Am J Nucl Med Mol Imaging 2014;4(3):213-224
www.ajnmmi.us /ISSN:2160-8407/ajnmmi1312001

Original Article

Quantitative ^{99m}Tc DTPA renal transplant scintigraphic parameters: assessment of interobserver agreement and correlation with graft pathologies

Sandeep K Gupta[1], Guy Lewis[1], Kerry M Rogers[1], John Attia[2,3], Kirk Rostron[1], Leanne O'Neill[1], Annah Skillen[1], Suresh Viswanathan[1]

[1]Department of Nuclear Medicine and PET, John Hunter Hospital, Newcastle, New South Wales, Australia; [2]Department of Medicine, John Hunter Hospital, Newcastle, New South Wales, Australia; [3]Centre for Clinical Epidemiology and Biostatistics, Hunter Medical Research Institute, University of Newcastle, Newcastle, New South Wales, Australia

Received December 9, 2013; Accepted February 19, 2014; Epub April 25, 2014; Published April 30, 2014

Abstract: Various ^{99m}Tc DTPA scintigraphic quantitative parameters for renal graft function assessment have been recommended, but none is universally accepted. In this study, 439 dynamic renal transplant scintigraphies (DRTS) were retrospectively analysed. In the first set of studies, four observers analysed the 47 random DRTS and interobserver agreement of eleven derived parameters was assessed. In the other set of studies, 181 instances of DRTS, performed on 127 recipients with renal biopsies within five days of each other were selected for correlation with pathology. Hilson's Perfusion index (HI), ΔP, P:PI, P:U & T10 were selected for this analysis. The pathologies were categorized into renal vascular compromise (RVC; n = 20), acute tubular necrosis (ATN; n = 40), vascular rejection (VR; n = 34), interstitial rejection (IR; n = 33), normal (NOR; n = 36) and unclassified pathologies (n = 18). A majority of the parameters showed good Intraclass correlation (ICC). HI differentiated well between grafts with RVC and the remainder of the study cohort, ($p < 0.0001$; AUC = 0.84); at a cut-off > 278, it had 84% sensitivity and 78% specificity (Likelihood ratio = 3.8). At < 278, it had 98% 'negative' predictive value for RVC. HI also showed reasonable association with VR ($p = 0.02$; AUC = 0.62) and IR ($p = 0.009$; AUC = 0.65). However, significant overlap of HI values between various subgroups was noted. Other parameters had good ICC but were not effective in differentiating graft pathologies. Of the measured parameters, only HI proved to be useful for the pathological assessment, particularly in the identification of vascular compromise. This parameter, however, has lower specificity in differentiating the other pathologies.

Keywords: Acute tubular necrosis, Hilson's index, interobserver agreement, quantitative renal transplant DTPA scintigraphy, rejection, renal artery stenosis, renal graft

Introduction

Various pathologies may complicate a successful renal transplantation and both early detection and accurate identification are essential for optimal management and prevention of loss of graft function [1]. Early, accurate diagnosis of complications of renal transplantation is, however, difficult to achieve. The current gold standard test, percutaneous needle biopsy, is invasive in nature and may lead to additional complications (e.g. perirenal haemorrhage, arteriovenous fistula, pseudoaneurysm, and collecting system laceration etc.); sampling errors and inter-observer variations in biopsy reporting are additional concerns [2, 3]. Imaging e.g. nuclear medicine scintigraphy and doppler ultrasound (US) form an integral part of the diagnostic evaluation in the non-invasive assessment of graft pathologies [4]. Doppler US is very useful in delineating structural pathologies but it has a limited role in diagnosing and differentiating various parenchymal processes [5].

Dynamic renal transplant scintigraphy (DRTS) provides simple, non-invasive and safe assessment of the function of renal grafts, but has

been criticised for its subjective nature and reliance on visual interpretation. Also, visual comparisons are insensitive to temporal changes in perfusion and an objective assessment is preferable [6, 7]. To overcome this problem, many objective scintigraphic parameters have been described previously but none has been universally accepted. Furthermore, there are important methodological variations in the derivation of these parameters. Due to a lack of comparative studies, the last consensus report from the Radionuclides in Nephrourology meeting in 1998 was unable to provide guidelines on quantitative data analysis of DRTS [8].

In order to address the lack of published literature regarding the validity of various parameters, we designed a retrospective study assessing and comparing the value of eleven scintigraphic parameters, selected after review of the literature. Many other parameters were not be selected either due to differences in the acquision protocol or due to more complicated analysis e.g. deconvolution analysis. Firstly, we investigated the interobserver agreement (IOA) of the selected parameters, as a measure of reproducibility. Secondly, as differences in study protocols and analysis programs could lead to between-institution differences, even in highly reproducible parameters, we calculated reference values for our study cohort and compared these with published reference values. And finally, a subset of parameters, were correlated with the findings of percutaneous needle biopsy.

Methods

In the Department of Nuclear Medicine & PET at John Hunter Hospital, Newcastle, Australia, DRTS are performed routinely as a protocol on day 1 and day 4 post-transplantation (release of vascular clamps occurs on day 0), and subsequently if required. The images have been acquired on LEHR parallel-hole collimation using 128 x 128 matrix on Siemens ECAM (Siemens Medical Solutions Inc., Signature series, Erlangen, Germany), with 140 keV photopeak and 15% acceptance window. The studies prior to 2002 were acquired on Elscint SP-4 and Elscint SP-6 gamma cameras (Haifa, Israel). 300-400 MBq of ^{99m}Tc DTPA is intravenously administered and dynamic images with 2 seconds per frame for one minute (perfusion phase) and further 1 minute frames for another 19 minutes (clearance phase) are acquired in the anterior projection with the patient lying supine. If the patient is unable to lie flat, camera position is adjusted to obtain the true anterior image. The bolus is given by a single push of approximately 0.2-0.5 mL of tracer, followed by quick 10 ml normal saline flush. This method is routinely used in our institution and has been found to provide satisfactory bolus for perfusion phase assessment.

