National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute (U01-DK-66143, U01-DK-66174, U01-DK-82194, U01-DK-66116). The CKiD Web site is located at http://www.statepi.jhsph.edu/ckid. Our sincere thanks to the CKiD steering committee and staff of the DCC, including Matthew Matheson and Judith Jerry Fluker for making this ancillary pilot study possible.

SUPPLEMENTARY MATERIAL

Supplementary Material. Study methods, study design, missing value imputation and statistical analyses, and supplementary references.

Table S1. Significant differences in plasma metabolites between chronic kidney disease subgroups (CKD stage and etiology; significance by *post hoc* testing $P < 0.05$).

Table S2. Significant differences in plasma metabolite ratios between chronic kidney disease subgroups (CKD stage and etiology; significance by *post hoc* testing $P < 0.05$).

Figure S1. Schematic of data collection methodologies using the Biocrates p180 kit, including (A) flow-injection MS/MS and (B) LC-MS/MS.

Figure S2. Schematic depicting quantitative methodologies used for the Biocrates p180 kit using (A) flow-injection analysis and (B) LC-MS/MS analysis.

Figure S3. (A–H) Boxplots of plasma metabolites and their ratios that differ between chronic kidney disease subgroups by stage and etiology (*post hoc* $P < 0.05$).

Supplementary material is linked to the online version of the paper at www.kireports.org.

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Performance of the Automated Urinalysis in Diagnosis of Proliferative Glomerulonephritis

To the Editor: The examination of urine to diagnose disease is an age-old practice, dating back thousands of years in primitive forms, and arguably represents

Table 1. Baseline characteristics of study cohort

Characteristic	PGN (n = 134)	Other kidney disease (n = 378)	*P* value
Age (yr)	50.5 ± 17.5	55.1 ± 15.2	<0.01
Female (%)	46.3	46.3	0.99
Race (%)			<0.01
White	66.7	69.3	
Black	11.6	21.4	
Other	21.7	9.3	
Median serum creatinine (μmol/l)	138 (97–203)	144 (88–214)	0.73
Median eGFR (ml/min per 1.73 m^2)	47.6 (29.3–69.2)	42.5 (24.8–77.4)	0.54
Median proteinuria (g/g creatinine)	1.8 (0.8–3.7)	2.1 (0.5–5.5)	0.69
Median urine RBC count per HPF	18 (6–60)	2 (1–10)	<0.01
Urine dipstick blood (%)			<0.01
None or trace	8.3	43.6	
1+	8.3	18.4	
2+	21.8	17.8	
3+	61.6	20.2	
DM (%)	10.5	28.3	<0.01
HTN (%)	43.3	56.4	<0.01
ACEI/ARB (%)	37.3	47.1	0.05
Indications for biopsy[a] (%)			<0.01
Proteinuria	67.9	52.9	
Hematuria	46.3	16.9	
Abnormal GFR	50.8	54.5	
Most common primary clinicopathologic diagnoses	IgA nephropathy (n = 74) ANCA-associated vasculitis (n = 19) Proliferative lupus nephritis (n = 11) Immune complex GN (n = 11) Cryoglobulinemic GN (n = 4)	Diabetic nephropathy (n = 63) Membranous nephropathy (n = 38) Secondary FSGS (n = 35) Advanced chronic changes (n = 29) Vascular sclerosis (n = 26)	

ACEI, angiotensin-converting enzyme inhibitor; ANCA, antineutrophil cytoplasmic antibody; ARB, angiotensin II receptor blocker; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; GN, glomerulonephritis; HPF, high-power field; HTN, hypertension; PGN, proliferative glomerulonephritis.
[a]Individual patients may have more than 1 indication for biopsy.

the genesis of laboratory medicine.[1] Microscopic evaluation of urine was introduced in the 19th century, and in the 20th century became a cornerstone of the nephrologist's armamentarium for diagnosing kidney disease. Since the introduction of automated urine analyzers, manual examination of the urine sediment has rapidly fallen out of favor among clinicians.[2–4] Despite its central role in the evaluation of patients with kidney disease, limited data are available in the literature on the test performance characteristics of the modern urinalysis (UA) as reported by laboratories using automated analyzers.[5] In a cross-sectional analysis, we studied how well automated UAs distinguished proliferative glomerulonephritis (PGN) from other forms of kidney disease in a cohort of adult patients who had not yet been initiated on immunosuppressive therapy, and for whom clinicopathologic diagnoses were uniformly adjudicated by native kidney biopsies.

