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Diagnostic performances and clinical usefulness of comprehensive non-commercial software for renogram analysis: values of renal output efficiency and normalized residual activity in suspected kidney outflow obstruction

Клиничка евалуација новог софтвера за анализу динамске сцинтиграфије бубрега: значај ефикасности бубрежне елиминације и нормализоване резидуалне активности у дијагностици опструкције уринарног тракта

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SUMMARY

Introduction/Objective Nuclear Medicine Section of IAEA has developed the software for dynamic renal scintigraphy, which allows calculation of advanced parameters of drainage: renal output efficiency (OE) and normalized residual activity (NORA).

The aim of this study was to validate IAEA software by comparing results of parameters of renal drainage in normal subjects against their established reference values and to assess diagnostic accuracy of OE and NORA in distinguishing between obstruction/unobstruction.

Methods 55 patients with suspected obstruction and 36 kidney donors were investigated. Group A consisted of 24 obstructed kidneys, Group B of 37 kidneys with dilated urinary tract and Group C of 72 normal kidneys. 40min acquisition was applied. Furosemide was administered after 20min. Post-micturition image was acquired at 50min. Parameters analyzed were: OE at 20min (OE_{20}) and at the end of furosemide test (OE_{40}), NORA at 20min ($NORA_{20}$) and after micturition ($NORA_{PM}$). One-way ANOVA was used for evaluating differences between Groups. Ability of OE_{40} and $NORA_{PM}$ to distinguish between obstruction/unobstruction was determined by ROC curve analysis. The sensitivity, specificity, area under the curve and cutoff values were analyzed.

Results Excellent agreement of our results with established OE and NORA values was found. Difference between Groups was significant for OE_{20}, OE_{40} $NORA_{20}$ and $NORA_{PM}$ ($p < 0.001$). Cut-off values for obstruction were 82% and 0.11 for OE_{40} and $NORA_{PM}$, respectively.

Conclusion IAEA software gives reliable analysis of diuretic renography and helps to better diagnose obstruction. IAEA should be encouraged to produce final version of the software and to release it through Web site.

Keywords: Radionuclide renography, uroobstruction, output efficiency, normalized residual activity

САЖЕТАК

Увод/Циљ У Одсеку за нуклеарну медицину Међународне агенције за атомску енергију (*IAEA*) направљен је софтвер за анализу динамске сцинтиграфије бубрега, који омогућава израчунавање нових, прецизнијих показатеља бубрежног излучивања – ефикасности елиминације (*OE*) и нормализоване резидуалне активности (*NORA*).

Циљ нашег рада је валидирање *IAEA* софтвера, поређењем вредности параметара ренограма код здравих испитаника са њиховим референтним вредностима и процена значаја *OE* и *NORA* у диференцијалној дијагностици уроопструкције.

Методе Анализиран је 91 испитаник, 55 пацијената са суспектном опструкцијом уринарног тракта и 36 давалаца бубрега. У Групи *A* је било 24 опструктивна бубрега, у Групи *B* 37 бубрега са неопструктивном дилатацијом, у Контролној групи *C* 72 нормална бубрега. Сцинтиграфија је рађена током 40. минута после *i.v.* убризгавања ^{99m}Tc-*MAG*-3, Фуросемид је убризган у 20. минуту, а постмикциона сцинтиграфија снимљена у 50. минуту. За обраду је коришћен *IAEA* софтвер Анализирани су: *OE* у 20. минуту (OE_{20}) и 20 минута после фуросемида (OE_{40}), *NORA* у 20. минуту ($NORA_{20}$) и после микције ($NORA_{PM}$). У процени резултата истраживања коришћене су методе дескриптивне и аналитичке статистике.

Резултати Поређење наших резултата са референтним вредностима *OE* и *NORA*,показало је висок степен сагласности. Разлика између група је била статистички значајна за OE_{20}, OE_{40} $NORA_{20}$ и $NORA_{PM}$ ($p < 0.001$). *Cutoff* вредности за дијагнозу опструкције биле су 82% za OE_{40} i 0.11 za $NORA_{PM}$.

