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ORIGINAL RESEARCH

Evaluation of Contrast-Enhanced Ultrasound in Diagnosis of Acute Kidney Injury of Patients in Intensive Care Unit

Ye Song[1], Jiangjun Mei[1], Dongwei Xu[2], Ying Ma[1]

[1]Department of Ultrasonography, Shanghai Pudong New Area Zhoupu Hospital, Shanghai University of Medicine & Health Sciences, Shanghai, 201318, People's Republic of China; [2]Department of Critical Care Medicine, Shanghai Pudong New Area Zhoupu Hospital, Shanghai University of Medicine & Health Sciences, Shanghai, People's Republic of China

Correspondence: Ye Song, Tel +86 13818086439, Email songye@tongji.edu.cn

Background: Ultrasound can assess renal perfusion, but its role in the evaluation of acute kidney injury (AKI) is still unclear. This prospective cohort study was to investigate the value of contrast-enhanced ultrasound (CEUS) in the evaluation of AKI in intensive care unit (ICU) patients.

Methods: Fifty-eight patients were recruited from ICU between October 2019 and October 2020, and CEUS was used to monitor the renal microcirculation perfusion within 24h after admission. Parameters included rise time (RT), time to peak intensity (TTP), amplitude of peak intensity (PI), area under the curve (AUC), time from peak to one half (TP1/2) of renal cortex and medulla. Ultrasonographical findings, demographics, laboratory, etc were collected for further analysis.

Results: There were 30 patients in the AKI group and 28 patients in the non-AKI group. The TTP, PI, TP1/2 of the cortex and the RT, TTP, TP1/2 of the medulla in the AKI group were significantly longer than in the non-AKI group ($P < 0.05$);. The TTP (OR = 1.261, 95% CI: 1.083–1.468, P = 0.003) (AUCs 0.733, Sen% 83.3, Spe%57.1), TP1/2 (OR = 1.079, 95% CI: 1.009–1.155, P = 0.027) (AUCs 0.658, Sen% 76.7, Spe%50.0) of the cortex and RT (OR = 1.453, 95% CI: 1.051–2.011, P = 0.024) (AUCs 0.686, Sen% 43.3, Spe% 92.9) of the medulla were related to the AKI. Eight new-onset AKI cases occurred in the non-AKI group within 7 days, the RT, TTP, TP1/2 of the cortex and medulla were significantly longer in the new-onset AKI group than in the non-AKI group ($P < 0.05$), but serum creatinine and blood urea nitrogen were no differences between groups ($P > 0.05$).

Conclusion: This study indicates CEUS can assess the renal perfusion in AKI. TTP and TP1/2 of the cortex and RT of the medulla can aid the diagnosis of AKI in ICU patients.

Keywords: contrast-enhanced ultrasound, acute kidney injury, intensive care unit

Introduction

According to the Improving Global Outcomes clinical practice guidelines, acute kidney injury (AKI) involves a rapid deterioration of kidney function. About 15% of adults and 25% of children develop AKI after hospitalization.[1,2] In addition, AKI has been a common disease and a complication in the intensive care unit (ICU) patients; it is associated with significant increases in mortality and risk for chronic kidney disease (CKD) and hemodialysis after discharge; it also increases medical cost and resource utilization.[3–8] In the hemodynamic resuscitation of ICU patients, the renal microcirculation is less monitored, which may be ascribed to the unavailable bedside assessment. Thus, it is imperative to develop a convenient diagnostic tool for the assessment of renal perfusion.

Studies have investigated the use of serum and/or urine biomarkers in the assessment of kidney injury. The expression of metalloproteinases-2 (TIMP-2) and insulin like growth factor binding protein 7 (IGFBP7) changes prior to AKI, and may predict the risk for AKI.[9] It has been reported that the combined use of these biomarkers can predict the AKI from moderate to severe in critically ill patients within 12 h.[10–12]

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Imaging techniques have some disadvantages such as high cost, long time for scanning, inconvenience and toxicities associated with contrast agents, and therefore the use of radiological examinations is limited in clinical practice. Ultrasonography (US) of the kidney is a simple and convenient examination with low cost and it has been the most widely used imaging modality in the initial workup of AKI. Doppler ultrasonography is a simple examination to detect the gross vascular abnormalities in the kidney, which can provide indirect evidence on microvascular disorders. Several studies have shown that an elevated renal resistive index (RRI) is associated with the increased risk for AKI.[13] Due to the limitations of the patient's imaging conditions and the operator's technique, accurate measurement becomes difficult. More effective, convenient, safe and economical imaging methods are needed for the clinical examinations.