RESULTS

A total of 512 patients were included in the analysis, 511 of whom had automated urine test strip results available and 421 of whom had urine red blood cell (RBC) counts available within 30 days before undergoing native kidney biopsy (Supplementary Figure S1). Of the 512 patients included in the analysis, 134 had PGN. The most common PGN diagnoses were IgA nephropathy (n = 74), antineutrophil cytoplasmic antibody–associated vasculitis (n = 19), and proliferative forms of lupus nephritis (n = 11). The most common non-PGN diagnoses were diabetic nephropathy (n = 63), membranous nephropathy (n = 38), and secondary focal segmental glomerulosclerosis (n = 35) (Supplementary Table S1). The mean age of the cohort was 53.9 ± 15.9 years, 46.3% were female, and 68.6% were white. The median estimated glomerular filtration rate was 44.9 (interquartile range [IQR] 26.3–76.8) ml/min per 1.73 m^2, and median proteinuria was 2.0 (IQR 0.6–5.0) g/g creatinine (Table 1).

Patients with PGN had a median urine RBC count of 18 (IQR 6–60) per high-power field (HPF), whereas those with other forms of kidney disease had a median urine RBC count of 2 (IQR 1–10) per HPF ($P < 0.01$). Moreover, among the patients with PGN, we found a trend toward higher RBC counts in patients with crescentic disease compared to those without glomerular crescents (median [IQR] 23.5 (11.5–92.5) vs. 15 (4–60) RBCs/HPF, respectively, $P = 0.06$). Of the patients with PGN, 8.3% had less than 1+ blood on their

Table 2. Sensitivity (Sens), specificity (Spec), positive predictive value (PPV), negative predictive value (NPV), postive likelihood ratio (LR+), and negative likelihood ratio (LR−) at different thresholds of test strip protein and blood for diagnosis of proliferative glomerulonephritis

	Blood ≥0	Blood ≥TR	Blood ≥1+	Blood ≥2+	Blood 3+
Protein ≥0					
Sens/Spec (%)		94.7/29.0	91.7/43.6	83.5/62.0	61.7/79.8
PPV/NPV (%)		32.1/94.0	36.5/93.7	43.7/91.4	51.9/85.5
LR+/LR−		1.33/0.18	1.71/0.18	2.18/0.27	3.05/0.48
Protein ≥TR					
Sens/Spec (%)	94.7/14.6	90.9/37.0	88.6/50.0	81.1/65.4	59.9/82.2
PPV/NPV (%)	28.1/88.7	33.6/92.1	38.4/92.6	45.2/90.8	54.1/85.4
LR+/LR−	1.11/0.36	1.44/0.25	1.77/0.23	2.34/0.29	3.37/0.49
Protein ≥1+					
Sens/Spec (%)	85.7/24.4	81.8/43.1	81.1/54.8	74.2/68.9	55.3/84.3
PPV/NPV (%)	28.6/82.9	33.5/87.1	38.6/89.2	45.6/88.4	55.3/84.3
LR+/LR−	1.13/0.59	1.44/0.42	1.79/0.34	2.39/0.37	3.52/0.53
Protein ≥2+					
Sens/Spec (%)	73.7/36.1	70.5/49.5	69.7/59.6	63.6/71.8	47.7/85.9
PPV/NPV (%)	28.9/79.5	32.9/82.7	37.7/84.9	44.2/84.9	54.3/82.4
LR+/LR−	1.15/0.73	1.40/0.60	1.73/0.51	2.26/0.51	3.38/0.61
Protein ≥3+					
Sens/Spec (%)	39.1/61.3	36.4/66.2	36.4/72.6	33.3/80.3	25.0/91.2
PPV/NPV (%)	26.3/74.0	27.4/74.8	31.8/76.5	37.3/77.4	50.0/77.6
LR+/LR−	1.01/0.99	1.08/0.96	1.33/0.88	1.69/0.83	2.84/0.82

TR, trace.

test strip compared to 43.6% of those with other forms of kidney disease. The Spearman correlation coefficient between test strip blood measurements and the urine RBC count was 0.66.

