Prognostic Value of Effective Renal Plasma Flow for First-year Renal Outcome in Kidney Allograft Recipients

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ABSTRACT

Introduction. Many studies have suggested that post-transplantation renal allograft function is associated with long-term allograft outcomes. However, accurate examination through non-invasive methods remains rare. The aim of the present study is to assess the association between ^{99m}Tc mercaptoacetyltriglycine (MAG3) effective renal plasma flow (ERPF) and first-year post-transplantation renal allograft function.

Methods. We conducted a retrospective cohort study at our center between January 2011 and December 2016. Kidney transplant recipients without an ERPF examination within 14 days post-transplantation, or those with less than 1 year of follow-up were excluded. Eligible cases were divided into 3 groups according to first-year eGFR <45, 45 < eGFR <60, eGFR >60. The Kruskal-Wallis test and χ^2 were used for comparisons between continuous and categorical variables.

Results. A total of 123 patients were analyzed. Each group received 41 patients. The baseline characteristics were comparable in the 3 groups, except for repeated transplantation and delayed graft function. The results of the ERPF median (interquartile range) for the 3 groups were 193 (140.0–244.5) in the eGFR < 45 group, 236 (182.5–301.0) in the 45 < eGFR < 60 group, and 294 (202.5–384.5) in the eGFR > 60 group ($P < .001$). The receiver operating characteristic analysis showed that a cutoff ERPF value of >276 exhibited the best sensitivity (65.85%) and specificity (75.61%) for predicting first-year eGFR > 60 mL/min/1.73 m^2, with an area under the receiver operating characteristic curve of .712, $P < .0001$.

Conclusion. Our findings suggest that an ERPF value of more than 276 is likely to be associated with a favorable first-year renal graft outcome after transplantation. The ^{99m}Tc MAG3 ERPF may be a non-invasive alternative to sequential protocol biopsies.

KIDNEY transplantation is generally perceived as the treatment of choice for end-stage kidney disease. Long-term renal allograft survival has long been of primary concern [1]. To address this issue, examinations are crucial to predict long-term survival and allow early identification of patients with potential poor long-term outcome. Previous studies have suggested that peritransplant parameters such as first-year post-transplantation renal allograft function are associated with long-term allograft outcomes [2]. Monitoring via sequential protocol biopsies may provide abundant information; however, biopsies carry the risks of bleeding and infection. Such complications, though infrequent, may be detrimental to graft outcomes [3]. On the other hand, non-invasive examinations such as Doppler ultrasound have been tested to provide a possible alternative, but they are not without limitations. ^{99m}Tc mercaptoacetyltriglycine (MAG3), with its high extraction fraction and rapid plasma clearance, is widely available, inexpensive, and may

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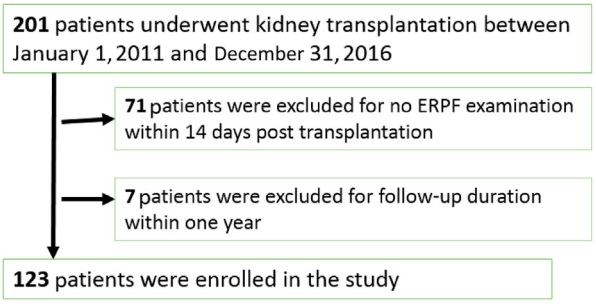

Fig 1. The steps followed in selecting patients.

be another feasible method. The aim of the present study is to investigate the association between ^{99m}Tc MAG3 effective renal plasma flow (ERPF) and first-year post-transplantation renal allograft function.

METHODS

We conducted a retrospective cohort study to investigate ERPF data and first-year renal allograft function in our kidney transplantation recipients at Taichung Veterans General Hospital, Taiwan, between January 2011 and December 2016. All adult Taiwanese recipients aged 18–65 who underwent primary or second kidney transplantation from living related and deceased donors