US contrast agent without risk for nephrotoxicity has been used in the semi-quantitative and functional assessment of renal microvascular perfusion.[14,15] Contrast-enhanced ultrasound (CEUS) is easy to operate and cost-effective. This study was to compare the renal perfusion between patients with AKI and those without AKI in ICU, aiming to investigate the value of CEUS in the diagnosis of AKI in ICU patients.

Methods

Study Subjects

This study was a prospective cohort study and all participants were consecutively recruited between October 2019 and October 2020. Patients were from the ICU of Zhoupu Hospital and received CEUS examination. Patients were diagnosed with AKI according to the criteria published elsewhere;[16] The inclusion criteria were as follows: 1) Baseline serum creatinine levels within 6 months prior study were available; 2) Patients were not younger than 18 years. The exclusion criteria were as follows: 1) Patients received kidney transplantation, chronic kidney disease, urinary tract obstruction before admission; 2) Patients had a history of cardiac shunt, cardiogenic shock, or severe heart failure within 72 h; 3) Pregnant women, lactating women, and patients with mental disabilities were excluded; 4) Patients had respiratory failure, hypersensitivity or contraindications to US contrast agents; 5) patients had drug poisoning; and 6) Patients withdrew from the study or clinical information was unavailable.

This study was approved by the Ethics Committee of our hospital (ZPYYLL-2018-02; April 2019), and all patients signed an informed consent form before study.

Methods

All patients received bundle care within 6 h after admission, and the mean arterial pressure (MAP), blood lactic acid (Lac) and central venous oxygen saturation ($ScvO_2$) were recorded. CEUS perfusion imaging was performed within 24 h after admission. Blood samples were collected for the detections of renal function, NGAL, KIM-1, CysC and IL-18, and the creatinine clearance rate (CCr) and urine volume per hour were also recorded. Patients were divided into AKI group and non-AKI group based on the occurrence of AKI within 24 h after admission. Each patient was followed up with regular blood tests, including serum creatinine, blood urea nitrogen, urine volume, and biological indicators of early renal injury, and the hemodynamics were continuously monitored within 7 days after admission. The MAP was maintained at ≥60 mmHg (1 mmHg = 0.133 kPa). Non-AKI patients were re-diagnosed according to AKI diagnostic criteria in 7 days after admission. The clinical context, medical history, physical examination, and laboratory findings of blood and urine examinations were used to assess the cause of AKI. The interval of follow-up was determined according to the physician's judgement, and the frequency of follow-up differed between patients. The demographics and comorbid conditions were also collected and compared between patients. CKD was defined by the presence of impaired estimated glomerular filtration rate (eGFR) for >3 months.[17] The study design is presented in Figure 1.

Procedures for CEUS

All patients received CEUS with Philips EPIC 7 ultrasound machine using a 1–5 MHz convex transducer. The same machine was operated by the same technician throughout the study, and the pulse inversion harmonic imaging was used. With mechanical index (MI) at 0.06, frequency general, dynamic range at 67, and gain at 52. Transform image depth, focus, and gain were determined according to the patients' conditions, but they remained unchanged in the same examination. The longest longitudinal section of the kidney was captured, including the entire kidney and the trunk and branches of the renal