Study cohort & analysis programme

Four hundred and thirty nine DRTS, performed on 214 patients between 1995 and 2008, were investigated. DRTS with non-viable grafts (identified visually as photopaenic defects at the site of transplant), were excluded because quantitative analysis of these scans is neither feasible nor clinically required. An in-house programme, which accommodated as many scintigraphic factors as possible, was designed using a Programmable Interactive X-Windows Imaging Environment (PIXIE). Regions of interest (ROIs) are manually drawn over the kidney (whole graft), background (half perirenal lateral to the graft) and arteries (the distal aorta and the ipsilateral iliac artery distal to the graft). The iliac artery ROI is drawn manually in the zoomed image after operator selects the best visualized frame. The length of this ROI is approximately third of the renal length and is drawn immediately distal to the kidney. Since pixel corrected counts are used for all the analyses, both renal and arterial ROIs are tightly drawn and inclusion of count poor adjoining pelvic tissue is carefully avoided. This guide was followed for more accurate quantitative assessment and to reduce intra- and interobserver differences. Perfusion- and background-corrected clearance time-activity curves are generated and HI (Hilson's Index) [6], KI (Kirchner's Index) [9], KAR (Kidney to Arterial Ratio) [10], ΔP (Delta P) [11, 12], T_{pmax} (Time to Peak perfusion) [12], GW t½ (Graft Washout t½) [11], P:Pl (Peak perfusion to Plateau ratio) [11, 13], P:U (Peak perfusion to uptake ratio) [13], R20/3 (Renal count ratio at 20 min to 3 min) [8, 14, 15], T10 (% Excretion at 10 min from peak uptake) [16] and T20 (% Excretion at 20 min from peak uptake) [16] were derived. These parameters have been further elaborated in our previous paper [17]. For analyses of perfusion parameters, studies with poor boluses (defined as half-time of the down-slope on the iliac perfusion time-activity curve > 18 seconds) were excluded.

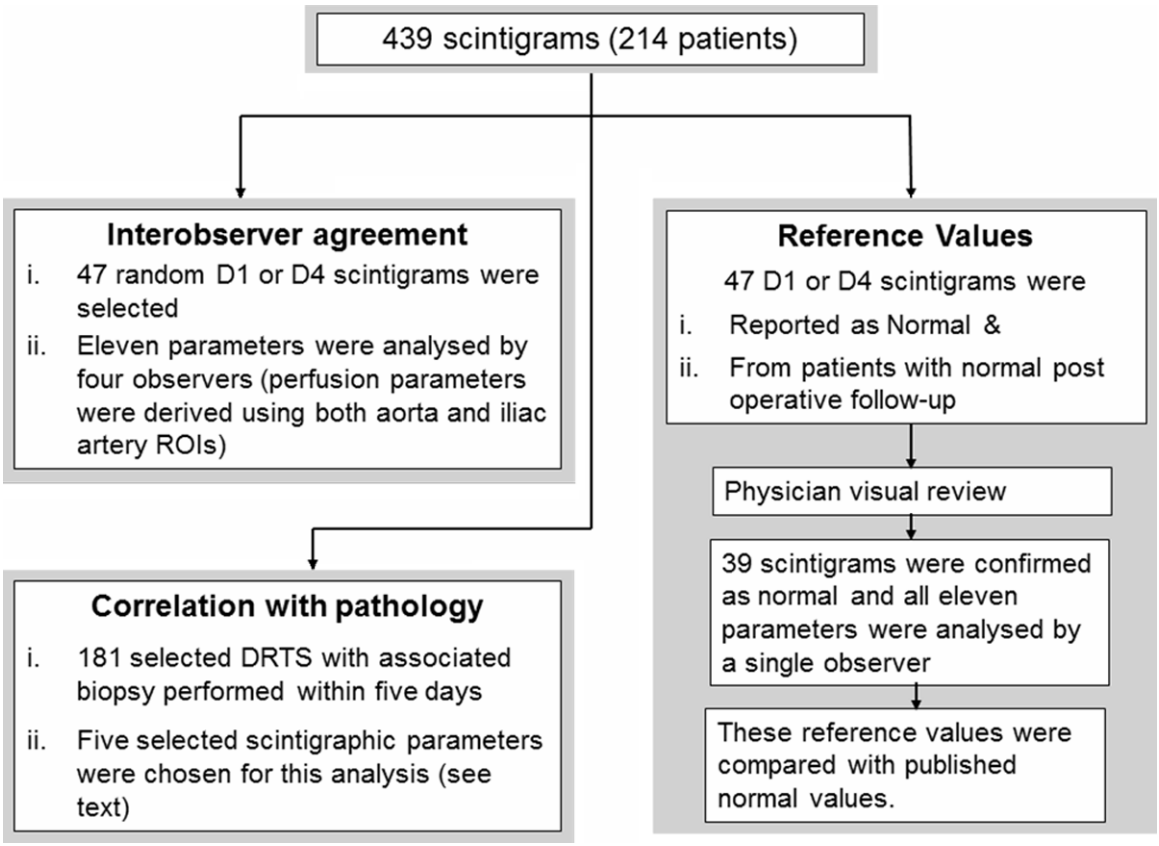

Figure 1. Flowchart demonstrating the method of the study. (DRTS, Dynamic renal transplant scintigraphy).

Interobserver agreement

Of the study cohort, 47 D1 or D4 protocol studies were randomly selected and were analysed independently by four observers (SG, KR, LS, AS) (**Figure 1**). Intraclass correlation coefficients (ICC) were calculated as a measure of IOA. For a few of these studies, graft function was very poor, resulting in difficulties in accurately identifying the renal ROI. This resulted in some extreme values (occasionally several orders of magnitude outside the normal range) with substantial inter-rater variability, particularly in parameters calculated with renal counts as denominator (e.g. HI). In clinical practice, these studies would be visually identified as highly abnormal, and calculated parameters would be clinically unimportant. In recognition of the difficulties in reading these highly abnormal studies, we calculated Intraclass Correlation Coefficients (ICC) for each parameter twice, firstly including and then excluding scintigraphies classed as "severe outliers" by all observers. Values less than the 25th percentile minus three times the interquartile range or greater than the 75th percentile plus three times the interquartile range (for this sample) were classified as 'severe outliers', in accordance with a statistical definition given by Sheskin [18].

Reference values of parameters

For the purpose of assessment of reference values of the parameters in our study population, reports for all available day 1 and day 4 protocol DRTS performed between 1995 and 2008 were reviewed and studies reported as normal or near normal were selected. These DRTS were further screened and those from patients with uncomplicated post-operative stays and serum creatinine values < 132 mmol/L at one year were considered as potentially normal. The 47 selected studies were reviewed by an experienced physician (SV), who confirmed 39 normal studies, which were then analysed by single operator (SG) to derive scintigraphic parameters (**Figure 1**).

