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Diagnostic performance of renal ultrasonography in detecting chronic kidney disease of various severity

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Abstract

Background: Association between early diagnosis of chronic kidney disease (CKD) and low morbidity and mortality rate has been proven. Thus, tools for early CKD diagnosis are vital. Ultrasonography has been widely used to diagnose and monitor the progression of CKD.

Objectives: To determine the performance of selected renal ultrasonographic parameters for the diagnosis of early CKD.

Methods: In a cohort of patients diagnosed with CKD ($n = 100$), diagnostic performance of ultrasonographically measured renal length (RL), renal cortical thickness (RCT), and parenchymal thickness (PT) was determined using receiver operating curve analysis; correlation of each parameter with the associated comorbidities and serum creatinine (Scr) levels was also determined. Severity of CKD was graded with estimated glomerular filtration rates (eGFR).

Results: Of all patient participants, 85 had severity grades 2 or 3. Mean (standard deviation) Scr was 1.88 (0.60) mg/dL; eGFR was 43.3 (11.85) mL/min/1.73 m². RL was 9.01 (0.83) cm, PT was 1.32 (0.22) cm, and RCT was 6.0 (0.10) mm. PT and RCT were positively correlated with eGFR ($P = 0.01$ and 0.002 , respectively). Early CKD was better predicted by PT (area under the curve (AUC) 0.735; 82% sensitivity; 30% specificity; 68% positive predictive value (PPV)) and RCT (AUC 0.741; 82% sensitivity; 48% specificity; 51% PPV); severe CKD was better predicted by RL (AUC 0.809; 67% sensitivity; 26% specificity, 45% PPV; 13% negative predictive value).

Conclusion: Index ultrasonic parameters show a diagnostic role in different stages of CKD. The index ultrasound and biochemical parameters showed a complementary role in predicting renal dysfunction.

Keywords: creatinine; kidney cortex; renal insufficiency, chronic; renal parenchyma; ultrasonography

Chronic kidney disease (CKD) is increasingly recognized as a global health problem. The rising incidence of CKD is associated in part with the ageing global population and the epidemic spread of noncommunicable diseases, such as type 2 diabetes mellitus (DM) and hypertension [1]. A recognized major sequel of CKD is end-stage renal failure. To ensure

the survival of patients in end-stage renal failure, either renal replacement therapy or renal transplantation is mandatory. The subsequent development of cardiovascular diseases further increases the CKD related morbidity and mortality. Early diagnosis and timely treatment is known to prevent or delay the morbidity and mortality of CKD [1, 2].

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To diagnose CKD, the findings of clinical examination, biochemical, and imaging investigation are complementary [3]. As diagnostic tools, renal ultrasound parameters, such as length, cortical echogenicity, and corticomedullary demarcation are used traditionally, whereas serum creatinine level (Scr) is the most frequently used biochemical variable [3–5]. While some studies have challenged the reliability of using routine investigation findings (such as, ultrasonography and Scr) in early CKD diagnosis [4–6], some have pointed out the credibility of using renal cortical and parenchymal thicknesses as tools for the diagnosis of early CKD [7–11]. The etiology of CKD is multifactorial; some etiological factors such as comorbidities (e.g., DM) have demonstrated a correlation with renal length (RL) [3, 12, 13]. Hence, the renal cortical and parenchymal thickness (PT) may also be correlated with these comorbidities.

Despite recognizing ultrasonography as a safe, accurate, noninvasive, and freely available imaging modality, uncertainty has remained with regard to the best ultrasound parameter with which to evaluate and monitor renal function in CKD [14, 15]. Although a few preliminary studies have evaluated renal cortical and parenchymal thicknesses, none of them was focused on assessing the correlation with either etiological factors or the severity of CKD. Therefore, practical applications (in diagnosis) of ultrasound parameters, such as renal cortical and parenchymal thicknesses have remained limited. Importantly, there is a scarcity of data for ultrasound parameters for Sri Lankan patients with CKD. Considering the possibility of geographical and ethnic variations in renal ultrasound parameters, an accurate understanding of ethnic-specific variations for both healthy and diseased individuals is important.