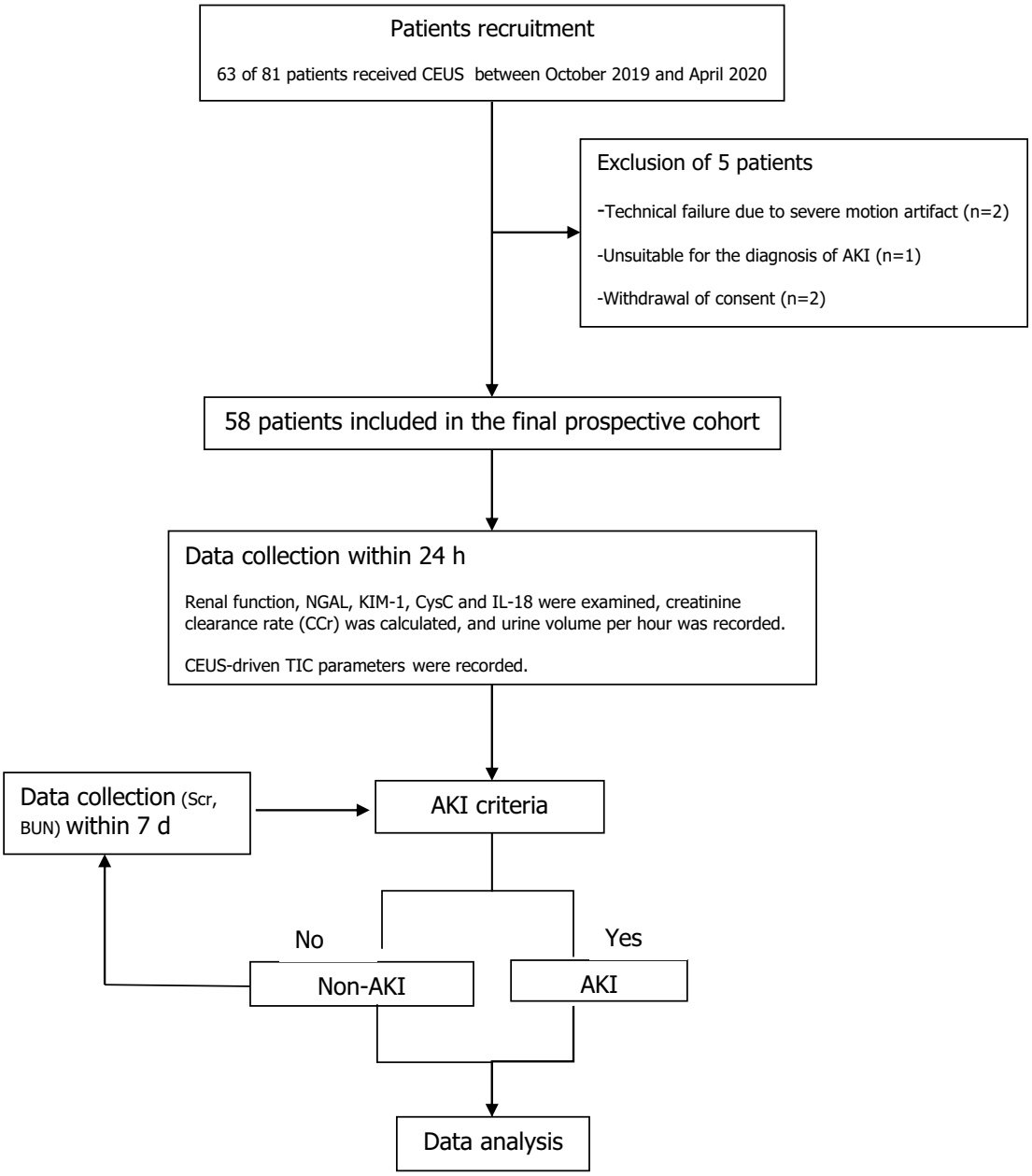

Figure 1 Flow diagram of study.

blood vessels. The probe was fixed in the same plane while the patient breathed as lightly as possible. Then, SonoVue (Bracco, Milan, Italy) (0.02 mL/kg body weight) was rapidly injected via the antecubital vein, followed by flush with 5 mL of 0.9% normal saline. The data were stored at the same time, and recorded within 3 min. Images of all the patients were stored, and the QLAB software was used for further analysis. Only one kidney was examined.

QLAB software enables the motion compensation, three regions of interest (ROIs) of similar size (5×5 mm^2) were delineated in the similar depth of renal cortex and medulla, the time-intensity curves (TIC) were generated, and the parameters were obtained by gamma fitting. Image fit was greater than 75% and data from three measurements were averaged to minimize heterogeneity. The parameters included rise time (RT, time from injection until the peak of enhancement; units), time to peak intensity (TTP, time to maximum enhancement; units), amplitude of peak intensity (PI, maximum intensity of the curve; dB), time from peak to one half (TP1/2; s), and area under the curve (AUC, area under the TIC that is proportional to the total volume of blood flow in the ROI; dB).

