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Original Investigation

Predicting Kidney Transplantation Outcomes Using Proteinuria Ascertained From Spot Urine Samples Versus Timed Urine Collections

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Background: Proteinuria has been associated with transplant loss and mortality in kidney transplant recipients. Both spot samples (albumin-creatinine ratio [ACR] and protein-creatinine ratio [PCR]) and 24-hour collections (albumin excretion rate [AER] and protein excretion rate [PER]) have been used to quantify protein excretion, but which measurement is a better predictor of outcomes in kidney transplantation remains uncertain.

Study Design: Observational cohort study.

Setting & Participants: Tertiary care center, 207 kidney transplant recipients who were enrolled in a prospective study to measure glomerular filtration rate. Consecutive patients who met inclusion criteria were approached.

Predictors: ACR and PCR in spot urine samples, AER and PER in 24-hour urine collections.

Outcomes: Primary outcome included transplant loss, doubling of serum creatinine level, or death.

Measurements: Urine and serum creatinine were measured using a modified Jaffé reaction that had not been standardized by isotope-dilution mass spectrometry. Urine albumin was measured by immunoturbidimetry. Urine protein was measured by pyrogallol red molybdate complex formation using a timed end point method.

Results: Mean follow-up was 6.4 years and 22% developed the primary end point. Multivariable-adjusted areas under the receiver operating characteristic curves were similar for the different protein measurements: ACR (0.85; 95% CI, 0.79-0.89), PCR (0.84; 95% CI, 0.79-0.89), PER (0.86; 95% CI, 0.80-0.90), and AER (0.83; 95% CI, 0.78-0.88). C Index values also were similar for the different proteinuria measurements: 0.87 (95% CI, 0.79-0.95), 0.86 (95% CI, 0.79-0.94), 0.88 (95% CI, 0.82-0.94), and 0.86 (95% CI, 0.77-0.95) for log(ACR), log(PCR), log(PER), and log(AER), respectively.

Limitations: Single-center study. Measurement of proteinuria was at variable times posttransplantation.

Conclusions: Spot and 24-hour measurements of albumin and protein excretion are similar predictors of doubling of serum creatinine level, transplant loss, and death. Thus, spot urine samples are a suitable alternative to 24-hour urine collection for measuring protein excretion in this population.

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INDEX WORDS: Proteinuria; albuminuria; kidney graft survival; outcomes; protein-creatinine ratio (PCR); albumin-creatinine ratio (ACR); albumin excretion rate (AER); protein excretion rate (PER); spot urine sample; 24-hour urine collection; end-stage renal disease (ESRD).

Both proteinuria and albuminuria are strong risk factors for the development of kidney failure in the general population.[1-3] Similarly, in kidney transplant recipients, total urinary albumin and protein excretion have been associated with progressive decreases in kidney function, transplant loss, and mortality.[4-6] At 1 year posttransplantation, proteinuria with protein excretion $>$ 150 mg/d is present in $\sim$40% and therefore is a common complication of kidney transplantation. Studies to date have shown that proteinuric kidney transplant recipients have a 2- to 5-fold increased risk for developing transplant failure.[6] Therefore, estimation of urinary albumin or protein loss remains an important tool for prognostication.

Timed urine specimens are considered the gold standard for measuring proteinuria and albuminuria. Because of convenience and cost, spot urine samples such as albumin-creatinine ratio (ACR) and protein-creatinine ratio (PCR) increasingly are being used for quantification of albuminuria and proteinuria. A recent KDIGO (Kidney Disease: Improving Global Outcomes) guideline suggests that ACR and PCR may be reasonable alternatives to 24-hour urine collection in kidney transplant recipients.[7] These spot measures of protein excretion have been reported to

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Table 1. Baseline Characteristics

