Quantitative Assessment of Renal Function In Children with UPJO By Contrast-enhanced Ultrasound: A Pilot Study

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Research article

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Abstract

Background: Contrast-enhanced ultrasonography (CEUS) is a new potential modality for the quantitative evaluation of the microvascular perfusion of a parenchymal organ.

Objective: To prospectively evaluate the diagnostic value of CEUS in assessing renal function in patients with ureteropelvic junction obstruction (UPJO).

Methods: The study protocol was approved by the local ethics committee, and written informed consent was obtained from the patients' parents or guardians.Ultrasonography (US), CEUS, and radioisotope renography were performed in 51 children (42 boys, 9 girls; mean age, 6.75 ± 4.14 years) with unilateral UPJO. The slope of the ascending curve (A), time to peak (TTP), peak intensity (PI), and area under the curve (AUC) were recorded during CEUS; the quantitative data were calculated by the QLAB system (semiautomated border tracking, Philips Healthcare) software. Sensitivity and specificity values were determined for CEUS and compared with radioisotope renography.

Results: CEUS depicted 102 kidneys in 51 patients, in whom the perfusion time-intensity curve（TIC）was determined. The TIC of renal cortical perfusion in all groups showed an asymmetrical single-peak curve, which could be clearly distinguished between the experimental group and the control group. Compared to the control group, the TTP was markedly prolonged but A was significantly decreased in the experimental group ($P < 0.05$). The ROC curve drawn to differentiate the differential renal function (DRF) using the TTP value provided an area under the ROC curve (AUROC) of 0.86. The diagnostic performance of contrast-enhanced US was better than that of US, as the sensitivity and specificity values were 92.86% and 76.14%, respectively.

Conclusions: This preliminary experience represents the first report of evaluating the diagnostic value of CEUS in assessing renal function in children with UPJO. CEUS is a highly sensitive, rapid, and cost-effective diagnostic imaging modality for detecting and monitoring renal function noninvasively.

Background

Ureteropelvic junction obstruction (UPJO) is a common cause of upper urinary obstruction in children and is usually detected by antenatal or neonatal ultrasound screening. The incidence of antenatal hydronephrosis (ANH) is approximately between 1% and 5%[1]. Diuretic renography (DRG) is the only diagnostic tool for evaluating differential renal function and upper urinary drainage in UPJO patients. Due to the possibility of overestimation, the DRG results are sometimes inconsistent with the actual degree of renal function[2]. Therefore, clinicians must consider other options to evaluate differential renal function.

With technical improvements, contrast-enhanced ultrasound (CEUS) has become widely used to investigate renal vessels and parenchymal abnormalities[3–5]. The contrast agent, microspheres, which are approximately the size of red blood cells and are not filtered or secreted by the kidneys, allow visualization of the renal parenchyma without interfering with the collecting system. It has been shown to

be a cost-effective modality for evaluating renal function impairment (RFI)[6]. Studies have shown that contrast-enhanced US is almost as sensitive as radioisotope renography in the quantitative diagnosis of chronic renal insufficiency, and correspondingly, contrast-enhanced US could be a useful tool for the assessment of renal function in children with UPJO[7–9]. Ionizing radiation exposure is a known risk factor for patients with leukaemia and brain tumours, especially for children with a higher radiation sensitivity and longer life expectancy[10, 11].The EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) release guidelines state that intravenous CEUS is safe and effective in paediatric populations and can be used effectively to avoid ionizing radiation exposure[11].

Thus, the purpose of our study was to prospectively evaluate the diagnostic value of contrast-enhanced US in the evaluation of renal function in children with UPJO.

Methods

Patients

A total of 51 patients with unilateral hydronephrosis (42 boys, 9 girls; mean age, 6.75 ± 4.14 years; age range, 1–14 years) who presented to the department of paediatric urology between January and April 2018 were prospectively included. This study was approved by the ethics board of our institution. Written informed consent was obtained from each patient. Inclusion criteria: (i) unilateral UPJO; (ii) normal functioning of contralateral kidney; (iii) no surgical treatment. Exclusion criteria: (i) bilateral UPJO; (ii) drug contraindications; (iii) other urinary system malformations; (iv) severe cardiopulmonary reactions.Urinary ultrasonography, intravenous pyelogram (IVP), and bilateral kidney CEUS were performed in all cases. The glomerular filtration rate (GFR) and DRF were determined by 99mTc DTPA renography.

