Assessment of Kidney Function After Allograft Transplantation by Texture Analysis

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Introduction. Ultrasonography is the preferable imaging technique for monitoring and assessing complications in kidney allograft transplants. Computer-aided diagnostic system based on texture analysis in ultrasonographic imaging is recommended to identify changes in kidney function after allograft transplantation.
Materials and Methods. A total of 61 biopsy-proven kidney allograft recipients (11 rejected and 50 unrejected) were assessed by a computer-aided diagnostic system. Up to 270 statistical texture features were extracted as descriptors for each region of interest in each recipient. Correlations of texture features with serum creatinine level and differences between rejected and unrejected allografts were analyzed. An area under the receiver operating characteristic curve was calculated for each significant texture feature. Linear discriminant analysis was employed to analyze significant features and increase discriminative power. Recipients were classified by the first nearest neighbor classifier.
Results. Fourteen texture features had a significant correlation with serum creatinine level and 16 were significantly different between the rejected and unrejected allografts, for which an area under the curve values were in the range of 0.575 for difference entropy S(4,0) to 0.676 for kurtosis. Using all 16 features, linear discriminant analysis indicated higher performance for classification of the two groups with an area under the curve of 0.975, which corresponded to a sensitivity of 90.9%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 98.0%.
Conclusions. Texture analysis was a reliable method, with the potential for characterization, and can help physicians to diagnose kidney failure after transplantation on ultrasonographic imaging.

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INTRODUCTION

In cases end-stage renal disease (ESRD), kidney transplantation presents a better choice of treatment than hemodialysis or peritoneal dialysis in terms of improving quality of life and offering a better chance of survival.[1] Despite recent improvements to immunosuppressive drugs and therapies, acute rejection remains at 12% for all allografts.[2]

Serum creatinine concentration remains the most commonly used endogenous filtration marker to monitor graft function after kidney transplant. Progressive allograft disorder appears with increasing interstitial fibrosis and tubular atrophy detectable by an increased level of creatinine.[3,4] It seems that interstitial fibrosis and tubular atrophy can affect the properties of medical images. Allograft biopsies are usually performed if there is no other explanation for an increased level of creatinine.[5]

Ultrasonography, computed tomography, nuclear medicine, and magnetic resonance imaging are diagnostic imaging techniques used to evaluate kidney allograft transplantation. Ultrasonography is the preferable technique for monitoring complications in kidney allograft transplants; it is often the first and sometimes the only imaging test required after transplantation, because it is taken in real time and it is radiation-free, noninvasive, widely available, low cost, portable, and convenient.[6] Ultrasonography image comprises diverse gray-level intensity, and different tissues have different texture. There is no precise mathematical definition of texture, and it is simply assessed by human eye. Image texture can be described by various patterns: coarse, fine, smooth, or spatial variations in pixel intensity of objects within an image. Structural abnormalities in ultrasound image can be extracted by visual inspection, but complex patterns are difficult to interpret.

To avoid unnecessary biopsy, laboratory tests, and assuage anxiety, and to increase diagnostic confidence, computer-aided diagnosis (CAD) systems have been developed. These refer to using computer technology to assist identification of subtle changes in tissue and abnormalities. In this regard, computerized texture analysis (TA) is a useful technique to detect pathological changes that cannot be perceived by the human eye using conventional ultrasonography imaging.[7,8]

Recent studies have employed TA to differentiate kidney diseases and monitor progression of the stages of chronic kidney disease.[9-17] It is shown that texture features extracted from an ultrasonography image have the potential to differentiate between normal kidneys, medical kidney disease (MKD), and cortical cyst (CC),[9-11] as well as to diagnose presence of cysts and calculi and bacterial infections.[12,13] Interstitial fibrosis and tubular atrophy caused by allograft disorders can affect the texture of an ultrasonographic kidney image. The aim of this study was to evaluate textures ability and this presents a noninvasive method to detect changes in ultrasonographic kidney images of patients who had kidney allograft transplantation and to determine interrelationships between such changes and serum creatinine level. To the best of our knowledge, this was the first study to apply TA to evaluate kidney allograft recipients.

