Urine Albumin Creatinine Ratio May Predict Graft Function After Kidney Transplant

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ABSTRACT

Background. The albumin to creatinine ratio (ACR) has been shown to be an important prognostic marker in kidney disease. The ACR has been shown to predict graft failure and patient death after kidney transplant.

Methods. From March 1, 2011, to December 31, 2013, we checked the urine ACR and blood for highly sensitive C-reactive protein in 93 kidney recipients who regularly follow up at out institute. We tested the linear correlations of these parameters with estimated glomerular filtration rate. Furthermore, we used multivariate linear regression to examine its value in predicting graft function. Finally, we used receiver operating characteristic curve analysis to validate their predictive value on creatinine clearance $>$ 45 mL/min.

Results. With multivariate linear regression, the latest estimated glomerular filtration rate has a strong linear relationship with initial ACR (B = −0.032; P = .02), suggesting each unit rise in ACR with a decrease in creatinine clearance by 0.032 mL/min. To investigate their value in predicting good functional graft defined as creatinine clearance >45 mL/min, a receiver operating characteristic curve analysis was applied on these parameters. The area under curve for age is 0.496, for body weight is 0.539, and for highly sensitive C-reactive protein is 0.582, which are all around the chance of 0.5 by flipping coins. The area under ACR curve is 0.825, better than above parameters, and only second to serum creatinine level.

Conclusions. Urine ACR is a simple and effective measure to predict graft function after a kidney transplant. It has similar independent strong correlations to creatinine clearance comparing with serum creatinine without requirement of a blood draw.

PROTEINURIA is currently considered the most important isolated prognostic marker in chronic renal disease in native kidneys and end-stage renal disease [1]. Microalbuminuria is a term to describe a moderate increase in the level of urine albumin. It occurs when the kidney leaks small amounts of albumin into the urine, in other words, when there is an abnormally high permeability for albumin in the renal glomerulus. Microalbuminuria is a marker of cardiovascular and renal outcome and was shown to be associated with total mortality and noncardiovascular mortality [2–5].

After kidney transplant, once the acute rejection problem has decreased with the introduction of immunosuppressants, the main cause for graft loss is death with a functioning graft and chronic allograft dysfunction. The presence of any grade of proteinuria in any moment of a renal transplant is associated with worse graft survival compared with the nonproteinuric population. However, there are no specific guidelines in renal transplants because the association between microalbuminuria (especially in nonproteinuric patients), patient, and graft survival has never been assessed in renal transplants. Nevertheless,

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Table 1. Divided Two Groups by ACR 30 mg/g as Cut-Off Value

	ACR ≤30 mg/g	ACR >30 mg/g	*P* Value
Age, mean (SD), y	30.40 (15.25)	36.63 (14.31)	.24
Sex, M:F	47	40	.90
Height, mean (SD), cm	158.78 (14.22)	160.25 (13.81)	.64
Weight, mean (SD), kg	56.78 (14.64)	58.85 (14.11)	.51
BMI, mean (SD)	22.08 (3.92)	22.27 (3.47)	.82
HS-CRP, mean (SD), mg/dL	4.29 (11.05)	6.94 (13.65)	.35
eGFR nadir, mean (SD), mL/min/1.73 m^2	66.33 (29.33)	66.87 (56.62)	.96
eGFR latest, mean (SD), mL/min/1.73 m^2	58.42 (25.23)	42.51 (32.65)	.01*

Abbreviations: ACR, albumin to creatinine ratio; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; F, female; HS-CRP, highly sensitive C-reactive protein; M, male.
*P value <.05.

massive proteinuria has been recognized as a risk factor for long-term graft loss [6].

The urine albumin to creatinine ratio (ACR) has been shown to be an important prognostic marker in kidney disease. An ACR of more than 30 mg/g, a value 2 to 3 times higher than albuminuria levels in adult, indicates renal injury and has been associated with the risk of progression to higher levels of proteinuria and glomerular filtration rate decrease. The ACR has been shown to predict graft failure and patient death after kidney transplant. Our aim is to test its value on predicting graft function rather than prognosis alone.