Закључак Примена *IAEA* софтвера повећава дијагностичку тачност диурезне ренографије и доприноси прецизнијој дијагностици уроопструкције. С обзиром да одељења нуклеарне медицине у многим земљама не поседују савремене софтвере за сцинтиграфију бубрега, било би значајно да *IAEA* омогући преузимање софтвера преко електронског сајта (*IAEA Web site*).

Кључне речи: Радиоизотопна ренографија, уроопструкција, ефикасност елиминације, нормализована резидуална активност

INTRODUCTION

Diuretic renography is old nuclear medicine technique, which is still widely used in the diagnosis of upper urinary tract obstruction. The differentiation between obstruction and non obstructive dilatation is assessed by the analysis of the down-slope of renogram curve after injection of furosemide [1]. The advanced quantitative parameters of kidney drainage, i.e. renal output efficiency (OE) and normalized residual activity (NORA) were proposed some time ago. They were shown to be the least dependent of the underlying single kidney function in comparison with other parameters [2, 3].

Nonetheless, these parameters have not been routinely used, since the majority of software for the analysis of diuretic renography didn't incorporate the tools for their calculation. In the meanwhile, the Nuclear Medicine and Diagnostic Imaging Section of the International Atomic Energy Agency (IAEA) has developed non-commercial software for renogram processing on a simple p-computer, which gave the opportunity of calculating OE and NORA [4]. However, neither this software was fully completed, nor the quality of its quantitative indices was validated in comparison with any commercial software package.

In this study we used MAG-3 and a specific time for injecting furosemide and studied the performances and clinical reliability of the use of IAEA Software Package in detecting urine flow obstruction. The aims were: a) to validate the numerical outputs of this software by comparing the results of parameters of renal drainage in normal subjects against their established reference values and b) to assess the diagnostic accuracy of OE and NORA in distinguishing between obstructed and patent upper urinary tract.

Patients and method

Patients enrolled in this study were referred from the Urology department Between November 2011 and July 2014 with the diagnosis of unilateral or bilateral urological disorder which caused the dilatation of the collecting system and suspected upper urinary tract obstruction. They had undergone ^{99m}Tc-MAG-3 dynamic scintigraphy with furosemide stimulation. The criteria for inclusion in the patients' Groups were: age over 18 years, renal function tests (serum creatinine level sCr, creatinine clearance cCr) and at least two imaging tests which findings suggested obstruction. The exclusion criteria were recent renal or ureteral surgery and high grade of vesicoureteric reflux. There were 55 patients, 23 males and 32 females, aged from 21 to 73 years (mean: 44.4±16.0 years). For the control Group, we selected 36 healthy subjects who were candidates for kidney donation. They had no structural abnormality of kidneys on ultrasound examination as well as no history of kidney, urinary or cardiovascular disorder, autoimmune disease or diabetes. There were 16 males and 20 females (age range: 35 to 73 years; mean: 51.7±10.6 years) in the control Group.

Ethical approval for this study was obtained from the Ethics Committee of Clinical Center of Serbia (approval number: 668/6/2018), and the written informed consent was obtained.

Each subject received 500 ml water 60 minutes before the study and emptied the bladder just before the acquisition. A large field of view γ camera (Siemens Orbiter 7500, Siemens, Erlangen, Germany) was set up with low-energy all-purpose collimator. The subject was in the supine position above the camera, which was positioned to include the left ventricle and both kidneys. A forty minutes acquisition protocol with 240 10-sec images in 128x128 matrix size was applied. The dose of ^{99m}Tc-MAG-3 was adjusted for body weight, with minimum of 74 MBq (2 mCi) and maximum of 200 MBq (5.5mCi), according to the respective guidelines [5, 6]. Furosemide was administered at twenty minute of acquisition. Post-void static image of 1 minute duration was acquired 50 minutes after tracer injection.