Table 2 demonstrates the performance characteristics of automated urine test strip protein and blood at different thresholds for diagnosis of PGN versus other causes of kidney disease. Table 3 shows the same performance characteristics for quantitative proteinuria measurements and automated urine RBC counts. Figure 1 shows receiver operating characteristic (ROC) curves for diagnosis of PGN versus other causes of kidney disease using test strip blood or the automated urine RBC count as predictors. The areas under these ROC curves were 0.77 and 0.75, respectively. The difference in the ROC curves was not significant when compared among patients who had both tests performed ($P = 0.15$). Using the laboratory's conventional threshold of >2 RBCs/HPF to define abnormal hematuria, the RBC count had 86% sensitivity, 51% specificity, 39% positive predictive value (PPV), and 91% negative predictive value (NPV) for PGN. Among patients with proteinuria <0.5 g/g creatinine, NPV increased to 96%. Analogously, a negative test strip for blood had 95% sensitivity, 29% specificity, 32% PPV, and 94% NPV. The NPV increased to 96% when restricted to patients with proteniuria <0.5 g/g creatinine.

When test strip blood was added to a clinical prediction model of PGN which included age, sex, race (black vs. nonblack), proteinuria (<1 vs. ≥1 g/g creatinine), estimated glomerular filtration rate, acute kidney injury as the reason for biopsy, diabetes

Table 3. Sensitivity (Sens), specificity (Spec), positive predictive value (PPV), negative predictive value (NPV), postive likelihood ratio (LR+), and negative likelihood ratio (LR−) for different thresholds of quantitative proteinuria and urine RBC counts for diagnosis of proliferative glomerulonephritis

	RBCs ≥0/HPF	RBCs >2/HPF	RBCs >5/HPF	RBCs >10/HPF	RBCs >15/HPF
Protein ≥0 g/g					
Sens/Spec (%)		85.7/51.4	76.2/62.3	61.0/75.7	50.5/81.2
PPV/NPV (%)		38.8/90.9	42.1/87.9	47.4/84.4	49.1/82.0
LR+/LR−		1.76/0.28	2.02/0.38	2.51/0.52	2.69/0.61
Protein ≥0.5 g/g					
Sens/Spec (%)	86.7/23.3	74.3/61.6	65.7/71.6	51.4/80.1	41.9/84.9
PPV/NPV (%)	28.9/82.9	41.1/87.0	45.4/85.3	48.2/82.1	50.0/80.3
LR+/LR−	1.13/0.57	1.93/0.42	2.31/0.48	2.58/0.61	2.77/0.68
Protein ≥1.0 g/g					
Sens/Spec (%)	72.4/35.3	61.9/66.4	54.3/75.0	43.8/82.9	35.2/87.3
PPV/NPV (%)	28.7/78.0	39.9/82.9	43.9/82.0	47.9/80.4	50.0/79.0
LR+/LR−	1.12/0.78	1.84/0.57	2.17/0.61	2.56/0.68	2.77/0.74
Protein ≥2.0 g/g					
Sens/Spec (%)	48.6/47.6	41.9/72.3	40.0/78.8	30.5/86.6	23.8/90.4
PPV/NPV (%)	25.0/72.0	35.2/77.6	40.4/78.5	45.1/77.6	47.2/76.4
LR+/LR−	0.93/1.08	1.51/0.80	1.89/0.76	2.28/0.80	2.48/0.84
Protein ≥3.5 g/g					
Sens/Spec (%)	28.6/62.0	26.7/78.4	25.7/83.9	20.0/90.1	16.2/93.8
PPV/NPV (%)	21.3/70.7	30.8/74.8	36.5/75.9	42.0/75.8	48.6/75.7
LR+/LR−	0.75/1.15	1.24/0.93	1.60/0.89	2.02/0.89	2.61/0.89

HPF, high-power field; RBC, red blood cell.

