RESEARCH ARTICLE

Evaluation of the URiSCAN 2 ACR Strip to estimate the urine albumin/creatinine ratios

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Background: The urine albumin/creatinine ratio (ACR) test is used to screen patients with chronic diseases, such as diabetes, hypertension and cardiovascular diseases that put them at an increased risk of developing kidney disease. Here, we evaluated the performance of the URiSCAN 2 ACR Strip (URiSCAN; YD diagnostics, Yongin, Korea), a semiquantitative point-of-care testing (POCT) assay, and we compared to an existing POCT assay and a quantitative assay.

Materials and Methods: A total of 1,020 random urine specimens were analyzed using the semiquantitative URiSCAN 2 ACR Strip and semiquantitative CLINITEK Microalbumin 2 Strip (CLINITEK; Siemens, New York, USA). We evaluated the precision of the URiSCAN 2 ACR Strip and compared the results of the ACR obtained from URiSCAN to those of CLINITEK with the quantitative results of a quantitative assay as a reference.

Results: The precision evaluation of the URiSCAN revealed a range between the cutoff (C_{50})–20% and C_{50} +20% bounds, the C_5 – C_{95} interval, with 85.8% confidence. URiSCAN and CLINITEK showed sensitivity and specificity of 87.7% and 72.2%, and 90.2% and 83.0%, respectively. The concordance rates of URiSCAN with CLINITEK and the quantitative assay were 75.6% and 79.1%, respectively. The concordance rate in the abnormal range (≥ 30 mg/g) between URiSCAN and the quantitative assay were higher than that between CLINITEK and the quantitative assay (78.8% vs 75.4%).

Conclusions: URiSCAN showed good precision and comparable sensitivity with lower specificity than those of CLINITEK.

KEYWORDS

albumin/creatinine ratio, kidney disease, moderately increased albuminuria, point-of-care testing, random urine

1 | INTRODUCTION

The most common risk factors of chronic kidney disease are diabetes and hypertension.¹ Preventing chronic kidney disease and early diagnosis of kidney damage are an important goal in primary health care. According to the Korea Health Insurance Review and Assessment Service, the number of Korean patients with chronic kidney disease

increased by 37.1%, and total medical expenses increased by 47.6%, from 2006 to 2010. The average annual growth rate for the 5-year period is of about 8.2% and 10.2%, respectively. According to the 2012 data, the total expenses for medical treatment of patients with end-stage renal failure is similar to those of all cancer patients, and the expenses of medical treatment per patient are the highest among all diseases.^{2,3} Therefore, in patients with a high potential risk of kidney

function, it is essential to periodically monitor the kidney function and to treat the progressive slowing down of the renal function as early as possible.^{1,4-8} An increased excretion of urinary protein, especially albumin, is an early finding of renal damage, and measurement of urinary albumin has been a useful marker for diagnosis and follow-up of renal failure with estimated glomerular filtration rate.^{4,9} The urine albumin/creatinine ratio (ACR) test is also used to screen patients with chronic diseases that put them at an increased risk of developing kidney disease. ACR is a surrogate marker of urine albuminuria.⁶ A quantitative evaluation of moderately increased albuminuria requires the use of expensive biochemical instruments and reagents, making it difficult to perform in small or medium-sized clinics. Even if an evaluation has been performed, it needs to be sent to a central clinical laboratory, so it is difficult to conduct an early diagnosis and frequent monitoring.

As such, the availability of point-of-care testing (POCT) instruments is important. POCT tools are rapidly expanding, and the availability of quick results appears to improve patient outcomes.^{10,11} Hence, evidence for POCT instruments of analytical quality is necessary to achieve good patient outcomes. In this study, we evaluated the performance of the URiSCAN 2 ACR Strip (URiSCAN; YD diagnostics, Yongin, Korea), a semiquantitative point-of-care testing (POCT) assay, and compared its results to those of an existing POCT assay and a quantitative assay.

