Original Paper

Quantitative Renal Echogenicity as a Tool for Diagnosis of Advanced Chronic Kidney Disease in Patients with Glomerulopathies and no Liver Disease

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Key Words

Chronic renal failure • Glomerular disease • Ultrasound

Abstract

Background/Aims: Glomerulopathy patients are prone to developing transitory reduced glomerular filtration rate (GFR), which can be difficult to differentiate from irreversible chronic kidney disease (CKD). Renal ultrasound can be useful, but differently from renal length, quantitative renal echogenicity has not been formerly evaluated regarding its capacity to identify irreversible advanced CKD. **Methods:** A prospective study was performed, where quantitative renal echogenicity was performed during renal biopsy in patients with suspected glomerular disease (n=197). Quantitative echogenicity was measured as the inverse of the ratio between the mean pixel densities of the renal cortex and adjacent liver using ScionImage software. Patients were followed during a six-months period to ascertain irreversible advanced CKD. Quantitative renal echogenicity and histopathology parameters discriminatory capacity were compared regarding their capacity to detect advanced and irreversible CKD - estimated GFR less than 30mL/min/1.73m² confirmed after a six-month follow-up. **Results:** At renal biopsy, the mean eGFR was 53.9±33.6 mL/min/1.73m² and 63 (32.0%) patients had an eGFR less than 30 mL/min/1.73m². Mean kidney/liver echogenicity ratio was 1.06±0.19 and it was inversely correlated with eGFR at follow-up (r=-0.684, p<0.001). Multivariate analysis was performed to create a histopathology index that correctly identifies irreversible advanced CKD. Renal echogenicity discriminatory capacity to identify irreversible advanced CKD was 0.793 (0.719 -0.867), similar to the histopathology index. Elevated renal echogenicity with best discriminatory capacity was a kidney/liver ratio greater than 1.15. This cutoff had a predictive positive value of 92% in patients with eGFR less than 30mL/min/1.73m².

Conclusion: Quantitative renal echogenicity can be a useful tool in patients with glomerular disease and normal kidney size (>8cm) to identify those patients with irreversible advanced CKD.

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Introduction

In adult glomerular disease, kidney biopsy is mandatory for the diagnosis and assessment of “lesion chronicity”, i.e. whether the lesion is or not reversible or treatable. As glomeruli become scarred, there is consequent atrophy of the remainder of the nephron with interstitial fibrosis, and the degree of chronic irreversible damage is generally assessed based on the amount of tubular atrophy/interstitial fibrosis. Although histological evaluation is recommended, there is a concept of “point of no return”, where extensive and irreversible kidney scarring indicates immunosuppressive therapeutic ineffectiveness [1]. The “point of no return” is currently defined as an estimated glomerular filtration rate (eGFR) less than 30mL/min/1.73m² and irreversible lesions in renal histology [1].

Although it is almost a universal consensus not to perform kidney biopsy in patients with GFR < 30mL/min and a reduced kidney size, many patients with advanced chronic kidney disease due to glomerular disease can have normal kidney length [2]. In these patients, it is a clinical challenge to differentiate patients with mainly irreversible chronic lesions from those with reversible reduced glomerular filtration rate (GFR) due hemodynamic alterations, for example.

In the setting of renal failure, sonographic evaluation is largely used in clinical practice [3]. In addition to excluding obstructive and cystic nephropathies, the sonographic assessment can provide information about renal size and parenchymal thickness, indicating irreversible chronic kidney disease. Another sonographic feature believed to be associated with irreversible renal lesions is echogenicity. However, there is little information about patients with renal echogenicity alterations only [4].

Few studies have evaluated the correlation between renal echogenicity and irreversible renal failure [5-8]. Also, Hricak et al [9] disclosed a correlation between renal echogenicity with tubular atrophy, glomerular sclerosis, hyaline casts and leukocyte infiltration. However, renal echogenicity in these studies was assessed qualitatively by the human eye, which is very unreliable. In 2001, Manley and O'Neill described a quantitative method to assess renal cortex echogenicity in relation to that of the liver [10]. Subsequently, the same group correlated renal cortex echogenicity with histopathological findings [2]. Increased renal echogenicity was mainly determined by tubular atrophy and interstitial inflammation. In this same study, the authors concluded that a reduced kidney length combined with a renal cortex echogenicity greater than that of the liver was associated with severe chronic kidney disease. However, the study design limits its clinical applicability when using renal echogenicity to determine lesion reversibility due to: (1) advanced CKD definition was based on histological parameters; (2) its cross-sectional design and (3) lack of data about GFR.

In the present study, we aimed to evaluate the performance of quantitative renal echogenicity in predicting irreversible advanced CKD in patients with glomerulopathy in whom any therapy will be needless and potential harmful. To answer this question, we performed a renal sonography concomitantly with a renal biopsy and followed these patients for 6 months to confirm or not the presence of advanced and irreversible CKD.