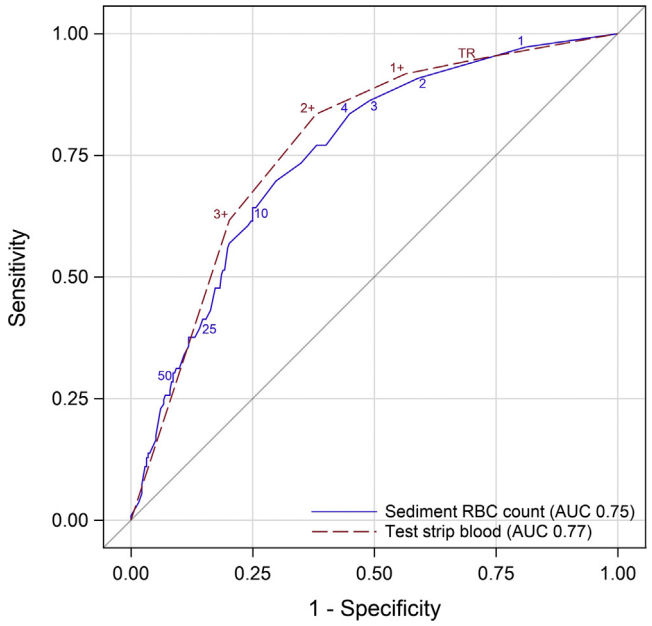

Figure 1. Receiver operating characteristic curves demonstrating fair performance of the automated urine red blood cell (RBC) count and urine test strip blood for diagnosis of proliferative glomerulonephritis versus other forms of kidney disease. Depicted thresholds for the RBC count are given as the number per high-power field. AUC, area under the curve; TR, trace.

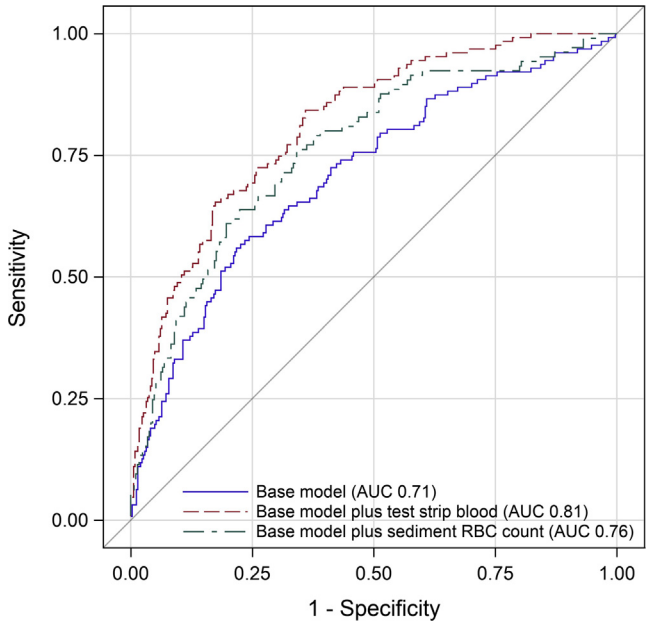

Figure 2. A clinical prediction model of proliferative glomerulonephritis that included age, sex, race (black vs. nonblack), proteinuria (<1 vs. ≥1 g/g creatinine), estimated glomerular filtration rate, acute kidney injury as the reason for biopsy, diabetes mellitus, hypertension, systemic lupus erythematosus, vasculitis, and hepatitis C significantly improved with the addition of test strip blood ($P < 0.01$) to the model, as well as with the addition of the sediment red blood cell (RBC) count among patients for whom this was available ($P < 0.01$). AUC, area under the curve.

mellitus, hypertension, systemic lupus erythematosus, vasculitis, and hepatitis C, the area under the ROC curve increased from 0.71 for the base model alone up to 0.81 ($P < 0.01$). Among patients for whom automated urine RBC counts were available, the addition of the RBC count instead of test strip blood to the same clinical prediction model increased the area under the ROC curve from 0.71 to 0.76 ($P < 0.01$) (Figure 2).

