

# Diffusion Tensor Imaging Generated by Gadolinium-Based Magnetic Resonance Imaging Diagnosis for Patients with Chronic Kidney Disease

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## ARTICLE INFO

**Received:**  June 21, 2021

**Published:**  June 29, 2021

**Citation:** Liu He, Gao Dan, Sun Yuanbo, Tang Fengqiong, Hu Mingcheng, Li Hongyi. Diffusion Tensor Imaging Generated by Gadolinium-Based Magnetic Resonance Imaging Diagnosis for Patients with Chronic Kidney Disease. Biomed J Sci & Tech Res 36(5)-2021. BJSTR. MS.ID.005914.

**Keywords:** Chronic Kidney Disease; Diffusion Tensor Imaging; DTI-GBMRI; Renal Function; RBF; eGFR

## ABSTRACT

Chronic kidney disease (CKD) can lead to systemic inflammatory responses and other cardiovascular disease. Diffusion tensor imaging findings generated by gadolinium-based MRI (DTI-GBMRI) is regarded as a standard method for assessing the pathology of CKD. To evaluate the diagnostic value of DTI-MRI for renal histopathology and renal efficiency, renal fibrosis and damage, noninvasive quantification of renal blood flow (RBF) were investigated in patients with CKD. CKD patients (n = 186) were recruited and underwent diagnosis of renal DTI-GBMRI or DTI-MRI to identify the pathological characteristics and depict renal efficiency. The cortical RBFs and estimated glomerular filtration rate (eGFR) were compared in CKD patients undergone DTI-GBMRI (n=92) or DTI-MRI (n=94). Results showed that gadolinium enhanced the diagnosis generated by DTI-MRI in renal fibrosis, renal damage and eGFR. The superiority in sensitivity and accuracy of DTI-GBMRI method in assessing renal function and evaluating renal impairment was observed in CKD patients compared with DTI-MRI. Outcomes demonstrated that DTI-GBMRI had higher accuracy, sensitivity and specificity than DTI-MRI in diagnosing patients with CKD. In conclusions, these outcomes indicate that DTI-GBMRI is a potential noninvasive method for measuring renal function, which can provide valuable information for clinical CKD diagnosis.

**Abbreviations:** CKD: Chronic Kidney Disease; DTI-GBMRI: Diffusion Tensor Imaging Findings Generated by Gadolinium-Based MRI; eGFR: Estimated Glomerular Filtration Rate; ASCVD: Atherosclerotic Cardiovascular Disease; US: Using Ultrasonography; CEUS: Contrast-Enhanced Ultrasound; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; CMR: Cardiovascular Magnetic Resonance; MTT: Mean Transit Time; RBF: Renal Blood Flow; ROC: Receiver Operating Characteristic; BMI: Body Mass Index

## Introduction

Chronic kidney disease (CKD) is a public health problem worldwide, which is a gradual impairment of renal function [1]. Patients with CKD are at increased risk of cardiovascular disease other chronic conditions with their daily lives [2]. Clinically, CKD

is characterized by a low estimated glomerular filtration rate (eGFR, <60 mL/min/1.73 m<sup>2</sup>), which may progress at varying rates depending on blood pressure (BP) management, history of decreased GFR, level of proteinuria [3]. CKD may result in

abnormalities of multiple physiological processes including removal of waste products of metabolism, heterogeneous disorders on kidney structure and function, electrolyte balance that substantially increases mortality risk due to atherosclerotic cardiovascular disease (ASCVD) [4]. Therefore, CKD patients require imaging monitoring to accurately predict risk of declining renal function and guide therapeutic schedules. CKD is generally diagnosed by imaging of the kidney using ultrasonography (US), contrast-enhanced ultrasound (CEUS), computed tomography (CT), or magnetic resonance imaging (MRI) [5].