MATERIAL AND METHODS

Study Design and Image Acquisition

Considered for this study were biopsy-proven kidney allograft recipients at Imam Khomeini Hospital Between July 2012 and July 2014. This study was conducted with an approval from the Ethics Committee of the Urmia University of Medical Sciences. Patient consent was not needed as the study was retrospective and used archived data. Inclusion criteria included the following: (1) all of the patients had received an allograft from a living donor; (2) all of the patients received similar immunosuppressive therapy treatments, based on steroids, mycophenolate, mofetil, and tacrolimus; and (3) serum creatinine level testing was done as the standard care for patients with decreased allograft function or suspicion of rejection. Patients with significant arrhythmia, large perinephric collections, chronic inflammatory, human immunodeficiency virus-positive, a current infection, diabetes mellitus, retransplant, hydronephrosis, and alcohol dependence or smoking habit were not included in the study.

A nephrologist or transplant surgeon referred patients for kidney ultrasonography and a serum creatinine test as standard care procedure for patients with decreased allograft function or suspicion of rejection. A longitudinal view of ultrasonography images were acquired using an Accuvix V20 device (Medison, Seoul, Korea) equipped with 7-MHz to 11-MHz L5-13IS linear transducer. Serum creatinine level were determined moments before ultrasonography examination and were measured using the standard laboratory method (Jaffe) using a kinetic colorimetric assay in the central laboratory of the Imam Khomeini Hospital. Body mass index (BMI) was calculated and all body weight measurements were taken with patients wearing light clothing to the nearest 0.1 kg and body heights were determined without shoes to the nearest 0.5 cm using a stadiometer.

Texture Feature and Regions of Interest Selection

Ultrasonography images were input in MaZda software, version 4.6 (Technical University of Lodz, Institute of Electronics) for TA. All regions of interest (ROI) were identified and placed on the cortex area with the help of an expert radiologist. One ROI was selected for each patient. Up to 300 texture features were extracted based on histogram, absolute gradient (spatial variation of grey level values), run-length matrix (counts of pixel runs with the specified gray scale value and length in a given direction), co-occurrence matrix (information about the distribution of pairs of pixels separated by given distance and direction), autoregressive model (description of correlation between neighboring pixels), and wavelets (decomposition image frequency at different scales).[7,8]

Texture Analysis and Classification

Texture features that showed a significant differences between the two groups were used for a computerized TA method. The linear discriminant analysis (LDA) was used to transform raw texture features to lower-dimensional spaces and to increase discriminative power, LDA seeks the most efficient directions for maximal separation of features. By LDA, the variability among feature vectors of the same class (within-class scatter) was minimized and variability among the feature vectors of different classes (between-class scatter) was maximized. Features processed by LDA were considered useful for pattern recognition and classification as they make data of the same class closer together and the data of different classes further apart.

The first nearest neighbor classifier was used for the features resulting from LDA. In order to compare the performance of diagnostic, 5 well-known indexes were calculated: accuracy, sensitivity, specificity, positive predictive value, and negative predictive value. An AUCvalue was also calculated to evaluate the overall performance of proposed TA method.[18] Figure 1 shows the CAD processing steps.

