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Renogram image characteristics and the reproducibility of differential renal function measurement

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Purpose **Patient factors such as age and glomerular filtration rate (GFR), have been implicated as causes for poor reproducibility of differential renal function (DRF) estimates on ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) renography. This study aims to investigate factors associated with the reproducibility of DRF measurements.**

Methods **The association between age, GFR and imaged derived image characteristics and reproducibility of repeated DRF estimates calculated using the area under the curve method and the Rutland Patlak method was analysed for cohort 1 (n=127). The association between these variables and reproducibility of DRF was tested with univariate linear regression. The univariate linear regression results were used to plan the multiple linear regression combinations.**

The associations between variables identified and reproducibility of DRF values were then tested in a second cohort (n=227).

Results **The R^2 values for goodness-to-fit for the multiple regression models ranged from 0.33 to 0.49 for cohort 1 and from 0.17 to 0.22 for cohort 2. Left kidney to background ratio (LKTBR) was significant in all the multiple linear regression combinations (P<0.05). Right kidney to background ratio (RKTBR), right renal margins well defined, right renal margins poorly visualised, time visualisation right calyces and age were significant in most combinations. The reproducibility of DRF measurement was decreased when the kidney to background ratio (KTBR) was ≤2.**

Conclusion **Only LKTBR, RKTBR, right renal margins well defined, time visualisation right calyces and age predicted reproducibility for the measurement of DRF on ^{99m}Tc-MAG3 renograms. The KTBR should be incorporated into the renal processing software as a quality control step. The DRF values should be interpreted with caution if the KTBR is ≤2.0. *Nucl Med Commun* 42: 866–876 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Differential renal function (DRF) is a measurement of each kidney's ability to extract tracer from blood and therefore reflects renal function [1]. DRF in the 45–55% range is regarded as normal.

Renograms are performed in a wide range of renal diseases and DRF is used to guide clinical decision making. For example, in children with unilateral hydronephrosis and a normal DRF, a watch and wait approach is followed [2]. Some institutions will intervene if the DRF is below 40% in the first renogram. Changes in DRF indicating the need for surgical intervention have been established empirically [3]. A drop in DRF of 10% from initial DRF value is an established indication for surgical intervention [4–6].

Multiple methods for calculating DRF have been proposed [7]. Currently, two methods, Rutland Patlak Plot method and the integral method, are recommended by international guidelines [8].

A number of patient and renal characteristics have been proposed in the literature as possible factors which could impact on the reproducibility of DRF measurements. These factors include renal immaturity, impaired renal function and severe renal dilatation [9–11]. We have previously established that the DRF calculation is usually reproducible but in a small number of renograms reproducibility is poor [12].

Different methods for establishing reproducibility have been proposed. Most include processing a renogram with more than one method or processing a renogram repeatedly [10,12–14]. From clinical experience, we expect that some visual characteristics are associated with good reproducibility and others with poor reproducibility of DRF. This research project will investigate which

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imaging characteristics are associated with good or poor reproducibility.

Method

The study was done in two stages. The first step was to evaluate the image characteristics and reproducibility of the DRF estimates of the children included in our previous study to identify the characteristics associated with reproducibility. The second was to test these associations between the image characteristics and reproducibility in a new group of patients.

Patients

In our previous study, we selected 172 patients as a stratified sample from all renograms done in our department between December 2000 and November 2008 to ensure patients at the extremes of DRF, age and glomerular filtration rate (GFR) were included [12]. The Hermes software truncated any negative values for DRF to zero. Therefore, patients with solitary kidneys were excluded from the analysis. This left 133 patients in cohort 1.

Cohort 2 was selected from renograms recorded in our department between July 2012 and September 2015. The children included had two kidneys in the normal anatomical position, a measured or estimated GFR within 1 month of the renogram study, and a complete dataset. Patients were only used once. No patient used in cohort 1 was included.

The renograms used were acquired according to the relevant European Association of Nuclear Medicine (EANM) guidelines for standard and diuretic renography at the time of acquisition [13,15]. The ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) dose used was calculated using the applicable EANM dose card [16,17]. The children were imaged on the same Philips Axis Dual Head camera (previously known as Picker and then Marconi) using a low-energy high-resolution collimator. Posterior images were recorded in a 128×128 matrix at 1 s per frame for the first 2 min. Thereafter, the images were recorded at 15 s per frame for 40 min. When clinically indicated furosemide was administered 20 min after the injection of ^{99m}Tc-MAG3.

All renograms were processed using the HERMES kidney analysis program, renography V5.2L/IS 7 April 2008, and the categorical and continuous variables were categorised and measured using the HERMES hybrid viewer PDR2.2.C.21. (Hermes Medical Solutions AB, Stockholm, Sweden). To calculate the DRF values, the renal region of interests (ROIs) were drawn on the 1–2 min summed image to include the whole kidney. The renal background ROIs were positioned automatically as perirenal C-shaped ROIs including both poles of the kidney. The background ROIs were 1–2 pixels wide and were placed 1–2 pixels apart from the renal ROI. A cardiac ROI was drawn over the pixels with maximal counts in the heart. In the straight-line fit display of the Rutland Patlak plot, the interval was manually manipulated to achieve the best fit. The renograms were processed five times at least 1 month apart by one operator, and five values of DRF, calculated using the Hermes area under the curve (HAUC) and Hermes Rutland Patlak (HRP) methods, were obtained. The maximum difference between the five measurements of DRF was used as a measure of the reproducibility of the calculation of DRF. This value was defined as *maxminhauc* for the HAUC method and *maxminhrp* for the HRP method.

The dynamic images recorded between 60 and 120 s post-injection were summed to form a 1- to 2-min static image, which was visually inspected to define the categorical variables and processed to obtain the values of the continuous variables.

Categorical variables

The appearance of the renal margins of the left and right kidneys was categorised as smooth or irregular and well defined or poorly visualised. The results of the individual variables were then combined to generate the variables, *both renal margins smooth* if both kidneys had smooth margins. *Renal margins smooth* was defined as a renal margin seen as a smooth line. Most of these patients had normal renal contours but a well-defined renal cortical defect such as a clearly defined wedge-shaped defect was also classified as renal margins smooth. The variable *renal margins irregular* was reserved for kidneys where the renal margins appeared jagged or scalloped. The variable *renal margin well defined* was defined as a kidney that was clearly seen above background activity and the margins could be easily delineated. In contrast, the term *renal margin poorly visualised* was used when the operator could not clearly see the kidney above background or identify the renal margin. The variables defined were; *left/right/both renal margins smooth; left/right/both renal margins irregular; left/right/both renal margins well defined* and *left/right/both renal margins poorly visualised*.