Cardiovascular magnetic resonance (CMR) is a standard method for imaging impairment in kidney function, renal injury and fibrosis [6]. MRI technique in particular has the potential to present both structural and functional parameters in the kidney by using targeted magnetic nanoparticles [7]. Gadolinium (GB)-based contrast agents are frequently used to enhance the diagnostic efficacy of MRI in patients with kidney diseases [8]. A potential alternative imaging modality for evaluating GFR and renal fibrosis is diffusion tensor imaging findings generated by Gadolinium-based MRI (DTI-GBMRI) [9]. Thus, DTI-GBMRI may be ideal for renal function assessment in patients with CKD. This purpose of this study was to comprehensively assess renal histopathology and renal efficiency, renal fibrosis and damage, noninvasive quantification of renal blood flow in patients with CKD using DTI-GBMRI. The sensitivity and accuracy between DTI-GBMRI and DTI-MRI method in assessing renal function and evaluating renal impairment was compared in CKD patients. The association between RBF value and eGFR was analyzed in patients with CKD.

## Materials and Methods

### Patients

A total of 186 CKD patients were recruited in Hongqi Hospital Affiliated To Mudanjiang Medcial University between January 2017 and May 2019. The inclusion criteria were as follows:

- 1) Age > 18 years;
- 2) Stage 1 of CKD ( $eGFR \geq 90 \text{ ml/min/1.73 m}^2$ ); Stage 2 of CKD ( $60 \text{ ml/min/1.73 m}^2 \leq eGFR < 90 \text{ ml/min/1.73 m}^2$ ); The exclusion criteria were as follows:
  1. Patients with HIV infection, polycystic kidney disease, cancer
  2. Patients with transplant recipients
  3. Pregnant and breastfeeding women
  4. History of adverse reaction to gadolinium. The protocol was approved by the ethics committee of Hongqi Hospital Affiliated To Mudanjiang Medcial University. CKD patients received DTI-GBMRI (n=92) or DTI-MRI (n=94) diagnosis. All participants signed written informed consent.

### Magnetic Resonance Imaging

MR examinations were performed using a 3 T unit (Canon Medical Systems, Tustin, CA, USA). Diffusion-weighted imaging/diffusion tensor imaging scans were obtained by using the following parameters: 256 diffusion directions, TR: 8000 ms, TE: 60 ms, 8 diffusion weighted b-values in steps of  $200 \text{ s/mm}^2$  ranging from b: 0–14000  $\text{s/mm}^2$ , flip angle:  $90^\circ$ ; bw: 1860 Hz/px, transversal base resolution matrix: 128 x 128. For DTI-GBMRI, A bolus injection of 0.2 mL/kg body weight gadolinium (Omniscan; Bracco, Daiichi-San-kyo Co., Ltd, Tokyo, Japan) was intravenously administered, followed by a 20-mL saline flush at 2 mL/sec. MR renography was obtained from all CKD patients to analyze renal histopathology and renal efficiency, renal fibrosis and damage, noninvasive quantification of renal blood flow.

### Outcomes

Kidney volume, the number, diameter, and volume of glomeruli in CDK patients were automatically analyzed using MRI image data. The eGFR was calculated using the estimation equation for CKD patients were determined on MRI image data. The GFR was calculated for each kidney by three radiologists by using Mirage software [10]. The mean transit time (MTT) was used to evaluate function of kidney in CKD patients as described previously [11]. Renal blood flow (RBF) was determined by MRI image data [12]. The procedure includes preprocessing of image data, segmentation of the kidney region, segmentation of the glomeruli, and quantification of the segmented regions as described previously [7]. All parameters were automatically analyzed by Syngo software (Siemens, Erlangen, Germany).

### Statistical Analyses

Data are expressed means  $\pm$  SD or n (%). All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Inc., Tokyo, Japan). The P values were calculated via independent sample t test for continuous variables and chi-square test for categorical variables. Receiver operating characteristic (ROC) analyses were used to analyze the diagnostic performance of the DTI-GBMRI diagnosis. The cutoff was determined according to ROC curve, and then the specificity and sensitivity of various scoring systems were calculated separately. Statistical significance was defined as a P-value <0.05.

