

Renogram Image Characteristics and the Reproducibility of Differential Renal Function Measurement

Anita Brink

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Supervisors: Prof. M Levin

Prof. MD Mann

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Abstract

Aim

The reproducibility of differential renal function (DRF) estimates on ^{99m}Tc -mercaptoacetyltriglycine (^{99m}Tc -MAG3) is good in the majority of children. There is however a small but important group with poor reproducibility which, if not recognized, could affect clinical decision making. Some factors, such as age and glomerular filtration rate (GFR), have been implicated as causes for poor reproducibility. The aim of this study is to formally investigate image characteristics associated with the reproducibility of DRF measurements.

Patients and methods

The image characteristics and reproducibility of the DRF estimates of the 127 patients in cohort 1 was used to identify the characteristics associated with reproducibility. The associations between these image characteristics and reproducibility were then tested in a second cohort of 227 patients.

The DRF measurements were calculated using two internationally accepted methods for calculating DRF, the HERMES area under the curve (HAUC) method and the HERMES Rutland Patlak (HRP) method.

The images were visually inspected to categorise the categorical variables and processed to obtain the values of the continuous variables. The variables investigated included two non-imaging variables, age (in months) and GFR which included measured or estimated GFR values.

The association between each variable and the reproducibility of DRF measurement for both the HAUC and the HRP methods was tested with univariate linear regression. The results of the univariate linear regression were used to plan the multiple linear regression combinations. All possible combinations were tested with multiple linear regression.

Results

The goodness-to-fit for the multiple regression models were much higher for all the combinations analysed in cohort 1 than in cohort 2. In cohort 1 the R^2 -values ranged from 0.3510 to 0.4906 for log MAXMINHAUC and 0.3284 to 0.4500 for log MAXMINHRP. In cohort 2, they ranged from 0.1675 to 0.2163 for log MAXMINHAUC, and 0.1706 to 0.2191 for log MAXMINHRP. The combinations with the highest R^2 -value for multiple linear regression analyses were similar in cohort 1 and 2.

The only individual variable which was significant in all the multiple linear regression combinations for cohort 1 and 2 for both log MAXMINHAUC and log MAXMINHRP was LEFT KIDNEY TO BACKGROUND RATIO. RIGHT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL MARGINS WELL DEFINED, RIGHT RENAL MARGINS POORLY VISUALISED and TIME VISUALISATION RIGHT CALYCES were significant in most of the combinations analysed. A high kidney to background ratio, RIGHT RENAL MARGINS WELL DEFINED and higher AGE predicted a good reproducibility. A low kidney to background ratio and later TIME VISUALISATION RIGHT CALYCES predicted poor reproducibility.

The variables LEFT RENAL AREA, LEFT BACKGROUND AREA, BOTH RENAL MARGINS SMOOTH and RIGHT RENAL MARGINS IRREGULAR were not-significant in any combinations analysed cohort 1 and 2 for both log MAXMINHAUC and log MAXMINHRP.

The remaining variables inconsistently predicted reproducibility in log MAXMINHAUC and log MAXMINHRP for both cohort 1 and 2.

Conclusion:

The only variables which consistently predicted good and poor reproducibility for the measurement of DRF on ^{99m}Tc -MAG3 renograms performed according to the EANM guidelines for both log MAXMINHAUC and log MAXMINHRP were AGE, LEFT KIDNEY TO BACKGROUND RATIO, RIGHT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL MARGINS WELL DEFINED and TIME VISUALISATION RIGHT CALYCES.

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

Renogram Image Characteristics and the Reproducibility of Differential Renal Function Measurement

Structured Literature review

Introduction:

The external probe renogram using ^{131}I -Urokon and ^{131}I -Diodrast was first described in 1956 by Kade et al.¹. Renography performed with external probes was technically challenging and the radiopharmaceuticals were suboptimal. The development of the Anger gamma camera connected to an external computer led to vast improvements in the imaging and processing of the renogram². The addition of a diuresis challenge to renography increased the use of this investigation further³.

Parallel to the development of the gamma camera was the development of radiopharmaceuticals. Para-aminohippuric acid (PAH) is the gold standard for measurement of tubular function. PAH is excreted through tubular secretion (80%) and glomerular filtration (20%) and 90% of it is eliminated from the plasma with one pass through the kidney. PAH is given as a constant infusion and clearance is measured in blood and urine cohorts. PAH is not an imaging agent. PAH is not useful for routine clinical work and was soon replaced with ^{131}I o-iodohippuric acid (OIH) also known as hippuran. OIH has slightly lower plasma clearance values, 85%, than PAH⁴. ^{131}I -OIH was widely used in the 1970's and eighties but it had some problems. The ^{131}I decays with beta minus and gamma emissions and the half-life is 8.02 days. The principle gamma ray has an energy of 364 keV (abundance of 81%). The beta-emissions and photons are not optimally suited for the gamma camera and leads to decreased spatial resolution. The associated beta emission increases the radiation dose the patient receives from this agent. Using ^{123}I -OIH seemed a logical solution to the problem, but ^{123}I has a short half-life, limited availability and high cost⁵.

Due to its lower price ^{99m}Tc -diethylenetriaminepentaacetic acid (DTPA) is the most widely used radiopharmaceutical for adult renography worldwide. ^{99m}Tc -DTPA is cleared by glomerular filtration so has a low plasma extraction rate. It also diffuses from the intravascular space into extracellular fluid. These factors lead to a decreased kidney to background ratio. This decreased ratio is problematic in children with poor renal function and children younger than 6 months. Tubular agents such as ^{99m}Tc -ethylenedicycysteine (^{99m}Tc -EC), ^{99m}Tc -mercaptoacetyltriglycine (^{99m}Tc -MAG3) and ^{123}I -OIH have a better plasma extraction rate and kidney to background ratio⁶.

^{99m}Tc -MAG3 has high protein binding, 79 to 90%. This leads to a high intravascular concentration of the agent and there is very little diffusion of the agent in the extravascular space. This improves the kidney to background ratio. Due to the high protein binding only a small percentage is filtered by the kidney. This agent is secreted into urine by tubular secretion. The initial plasma extraction ratio is 60% but it decreases to 40% within 30 minutes after the injection of the agent⁷.

^{99m}Tc -EC and ^{99m}Tc -MAG3 are currently the recommended radiopharmaceuticals for paediatric radionuclide renography. The current combined European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) guideline states that ^{99m}Tc -DTPA may be used if ^{99m}Tc -EC and ^{99m}Tc -MAG3 are not available⁸. ^{99m}Tc -EC is only commercially available in a few countries and therefore ^{99m}Tc -MAG3 is the tubular agent used in most countries^{6,9-11}.

Renograms are performed to evaluate a variety of renal problems. These include hydronephrosis caused by; pelvi-ureteric junction stenosis, vesico-ureteric stenosis, bladder dysfunction, posterior urethral valves, complicated duplex kidneys. Renograms are also performed to assess the effects of renal infection and vesico-ureteric reflux (VUR) on kidneys and are frequently performed as a precursor to indirect cystography¹².

Differential renal function (DRF) is a measurement of each kidney's ability to extract tracer from blood and therefore reflects renal function¹³. This value is used to guide clinical decision making. In children with unilateral hydronephrosis and a normal DRF, where the DRF for the two kidneys fall in the 45 to 55% range, a watch and wait approach is followed¹⁴. Some institutions will intervene if the DRF is below 40%, which is essentially a drop of 5% from the lower limit of normal DRF. A comprehensive metareview done by Josephson shows that only 25% of patients with an initial DRF of less than 40% on whom conservative approach was followed needed a pyeloplasty¹⁵. The levels for a drop in DRF before surgical intervention have been established empirically¹⁶. A drop in DRF of 10% from initial DRF value is an established indication for surgical intervention¹⁷⁻¹⁹.

Multiple methods for calculating DRF have been proposed²⁰. Currently two methods are recommended by international guidelines. These are the Rutland Patlak Plot (RP) method and the integral method¹².

The integral method is also referred to as the area under the curve method (AUC). The integral method is calculated using the area under the background-corrected curve of each kidney for a selected time period, usually 60 to 120 seconds after injection of ^{99m}Tc-MAG3, or 60 to 150 seconds after injection of DTPA. The RP method is the mean slope of the ascending portion of the curve plotting the background-corrected kidney region of interest (ROI) counts $[R(t)]$ divided by the cardiac ROI counts $[H(t)]$ as a function of the integral of the cardiac ROI counts divided by $[H(t)]$ ^{12,21}. In theory the RP method should be more accurate than the integral method as there is a correction for the vascular component of renal counts. In practice the slope of the RP method is more sensitive to errors because of poor statistics. It is therefore prone to errors in patients with decreased or immature renal function^{6,22}.

We have previously established that the DRF calculation is usually reproducible but in a small number of renograms reproducibility is poor²³. Different methods for establishing reproducibility have been proposed. Most include processing a renogram with more than

one method or processing a renogram repeatedly^{6,23–25}. From clinical experience we expect that some visual characteristics are associated with a good reproducibility and others with poor reproducibility of DRF measurements. This research project will investigate which imaging characteristics are associated with good or poor reproducibility.

Objectives of the literature review:

Only a few articles have been published on the reproducibility of DRF. Some of the factors implicated to affect reproducibility are the size of the kidney, or size of the renal pelvis. Another factor is the kidney to background ratio which is correlated to the renal function. In kidneys with impaired renal function, uptake of tracer from blood is decreased. This leads to a small difference between the kidney and background counts.

This literature review aims to collect articles which investigate visual or clinical factors which may influence the reproducibility of DRF measurements of ^{99m}Tc-MAG3 renograms. These factors include renal size, degree of hydronephrosis, global renal function, best described by the glomerular filtration rate (GFR), functional impairment of an individual kidney, renal immaturity, and cortical defects.

Literature search strategy:

Information sources:

A systematic review of articles on MEDLINE Pubmed and Cochrane database using the following terms was performed:

1. “Reproducibility of renogram”

MEDLINE Pubmed was searched using the term “Reproducibility of Renogram”. This retrieved 37 articles. A total of six articles were included. The remaining papers were excluded as they described drainage parameters (10), did not describe reproducibility of DRF measurement (9), described estimated renal plasma flow (ERPF) or GFR measurements and did not discuss associations between ERPF or GFR and reproducibility of DRF measurements (7), did not describe ^{99m}Tc-MAG3 renography (4) and transplant renography (1,) Table 1. The Cochrane database was searched using the same terms and eleven articles were found. Eight articles were duplicates of entries found in the Pubmed search. The remaining three papers did not describe reproducibility of DRF measurement. Both data bases were searched on 23 May 2019.

2. “Reproducibility, renogram, MAG3”

Both listed databases were also searched for the keywords “reproducibility, renogram, MAG3” on 23 May 2019. This search yielded nine articles from MEDLINE Pubmed, Table 1, four papers on the Cochrane database. No new articles were found.

3. “Renal scintigraphy reproducibility”

A MEDLINE Pubmed search using “renal scintigraphy reproducibility” was performed on 24 May 2019. This listed 452 articles and 20 were included for review. The remaining articles were excluded because they did not describe factors affecting reproducibility of DRF measurement (34), did not describe ^{99m}Tc -MAG3 renography (285), focussed on GFR or ERPF measurements and did not discuss associations between GFR or ERPF and reproducibility of DRF measurements (49), focussed on captopril renography (14), described drainage parameters (11), were identified and included in search one (6) and excluded in search one (21), transplant renography (5), comments on articles (4). Three articles were classified as miscellaneous, one was on the topic of exercise renography, one describes the pitfalls in patients with ectopic kidneys and the last was a comparison between ^{99m}Tc -MAG3 and ^{99m}Tc -DMSA studies, Table 1.

Using the same search terms on the Cochran database on 24 May 2019, produced 17 articles, all were already identified and excluded in the MEDLINE Pubmed search.

4. “Differential renal function and renography”

The search was performed on 24 May 2019. A total of 306 articles were found on MEDLINE Pubmed, 15 of these were included. The reasons for excluding the other articles were; they did not describe reproducibility of DRF measurement (108), did not describe ^{99m}Tc -MAG3 renography (80), captopril renography (40), excluded before (17), transplant renography (15), drainage parameters (13), already included (11), not discuss associations between GFR and reproducibility of DRF measurements (3) and miscellaneous (4). The miscellaneous articles were two articles published in 1970 and we could not find copies of the articles, one published in 1984 in German and one article which only described perfusion parameters of renography, Table 1.

The Cochrane database, searched on 24 May 2019, gave 12 articles. Ten were duplicates from the MEDLINE Pubmed search. The remaining two did not describe reproducibility of DRF measurement.

5. “Differential renal function and renogram and scintigraphy”

Pubmed was searched for the keywords “Differential renal function and renogram and scintigraphy” on 24 May 2019 and 67 results found. Of the 67 articles retrieved ten were excluded because they did not describe reproducibility of DRF measurement, they discussed captopril renography (2) or they did not describe ^{99m}Tc -MAG3 renography (3). Forty three articles were excluded before and nine articles were included in previous searches, Table 1.

A Cochrane database search on 24 May 2019 produced one article. This article was a duplicate from the MEDLINE Pubmed search.

Table 1. A summary of the MEDLINE Pubmed search results.

Search term	Included	Excluded: Duplicate	Excluded: Do not describe reproducibility of DRF	Excluded: Drainage parameters	Excluded: GFR or ERPF	Excluded: Other modality	Excluded: Other*
Reproducibility of renogram	6	0	9	10	7	4	1
Reproducibility, renogram, MAG3	0	9	0	0	0	0	0
Renal scintigraphy reproducibility	20	27	34	11	49	285	26
Differential renal function and renography	15	28	108	13	3	80	59
Differential renal function and renogram and scintigraphy	0	52	10	0	0	3	2

*Excluded Other: Included transplant renography, captopril renography and articles classified as miscellaneous.

In summary:

“Search terms” search engines (number of articles)

“Reproducibility of renogram” MEDLINE pubmed (37), Cochrane (11)

“Reproducibility, renogram, MAG3” MEDLINE pubmed (9), Cochrane (4)

“Renal scintigraphy reproducibility” MEDLINE pubmed (452), Cochrane (17)

“Differential renal function and renography” MEDLINE pubmed (306), Cochrane (12)

“Differential renal function and renogram and scintigraphy” MEDLINE pubmed (67), Cochrane (1)



Exclusion criteria:

Did not describe reproducibility of DRF measurement:
175

Duplicates: 156

Did not describe ^{99m}Tc-MAG3 renography: 363

ERPF and GFR: 59

Captopril renography: 56

Drainage parameters: 34

Transplant renography: 21

Comments on articles: 4

Miscellaneous: 7



Included articles: 41

The reference lists of articles included from the database searches were reviewed and additional relevant articles were also added.

Literature review

Radionuclide renography is an established investigation for children with various renal diseases. The estimate of DRF is the most reliable parameter obtained from renography. The initial DRF value as well as changes in DRF are used to guide treatment decisions and to follow-up patients²⁶. The reproducibility of this measurement is therefore of vital importance.

Current recommendations for calculating DRF:

DRF is the percentage that each kidney contributes to total renal function. In 1999 the International Consensus Committee from the Scientific Committee of Radionuclides in Nephrourology (ISCORN) released a document on quality control of measurements in renography. It states that the time interval for calculating DRF with ^{99m}Tc-MAG3, ^{99m}Tc-DTPA and ¹²³I-OIH should be between one and two minutes 30 seconds after peak cardiac activity unless the time to peak of the renogram curve has been reached. The starting point of this time interval should not be too early. In patients with poor renal function the renal vascular transit time is decreased, leading to an artefactual increase in the DRF values if the time interval used to calculate DRF starts earlier than 40 seconds after peak cardiac activity. The end point of this time interval should be selected before there is any escape of tracer from the nephron into the renal collecting system²⁷.

More recent guidelines have moved the acceptable end time point for ^{99m}Tc-MAG3 from two minutes 30 seconds to two minutes. So the current recommendation for the time interval for DRF calculation on ^{99m}Tc-MAG3 renography is 60 to 120 seconds after the peak cardiac activity of the ^{99m}Tc-MAG3 bolus. If a diuretic is given at the same time as the ^{99m}Tc-MAG3 injection, F0 renography, there may be rapid transit of activity through the

nephron leading to early accumulation of ^{99m}Tc -MAG3 in the renal collecting system. In these cases the DRF should be calculated at 40 to 100 seconds after peak cardiac activity¹².

The integral and RP methods for calculating DRF are the only two accepted methods. The integral method determines the area under the background corrected renogram curve over a selected time period²⁷.

The Rutland-Patlak plot is defined as:

$$\frac{R(t)}{B(t)} = F + K \frac{\int_0^t B(t) dt}{B(t)}$$

$R(t)$ is the renal activity corrected for peri-renal background

$B(t)$ is the plasma activity derived from the cardiac curve.

F is the blood background subtraction factor.

K is the fraction of blood activity taken up per second²¹.

It is important to understand that renal background has two components. One is extrarenal and the other intrarenal. Depending on the placement of the background ROI the extrarenal component consists of the organs surrounding the kidneys for instance liver, spleen, bowel and abdominal vessels. The activity in the different components of the background is constantly changing. Shortly after injection of radiopharmaceutical there is a drop in the amount of activity in the intravascular space as the activity is taken up by the nephrons. In the case of ^{99m}Tc -DTPA the drop in the intravascular space is also due to diffusion of the ^{99m}Tc -DTPA into the interstitial space²⁷.

The current recommendation for drawing the renal ROI is a peri-renal ROI. The renal ROI should not cut the kidney and should preferably be drawn with a ROI that is slightly bigger than the kidney. The recommended background ROIs is a C-shaped ROI which does not include the renal hilum⁸. The background ROIs should be separated from the kidney with one or two pixels, depending on matrix size, to avoid scatter from the kidney²⁷. Scatter from the kidney into the background ROI will result in overestimation of background activity. The

guidelines state that it is unacceptable to process the renogram without any background correction or using the infero-lateral background correction⁸. The infero-lateral background should not be used as it will lead to a significant overestimation of the DRF of the kidney with decreased function if there is asymmetrical renal function. Careful attention should be paid that the background ROI does not extend outside the body outline especially in patients with marked hydronephrosis^{12,24}.

Phantom studies investigating reproducibility of DRF:

Numerous physical phantoms for quality control of renograms have been developed. In 2004 Heikkinen described tests performed on a phantom he developed. The same pre-programmed renogram simulation was run three times. The reproducibility of ^{99m}Tc-MAG3 DRF values, expressed as the average root mean square of the coefficient of variation of the three measurements calculated by the RP method using Hermes software, was 3.3%²⁸.

In 2014 Nykänen used the phantom developed by Heikkinen and did imaging studies in 20 different nuclear medicine departments. All the departments were asked to image the phantom per their protocol and calculate different parameters. There were three simulations programmed in the phantom. The first simulated normal kidney function, the second obstruction and the third a dilated pelvis. With all three simulations the function of the left kidney was overestimated from the true value, the mean difference in results from the true DRF to the calculated DRF varied from 3.6 to 9.6% with a standard deviation from the different measurements of DRF in different hospitals varying from 3 to 3.9 %. Seventeen of the 20 hospitals used the HERMES software for evaluation of DRF. Background subtraction between the hospitals differed from peri-renal C-shaped, inferolateral to no background correction, and the difference in background correction did not influence the DRF in this study. In one simulation the RP method provided more accurate results and in the other two the more accurate results were provided by the integral method²⁹.

Recently a study using digital phantom studies was published. Three digital phantoms were programmed. Two had normal renal plasma clearance of ^{99m}Tc-MAG3, one was a female

with normal DRF (phantom A) the other a male with asymmetrical DRF (phantom B). The third phantom was a simulation of a male with normal DRF but a decreased renal plasma clearance of ^{99m}Tc -MAG3 in keeping with renal impairment (phantom C). A unique set of posterior projection data specifically tailored to match these parameters was then generated for each participant and camera configuration. These studies were then processed by 21 different nuclear medicine departments. The measured DRFs for the left kidney were $55.4\% \pm 1.6$ for phantom A, $39.3\% \pm 2.2$ for phantom B and 60.8 ± 4.4 for phantom C. The true values for uptake by the left kidney were 50% (phantom A), 33.3% (phantom B) and 55% for Phantom C. The systematic overestimation of function on the left was attributed to the difference in renal depth between the right and left kidneys. The phantom with decreased renal function, phantom C, had decreased precision of DRF measurements compared to the other phantoms. This decrease in precision was attributed to a decreased kidney to background ratio coupled with increased background activity which in turn makes placing accurate background ROIs more challenging³⁰.

A similar paper used two digital phantom studies and three anonymised patient studies. The patients were diagnosed with hydronephrosis, VUR and obstruction. These studies were then analysed by 34 different medical centres from a total of 21 countries. The method of background subtraction between the different departments varied from, peri-renal (40%), none (21%), sub-renal (18%), background determined by interpolation or other methods (15%) and central (6%). The researcher received 136 reports for the five renograms. The DRF values for the right kidney for the five studies were 68% (67.1 to 68.5%), 31% (28.1 to 32.9%), 48% (47.2 to 48.8%), 50% (49.9 to 50.1%) and 21% (20.1 to 21.9%). The 95% confidence interval is indicated in brackets. The best agreement between centres was for a phantom study with a DRF of 50%, the highest deviations in values were in the two studies with impaired function of the right kidney. The one renogram with impaired function on the left had a smaller deviation in values than that of the right kidneys with impaired function. The authors attributed the larger variation in values in the right kidneys with decreased function to the adjacent liver and the larger contribution of background counts to the number of counts in the renal ROI¹³.

A national audit of nuclear medicine departments in the United Kingdom investigated the reproducibility of various renogram parameters in 10 patient studies. The study included five ^{99m}Tc -DTPA and five ^{99m}Tc -MAG3 renograms. The renograms included represented normal and pathological renal function. The participating hospitals were asked to measure DRF, whole kidney mean transit time (MTT) and time to peak. A total of 180 responses were received from 81 hospitals. Relative function was measured by various algorithms including the integral method, RP method, deconvolution, renogram slope, renogram peak counts, counts at a fixed time and multiple regression analysis. There was also little consistency in the site and shape of background ROIs. The authors found that of all the measurements tested the measurement of DRF had the best consistency. The actual values for DRF were not reported but depicted with histograms illustrating that in some cases there was a difference of close to 20% in the value obtained for DRF of the same left kidney by different hospitals. The authors did not state which renograms were performed with ^{99m}Tc -DTPA or ^{99m}Tc -MAG3. The audit found that factors influencing the measurement of DRF were the software origin (in-house or commercial), hospital, computer, background ROI site, UK region, number of smooths and method/algorithm used to calculate DRF³¹.

In summary the reproducibility of renograms on phantom studies is usually good. There are many factors which influence reproducibility. These include the method used to calculate the DRF, integral vs. RP. There is a difference in the calculation of DRF when using the same method supplied by different software programs. The method of drawing background ROIs is also an important factor. If there is decreased renal function there is a decrease in the reproducibility of measurements. The side of the kidney with decreased function is also important especially in cases with decreased renal function. In simulations where the right kidney has decreased function there is a decrease in the reproducibility of the measurements.

Current recommendations to assess reproducibility of DRF measurements:

The calculation of DRF is a robust measurement as shown with the phantom studies. However careful attention should be paid to placing the kidney and background ROIs in the

correct position. When using the RP method correct fitment of the RP plot is essential. The following quality control steps for the calculation of DRF have been recommended.

The DRF is usually calculated using the one to two minute interval after injecting ^{99m}Tc -MAG3. In studies where the diuretic was injected at the same time as the ^{99m}Tc -MAG3 and there is rapid transit of tracer through the kidney the DRF should be calculated at 40 to 100 seconds. A suggested quality control measure for DRF for the integral method is to calculate the DRF for each 10 second frame of the one to two minute or 40 to 100 second time period. A DRF which is constant, defined as a difference of less than 5% between the frames, is an indication of stability of the method. The method of quality control is however not very practical in an average clinical department and most software packages do not have this functionality ^{6,12}.

The slope of the RP curve represents the background corrected clearance of activity from the kidneys and the intercept of the line represents the non-corrected vascular activity. If the intercept is greater than zero there is under correction for background activity and if it is less than zero too much background has been subtracted from the curve. The points plotted for the RP plot in normal patients are distributed fairly well along a straight line. Most software packages provide a linear regression estimate of how well the points plotted fits the straight line (R^2). A value of greater than 0.95 is preferred. The first two points, which represent the first 40 seconds of the renogram, are influenced by high extra renal activity and should not be ignored if they alter the straight line fit. The later points are influenced by activity leaving the kidney and the goodness of fit increases if later points are omitted. After ten points the points usually fall below the straight line. In this short time interval for optimal straight line fit significant errors can be made if there is statistical noise, for instance in cases of poor renal function. The quality control therefore is to check visually that the plotted slope intercepts the points plotted, if it does not the renal and background ROIs should be redrawn to improve the fit ^{6,25}.

Comparing the DRF results obtained by the integral and RP methods provides additional quality control. The EANM guidelines recommend that if the results are discordant, $\geq 5\%$

difference between the two methods, the studies should be reprocessed with careful attention to placing the regions of interest and the fit of the RP plot^{6,12}.

Another way of identifying studies with poor reproducibility is to process each study more than once; preferably with more than one method and to see if the values obtained for DRF are robust²³.

Studies investigating the reproducibility of DRF:

A small number of studies have investigated the reproducibility of DRF measurements of ^{99m}Tc-MAG3 renograms in humans. In 1999 Piepsz and co-workers did a study on 13 healthy adult volunteers (21 to 30 years). These volunteers had two ^{99m}Tc-MAG3 renograms performed one week apart. The mean difference of DRF between the two renograms was less than 0.3% for both the integral and the RP plot method. The standard deviation of the difference was 1.7 for the integral method using a peri-renal region for background correction and 2.8 if four early points of the renogram were used in the RP plot method³².

In 2007 Dissing et al., investigated the reproducibility and repeatability of estimates of DRF in 4-week-old piglets. In this study renal scintigraphy was performed with ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) and ^{99m}Tc-DTPA. In eight animals three alternating ^{99m}Tc-DMSA scintigrams and ^{99m}Tc-DTPA renograms were performed daily over six days. The DRF was calculated using superior and inferior background regions of interest of different sizes and once without any background correction. This led to 19 different combinations of background ROIs. The average coefficient of variation (CV) of DRF for the 19 different background combinations with ^{99m}Tc-DMSA scintigraphy was 2.3% (range 0.8 to 3.9%). The coefficient of variation of ^{99m}Tc-DTPA scintigraphy ranged from 0.5 to 35.9% when using the AUC method and 1.6 to 37.2% for the RP method. The repeatability coefficient (RC) was calculated for each of the methods of background correction. The lowest RC for ^{99m}Tc-DMSA was 3.4%. For ^{99m}Tc-DTPA the lowest RC for DRF calculated with the AUC method was 14.9% and with the Rutland Patlak plot method it was 9.4%³³. The background ROIs which gave the lowest RC values for all three methods were the two pixel wide ROIs placed superiorly and inferiorly. A lateral ROI was not used in this study; due to

the size of the animals it would have extended outside the body outline. The large variation in DRF measured using ^{99m}Tc -DTPA was attributed to the poor kidney to background ratio in the immature animals ³⁴. The reproducibility and repeatability parameters in these immature animals were so poor that the authors extrapolated that the use of ^{99m}Tc -DTPA in immature patients could not be recommended. It is expected that the reproducibility and repeatability would be slightly better if ^{99m}Tc -MAG3 with its higher extraction ratio and higher protein binding is used^{5,35}.

Lezaic et al. also showed that immaturity affects the reproducibility of DRF measurements on ^{99m}Tc -MAG3 renograms. They evaluated reproducibility of various renogram parameters in 50 adult and 50 paediatric patients. The ^{99m}Tc -MAG3 renograms of successive patients were processed twice by three observers using the integral method. The patients had a wide range of DRF. The intraobserver and interobserver agreement for DRF measurement was calculated using an intraclass correlation coefficient (ICC). The agreement between observers for the adult population was very good with an ICC of 0.99. The average ICC values for the paediatric population was also very good, they were 0.98 for the intraobserver and 0.97 for the interobserver analysis. In this paper intra and interobserver variation in DRF measurement was quantified by a within subject standard deviation (SD) and repeatability parameter. The repeatability parameter was defined as 2.77XSD ³³. Repeatability of DRF measurement in the entire paediatric subgroup was acceptable for a single observer (4.76%) but was high between observers (7.80%). The influence of immaturity of renal function was tested by dividing the paediatric patients into two equal subgroups of patients younger than six months and patients between six months and six years. No striking difference in repeatability was found. The authors divided the patients into those with good and poor drainage. Inter and intraobserver analysis showed that DRF estimates were lower in the poor drainage group. The intraobserver SD of the DRF estimates did not vary across drainage groups but the interobserver SD did vary across the groups. The interaction of factors with possible effect on DRF variability were analysed with ANOVA. The factors analysed were the DRF values, patient age, DRF asymmetry and drainage. Drainage categories and DRF were found to be significant factors in intraobserver analysis but in the interobserver analysis these factors only had borderline significance. The other factors were not significant³⁶.

In a study of 24 adult urology patients with stable renal function, each patient had two ^{99m}Tc -MAG3 renograms within a month. There was no significant difference between the baseline and follow-up measurements of DRF. Pearson correlation between the measurements of relative uptake of the two studies was 0.98 for both kidneys. The patients were divided into two groups, those with normal (13) and elevated creatinine (11) and there was no difference in mean error of DRF measurement between these two small groups. The error was calculated as the difference between the two measurements. Each study was only processed once. The 95% confidence interval of the two measurements was $\pm 5.64\%$ for the right kidney and $\pm 6.01\%$ for the left. This led to the conclusion that if appropriate software is used in combination with careful attention to quality control, a difference in DRF of more than 7% between studies in a patient is probably pathological and a conservative cut-off of a change of $\geq 9\%$ is recommended¹⁷.

In 1999 Lythgoe et al., compared DRF measurement when using ^{99m}Tc -MAG3 to DRF measurements on ^{99m}Tc -DMSA scintigraphy. The study population consisted of two groups, one group with a single functioning kidney (35) and the other with two kidneys with normal GFR (20). In the group with single kidneys only eight had normal renal function, ten had a GFR of $< 50 \text{ ml/min/1.73m}^2$ and remaining 17 patients were under one year and thus assumed to have immature renal function. The renal function of these 17 patients was however not provided in the paper. A ^{99m}Tc -DMSA scan recorded within a month of the ^{99m}Tc -MAG3 renogram was used as the reference value for DRF calculation in the group with two kidneys. All the renograms were then analysed using six different methods for calculating DRF. These included the RP method, deconvolution analysis (by matrix method), differential method, integral method, slope method and area under the curve method. The assignment of method names in the study may lead to confusion as the area under the curve method described by the authors, the area under the renogram $R(t)$, is not the same as area under the curve method which is referred to as the integral method in the international guidelines. Each renogram was then processed using the six methods in combination with rectangular and irregular renal ROIs. The rectangular renal ROIs were then combined with rectangular background and the irregular ROIs with a C-shaped peri-renal

background. Both renal ROIs were also processed without background correction. Therefore each renogram was processed with 24 different methods by three different operators. The group with single kidneys were processed as if they had two kidneys. The relative function for these patients should intuitively be 100% if the measurement parameters are correct. The data was analysed using paired differences between each of the three operators. In the group with normal renal function and two kidneys all analysis were performed on the difference between paired ^{99m}Tc -DMSA and ^{99m}Tc -MAG3 data. The DRF values for the left kidney obtained by the three observers for each of the 24 methods were not significantly different. The $\text{Mean}_{\text{maxdiff}}$ between any two observers ranged from 0.2 to 0.9% and the $\text{SD}_{\text{maxdiff}}$ values ranged from 0.6% to 1.9 %. This indicated that in children with two kidneys and normal renal function difference between methods and observers were small. In comparison the single kidney group where 77% of the patients had a low GFR, the $\text{Mean}_{\text{maxdiff}}$ ranged from 0.6% to 5.9% and $\text{SD}_{\text{maxdiff}}$ values ranged from 2.3% to 11.1% respectively. The $\text{Mean}_{\text{intramethod}}$ DRF for the absent kidney when using the 12 methods with background correction was 0.1 to 6.1% and when no background subtraction was used the corresponding values were 7.9 to 25%. The authors concluded that background subtraction has an effect in children with one kidney and poor renal function³⁷.

In a study performed in our institution 172 renograms were processed five times each with different software packages for the integral (four different software programs) and RP method (three different software programs) for calculating DRF. These studies were processed by a single observer. The maximum difference between the five measurements for DRF was calculated for each method. The maximum differences between the repeated measurements of the same renogram were; 69% Philips AUC, 14% experimental AUC, 22% Hermes AUC, 46% International Atomic Energy Agency (IAEA) AUC and 7% experimental RP, 24% Hermes RP, 26% IAEA RP. The median values of the maximum difference between repeated measurements were 3% Philips AUC, 1% experimental AUC, 3% Hermes AUC, 3% IAEA AUC and 1% experimental RP, 4% Hermes RP, 4% IAEA RP. Of concern was the 90th centile in commercial methods. These max-min values were between 7 to 9%, a level which would impact clinical management. In a small number of renograms, 26, we found that the difference in DRF was greater than the 95th centile in one or more of the seven software packages. Eight of the 26 patients had differences greater the 95th centile in three or more

software packages. There was an association between younger age, lower GFR and poor reproducibility of DRF. This would suggest that patients with poor reproducibility had higher background activity and the kidney could not be as clearly defined above background. The increased background activity could also increase the error in appropriately correcting for background. A limitation of the study was that in most cases the GFR was an estimated GFR and not a measured GFR²³.

In a study by Ozcan and co-workers, 394 ^{99m}Tc-MAG3 renograms performed on 101 children with a prenatal diagnosis of unilateral hydronephrosis were processed once by one person using the RP method and integral method. The DRF value was classified as impaired (< 45%), normal (45 to 55%) or supranormal (> 55%). The agreement in DRF classification between the two methods in the initial study performed on any patient was only 54.5%. In the final study, when the patients were older, the methods agreed in 86.1% of cases. This supports other findings that renal maturation leads to better renal function and thus higher uptake by the kidneys which improves the reproducibility of DRF measurements. Another factor which could in addition account for the improved agreement in DRF classification is the physiological improvement of the unilateral hydronephrosis which is known to occur in some patients. The mean difference in calculating DRF between the two methods was - 0.8%. It was found that a discrepancy in DRF of greater than 5% between the two methods was more frequent in children under one year old than in the group older than one, 23% vs. 9.9%. The RP gave values higher than 55% in 8.4% and the AUC method gave values in this supranormal DRF group in 11.2% of the studies. A possible reason for this could be that if there is asymmetrical renal size the RP with its subtraction of vascular activity better corrects for possible increased vascular activity in the larger kidney³⁸.

A recent study evaluated the inter- and intra-observer reproducibility of quantitative measurements of DRF and drainage of ^{99m}Tc-MAG3 renography. The DRF was calculated with the integral and RP methods. Four observers processed the studies once to establish inter-observer reproducibility and two of the four observers then reprocessed the studies two months later to establish the intra-observer reproducibility. There was no statistical difference between observers. For 95% of the studies the observed differences in DRF were between -5 and +5% for the left kidney. The outliers for DRF and outflow measurements

were few and tended to be seen more frequently with the RP plot method than the integral method. The outliers were renograms of patients who had a very low GFR ($< 20\text{ml/min/1.73m}^2$), or were very young (first days of life), had huge mega ureters, normalised residual activity (NORA) values > 2.0 , renal output efficiency (ROE) below 60% or ectopic kidneys with a bladder overlying the renal ROI. The mean difference between two observers was -0.01 (SD 1.83) in children under six months and 0.03 (SD 1.2) in children older than six months for the integral method. The values for the RP method were -0.49 (SD 2.77) in children younger than six months and -0.13 (SD 2.17) in children older than six months. In patients with a $\text{GFR} \leq 50\text{ml/min/1.73m}^2$ the mean differences were -1.14 (SD 1.68) for the integral method and -2.43 (SD 4.31) for the RP method. The corresponding values for patients with a GFR above 50ml/min/1.73m^2 were 0.01 (SD 1.51) integral method and -0.30 (SD 2.27) for the RP method. The p-values for these differences calculated with Student's t-test of risk stratification for poor reproducibility, age below and above six months, GFR below and above 50ml/min/1.73m^2 , and asymmetrical uptake were not statistically significant³⁹.

A study investigating the reproducibility of DRF measurements in children when renography was performed using $^{99\text{m}}\text{Tc-EC}$ showed that the interobserver reproducibility of DRF measurements was good. The mean difference in DRF between the three observers ranged from $0.189 - 0.545\%$ (SD 1.63 -2.25%). All the children included in the study were older than 1 year. In total 109 renograms were analysed. There were six and seven outliers in which the difference between DRF measurements between any two raters was greater than 5%. The study population did not include children with impaired renal function⁴⁰.

Supranormal DRF:

The controversy around supranormal/contradictory DRF has shed some light on some of the inherent problems of processing renograms. Steckler et al., from Toronto in Canada, published the first paper on this topic in 1994. Their study population consisted of 13 patients younger than two years with uncomplicated unilateral hydronephrosis. The patients had $^{99\text{m}}\text{Tc-DTPA}$ renograms and five of the 13 patients had a DRF $> 55\%$ in the

hydronephrotic kidney. Background correction on these renograms was performed using interpolative subtraction. The background ROIs excluded spleen and liver activity. No explanation for this phenomenon of supranormal DRF was given⁴¹. It should be noted that these authors investigated the children with ^{99m}Tc-DTPA which is known to be suboptimal in patients with immature renal function. The background ROIs were not peri-renal as is recommended by current guidelines¹².

Another early study on this topic was done by Gluckman et al., Their study group consisted of 29 patients, 22 had DRF values < 50% and seven patients had DRF > 50%. The individual values for the seven kidneys with supranormal DRF values were not given, only a range 52 to 72%. Six of the seven kidneys with “supranormal” DRF were right sided kidneys. Background correction was performed with infero-laterally placed background ROIs. The authors concluded that the “supranormal” DRF was probably due to the high background from the adjacent liver on the right and therefore technical⁴². One of the problems with this study was the definition of supranormal DRF as > 50% as the current accepted normal range is 45 to 55%¹⁴. Another was the use of the inferolateral background ROI which will not adequately correct for background activity¹².

A follow-up study on contradictory supernormal DRF was published by the group from Toronto, Canada, who initially described supernormal DRF. The study population included 16 patients with unilateral hydronephrosis who had both ^{99m}Tc-DTPA and ^{99m}Tc-DMSA scans. The ^{99m}Tc-DMSA scan was done two days to six months (median interval 1.8 months) after the ^{99m}Tc-DTPA. The ^{99m}Tc-DMSA scan was used as the “gold standard”. With all the patients the ^{99m}Tc-DMSA DRF was lower than the corresponding ^{99m}Tc-DTPA DRF. The mean ^{99m}Tc-DTPA DRF was 58.3% (range 53 to 66%) and the mean DRF for ^{99m}Tc-DMSA was 51.1% (range 42 to 57%). The background correction employed was a two to three pixel wide semi-circular region which extended from the upper to the lower pole of the kidney. The difference in results were attributed to the higher kidney to background ratio of ^{99m}Tc-DMSA compared to ^{99m}Tc-DTPA as the ^{99m}Tc-DMSA images were recorded at a later time interval reducing the residual activity in the liver and spleen. The authors did not take into account that the median time interval between the two studies was 1.8 months and

maturation of tubular function, with associated improvement of kidney to background ratio, especially with the cortical agent, would have occurred in cases with a prolonged time interval between the ^{99m}Tc -DTPA and ^{99m}Tc -DMSA scan⁴³.