A group of variables described the presence or absence of cortical defects as well as the number of cortical defects. A kidney was classified as having islands of functioning tissue if there was extensive cortical destruction. The variables describing cortical defects were: *left/right no cortical defects*, *left/right <2 cortical defects*, *left/right ≥2 cortical defects* and *left/right islands of functioning tissue*.

Continuous variables

The variables investigated included two nonimaging variables, *age* (in months) and *GFR* which included measured or estimated GFR values. The measured GFRs (mGFR) were measured using ^{51}Cr-ethylenediaminetetraacetic acid, and the two blood sample methods according to the EANM guidelines [18]. The estimated GFR values (eGFR) were calculated using the modified Schwartz method [19]. All GFR values were corrected for body surface area.

Asymmetry (*asymmetry drf*) in uptake of tracer between the two kidneys was calculated as the absolute difference between the mean of the five measurements of DRF on each side.

The number of counts and the size in cm^2 of each region of interest were recorded. The variables defined were *left/right renal area* and *left/right background area*. *Left kidney to background ratio (LKTBR)* and *right kidney to background ratio (RKTBR)* were calculated as the ratio of mean counts per pixel in the renal ROI divided by the mean counts per pixel in the background ROI for that kidney. The times at which calyceal activity and renal pelvis activity were first visualised were recorded for each kidney; *time visualisation left calyces*, *time visualisation right calyces*, *time visualisation left pelvis* and *time visualisation right pelvis*.

Statistical analysis

Statistical analysis was performed using STATA 12 (StataCorp. 2011. Stata: Release 12. Statistical Software; StataCorp LP, College Station, Texas, USA) and Statistica (Dell Inc. (2016). Dell Statistica (data analysis software system), version 13. software.dell.com.

The distributions of the dependent variables were not normal. Log transformation, ($\log_{10}$), of the dependent variables improved the distribution.

The association between each variable and the reproducibility of each method of DRF measurement was tested with univariate linear regression. The results of the univariate linear regression were used to plan the multiple linear regression combinations. Therefore, the building of the multiple linear regression models was finalised after the univariate linear regression results were available. Variables with a P value for the univariate regression coefficient ≤0.2 were included in the multiple linear regression analysis.

The multiple linear regression analysis was done in groups and combinations that avoided overfitting the model. One variable was included per 15 cases, that is, a maximum of 8–9 variables per model, for the sample size $n = 133$. To avoid collinearity, independent variables showing a strong correlation ($r \geq 0.80$) were identified. Each of these variables was added to the model without the other to test if a significant association was established with the dependent variable, reproducibility. For example, the variables *LKTBR* and *RKTBR* could not be used in the same combination.

The multiple linear regression analyses were performed using three different methods. First, straight multiple linear regression using all the variables in the combination was performed. This was followed by step-up and step-down multiple linear regression models using a significance level of $P \leq 0.2$ ($P > |t|$) for each variable included in the combinations, adding them in the step-up or removing them in the step-down multiple regression models.

Testing the assumptions of multiple linear regression models cohort 1 are as follows:

(1) Normality and constant variance of the residuals were checked. The regression residual values of all the cases were plotted against a normal distribution plot.
(2) Outliers and influential observations were identified with variance inflation factor (VIF) >|5|. The residuals were also plotted against each continuous variable to assist in identifying outliers in the analysis.
(3) A VIF was calculated to establish if there was significant multicollinearity between the different variables included in the regression analysis, VIF >10.
(4) Heteroscedasticity, skewness and kurtosis were tested using the Cameron and Trivedi algorithm.

Results

Patients – cohort 1

A total of 133 patients were eligible for inclusion in cohort 1. Six patients were excluded as the uptake was too poor to assess the number of cortical defects or categorise the renal margins. This left a total of 127 renograms for analysis in cohort 1.

The ages of the patients ranged from zero to 195 months. A total of 17 (13%) were less than two, 13 (10%) between two and six, 11 (9 %) between 6 and 12, and 11 (9 %) between 12 and 18 months.

The GFR values of the patients included in cohort 1 ranged between 19 and 230 mL/min/1.73 m^2. Eleven (9%) had a GFR < 60 mL/min/1.73 m^2, 20 patients (12%) had a GFR between 60 and 80 mL/min/1.73 m^2. Of the 31 patients with GFR values <80 mL/min/1.73 m^2, 9 were older than 12 months. Fourteen (11%) of the patients had mGFRs and the other 113 patients eGFRs.

The *LKTBR* ranged from 1.15 to 5.33 and the *RKTBR* ranged from 1.03 to 4.95.

Patients – cohort 2

The ages of the 227 patients selected for cohort 2 ranged from 0 to 245 months, with a median age of 49 months. In total, 18 (8%) were younger than two, 21 (9%) were between 2 and 6, 22 (10%) were between 6 and 12, and 13 (6%) were between 12 and 18 months.

The GFR values were between 12 and 358 mL/min/1.73 m^2. Only 19 patients (8%) had a GFR <60 mL/min/1.73 m^2 and 20 patients (9%) had a GFR between 60 and 80 mL/min/1.73 m^2. Twenty-three of the patients with GFR values <80 mL/min/1.73 m^2 were older than 12 months. Thirty-six (16%) of the patients had mGFRs, the remaining 191 patients eGFRs.