MATERIALS AND METHODS

From March 1, 2011, to December 31, 2013, we checked the urine ACR and blood for highly sensitive C-reactive protein (HS-CRP) levels in 358 kidney recipients who regularly follow up at our institute. Because some biochemistry data were lost, we were only able to collect the parameters from 93 patients. We first checked the urine ACR after 1 to 6 months after renal transplant when graft kidney function was stable. Then we checked urine ACR regularly around every 6 to 12 months for deterioration of graft kidney function. The urine ACR (ACR-change) was also recorded while we changed the immunosuppressant drugs. The last urine ACR was checked before we recorded the last creatinine of these patients. Other parameters were recorded, such as age, body weight, body mass index, sex, and creatinine. We tested the linear correlations of these parameter with the latest estimated glomerular filtration rate (eGFR). The eGFR was estimated by Modification of Diet in Renal Disease formula. Furthermore, we use univariate and multivariate linear regression to examine each parameter in predicting graft function. Besides, urine ACR (mg/g creatinine) was calculated as albumin concentration (mg/L) divided by creatinine concentration (g/L). A receiver operating characteristic (ROC) curve analysis was used to estimate the discriminative power of each parameter to detect graft renal function. The eGFR cutoff value was defined as 30 mL/min/1.732 m^2, 45 mL/min/1.732 m^2, and 60 mL/min/1.732 m^2, corresponding with chronic kidney disease stage IIIb, stage IIIa, and stage II, respectively. The optimal cutoff point was defined as the measurement that corresponds to the point on the ROC curve closest to the top left corner (ie, closest to the point with 100% sensitivity and 100% specificity). Statistical analysis was performed using SPSS version 20 (IBM, Armonk, NY, United States).

RESULTS

The urine ACR was defined as 30 mg/g in both sexes [7–9]. When using 30 mg/g as the cutoff value of urine ACR, the initial urine ACR was strongly correlated with the latest eGFR ($P = .01$) (Table 1) In Van Ree's study, changes in serum creatinine during follow-up were −0.45 μmol/L/y (range, −4.83 to 4.76 μmol/L/y) in 172 subjects with CRP <1.0 mg/L, 1.04 μmol/L/y (range, −3.36 to 6.12 μmol/L/y) in 184 subjects with CRP 1.0 to −3.0 mg/L, and 2.34 μmol/L/y (−3.33 to 9.07 μmol/L/y) in 219 subjects with CRP >3.0 mg/L (significantly different between the 3 groups) [10]. However, in our study, the latest eGFR was not correlated with HS-CRP with cutoff value of 3 mg/L (Table 2).

With univariate linear regression, the latest eGFR has strong linear relationship with initial ACR ($B = -0.032$; $P = .02$). Using multivariate linear regression model, initial

Table 2. Divided Two Groups by HS-CRP 3 mg/L as Cut-Off Value

	HS-CRP < 3 mg/L	HS-CRP ≥ 3 mg/L	*P* Value
Age, mean (SD), y	39.93 (14.74)	39.12 (15.38)	.81
Sex, M:F	43	34	.23
Height, mean (SD), cm	157.54 (13.78)	160.00 (14.29)	.46
Weight, mean (SD), kg	54.42 (14.26)	60.89 (14.14)	.05
BMI, mean (SD)	21.28 (3.92)	23.18 (3.25)	.03*
HS-CRP, mean (SD), mg/dL	161.31 (306.9)	139.97 (227.38)	.78
eGFR nadir, mean (SD), mL/min/1.73 m^2	65.79 (27.07)	68.44 (61.80)	.80
eGFR latest, mean (SD), mL/min/1.73 m^2	53.62 (30.16)	50.79 (30.09)	.69

Abbreviations: ACR, albumin to creatinine ratio; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; F, female; HS-CRP, highly sensitive C-reactive protein; M, male.
*P value <.05.