Materials and Methods

Subjects

This was a prospective study performed from October 2010 through July 2013. All adult patients (age > 18 years) submitted to native renal biopsy due to glomerular diseases were included. Renal biopsy indications

for glomerular disease in our service are: unexplained 24h-urine protein excretion rate greater than 1 g and unexplained renal injury associated with hematuria or any degree of proteinuria. Because only few patients were submitted to renal biopsy due to unexplained AKI without alterations suggesting glomerular disease (n=8), they were excluded. Also, patients with advanced renal disease (glomerular filtration rate less than 30 mL/min/1.73m²) associated with combined renal length less than 16 cm were not routinely considered for renal biopsy. In patients submitted to more than one renal biopsy, only the first one was considered. Patients with known liver disease were excluded. All renal biopsies were indicated after independent nephrology consultation. The Institutional Ethical Committee approved this study and informed consent was applied.

Clinical and Laboratory Data

Laboratory data about renal function, 24h-urine protein excretion rate, and serum albumin were collected from patients on the three days before and between three and six months after the renal biopsy was performed. Patients were considered as having irreversible advanced CKD if they had: eGFR less than 30mL/min/1.73m² at renal biopsy which was maintained after a six-months follow-up. Patients with eGFR less than 30 mL/min/1.73m² at renal biopsy, but not at 6 months of follow-up were considered as having AKI or acute-on-CKD. Patients with an eGFR higher than 40 mL/min/1.73m² at renal biopsy and less than 30mL/min/1.73m² after three to six months were considered as rapid progression and not as irreversible advanced CKD. Patients in whom it was not possible to perform this evaluation due to unavailable data about renal function were excluded. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI equation [11].

Histopathological Evaluation

Tissue specimens for light microscopic examination were immersed in formalin, dehydrated in graded alcohols, cleared in xylene, and infiltrated with paraffin using automated procedures. Paraffin-embedded tissues were cut into 3-micron slices and stained with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS) reagent, Masson's trichrome, and Jones' methenamine silver stain. Each biopsy contained at least 12 glomeruli. Biopsies were evaluated regarding 4 parameters: (1) glomerular sclerosis, (2) tubular atrophy, (3) interstitial fibrosis, and (4) inflammatory infiltrate. Each parameter was measured in every biopsy using a semiquantitative grading scale ranging from 0 to 4, where a score of 0 signified that 5% or less of the biopsy specimen was affected; a score of 1, between 6% and 25%; a score of 2, between 26% and 50%; a score of 3, between 51% and 75%; and a score of 4, greater than 75%.

Sonographic Evaluation

Patients underwent ultrasound-guided renal biopsy. Prior to the procedure, patients were submitted to food and water deprivation for 8 hours. All sonograms were performed using a PICO Mycolor 202 system (Medison CO LTD, Seoul, Korea) using a 5.0 MHz wide-frequency band and a phased array probe. Output was onto thermal printer paper. All studies were performed immediately before renal biopsies performed by a single nephrologist responsible for the procedures. Kidney length was determined as the maximum longitudinal dimension and parenchymal thickness was determined as the shortest distance from the renal sinus fat to the renal capsule. These parameters were measured at the time of the sonogram. The investigator performing these measurements was blinded to pathological findings. These measurements were made on the kidney that was biopsied. Echogenicity was quantified as previously described [10]. Briefly, echogenicity was measured as the inverse of the ratio between the mean pixel densities of the renal cortex and adjacent liver using ScionImage software (Scion Corp., Frederick, MD, USA) after images were stored in tag format. Because comparison to the liver is required, echogenicity was analyzed only in the right kidney. For each patient, three different area from kidney and liver were selected. Each sonographic parameter was measured by a single investigator to avoid interobserver variability.

Statistical Analysis

Analysis was performed using SPSS 19.0 for Windows. All variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally or near-normally distributed variables are reported as means with standard deviations (SD). Categorical data were reported as proportions and compared using Fisher's exact test. Univariate analysis is shown as Pearson's or Spearman's coefficient when indicated.

Discrimination was assessed by the area under the receiver operator characteristic (AuROC) curve and comparison of discriminatory capacity was performed using the non-parametric method. For each predictor parameter, cutoff points were chosen according to the highest Youden index, which was calculated as $[1 - (1 - \text{sensitivity}) + (1 - \text{specificity})]$. Sensitivity, specificity, positive and negative predictive values are expressed as percentage. A backward stepwise multivariate regression was performed to identify the independent histopathological parameters were associated with advanced CKD. Data are shown as odds ratios (OR) with 95% confidence intervals (CI). A p-value < 0.05 was considered statistically significant for all comparisons.

