

The following manuscript was accepted for publication in Pharmaceutical Sciences. It is assigned to an issue after technical editing, formatting for publication and author proofing.  
Citation: Fakhari A, Gharepapagh E, Gilani N, Mirfakhraei N, Farajbakhsh Mamaghani F, Dabiri Oskuei S. Impact of storage conditions on a new child-friendly dispersible tablet for treating Tuberculosis in pediatrics., Pharm Sci. 2021, doi: 10.34172/PS.2021.47

## **The Association of Kidney's GFR and Serum Creatinine Levels with Renal Scarring through <sup>99m</sup>Tc-Glucoheptonate Radiopharmaceutical Scan in Patients with Urinary Tract Infection**

Ashraf Fakhari<sup>1,2</sup>, Esmail Gharepapagh<sup>1,2\*</sup>, Neda Gilani<sup>3</sup>, Nardin Mirfakhraei<sup>1,2</sup>, Farzad Farajbakhsh Mamaghani<sup>5</sup>, Shahram Dabiri Oskuei<sup>1,2</sup>

<sup>1</sup>Medical Radiation Sciences Research Team, Tabriz University of Medical Sciences, Tabriz, Iran

<sup>2</sup>Department of Radiology, Medical School, Tabriz University of Medical Sciences, Tabriz, Iran

<sup>3</sup>Department of Statistics and Epidemiology, Faculty of Health, Tabriz University of Medical Sciences, Tabriz, Iran

<sup>4</sup>Radiopharmaceutical Kits Production, Pars Isotope Company, Tehran, Iran

\*Corresponding author: Email: [gharepapaghe@tbzmed.ac.ir](mailto:gharepapaghe@tbzmed.ac.ir)

## Abstract

UTI (urinary tract infection) is a leading cause of renal scarring. Most of nephrons are found in kidney cortex, so it is important for early diagnosis of scarring. In this study, we investigated if scarring affects GFR (glomerular filtration rate) and serum level of creatinine through dual multipurpose  $^{99m}\text{Tc}$ -GH ( $^{99m}\text{Tc}$ -Glucoheptonate) scintigraphy in patients with UTI.

**Methods:** During this study 21 patients with UTI were studied by  $^{99m}\text{Tc}$ -GH scan. For performing scintigraphy, the patient was injected by 370-555 MBq of  $^{99m}\text{Tc}$ -GH and studied through two steps including dynamic (immediately after injection) and static (2-3h after injection) phases. The results were evaluated by appropriate analytical methods. Moreover, five patients were studied by both  $^{99m}\text{Tc}$ -DMSA/GH ( $^{99m}\text{Tc}$ -dimercaptosuccinic acid and  $^{99m}\text{Tc}$ -Glucoheptonate) to show  $^{99m}\text{Tc}$ -GH scan is beneficial for detection of additional problems.

**Results:** The results showed that there is an association between right/left kidney scarring and related GFR. Furthermore, the odds of decreased right and left kidney GFR with scarring is 12.64 and 11.89 times more than normal kidney respectively. Also, there is a significant association between renal scarring and serum level of creatinine. The study showed that the odds of increased serum level of creatinine in patients with scarring are 6.75 times more than patients without scarring. Moreover, the survey of five patients with both  $^{99m}\text{Tc}$ -DMSA/GH scans showed  $^{99m}\text{Tc}$ -GH could be helpful with diagnosis of some renal problems as well as scarring.

**Conclusion:** Through this study by  $^{99m}\text{Tc}$ -GH, it was demonstrated that kidney glomerular filtration rate and serum level of creatinine are associated with renal scarring. Furthermore, it was shown that  $^{99m}\text{Tc}$ -GH scintigraphy could detect dilatation and abstraction of collection system in addition to renal scarring through static/dynamic renal scintigraphy.

**Keywords:** Glomerular Filtration Rate, Urinary Tract Infection, Radionuclide Imaging, Creatinine, Radiation Protection

## Introduction:

Renal scarring as a serious renal problem, leads to essential problems like chronic renal failure and hypertension (1). There are some important etiologies of renal scarring including UTI (urinary tract infection), pyelonephritis, nephrolithiasis, hypertension, vesicoureteral reflux and diabetes (2). Due to highly localization of nephrons in kidney's parenchyma, early diagnosis of cortical lesions could prevent permanent scars as a leading cause of renal failure. Moreover, renal scarring would lead to proteinuria, hematuria, electrolyte imbalance and hypertension (3). Basically, the origin of renal scarring is determined by biopsy, but it isn't preferable because of being invasive method. Generally, various diagnostic methods including urography, sonography, CT (computed tomography), MRI (Magnetic resonance imaging) and renal scintigraphy are used to detect renal scarring (4). Renal scintigraphy as a functional imaging is used for kidney clearance assay, renal tubular secretion and morphological studies (5). Mainly, renal scintigraphy is classified into dynamic (perfusion and function scintigraphy) and static (renal cortical scintigraphy) studies (6). There are different types of radiopharmaceuticals determined to targeted renal scintigraphy, Fig.1. Dynamic scintigraphy is performed to evaluate GFR (glomerular filtration rate) and tubular secretion. The common radiopharmaceutical for calculation of GFR is  $^{99m}\text{Tc}$ -DTPA, but the  $^{99m}\text{Tc}$ -GH could be also used. The  $^{99m}\text{Tc}$ -GH ( $^{99m}\text{Tc}$ -Glucoheptonate) as a radiolabeled carbohydrate, is eliminated by glomerular filtration (>80%) and binds to kidney tubules (10%-15%). Therefore,  $^{99m}\text{Tc}$ -GH as a multi-purpose radiopharmaceutical could be used to evaluate both renal function and cortical scar just via one-dose i.v. injection. It should be mentioned when the renal scintigraphy is just performed for functional study, the  $^{99m}\text{Tc}$ -DTPA is preferable. For evaluation of both renal function and morphology, the  $^{99m}\text{Tc}$ -GH is preferred in order to provide both dynamic and static scintigraphy. Renal cortical scintigraphy is performed to evaluate renal morphology, especially for diagnosis of renal scarring.  $^{99m}\text{Tc}$ -DMSA ( $^{99m}\text{Tc}$ -dimercaptosuccinic acid) as common radiopharmaceutical is commonly used to perform cortical scintigraphy for diagnosis of renal scarring. After i.v. injection, the  $^{99m}\text{Tc}$ -DMSA binds to  $\alpha$ 1-microglobulin in blood by sulfhydryl groups. The assembly ( $^{99m}\text{Tc}$ -DMSA- $\alpha$ 1-microglobulin) aggregates in tubules of renal parenchyma by megalin/tubulin-mediated endocytosis that leads to parenchymal retention of  $^{99m}\text{Tc}$ -DMSA by 50 percent. Free  $^{99m}\text{Tc}$ -DMSA and trace amounts of assembly are secreted in tubular fluid (7). Generally, the study of renal function has been performed by glomerular radiopharmaceuticals, especially by  $^{99m}\text{Tc}$ -DTPA with regard to GFR's calculation. The