Regions of interest (ROI) were drawn over the left ventricle and both kidneys. The renal ROI included the kidney cortex and pelvis. From the generated renograms, the time to maximum activity (T_{max}) and to half maximum ($T_{1/2}$) were calculated. Differential renal function (DRF) was determined using the Rutland-Patlak plot (RP) method [7].

Three experienced physicians (two nuclear medicine specialists and one urologist) analyzed each patient and classified the kidneys into two categories. The division was based on the analysis of the pattern of excretion on diuretic renography after furosemide (by visual assessment of dynamic images and curves, T_{max} and $T_{1/2}$ values) and imaging tests other than renography (ultrasound, IVU, CT, MRU). Kidneys with poor drainage after furosemide and clinical/radiological signs of obstruction were classified into Group A. They were characterized by progressive accumulation of radiopharmaceutical in the collecting system on dynamic scintigraphy and retention of tracer on post-micturition images. Other imaging tests showed significant dilatation of pelvi-calyceal system and lack of appearance of radiology contrast media in the lower urinary tract. Group B consisted of hypotonic unobstructed kidneys with good drainage of the pelviureteric system after furosemide on dynamic scintigraphy images, followed by significant further drainage on post-micturition images. Radiology imaging tests revealed moderate pelvic dilatation and signs of patent urinary tract.

For the OE and NORA, the International atomic energy agency (IAEA) software package was used (Figure 1). These parameters were determined at 2 time points: OE at 20min (OE_{20}) and at 40min (20min after furosemide injection, OE_{40}), NORA at 20min ($NORA_{20}$) and on the post-micturition acquisition ($NORA_{PM}$).

Statistical analysis

For assessing the results of the research, descriptive and analytical statistics (SPSS version 20) was used. The default level of significance has been put below 0.05 level. We used the one-way ANOVA for evaluating the differences between the Groups. The unpaired *t*-test was used to compare the values between the Groups A and B. The relationship between OE_{20} and $NORA_{20}$ was assessed by Pearson correlation coefficient and linear regression analysis. The ability of the OE_{40} and $NORA_{PM}$ to distinguish between obstruction/unobstruction was determined by receiver operating characteristics (ROC) curve analysis. The sensitivity, specificity, the area under the curve (AUC) with 95% confidence interval and cutoff values were analyzed.

RESULTS

Subjects

Fifty-five patients presented with 61 hydronephrotic kidneys (49 patients with unilateral, 6 with bilateral HN). The underlying clinical diagnosis were: pelviureteric junction (PUJ) narrowing (51%), renal calculus's (38%), ureteral stenosis (4%) and others (7%). Twenty-four kidneys had the signs of obstruction and were classified into Group A, while Group B consisted of 37 kidneys with dilated but unobstructed upper urinary tracts. The control Group C consisted of 36 subjects with 72 renal units (RU). In total, 91 subjects and 133 renal units were analyzed.

Parameters of renal washout in control subjects

There were 72 kidneys in the Group C (36 on the left and on the right side). In all kidneys the differential renal function (DRF) was normal, between 43% and 57%. Table 1 shows the mean and standard deviation (SD), the minimum and maximum values for T_{max}, $T_{1/2}$,

OE_{20}, OE_{40}, $NORA_{20}$, $NORA_{PM}$ and DRF. As expected, the values for NORA were low, whereas OE was high.

Parameters of kidney washout in patients

Group A consisted of 23 kidneys, and Group B of 36 kidneys. The results of $NORA_{20}$, OE_{20}, OE_{40} and $NORA_{PM}$ are shown in Table 2.

The one-way ANOVA comparison between the Groups, taking normal Group C as reference, showed significant difference for the OE_{20}, OE_{40} $NORA_{20}$ and $NORA_{PM}$ ($P<0.001$, Figure 2). Comparing the values between Groups A and B, the significant difference was obtained for the values of OE_{40} and $NORA_{PM}$ ($p<0.001$).