Table 1. Patient Demographics and Effective Renal Plasma Flow Data

			eGFR						
	Total (N = 123)		<45 (n = 41)		45–60 (n = 41)		>60 (n = 41)		
	n	%	n	%	n	%	n	%	*P* Value
Sex									.745
F	57	(46.3%)	20	(48.8%)	17	(41.5%)	20	(48.8%)	
M	66	(53.7%)	21	(51.2%)	24	(58.5%)	21	(51.2%)	
Recipient age, median (IQR)*	47.0	(35.0–54.0)	47.0	(34.0–54.0)	47.0	(37.0–53.0)	48.0	(33.0–55.5)	.993
HLA mismatch, median (IQR)*	2.0	(2.0–4.0)	2.0	(1.0–4.0)	3.0	(2.0–4.0)	2.0	(1.5–4.0)	.554
ERPF days post-transplant, median (IQR)*	5.4	(3.3–5.5)	5.3	(2.6–5.4)	5.4	(3.5–5.6)	5.4	(2.9–5.5)	.340
ERPF report, median (IQR)*	239.0	(175.0–311.0)	193.0	(140.0–244.5)	236.0	(182.5–301.0)	294.0	(202.5–384.5)	<.001‡
≤150	21	(17.1%)	12	(29.3%)	6	(14.6%)	3	(7.3%)	.016†
150–200	26	(21.1%)	10	(24.4%)	10	(24.4%)	6	(14.6%)	
>200–250	22	(17.9%)	10	(24.4%)	7	(17.1%)	5	(12.2%)	
>250–300	21	(17.1%)	4	(9.8%)	8	(19.5%)	9	(22.0%)	
>300	33	(26.8%)	5	(12.2%)	10	(24.4%)	18	(43.9%)	
Primary or secondary transplantation									.046†
Primary transplantation	120	(97.6%)	38	(92.7%)	41	(100.0%)	41	(100.0%)	
Second transplantation	3	(2.4%)	3	(7.3%)	0	(.0%)	0	(.0%)	
Delayed graft function									.019†
N	89	(72.4%)	25	(61.0%)	28	(68.3%)	36	(87.8%)	
Y	34	(27.6%)	16	(39.0%)	13	(31.7%)	5	(12.2%)	
Living related or deceased donors									.364
Deceased donor	59	(48.0%)	22	(53.7%)	16	(39.0%)	21	(51.2%)	
Living related donor	64	(52.0%)	19	(46.3%)	25	(61.0%)	20	(48.8%)	
Induction therapy									.483
IL-2RA (basiliximab)	60	(48.8%)	21	(51.2%)	18	(43.9%)	21	(51.2%)	
Anti-thymocyte globulin	30	(24.4%)	12	(29.3%)	8	(19.5%)	10	(24.4%)	
CNI									.359
Tacrolimus	120	(97.6%)	41	(100.0%)	40	(97.6%)	39	(95.1%)	
Cyclosporin	3	(2.4%)	0	(.0%)	1	(2.4%)	2	(4.9%)	
Certican									.934
Y	17	(13.8%)	5	(12.2%)	6	(14.6%)	6	(14.6%)	
N	106	(86.2%)	36	(87.8%)	35	(85.4%)	35	(85.4%)	
Sirolimus									.207
Y	6	(4.9%)	4	(9.8%)	1	(2.4%)	1	(2.4%)	
N	117	(95.1%)	37	(90.2%)	40	(97.6%)	40	(97.6%)	
MMF/mycophenolate sodium									.345
MMF/mycophenolate sodium	45	(36.6%)	15	(36.6%)	18	(43.9%)	12	(29.3%)	
Mycophenolate sodium	62	(50.4%)	18	(43.9%)	20	(48.8%)	24	(58.5%)	

Abbreviations: CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration; ERPF, effective renal plasma flow; IL-2RA, interleukin-2 receptor antagonist; IQR, interquartile range; MMF mycophenolate mofetil.

*Kruskal-Wallis test.

†$P < .05$.

‡$P < .01$.

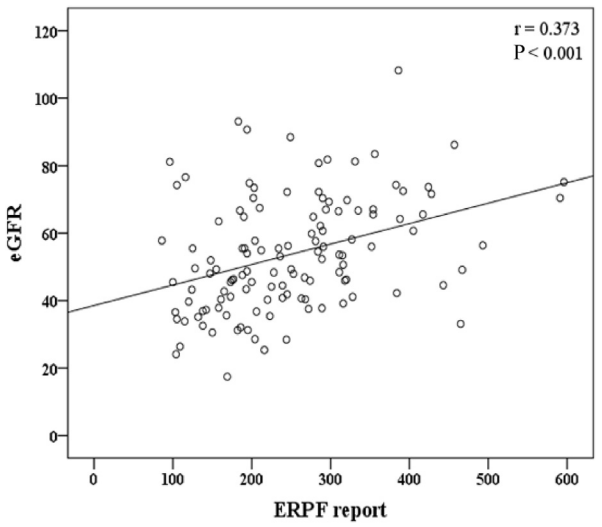

Fig 2. The Pearson correlation coefficients of the eGFR and ERPF.

were studied. The exclusion criteria were recipients without an ERPF examination within 14 days post transplantation, or follow-up for less than 1 year.