2 | MATERIALS AND METHOD

2.1 | Specimens from patients

We analyzed random, midstream urine specimens among those requested for quantitative ACR tests from March 1, 2016, to November 15, 2016 at the Department of Laboratory Medicine, Kangbuk Samsung Hospital. Urine specimens were selected so that the same number of test results per each albumin grade (negative, 1+, 2+, and 3+) could be obtained using a quantitative analyzer, Cobas Integra 800 (Roche Diagnostics, Basel, Switzerland) according to CLSI EP12-A2.¹² All tests were completed within two hours after urine collection, and a total of 1020 specimens were selected by applying the following exclusion criteria:

1. showing positive for hemoglobin or myoglobin (≥ 5 mg/dL);
2. with a high urine specific gravity (SG ≥ 1.030);
3. with a urine pH ≥ 9.0 ;
4. specimens showing positive for vitamin C (>100 mg/dL);
5. specimens showing positive for bilirubin (>5 mg/dL).

2.2 | Assays

2.2.1 | Quantitative assay

Urine albumin and creatinine were measured with the quantitative Tina-quant Albumin Gen.2 and COBAS INTEGRA Creatinine Jaffe Gen.2 (Roche Diagnostics, Basel, Switzerland) using a quantitative

analyzer, Cobas Integra 800. Urine albumin was measured using an immunoturbidimetric principle and its analytical range was 3.0–210.0 mg/L. Urine creatinine was quantitated using the Jaffe-kinetic method, and its analytical range was 0.31–367 mg/dL. Specimens showing concentrations above the analytical measurement limit were repeatedly measured after 1:10 dilution with normal saline.

2.2.2 | Semiquantitative assays

Urine albumin and creatinine were measured via the colorimetric method using sulfonephthalein dye-binding and creatinine-metal complex in the URiSCAN 2 ACR Strip and CLINITEK Microalbumin 2 Strip (CLINITEK; Siemens, New York, NY, USA), respectively. The color change made by the reaction was measured with the corresponding analyzers, URiSCAN New Pro (YD diagnostics, Yongin, Korea) and Clinitek status plus (Siemens). The albumin-to-creatinine ratio (albumin/creatinine, ACR) was calculated according to the unique interpretation criteria of each manufacturer. URiSCAN classifies the results of the albumin concentration into four categories (0, 30, 80, and 150 mg/L), and the results of the creatinine concentration into five categories (10, 50, 100, 200, and 300 mg/dL), which allows for semiquantitative estimation. It finally estimates the ACR as three categories (<30 , 30–300, and >300 mg/g).

CLINITEK classifies the results of albumin, creatinine, and ACR using the same categories as those of URiSCAN. The normal value of ACR was defined as <30 mg/g,¹³ and abnormal values were defined as 30–300 mg/g and >300 mg/g in both strips.

2.3 | Precision of the URiSCAN 2 ACR Strip

To evaluate the precision, albumin and creatinine solutions of three concentrations (cutoff, C_{50} ; $C_{50}-20\%$; $C_{50}+20\%$) using quality control materials (Bio-rad, Irvine, USA) were prepared. Each concentration was repeatedly measured 40 times using URiSCAN according to the Clinical and Laboratory Standards Institute (CLSI) EP12-A2; User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline. To verify the good precision of a qualitative reagent, we should prove that C_5 – C_{95} interval should be included within the concentration range between $C_{50}-20\%$ and $C_{50}+20\%$ and concentrations 20% or more away from C_{50} should yield consistent results. C_5 is the concentration at which 5% of the tests showed positive and 95% showed negative results when many replicates of a single sample at the concentration are tested. C_{95} is the concentration at which 95% of tests showed positive and 5% showed negative results.

2.4 | Concordance among assays

Quantitative albumin concentration measurements of <20 , ≥ 20 – <56 , ≥ 56 – <116 , and ≥ 116 mg/L were assigned categories defined by negative, 1+, 2+, and 3+ according to semiquantitative assay grades, respectively. Quantitative creatinine concentration measurements of <30 , ≥ 30 – <81 , ≥ 81 – <181 , ≥ 181 – <281 , and ≥ 281 mg/dL were matched to categories defined by negative, 1+, 2+, 3+, and 4+, according to

semiquantitative assay grades, respectively. Quantitative ACR results of <30, 30-300, and >300 mg/g were regarded as normal, moderately increased albuminuria, and proteinuria, respectively. We compared the grades of albumin, creatinine, and ACR results of the URiSCAN to those of CLINITEK. The concordance rate between the quantitative and each semiquantitative method was also evaluated after converting the quantitative results to semiquantitative grades.