Significant inverse linear correlation between $NORA_{20}$ and OE_{20} was obtained by linear regression analysis ($r = -0.982$; $y = 99.1 – 20.2x$) at 0.001 level. The dispersion of the values along the line of regression slightly increased when the quality of drainage decreased (Figure 3).

The ability of the OE_{40} and $NORA_{PM}$ to distinguish between obstructed and unobstructed kidneys were analyzed by ROC curve analysis. The areas under the curves (AUC) with 95% confidence interval (95% CI), optimal cutoff values, sensitivity and specificity are summarized in Table 3.

DISCUSSION

We studied in the adult patients with suspected upper urinary tract obstruction the performances of the IAEA software for the comprehensive analysis of radionuclide renography and validated the reliability of its numerical outputs for characterization kidney drainage, by comparing with reference values for ^{99m}Tc- MAG-3. The obtained results revealed excellent agreement with established normal ranges of OE and NORA. Normal kidneys presented with

OE_{20} values higher than 83%, OE_{40} higher than 91%, $NORA_{20}$ lower than 0.70 and $NORA_{PM}$ lower than 0.07. In kidneys with obstruction, OE_{40} was lower than 83% and $NORA_{PM}$ higher than 0.17. Furthermore, OE_{40} and showed high sensibility and specificity in verifying insufficient drainage. The calculated cutoff values for predicting poor drainage were shown to be ≤82% and >0.10 for OE_{40} and $NORA_{PM}$, respectively.

The traditional way to analyze the diuretic renogram consisted of visual interpretation of dynamic images and time/activity curves as well as the calculation of T_{max} and $T_{1/2}$ values [8]. The problem appears in the case of reduced renal function or grossly dilated renal pelvis when $T_{1/2}$ is prolonged, even in the absence of obstruction, which leads to equivocal findings of diuresis renography [9]. The output efficiency index and the normalized residual activity are two measurements that have been proposed by the International Scientific Committee of Radionuclides in Nephro-urology (ISCORN) to compensate for slower rates of clearance due to reduced renal function [5]. Some commercial software packages incorporated the tools for calculating these two parameters, but the users in developing countries couldn't afford them due to high price. IAEA released the non-commercial "Software Package for the Analysis of Scintigraphic Renal Dynamic Studies" as a draft version on 2010 [4]. However, to date, the software has not been completed, probably due to the lack of interest in nuclear medicine centers in developed countries to apply the software, since their departments are equipped with high-quality commercial software packages. In our department, there has been considerable interest to apply the advanced analysis of diuretic renography. As for our knowledge, this is the first study about the validation of numerical indices of IAEA software in patients with impaired drainage.

In the previously published studies about OE and NORA, various protocols were used, with the differences in duration of acquisition and in the time of diuretic challenge. This invalidates the comparison between studies and avoids the determination of cut-off values of these parameters for differentiation between obstruction/unobstruction. In the newest Guidelines for diuresis renography, three time points were specified for the calculation of renogram parameters: 20 minutes after start of the acquisition, 20 minutes after diuretic challenge, and on the post-micturition scan. The current version of the IAEA offers the calculation of OE_{20} and OE_{40}, $NORA_{20}$ and $NORA_{PM}$ [5, 10]. According to these time points, we calculated the present results.

The normal ranges for parameters of ^{99m}Tc- MAG-3 renogram were reported in several studies, mainly for T_{max} and $T_{1/2}$ [11-15]. The results calculated in our study with the use of IAEA software showed the substantial agreement with these values (Table 4).

For the OE, in the study that validated this index as an objective quantitative parameter of kidney drainage, Chaiwatanarat et al. reported the normal values in 22 kidneys of healthy control subjects to be 91.6±4.6%; that were in complete agreement with our results [2]. In obstructed kidneys, they obtained somewhat lower values in comparison with present study, probably due to shorter time for diuretic challenge (30 minutes acquisition instead of 40 minutes in our protocol). In the study of output efficiency as a method for clarifying equivocal renograms, the 30 minutes acquisition protocol was also applied and the reported cut-off value for excluding obstruction was lower than in our study [16].