We hypothesized that the early renal function deterioration is better evaluated by assessing renal cortical and parenchymal thicknesses than by traditional parameters, such as RL. We also hypothesized the possibility of comorbidity-related changes in renal cortical thickness (RCT). Thus, the main objective of this study was to identify the diagnostic performance of ultrasound parameters (e.g., absolute RL, relative RL, RCT, and renal PT) in the diagnosis of early and severe stages of CKD. We also evaluated the renal ultrasonic parameters to identify the following associations: between renal function and renal ultrasonic parameters (absolute RL, relative RL, RCT, and renal PT); between RCT and the severity of CKD; and between RCT and common associated comorbidities (such as etiological factors of CKD).

Methods

Following approval by the Ethical Review Committee of the Faculty of Medicine, University of Ruhuna (approval

reference No. 19.12.2016: 3.8), this descriptive cross-sectional, prospective, observational study was conducted at the Radiology Unit of Base Hospital Tissamaharama, Sri Lanka, from March 2017 to March 2018 and followed the principles of the contemporary revision of the Declaration of Helsinki. Before data collection, informed written consent obtained from all the studied patient participants. The eligible population presenting during the study period was incorporated as the study sample. All the patients ($n = 961$) who presented for renal ultrasound scan during the study period, with various indications, were screened to identify their eligibility. From these, adult patients diagnosed with CKD ($n = 100$) were recruited using convenience sampling of consecutive patients after excluding the following conditions: those <18 years old, with past history of renal surgery, currently diagnosed with either acute renal insufficiency or on renal replacement therapy (hemodialysis and peritoneal dialysis), history of renal transplantation, patients with obstructive uropathy, renal calculi disease, diagnosed fatty liver or chronic liver disease, and those unwilling to participate. Diagnosis of CKD in all patients was made by a physician according to the standard diagnostic guidelines [16]. Their sociodemographic data such as age, sex, height, weight, and associated comorbidities were recorded. For standardization, the Scr level was recorded if it was assessed within the past 3 months, at the day lab of the Base Hospital Tissamaharama. The Jaffe method used to calculate the Scr levels and the following procedure was performed to standardize the Scr measurements: the lab measurements were regularly validated against standard strength solutions and showed no deviations around the levels of clinical importance.

Definition and classification of CKD

Renal function expressed as glomerular filtration rate (eGFR) was calculated using CKD Epidemiology Collaboration equation (CKD-EPI) and a modified Modification of Diet in Renal Disease Study (MDRD) formula. eGFR was expressed in mL/min/1.72 m² body surface area. CKD was defined when eGFR < 60 mL/min/1.72 m² for more than 3 months and with structural or functional abnormality other than the abnormal eGFR [16]. CKD was categorized according to eGFR using the MDRD formula [16]. To avoid bias, patient clinical details or ultrasound findings were not available during such categorization.

Ultrasound protocol

Ultrasound scans were performed by a single experienced radiologist, who was blinded to the patient's Scr levels and

CKD grade. A Mindray DC 60 ultrasound unit (released to the market in December 2016) was used with 3.5 MHz curved array transducer: grayscale amplification and a time gain compensation curve were adjusted to acquire the best quality images, the single focus point was adjusted at the level of the kidney, while routinely using tissue harmonic effects. All subjects were well hydrated and with a full urinary bladder when they scanned. The right kidney scanned in left lateral recombinate position and vice versa for the left kidney.

Ultrasound renal measurements obtained from a frozen image: pole-to-pole length or the absolute RL measured to the nearest millimeter (**Figure 1A**), the renal PT was measured from the renal hilar fat-parenchymal interphase to the maximum outer convex border of the kidney, to the nearest 0.1 mm. RCT was measured over a medullary pyramid, from the corticomedullary interphase to the renal capsule, perpendicular to the renal capsule, to the nearest 0.1 mm (**Figure 1B**). Both parenchymal and cortical thicknesses were measured in the mid-region of the kidney, parallel to each other and perpendicular to the longitudinal renal measurement using a magnified frozen image. All ultrasound measurements were recorded 3 times, and the average of these was taken for

calculations. The relative RL was calculated: the absolute length (in mm) divided by the height of the patient (in cm); expressed in mm/cm.