Table 1 The patient demographics of the 127 patients included in cohort 1 and the 227 patients included in cohort 2

	Median		25% Quartile		75% Quartile		
Variable	Cohort 1	Cohort 2	Cohort 1	Cohort 2	Cohort 1	Cohort 2	*P* value *U*-test[a]
Age (months)	31	49	7	11	84	95	0.08
GFR (mL/min/1.73 m^2)	99	121	81	93	122	140	0.00
DRF HAUC (%)[b]	53	52	43	48	67	58	0.54
DRF HRP (%)[b]	53	53	43	47	65	58	0.53
maxminhauc	3	4	2	3	5	6	0.02
maxminhrp	4	4	3	3	6	6	0.90
LKTBR	2.96	3.57	2.32	2.62	3.74	4.35	0.30
RKTBR	2.51	2.78	1.90	2.15	3.09	3.27	0.09

[a]Mann–Whitney *U* test (*U* test).
[b]The values given for DRF HAUC (%) and DRF HRP (%) The values given for DRF HAUC and DRF HRP are the mean of the five values measured for the left kidney.
DRF, differential renal function; GFR, glomerular filtration rate.

The cohort 2 *LKTBR* ranged from 1.02 to 8.45 and *RKTBR* ranged from 0.93 to 6.45.

There was no difference in the values obtained in cohorts 1 and 2 for age, mean DRF HAUC, mean DRF HRP, *maxminhrp*, *LKTBR* and *RKTBR* but *GFR* and *maxminhauc* differed. *Maxminhauc* was ≤5 in 78% of the children in cohort 1 and 70% of those in cohort 2, Table 1.

One patient had a *maxminhrp* value of 0. This value could not be transformed by the log transformation and the patient was excluded from the log *maxminhrp* analyses.

Univariate linear regression results

The variables *left islands of functioning tissue* (six patients), *right islands of functioning tissue* (5), *left ≥2 cortical defects* (8), *right ≥2 cortical defects* (15) and *both renal margins poorly visualised* (9) were excluded as the number of children with these characteristics was too small for statistical analysis.

The beta-coefficients of 14 variables had $P \leq 0.2$ with univariate linear regression for log *maxminhauc* and log *maxminhrp* in cohorts 1 and 2. The categorical variables were; *both renal margins irregular*, *both/left/right renal margins well defined*, *left/right renal margins poorly visualised*, and *right renal margins smooth*. The continuous variables were; *LKTBR*, *RKTBR*, *left background area*, *time visualisation right calyces*, *left renal area*, *GFR* and *age*. These variables were eligible for inclusion in multiple linear regression in both cohorts, Tables 2 and 3.

Right <2 cortical defects and *asymmetry drf*, had $P > 0.2$ with univariate linear regression for both methods in cohorts 1 and 2 and were excluded from the multiple linear regression models. The *P* value of the beta-coefficient of the remaining variables was inconsistent. In some methods and/or cohorts it was ≤0.2 and in others it was >0.2, Tables 2 and 3.

Selection of variables for multiple linear regression

The 594 multiple linear regression combinations for log *maxminhauc* were compiled by combining one dependent variable with seven independent variables as follows:

Dependent variable: log *maxminhauc*

Independent variables

(1) *age*,
(2) *GFR*,
(3) *LKTBR* or *RKTBR*,
(4) *left renal area* or *right renal area* or *left background area*,
(5) *left no cortical defects* or *right no cortical defects* or *left <2 cortical defects*,
(6) One variable describing the renal margins; for instance *right renal margin smooth*,
(7) *time visualisation left pelvis* or time visualisation left calyces or time visualisation right calyces.

An example of a combination for log *maxminhauc* is: *age* and *GFR* and *LKTBR* and *left renal area* and *left no cortical defects* and *right renal margin smooth* and *time visualisation left pelvis*.

There were 240 multiple linear regression combinations for log *maxminhrp*. The differences between the multiple linear regression combinations for log *maxminhauc* and log *maxminhrp* were the exclusion of *left <2 cortical defects*, *right renal margins irregular*, *right renal area* and *time visualisation right calyces* from the log *maxminhrp* combinations analysed.

Multiple linear regression results

The different methods of multiple linear regression, straight, step-down and step-up, gave similar results for each combination. The multiple linear regression analysis for cohort 1 was performed using the same combinations of variables as cohort 2.

For the dependent variable log *maxminhauc* the R^2-values for the 594 different combinations ranged between 0.35 and 0.49 for cohort 1. All the R^2-values of cohort 2 were lower, they ranged from 0.17 to 0.22.

For the cohort 1 combination with the highest R^2, 0.49, the independent variables were *age*, *GFR*, *LKTBR*, *left renal area*, *right renal margins well defined*, *left no cortical defects* and *time visualisation right calyces*. All the variables

Table 2 Univariate linear regression of the 15 categorical variables and log *maxminhauc* and log *maxminhrp* – cohorts 1 and 2

	log *maxminhauc* – cohort 1				log *maxminhauc* – cohort 2				log *maxminhrp* – cohort 1				log *maxminhrp* – cohort 2			
Variable	Beta	SE	*t*	*P*>|t|	Beta	SE	*t*	*P*>|t|	Beta	SE	*t*	*P*>|t|	Beta	SE	*t*	*P*>|t|
Both renal margins irregular	**0.71**	**0.20**	**3.58**	**<0.01**	**0.50**	**0.17**	**2.98**	**<0.01**	**0.55**	**0.24**	**2.28**	**0.02**	**0.49**	**0.15**	**3.35**	**<0.01**
Both renal margins well defined	**−0.63**	**0.13**	**−5.00**	**<0.01**	**−0.40**	**0.11**	**−3.56**	**<0.01**	**−0.60**	**0.11**	**−5.42**	**<0.01**	**−0.40**	**0.11**	**−3.65**	**<0.01**
Left renal margins well defined[a]	**−0.58**	**0.15**	**−3.92**	**<0.01**	**−0.24**	**0.17**	**−1.41**	**0.16**	**−0.53**	**0.13**	**−4.26**	**<0.01**	**−0.23**	**0.17**	**−1.40**	**0.16**
Right renal margins well defined[a]	**−0.57**	**0.16**	**−3.47**	**<0.01**	**−0.57**	**0.13**	**−4.49**	**<0.01**	**−0.61**	**0.15**	**−4.19**	**<0.01**	**−0.54**	**0.12**	**−4.52**	**<0.01**
Left no cortical defects	−0.53	0.12	−4.35	<0.01	−0.14	0.11	−1.23	0.22	−0.37	0.12	−3.05	<0.01	−0.10	0.10	−0.96	0.34
Left renal margins smooth	−0.52	0.13	−4.03	<0.01	−0.18	0.15	−1.24	0.22	−0.38	0.13	−2.84	0.01	−0.22	0.13	−1.69	0.09
Left renal margins irregular	0.50	0.13	3.76	<0.01	0.18	0.15	1.24	0.22	0.35	0.14	2.49	0.01	0.22	0.13	1.69	0.09
Both renal margins smooth	−0.35	0.13	−2.75	<0.01	−0.09	0.11	−0.81	0.42	−0.29	0.12	−2.42	0.02	−0.18	0.10	−1.76	0.08
Right no cortical defects	−0.34	0.16	−2.17	0.03	0.01	0.10	−0.10	0.92	−0.30	0.15	−2.00	0.05	−0.09	0.10	−0.90	0.37
Left < 2 cortical defects	0.31	0.12	2.51	0.01	0.14	0.11	1.22	0.22	0.16	0.13	1.26	0.21	0.09	0.11	0.80	0.43
Right renal margins smooth	**−0.28**	**0.16**	**−1.75**	**0.08**	**−0.24**	**0.12**	**−1.97**	**0.05**	**−0.30**	**0.14**	**−2.12**	**0.04**	**−0.31**	**0.11**	**−2.85**	**0.01**
Right renal margins irregular	0.23	0.17	1.36	0.18	0.24	0.12	1.97	0.05	0.19	0.16	1.17	0.25	0.31	0.11	2.85	0.01
Right < 2 cortical defects	**0.12**	**0.15**	**0.81**	**0.42**	**0.07**	**0.11**	**0.66**	**0.51**	**0.11**	**0.15**	**0.73**	**0.47**	**−0.10**	**0.12**	**−0.84**	**0.40**