US and contrast-enhanced US

US and CEUS were performed with a standard abdominal C5-1 convex probe (3.5–5.0 MHz) using an IU 22 system (Philips, Bothell, WA) by one experienced radiologist was blinded to the patients' clinical and pathological information. A 24-gauge cannula was used for the contrast injection. A bolus dose of 0.03 mL/kg of microbubbles containing sulphur hexafluoride (SonoVue, Bracco, Milan, Italy) was injected intravenously into an antecubital vein, followed by a flush with 5 ml of normal saline. At the time of examination, the younger children who were unable to cooperate were orally sedated with chloralhydrate (0.5 mL/kg). Raw images were observed and captured in real-time for 1 minute and then stored digitally in DICOM format. Then, all patients underwent 30 minutes of clinical observation. The contralateral kidney was evaluated after at least 15 minutes. Raw images were stored digitally in DICOM format, and all patients underwent 30 minutes of clinical observation.

Image analysis

All video clips were stored digitally for subsequent analysis. An integrated computer workstation (QLab) was used to perform the perfusion TIC analysis. Ultrasound was performed to obtain the ratio of the

depth of calyces to the thickness of the parenchyma (C/P ratio). For the TIC of the CEUS data, regions of interest were drawn located in the renal cortex using QLab software. The regions of interest(ROIs) were placed as close to the same depth as possible in accordance with greyscale images and contrast images. Five ROIs in the peripheral renal cortex were selected with the same size and shape (5 mm × 5 mm square), and then the mean value of each perfusion parameter was obtained. TICs for the experimental group and the control group were generated (Figs. 1, 2). The following perfusion parameters of the TIC were recorded: slope of the ascending curve (A), area under the curve (AUC), peak intensity (PI) and time to peak (TTP). For each ROI, the analysis was repeated five times, and then the mean value of each perfusion parameter was obtained.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 23.0, IBM, USA). A two-sided P value of less than or equal to 0.05 was considered to indicate a significant difference. Conventional CEUS quantitative parameters were analysed. One-way analysis of variance (ANOVA) and receiver operating characteristic (ROC) curves were used. Receiver operating characteristic (ROC) curves were constructed to determine the optimal cutoff value for evaluating the severity of kidney damage in UPJO patients.

Results

A total of 51 hydronephrotic kidneys matched with 51 contralateral kidneys were evaluated by US, DRG and CEUS. The APD of the hydronephrotic side was between 9 mm and 70 mm (mean: 34.2 ± 13.1). A total of 42 boys and 9 girls with a mean age (± standard deviation) of 6.75 years ± 4.14 (range 1–14 years) were included in this study. The image quality was high enough for independent US and CEUS readings. A 14-year-old boy felt warmth at the injection site. No patients needed multiple applications. There were no serious adverse reactions to the ultrasound contrast agent application.

CEUS parameters analysis

Among the cortical perfusion parameters, the differences in the TTP and A between the control group and the experimental group were significant ($P < 0.05$) (Table 1). However, there was no significant difference in the AUC or PI between the two groups.

Table 1. CEUS parameters between the control group and the experimental group (±s).

Parameter	Experimental group	Control group	P	T
AUC (dB s)	545.244±204.555	540.526±198.299	0.906	0.118
TTP (s)	25.619±9.199	16.022±4.818	<0.001*	6.600
PI (dB)	13.256±3.604	13.057±3.338	0.773	0.289
A (dB/s)	1.321±0.883	2.660±1.106	<0.001*	-6.758

CEUS, contrast-enhanced ultrasound; PI, peak intensity; AUC, area under the time-intensity curve; A, slope of the ascending curve; TTP, time to peak

* P < 0.05, compared to the control group

ROC curve analysis

The ROC curve drawn to differentiate DRF values of <40% and ≥40% using TTP and A values provided an area under the ROC curve (AUROC) of 0.86 and 0.85 (Figs. 3, 4), with optimal cutoffs of 23.459 s and 0.92 dB/s. Table 2 shows the observed AUROC, sensitivity, and specificity for the optimal cutoff values for each of the ROC curves.