Table 1. Interobserver agreement for early post-operative period scintigraphic parameters

	Parameters	Intraclass correlation (Confidence interval)		Number of severe outliers	Cut off for the severe outlier value
		All patients	Excluding severe outliers*		
Perfusion parameters using Aortic ROI	HI	0.43 (0.28-0.59)	0.77 (0.66-0.85)	3	> 888
	KI	0.83 (0.75-0.89)		0	†
	KAR	0.89 (0.83-0.93)		0	†
	ΔP (Sec)	0.67 (0.55-0.79)	0.61 (0.47-0.74)	1	> 11.8
Perfusion parameters using Iliac artery ROI	HI	0.73 (0.63-0.83)	0.86 (0.79-0.91)	2	> 557
	KI	0.94 (0.90-0.96)		0	†
	KAR	0.94 (0.90-0.96)		0	†
	ΔP (Sec)	0.6 (0.4-0.7)		0	> 9.4
Other perfusion parameter	T_{pmax} (Sec)	0.36 (0.22-0.53)	0.30 (0.15-0.47)	1	> 17.0
Filtration/Washout Phase Parameters	P:PI	0.75 (0.63-0.84)	0.61 (0.46-0.75)	1	< 0.27
	GW t½ (Sec)	0.45 (0.26-0.62)	0.81 (0.72-0.82)	1	> 49.5
Extraction/Uptake parameter	P:U	0.97 (0.95-0.98)		0	†
Excretion/Clearance parameter	R20/3	0.86 (0.78-0.91)		0	†
	T10	0.95 (0.92-0.97)		0	†
	T20	0.84 (0.75-0.90)		0	< 0.67

*Severe outliers were defined as those scored as follows by all raters: [< 25th percentile – 3x interquartile range] or [> 75th percentile + 3x interquartile range] (see text).
†Not applicable: statistically identified cut-off was negative number.

Table 2. Reference values for early post-operative period scintigraphic parameters in our study cohort

	Variable	Reference values (current study population)			Mean value described in literature
		Median	5 percentile	95 percentile	
Perfusion parameters using Aortic ROI	HI	254	93	674	*
	KI	0.69	0.35	1.45	0.87 [9]
	KAR	0.85	0.45	1.7	1.13 [10]
	ΔP (Sec)	4	2	6.01	*
Perfusion parameters using Iliac artery ROI	HI	116	57	269	96 [6]
	KI	0.89	0.48	1.84	*
	KAR	1.15	0.7	2.3	*
	ΔP (Sec)	3.7	1.7	6.1	2.4-3.4 [11]
Other perfusion parameter	T_{pmax} (Sec)	9.1	7.1	12.0	*
Filtration/Washout Phase Parameters	P:PI ratio	1.55	1.14	2.74	1.48-1.62 [11]
	GW T½ (Sec)	14.0	6.9	28.4	< 17 [11]
Extraction/Uptake parameter	P:U ratio	0.038	0.029	0.059	1.03 [13]
Excretion/Clearance parameter	R20:3	0.51	0.39	0.78	0.8 [15]
	T10	40.6	11.7	55.5	*
	T20	49.2	22.3	63.0	*

*Mean values of these parameters could not be identified in the published literature.

Pathological correlation

Of the study cohort, patients who had renal biopsy and renal scintigraphy performed within five days of each other were selected. Of the many parameters (**Table 1**), HI, ΔP, P:PI, P:U and T10 were selected for this analysis. Selection of these parameters was based on good IOA (**Table 1**) and their value in the prognosis [17]. The perfusion parameters were assessed using iliac ROI as in general, these had better ICCs than the equivalent aortic values. The final diagnosis of the graft pathology was based on histopathology results. Concurrent radiological imaging (e.g. MRI, Angiography or Doppler etc.) reports were reviewed for all

Table 3. Median values of scintigraphic parameters in various graft pathologies*

		HI**	ΔP**	P:PI	T10	P:U
Normal biopsy (NOR; n = 36)	Median (Range)	169 (56-470)	4.2 (2.0-28.1)	1.43 (0.94-1.95)	29.5 (1.7-61.7)	0.037 (0.000-0.060)
	Significance***	**p = 0.02**	N.S	N.S	N.S	N.S
Interstitial rejection (IR; n = 33)	Median (Range)	154 (77-431)	4.0 (2.0-16.0)	1.25 (1.02-1.81)	20.5 (1.0-46.3)	0.035 (0.022-0.052)
	Significance***	**p = 0.009**	N.S	N.S	N.S	N.S
Renal vascular compromise (RVC; n = 20)	Median (Range)	377 (158-1467)	6.1 (2.0-20.1)	1.37 (0.78-3.16)	23.0 (-13.7-47.3)	0.039 (0.024-0.058)
	Significance***	**p < 0.0001**	**p = 0.02**	N.S	N.S	N.S
Vascular rejection (VR; n = 34)	Median (Range)	220 (84-600)	4.2 (0.4-15.6)	1.40 (0.75-2.95)	22.7 (3.8-46.8)	0.043 (0.012-0.063)
	Significance***	**p = 0.02**	N.S	N.S	N.S	N.S
Acute tubular necrosis (ATN; n = 40)	Median (Range)	196 (94-496)	6.0 (1.8-18.2)	1.39 (0.86-3.93)	30.2 (4.2-52.1)	0.043 (0.019-0.080)
	Significance***	N.S	N.S	N.S	N.S	N.S

*18 studies of unclassified pathologies subgroup were not separately analysed (see text). **Perfusion parameters derived using iliac artery ROIs. ***Significance of difference from remainder of the study cohort using Mann-Whitney test (the significant values are highlighted in bold).

Table 4. Accuracy of scintigraphic parameters in assessment of various graft pathologies as measured by Receiver Operator Characteristic curve analysis (ROC analysis)*

	HI				ΔP
	RVC	Vascular rejection	Interstitial rejection	All abnormal***	RVC
AUC (95% CI)	0.84 (0.76 to 0.92)	0.62 (0.51 to 0.73)	0.65 (0.50 to 0.79)	0.62 (0.52 to 0.73)	0.67 (0.55 to 0.79)
Cut-off selected**	278	194	189	259	4.1
Sensitivity (95% CI)	84% (60 to 97)	70% (51 to 84)	75% (57 to 89)	36% (28 to 45)	84% (60 to 97)
Specificity (95% CI)	78% (71 to 85)	54% (45 to 63)	56% (48 to 65)	88% (73 to 97)	50% (41 to 58)
Positive likelihood ratio	3.8	1.5	1.7	3	1.7
Negative likelihood ratio	0.2	0.6	0.5	0.7	0.3

*Only parameters, found to be significant on Mann-Whitney test (**Table 3**) are included for this analysis. These perfusion parameters were derived using iliac artery ROIs. **Higher values than the cut-offs are abnormal. ***I.e. normal biopsies in the study cohort versus remainder of the cohort.

patients and if needed, patients' notes were reviewed for clarification. The biopsy results were categorized as normal (NOR), vascular rejection (VR), acute tubular necrosis (ATN), interstitial rejection (IR) or unclassified pathologies. However, if there was evidence of significant renal vascular compromise (RVC; e.g. extrinsic compression, renal artery stenosis or renal vein thrombosis) on concurrent imaging and clinically, the diagnosis was categorized as RVC. For the duration of study period, the post-operative management protocol of transplant recipients has changed and there is a trend to use more potent induction immunosuppression with tracrolimus, MMF and anti-CD-25 antibodies [19]. Previous and current management protocols, including immuno-suppression medications, can be assessed online at the Australia & New Zealand Dialysis and Transplant Registry (ANZDATA) website www.anzdata.org.au.

