Research Article

Ari Chong, Jung-Min Ha*, Nam kyu Choi, Min ho Shin

Using post transplant 1 week Tc-99m DPTA renal scan as another method for predicting renal graft failure

Abstract: Purpose. The aims of this study were to determine whether post transplant renal scan performed at around 1 week can predict graft failure, and to identify the best predictive factors among easy-to-measure variables.

Materials and methods. We retrospectively evaluated patients who underwent Tc-99m DTPA renal scan at approximately 1 week after renal transplantation. They were separated into two categories at 3 months after the operation; graft failure and non-failure. Graft failure was confirmed by biopsy (rejection). Non-failure was confirmed either by biopsy or clinical follow-up with serum creatine (Cr). Scan parameters including glomerular filtration rate (GFR), Hilson perfusion index, peaks of the iliac and graft perfusion curves were analyzed. Clinical variables including age, sex, height, weight, systolic blood pressure, serum Cr, type of donated kidney, side of transplant, and immunosuppressant were also analyzed.

Results. Among total 45 patients, graft failure was present in 11 cases. The serum Cr level was significantly higher in the failure group. Among scan variables, only the GFR was significantly different between groups. GFR of <44.48 mL/min was predictive of graft failure (sen 88.9%). Serum Cr level >2.13 mg/dL was also predictive (sen 72.7%).

Conclusion. GFR on renal scan at approximately 1 week after kidney transplant can predict graft failure.

Keywords: Kidney Transplantation; Radionuclide Imaging; Kidney Function Tests

*Corresponding author: Jung-Min Ha, Department of Nuclear Medicine, Chosun University Hospital, 588 Seoseok-dong, dong-gu, Gwangju, Republic of Korea, 501-757, C.P: +82+1046115140, Office: +82+622203589, Fax: +82-62+232-9797, Email: jmha@chosun.ac.kr
Ari Chong, Department of Nuclear medicine, Chosun University Hospital, Gwangju, Korea
Nam kyu Choi, Min ho Shin, Department of Surgery, Chosun University Hospital, Gwangju, Korea

1 Introduction

Graft rejection after kidney transplant is a major problem, and a reliable predictor of graft function is necessary for optimal management of renal transplant patients [1]. The current gold standard for the diagnosis of transplant rejection is invasive core needle biopsy, which carries a risk of graft injury and, furthermore, is not immediately feasible in patients who are taking anticoagulants [2]. A non-invasive method to predict rejection after kidney transplant would be ideal.

Renal scintigraphy (scan) is now widely used to evaluate graft function [3]. Technetium-99m (Tc-99m) diethylenetriaminepentaacetic acid (DTPA) is a reliable tracer for renal scintigraphy, as is technetium-99m mercaptoacetyltriglycine (MAG3). Previous studies have revealed good results with scintigraphy in transplanted kidneys. Most of these studies have relied on early scanning, which was performed within 4 days, and even at 1 day, post transplant [3-11], and a comparison of post transplant scans at 3 days and 7 days postoperatively in the same patient seemed to show that only the post transplant day-3 scan could predict the graft outcome [10]. However, for various reasons, early scanning is not always possible, as is the situation at our institution, where renal scans are not routinely performed until approximately 1 week after transplant.

Among the parameters from DTPA scan, Kirchner's index, Hilson's index, the kidney-to-aorta ratio, graft washout, time difference between peak renal perfusion count and peak arterial count, peak renal perfusion count/counts at plateau, peak renal perfusion/peak renal uptake, renal counts at 20 min/renal counts at 3 min, and others, may be evaluated to assess graft function [8]. One group has recently reported a new index for predicting graft function based on a formula using existing variables [5], but as yet, there has been no consensus about which indices are most useful [6, 12]. In addition, in routine clinical practice, the parameters mentioned above are not all easy to obtain.

An easily measured parameter from renal scintigraphy performed at about 1 week after transplantation is needed. The aims of this study were to find out whether a renal scan performed at approximately 1 week post transplant can be used to predict graft failure and to identify the best predictive factors among easy-to-measure variables.