Table 2. Diagnostic performance of TTP and A values

Parameter	AUROC	95% CI	P	Sensitivity (%)	Specificity (%)	Cutoff
TTP (s)	0.86	0.754-0.968	<0.001	92.86	76.14	23.459
A (dB/s)	0.85	0.729-0.978	<0.001	86.36	78.57	0.920

Discussion

Ureteropelvic junction obstruction (UPJO) is the most common cause of hydronephrosis in the paediatric population and is characterized by impairment of urine drainage, leading to hydronephrosis and obstructive changes in the renal parenchyma and loss of differential renal function of the affected side. At present, the most sensitive imaging modality for evaluating DRF is ECT. 99mTc-DTPA has been shown to correlate well with the renal clearance of inulin. In children with hydronephrosis, DTPA diuretic renography is used to calculate the differential renal function (DRF) and to assess drainage. T 1/2 can be used more reliably to assess hydronephrosis with UPJO to make a decision regarding surgical intervention. The DFR determined by 99mTc-DTPA is inaccurate because of the inability to assure quantitative emptying of the bladder and the overestimation caused by the selection of regions of interest, especially in children. Overestimated and supernormal DRF values are related to patient age, asymmetrical kidney size, renal insufficiency, and type of background correction method, especially for higher hydronephrosis grades or patients younger than 2 years old[2, 12]. The majority of cases only need

conservative management or close follow up. For this reason, it is very important to differentiate between those with and without kidney damage without the use of ionizing radiation[13]. However, there is no dependable substitute for an accurately determined GFR, and diuretic renography is still the gold standard for evaluating the split differential renal function (sDRF) of children with hydronephrosis.

The renal cortical blood supply accounts for approximately 90% of all renal blood flow. In normal physiological conditions, the cortical blood supply remains within a relatively constant range. Increased intrarenal vascular resistance is responsible for reduced microvascular perfusion in the renal cortex. Cortical perfusion gradually decreases with increasing renal insufficiency. Contrast-enhanced US has been used to assess ischaemic renal disorders, complex cysts, and indeterminate renal lesions, as well as for the follow-up examination of non-surgical renal lesions[14]. US contrast agents are blood pool agents that are used to identify subtle vascular alterations. The major strength of contrast-enhanced US is that it can provide precise information about the renal cortical blood supply. It is able to depict the degree of enhancement compared with the surrounding tissues as well as the contrast distribution. While CEUS has been widely used in renal diseases, including vesicoureteral reflux, diabetic kidney disease (DKD), complex cysts, renal tumours, chronic kidney disease (CKD), ischaemic renal disorder and kidney transplantation, to provide information regarding cortical perfusion, no studies have shown that CEUS could reliably demonstrate perfusion alterations in UPJO. As a tracer to assess tissue perfusion, microbubbles provide signals reflecting the tissue blood volume fraction (BVF). The actual tissue nutrient blood flow (NBF) is equal to the product of the microbubble velocity and the BVF. Therefore, it would be significant to quantitatively evaluate blood perfusion changes in the renal cortex to identify renal microcirculation perfusion changes, which can be used to diagnose renal damage early.

In the present study, enhanced and non-enhanced images of the renal cortex microvascular beds in both the control group and the experimental group were examined, and the TIC of renal perfusion could easily discriminate between the different levels of kidney injury (Fig. 5). The TIC could be used for the measurement of renal damage. Quantitative analysis showed significant increases in the TTP but decreases in A in patients in the experimental group compared with patients in the control group ($P < 0.05$). Unlike in previous studies, in this study, there was no significant difference in the AUC or PI between the control group and the experimental group ($P > 0.05$). Both an increase and a decrease in the AUC have been described in CKD, DKD and ischaemic renal disorder. This may be explained by the fact that the AUC is influenced by the blood flow velocity, microbubble distribution volume, and interception time. To reduce the bias caused by the interception time, this study selected the first minute after the injection of the contrast agent as the interception time. Only the perfusion images could be obtained; contrast-reduced images and the slope of the descending curve could not be obtained. Therefore, the renal blood perfusion could not be evaluated overall. More importantly, the TTP and GFR showed a very strong positive correlation, which strongly suggests that CEUS could accurately assess the microvascular perfusion and haemodynamic characteristics of the renal cortex. Quantitative analysis demonstrated that the change in A and the TTP in the UPJO group became more obvious as the disease progressed, which may be related to renal microvascular ischaemia and inhibited perfusion.