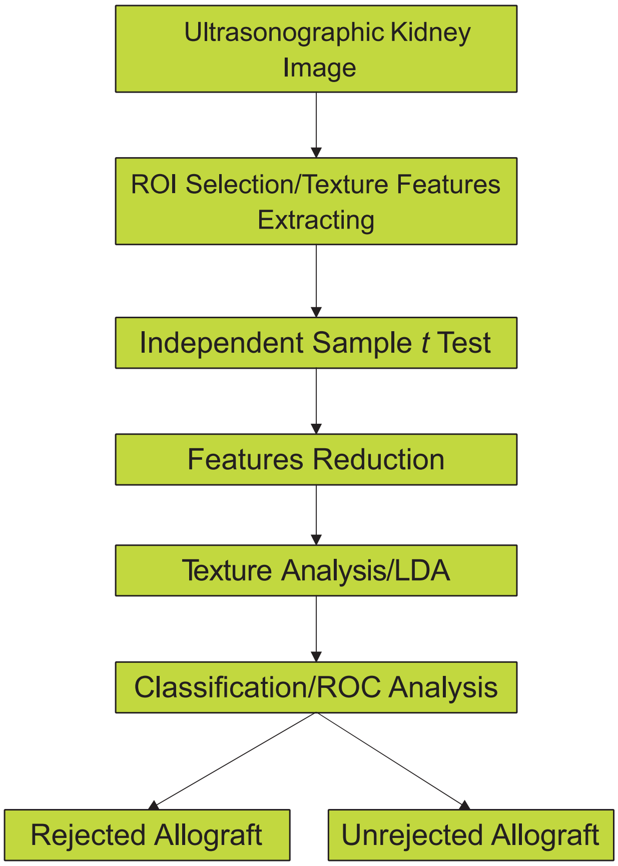

Figure 1. The computer-aided diagnosis processing steps. ROI indicates regions of interest; LDA, linear discriminant analysis; and ROC, receiver operating characteristic curve.

Statistical Analysis

Data were tested for normality by the Kolmogorov-Smirnov test. The 2-tailed independent samples *t* test was done to compare differences of texture features, age, BMI, and serum creatinine level between the two groups (rejected and intact allograft transplantations). The area under the receiver operating characteristic (ROC) curve was calculated for each significant texture feature in order to evaluate overall performance of classification between the two groups.[18] The area under the curve (AUC) values were estimated beyond the 95% confidence level. The 2-tailed Pearson correlation test was used to find correlation between significant texture features and serum creatinine level. The Fisher exact and the chi-square tests were used to evaluate sex distribution between the two groups. A *P* value less than .05 was considered significant. Statistical analyses were performed with the SPSS software (Statistical Package for the Social Sciences, version 19.0, SPSS Inc, Chicago, IL, USA).

RESULTS

Patients Characteristics

This retrospective study included 61 biopsy-proven kidney allograft transplant recipients (40 men and 21 women) who had been followed up for a mean of 5.6 ± 3.9 years. Of the 61 patients, the transplanted kidney had been rejected in 11 patients (6 men and 5 women) with a mean age of 36.2 ± 15.2 years and a serum creatinine level of 7.43 ± 1.82 mg/dL. Although kidney transplant rejection was slightly more prevalent in the men than in the women, the difference did not reach a level of significance (*P* = .40; Table 1). The mean age of the recipients in the rejected group was slightly lower than that in the unrejected group (36.2 ± 15.2 years versus 43.3 ± 14.8 years; *P* = .16). The mean BMI of the patients were not significantly different between the two groups (Table 1).

Texture Features and Pathological Changes

Since 1 ROI was selected for each patient, 61 nonoverlap ROIs were selected for statistical analysis. Sixteen texture features were significantly different between rejected and unrejected kidney transplants: Teta3 (*P* = .003) and Teta4 (*P* < .001) from autoregressive model; short run emphasis in horizontal direction (*P* = .006), fraction in horizontal direction (*P* = .009), and long run emphasis in horizontal direction (*P* = .04) from run-length matrix; kurtosis (*P* = .03) and skewness (*P* = .047) from histogram and difference entropy S(4,0), *P* = .01), difference entropy S(5,0) (*P* = .01), difference entropy S(3,0) (*P* = .02), difference entropy S(2,0) (*P* = .04), inverse difference moment S(5,0) (*P* = .002), inverse difference moment S(4,0) (*P* = .002), inverse difference moment S(3,0) (*P* = .005), inverse difference moment S(2,0) (*P* = .012), inverse difference moment S(1,0) (*P* = .03) from co-occurrence matrix (Tables 2 and 3), where S(i j) shows the direction of matrix construction and inter pixel distance *i* along rows and *j* along columns of the matrix.