Listed in ascending order of the *P* value of the beta-coefficient of cohort 1. The variables for which *P* were ≤0.2 or >0.2 for all are in bold. A negative beta-coefficient predicted good reproducibility and a positive beta-coefficient predicted decreased reproducibility.
Beta, beta-coefficients.
[a]The beta-coefficients and *t*-values of left renal margins well defined and left renal margins poorly visualised, right renal margins well defined and right renal margins poorly visualised were equal in magnitude but of opposite sign. Therefore, only the results of left renal margins well defined and right renal margins well defined are presented.

Table 3 Univariate linear regression of the 13 continuous variables and log *maxminhauc* and log *maxminhrp* – cohorts 1 and 2

	log *maxminhauc* – cohort 1				log *maxminhauc* – cohort 2				log *maxminhrp* – cohort 1				log *maxminhrp* – cohort 2			
Variable	Beta	SE	*t*	*P*>|t|	Beta	SE	*t*	*P*>|t|	Beta	SE	*t*	*P*>|t|	Beta	SE	*t*	*P*>|t|
LKTBR	**−0.42**	**0.06**	**−6.91**	**<0.01**	**−0.17**	**0.04**	**−4.64**	**<0.01**	**−0.36**	**0.06**	**−6.40**	**<0.01**	**−0.16**	**0.04**	**−4.63**	**<0.01**
RKTBR	**−0.36**	**0.08**	**−4.55**	**<0.01**	**−0.27**	**0.05**	**−5.40**	**<0.01**	**−0.39**	**0.08**	**−4.92**	**<0.01**	**−0.26**	**0.05**	**−5.10**	**<0.01**
Time visualisation left calyces	0.09	0.05	1.83	0.07	0.01	0.04	0.11	0.91	0.10	0.04	2.39	0.02	<−0.01	0.04	−0.03	0.98
Left background area	**−0.08**	**0.02**	**−3.44**	**<0.01**	**−0.08**	**0.02**	**−3.82**	**<0.01**	**−0.06**	**0.02**	**−2.74**	**0.01**	**−0.08**	**0.02**	**−3.57**	**<0.01**
Right background area	−0.04	0.03	−1.28	0.20	−0.07	0.02	−4.11	<0.01	−0.03	0.03	−1.07	0.29	−0.08	0.02	−4.38	<0.01
Time visualisation left pelvis	0.04	0.02	2.11	0.04	−0.01	0.01	−0.75	0.46	0.03	0.17	1.90	0.06	−0.01	0.01	−1.25	0.21
Time visualisation right calyces	**0.03**	**0.02**	**1.70**	**0.09**	**0.03**	**0.01**	**3.65**	**<0.01**	**0.03**	**0.02**	**1.49**	**0.14**	**0.03**	**0.01**	**4.02**	**<0.01**
Left renal area	**−0.01**	**0.01**	**−2.48**	**0.01**	**−0.01**	**<0.01**	**−3.68**	**<0.01**	**−0.01**	**0.01**	**−2.30**	**0.02**	**−0.01**	**<0.01**	**−3.80**	**<0.01**
Time visualisation right pelvis	0.01	0.01	1.05	0.30	0.01	0.01	1.29	0.20	0.01	0.01	1.17	0.25	0.01	0.01	0.84	0.40
GFR	**−0.01**	**0.02**	**−5.39**	**<0.01**	**<−0.01**	**<0.01**	**−2.81**	**0.01**	**−0.01**	**0.02**	**−4.36**	**<0.01**	**<−0.01**	**<0.01**	**−2.94**	**<0.01**
Right renal area	−0.01	0.01	−1.78	0.08	−0.01	<0.01	−3.89	<0.01	−0.01	0.01	−1.17	0.25	−0.01	<0.01	−4.27	<0.01
Age	**−0.01**	**<0.01**	**−3.57**	**<0.01**	**<−0.01**	**<0.01**	**−4.71**	**<0.01**	**<−0.01**	**<0.01**	**−3.00**	**<0.01**	**<−0.01**	**<0.01**	**−4.62**	**<0.01**
Asymmetry drf	**<0.01**	**<0.01**	**0.43**	**0.67**	**<−0.01**	**0.002**	**−1.20**	**0.23**	**<0.01**	**<0.01**	**0.67**	**0.51**	**<−0.01**	**<0.01**	**−0.51**	**0.61**

Listed in ascending order of the P value of the beta-coefficient of cohort 1. The variables for which P were ≤2 or >0.2 for all are in bold. A negative beta-coefficient predicted good reproducibility and a positive beta-coefficient predicted decreased reproducibility.
DRF, differential renal function; GFR, glomerular filtration rate LKTBR, left kidney to background ratio; RKTBR, right kidney to background ratio.