The size of the renal ROI has also been implicated as a factor which influences the measurement of DRF. ^{99m}Tc -MAG3 renograms of 18 children with unilateral hydronephrosis who underwent a total of 57 renograms were reviewed. Three operators drew rectangular ROIs over each kidney. The first two ROIs were tight ROIs around the kidney that did not cut the kidney. A third ROI was then placed over the normal sized kidney but the ROI was the same size as ROI of the hydronephrotic kidney. Background correction was done using a two pixel wide background ROI around each renal ROI. Eight different DRF values for the hydronephrotic kidney were obtained from each renogram. The values were calculated using the following; RP and AUC calculations with tight ROIs around both kidneys and RP and AUC calculations with tight ROIs around the hydronephrotic kidney and a ROI the same size as the hydronephrotic kidney ROI over the normal kidney. All processing was done once with and once without background correction. The AUC methods with and without background correction had a progressive increase in DRF if there was a size difference between the ROI of the hydronephrotic and normal kidneys. This suggests that as one increases the size of the renal ROI with this method one adds function which is artefactual. When the RP method with and without background correction was compared there was little or no effect on DRF values when the kidney ROI size was increased but there was a bigger spread of differences between the two values of DRF. The increase in scatter of values may be due to the peri-renal background being inappropriate for a large kidney or the increase in statistical noise in the processing. These results suggest that technical factors, including the size of the region of interest, may affect DRF, and may, in part, explain reports of supranormal DRF ²⁰.

A study by Oh et al., further investigated the phenomenon of supranormal DRF on ^{99m}Tc -MAG3 renograms. They included 44 patients with unilateral congenital hydronephrosis. This was a young patient population, average 2.6 months with a range of one to nine months. They processed the kidneys using three options of background

correction, peri-renal, lateral which extended from the upper to the lower pole without extending above and below the poles of the kidneys as well as no background correction. The renal ROIs were drawn to include the whole kidney. The DRF was then calculated with the AUC method at different time intervals 30 to 60, 60 to 90, 90 to 120, 120 to 150 and 150 to 180 seconds. In addition they graded the degree of hydronephrosis by a renal area ratio which is defined as the ratio of the number of pixels within the ROI of the hydronephrotic kidney divided by that of the normal contralateral kidney. They found that the DRF increased with the later time intervals when no background correction or the peri-renal background was used. It went from $47.8 \pm 9.4\%$ (range 13.1 to 64.1%) at 30 to 60 seconds to $49.5\% \pm 11.6\%$ (range 13.1 to 78.6%) for the 150 to 180 second interval. The lateral method of background correction gave higher values in all the time intervals, $53.3 \pm 16\%$ (range 9.0 to 84.4%) for the 30 to 60 second interval, and there was no significant increase in DRF value at later time intervals. Size of the kidney was found to be a factor for increased DRF, the DRF increased as the renal area ratio increased. This effect was more pronounced on the later time intervals. The authors postulated that the lateral region of interest may have overestimated the right hepatic background activity and therefore overestimated the DRF of the left hydronephrotic kidneys⁴⁴.

Khan et al., in a retrospective review of 57 patients with unilateral hydronephrosis did not find any patient with supranormal DRF on ^{99m}Tc -MAG3 renograms. The background ROIs were peri-renal and placed automatically around the manually drawn renal ROIs. The DRF was calculated on the one to two minute image. The authors do not state which method was used to calculate the DRF. The ages of the patients were also not given so one cannot assess the percentage of patients with immature renal function included in their study. They concluded that if one uses ^{99m}Tc -MAG3 with its favourable plasma extraction and draws peri-renal background ROIs the phenomenon of supranormal DRF can be avoided⁴⁵.

Inanir et al. found that supranormal DRF was only seen in seen younger patients, 8.1 ± 6.7 months. Their study population consisted of 67 patients investigated with ^{99m}Tc -MAG3 renography. Four different methods of background ROIs were used, peri-renal, lateral, C-shaped and inferolateral and the DRF was calculated at one to two minutes and two to

three minutes. Each renogram was therefore processed eight times. Ten kidneys had an estimate of supranormal DRF, mean $56.7\% \pm 1.3\%$ with a range of 55.1 to 61.3%, with one or more of the combinations of background ROI and time interval. The DRF measurement for the hydronephrotic kidney was higher when using the inferolateral background ROI than with the other background ROIs and the higher DRF was more pronounced in children with right hydronephrosis. These results once again confirm that the use of the inferolateral background ROI is suboptimal. There was a difference between the DRF measured at one to two minutes and two to three minutes with higher median values for DRF of the hydronephrotic kidney for all methods at the two to three minutes interval. The kidneys with supranormal DRF also had a higher renal area ratio 1.24 ± 0.24 than those with renal function $\leq 55\%$, 1.07 ± 0.21 . It is again speculated that the higher DRF in the enlarged kidneys may be due to an increase in the vascular component. Unfortunately the renograms were only processed using the AUC method which does not correct for vascular background⁴⁶.

Piepsz et al., also investigated supranormal DRF in 72 patients with 89 renograms who had $^{99m}\text{Tc-MAG3}$ and $^{51}\text{Cr-EDTA}$ GFR, single sample method, on the same day. Of these patients four had a DRF of the hydronephrotic kidney which was greater than 55%. The patients with supranormal DRF were between one and 11 years and the GFRs of these patients ranged from 73 to 105 ml/min/1.73m². All had hydronephrosis on the left. One patient had three renograms which all showed supranormal DRF. Therefore six studies were available for analysis. All studies were processed using the AUC method, with a peri-renal background ROI and DRF was calculated at the one to two minute interval. It should be noted that none of the 21 children younger than one year age, twenty five renograms, had supranormal DRF. This study illustrates that supranormal DRF is relatively infrequent and points to certain patient factors being involved, as shown by one patient who had three renograms with supranormal DRF. The DRF was only calculated once and the question arises what the range of DRF would have been if the studies were processed repeatedly⁴⁷.

In summary supranormal DRF appears to be artefactual in most cases. Reasons for this include using $^{99m}\text{Tc-DTPA}$ with its decreased kidney to background ratio in children with

immature renal function or using inadequate background correction, most notably the background ROI placed inferolateral to the kidney. Another reason for supranormal DRF is calculating the DRF at a time interval when some of the tracer may have left the renal ROI, for instance two to three minutes for ^{99m}Tc -MAG3. Some factors have not been fully addressed such as the effect of the method used to calculate the DRF. Supranormal DRF appears to be less frequent if the RP plot is used. The notion that an increased renal area is a factor should be investigated further. Finally there are conflicting results as to the importance of renal immaturity, some authors find a strong correlation between renal immaturity and the phenomena of supranormal DRF and others not. The reproducibility of DRF measurement in the setting of supranormal DRF was not investigated.

The effect of normal renal maturation on ^{99m}Tc -MAG3 clearance:

By 36 weeks' gestation the foetal kidney has the same number of nephrons as an adult kidney. Renal growth is by hyperplasia of the tubules and glomeruli⁴⁸. In normal people the GFR corrected for body surface area increases from birth until it reaches mature levels at two years⁴⁹.

It is believed that maturation of the tubules is more rapid than that of the glomeruli. There is already good clearance of ^{99m}Tc -MAG3 by one month age, and ^{99m}Tc -DTPA lags behind ^{99m}Tc -MAG3 in the age related increase in clearance. Infants have a relatively large extravascular space and ^{99m}Tc -DTPA is freely diffusible between the intra and extravascular space. The lag in ^{99m}Tc -DTPA clearance and large extravascular space in infants results in a decreased plasma concentration of ^{99m}Tc -DTPA, lower uptake of ^{99m}Tc -DTPA, and higher background activity leading to a poor kidney to background ratio⁴⁸. Therefore ^{99m}Tc -MAG3 is the agent of choice in children with immature renal function^{12,24}.

The tubular extraction rate (TER) for ^{99m}Tc -MAG3 was first described by Bubeck et al. The TER is defined as; the virtual plasma volume per minute from which a substance, related to its plasma concentration in the renal artery, is completely removed by tubular extraction⁵⁰. In a population of paediatric patients expected to have normal renal function it was shown that there is a progressive increase in renal clearance of ^{99m}Tc -MAG3 throughout childhood. The values were calculated using a single plasma sample method. The mean clearance in children younger than two months of age was 208 ml/min/1.73m² and it increased to 311 ml/min/1.73m² by one year. Therefore the maturation of renal clearance of ^{99m}Tc -MAG3 is complete by one year of age. The mean clearance value of the eight children younger than two months age was also two thirds of the adult value. It was also found that 68% of the adult value for TER was already achieved by two months of age⁵¹.

In cases of severe hydronephrosis some authors go as far as recommending that a ^{99m}Tc -MAG3 renogram may be performed as early as one week of life. This is done not to accurately determine the DRF but to establish if a markedly abnormal kidney is functioning^{6,18}.

The effect of renal function on the reproducibility of DRF measurements:

In patients with severely decreased renal function there is a decrease in the kidney to background ratio and the kidney is not as clearly seen above the background. It is therefore intuitive that drawing both renal and background ROIs becomes more difficult and the reproducibility of the DRF calculation will be decreased. A small number of studies have investigated this problem.

To assess the difference in reproducibility of DRF measurements using manual and automated background correction a small population of 16 patients with a range of DRF and GFR values were investigated. Each renogram was reprocessed three times by three different operators. Standard deviations of the resulting nine measurements for each

patient were calculated as an index of variability. The variability of DRF using manually drawn background ROIs in ^{99m}Tc -DPTA renography was 32% in adult patients with a single kidney glomerular filtration rate (SKGFR) $\leq 15\text{ ml/min}$ compared to 6% in patients with a SKGFR between 15 and 40 ml/min. The corresponding values when using automated background correction were 11% and 7%. These patients were all known with hypertension. A background crescentic ROI lateral to each kidney was drawn by the operator. DRF was calculated with the AUC method. The increase in variability in the DRF measurement in patients with decreased renal function was attributed to the fact that drawing accurate renal outlines in these patients was problematic⁵².

^{99m}Tc -DMSA is an agent used to image the renal cortex. This imaging agent is taken up by and remains in the proximal convoluted tubule and only a small amount of activity is excreted in the urine. The time interval for imaging patients with ^{99m}Tc -DMSA differs from that with ^{99m}Tc -MAG3. The patients are imaged with static images recorded over five to ten minutes, depending on institution and type of collimator used, two to four hours after injection⁵³. This delay between injection and scanning as well as the prolonged retention of activity in the tubular cells with the low rate of renal excretion and longer imaging time leads to a good kidney to background ratio. Calculation of DRF with ^{99m}Tc -DMSA in normal patients is robust⁵⁴. However, it should be noted that ^{99m}Tc -DMSA may overestimate function in patients with hydronephrosis due to pelvic retention of the activity excreted into the urine^{18,53}. The degree to which ^{99m}Tc -DMSA overestimates DRF in hydronephrotic kidney has been debated^{55,56}.

An elegant study investigated the calculation of DRF when using ^{99m}Tc -MAG3 renogram in 100 adult patients, with diverse nephropathies, who had both a ^{99m}Tc -MAG3 renogram and a ^{99m}Tc -DMSA scan within one day of each other. Patients with hydronephrosis were excluded from this study. All patients had an ERPF calculated from ^{125}I -OIH injection and multiple blood samples. The patients were divided into three groups; ERPF $\geq 250\text{ ml/min}$, ERPF between 100 and 250 ml/min and ERPF $\leq 100\text{ ml/min}$. Group one consisted of 36 patients and had a mean ERPF value of 308ml/min (SD 43.46), group two had 45 patients, mean ERPF 182.62ml/min (SD 40.33) and group three, 19 patients, mean ERPF of

67.73ml/min (SD 22.62). The DRF calculated with ^{99m}Tc -MAG3 renogram and ^{99m}Tc -DMSA correlated well, $r = 0.97$. In the group with an ERPF ≥ 250 ml/min the mean difference between the DRF values for ^{99m}Tc -MAG3 and ^{99m}Tc -DMSA was 1.51% with a SD of 0.72. In the group with an ERPF between 100 and 250 ml/min the corresponding values were 1.8% and 0.82 and when the ERPF was ≤ 100 ml/min the values were 2.4% and 1.1. It was noted that on ^{99m}Tc -MAG3 studies the DRF value for the right kidney was usually higher than on ^{99m}Tc -DMSA and that this difference in values was more apparent in patients with impaired renal function. This finding was attributed to the inclusion of the adjacent hepatic activity in the right renal ROI on a ^{99m}Tc -MAG3 renogram. The authors argued that hepatic activity mentioned was not due to hepatic uptake of ^{99m}Tc -MAG3 isomers, as this problem is usually seen on the later images of ^{99m}Tc -MAG3 renography and should not influence the calculation of DRF at one to two minutes after ^{99m}Tc -MAG3 injection⁵⁷.

Gordon et al. compared DRF assessed by ^{99m}Tc -MAG3 and ^{99m}Tc -DMSA studies performed within four weeks of each other in 58 children aged 0.1 to 14 years with a median age of 5.3 years scanned for urinary tract infections. The DRF on the ^{99m}Tc -MAG3 renogram was calculated using the RP plot, 40 to 120 seconds after ^{99m}Tc -MAG3 injection, using peri-renal background ROIs. There was a good agreement between the DRF obtained with both methods. Simple linear regression analysis found $R^2 = 0.97$ ($p = < 0.001$)⁵⁸.

The reproducibility of DRF measurements using the ^{99m}Tc -DMSA studies of ten adults and 39 children, processed by 15 different nuclear physicians was investigated. The ^{99m}Tc -DMSA imaging was performed in cases with acute UTI or follow-up after acute infection. The nuclear physicians used the same software packages and background correction techniques that were routinely used for clinical studies in their departments to calculate DRF. There was a wide range of DRF for the left kidney (29 to 72%). The maximum difference in the 15 measurements, one for each observer, ranged from 1.7 to 12%, and was less than 6% in more than 70% of the patients. The two patients with the highest difference, 11 and 12%, were two adults with severe chronic renal impairment. There was also an increase in the variability of DRF measurements in patients with asymmetrical function. It should however

be noted that the nuclear physicians used different methods for background correction, peri-renal, sub-renal, supra-renal and none, to calculate the DRF⁵⁴.

In 1993 Sennewald and Taylor described a case where a lady with acute deterioration of renal function was imaged with ^{99m}Tc-MAG3. At the time of renography her creatinine was 769 µmol/l. The authors calculated her DRF at two to three minutes with different background correction methods, inferior, lateral and elliptical. The value for the left kidney ranged from 41 to 98% depending on the method of background correction⁵⁹.

Due to the impact of impaired renal function on ^{99m}Tc-MAG3 renography image quality, one of the earliest consensus statements on diuresis renography recommended that serum creatinine should be measured before paediatric renograms to exclude azotaemia. In young babies with immature renal function the initial GFR is low, so it was previously recommended that the patient should be at least one month old before performing ^{99m}Tc-MAG3 renography⁶⁰.

It could be argued that the RP method should be used in cases where there is decreased renal function. The additional correction of the vascular background with the RP method may be useful to correct for the high residual vascular background in cases with decreased renal function or when performing ^{99m}Tc-DTPA renography. This theoretical advantage is however not proven in clinical practice as the RP method is not more robust than the integral method. In severe renal failure no method to calculate DRF is valid⁶¹.

The recent SNMMI procedure standard/ EANM practice guideline for diuretic renal scintigraphy in adults recommends that in patients with bilaterally impaired renal function and subsequent delayed tracer uptake and excretion that DRF should be calculated at a later time frame than the one to two, one to two and a half or one to three minute time interval. They recommend that the DRF should be calculated on the image recorded one minute

before any tracer leaves the renal ROI. This is done to ensure that DRF is calculated using the image with the best kidney to background ratio⁶².

It has been shown with multiple methods and multiple radiopharmaceuticals that decreased renal function adversely affects the reproducibility of DRF calculations. We also know that if there is a marked decrease in renal function all methods are invalid. However the level of impairment at which methods are no longer reproducible has not been established¹².

The effect of severe renal dilatation:

It is known that in cases where the child has severe dilatation of a kidney one can have difficulty drawing a background ROI that stays within the confines of the body outline. If the ROI extends outside the body outlines it leads to an inaccurate assessment of the DRF. One of the recommendations is to draw a background ROI above and below such a distended kidney^{14,24}. In addition there is inhomogeneous tracer distribution within the kidney due to the large photopaenic calyces and pelvis on the initial images. This would also lead to over subtraction of background in the calyceal and pelvic pixels. None of the authors describe this as contributory factor to the inaccuracies in DRF calculation in children with very severe hydronephrosis.

In the debate around supranormal DRF more than one author eluded to the possibility that a marked difference in renal size may lead to an artefactual increase in DRF of the larger kidney due to an increase in the vascular background in the larger kidney^{20,46}.

The effect of administered activity:

One published abstract investigated the effect of the administered activity on the precision on DRF when using ^{99m}Tc -MAG3 and ^{99m}Tc -DTPA. This simulation study investigated the statistical noise at different levels of administered activity. It was generally less than 3% at doses used for routine adult renograms. The effect of decreased renal function on the statistic noise was not investigated⁶³.

As part of the “Image Wisely” campaign Taylor et al., investigated if there was a difference in the DRF values obtained between studies acquired using low (62.9 ± 40.7 MBq) and high doses ($303,4 \pm 48.1$ MBq) of ^{99m}Tc -MAG3 in adults. The mean difference in DRF values obtained with the AUC method was small, 0.75 % (95% CI -0.734 to 2.34 %) ⁶⁴.

The role of appropriate selection of background regions of interest:

The use of background correction has been debated through the years. There is a school of thought that advocates no background correction. Most nuclear physicians and physicists recommend some form of background correction reasoning that extrarenal activity is added to the renal signal if no background correction is applied. If no background correction is applied there is a smaller difference between the two kidneys and the function of the poorly functioning kidney will be overestimated⁶.

The background anatomy of the two kidneys differs. At the upper pole of kidneys there is the overlapping liver on the right and spleen on the left which are more pronounced in children. Along the medial margin there are the large vessels and intestine. The lateral margin usually consists of gut activity but may also contain some liver activity adjacent to the right kidney. In front of and behind the kidneys there are several layers of muscle, skin and fat. In each patient the contribution of activity from the organs and structures differs. On angiography it is clearly demonstrated that the kidney is a vascular organ and it has a

greater blood supply than interstitial tissue and bowel in the tissue adjacent to the lower poles of the kidney. The spleen and liver which overlap with the upper poles of the kidneys are highly vascular organs. The kidneys and spleen have arterial blood supply compared to the liver which has predominant portal venous blood supply. This difference leads to a difference in peak blood pool activity in the organs which overlap the upper poles of the kidneys, with peak blood pool activity in the liver being later than that of the spleen. Therefore the peri-renal background correction underestimates the vascular component in the kidney. This has led to the addition of a vascular ROI such as employed by the RP method. Using both a peri-renal and a vascular ROI introduces more assumptions to the equations. It assumes that the tissue activity is the same in the renal and background areas, and that the vascular component of the kidney behaves exactly the same as the cardiac region⁶⁵.

Numerous articles have been published investigating the role of background correction. Gates described a camera based method for determining GFR using a ^{99m}Tc-DTPA renogram comparing his results with 24 hour creatinine clearance⁶⁶. The use of creatinine clearance as a reference value is a limitation of the study. There are multiple inherent problems with the creatinine clearance measurements⁴⁹. The influence of different time frames for calculating DRF on the estimated GFR results was investigated. Gates found that one to two, two to three and the one to three minute time interval gave the most accurate GFR results. Other time intervals zero to one, three to four and one to four minutes were less accurate. The second factor investigated was the influence of different methods of background correction, semilunar ROI inferior to the kidney or peri-renal ring ROI, on the GFR calculation. The semilunar inferior background ROI gave GFR values with a slightly better correlation coefficient (0.94 vs. 0.93) with creatinine clearance and lower standard error (9.5 vs. 10.3) than the peri-renal ring background ROI⁶⁶.

The role of background correction is particularly important when one performs renography using ^{99m}Tc-DTPA. In the first minutes of a ^{99m}Tc-DTPA renogram the background consists of decreasing intravascular activity and rising extravascular activity as the ^{99m}Tc-DTPA which is

not protein bound diffuses to the extravascular space. Peters et al. showed that a peri-renal background ROI best corrects for background activity⁶⁷.

In 1990 Piepsz et al. investigated the effect of background correction on separate ^{99m}Tc-DTPA clearance. A total of 53 renograms were processed by three different algorithms, area ratio, adjustment and the RP method (referred to as the double correction method in this paper). These methods are all modifications of the basic renal clearance calculation.

The basic renal clearance calculation is:

$$R(c) = C \times \int P(t)dt$$

C is the renal clearance

Rc(t) is the background corrected renal activity at time t

P(t) is the plasma activity at time t.

This equation is valid as long as no tracer escapes from the kidney.

The area ratio method is defined as:

$$Rc(t) = Rb(t) - Q.Bg(t)$$

Rb(t) is the non-corrected renal activity

Bg(t) is the activity in the background ROI

$Q = S_r/S_b$, S_r is the renal surface area and S_b is surface area of the background ROI

The adjustment method is a modification of the renal clearance calculation:

If the clearance is constant during the interval of time when the clearance is measured and no escape of activity has occurred from the renal area the Rc(t) is proportional to I(t).

$$I(t) = \int P(t)dt$$

Then:

$$C \times I(t) + QBg(t) = Rb(t)$$

The renograms were also processed using different background correction methods; supra-renal, one pixel peri-renal area, and a sub-renal area. The authors presented the ^{99m}Tc -DTPA clearance values and not DRF. They found that when sub-renal background was used in combination with the area method and the adjustment method there was an underestimation of the clearance values and they even recorded some negative values. This underestimation was not seen if sub-renal background was used in combination with the double background method. Supra-renal background correction led to an overestimation of the clearance in all methods⁶⁵.

In another study investigating the SKGFR of DTPA, 83 adult patients who had both ^{99m}Tc -DTPA and ^{51}Cr -EDTA studies within two months of each other were investigated. The RP method was used to calculate clearance. Three different methods of background correction were compared. Method one used a cardiac ROI and manually drawn renal ROI to determine clearance. Method two the same cardiac and renal ROIs with the addition of an automatically drawn peri-renal background ROI two pixels wide placed one pixel away from the renal ROI. Method three used the same cardiac ROI, renal ROI, and renal background ROI with an additional correction for kidney depth. In this paper terminology is slightly different as the authors refer to the RP method as the method used by Rehling et al., and the SKGFR is referred to as the uptake index (UI). The sum of the SKGFR results were compared the measured GFR. The equations of two regression lines of the RP method showed that if no extrarenal background was used there was a systematic bias corresponding to an 14ml/min overestimation of the summed SKGFR value⁶⁸.

A study investigating the accuracy of determining extrarenal background activity when performing ^{99m}Tc -DTPA renography was conducted by Moonen et al. The study population

was 21 adult patients with solitary kidneys. They had undergone nephrectomies years earlier. The authors compared the activity in the background ROIs drawn around the functioning kidney with the background activity around the empty renal bed. The renal ROI used over the empty bed was drawn using a set ROI size. The size of the ROI was determined from 33 adult control patients who had two normal kidneys. For all the background ROIs the results were normalised for the number of pixels of the ROI of the empty renal bed. It was assumed that no difference between the background ROI and the empty renal ROI would signify correct background correction. The background ROIs were drawn as semilunar ROIs under the renal ROIs, a single ROI between the renal ROIs, rectangular ROIs around the renal ROIs, two pixel wide peri-renal ROIs drawn next to the renal ROIs, and a peri-renal ROI one pixel apart from the renal ROIs and two pixels wide. Heart and liver ROIs were drawn over the area in the each organ with the highest activity. The liver ROI was only used to describe its clearance curve. The DRF was calculated using the AUC and RP plot methods. Activity in the semilunar ROIs under the kidneys was much lower than the empty renal ROI. Not surprisingly activity in the liver and heart ROI was much higher than the empty renal bed. There was no significant difference in activity in the empty renal ROI and the rectangular or the two different peri-renal ROIs⁶⁹. A criticism to this study may be that using an empty renal bed to compare for adequate background correction neglects the fact that the anatomy is disturbed and the intravascular renal background component is missing⁶⁷.

Another study by Moonen et al., compared three different methods for calculating SKGFR when using ^{99m}Tc-DTPA. The methods were the integral method, the slope method and the RP method (once again referred to as the UI method). The slope method was defined as the slope value of the background corrected renogram, calculated by linear regression during the uptake interval. Four groups of patients were selected. Group A, the control group, were 32 consecutive patients with a variety of renal problems. Group B were 38 patients with a unilateral malignant renal tumour for nephrectomy. Group C were a small subset, three patients, from group A with unilateral parenchymal disease and different GFRs. Finally group D consisted of seven patients who underwent renography and ⁵¹Cr-EDTA GFR before nephrectomy and a ⁵¹Cr-EDTA GFR within a year after the nephrectomy. For all the groups

except group C the ROIs were drawn once and the time interval used to calculate the DRF was between the arrival of the ^{99m}Tc -DTPA bolus and ended before the renogram slope decreased, no later than 180 seconds after the starting point of the renogram. In Group C the ROIs were drawn in six times and the DRF was measured at six different time intervals, up to 200 seconds after injection. For group D the mean difference between the estimated GFR and the measured GFR after the nephrectomy was taken as the accuracy of each of the three methods used to calculate the SKGFR. The precision was tested on group C which only consisted of three patients and was found to be good 0.8, 1.5 and 0.7% for the different ROIs and 0.4, 1.2 and 0.7% for the different time intervals. The accuracy as measured by group D was 4.6 ± 4.2 ml/min (mean $\pm$ SD) for the integral method, 0.9 ± 4.2 ml/min for the slope method and 2.0 ± 4.2 ml/min for the RP method. The comparison between group A (the control) and group B showed that all three methods correlated well in the control group (correlation coefficients were 0.99 to 0.97). The correlation was not as good in the group with renal tumours (0.51 to 0.88) and the integral method systematically estimated a higher value for the side with the tumour. This was attributed to an abnormal blood volume in the kidneys with renal tumours and the authors recommended that correction for blood volumes should be added to calculation of DRF. The RP method is recommended as the method of choice for performing SKGFR⁷⁰.

It should be noted that there are several algorithms for calculating single kidney function and camera based methods for calculating single kidney function are less precise than creatinine-based formulae and results of studies using only camera based formulae should be interpreted with caution⁶¹.

The increasing use of ^{99m}Tc -MAG3 led to a renewed debate around optimal background correction. In 1997 Taylor et al., investigated the optimal placement for background ROIs in ^{99m}Tc -MAG3 and found similar results to those reported with ^{99m}Tc -DTPA. They included 15 adult patients with unilateral nephrectomies and a phantom kidney was drawn at the expected position of the absent kidney using the approximate size of a normal kidney. Different background regions were drawn including, no background, inferior and lateral backgrounds (drawn manually) and elliptical and peri-renal ROIs (placed automatically). The

DRF was also calculated at different time intervals one to two, one to two and a half, one and a half to two and a half and two to three minutes after ^{99m}Tc -MAG3 injection. The studies were processed by two observers. The mean errors associated with no background correction and inferior background correction were large, respectively $31.7\% \pm 16.7\%$ and $16.3\% \pm 10.9\%$. The mean error and SD for the peri-renal ($-1.3\% \pm 6.7\%$), lateral ($-1.2\% \pm 8.1\%$) and elliptical ($-2.1\% \pm 9.9\%$) background ROIs, were not significantly different and also not statistically different from 0%. The authors point out that peri-renal and elliptical background will overestimate background in the later time periods of the renogram if there is a dilated renal pelvis or ureter or a bladder in case of ectopic and transplant kidneys. They suggest that one should be able to manipulate automatic ROIs to exclude the renal pelvis and ureter. There was no significant difference in results for the different time intervals. However, the authors did note that in well hydrated patients activity can be seen in the collecting system at three minutes so they recommended the one to two and a half minute interval for the calculation of DRF⁷¹.

In a small study of 23 children who had ^{99m}Tc -MAG3 renograms, Nguyen et al., drew two rectangular background ROIs above and below the poles of the kidneys and another ROI lateral to the kidneys. The DRF was calculated with three different background regions, only the superior ROI, only the inferior ROI or average count between the superior, inferior and lateral ROIs. The DRF values obtained with three different ROIs were then compared to the DRF value obtained with standard renal processing software provided by Siemens Medical Systems, Inc., Iselin, New Jersey which only employed an inferior background ROI. In patients with left hydronephrosis the values obtained for the kidney were systematically less when the superior and average ROIs were used. Not surprisingly the values obtained with the inferior background technique were similar to values obtained by the commercial software. Comparing the DRF values obtained with different ROIs to a value calculated only using inferior ROIs is a major limitation of this study. They concluded that if one used only the inferior ROI it could be a cause for “supranormal DRF” and recommended peri-renal ROIs⁷².

A study comparing the DRF of ^{99m}Tc -MAG3 and ^{99m}Tc -DTPA renograms with DRF values obtained from cortical imaging using ^{99m}Tc -DMSA was performed. The population consisted of 83 patients, 37 of whom also had a ^{99m}Tc -DMSA scan within a month of the renogram. A total of 42 patients had a renogram using ^{99m}Tc -DTPA and 41 using ^{99m}Tc -MAG3. The authors did not define the number of paediatric patients included in the study but in the method section alluded to the fact that paediatric patients were included. The renograms were processed by the integral method using an inferior background ROI and a C-shaped peri-renal ROI. The DRF values on the ^{99m}Tc -DMSA scans were calculated without background correction. The mean DRF values for both kidneys and SD from the mean DRF were calculated. When using ^{99m}Tc -MAG3 there was a smaller SD of the mean DRF compared to ^{99m}Tc -DTPA. When using ^{99m}Tc -DTPA with the peri-renal background correction, mean DRF values and SD for the left kidney were $55.5 \pm 9.19\%$ (n 9) for normal kidneys, $60.44 \pm 9.28\%$ (n 18) in cases with right hydronephrosis, $45.80 \pm 11.55\%$ (n 15) in cases with left hydronephrosis and $51.14 \pm 22.03\%$ (n 7) if there was bilateral hydronephrosis. The corresponding values for a different population using ^{99m}Tc -MAG3 and peri-renal background correction were; $52.43 \pm 6.29\%$ (n 7), $54.75 \pm 8.97\%$ (n 8), $51.65 \pm 8.73\%$ (n 17) and $55.67 \pm 6.76\%$ (n 9). Differences were seen between DRF estimates with sub-renal and peri-renal background ROIs. The values given were for ^{99m}Tc -MAG3 and ^{99m}Tc -DTPA studies combined. For normal kidneys the mean difference between the DRF when using the sub-renal and peri-renal background was 5.33 ± 4.24 (n 9), in cases with left hydronephrosis it was 2.25 ± 3.54 (n 32), in cases with right hydronephrosis it was 7.96 ± 5.25 (n 26) and if there was bilateral hydronephrosis the values was 4.56 ± 6.18 (n 16). The mean difference between the two methods of background correction was 4.81 ± 5.26 (n 83), with a range of -7 to +25. In the small group of patients who also had a ^{99m}Tc -DMSA scan the sub-renal background correction on the renogram overestimated the DRF on the right side at an average of 4.8%. Unfortunately DRF values of the ^{99m}Tc -DMSA scans were not calculated as recommended by the guidelines as they were calculated without background correction⁵³. In conclusion the inferior background ROI was found to be suboptimal for both ^{99m}Tc -MAG3 and ^{99m}Tc -DTPA renograms especially in patients with right hydronephrosis⁷³.

The renal curve should start at the origin of the y-axis on the time activity curve (TAC). If the TAC intercepts at a higher level than zero background is underestimated and if the curve has a negative intercept background is overestimated. This fact was used to analyse different methods of background correction. A total of 134 renograms were processed with four different methods, the integral method with peri-renal and manually drawn ROIs (position not specified in the abstract) and the RP with cardiac or splenic vascular ROIs. No mention is made of the renal background ROI used with the RP method, if any. The percentage of curves with under-estimation, ideal results and overestimation of background activity is presented in Table 2. No gold standard was used to confirm the findings of under-estimation, ideal results and overestimation of background activity. The four methods agreed when the renal function was good but significant differences between the methods were seen if renal function was reduced. This is a summary of an abstract of a congress proceeding and extensive definitions of methods used were not given⁷⁴.

Table 2. The percentage of curves with under-estimation, ideal results and overestimation of background activity.

Method	Integral method with peri-renal background	Integral method with manual background	RP method using cardiac vascular region	RP method using splenic vascular region
Under estimation	39%	38%	61%	13%
Ideal results	48.5%	45%	38%	87%
Over estimation	12.5%	17%	< 1%	0

Repeatability and reproducibility of DRF measurements are operator dependent especially when the program uses manually drawn ROIs. The repeatability of ROIs was tested on 20 ^{99m}Tc-DTPA renograms. Each renogram was processed twice by two operators. There was a gap of one month between the renogram being processed the first and second time by the

same operator. The variation in ROI drawing was calculated by a “success factor” which was the coincident pixels between any two ROIs determined by dividing the number of pixels common to both regions by the mean number of pixels in the two. In addition masks of the pixels were drawn and compared to see if the same pixels were included in the ROI. The success factor was good for the background ROIs, 0.95 for intraoperator and 0.94 for interoperator values. It was also good for the kidney ROIs, 0.94 for intraoperator and 0.93 for the interoperator values. These findings show that renal and background ROIs drawn by experienced nuclear medicine technicians show a high degree of reproducibility⁷⁵.

With improvements in software, studies were performed comparing semi-automated renal processing and manually drawn ROIs. The manual renal ROIs were drawn by three different operators with different levels of experience. In the manual processing peri-renal background ROIs were placed automatically and the calculation was performed on the one to two minute interval. The ^{99m}Tc-MAG3 renograms were studies of 33 adults. There was a significant difference in the clearance values between the three operators when manually drawn ROIs were used, one way repeated measure ANOVA was $p < 0.0001$. In the semi-automated method the operator clicked with the mouse on the centre of the kidney and the renal processing program used the double threshold method to place the ROIs. The double threshold method, with a first and second threshold of 50 and 60% of maximal renal counts, on the one to two minute images failed in three kidneys with markedly reduced function. This left 59 kidneys that could be processed with the semi-automated method. The results for the semi-automated method showed complete reproducibility in 58 of the 59 kidneys. The one way repeated measures ANOVA for the semi-automated group was $p > 0.9999$. Unfortunately this paper did not report the DRF measurements but illustrated that if there is good renal function semi-automated methods provide more reproducible results than manual methods⁷⁶.

An American research group developed an automated program, RENEX, to define ROIs automatically. The algorithm used to generate the renal ROI employs five steps. In step one the dynamic frames recorded between two and three minutes after ^{99m}Tc-MAG3 injection are summed to form a one minute image and another summed image is produced of the

frames recorded between 18 and 20 minutes after ^{99m}Tc -MAG3 injection. Step two to five utilizes various edge detection methods to define the renal outlines and draw a peri-renal ROI around the identified renal margins. The five steps to automatically define the kidney margins failed in 22 of the 194 kidneys from an adult population. In these cases an operator would then identify a single pixel along the superior poles of the relevant kidneys making sure that the pixel was between the liver and the right kidney. The automatically drawn ROIs were compared to a reference standard which was manually drawn ROIs by an experienced technologist and a nuclear physician. Error was defined as the difference between the renal border defined by the reference standard, the automatically drawn ROI and the nuclear physician. The error difference for the entire group between the automatically placed ROI and the nuclear physician was not statistically significant. The 22 kidneys which needed operator intervention all had markedly decreased function and 15 were right kidneys. The ^{99m}Tc -MAG3 clearance values were 27.7 ± 20.5 (range 6 - 85) ml/min/1.73m² for the right kidney and 23.4 ± 12.6 (range 9 - 46) ml/min/1.73m² for the left. The normal range given for these values was 113 to 220 ml/min/1.73m². The authors concluded that in cases with poor renal function the renal borders are poorly defined due to a low kidney to background ratio. The high background activity, particularly in the liver, makes drawing of automatic ROIs for the right kidney more difficult ⁷⁷.

In conclusion most guidelines and consensus statements agree that the background ROI should be peri-renal, elliptical, peri-renal rectangular or C-shaped, including both poles of the kidneys and one or two pixels away from the kidney to avoid scatter from renal activity^{12,24,27,78}. The development of software for the placement of renal and background ROIs is promising and should hopefully help to decrease the variability in placement of ROIs. Currently the drawing of renal and background ROIs is operator dependent and can be problematic if there is decreased renal function, especially if the right kidney has impaired function.

Conclusion:

The reproducibility of DRF estimates is good in the majority of children and adults. There is however a small but important group with poor reproducibility which, if not recognized, could affect clinical decision making.

Some factors, such as age and GFR, have been implicated as causes for poor reproducibility. We could not find any study which formally investigates image characteristics associated with the reproducibility of DRF measurements.

Method

Objectives

The study was done in two stages. The first step was to evaluate the image characteristics and reproducibility of the DRF estimates of the 172 patients 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 227 patients.

Patients - Cohort 1:

In our previous study we selected 172 patients as a stratified sample from an electronic archive containing the raw data of all renograms done in our Department between December 2000 and November 2008 to ensure patients at the extremes of DRF, age and GFR were included²³.

The renograms used in cohort 1 were previously processed five times at least one 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. All renograms were processed using HERMES kidney analysis program, renography V5.2L/ IS 7 April 2008 and the categorical and continuous variables were categorised and measured using HERMES hybrid viewer PDR2.2.C.21. (Hermes Medical Solutions AB, Stockholm, Sweden). The maximum difference between the five measurements of DRF was used as a measure of the reproducibility of the calculation of DRF.

The Hermes software truncated any negative values for DRF to zero. The truncation of the DRF results by the software influenced the reproducibility of the measurement of DRF in solitary kidneys. There were 20 patients with left and 19 with right solitary kidneys. It was decided to exclude this group of patients from the analysis. This left 133 patients with two kidneys in the cohort.

Patients - Cohort 2:

The population of cohort 2 was selected to have a similar spread of DRF values to patients tested in cohort 1. All renograms recorded in our department between 25 July 2012 and 1 September 2015 were eligible for inclusion, if the child had two kidneys in the normal anatomical position, a measured or estimated GFR within one month of the renogram study, and all image characteristics analysed in cohort 1 could be recorded. In cohort 1 85% of the population had a mean DRF measurement for the left kidney between 30 and 70%. The study population for cohort 2 was selected so the proportion of patients with a DRF value between 30 and 70% for the left kidney did not exceed 85%. Patients were only used once. No patient used in cohort 1 was included.

Acquisition of Renograms – Cohort 1 and Cohort 2:

The renograms used in cohort 1 and cohort 2 were acquired according to the relevant EANM guidelines for standard and diuretic renography at the time of acquisition^{12,24}. The ^{99m}Tc-MAG3 dose used was calculated using the applicable EANM dose card^{79,80}. 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 x 128 matrix at one second per frame for the first two minutes. Thereafter the images were recorded at 15 seconds per frame for 40 minutes. When clinically indicated furosemide was administered 20 minutes after the injection of ^{99m}Tc-MAG3.

Renogram Processing – Cohort 1 and Cohort 2:

The raw data of the renograms of the patients in cohort 1 and cohort 2 were retrieved from the electronic archive and one to two minute images, and 20 to 21 minute images were summed to form one minute static images of these time frames. These images were visually

inspected to categorise the categorical variables and processed to obtain the values of the continuous variables.

Categorical variables:

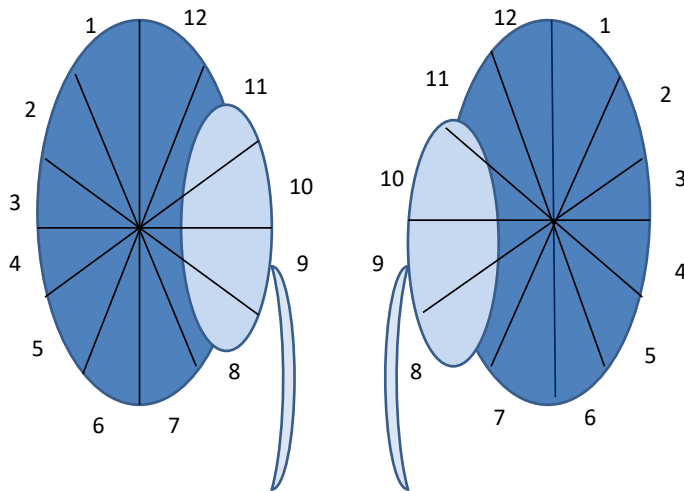
The appearance of the renal margins was categorised as smooth or irregular and well defined or poorly visualised. RENAL MARGINS SMOOTH was defined as a renal margin seen as a smooth line. Most of these patients had normal renal contours but a well-defined renal cortical defect such as a clearly defined 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.