2.5 | Statistical analysis

Sensitivity, specificity, positive predictability, negative predictability, and likelihood ratios with 95% confidence interval were calculated for each semiquantitative method based on the quantitative assay results. STATA version 14.0 (StataCorp LP, College Station, TX, USA) was used for the calculation.

3 | RESULTS

3.1 | Precision of the URiSCAN 2 ACR Strip

The C_{50} concentrations were albumin concentrations of 20 mg/L and creatinine concentrations of 30 mg/dL. Tests with $C_{50}+20\%$ concentrations were performed 40 times and 40/40 (100%) tests were all positive. Tests with $C_{50}-20\%$ concentrations were also performed, and 40/40 (100%) tests showed negative. The range between $C_{50}-20\%$ and $C_{50}+20\%$ bounded the C_5-C_{95} interval with 85.8% confidence.

3.2 | Comparison of the quantitative and semiquantitative method

The distribution of albumin concentrations of 1,020 random urine specimens were measured using a quantitative assay as follows: 300 (29.4%) specimens of < 20 mg/L, 240 (23.5%) specimens of 20-56 mg/L, 240 (23.5%) specimens of 56-116 mg/L, and 240 (23.5%) specimens of > 116 mg/L. The proportion of specimens with positive albuminuria was 70.6%. With URiSCAN, there were 393 (38.5%) specimens with albumin concentration of 0 mg/L (negative), 197 (19.3%) specimens of 30 mg/L (1+), 144 (14.1%) specimens of 80 mg/L (2+) and 286 (28.0%) specimens of 150 mg/L (3+). The proportion of specimens with positive albuminuria was 60.5%, which was lower than that of the quantitative assay. On the other hand, with the semiquantitative CLINITEK, there were 237 (23.2%) specimens with albumin concentration of <10 mg/L (negative), 262 (25.7%) specimens of 30 mg/L (1+), 295 (28.9%) specimens of 80 mg/L (2+) and 226 (22.2%) specimens of 150 mg/L (3+). The proportion of specimens with positive albuminuria was 76.8%, which was higher than that of the quantitative assay and URiSCAN ($P<.0001$, $P<.0001$).

The concordance rates between the URiSCAN and the quantitative assay on the albumin and creatinine were 65.7% (95%CI: 62.7%-68.7%) and 53.4% (95%CI: 50.1%-56.3%), respectively. For ACR, the overall concordance rate was 75.6% (95%CI: 72.8%-78.2%), and that for the ACR $\geq 1+$ (≥ 30 mg/g) grades was 78.8% (95%CI: 75.1%-82.3%) (Table 1, Figure 1). False-negative ACR results with URiSCAN

TABLE 1 Comparison of the ACR results (n=1020) between the semiquantitative assays and the quantitative assay

Semiquantitative assays	Quantitative assay		
	<30 mg/g	30-300 mg/g	>300 mg/g
URiSCAN 2 ACR Strip			
<30 mg/g	361	63	1
30-300 mg/g	139	307	5
>300 mg/g	0	41	103
CLINITEK Microalbumin 2 Strip			
<30 mg/g	451	49	2
30-300 mg/g	84	301	16
>300 mg/g	1	61	91

Bold characters: number of concordant results. Abbreviations: ACR, albumin-to-creatinine ratio; CI, confidence interval.