Table 3. Regressions of Final eGFR

Final eGFR	Univariate Linear Regression		Multivariate Linear Regression		
Parameter	B	*P* Value	B	95% CI	*P* Value
Age	−0.109	.606	0.074	−0.689 ~ 0.540	.81
Sex	0.509	.937	5.378	−13.755 ~ 24.512	.57
Height	−0.688	.003	−0.735	−1.690 ~ 2.220	.13
Weight	−0.396	.083	−0.161	−0.811 ~ 1.132	.74
HTN	−1.234	.848	−12.736	−28.734 ~ 3.262	.12
DM	−7.057	.457	−11.151	−34.563 ~ 12.261	.34
HS-CRP	−0.078	.784	0.064	−0.695 ~ 0.823	.87
ACR	−0.032	.019	−0.035	−0.066 ~ −0.005	.02*

Abbreviations: ACR, albumin to creatinine ratio; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HS-CRP, highly sensitive C-reactive protein; HTN, hypertension.
**P* value <.05.

ACR remained inside parameters that could affect latest eGFR independently (Table 3). The age, sex, body weight, body height, diabetes mellitus, hypertension, and inflammation factors (HS-CRP) had no significant relation with the latest eGFR. The multivariate linear regression showed each unit rise in ACR with a decrease in creatinine clearance by 0.032 mL/min/1.732 m^2.

To investigate their value in predicting graft function defined eGFR <30 mL/min/1.732 m^2, <45 mL/min/1.732 m^2, and or <60 mL/min/1.732 m^2, a ROC curve analysis was applied on these parameters (Table 4). When predicting eGFR <30 mL/min/1.732 m^2, the area under the curve for age was 0.625, for body weight was 0.587, for HS-CRP was 0.646, for initial urine ACR was 0.767, and for latest urine ACR was 0.858 (Fig 1A). Beyond latest creatinine, the initial and latest ACR were the most accurate predictive factor of graft renal function. While predicting eGFR <45 mL/min/1.732 m^2, the area under curve was 0.825 and 0.837,

Table 4. True Positive and False Negative Rates of Different eGFR Cut-Offs

eGFR< 30 mL/min/1.73 m^2 (Fig 1A)	AUC	True Positive Rate	False Negative Rate	*P* Value
ACR first	0.767	0.833	0.375	.03*
ACR last	0.858	0.833	0.083	.005*
Age	0.625	0.833	0.438	.32
Weight	0.587	0.500	0.167	.29
HS-CRP	0.646	0.500	0.188	.44
ACR change	0.748	0.667	0.313	.049*
eGFR <45 mL/min/1.73 m^2 (Figure 1B)	**AUC**	**True Positive Rate**	**False Negative Rate**	***P* Value**
ACR first	0.825	0.667	0.143	.001*
ACR last	0.837	0.583	0.095	<.001*
Age	0.496	0.167	0.119	.97
Weight	0.539	0.417	0.167	.68
HS-CRP	0.582	0.333	0.071	.39
ACR change	0.811	0.50	0.095	.001*
eGFR <60 mL/min/1.73 m^2 (Fig 1C)	**AUC**	**True Positive Rate**	**False Negative Rate**	***P* Value**
ACR first	0.606	0.400	0.138	.18
ACR last	0.541	0.120	0.034	.61
Age	0.576	0.160	0.103	.34
Weight	0.464	0.400	0.138	.07
HS-CRP	0.577	0.280	0.069	.34
ACR change	0.606	0.400	0.172	.18
eGFR <75 mL/min/1.73 m^2 (Fig 1D)	**AUC**	**True Positive Rate**	**False Negative Rate**	***P* Value**
ACR first	0.468	0.179	0.067	.72
ACR last	0.441	0.256	0.133	.50
Age	0.395	0.947	0.800	.24
BW	0.587	0.359	0.133	.32
HS-CRP	0.442	0.282	0.200	.50
ACR change	0.518	0.179	0.067	.84

Abbreviations: ACR, albumin to creatinine ratio; AUC, area under the curve; eGFR, estimated glomerular filtration rate; HS-CRP, highly sensitive C-reactive protein.
**P* < .05.