Mann-Whitney analyses were performed to compare parameters for studies within or outside diagnostic categories (i.e. NOR/abnormal; RVC/no RVC; IR/no IR; VR/no VR; ATN/no ATN). Receiver Operator Characteristic (ROC) curve analysis was used to quantify the agreement of scintigraphic parameters with the biopsy-derived diagnosis and cut-off values that maximised the sum of sensitivity and specificity were derived. Sensitivities, specificities and likelihood ratios were calculated using the selected cut-offs. Based on the area under the ROC curve (AUC), parameters were classed as inaccurate (AUC < 0.5), of low accuracy (AUC = 0.5-0.7) or moderately accurate (AUC = 0.7-0.9) [20].

All statistical analyses were performed with the StatsDirect statistical package (Version 2.7.7, Altrincham-England: StatsDirect Ltd. 2009).

Results

Interobserver agreement

Forty seven DRTSs, performed on 27 renal transplant recipients (median age 50 yrs; range 21 to 70 years, M:F = 21:6; Living : Deceased donor = 20:7) were analysed (**Table 1**).

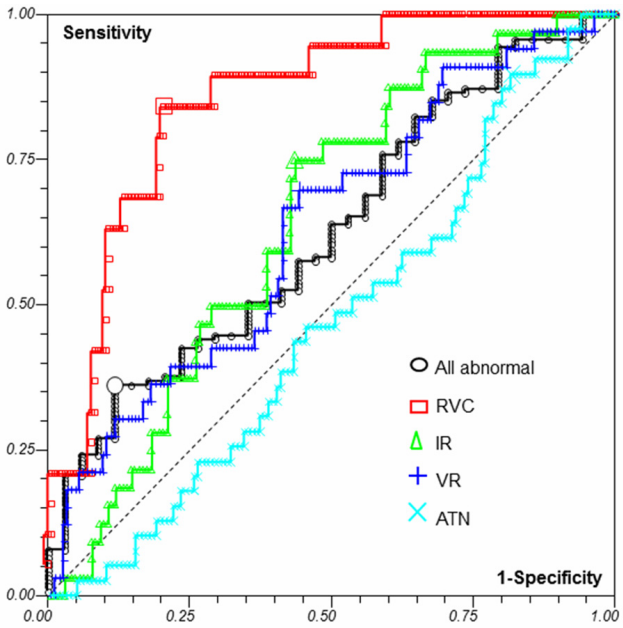

Figure 2. ROC curves Hilson's Perfusion Index (HI) measurements in various pathologies (see also **Table 4**).

Among perfusion parameters, IOA was excellent for KI & KAR calculated using iliac arterial ROIs, (ICC: 0.94 & 0.94 respectively). The IOA was slightly poorer for the same parameters calculated using aortic ROIs (ICC: 0.83 & 0.89 respectively). The IOA was worse for HI calculated using iliac arterial ROIs (ICC - 0.73) but exclusion of two severe outliers improved the ICC to 0.86. Although KI and KAR appear better than HI on the basis of intraclass correlation when all scintigrams are included, ICC for HI is improved after the exclusion of the most severe outliers, suggesting that the reliability of this parameter is acceptable except in the case of severely impaired grafts. ICC was relatively low for ΔP and was poor for T_{pmax} (0.36).

ICC was poorer for filtration parameters than for perfusion parameters. P:PI had an ICC of 0.75, which reduced to 0.61 after the exclusion of a severe outlier. GW t½ ICC improved from 0.45 to 0.81 after exclusion of a severe outlier. ICC was excellent for the extraction and excretion parameters, and no severe outliers were identified (**Table 1**).

Reference scintigraphic values

Reference values were derived from 39 normal studies, performed on 26 patients (Mean age 47; M:F = 11:15; Living : Deceased donor = 20:6) and compared, whenever possible, with the values reported in the original descriptions (**Table 2**). Median values of iliac arterial HI and ΔP and aortic KI & KAR (116, 3.7 sec, 0.69 and 0.85 respectively), were similar to the values reported in the original descriptions (96, 2.4 to 3.4 sec, 0.87 and 1.13 respectively). Similarly, median values of non-perfusion parameters (P:PI - 1.55; GW t½ - 14.0; R20/3 - 0.51) were comparable to published values. A substantial difference was observed between median P:U in our study (0.038) and the published value (1.03), which probably results from a difference in frame timing (2 seconds frame for perfusion in our study, compared with one minute for the published study [13]).

Pathological correlation

181 DRTS on 127 recipients (M:F = 74:53; mean age 46 years, Live : Deceased Donor = 58:69) were analysed. 154 (85%) of these studies were performed on the day or within 3 days of the biopsy (**Figure 1**). The scintigraphies were performed on average 39.6 days post renal transplantation (median 5 days); 158/181 (87%) scintigraphies were performed within one month of the transplantation. For each parameter, **Table 3** presents median values, ranges and significance in each pathology subgroups. 18 studies had other primary diagnoses on biopsy, with sample sizes that were too small for subgroup analyses (unclassified pathologies). These subgroups included – Interstitial disease/fibrosis (n = 7), mixed pathologies (n = 8) and unspecified thrombotic microangiopathy (n = 3).

The median HI for abnormal biopsy was higher compared to HI for normal biopsies (201 versus 169 respectively, p = 0.02; **Table 3**). There were significant differences in HI between patients with each pathology subgroup (RVC, IR and VR) versus remainder of study cohort with the exception of ATN. ΔP could only differentiate between patients with RVC and patients without RVC (median value 6.1 sec; p = 0.02), although median values of ΔP in the ATN subset were also noted to be higher (Median value 6.0, p = NS). Median P:PI, T10 and P:U values in each diagnostic subset were not significantly different from the remainder of the study cohort

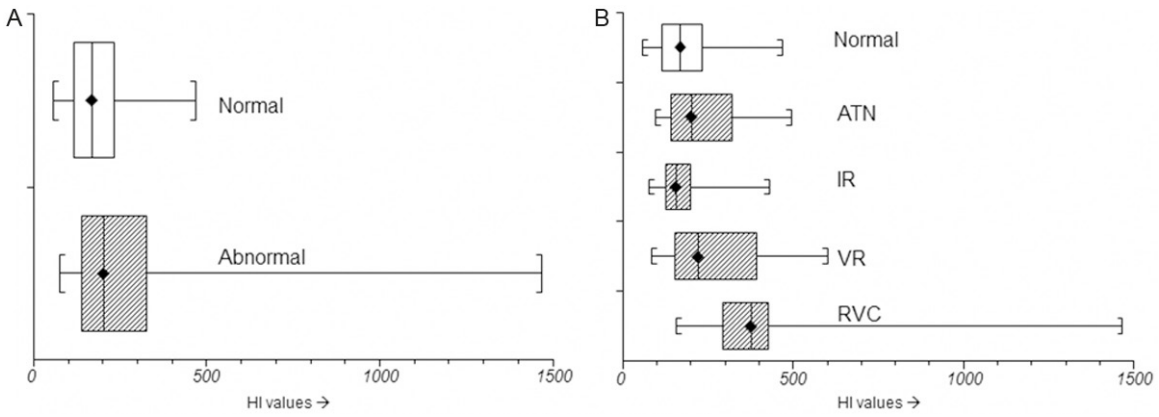

Figure 3. Box & whisker plot demonstrating spread of HI values in A. Normal biopsy versus abnormal biopsy (including RVC) and B. Various pathologies.