The NORA index was proposed as robust parameter of renal drainage and simpler for calculation than OE. This parameter hasn't been widely assessed in the literature. The more frequently used was residual activity index expressed as a percentage of the maximal activity, but it didn't take into account the value of renal clearance [17]. The reported normal threshold for $NORA_{20}$ was 0.70 [18], which was identical with the result of present study.

Since in the literature a significant correspondence was reported between NORA and OE [19], we correlated the values of these two parameters at calculated at 20min and obtained high values of Pearson correlation coefficient. This correlation confirmed the statement of the possibility to replace the OE with NORA, when deconvolution method for calculation of OE could not be applied or is not available [20].

We have determined the optimal cutoff values for OE_{40} and $NORA_{PM}$ to distinguish between hypotonic unobstructed kidneys and kidneys with obstruction. They were similar with the previously reported cutoff values for obstruction [18] and yielded a sensitivity and specificity of almost 100%, thus affirming the use of these parameters in evaluation of kidney drainage.

CONCLUSION

This study demonstrates that the implementation of the new algorithm for quantification of renal drainage, incorporated in the IAEA software package provides comprehensive, high-quality quantitative analysis of diuretic renography. Renal output efficiency and normalized residual activity are accurate parameters of renal drainage, which contribute to the diagnosis of kidney outflow obstruction. The calculation of these quantitative indices should become a part of routine analysis of dynamic renal scintigraphy. They would facilitate the comparison between studies during follow-up and monitoring the response to surgical treatment. In addition, the use of this software can help to standardize the protocols for acquisition and processing of the diuretic renrography and to avoid the measurement of excretory parameters at various times after diuretic challenge, which hampers the comparison of studies between centers. The harmonization of the scintigraphy reports could enable the exchange of quantitative data between physicians and departments. We would appeal to the Nuclear Medicine and Diagnostic Imaging section of the IAEA to complete the work on the software and to release it through IAEA Web site.

Conflict of interest: None declared.

