Assessment of Chronic Allograft Injury in Renal Transplantation Using Diffusional Kurtosis Imaging

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Abstract

Background: Chronic allograft injury (CAI) is a significant reason for which many grafts were lost. The study was conducted to assess the usefulness of diffusional kurtosis imaging (DKI) technology in the non-invasive assessment of CAI.

Methods: Between February 2019 and October 2019, 110 renal allograft recipients were included to analyze relevant DKI parameters. According to estimated glomerular filtration rate (eGFR) (mL/min/ 1.73m^2) level, they were divided to 3 groups: group 1, eGFR≥60 (n=10); group 2, eGFR 30–60 (n=69); group 3, eGFR<30 (n=31). We performed DKI on a clinical 3T magnetic resonance imaging (MRI) system. We measured the area of interest to determine the mean kurtosis (MK), mean diffusivity (MD), and apparent diffusion coefficient (ADC) of the renal cortex and medulla. We performed a Pearson correlation analysis to determine the relationship between eGFR and the DKI parameters. We used the receiver operating characteristic (ROC) curve to estimate the predicted values of DKI parameters in the CAI evaluation. We randomly selected five patients from group 2 for biopsy to confirm CAI.

Results: With the increase of creatinine, ADC, and MD of the cortex and medulla decrease, while MK of the cortex and medulla gradually increase. Among the three different eGFR groups, significant differences were found in cortical and medullary MK (P =0.039, P <0.001, P <0.001, respectively). Cortical and medullary ADC and MD are negatively correlated with eGFR (r=-0.49, -0.44, -0.57, -0.57, respectively; P<0.001), while cortical and medullary MK are positively correlated with eGFR (r=0.42, 0.38; P<0.001). When 0.491 was set as the cutoff value, MK's CAI assessment showed 87% sensitivity and 100% specificity. All five patients randomly selected for biopsy from the second group confirmed glomerulosclerosis and tubular atrophy/interstitial fibrosis.

Conclusion: The DKI technique is related to eGFR as allograft injury progresses, and is expected to become a potential non-invasive method for evaluating CAI.

Background

Kidney transplantation might be the most suitable treatment option for patients with end-stage renal disease. When the dialysis method is different, kidney transplantation can provide unparalleled results, such as survival rate, personal satisfaction, quality of life, and cost suitability[1].

Despite advances in surgical techniques and immunosuppressive agents, kidney allografts' long-term effects have not been wholly improved in the past two decades. This may be caused to a certain extent by chronic allograft injury (CAI), which is the main reason for the failure of the renal allograft.

The characteristics of CAI is glomerulosclerosis, tubular atrophy, vascular occlusive changes, and interstitial fibrosis. Early detection and exact evaluation of CAI are critical to manage treatment and to postpone or prevent irreversible damage to the transplanted renal[2][3].

Current methods for evaluating CAI have significant impediments. Estimation of serum creatinine level and the estimated glomerular filtration rate (eGFR) are the most commonly used techniques for checking the function of the allograft. However, they are known to be affected by many factors, and their predictive value for allograft injury is low. When the serum creatinine has expanded, or the eGFR has decreased, the degree of allograft injury may have already gotten advanced and irreversible[4]. Accordingly, allograft biopsy was considered the golden choice to analyze allograft injury and differentiate among the different etiologies, despite its impediments, such as infection, bleeding, and even allograft loss[5]. But the regular evaluation of CAI still can not be exactly. Like the eGFR might not be sensitive enough to evaluate CAI change, and the standard golden biopsy also seems to have significant risks. Hence, a critical need is needed to find non-invasive and precise techniques for diagnosing CAI to guide timely intervention.

Magnetic resonance imaging (MRI) has been proven to provide the morphological, microstructural, and functional characteristics of renal allografts. Ionizing radiation is not used in MRI, so it allows repeated imaging during follow-up after the patient has received a kidney transplant[6][7].

Diffusional kurtosis imaging (DKI) extends the conventional diffusion tensor imaging (DTI) model by considering the non-gaussian behavior of water molecules and can provide a more accurate and sensitive measurement of microstructural complexity and diffusional heterogeneity. DKI requires at least three b-values, and the maximum b-value is more significant than diffusion-weighted imaging (DWI). Although there are standard DTI metrics such as mean diffusivity (MD) and apparent diffusion coefficient (ADC), DKI can provide parameters identified by mean kurtosis (MK). Among these parameters, MK is the significant one obtained from DKI, which renal allografts believed to be a natural complexity. The more complex the structure and the higher the MK value, the higher the degree of diffusion restriction on the non-Gaussian distribution of water molecules[8]. So, we supposed that the microstructural change in CAI might be demonstrated by the DKI technique more precisely than eGFR, and the DKI technique might be a non-invasive method for evaluating CAI

This study is planned to evaluate the correlation between eGFR and DKI parameters and the potential feasibility of the DKI technique in non-invasive assessment for CAI.

Methods

Participants

All the patients included in the analysis received kidney transplantation approved by the Institutional Review Board of Beijing Chao-Yang Hospital, Capital Medical University. They conformed to the tenets of the Declaration of Helsinki. Before allograft biopsy and functional MRI, written informed consent from all patients should be collected.

In this prospective single-center study conducted from February 2019 to October 2019, a total of 130 adult patients after kidney transplantation agreed to participate and had no MRI contraindications were inrolled. Exclusion criteria were the presence of MRI-incompatible equipment, claustrophobia, rejection of patients,

and the interval between transplantation and MRI for less than three months. When the MRI slot is available, select eligible patients who did not meet the exclusion criteria. The final analysis included only kidneys known to have been procured with the consent of the donors or their family members. The data from patients with kidney transplantation from unknown sources were excluded from the final analysis.