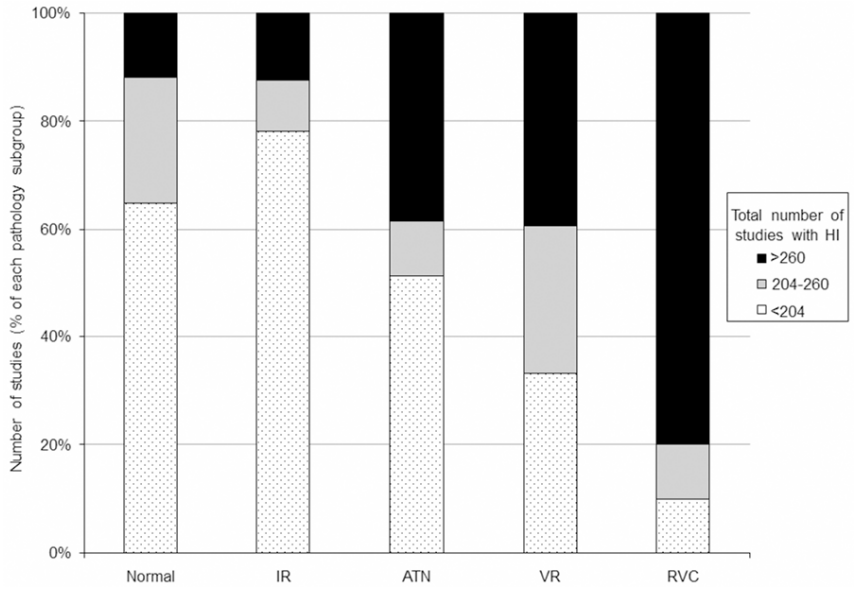

Figure 4. Bar chart showing number of studies at two HI cut-offs in each pathology subgroup. On X-Axis, pathology subgroups and on the Y-axis, total number of studies in percentage compared to all studies of that subgroup.

on Mann-Whitney analyses (**Table 3**). Given the multiple tests being done (5 parameters and 5 pathologies = 25 tests) only the significant result for HI in differentiating between patients with and without RVC survived Bonferroni correction (0.05/25 = 0.002).

ROC analysis was performed only on the parameters (HI & ΔP) that had shown significance on Mann-Whitney test. On analysis of individual pathology subgroups, HI showed fairly robust AUC for identification of RVC (0.84), and relatively lower accuracy in identifying VR (AUC - 0.62) & IR (AUC - 0.65) (**Table 4**; **Figure 2**). HI below the cut off of 278 had an excellent 'negative' predictive value for RVC (98%; 95% CI 93.3-99.5). HI values above 259 was highly specific (88%) for detection of a biopsy-defined abnormality or RVC. A cut off value of HI, below which graft abnormalities are excluded, could not be identified. Discrimination between grafts with RVC and those without on the basis of ΔP was also acceptable, (AUC = 0.67; 95% CI = 0.55 to 0.79); although this is significantly less compared to the HI.

ROC analysis of RVC + VR subgroup versus remainder of the study cohort showed moderate accuracy (AUC = 0.76). At a cut off above 204, HI showed a sensitivity of 75% and a specificity of 66% for the combination of RVC and VR (positive likelihood ratio 2.2). This analysis was performed to assess value of higher HI in the detection of VR if RVC can be excluded with other non-invasive imaging. ROC analysis after the exclusion of the RVC subgroup was also performed. In RVC, the values were higher, which could lead to underestimation of the parameter values for other pathology categories. Another reason for this analysis was to