These variables describing renal margins were defined separately for the left and right kidney. The results of the individual variables were then combined to generate the variables, BOTH RENAL MARGINS SMOOTH, BOTH RENAL MARGINS IRREGULAR, BOTH RENAL MARGINS WELL DEFINED and BOTH RENAL MARGINS POORLY VISUALISED. This was done in the following manner, if the patient had two kidneys that were both well-defined it was coded yes, if the patient had one kidney that was well defined and one which was poorly defined it was termed “no”, if both the patient’s kidneys were not well defined it was termed “no”.

The next group of variables described the presence or absence of cortical defects as well as the number of cortical defects. The variables were; NO CORTICAL DEFECTS, < 2 CORTICAL DEFECTS, ≥ 2 CORTICAL DEFECTS and ISLANDS OF FUNCTIONING TISSUE. A kidney was classified as having islands of functioning tissue if there was extensive cortical destruction.

In patients with cortical defects, the position of the cortical defect was described using this figure (Figure 1) which divides each kidney into twelve segments.

Figure 1: a schematic display of how the kidneys were divided into 12 segments



List of categorical variables:

- LEFT RENAL MARGINS SMOOTH
- RIGHT RENAL MARGINS SMOOTH
- BOTH RENAL MARGINS SMOOTH
- LEFT RENAL MARGINS IRREGULAR
- RIGHT RENAL MARGINS IRREGULAR
- BOTH RENAL MARGINS IRREGULAR
- LEFT RENAL MARGINS WELL DEFINED
- RIGHT RENAL MARGINS WELL DEFINED
- BOTH RENAL MARGINS WELL DEFINED
- LEFT RENAL MARGINS POORLY VISUALISED
- RIGHT RENAL MARGINS POORLY VISUALISED
- BOTH RENAL MARGINS POORLY VISUALISED
- LEFT NO CORTICAL DEFECTS
- RIGHT NO CORTICAL DEFECTS
- LEFT < 2 CORTICAL DEFECTS
- RIGHT < 2 CORTICAL DEFECTS
- LEFT ≥ 2 CORTICAL DEFECTS
- RIGHT ≥ 2 CORTICAL DEFECTS
- LEFT ISLANDS OF FUNCTIONING TISSUE
- RIGHT ISLANDS OF FUNCTIONING TISSUE
- POSITION OF CORTICAL DEFECTS

Continuous variables:

The DRF values were obtained from the HERMES renogram processing. The renal ROIs were drawn on the one to two minute summed image. Care was taken to ensure that the renal ROI included the whole kidney. The renal background ROIs were positioned automatically in the kidney analysis program as peri-renal C-shaped ROIs including both the upper and lower

pole of the kidney. The background ROIs were one to two pixels wide and were placed one to two pixels apart from the renal ROI. The images were inspected to confirm that the background ROIs did not extend outside the body outline of the patient. 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. All renograms analysed were processed five times at least one month apart by one operator, and the DRF values were recorded for both the HAUC and HRP method. 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

Asymmetry in uptake of tracer between the two kidneys was calculated as the absolute difference between the mean of the five measurements of DRF of the left kidney and the mean of the DRF measurements of the right kidney.

Additional processing to define continuous variables:

Continuous variables derived from the one to two minute summed image:

Renal and background ROIs were drawn three times at least one month apart by one operator on the summed one to two minute image displayed on the HERMES hybrid viewer display in the same manner as described for renogram processing. The number of counts and the size in cm^2 of each region were recorded.

LEFT KIDNEY TO BACKGROUND RATIO and RIGHT KIDNEY TO BACKGROUND RATIO 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 variables SD TOTAL COUNTS LEFT RENAL ROI, SD TOTAL COUNTS RIGHT RENAL ROI, SD TOTAL COUNTS LEFT BACKGROUND ROI and SD TOTAL COUNTS RIGHT BACKGROUND ROI were calculated as the standard deviation of the total counts of the three measurements of renal and background ROIs.

The pole to pole length of each kidney and distance between the lateral margin of the mid-pole of the kidney and the body outline was also measured on the summed one to two minute image.

Continuous variables derived from the 20 to 21 minute summed image:

Two measurements of renal pelvis size were recorded on the 20 to 21 minutes after ^{99m}Tc -MAG3 injection summed image, the pole to pole length of the pelvis and the maximal width of the pelvis measured in an axis perpendicular to the pelvis length measurement.

Continuous variables derived from visual assessment:

The times at which calyceal activity and renal pelvis activity were first visualised were recorded for each kidney.

Non-imaging continuous variables:

The variables investigated included two non-imaging variables, AGE (in months) and GFR which included measured or estimated GFR values. The measured GFRs (mGFR) were measured using ^{51}Cr -EDTA, and the two blood sample method according to the EANM guidelines⁸¹. The estimated GFR values (eGFR) were calculated using the modified Schwartz method⁸². All GFR values were corrected for body surface area.

List of continuous variables:

- MAXMINHAUC
- MAXMINHRP
- AGE
- GFR
- LEFT RENAL AREA
- RIGHT RENAL AREA
- LEFT BACKGROUND AREA
- RIGHT BACKGROUND AREA
- LEFT KIDNEY TO BACKGROUND RATIO
- RIGHT KIDNEY TO BACKGROUND RATIO
- SD TOTAL COUNTS LEFT RENAL ROI
- SD TOTAL COUNTS RIGHT RENAL ROI
- SD TOTAL COUNTS LEFT BACKGROUND ROI
- SD TOTAL COUNTS RIGHT BACKGROUND ROI
- LEFT KIDNEY LENGTH
- RIGHT KIDNEY LENGTH
- DISTANCE BETWEEN LATERAL MARGIN LEFT KIDNEY AND BODY OUTLINE
- DISTANCE BETWEEN LATERAL MARGIN RIGHT KIDNEY AND BODY OUTLINE
- LEFT RENAL PELVIS LENGTH
- RIGHT RENAL PELVIS LENGTH
- WIDTH LEFT RENAL PELVIS
- WIDTH RIGHT RENAL PELVIS
- ASYMMETRY DRF
- TIME VISUALISATION LEFT CALYCES
- TIME VISUALISATION RIGHT CALYCES
- TIME VISUALISATION LEFT PELVIS
- TIME VISUALISATION RIGHT PELVIS

All processing for cohort 1 and 2 was performed by a single operator.

Statistical analysis – Cohort 1:

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

Univariate linear regression – Cohort 1:

The association between each variable and the reproducibility of DRF measurement for both the HAUC and the HRP methods was tested with univariate linear regression.

Multiple linear regression - Cohort 1:

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, i.e. a maximum of eight to nine 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 LEFT KIDNEY TO BACKGROUND RATIO and RIGHT KIDNEY TO BACKGROUND RATIO could not be used in the same combination.

All possible combinations were tested. The combinations always included AGE and GFR. The next variable included was LEFT KIDNEY TO BACKGROUND RATIO OR RIGHT KIDNEY TO BACKGROUND RATIO. This was followed by a variable describing the size of the ROIs i.e. LEFT RENAL AREA OR RIGHT RENAL AREA OR LEFT BACKGROUND AREA OR RIGHT BACKGROUND AREA. The next variable included in the combinations was TIME VISUALISATION LEFT CALYCES OR TIME VISUALISATION RIGHT CALYCES OR TIME VISUALISATION LEFT PELVIS OR TIME VISUALISATION RIGHT PELVIS. The next variable added was SD TOTAL COUNTS LEFT RENAL ROI OR SD TOTAL COUNTS RIGHT RENAL ROI OR SD OF TOTAL COUNTS LEFT BACKGROUND ROI OR SD TOTAL COUNTS RIGHT BACKGROUND ROI. ASYMMETRY DRF was added as a separate variable. For the categorical variables describing RENAL MARGINS only one was used in each combination. This same principle applied for the number of cortical defects in each kidney.

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:

- 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.

The distributions of the dependent variables were not normal, Figure 2 and 3. The residual values plotted on the normality plot deviated from the expected line, Figure 4. There was also heteroscedasticity for both MAXMINHAUC and MAXMINHRP. The heteroscedasticity was so severe that the models had to be rejected, Table 3 and Table 4.

Figure 2. The histogram of MAXMINHAUC

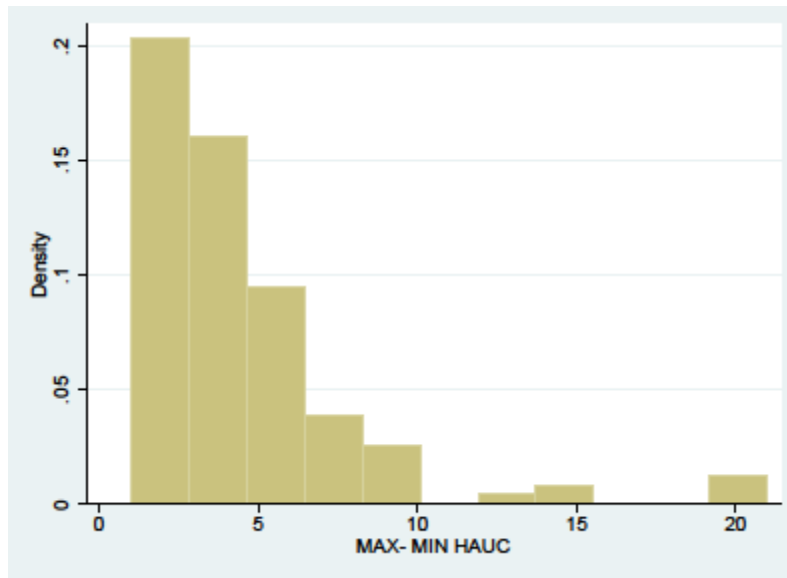


Figure 3. The histogram of MAXMINHRP

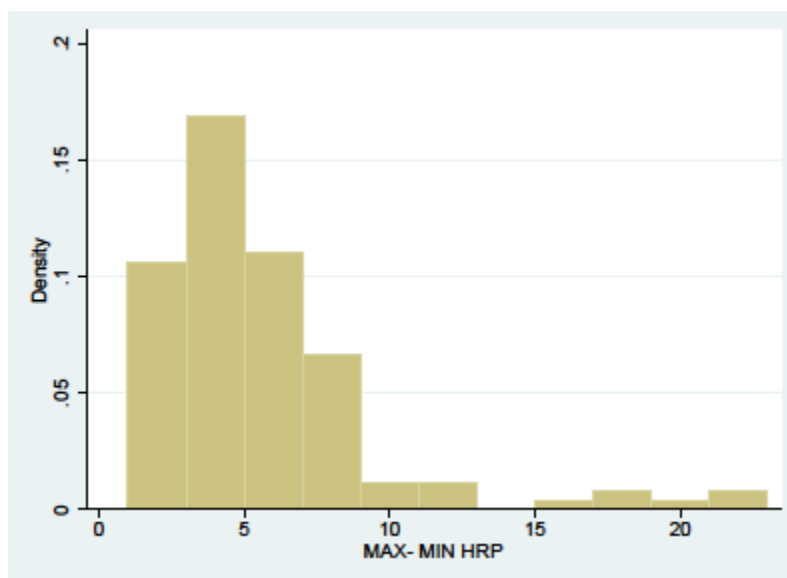
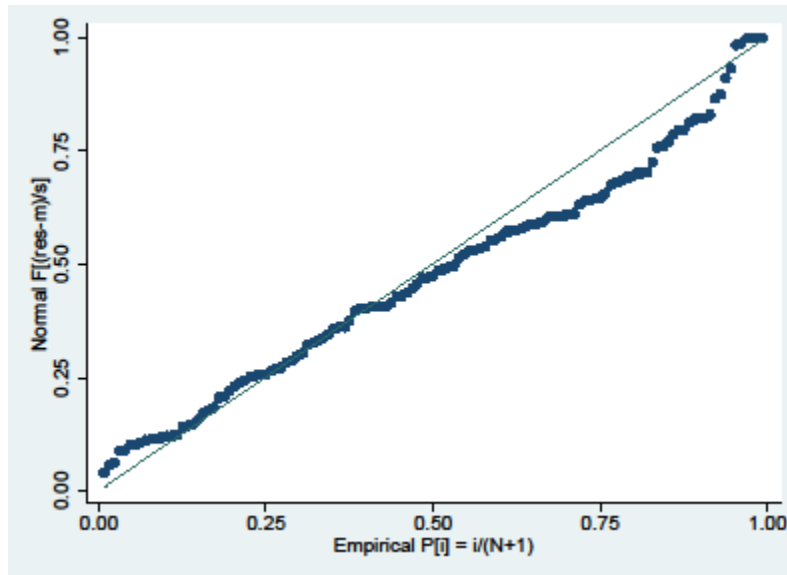


Figure 4. The residual values for the combination with the highest R^2 , MAXMINHAUC, plotted on a normal probability plot.



The normal probability plot for the residuals of the MAXMINHRP was very similar to the one for MAXMINHAUC and is not shown here.

Table 3. Cameron and Trivedi's decomposition of IM – test for the multiple linear regression combination with the highest R^2 for MAXMINHAUC (untransformed).

Source	χ^2	df	p
Heteroscedasticity	59.43	33	0.003
Skewness	23.38	7	0.002
Kurtosis	3.12	1	0.077
Total	85.93	41	<0.001

Table 4. Cameron and Trivedi's decomposition of IM – test for the combination with the highest R^2 for MAXMINHRP (untransformed).

Source	χ^2	df	p
Heteroscedasticity	55.01	33	0.010
Skewness	25.19	7	0.001
Kurtosis	2.91	1	0.088
Total	83.12	41	<0.001

Log transformation, ($\log_{10}$), of the dependent variables improved the distribution, Figures 5 and 6.

Figure 5. The histogram of log transformed MAXMINHAUC.

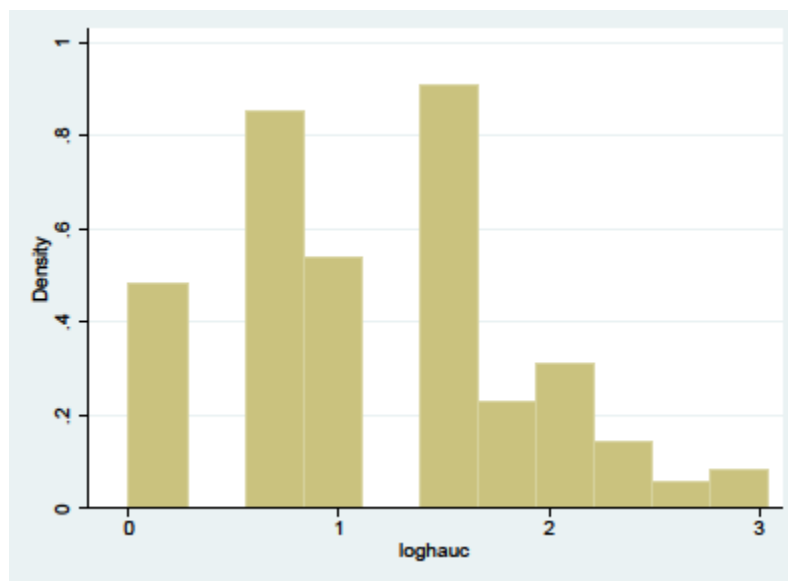
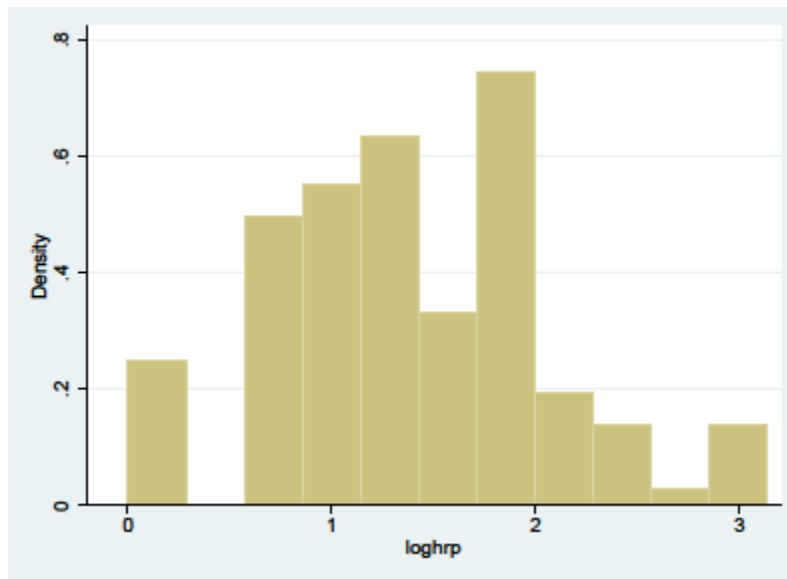


Figure 6. The histogram of log transformed MAXMINHRP.



The univariate and multiple linear regression analyses described above were repeated on the cohort 1 data using log transformed dependent variables. Log transformed dependent variables were used in the analysis of the cohort 2 data.

Results

Patients - Cohort 1:

The age, GFR, DRF and MAXMINHAUC and MAXMINHRP of the 133 patients in the cohort are summarised in Table 5. The values given for DRF are the mean of the five values recorded for the left kidney. Thirty-three children were less than six months and 13 between six and 12 months. There were 14 with a GFR < 60 ml/min/1.73m² and 22 with a GFR between 60 and 80 ml/min/1.73m².

Table 5. The patient demographics of the 133 patients.

Variables	Median	25% Quartile	75% Quartile
AGE (months)	26	7	83
GFR (ml/min/1.73m ²)	97	78	120
DRF* HAUC (%)	53	43	68
DRF* HRP (%)	53	43	67
MAXMINHAUC	4	2	6
MAXMINHRP	4	3	7

* DRF of left kidney

In six of these patients the number of cortical defects could not be ascertained with certainty. In three of these six patients we could also not categorise the renal margins as smooth or irregular as uptake was too poor. These patients with absent observations were not included in the univariate linear and multiple linear regression analyses. The categorisations of the categorical variables RENAL MARGINS IRREGULAR and RENAL MARGINS POORLY VISUALISED and the values of continuous variables AGE, GFR, MAXMINHAUC and MAXMINHRP for

these six patients are listed in Table 6. Exclusion of these six children left a total of 127 renograms in the analysis in cohort 1.

Table 6. Demographics of the six patients with absent observations who were excluded in cohort 1.

AGE (months)	GFR (ml/min/1.73m ²)	RENAL MARGINS IRREGULAR		RENAL MARGINS POORLY VISUALISED		MAXMINHAUC	MAXMINHRP
		Left	Right	Left	Right		
7.72	59	yes	no	no	yes	16	19
2.33	63	no	no	yes	yes	4	5
2.56	74	no	*	no	yes	6	7
2.50	48	*	no	yes	no	13	11
9.66	70	no	*	no	yes	6	10
84.60	51	yes	yes	yes	yes	10	9

* kidney too poorly visualised to categorise the smoothness/irregularity of the renal margin.

The patient demographics of the 127 patients in the analysis in cohort 1 are summarised in Table 7. 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 months, 11 (9 %) between 6 and 12 months, and 11 (9 %) between 12 and 18 months.

The GFR values of the patients included in cohort 1 ranged between 19 – 230 ml/min/1.73m². A total of 11 (9%) had a GFR < 60ml/min/1.73m², 20 patients (12%) had a GFR between 60 and 80ml/min/1.73m². Of the 31 patients with GFR values < 80ml/min/1.73m², nine were older than 12 months. Fourteen (11%) of the patients had mGFRs and the other 113 patients eGFRs.

The LEFT KIDNEY TO BACKGROUND RATIO ranged from 1.15 to 5.33 and the RIGHT KIDNEY TO BACKGROUND RATIO ranged from 1.03 to 4.95.

Table 7. The patient demographics of the 127 patients included in cohort 1.

Variables	Median	25% Quartile	75% Quartile
AGE (months)	31	7	84
GFR (ml/min/1.73m ²)	99	81	122
DRF* HAUC (%)	53	43	67
DRF* HRP (%)	53	43	65
MAXMINHAUC	3	2	5
MAXMINHRP	4	3	6
LEFT KIDNEY TO BACKGROUND RATIO	2.96	2.32	3.74
RIGHT KIDNEY TO BACKGROUND RATIO	2.51	1.90	3.09

* DRF of left kidney

Categorical variables - cohort 1:

Some categorical variables could not be used in univariate linear regression of the 127 patients remaining in the cohort 1 dataset as the number of children was too small for statistical analysis. These variables were: LEFT ISLANDS OF FUNCTIONING TISSUE (3 patients) RIGHT ISLANDS OF FUNCTIONING TISSUE (2), LEFT ≥ 2 CORTICAL DEFECTS (5), RIGHT ≥ 2 CORTICAL DEFECTS (4) and BOTH RENAL MARGINS POORLY VISUALISED (6). These variables were excluded from further analysis. The AGE, GFR, MAXMINHAUC and MAXMINHRP of the patients with one or more of these variables are given in Table 8.

Table 8. The AGE, GFR, MAXMINHAUC and MAXMINHRP of the patients that had one or more of the variables excluded from further analysis in cohort 1

PATIENT NUMBER	AGE (months)	GFR (ml/min/1.73m ²)	MAXMINHAUC	MAXMINHRP	LEFT KIDNEY TO BACKGROUND RATIO	RIGHT KIDNEY TO BACKGROUND RATIO
LEFT ISLANDS OF FUNCTIONING TISSUE						
75	25	89	4	4	1.43	3.15
155	75	79	6	7	1.97	2.37
LEFT ≥ 2 CORTICAL DEFECTS						
45	33	230	4	6	2.35	3.16
151	1	39	7	8	1.58	1.70
152	2	46	12	11	2.24	1.46
167	63	68	2	2	2.78	2.36
RIGHT ≥ 2 CORTICAL DEFECTS						
66	116	135	2	2	4.02	2.57
82	133	127	2	2	5.33	2.47
138	1	58	7	7	2.36	1.61
153	<1	77	7	8	3.93	1.49
BOTH RENAL MARGINS POORLY VISUALISED						
49	12	144	3	6	2.05	2.47
53	81	90	6	6	1.91	2.34
68	30	81	4	7	2.75	1.44
146	2	37	10	18	1.69	1.44
LEFT AND RIGHT ISLANDS OF FUNCTIONING TISSUE and BOTH RENAL MARGINS POORLY VISUALISED						
169	3	19	21	20	1.28	1.04
RIGHT ISLANDS OF FUNCTIONING TISSUE, and LEFT ≥ 2 CORTICAL DEFECTS and BOTH RENAL MARGINS POORLY VISUALISED						
148	191	57	15	21	2.05	1.18

The number of cortical defects recorded for each of the 12 defined renal segments was too low for statistical analysis. There were 48 patients with one or more cortical defects in the

left kidney and 34 patients with one or more defects in the right kidney. The majority of the kidneys with cortical defects, 37 left kidneys and 28 right kidneys, only had one defect. Therefore, the variable describing the POSITION OF CORTICAL DEFECTS was excluded.

In total, 15 categorical variables were available for analysis.

Continuous variables – cohort 1:

A number of the predefined continuous variables could not be used in the statistical analyses. The variables KIDNEY LENGTH and DISTANCE BETWEEN LATERAL MARGIN KIDNEY AND BODY OUTLINE could not be measured on the left in eight patients and on the right in ten. We were able to measure LEFT RENAL AREA and RIGHT RENAL AREA in all patients and we elected to use them to measure kidney size instead of KIDNEY LENGTH.

The variables PELVIS WIDTH and PELVIS LENGTH were also problematic. They were measured on the 20 to 21 minute summed image and in most patients with normal kidneys the renal pelvis cleared before this timeframe and could not be visualised. On the left there were 27 patients where all activity had cleared from the pelvis at this time interval and in two patients the uptake was too poor to define the pelvis width and length accurately. On the right the corresponding numbers were 28 and two. Therefore, these variables were also excluded leaving 17 continuous variables available for analysis.

The 32 categorical and continuous variables were screened using univariate linear regression to identify possible predictors of the dependent variables log MAXMINHAUC and log MAXMINHRP.

Results for log MAXMINHAUC – cohort 1

Univariate linear regression results for categorical variables and log MAXMINHAUC – cohort 1:

The univariate linear regression results for the 15 categorical variables are listed in ascending order of p-value of the beta-coefficient in Table 9. Most of the variables had p-values ≤ 0.001 . They were; BOTH RENAL MARGINS WELL DEFINED, LEFT NO CORTICAL DEFECTS, LEFT RENAL MARGINS SMOOTH, LEFT RENAL MARGINS WELL DEFINED, LEFT RENAL MARGINS POORLY VISUALISED, LEFT RENAL MARGINS IRREGULAR, BOTH RENAL MARGINS IRREGULAR, RIGHT RENAL MARGINS WELL DEFINED and RIGHT RENAL MARGINS POORLY VISUALISED. The variables BOTH RENAL MARGINS SMOOTH, LEFT < 2 CORTICAL DEFECTS, RIGHT NO CORTICAL DEFECTS, RIGHT RENAL MARGINS SMOOTH, and RENAL MARGINS IRREGULAR had higher values of p but the values were ≤ 0.2 . All these variables were therefore included in the multiple linear regression analysis

The only categorical variable excluded from multiple linear regression was RIGHT < 2 CORTICAL DEFECTS.

The beta-coefficients and t-values of the variables LEFT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS POORLY VISUALISED were equal in magnitude but of opposite sign. The same pattern was found with RIGHT RENAL MARGINS WELL DEFINED and RIGHT POORLY VISUALISED, which also had values of equal magnitude but of opposite sign for the beta-coefficients and t-values.

A negative beta-coefficient predicted good reproducibility and a positive beta-coefficient predicted decreased reproducibility.

Table 9. Univariate linear regression of the 15 categorical variables and log MAXMINHAUC cohort 1. The variables are listed in ascending order of the p-value of the beta-coefficient.

Variable	Beta-coefficient.	Standard error	t	p > t
BOTH RENAL MARGINS WELL DEFINED	-0.632	0.126	-5.00	<0.001
LEFT NO CORTICAL DEFECTS	-0.533	0.123	-4.35	<0.001
LEFT RENAL MARGINS SMOOTH	-0.519	0.129	-4.03	<0.001
LEFT RENAL MARGINS WELL DEFINED	-0.579	0.148	-3.92	<0.001
LEFT RENAL MARGINS POORLY VISUALISED	0.579	0.148	3.92	<0.001
LEFT RENAL MARGINS IRREGULAR	0.495	0.131	3.76	<0.001
BOTH RENAL MARGINS IRREGULAR	0.706	0.197	3.58	<0.001
RIGHT RENAL MARGINS WELL DEFINED	-0.569	0.164	-3.47	0.001
RIGHT RENAL MARGINS POORLY VISUALISED	0.569	0.164	3.47	0.001
BOTH RENAL MARGINS SMOOTH	-0.351	0.128	-2.75	0.007
LEFT < 2 CORTICAL DEFECTS	0.305	0.122	2.51	0.014
RIGHT NO CORTICAL DEFECTS	-0.340	0.157	-2.17	0.032
RIGHT RENAL MARGINS SMOOTH	-0.278	0.159	-1.75	0.083
RIGHT RENAL MARGINS IRREGULAR	0.226	0.166	1.36	0.175
RIGHT < 2 CORTICAL DEFECTS	0.122	0.152	0.81	0.422

Univariate linear regression for continuous variables and log MAXMINHAUC – cohort 1:

The univariate linear regression results of the 17 continuous variables are presented in Table 10. The variables are listed in ascending order of the p-value of the beta-coefficient. The variables which had p-values ≤ 0.001 were LEFT KIDNEY TO BACKGROUND RATIO, GFR, RIGHT KIDNEY TO BACKGROUND RATIO, AGE and LEFT BACKGROUND AREA. Variables with higher values of p, but still ≤ 0.2 were LEFT RENAL AREA, TIME VISUALISATION LEFT PELVIS, TIME VISUALISATION LEFT CALYCES,

RIGHT RENAL AREA, and TIME VISUALISATION RIGHT CALYCES. All these variables were therefore included in the multiple linear regression analysis.

The continuous variables RIGHT BACKGROUND AREA, SD TOTAL COUNTS LEFT RENAL ROI, TIME VISUALISATION RIGHT PELVIS, SD TOTAL COUNTS RIGHT BACKGROUND ROI, ASYMMETRY DRF, SD TOTAL COUNTS LEFT BACKGROUND ROI and SD TOTAL COUNTS RIGHT RENAL ROI were excluded from the multiple linear regression analyses.

Table 10. Univariate linear regression of the 17 continuous variables and log MAXMINHAUC cohort 1. The variables are listed in ascending order of the p-value of the beta-coefficient.

Variable	Beta-coefficient.	Standard error.	t	p > t
LEFT KIDNEY TO BACKGROUND RATIO	-0.416	0.060	-6.91	<0.001
GFR	-0.011	0.020	-5.39	<0.001
RIGHT KIDNEY TO BACKGROUND RATIO	-0.364	0.080	-4.55	<0.001
AGE	-0.005	0.001	-3.57	0.001
LEFT BACKGROUND AREA	-0.081	0.024	-3.44	0.001
LEFT RENAL AREA	-0.013	0.005	-2.48	0.014
TIME VISUALISATION LEFT PELVIS	0.038	0.018	2.11	0.037
TIME VISUALISATION OF LEFT CALYCES	0.093	0.051	1.83	0.070
RIGHT RENAL AREA	-0.010	0.006	-1.78	0.077
TIME VISUALISATION RIGHT CALYCES	0.028	0.016	1.70	0.092
RIGHT BACKGROUND AREA	-0.042	0.033	-1.28	0.202
SD TOTAL COUNTS LEFT RENAL ROI	-0.001	0.001	-1.16	0.248
TIME VISUALISATION RIGHT PELVIS	0.012	0.011	1.05	0.298
SD TOTAL COUNTS RIGHT BACKGROUND ROI	-0.001	0.001	-0.77	0.444
ASYMMETRY DRF	0.001	0.002	0.43	0.666
SD TOTAL COUNTS LEFT BACKGROUND ROI	0.001	0.001	-0.42	0.674
SD TOTAL COUNTS RIGHT RENAL ROI	0.000	0.001	0.38	0.707

Selection of variables for multiple linear regression log MAXMINHAUC - cohort 1:

The multiple linear regression combinations were compiled by combining one dependent variable with eight independent variables as follows;

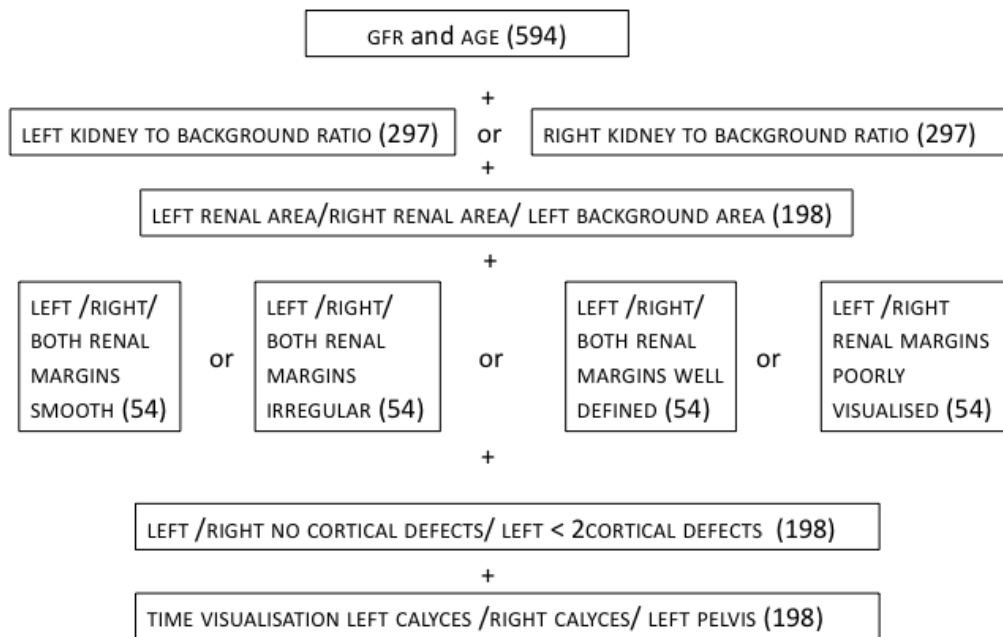
Dependent variable: log MAXMINHAUC

Independent variables

1. AGE
2. GFR
3. LEFT KIDNEY TO BACKGROUND RATIO or RIGHT KIDNEY TO BACKGROUND RATIO,
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

The plan for compiling the combinations of the variables is depicted in Figure 7. An example of a combination for log MAXMINHAUC is: AGE and GFR and LEFT KIDNEY TO BACKGROUND RATIO and LEFT RENAL AREA and LEFT NO CORTICAL DEFECTS and RIGHT RENAL MARGIN SMOOTH and TIME VISUALISATION LEFT PELVIS. A total of 594 different combinations were analysed with multiple linear regression, step-down multiple linear regression and step-up multiple linear regression. The 594 different combinations tested for log MAXMINHAUC are listed in the appendix in Table 43.

Figure 7. A schematic display to show how the 594 combinations used in multiple linear regression for log MAXMINHAUC were compiled.



Multiple linear regression results - log MAXMINHAUC - cohort 1:

The different methods of multiple linear regression, straight, step-down and step-up, gave similar results for cohort 1 for each combination.

The beta-coefficients and t-values of the variables RIGHT RENAL MARGINS WELL DEFINED and RIGHT RENAL MARGINS POORLY VISUALISED, were equal in magnitude but of opposite sign. The same pattern was found with LEFT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS POORLY VISUALISED so only the results for the combinations with the variables RIGHT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS WELL DEFINED are presented.

The combination with the highest R^2 for log MAXMINHAUC - cohort 1:

For the dependent variable log MAXMINHAUC the R^2 -values for the 594 different combinations ranged between 0.3510 and 0.4906. In the log MAXMINHAUC combination with the highest R^2 , 0.4906, the independent variables were AGE, GFR, LEFT KIDNEY TO BACKGROUND RATIO, LEFT RENAL AREA, RIGHT RENAL MARGINS WELL DEFINED, LEFT NO CORTICAL DEFECTS and TIME VISUALISATION RIGHT CALYCES. The beta-coefficients, robust standard errors and p-values of the variables in this combination are given in Table 11.

Table 11. Multiple linear regression for the combination with the highest R^2 for log MAXMINHAUC cohort 1.

Variable	Beta-coefficient	Robust Standard Error	p-value
LEFT KIDNEY TO BACKGROUND RATIO	-0.316	0.061	<0.001
RIGHT RENAL MARGINS WELL DEFINED	-0.399	0.121	0.001
GFR	-0.005	0.002	0.004
AGE	-0.003	0.001	0.009
TIME VISUALISATION RIGHT CALYCES	0.033	0.014	0.019
LEFT NO CORTICAL DEFECTS	-0.124	0.104	0.233
LEFT RENAL AREA	0.004	0.005	0.360

Results of the individual variables in the different combinations for log MAXMINHAUC – cohort 1:

The multiple linear regression results of the 594 combinations analysed against the dependent variable log MAXMINHAUC are summarised in Table 12. The variables found to be significant in all combinations in which they were included were GFR (594 combinations), LEFT KIDNEY TO BACKGROUND RATIO (297) and BOTH RENAL MARGINS WELL DEFINED (54).

RIGHT KIDNEY TO BACKGROUND RATIO was significant in 261 of the 297 combinations in which it was included. The R^2 -values of the 36 combinations in which RIGHT KIDNEY TO BACKGROUND RATIO was not significant ranged from 0.3554 to 0.4160. They contained the following variables in addition to AGE and GFR:

- LEFT RENAL AREA (21) and LEFT BACKGROUND AREA (15)
- TIME VISUALISATION RIGHT CALYCES (20), TIME VISUALISATION LEFT CALYCES (4) and TIME VISUALISATION LEFT PELVIS (12)
- RIGHT NO CORTICAL DEFECTS (13), LEFT < 2 CORTICAL DEFECTS (13) and LEFT NO CORTICAL DEFECTS (10)
- RIGHT RENAL MARGINS WELL DEFINED (14), RIGHT RENAL MARGINS POORLY VISUALISED (14), BOTH RENAL MARGINS WELL DEFINED (6) and BOTH RENAL MARGINS IRREGULAR (2)

AGE and BOTH RENAL MARGINS IRREGULAR were significant in 55% and 67% of the combinations in which they were included, respectively. RIGHT RENAL AREA, LEFT NO CORTICAL DEFECTS, LEFT RENAL MARGINS SMOOTH, LEFT RENAL MARGINS IRREGULAR, LEFT RENAL MARGINS WELL DEFINED, RIGHT RENAL MARGINS WELL DEFINED, TIME VISUALISATION LEFT CALYCES, TIME VISUALISATION RIGHT CALYCES and TIME VISUALISATION LEFT PELVIS were significant in 33 to 50% of the combinations in which they were included. LEFT < 2 CORTICAL DEFECTS was only significant in three of the 198 combinations in which it was included.

The variables which were not significant in any of the combinations were LEFT RENAL AREA, LEFT BACKGROUND AREA, RIGHT NO CORTICAL DEFECTS, RIGHT RENAL MARGINS SMOOTH, BOTH RENAL MARGINS SMOOTH and RIGHT RENAL MARGINS IRREGULAR.

Table 12. Multiple linear regression results for the 594 combinations for log MAXMINHAUC cohort 1. The number of combinations in which each variable was included is given in brackets. The range of p-values of the beta-coefficients and the number of times a variable had a p-value ≤ 0.05 are also listed.

Variable (n)	p range	p-value ≤ 0.05 (n)
AGE (594)	<0.001 - 0.461	329
GFR (594)	<0.001 - 0.007	594
LEFT KIDNEY TO BACKGROUND RATIO (297)	<0.001 - 0.005	297
RIGHT KIDNEY TO BACKGROUND RATIO (297)	<0.001 - 0.093	261
LEFT RENAL AREA (198)	0.198 - 0.999	0
RIGHT RENAL AREA (198)	0.004 - 0.998	86
LEFT BACKGROUND AREA (198)	0.332 - 0.991	0
LEFT NO CORTICAL DEFECTS (198)	0.003 - 0.428	59
RIGHT NO CORTICAL DEFECTS (198)	0.086 - 0.998	0
LEFT < 2 CORTICAL DEFECTS (198)	0.036 - 0.995	3
LEFT RENAL MARGINS SMOOTH (54)	0.001 - 0.495	18
RIGHT RENAL MARGINS SMOOTH (54)	0.135 - 0.530	0
BOTH RENAL MARGINS SMOOTH (54)	0.132 - 0.999	0
LEFT RENAL MARGINS IRREGULAR (54)	0.003 - 0.719	17
RIGHT RENAL MARGINS IRREGULAR (54)	0.181 - 0.889	0
BOTH RENAL MARGINS IRREGULAR (54)	0.006 - 0.218	36
LEFT RENAL MARGINS WELL DEFINED (54)	<0.001 - 0.613	27
RIGHT RENAL MARGINS WELL DEFINED (54)	<0.001 - 0.433	27
BOTH RENAL MARGINS WELL DEFINED (54)	<0.001 - 0.021	54
TIME VISUALISATION LEFT CALYCES (198)	0.002 - 0.839	77
TIME VISUALISATION RIGHT CALYCES (198)	0.003 - 0.775	99
TIME VISUALISATION LEFT PELVIS (198)	0.001 - 0.762	59

Testing the assumptions of the multiple linear regression models - log MAXMINHAUC - cohort 1:

Residual values - log MAXMINHAUC - cohort 1:

The residual values, the differences between the predicted and observed values for each patient, in the combination with the highest R^2 -value for log MAXMINHAUC were calculated and plotted on a normal probability plot (Figure 8). The residual values did not depart significantly from the expected normal distribution.

The residual values were also plotted against the continuous variables AGE, GFR, LEFT KIDNEY TO BACKGROUND RATIO, LEFT RENAL AREA and TIME VISUALISATION RIGHT CALYCES, (Figures 9 through 13). None of the patients had high residual values.