Functional MRI examinations were performed within one week before the biopsy. In all patients, blood samples were collected on the day of the MR examination, and eGFR was calculated by modifying the renal disease equation[9]. Patients were divided to three groups according to the function of allograft: Group 1 consisted of patients with good allograft function eGFR > 60 (mL/min/1.73 m^2), Group 2 consisted of patients with moderate allograft function 30 < eGFR < 60 (mL/min/1.73 m^2), while patients with heavily impaired renal function eGFR < 30 (mL/min/1.73 m^2) were classified into Group 3. Clinical status and renal function were monitored every 1–4 weeks in the first year after transplantation and every month after that. A minimum of 3 months of follow-up was available for all patients.

MRI Protocols

All MRI examinations were performed on the 3T Prisma MRI scanner (Siemens Healthineers, Erlangen, Germany) using a 16-channel phased-array coil positioned over the pelvis. The anatomic images were obtained using transverse T1-weighted imaging (TR/TE = 700/12 ms, slice thickness = 5.0 mm, slice spacing = 0 mm, FOV = 240mm^2,matrix size = 256 × 256) and transverse T2-weighted imaging (TR/TE = 3770/101 ms, slice thickness = 5.0 mm, slice spacing = 0 mm, FOV = 240mm^2, matrix size = 320 × 320) covering the transplant kidney. Following the anatomic scans, DWI was performed with single-shot echo-planar imaging (EPI) in the transverse plane, with locations identical to those prescribed for the transverse T2-weighted imaging, using six *b*-values (0_4, 400_6, 800_8, 1200_{10}, 2000_{10} and 3000_{12} s/mm^2, where the subscript denotes the number of averages). The other key acquisition parameter for DWI were: TR/TE = 3100/68 ms, slice thickness = 3.5 mm, slice spacing = 0 mm, matrix size = 120 × 120, FOV = 350 mm, and the scan time∼9 min.

Functional MRI Image Analyses

All MR images were analyzed by two radiologists (with more than ten years of experience in the field of abdominal imaging) who did not know the diagnosis or pathophysiologic grade. Regions of interest (ROI) were manually drawn on DWI with *b* value = 0 s/mm^2, and then copied onto the corresponding position on all parameter maps. 18 ROIs were positioned on three parts (upper pole, central area, and lower pole) of transplant kidney: for each segment, three ROIs (anterior labrum, posterior labrum and, intermediate site) were drawn on the cortex and another three on the medulla. Finally, the values of ADC and DKI parameters (MK and MD) were calculated as an average of all voxels contributing to the ROI, and then did further quantitative analysis detailed below. Artifacts were avoided when placing ROIs. All measurements were repeated twice, and the values of K, D, and ADC were recorded.

Histopathological analysis

We performed biopsy randomly in patients of Group 2 to confirm the histopathological changes. The indication of the biopsy was eGFP < 60 (mL/min/1.73 m2) with or without gradual deterioration during the follow-up and patient consent. Kidney tissue was obtained by needle biopsy and fixed in 4% buffered formaldehyde. Then the tissue was embedded in paraffin and cut into 2-μm-thick serial sections. The sections were stained in a routine manner, with hematoxylin and eosin (H&E) and periodic acid silver methenamine (PASM), to assess glomerulosclerosis and tubular atrophy, respectively, and with Masson-Goldner's trichrome to quantify interstitial fibrosis. The diagnosis procedures were performed according to the standard protocols of the renal pathology laboratory, as reported previously[10]. Pathologic diagnoses were performed by two experienced neuropathologists with 15 years and 18 years of experience, respectively, according to the Banff 2015 scheme[11] without referring to functional MRI results.

The inter-reader agreement assessment

We evaluated the repeatability of MRI parameters using interclass correlation coefficients(ICCs). The ICC was classified as good consistency when it was larger than 0.80.

Statistical analysis

SPSS 24.0 for Windows (SPSS, Chicago, IL, USA) was used for statistical data analysis. We used the Kolmogorov-Smirnov test to testify the normality of data. Normally distributed variables are expressed as mean values with standard deviations. Categorical variables are described as a percentage. We used Two-tailed paired Student *t*-tests to compare cortical and medullary DKI parameters. A one-way analysis of variance (ANOVA) was performed to test the difference in ADC, Mean K, and Mean D values between the three groups. A Pearson correlation analysis was performed to determine the relationship between the MRI parameters and eGFR. The receiver operating characteristic (ROC) curve analysis of diffusional kurtosis parameters was performed to predict normal and mildly impaired renal function in the recipients to evaluate the diagnostic performances of diffusional kurtosis parameters in predicting impaired renal function without the server impaired renal function group. P < 0.05 indicated that the difference was statistically significant.

Results

Patient Demographics, Clinical Characteristics, and Laboratory Characteristics

A total of 130 patients were included in this cohort, and if there were MRI-incompatible devices, claustrophobia, and patient refusal(n = 20), they were excluded. Finally, the functional MRI data of 110 patients (mean age, 44.32±9.562 years) were analyzed (Fig. 1), including 82 males (mean age,

43.50±9.535 years) and 28 females (mean age, 46.71±9.40 years). The time interval between renal transplantation and MR examination was three months to 300 months, with a median of 42.29 months. No statistically significant difference was observed between these three groups about donor demographics, recipient age, sex, kidney transplant type, and immunosuppressive regimens used. (Table 1)

Table 1
Patient demographics, clinical features, and laboratory characteristics in 110 patients who underwent functional magnetic resonance imaging