$^{99m}\text{Tc}$ -DTPA ( $^{99m}\text{Tc}$ -diethylenetriaminepentaacetic acid) was glomerularly filtered by %95 (about 5% of  $^{99m}\text{Tc}$ -DTPA binds to plasma proteins), so it provides ability to calculate GFR and assay urine flow through pyelocalyceal system in order to detect obstructive problems (8). In comparison to renal scintigraphy, the CT scan can be used to study functional and morphological statuses of unilateral chronic renal obstruction, but  $^{99m}\text{Tc}$ -DTPA scan is preferable because of low radiation exposure dose. Furthermore, it was noted "comparative studies are needed to assess the role of CT-based parenchymal volume in evaluation of individual renal functions in patients with acute obstruction, bilateral nephropathy and renal impairment" (9). However, it is possible to study morphology and hemodynamics of kidney due to developments in ultrasound modalities, but the  $^{99m}\text{Tc}$ -DTPA scan is necessary for assessment of clearance rate and accurate function of kidney (10). Although the renal magnetic resonance imaging could be used to perform the functional imaging by gadolinated tracers, it is accompanied by lack of linearity, therefore the  $^{99m}\text{Tc}$ -DTPA scan still remains as a gold standard in this domain (11). Moreover, from radiation protection point of view, radiation dose from  $^{99m}\text{Tc}$ -GH is less than sums of  $^{99m}\text{Tc}$ -DTPA and  $^{99m}\text{Tc}$ -DMSA scans, because the recommended dose for  $^{99m}\text{Tc}$ -GH scan is 370-555 MBq (the recent literature also recommended 296 MBq for  $^{99m}\text{Tc}$ -GH (7)) (12). Therefore, when there is necessity to perform both  $^{99m}\text{Tc}$ -DTPA and  $^{99m}\text{Tc}$ -DMSA scans, the  $^{99m}\text{Tc}$ -GH scan could be just performed instead. Urinary tract infections (UTI) and acute pyelonephritis (APN) are the leading cause of renal scarring, especially in children. In general, 15-60% of children with UTI develop renal scarring (13,14). So, the early detection of scarring can prevent related problems as well as renal dysfunction due to parenchymal damage (15). Because patients with renal scarring have been routinely studied by  $^{99m}\text{Tc}$ -DMSA scan, so the renal perfusion and GFR (that could be decreased) are missed during evaluation. During this study, we attempted to detect renal scarring and evaluate association of that with GFR and serum level of creatinine by individual  $^{99m}\text{Tc}$ -GH renal scan that could gather more data about morphology and function of kidney simultaneously. This study showed how missed  $^{99m}\text{Tc}$ -GH radiopharmaceutical could be useful in diagnosis of urinary tract complications and kidney functions as well as renal scarring just through single scintigraphy instead of both separated  $^{99m}\text{Tc}$ -DTPA and  $^{99m}\text{Tc}$ -DMSA scintigraphy. Ultimately,  $^{99m}\text{Tc}$ -GH scintigraphy as an alternative leads to reduce radiation exposure in patient candidate for both  $^{99m}\text{Tc}$ -DTPA and  $^{99m}\text{Tc}$ -DMSA scintigraphy.

## Methods:

During this retrospective study, 21 patients with UTI who had referred to our nuclear medicine division were studied during one year to find if renal scarring correlates with GFR and serum level of creatinine through  $^{99m}\text{Tc}$ -GH renal scan. Ethical approval for this study was obtained from Research Ethics Committee of our institution. The participants were informed on data publishing.

Inclusion criteria: all patients with confirmed UTI by positive urine culture, and creatinine serum level of them had been determined prior to scintigraphy. All patients didn't have any systemic disease and hadn't consumed antibiotic recently.

Exclusion criteria: the pregnant patients

The GH vacuumed cold kits were obtained from Pars Isotope Co. and radiolabeled with fresh  $^{99m}\text{TcO}_4^-$  ( $^{99m}\text{Tc}$ -Technetium pertechnetate) from  $^{99}\text{Mo}/^{99m}\text{Tc}$  generator according to kit instruction. All patients were evaluated by both dynamic and static scintigraphy after 370-555 MBq of  $^{99m}\text{Tc}$ -GH i.v. injection (16). The dynamic renal scan was subsequently performed after bolus i.v. injection of radiopharmaceutical at perfusion, parenchymal and excretory phases at posterior views. The split renal GFR was calculated via Gates method. The cortical scintigraphy was performed 2h after  $^{99m}\text{Tc}$ -GH i.v. injection at Ant (anterior), Post (posterior), LPO (left posterior oblique) and RPO (right posterior oblique) views. The Siemens SPECT E.Cam Dual Head gamma camera with low-energy and high-resolution collimator was used in this study. It should be mentioned the normal serum level of creatinine was considered at 0.7-1.3 mg/dL (17). Also, the threshold for lowered GFR was considered as  $\text{GFR } 90 \geq \text{ mL/min}$  (18). For radiolabeling of GH cold kit, 1110-1850 MBq (30-50 mCi) of fresh  $^{99m}\text{TcO}_4^-$  (up to 4 mL) was added to GH cold kit and shaken for 1 min then left in room temperature for 10 min to complete ligand/radioisotope incubation. For radiolabeling of DMSA cold kit, 1480 MBq of fresh  $^{99m}\text{TcO}_4^-$  (up to 3 mL) was added to DMSA cold kit and shaken for 1-2 min then left in room temperature for 15-20 min to complete ligand/radioisotope incubation. The quality of radiolabeled kits were assayed by two systems of chromatography (by ITLC) (19).

Moreover, Schwartz formula (that it was considered as a confirmed standard way, Eq 1) was used to find out if the calculated GFR (based  $^{99m}\text{Tc}$ -GH renal scan) is reliable (20). In this Equation the "K" is defined as 0.419 if males aged >13 years and otherwise considered at 0.373, the "Scr" and "L" are defined as serum level of creatinine and patient's height (cm) respectively.

Eq 1: Schwartz formula:  $eGFR = kL/Scr$

Through this investigation five patients were studied by either  $^{99m}Tc$ -GH or  $^{99m}Tc$ -DMSA renal scan after getting permission from vulnerable patients to show if  $^{99m}Tc$ - GH renal scan is beneficial for some patients in addition to renal scarring detection.

**Determination of serum creatinine:** The serum level of creatinine had been determined by autoanalyzer system (model: BS-800, Mindray factory, China) and enzymatic method.

**Preparation of patient for scintigraphy:** There is no special patient preparation for  $^{99m}Tc$ -GH renal scan, but it is recommended that the patients should be hydrated by drinking 5-10 mL/kg of water 30-60 min prior to scintigraphy (21).

**Statistical Analysis:** The obtained data were analyzed by descriptive statistics methods as mean  $\pm$ SD and frequency (percent). For inferential statistics Fisher's exact test, Pearson correlation test and logistic regression analysis were used by SPSS 16 (SPSS Inc., Chicago, IL) Software. The Shapiro-Wilk test was used to evaluate normal distribution of data. In all analysis, p-values less than 0.05 ( $P < 0.05$ ) were considered as significant.

