A3. Wayne, PA CLSI; 2013. https://clsi.org/media/2293/ep09ed3ce_sample.pdf
22 Burkhardt AE, Johnston KG, Waszak CE, *et al*. A reagent strip for measuring the specific gravity of urine. *Clin Chem* 1982;28:2068–72.
23 Dorizzi RM, Caputo M. Measurement of urine relative density using refractometer and reagent strips. *Clin Chem Lab Med* 1998;36:925–8.
24 McTaggart MP, Price CP, Pinnock RG, *et al*. The diagnostic accuracy of a urine albumin-creatinine ratio point-of-care test for detection of albuminuria in primary care. *Am J Kidney Dis* 2012;60:787–94.
25 Graziani MS, Gambaro G, Mantovani L, *et al*. Diagnostic accuracy of a reagent strip for assessing urinary albumin excretion in the general population. *Nephrol Dial Transplant* 2009;24:1490–4.
26 Guy M, Newall R, Borzomato J, *et al*. Diagnostic accuracy of the urinary albumin: creatinine ratio determined by the CLINITEK Microalbumin and DCA 2000+ for the rule-out of albuminuria in chronic kidney disease. *Clin Chim Acta* 2009;399:54–8.
27 Le Floch JP, Marre M, Rodier M, *et al*. Interest of Clinitek Microalbumin in screening for microalbuminuria: results of a multicentre study in 302 diabetic patients. *Diabetes Metab* 2001;27:36–9.
28 Croal BL, Mutch WJ, Clark BM, *et al*. The clinical application of a urine albumin:creatinine ratio point-of-care device. *Clin Chim Acta* 2001;307:15–21.
29 Nah E-H, Cho S, Kim S, *et al*. Comparison of urine albumin-to-creatinine ratio (ACR) between ACR strip test and quantitative test in prediabetes and diabetes. *Ann Lab Med* 2017;37:28–33.
30 Oyaert M, Delanghe JR. Semiquantitative, fully automated urine test strip analysis. *J Clin Lab Anal* 2019;33:e22870.
31 Currin SD, Gondwe MS, Mayindi NB, *et al*. Diagnostic accuracy of semiquantitative point of care urine albumin to creatinine ratio and urine dipstick analysis in a primary care resource limited setting in South Africa. *BMC Nephrol* 2021;22:103.