Texture Features and Serum Creatinine Levels

Among the 16 significant texture features, 7

Table 1. Main demographic characteristics and laboratory data of rejected and unrejected kidney transplant recipients.

Characteristics	All	Rejected Allografts	Unrejected Allografts	*P*
Age, y	41.98 ± 15.05	36.18 ± 15.18	43.26 ± 14.84	.16
Sex				
Female	21 (34.4)	5 (45.5)	16 (32.0)	
Male	40 (65.6)	6 (54.5)	34 (68.0)	.40
Body mass index, kg/m^2	24.25 ± 03.95	24.94 ± 04.99	24.10 ± 03.73	.53
Serum creatinine, mg/dL	03.32 ± 02.43	07.43 ± 01.38	02.42 ± 01.38	.01

Table 2. Texture Features in Kidney Transplant Recipients With Direct Correlations With Serum Creatinine Level

Texture Feature Group	Texture Feature Name	*P* for Correlation With Creatinine	Independent Sample *t* Test *P*	Area Under Curve (95% Confidence Interval)
Autoregressive model	Teta3	0.300 (.02)	.003	0.644 (0.483 to 0.805)
Run-length matrix	Short run emphasis in horizontal direction	0.293 (.02)	.006	0.589 (0.376 to 0802)
Run-length matrix	Fraction in horizontal direction	0.280 (.03)	.009	0.587 (0.374 to 0.801)
Co-occurrence matrix	Difference entropy S(4,0)	0.265 (.04)	.01	0.575 (0.385 to 0.765)
Co-occurrence matrix	Difference entropy S(5,0)	0.265 (.04)	.01	0.582 (0.400 to 0.764)
Co-occurrence matrix	Difference entropy S(3,0)	0.264 (.04)	.02	0.576 (0.381 to 0.771)
Histogram	Kurtosis	… (0.16)	.03	0.676 (0.525 to 0.828)
Co-occurrence matrix	Difference entropy S(2,0)	0.259 (.04)	.04	0.582 (0.387 to 0.776)

Table 3. Texture Features in Kidney Transplant Recipients With Inverse Correlations With Serum Creatinine Level

Texture Feature Group	Texture Feature Name	Pearson Coefficient (*P*)	Independent Sample *t* Test *P*	Area Under Curve
Autoregressive model	Teta4	-0.334 (.009)	< .001	0.665 (0.510 to 0.821)
Co-occurrence matrix	Inverse difference moment S(5,0)	-0.293 (.02)	.002	0.604 (0.398 to 0.809)
Co-occurrence matrix	Inverse difference moment S(4,0)	-0.293 (.02)	.002	0.600 (0.396 to 0.804)
Co-occurrence matrix	Inverse difference moment S(3,0)	-0.29 (.02)	.005	0.589 (0.384 0.794)
Co-occurrence matrix	Inverse difference moment S(2,0)	-0.285 (.03)	.01	0.591 (0.385 to 0.796)
Co-occurrence matrix	Inverse difference moment S(1,0)	-0.276 (.31)	.03	0.595 (0.387 to 0.802)
Run-length matrix	Long run emphasis in horizontal direction	-0.27 (.04)	.04	0.580 (0.367 to 0793)
Histogram	Skewness	… (.40)	.047	0.673 (0.509 to 0.836)

*Numbers in parentheses are 95% confidence intervals.

indicated a significant positive correlation between serum creatinine and Teta3 (r = 0.300, *P* = .02), short run emphasis in horizontal direction (r = 0.293, *P* = .02), fraction in horizontal direction (r = 0.280, *P* = .03), difference entropy S(4,0) (r = 0.265, *P* = .04), difference entropy S(5,0) (r = 0.265, *P* = .04), difference entropy S(3,0) (r = 0.264, *P* = .04), difference entropy S(2,0) (r = 0.259, *P* = .04) (Table 2). Also 7 texture features indicated a significant negative correlation between serum creatinine and Teta4 (r = -0.334, *P* = .009), inverse difference moment S(5,0) (r = -0.293, *P* = .02), inverse difference moment S(4,0) (r = -0.293, *P* = .02), inverse difference moment S(3,0) (r = -0.290, *P* = .023), inverse difference moment S(2,0) (r = -0.285, *P* = .03), inverse difference moment S(1,0) (r = -0.276, *P* = .03), long run emphasis in horizontal direction (r = -0.27, *P* = .04) (Table 3).