2 Materials and methods

2.1 Patients

This retrospective observational study was carried out in accordance with the Declaration of Helsinki. Patients who met all of the following inclusion criteria were enrolled: 1) renal transplantation performed at our institution between the years 2005 to 2010; 2) renal scan performed at approximately 1 week (5 to 8 days) after transplantation; 3) follow-up performed at our institution at approximately 3 months post transplant. We excluded patients whose follow-up data were missing and those whose renal scans were considered incorrect due to failure of DTPA bolus injection. They were categorized into two groups based on the status 3 months after the operation; graft failure group vs non-failure group. Graft failure was confirmed by renal biopsy (rejection). Non-failure group was confirmed either by renal biopsy or by clinical follow-up with normal serum creatinine (Cr) levels (<1.5 mg/dL) over 1 year. The study methods of patient enrolment and grouping is shown in Figure 1.

2.2 Renal scintigraphy (Renal scan)

Patients were instructed to have adequate hydration before scanning. Gamma camera (Dual head SPECT, INFINIA GP3, GE) Tc-99m DTPA (340 MBq intravenous bolus) scans, anterior views, were performed with patients lying in a supine position on the camera bed. The gamma camera was equipped with a low-energy, parallel-hole, all-purpose collimator. Sequential 60-s perfusion images (1 s/frame) and sequential 20-min images (30 s/frame) were obtained. Image processing was performed using Exeleris Functional Imaging Workstation software (GE). Regions-of-interest (ROIs) were defined for the cortex of the transplanted kidney, iliac artery, and background. Each ROI was firstly drawn automatically and then manually corrected by the same technician, and in every case, the same nuclear medicine physician confirmed the ROIs.

Once the ROIs were drawn, the software automatically calculated the glomerular filtration rate (GFR), the Hilson perfusion index [9] (100 × [area under arterial curve to peak] / [area under renal curve]), time (s) between the peaks of the iliac and graft perfusion curves (ΔP)[13], and time (s) for the declining counts on the renal perfusion curve to reach half of the peak value (T½ of graft washout; GW½) [5, 13] of renal perfusion.

2.3 Statistical analysis

2.3.1 Variables

Variables from renal scan including GFR, Hilson perfusion index, ΔP, and GW½, were analyzed, along with clinical variables including age, sex, height, weight, diabetes mellitus, underlying renal disease, systolic blood pressure, serum Cr level at the time of the renal scan, type of donated kidney, side of the transplant, regimen of immunosuppressive therapy, infection, surgical complication and accompanying disease. In addition, we analyzed whether they had an episode of acute kidney injury (AKI) during the 3 months after transplantation (AKI was defined as increase in serum Cr by ≥0.3 mg/dl within 48 hours or increase in serum Cr to 1.5 times from baseline which is known or presumed to have occurred within the prior 7 days or urine volume <0.5 ml/kg/h for 6 h) [14]. P<0.05 was considered significant.