## Results

### Characteristic of Patients with CKD

A total of 186 CKD patients were enrolled in this study. All CKD patients in stage 1 or 2 were enrolled between May 2017 and June 2019. A flowchart of CKD patient recruitment is shown in Figure 1. The age of CKD patients was 46.5 years old (range, 30-65 years). CKD patients voluntarily received DTI-GBMRI (n=92) or DTI-MRI (n=94) diagnosis. Table 1 shows the demographics and characteristics of

patients with CKD. There were no significant differences in BMI, age, sex, blood pressure, cerebrovascular disease, and intraocular

pressure between two groups. Signalment and renal biomarkers in two groups were not significant difference.

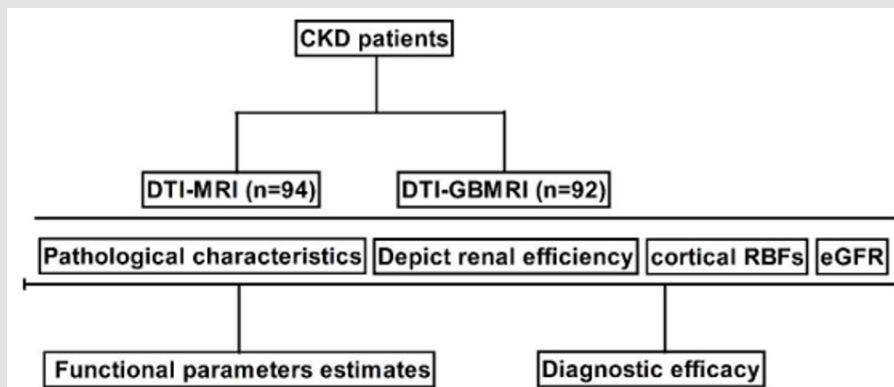


Figure 1: Flow diagram showing CKD patients in this study.

Table 1: Characteristic of CKD patients.

	DTI-MRI	DTI-GBMRI
Number	94	92
Male/female	54/40	53/39
Age (years)	52 ± 10	52 ± 10
BMI (Kg/m <sup>2</sup> )	25.2 ± 2.6	25.8 ± 3.1
<b>Blood pressure (mm Hg)</b>		
Systolic	132.3 ± 8.5	130.8 ± 9.0
Diastolic	82.6 ± 5.8	84.2 ± 6.5
Cerebrovascular disease	10 (10.6%)	9 (9.8%)
Intraocular pressure (mm Hg)	14.5 ± 2.6	14.8 ± 3.1
Smoking, n (%)	10 (10.6%)	10 (10.9%)
<b>CKD stages</b>		
2 (mild)	50 (53.2%)	50 (54.3%)
3a (mild to moderate)	44 (46.8%)	42 (45.7%)

Note: Data are expressed as mean ± or n (%). The P values were calculated via independent sample t test for continuous variables and chi-square test for categorical variables.

### The Pathological Characteristics and Depict Renal Efficiency Diagnosed by DTI-GBMRI

We compared the pathological characteristics and depict renal efficiency in CKD patients diagnosed by DTI-GBMRI or DTI-MRI. CKD patients diagnosed by DTI-GBMRI showed more renal vascular lesions and bigger diameters of lesions than those patients in DTI-MRI group. The average diameter diagnosed by DTI-GBMRI was

3.28 cm, while was in 3.02 cm in CKD patients diagnosed by DTI-MRI. DTI-GBMRI had significantly better performance than DTI-MRI in measuring lumen depiction scores (4.8 ± 0.2 vs 3.2 ± 0.2 for arterial inflow, 4.2 ± 0.1 vs 1.8 ± 0.2 for arterial outflow, 3.8 ± 0.3 vs 2.0 ± 0.3 for anastomosis, and 4.4 ± 0.2 vs 2.2 ± 0.2 for venous outflow; P<0.01), intraluminal signal homogeneity (0.24 ± 0.03 vs 0.40 ± 0.05, P<0.01), and CNR efficiency in the venous outflow (5.2 ± 0.3 vs 2.6 ± 0.3, P<0.01) (Table 2).