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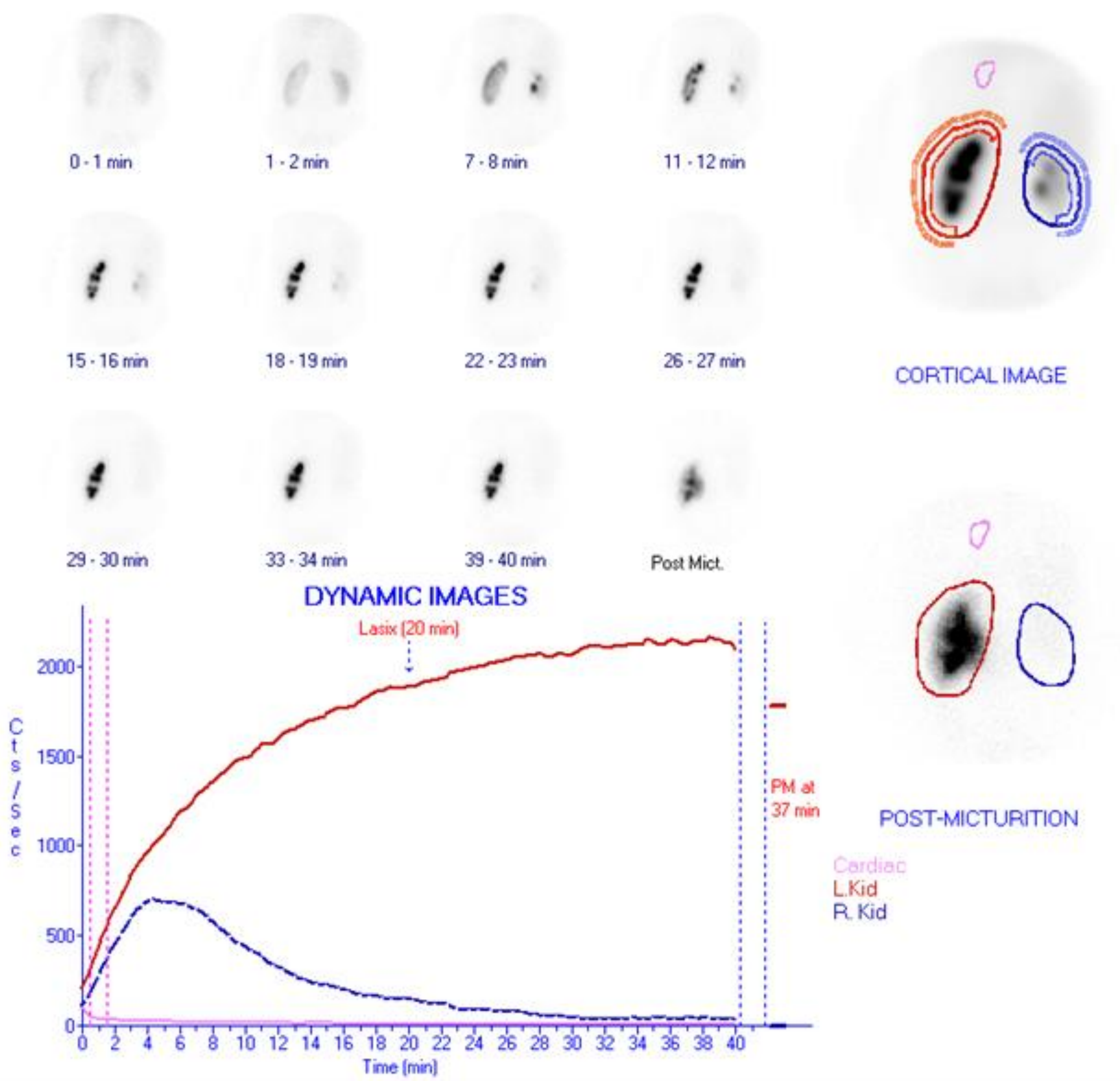

Figure 1 A structured display of IAEA Software Package review screen. Serial 1-minute images of kidneys enable the estimation of tracer kinetics. Composite parametric image with ROIs over kidneys, left ventricle and background; postmicturition image; renogram curves