In our study, we evaluated the diagnostic efficiency and value of CEUS parameters and found that the TTP is a sensitive indicator of impaired renal function with a cutoff value of 1.77. The sensitivity, specificity, and positive and negative predictive values of contrast-enhanced US play a crucial role in the assessment of renal function, with good agreement with the 99mTc-DTPA findings. CEUS has been used for recognizing morphological defects, determining the indications for surgical intervention and measures of renal damage and performing post-operative follow-up examinations. CEUS is a new method showing safety, accuracy, and reproducible precision.

There was only one patient with contrast agent incompatibility (injection site warmth). No severe adverse effects were observed in our study. The relative rate of adverse reactions is reportedly much lower than in any other image diagnosis method[15]. A European survey confirmed that there were no adverse reactions in more than 4,000 intracavitary paediatric applications, and five of the nearly 1,000 intravenous medications had six minor adverse reactions[16]. A large study from Europe consisting of approximately 24,000 examinations reported a low rate of adverse events (3/23188, 0.013%) and severe adverse events (0.0086%)[17], which are significantly lower than the corresponding rate observed with CT contrast agents (1969/286087, 0.69%), with no risk of contrast-related nephropathy or nephrogenic systemic fibrosis[18]. Their only contraindication is severe respiratory failure. Patients are not exposed to radiation or put at risk by nephrotoxic contrast agents. Furthermore, they are not excreted through the kidneys, provide an excellent depiction of renal perfusion and are safe for patients with renal insufficiency[19]. Because the equipment required for the procedure is common, the procedure can be performed at the patient's bedside, e.g., in the intensive care unit.

CEUS has many important advantages, including serving as an ideal imaging modality for monitoring patients treated conservatively and reducing the number of follow-up diuretic renograms, especially in young (under 18 years) patients and women. The technique may represent a useful alternative to DMSA for follow-up examinations to spare nonoperative and postoperative paediatric from radiation exposure. Therefore, CEUS is effective and accurate in children, with the advantages of not requiring radiation exposure or the use of nephrotoxic contrast agents. On the other hand, CEUS is unable to evaluate glomerular filtration, active tubular secretion and reabsorption. Our study is an initial experience with a limited number of patients. There is a critical need for further exploration in future studies. We believe that future prospective studies are necessary to expand the clinical applications of CEUS in many areas in the paediatric population.

Conclusions

This preliminary experience shows a new method for measuring renal function noninvasively using ultrasound. Our study suggests that the method may represent a useful and accurate alternative to diuretic renography in evaluating renal function without radiation exposure.

Abbreviations

A.the slope of the ascending curve; ANH:antenatal hydronephrosis; ANOVA:One-way analysis of variance; AUC:area under the curve; AUROC:an area under the ROC curve; BVF:blood volume fraction; CEUS:Contrast-enhanced ultrasonography; CKD:chronic kidney disease; DKD:diabetic kidney disease; DRF:the differential renal function; EFSUMB:European Federation of Societies for Ultrasound in Medicine and Biology; GFR:glomerular filtration rate; IVP:intravenous pyelogram; NBF:nutrient blood flow; PI:peak intensity; QLAB:Philips advanced ultrasound quantification software; RFI:renal function impairment; TTP:time to peak; TIC:time-intensity curve; UPJO:ureteropelvic junction obstruction; US:Ultrasonography

Declarations

Ethics approval and consent to participate

This study and the use of SonoVue were approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University (National Center for Children's Health of China, Beijing). Written informed consent was provided by each child's parents.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

SFC and DFL conceived of the study, and performed the experiments and wrote the manuscript. PL and QLL carried out the acquisition of data, or analysis and interpretation of date. MLL, XMW, WPZ, HCS and ZWL participated in the design of the study and provided technical advices. NS participated in the design of the study, in discussions and reviewed the manuscript. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, all tables are only available for download from the Supplementary Files section.