The intraclass correlation coefficient (ICC) has been advocated as a statistic for assessing agreement or consistency between two methods of GFR measurement. For calculation ICC, a two-way mixed-effect model based on single ratings assessed was used. Mean estimation along with 95% confidence intervals (CI) were reported for the ICC. Interpretation was as follows:  $< .50$ , poor; between 0.50 and 0.75, fair; between 0.75 and 0.90 good; above 0.90, excellent (22).

## Results:

During this study, 21 patients with UTI, 11 female (52.4%) with mean of age  $23.2 \pm 14.7$  years and 10 (47.6%) male patients with mean of age  $21.3 \pm 15.9$  years were studied. The mean of GFR in patients with renal scarring (A) were calculated at  $25.58 \pm 11.90$  ml/min and  $28.75 \pm 20.46$  ml/min for right and left kidney respectively. The mean of GFR in patients without renal scarring (B) were calculated at  $42.56 \pm 11.90$  ml/min and  $43.15 \pm 20.51$  ml/min for right and left kidney respectively. Moreover, there was no significance difference between the mean serum level of creatinine for patients with ( $1.64 \pm 0.72$  mg/dl) and without ( $1.5 \pm 0.94$  mg/dl) renal scarring ( $p$ -value=0.751). Among 21 patients, 11 patients (52.4%) were demonstrated decreased right kidney's GFR. As Table 1 shows, 85.7% of patients with right

renal scarring had decreased right kidney's GFR and 14.3% had normal GFR. Based on Fisher's exact test, there is a significant association between right kidney's GFR and renal scarring (p-value=0.031). Among all patients, 61.9% (11 patients) showed decreased left kidney's GFR. As Table 1 shows, 87.5% of patients with left renal scarring had decreased left kidney's GFR. Based on Fisher's exact test, there is also a significant association between left kidney's GFR and renal scarring (p-value=0.047).

Moreover, after adjustments for sex and age, the results showed the odds of decreased right kidney's GFR in patients with right kidney scar is 12.64 times more than patients without that diagnosis (OR=12.64, p-value=0.043). Also, the results demonstrated that sex and age of the patients didn't affect right kidney's GFR, Table 2 (p-value<sub>(sex)</sub>=0.845, p-value<sub>(age)</sub>=0.165). Furthermore, the results indicated that the odds of decreased left kidney's GFR in patients with left kidney's scar is 11.89% times more than patients without that diagnosis (OR=11.89, p-value=0.046) through moderation of age and sex effects. Also, the results showed that sex and age of the patients didn't affect left kidney's GFR, Table 2 (p-value<sub>(sex)</sub>=0.308, p-value<sub>(age)</sub>=0.236).

Among all patients (n=21), 47.6% (11 patients) demonstrated increased serum level of creatinine. As Table 3 shows, 66.7% of patients with renal scarring associated with increased serum level of creatinine. According to Fisher's exact test, there is a significant association between renal scarring and serum level of creatinine (p-value =0.030). Also, we developed a survey to find if there is correlation between right/left kidney's GFR and serum level of creatinine. According to Shapiro-Wilk test, normal distribution of variables including right kidney's GFR, left kidney's GFR and serum level of creatinine were concluded. Correlation between variables was assessed by Pearson correlation test. As Table 4 shows there is a negative correlation between right/left kidney's GFR and serum level of creatinine (right kidney's GFR: r=-0.54, p-value=0.011; left kidney's GFR: r=-0.50, p-value=0.022). However, there is not significant correlation between left and right kidney's GFR (r=-0.01, p-value=0.982). Moreover, percent prediction (determination coefficient) of creatinine serum level by right/left kidney's GFR were calculated to be 25% and 29%, respectively. Following that, after adjustments of sex and age, the odds of increased serum level of creatinine in patients with renal scarring is 6.75 times more than patients without renal scarring (OR=6.75, p-value=0.032). Also, the results demonstrated that sex and age of patients didn't affect serum level of creatinine, Table 5 (p-value<sub>(sex)</sub>=0.362, p-value<sub>(age)</sub>=0.349).

Also, the intraclass correlation coefficient was computed to assess the consistency between two GFR measurement methods (calculated GFR from  $^{99m}\text{Tc}$ -GH scan and estimated GFR from Schwartz formula). The ICC was between fair and good being 0.81 (0.56-0.92), for calculated GFR (by  $^{99m}\text{Tc}$ -GH scintigraphy) and estimated GFR (by Schwartz formula).

Moreover, during this study, five patients that had been studied by both  $^{99m}\text{Tc}$ -GH and  $^{99m}\text{Tc}$ -DMSA scans, developed valuable results demonstrating  $^{99m}\text{Tc}$ -GH renal scan could be beneficial for patients with some kidney problems as well as renal scarring.  $^{99m}\text{Tc}$ -GH scan could evaluate renal perfusion-function in addition to renal cortical surveys (figs 2-6). In all patients  $^{99m}\text{Tc}$ -GH scan was performed at least 48h after  $^{99m}\text{Tc}$ -DMSA scan in order to assay whether  $^{99m}\text{Tc}$ -GH shows renal cortical uptake similar to  $^{99m}\text{Tc}$ -DMSA scan.

Fig.2 (a-c) illustrates both  $^{99m}\text{Tc}$ -GH and  $^{99m}\text{Tc}$ -DMSA for a same patient. As shown, there is a decreased  $^{99m}\text{Tc}$ -DMSA uptake in corticomedial parenchyma of left kidney that tends to be seemed as a scar. During  $^{99m}\text{Tc}$ -GH scan, the early dynamic phases demonstrated the retention of  $^{99m}\text{Tc}$ -GH in the mentioned region of left kidney. Following i.v. injection of diuretic at 10<sup>th</sup> min of study, completed clearance of radiotracer from corticomedial parenchyma of left kidney was shown. So it is concluded that the decreased parenchymal uptake is resulted from collecting system dilatation instead of renal cortical scar.

Fig.3 (a-c) illustrates a large cortical defect in the upper pole of right kidney in both  $^{99m}\text{Tc}$ -GH (in static phase) and  $^{99m}\text{Tc}$ -DMSA scans. Dynamic phase of  $^{99m}\text{Tc}$ -GH scan showed accumulation of radiopharmaceutical in the mentioned defect that ruled out the probability of renal scarring. After Lasix injection, retention of  $^{99m}\text{Tc}$ -GH in pelvis demonstrated obstructive problems like ureteropelvic junction stenosis (UPJS).

Fig.4 (a-c) shows small region of decreased cortical radiotracer uptake in the upper pole of left kidney in both static  $^{99m}\text{Tc}$ -GH and  $^{99m}\text{Tc}$ -DMSA scans (Figs a,b) that is suspicious of cortical scar. Both kidneys were also considered as normal at  $^{99m}\text{Tc}$ -GH dynamic phase that ruled out renal scarring. Therefore, it is concluded that such small defects could be due to partial dilatation of collecting system.

Fig.5 (a-c) illustrates normal uptake of radiopharmaceutical in kidneys cortex in both renal cortical scans (a,b). In addition, the  $^{99m}\text{Tc}$ -GH dynamic phase demonstrated normal perfusion-function of right kidney and mild decreased perfusion-function and GFR for left kidney.

