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● *Original Contribution*

PREDICTION OF TUBULOINTERSTITIAL INJURY IN CHRONIC KIDNEY DISEASE USING A NON-INVASIVE MODEL: COMBINATION OF RENAL SONOGRAPHY AND LABORATORY BIOMARKERS

Wen-Qi Yang,*[,1] Shan Mou,[†,1] Li Xu,* Feng-Hua Li,* and Hong-Li Li*

* Department of Ultrasound, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China; and [†] Department of Nephrology, Molecular Cell Lab for Kidney Disease, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China

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Abstract—The goal of the study described here was to evaluate the degree of tubulointerstitial injury in patients with chronic kidney disease (CKD) using a more accurate model that combines renal sonographic parameters and laboratory biomarkers. A total of 308 patients were enrolled. The study protocol included conventional ultrasound, contrast-enhanced ultrasonography and renal biopsy. CKD patients were divided into normal and mild (≤25%), moderate (26%–50%) and severe (>50%) tubulointerstitial injury groups. We created a model comprising peak intensity, time to peak, urinary retinol-binding protein and β_2-microglobulin that could discriminate severe (>50%) tubulointerstitial injury. The area under the receiver operating characteristic curve of this model was 0.832, which had better accuracy than other individual indexes, and the sensitivity and specificity were 74.2% and 82.8%, respectively. Therefore, this model may be used to evaluate the severity of tubulointerstitial injury and may have the potential to serve as an effective auxiliary method to help nephrologists evaluate patients with CKD. (E-mail: lihliwl@163.com) **© 2018 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

Key Words: **Conventional renal ultrasonography, Contrast-enhanced ultrasonography, Chronic kidney disease, Tubulointerstitial injury.**

INTRODUCTION

Chronic kidney disease (CKD) is a major global public health problem. It also can progress to end-stage renal disease (Menzilcioglu et al. 2015). The tubulointerstitial lesion is a crucial pathologic feature of progressive renal injury in most glomerulopathies. It is reported that the extent of a tubulointerstitial lesion correlates closely with the progression of CKD (Healy and Brady 1998; Norman and Fine 2006; Thoeny et al. 2005). Patients with severe tubulointerstitial injury tend to have a poor prognosis in glomerular disease (D'Amico 2000; D'Amico et al. 1995; Healy and Brady 1998). Thus, accurate assessment of tubulointerstitial injury is required for improved diagnosis, progression monitoring and treatment of patients with CKD.

To date, renal biopsy is considered the gold standard for the evaluation of tubulointerstitial injury. However, as an invasive tool, renal biopsy is extremely inconvenient to the patient because it carries risks such as hemorrhage and infection and is expensive. (Wang et al. 2014). As a consequence, non-invasive methods are preferable for assessment of tubulointerstitial injury in patients with CKD.

Many non-invasive approaches, such as laboratory tests and imaging techniques, have been proposed as alternatives to renal biopsy (D'Amico and Bazzi 2003; Gao et al. 2013; Prabahar et al. 2008; Theilig et al. 2007). Urinary microproteins are measured with the urine test, which can mirror alterations in functional tubules, and functional alterations are associated with the degree of tubulointerstitial injury (Healy and Brady 1998). No single laboratory biomarkers can achieve perfect diagnostic performance.

Recent studies have reported that Doppler ultrasound (US) could be applied to predict the severity of tubulointerstitial injury in glomerular disease (Prabahar et al. 2008) and lupus nephritis (Gao et al. 2013). Nevertheless, Doppler US parameters, such as the resistance index, can reflect macrovascular flow indirectly. Unfortunately, it is limited in the detection of smaller vessels and even capillary blood flow (Basiratnia et al. 2006).

Address correspondence to: Hong-Li Li, Department of Ultrasound, Renji Hospital, School of Medicine, Shanghai Jiaotong University, 160 Pujian Road, Shanghai, 200127, China. E-mail: lihliwl@163.com

[1] These authors contributed equally to this work.