Area Under the Curve and Correlated Texture Features

The ROC analysis indicated that texture features of histogram (kurtosis and skewness) and autoregressive model (Teta4 and Teta3) had higher AUC values in terms of difference between the rejected and unrejected cases of kidney transplant. The AUC value of kurtosis, skewness, Teta4, and Teta3 were 0.676, 0.673, 0.665, and 0.644 respectively (Figure 2). The AUC values of other texture features are listed in Tables 2 and 3. All of the 16 texture features had AUC values greater than 0.57. The lowest AUC value belonged to difference entropy S(4,0) and difference entropy S(3,0) with AUC values of 0.575 and 0.576, respectively.

Texture Analysis and Classification

Discrimination power of diagnostic performance of the CAD system for classifying and making comparisons between rejected and unrejected groups was achieved with a sensitivity of 90.90%, a specificity of 100%, an accuracy of 98.36%, a positive predictive value of 100%, and a negative predictive value of 98.03%. Figure 3 shows ROC curves of the proposed CAD system and demonstrated excellent performance in classification with and AUC of 0.975. Discrimination distributions for LDA are illustrated in Figure 4 and these showed that LDA was powerful in making discriminations between rejected and unrejected groups of kidney transplant recipients.

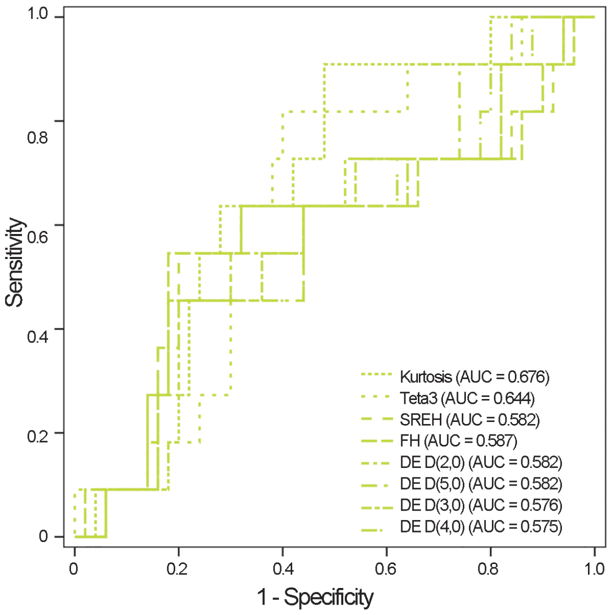

Figure 2. The receiver operating characteristic curves and area under the curves (AUCs) of texture features for kidney allograft rejection. SREH indicates short run emphasis in horizontal direction; FH, fraction in horizontal direction; and DE, difference entropy.