Table 4 Multiple linear regression result for the combination with the highest R^2 for log *maxminhauc* cohorts 1 and 2

Log *maxminhauc* cohort 1				Log *maxminhauc* cohort 2			
Variable	Beta	SE	*P* value	Variable	Beta	SE	*P* value
LKTBR	−0.32	0.06	<0.01	LKTBR	−0.12	0.04	<0.01
Right renal margins well defined	−0.40	0.12	<0.01	Right renal margins well defined	−0.40	0.13	<0.01
GFR	<−0.01	<0.01	<0.01	Time visualisation left pelvis	−0.02	0.01	0.06
Age	<−0.01	<0.01	0.01	Age	<−0.01	<0.01	0.12
Time visualisation right calyces	0.03	0.01	0.02	Right no cortical defects	0.14	0.10	0.16
Left no cortical defects	−0.12	0.10	0.23	GFR	<−0.01	<0.01	0.25
Left renal area	<0.01	0.01	0.36	Right renal area	<−0.01	<0.01	0.37

Presented in asending order or the *P* value.
Beta, beta-coefficient; GFR, glomerular filtration rate; SE, robust standard error.

Table 5 Multiple linear regression result for the combination with the highest R^2 for log *maxminhrp* cohorts 1 and 2. Presented in asending order or the *P* value

Variable	Beta	SE	*P* value	Variable	Beta	SE	*P* value
LKTBR	−0.32	0.06	<0.01	LKTBR	−0.12	0.04	<0.01
Right renal margins well defined	−0.52	0.11	<0.01	Right renal margins well defined	−0.33	0.12	0.01
Age	<−0.01	<0.01	0.01	Time visualisation left pelvis	−0.02	0.01	0.02
GFR	<−0.01	<0.01	0.06	Age	<−0.01	<0.01	0.09
Time visualisation right calyces	0.04	0.02	0.02	GFR	<−0.01	<0.01	0.21
Left no cortical defects	0.04	0.11	0.76	Left renal area	<−0.01	<0.01	0.56
Left background area	0.03	0.02	0.22	Left no cortical defects	0.06	0.11	0.59

Beta, beta-coefficient; GFR, glomerular filtration rate; SE, robust standard error.

except *left no cortical defects* and *left renal area* were significant in this combination. The cohort 2 combination with the highest R^2-value, 0.22, was *age*, *GFR*, *right renal area*, *LKTBR*, *right renal margins well defined*, *right no cortical defects* and *time visualisation left pelvis*. The only variables which were significant in this combination were *LKTBR* and *right renal margins well defined*, Table 4.

For the dependent variable log *maxminhrp* the R^2-values for the 240 different combinations ranged between 0.33 and 0.45 for cohort 1. The R^2-values of cohort 2 ranged from 0.17 to 0.22.

The log *maxminhrp* cohort 1 combination with the highest R^2 value, 0.45, included the variables *age*, *GFR*, *LKTBR*, *right renal margins well defined*, *left no cortical defects*, *time visualisation right calyces* and *left background area*. All the variables except *left no cortical defects* and *left background area* were significant in this combination. The cohort 2 combination with the highest R^2 value, 0.22, was *age*, *GFR*, *left renal area*, *LKTBR*, *right renal margins well defined*, *left no cortical defects* and *time visualisation left pelvis*. In this combination the variables *GFR*, *left renal area* and *left no cortical defects* were not significant (NS), Table 5.

On review of the results of the individual variables included in the multiple linear regression combinations it was found that there was a clear pattern of variables which predict reproducibility, some which may predict reproducibility, some which probably do not predict reproducibility and those who do not predict reproducibility.

The variable *LKTBR* was significant in all combinations in which it was included. *RKTBR* was significant in all log *maxminhrp* combinations. *RKTBR* was significant in 261 of 297 of the log *maxminhauc* combinations cohort 1. It was significant in all the log *maxminhauc* combinations for cohort 2, Tables 6 and 7.

Right renal margins well defined and *right renal margins poorly visualised* were significant in 50% of the combinations cohort 1. These variables were significant in more than 80% of the combinations for cohort 2. *Time visualisation right calyces* was significant in 50% of the combinations in cohort 1. In cohort 2, it was significant in 91% of the log *maxminhauc* and 89% of the log *maxminhrp* combinations. *Age* was significant in 40, 55, 80 and 85% of the combinations, Tables 6 and 7.

GFR was significant in all 100% combinations for log *maxminhauc* and 95% of the combinations for log *maxminhrp* cohort 1 but in cohort 2 it was only significant in 1 and 3% of the combinations. The variables *both renal margins well defined*, *left renal margins well defined*, *left renal margins poorly visualised*, *both renal margins* irregular, *time visualisation left calyces*, *time visualisation left pelvis* were significant in some but not all the combinations in which they were included, Tables 6 and 7. These variables may predict reproducibility of DRF measurements.

Left no cortical defects, *right no cortical defects*, *left <2 cortical defects*, *left renal margins smooth*, *right renal margins smooth*, *left renal margins irregular* and *right renal area* were NS in the majority of combinations in which they were included for both cohorts and for both methods, Tables 6 and 7. These variables probably did not predict reproductivity of DRF measurements.

Left renal area, *left background area*, *both renal margins smooth*, and *right* renal margins irregular did not predict

Table 6 Multiple linear regression results for the 594 combinations analysed for log *maxminhauc* in cohorts 1 and 2