Statistics

SPSS version 19.0 and MedCalc were used for statistical analysis. Quantitative data are expressed as mean ± standard deviation and qualitative data as percentiles (%). Data were compared using an independent sample *t*-test or Chi square test. The predictive power of each parameter for AKI was evaluated based on the AUC. The cut-off value was used as the diagnostic reference. Pearson correlation coefficient was used to calculate the correlation coefficient. A value of two-tailed P <0.05 was considered statistically significant.

Results

General Conditions

A total of 58 patients were included in this study (Table 1). The incidence of AKI was 51.72% (30/58), including myolysis (n = 1), trauma (n = 4), postoperative (n = 5), infection (n = 20). The serum creatinine and blood urea nitrogen on admission were significantly higher in the AKI group than in the non-AKI group (P < 0.05). However, there were no significant differences in the age, body mass index (BMI) and gender between groups (P > 0.05).

CEUS-Driven TIC Parameters

As shown in Table 2, the TTP, PI and TP1/2 of the cortex and medulla were significantly different between two groups, and they were longer in the AKI group than in the non-AKI group (P < 0.05). PI of the cortex in the AKI group was

Table 1 Demographic and Biochemical Findings on Admission in Two Groups

	Non-AKI (n=28)	AKI (n=30)	*P*
Age (yr)	70.36 ±14.58	68.93 ±16.60	NS
Body mass index (kg/m^2)	25.64 ±5.30	24.27 ±4.88	NS
Gender [% (n)]			NS
Female	19.0 (11)	29.3 (17)	
Male	17.2 (10)	34.5 (20)	NS
Scr (μmol/L)	107.59±35.79	265.93±160.90	0.000
BUN (mmol/L)	8.57±2.79	27.89±25.53	0.000

Note: Data are expressed as mean ± SD.
Abbreviations: Scr, serum creatinine; BUN, blood urea nitrogen.

Table 2 CEUS-Related Parameters Within 24 h After Admission in Two Groups

	Non-AKI (n=28)	AKI (n=30)	*P*
Cortex			
RT (s)	6.21±1.36	6.49±1.44	0.449
TTP (s)	15.00±3.29	18.90±4.86	0.001
PI (dB)	48.28±23.24	37.77±15.08	0.018
TP 1/2 (s)	36.24±7.01	41.64±9.86	0.020
AUC (dB)	2796.78±853.53	2484.64±772.37	0.149
Medulla			
RT (s)	7.69±1.44	9.63±3.51	0.009
TTP (s)	20.91±15.07	30.61±8.38	0.003
PI (dB)	43.50±21.01	35.85±15.36	0.117
TP 1/2 (s)	48.25±29.53	64.35±15.57	0.011
AUC (dB)	2647.37±756.63	2456.96±807.82	0.359

Note: Data are expressed as mean ± SD.
Abbreviations: RT, Rise time, the time from injection until the peak of enhancement; TTP, time to peak intensity, time to maximum enhancement; PI, amplitude of peak intensity, the maximum intensity of the curve; TP1/2, time from peak to one half; AUC, area under the curve, the area under the TIC that was proportionate to the total volume of blood flow in the ROI.

significantly lower than in the non-AKI group (P < 0.05). There were no marked differences in the RT and AUC of the cortex and in the PI and AUC of the medulla between two groups (P > 0.05).

Predictive Value of CEUS in AKI

Multiple logistic regression analysis was performed to explore the CEUS parameters that can be used to predict the AKI. Results showed TTP (OR = 1.261, 95% CI: 1.083–1.468, P = 0.003) and TP1/2 of the cortex (OR = 1.079, 95% CI: 1.009–1.155, P = 0.027) and RT of the medulla (OR = 1.453, 95% CI: 1.051–2.011, P = 0.024) were closely related to the AKI (P < 0.05).

As shown in Table 3, the TTP and TP1/2 of the cortex and the RT, TTP and TP1/2 of the medulla yielded the AUCs of 0.733, 0.658, 0.686, 0.868 and 0.838, respectively, in the prediction of AKI (P < 0.05); thus, the progressive 95% CI did not include 0.5. The AUCs of remaining parameters were higher than 0.5; TTP of the cortex and RT, TTP and TP1/2 of the medulla were significant (P < 0.05).