DISCUSSION

Our data show that the automated UA has fair ability to differentiate PGN from other kidney diseases. A negative urine RBC count or dipstick for blood had high negative predictive value, especially among patients with low levels of proteinuria, despite our cohort having a high proportion of patients with PGN. Both tests, however, had limited specificity and positive predictive value, and similar performance overall. It is possible that specificity and PPV would be higher in nonbiopsied chronic kidney disease cohorts, as most patients with diseases such as diabetic nephropathy or hypertensive nephrosclerosis do not undergo biopsy, and our cohort is thus likely to be enriched for atypical presentations of these diseases. Although this could affect the generalizability of our findings, the inclusion of only patients with biopsy-proven disease is a fundamental strength of our analysis. Without being able to compare our automated UA results to the results of the gold standard diagnostic method, ascertainment bias could lead to invalid estimates of the test performance characteristics.

Despite its limitations as a diagnostic test, the automated UA added significantly to a basic clinical prediction model of PGN. Among patients with PGN, we furthermore found a trend toward an association between higher levels of hematuria and more severe disease, as indicated by the presence of glomerular crescents. Although this finding was not statistically significant, our study may not have been adequately powered to detect a statistically significant difference. Taken together, our data demonstrate quantitatively how the automated UA may aid clinicians, albeit imperfectly, when determining the appropriateness of additional workup for kidney disease, such as serological studies and, ultimately, a kidney biopsy.

Interestingly, we found no difference between the performance characteristics of the urine RBC count and the semiquantitative test strip blood measurements for diagnosis of PGN. Because automated analyzers do not reliably detect less common but more specific features of PGN in the urine sediment, such as acanthocytes and

RBC casts,[6,7] further studies are needed to compare the performance characteristics of the manual sediment examination when carried out by trained nephrologists to those of modern laboratory-based automated analyzers.

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DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary Methods.

Figure S1. Overview of analysis cohort.

Table S1. Primary clinicopathologic diagnoses of patients in the analysis cohort.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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Epidemiology and Outcome of CKD in Omani Children

To the Editor: Chronic kidney disease (CKD) is a public health problem worldwide. It is due to permanent kidney damage which ultimately leads to end-stage renal disease (ESRD).The Kidney Disease Improving Global Outcomes initiative defines CKD as structural or functional abnormalities of the kidney that last for 3 months or more and affect the well-being of the patient.[1] Children with CKD constitute a small but very important proportion of the CKD population. These children are at risk of long-term complications, such as growth retardation and alteration of cognitive development.[2–4]

There are limited data on the epidemiology of CKD in children, especially for early stages, as most children are asymptomatic.[5] Most earlier studies on pediatric CKD were based on hospital records, largely representing children presenting in late stages, and used different definitions for CKD.[5] More recent publications, however, have been using the CKD classification published by the National Kidney Foundation's Kidney Disease Outcome Quality Initiative in 2003.[6,7]

Oman is one of the Arab Countries located in the southeastern corner of the Arabian Peninsula. According to the 2018 Statistical Yearbook report of the National Center for Statistics and Information, in mid-year 2017, the population size was 4.55 million with a population of approximately 1 million age 14 years and younger.[8]

The aim of this study was to establish data about CKD in children in Oman, including the annual incidence, etiology, and long-term outcomes based on the experience at a major tertiary referral center that provides pediatric nephrology services for the entire population being the only pediatric nephrology center catering for children with CKD.

RESULTS

Over a study period of 12 years (between 2004 and 2015) there were 208 cases of CKD, the patient demographics are illustrated in Table 1.The mean