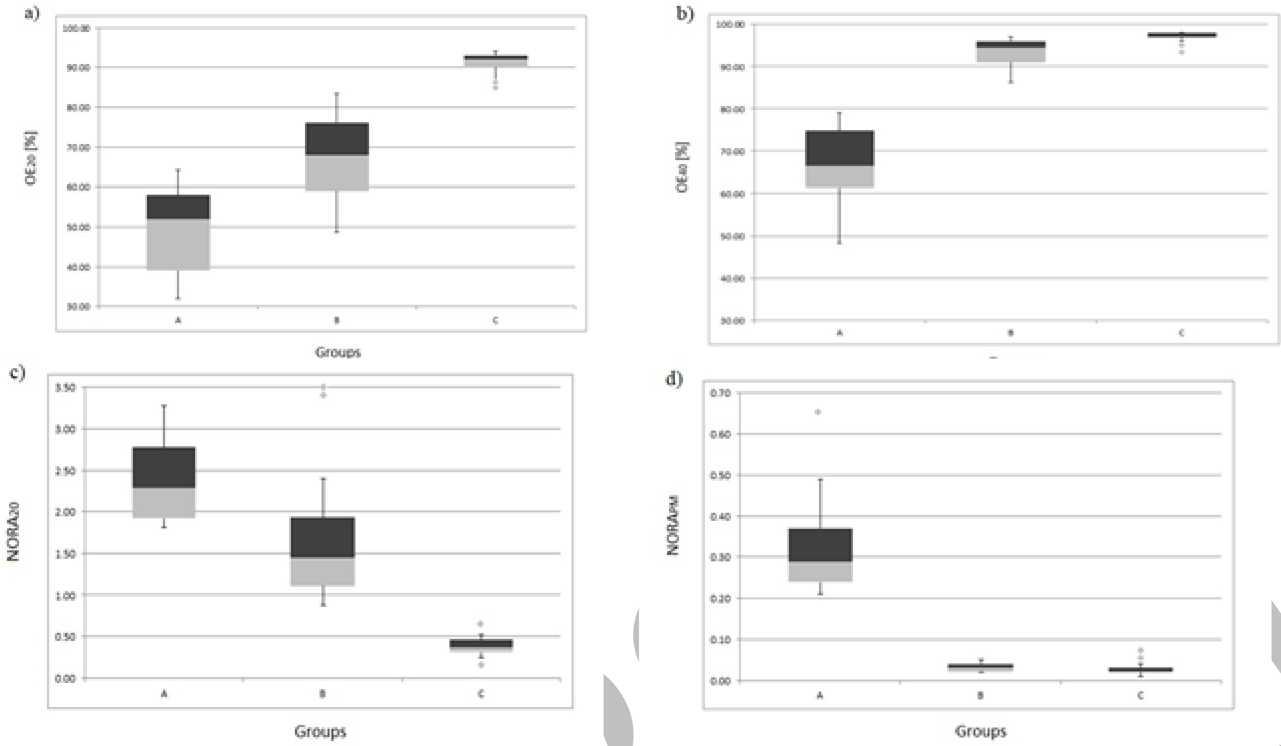

Figure 2 In (a–d), the values of output efficiency $(OE)_{20}$, output efficiency $(OE)_{40}$, normalized residual activity $(NORA)_{20}$ and NORA postmicturition (PM) are, respectively, represented for the Groups of patients A, B and C. OE is given in percentage and NORA in units