Variable (*n*)	*P* range cohort 1	*P* value ≤0.05 cohort 1	% combinations cohort 1	*P* range cohort 2	*P* value ≤0.05 cohort 2	% combinations cohort 2
Age (594)	<0.001–0.461	329	55	0.004–0.160	475	80
GFR (594)	<0.001–0.007	594	100	0.046–0.416	3	1
LKTBR (297)	**<0.001–0.005**	**297**	**100**	**<0.001–0.023**	**297**	**100**
RKTBR (297)	<0.001–0.093	261	88	<0.001–0.009	297	100
Left renal area (198)	**0.198–0.999**	**0**	**0**	**0.587–0.999**	**0**	**0**
Right renal area (198)	0.004–0.998	86	43	0.092–0.992	0	0
Left background area (198)	**0.332–0.991**	**0**	**0**	**0.576–0.999**	**0**	**0**
Left no cortical defects (198)	0.003–0.428	59	30	0.256–0.997	0	0
Right no cortical defects (198)	0.086–0.998	0	0	0.034–0.998	8	4
Left <2 cortical defects (198)	0.036–0.995	3	2	0.341–0.993	0	0
Left renal margins smooth (54)	0.001–0.495	18	33	0.614–0.929	0	0
Right renal margins smooth (54)	**0.135–0.530**	**0**	**0**	**0.187–0.994**	**0**	**0**
Both renal margins smooth (54)	**0.132–0.999**	**0**	**0**	**0.283–0.725**	**0**	**0**
Left renal margins irregular (54)	0.003–0.719	17	31	0.614–0.929	0	0
Right renal margins irregular (54)	**0.181–0.889**	**0**	**0**	**0.187–0.944**	**0**	**0**
Both renal margins irregular (54)	0.006–0.218	36	67	0.023–0.123	15	28
Left renal margins well defined (54)	<0.001–0.613	27	50	0.443–0.998	0	0
Right renal margins well defined (54)	<0.001–0.433	27	50	<0.001–0.093	48	89
Both renal margins well defined (54)	<0.001–0.021	54	100	0.087–0.555	0	0
Time visualisation left calyces (198)	0.002–0.839	77	39	0.107–0.347	0	0
Time visualisation right calyces (198)	0.003–0.775	99	50	<0.001–0.235	180	91
time visualisation left pelvis (198)	0.001–0.762	59	30	0.042–0.117	18	9

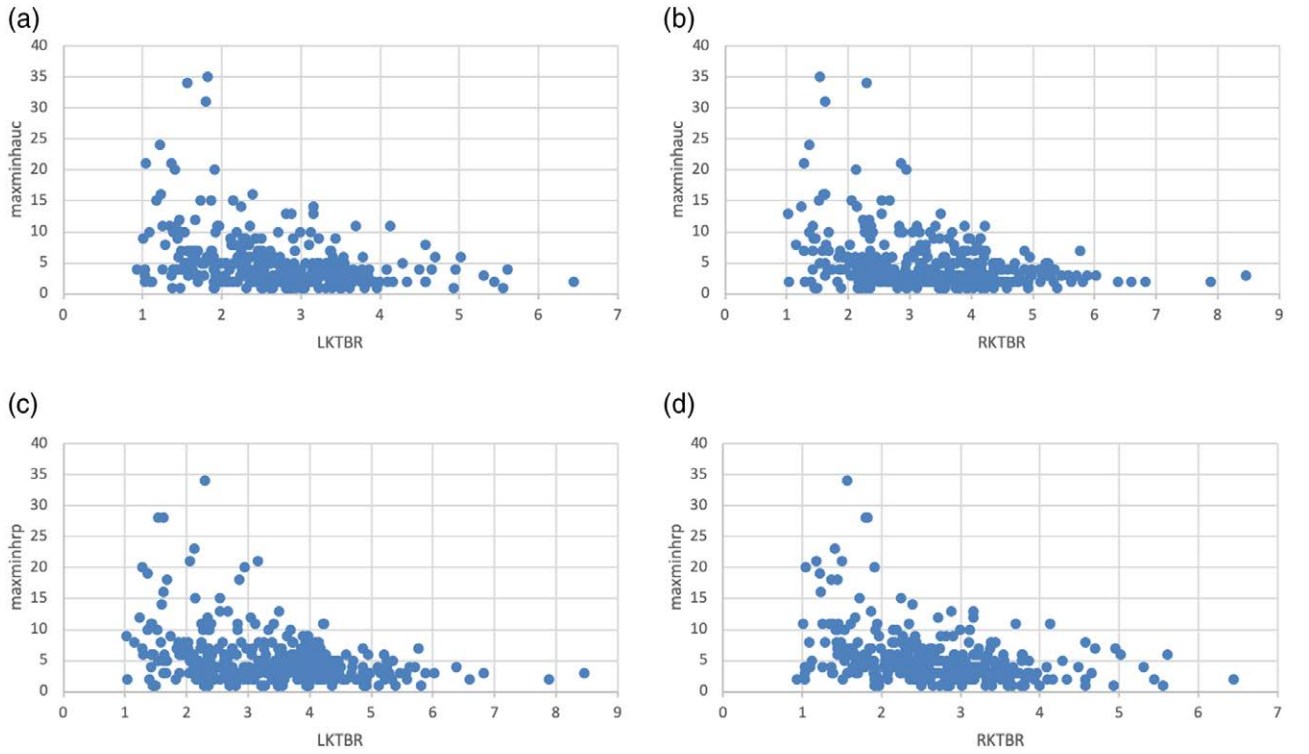
The number of combinations in which each variable was included is given in brackets. The range of *P* values and the number of times a variable had a *P* value ≤0.05 is also listed. The variables with the same number of combinations in cohorts 1 and 2 in which the *P* value of the beta coefficient was ≤0.05 or >0.05 are presented in bold. The percentage of combinations in which each variable was significant is also given.

Table 7 Multiple linear regression results for the 240 combinations analysed for log *maxminhrp* in cohort 1 and cohort 2

Variable (*n*)	*P* range cohort 1	*P* value ≤0.05 cohort 1	% combinations cohort 1	*P* range cohort 2	*P* value ≤0.05 cohort 2	% Combinations cohort 2
Age (240)	0.008–0.358	96	40	0.005–0.119	205	85
GFR (240)	0.005–0.075	227	95	0.034–0.285	6	3
LKTBR (120)	**<0.001–0.005**	**120**	**100**	**<0.001–0.030**	**120**	**100**
RKTBR (120)	**<0.000–0.033**	**120**	**100**	**<0.001–0.013**	**120**	**100**
Left renal area (120)	**0.238–0.987**	**0**	**0**	**0.381–0.895**	**0**	**0**
Left background area (120)	**0.218–0.998**	**0**	**0**	**0.494–0.999**	**0**	**0**
Left no cortical defects (120)	**0.123–0.992**	**0**	**0**	**0.146–0.976**	**0**	**0**
Right no cortical defects (120)	**0.079–0.903**	**0**	**0**	**0.254–0.994**	**0**	**0**
Left renal margins smooth (24)	0.032–0.804	4	17	0.383–0.996	0	0
Right renal margins smooth (24)	0.049–0.488	1	4	0.068–0.354	0	0
Both renal margins smooth (24)	**0.224–0.920**	**0**	**0**	**0.567–0.995**	**0**	**0**
Left renal margins irregular (24)	**0.088–0.996**	**0**	**0**	**0.383–0.996**	**0**	**0**
Both renal margins irregular (24)	0.144–0.544	0	0	0.013–0.070	21	88
Left renal margins well defined (24)	<0.001–0.284	12	50	0.424–0.939	0	0
Right renal margins well defined (24)	<0.001–0.138	12	50	0.002–0.129	20	83
Both renal margins well defined (24)	<0.001–0.008	24	100	0.105–0.497	0	0
Time visualisation left calyces (80)	<0.001–0.639	40	50	0.089–0.288	0	0
Time visualisation right calyces (80)	0.012–0.750	40	50	<0.001–0.216	71	89
Time visualisation left pelvis (80)	0.013–0.839	24	30	0.011–0.057	77	96