Figure 8. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHAUC cohort 1, plotted on a normal probability plot.

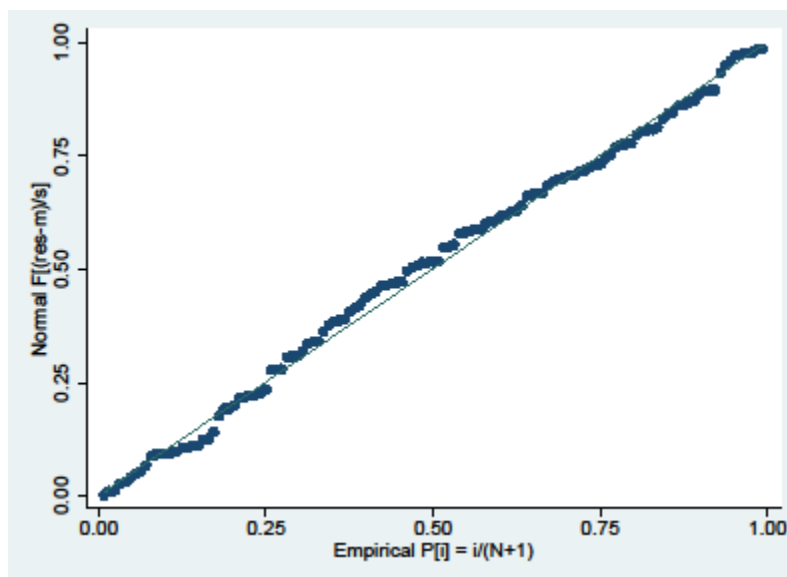


Figure 9. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHAUC cohort 1, plotted against AGE.

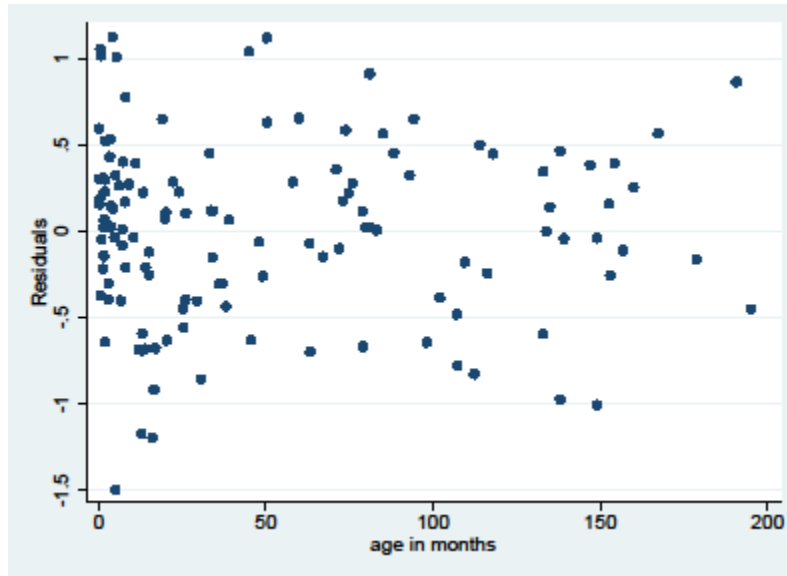


Figure 10. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHAUC cohort 1, plotted against GFR.

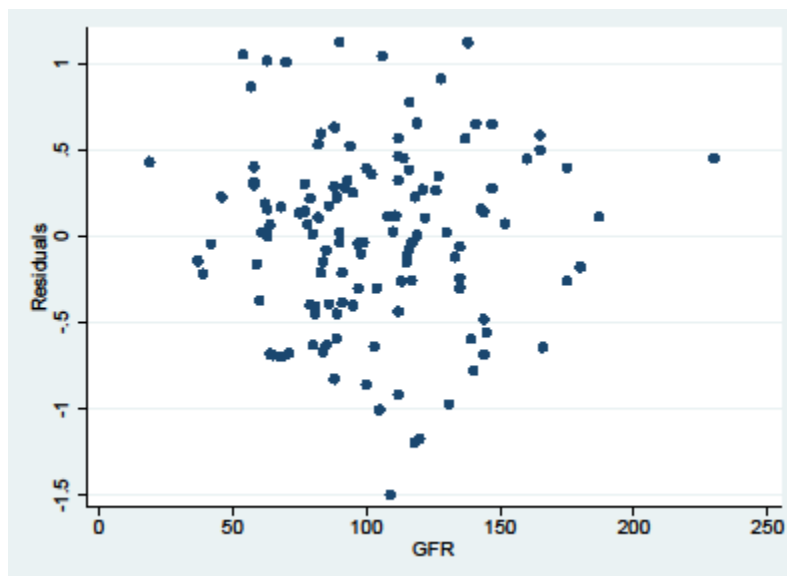
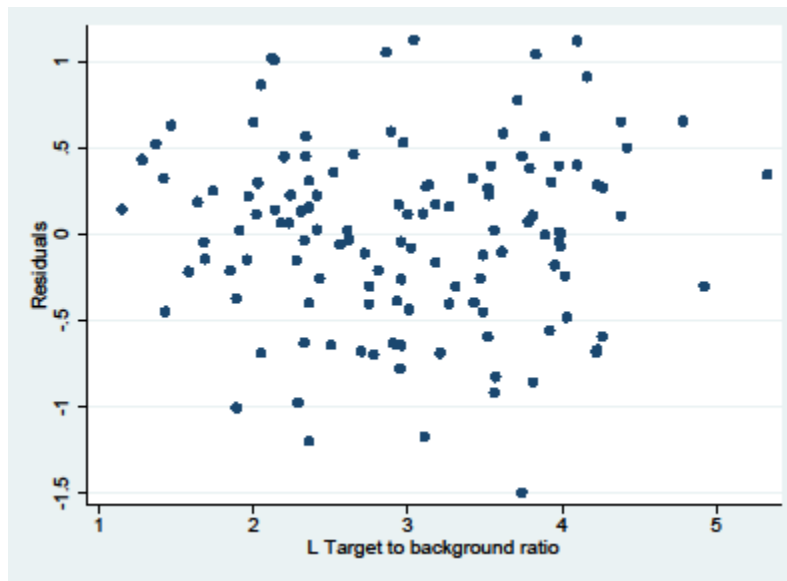


Figure 11. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHAUC cohort 1, plotted against LEFT KIDNEY TO BACKGROUND RATIO.



*L Target to background ratio = LEFT KIDNEY TO BACKGROUND RATIO.

Figure 12. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHAUC cohort 1, plotted against LEFT RENAL AREA.

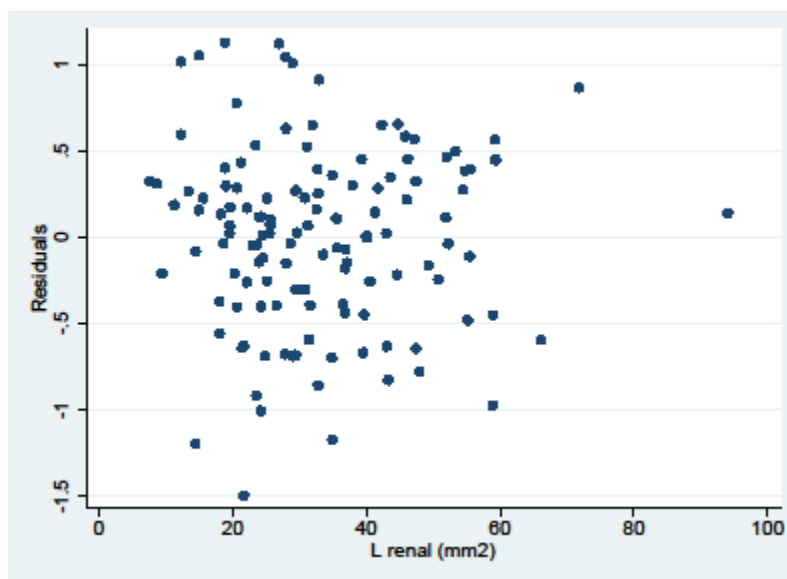
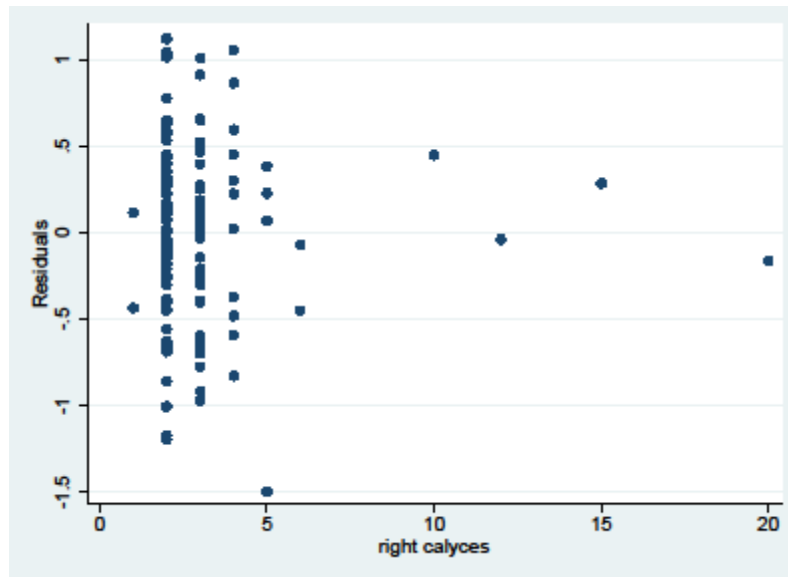


Figure 13. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHAUC cohort 1, plotted against TIME VISUALISATION RIGHT CALYCES.



Homoscedasticity - log MAXMINHAUC – cohort 1:

Cameron and Trivedi's test illustrates that there was no heteroscedasticity between the different variables included in the analysis, Table 13.

Table 13. Cameron and Trivedi's decomposition of IM – test for the combination with the highest R^2 for log MAXMINHAUC cohort 1.

Source	χ^2	df	p
Heteroscedasticity	23.27	33	0.896
Skewness	7.04	7	0.425
Kurtosis	0.03	1	0.858
Total	30.34	41	0.889

Multicollinearity - log MAXMINHAUC – cohort 1:

The VIF was calculated for each of the independent variables used in the combination with the highest R²-value. The results are presented in Table 14. For all the variables the VIF values were less than |5|. This indicates there is no multicollinearity between these variables.

Table 14. VIF for the combination with the highest R² for log MAXMINHAUC cohort 1.

Variable	VIF	1/VIF
AGE	2.29	0.437
GFR	1.53	0.655
LEFT KIDNEY TO BACKGROUND RATIO	1.30	0.766
LEFT RENAL AREA	2.34	0.427
TIME VISUALISATION RIGHT CALYCES	1.19	0.837
LEFT NO CORTICAL DEFECTS	1.24	0.807
RIGHT RENAL MARGINS WELL DEFINED	1.17	0.852
Mean VIF	1.58	

The collinearity between the variables was tested further, Table 15. There was no significant collinearity (> 0.800) between the variables. Of note, the collinearity between AGE and GFR was only - 0.144.

Table 15. Correlation matrix of collinearity coefficients of the regression model for the combination with the highest R^2 for log MAXMINHAUC cohort 1.

Variable	AGE	GFR	LEFT KIDNEY TO BACKGROUND RATIO	LEFT RENAL AREA	TIME VISUALISA- TION RIGHT CALYCES	LEFT NO CORTICAL DEFECTS	RIGHT RENAL MARGINS WELL DEFINED	-CONS
AGE	1.000							
GFR	-0.144	1.000						
LEFT KIDNEY TO BACKGROUND RATIO	-0.235	-0.260	1.000					
LEFT RENAL AREA	-0.512	-0.386	0.105	1.000				
TIME VISUALISATION RIGHT CALYCES	-0.359	0.415	-0.078	-0.171	1.000			
LEFT NO CORTICAL DEFECTS	0.015	-0.136	-0.363	0.007	0.002	1.000		
RIGHT RENAL MARGINS WELL DEFINED	-0.055	0.129	0.157	0.089	0.009	-0.084	1.000	
-CONS	0.445	-0.207	-0.570	-0.360	-0.228	0.173	-0.507	1.000

Conclusion regression diagnostics log MAXMINHAUC – cohort 1:

The multiple linear regression models met the necessary statistical assumptions.

Summary of the different combinations analysed with multiple linear regression log MAXMINHAUC - cohort 1:

For the log MAXMINHAUC combination with the highest R^2 -value in cohort 1, three variables, LEFT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL MARGINS WELL DEFINED and GFR, were highly

significant with p-values of the beta-coefficient of < 0.001 , 0.001 and 0.004 . Two variables, AGE and TIME VISUALISATION RIGHT CALYCES, had strong significance with p-values of 0.009 and 0.019 . The other two variables in this combination, LEFT NO CORTICAL DEFECTS and LEFT RENAL AREA, had non-significant p-values of 0.233 and 0.360 .

The analysis of the 594 combinations with log MAXMINHAUC showed a striking pattern in cohort 1: the individual variables GFR, LEFT KIDNEY TO BACKGROUND RATIO, and BOTH RENAL MARGINS WELL DEFINED were significant in every combination in which the variable was present. RIGHT KIDNEY TO BACKGROUND RATIO was significant in the vast majority of the combinations in which it was included. Conversely the variables LEFT RENAL AREA, LEFT BACKGROUND AREA, RIGHT NO CORTICAL DEFECTS, RIGHT RENAL MARGINS SMOOTH, BOTH RENAL MARGINS SMOOTH, RIGHT RENAL MARGINS IRREGULAR and BOTH RENAL MARGINS IRREGULAR were not significant in any of the combinations in which they were included.

Results for log MAXMINHRP – cohort 1

Univariate linear regression results for categorical variables and log MAXMINHRP - cohort 1:

The univariate linear regression results for the 15 categorical variables are listed in ascending order of the p-value of the beta-coefficient in Table 16. The variables which had p-values < 0.001 were BOTH RENAL MARGINS WELL DEFINED, LEFT RENAL MARGINS WELL DEFINED, LEFT RENAL MARGINS POORLY VISUALISED, RIGHT RENAL MARGIN WELL DEFINED, and RIGHT RENAL MARGINS POORLY VISUALISED. The p-values for LEFT NO CORTICAL DEFECTS, LEFT RENAL MARGINS SMOOTH, LEFT RENAL MARGINS IRREGULAR, BOTH RENAL MARGINS SMOOTH, BOTH RENAL MARGINS IRREGULAR, RIGHT RENAL MARGIN SMOOTH and RIGHT NO CORTICAL DEFECTS were higher but still ≤ 0.2 . All these variables were therefore included in the multiple linear regression models

The p-values for LEFT < 2 CORTICAL DEFECTS, RIGHT RENAL MARGINS IRREGULAR, and RIGHT < 2 CORTICAL DEFECTS were > 0.2. They were not included in the multiple linear regression models.

Table 16. Univariate linear regression of the 15 categorical variables and log MAXMINHRP cohort 1.

The variables are listed in ascending order of the p-value of the beta-coefficient.

Variable	Beta -coefficient.	Standard error	t	p > t
BOTH RENAL MARGINS WELL DEFINED	-0.603	0.111	-5.42	<0.001
LEFT RENAL MARGINS WELL DEFINED	-0.533	0.125	-4.26	<0.001
LEFT RENAL MARGINS POORLY VISUALISED	0.533	0.125	4.26	<0.001
RIGHT RENAL MARGINS WELL DEFINED	-0.608	0.145	-4.19	<0.001
RIGHT RENAL MARGINS POORLY VISUALISED	0.608	0.145	4.19	<0.001
LEFT NO CORTICAL DEFECTS	-0.374	0.123	-3.05	0.003
LEFT RENAL MARGINS SMOOTH	-0.375	0.131	-2.84	0.005
LEFT RENAL MARGINS IRREGULAR	0.346	0.139	2.49	0.014
BOTH RENAL MARGINS SMOOTH	-0.289	0.119	-2.42	0.017
BOTH RENAL MARGINS IRREGULAR	0.551	0.241	2.28	0.024
RIGHT RENAL MARGINS SMOOTH	-0.304	0.143	-2.12	0.036
RIGHT NO CORTICAL DEFECTS	-0.302	0.151	-2.00	0.047
LEFT <2 CORTICAL DEFECTS	0.160	0.127	1.26	0.211
RIGHT RENAL MARGINS IRREGULAR	0.190	0.163	1.17	0.246
RIGHT <2 CORTICAL DEFECTS	0.108	0.149	0.73	0.467

* The corresponding Table for log MAXMINHAUC cohort 1 is Table 8.

Univariate linear regression results for continuous variables and log MAXMINHRP - cohort 1:

The univariate linear regression results of the 17 continuous variables are presented in Table 17. The variables are listed in ascending order of the p-value of the beta-coefficient. The variables with p-values < 0.001 were LEFT KIDNEY TO BACKGROUND RATIO, RIGHT KIDNEY TO BACKGROUND RATIO and GFR. The p-values for AGE, LEFT BACKGROUND AREA, TIME VISUALISATION LEFT CALYCES, LEFT RENAL AREA, TIME VISUALISATION LEFT PELVIS and TIME VISUALISATION RIGHT CALYCES were

higher, between 0.003 and 0.139. All these variables were included in the multiple linear regression models.

TIME VISUALISATION RIGHT PELVIS, RIGHT RENAL AREA, RIGHT BACKGROUND AREA, SD TOTAL COUNTS LEFT RENAL ROI, ASYMMETRY DRF, SD TOTAL COUNTS LEFT BACKGROUND ROI, SD TOTAL COUNTS RIGHT BACKGROUND ROI, and SD TOTAL COUNTS RIGHT RENAL ROI were excluded from the multiple linear regression models.

The coefficients and t-values of the variables LEFT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS POORLY VISUALISED were equal in magnitude but of opposite sign for log MAXMINHRP too. The same pattern was found with RIGHT RENAL MARGINS WELL DEFINED and RIGHT POORLY VISUALISED, which also had values of equal magnitude but of opposite sign for the coefficient and t-values for both log MAXMINHAUC and log MAXMINHRP.

A negative beta-coefficient predicted good reproducibility and a positive beta-coefficient predicted decreased reproducibility.

Table 17. Univariate linear regression of the 17 continuous variables and log MAXMINHRP cohort 1.
The variables are listed in ascending order of the p-value of the beta-coefficient.

Variable	Beta-coefficient.	Standard error	t	p > t
LEFT KIDNEY TO BACKGROUND RATIO	-0.358	0.056	-6.40	<0.001
RIGHT KIDNEY TO BACKGROUND RATIO	-0.387	0.079	-4.92	<0.001
GFR	-0.008	0.020	-4.36	<0.001
AGE	-0.004	0.001	-3.00	0.003
LEFT BACKGROUND AREA	-0.061	0.022	-2.74	0.007
TIME VISUALISATION LEFT CALYCES	0.098	0.041	2.39	0.019
LEFT RENAL AREA	-0.011	0.005	-2.30	0.023
TIME VISUALISATION LEFT PELVIS	0.032	0.169	1.90	0.060
TIME VISUALISATION RIGHT CALYCES	0.034	0.022	1.49	0.139
TIME VISUALISATION RIGHT PELVIS	0.014	0.012	1.17	0.245
RIGHT RENAL AREA	-0.006	0.005	-1.17	0.246
RIGHT BACKGROUND AREA	-0.032	0.031	-1.07	0.288
SD TOTAL COUNTS LEFT RENAL ROI	0.001	0.001	-1.06	0.291
ASYMMETRY DRF	0.001	0.002	0.67	0.506
SD TOTAL COUNTS LEFT BACKGROUND ROI	0.001	0.001	-0.46	0.648
SD TOTAL COUNTS RIGHT BACKGROUND ROI	<0.001	0.001	0.39	0.699
SD TOTAL COUNTS RIGHT RENAL ROI	<-0.001	0.001	-0.39	0.699

* The corresponding Table for log MAXMINHAUC cohort 1 is Table 10.

Similarities and differences between the univariate linear regression results for log MAXMINHAUC and log MAXMINHRP – cohort 1:

The categorical variables which had a p-value of the beta coefficient ≤ 0.2 for log MAXMINHAUC and log MAXMINHRP cohort 1 were LEFT RENAL MARGINS WELL DEFINED, RIGHT RENAL MARGINS WELL DEFINED, BOTH RENAL MARGINS WELL DEFINED, LEFT RENAL MARGINS POORLY VISUALISED, RIGHT RENAL MARGINS POORLY VISUALISED, LEFT RENAL MARGINS SMOOTH, RIGHT RENAL MARGINS SMOOTH, BOTH RENAL MARGINS SMOOTH, LEFT RENAL MARGINS IRREGULAR, BOTH RENAL MARGINS IRREGULAR, LEFT NO CORTICAL DEFECTS and RIGHT NO CORTICAL DEFECTS.

The only categorical variable with $p > 0.2$ for log MAXMINHAUC and log MAXMINHRP cohort 1 was RIGHT < 2 CORTICAL DEFECTS.

The variables LEFT < 2 CORTICAL DEFECTS and RIGHT RENAL MARGINS IRREGULAR had p-values ≤ 0.2 for log MAXMINHAUC but > 0.2 for log MAXMINHRP cohort 1.

The continuous variables which had a p-value of the beta-coefficient ≤ 0.2 for log MAXMINHAUC and log MAXMINHRP cohort 1 were LEFT KIDNEY TO BACKGROUND RATIO, RIGHT KIDNEY TO BACKGROUND RATIO, GFR, AGE, LEFT RENAL AREA, LEFT BACKGROUND AREA, TIME VISUALISATION LEFT PELVIS and TIME VISUALISATION LEFT CALYCES.

The variables which had a $p > 0.2$ for log MAXMINHAUC and log MAXMINHRP cohort 1 were RIGHT BACKGROUND AREA, SD TOTAL COUNTS LEFT RENAL ROI, SD TOTAL COUNTS RIGHT RENAL ROI, SD TOTAL COUNTS LEFT BACKGROUND ROI, SD TOTAL COUNTS RIGHT BACKGROUND ROI, TIME VISUALISATION RIGHT PELVIS, and ASYMMETRY DRF.

RIGHT RENAL AREA and TIME VISUALISATION RIGHT CALYCES had a $p \leq 0.2$ for log MAXMINHAUC cohort 1 but for log MAXMINHRP cohort 1 the p-values for these variables were > 0.2 .

Selection of variables for multiple linear regression log MAXMINHRP - cohort 1:

The multiple linear regression combinations were compiled by combining one dependent variable with seven independent variables as follows;

Dependent variable: log MAXMINHRP

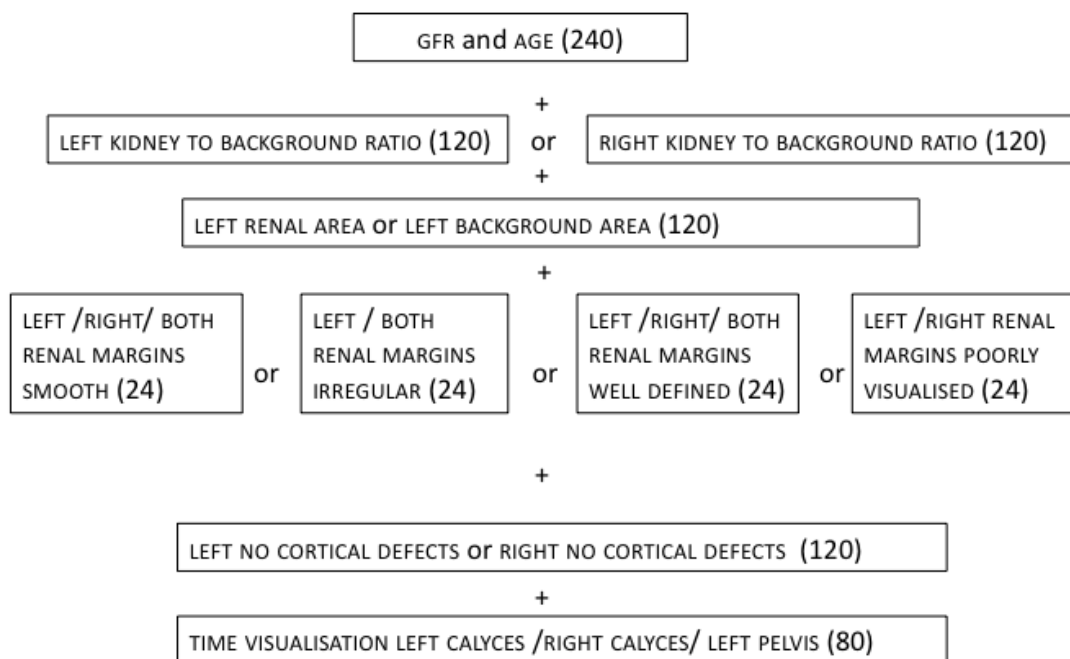
Independent variables

1. AGE
2. GFR
3. LEFT KIDNEY TO BACKGROUND RATIO OR RIGHT KIDNEY TO BACKGROUND RATIO,
4. LEFT RENAL AREA OR LEFT BACKGROUND AREA
5. LEFT NO CORTICAL DEFECTS OR RIGHT NO CORTICAL DEFECTS
6. One variable describing the renal margins; for instance, RIGHT RENAL MARGIN SMOOTH
7. TIME VISUALISATION LEFT CALYCES OR TIME VISUALISATION RIGHT CALYCES OR TIME VISUALISATION LEFT PELVIS.

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.

The combination of the variables is depicted in Figure 14. An example of a combination for log MAXMINHRP is: AGE and GFR and LEFT KIDNEY TO BACKGROUND RATIO and LEFT RENAL AREA and LEFT NO CORTICAL DEFECTS and RIGHT RENAL MARGIN SMOOTH and TIME VISUALISATION LEFT PELVIS. A total of 240 different combinations were analysed with multiple linear regression, step-down multiple linear regression and step-up multiple linear regression. The 240 different combinations tested for log MAXMINHRP are listed in the appendix in Table 44.

Figure 14. A schematic display to show how the 240 combinations used in multiple linear regression for log MAXMINHRP were compiled.



Multiple linear regression results - log MAXMINHRP - cohort 1:

The different methods of multiple linear regression, straight, step-down and step-up, gave similar results for cohort 1 for each combination.

The beta-coefficients and t-values of the variables RIGHT RENAL MARGINS WELL DEFINED and RIGHT RENAL MARGINS POORLY VISUALISED, were equal in magnitude but of opposite sign. The same pattern was found with LEFT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS POORLY VISUALISED so only the results for the combinations with the variables RIGHT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS WELL DEFINED are presented.

The combination with the highest R^2 for log MAXMINHRP – cohort 1:

For the dependent variable log MAXMINHRP the R^2 -values for the 240 different combinations ranged from 0.3284 to 0.4500. In the log MAXMINHRP combination with the highest R^2 -value, 0.4500, the independent variables were AGE, GFR, LEFT KIDNEY TO BACKGROUND RATIO, LEFT BACKGROUND AREA, RIGHT RENAL MARGINS WELL DEFINED, LEFT NO CORTICAL DEFECTS and TIME VISUALISATION RIGHT CALYCES. The beta-coefficients, robust standard errors and p-values of the beta-coefficients of the variables in this combination are given in Table 18.

This combination was similar to the one which had the highest R^2 -value for log MAXMINHAUC. The only difference was the inclusion of LEFT BACKGROUND AREA instead of LEFT RENAL AREA. The results of the individual variables was also remarkably similar except for GFR which had a p-value of 0.060 in the log MAXMINHRP combination and 0.004 in the log MAXMINHAUC combination.

Table 18. Multiple linear regression for the combination with the highest R^2 for log MAXMINHRP cohort 1.

Variable	Beta-coefficient	Robust Standard Error	p-value
LEFT KIDNEY TO BACKGROUND RATIO	-0.323	0.058	<0.001
RIGHT RENAL MARGINS WELL DEFINED	-0.523	0.113	<0.001
AGE	-0.003	0.001	0.010
TIME VISUALISATION RIGHT CALYCES	0.039	0.016	0.018
GFR	-0.003	0.002	0.060
LEFT BACKGROUND AREA	0.028	0.023	0.218
LEFT NO CORTICAL DEFECTS	0.035	0.112	0.757

*The corresponding Table for log MAXMINHAUC cohort 1 is Table 11.

Results of the individual variables in the different combinations for log MAXMINHRP – cohort 1:

The results of all combinations analysed against the dependent variable log MAXMINHRP are summarised in Table 19. LEFT KIDNEY TO BACKGROUND (120 combinations), RIGHT KIDNEY TO BACKGROUND RATIO (120) and BOTH RENAL MARGINS WELL DEFINED (24) were significant in all combinations in which these variables were included for analyses for MAXMINHRP.

GFR was significant in the vast majority of the combinations, 227 out of 240 combinations.

The 13 combinations in which GFR was not significant contained the following variables in addition to AGE and GFR:

- LEFT KIDNEY TO BACKGROUND RATIO (11) and RIGHT KIDNEY TO BACKGROUND RATIO (2)
- LEFT RENAL AREA (8) and LEFT BACKGROUND AREA (5)
- TIME VISUALISATION RIGHT CALYCES (13)

- RIGHT NO CORTICAL DEFECTS (8) and LEFT NO CORTICAL DEFECTS (5)
- RIGHT RENAL MARGINS WELL DEFINED (4), RIGHT RENAL MARGINS POORLY VISUALISED (4), RIGHT RENAL MARGINS SMOOTH (3), LEFT RENAL MARGINS WELL DEFINED (1) and LEFT RENAL MARGINS POORLY VISUALISED (1)

LEFT RENAL MARGINS WELL DEFINED, RIGHT RENAL MARGINS WELL DEFINED, TIME VISUALISATION LEFT CALYCES, and TIME VISUALISATION RIGHT CALYCES were all significant in 50% of the combinations in which they were included. AGE was significant in less than half, 96 out of 240 combinations. LEFT RENAL MARGINS SMOOTH, RIGHT RENAL MARGINS SMOOTH and TIME VISUALISATION LEFT PELVIS were only significant in a small number of the combinations in which they were analysed, four out of 24, one out of 24 and 24 out of 80 respectively.

The variables which were not significant in any of the log MAXMINHRP combinations were LEFT RENAL AREA (120), LEFT BACKGROUND AREA (120), LEFT NO CORTICAL DEFECTS (120), RIGHT NO CORTICAL DEFECTS (120), BOTH RENAL MARGINS SMOOTH (24), LEFT RENAL MARGINS IRREGULAR (24) and BOTH RENAL MARGINS IRREGULAR (24).

Table 19. Multiple linear regression results for the 240 combinations for log MAXMINHRP cohort 1.

The number of combinations in which each variable was included is given in brackets. The range of p-values of the beta-coefficient and the number of times a variable has a p-value ≤ 0.05 are also listed.

Variable (n)	p range	p-value ≤ 0.05
AGE (240)	0.008 - 0.358	96
GFR (240)	0.005 - 0.075	227
LEFT KIDNEY TO BACKGROUND RATIO (120)	<0.001 - 0.005	120
RIGHT KIDNEY TO BACKGROUND RATIO (120)	<0.000 - 0.033	120
LEFT RENAL AREA (120)	0.238 - 0.987	0
LEFT BACKGROUND AREA (120)	0.218 - 0.998	0
LEFT NO CORTICAL DEFECTS (120)	0.123 - 0.992	0
RIGHT NO CORTICAL DEFECTS (120)	0.079 - 0.903	0
LEFT RENAL MARGINS SMOOTH (24)	0.032 - 0.804	4
RIGHT RENAL MARGINS SMOOTH (24)	0.049 - 0.488	1
BOTH RENAL MARGINS SMOOTH (24)	0.224 - 0.920	0
LEFT RENAL MARGINS IRREGULAR (24)	0.088 - 0.996	0
BOTH RENAL MARGINS IRREGULAR (24)	0.144 - 0.544	0
LEFT RENAL MARGINS WELL DEFINED (24)	<0.001 - 0.284	12
RIGHT RENAL MARGINS WELL DEFINED (24)	<0.001 - 0.138	12
BOTH RENAL MARGINS WELL DEFINED (24)	<0.001 - 0.008	24
TIME VISUALISATION LEFT CALYCES (80)	<0.001 - 0.639	40
TIME VISUALISATION RIGHT CALYCES (80)	0.012 - 0.750	40
TIME VISUALISATION LEFT PELVIS (80)	0.013 - 0.839	24

*The corresponding Table for log MAXMINHAUC cohort 1 is Table 12.

Testing the assumptions of the multiple linear regression models – log MAXMINHRP - cohort 1:

Residual values log MAXMINHRP – cohort 1:

The residual values, the difference between the predicted and observed value, for each patient, in the combination with the highest R^2 -value for log MAXMINHRP cohort 1 were calculated and plotted on a normal probability plot (Figure 15). The residual values did not depart significantly from the expected normal distribution.

The residual values were also plotted against the continuous variables AGE, GFR, LEFT KIDNEY TO BACKGROUND RATIO, LEFT BACKGROUND AREA and TIME VISUALISATION RIGHT CALYCES, (Figures 16 through 20). None of the patients had high residual values.

Figure 15. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHRP cohort 1, plotted on a normal probability plot.

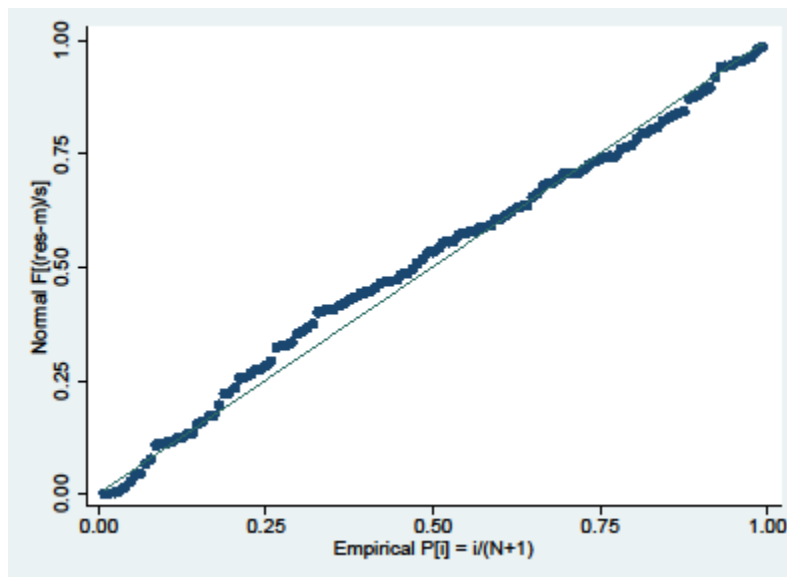


Figure 16. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHRP cohort 1, plotted against AGE.

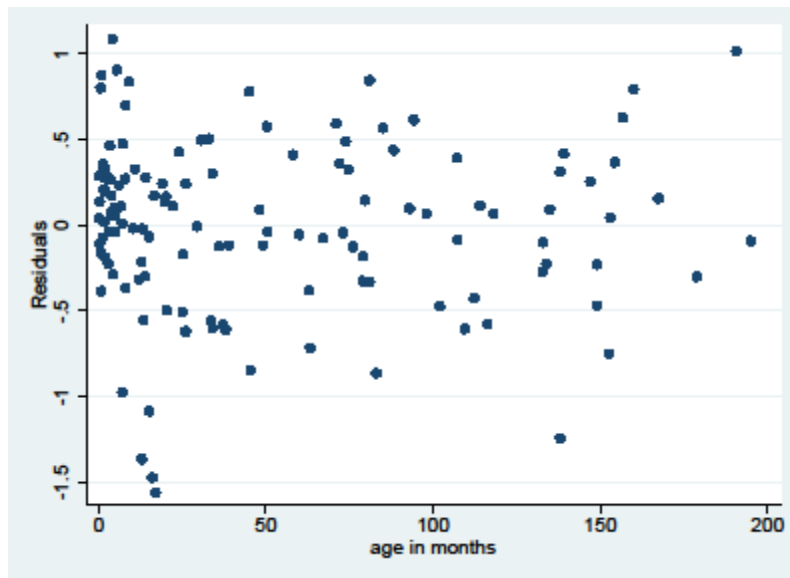


Figure 17. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHRP cohort 1, plotted against GFR.

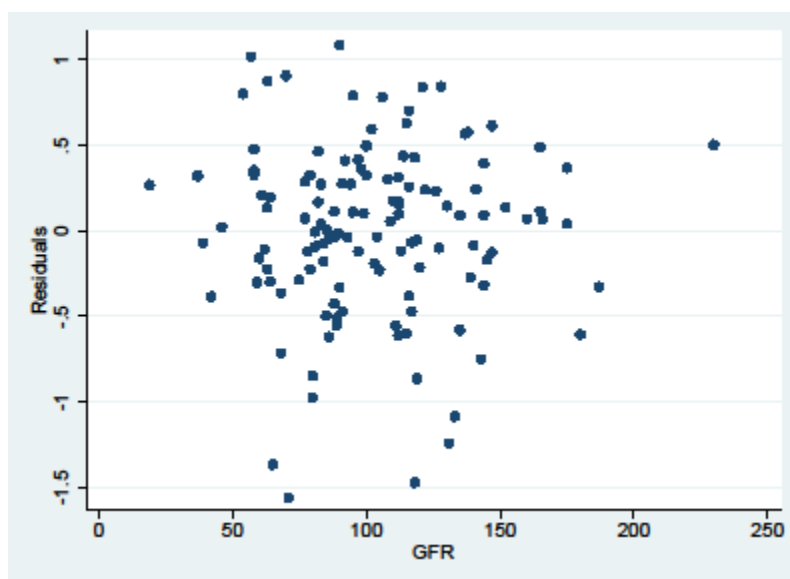
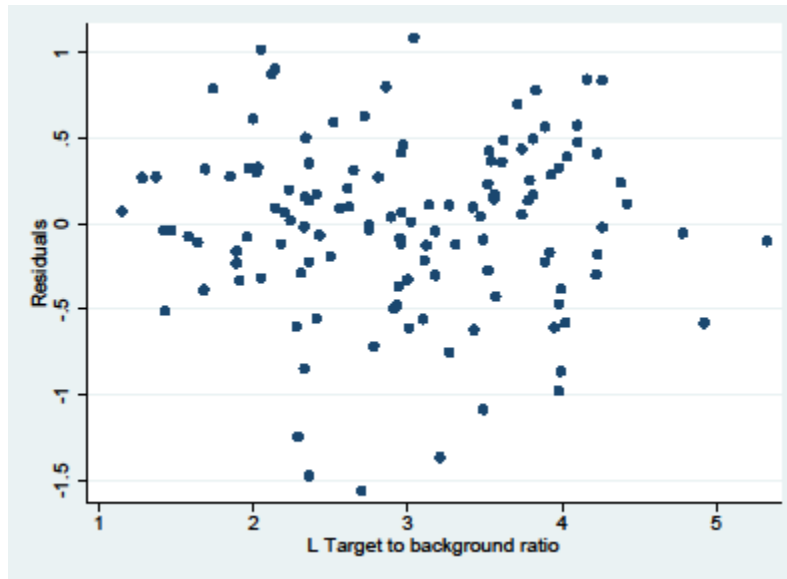


Figure 18. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHRP cohort 1, plotted against LEFT KIDNEY TO BACKGROUND RATIO.



*L Target to background ratio = LEFT KIDNEY TO BACKGROUND RATIO.

Figure 19. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHRP cohort 1, plotted against LEFT BACKGROUND AREA.