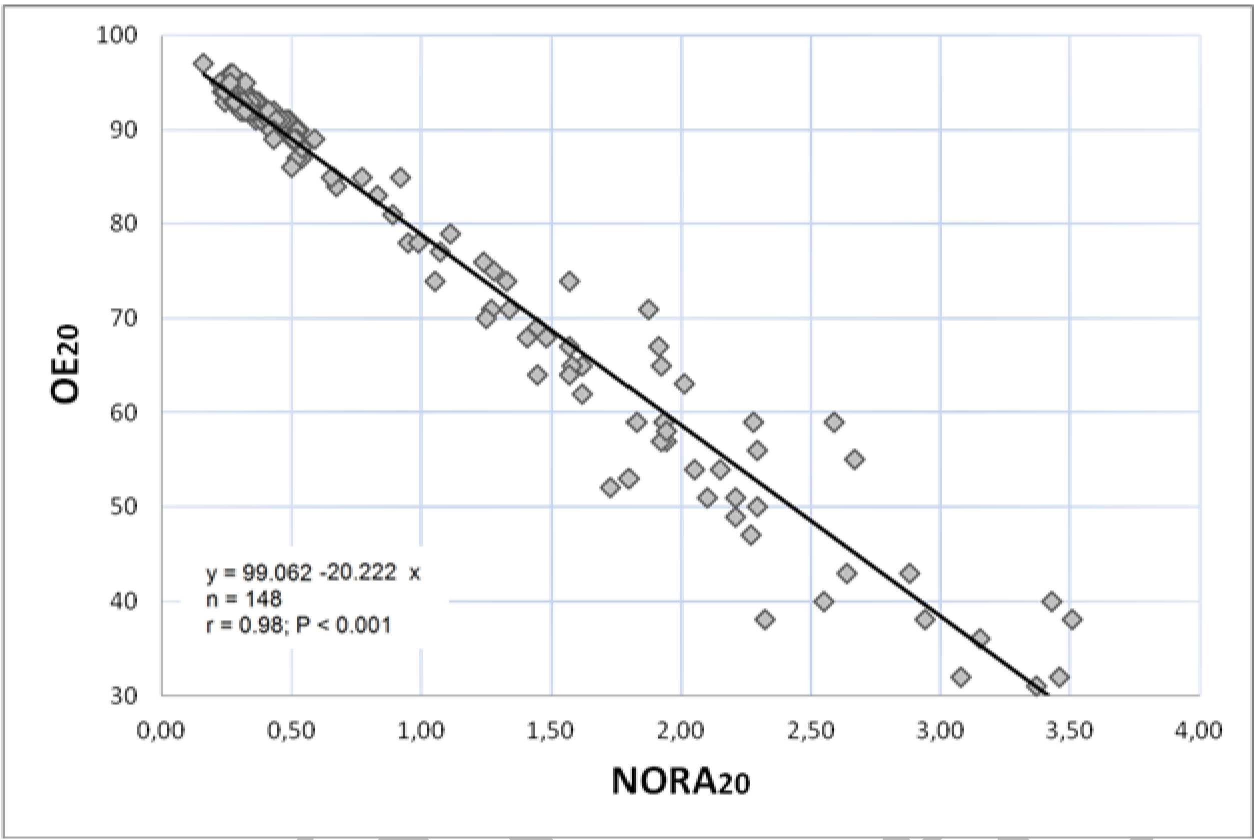

Figure 3 Correlation between output efficiency $(OE)_{20}$ and normalized residual activity $(NORA)_{20}$. The Pearson's correlation coefficient was high (r = - 0.982, $p < 0.001$)

Table 1. Parameters of ^{99m}Tc-MAG-3 renogram in normal kidneys

Values	T_{max} (min)	$T_{1/2}$ (min)	OE_{20} (%)	OE_{40} (%)	$NORA_{20}$	$NORA_{PM}$	DRF (%)
N	72	72	72	72	72	72	72
Mean	3.57	6.61	91.29	97.06	0.38	0.02	50.23
SD	0.66	1.75	2.77	1.25	0.11	0.01	3.43
Min	0.7	2.5	84	92	0.16	0.01	43
Max	5.2	11.0	97	98	0.69	0.06	57

Table 2. OE and NORA in kidneys with obstructed or dilated urinary tract

Groups	**OE$_{20}$** (%)	**OE$_{40}$** (%)	**NORA$_{20}$**	**NORA$_{PM}$**
Group A (obstructed)				
N	24	24	24	24
Mean	49.61	66.18	2.40	0.32
SD	12.20	10.64	0.54	0.11
Min	31	47	1.73	0.17
Max	71	82	3.46	0.65
Group B (dilated)				
N	37	37	37	37
Mean	66.92	93.31	1.57	0.03
SD	12.75	3.70	0.66	0.01
Min	38	84	0.42	0.01
Max	91	98	3.51	0.06
P value	<0.001	<0.001	<0.001	<0.001

p significance level from comparison of kidneys with good and poor drainage

Table 3. Receiver operating characteristics analysis for OE_{40} and $NORA_{PM}$

Predictor variables	N	AUC	95% CI	P	Optimal cut-off value	Sensitivity (%)	Specificity (%)
OE_{40} (%)	61	0.992	0.934-1.000	<0.001	≤82	98	91
$NORA_{PM}$	61	1.00	0.852-1.000	<0.001	>0.10	97	95

Table 4. Comparison with related studies for T_{max} and $T_{1/2}$

Studies	T_{max} (min)			$T_{1/2}$ (min)		
Author, year	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Klingensmith et al. 1994.	36	3.6	2.2	36	6.0	2.5
Clausen et al. 2002.	82	3.2	0.6	-	-	-
Jung et al. 2005.	22	3.8	1.2	22	6.2	2.5
Esteves et al. 2005.	106	3.8	1.9	106	6.5	4.1
Rewers et al. 2015.	48	3.1	0.5	-	-	-
Present study	72	3.6	0.7	72	6.6	1.7