Statistical analyses

Data analysis was conducted with IBM SPSS Statistics for Windows (version 20). Continuous variables are reported as mean (standard deviation (SD)); categorical variables are reported as percentages. Normally distributed variables were compared between groups (diabetic, nondiabetic, and cardiovascular groups) using independent and paired-sample *t* tests, Pearson correlation coefficients, and χ^2 analysis. Receiver operating curve (ROC) analyses were conducted to determine the diagnostic performance of the various tests in predicting the renal function abnormality; results are expressed as area under the curve (AUC) with 95% confidence interval (CI). Cutoff values were calculated using ROC analysis. Sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) were calculated for each cutoff value. Because ultrasound scan results of all participants were available, no analysis for missing data was necessary. For all analysis, $P < 0.05$ was considered as significant.

Results

The study recruited adult patients diagnosed with CKD ($n = 100$); of whom 30% were female (**Table 1**). Their mean age (SD) was 68 (8) years, and ranged from 50 to 89 years. Scr was 1.88 (0.60) mg/dL and ranged 4.4–1.3 mg/dL; eGFR was 43.3 (11.85) mL/min/1.72 m²; eGFR ranged 60–16. Bland–Altman plot analysis was performed to compare the accuracy of eGFR

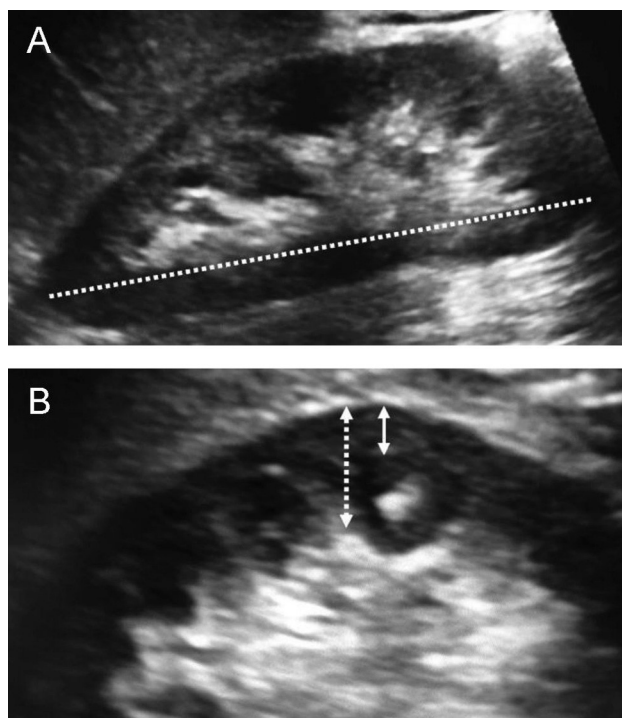


Figure 1. Representative ultrasound images of the kidney. **A.** Showing absolute renal length (RL) measurement. The white dotted line indicates the absolute RL. **B.** Showing cortical and parenchymal thickness measurements. The white dotted arrow indicates the renal parenchymal thickness; white solid arrow indicates renal cortical thickness.

Table 1. Baseline parameters of male and female patient populations

Parameter	Male (n = 70)	Female (n = 30)
Age (years)	67 (9)	68 (9)
Serum creatinine (mg/dL)	1.91 (0.66)	1.78 (0.46)
eGFR (mL/min/1.72 m ²)	46.4 (12.0)*	36.2 (7.8)
Absolute length (cm)		
Right kidney	9.0 (0.81)	8.9 (0.99)
Left kidney	9.1 (0.84)	8.9 (0.99)
Relative length (mm/cm)		
Right kidney	0.57 (0.05)	0.60 (0.06)
Left kidney	0.57 (0.05)	0.60 (0.06)

Results are expressed as mean (standard deviation); eGFR: estimated glomerular filtration rate.

* $P = 0.031$.

measurements calculated using MDRD and CKD-EPI equations. Because equal accuracy was found for calculating eGFR by either MDRD or CKD-EPI equations (bias -1.36 ; precision 1.642 ; 95% CI 1.86 to -4.58); the MDRD equation was used for further analysis. The Scr levels in male and female patients were not significantly different, but compared with men, women were found to have a significantly lower eGFR (**Table 1**). The severity of CKD in patients included in the study group was as follows: 11% in CKD grade 2; 35% in grade 3a; 39% in grade 3b; 15% in grade 4; 0% in grade 5. The vast majority of CKD patients (88%) were diagnosed to have one or more associated comorbidity; hypertension being the most frequent ($n = 72$), followed by DM ($n = 46$); the remaining reported comorbidities were ischemic heart disease ($n = 13$), bronchial asthma ($n = 3$), hypothyroidism ($n = 2$), and rheumatoid arthritis ($n = 1$).