Fig.6 (a-c) indicates a large region of cortical defect in upper pole of right kidney in both  $^{99m}\text{Tc}$ -DMSA and  $^{99m}\text{Tc}$ -GH (in static phase) scans. Moreover, the  $^{99m}\text{Tc}$ -GH dynamic phase showed normal perfusion-function of left kidney as well as non-obstructive partially



dilatation of collecting system in right kidney. Consequently, there is correspondence between  $^{99m}\text{Tc}$ -GH static phase and  $^{99m}\text{Tc}$ -DMSA scans results.

### **Discussion:**

During this investigation it was concluded that 1) the mean of GFR in normal patients is supposedly higher than patients with renal scarring and also, the mean of creatinine serum level is elevated for patients with renal scarring, 2) the age and sex are not affected the GFR and serum level of creatinine, 3) the separated GFR is associated with related kidney's scarring, and 4) the GFR and serum level of creatinine are not correlated with together. Similar to this findings, there are some similar studies. Because patients with UTI are susceptible to renal scarring (23), there are numerous studies in this field. Balakrishna et al. studied the presence of renal scarring in children with UTI by  $^{99m}\text{Tc}$ -DMSA scan. They reported the renal scarring associated closely with hydronephrosis (100%), febrile UTI (34%), younger age group (67.5%) and *E. coli* UTI (86%). They also noted that cortical renal scintigraphy as a non-invasive method is preferable for investigation of renal scarring in children with first and recurrent UTI (24). Shaikh et al. expressed the delayed antibiotic treatment of febrile UTI will be firmly associated with renal scarring. They mentioned that "understanding the association between the number of episodes of febrile UTI and the risk for renal scarring can help develop evidence-based management strategies for children with this frequently occurring problem" (25). Najafi et al. did a meta-analysis to find the prevalence of kidney scarring caused by UTI in Iranian children. Their survey concluded that one-third of children with UTI involved with renal scarring and the odds of renal scarring in patients with urinary tract reflux is about four times (26). Recently, during a review article by Vasikar et al. it was mentioned UTI as a common problem of hospitalized children could affect bladder and kidney if it is severe. The infection could destroy kidney's tissue by replacing of nephrons through deposition of extra cellular matrix as renal scar (27). Therefore, UTI could lead to renal scarring resulting in decreased GFR and elevated serum level of creatinine. Similar to our investigation, there are similar studies that noted the renal scarring affect kidney's function through decreasing GFR. Relevantly, Masaaki et al. showed the renal scarring confirmed by  $^{99m}\text{Tc}$ -DMSA scan leads to decrease GFR in related patients (28). Hadi et al. noted the nephrons losing cause to increase in single nephron glomerular filtration rate (SNGFR) as a compensatory mechanism to prevent decreasing of total GFR, but this mechanism could lead to hypertension or CKD (chronic kidney disease) if there is severe or

long lasting of nephrons losing (29). Based on inherent characteristics of  $^{99m}\text{Tc}$ -GH, both functional and morphological studies could be performed by  $^{99m}\text{Tc}$ -GH scan. Related that, our study showed the calculated GFR by  $^{99m}\text{Tc}$ -GH scan is in correlation with estimated GFR (from Schwartz formula). According to Schwartz equation, there is an inverse relationship between GFR and serum level of creatinine. So, the result could be considered as a validation for our study, and the odds of increased serum level of creatinine in patients with renal scarring was 6.75. Although no research found a relationship between renal scarring and serum level of creatinine directly, it seems that the renal scarring could affect serum level of creatinine through causing an injury to nephrons and decreasing GFR at least. Because the serum level of creatinine could be affected by several factors including age, gender, race, protein intake, muscle mass, infections, and inflammatory status, therefore the used of creatinine as real function's marker would be as a controversy especially in patients with acute kidney injury (AKI). Sagheb et al studied the Cystatin C as a marker of renal function in critically patients with normal serum creatinine. Their study showed serum cystatin C is not superior to serum creatinine in the early detection of renal dysfunction (30,31). Also, during our study the participants did not have any systemic disease. However,  $^{99m}\text{Tc}$ -DMSA scintigraphy is considered as a gold standard to detection of renal scarring (32),  $^{99m}\text{Tc}$ -GH scintigraphy could show the kidney's cortex due to about 20% cortex retention too. Through our study by  $^{99m}\text{Tc}$ -GH the valuable results were gained regarding the kidney's function, cortical disorders and obstructive problems. Therefore, this study suggests that it is better to investigate both kidney's cortex and perfusion in patients with risk factors of renal scarring rather than just cortical study. Generally, the strength of this study was determined to evaluate both GFR (for evaluating kidney function) and kidney's cortex (for evaluating renal scarring) just by  $^{99m}\text{Tc}$ -GH scan instead of separated  $^{99m}\text{Tc}$ -DTPA and  $^{99m}\text{Tc}$ -DMSA scans, and we investigated the association of Kidney's GFR and serum level of creatinine with renal scarring just through one scintigraphy based on characteristics of  $^{99m}\text{Tc}$ -GH radiopharmaceutical.

This study had some limitations. Firstly, the characteristics of patients were only sex and age, so other confounder factors which may affect renal function were not included in statistical analysis. Secondly, the creatinine serum level could be affected by several factors that were not considered during this study. Thirdly, the scintigraphy was limited in pregnant and breastfeeding patients (33).

**Conclusion:**

In this study by  $^{99m}\text{Tc}$ -GH renal scan some qualitative and quantitative findings were obtained. The study of patients with UTI by  $^{99m}\text{Tc}$ -GH scintigraphy demonstrated that renal scarring has more effect on GFR. As this study shown, the GFR and serum level of creatinine is associated with renal scarring, also renal scarring and elevated serum level of creatinine correlated. Moreover, patients who were studied by  $^{99m}\text{Tc}$ -GH developed both perfusion and cortical scans. During this study, limited survey of cortical study by both  $^{99m}\text{Tc}$ -GH and  $^{99m}\text{Tc}$ -DMSA scans in patients with UTI demonstrated that  $^{99m}\text{Tc}$ -GH could show renal scarring if there is. Furthermore, dynamic phase of  $^{99m}\text{Tc}$ -GH scan could detect additional problems like dilatation and obstruction of urinary tract. It is suggested that this kind of expanded renal scintigraphy via  $^{99m}\text{Tc}$ -GH gives chance to detect perfusion-functional disorders that would cause in serious kidney's problems in addition to cortical studies. Moreover, the patients are determined to be studied by both  $^{99m}\text{Tc}$ -DMSA and  $^{99m}\text{Tc}$ -DTPA scans could be replaced just by  $^{99m}\text{Tc}$ -GH scan because of saving time and cost as well as decreased radiation exposure dose. Furthermore, reliability and consistency of GFR based on both  $^{99m}\text{Tc}$ -GH renal scan and Schwartz formula was calculated. The ICC was between fair and good.

**Ethical approval and consent to participate:**

The study had been approved by Tabriz University of Medical Sciences ethics committee and the necessary permission was obtained from patients to publish their findings.