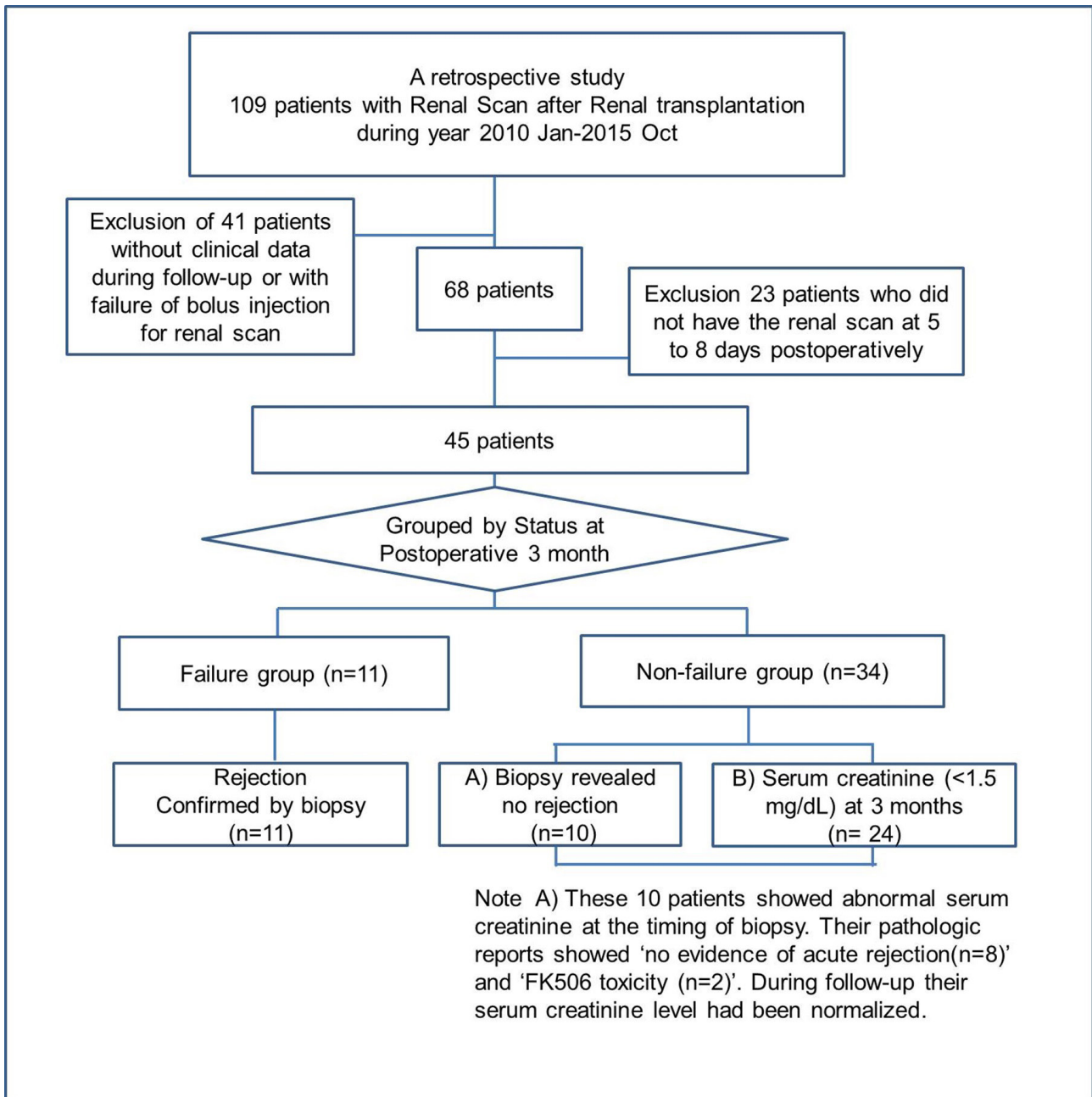### 2.3.2 Statistical analysis

We used Shapiro-Wilk normality test to evaluate data for parametric tests including t-test, chi-squared, chi-square for trend, or simple correlation. Data rejected by the normality test were analyzed by non-parametric tests including the Mann-Whitney U test, Fisher's exact test, or Wilcoxon signed-rank test. Receiver-operator curve (ROC) analysis was also performed. MedCalc software (ver. 13.3.3.0; MedCalc, Inc., Ostend, Belgium) was used for the analyses and p-values <0.05 were considered to be statistically significant.

2.4 Results

2.4.1 Enrolled patients

As shown in Figure 1, a total of 109 patients underwent renal scan after kidney transplantation at our institution

A retrospective study
109 patients with Renal Scan after Renal transplantation
during year 2010 Jan-2015 Oct

Exclusion of 41 patients without clinical data during follow-up or with failure of bolus injection for renal scan

68 patients

Exclusion 23 patients who did not have the renal scan at 5 to 8 days postoperatively

45 patients

Grouped by Status at Postoperative 3 month

Failure group (n=11)

Non-failure group (n=34)

Rejection Confirmed by biopsy (n=11)

A) Biopsy revealed no rejection (n=10)

B) Serum creatinine (<1.5 mg/dL) at 3 months (n= 24)

Note A) These 10 patients showed abnormal serum creatinine at the timing of biopsy. Their pathologic reports showed 'no evidence of acute rejection(n=8)' and 'FK506 toxicity (n=2)'. During follow-up their serum creatinine level had been normalized.