The number of combinations in which each variable was included is given in brackets. The range of *P* values and the number of times a variable had a *P* value ≤0.05 is also listed. The variables with the same number of combinations in cohorts 1 and 2 in which the *P* value of the beta coefficient was ≤0.05 or >0.05 are presented in bold. The percentage of combinations in which each variable was significant is also given.GFR, glomerular filtration rateLKTBR, left kidney to background ratio; RKTBR, right kidney to background ratio.

Fig. 1



(a) The *LKTBR* plotted against the dependent variable *maxminhauc*. (b) The *RKTBR* plotted against the dependent variable *maxminhauc*. (c) The *LKTBR* plotted against the dependent variable *maxminhrp*. (d) The *RKTBR* plotted against the dependent variable *maxminhrp*.

reproducibility in any of the combinations in which they were included, Tables 6 and 7.

Testing the assumptions of the multiple linear regression models

The residual values, the differences between the predicted and observed values for each patient, in the combinations with the highest R^2 value for both methods and cohorts were calculated and plotted on a normal probability plot. The residual values did not depart significantly from the expected normal distribution. The residual values were also plotted against the continuous variables included in the combinations with the highest R^2 values. None of the patients had high residual values.

Cameron and Trivedi's test illustrated that there was no heteroscedasticity between the different variables included in the different analyses.

The VIF was calculated for each of the independent variables used in the combinations with the highest R^2 value. For all the variables the VIF values were less than |5|. This indicates there is no multicollinearity between these variables.

The collinearity between the variables was tested. There was no significant collinearity (>0.80) between the variables. Of note, there was no collinearity between age and GFR, the collineariarity coefficients ranged from −0.14 to 0.31.

Clinical implication of results

The results presented in this document were compiled after log transforming the dependent variables. The continuous variables *LKTBR* and *RKTBR* were re-analysed using the untransformed dependent variables so that the results could be translated into clinical practice.

The patients in cohorts 1 and 2 were combined in a single datasheet. *LKTBR* and *RKTBR* were plotted on scatterplots against the untransformed dependent variables *maxminhauc* and *maxminhrp*. The plots demonstrate that if the patient has a kidney to background ratio (KTBR) ≥5, no patient has a *maxminhauc* and *maxminhrp* ≥10. Most notably poorest reproducibility of DRF values, *maxminhauc* and *maxminhrp* ≥15, is seen if the KTBR is ≤3, Fig. 1.

The only categorical variables which were significant in most of the combinations in which they were present were right renal margins well defined and right renal margins poorly visualised. The ability to see the kidney clearly is dependent on the KTBR. There were 66 kidneys classified as right renal margins poorly visualised. The *RKTBR* for these kidneys ranged between 1.01 and 6.45, with 51 (77%) having an *RKTBR* ≤2. In contrast, the 288 kidneys classified as right renal margins well defined

had an RKTBR between 0.93 and 5.61 and only 36 (12%) patients had an RKTBR ≤2.

Discussion

The DRF value is used in clinical decision-making in a wide variety of renal diseases [15]. Several variables such as renal immaturity, decreased renal function, and a very big dilated renal pelvis have been implicated in the literature as possible reasons for poor reproducibility of DRF measurement [9,20].

We found that *LKTBR* predicted reproducibility in every combination analysed. *RKTBR* predicted reproducibility in most of the combinations in which it was included, except for log *maxminhauc* cohort 1 where it predicted reproducibility in 88% of the combinations. The KTBR value of the right kidney is consistently lower than that of the left kidney due to the high liver blood pool activity adjacent to the right renal ROI.

The calculated KTBR is a simple and objective method for quantifying uptake in each kidney. Of all the categorical and continuous variables examined, this variable is the most basic and most closely linked to renal activity, which depends on the function of that kidney.

In the first half of the 20th century, Rose developed a model to assess the threshold for detection of objects above noise in imaging. This was refined by Moran for medical imaging. The proposed signal to noise range for detection of a target object was given as 2.8–7 [21]. The range is comparable to the KTBRs found in this project. In 77% of the kidneys classified as right renal margins poorly visualised the target to background ratio was ≤2. In the current project, the decrease in reproducibility when the KTBR was ≤3 was clearly demonstrated.

In the early 1990s, Gordon *et al*. published a paper that addressed the importance of KTBR on the reproducibility of DRF measurement. The renograms were performed using ^{99m}Tc-DTPA. A drop of DRF of >10% was used as a criterion for surgical intervention. The authors described this change in DRF as a 'rather generous value'. The reason given for this cutoff was that in cases with low KTBR one encounters difficulty interpreting a renogram. The impact of the poor KTBR on image quality and DRF measurements when using ^{99m}Tc-DTPA in patients with immature renal function has led to the recommendation that a tracer with a higher extraction rate by the kidney, such as ^{99m}Tc-MAG3, ^{99m}Tc-EC or ^{123}I-Hippuran, should be used in children with immature function [22]. ^{99m}Tc-MAG3 is removed from blood by tubular secretion with an extraction fraction of 40–50%. Maturation of tubular function is fast in the first three weeks of life and it reaches a plateau at 12 months. Therefore, one frequently has a good KTBR even in young infants when using ^{99m}Tc-MAG3. In addition, ^{99m}Tc-MAG3 is highly protein-bound and the tracer remains in the intravascular space. This means that the overall KTBR for this tracer is high. However, blood pool activity in the heart, spleen and liver is more prominent on the early images, especially in patients with impaired renal function. This may make drawing ROIs difficult in patients with impaired renal function [23].