Figures

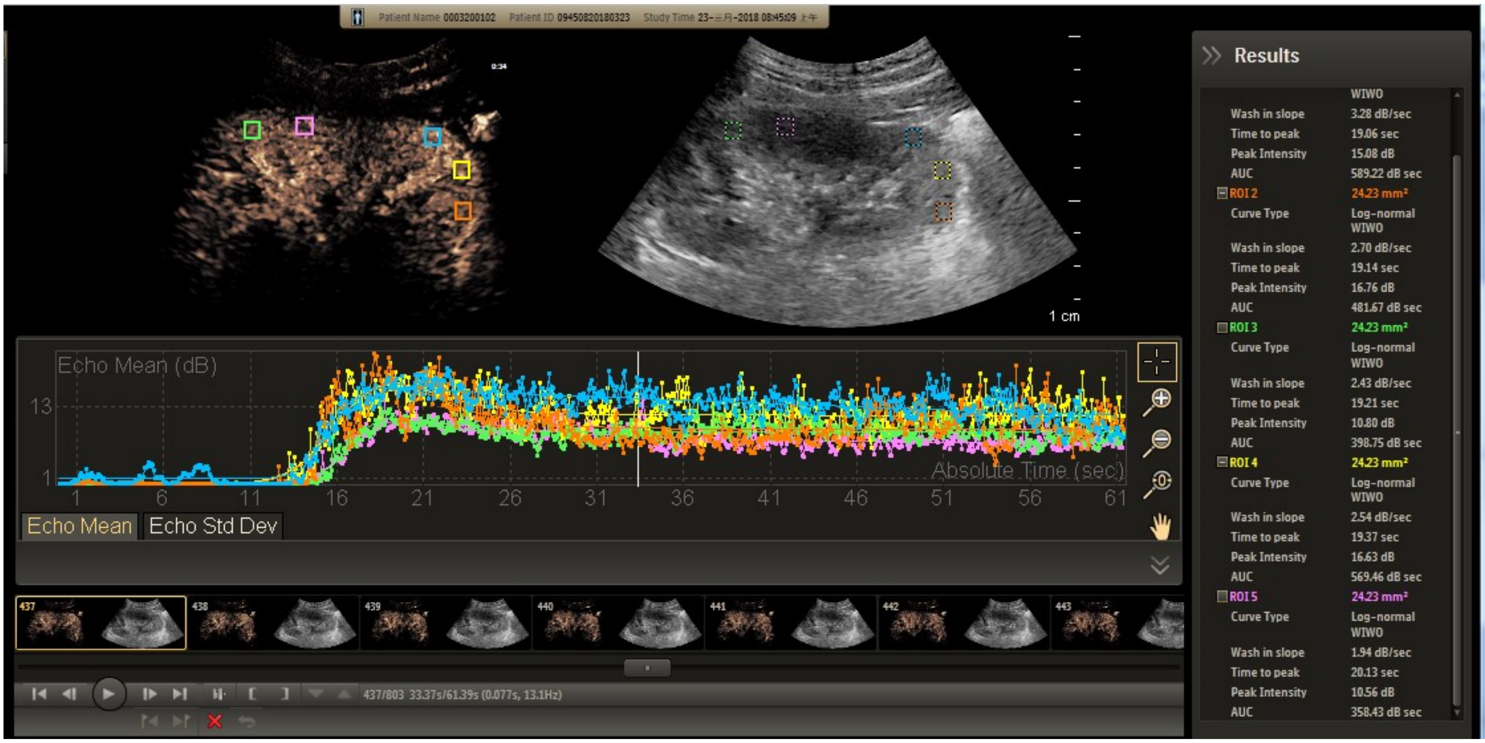

Figure 1

Time-intensity curves (TICs) of the unaffected kidney. Different colour curves represent the TICs of different ROIs.