**Acknowledgment:**

The authors thank Medical Radiation Sciences Research Team and Tabriz University of Medical Sciences for their support. There is no potential conflict of interest in this investigation.

**Availability of data:**

The data that support the findings of this study are available on request from the corresponding author.

**Authors' Contribution:**

Fakhari designed the work and was a major contributor in drafting the work. Gharepapagh interpreted the scintigraphy regarding the  $^{99m}\text{Tc}$ -GH and  $^{99m}\text{Tc}$ -DMSA renal scans. Mirfakharei contributed in acquisition of all patient's documents and Gilani was done statistical analysis of the work. Farajbakhsh Mamaghani participated in performing of scintigraphy and Dabiri Oskuei revised the draft.

### References:

- 1: Jacobson SH, Eklof O, Eriksson CG, Lins LE, Tidgren B, Winberg J. Development of hypertension and uraemia after pyelonephritis in childhood: 27 year follow up. *BMJ*. 1989;299(6701): 703–706. doi: 10.1136/bmj.299.6701.703
- 2: Effects of Scarring on the Kidneys. <https://healthfully.com/effects-of-scarring-on-the-kidneys-4189099.html>. Accessed 18 December 2018.
- 3: Park YS. Renal scar formation after urinary tract infection in children. *Korean J Pediatr*. 2012; 55(10):367-70. doi: 10.3345/kjp.2012.55.10.367
- 4: Stokland E, Hellström M, Jakobsson B, Sixt R. Imaging of renal scarring. *Acta Paediatr Suppl*. 1999;88(431):13-21. doi: 10.1111/j.1651-2227.1999.tb01314.x
- 5: Andrew T. Taylor. Radionuclides in Nephrourology, Part 1: Radiopharmaceuticals, Quality Control, and Quantitative Indices. *J NUCL Med*. 2014;55 (4) 608-615; doi: <https://doi.org/10.2967/jnumed.113.133447>
- 6: Alsabea H. Type of Renal Scintigraphy. *J Nucl Med Radiat Ther*. 2017;8(6): 1-8. doi:10.4172/2155-9619.1000347
- 7: Weyer K, Nielsen R, Petersen SV, Christensen EI, Rehling M, Birn H. Renal uptake of  $^{99m}\text{Tc}$ -dimercaptosuccinic acid is dependent on normal proximal tubule receptor-mediated endocytosis. *J Nucl Med*. 2013 Jan;54(1):159-65. doi: 10.2967/jnumed.112.110528. Epub 2012 Dec 11
- 8: Banker H, Sheffield EG, Cohen HL. Nuclear Renal Scan. *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2021 Jan.2020 Sep 5.
- 9: Galil Hamed MA. Assessment of the individual renal function in chronic unilateral renal obstruction using functional CT as compared to  $^{99m}\text{Tc}$ -DTPA renal scan. *Iran J Nucl Med*. 2014;22(2):57-63.
- 10: Anjum S, Ahmad A, Anwar F, Jabeen, Z, Bacha R, Ayaz M. Effectiveness of Nuclear Scan  $^{99m}\text{Tc}$ -DTPA in the Evaluation of Renal Function. *AJAHS*. 2018; 3(2):50-54.

- 11: Durand E, Chaumet-Riffaud P, Grenier N. Functional Renal Imaging: New Trends in Radiology and Nuclear Medicine. *Seminars in Nuclear Medicine*. 2011;41(1):61-72. doi: 10.1053/j.semnuclmed.2010.08.003.
- 12: Malley JO, Ziessman H. Nuclear medicine and molecular imaging, *The Requisites*, 5th ed, Philadelphia: Elsevier; 2021.p.493&502.
- 13: Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: a systematic review. *Pediatrics*. 2010;126(6):1084-91. doi: 10.1542/peds.2010-0685.
- 14: Faust WC, Diaz M, Pohl HG. Incidence of post-pyelonephritic renalscarring: a meta-analysis of the dimercapto-succinic acid literature. *J Urol*. 2009;181(1):290-7. doi: 10.1016/j.juro.2008.09.039
- 15: Kitao T, Kimata T, Yamanouchi S, Kato S, Tsuji S, Kaneko K. Urinary Biomarkers for Screening for Renal Scarring in Children with Febrile Urinary Tract Infection. Pilot Study. *J Urol*. 2015;194(3):766-771. doi: 10.1016/j.juro.2015.04.091
- 16: Mandell GA, Egli DF, Gilday DL, Heyman S, Leonard JC, John H, et al. Procedure Guideline for Renal Cortical Scintigraphy in Children. *J Nucl Med*. 1997;38(10): 1644-1646.
- 17: Reference Ranges. <https://annualmeeting.acponline.org/educational-program/handouts/reference-ranges-table> Accessed 2011-2021.
- 18: Fenton A, Montgomery E, Nightingale, Peters A, Sheerin N, Wroe A, et al. Glomerular filtration rate: new age- and gender- specific reference ranges and thresholds for living kidney donation. *BMC Nephrology*. 2018;19(336): 1-8. doi:org/10.1186/s12882-018-1126-8
- 19: Technetium-99m Radiopharmaceuticals: Manufacture of Kits. International Atomic Energy Agency; 2008.
- 20: George J. Schwartz. Height: the missing link in estimating glomerular filtration rate in children and adolescents. *Nephrol. Dial. Transplant*. 2014;29(5): 944–947. doi.org/10.1093/ndt/gft530
- 21: Ahmadzadehfar H, Biersach H, M.Freeman L, S.Zuckier L. *Clinical Nuclear Medicine*, 2<sup>nd</sup> ed. Switzerland: Springer Nature; 2020.p.326.
- 22: Perinetti G. StaTips Part IV: Selection, interpretation and reporting of the intraclass correlation coefficient. *SEJODR*. 2018;5(1):3-5.
- 23: Kosmeri C, Kalaitzidis R, Siomou E. An update on renal scarring after urinary tract infection in children: what are the risk factors?. *J Pediatr Urol*. 2019;15(6):598-603. doi: 10.1016/j.jpuro.2019.09.010