were observed in 139 cases with concentrations of 6.5-29.98 (median; 19.01) mg/g, and false-positive ACR results were observed in 64 cases with concentrations of 30.89-550.93 (median, 64.95) mg/g. The concordance rates between CLINITEK and the quantitative assay for albumin and creatinine were 75.2% (95%CI: 72.4-77.8%) and 62.6% (95%CI: 59.6-65.6%), respectively. For ACR, the overall concordance rate was 79.1% (95%CI: 76.5-81.6%), and for the ACR $\geq 1+$ (≥ 30 mg/g) grades was 75.4% (95%CI: 71.4-79.0%) (Table 1, Figure 2). False-negative ACR results with CLINITEK were observed in 85 cases with concentrations of 6.05-29.98 (median; 20.81) mg/g, and false-positive results were observed in 51 with concentrations of 30.76-550.93 (median; 63.08) mg/g. The sensitivities, specificities, positive predictabilities, negative predictabilities for URiSCAN and the CLINITEK are described in Table 2.

3.3 | Comparison of the ACR results between the URiSCAN 2 ACR Strip and the CLINITEK microalbumin 2 Strip

The overall concordance rate of the ACR results between the two semiquantitative POCT assays was 75.3% (95%CI: 72.5%-77.9%). Among 107 specimens showing discrepancies in the results between the two assays, 105 specimens showed ACR of 30-300 mg/g with URiSCAN and ACR of < 30 mg/g using CLINITEK. Among 105 specimens, an ACR of less than 30 mg/g was observed in 74 specimens (7.25% of total specimens) using a quantitative assay, which meant that 74 results were false-positives using URiSCAN. The range of quantitative ACR values of the false-positive results varied from 6.5 to 28.84 (median; 16.76) mg/g. The remaining two specimens showed concentrations of 443.16 mg/g and 34.27 mg/g, respectively. The ACR $\geq 1+$ (≥ 30 mg/g) grade concordance between the two assays was 73.8% (95%CI: 70.0-77.4%), which was similar to the overall concordance rate. Among 60 specimens with an ACR in a range of 30-300 mg/g with CLINITEK and of < 30 mg/g with URiSCAN, only 20 specimens showed a value of less than 30 mg/g using the quantitative assay. That is, false-negative results with URiSCAN were observed in

FIGURE 1 Comparison of the ACR results (n=1020) between the URiSCAN and the quantitative assay. Abbreviation: ACR, albumin/creatinine ratio

FIGURE 2 Comparison of the ACR results (n=1020) between the CLINITEK and the quantitative assay. Abbreviation: ACR, albumin/creatinine ratio

TABLE 2 Sensitivities, specificities, positive predictabilities, negative predictabilities, and likelihood ratios of the URiSCAN and the CLINITEK

	URiSCAN 2 ACR Strip	CLINITEK Microalbumin 2 Strip
Sensitivity (%)	87.7 (95%CI: 84.6-90.4%)	90.2 (95% CI: 87.3-92.6%)
Specificity (%)	72.2 (95%CI: 68.0-76.1%)	83.0 (95% CI: 79.4-86.2%)
Positive predictability (%)	76.6 (95%CI: 73.0-80.0%)	84.7 (95% CI: 81.4-87.6%)
Negative predictability (%)	84.9 (95%CI: 81.2-88.2%)	89.1 (95% CI: 85.9-91.7%)
Positive likelihood ratio	3.15 (95%CI: 2.73-3.65)	0.17 (95% CI: 0.14-0.22)
Negative likelihood ratio	5.31 (95%CI: 4.36-6.45)	0.12 (95% CI: 0.10-0.15)

ACR, albumin-to-creatinine ratio; CI, confidence interval.

TABLE 3 Comparison of ACR results (n=1020) between the URiSCAN 2 ACR Strip and the CLINITEK Microalbumin 2 Strip

	CLINITEK Microalbumin 2 Strip		
	<30 mg/g	30-300 mg/g	>300 mg/g
URiSCAN 2 ACR Strip			
<30 mg/g	359	60	6
30-300 mg/g	105	304	42
>300 mg/g	2	37	105

Bold characters: number of concordant results.
ACR, albumin-to-creatinine ratio; CI, confidence interval.

40 specimens (3.92% of total specimens). In addition, six specimens showed results of an ACR greater than 300 mg/g with CLINITEK and less than 30 mg/g with URiSCAN. These specimens showed quantitative ACR concentrations between 75.42 and 204.37 (median; 112.17) mg/g, which were also false-negative results for URiSCAN (Table 3).