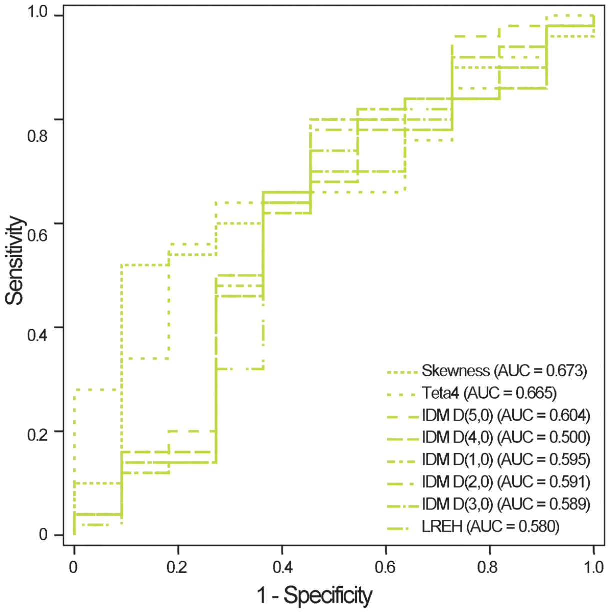

Figure 3. receiver operating characteristic curves of the proposed C computer-aided diagnosis system. AUC indicates area under the curve; LREH long run emphasis in horizontal direction; and IDM, inverse difference moment.

DISCUSSION

The primary objective of this study was to evaluate texture ability, a noninvasive method to monitor kidney allograft transplant among recipients using ultrasonographic imaging. Results

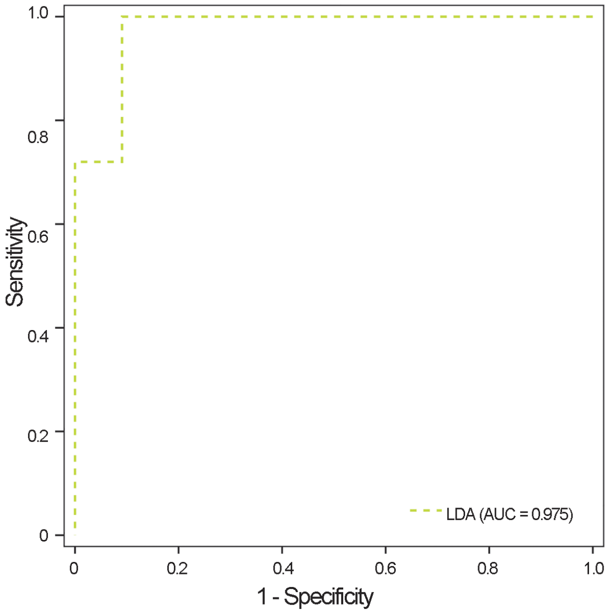

Figure 4. Discrimination distributions of linear discriminant analysis (LDA) for kidney allograft rejection. AUC indicates area under the curve.

demonstrated that texture features were correlated with serum creatinine level of kidney in allograft kidney transplant recipients. Three hundred texture features were extracted from among many groups and classes of texture and 16 of these texture features were significantly different between rejected and unrejected groups of kidney transplant recipients. The AUC values of these 16 features were determined in the rang of 0.575 (difference entropy S[4,0]) to 0.676 (kurtosis). The AUC values, ordered by LDA using all 16 texture features, had a higher level of performance than did each of the texture features alone to classification rejected and unrejected groups with and AUC of0.975, which corresponded to a sensitivity evaluation of 90.90%, specificity of 100%, accuracy of 98.36%, positive predictive value of 100%, and negative predictive value of 98.03%. Since the mean age, BMI, and sex were not significantly different between the rejected and unrejected groups of kidney transplant recipients, these parameters were not determined as confounding factors in this study.

Among 16 texture features which were significant between rejected and unjerected groups, 2 texture features from histogram group (kurtosis and skewness) have no significant correlation with serum creatinine level. Based on Kee and colleagues' study, there is a subgroup of subclinical rejection defined as when histologic changes of acute rejection observed in the absence of an increased serum creatinine concentration.[19] It seems that pathological evidence of rejection in kidney allograft is not correlated with serum creatinine test based on this reference.