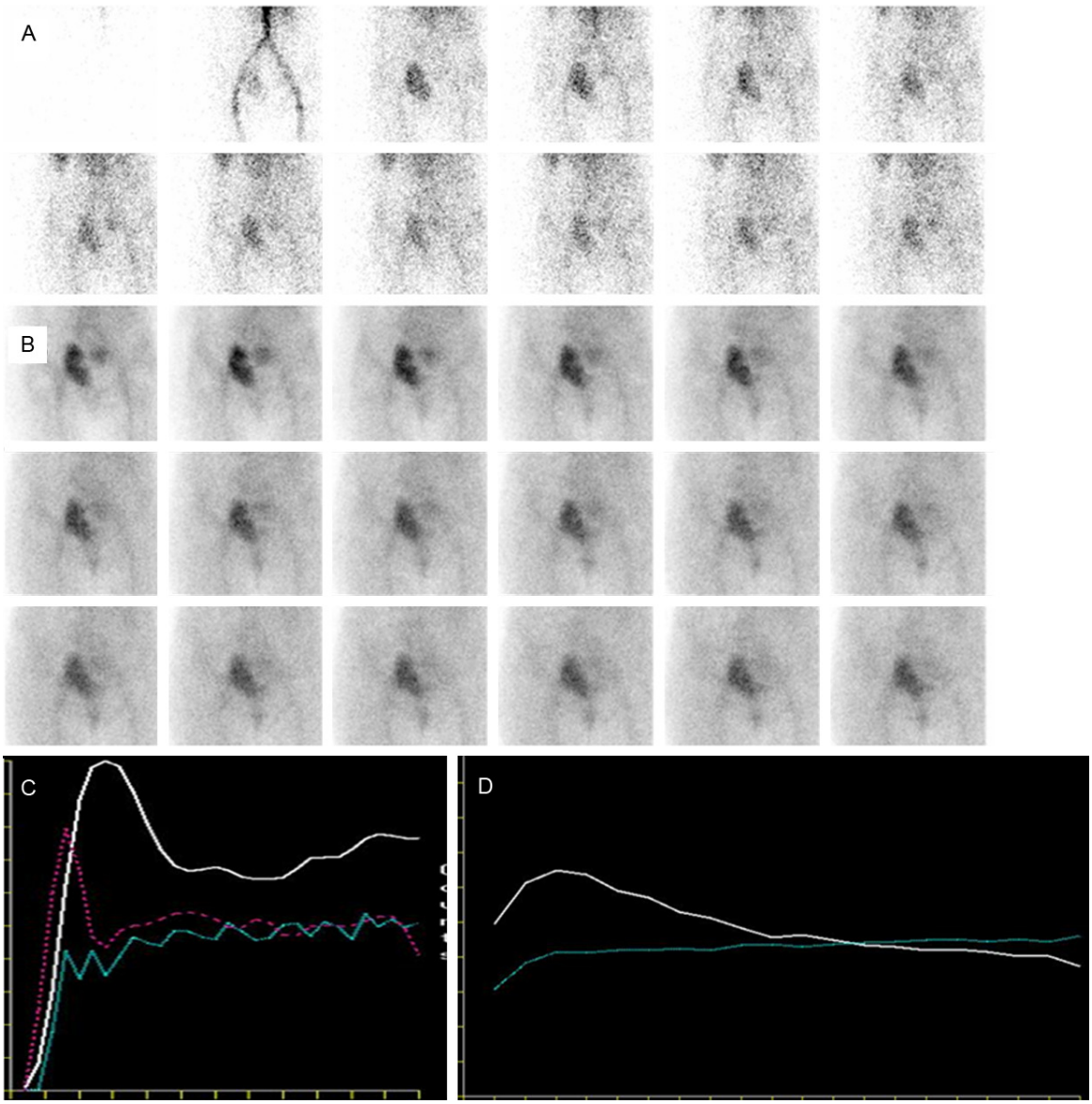

Figure 5. DRTS of a case of impaired graft function eight days post live donor transplantation showed high HI of 259. The biopsy showed findings consistent with vascular rejection. A. Perfusion phase (shown in 4 second per frame) show slightly delayed flow of tracer to the renal graft in the right iliac fossa. B. Clearance phase (1 minute per frame) show good extraction of tracer with some excretion of tracer activity over 20 minutes. C. Perfusion phase curves: pink- Iliac artery, white- renal and blue- background. D. Clearance phase curves: white- renal and blue- background.

assess the parameter value if RVC has been excluded by sonography prior to scintigraphy. Only HI differentiated between patients with VR and those without (at cut off = 204, AUC = 0.68; sensitivity 67% & specificity 65%) (Data not shown). Various other combinations of the parameters were not found to be significant for diagnosis of a particular pathology (Data not shown).

Since only HI showed significance on Mann-Whitney and ROC analyses, we examined the spread of its values using Box and whisker plots and bar charts after categorizing each pathology subgroup using a cut-off of 204 and 260. As depicted in **Figure 3**, HI values in the RVC subset were strikingly different from the other diagnostic subsets. However, HI values overlapped for the other subgroups. In the bar chart (**Figure 4**), a majority of studies in NOR or IR subgroups had HI of < 204. In contrast, a majority of patients in the RVC subgroup had HI > 260. However, in the ATN and VR subgroups, almost similar number of studies (approximate-

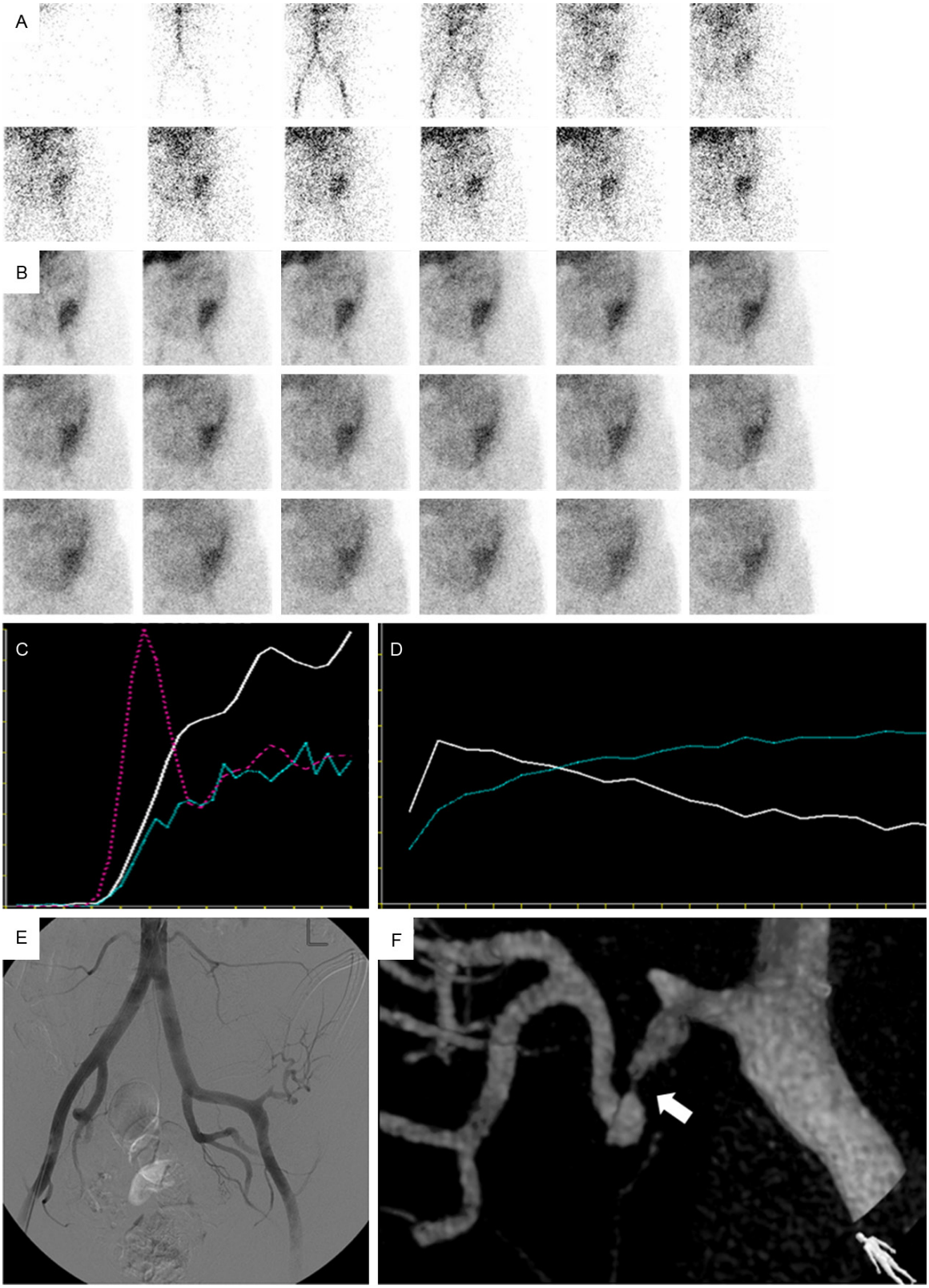

Figure 6. DRTS of a case of poor graft function four months post deceased donor transplantation showed high HI of 563. (A) Perfusion phase (shown in 4 second per frame) show delayed flow of tracer to the renal graft in the left iliac fossa. (B) Clearance phase (1 minute per frame) show reasonable extraction of tracer with reduction of tracer

activity over 20 minutes together with increased background activity. (C) Perfusion phase curves: pink- Iliac artery, white- renal and blue- background. (D) Clearance phase curves: white- renal and blue- background. (E) Angiogram revealed reduced perfusion to the graft due to a 95% stenosis just proximal to the U bend in the vessel, which is better appreciated in the supplementary 3D angiography film run (F, arrow).