Right renal margins well defined and *right renal margins poorly visualised* were the strongest categorical predictors of reproducibility. Kidneys with poorly visualised margins usually have a low KTBR. If the right kidney is not well defined the measurement of DRF becomes less reproducible. This illustrates that being able to clearly see the right kidney above background makes it easier to draw the ROIs and therefore leads to reproducible measurements of DRF irrespective of the method used to calculate DRF.

We postulate that the reason only *time visualisation right calyces* predicted poor reproducibility may again be related to the decreased kidney to background. The ability to see activity in the right calyces depends on the ability to see activity above the adjacent renal background which in this case is a combination of renal parenchymal activity superimposed on the liver blood pool activity background. Therefore, in patients with decreased kidney to background the calyceal activity on the right would be visualised slightly later than on the left.

Higher age strongly predicted good reproducibility for both methods in both cohorts. The literature pertaining to ^{99m}Tc-DTPA shows there is a higher variation in DRF measurements in infants due to renal immaturity [2,24]. The effect of renal immaturity on the reproducibility of ^{99m}Tc-MAG3 has not been extensively investigated. Lezaic *et al*. found that the variable age was NS in analysis of variance analyses used to assess factors that affected reproducibility of DRF on ^{99m}Tc-MAG3 renography. There was no difference in the SD of DRF in 25 children less than 6 months compared to 25 children older than 6 months [9]. A recent study by Tondeur *et al*. [25], also found that age younger than 6 months did not affect the reproducibility of DRF on ^{99m}Tc-MAG3 renography.

Piepsz has shown that most patients reach mature GFR at 12 months of age but maturation can continue until 24 months [26]. About 60% of the patients included were older than 18 months. It can therefore be assumed that they had mature glomerular filtration at the time the renograms were performed. Maturation of tubular function is faster and by 2 months 68% of the mature clearance of ^{99m}Tc-MAG3 is reached [27]. Less than 15% of the children in both cohorts were younger than 2 months. The effect of immature tubular function on reproducibility was therefore not adequately tested in this project.

A higher GFR was a strong predictor of good reproducibility for both methods in cohort 1 but not in cohort 2. Several reasons for this have been identified, such as a

difference in the cohort populations and the predominant use of eGFRs. The method for measuring creatinine differed between the two cohorts. Our laboratory changed from the Jaffe method to an enzymatic method in 2010.

The literature identifies a very low GFR as a cause for poor reproducibility on ^{99m}Tc-MAG3 renography [28]. It has been shown that mild to moderately impaired GFR does not affect the reproducibility of DRF measurements. Taylor *et al*. investigated reproducibility in 24 adult patients, 11 of whom had raised creatinine levels of between 114 and 248 µmol/L. There was no difference in the mean error of DRF measurement between the 13 patients with normal GFRs and the 11 patients with raised GFRs [4]. Even when using ^{99m}Tc-DTPA instead of ^{99m}Tc-MAG3, it appears that adult patients with mild to moderately impaired GFR, 15–40 mL/min, had better reproducibility of DRF measurement with a 6% coefficient of variation compared to 32% coefficient of variation in patients with a GFR ≤15 mL/min [29].

The variables renal margins smooth or irregular are subjective and may not be consistently assigned by any single observer. In this study, all these variables were assigned by a single observer. From our results, it is clear that an objectively measured KTBR is a better predictor of reproducibility than these subjective variables.

The absence of cortical defects or the presence of only one cortical defect does not affect the ability to clearly visualise the kidney above background and had no impact on the reproducibility of DRF measurements.

The unexpected finding that the size of the kidney did not impact on reproducibility in our cohorts could be explained by the fact that the cohorts were taken from a mixed population of children which included children with hydronephrotic kidneys, normal kidneys and small dysplastic kidneys. Of these, only a small number had severe hydronephrosis which made the drawing of ROIs difficult in those patients. The effect of large renal size due to hydronephrosis was not effectively investigated by this population. A study that investigates differences in reproducibility in children without hydronephrosis and children with varying degrees of hydronephrosis would be more appropriate.

In contrast to the literature, the variable *asymmetry drf* did not predict reproducibility. In 1999, Piepsz *et al*. did a small study in 13 healthy adult volunteers to assess the accuracy and reproducibility of ^{99m}Tc-MAG3 compared to ^{99m}Tc-DMSA. Higher systematic biases were seen in five patients with asymmetrical renal function when the renograms were processed without background correction [30]. If there is very severe asymmetry, then the KTBR of the affected kidney would be poor. However, in small dysplastic kidneys, the asymmetry in renal function can be attributed to the difference in functional renal mass instead of poor KTBR. These kidneys can still be clearly identified above background if uptake of ^{99m}Tc-MAG3 by the remaining renal tissue is still good.

Limitations

A limitation of this study was the fact that most of the patients, 89%, had eGFRs.

The R^2 values of the cohort 2 multiple linear regression models were low. This means that there are one or more factors that impact on the reproducibility that were not examined by these multiple regression models.

Recommendations and future perspective

Future studies should investigate the relationship between mGFR and the reproducibility of DRF measurements. These studies should contain large enough populations with decreased mGFR to confirm any effect of low mGFR on reproducibility.

It is recommended that the KTBR should be incorporated into the renal processing screen display as a valuable quality control step. The DRF values should be interpreted with caution, or the renogram should be reprocessed repeatedly to determine reproducibility of the DRF value if the KTBR is ≤2.0.

Conclusion

The only variables which consistently predicted good and poor reproducibility for the measurement of DRF of children on ^{99m}Tc-MAG3 renograms performed according to the SNMMI and EANM guidelines were *LKTBR, RKTBR*, *right renal margins well defined*, *time visualisation right calyces* and *age*.

Consideration should be given to incorporating the KTBR into the renal processing screen display as a valuable quality control step. The DRF values should be interpreted with caution if the KTBR is ≤2.0.

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Conflicts of interest

There are no conflicts of interest.

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