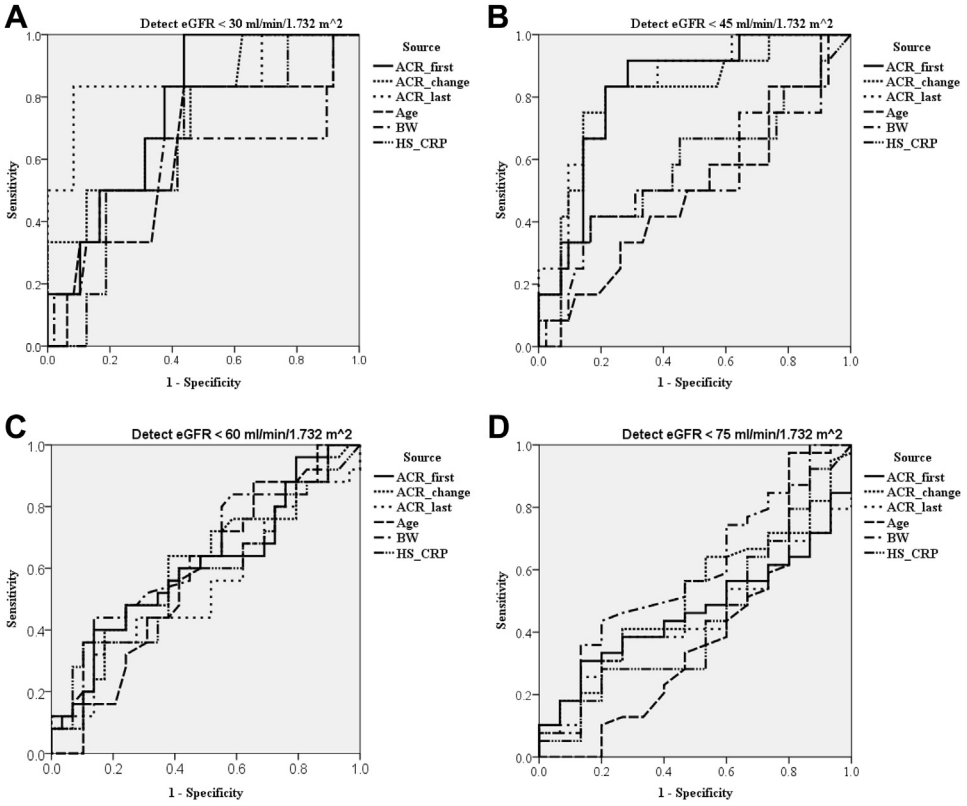

Fig 1. ROC curve to detect renal graft dysfunction. ROC, receiver operating curve.

which meant that it was more accurate than predicting eGFR <30 mL/min/1.732 m^2 (Fig 1B). However, to predict eGFR <60 mL/min/1.732 m^2, the area under the curve of initial ACR and latest ACR reduced to 0.606 and 0.541, respectively (Fig 1C). While predicting eGFR <75 mL/min/1.732 m^2, poor accuracy was noted in every parameter (Fig 1D).

DISCUSSION

The predictors of graft renal dysfunction were included donor and recipient age, donor type, cause of kidney failure, cold ischemia time, dialysis duration prior to kidney transplant, and body mass index of the donor and the recipient. Other predictors were measured shortly after transplant, such as creatinine in the first week after transplant [11,12], serum creatinine at 6 months [12,13] or at 1 year [14], blood pressure, and proteinuria at 1 year [15].