ly 40%) had HI > 260; although number of studies with HI between 204 and 260 is higher in VR. This indicates that a higher HI, even after exclusion of RVC, may not be able to differentiate ATN versus VR. A couple of cases have been depicted in **Figures 5** and **6**.

Discussion

We found good to excellent inter-observer agreement among the majority of scintigraphic parameters including HI. Previously, HI was reported to have lower IOA by Ellam et al in 1983 [21] and good IOA by El-Maghraby et al in 1998 [12]. Reliability in calculation of perfusion parameters has been predicted to improve with use of the aortic rather than iliac arterial ROI, due to easier visualisation [22]. However in this study, the IOA was better for perfusion parameters calculated using iliac arterial ROIs, possibly because overlying soft tissue structures and mesenteric vasculature increase the uncertainty in aortic counts with variations in ROIs. The IOA for most non-perfusion parameters was better than agreement for perfusion parameters, because the latter are dependent on accurate identification of arterial ROIs in addition to renal ROIs.

In a separate sub-study, we calculated reference parameters and compared these with published reference values, where available (**Table 2**). Our values were similar to the published values, but often indicative of slightly worse renal function, which could be due to our restriction of the cohort to early post-operative studies.

For the assessment of graft pathologies, only HI showed significant differences in values in a pathology subgroup compared to the remainder of the study cohort (**Table 3**). A higher HI value indicates graft pathology (ATN, VR or RVC) and lower values correlate with normal biopsy or IR. However, even at the optimum cut-offs identified using the ROC analysis, this parameter appeared non-specific in differentiating between various graft pathologies (**Figure 4**). Nonetheless, much clinically useful information can be derived using this parameter, e.g. a value $\geq$ 260 has 88% specificity for an abnormality (RVC or a parenchymal pathology) and a value < 278 has 98% negative predictive value for RVC. In conjunction with a very good correlation with graft survival [17], this parameter may be considered the most useful scintigraphic parameter for the graft function assessment. Although ΔP showed some significance for RVC, the significance of this correlation as well as the AUC was weaker than for HI. Aktas et al [23] and Jackson et al [24], in contrast to our study, had shown that P:PI is more sensitive and specific for identifying acute rejection than HI. We failed to replicate these results, probably due to inclusion of a variety of pathologies rather than inclusion of paired pathologies. A recent study by Yazici B et al showed good sensitivity of GW t½ and R20/3 for ATN and AR, compared to the normal grafts [25]. We didn't include these parameters for pathological assessment due to lower interobserver correlation with the former and no relation with graft survival with the later parameter.

HI was originally described by Hilson et al in 1978, in a retrospective study on 276 DRTS [6]. They found a mean HI of 96 for normal grafts, 153 for the ATN group, 256 for the rejection group and 255 for the patients with renal artery stenosis. Subsequent studies show mixed results; Gedroyc et al in 1986 studied 43 grafts and found no significant differences in values of rejection, cyclosporine nephrotoxicity [26], whereas in 1993, Al-Nahhas et al, showed that HI had 86% sensitivity and 94% specificity in differentiating VR and cyclosporine nephrotoxicity [27]. The methodology of our study is different to the earlier studies as we included 'all' grafts, rather than grafts with 'paired' or 'selected' pathologies; this should closely replicate the clinical practice and avoid falsely inflated diagnostic properties.

ATN has been described to be associated with normal perfusion [6]. Our study showed impaired perfusion in this pathology as well, which may be due to the higher number of early post-operative DRTS in our study. Some of the impaired perfusion may be explained by early post-operative inflammation/oedema and a

compartment effect leading to reduced perfusion in ATN. In interstitial rejection, the HI was not elevated, which may be explained by involvement of the interstitium, and relative sparing of arterioles and arteries [28]; therefore, a lower HI cannot exclude this pathology.

There are a few limitations of the study subgroup, correlating parameter values with the pathology. Firstly, the biopsy results in the study were reported over a 15 years period and could not be standardized. Some of the biopsies showed mixed findings; although the predominant pathology was chosen as the final diagnosis in those cases, this may reduce the specificity of the test. Secondly, a majority of DRTS in our study were performed within the 30 days post-operatively (approximately 87%) and there is lack of subacute to chronic graft pathologies (e.g. chronic allograft nephropathies or cyclosporine toxicity etc.) in our study. Thirdly, the final diagnosis in our study was based on graft pathology rather than clinical diagnosis. Other clinical factors e.g. sepsis, drug toxicities, dopamine infusion, hypertension, hematoma/lymphocele etc may also affect the graft perfusion and function. Finally, the patients in this study had a biopsy because of higher clinical suspicion of an abnormality. It should be noted that a normal biopsy report may not exclude abnormal pathology as there may be sampling error e.g. inadequate specimen or a non-uniform pathology. This is also evident with the higher median HI values of 169 in this study group with normal biopsies, compared to the 116 in reference normal grafts. This may have impacted on sensitivity and specificity in the differentiation of normal and abnormal kidneys.

Nevertheless this study had a larger sample size and there was a very good temporal association between the biopsies and the scintigraphies; approximately 85% DRTS were performed within three days of biopsy. This study also avoids the tendency to inflate the diagnostic properties of these measures that occurs when comparing a particular pathology group to a completely normal group. In clinical practice, physicians need to identify particular pathologies from a set of mixed cases.

In conclusion, a majority of parameters show good interobserver agreement. Only HI shows value in graft pathology assessment, particularly for the assessment of vascular compromise. However, the specificity of HI for differentiating the various pathologies is lower, which may be improved by incorporation of clinical "probability of pathologies" or other non-scintigraphic parameters. This possibility needs to be assessed in future studies.

Disclosure of conflict of interest

Authors declare that they have no conflict of interest.

Abbreviations

DRTS, Dynamic Renal Transplant Scintigraphy; DTPA, Diethylene Triamine Pentaacetic Acid; HI, Hilson's Index; ΔP, Delta P; ROI, Region Of Interest; RVC, renal vascular compromise; VR, Vascular rejection; IR, Interstitial rejection; ATN, Acute tubular necrosis; NOR, Normal biopsy.