New-Onset AKI Within 7 Days After Admission in Non-AKI Patients

The incidence of new-onset AKI within 7 days in the non-AKI group was 28.57% (8/28), and the causes of the new case were as follows: trauma (n = 2), postoperative liver surgery (n = 1) and infection (n = 5). There were no significant differences in the age, body mass index (BMI), gender, serum creatinine and blood urea nitrogen between new-onset AKI patients and non-AKI patients (P > 0.05) (Table 4).

Table 3 ROC Curve Analysis of CEUS-Related Parameters Regarding AKI

	Area%	95% CI	P	Cut-off Point	Sen%	Spe%
Cortex						
RT	0.594	0.457–0.721	0.225	6.54	46.7	78.6
TTP	0.733	0.601–0.841	0.001	14.82	83.3	57.1
PI	0.621	0.484–0.745	0.112	58.56	96.7	32.1
TP 1/2	0.658	0.522–0.778	0.028	34.44	76.7	50.0
AUC	0.605	0.468–0.731	0.167	2493.48	63.3	60.7
Medulla						
RT	0.686	0.551–0.802	0.008	9.37	43.3	92.9
TTP	0.868	0.753–0.942	0.001	26.97	73.3	92.9
PI	0.589	0.452–0.717	0.243	59.45	96.7	25.0
TP 1/2	0.838	0.717–0.921	0.001	50.12	73.3	89.3
AUC	0.540	0.405–0.672	0.608	2378.12	66.7	60.7

Abbreviations: RT, Rise time, the time from injection until the peak of enhancement; TTP, time to peak intensity, time to maximum enhancement; PI, amplitude of peak intensity, the maximum intensity of the curve; TP1/2, time from peak to one half; AUC, area under the curve, the area under the TIC that was proportionate to the total volume of blood flow in the ROI.

Table 4 Baseline Characteristics of New-Onset AKI Patients and Non-AKI Patients Within 7 Days After Admission

	Non-AKI (n=20)	New-onset AKI (n=8)	*P*
Age (yrs)	67.55 ±14.95	77.38 ±11.59	NS
Body mass index (kg/m^2)	25.05 ±5.33	27.10 ±5.30	NS
Gender [% (n)]			NS
Female	25.0 (7)	14.3 (4)	
Male	46.4 (13)	14.3 (4)	NS
Scr (μmol/L)	112.38±27.66	100.28±51.83	0.000
BUN (mmol/L)	8.79±3.10	8.04±1.89	0.000

Note: Data are expressed as mean ± SD.
Abbreviations: Scr, serum creatinine; BUN, blood urea nitrogen.

Table 5 CEUS-Related Parameters of New-Onset AKI Patients and Non-AKI Patients Within 7 Days After Admission

	Non-AKI (n=20)	New-onset AKI (n=8)	*P*
Cortex			
RT (s)	5.73±1.07	7.44±1.29	0.001
TTP (s)	14.09±2.62	17.28±3.86	0.018
PI (dB)	50.18±25.05	43.53±18.55	0.504
TP 1/2 (s)	33.95±5.40	42.00±7.58	0.004
AUC (dB)	2858.44±896.25	2642.64±769.20	0.556
Medulla			
RT (s)	7.19±1.31	8.98±0.88	0.002
TTP (s)	17.30±3.25	21.17±5.16	0.024
PI (dB)	45.29±22.82	39.02±16.02	0.486
TP 1/2 (s)	41.34±5.50	48.04±5.95	0.008
AUC (dB)	2702.20±774.47	2510.30±741.68	0.554

Abbreviations: RT, Rise time, the time from injection until the peak of enhancement; TTP, time to peak intensity, time to maximum enhancement; PI, amplitude of peak intensity, the maximum intensity of the curve; TP1/2, time from peak to one half; AUC, area under the curve, the area under the TIC that was proportionate to the total volume of blood flow in the ROI.

CEUS-Driven TIC Parameters

As shown in Table 5, the RT, TTP and TP1/2 of the cortex and medulla were significantly different between new-onset AKI patients and non-AKI patients, and they were longer in the new-onset AKI group than in the non-AKI group ($P < 0.05$). There were no marked differences in the PI and AUC of the cortex and medulla between two groups ($P > 0.05$).

Discussion

In this study, CEUS was employed to detect the kidney perfusion of ICU patients on admission. The predictive value of CEUS-related parameters for AKI was evaluated by comparing these parameters between AKI group and non-AKI group. In this prospective study, results showed TTP and TP1/2 of the renal cortex and RT of the renal medulla could be used to assess the severity of AKI.