In 2008, Hsu et al [16] identified 1764 patients who developed hospital-acquired acute kidney injury (AKI) treated with dialysis from 1996 to 2003 compared with 600,820 hospitalized patients who did not develop AKI requiring dialysis. The adjusted odds ratio of dialysis-requiring AKI for patients with documented proteinuria was 2.79 (compared with referent patients without proteinuria). Cantarovich et al [17] found that proteinuria was also strongly associated with patient survival (hazard ratio, 3.30; 95% CI, 1.94–5.62; $P < .001$). Proteinuria was a stronger predictor of outcome than either baseline serum creatinine or creatinine 1 month after rejection as Oblak et al [18] reviewed proteinuria among 83 patients with biopsy-proven acute rejection.

To our knowledge, the prognostic value of microalbuminuria or macroalbuminuria had never been assessed in renal transplant, and microalbuminuria has never been directly linked to end-stage renal disease. However, it must be noted that only indirect evidence links microalbuminuria to end-stage renal disease. Patients with microalbuminuria were more prone to develop proteinuria or renal impairment than those with normoalbuminuria [19–22].

The magnitude of the associations of ACR with outcomes of tubular injury was found in a subset of the FAVORIT trial [23,24]. In our study, the urine ACR was strongly correlated with latest eGFR using 30 mg/g as a cutoff value. The multivariate analysis also revealed negative regression between urine ACR and graft renal function, as in the FAVORIT trial. However, because of the relatively small number of participants, the linear slope was slow ($B = -0.032$). In statistics, there was no significant effect from age, body weight, diabetes mellitus, hypertension, or inflammation factor, but these factors presented a negative effect on graft kidney function.

Nauta et al [25] found that ACR predicted graft loss in a single-center study of 606 kidney transplant recipients with

42 graft failure events. The FAVORIT trial showed that a simple measure of ACR was strongly associated not only with allograft failure, but also with cardiovascular disease events and mortality.

Inflammation was also a factor of graft renal dysfunction. No universally accepted cutoff values for inflammatory markers in renal transplant recipients exist, but regarding cardiovascular outcomes in the general population, CRP <1 mg/dL confers low risk, CRP 1 to 3 mg/dL confers average risk, and CRP >3 mg/dL confers high risk [10,26]. After adjustment for traditional risk factors, HS-CRP was independently associated with death-censored graft loss, the composite endpoints graft loss or death, and doubling of serum creatinine, graft loss, or death [27]. Although there was no statistically significant effect between HS-CRP and latest eGFR, when dividing at a high risk of inflammation (HS-CRP) it showed strong effect on final eGFR.

The accuracy of ACR in kidney recipients has been validated by Erman et al [28] in Israel. In our analysis, the correlation with eGFR is as great as serum creatinine by univariate linear regression. Multivariate analysis also confirmed its independent negative correlation role with eGFR. The multiple factor of ROC curve could predict accuracy of each parameter. The urine ACR of ROC area was higher than other parameters, such as age, weight, or inflammation. When detecting stage IIIa chronic kidney disease (CKD) after renal transplant, the urine ACR of ROC area was higher than detecting stage II and stage IIIb CKD. The FAVORIT trial showed that eGFR <45 mL/min/1.73 m^2 was associated with increased risk for cardiovascular disease [29]. No study showed which of cutoff value of eGFR was more strongly correlated with urine ACR. According to CKD stage, we knew eGFR <45 mL/min/1.73 m^2 had more correlation with urine ACR than eGFR <30 mL/min/1.73 m^2 or <60 mL/min/1.73 m^2. As shown in Table 4, we could use initial urine ACR and the latest ACR to successfully detect graft function below CKD stage IIIa or stage IIIb but not for stage II.

The urine ACR also has the advantage of convenience as neither blood draw nor 24-hour urine collection is required. This test was adopted because of its simplicity and is recommended by various guidelines in diabetic and nondiabetic patients for the detection of microalbuminuria, which can be a good predictor for kidney function.

CONCLUSIONS

The urine ACR is a simple and effective measure to predict graft function after kidney transplant. It has independent correlations to eGFR comparing to serum creatinine without the requirement of a blood draw.

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