Recent studies have reported on application of TA to diagnose kidney diseases and these reports indicate that many types of texture feature extracted from ultrasonographic images were useful for kidney characterization. Raja and coworkers[10] showed that Gabor wavelet features can classify normal, MKD, and CC with 86.66%, 76.66%, and 83.33% classification efficiency, respectively. Also with the same purpose they utilized 36 features and indicated that a fuzzy-neural system can classify normal, MKD, and CC with efficiency determinations of 96.15%, 92.31%, and 96.15% respectively.[11]

Texture features can also help radiologists to distinguish lesions. Accordingly, Attia and coworkers used a discrete wavelet transform-based feature and achieved correct classification rate of 83% for stone and 94% for cyst.[13] Hafizah and colleagues reported that co-occurrence matrix and histogram-based features had the potential to diagnose cyst, stone, and bacterial infections.[12]

Chronic kidney disease is defined as kidney damage that leads to loss of kidney function. Progressive chronic kidney disease can lead to ESRD that then requires transplantation or dialysis treatment.[20] In this regard, texture feature of an ultrasonographic image can diagnose stages of chronic kidney disease. As the stage of disease progresses, average brightness, contrast, homogeneous, energy and area ratio all show an increase,[17] while the white-black ratio shows a decrease.[15,16]

Over the past few decades, ultrasonography has become the primary and first imaging technique for making initial evaluations, routine follow-ups and to monitor a kidney transplant.[6] Accordingly, advanced ultrasonography techniques such as elastography and Doppler can also be used to evaluate kidneys. Elastographic features contain information about tissue stiffness. Ultrasonography elastography is a noninvasive technique used to achieve tissue deformation in response to compression.[21] Fibrosis and tubular atrophy can be present due to kidney allograft loss in transplant recipients.[22] Although some effort has been made to investigate correlations between kidney stiffness and pathological changes, findings are quite controversial in the literature. In this regard, Syversveen and colleagues[23] used acoustic radiation force impulse and indicated no correlation between kidney stiffness and pathological changes. Grenier and associates[24] reached the same conclusion, whereas Stock and colleagues[25] and Sommere and colleagues[26] reported a positive and moderate correlation. In the Wan-Yuan and coworkers' study,[27] shear wave velocity or kidney stiffness showed a highly significant negative correlation between estimated glomerular filtration rate that is indicative of kidney function. In general, elastography is a promising technique for monitoring kidney function, but it can be influenced by factors such as skin-allograft distance and perirenal or intrarenal fluid.[26]

Doppler ultrasonography can be used to assess blood flow in the kidney by markers such as the resistance index (RI), which measures the ratio of the end diastolic flow to the peak systolic flow and may be useful for diagnosing acute rejection.[28] Cano and colleagues[29] indicated that measurement of RI at 12 to 18 months after transplantation was a reliable marker to assess kidney function, but results reported in Matar and colleagues showed the opposite.[30] In addition, Gao and colleagues[31] determined no correlation between fibrosis, tubular atrophy, and RI, or amount of fibrosis. Although RI is still used in many centers, there remains the need for further research in this field.

The ability to detect and monitor kidney function after transplantation is one of the most critical factors to improving accuracy of an initial diagnosis. In this study, TA was used and it was found to have the potential to assess kidney function after transplantation. Further studies using larger datasets are needed to confirm these results. Ultrasonographic classification was compared with pathology. Also, evaluations of serum creatinine level were used to assess kidney function and applied to correlation analysis with serum creatinine. As serum creatinine level can be influenced by sex, muscle mass, age, and medication,[32,33] cystatin C may be a reflection of the true glomerular filtration rate that has an advantage over serum creatinine.[34,35] Definitive results require comparison with cystatin C.

Since physician-referred cases were based on clinical indications, other kidney characteristic features did not have any additional information and were not considered for TA and classification. This method is not suggested as an alternative to biopsy or serum examination, but it can be applied to help physicians identify kidney dysfunction or rejection in patients after allograft transplantation.

CONCLUSIONS

A new approach based on TA is proposed for evaluation of kidney function after transplantation using 2-dimensional ultrasonography. Preliminary results indicate that texture features of a conventional ultrasound image can be used as a supplementary technique to improve understandings of conventional ultrasound imaging and to assist with Doppler and elastography ultrasonography.

CONFLICT OF INTEREST

None declared.

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