Table 2: The pathological characteristics and depict renal efficiency diagnosed by DTI-GBMRI.

	DTI-MRI	DTI-GBMRI	P value
Diameters of lesions (cm)	3.02 ± 0.32	3.28 ± 0.24	0.0045
Depiction scores	3.2 ± 0.2	4.8 ± 0.2	0.0032
Arterial inflow	1.8 ± 0.2	4.2 ± 0.1	0.0010
Arterial outflow	2.0 ± 0.3	3.8 ± 0.3	0.0041
Venous outflow	2.2 ± 0.2	4.4 ± 0.2	0.0036

Intraluminal signal homogeneity	0.40 ± 0.05	0.24 ± 0.03	0.0057
CNR efficiency	2.6 ± 0.3	5.2 ± 0.3	0.0028

**Note:** Data are reported as mean ± SD. The p values were analyzed using independent sample t test.

### Kidney Volume and Functional Parameters Estimates

Kidney volumes and functional parameters estimates were compared in CDK patients between DTI-GBMRI and DTI-MRI groups (Table 3). The mean kidney volumes of CDK patients in DTI-GBMRI and DTI-MRI were 2046 ± 214 ml and 1868 ± 224 ml, respectively (p<0.01). Creatinine levels were not significantly different between DTI-GBMRI and DTI-MRI groups. The total glomerular count in CKD patients diagnosed by DTI-GBMRI and DTI-MRI was around 16320 ± 12350 and 14560 ± 10180, respectively (p<0.01). MTTK was

significantly higher in the DTI-MRI group (186.2 ± 40.5 seconds) than in the DTI-GBMRI group (137.6 ± 30.6 seconds). DTI-GBMRI revealed stronger impairment of renal perfusion (156 ± 7 vs 293 ± 44 mL/[min × 100 g]; P < 0.01) and more pronounced increases in T2 (60.1 ± 2.0 vs 45.7 ± 1.2 milliseconds, P < 0.01) and T1 relaxation times (1938 ± 53 vs 1350 ± 27 milliseconds, P < 0.01) than DTI-MRI. Apparent diffusion coefficient was 1.39 ± 0.14 × 10<sup>-3</sup> mm<sup>2</sup>/s and 1.83 ± 0.05 × 10<sup>-3</sup> mm<sup>2</sup>/s in kidneys in DTI-GBMRI group and DTI-MRI group, respectively (P < 0.05).

**Table 3:** Kidney volume and functional parameters estimates diagnosed by DTI- GBMRI.

	DTI-MRI	DTI-GBMRI	P value
kidney volumes (ml)	1868 ± 224	2046 ± 214	0.0008
Creatinine (mg/dL)	1.68 ± 0.32	1.75 ± 0.40	0.0091
MTTK	186.2 ± 40.5	137.6 ± 30.6	0.0025
<b>Impairment of renal perfusion</b>			
(mL/[min])	293 ± 44	156 ± 7	0.0010
T2 pronounce (milliseconds)	45.7 ± 1.2	60.1 ± 2.0	0.0040
<b>T1 relaxation times</b>			
(milliseconds)	1938 ± 53	1350 ± 27	0.0012
CNR efficiency (mm <sup>2</sup> /s)	1.83 ± 0.05 × 10 <sup>-3</sup>	1.39 ± 0.14 × 10 <sup>-3</sup>	0.0085