Serum creatinine level and urine volume are two important parameters used for the diagnosis of AKI. They are neither sensitive nor specific to AKI,[2] and changes in serum creatinine are not closely associated with the severity of renal impairment and do not reflect the cause of AKI.[18,19] In this study, the serum creatinine and blood urea nitrogen in the AKI group were higher than in the non-AKI group on admission, but there were no significant differences in new-onset AKI within 7 days of admission.

The incidence of AKI and the AKI-related mortality are increasing,[20] which has been reported to be ascribed to the abnormal renal perfusion.[21] Currently, there are still no effective tools that can be used to assess the renal perfusion. CEUS is a new imaging tool, and has been widely used in the clinical practice due to its simple operation, convenience and low cost. CEUS has been used to assess the kidney perfusion, available in blood gas microbubble generated by nonlinear effect and strong backscattering contrast of image, combined with low mechanical index monitoring method. CEUS can identify the renal hemoperfusion in the early stage of AKI and is more sensitive to small vessel lesions.[22] It is also useful for the visualization and quantification of organ perfusion. Compared with conventional angiography, CEUS is an economic, rapid, noninvasive, and non-nephrotoxic technique that can be safely used in patients with contra-indications to iodine or gadolinium contrast or with renal impairment.[23] The impaired renal microcirculation perfusion has been reported in AKI patients and animal models[24–27] and the renal perfusion impairment is closely related to the renal histological injury and CKD progression.[26]

Our results showed the TTP and TP1/2 of the cortex and the RT, TTP and TP1/2 of the medulla in the AKI group were significantly longer than in the non-AKI group ($P < 0.05$); the PI of the cortex in the AKI group was markedly lower than in the non-AKI group ($P < 0.05$). These findings were consistent with those previously reported.[14,28,29] In the

early stage of AKI, the vascular perfusion of the renal cortex begins to decline, leading to a decrease in the renal perfusion. Therefore, even if the patients did not develop AKI in the early stage, the speed of renal perfusion had been significantly prolonged, which was reflected in new-onset AKI cases within 7 days, although the sample size was relatively small. Moreover, the intra-renal stasis slows down the metabolism of contrast agent, which may be ascribed to the higher TTP and TP1/2 of renal cortex and higher RT, TTP and TP1/2 of renal medulla in the AKI group than in the non-AKI group. PI reflects the highest blood perfusion intensity in ROI. PI is affected by multiple factors such as circulation status. In the present study, PI in the AKI group was lower than in the non-AKI group, which may be related to the decreased overall perfusion and persistent hypoperfusion in the injured kidney.[30,31]

Renal evaluation is an important part in the assessment of ICU patients on admission and is generally performed within 12–24 h after admission. Therefore, in addition to traditional biomarkers, more effective, convenient, safe and economical imaging techniques are needed for the assessment of renal injury. Imaging techniques, such as Doppler ultrasound, blood oxygenation level dependent (BOLD) MRI, and diffusion-weighted imaging (DWI) have been used to assess the renal function in AKI and CKD.[32] Due to the high cost and inconvenience, the use of these techniques in ICU patients is limited. CEUS is the most suitable method and has become a valuable diagnostic tool for ICU patients. CEUS can be used to assess risk for AKI and predict the prognosis of AKI patients. It can be used for bedside examination, which is convenient and can be employed for dynamic, real-time and repeatable evaluation of ICU patients.

There were several limitations in this study. First, the sample size in the study was still small, and our results should be further confirmed in more studies with large sample size. Second, patients were asked to hold their breath during the measurements, aiming to minimize the motion artifacts, and thus it is not applicable in ICU patients without spontaneous respiration.[33] Third, the regions of interests of the perfusion map were selected subjectively in the kidney and this might very well represent local microheterogeneities.[34]

Conclusions

CEUS is more sensitive to accurately display the early renal blood perfusion in ICU patients with AKI and can be used for the early assessment of renal injury. TTP and TP1/2 of the cortex and the RT of the medulla are helpful for the diagnosis of AKI in ICU patients.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Independent Ethics Committee of Shanghai Pudong New Area Zhoupu Hospital (ZPYYLL-2018-02; April 2019).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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Disclosure

The authors declare no conflict of interest.

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