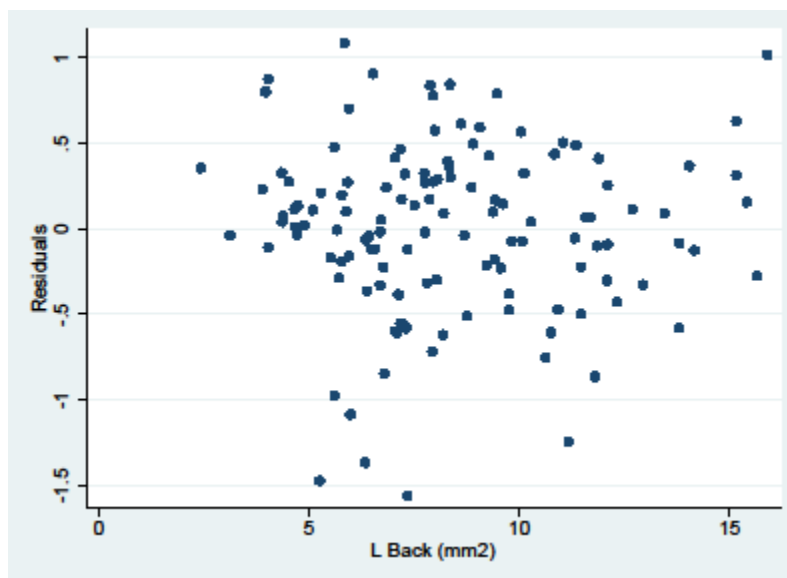
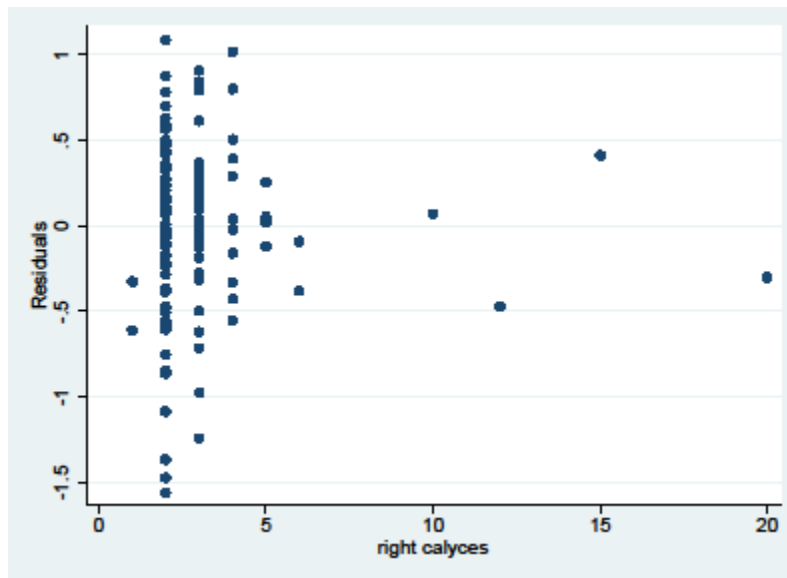


Figure 20. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHRP cohort 1, plotted against TIME VISUALISATION RIGHT CALYCES.



Homoscedasticity – log MAXMINHRP - cohort 1:

Cameron and Trivedi's test proves that there was no heteroscedasticity between the different variables included in the analysis, Table 20.

Table 20. Cameron and Trivedi's decomposition of IM – test for the combination with the highest R^2 for log MAXMINHRP cohort 1.

Source	χ^2	df	p
Heteroscedasticity	20.03	33	0.9631
Skewness	8.88	7	0.2611
Kurtosis	2.41	1	0.1204
Total	31.32	41	0.8625

* The corresponding Table for log MAXMINHAUC cohort 1 is Table. 13.

Multicollinearity - log MAXMINHRP – cohort 1:

The VIF was calculated for each of the independent variables used in the log MAXMINHRP cohort 1 combination with the highest R^2 -value. The results are presented in Table 21. For all the variables the VIF values were less than |5|. This indicates there was no multicollinearity between these variables.

Table 21. VIF for the combination with the highest R^2 for log MAXMINHRP cohort 1.

Variable	VIF	1/VIF
AGE	2.83	0.354
GFR	1.50	0.655
LEFT KIDNEY TO BACKGROUND RATIO	1.32	0.756
LEFT BACKGROUND AREA	2.92	0.342
TIME VISUALISATION RIGHT CALYCES	1.18	0.844
LEFT NO CORTICAL DEFECTS	1.25	0.798
RIGHT RENAL MARGINS WELL DEFINED	1.18	0.850
Mean VIF	1.74	

* The corresponding Table for log MAXMINHAUC cohort 1 is Table 14.

The collinearity between the different variables included in the analysis were tested further, Table 22. There was no significant collinearity (> 0.800) between the variables. Of note the collinearity between AGE and GFR was only - 0.030.

Table 22. Correlation matrix of collinearity coefficients of the regression model for the combination with the highest R^2 for log MAXMINHRP cohort 1.

Variable	AGE	GFR	LEFT KIDNEY TO BACKGROUND RATIO	LEFT BACKGROUND AREA	TIME VISUALIS- TION RIGHT CALYCES	LEFT NO CORTICAL DEFECTS	RIGHT RENAL MARGINS WELL DEFINED	-cons
AGE	1.000							
GFR	-0.030	1.000						
LEFT KIDNEY TO BACKGROUND RATIO	-0.136	-0.233	1.000					
LEFT BACKGROUND AREA	-0.584	-0.379	-0.055	1.000				
TIME VISUALISATION RIGHT CALYCES	-0.308	0.254	-0.059	-0.053	1.000			
LEFT NO CORTICAL DEFECTS	-0.153	-0.025	-0.492	0.069	0.155	1.000		
RIGHT RENAL MARGINS WELL DEFINED	-0.127	-0.078	0.343	-0.087	0.117	-0.277	1.000	
-CONS	0.519	-0.265	-0.489	-0.361	-0.356	0.164	-0.419	1.000

*The corresponding Table for log MAXMINHAUC cohort 1 is Table 15.

Conclusion regression diagnostics log MAXMINHRP – cohort 1:

The multiple linear regression models for log MAXMINHRP met the necessary statistical assumptions.

Summary of the different combinations analysed with multiple linear regression log MAXMINHRP - cohort 1:

For the log MAXMINHRP combination with the highest R^2 -value in cohort 1 four individual variables were highly significant with p-values of < 0.001 . They were LEFT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL MARGINS WELL DEFINED, AGE and TIME VISUALISATION RIGHT CALYCES. GFR had borderline significance with a p-value of 0.06. The other variables, LEFT BACKGROUND AREA and LEFT NO CORTICAL DEFECTS, had non-significant p-values of 0.218 and 0.757.

The individual variables LEFT KIDNEY TO BACKGROUND RATIO, RIGHT KIDNEY TO BACKGROUND RATIO and BOTH RENAL MARGINS WELL DEFINED were significant in every combination in which the variable was present. GFR was significant in the vast majority of the combinations in which it was included. Conversely the individual variables LEFT RENAL AREA, LEFT BACKGROUND AREA, LEFT NO CORTICAL DEFECTS, RIGHT NO CORTICAL DEFECTS, BOTH RENAL MARGINS SMOOTH, LEFT RENAL MARGINS IRREGULAR and BOTH RENAL MARGINS IRREGULAR were not significant in any of the combinations in which these variables were included.

Final conclusion – cohort 1:

In cohort 1 univariate linear regression identified 24 variables which may have had an impact on the reproducibility of log MAXMINHAUC and 21 variables which possibly impacted on log MAXMINHRP.

A total of 12 categorical variables had univariate linear regression p-values ≤ 0.2 for both log MAXMINHAUC and log MAXMINHRP. They were RIGHT RENAL MARGINS WELL DEFINED, LEFT RENAL MARGINS WELL DEFINED, BOTH RENAL MARGINS WELL DEFINED, LEFT RENAL MARGINS POORLY VISUALISED, RIGHT RENAL MARGINS POORLY VISUALISED, LEFT RENAL MARGINS SMOOTH, RIGHT RENAL MARGINS SMOOTH, BOTH RENAL MARGINS SMOOTH, LEFT RENAL MARGINS IRREGULAR, BOTH RENAL MARGINS IRREGULAR, LEFT NO CORTICAL DEFECTS and RIGHT NO CORTICAL DEFECTS. There was one categorical variable, RIGHT < 2 CORTICAL

DEFECTS, which had a p-value > 0.2 for both log MAXMINHAUC and log MAXMINHRP. LEFT < 2 CORTICAL DEFECTS and RIGHT RENAL MARGINS IRREGULAR had p-values > 0.2 for log MAXMINHAUC only.

There were nine continuous variables which had univariate linear regression p-values ≤ 0.2 for both log MAXMINHAUC and log MAXMINHRP. They were LEFT KIDNEY TO BACKGROUND RATIO, RIGHT KIDNEY TO BACKGROUND RATIO, GFR, AGE, LEFT BACKGROUND AREA, TIME VISUALISATION LEFT CALYCES, LEFT RENAL AREA, TIME VISUALISATION LEFT PELVIS, and TIME VISUALISATION RIGHT CALYCES. The variables TIME VISUALISATION RIGHT PELVIS, RIGHT BACKGROUND AREA, SD TOTAL COUNTS LEFT RENAL ROI, ASYMMETRY DRF, SD TOTAL COUNTS LEFT BACKGROUND ROI, SD TOTAL COUNTS RIGHT BACKGROUND ROI, and SD TOTAL COUNTS RIGHT RENAL ROI had p-values > 0.2 for both log MAXMINHAUC and log MAXMINHRP. RIGHT RENAL AREA had a p-value ≤ 0.2 for log MAXMINHAUC only.

Multiple linear regression models were compiled using the variables identified with univariate linear regression. The results of the multiple linear regression analyses of cohort 1 show that the variables LEFT KIDNEY TO BACKGROUND RATIO and BOTH RENAL MARGINS WELL DEFINED predict good reproducibility for both log MAXMINHAUC and log MAXMINHRP and combinations which included the LEFT KIDNEY TO BACKGROUND RATIO had a better fit than those which contained the variable RIGHT KIDNEY TO BACKGROUND RATIO. However RIGHT KIDNEY TO BACKGROUND RATIO was significant in all the combinations for log MAXMINHRP and in the vast majority of log MAXMINHAUC combinations. Similarly, GFR was significant all the combinations for log MAXMINHAUC and in the vast majority of log MAXMINHRP combinations. The variables LEFT RENAL AREA, LEFT BACKGROUND AREA, RIGHT NO CORTICAL DEFECTS, BOTH RENAL MARGINS SMOOTH, LEFT RENAL MARGINS IRREGULAR, and BOTH RENAL MARGINS IRREGULAR did not have a significant relationship with reproducibility in any of the combinations in which these variables were included for either log MAXMINHAUC or log MAXMINHRP.

Cohort 2:

Cohort 2 - Patients:

The patients for cohort 2 were selected from 654 renograms performed in our department between 25 July 2012 and 1 September 2015. The patients were selected using the same criteria used in cohort 1 and the image characteristics identified as in cohort 1. The following renograms were excluded from analysis: no GFR (142), solitary kidneys (81), transplant renograms (34), fused or ectopic kidneys (28), patient used in cohort 1 (12), could not visualise the kidneys well enough to define parameters (9), studies lost from electronic archive containing the raw data of all renograms (7), poor technical quality (6), creatinine level below the limit of accurate detection, $< 9 \mu\text{mol/l}$, (2) and a renogram on a patient already included (44). Therefore 289 studies were available for inclusion.

The population in cohort 1 was a stratified sample to prevent the population from being dominated by patients with normal renograms. To ensure that the population in cohort 2 was comparable to the population of cohort 1, 62 patients with a DRF value between 30 and 70% were excluded. A total of 227 patients were included for further analysis in 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 months, 21 (9%) were between 2 and six months, 22 (10%) were between six and 12 months and 13 (6%) were between 12 and 18 months.

The GFR values were between 12 and 358 ml/min/1.73m². Only 19 patients (8%) had a GFR $< 60 \text{ ml/min/1.73m}^2$, 20 patients (9%) had a GFR between 60 and 80 ml/min/1.73m². Twenty-three of the patients with GFR values $< 80 \text{ ml/min/1.73m}^2$ were older than 12 months.

Thirty-six (16%) of the patients had mGFRs, the remaining 191 patients eGFRs.

MAXMINHAUC for the left kidney varied from one to 35 and MAXMINHRP from zero to 34. The majority of the renograms, 159 renograms (70%) for the HAUC method and 153 (67%) for the HRP method, had a MAXMINHAUC and MAXMINHRP difference of five or less, Table 23.

The cohort 2 LEFT KIDNEY TO BACKGROUND RATIO ranged from 1.02 to 8.45 and the RIGHT KIDNEY TO BACKGROUND RATIO ranged from 0.93 to 6.45.

Table 23. The patient demographics of the 127 patients included in cohort 1 and the 227 patients included in cohort 2.

Variable	Median		25% Quartile		75% Quartile		p-value U-test*
	Cohort 1	Cohort 2	Cohort 1	Cohort 2	Cohort 1	Cohort 2	
AGE (months)	31	49	7	11	84	95	0.08
GFR (ml/min/1.73m ²)	99	121	81	93	122	140	0.00
DRF HAUC (%)	53	52	43	48	67	58	0.54
DRF HRP (%)	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
LEFT KIDNEY TO BACKGROUND RATIO	2.96	3.57	2.32	2.62	3.74	4.35	0.30
RIGHT KIDNEY TO BACKGROUND RATIO	2.51	2.78	1.90	2.15	3.09	3.27	0.09

*Mann-Whitney U-test (U-test)

Comparison of the two study populations:

There was no difference in the values obtained in cohort 1 and 2 for AGE, mean DRF HAUC, mean DRF HRP, MAXMINHRP, LEFT KIDNEY TO BACKGROUND RATIO and RIGHT KIDNEY TO BACKGROUND RATIO but GFR and MAXMINHAUC differed.

MAXMINHAUC was 5 or less in 78% of the children in cohort 1 and 70% of those in cohort 2.

Transformation of the dependent variables cohort 2:

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. The patient was 118 months old, had an eGFR of 173 ml/min/1.73m² and DRF of the left kidney of 52%. Therefore 226 patients were analysed for log MAXMINHRP.

Categorical variables - cohort 2:

Although the categorical variables LEFT ISLANDS OF FUNCTIONING TISSUE, RIGHT ISLANDS OF FUNCTIONING TISSUE, LEFT ≥ 2 CORTICAL DEFECTS, RIGHT ≥ 2 CORTICAL DEFECTS and BOTH RENAL MARGINS POORLY VISUALISED were not used in the analysis of cohort 1 because the numbers of patients with these variables were too small, we did record the data in cohort 2. The number of patients that had these variables was once again too small for analysis in cohort 2. The number of patients for which these variables were recorded was LEFT ISLANDS OF FUNCTIONING TISSUE (3), RIGHT ISLANDS OF FUNCTIONING TISSUE (3), LEFT ≥ 2 CORTICAL DEFECTS (3), RIGHT ≥ 2 CORTICAL DEFECTS (11) and BOTH RENAL MARGINS POORLY VISUALISED (9). Therefore, these variables were again excluded from further analysis. The AGE, GFR, MAXMINHAUC and MAXMINHRP of the patients with one or more of these variables are given in Table 24.

Table 24. The AGE, GFR, MAXMINHAUC and MAXMINHRP of the patients that had one or more of the variables excluded from further analysis cohort 2.

PT NUMBER	AGE (months)	GFR (ml/min/1.73m ²)	MAXMINHAUC	MAXMINHRP	LEFT KIDNEY TO BACKGROUND RATIO	RIGHT KIDNEY TO BACKGROUND RATIO
LEFT ISLANDS OF FUNCTIONING TISSUE						
146	6	107	2	6	1.30	3.03
RIGHT ISLANDS OF FUNCTIONING TISSUE						
47	59	102	3	4	4.06	1.37
220	156	118	2	2	1.04	6.45
LEFT ≥ 2 CORTICAL DEFECTS						
28	81	107	5	4	3.61	3.47
70	159	135	3	2	3.08	2.80
RIGHT ≥ 2 CORTICAL DEFECTS						
14	77	108	2	3	6.83	2.96
20	86	64	1	3	2.22	2.31
108	132	67	2	4	2.40	2.15
132	32	51	5	5	1.53	1.54
187	7	85	5	5	3.44	1.78
188	4	89	6	6	3.05	1.45
213	133	46	7	5	3.17	1.68
BOTH RENAL MARGINS POORLY VISUALISED						
86	48	24	9	11	1.43	1.01
88	89	183	6	6	2.50	4.49
124	17	53	15	15	2.55	1.73

148	11	103	6	5	2.39	1.90
207	16	26	16	16	1.63	1.23
217	2	78	15	10	1.52	2.14
BOTH ≥ 2 CORTICAL DEFECTS						
119	118	79	2	3	2.62	2.64
RIGHT ≥ 2 CORTICAL DEFECTS and BOTH RENAL MARGINS POORLY VISUALISED						
16	100	137	2	2	1.83	3.56
219	6	62	4	8	2.24	1.43
LEFT ISLANDS OF FUNCTIONING TISSUE and RIGHT ≥ 2 CORTICAL DEFECTS						
37	76	55	7	7	4.12	3.16
BOTH KIDNEYS ISLANDS OF FUNCTIONING TISSUE and BOTH RENAL MARGINS POORLY VISUALISED						
35	65	12	24	19	1.37	1.22

*The corresponding Table for cohort 1 is Table 8.

The univariate linear regression analysis done in cohort 1 was repeated in cohort 2 with the same 32 variables.

Results for log MAXMINHAUC – cohort 2

Univariate linear regression results for categorical variables and log MAXMINHAUC- cohort 2:

The cohort 2 univariate linear regression results of the 15 categorical variables are listed in ascending order of the p-value of the beta-coefficient in Table 25. The variables with p-values < 0.001 were RIGHT RENAL MARGINS WELL DEFINED, RIGHT RENAL MARGINS POORLY VISUALISED and BOTH RENAL MARGINS WELL DEFINED. Variables with higher values for p, but still < 0.2 were BOTH RENAL MARGINS IRREGULAR, RIGHT RENAL MARGINS SMOOTH, RIGHT RENAL MARGINS IRREGULAR, LEFT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS POORLY VISUALISED. The remaining variables LEFT RENAL MARGINS SMOOTH, LEFT RENAL MARGINS IRREGULAR, LEFT NO CORTICAL DEFECTS, LEFT < 2 CORTICAL DEFECTS, RIGHT < 2 CORTICAL DEFECTS, and RIGHT NO CORTICAL DEFECTS had p-values > 0.2.

The beta-coefficients of eight categorical variables had $p \leq 0.2$ with univariate linear regression for log MAXMINHAUC in cohort 1 and 2. These variables were therefore eligible for inclusion in multiple linear regression in both cohorts. They were RIGHT RENAL MARGINS WELL DEFINED, RIGHT RENAL MARGINS POORLY VISUALISED, BOTH RENAL MARGINS WELL DEFINED, BOTH RENAL MARGINS IRREGULAR, RIGHT RENAL MARGINS SMOOTH, RIGHT RENAL MARGINS IRREGULAR, LEFT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS POORLY VISUALISED.

One categorical variable, RIGHT < 2 CORTICAL DEFECTS, was not eligible of inclusion in the multiple linear regression model in cohort 1 and 2.

There were no categorical variables with $p > 0.2$ in cohort 1 and ≤ 0.2 in cohort 2.

Six categorical variables had a p-value ≤ 0.2 in cohort 1 and > 0.2 in cohort 2. They were LEFT RENAL MARGINS SMOOTH, LEFT RENAL MARGINS IRREGULAR, LEFT NO CORTICAL DEFECTS, LEFT < 2 CORTICAL

DEFECTS, BOTH RENAL MARGINS SMOOTH and RIGHT NO CORTICAL DEFECTS. They are listed in bold in Table 23. These variables would not have been included in the multiple linear regression model if the model was determined using cohort 2. However, the purpose of the cohort 2 was to validate the results of the model determined in cohort 1. Therefore, these variables were still included in the cohort 2 analyses.

Comparison of these six variables showed the following:

1. For the beta-coefficient of the variable LEFT RENAL MARGINS SMOOTH, p was < 0.001 in cohort 1. In cohort 2 it was 0.216. In cohort 1, 94 (74%) patients had LEFT RENAL MARGINS SMOOTH and in cohort 2 the number was 191 (84%). The difference between the two populations was highly significant ($p = 0.021$, Pearson's χ^2).
2. In cohort 1 the variable LEFT RENAL MARGINS IRREGULAR had a p -value of < 0.001 . In cohort 2, the p -value was 0.216. For cohort 1, 30 (24%) patients had LEFT RENAL MARGINS IRREGULAR and for cohort 2, the corresponding number was 36 (16%). This difference was calculated as not significant ($p = 0.072$, Pearson's χ^2).
3. In cohort 1 the variable LEFT NO CORTICAL DEFECTS had p -value of < 0.001 . In cohort 2, the p -value was 0.221. For cohort 1, 48 (38%) patients had cortical defects on left and for cohort 2, the corresponding number was 49 (22%). This difference was calculated as highly significant ($p < 0.001$, Pearson's χ^2).
4. In cohort 1 the variable LEFT < 2 CORTICAL DEFECTS had a p -value of 0.014. In cohort 2 it was 0.224. For cohort 1, 37 (29%) patients had LEFT < 2 CORTICAL DEFECTS and for cohort 2, the corresponding number was 42 (19%). The difference in the populations was calculated as highly significant ($p = 0.021$, Pearson's χ^2).
5. BOTH RENAL MARGINS SMOOTH had a p -value of 0.007 in cohort 1. It changed to 0.417 in cohort 2. In cohort 1, 71 (56%) and for cohort 2, 168 (74%) patients had BOTH RENAL MARGINS SMOOTH. The population difference was calculated as highly significant ($p < 0.001$, Pearson's χ^2).
6. RIGHT NO CORTICAL DEFECTS had a p of 0.032 in cohort 1 and 0.923 in cohort 2. For cohort 1, 34 (27%) and for cohort 2, 55 (24%) patients had cortical defects. This difference was not significant ($p = 0.597$, Pearson's χ^2).

In cohort 2, 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, LEFT RENAL MARGINS SMOOTH and LEFT RENAL MARGINS IRREGULAR, RIGHT RENAL MARGINS SMOOTH and RIGHT RENAL MARGINS IRREGULAR were equal in magnitude but of opposite sign.

A negative beta-coefficient predicted good reproducibility and a positive beta-coefficient predicted decreased reproducibility.

Table 25. Univariate linear regression of the 15 categorical variables and log MAXMINHAUC - cohort 2 and cohort 1. Listed in ascending order of the p-value of the beta-coefficient of cohort 2. The variables for which p changed from > 0.2 to ≤ 0.2 or from ≤ 0.2 to > 0.2 are in bold.

	Cohort 2				Cohort 1			
Variable	Beta-coefficient	Standard error	t	p > t	Beta-coefficient	Standard error	t	p > t
RIGHT RENAL MARGINS WELL DEFINED	-0.567	0.126	-4.49	<0.001	-0.569	0.164	-3.47	0.001
RIGHT RENAL MARGINS POORLY VISUALISED	0.567	0.126	4.49	<0.001	0.569	0.164	3.47	0.001
BOTH RENAL MARGINS WELL DEFINED	-0.403	0.113	-3.56	<0.001	-0.632	0.126	-5.00	<0.001
BOTH RENAL MARGINS IRREGULAR	0.502	0.168	2.98	0.003	0.706	0.197	3.58	<0.001
RIGHT RENAL MARGINS SMOOTH	-0.243	0.123	-1.97	0.050	-0.278	0.159	-1.75	0.083
RIGHT RENAL MARGINS IRREGULAR	0.243	0.123	1.97	0.050	0.226	0.166	1.36	0.175
LEFT RENAL MARGINS WELL DEFINED	-0.242	0.172	-1.41	0.160	-0.579	0.148	-3.92	<0.001
LEFT RENAL MARGINS POORLY VISUALISED	0.242	0.172	1.41	0.160	0.579	0.148	3.92	<0.001
LEFT RENAL MARGINS SMOOTH	-0.181	0.146	-1.24	0.216	-0.519	0.129	-4.03	<0.001
LEFT RENAL MARGINS IRREGULAR	0.181	0.146	1.24	0.216	0.495	0.131	3.76	<0.001
LEFT NO CORTICAL DEFECTS	-0.135	0.110	-1.23	0.221	-0.533	0.123	-4.35	<0.001
LEFT < 2 CORTICAL DEFECTS	0.138	0.113	1.22	0.224	0.305	0.122	2.51	0.014
BOTH RENAL MARGINS SMOOTH	-0.092	0.111	-0.81	0.417	-0.351	0.128	-2.75	0.007
RIGHT < 2 CORTICAL DEFECTS	0.072	0.109	0.66	0.509	0.122	0.152	0.81	0.422
RIGHT NO CORTICAL DEFECTS	0.010	0.104	-0.10	0.923	-0.340	0.157	-2.17	0.032

* The corresponding Table for cohort 1 is Table 9.

Univariate linear regression results for continuous variables and log MAXMINHAUC - cohort 2:

The cohort 2 univariate linear regression results of the 17 continuous variables are presented in Table 26. The variables are listed in ascending order for the p-value of the beta-coefficient of the cohort 2 results. The variables with p-values of the beta-coefficient < 0.001 were AGE, LEFT KIDNEY TO BACKGROUND RATIO, RIGHT KIDNEY TO BACKGROUND RATIO, RIGHT BACKGROUND AREA, RIGHT RENAL AREA, LEFT BACKGROUND AREA, LEFT RENAL AREA, and TIME VISUALISATION RIGHT CALYCES. Variables with higher values for p, but still < 0.2 were GFR, SD OF TOTAL COUNTS LEFT RENAL ROI and TIME VISUALISATION RIGHT PELVIS. The variables ASYMMETRY DRF, SD OF TOTAL COUNTS LEFT BACKGROUND ROI, SD TOTAL COUNTS RIGHT RENAL ROI, TIME VISUALISATION LEFT PELVIS, SD TOTAL COUNTS RIGHT BACKGROUND ROI, and TIME VISUALISATION LEFT CALYCES all had $p > 0.2$.

There were eight continuous variables which had a p-value of the beta-coefficient of ≤ 0.2 for log MAXMINHAUC in cohort 1 and 2. These variables were therefore eligible for inclusion in multiple linear regression in both cohorts. They were AGE, LEFT KIDNEY TO BACKGROUND RATIO, RIGHT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL AREA, LEFT BACKGROUND AREA, LEFT RENAL AREA, TIME VISUALISATION RIGHT CALYCES and GFR.

Four continuous variables had a p-value > 0.2 for log MAXMINHAUC in cohort 1 and 2. They were ASYMMETRY DRF, SD OF TOTAL COUNTS LEFT BACKGROUND ROI, SD OF TOTAL COUNTS RIGHT RENAL ROI and SD OF TOTAL COUNTS RIGHT BACKGROUND ROI. They were not eligible for inclusion in the multiple linear regression model in cohort 1 and 2.

There were three continuous variables for log MAXMINHAUC with p-values > 0.2 in cohort 1 which now had p-values ≤ 0.2 in cohort 2.

1. The p-value of SD TOTAL COUNTS LEFT RENAL ROI was 0.248 in cohort 1 and 0.129 in cohort 2.
2. There was no difference in the two populations for this variable ($p = 0.889$, U-test).

2. TIME VISUALISATION RIGHT PELVIS had a p-value of 0.298 in cohort 1 and 0.198 in cohort 2. There was no difference in the two populations ($p = 0.881$, U-test).
3. RIGHT BACKGROUND AREA had a p-value of 0.202 in cohort 1 and < 0.001 in cohort 2. There was a significant difference in the two populations for this variable ($p < 0.001$, U-test).

These variables would have been included in the multiple linear regression model if the model was determined using cohort 2. However, the purpose of the cohort 2 was to validate the results of the model determined in cohort 1. Therefore, these variables were still excluded in the cohort 2 analyses.

There were two continuous variables for log MAXMINHAUC with p-values ≤ 0.2 in cohort 1 which now had p-values > 0.2 in cohort 2.

1. In cohort 1 TIME VISUALISATION LEFT PELVIS had a p-value of 0.037. The p-value was 0.455 in cohort 2. There was no difference in the two populations for this variable ($p = 0.090$, U-test).
2. The p-value of TIME VISUALISATION LEFT CALYCES was 0.070 in cohort 1 and 0.909 in cohort 2. There was no difference in the two populations for this variable ($p = 0.499$, U-test).

These variables would not have been included in the multiple linear regression model if the model was determined using cohort 2. However, the purpose of cohort 2 was to validate the results of the model determined in cohort 1. Therefore, these variables were still included in the cohort 2 analyses.

Table 26. Univariate linear regression of the 17 continuous variables and log MAXMINHAUC - cohort 2 and cohort 1. Listed in ascending order of the p-value of the beta-coefficient of cohort 2. The variables for which p changed from > 0.2 to ≤ 0.2 or from ≤ 0.2 to > 0.2 are in bold.

	Cohort 2				Cohort 1			
Variable	Beta-coefficient	Standard error	t	p > t	Beta-coefficient	Standard error	t	p > t
AGE	-0.004	0.001	-4.71	<0.001	-0.005	0.001	-3.57	0.001
LEFT KIDNEY TO BACKGROUND RATIO	-0.170	0.037	-4.64	<0.001	-0.416	0.060	-6.91	<0.001
RIGHT KIDNEY TO BACKGROUND RATIO	-0.265	0.049	-5.40	<0.001	-0.364	0.080	-4.55	<0.001
RIGHT BACKGROUND AREA	-0.074	0.018	-4.11	<0.001	-0.042	0.033	-1.28	0.202
RIGHT RENAL AREA	-0.011	0.003	-3.89	<0.001	-0.010	0.006	-1.78	0.077
LEFT BACKGROUND AREA	-0.084	0.022	-3.82	<0.001	-0.081	0.024	-3.44	0.001
LEFT RENAL AREA	-0.012	0.003	-3.68	<0.001	-0.013	0.005	-2.48	0.014
TIME VISUALISATION RIGHT CALYCES	0.030	0.008	3.65	<0.001	0.028	0.016	1.70	0.092
GFR	-0.003	0.001	-2.81	0.005	-0.011	0.020	-5.39	<0.001
SD TOTAL COUNTS LEFT RENAL ROI	<0.001	<0.001	1.52	0.129	-0.001	0.001	-1.16	0.248
TIME VISUALISATION RIGHT PELVIS	0.014	0.011	1.29	0.198	0.012	0.011	1.05	0.298
ASYMMETRY DRF	-0.002	0.002	-1.20	0.232	0.001	0.002	0.43	0.666
SD TOTAL COUNTS LEFT BACKGROUND ROI	-0.001	0.001	-0.94	0.347	0.001	0.001	-0.42	0.674
SD TOTAL COUNTS RIGHT RENAL ROI	<0.001	<0.001	0.84	0.400	0.000	0.001	0.38	0.707
TIME VISUALISATION LEFT PELVIS	-0.007	0.009	-0.75	0.455	0.038	0.018	2.11	0.037
SD TOTAL COUNTS RIGHT BACKGROUND ROI	0.001	0.001	-0.73	0.467	-0.001	0.001	-0.77	0.444
TIME VISUALISATION LEFT CALYCES	0.005	0.040	0.11	0.909	0.093	0.051	1.83	0.070

*The corresponding Table for Cohort 1 is Tables 10

Multiple linear regression results - log MAXMINHAUC - Cohort 2:

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

The R^2 -values of the 594 combinations ranged from 0.1675 to 0.2163. All were lower than those recorded in cohort 1 which ranged from 0.3510 to 0.4906.

In cohort 2 the beta-coefficients and t-values of the variables RIGHT RENAL MARGINS WELL DEFINED and RIGHT RENAL MARGINS POORLY VISUALISED, LEFT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS POORLY VISUALISED, LEFT RENAL MARGINS SMOOTH and LEFT RENAL MARGINS IRREGULAR were equal in magnitude but of opposite sign.

Three combinations for log MAXMINHAUC are presented. First, the combination with the highest R^2 -value in cohort 2. The combinations with the highest R^2 in both cohorts were then repeated for the other cohort and compared. Therefore, the result of the cohort 1 combination with the highest R^2 value was compared to the result of the same combination analysed using cohort 2. The results of the cohort 2 combination with the highest R^2 value was then compared to the result of the same combination analysed using cohort 1.

The combination with the highest R^2 for log MAXMINHAUC – cohort 2:

The combination for the dependent variable log MAXMINHAUC with the highest R^2 -value, 0.2163, for cohort 2 was a combination of AGE, GFR, RIGHT RENAL AREA, LEFT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL MARGINS WELL DEFINED, RIGHT NO CORTICAL DEFECTS and TIME VISUALISATION LEFT PELVIS. The only variables which were significant in this combination were LEFT KIDNEY TO BACKGROUND RATIO and RIGHT RENAL MARGINS WELL DEFINED, Table 27.

Table 27. Multiple linear regression for the combination with the highest R^2 for log MAXMINHAUC cohort 2.

Variable	Beta coefficient	Robust Standard Error	p-value
LEFT KIDNEY TO BACKGROUND RATIO	-0.120	0.038	0.002
RIGHT RENAL MARGINS WELL DEFINED	-0.404	0.126	0.002
TIME VISUALISATION LEFT PELVIS	-0.017	0.009	0.055
AGE	-0.002	0.001	0.117
RIGHT NO CORTICAL DEFECTS	0.140	0.101	0.164
GFR	-0.001	0.001	0.248
RIGHT RENAL AREA	-0.004	0.004	0.367

* The corresponding Table for log MAXMINHAUC cohort 1 is Table 11.

Comparison of the cohort 2 results for the log MAXMINHAUC combination with the highest R^2 in cohort 1:

The combination with the highest R^2 -value for log MAXMINHAUC in cohort 1 included the variables AGE, GFR, LEFT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL MARGINS WELL DEFINED, LEFT NO CORTICAL DEFECTS, TIME VISUALISATION RIGHT CALYCES and LEFT RENAL AREA. In cohort 1 this combination had a R^2 -value of 0.4906. In cohort 2 the result of this combination was very different. R^2 was 0.1992, Table 28. RIGHT RENAL MARGINS WELL DEFINED, LEFT KIDNEY TO BACKGROUND RATIO and AGE were significant in both cohorts. GFR and TIME VISUALISATION RIGHT CALYCES were

not significant in cohort 2. LEFT NO CORTICAL DEFECTS and LEFT RENAL AREA were not significant in cohort 1 and cohort 2.

Table 28. The cohort 2 multiple linear regression results for the log MAXMINHAUC combination with the highest R^2 in cohort 1

	Cohort 2			Cohort 1		
Variable	Beta-coefficient	Robust Standard Error	p-value	Beta-coefficient	Robust Standard Error	p-value
RIGHT RENAL MARGINS WELL DEFINED	-0.338	0.123	0.007	-0.399	0.121	0.001
LEFT KIDNEY TO BACKGROUND RATIO	-0.103	0.042	0.014	-0.316	0.061	<0.001
AGE	-0.003	0.001	0.047	-0.003	0.001	0.009
TIME VISUALISATION RIGHT CALYCES	0.014	0.009	0.131	0.033	0.014	0.019
GFR	-0.001	0.001	0.367	-0.005	0.002	0.004
LEFT RENAL AREA	-0.002	0.004	0.588	0.004	0.005	0.360
LEFT NO CORTICAL DEFECTS	0.042	0.123	0.731	-0.124	0.104	0.233

*The corresponding Table for log MAXMINHAUC Cohort 1 is Table 11

Comparison of the cohort 1 results for the log MAXMINHAUC combination with the highest R^2 in cohort 2:

The combination for the dependent variable log MAXMINHAUC with the highest R^2 -value, 0.2163, for cohort 2 was a combination of AGE, GFR, RIGHT RENAL AREA, LEFT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL MARGINS WELL DEFINED, RIGHT NO CORTICAL DEFECTS and TIME VISUALISATION LEFT PELVIS. In cohort 1 the result of this combination was very different. R^2 was 0.4719, Table 29. RIGHT RENAL MARGINS WELL DEFINED, LEFT KIDNEY TO BACKGROUND RATIO and AGE were significant in both cohorts. GFR and AGE were significant in cohort 1 but not in cohort 2. TIME VISUALISATION LEFT PELVIS and RIGHT RENAL, AREA RIGHT NO CORTICAL DEFECTS, were not significant in cohort 1 and 2.

Table 29. The cohort 1 multiple linear regression results for the log MAXMINHAUC combination with the highest R² in cohort 2

	Cohort 1			Cohort 2		
Variable	Beta coefficient	Robust Standard Error	p-value	Beta coefficient	Robust Standard Error	p-value
LEFT KIDNEY TO BACKGROUND RATIO	-0.311	0.0623	<0.001	-0.120	0.038	0.002
RIGHT RENAL MARGINS WELL DEFINED	-0.495	0.134	<0.001	-0.404	0.126	0.002
GFR	-0.005	0.002	0.003	-0.001	0.001	0.248
AGE	-0.002	0.001	0.044	-0.002	0.001	0.117
TIME VISUALISATION LEFT PELVIS	0.014	0.016	0.373	-0.017	0.009	0.055
RIGHT NO CORTICAL DEFECTS	0.040	0.127	0.754	0.140	0.101	0.164
RIGHT RENAL AREA	0.001	0.005	0.887	-0.004	0.004	0.367

The corresponding Table for log MAXMINHAUC Cohort 2 is Table 27

Results of the individual variables in the different combinations for log MAXMINHAUC – cohort 2:

The results of the individual variables in the 594 combinations for log MAXMINHAUC cohort 2 are presented in Table 30. The variables with the same number of combinations in cohort 1 and 2 in which the p-value of the beta-coefficient was ≤ 0.05 are presented in bold.

The variable LEFT KIDNEY TO BACKGROUND RATIO was highly significant in all combinations for cohort 1 and 2.

RIGHT KIDNEY TO BACKGROUND RATIO was significant in all the combinations for cohort 2. In cohort 1 it was significant in 261 of 297 combinations.

AGE was significant in the majority of the combinations in cohort 2, 475 out of 594 combinations. In cohort 1 it was significant in 329 combinations of the 594 combinations.

TIME VISUALISATION RIGHT CALYCES and RIGHT RENAL MARGINS WELL DEFINED were significant in more than 50% of the combinations in which they were included in cohort 1 and 2.

TIME VISUALISATION LEFT PELVIS was significant in less than 50% of the combinations in which it was included in cohort 1 and 2.

GFR was significant in all 594 combinations for cohort 1 but in cohort 2 it was only significant in 3 of the 594 combinations. BOTH RENAL MARGINS IRREGULAR was significant in 36 of the combinations for cohort 1 but it was only significant in 15 combinations in cohort 2. BOTH RENAL MARGINS WELL DEFINED was significant in all 54 combinations for cohort 1 but was not significant in any combinations in cohort 2.

RIGHT RENAL AREA, LEFT NO CORTICAL DEFECTS, LEFT < 2 CORTICAL DEFECTS, LEFT RENAL MARGINS SMOOTH, LEFT RENAL MARGINS IRREGULAR, LEFT RENAL MARGINS WELL DEFINED, and TIME VISUALISATION LEFT CALYCES were significant in some but not all combinations in cohort 1 and not significant in any combinations in cohort 2.

Finally LEFT RENAL AREA, LEFT BACKGROUND AREA, RIGHT RENAL MARGINS SMOOTH, BOTH RENAL MARGINS SMOOTH, and RIGHT RENAL MARGINS IRREGULAR were not significant in any combinations in cohort 1 and cohort 2.

Table 30. Multiple linear regression results for the 594 combinations analysed for log MAXMINHAUC in cohort 1 and 2. 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 cohort 1 and 2 in which the p-value of the beta coefficient was ≤ 0.05 are presented in bold. The percentage of combinations in which each variable was significant is also given.

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
LEFT KIDNEY TO BACKGROUND RATIO (297)	<0.001 - 0.005	297	100	<0.001 - 0.023	297	100
RIGHT KIDNEY TO BACKGROUND RATIO (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 corresponding Table for log MAXMINHAUC cohort 1 is Table 12.

Testing the assumptions of the multiple linear regression models – log MAXMINHAUC - cohort 2:

Residual values log MAXMINHAUC cohort 2:

The residual values for each patient, in the combination with the highest R^2 -values for log MAXMINHAUC cohort 2 were calculated and plotted on a normal probability plot (Figure 21). The residual values did not depart significantly from the expected normal distribution.

The residual values were also plotted against the continuous variables AGE, GFR, LEFT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL AREA and TIME VISUALISATION LEFT PELVIS, (Figures 22 through 26). None of the patients had high residual values.

Figure 21. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHAUC cohort 2, plotted on a normal probability plot.