Table 1 shows absolute and relative RL distribution according to sex. Regardless of sex, no significant difference was found in either absolute or relative RLs of either kidney. **Table 2** compares the ultrasound parameters of right and left kidneys. Although the absolute RL difference between the right and the left kidney was not significant; the PT ($P < 0.001$) and the RCT ($P < 0.05$) differences were significant. The relative RLs of the right and left kidneys showed an equivalent value.

Table 3 shows the correlations between index renal ultrasound parameters and biochemical parameters. Absolute RL, relative RL, and renal PT showed a weak negative correlation with Scr ($P > 0.05$); by contrast, RCT showed a weak negative correlation with Scr ($P = 0.043$). Although there was a weak correlation between absolute RL, relative RL, and eGFR; there was a positive correlation between PT ($P = 0.01$), cortical thicknesses ($P = 0.002$), and eGFR.

To diagnose early CKD, we evaluated the diagnostic performance of renal ultrasound parameters (absolute RL, relative RL, RCT, and renal PT) and serum creatinine, considering eGFR of $60 \text{ mL/min/1.72 m}^2$ as the cutoff value (**Figure 2**). RCT (AUC 0.741 ; 95% CI 0.623 – 0.859) and the renal PT (AUC 0.735 ; 95% CI 0.624 – 0.845) showed a better diagnostic performance than the rest of the ultrasound parameters studied; but Scr (AUC 0.028 ; 95% CI <0.001 – 0.058), absolute RL (AUC 0.628 ; 95% CI 0.499 – 0.757), and relative RL (AUC

0.570 ; 95% CI 0.424 – 0.717) showed limited diagnostic performance. The calculated cutoff value for renal PT was 1.4 cm (30% specificity and 82% sensitivity; 68% PPV); and for RCT was 6.1 mm (48% specificity and 82% sensitivity; 51% PPV). Because the study group contained only diseased patients, NPVs above cutoff values were not calculated.

Similarly, the diagnostic performance of the same parameters was assessed to diagnose severe CKD, considering eGFR of $45 \text{ mL/min/1.72 m}^2$ as the cutoff value: the absolute RL (AUC 0.809 ; 95% CI 0.664 – 0.955) performed better than relative RL (AUC 0.794 ; 95% CI: 0.593 – 0.994); PT (AUC 0.570 ; 95% CI 0.179 – 0.962), RCT (AUC 0.572 ; 95% CI 0.213 – 0.932), and Scr (AUC 0.442 ; 95% CI 0.140 – 0.744). Cutoff values calculated for absolute and relative RLs were 9.5 cm (specificity 26% and 67% sensitivity; 45% PPV; 13% NPV) and 0.6 mm/cm (specificity 31% and 67% sensitivity, 40% PPV, 17% NPV) respectively.

The present study evaluated the following associations: first, that between RCT and the severity of CKD; second, that between RCT and commonly associated comorbidities, such as diabetic and cardiovascular diseases. For such evaluations, a RCT of 6 mm was considered as the reference value [4]. We found a progressive thinning of renal cortex with the progression of CKD ($\chi^2 = 12.34$, $P < 0.05$): all (100%) patients with

Table 2. Ultrasound parameters of right and left kidneys

Parameter	Right kidney	Left kidney
Absolute renal length (cm)	9.06 (0.87)	9.07 (0.89)
Relative renal length (mm/cm)	0.58 (0.05)	0.58 (0.05)
Renal parenchymal thickness (cm)	1.29 (0.23)**	1.35 (0.25)
Renal cortical thickness (cm)	0.59 (0.1)*	0.61 (0.1)

Parameters are expressed as mean (SD).

* $P = 0.029$, ** $P < 0.001$.