4 | DISCUSSION

Moderately increased albuminuria is considered as a screening marker for kidney damage, and it is used as the first clinical indicator for diabetic kidney disease.¹⁴⁻¹⁶ The 2015 American Diabetes Association (ADA) guideline recommends at least an annual albuminuria screen with a random spot urine sample for urine ACR in patients with 5 years of diabetes,¹⁷ and a POCT that can obtain ACR results within a few minutes is also available.

When compared to the CLINITEK, URiSCAN showed a higher sensitivity with quantitative assay in the specimens with ACR $\geq 1+$ (≥ 30 mg/g) grades (78.8% vs 75.4%) than that in all specimens (75.6% vs 79.1%), which was similar to the comparison between URiSCAN and the quantitative assay. Compared to the previous evaluation,¹⁷ the gaps in the sensitivity and specificity between CLINITEK and URiSCAN both decreased, although the specificity was reversed. In the cases with false-positive ACR specimens, URiSCAN measured urinary albumin one or two grades higher than those with CLINITEK, and the creatinine grade measured by URiSCAN was lower than with CLINITEK. These higher albumin grades with a lower creatinine grade might result in false-positive ACR results.

In a study evaluating CLINITEK, a lower sensitivity (83.2% vs 90.2%) and similar specificity (80.0% vs 83.0%) were observed compared to our results, which might also be due to the lower positive rate of albuminuria (20.2% vs 70.6%).¹¹ In addition, 64 false-negatives of URiSCAN 2 ACR Strip and 51 false-negatives of CLINITEK Microalbumin 2 Strip had ACR values higher than the detection limit (0.82 mg/g) from the quantitative assay.

In this study, the overall concordance rate between the URiSCAN and the quantitative assay on ACR was 75.6%, and that for ACR $\geq 1+$ (≥ 30 mg/g) grades was 78.8%, and these results were much improved since the first evaluation totaling 219 urine specimens. In the first evaluation, the overall concordance rate was 74.0%, and that for ACR $\geq 1+$ grades was 45.9%. In addition, the analytical sensitivity also improved (87.7% vs 45.9%), but the specificity decreased (72.2% vs 84.8%).¹⁸ Although the above changes might be partially a result of a higher positive rate of albuminuria (70.6% vs 27.9%), the improvement in the strips may result in a dramatic increase in the sensitivity. URiSCAN changed the formulation to decrease the lot-to-lot variation and reduce the effect of urine buffering capacity and urine pH. This improvement allows a reduction in the false-negative results and an improvement in the sensitivity over the previous strip version, while the frequency of false-positives increased due to a low specificity. Semiquantitative ACR assays, including URiSCAN used in this study, measure moderately increased albuminuria or severely increased albuminuria with earlier and user-friendly convenience than sending to the main laboratory. The response time for URiSCAN is 90 seconds per test, which is longer than that of CLINITEK at 48 seconds per test. However, the total number of tests per hour is 720 for URiSCAN and 72 for CLINITEK. While only one specimen can be loaded during measurement in CLINITEK, continuous loading of specimens is possible during measurement in URiSCAN. Therefore, final throughput of URiSCAN is much more than that of CLINITEK.

This convenience and speed are expected to be useful in health care centers, major medical centers or medium-sized clinics performing more than 50 tests per hour. In particular, patients living in regions with little access to hospitals could use this ACR Strip as a self-screening test. In spite of advantages of the URiSCAN, any error in the measurement can be magnified and followed by an underestimation or overestimation, because semiquantitative ACR assays do not report albumin and creatinine levels as quantitative values but as grades.

In summary, URiSCAN showed a comparable sensitivity and lower specificity than CLINITEK. Since URiSCAN showed a relatively low positive predictive value and a high negative predictive value, the frequency of false-positive results was high. Therefore, URiSCAN would be appropriate as a screening test to exclude albuminuria, but additional tests will be necessary to confirm albuminuria. Also, it is thus necessary to improve the test strips to decrease the false-positive results by improving the specificity for albumin.

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