Address correspondence to: Dr. Sandeep K Gupta, Department of Nuclear Medicine & PET, John Hunter Hospital, Newcastle, NSW, Australia. Tel: +61 2 49213390; Fax: +61 2 49213392; E-mail: Sandeep.Gupta@hnehealth.nsw.gov.au

References

[1] Brown ED, Chen MY, Wolfman NT, Ott DJ, Watson NE Jr. Complications of renal transplantation: evaluation with US and radionuclide imaging. Radiographics 2000; 20: 607-622.

[2] Sorof JM, Vartanian RK, Olson JL, Tomlanovich SJ, Vincenti FG, Amend WJ. Histopathological concordance of paired renal allograft biopsy cores. Effect on the diagnosis and management of acute rejection. Transplantation 1995; 60: 1215-1219.

[3] Furness PN, Taub N. International variation in the interpretation of renal transplant biopsies: report of the CERTPAP Project. Kidney Int 2001; 60: 1998-2012.

[4] Nezami N, Tarzamni MK, Argani H, Nourifar M. Doppler ultrasonographic indices after renal transplantation as renal function predictors. Transplant Proc 2008; 40: 94-99.

[5] Irshad A, Ackerman S, Sosnouski D, Anis M, Chavin K, Baliga P. A review of sonographic evaluation of renal transplant complications. Curr Probl Diagn Radiol 2008; 37: 67-79.

[6] Hilson AJ, Maisey MN, Brown CB, Ogg CS, Bewick MS. Dynamic renal transplant imaging with Tc-99m DTPA (Sn) supplemented by a transplant perfusion index in the management

of renal transplants. J Nucl Med 1978; 19: 994-1000.
[7] Ash J, DeSouza M, Peters M, Wilmot D, Hausen D, Gilday D. Quantitative assessment of blood flow in pediatric recipients of renal transplants. J Nucl Med 1990; 31: 580-585.
[8] Dubovsky EV, Russell CD, Bischof-Delaloye A, Bubeck B, Chaiwatanarat T, Hilson AJ, Rutland M, Oei HY, Sfakianakis GN, Taylor A Jr. Report of the Radionuclides in Nephrourology Committee for evaluation of transplanted kidney (review of techniques). Semin Nucl Med 1999; 29: 175-188.
[9] Kirchner PT, Goldman MH, Leapman SB, Kiepfer RF. Clinical application of the kidney to aortic blood flow index (K/A ratio). Contrib Nephrol 1978; 11: 120-126.
[10] Koizumi K, Kakiuchi H, Saguchi T, Inoue S, Fuse S, Kawakami E, Yamazaki A, Kozaki K, Nagao T. A simple objective parameter for perfusion study of renal transplant. Ann Nucl Med 2001; 15: 27-32.
[11] Preston DF, Luke RG. Radionuclide evaluation of renal transplants. J Nucl Med 1979; 20: 1095-1097.
[12] El-Maghraby TA, de Fijter JW, van Eck-Smit BL, Zwinderman AH, El-Haddad SI, Pauwels EK. Renographic indices for evaluation of changes in graft function. Eur J Nucl Med 1998; 25: 1575-1586.
[13] Aktas A, Aras M, Colak T, Gencoglu A, Moray G. Indicators of acute rejection on Tc-99m DTPA renal scintigraphy. Transplant Proc 2006; 38: 443-448.
[14] Russell CD, Yang H, Gaston RS, Hudson SL, Diethelm AG, Dubovsky EV. Prediction of renal transplant survival from early postoperative radioisotope studies. J Nucl Med 2000; 41: 1332-1336.
[15] Li Y, Russell CD, Palmer-Lawrence J, Dubovsky EV. Quantitation of renal parenchymal retention of technetium-99m-MAG3 in renal transplants. J Nucl Med 1994; 35: 846-850.
[16] el Maghraby TA, van Eck-Smit BL, de Fijter JW, Pauwels EK. Quantitative scintigraphic parameters for the assessment of renal transplant patients. Eur J Radiol 1998; 28: 256-269.
[17] Gupta SK, Lewis G, Rogers K, Attia J. Quantitative Tc-99m DTPA renal transplant scintigraphy predicts graft survival in the very early postoperative period. Nucl Med Commun 2012; 33: 1292-1299.
[18] Sheskin D. Handbook of parametric and nonparametric statistical procedures. 3rd edition. Florida: Chapman and Hall/CRC 2004, pp: 41.
[19] Chang SH, Russ GR, Chadban SJ, Campbell S, McDonald SP. Trends in adult post-kidney transplant immunosuppressive use in Australia, 1991-2005. Nephrology (Carlton) 2008; 13: 171-176.
[20] Akobeng AK. Understanding diagnostic tests 3: Receiver operating characteristic curves. Acta Paediatr 2007; 96: 644-647.
[21] Ellam SV, Maisey MN, Mistry R. Measurement of changes of blood flow in renal transplants. Eur J Nucl Med 1983; 8: 84-86.
[22] Hamilton D, Miola UJ, Payne MC. The renal transplant perfusion index: reduction in the error and variability. Eur J Nucl Med 1994; 21: 232-238.
[23] Aktas A, Karakayali H, Bilgin N, Akkoc H, Moray G, Emiroglu R. Serial radionuclide imaging in acute renal allograft dysfunction. Transplant Proc 2002; 34: 2102-2105.
[24] Jackson SA, Ehrlich L, Martin RH. The renal washout parameter as an indicator of transplant rejection. Eur J Nucl Med 1986; 12: 86-90.
[25] Yazici B, Yazici A, Oral A, Akgun A, Toz H. Comparison of renal transplant scintigraphy with renal resistance index for prediction of early graft dysfunction and evaluation of acute tubular necrosis and acute rejection. Clin Nucl Med 2013; 38: 931-935.
[26] Gedroyc W, Taube D, Fogleman I, Neild G, Cameron S, Maisey M. Tc-99m DTPA scans in renal allograft rejection and cyclosporine nephrotoxicity. Transplantation 1986; 42: 494-497.
[27] al-Nahhas AM, Kedar R, Morgan SH, Landells WN, al-Murrani B, Heary T, Wright A, Cosgrove DO, Bending MR, McCready VR. Cellular versus vascular rejection in transplant kidneys. Correlation of radionuclide and Doppler studies with histology. Nucl Med Commun 1993; 14: 761-765.
[28] Thomsen HS, Frokicer J. Renal transplant evaluation. In: Ell PJ, Gambhir SS, editors. Nuclear Medicine In Clinical Diagnosis And Treatment. 3rd edition. London: Churchill Livingston 2004, pp: 359-400.