Table 3. Correlations between age, renal ultrasound measurements, eGFR, and serum creatinine

Parameter	Serum creatinine		eGFR	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Age	−0.129	0.19	0.033	0.75
Absolute renal length				
Right kidney	−0.166	0.10	0.241	0.02*
Left kidney	−0.098	0.33	0.204	0.054
Mean right and left kidneys	−0.138	0.20	0.212	0.03*
Relative renal length				
Right kidney	−0.179	0.25	−0.09	0.51
Left kidney	−0.111	0.08	−0.06	0.88
Mean right and left kidneys	−0.154	0.16	0.028	0.75
Parenchymal thickness				
Right kidney	−0.130	0.20	0.265	0.01*
Left kidney	−0.115	0.25	0.233	0.02*
Mean right and left kidneys	−0.129	0.18	0.264	0.01*
Cortical thickness				
Right kidney	−0.178	0.08	0.274	0.01*
Left kidney	−0.191	0.06	0.275	0.01*
Mean right and left kidneys	−0.202	0.043*	0.300	0.002*

eGFR, estimated glomerular filtration rate.

* $P < 0.05$.

CKD grade 2 had normal RCT compared with patients with CKD grade 4 (33% had normal thickness; **Figure 3**). The RCT difference between patients in the DM and non-DM groups was significant ($\chi^2 = 14.72$, $P < 0.05$): 77% of patients in the DM group had normal RCT; whereas, 51% of patients in the non-DM group had a normal RCT (**Figure 4A**). Patients in the group with cardiovascular disease (ischemic heart disease and hypertension) had thinner renal cortices ($\chi^2 = 14.32$, $P < 0.05$) compared with those in the group without cardiovascular disease (**Figure 4B**): 64% of those in the group with cardiovascular disease had normal RCT; whereas, 75% of those in the group without cardiovascular disease had normal RCT.

Discussion

Considering the priority for early diagnosis and prompt management of CKD to retard the progression of the disease, we aimed to evaluate selected noninvasive diagnostic tools for early CKD diagnosis [1, 2, 17, 18]. The findings of the present study support our suggested hypothesis that early renal function deterioration is better evaluated with renal cortical and parenchymal thicknesses than traditional parameters. By contrast, absolute and relative RLs were better for predicting late CKD.

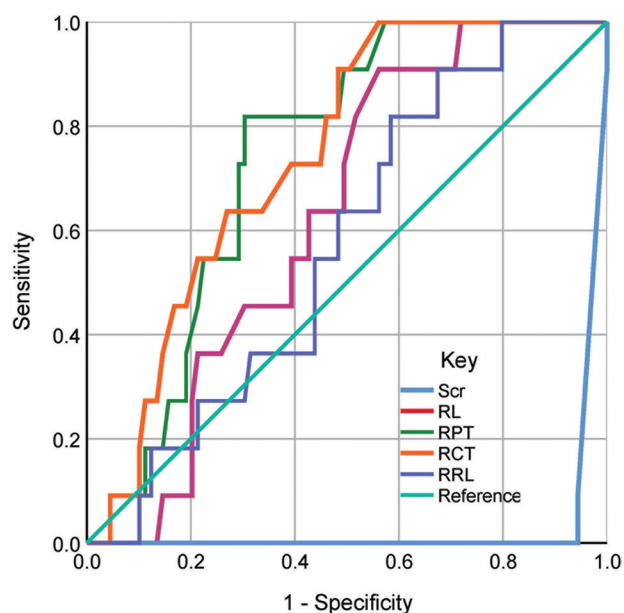


Figure 2. Receiver operating characteristic curves of sonographic parameters and serum creatinine level in predicting early chronic kidney disease. RL, absolute renal length; RPT, renal parenchymal thickness; RRL, relative renal length; RCT, renal cortical thickness; Scr, serum creatinine level.

Our secondary hypothesis was that we could identify a comorbidity-related change in renal cortical thicknesses. Prolonged diabetes and ischemic renal conditions (such as

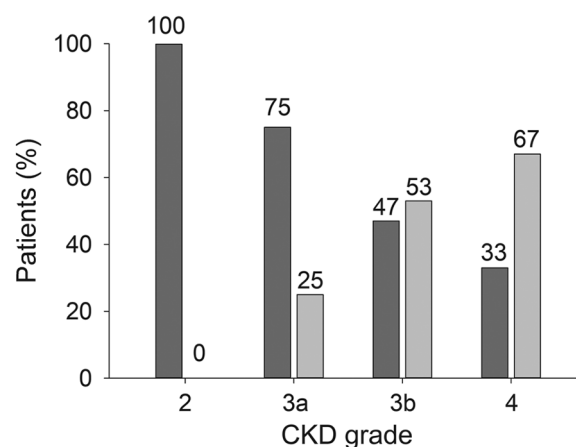


Figure 3. Renal cortical thicknesses in different chronic kidney disease (CKD) grades. Dark gray bar ≥ 6.0 mm; light gray bar < 6.0 mm.