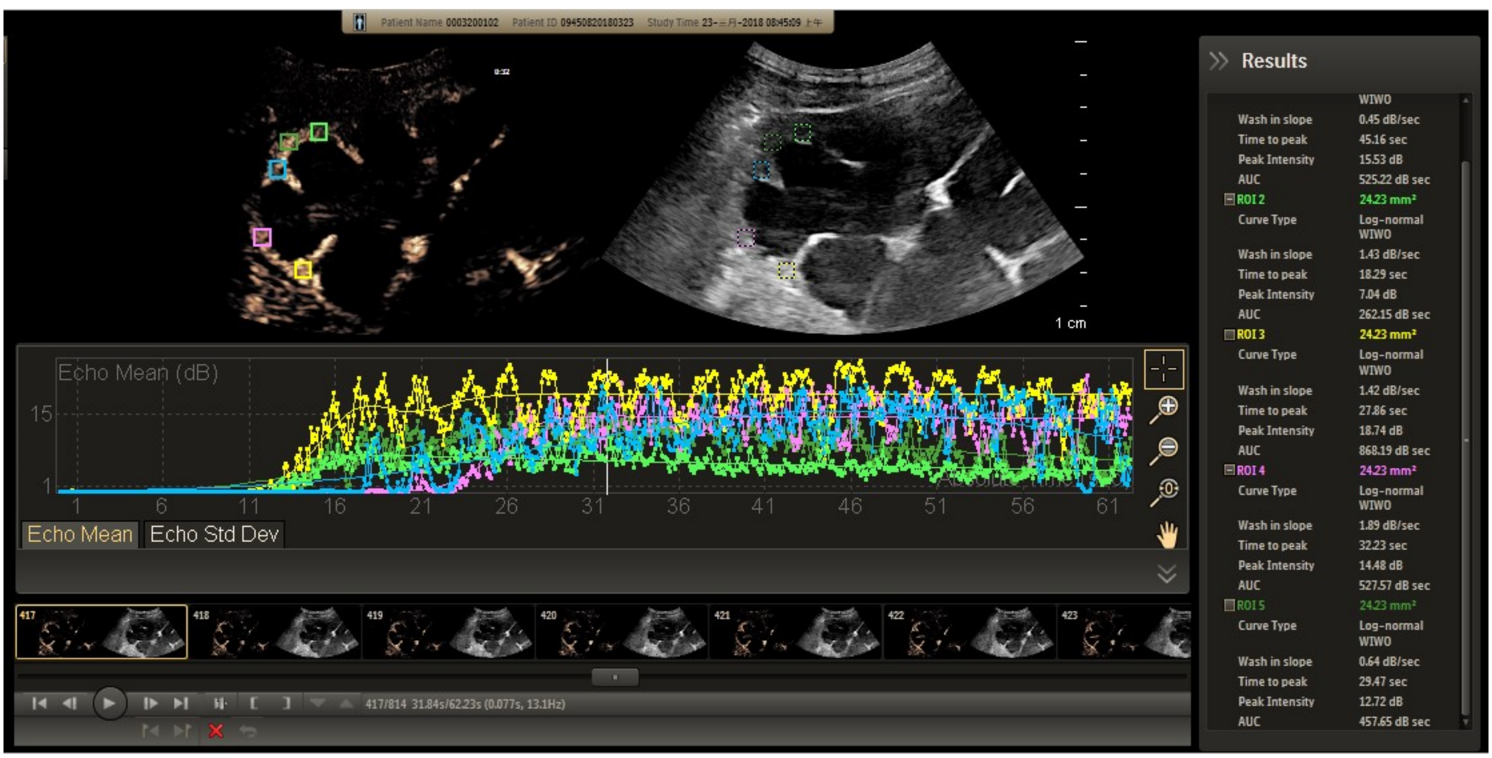

Figure 2

Time-intensity curves (TICs) of the affected kidney.