**Note:** Data are reported as mean ± SD. The p values were analyzed using independent sample t test.

### Cortical RBFs and eGFR

The cortical RBFs and estimated glomerular filtration rate (eGFR) were compared in CKD patients undergone DTI-GBMRI (n=92) or DTI-MRI (n=94). The cortical RBF values of CKD patients in DTI-GBMRI group were lower than patients in DTI-MRI group

(315.8 ± 23.6 vs. 503.5 ± 32.4, p<0.01). Outcomes demonstrated that eGFR was significantly lower in CDK patients undergone DTI-GBMRI than those undergone DTI-MRI (36.4 ± 20.8 vs 44.7 ± 16.5 mL/min) (Table 4). Results showed that gadolinium enhanced the diagnosis generated by DTI-MRI in renal fibrosis, renal damage and eGFR.

**Table 4:** Analysis of Cortical RBFs and eGFR in CDK patients.

	DTI-MRI	DTI-GBMRI	P value
Serum creatinine (mg/dL)	1.68 ± 0.32	1.75 ± 0.40	0.0058
eGFR (mL/min/1.73 m <sup>2</sup> )	36.4 ± 20.8	44.7 ± 16.5	0.0072
BRF (ml/min)	503.5 ± 32.4	315.8 ± 23.6	0.0020

**Note:** Data are reported as mean ± SD. The p values were analyzed using independent sample t test.

### Diagnostic Efficacy of DTI-GBMRI

Receptor operating characteristics (ROC) curve was used to determine the diagnostic efficacy between DTI-MRI and DTI-GBMRI groups in CDK patients. DTI-GBMRI method showed the superior diagnostic accuracy compared to DTI-MRI. Outcomes demonstrated that DTI-GBMRI had higher sensitivity and specificity than DTI-MRI in diagnosing patients with CKD (Table 5). From the curve, the cut-off value for and DTI-GBMRI were determined with maximum sensitivity and specificity to be 0.92 and 0.85,

respectively (Figure2).

**Table 5:** Diagnostic efficacy of DTI-GBMRI in CKD patients.

	DTI-MRI	DTI-GBMRI	P value
Sensitivity (%)	86.8	98.5	0.0048
Specificity (%)	88.3	98.2	0.0070

**Note:** Sensitivity and specificity differences between DTI-MRI and DTI-GBMRI were analyzed using Pearson nonparameter correlation analysis

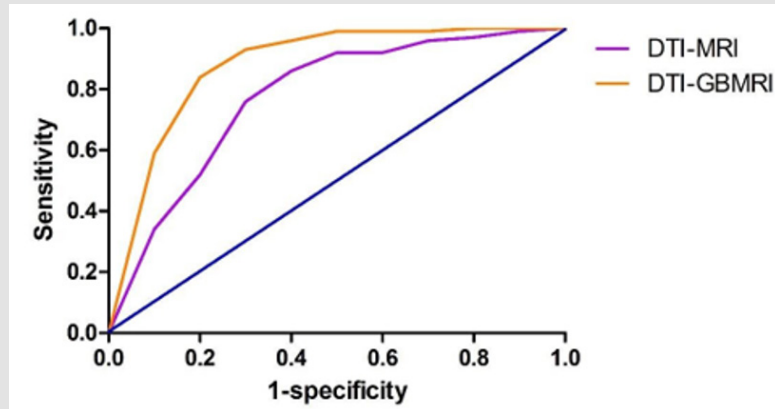


Figure 2: Receiver operating characteristic curve of DTI-GBMRI and DTI-MRI for the diagnosis of CKD patients.