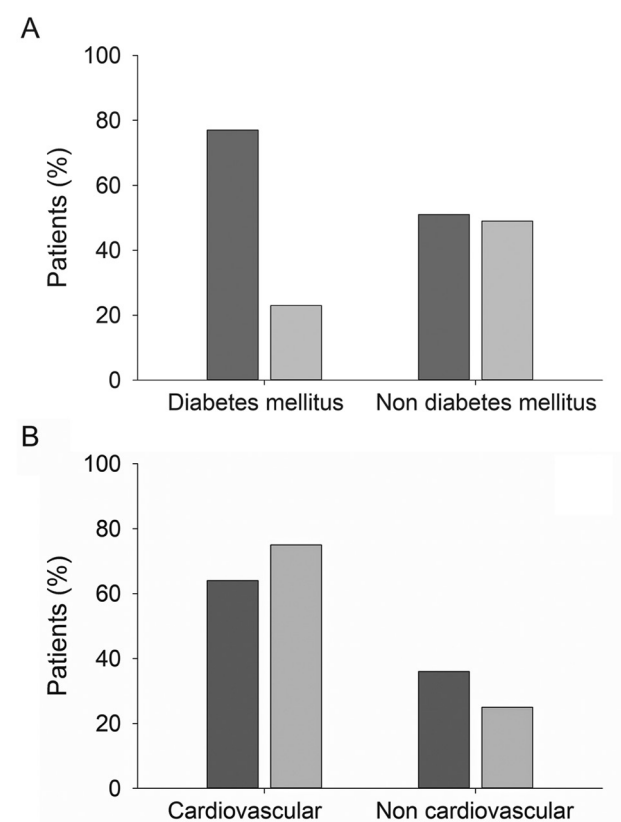


Figure 4. Renal cortical thicknesses. **A.** In groups of diabetic and nondiabetic patients with chronic kidney disease. Dark gray bar ≥ 6.0 mm; light gray bar < 6.0 mm. **B.** In groups of patients with cardiovascular and without cardiovascular disease, but both with chronic kidney disease. Dark gray bar ≥ 6.0 mm; light gray bar < 6.0 mm.

ischemic heart disease and hypertension) are recognized major etiological factors of CKD, which emphasizes the need for early diagnosis of diabetic and ischemic nephropathy. Previous studies evaluated kidneys of diabetic patients (DM) using renal biopsies and described a dynamic change in renal size including renal enlargement in early DM, followed by a progressive reduction in renal size [3, 19, 20]. Nevertheless, only a few preliminary ultrasound studies, which were with several limitations, were available for noninvasive assessment [7, 8]. Korkmaz et al. separated patients with CKD into 2 groups: “DM” (n = 4) and “DM with hypertension” (n = 2) and reported a low incidence of renal parenchymal atrophy in patients with “DM.” However, the small sample size of their study is a noteworthy limitation [7]. The high proportion of patients with diabetic nephropathy is a probable reason for higher mean RCT measurements (6 mm) and high cutoff value (6.1 mm) to diagnose early CKD [4].

By contrast with DM, thin renal cortices were reported in conditions of renal ischemia, such as in renal artery stenosis (computed tomographic (CT) study) [12]. Use of CT in renal assessment is more restricted than ultrasonography because of ionizing radiation, less availability, and the high cost of CT [21]. Therefore, ultrasonographic renal assessment as a noninvasive tool has not been challenged. In agreement with previous studies, we found a distinct comorbidity-related change in RCT: thick renal cortices in patients DM and thin renal cortices in those with hypertension.

An effective screening procedure would accomplish early CKD diagnosis. In addition to early diagnosis, a successful screening procedure would provide a better patient outcome at a low cost. Patients with asymptomatic CKD, identified in a population-based screening program, can be referred for more invasive (biochemical and histological) investigations [22]. Although renal cortical and parenchymal thicknesses are noninvasive reproducible ultrasound parameters, to our knowledge, they were never previously evaluated as a screening tool [7–10]. The high sensitivity and specificity of the cutoff values of renal cortical and parenchymal thicknesses (of early CKD patients) accomplish the criteria of an ideal screening tool [23]. However, considering the influence of comorbidity on RCT, further studies are recommended to establish comorbidity-specific cutoff values. Because renal cortical and parenchymal thicknesses had shown a reciprocal correlation to disease severity, even before establishing disease-specific cutoff values, they can be used to monitor the progression of early CKD.