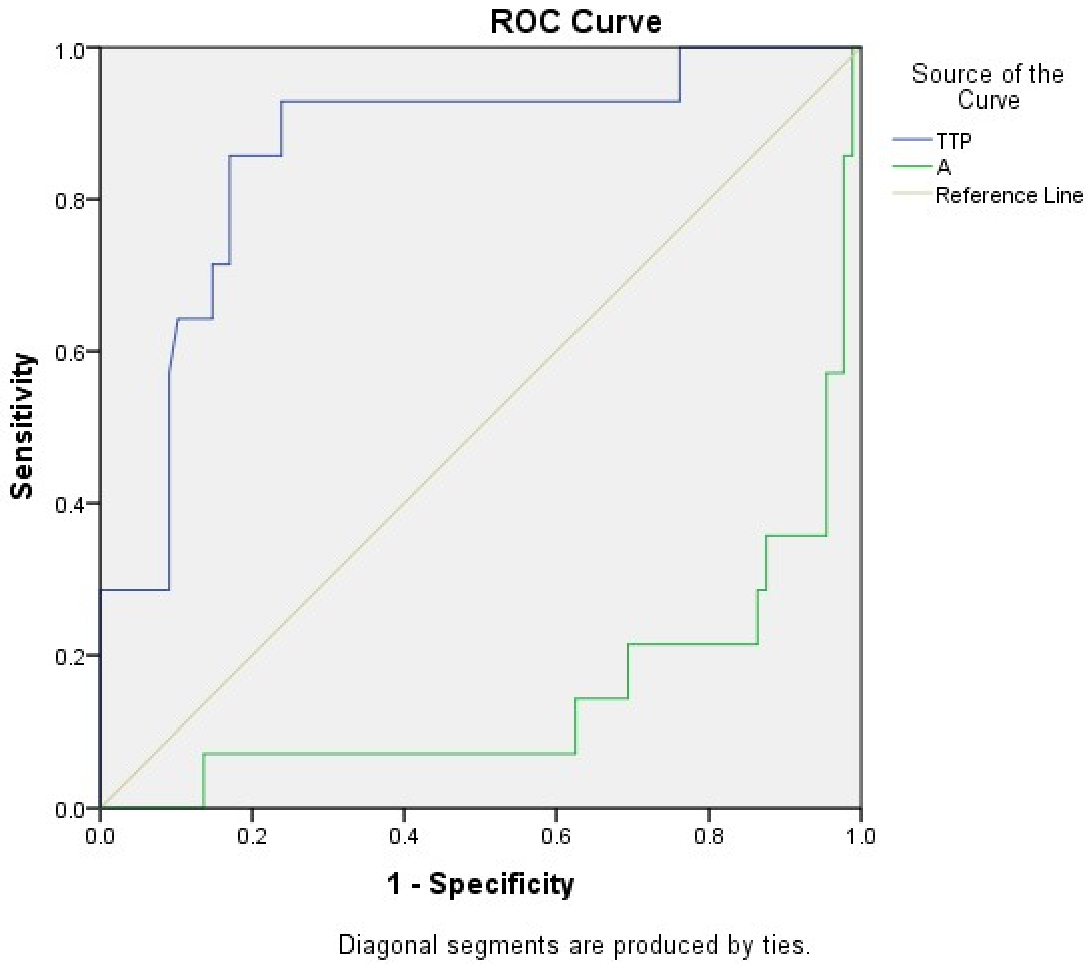

Figure 3

Receiver operating characteristic (ROC) curves of TTP and A values discriminating between DRF values of <40% and DRF values of ≥40%. The positive actual state is DRF<40%.