Characteristics/Findings	Group 1	Group 2	Group 3
No. of patients	10	69	31
Sex (men: women)	5:5	11:58	12:19
Age(months)	50.4±5.4	43.1±9.5	44.9±10.3
Time post transplantation(months)	35±25.8	31.96±26.1	67.32±47.2
Immunosuppressive regimens			
Pre + MMF + FK506, n (%)	8(80)	60(87)	27(87.1)
Pre + MMF + CsA, n (%)	0	6(8.7)	2(6.5)
Other, n (%)	2(20)	3(4.3)	2(6.5)
Serum creatinine, mg/dl, mean±SD	65.3±4.6	108.8±33.6	168.4±104.6
eGFR, ml/min/1.73 m^2, mean±SD	65.6±5.1	41.7±8.8	24.3±8.1
Hemoglobin level, g/dl, mean±SD	143.6±12.7	145.26±20.5	117±22.8
Pre: Prednisone, MMF: Mycophenolate mofetil			

Unsurprisingly, the mean hemoglobin level of Group 3 was much lower than that of both Gourp1 and Group2.

Diffusional Kurtosis Imaging

The corticomedullary difference is displayed by diffusional kurtosis imaging. (Fig. 2)

Table 2 demonstrated the value of different cortical and medullary DKI parameters in three groups. Except for the mean D of the medulla of group 3 ($p = 0.277$), the renal cortex parameters (including MK and MD values) of the subjects in all three groups were significantly higher than the medulla of the subjects ($p < 0.05$). But the cortical ADC was lower than medullary ADC ($p < 0.05$). ADC and Mean D values of the renal

cortex and medulla decreased gradually with the increase of creatinine. In contrast, the Mean K values of the renal cortex and medulla increased gradually with creatinine.

Table 2.
Comparison of diffusional kurtosis parameters of renal cortex and medulla in each group

	ADC (10^{-3} mm^2/s)		Kurtosis (10^{-3} mm^2/s)		D (10^{-3} mm^2/s)	
	Cortex	Medulla	Cortex	Medulla	Cortex	Medulla
Group 1	1.192±0.049	1.236±0.063	0.470±0.013	0.458±0.017	2.778±0.409	2.625±0.377
	(p=0.000)		(p=0.039)		(p=0.000)	
Group 2	1.141±0.097	1.155±0.116	0.521±0.044	0.511±0.041	2.585±0.237	2.533±0.230
	(p=0.25)		(p=0.000)		(p=0.001)	
Group 3	1.016±0.116	1.049±0.105	0.554±0.042	0.535±0.039	2.183±0.323	2.178±0.197
	(p=0.002)		(p=0.000)		(p=0.27)	
Statistical analysis was employed using the t-test. Data presented as mean±SD. A p<0.05 was considered statistically significant.						

As showed in Fig. 3, all parameters showed significant differences ($p < 0.05$) except Cortical ADC and Medullary Mean D between Group 1 and Group 2 ($p = 0.117$, $p = 0.257$, respectively).

Correlations of DKI parameters with eGFR

The Mean K of renal cortex and medulla of all the patients showed positive correlations with eGFR ($r = 0.42, 0.38$; $P < 0.001$), while the ADC and MD of renal cortex and medulla all correlated negatively with eGFR ($r=-0.49, -0.44, -0.57, -0.57$, respectively; $P < 0.001$). (Fig. 4).

ROC Analysis Results

In each of these six parameters, the Mean K of the renal cortex showed the most prominent area under the stove of 0.967. In contrast, the medullary Mean K showed a comparable area under the curve of 0.960. When 0.491 was set as the cutoff value, the sensitivity of cortical Mean K to predict normal and mild impaired renal function is 87%, and the specificity is 100%. Meanwhile, When 0.499 was set as the cutoff value, the medullary Mean D demonstrated a sensitivity of 61% and specificity of 100% for predicting normal and mildly impaired renal function. (Fig. 5 and Table 3)

Table 3
Performances of Diffusion kurtosis Imaging parameters in Predicting Decreased Transplanted Kidney Function

Index	ADC (10^{-3} mm^2/s)		Kurtosis (10^{-3} mm^2/s)		D (10^{-3} mm^2/s)	
	Cortex	Medulla	Cortex	Medulla	Cortex	Medulla
AUC	0.218	0.142	0.967	0.960	0.282	0.344
Cut off value		1.429	0.491	0.499		
Sensitivity%		100%	87%	61%		
Specificity%		3%	100%	100%		
P value	(p=0.051)	(p=0.042)	(p=<0.022)	(p=<0.041)	(p=0.085)	(p=0.104)

The results of inter-reader agreement assessment

The results of the ICCs were displayed in the supplementary materials Table 1. The results of ICCs ranged from 0.83 to 0.99, representing good agreements for the measurement data.

Pathology Findings

We randomly selected five patients from group 2 to confirm the diagnose of CAI. The main pathologic findings in the five patients were glomerulosclerosis and tubular atrophy/interstitial fibrosis, which conform to the diagnose of CAI (Fig. 6).

Discussion

The present study first proposed the non-Gaussian DKI model as a potential non-invasive method for evaluating of CAI.

Jensen et al. first proposed DKI in 2005[12], as an extension of conventional DWI, which requires ultrahigh b-values (> 1000 s/mm2) and a modified image post-processing procedure. The traditional model of DWI was established based on the assumption that water diffusion exhibits Gaussian behavior without any restriction and that the diffusion-weighted MRI signal mono-exponentially decreases with increasing b-values; however, a deviation from simple mono-exponential decay is readily identified in the kidney, under either healthy or pathological conditions[13]. DKI could be utilized to analyze non-Gaussian water diffusion with a polynomial model and has been used to identify the heterogeneity of cellularity and microstructural complexity[14][15].