Figure 1: Enrolled patients and grouping

from January 2010 to October 2015. Sixty-four patients were excluded due to lack of clinical data, failure of DTPA bolus injection, or too-long interval between transplantation and scan, and finally, 45 patients who underwent postoperative renal scan at approximately 1 week (day 5 to day 8) after kidney transplant were included.

There were 11 patients who had transplant rejection confirmed by biopsy (Graft failure group). The other 34 patients were in non-failure group. In the non-failure group, 10 patients underwent biopsy and their biopsy results were as follows; 'no evidence of acute rejection (n=8)' and 'FK506 (tacrolimus) toxicity (n=2)'. They under-

went renal biopsy due to increased serum Cr at that time and their serum Cr level had been normalized later. In all of the patients in the non-failure group, the serum Cr level remained normal through 1 year post operation. Table 1 shows the patient characteristics for both groups.

Their underlying renal diseases were chronic glomerulonephritis (n=10), hypertensive nephropathy (n=6), diabetic nephropathy (n=3), IgA nephropathy (n=2), chronic interstitial nephritis (n=1), lupus nephritis (n=1), obstructive nephropathy (n=1) and others were unknown origin. Surgical complications were shown in some patients as follows; seroma (n=4), lymphocele (n=3), hematoma (=1),

Table 1: Patient characteristics at the time of renal scan

Variable	
Male[a]	27 (60%)
Age[b]	45±10.2
Body weight, kg[b]	64.6 ± 13.7
Height, cm[b]	164.6 ±7.8
Body mass index (BMI)[b]	23.71 ± 4.0
Type of donated kidney[a]	
DDKT	38 (84.4%)
LDKT	4 (8.9%)
ABOi LDKT	3 (6.7%)
Side of transplant, right[a]	43 (95.6%)
Time from operation to renal biopsy[b,c]	1.27 ± 0.87 months (0.3 to 3.0 months)
Time from operation to DTPA scan[b]	7± 0.89 days (5 to 8 days)

[a] n (%)
[b] mean ± standard deviation
[c] Renal biopsy was performed in 21 patients
Abbreviations: scan, scintigraphy; DDKT, deceased donor kidney transplant; LDKT, living donor kidney transplant; ABOi LDKT, ABO-incompatible LDKT.

leakage (n=1), hydronephrosis (n=1), and wound infection (n=1). Accompanying disease before kidney transplantation were shown in some patients as follows; chronic hepatitis C (n=2), dilated cardiomyopathy (n=2), gout (n=3), hepatitis B virus carrier (n=1), hypothyroidism (n=1), overlap syndrome of rheumatoid arthritis and systemic lupus erythematosus (n=1), thyroid cancer (n=2), Crohn's disease (n=1).

Infection during follow-up were shown in some patients as follows; cytomegalovirus infection (n=1), pulmonary fungal infection (n=1), influenza (n=1), MRSA (n=1), VRE (n=1), and suprapubic abscess (n=1).

2.4.2 Comparison between groups

Table 2 shows the comparison of results between groups. Among clinical variables, serum Cr level at the time of renal scan was significantly higher in the Graft failure group, and type of kidney donation was also significantly different (p=0.0208) between groups. The extended chi-

square test showed significantly different ratios of graft failure between donor types, and ABO-incompatible living donor showed a higher level of graft failure. The other clinical variables were not different between groups (Table 2).

Underlying renal disease was not significantly different between groups (chi-squared test, p=0.0601). Surgical complication was not significantly different between groups (chi-squared test, p=0.2192). Accompanying disease and infection were not significantly different between groups either.

Among renal scan variables, GFR was significantly different between groups, while there were no significant between-group differences in other renal scan variables. In two cases of failure group (rejection), the renal uptake was too low. The program could not calculate GFR. Therefore, GFR of failure group was calculated with the scan of 9 patients.