## Discussion

The assessment of early CKD damage is of crucial importance in preventing CKD-induced diseases [13]. In this study, we investigated the diagnostic efficacy of DTI-GBMRI in evaluating histopathology and renal efficiency in patients with in CKD patients. Functional parameters associated with renal impairment in kidney function were analyzed in DTI-GBMRI-diagnosed CKD patients with CKD. Findings in this study found DTI-GBMRI accurately imaged the pathological characteristics and depict renal efficiency in CKD patients. Thus, DTI-GBMRI may be a potential noninvasive method for measuring renal function for CKD patients. CKD has been associated with increased visual impairment and cardiovascular disease [13]. Inflammation and dysfunction of glomerular cells contributes to the cardiovascular disease burden associated with CKD, which is one of the most important risk factors for mortality and morbidity in CKD patients [14]. Thus, it is very important to evaluate the degree of CKD and analyze abnormalities of kidney structure or function [15]. MRI methods have become available for renal functional evaluation for patients with CKD, which can access renal function combined with high-resolution morphological evaluation of the kidneys and the entire urinary tract [16]. In this study, we found that DTI-GBMRI presented higher efficacy in evaluating renal histopathology and renal efficiency, renal fibrosis and damage, noninvasive quantification of renal blood flow than DTI-MRI. Data reported that DTI-GBMRI clearly showed the diameters of lesions, good performance in measuring lumen depiction scores, intraluminal signal homogeneity, and CNR efficiency in CKD patients compared to DTI-MRI, suggesting DTI-GBMRI provided the possible origins of differences in estimates of CKD prevalence, and presented possible solutions for tackling the factors responsible for the reported variations in renal injury measurements. Previously, MRI allows the assessment of markers of perfusion without the use of contrast media [17]. A study highlighted the potential clinical benefits of early detection

in patients predisposed to CKD by using MRI techniques, which provided structural and functional information in the kidney [7]. Zhao et al found that diffusion-weighted MRI can be used to assess renal fibrosis in CKD patients [18].

Data in this study observed that DTI-GBMRI-diagnosed CKD patients had higher MTTK, stronger impairment of renal perfusion and more pronounced increases in T2 and T1 relaxation times than DTI-MRI in CKD patients. However, there was no significant difference in evaluating kidney volumes between DTI-GBMRI and DTI-MRI groups. A previous study demonstrated that MRI could classify renal function, identify eGFR and functional renal parenchyma RBF in CKD patients [18,19]. Findings in the current study demonstrated that DTI-GBMRI-diagnosed CKD patients showed lower cortical RBF values and eGFR than those patients diagnosed by DTI-MRI. MRI method has been used in diagnosing CKD for it is a noninvasive and accessible method [20-22]. However, its operator dependency and low sensitivity reduce its utility in research. This study introduced gadolinium-based MRI to improve operator dependency and low sensitivity in diagnosing cortical RBFs eGFR, renal fibrosis, renal damage and eGFR in CKD patients. The strategies of this study compared the diagnostic efficacy between DTI-GBMRI and DTI-MRI, and outcomes found that DTI-GBMRI method showed the superior diagnostic accuracy, sensitivity and specificity compared to DTI-MRI in patients with CKD. In conclusion, this study demonstrates the benefits of DTI-GBMRI in measuring renal histopathology and renal efficiency, renal fibrosis and damage, noninvasive quantification of renal blood flow in CDK patients. Outcomes find that DTI-GBMRI improves testing methodologies for more accurate assessment of cortical RBFs, GFR, pathological characteristics and depict renal efficiency than DTI-MRI, which further contributes to high sensitivity and specificity. These data suggest that DTI-GBMRI may be a reliable assessment of renal function combined with high-resolution morphological evaluation of the kidneys, as well as accurately identify stage CKD in certain clinical patients.

## Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Hongqi Hospital Affiliated To Mudanjiang Medical University.

## Funding

Mechanism of BMSC transformation of NRk-52e based on the role of gsk3beta in renal interstitial fibrosis (UNPYSCT-2018120).

## Acknowledgement

Not application.

## Human and Animal Rights

The present study was approved by the Committee on Human Rights Related to Research Involving Human Subjects (IRB Approval number: 20170111X).

## Informed Consent

Consent for tissue collection and use was collected prior to experimentation. All patients signed written informed consent and consent for publication.

## Conflict of Interest

The authors declare that they have no competing interests.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2021.36.005914

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