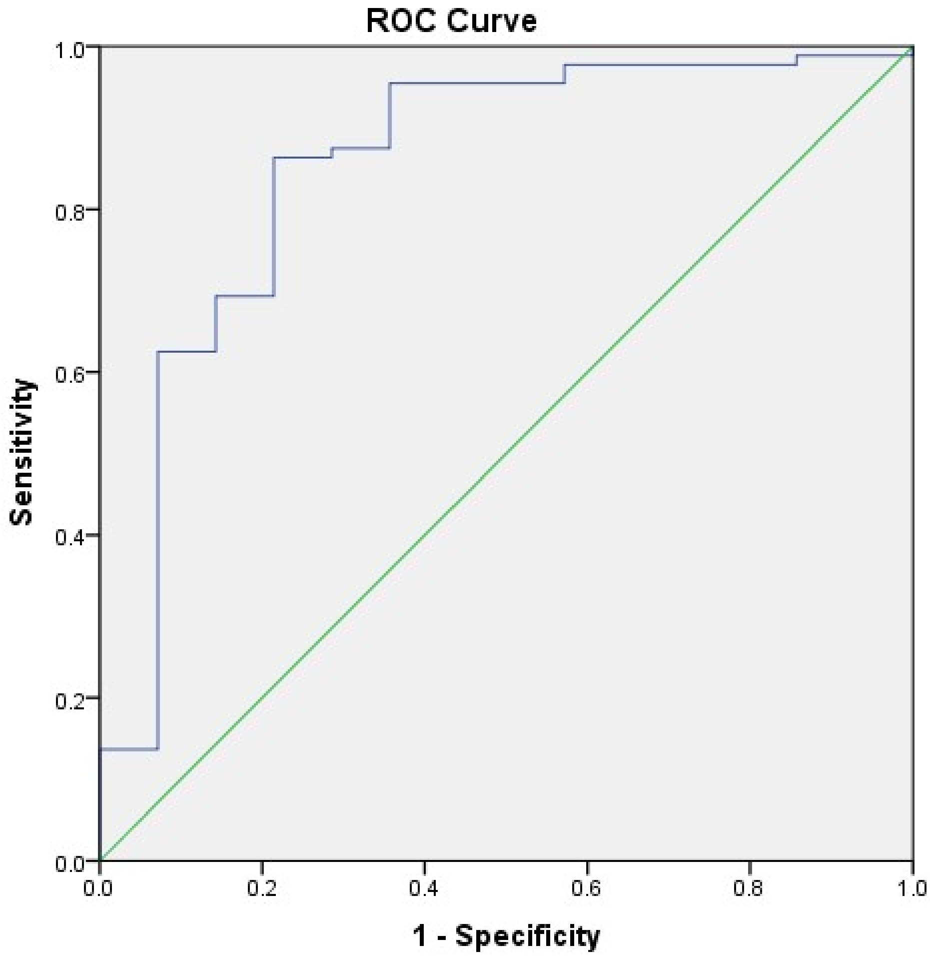

Figure 4

Receiver operating characteristic (ROC) curves of A values discriminating between DRF values of <40% and DRF values of ≥40%. The positive actual state is DRF>40%.

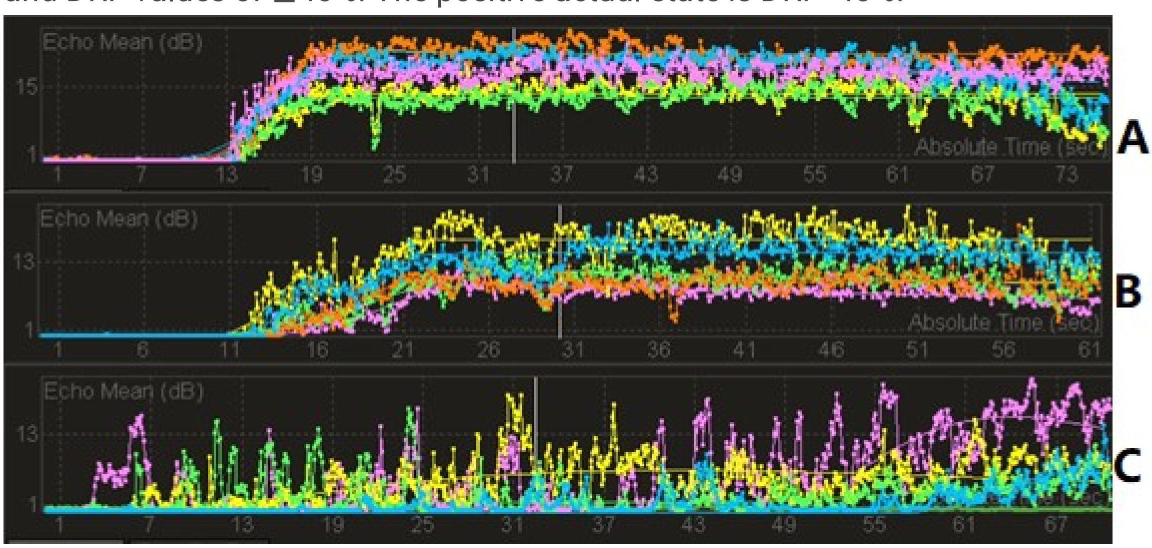

Figure 5

TIC of renal perfusion: (A) perfusion curve in the control group; (B) perfusion curve in the renal impairment group with DRF more than 40; (C) perfusion curve in the renal impairment group with DRF less than 40.

Supplementary Files

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- Table.docx