DKI can yield two characteristic variables: D and K. D is the diffusion coefficient corrected by a non-Gaussian bias, and K quantifies the deviation of tissue diffusion from a Gaussian pattern [12][15]. Recently, in animal models, DKI has been used to assess liver fibrosis[16][17], which demonstrated additional meaningful information different from that of conventional DWI. There were only two studies focused on DKI in healthy kidneys, which showed conflicting results[18][19]. And the results showed that whether the maximal b- values (600 and 1000s/mm) are sufficiently high remains controversial. Huang et al. [18] showed that in a normally functioning kidney, the MK value of the cortex is lower than that of the medulla. Among these diffusion kurtosis indicators, the difference between cortex and medulla is reliable with the presence of radially-oriented vessels, tubules, and collecting ducts in the medulla [18]. Interestingly, Pentang et al. [19] showed that the cortical MK is larger than the medullary MK.

As a particular metric of the DKI model, K has been hypothesized to represent the direct interaction of water molecules with the cell membrane intracellular compounds and expanded K recommends that the tissue has increasingly irregular and heterogeneous environments with numerous great interfaces. In tumor cells, an increased nuclear-cytoplasmic ratio and microstructural were revealed by K value [14][20]. The accurate underlying meaning of the diffusional kurtosis metrics is not yet mastered, and DKI acquisition still needs improvement.

Liu et al. [21]found that in the pathogenesis of IgAN, the progressive loss of glomerular capillary structures and the disappearance of glomerular cellular elements with replacement by an expanding extracellular matrix and fibrous tissue could result in more complex microstructure and marked variation in cell size and shape than in healthy kidneys, leading to increased K.

In our study, we found that the MK increased gradually with the deterioration of kidney function, which indicates the increase of a much more irregular and heterogeneous environment in renal allograft with the worsening of renal function. As we know, the primary pathology change of CAI is the glomerulosclerosis and tubular atrophy/interstitial fibrosis, which means a tendency of the more irregular and heterogeneous environment in the renal allograft.

Liu et al. also demonstrated that K showed better performance than ADC in glomerulosclerosis in terms of the diagnostic efficacy, with a relatively larger AUC and stronger correlation. However, the level of statistical significance was not achieved[21]. These results indicate that the K in the DKI model showed clinical potential for assessing the severity of renal sclerosis in the glomeruli and can provide more information compared with ADC.

In our study, we found that ADC and the Mean D value of cortex in patients with severely decreased eGFR were significantly lower than those in patients with higher eGFR. In comparison, the Mean K value in patients with higher eGFR was lower than in patients with severely reduced eGFR.

According to our research, although all the six parameters showed significant differences except cortical ADC and medullary Mean D between Group 1 and Group 2, the ROC's considerable differences were only found in ADC of Medulla and MK of cortex and medulla. But the ADC demonstrated an extremely low

specificity, and the MK of the cortex showed the largest AUC. Meanwhile, we performed a random autopsy to confirm the histography change of renal allograft. We found that there were glomerulosclerosis and tubular atrophy/interstitial fibrosis of the randomly selected patients, which confirmed that K increased with the deterioration of renal function and renal fibrosis progression. So, we suggested that Mean K showed excellent CAI prediction for the identification of both glomerulosclerosis and tubular atrophy/interstitial fibrosis.

At the same time, the higher Mean K value of patients with decreased renal function may be partially due to interstitial fibrosis. The higher cell density and collagen deposition may result in lower ADC values in renal allografts [22]. This showed that DKI parameters have broad clinical application prospects in the non-invasive screening of the function of renal allografts at various stages. When 0.491 was set as the cutoff value, the Mean K in the cortex demonstrated a sensitivity of 87% and specificity of 100% for predicting impaired allograft function.

There are limitations to this study. First, the number of patients with normal eGFR was little. And it limits the accuracy of ROC curves. Second, not all the patients were performed biopsy in this study to analyze the quantitative correlation between histopathologic results and DKI parameters.

So, although we confirmed that the DKI model was associated with the changes of eGFR and can assess CAI to some extent if the DKI model can evaluate the evolution of CAI more accurately before the change of eGFR still needs to be studied. In the future, we aim to perform a more extensive sample size research to explore if the micro-changes detected by the DKI model can stand for the change of CAI more accurately even earlier than eGFR.

Conclusions

In conclusion, the non-invasive KI model was closely associated with the eGFR as allograft injury progresses, as renal perfusion might be reduced. The parameter MK of the renal cortex can non-invasively assess CAI to some extent. The DKI technique is correlated with eGFR and can be expected to be a non-invasive method to evaluate CAI potentially.

Abbreviations

ADC = apparent diffusion coefficient

MK = mean kurtosis

MD = mean diffusivity

DTI = diffusion tensor imaging

eGFR = estimated glomerular filtration rate

CAI = chronic allograft injury

MRI = magnetic resonance imaging

ROC = receiver operating characteristic

Declarations

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Written informed consent was gathered from all patients before the functional MRI and allograft biopsies.

Consent for publication

There is no conflict of interest in this manuscript, which has been approved by all authors for publication. I would like to declare on behalf of all co-authors that the work described herein is an original research article that has not been published previously and is not under consideration for publication elsewhere, either in whole or in part.

Availability of data and material

All the data and materials can be offered if required.

Competing interests

The authors have no financial conflicts of interest.

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Authors' contributions

Guarantors of the integrity of the entire study, TJ, XPH; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of the final version of the submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, XZ, ML, TJ, XPH; clinical studies, XZ, ML, TJ, XPH; MRI studies, XZ, ML, PW, XNL; statistical analysis, XZ. ML; and manuscript editing, XZ, ML, QZ, SZ, TJ, XPH.