Table 3 shows that GFR of <44.48 mL/min at 1-week renal scintigraphy post operation could predict graft failure (sensitivity 88.9%, specificity 64.7%; AUC 0.724; p=0.0067); among the clinical variables, serum Cr level of >2.13 mg/dL also predicted graft failure (sensitivity 72.7%, specificity 82.4%; AUC, 0.734; p=0.0158). Predictive value of both criteria together (serum Cr >2.13 mg/dL and GFR <44.48 mL/min) and of at least one criteria (serum Cr >2.13 mg/dL or GFR <44.48 mL/min) were analyzed, and AUC values were highest for "at least one criteria positive" (0.753), although there was no significant difference between scenarios.

3 Discussion

Our results indicate that renal scan performed within 5 to 8 days after kidney transplant could predict graft failure. GFR <44.48 mL/min on renal scan can predict graft failure. Also, when it was impossible to get automatically calculated GFR due to too-low renal uptake, both of those two cases were all in failure group in our study. We also found that serum Cr level of >2.13 mg/dL predicted graft failure. Transplant recipients who meet either or both of these criteria should be closely monitored. Our result is well-correlated with previous studies that mention the importance of GFR as a prognostic factor in renal transplantation[15], and our study confirms that GFR measured by renal scan at approximately 1 week after transplantation can predict the graft outcome.

As mentioned above, in a previous study comparing post transplant on day-3 and day-7 scans, postoperative

Table 2: Comparison between groups

	Non-failure group (n=34)	Graft failure group (n=11)	P-value
Clinical variables			
Age[a]	45.4 ± 9.9	45.2 ±11.2	0.9489 [b]
Height[a]	163.0 ±7.3	168.0 ±6.1	0.0546[b]
Weight[a]	63.9 ±14.7	66.8 ±10.3	0.5453[b]
Body mass index (BMI)[a]	23.9 ±4.4	23.2 ±2.5	0.6251[b]
Diabetes mellitus (yes:no)	9:25	6:5	0.0896[c]
Hypertension (yes:no)	27:7	10:1	0.6568[d]
Serum creatinine (mg/dL) at the time of renal scintigraphy[e]	1.58 (0.55-5.886)	3 (1.1-13.3)	0.0208[f]
Systolic blood pressure (mmHg) at the time of renal scintigraphy[e]	135 (120-180)	140 (120-160)	0.2909[f]
Type of donated kidney[g] (DDKT, ABOi-LDKT, LDKT)	32, 0, 2	6, 3, 2	0.0022[c]
Right-sided transplant[g]	33	10	0.4333[d]
Episode of acute kidney injury(AKI)[h] (yes:no)	7:27	5:6	0.1089[c]
Regimen of immunosuppressant			0.6568[d]
Cyclosporine, MMF, PDS	7	1	
Tacrolimus, MMF, PDS	27	10	
Renal scan variables			
GFR[e,i]	54.3 (14.2-178.4)	34.2 (19.1-78.6)	0.0394[f]
Hilson perfusion Index[e]	130.5 (24.7-594.1)	141.4 (32.0-1002.5)	0.6369[f]
ΔP [e]	2.06 (1.09-4.48)	1.74 (1.13-4.48)	0.2259[f]
GW½	8.5 (3.5-93.81)	16.75 (3.33-88.48)	0.6446[f]

[a] mean ± standard deviation

[b] T-test

[c] Chi-square test

[d] Fisher's exact test

[e] median (range, minimum to maximum)

[f] Mann-Whitney test

[g] Number of cases

[h] Episode of AKI during 3 months after transplantation (AKI was defined as increase in serum Cr by ≥0.3 mg/dl within 48 hours or increase in serum Cr to 1.5 times from baseline which is known or presumed to have occurred within the prior 7 days or urine volume <0.5 ml/kg/h for 6 h [14]).

[i] In two cases of failure group, the renal uptake was too low. The program could not calculate GFR. Therefore, GFR of failure group was calculated with the scan of 9 patients.