In our study, 73.2% of patients received antibody induction therapy with either lymphocyte non-depleting interleukin-2 receptor antagonist (basiliximab) or lymphocyte-depleting polyclonal antibody anti-thymocyte globulin (Thymoglobulin, Sanofi, Paris, France). Maintenance immunosuppression consisted of calcineurin inhibitor (CNI, either tacrolimus 97.6% or cyclosporine 2.4%), a steroid, and mycophenolate mofetil/mycophenolate sodium. In addition, 18.7% of patients received CNI, a steroid, and mammalian target of rapamycin (mTOR) inhibitor. Eligible cases were divided into 3 groups based on first-year estimated glomerular filtration rate (eGFR): Group 1: eGFR < 45 mL/min/1.73 m^2; Group 2: 45 mL/min/1.73 m^2 < eGFR < 60 mL/min/1.73 m^2; Group 3: eGFR > 60 mL/min/1.73 m^2.

^{99m}Tc MAG3 ERPF procedures were performed using an intravenous administration dose in a range of 3–6 mCi. Dynamic images were acquired with a single-headed Siemens (Munich, Germany) gamma camera. A single plasma sample method was used by utilizing the 44th-minute blood sample [4].

First-year eGFR was calculated via the Modification of Diet in Renal Disease Study equation [5] and with the application of the first-year mean creatinine values. We used the Kruskal-Wallis test for continuous variables and χ^2 to analyze categorical variables. The correlation between ERPF and eGFR was identified using a Pearson correlation. In addition, a receiver operating characteristic curve analysis was conducted to evaluate the predictive value of ERPF when eGFR >60 mL/min/1.73 m^2.

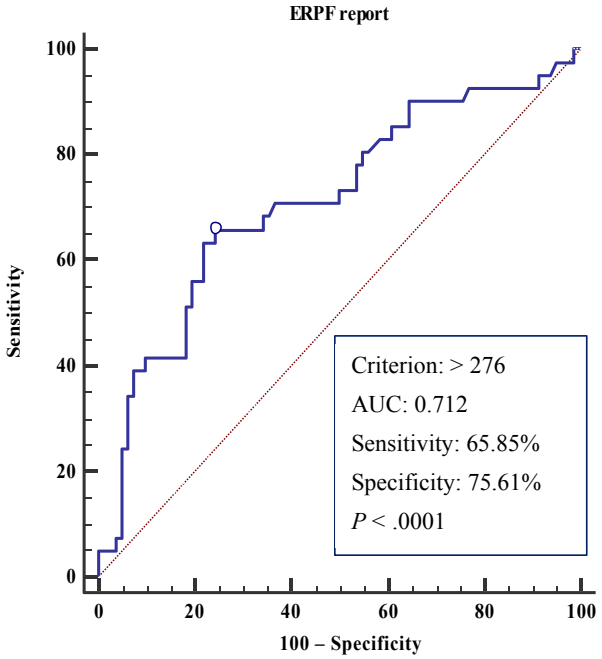

Fig 3. The receiver-operating characteristic curve of ERPF in predicting first-year eGFR >60 mL/min/1.73 m^2. A cutoff ERPF value of >276 was the most sensitive (65.85%) and specific (75.61%) in predicting first-year eGFR > 60 mL/min/1.73 m^2, with an area under the receiver operating characteristic curve of 0.712, $P < .0001$.

RESULTS

A total of 201 patients were enrolled in our study. Of these, 71 were excluded because of a lack of ERPF data within 14 days post-transplantation. Another 7 patients were excluded because they had a follow-up time of less than 1 year. Finally, 123 patients were analyzed, as shown in Figure 1. Each group received 41 patients based on first-year eGFR. Baseline demographic data are shown in Table 1. There were no differences in age, gender, dialysis duration, HLA mismatch, baseline CNI, antibody induction, or maintenance immunosuppression. However, Group 1 differed from the other 2 groups with 3 patients who underwent a second transplantation. The percentage of patients with delayed renal function was highest in Group 1 and lowest in Group 3.

The results of the ERPF medians (interquartile range) among the 3 groups were 193 (140.0–244.5) in Group 1, 236 (182.5–301.0) in Group 2, and 294 (202.5–384.5) in Group 3. The ERPF report in Table 1 also reveals that the higher the ERPF value is, the better the kidney function in the first year of tracking will be ($P < .016$). Figure 2 illustrates the Pearson correlation coefficient of the ERPF and first-year eGFR, which shows a weakly positive correlation (r = .373, $P < .001$). Accordingly, we can see the trend between the value of ERPF and first-year eGFR. The receiver operating characteristic analysis illustrated in Figure 3 shows an area under the curve of .712 (95% confidence interval .624-.790, $P < .0001$). A cutoff ERPF value of 276 proved to be the most sensitive (65.85%) and specific (75.61%) for predicting first-year eGFR > 60 mL/min/1.73 m^2.