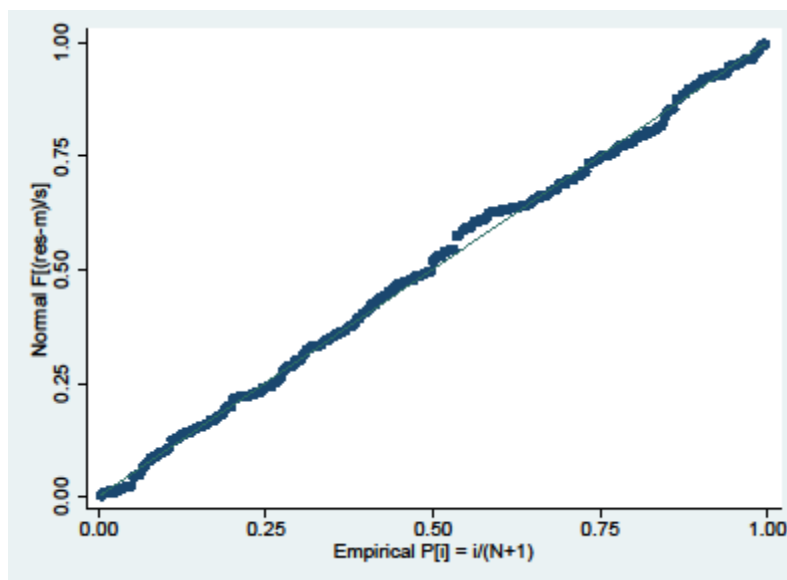


Figure 22. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHAUC cohort 2, plotted against AGE.

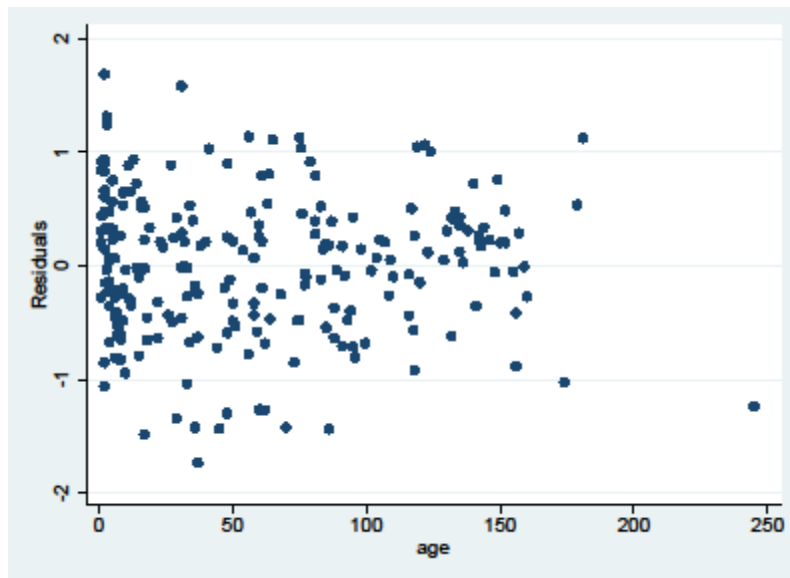


Figure 23. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHAUC cohort 2 plotted against GFR.

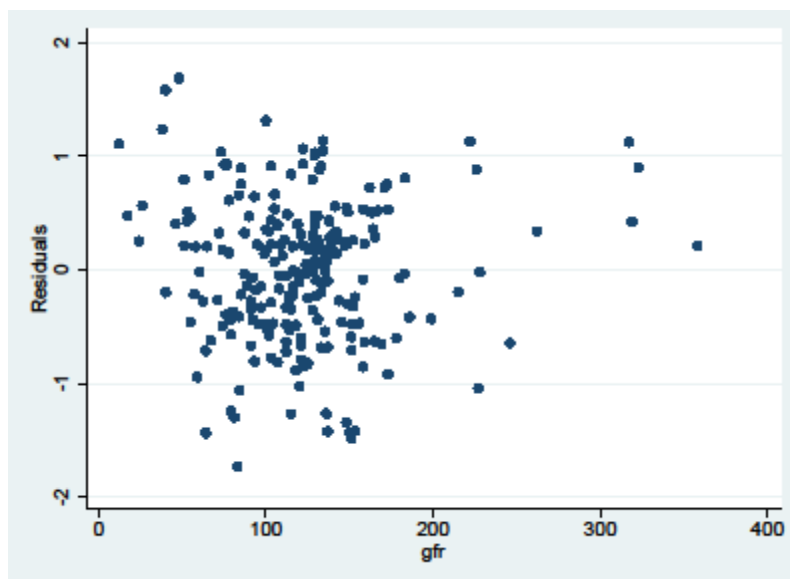
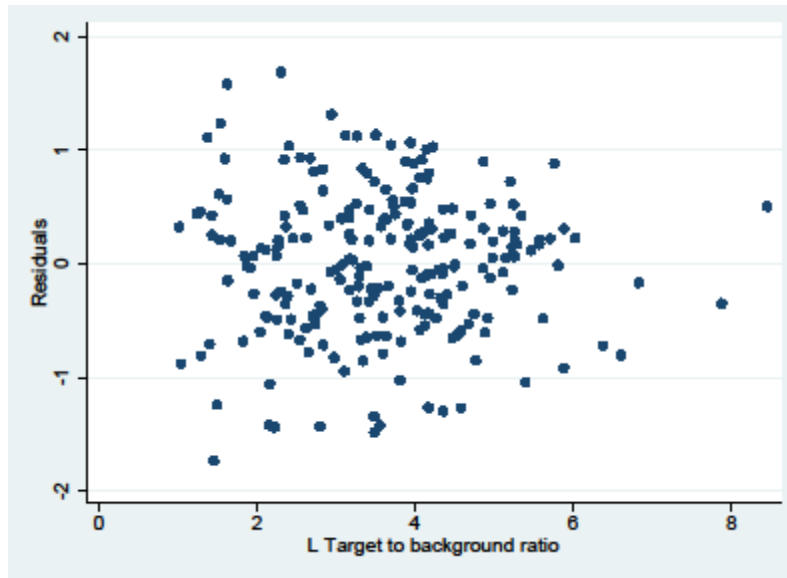


Figure 24. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHAUC cohort 2, plotted against LEFT KIDNEY TO BACKGROUND RATIO.



*L Target to background ratio = LEFT KIDNEY TO BACKGROUND RATIO.

Figure 25. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHAUC cohort 2, plotted against RIGHT RENAL AREA.

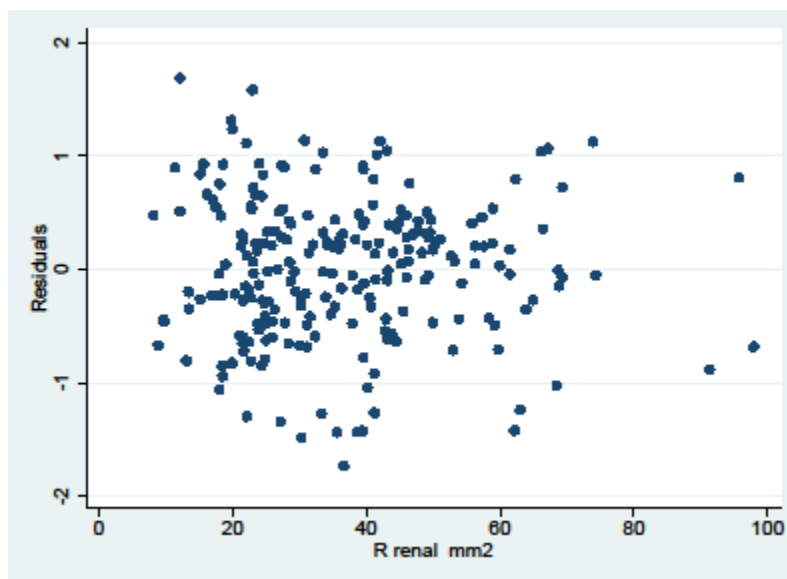
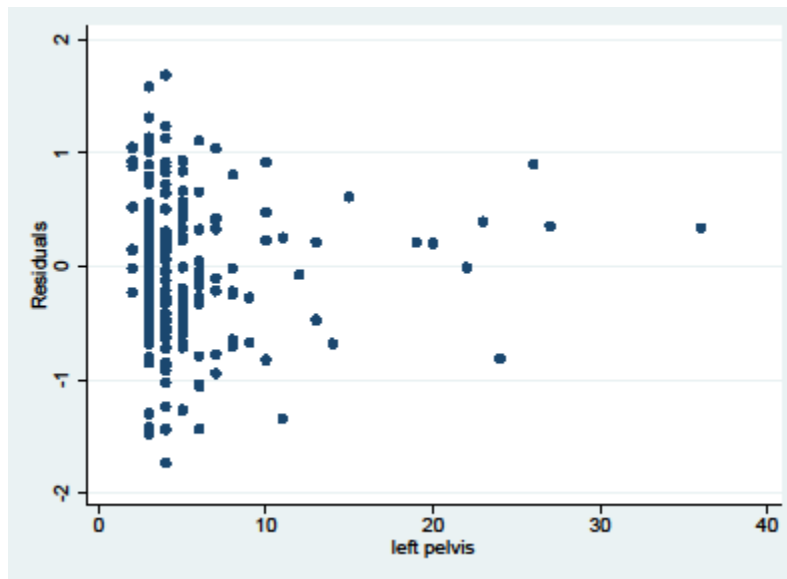


Figure 26. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHAUC cohort 2, plotted against TIME VISUALISATION LEFT PELVIS.



Homoscedasticity - log MAXMINHAUC - cohort 2:

Cameron and Trivedi's test was performed on the combination with the highest R^2 -value log MAXMINHAUC cohort 2. There was no heteroscedasticity between the different variables included in the analysis, Table 31.

Table 31. Cameron and Trivedi's decomposition of IM – test for the combination with the highest R^2 for log MAXMINHAUC cohort 2.

Source	χ^2	df	p
Heteroscedasticity	44.01	33	0.095
Skewness	6.13	7	0.525
Kurtosis	0.08	1	0.773
Total	50.22	41	0.153

*The corresponding Table for log MAXMINHAUC cohort 1 is Table 13.

Multicollinearity – log MAXMINHAUC - cohort 2:

The VIF was calculated for each of the independent variables used in the combination with the highest R²-value log MAXMINHAUC cohort 2. The results are presented in Table 32. For all the variables the VIF values were less than |5|, indicating there was no multicollinearity between these variables. The VIF values were similar to those in cohort 1.

Table 32. VIF for the combination with the highest R² for log MAXMINHAUC cohort 2.

Variable	VIF	1/VIF
AGE	2.29	0.437
GFR	1.38	0.724
LEFT KIDNEY TO BACKGROUND RATIO	1.37	0.729
RIGHT RENAL AREA	2.30	0.435
TIME VISUALISATION LEFT PELVIS	1.05	0.950
RIGHT NO CORTICAL DEFECTS	1.22	0.823
RIGHT RENAL MARGINS WELL DEFINED	1.32	0.759
Mean VIF	1.56	

* The corresponding Table for log MAXMINHAUC cohort 1 is Table 14.

The collinearity between the different variables included in the analysis were tested further, Table 33. As in cohort 1 there was no significant collinearity (> 0.800) between the variables.

Table 33. Correlation matrix of collinearity coefficients of the regression model for the combination with the highest R^2 for log MAXMINHAUC cohort 2.

Variable	AGE	GFR	LEFT KIDNEY TO BACKGROUND RATIO	RIGHT RENAL AREA	TIME VISUALI- SATION LEFT PELVIS	RIGHT NO CORTICAL DEFECTS	RIGHT RENAL MARGINS WELL DEFINED	-CONS
AGE	1.000							
GFR	0.156	1.000						
LEFT KIDNEY TO BACKGROUND RATIO	-0.302	-0.221	1.000					
RIGHT RENAL AREA	-0.700	-0.011	0.173	1.000				
TIME VISUALISATION LEFT PELVIS	-0.027	0.147	0.222	-0.095	1.000			
RIGHT NO CORTICAL DEFECTS	-0.012	-0.117	-0.071	0.023	0.044	1.000		
RIGHT RENAL MARGINS WELL DEFINED	-0.076	0.290	0.272	0.157	0.201	-0.294	1.000	
-CONS	0.267	-0.408	-0.525	-0.483	-0.345	0.210	-0.191	1.000

The corresponding Table for log MAXMINHAUC cohort 1 is Table 15.

Conclusion regression diagnostics log MAXMINHAUC –cohort 2:

The multiple linear regression models met the necessary statistical assumptions in cohort 2.

Conclusion of the different combinations analysed with multiple linear regression log MAXMINHAUC - cohort 1 and cohort 2:

In cohort 2, the R^2 values of all the combinations, 0.1675 to 0.2163, were much lower than the values in cohort 1, 0.3510 and 0.4906.

LEFT KIDNEY TO BACKGROUND RATIO was the only variable which was significant in all combinations in which it was present in cohort 1 and 2 and RIGHT KIDNEY TO BACKGROUND RATIO was significant in the majority of the combinations. Conversely LEFT RENAL AREA, LEFT BACKGROUND AREA, RIGHT RENAL MARGINS SMOOTH, BOTH RENAL MARGINS SMOOTH, and RIGHT RENAL MARGINS IRREGULAR were not significant in all log MAXMINHAUC combinations in cohort 1 and 2.

Of the variables identified in the literature as possible predictors of poor reproducibility of DRF measurements, AGE was significant in more than 50% of the combinations of cohort 1 and in most of the combinations for cohort 2. However, GFR was significant in all the combinations for cohort 1 but in cohort 2 it was significant in 0.5% of the combinations.

Results for log MAXMINHRP – cohort 2

Univariate linear regression results for categorical variables and log MAXMINHRP – cohort 2:

The cohort 2 univariate linear regression results of the 15 categorical variables and log MAXMINHRP are listed in ascending order of the p-value of the beta-coefficient in Table 34. The variables with p-values ≤ 0.001 were RIGHT RENAL MARGINS WELL DEFINED, RIGHT RENAL MARGINS POORLY VISUALISED, BOTH RENAL MARGINS WELL DEFINED and BOTH RENAL MARGINS IRREGULAR. The variables RIGHT RENAL MARGINS SMOOTH, RIGHT RENAL MARGINS IRREGULAR, BOTH RENAL MARGINS SMOOTH, LEFT RENAL MARGINS SMOOTH, LEFT RENAL MARGINS IRREGULAR, LEFT RENAL MARGINS WELL DEFINED, and LEFT RENAL MARGINS POORLY VISUALISED had p-values between 0.005 and 0.164. LEFT NO CORTICAL DEFECTS, RIGHT NO CORTICAL DEFECTS, LEFT < 2 CORTICAL DEFECTS and RIGHT < 2 CORTICAL DEFECTS had p-values > 0.2.

The beta-coefficients of 11 categorical variables had $p \leq 0.2$ with univariate linear regression for log MAXMINHRP, in cohort 1 and 2. These variables were therefore eligible for inclusion in multiple linear regression in both cohorts. They were RIGHT RENAL MARGINS WELL DEFINED, RIGHT RENAL MARGINS POORLY VISUALISED, BOTH RENAL MARGINS WELL DEFINED, BOTH RENAL MARGINS IRREGULAR, RIGHT RENAL MARGINS SMOOTH, BOTH RENAL MARGINS SMOOTH, LEFT RENAL MARGINS SMOOTH, LEFT RENAL MARGINS IRREGULAR, LEFT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS POORLY VISUALISED.

LEFT < 2 CORTICAL DEFECTS and RIGHT < 2 CORTICAL DEFECTS was not eligible for inclusion in the multiple linear regression model in cohort 1 and 2.

The p-value of the beta-coefficient of the variable RIGHT RENAL MARGINS IRREGULAR was > 0.2 in cohort 1. In cohort 2 it was ≤ 0.2 . For cohort 1, 30 (24%) patients had RIGHT RENAL MARGINS IRREGULAR and for cohort 2, the corresponding number was 46 (20%). This difference was

non-significant ($p = 0.461$, Pearson's χ^2). This variable would have been included in the multiple linear regression model if the model was determined using cohort 2.

There were two categorical variables which had a $p \leq 0.2$ in cohort 1 and a $p > 0.2$ in cohort 2. They were LEFT NO CORTICAL DEFECTS and RIGHT NO CORTICAL DEFECTS. Previously it was shown that there was a difference in the two populations for LEFT NO CORTICAL DEFECTS ($p = 0.001$, Pearson's χ^2) but no difference between the populations for RIGHT NO CORTICAL DEFECTS, ($p = 0.597$, Pearson's χ^2). These variables would not have been excluded from the multiple linear regression model if the model was determined using cohort 2. However, the purpose of cohort 2 was to validate the results of the model determined in cohort 1. Therefore, these variables were still included in the cohort 2 analyses.

In cohort 2 the values for the beta-coefficient and t-values of LEFT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS POORLY VISUALISED, RIGHT RENAL MARGINS WELL DEFINED and RIGHT POORLY VISUALISED, LEFT RENAL MARGINS SMOOTH and LEFT RENAL MARGINS IRREGULAR, RIGHT RENAL MARGINS SMOOTH and RIGHT RENAL MARGINS IRREGULAR were equal in magnitude but of opposite sign.

A negative beta-coefficient predicted good reproducibility and a positive beta-coefficient predicted decreased reproducibility.

Table 34. Univariate linear regression of the 15 categorical variables and log MAXMINHRP - cohort 2 and cohort 1. Listed in ascending order of the p-value of the beta-coefficient of cohort 2. The variables for which p changed from > 0.2 to ≤ 0.2 or from ≤ 0.2 to 0.2 are in bold.

	Cohort 2				Cohort 1			
Variable	Beta-coefficient	Standard error	t	p > t	Beta-coefficient	Standard error	t	p > t
RIGHT RENAL MARGINS WELL DEFINED	-0.536	0.119	-4.52	<0.001	-0.608	0.145	-4.19	<0.001
RIGHT RENAL MARGINS POORLY VISUALISED	0.536	0.119	4.52	<0.001	0.608	0.145	4.19	<0.001
BOTH RENAL MARGINS WELL DEFINED	-0.395	0.108	-3.65	<0.001	-0.603	0.111	-5.42	<0.001
BOTH RENAL MARGINS IRREGULAR	0.493	0.147	3.35	0.001	0.551	0.241	2.28	0.024
RIGHT RENAL MARGINS SMOOTH	-0.310	0.109	-2.85	0.005	-0.304	0.143	-2.12	0.036
RIGHT RENAL MARGINS IRREGULAR	0.310	0.109	2.85	0.005	0.190	0.163	1.17	0.246
BOTH RENAL MARGINS SMOOTH	-0.180	0.102	-1.76	0.080	-0.289	0.119	-2.42	0.017
LEFT RENAL MARGINS SMOOTH	-0.220	0.130	-1.69	0.092	-0.375	0.131	-2.84	0.005
LEFT RENAL MARGINS IRREGULAR	0.220	0.130	1.69	0.092	0.346	0.139	2.49	0.014
LEFT RENAL MARGINS WELL DEFINED	-0.232	0.166	-1.40	0.164	-0.533	0.125	-4.26	<0.001
LEFT RENAL MARGINS POORLY VISUALISED	0.232	0.166	-1.40	0.164	0.533	0.125	4.26	<0.001
LEFT NO CORTICAL DEFECTS	-0.100	0.104	-0.96	0.337	-0.374	0.123	-3.05	0.003
RIGHT NO CORTICAL DEFECTS	-0.090	0.100	-0.90	0.371	-0.302	0.151	-2.00	0.047
RIGHT <2 CORTICAL DEFECTS	-0.096	0.115	-0.84	0.402	0.108	0.149	0.73	0.467
LEFT <2 CORTICAL DEFECTS	0.086	0.108	0.80	0.426	0.160	0.127	1.26	0.211

* The corresponding Table for cohort 1 is Table 16.

Univariate linear regression results for continuous variables and log MAXMINHRP - cohort 2:

The cohort 2 univariate linear regression results of the 17 continuous variables analysed are presented in Table 35. The variables are listed in ascending order for the p-value of the beta-coefficient of the cohort 2 results. The variables with p-values of the beta-coefficient < 0.001 in cohort 2 were LEFT KIDNEY TO BACKGROUND RATIO, RIGHT KIDNEY TO BACKGROUND RATIO, AGE, RIGHT BACKGROUND AREA, RIGHT RENAL AREA, TIME VISUALISATION RIGHT CALYCES, LEFT RENAL AREA and LEFT BACKGROUND AREA. GFR had a p-value of 0.04. The variables TIME VISUALISATION LEFT PELVIS, TIME VISUALISATION RIGHT PELVIS, SD OF TOTAL COUNTS LEFT BACKGROUND ROI, SD TOTAL COUNTS RIGHT BACKGROUND ROI, SD TOTAL COUNTS LEFT RENAL ROI, ASYMMETRY DRF, SD TOTAL COUNTS RIGHT RENAL ROI, and TIME VISUALISATION LEFT CALYCES had a p-value > 0.2 .

There were seven continuous variables which had a p-value of ≤ 0.2 for log MAXMINHRP cohort 1 and 2. These variables were therefore eligible for inclusion in multiple linear regression models in both cohorts. They were LEFT KIDNEY TO BACKGROUND RATIO, RIGHT KIDNEY TO BACKGROUND RATIO, AGE, TIME VISUALISATION RIGHT CALYCES, LEFT RENAL AREA, LEFT BACKGROUND AREA and GFR.

Six continuous variables had a p-value > 0.2 for the beta-coefficient for log MAXMINHRP in cohort 1 and 2. They were TIME VISUALISATION RIGHT PELVIS, SD OF TOTAL COUNTS LEFT BACKGROUND ROI, SD OF TOTAL COUNTS RIGHT BACKGROUND ROI, SD OF TOTAL COUNTS LEFT RENAL ROI, ASYMMETRY DRF, and SD OF TOTAL COUNTS RIGHT RENAL ROI. They were not eligible for inclusion in the multiple linear regression model in cohort 1 and 2.

There were two continuous variables for log MAXMINHRP with p-values > 0.2 in cohort 1 which now had p-values of ≤ 0.2 in cohort 2, Table 33 (presented in bold).

1. In cohort 1 the variable RIGHT BACKGROUND AREA had a p-value of 0.228. This variable had a p-value < 0.001 in cohort 2. There was a significant difference in the two populations for this variable ($p < 0.001$, U-test).
2. In cohort 1 the variable RIGHT RENAL AREA had a p-value of 0.246, $p < 0.001$ in cohort 2. There was a significant difference between the two populations for this variable too ($p = 0.001$, U-test).

These variables would have been included in the multiple linear regression model if the model was determined using cohort 2. However, the purpose of cohort 2 was to validate the results of the model determined in cohort 1. Therefore, these variables were still excluded in the cohort 2 analyses.

The variables TIME VISUALISATION LEFT PELVIS and TIME VISUALISATION LEFT CALYCES had p-values of the beta-coefficient, ≤ 0.2 in cohort 1, in cohort 2 it was > 0.2 .

1. TIME VISUALISATION LEFT PELVIS had a p-value of 0.060 in cohort 1 for cohort 2 the p-value was 0.213. There was no difference in the two populations for this variable ($p = 0.090$, U-test).
2. TIME VISUALISATION LEFT CALYCES. In cohort 1 this variable had a p-value of 0.019 in cohort 1, in cohort 2 it was 0.977. There was no difference in the two populations for this variable ($p = 0.499$, U-test).

These variables would not have been included in the multiple linear regression model if the model was determined using cohort 2. However, the purpose of cohort 2 was to validate the results of the model determined in cohort 1. Therefore, these variables were still included in the cohort 2 analyses.

Table 35. Univariate linear regression of the 17 continuous variables and log MAXMINHRP - cohort 2 and cohort 1. Listed in ascending order of the p-value of the beta-coefficient of cohort 2. The variables in which the univariate linear regression results changed are presented in bold

Variable	Cohort 2				Cohort 1			
	Beta-coefficient	Standard error	t	p > t	Beta-coefficient	Standard error	t	p > t
LEFT KIDNEY TO BACKGROUND RATIO	-0.161	0.035	-4.63	<0.001	-0.358	0.056	-6.40	<0.001
RIGHT KIDNEY TO BACKGROUND RATIO	-0.258	0.051	-5.10	<0.001	-0.387	0.079	-4.92	<0.001
AGE	-0.004	0.001	-4.62	<0.001	-0.004	0.001	-3.00	0.003
RIGHT BACKGROUND AREA	-0.076	0.017	-4.38	<0.001	-0.032	0.031	-1.07	0.288
RIGHT RENAL AREA	-0.011	0.003	-4.27	<0.001	-0.006	0.005	-1.17	0.246
TIME VISUALISATION RIGHT CALYCES	0.029	0.007	4.02	<0.001	0.034	0.022	1.49	0.139
LEFT RENAL AREA	-0.012	0.003	-3.80	<0.001	-0.011	0.005	-2.30	0.023
LEFT BACKGROUND AREA	-0.078	0.022	-3.57	<0.001	-0.061	0.022	-2.74	0.007
GFR	-0.003	0.001	-2.94	0.004	-0.008	0.020	-4.36	<0.001
TIME VISUALISATION LEFT PELVIS	-0.012	0.009	-1.25	0.213	0.032	0.169	1.90	0.060
TIME VISUALISATION RIGHT PELVIS	0.009	0.011	0.84	0.401	0.014	0.012	1.17	0.245
SD OF TOTAL COUNTS LEFT BACKGROUND ROI	-0.001	0.001	-0.82	0.415	0.001	0.001	-0.46	0.648
SD OF TOTAL COUNTS RIGHT BACKGROUND ROI	0.001	0.001	-0.76	0.450	<0.001	0.001	0.39	0.699
SD OF TOTAL COUNTS LEFT RENAL ROI	<0.001	<0.001	-0.69	0.493	0.001	0.001	-1.06	0.291
ASYMMETRY DRF	-0.001	0.002	-0.51	0.611	0.001	0.002	0.67	0.506
SD TOTAL COUNTS RIGHT RENAL ROI	<-0.001	<0.001	-0.21	0.833	<-0.001	0.001	-0.39	0.699
TIME VISUALISATION LEFT CALYCES	-0.001	0.036	-0.03	0.977	0.098	0.041	2.39	0.019

*The corresponding Table for Cohort 1 is Table 17

Multiple linear regression results log MAXMINHRP - Cohort 2:

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

The R^2 -values of the 240 combinations for log MAXMINHRP cohort 2 ranged from 0.1706 to 0.2191. All were lower than those recorded in cohort 1 which ranged from 0.3284 to 0.4500.

In cohort 2 the beta-coefficient and t-values of the variables RIGHT RENAL MARGINS WELL DEFINED and RIGHT RENAL MARGINS POORLY VISUALISED, LEFT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS POORLY VISUALISED, LEFT RENAL MARGINS SMOOTH and LEFT RENAL MARGINS IRREGULAR were equal in magnitude but of opposite sign.

Three combinations for log MAXMINHRP are presented. First, the combination with the highest R^2 -value in cohort 2. The combinations with the highest R^2 in both cohorts were then repeated for the other cohort and compared. Therefore, the result of the cohort 1 combination with the highest R^2 value was compared to the result of the same combination analysed using cohort 2. The results of the cohort 2 combination with the highest R^2 value was then compared to the result of the same combination analysed using cohort 1.

The combination with the highest R^2 log MAXMINHRP – cohort 2:

The log MAXMINHRP combination with the highest R^2 -value, 0.2191, for cohort 2 was a combination of AGE, GFR, LEFT RENAL AREA, LEFT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL MARGINS WELL DEFINED, LEFT NO CORTICAL DEFECTS and TIME VISUALISATION LEFT PELVIS. The variables LEFT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL MARGINS WELL DEFINED and TIME VISUALISATION LEFT PELVIS were significant in this combination, Table 36.

Table 36. Multiple linear regression for the combination with the highest R^2 for log MAXMINHRP cohort 2.

Variable	Beta coefficient	Robust Standard Error	p-value
LEFT KIDNEY TO BACKGROUND RATIO	-0.115	0.039	0.004
RIGHT RENAL MARGINS WELL DEFINED	-0.330	0.117	0.005
TIME VISUALISATION LEFT PELVIS	-0.022	0.009	0.016
AGE	-0.002	0.001	0.086
GFR	-0.001	0.001	0.210
LEFT RENAL AREA	-0.003	0.004	0.562
LEFT NO CORTICAL DEFECTS	0.062	0.114	0.589

*The corresponding Table for log MAXMINHRP cohort 1 is Table 18.

Comparison of the cohort 2 results for the log MAXMINHRP combination with the highest R^2 in cohort 1:

The combination with the highest R^2 -value for log MAXMINHRP cohort 1 included the variables AGE, GFR, LEFT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL MARGINS WELL DEFINED, LEFT NO CORTICAL DEFECTS, TIME VISUALISATION RIGHT CALYCES and LEFT BACKGROUND AREA. In cohort 1 this combination had a R^2 value of 0.4500. In cohort 2 the results of this combinations was very different. R^2 value was 0.2002, Table 37. AGE, LEFT KIDNEY TO BACKGROUND RATIO and RIGHT RENAL MARGINS WELL DEFINED were significant in both combinations analysed. TIME VISUALISATION RIGHT CALYCES was significant in cohort 1 but not in cohort 2. GFR, LEFT BACKGROUND AREA and LEFT NO CORTICAL DEFECTS were not significant in cohort 1 and cohort 2.

Table 37. The cohort 2 multiple linear regression results for the log MAXMINHRP combination with the highest R² in cohort 1

	Cohort 2			Cohort 1		
Variable	Beta-coefficient	Robust Standard Error	p-value	Beta-coefficient	Robust Standard Error	p-value
LEFT KIDNEY TO BACKGROUND RATIO	-0.104	0.040	0.011	-0.323	0.058	<0.001
RIGHT RENAL MARGINS WELL DEFINED	-0.300	0.120	0.013	-0.523	0.113	<0.001
AGE	-0.003	0.001	0.023	-0.003	0.001	0.010
GFR	-0.002	0.001	0.186	-0.003	0.002	0.060
TIME VISUALISATION RIGHT CALYCES	0.011	0.009	0.216	0.039	0.016	0.018
LEFT NO CORTICAL DEFECTS	0.091	0.117	0.437	0.035	0.112	0.757
LEFT BACKGROUND AREA	0.009	0.033	0.791	0.028	0.023	0.218

* The corresponding Table log MAXMINHRP for cohort 1 is Table 18.

Comparison of the cohort 1 results for the log MAXMINHRP combination with the highest R^2 in cohort 2:

The combination for the dependent variable log MAXMINHRP with the highest R^2 -value, 0.2191, for cohort 2 was AGE, GFR, LEFT RENAL AREA, LEFT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL MARGINS WELL DEFINED, LEFT NO CORTICAL DEFECTS and TIME VISUALISATION LEFT PELVIS. In cohort 1 the results of this combination were very different. R^2 was 0.4340, Table 38. LEFT KIDNEY TO BACKGROUND RATIO and RIGHT RENAL MARGINS WELL DEFINED were significant in both cohorts. GFR and AGE were significant in cohort 1 but not in cohort 2. TIME VISUALISATION LEFT PELVIS was significant in cohort 2 but not in cohort 1. LEFT RENAL AREA and LEFT NO CORTICAL DEFECTS, were not significant in cohort 1 and 2.

Table 38. The cohort 1 multiple linear regression results for the log MAXMINHAUC combination with the highest R^2 in cohort 2

Variable	Cohort 1			Cohort 2		
	Beta-coefficient	Robust Standard Error	p-value	Beta-coefficient	Robust Standard Error	p-value
LEFT KIDNEY TO BACKGROUND RATIO	-0.297	0.067	<0.001	-0.115	0.039	0.004
RIGHT RENAL MARGINS WELL DEFINED	-0.550	0.114	<0.001	-0.330	0.117	0.005
AGE	-0.002	0.001	0.036	-0.002	0.001	0.086
GFR	-0.004	0.002	0.037	-0.001	0.001	0.210
LEFT RENAL AREA	0.004	0.004	0.338	-0.003	0.004	0.562
TIME VISUALISATION LEFT PELVIS	0.007	0.013	0.584	-0.022	0.009	0.016
LEFT NO CORTICAL DEFECTS	0.009	0.115	0.938	0.062	0.114	0.589

*The corresponding Table for log MAXMINHRP cohort 2 is Table 36.

Results of the individual variables in the different combinations for log MAXMINHRP – cohort 2:

The results of the individual variables analysed in the 240 combinations for log MAXMINHRP cohort 2 are presented in Table 39. The variables with the same number of combinations in cohort 1 and 2 in which the p-value of the beta-coefficient was ≤ 0.05 are presented in bold.

The variables LEFT KIDNEY TO BACKGROUND RATIO and RIGHT KIDNEY TO BACKGROUND RATIO were highly significant in all MAXMINHRP combinations analysed for cohort 1 and 2.

AGE was significant in the majority of the combinations in cohort 2, 205 out of 240 combinations. The 35 combinations in which AGE was not significant contained the following variables in addition to AGE and GFR:

- LEFT KIDNEY TO BACKGROUND RATIO (21) and RIGHT KIDNEY TO BACKGROUND RATIO (14)
- LEFT RENAL AREA (35)
- TIME VISUALISATION LEFT CALYCES (14), TIME VISUALISATION RIGHT CALYCES (11) and TIME VISUALISATION LEFT PELVIS (10)
- RIGHT NO CORTICAL DEFECTS (19) and LEFT NO CORTICAL DEFECTS (16)
- RIGHT RENAL MARGINS WELL DEFINED (12), RIGHT RENAL MARGINS POORLY VISUALISED (12), BOTH RENAL MARGINS WELL DEFINED (9), LEFT RENAL MARGINS SMOOTH (1) and LEFT RENAL MARGINS IRREGULAR (1)

In cohort 1 AGE was significant in less than 50% of the combinations, 96 combinations of the 240 combinations analysed.

TIME VISUALISATION RIGHT CALYCES was significant in most of the combinations for cohort 2, 71 of 80 combinations. In cohort 1 this variable was significant in 50% of the combinations, 40 of the 80 combinations. RIGHT RENAL MARGINS WELL DEFINED was significant in 20 of the 24 combinations for cohort 2. In cohort 1 this variable was significant in 50% of the combinations, 12 of the 24 combinations.

TIME VISUALISATION LEFT PELVIS was significant all but three of the combinations for cohort 2, 77 out of 80 combinations. In cohort 1 it was significant in a third of the combinations, 24 of the 80 combinations analysed.

BOTH RENAL MARGINS IRREGULAR was significant in the majority of the combination in cohort 2, 21 of the 24 combinations. In cohort 1 it was not significant in any combination.

GFR was only significant in six of the 240 combinations in cohort 2. In contrast it was significant in the majority, 227 of the 240 combinations, for cohort 1.

LEFT RENAL MARGINS SMOOTH, RIGHT RENAL MARGINS SMOOTH, LEFT RENAL MARGINS WELL DEFINED, BOTH RENAL MARGINS WELL DEFINED, and TIME VISUALISATION LEFT CALYCES were significant in none of the combinations for cohort 2. In cohort 1 these variables were significant in some but not all combinations.

LEFT RENAL AREA, LEFT BACKGROUND AREA, LEFT NO CORTICAL DEFECTS, RIGHT NO CORTICAL DEFECTS, BOTH RENAL MARGINS SMOOTH, and LEFT RENAL MARGINS IRREGULAR were not significant in all MAXMINHRP combinations cohort 1 and 2.

Table 39. Multiple linear regression results for the 240 combinations analysed for log MAXMINHRP in cohort 1 and cohort 2. 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 cohort 1 and 2 in which the p-value of the beta coefficient was ≤ 0.05 are presented in bold. The percentage of combinations in which each variable was significant is also given.

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
LEFT KIDNEY TO BACKGROUND RATIO (120)	<0.001 - 0.005	120	100	<0.001 - 0.030	120	100
RIGHT KIDNEY TO BACKGROUND RATIO (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 corresponding Table for log MAXMINHRP for cohort 1 is Table 19

Testing the assumptions of the multiple linear regression models - log MAXMINHRP - cohort 2:

Residual values log MAXMINHRP - cohort 2:

The residual values for each patient, in the combination with the highest R^2 -value for log MAXMINHRP cohort 2 were calculated and plotted on a normal probability plot (Figure 27). The residual values followed the expected normal distribution.

The residual values were also plotted against the continuous variables AGE, GFR, LEFT KIDNEY TO BACKGROUND RATIO, LEFT RENAL AREA and TIME VISUALISATION LEFT PELVIS, (Figures 28 through 32). None of the patients had high residual values.

Figure 27. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHRP cohort 2, plotted on a normal probability plot.

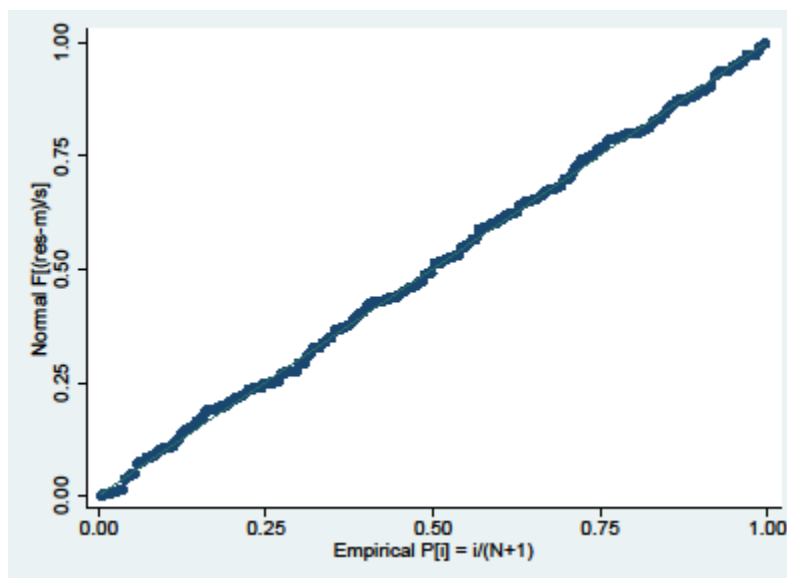


Figure 28. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHRP cohort 2, plotted against AGE.

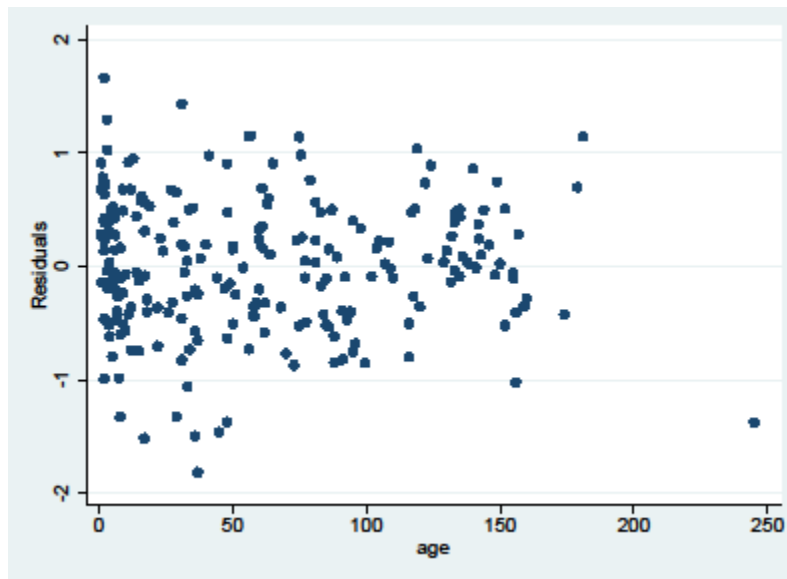


Figure 29. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHRP cohort 2, plotted against GFR.