Abbreviations: BMI, body mass index; DDKT, deceased donor kidney transplant; LDKT, living donor kidney transplant; ABOi-LDKT, ABO-incompatible LDKT; GFR, glomerular filtration rate; ΔP, time (s) between the peaks of the iliac and graft perfusion curves; GW½, time (s) for declining counts on the renal perfusion curve to reach half of the peak value (T½ of graft washout); MMF, Mycophenolate mofetil; PDS, prednisolone

Table 3: ROC analysis to predict graft failure

Variable	AUC	SE	95% CI	p
Serum Cr[a]	0.734	0.0970	0.581 to 0.854	0.0158
GFR[b]	0.725	0.0832	0.568 to 0.850	0.0067
Positive both criteria[c]	0.730	0.0830	0.577 to 0.083	0.0056
Positive at least one criteria[d]	0.763	0.0621	0.613 to 0.877	<0.0001

Foot note
a, Serum Cr at the time of renal scan >2.13 ng/dL
b, GFR on renal scan <44.48 mL/min (n=43)
 In two cases, renal uptake was so low that GFR could not be calculated.
c, serum Cr >2.13 ng/dL AND GFR<44.48 mL/min
d, serum Cr >2.13 ng/dL or GFR<44.48 mL/min
Abbreviation: AUC, area under curve; SE, standard error; CI, confidence interval

day-3 scans could predict graft failure, while the day-7 scans could not [10]. That study defined graft failure by long term follow-up (average follow-up duration approximately 67.4 months), whereas the follow-up to graft failure in our study (approximately 3 months) was much shorter. In addition, the previous study used a MAG3 tracer, but it has been reported that DTPA is more sensitive than MAG3 for diagnosing dysfunction [16]. These differences of follow-up period and tracer might have caused the different results, and additional study with a larger number of patients and longer follow-up is needed.

Other variables from renal scintigraphy, including the Hilson perfusion index, ΔP, and GW½, did not predict graft failure in our study. Yazici et al. have reported that patients whose grafts were failing at 3 months after transplant had high GW½ or high ΔP on renal scans performed within 2 days after transplant [6]. Those authors determined graft function by serum Cr levels. GW½ and ΔP were also high in the failure group in our study, but the finding was not statistically significant. Gupta SK et al. have also reported that among several variables, only Hilson's perfusion index proved to be useful for correlation with pathologic results [7]. However, the goal was correlation between renal scan and pathologic results. Therefore, in their study, most of the enrolled patients underwent biopsy, and the interval between renal scan and biopsy was short (within five days). In our study, the goal was to predict graft failure and not to compare the results of examinations which were done at almost the same time.

In analyzing renal function by scintigraphy, it is very important to draw the ROI in the right place [17]. A purely automated definition of the ROI cannot accurately identify the boundaries of the kidneys [18]. We used a combination of automatic and manual methods, and the same technician drew the ROIs, all of which were confirmed by a nuclear medicine physician.

Three of the patients who had ABO-incompatible living donor transplants had graft failure in this study. Due to the small number of cases, we did not analyze this type of transplant separately. Once again, further study with a larger number of cases and more information will be needed.

There are several limitations in this study. This is a retrospective study. In some cases, clinical information, such as the need for dialysis in the first week, was not available. Delayed graft function is typically defined in patients who need dialysis in the first week after transplant, and lacking those clinical data, we could not distinguish delayed graft function in our analysis. Renal scans were performed 5 to 8 days after transplantation, so patients with delayed graft function might have been included among the patients who were categorized as non-failure group in our analysis. However, in all of the patients in the non-failure group, the serum Cr level remained normal during the 1st year post operation which means our "non-failure group" was really "non-failure" and remained "non-failure" for a year. Acute tubular necrosis (ATN), also known as acute vasomotor nephropathy, is a common cause of delayed graft function [5, 17], but the presence of ATN was not analyzed in our study because of the timing (3 months post

transplant) of the renal biopsy. Patients with other complications, including cyclosporin toxicity, were also categorized as non-failure group because of these limitations. The small study population is also a limitation.

4 Conclusion

DTPA renal scan performed at approximately 1 week after renal transplantation can predict graft outcome at 3 months. Lower GFR can be used to predict graft failure at 3 months.

Conflict of Interest: The authors declare that they have no conflicts of interest.

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