DISCUSSION

As shown in our study, ^{99m}Tc MAG3 ERPF overcame the limitations of other commonly practiced measures. First of

all, ^{99m}Tc MAG3 ERPF, as a means of non-invasive examination, may prevent the risks of bleeding and infection caused by protocol biopsies. Second, ^{99m}Tc MAG3 ERPF, compared to other non-invasive examinations, could be more feasible in its accuracy and simplicity. For example, resistance index as measured by Doppler ultrasound is a valuable marker for determining renal graft function. Nevertheless, ultrasonography is operator dependent, and could not differentiate between graft and extrarenal factors (e.g., arterial stiffness, left ventricular hypertrophy, age of the recipient, etc) [6], both of which make interpretation of the results much more complicated. Another non-invasive examination, ^{99m}Tc diethylenetriaminepentaacetic acid, which is performed within 2 days after transplantation, is useful in the prediction of long-term graft function, and the result is more predictive than the resistance index as obtained by Doppler ultrasound [7]. However, compared to ^{99m}Tc diethylenetriaminepentaacetic acid, ^{99m}Tc MAG3 has a higher extraction fraction and rapid plasma clearance, and has gradually replaced ^{99m}Tc diethylenetriaminepentaacetic acid in most transplantation centers in Taiwan. With these strengths, ^{99m}Tc MAG3 ERPF may be more feasibly adopted as a peritransplant examination tool to predict the first-year outcome of renal transplantation.

Russel et al demonstrated the significant predictive value of renal allograft survival at 1 year with ^{99m}Tc MAG3 ERPF for deceased donors, but not for living related donor transplants [8]. The present study is different from the previous one in 2 respects, which may explain the disparities of the results. First, antibody induction therapy in the study by Russell et al comprised Orthoclone OKT3 (Ortho Pharmaceutical, Raritan, NJ, United States), but our study used mainly interleukin-2 receptor antagonist or antithymocyte globulin, which are more compatible with kidney transplantation in contemporary practice [8,9]. Second, the previous study used cyclosporine as maintenance immunosuppression, while 97.6% of the patients in our study used tacrolimus. Although both are agents are calcineurin inhibitors, tacrolimus is more potent, with less early CNI nephrotoxicity and fewer rejection episodes [10].

Our findings shed light on first year post-transplantation renal allograft function, yet some issues should be addressed. First, due to the innate nature of retrospective studies, baseline demographic data are similar in our 3 groups, but unforeseen confounders could potentially bias the findings. Second, as our ERPF examination has only been implemented since 2011, the follow-up duration has not yet enabled us to conduct a 5-year or even a 10-year survival analysis. A follow-up study will address these issues and provide further insight.

CONCLUSION

Our findings suggest that an ERPF value of more than 276 is likely to be associated with a favorable first-year post-transplantation renal graft outcome in contemporary practice. The non-invasive ^{99m}Tc MAG3 ERPF may be a more feasible alternative to sequential protocol biopsies.

REFERENCES

[1] Lamb KE, Lodhi S, Meier-Kriesche HU. Long-term renal allograft survival in the United States: a critical reappraisal. Am J Transplant 2011;11:450–62.

[2] Salvadori M, Rosati A, Bock A, Chapman J, Dussol B, Fritsche L, et al. Estimated one-year glomerular filtration rate is the best predictor of long-term graft function following renal transplant. Transplantation 2006;81:202–6.

[3] Furness PN, Philpott CM, Chorbadjian MT, Nicholson ML, Bosmans JL, Corthouts BL, et al. Protocol biopsy of the stable renal transplant a multicenter study of methods and complication rates. Transplantation 2003;76:969–73.

[4] Russell CD, Taylor A, Eshima D. Estimation of technetium-99m-MAG3 plasma clearance in adults from one or two blood samples. J Nucl Med 1989;30:1955–9.

[5] Poggio ED, Wang X, Weinstein DM, Issa N, Dennis VW, Braun WE, et al. Assessing glomerular filtration rate by estimation equations in kidney transplant recipients. Am J Transplant 2006;6:100–8.

[6] Cano H, Castañeda DA, Patiño N, Pérez HC, Sánchez M, Lozano E, et al. Resistance index measured by Doppler ultrasound as a predictor of graft function after kidney transplantation. Transplant Proc 2014;46:2972–4.

[7] Yazici B, Oral A, Gokalp C, Akgün A, Toz H, Ozbek SS, et al. Evaluation of renal transplant scintigraphy and resistance index performed within 2 days after transplantation in predicting long-term graft function. Clin Nucl Med 2015;40:548–52.

[8] Russell CD, Yang H, Gaston RS, Hudson SL, Diethelm AG, Dubovsky EV, et al. Prediction of renal transplant survival from early postoperative radioisotope studies. J Nucl Med 2000;41:1332–6.

[9] Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9: S1–155.

[10] Nankivell BJ, P'Ng CH, O'Connell PJ, Chapman JR. Calcineurin inhibitor nephrotoxicity through the lens of longitudinal histology: comparison of cyclosporine and tacrolimus eras. Transplantation 2016;100:1723–31.