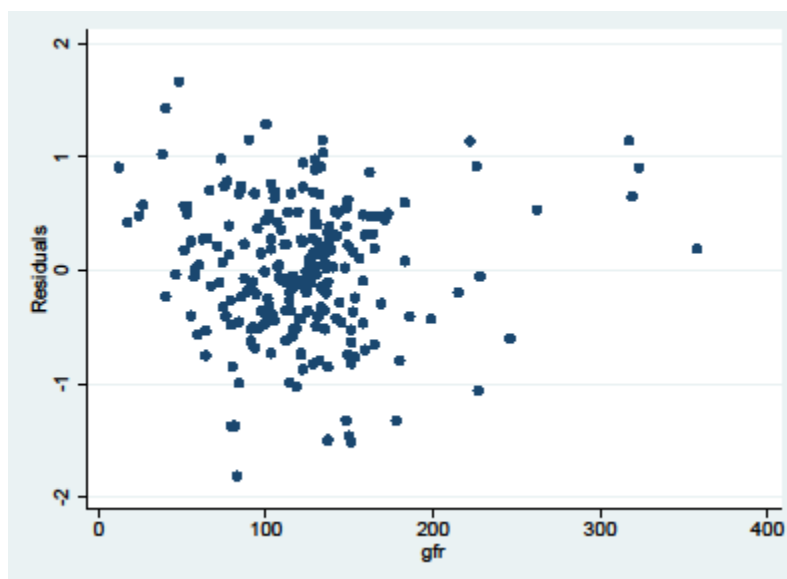
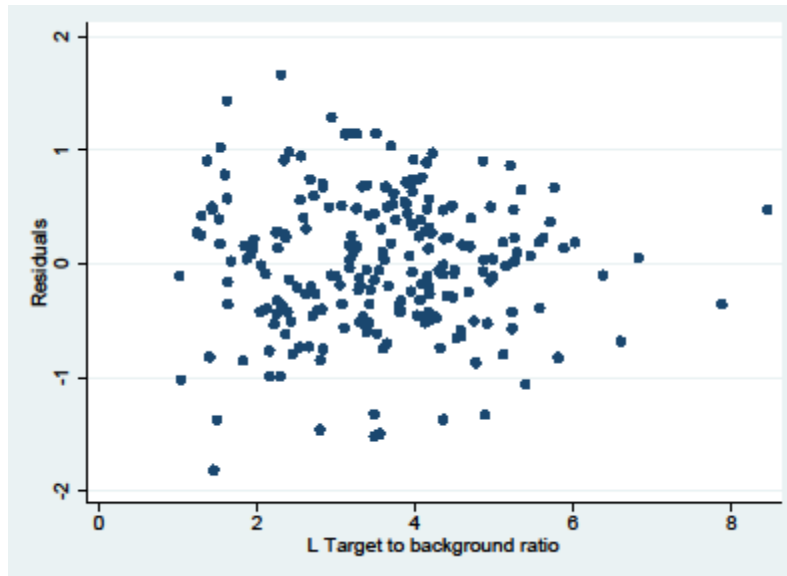


Figure 30. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHRP cohort 2, plotted against LEFT KIDNEY TO BACKGROUND RATIO.



*L Target to background ratio = LEFT KIDNEY TO BACKGROUND RATIO.

Figure 31. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHRP cohort 2, plotted against LEFT RENAL AREA.

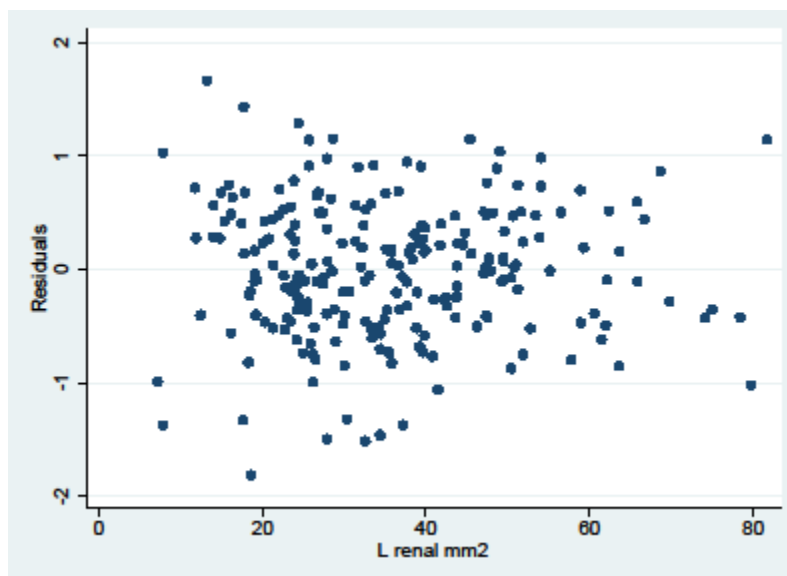
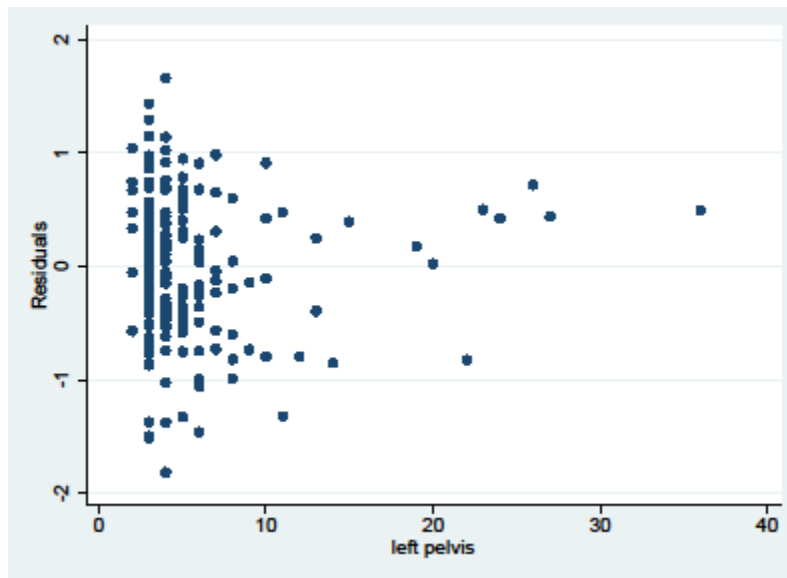


Figure 32. The residual values for the combination with the highest R^2 for the dependent variable log MAXMINHRP cohort 2, plotted against TIME VISUALISATION LEFT PELVIS.



Homoscedasticity - log MAXMINHRP - cohort 2:

Cameron and Trivedi's test illustrates that there was some heteroscedasticity, $p = 0.046$, between the different variables included in the log MAXMINHRP combination with the highest R^2 value in cohort 2, Table 40

Table 40. Cameron and Trivedi's decomposition of IM – test for the combination with the highest R^2 for log MAXMINHRP cohort 2.

Source	χ^2	df	p
Heteroscedasticity	47.77	33	0.046
Skewness	6.26	7	0.510
Kurtosis	0.27	1	0.605
Total	54.29	41	0.080

*The corresponding Table for log MAXMINHRP cohort 1 is Table 20.

Multicollinearity - log MAXMINHRP - cohort 2:

The VIF was calculated for each of the independent variables used in the log MAXMINHRP combination with the highest R²-value cohort 2. The results are presented in Table 41. For all the variables the VIF values were less than |2|. This indicates there is no multicollinearity between these variables.

Table 41. VIF for the combination with the highest R² for log MAXMINHRP cohort 2.

Variable	VIF	1/VIF
AGE	1.88	0.533
GFR	1.36	0.736
LEFT KIDNEY TO BACKGROUND RATIO	1.38	0.724
LEFT RENAL AREA	1.90	0.526
TIME VISUALISATION LEFT PELVIS	1.05	0.948
LEFT NO CORTICAL DEFECTS	1.21	0.828
RIGHT RENAL MARGINS WELL DEFINED	1.20	0.832
Mean VIF	1.43	

* The corresponding Table for log MAXMINHRP cohort 1 is Table 21.

The collinearity between the different variables included in the analysis were tested further, Table 42. There was no significant collinearity (> 0.800) between the variables

Table 42. Correlation matrix of collinearity coefficients of the regression model for the combination with the highest R² for log MAXMINHRP cohort 2.

Variable	AGE	GFR	LEFT KIDNEY TO BACKGROUND RATIO	LEFT RENAL AREA	TIME VISUALI- SATION LEFT PELVIS	LEFT NO CORTICAL DEFECTS	RIGHT RENAL MARGINS WELL DEFINED	-CONS
AGE	1.000							
GFR	0.306	1.000						
LEFT KIDNEY TO BACKGROUND RATIO	-0.162	-0.149	1.000					
LEFT RENAL AREA	-0.735	-0.194	0.013	1.000				
TIME VISUALISATION LEFT PELVIS	0.026	0.131	0.247	-0.058	1.000			
LEFT NO CORTICAL DEFECTS	-0.136	-0.195	-0.434	0.074	0.057	1.000		
RIGHT RENAL MARGINS WELL DEFINED	-0.246	-0.388	-0.203	0.005	-0.117	0.222	1.000	
-CONS	0.283	-0.310	-0.381	-0.442	-0.458	-0.112	-0.026	1.000

*The corresponding Table for log MAXMINHRP cohort 1 is Table 22.

Conclusion regression diagnostics log MAXMINHRP – cohort 2:

The multiple linear regression models for log MAXMINHRP cohort 2 showed minor heteroscedasticity despite the log transform of the dependent variable. The model met all the other necessary statistical assumptions.

Conclusion of the different combinations analysed with multiple linear regression log MAXMINHRP - cohort 1 and cohort2:

The R^2 -values for log MAXMINHRP cohort 2 ranged from 0.1706 to 0.2191. These values were much lower than the values in cohort 1, 0.3284 to 0.4500.

The only variables which were significant in the majority of combinations in which they were present in cohort 1 and 2 were LEFT KIDNEY TO BACKGROUND RATIO and RIGHT KIDNEY TO BACKGROUND RATIO. The individual variables LEFT RENAL AREA, LEFT BACKGROUND AREA, LEFT NO CORTICAL DEFECTS, RIGHT NO CORTICAL DEFECTS, BOTH RENAL MARGINS SMOOTH, and LEFT RENAL MARGINS IRREGULAR were not significant in any log MAXMINHRP combinations in which they were present in cohort 1 and 2.

Of the variables identified as possible predictors of poor reproducibility of DRF measurements in the literature, AGE was significant in 40% of the combinations of cohort 1 and it was significant in the vast majority of the combinations for cohort 2. However, GFR was significant in all combinations in cohort 1 but in cohort 2 it was significant in only 3 % of the combinations.

Summary results cohort 1 and 2:

Variables which do not predict reproducibility of DRF measurements:

LEFT RENAL AREA, LEFT BACKGROUND AREA, BOTH RENAL MARGINS SMOOTH, and RIGHT RENAL MARGINS IRREGULAR did not predict reproducibility in any of the combinations in which they were included.

Variables which probably do not 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 not significant in the majority of combinations in which they were included for both cohorts and for both methods. Therefore, these variables most probably do not predict reproducibility of DRF measurements.

Variables which may predict reproducibility of DRF measurements:

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 and GFR were significant in some but not all the combinations in which they were included. For instance, GFR was significant in most of the combinations in cohort 1 but in only a few for cohort 2.

Variables which predict reproducibility of DRF measurements:

The only individual variable which consistently predicted reproducibility in all combinations in which it was included for both methods was LEFT KIDNEY TO BACKGROUND RATIO. RIGHT KIDNEY TO BACKGROUND RATIO was significant in the majority of the combinations in which it was included.

RIGHT RENAL MARGINS WELL DEFINED, RIGHT RENAL MARGINS POORLY VISUALISED and TIME VISUALISATION RIGHT CALYCES were significant in at least 50% of the combinations in which they were included in cohort 1 and 2 for both methods. AGE was significant in 55% and 40% of the combinations for cohort 1 and in $\geq 80\%$ of the combinations for cohort 2.

Clinical implication of results:

The results presented in this document were compiled after log transforming the dependent variables. The continuous variables which were significant in most of the multiple linear regression combinations for cohort 1 and 2 for both log MAXMINHAUC and log MAXMINHRP: LEFT KIDNEY TO BACKGROUND RATIO, RIGHT KIDNEY TO BACKGROUND RATIO, TIME VISUALISATION RIGHT CALYCES and AGE were re-analysed using the untransformed dependent variables so that the results could be translated into clinical practice.

The patients in cohort 1 and 2 were combined in a single datasheet. The continuous variables LEFT KIDNEY TO BACKGROUND RATIO, RIGHT KIDNEY TO BACKGROUND RATIO, TIME VISUALISATION RIGHT CALYCES and AGE were plotted on scatterplots against the untransformed dependent variables MAX-MIN HAUC and MAX-MIN HRP, Figure 33 through 42.

The plots demonstrate that if the patient has a kidney to background ratio ≥ 5 , no patient has a MAX-MIN HAUC and MAX-MIN HRP ≥ 10 . Most notably poorest reproducibility of DRF values, MAX-MIN HAUC and MAX-MIN HRP ≥ 15 , is seen if the kidney to background ratio is ≤ 3 , Figure 34 through 37.

The plots show that decreased reproducibility of DRF measurement is seen in patients with prompt and slightly delayed visualisation of the right calyces. None of the patients whom had visualisation in the calyces after 12 minutes had a poor reproducibility, Figure 38 and 39.

One sees poor reproducibility, MAX-MIN HAUC and MAX-MIN HRP ≥ 10 , at all ages, Figure 40 and 41. On closer inspection of the children under 24 months age one see that there is a large number of cases with very poor reproducibility, MAX-MIN HAUC and MAX-MIN HRP ≥ 15 , in children $\leq$ four months age, Figure 42 and 43.

Figure 33. The LEFT KIDNEY TO BACKGROUND RATIO plotted against the dependent variable MAX-MIN HAUC.

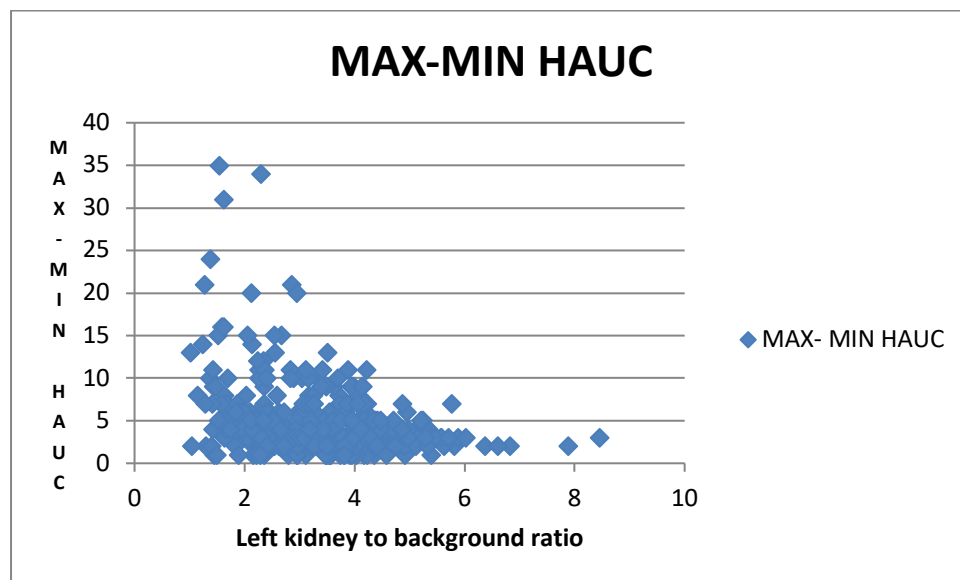


Figure 34. The LEFT KIDNEY TO BACKGROUND RATIO plotted against the dependent variable MAX-MIN HRP.

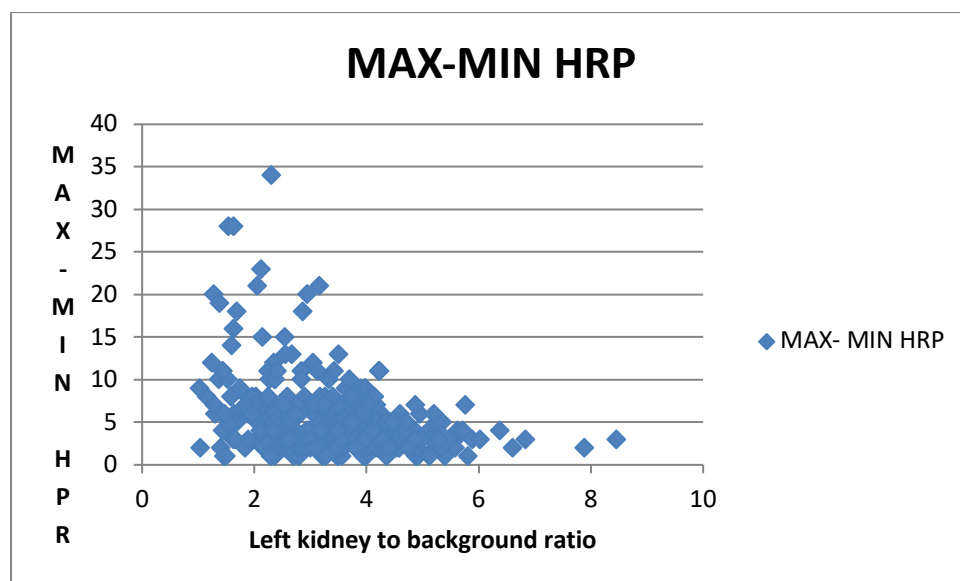


Figure 35. The RIGHT KIDNEY TO BACKGROUND RATIO plotted against the dependent variable MAX-MIN HAUC.

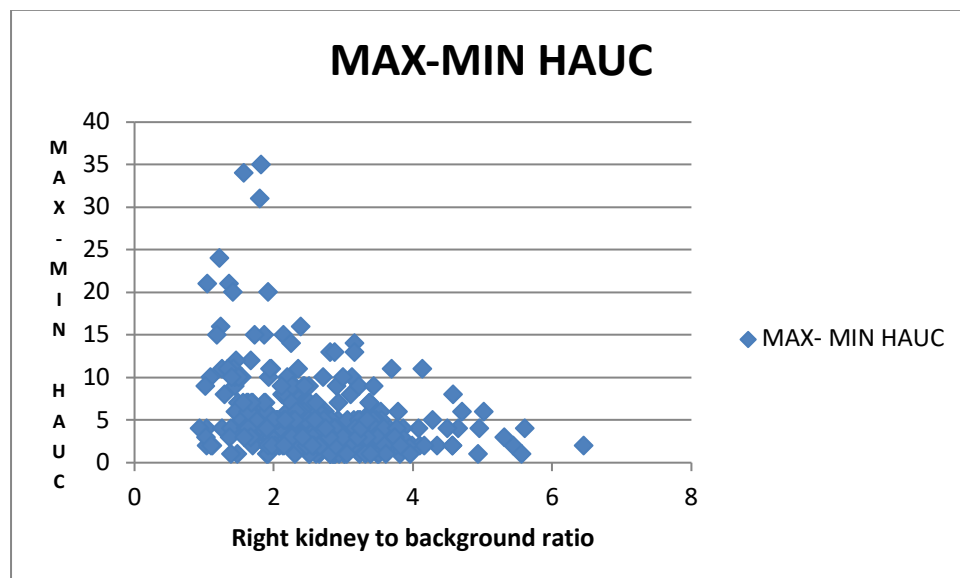


Figure 36. The RIGHT KIDNEY TO BACKGROUND RATIO plotted against the dependent variable MAX-MIN HRP.

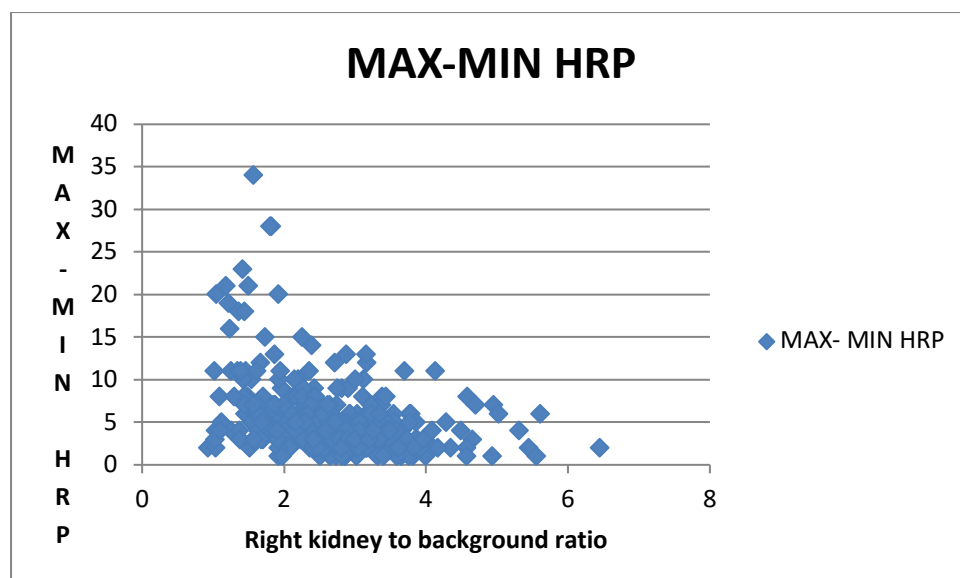


Figure 37. The TIME VISUALISATION RIGHT CALYCES plotted against the dependent variable MAX-MIN HAUC.

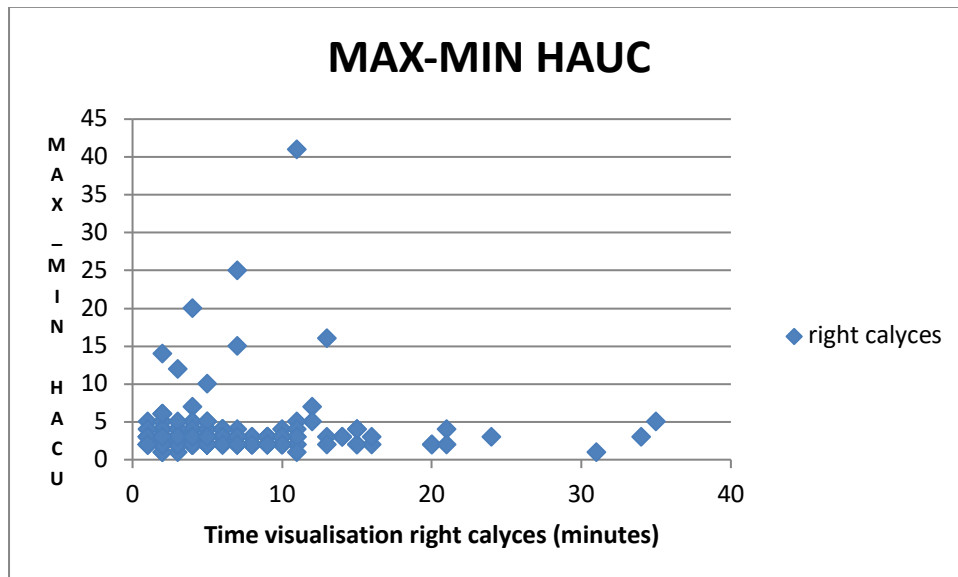


Figure 38. The TIME VISUALISATION RIGHT CALYCES plotted against the dependent variable MAX-MIN HRP.

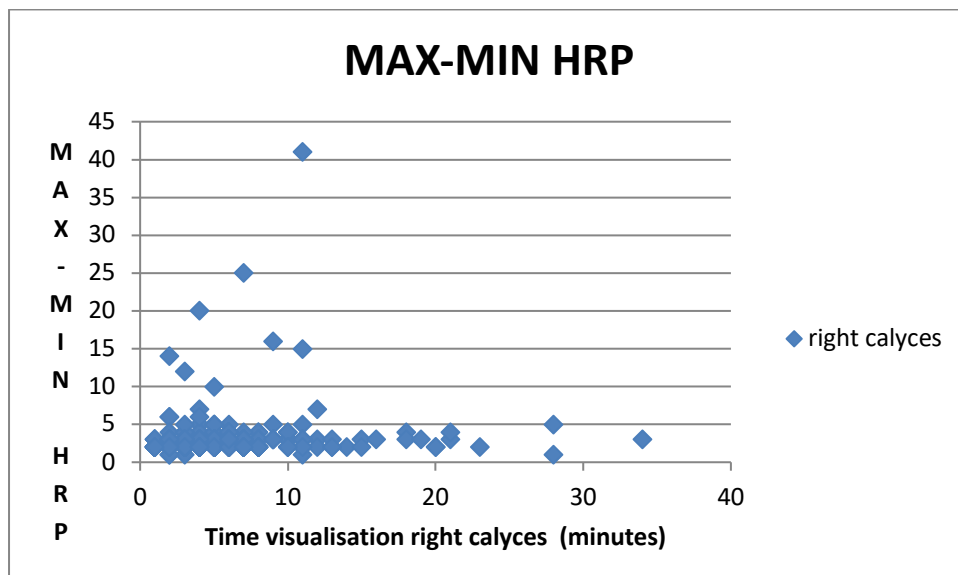


Figure 39. The AGE, all the patients, plotted against the dependent variable MAX-MIN HAUC.

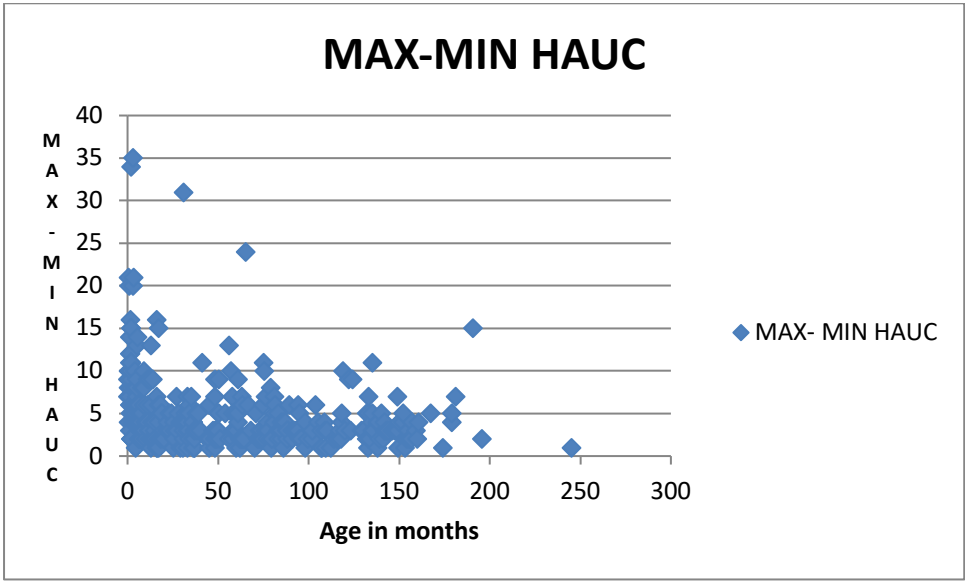


Figure 40. The AGE, all the patients, plotted against the dependent variable MAX-MIN HRP.

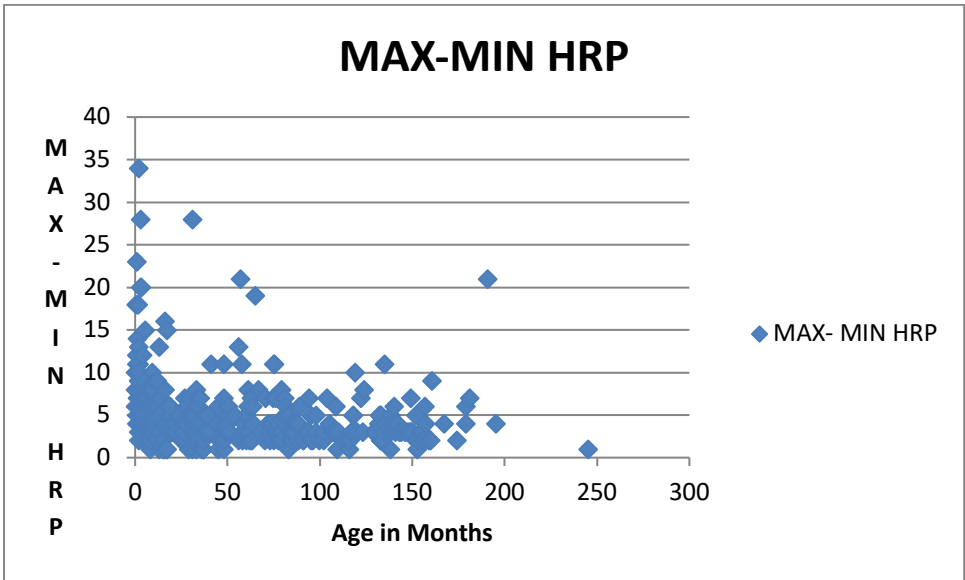


Figure 41. The AGE, all patients younger than 24 months, plotted against the dependent variable
MAX-MIN HAUC.

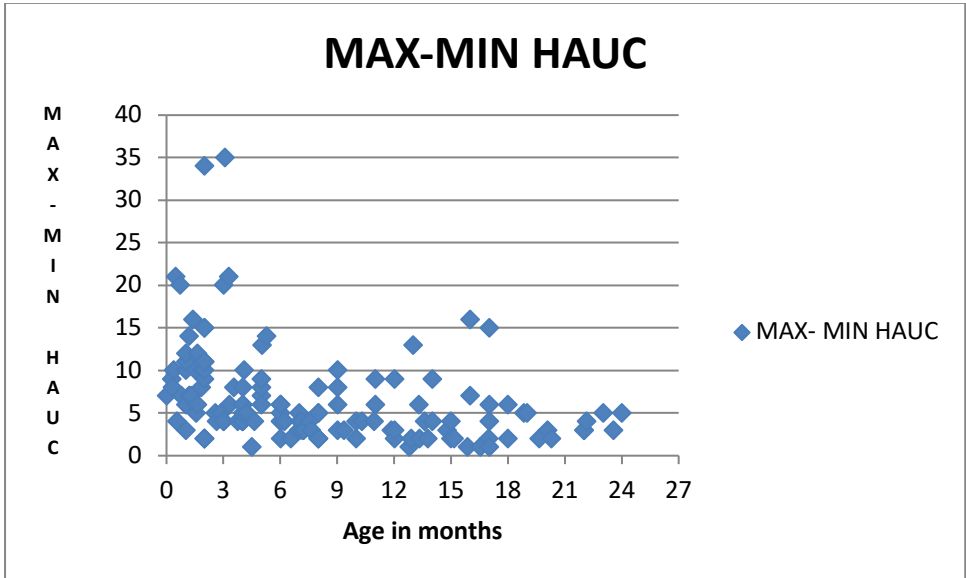
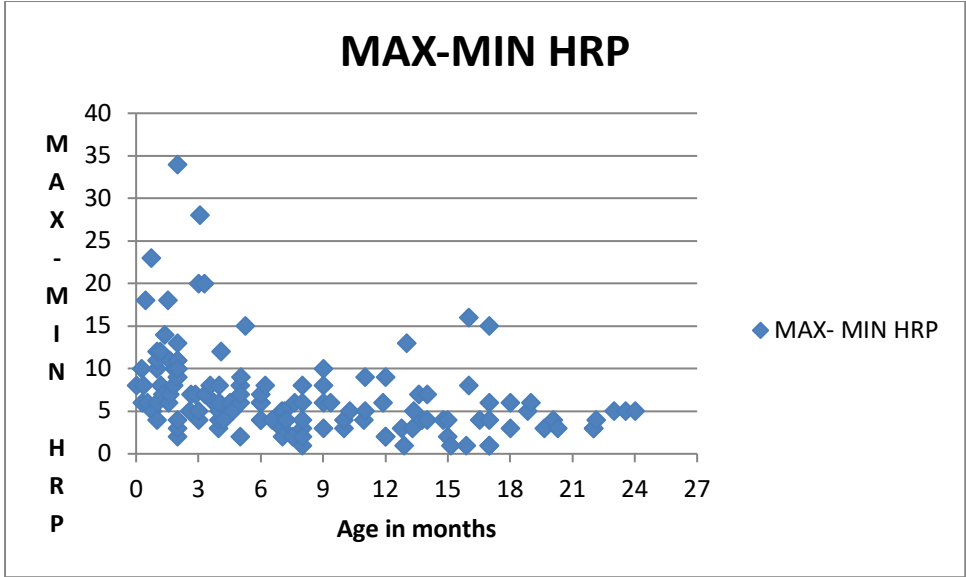


Figure 42. The AGE, all patients younger than 24 months, plotted against the dependent variable
MAX-MIN HAUC.



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 kidney to background ratio. There were 28 kidneys classified as RIGHT RENAL MARGINS POORLY VISUALISED in cohort 1, the RIGHT KIDNEY TO BACKGROUND RATIO for these kidneys ranged between 1.03 and 2.57, with 21 of the 28 having a RIGHT KIDNEY TO BACKGROUND RATIO ≤ 2 . In cohort 2, 38 kidneys were classified as RIGHT RENAL MARGINS POORLY VISUALISED the RIGHT KIDNEY TO BACKGROUND RATIO for these kidneys ranged between 1.01 and 6.45, 30 of these kidneys had a RIGHT KIDNEY TO BACKGROUND RATIO of ≤ 2 . In contrast the 99 kidneys classified as RIGHT RENAL MARGINS WELL DEFINED cohort 1 had a RIGHT KIDNEY TO BACKGROUND RATIO between 1.38 and 4.95 and only 16 patients had a RIGHT KIDNEY TO BACKGROUND RATIO ≤ 2 . In cohort 2, 189 kidneys were classified as RIGHT RENAL MARGINS WELL DEFINED they had a RIGHT KIDNEY TO BACKGROUND RATIO between 0.93 and 5.61 and only 20 patients had a RIGHT KIDNEY TO BACKGROUND RATIO ≤ 2 .

Final conclusion

The goodness-to-fit for the multiple regression models were much higher for all the combinations analysed in cohort 1 than in cohort 2. In cohort 1 the R^2 -values ranged from 0.3510 to 0.4906 for log MAXMINHAUC and 0.3284 to 0.4500 for log MAXMINHRP. In cohort 2, they ranged from 0.1675 to 0.2163 for log MAXMINHAUC, and 0.1706 to 0.2191 for log MAXMINHRP. The combinations with the highest R^2 -value for multiple linear regression analyses were similar in cohort 1 and 2.

The only variable which was significant in all the multiple linear regression combinations for cohort 1 and 2 for both log MAXMINHAUC and log MAXMINHRP was LEFT KIDNEY TO BACKGROUND RATIO. RIGHT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL MARGINS WELL DEFINED, RIGHT RENAL MARGINS POORLY VISUALISED and TIME VISUALISATION RIGHT CALYCES were significant in most of the combinations in which they were present. RIGHT RENAL MARGINS WELL DEFINED and higher AGE

predicted a good reproducibility. A low kidney to background ratio predicted poor reproducibility.

The variables LEFT RENAL AREA, LEFT BACKGROUND AREA, BOTH RENAL MARGINS SMOOTH and RIGHT RENAL MARGINS IRREGULAR were not significant in any combinations in which they were present for cohort 1 and 2 for both log MAXMINHAUC and log MAXMINHRP.

The remaining variables inconsistently predicted reproducibility in log MAXMINHAUC and log MAXMINHRP for both cohort 1 and 2.

Discussion

The DRF value is used in clinical decision making in a wide variety of renal diseases, such as hydronephrosis caused by pelvi-ureteric junction stenosis, vesico-ureteric stenosis, bladder dysfunction, posterior urethral valves and complicated duplex kidneys¹². From the literature and clinical experience, we know that there is a small group of children in whom the measurement of DRF is not reproducible. 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 in these patients^{36,38}.

The impact of all the variables on DRF was examined for both the AUC method and the Rutland Patlak Plot method. These are the two accepted methods for calculating DRF^{8,12}. The mathematical assumptions of the two methods and therefore the calculation of DRF differ. The AUC method calculates DRF from the area under the background corrected renal curve²⁷. The RP method calculates the DRF from the background corrected renal activity and a correction for blood pool activity derived from the cardiac blood pool²¹. In theory the additional correction of the vascular background with the RP method may be useful to correct for the high residual vascular background in cases with decreased renal function. However, the additional blood pool correction decreases the total counts used in the DRF calculation. This decrease in counts makes the RP more sensitive to slight errors than the AUC method^{12,25,39}. Therefore, it was not surprising that the variables which predicted reproducibility of DRF measurement differed between the two methods.

Variables which predict reproducibility:

LEFT KIDNEY TO BACKGROUND RATIO and RIGHT KIDNEY TO BACKGROUND RATIO:

LEFT KIDNEY TO BACKGROUND RATIO predicted reproducibility in all of the combinations log MAXMINHAUC and log MAXMINHRP cohort 1 and 2. RIGHT KIDNEY TO BACKGROUND RATIO was significant in 261 of the 297 combinations analysed for log MAXMINHAUC cohort 1 and all of the combinations analysed for log MAXMINHAUC cohort 2 as well as all of the 120 combinations analysed log MAXMINHRP cohort 1 and 2.

Most nuclear medicine studies reflect differences in the extraction of a tracer from blood by normal and abnormal tissues and organs. In renal studies, as the tracer is taken up by the kidney, activity in the kidney increases, activity in the adjacent tissues, the background, decreases and the kidney to background ratio increases. 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 to 7. The range is comparable to the kidney to background ratios found in this project. The kidney to background ratio for the right kidney was lower with close to a quarter of the renograms having a kidney to background ratio ≤ 2 , which in theory makes visual detection difficult⁸³. In the current project the decrease in reproducibility when the kidney to background ratio was ≤ 2 was clearly demonstrated in the scatterplots of the raw data of the both cohorts for both the HAUC and HRP methods.

Kidney to background ratio values are derived from two measurements, each with their own associated error in count statistics. In this thesis, LEFT KIDNEY TO BACKGROUND RATIO and RIGHT KIDNEY TO BACKGROUND RATIO 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. Usually the mean counts in the kidney (target organ) are much higher those in the background and

therefore the error in renal counts is much lower than that of the background counts. Despite the inherent errors in the derived value it was still the most robust predictor of reproducibility of DRF. It should be noted that the error of the individual measurements, the SD of the total counts in each individual ROI, SD OF TOTAL COUNTS LEFT RENAL ROI, SD OF TOTAL COUNTS RIGHT RENAL ROI, SD OF TOTAL COUNTS LEFT BACKGROUND ROI and SD OF TOTAL COUNT RIGHT BACKGROUND ROI did not predict reproducibility of DRF measurements.

The calculated kidney to background ratio 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 early 1990's Gordon et al. published a paper which assessed how DRF and drainage could guide clinical management. Their paper addressed the importance of kidney to background ratio 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 cut-off was that in cases with low kidney to background ratio one encounters difficulty interpreting a renogram. Causes for poor kidney to background ratio were identified as renal immaturity and the higher volume of interstitial fluid in babies as ^{99m}Tc -DTPA diffuses freely into interstitial fluid¹⁶. In contrast ^{99m}Tc -MAG3 is highly protein bound and therefore it remains in the intravascular space. In addition the maturation of tubular function is faster than that of glomerular function so renal immaturity should not impact the reproducibility of DRF on a ^{99m}Tc -MAG3 renogram as much as on a ^{99m}Tc -DTPA renogram^{48, 5}.

In a study investigating the reproducibility of DRF measurement in 4-week-old piglets it was shown that a high kidney to background ratio was a very important predictor of good reproducibility of DRF measurements. ^{99m}Tc -DMSA scans and ^{99m}Tc -DTPA renograms were done on the same animals. The day to day variation of DRF measurements on ^{99m}Tc -DMSA

scans was small with an average coefficient of variation of 2.3% (range 0.8 – 3.9%). The kidney to background ratio was high as 90% of the injected activity being taken up in the proximal convoluted tubules³⁴.

In contrast the DRF values for the ^{99m}Tc-DTPA renograms were not reproducible. The coefficient of variation ranged between 0.5 and 35.9% for the AUC method and 1.6% to 37.2% for the RP method. DRF was calculated during a 70 -100 second interval which started 30 to 50 seconds after peak cardiac counts. The plasma extraction fraction of ^{99m}Tc-DTPA is determined by the glomerular filtration rate of that particular kidney. In patients with mature glomerular function it is 20%. This value is lower in subjects with immature function. During the time frame used to calculate the DRF there is considerable plasma background activity. The authors concluded that the unfavourable kidney to background ratio when using ^{99m}Tc-DTPA led to the poor reproducibility of DRF in these immature animals³⁴.