Contrast-enhanced ultrasonography (CEUS) is a non-invasive imaging method for quantitative evaluation of microvascular perfusion of a parenchymal organ (Schneider et al. 2012). Microbubbles are pure blood-pool contrast agents, allowing direct assessment of renal microvascular perfusion (Greis 2009). Studies have reported that CEUS could be used to evaluate renal microvascular perfusion in CKD (Dong et al. 2014; Tsuruoka et al. 2010). Ma et al. (2013) evaluated renal microvascular perfusion in diabetic rats with CEUS and found that perfusion parameters were associated with renal histopathology. The reduction of peritubular capillaries was a vital pathologic feature of tubulointerstitial injury (Bohle et al. 1996). We hypothesize that CEUS can be helpful in monitoring the perfusion of capillaries and assessing the severity of tubulointerstitial injury.

Tubulointerstitial injury is characterized by tubular atrophy, inflammatory infiltration and interstitial fibrosis. Therefore, a combination of different approaches may be better than an individual method because these methods can provide complementary information on tubulointerstitial injury status. However, the literature on investigating prediction of the degree of tubulointerstitial injury by the use of US parameters combined with laboratory biomarkers in CKD is limited.

The purpose of the study described here was to evaluate the application of CEUS quantitative parameters in the assessment of tubulointerstitial injury and further establish a non-invasive model for predicting the degree of tubulointerstitial injury in CKD patients.

METHODS

Study design and patients involved

This retrospective study was approved by the institutional review board and ethics committee of the Renji Hospital, School of Medicine, Shanghai Jiaotong University. Written informed consent was obtained from all patients before examination.

From March 2014 to March 2017, patients with CKD were enrolled through the Department of Nephrology. To be included, patients had to have had (i) albuminuria and/or elevated serum creatinine or blood serum urea nitrogen levels, and/or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 for >3 mo; (ii) age ≥18 y; and (iii) body mass index between 18.5 and 26.9.

Excluded from this study were (i) patients with contraindications to the contrast agent SonoVue, such as a history of cardiac failure, respiratory disorders, hypersensitivity and contraindications according to the approved labeling (Lassau et al. 2017); (ii) patients with a solitary kidney, polycystic kidneys, acute kidney injury, renal amyloidosis, hydronephrosis, renovascular nephropathy, renal transplantation or obesity-related glomerulopathy; (iii) patients with asymmetry in renal size, which is defined as a difference ≥2 cm between kidneys; (iv) patients with comorbid conditions such as cardiac insufficiency and liver disease; (v) patients not able to cooperate fully in breathing motion; and (6) patients with contraindications to renal biopsy. Finally, a total of 308 patients were included in this study.

Twenty-four-hour total urinary protein (UPE), urinary retinol-binding protein (RBP), urinary *N*-acety1-β-D-glucosaminidase (NAG), urinary β_2-microglobulin (β_2-MG) and urinary microalbumin (MALB) were measured using standard methods in a certified laboratory before US examinations in CKD patients.

The eGFR was calculated in accordance with the modification of diet in renal disease formula (Ma et al. 2006).

Conventional US and CEUS examinations

Conventional US and CEUS were performed with an iU 22 (Philips, Bothell, WA, USA), using a 1- to 5-MHz convex probe. All scanning procedures were performed before renal biopsy by one radiologist (H.L.L., more than 10 y of diagnostic experience in renal US), who was not aware of patient's clinical information. First, both the right and left sides of the kidney were scanned longitudinally and cross-sectionally by conventional US. The size, position, echogenicity and cortical thickness of the kidneys were noted. Patients were examined in the prone position. Renal size was determined as the maximum longitudinal dimension. Renal length was measured as the greatest pole-to-pole distance in the sagittal plane. Renal thickness was measured perpendicular to renal length at the mid-level of the kidney, which represented renal anteroposterior diameter. Cortical thickness was measured at the mid-level of the kidney as described by Moghazi et al. (2005). The measurement was perpendicular to the renal capsule as the shortest distance from the base of a medullary pyramid to the renal capsule. Conventional US parameters recorded in our study were renal length, renal thickness and cortical thickness. Renal length, renal thickness and cortical thickness were measured three times, and the average of three measurements was calculated. Dynamic range, gain and frequency were kept constant to minimize variation. The focus position was set on the level of the kidney. Time-gain compensation control settings were maintained in a neutral position. No parameters were changed during all examinations.

Second, CEUS was performed on patients in the prone position. We selected a maximum longitudinal scanning section that included the entire kidney. The mechanical index was set at 0.06. All CEUS examinations were performed on the left kidney. The contrast agent used in this study was SonoVue (Bracco, Milan, Italy), which contains sulfur hexafluoride microbubbles stabilized in a phospholipid shell (McArthur and Baxter 2012). After