As the article is a comprehensive work of both Urology and Radiology, it needs the cooperation of both departments. Dr. XZ and Dr. ML from Urology and Radiology, separately, cooperated very well in all the process of this research. Dr. XZ attributed more work regarding the collection of clinical data, while Dr. ML attributed more work regarding the collection of MRI data. Furthermore, Dr. XZ wrote the clinical part of the article, and Dr. ML wrote the piece of MRI protocols. Then they incorporated in the discussion parts of the article. So, we think they attributed equal to the article and should be the co-first author.

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Consent to participate (include appropriate statements)

Written informed consent was gathered from all patients before performing allograft biopsies and the functional MRI.

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Figures

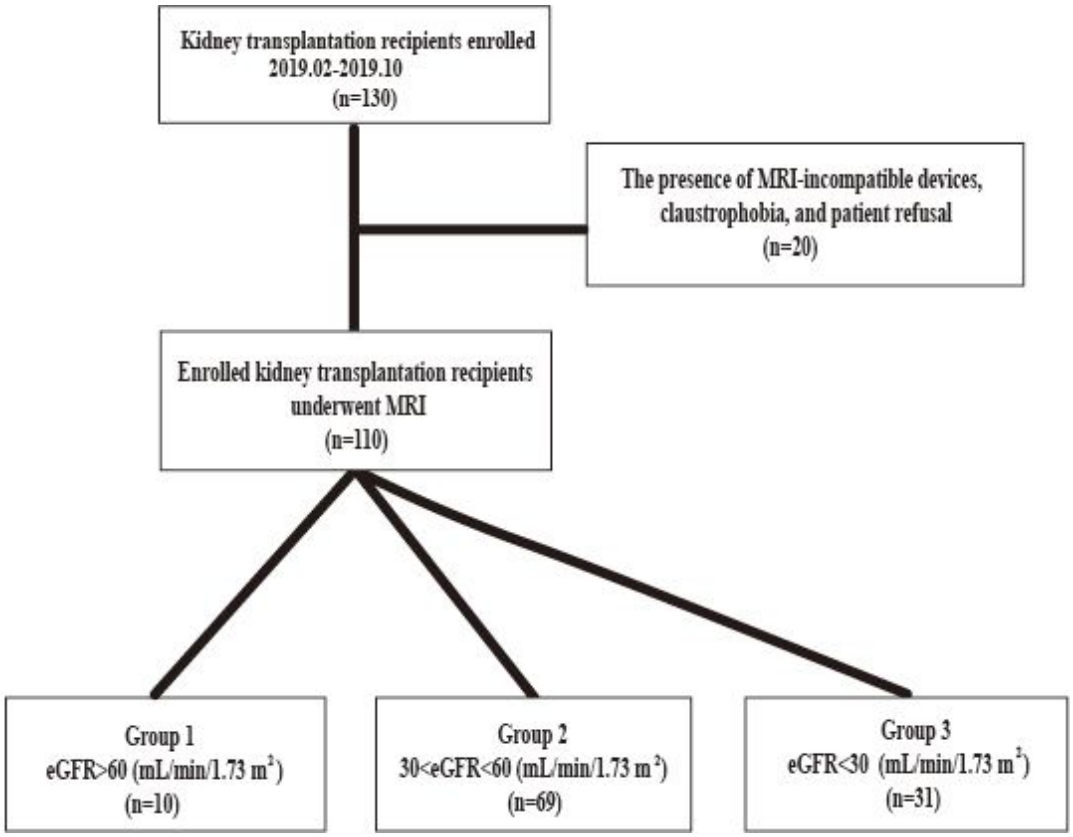


Figure 1

functional MRI data

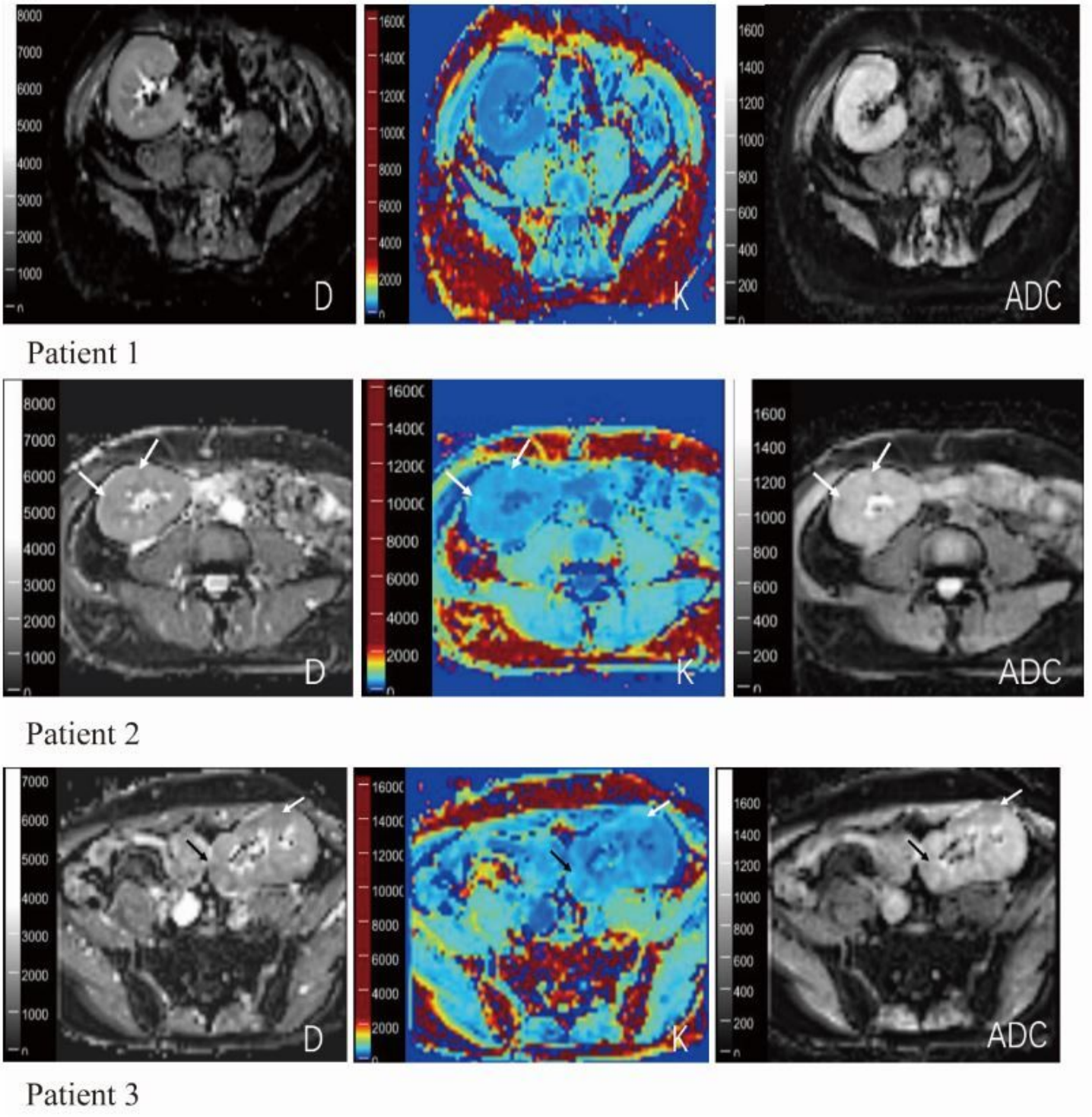


Figure 2

The corticomedullary difference is displayed by diffusional kurtosis imaging.

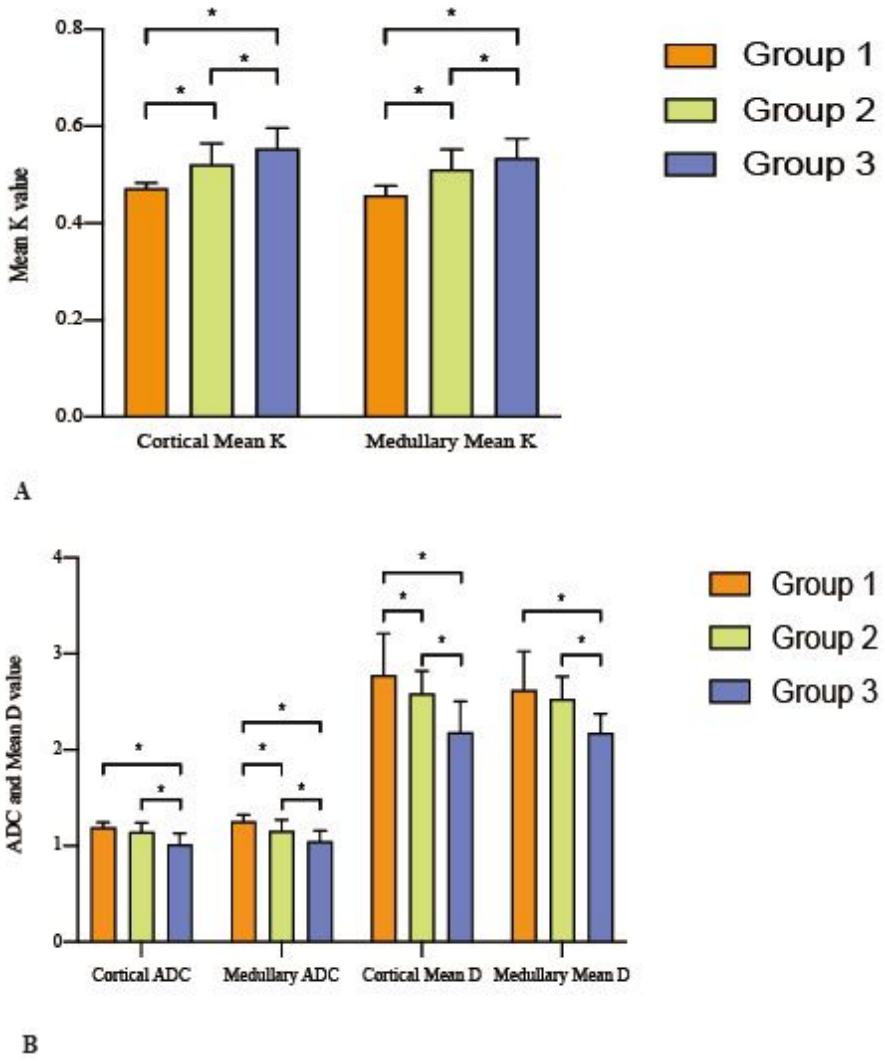


Figure 3

parameters showed significant differences ($p<0.05$) except Cortical ADC and Medullary Mean D between Group 1 and Group 2 ($p=0.117$, $p=0.257$, respectively).