- 24: Bandari B, Sindgikar SP, Kumar SS, Vijaya MS, Raghu Shankar. Renal scarring following urinary tract infections in children. *Sudan J Paediatr.* 2019;19(1):25-30. doi: 10.24911/SJP.106-1554791193.
- 25: Shaikh N, Mattoo TK, Keren R, Ivanova A, Cui G, Moxey-Mims M, Majd M, Ziessman HA, Hoberman A. Early Antibiotic Treatment for Pediatric Febrile Urinary Tract Infection and Renal Scarring. *JAMA Pediatr.* 2016;170(9):848-54. doi: 10.1001/jamapediatrics.2016.1181.
- 26: Najafi F, Sarokhani D, Dehkordi AH. The prevalence of kidney scarring due to urinary tract infection in Iranian children: a systematic review and meta-analysis. *J Pediatr Urol.* 2019;15(4):300-308. doi: 10.1016/j.jpuro.2019.05.011
- 27: Murugapoopathy V, McCusker C, Gupta IR. The pathogenesis and management of renal scarring in children with vesicoureteric reflux and pyelonephritis. *Pediatr Nephrol.* 2020;35(3):349-357. doi: 10.1007/s00467-018-4187-9
- 28: Imamura M, Hayashi C, Kim WJ, Yamazaki Y. Renal scarring on DMSA scan is associated with hypertension and decreased estimated glomerular filtration rate in spina bifida patients in the age of transition to adulthood. *J Pediatr Urol.* 2018;14(4):317.e1-317.e5. doi: 10.1016/j.jpuro.2018.07.023
- 29: Fattah H, Layton A, Vallon V. How Do Kidneys Adapt to a Deficit or Loss in Nephron Number?, *Physiology (Bethesda).* 2019;34(3):189-197. doi: 10.1152/physiol.00052.2018
- 30: Sagheb M, Namazi S, Geramizadeh B, Karimzadeh A, Oghazian M, Karimzadeh I. Serum Cystatin C as a Marker of Renal Function in Critically Ill Patients With Normal Serum Creatinine. *Nephrourol Mon.* 2014; 6(2): e15224. doi: 10.5812/numonthly.15224
- 31: Verma S, Kellum J. Defining Acute Kidney Injury. *Crit. Care Clin.* 2021;37(2):251-266. doi:org/10.1016/j.ccc.2020.11.001
- 32: Sepahi MA, Razavi MR, Fakher MS, Movahedi Z. The role of <sup>99m</sup>Tc dimercaptosuccinic acid scintigraphy in detection of vesicoureteral reflux in pediatrics with first episode of acute pyelonephritis. *J Nephroarmacol.* 2019;8(2):e27. doi: 10.15171/npj.2019.27
- 33: Taylor A, Brandon D, Palma D, Blaufox M, Durand E, Erbas B, et al. SNMMI Procedure Standard/EANM Practice Guideline for Diuretic Renal Scintigraphy in Adults With Suspected Upper Urinary Tract Obstruction 1.0. *Semin Nucl Med.* 2018 Jul; 48(4): 377–390. doi: 10.1053/j.semnuclmed.2018.02.010

## Tables:

**Table 1: The rate of right/left kidney's GFR in patients with and without right renal scarring**

Variable	Category	Kidney's GFR			p-value*
		Decreased	Normal	Total	
		Number (%)	Number (%)	Number (%)	
<b>Right kidney scarring</b>	A	6 (85.7)	1 (14.3)	7 (100)	0.031
	B	5 (35.7)	9 (64.3)	14 (100)	
	Total	11 (52.4)	10 (47.6)	21 (100)	
<b>Left kidney scarring</b>	A	7 (87.5)	1 (12.5)	8 (100)	0.047
	B	6 (46.2)	7 (53.8)	13 (100)	
	Total	13 (61.9)	8 (31.8)	21 (100)	

\*Results were based on Fisher's exact test

**Table 2: The effects of right /left kidney scar, gender and age on right and left kidney's GFR**

### The effects of right kidney scar, gender and age on right kidney's GFR

Variable	Category	OR*	95% CI**	p-value***
<b>Right kidney scar</b>	-		Reference	
	+	12.64	(1.12, 24.72)	0.043
<b>Sex</b>	Female		Reference	
	Male	1.27	(0.12, 13.54)	0.845
<b>Age (y)</b>		1.05	(0.98, 1.13)	0.165

### The effects of left kidney scar, gender and age on left kidney's GFR

<b>Left kidney scar</b>	-		Reference	
	+	11.89	(1.09,22.91)	0.046
<b>Sex</b>	Female		Reference	
	Male	3.55	(0.31, 40.56)	0.308
<b>Age (y)</b>		1.04	(0.98, 1.11)	0.236

\* Odds Ratio (OR)

\*\* confidence interval (CI)

\*\*\* Results were based on logistic regression

**Table 3:** The frequency (%) of creatinine serum level in patient with and without renal scarring

Variable		Serum level of creatinine			p-value*
		Increased	Normal	Total	
		Number (%)	Number (%)	Number (%)	
<b>renal scarring</b>	A	8 (66.7)	4 (33.3)	12 (100)	0.030
	B	2 (22.2)	7 (77.8)	9 (100)	
	Total	10 (47.6)	11 (52.4)	21 (100)	

\*Results were based on Fisher's exact test

**Table 4:** The Correlation of right/left kidney GFR and serum level of creatinine

Variable	1.		2.		3.	
	r*	p-value	r*	P-value	r*	p-value
<b>1.Right kidney GFR</b>	1		0.01	0.982	-0.50	0.022
<b>2.Left kidney GFR</b>			1		-0.54	0.011
<b>3.Creatinine</b>					1	

\*Pearson correlation coefficient

**Table 5:** The effects of right kidney scar, gender and age on creatinine serum level

Variable	Variable Series	OR*	95% CI**	p-value***
<b>Right kidney scar</b>	-	Reference		
	+	6.75	(1.31, 12.26)	0.032
<b>Gender</b>	Female	Reference		
	Male	0.36	(0.03, 3.89)	0.362
<b>Age (y)</b>		1.05	(0.98, 1.13)	0.349

\* Odds Ratio (OR)

\*\* confidence interval (CI)