The impact of the poor kidney to background ratio 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 ¹²³I-Hippuran, should be used in children with immature function⁶¹.

There are major differences between ^{99m}Tc-DTPA and ^{99m}Tc-MAG3. ^{99m}Tc-DTPA is removed from blood by glomerular filtration with an extraction fraction of about 20% in a mature kidney. ^{99m}Tc-DTPA has less than 10% protein binding and diffuses freely into the extravascular space⁸⁴. In the neonate, the glomerular filtration rate is 52.0 ± 9.0 ml/min/1.73m², increasing over the next 18 months to reach mature adult levels by 2 years⁴⁹. This combination of low renal uptake and high background results in a low kidney to background ratio, particularly in infants and in children with impaired renal function. In contrast, ^{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 kidney to background ratio 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 kidney to background ratio 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 function⁸⁴.

Approximately 3% of injected ^{99m}Tc -MAG3 is found in the liver, gall bladder and gastrointestinal tract in normal healthy volunteers. In patients with decreased renal function increased hepatic uptake of ^{99m}Tc -MAG3 has been described⁵. This could decrease the kidney to background ratio making the visualisation of the right kidney above liver background even more difficult in patients with decreased renal function.

The recent SNMMI procedure standard/ EANM practice guideline for diuretic renal scintigraphy in adults addresses the impact of poor kidney to background ratio on DRF measurement. This guideline recommends that in patients with bilaterally impaired renal function and subsequent delayed tracer uptake and excretion, DRF should be calculated at a later time frame than the one to two, one to two and a half or the one to three minute time interval. The DRF should be calculated on the frames recorded one minute before the tracer leaves the renal ROI. The authors made this recommendation since these patients have poor kidney to background ratio on the early frames due to decreased renal function⁶².

We found that high LEFT KIDNEY TO BACKGROUND RATIO predicted good reproducibility in every combination analysed. Although RIGHT KIDNEY TO BACKGROUND RATIO predicted good reproducibility in most of the combinations in which it was included, there was a percentage, 12% of combinations, in which it did not predict reproducibility for log MAXMINHAUC. The combinations in which RIGHT KIDNEY TO BACKGROUND RATIO did not predict reproducibility were varied and included the majority of the variables analysed for log MAXMINHAUC. The kidney to background ratio 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 left renal ROI has a smaller area of overlap with the spleen. The spleen also

has an arterial blood supply while the liver has an arterial and a portal venous blood supply. Peak background activity in the spleen is earlier than that of the liver⁸⁵. The predominantly portal blood supply to the liver means that there is higher background blood pool activity next to the right kidney during the one to two minutes that DRF is calculated and the liver is a much larger organ than the spleen. Therefore, the blood pool activity adjacent to kidney is much greater on the right than the left.

The difference between right and left background activity on ^{99m}Tc-MAG3 renography was used as a reason to suggest the use of different background corrections for each kidney instead of using a single background ROI⁴². In an early paper investigating DRF measurements on ^{99m}Tc-MAG3 renography, the authors concluded that the high liver background on the early images of the ^{99m}Tc-MAG3 renogram contributed to an over-estimation of DRF on the right. This study compared DRF measurements calculated on ^{99m}Tc-MAG3 renography and ^{99m}Tc-DMSA images and found that with ^{99m}Tc-MAG3 renography DRF measurements of the right kidney were systematically higher. The overall difference in DRF was 1.82 ± 0.57 %. It should be noted that DRF for both ^{99m}Tc-DMSA and ^{99m}Tc-MAG3 studies was calculated using an infero-lateral background ROI which would have underestimated the hepatic contribution to the background on the ^{99m}Tc-MAG3 renogram⁵⁷.

A study calculated the success factor (SF) for drawing ROIs on a 70 Kg reference man phantom renogram study. This factor represents the agreement between two operators for drawing ROIs. It is the fraction of the coincident pixels between the two ROIs, found by dividing the number of pixels common to both regions by the mean number of pixels in the two. The SF was slightly lower for the right renal ROI, 0.92, than for the left renal ROI, 0.95. The author concluded that the difference was due to the right kidney overlapping with the liver⁷⁵.

The higher liver background activity will also cause scatter of radioactivity into those renal pixels close to the liver but not necessarily overlapping with liver activity⁸⁶.

A few renograms were excluded from this study as the kidney to background ratio was so low, we could not clearly define the kidneys above background. Therefore, the result of this study can only be applied to renograms in which the operator is able to visualise the kidney(s) above background.

A number of papers have identified possible causes for poor reproducibility of DRF measurements such as poor and immature renal function^{13,23,25}. These factors are both associated with decreased kidney to background ratios. No paper has investigated kidney to background ratio as an independent factor. This is the first project which shows that this is the best predictor of reproducibility of DRF measurements.

In theory the ability to see the organ above background should be the same irrespective of the tracer used. It would be interesting to investigate if the same kidney to background values apply for different tracer such as ^{99m}Tc-EC, ^{99m}Tc-DTPA and ^{99m}Tc-DMSA.

The kidney to background ratio 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 kidney to background ratio is ≤ 2.0 .

RIGHT RENAL MARGINS WELL DEFINED and RIGHT RENAL MARGINS POORLY VISUALISED:

RIGHT RENAL MARGINS WELL DEFINED and RIGHT RENAL MARGINS POORLY VISUALISED were the strongest categorical predictors of reproducibility. These variables do not overlap, the group RIGHT RENAL MARGINS WELL DEFINED included no patients with RIGHT RENAL MARGINS POORLY VISUALISED and the group RIGHT RENAL MARGINS POORLY VISUALISED included no patients with RIGHT RENAL MARGINS WELL DEFINED. These variables are visual descriptors of kidney to background. If one can clearly see the kidney above background it is easy to place the ROIs. Being able see a kidney

clearly is dependent on the amount of uptake of by the kidney and the background activity. When using ^{99m}Tc -MAG3 good tubular function means that activity is cleared from the blood background quickly. This leads to a high kidney to background ratio and it is therefore easy to clearly visualise the kidneys. The margin of the right kidney overlaps liver background for most of the lateral margin and the upper pole of the kidney. The higher background activity next to the right kidney compared to the left means that one is frequently still able to visualise the left kidney clearly when one has problems identifying the right kidney. Kidneys with poorly visualised margins usually have a low kidney to background ratio. This could be seen in our results as 21 of the 28 in cohort 1 and 30 of the 38 patients in cohort 2 who were classified as RIGHT RENAL MARGINS POORLY VISUALISED had a RIGHT KIDNEY TO BACKGROUND RATIO ≤ 2 . 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.

The difference in the ability to detect the right renal border compared to the left renal border was also confirmed when using an automated system for detecting renal borders. In normal patients AUTROI had a lower error for detecting the left renal borders compared to the board certified nuclear physician ($p = 0.02$). This difference in error was not found for the detection of the right borders ($p = 0.08$). In adult patients with suspected obstruction there was no difference in the ability to detect the left renal margins between the AUTROI system and the experienced nuclear physician, $p = 0.71$, but there was a difference for detecting the right renal border, $p = 0.05^{77}$.

It would be worthwhile investigating if the change in DRF used as an indication for surgical intervention should differ depending on the side of pelvic ureteric junction stenosis.

TIME VISUALISATION RIGHT CALYCES:

Only one of the four variables defined to describe tissue tracer transit, TIME VISUALISATION RIGHT CALYCES consistently predicted reproducibility for both cohorts and both methods in patients with delayed tissue tracer transit.

The flow of urine in the renal tubule moves ^{99m}Tc -MAG3 from the proximal tubule to the renal collecting system. It has also been postulated that children with hydro-nephrosis due to obstruction at the junction of the renal pelvis and ureter would have increased pressure in the collecting system leading to a delay in transit of activity from the kidney to the pelvis^{87,88}.

In children with decreased renal function uptake of the ^{99m}Tc -MAG3 is decreased, leading to a decreased kidney to background ratio. If there is a decrease in GFR in addition to the decrease in ERPF there would be a slow washout of tracer from the renal tubule to the collecting system. Therefore there would be a later visualisation of the collecting system. 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.

In contrast TIME VISUALISATION RIGHT PELVIS did not predict good or bad reproducibility for both methods in cohort 1 and inconsistently for cohort 2. It is difficult to separate activity in the calyces from that in the renal pelvis on most paediatric renograms. In normal kidneys there may be significant overlap of these structures on the images recorded. This visual overlap in structures is exaggerated in children with hydronephrosis making the separation between calyces and pelvis even more difficult. To only assess the time of visualisation of activity in

the subcortical structures rather than assessing the time at which activity appeared in the pelves separate from the calyces seems to be a better parameter.

To our knowledge this is the first study which assessed if the visualisation of activity in the subcortical structures predicted reproducibility of DRF measurements.

AGE:

Higher AGE strongly predicted good reproducibility for both methods in both cohorts with univariate linear regression. In cohort 1 AGE was significant in 55% of the multiple linear regression combinations for log MAXMINHAUC and 40% of the multiple linear regression combinations for log MAXMINHRP. AGE was significant in $\geq 80\%$ of the multiple linear regression combinations in cohort 2 for both methods. This difference in results could not be attributed to differences between the two cohorts. The U-test showed that the ages of the two cohorts were comparable ($p = 0.08$).

The literature pertaining to ^{99m}Tc -DTPA shows there is a higher variation in DRF measurements in infants due to renal immaturity^{14,48}. 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 not significant in ANOVA analyses used to assess factors which 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 months³⁶. A recent study by Tondeur et al., also found that age younger than 6 months did not affect the reproducibility of DRF on ^{99m}Tc -MAG3 renography³⁹.

There is an association between age and maturation of renal function, although the maturation of renal function is not linear. Piepsz has shown that most patients reach mature GFR at 12 months age but maturation can continue until 24 months⁴⁹. About 60% of the patients included in the cohort 1 and 2, 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 reached⁵¹. Less than 15% of the children in cohort 1 and 2 were younger than two months. The effect of immature tubular function on reproducibility was therefore not adequately tested in this research project. However, on analysis of the raw data of both populations a trend of decreased reproducibility is clearly identified in children younger than 4 months for both the HAUC and HRP methods. The reporting physician should be aware of this potential pitfall in the reproducibility of DRF measurement in younger children but this should not discourage the use of ^{99m}Tc -MAG3 renography in children where indicated.

It is not only renal maturation which impacts on the reproducibility of DRF in young children. A number of physiological and anatomical factors also affect the technical quality of the images recorded. The kidneys of small children are small and close to the diaphragm. The kidneys move during normal respiration. The median respiratory rate of a neonate is 44 breaths per minute. There is a steep decline in the breaths per minute during the first two years of life. The median respiratory rate of a two year old is 26 breaths per minute. If the baby cries during the uptake part of the scan there are deeper and more frequent breaths and more pronounced movement of the kidneys⁸⁹. This movement causes the renal tissue to move in and out of the background ROI and can reduce the accuracy of the DRF measurement.

It should also be kept in mind that the children referred for renograms usually have history of significant renal disease and that this would also impact on the reproducibility of DRF measurement in these children.

In summary DRF measurement on a ^{99m}Tc -MAG3 study in young children is affected by many factors such as renal pathology, renal maturity, renal size and movement artefacts. The reproducibility of DRF measurements in children younger than 4 months is decreased.

Variables which may predict reproducibility:

BOTH RENAL MARGINS WELL DEFINED, LEFT RENAL MARGINS WELL DEFINED, LEFT RENAL MARGINS POORLY VISUALISED, and BOTH RENAL MARGINS IRREGULAR:

BOTH RENAL MARGINS WELL DEFINED was significant in all the combinations analysed for both methods in cohort 1 and none of the combinations analysed for cohort 2. The variable BOTH RENAL MARGINS WELL DEFINED was derived from the individual variables LEFT RENAL MARGINS WELL DEFINED and RIGHT RENAL MARGINS WELL DEFINED. The finding is therefore in keeping with the results of LEFT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS POORLY VISUALISED. LEFT RENAL MARGINS WELL DEFINED, LEFT RENAL MARGINS POORLY VISUALISED, RIGHT RENAL MARGINS WELL DEFINED and RIGHT RENAL MARGINS POORLY VISUALISED were significant in 50% of the combinations analysed for both methods cohort 1. RIGHT RENAL MARGINS WELL DEFINED and RIGHT RENAL MARGINS POORLY VISUALISED which were significant in $\geq 80\%$ of the combinations of cohort 2 but LEFT RENAL MARGINS WELL DEFINED and LEFT RENAL MARGINS POORLY VISUALISED were not significant in any combination analysed for cohort 2.

These findings show that the ability to clearly see the right kidney is a greater predictor of reproducibility than the ability to see the left kidney above background. One can frequently still visualise the left kidney clearly while having difficulty visualising the right kidney above liver background when there is a global decrease in ^{99m}Tc -MAG3 uptake.

BOTH RENAL MARGINS IRREGULAR was a strong predictor of poor reproducibility in most of the combinations in which it was analysed. In children with more severe renal impairment one frequently sees bilateral irregular renal margins.

The variables which describes the renal margins are subjective and the classification of well defined and poorly visualised and smooth or irregular may not be consistently assigned by any single observer.

The variables BOTH RENAL MARGINS WELL DEFINED, LEFT RENAL MARGINS WELL DEFINED, LEFT RENAL MARGINS POORLY VISUALISED OR BOTH RENAL MARGINS IRREGULAR did not consistently predict reproducibility. From our results it is clear that an objectively measured kidney to background ratio is a better predictor of reproducibility than these subjective variables.

TIME VISUALISATION LEFT CALYCES and TIME VISUALISATION LEFT PELVIS:

TIME VISUALISATION LEFT CALYCES and TIME VISUALISATION LEFT PELVIS inconsistently predicted both good and poor reproducibility in the combinations analysed for cohort 1. TIME VISUALISATION LEFT CALYCES predicted reproducibility in 39% of the combinations log MAXMINHAUC and 50% of the combinations log MAXMINHRP cohort 1 and none of the cohort 2 combinations. TIME VISUALISATION LEFT PELVIS was significant in 30% of the combinations analysed for log MAXMINHAUC and log MAXMINHRP cohort 1 for cohort 2 it was significant in 9% for log MAXMINHAUC but nearly all, 96%, of the combinations analysed for log MAXMINHRP.

It has been shown in animal models that the transit of ^{99m}Tc -MAG3 from the cortex to the collecting system is delayed if there is a drop in GFR but no drop in the effective renal plasma flow to the tubule. This is seen in response to obstruction and is a precursor to sclerosis of the nephron⁹⁰. If there is globally decreased GFR the transit of tracer through both kidneys will also be delayed.

The time at which one sees activity in the subcortical structures, calyces and pelves, is dependent on the GFR. The flow of urine through the nephron moves ^{99m}Tc -MAG3 from the proximal convoluted tubule through the rest of the nephron and into the collecting system. In kidneys with normal renal function and no obstruction one normally sees activity in the

calyces at two to three minutes if Furosemide was given at the same time as the ^{99m}Tc -MAG3 injection^{88,91,92}.

Later TIME VISUALISATION LEFT PELVIS and TIME VISUALISATION LEFT CALYCES were not consistent predictors of good or poor reproducibility in contrast to TIME VISUALISATION RIGHT CALYCES. The ability to see an increase in activity in a small subcortical structure above changing renal parenchymal activity may have caused this finding. In the early images the renal parenchymal activity is high and the subcortical structures may even be photopaenic. As the study progresses and the activity moves from the nephron to the collecting system the decrease in parenchymal activity makes the visualisation of the subcortical structures easier. It is therefore difficult to visualise the subcortical structures during the first couple of minutes of a renogram. In children with poor renal function activity in the renal parenchyma will persist for longer making visualisation of subcortical structure in these patients difficult.

Further studies which formally assess the relationship between mGFR and the time of visualisation of subcortical structure may be useful. In this project the vast majority of GFR values were eGFRs.

GFR:

Patients with higher GFR values usually have better uptake of ^{99m}Tc -MAG3. If both kidneys have good uptake of ^{99m}Tc -MAG3 they will be well defined above background and the kidney to background ratio will be high.

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 laboratory method used to measure creatinine between the two cohorts. The GFR values

between the two cohort populations differed. The use of eGFR in the majority of patients was suboptimal.

The GFR values in for the patients in cohort 1 ranged between 19 and 230 ml/min/1.73m². In cohort 2 the values ranged between 12 and 358 ml/min/1.73m². The median values of the cohort 1 and 2 were 99 ml/min/1.73m² and 121 ml/min/1.73m² respectively. The U-test showed that the GFR values of the two cohorts were different ($p < 0.001$). A reason for this difference in cohorts could be that cohort 1 was collected retrospectively and creatinine measurements were only performed on children in whom there was a concern regarding the renal function. For cohort 2 blood for creatinine measurement was taken if possible, at the time of the ^{99m}Tc-MAG3 renogram studies. Another reason for the difference in cohorts could be that eGFR was used as a measure of renal function for the majority of patients included for both cohort 1 and 2. The method for measuring creatinine used by our laboratory changed from the Jaffe method to an enzymatic method on 24 November 2010. Therefore, the method used for measuring the creatinine in cohort 1 was different to the method used in cohort 2.

The bedside isotope dilution mass spectrometric (IDMS)-traceable Schwartz method was used to calculate the eGFRs. This method has been shown to have a good conformity with measured GFRs at levels <60 ml/min/1.73m² but the error of the calculation increases at high GFR values⁹³. This error in calculation of GFRs in patients with low creatinine levels, high GFR values, could explain the unusually large GFR values that were obtained with some of the patients.

The literature identifies a very low GFR as a cause for poor reproducibility on ^{99m}Tc-MAG3 renography⁵⁹. 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 μ mol/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 GFRs¹⁷. The difference between DRF

measurements calculated from ^{99m}Tc -DMSA and ^{99m}Tc -MAG3 scintigraphy in adult patients without hydronephrosis showed that the difference between the measurements increased as renal function dropped and the difference between measurements was most pronounced in the group with an ERPF of the right kidney $\leq 100 \text{ ml/min}^{57}$.

Even when using ^{99m}Tc -DTPA instead of ^{99m}Tc -MAG3 it appears that 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 $\leq 15 \text{ ml/min}^{52}$.

Only 24% of the cohort 1 had a GFR below 80 and 9% a GFR $< 60 \text{ ml/min/1.73m}^2$. In cohort 2, 17% of the patients had GFR values $< 80 \text{ ml/min/1.73m}^2$. The effect of low GFR on reproducibility could therefore not be effectively tested in these populations.

In this project GFR was used as a measurement of renal function. However, ^{99m}Tc -MAG3 is uptake is by tubular secretion by the proximal tubules. The physiological maturation of tubular function is faster than that of GFR. The maturation of renal function as measured by normalisation of clearance of ^{99m}Tc -MAG3 is fast in the first three weeks of life and then reaches a plateau at the end of 12 months⁵¹.

Future studies which investigate the effect of GFR on the reproducibility of DRF measurements are needed. These studies should use only mGFRs and contain large enough populations with decreased GFR to confirm the effect of low GFR on reproducibility.

Variables which probably did not predict reproducibility:

LEFT NO CORTICAL DEFECTS, RIGHT NO CORTICAL DEFECTS and LEFT < 2 CORTICAL DEFECTS:

LEFT NO CORTICAL DEFECTS was significant in 30% of the combinations analysed for log MAXMINHAUC cohort 1 but, it was not significant log MAXMINHAUC cohort 2 or in log MAXMINHRP cohort 1 and 2. A larger proportion, 38%, of cohort 1 had cortical defects on left compared to 22% of cohort 2. RIGHT NO CORTICAL DEFECTS was significant in only 4% of the combinations analysed for log MAXMINHAUC cohort 2, it was not significant in any combination analysed for log MAXMINHAUC cohort 1 or log MAXMINHRP cohort 1 and 2. LEFT < 2 CORTICAL DEFECTS was significant in only 2% of the combinations analysed for log MAXMINHAUC cohort 1 and none of the combinations analysed for log MAXMINHAUC cohort 2. It was not included in the multiple linear regression for log MAXMINHRP.

Cortical defects are due to diseases, such as pyelonephritis, which cause regional damage to the cortex. They are associated with severe or repeated renal injury. 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 therefore has no impact on the reproducibility of DRF measurements. It is more difficult to detect cortical defects in the right kidney due to the lower kidney to background ratio. If there are multiple cortical defects the renal function of the affected kidney may be severely impaired, decreasing the kidney to background ratio and making the detection of cortical defects difficult. The detection of cortical defects is subjective in contrast to the objective measurement of the kidney to background ratio.

To our knowledge this is the first study to evaluate the impact of cortical defects on DRF. However, our study population was dominated by many patients with no cortical defects. The fact the number of patients with multiple cortical defects was too low for analysis was a

limitation. Future studies should be performed to assess if multiple cortical defects decrease reproducibility of DRF measurements.

LEFT RENAL MARGINS SMOOTH, RIGHT RENAL MARGINS SMOOTH and LEFT RENAL MARGINS IRREGULAR:

LEFT RENAL MARGINS SMOOTH predicted reproducibility in 33% of the combinations analysed for log MAXMINHAUC cohort 1 and 17% of the combinations analysed for log MAXMINHRP cohort 1 and none of the combinations analysed for cohort 2. LEFT RENAL MARGINS IRREGULAR predicted reproducibility in only 31% of the combinations analysed for log MAXMINHAUC cohort 1 and none of the other combinations. RIGHT RENAL MARGINS SMOOTH was only significant in 4% of the combinations analysed for log MAXMINHRP cohort 1 and none of the other combinations.

The description renal margins irregular was reserved for kidneys where the renal margins appeared jagged or scalloped. In practice the classification of renal margins smooth or irregular was more difficult than the classification renal margins well defined or poorly visualised. It is also more difficult to assess the smoothness of the border of the right kidney in comparison to the smoothness of the left renal margins. This could explain the reason why LEFT RENAL MARGINS SMOOTH and LEFT RENAL MARGINS IRREGULAR did predict reproducibility in some of the combinations in which they were included.

In this study the kidney to background and the ability to see the kidney impacted on the reproducibility of DRF irrespective of the smoothness of the renal margins.

This is the first study which investigates if the smoothness of renal margins has an impact on the reproducibility of DRF measurements. From this study it seems that the impact of the smoothness of the renal margins is probably not relevant on the reproducibility of DRF measurements.

A possible weakness of this analysis is that we did not create a variable SINGLE RENAL MARGINS SMOOTH, irrespective of side of the kidney. This may be analysed in a future project.

RIGHT RENAL AREA:

This variable was only included in the multiple linear regression combinations analysed for log MAXMINHAUC. In the multiple linear regression combinations it was significant in less than 50% of the combinations analysed for cohort 1 and none of the combinations analysed for cohort 2. This result could be in keeping with the fact the population tested had a wide range of renal sizes. It included hydronephrotic kidneys, normal kidneys and small dysplastic kidneys. The size of normal kidneys increases throughout childhood and adolescence so a larger renal size in this mixed patient population is more in keeping with renal growth than hydronephrosis⁹⁴. It was more difficult to draw renal ROIs around poorly functioning right kidneys. These kidneys had a decreased kidney to background ratio and they were not clearly visualised above the high liver background. If the right kidney is small the functioning tissue of this kidney is reduced, which leads to decreased uptake and a decreased kidney to background ratio.

The effect of large renal size due to hydronephrosis was not effectively investigated by this population. A study which investigates differences in reproducibility in children without hydronephrosis and children with varying degrees of hydronephrosis would be more appropriate.

Variables which did not predict reproducibility:

LEFT RENAL AREA and LEFT BACKGROUND AREA:

In the multiple linear regression models LEFT RENAL AREA and LEFT BACKGROUND AREA did not have an impact on the reproducibility of DRF measurements in any of the combinations in which they were included.

The sizes of the kidneys, and by default the background area, increase with age, unless the child has a dysplastic kidney, or a kidney severely affected by nephropathy in which case uptake by the kidney will be decreased. It has been postulated that in patients with very big kidneys the DRF would be overestimated due to the increased the vascular component²⁰. In addition, there may be an increase in blood flow to obstructed hydronephrotic kidneys as part of the pathophysiologic response to obstruction⁴⁵. Another problem with large kidneys is when a child has severe dilatation of the kidney one can have difficulty drawing a background ROI that stays within the confines of the body outline. If the ROI extends outside the body outline it leads to an inaccurate assessment of the DRF. It has been recommended that separate background ROIs above and below such a kidney should be drawn²⁴. We have postulated that inhomogeneous tracer distribution within the kidney due to the large photopaenic calyces and pelvis on the initial images could lead to over subtraction of background in the calyceal and pelvic pixels. These factors would negatively affect reproducibility but this has not been proved.

The unexpected finding that the size of the left kidney ROIs 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 and that only a proportion of the children were investigated for hydronephrosis. Of these only a small number had severe hydronephrosis which made the drawing of ROIs difficult.

To our knowledge this is the first project which formally investigates the effect of the renal size on the reproducibility of DRF measurements.

Future studies could be performed in children with hydronephrosis, investigating if there is an association between the degree of hydronephrosis and poor reproducibility.

BOTH RENAL MARGINS SMOOTH and RIGHT RENAL MARGINS IRREGULAR:

BOTH RENAL MARGINS SMOOTH and RIGHT RENAL MARGINS IRREGULAR were not significant in any of the combinations in which they were included.

As discussed previously the description of renal margins smooth or irregular was subjective. It is also more difficult to clearly visualise the right renal margins clearly above the liver background on the early cortical images.

This is the first study which investigates if the smoothness of renal margins has an impact on the reproducibility of DRF measurements. From this study it seems that the impact of the smoothness of the renal margins is probably not relevant on the reproducibility of DRF measurements.

The univariate linear regression result which contradicts findings in the literature:

ASYMMETRY DRF:

The variable ASYMMETRY DRF did not predict good or bad reproducibility in both methods and in both cohorts when analysed with univariate linear regression so this variable was not included in the combinations analysed.

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. Once perirenal background correction was applied this difference was $1.5 \pm 2.2\%$ for the integral method and $0.7 \pm 2.8\%$ for the Rutland Patlak method background correction³². The EANM guidelines for renography state that if there is asymmetry of renal function and/or reduced renal function only methods recommended by the guidelines can be used to calculate DRF¹². This implies that the ability to calculate DRF may be impaired if there is asymmetry in renal function.

The kidney to background ratio of either kidney was found to be a far more important factor than asymmetry in renal function. It can be argued that if there is very severe asymmetry then the kidney to background ratio of the affected kidney would be poor. However, in many small dysplastic kidneys the asymmetry in renal function can be attributed to the difference in functional renal mass instead of poor kidney to background ratio. Many small kidneys can still be clearly identified above background if uptake of ^{99m}Tc -MAG3 by the remaining renal tissue is still good.

The absence of collinearity between AGE and GFR:

There is extensive data which shows that GFR increases with AGE until 18 to 24 months age and that these factors are not independent physiologically^{48,49,51}. However, collinearity between AGE and GFR was not illustrated for the multiple linear regression models for both log MAXMINHAUC and log MAXMINHRP. One of the reasons for this may be that the 59% of cohort 1 was older than 18 months and only 24% was less than 6 months old. For cohort 2 67%, of the children were older than 18 months. So most of the patients included in cohort 1 and 2 had mature renal function.

Limitations:

A limitation of this study was the fact that most of the patients, 89%, had eGFRs. A large study by Pottel et al., which used ⁵¹Cr-EDTA measured GFR as a validation method, predicted that 61.3% of patients with an eGFR < 90ml/min/1.73m² and that 47.2% of the patients with an eGFR ≥ 90ml/min/1.73m² would fall within ± 30% of the ⁵¹Cr-EDTA mGFR values. They did however not include measured GFRs in children under two years⁹⁵.

Another limitation was the non-random exclusion of patients with poor uptake as some of the variables such as number of cortical defects could not be assessed. The impact of very poor uptake on DRF measurements could not be adequately investigated. The results of this study can therefore only be extrapolated to renogram studies showing enough uptake to allow the operator to draw the ROIs

The R²-value of the cohort 2 multiple linear regression models were low. This means that there are one or more factors which impact on the reproducibility that were not examined by these multiple regression models.

Recommendations and future perspective:

It is recommended that the kidney to background ratio 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 kidney to background ratio is ≤ 2.0 .

A number of questions have not been answered by this project and could be investigated in future:

1. Test the results of this project on novel DRF measurement methods.
2. It would be interesting to investigate if the same kidney to background values apply for different tracers such as $^{99m}\text{Tc-EC}$, $^{99m}\text{Tc-DTPA}$ and $^{99m}\text{Tc-DMSA}$.
3. It would be interesting to investigate if a similar target to background ratio would apply for different Nuclear Medicine investigations for example equilibrium gated radionuclide angiography (ERNA).
4. Should the change in DRF, used as an indication for surgical intervention, differ depending on the side of pelvic ureteric junction stenosis?
5. A formal assessment of the relationship between mGFR and the time of visualisation of subcortical structure may be useful.
6. Investigate the effect of mGFR on the reproducibility of DRF measurements. These studies should contain large enough populations with decreased mGFR to confirm the effect of low mGFR on reproducibility.
7. Investigate if multiple renal cortical defects decrease the reproducibility of DRF measurements.
8. Investigate if there are differences in reproducibility of DRF measurement in children without hydronephrosis compared to children with varying degrees of hydronephrosis.

Conclusion:

The only variables which consistently predicted good and poor reproducibility for the measurement of DRF on ^{99m}Tc -MAG3 renograms performed according to the EANM guidelines for both log MAXMINHAUC and log MAXMINHRP were AGE, LEFT KIDNEY TO BACKGROUND RATIO, RIGHT KIDNEY TO BACKGROUND RATIO, RIGHT RENAL MARGINS WELL DEFINED and TIME VISUALISATION RIGHT CALYCES.

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

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Appendix

Abbreviation key for Table 43 and 44:

- age: AGE
- gfr: GFR
- ltargettobackgroundratio: LEFT KIDNEY TO BACKGROUND RATIO
- rtargettobackgroundratio: RIGHT KIDNEY TO BACKGROUND RATIO
- lrenalmm2: LEFT RENAL AREA
- rrenalmm2: RIGHT RENAL AREA
- lbackmm2: LEFT BACKGROUND AREA
- leftcalyces: TIME VISUALISATION LEFT CALYCES
- rightcalyces: TIME VISUALISATION RIGHT CALYCES
- leftpelvis: TIME VISUALISATION LEFT PELVIS
- lnocorticaldefects: LEFT NO CORTICAL DEFECTS
- rnocorticaldefects: RIGHT NO CORTICAL DEFECTS
- lcorticaldefects2: LEFT < 2 CORTICAL DEFECTS
- lrenalmarginssmooth: LEFT RENAL MARGINS SMOOTH
- rrenalmarginssmooth: RIGHT RENAL MARGINS SMOOTH
- allsmooth: BOTH RENAL MARGINS SMOOTH
- lrenalmarginsirregular: LEFT RENAL MARGINS IRREGULAR
- rrenalmarginsirregular: RIGHT RENAL MARGINS IRREGULAR
- allirregular: BOTH RENAL MARGINS IRREGULAR
- lwelldefined: LEFT RENAL MARGINS WELL DEFINED
- rwelldefined: RIGHT RENAL MARGINS WELL DEFINED
- allwell: BOTH RENAL MARGINS WELL DEFINED
- lrenalmarginspoorlyvisualised: LEFT RENAL MARGINS POORLY VISUALISED
- rrenalmarginspoorlyvisualised: RIGHT RENAL MARGINS POORLY VISUALISED

Table 43. The 594 different combinations tested for log MAXMINHAUC.

The combinations tested for MAXMINHAUC
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, lrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, rrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, allsmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, lrenalmarginsirregular
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, rrenalmarginsirregular
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, allirregular
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, lwelldefined
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, rwelldefined
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, allwell
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, lrenalmarginspoorlyvisualised
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, rrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, lrenalmarginssmooth
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, rrenalmarginssmooth
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, allsmooth
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, lrenalmarginsirregular
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, rrenalmarginsirregular
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, allirregular
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, lwelldefined
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, rwelldefined

age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, allwell
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, lrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, Inocorticaldefects, rrenalmarginspoorlyvisualised
age, gfr, ltargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, lrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, rrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, allsmooth
age, gfr, ltargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, lrenalmarginsirregular
age, gfr, ltargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, rrenalmarginsirregular
age, gfr, ltargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, allirregular
age, gfr, ltargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, lwelldefined
age, gfr, ltargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, rwelldefined
age, gfr, ltargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, allwell
age, gfr, ltargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, lrenalmarginspoorlyvisualised
age, gfr, ltargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, rrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, lrenalmarginssmooth
age, gfr, rtargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, rrenalmarginssmooth
age, gfr, rtargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, allsmooth
age, gfr, rtargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, lrenalmarginsirregular
age, gfr, rtargettobackgroundratio, lbackmm2, leftpelvis, Inocorticaldefects, rrenalmarginsirregular

age, gfr, rtargettobackgroundratio, lbackmm2, leftpelvis, lnocorticaldefects, allirregular
age, gfr, rtargettobackgroundratio, lbackmm2, leftpelvis, lnocorticaldefects, lwelldefined
age, gfr, rtargettobackgroundratio, lbackmm2, leftpelvis, lnocorticaldefects, rwelldefined
age, gfr, rtargettobackgroundratio, lbackmm2, leftpelvis, lnocorticaldefects, allwell
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age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, lrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, rrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, allsmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, lrenalmarginsirregular
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, rrenalmarginsirregular
age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, allirregular
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age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, allwell
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age, gfr, ltargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, rrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, lrenalmarginssmooth
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, rrenalmarginssmooth
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, allsmooth

age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, lrenalmarginssirregular
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age, gfr, ltargettobackgroundratio, rrenalmm2, leftpelvis, lcorticaldefects2, allwell
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age, gfr, rtargettobackgroundratio, rrenalmm2, leftcalyces, lcorticaldefects2, lrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, rrenalmm2, leftcalyces, lcorticaldefects2, rrenalmarginspoorlyvisualised
age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, lrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, rrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, allsmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, lrenalmarginssirregular
age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, rrenalmarginssirregular

age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, allirregular
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age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, rwelldefined
age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, allwell
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age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, allirregular
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, lwelldefined
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, rwelldefined
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, allwell
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, lrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, lnocorticaldefects, rrenalmarginspoorlyvisualised

age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, Inocorticaldefects, lrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, Inocorticaldefects, rrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, Inocorticaldefects, allsmooth
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, Inocorticaldefects, lrenalmarginsirregular
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, Inocorticaldefects, rrenalmarginsirregular
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, Inocorticaldefects, allirregular
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age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, Inocorticaldefects, allirregular
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age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, lnocorticaldefects, rwelldefined
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age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, rwelldefined
age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, allwell
age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, lrenalmarginspoorlyvisualised
age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, rrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, lrenalmarginssmooth
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, rrenalmarginssmooth

age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, allsmooth
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, lrenalmarginsirregular
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, rrenalmarginsirregular
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, allirregular
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, lwelldefined
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, rwelldefined
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, allwell
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, lrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, rnocorticaldefects, rrenalmarginspoorlyvisualised
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, lrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, rrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, allsmooth
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, lrenalmarginsirregular
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, rrenalmarginsirregular
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, allirregular
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, lwelldefined
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, rwelldefined
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, allwell

age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, lrenalmarginspoorlyvisualised
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age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, rrenalmarginssmooth
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, allsmooth
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, lrenalmarginssirregular
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, rrenalmarginssirregular
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, allirregular
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, lwelldefined
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, rwelldefined
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, allwell
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, lrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, rnocorticaldefects, rrenalmarginspoorlyvisualised
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age, gfr, ltargettobackgroundratio, rrenalmm2, rightcalyces, lnocorticaldefects, allsmooth
age, gfr, ltargettobackgroundratio, rrenalmm2, rightcalyces, lnocorticaldefects, lrenalmarginssirregular

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age, gfr, ltargettobackgroundratio, rrenalmm2, rightcalyces, Inocorticaldefects, lwelldefined
age, gfr, ltargettobackgroundratio, rrenalmm2, rightcalyces, Inocorticaldefects, rwelldefined
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age, gfr, rtargettobackgroundratio, rrenalmm2, rightcalyces, rnocorticaldefects, allirregular
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age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, lcorticaldefects2, lwelldefined
age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, lcorticaldefects2, rwelldefined
age, gfr, ltargettobackgroundratio, lrenalmm2, rightcalyces, lcorticaldefects2, allwell
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age, gfr, rtargettobackgroundratio, lrenalmm2, rightcalyces, lcorticaldefects2, allirregular
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age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, lcorticaldefects2, lrenalmarginssmooth
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age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, lcorticaldefects2, allwell

age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, lcorticaldefects2, lrenalmarginspoorlyvisualised
age, gfr, ltargettobackgroundratio, lbackmm2, rightcalyces, lcorticaldefects2, rrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, lcorticaldefects2, lrenalmarginssmooth
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age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, lcorticaldefects2, allirregular
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, lcorticaldefects2, llwelldefined
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, lcorticaldefects2, rwelldefined
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, lcorticaldefects2, allwell
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, lcorticaldefects2, lrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, lbackmm2, rightcalyces, lcorticaldefects2, rrenalmarginspoorlyvisualised
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age, gfr, ltargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, rrenalmarginssmooth
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age, gfr, ltargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, lrenalmarginssirregular
age, gfr, ltargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, rrenalmarginssirregular

age, gfr, ltargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, allirregular
age, gfr, ltargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, lwelldefined
age, gfr, ltargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, rwelldefined
age, gfr, ltargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, allwell
age, gfr, ltargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, lrenalmarginspoorlyvisualised
age, gfr, ltargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, rrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, lrenalmarginssmooth
age, gfr, rtargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, rrenalmarginssmooth
age, gfr, rtargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, allsmooth
age, gfr, rtargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, lrenalmarginsirregular
age, gfr, rtargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, rrenalmarginsirregular
age, gfr, rtargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, allirregular
age, gfr, rtargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, lwelldefined
age, gfr, rtargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, rwelldefined
age, gfr, rtargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, allwell
age, gfr, rtargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, lrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, rrenalmm2, rightcalyces, lcorticaldefects2, rrenalmarginspoorlyvisualised

Table 44. The 240 different combinations tested for log MAXMINHRP.

The combinations tested for MAXMINHRP
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, rwelldefined
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, rnocorticaldefects, rrenalmarginspoorlyvisualised
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, lnocorticaldefects, rwelldefined
age, gfr, rtargettobackgroundratio, lrenalmm2, leftpelvis, lnocorticaldefects, rrenalmarginspoorlyvisualised
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age, gfr, ltargettobackgroundratio, lbackmm2, leftcalyces, lnocorticaldefects, rrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, leftcalyces, rnocorticaldefects, allsmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, leftcalyces, lnocorticaldefects, rrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, leftcalyces, lnocorticaldefects, allirregular
age, gfr, ltargettobackgroundratio, lbackmm2, leftcalyces, lnocorticaldefects, allsmooth
age, gfr, ltargettobackgroundratio, lbackmm2, leftcalyces, rnocorticaldefects, lwelldefined
age, gfr, ltargettobackgroundratio, lbackmm2, leftcalyces, rnocorticaldefects, lrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, leftcalyces, lnocorticaldefects, allsmooth

age, gfr, ltargettobackgroundratio, lbackmm2, leftcalyces, Inocorticaldefects, lrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lbackmm2, leftcalyces, Inocorticaldefects, lrenalmarginssirregular
age, gfr, ltargettobackgroundratio, lrenalmm2, leftcalyces, rnocorticaldefects, lwelldefined
age, gfr, ltargettobackgroundratio, lrenalmm2, leftcalyces, rnocorticaldefects, lrenalmarginsspoorlyvisualised
age, gfr, ltargettobackgroundratio, lrenalmm2, leftcalyces, Inocorticaldefects, lrenalmarginssmooth
age, gfr, ltargettobackgroundratio, lrenalmm2, leftcalyces, Inocorticaldefects, lrenalmarginssirregular
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age, gfr, ltargettobackgroundratio, lrenalmm2, leftcalyces, Inocorticaldefects, allwell