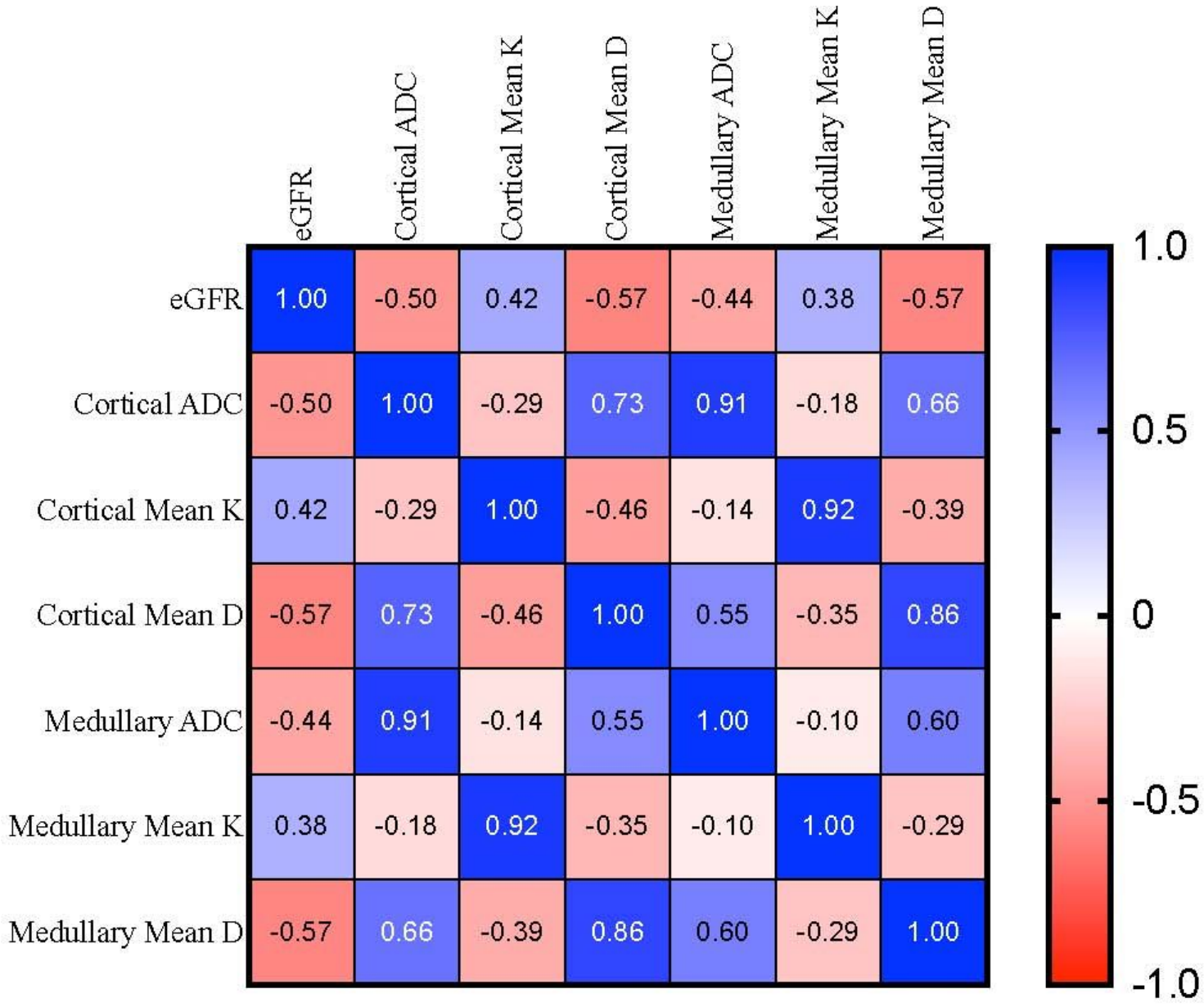


Figure 4

Correlations of DKI parameters with eGFR

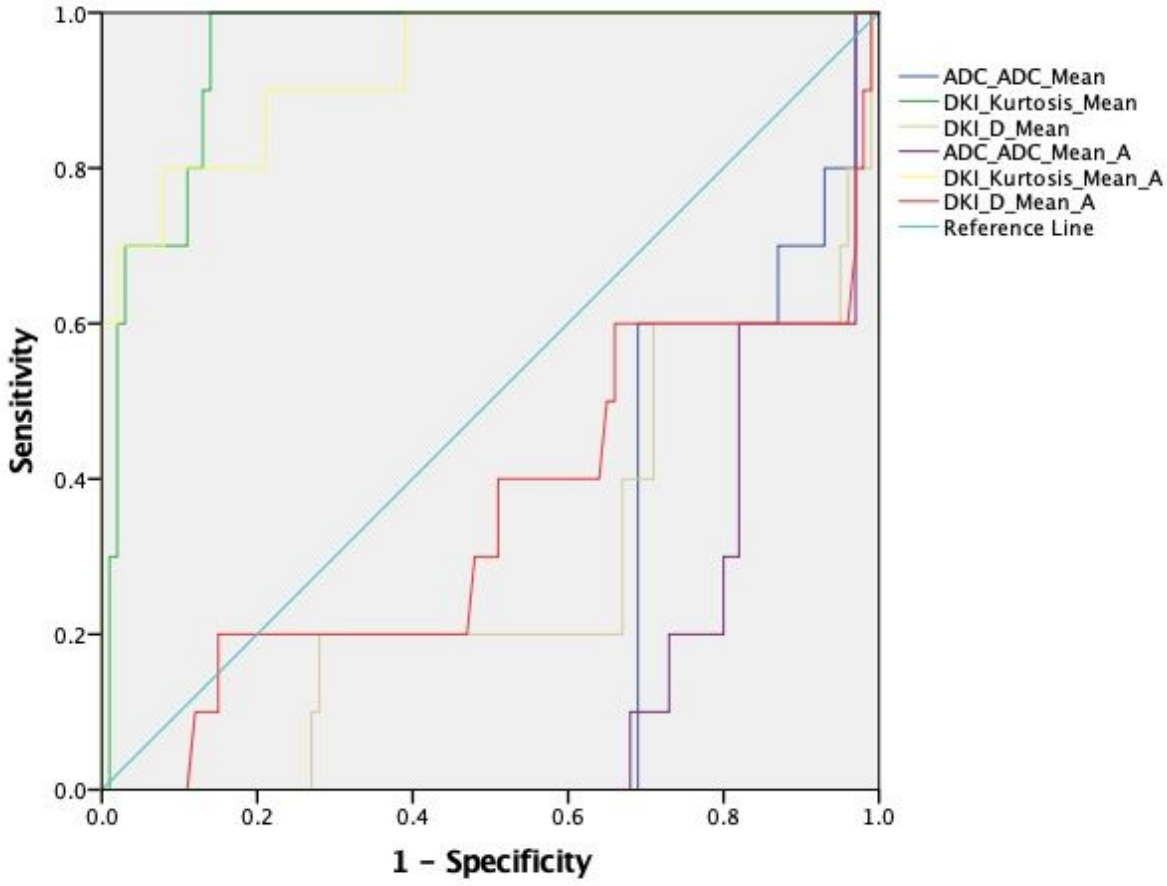
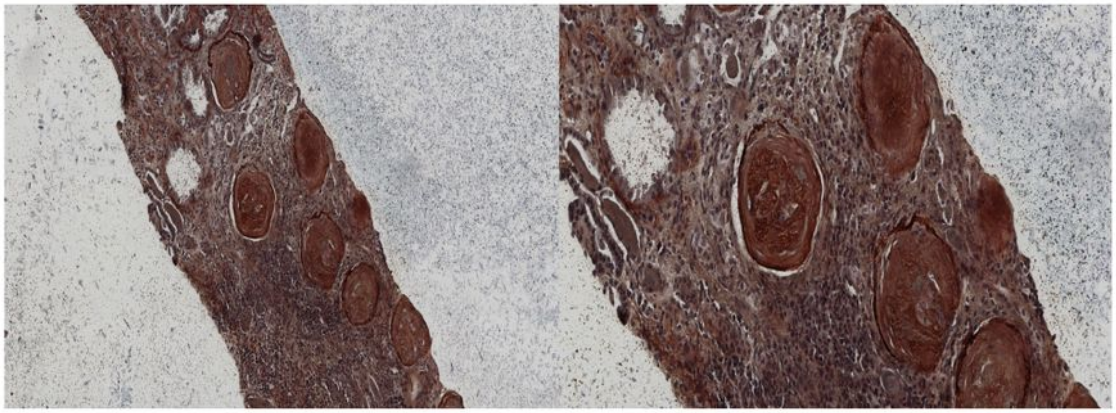
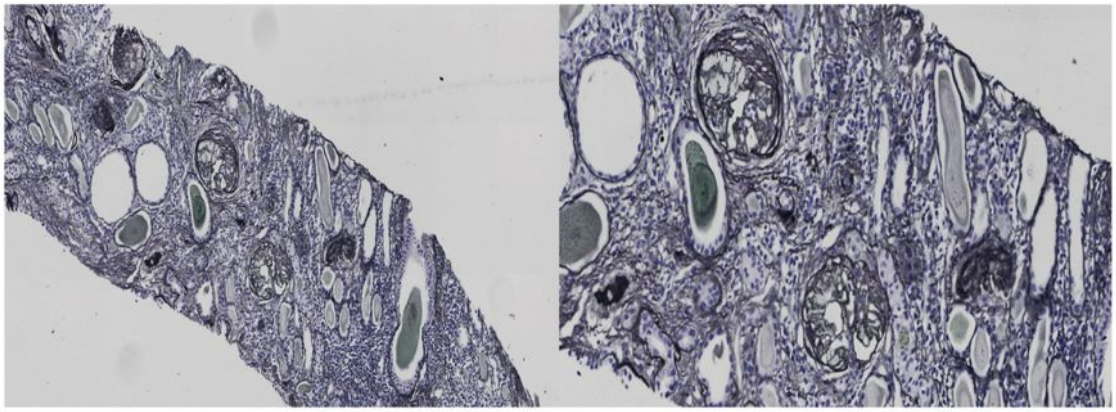