\*\*\* Results was gained upon logistic regression



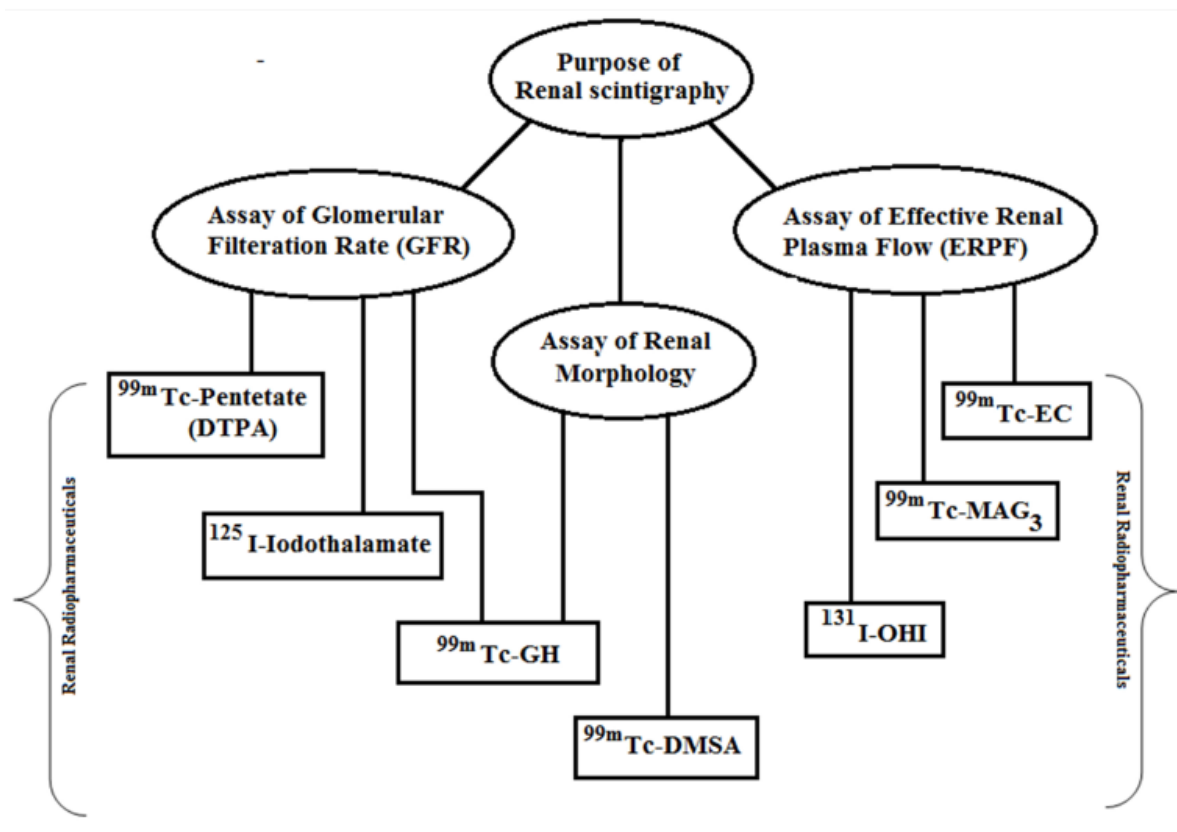


Figure 1. Renal radiopharmaceuticals

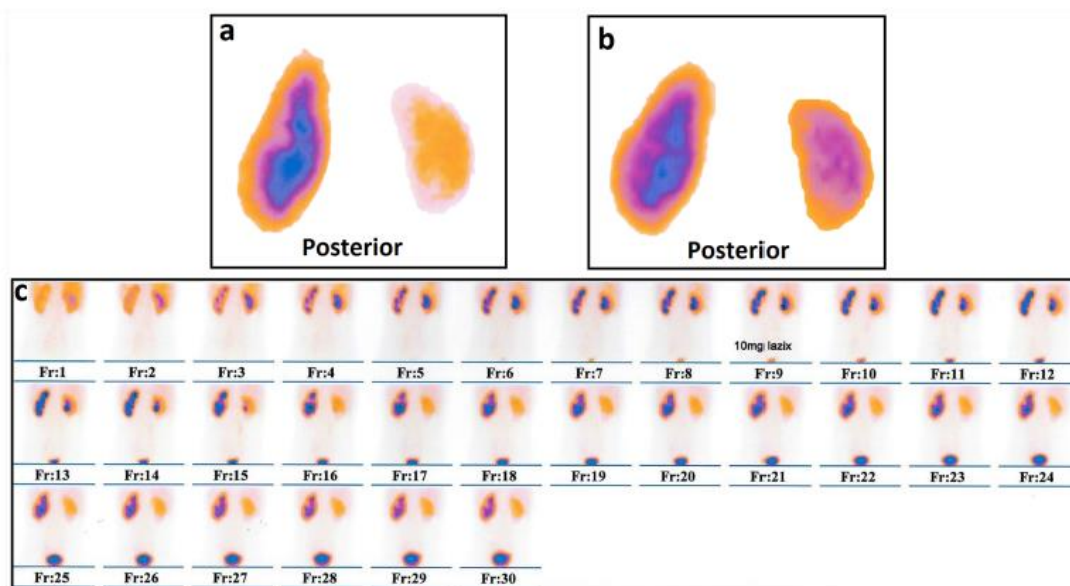
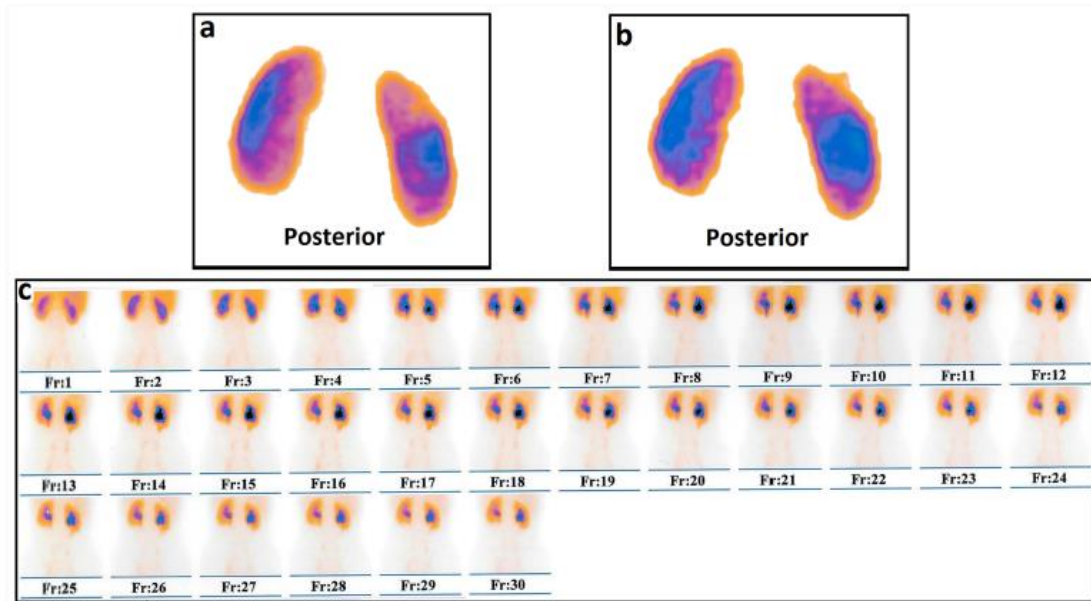
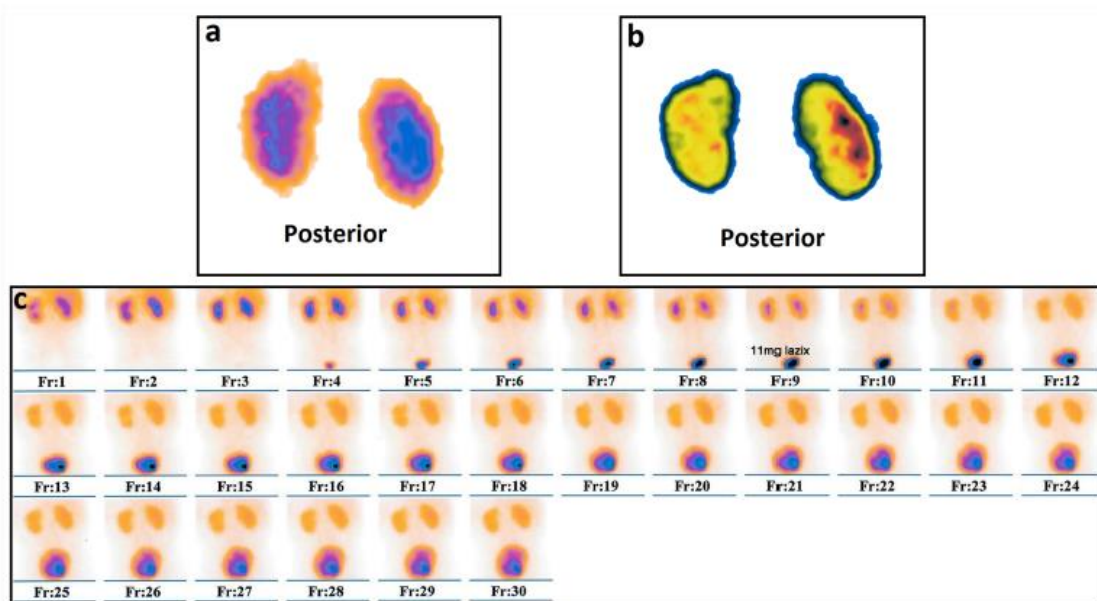