	All Patients (N=207)[a]	ACR < 30 (n=104)	ACR 30-300 (n=75)	ACR > 300 (n=21)	*P* for Trend
Mean age (y)	59.9 ± 12	60 ± 12	60.2 ± 12	59.1 ± 14	0.9
Male	135 (65)	62 (59.6)	51 (68)	16 (76.2)	0.5
Race					
White	190 (92)	92 (89)	71 (95)	20 (95)	0.8
Black	5 (2)	5 (4.8)	0 (0)	0 (0)	0.5
Asian	7 (3)	4 (3.9)	2 (3)	1 (5)	0.9
Other	5 (2)	3 (2.9)	2 (3)	0 (0)	0.5
Weight (kg)	79.9 ± 17	79 ± 19	82.5 ± 16	78.3 ± 17	0.6
Height (cm)	167 ± 10.2	168 ± 10.7	168 ± 9.3	164 ± 11	0.2
Body surface area (m^2)	1.89 ± 0.2	1.89 ± 0.2	1.92 ± 0.2	1.84 ± 0.2	0.9
Living donor	79 (38)	36 (34.6)	30 (40)	8 (38)	0.7
Time from Tx to study entry (y)	5.3 [9.1]	4.6 [5.9]	5.3 [8.9]	7.8 [10.7]	0.05
F/U after study entry (y)	6.2 [1.6]	6.3 [1.3]	6.5 [0.88]	6.2 [0.82]	0.3
Primary Tx	181 (87)	88 (84.6)	66 (88)	20 (95)	0.7
Cause of kidney disease					
Diabetes	27 (13)	13 (12.5)	7 (9)	4 (19)	0.8
Polycystic kidney disease	33 (16)	18 (17.3)	12 (16)	2 (10)	0.5
Glomerulonephritis	54 (26)	26 (25)	20 (27)	6 (29)	0.8
Hypertension	12 (6)	5 (4.8)	4 (5)	2 (10)	0.5
Other	81 (39)	42 (40.4)	32 (43)	7 (33)	0.9
Medication					
ACEi or ARB	72 (35)	31 (30)	28 (37)	10 (48)	0.3
Prednisone	204 (99)	103 (99)	74 (99)	20 (95)	0.9
Tacrolimus	80 (39)	40 (39)	28 (37)	8 (38)	0.9
Cyclosporine	107 (52)	51 (49)	41 (55)	12 (57)	0.6
Azathioprine	35 (17)	20 (19)	11 (15)	3 (14)	0.5
Mycophenolate mofetil	140 (68)	72 (69)	51 (68)	13 (62)	0.8
Sirolimus	6 (3)	1 (1)	3 (4)	1 (5)	0.2
GFR category					
≥90 mL/min/1.73 m^2	16 (8)	9 (9)	7 (9)	0 (0)	0.4
60-89 mL/min/1.73 m^2	81 (39)	48 (46)	28 (37)	4 (19)	0.2
30-59 mL/min/1.73 m^2	88 (42)	45 (43)	29 (39)	10 (48)	0.9
15-29 mL/min/1.73 m^2	18 (9)	2 (2)	10 (13)	4 (19)	0.002
<15 mL/min/1.73 m^2	4 (2)	0 (0)	1 (1)	3 (14)	<0.001
PER (mg/d)	210 [370]	100 [170]	270 [280]	1,330 [1,330]	<0.001
PCR (mg/g)	150 [216]	61 [82]	209 [179]	1,003 [901]	<0.001
AER (mg/d)	37 [124]	16 [20]	81 [165]	738 [968]	<0.001
Doubling of serum creatinine	14 (7)	2 (2)	6 (8)	5 (24)	<0.001
Transplant loss	14 (7)	2 (2)	4 (5)	7 (33)	<0.001
Death	17 (8)	5 (5)	8 (11)	3 (14)	0.1

Note: Continuous values given as mean ± standard deviation or median [interquartile range]; categorical values expressed as number (percentage). ACR given in mg/g of creatinine.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-creatinine ratio; AER, albumin excretion rate; ARB, angiotensin receptor blocker; F/U, follow-up; GFR, glomerular filtration rate; PCR, protein-creatinine ratio; PER, protein excretion rate; Tx, transplantation.

[a]Seven patients did not have ACR measured.

perform equally as predictors of both renal and patient outcomes in the nontransplantation population.[8] However, in the kidney transplant recipient population, the ability of spot measures of protein excretion to predict patient and transplant outcomes remains unclear. For instance, most transplant recipients are treated with steroids, which decrease muscle mass and thus would lead to lower creatinine excretion, affecting ACR and PCR. Accordingly, the objective of this study was to determine whether ACR and PCR were better than standard 24-hour measurements of urine protein or albumin (protein excretion rate [PER] and albumin excretion rate [AER], respectively) in predicting outcomes in kidney transplant recipients.