For several reasons, renal cortical and parenchymal thicknesses are not recommended for monitoring patients with severe CKD. First, because of the low diagnostic performance of renal cortical and parenchymal thicknesses. Second,

because of the low measurement accuracy: increased renal cortical echogenicity and poor corticomedullary demarcation obliterate the renal sinus fat-parenchymal and corticomedullary interphase leading to measurement difficulties [14, 15].

The mean absolute RL reported for the study population (right kidney 9.06 cm and left kidney 9.07 cm) was lower than that of a similarly aged healthy Sri Lankan population (9.47 cm) [24]. Even though a high diagnostic performance is reported for both absolute and relative RLs, such parameters are not recommended as screening tools to assess individuals with severe CKD due to low sensitivity, and the low positive and negative predictability of their cutoff values. Additionally, the relatively straightforward diagnosis of severe CKD using biochemical markers lowers the requirement for a screening tool.

Compared with absolute RL, relative RL has been described as a better parameter with which to assess renal size by considering the low sex and height variability [3, 14, 25]. However, we could not delineate a specific diagnostic advantage of relative RL over the absolute RL. In addition, the time needed to calculate the relative RL (relative RL = absolute RL/patient’s height) would hamper its use in busy clinics. Therefore, absolute RL is a more practical option for identifying individuals with severe CKD. Nevertheless, it needs to be stressed that the RL would not be useful as a screening tool.

The present study is in agreement with previous studies reporting the limited diagnostic performance of Scr, for both early and severe CKD [1, 26]. Because the studied ultrasound parameters have also shown several limitations, such as the influence of associated comorbidity; a collective interpretation of both biochemical and ultrasound findings would provide a better picture of any renal function abnormality.

Ultrasound measurement of renal cortical and parenchymal thicknesses have reported a fair accuracy with low interobserver variations [9]. The interobserver variation has been further minimized in the present study by employing an experienced radiologist to obtain all the measurements. However, validating the renal measurement accuracy by employing more than one radiologist would provide an even more accurate methodology. Other strengths of the present study are: adequate sample size; demonstration of fair weightage for each studied renal ultrasound parameter in different stages of CKD; identification of the comorbidity related changes in RCT. While being a pioneer study to describe renal cortical and parenchymal thicknesses for a Sri Lankan population with CKD, this study has several limitations. First, the duration of comorbidities was not considered in calculations, which explains the observed weak correlations between ultrasound parameters and renal function. Second, the study was limited to a

single geographical region in Sri Lanka, and therefore, would not represent the entire Sri Lankan population. Nevertheless, the reported comorbidity dependency in ultrasonic renal parameters is a timely stimulus for further studies, to strengthen the clinical significance and to establish comorbidity-specific cutoff values.

Conclusion

Each studied ultrasonic parameter demonstrated a reasonably defined role in determining different stages of CKD: renal cortical and parenchymal thicknesses are valuable to identify early stage disease, while the absolute RL is of value for identifying severe CKD. An individualized approach is prudent when selecting ultrasonic parameters to assess CKD, and should be done by taking into account the disease stage and the associated comorbidities. Interpreting ultrasound and biochemical investigations collectively would further improve their diagnostic accuracy for renal function abnormality.

Author contributions. All authors contributed substantially to the conception and design of the study. DTKG and IK contributed substantially to the collection of data, and all authors contributed substantially to its analysis and interpretation. All authors contributed substantially to drafting and critical revision of the manuscript, approved the final version submitted for publication and take responsibility for statements made in the published article.

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Conflicts of interest statement. Each author has completed and submitted an International Committee of Medical Journal Editors Uniform Disclosure Form for Potential Conflicts of Interest. None of the authors has any potential or actual conflict of interest concerning the published article to disclose.

Data sharing statement. The data sets generated or analyzed during the present study are included in this published article. Data that support the findings of this study are also available in figshare, with doi: 10.6084/m9.figshare.13100627; and all data are available from the corresponding author on a reasonable request after deidentification of data from any person whose data was included in the study.

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