Figure 5

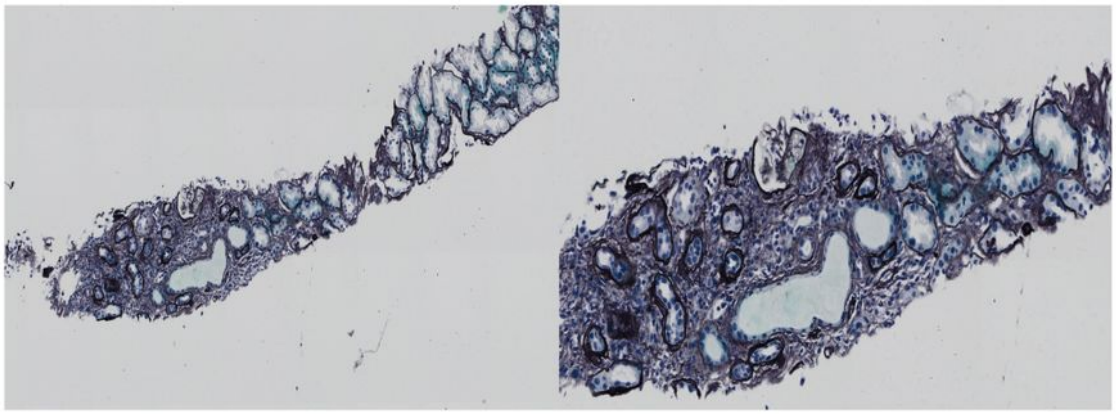
ROC Analysis Results



Patient 1



Patient 2



Patient 3

Figure 6

Pathology Findings

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplenment1.docx