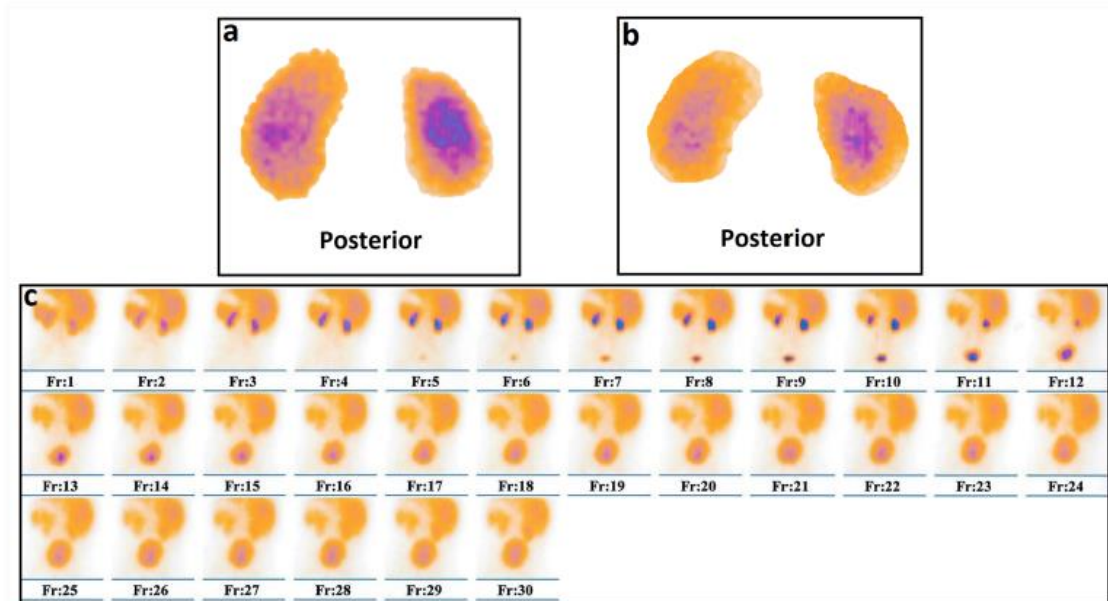
Figure 2. Both  $^{99m}\text{Tc}$ -GH and  $^{99m}\text{Tc}$ -DMSA scintigraphy for a same patient. (a):  $^{99m}\text{Tc}$ -DMSA Renal Scintigraphy, (b): Cortical (static) renal scintigraphy by  $^{99m}\text{Tc}$ -GH, (c): Dynamic functional renal scintigraphy by  $^{99m}\text{Tc}$ -GH.



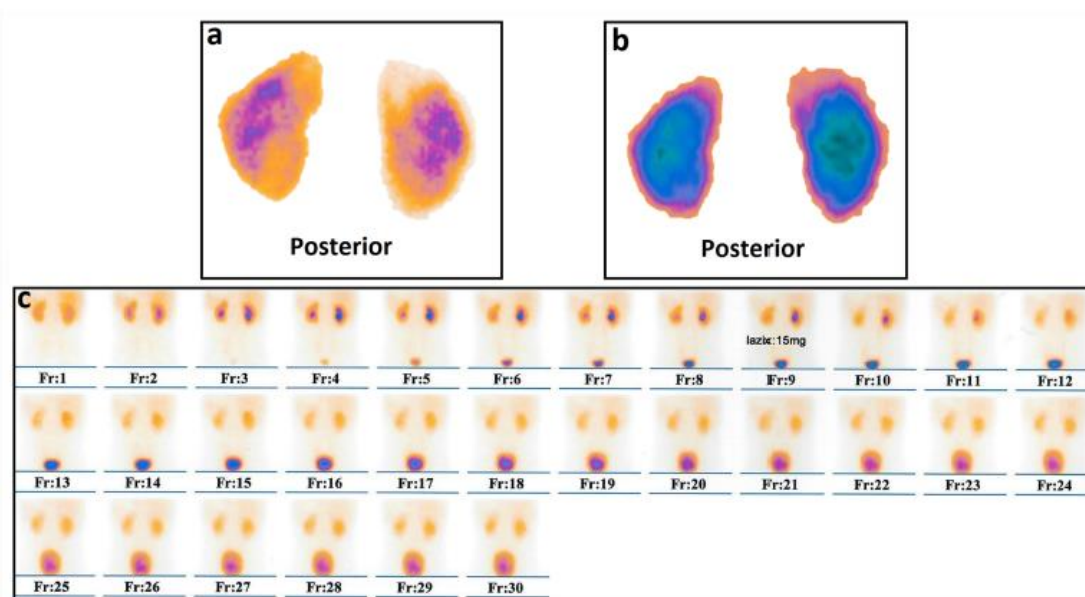
**Figure 3.** Both  $^{99m}\text{Tc}$ -GH and  $^{99m}\text{Tc}$ -DMSA scintigraphy for a same patient. (a):  $^{99m}\text{Tc}$ -DMSA Renal Scintigraphy, (b): Cortical (static) renal scintigraphy by  $^{99m}\text{Tc}$ -GH, (c): Dynamic functional renal scintigraphy by  $^{99m}\text{Tc}$ -GH.



**Figure 4.** Both  $^{99m}\text{Tc}$ -GH and  $^{99m}\text{Tc}$ -DMSA scintigraphy for a same patient. (a):  $^{99m}\text{Tc}$ -DMSA Renal Scintigraphy, (b): Cortical (static) renal scintigraphy by  $^{99m}\text{Tc}$ -GH, (c): Dynamic functional renal scintigraphy by  $^{99m}\text{Tc}$ -GH.



**Figure 5.** Both  $^{99m}\text{Tc}$ -GH and  $^{99m}\text{Tc}$ -DMSA scintigraphy for a same patient. (a):  $^{99m}\text{Tc}$ -DMSA Renal Scintigraphy, (b): Cortical (static) renal scintigraphy by  $^{99m}\text{Tc}$ -GH, (c): Dynamic functional renal scintigraphy by  $^{99m}\text{Tc}$ -GH.



**Figure 6.** Both  $^{99m}\text{Tc}$ -GH and  $^{99m}\text{Tc}$ -DMSA scintigraphy for a same patient. (a):  $^{99m}\text{Tc}$ -DMSA Renal Scintigraphy, (b): Cortical (static) renal scintigraphy by  $^{99m}\text{Tc}$ -GH, (c): Dynamic functional renal scintigraphy by  $^{99m}\text{Tc}$ -GH.