Results

Subjects Characteristics

A total of 255 renal biopsies were performed in native kidneys. After exclusions (figure 1), 197 patients were included in the final analysis. There was a predominance of females (56.9%) and the mean age was 39.0 ± 16.1 years. Renal biopsy diagnoses are disclosed in table 1. In relation to renal function at renal biopsy, the mean eGFR was 53.9 ± 33.6 mL/min/1.73m² and 63 (32.0%) patients had an eGFR less than 30 mL/min/1.73m².

After the follow-up period, 54 (27.4%) patients were considered as having irreversible advanced CKD (eGFR less than

Fig. 1. Flow-chart of patients.

Table 1: Glomerulopathy diagnosis.

Diagnosis	Number
Focal Segmental Glomerulosclerosis	35
Lupus Nephritis	34
Advanced, indeterminate disease	28
Minimal Lesion	18
Crescentic pauci-immune Glomerulonephritis	16
Membranous Glomerulonephritis	18
Iga Nephropathy	12
Diffuse Acute Glomerulonephritis	09
Membranoproliferative Glomerulonephritis	07
Diabetic Nephropathy	07
Thrombotic Microangiopathy	07
Other	06

Table 2. Spearman correlation coefficients for the relationships between cortical echogenicity and pathologic parameters

Histopathology Parameter	Correlation	p
Tubular Atrophy	0.402	<0.0001
Interstitial Fibrosis	0.211	0.005
Sclerosed Glomeruli	0.254	<0.0001
Inflammatory Infiltrate	0.264	<0.0001

30 mL/min/1.73m²) and among these patients, seven had an eGFR between 30-40mL/min at the renal biopsy. Seventeen patients recovered renal function, at least partially.

Histopathology and Sonographic Evaluation

Patients had a mean renal length of 10.3±1.12 cm and a mean parenchymal thickness of 16.4±0.5 mm. Mean kidney/liver echogenicity ratio was 1.06±0.29. In relation to histopathological parameters used to evaluate chronicity, some degree of interstitial fibrosis was disclosed in 66 (33.5%) patients, tubular atrophy in 70 (35.5%) and inflammatory infiltrate in 53 (26.9%). Eighty-three patients (42.1%) had more than 30% of globally sclerosed glomeruli.

As expected, there was a positive correlation between all histopathological parameters evaluated. The strongest correlation was found between interstitial fibrosis and tubular atrophy ($r=0.697$, $p<0.001$) and the weakest was found between sclerosed glomeruli and inflammatory infiltrate ($r=0.273$, $p<0.001$). Renal echogenicity was inversely correlated with renal length ($r=-0.266$, $p<0.001$), but not with parenchymal thickness ($r=-0.062$, $p=0.429$). Renal echogenicity correlated with all histopathological parameters (table 2). Moreover, renal echogenicity was directly correlated with 24h-proteinuria ($r=0.216$, $p=0.008$) and inversely with eGFR at follow-up ($r=-0.684$, $p<0.001$) and serum albumin ($r=-0.201$, $p=0.011$).

Histopathology Parameters and Advanced Irreversible Chronic Kidney Disease

Initially, each histopathological parameter was evaluated separately in relation to its discriminatory capacity to identify advanced CKD (table 3). Generally, they had moderate to good discriminatory capacity and similar capacity when compared to each other. The only trend in statistical difference was between the discriminatory capacities of interstitial fibrosis and tubular atrophy ($p=0.050$). The score with best discriminatory capacity was grade 3 or higher in all histopathological parameters and more than 30% of sclerosed glomeruli. These scores were used to calculate sensitivity, specificity, positive and negative predictive values for each parameter, as shown in Table 3.

In an attempt to analyze the entire renal histopathological capacity to identify advanced CKD and because the histological parameters were strongly linked, multivariate analysis was performed to determine their relative contributions in determining advanced CKD - Table 4. Only interstitial fibrosis and inflammatory infiltrate remained as significant independent predictors. They had similar standardized Beta coefficient values, so we calculated a combined index with equal contribution by interstitial fibrosis and inflammatory infiltrate (IF/II index). Even after calculating this composite index, it did not show a better performance than interstitial fibrosis alone - table 3.

Fig. 2. Discriminatory capacity of quantitative renal echogenicity in identifying advanced chronic kidney disease.

*Cortical
Echogenicity
and Advanced
Irreversible
Chronic
Kidney
Disease*

Renal echogenicity discriminatory capacity to identify advanced and irreversible CKD is shown in figure 2. Elevated renal echogenicity with best discriminatory capacity was a kidney/liver ratio

greater than 1.15. Using this cutoff, 65 (33.0%) patients had elevated renal echogenicity. Renal echogenicity had a moderate sensitivity and good specificity in identifying advanced CKD. In comparison to histopathological parameters, it had a better sensitivity than tubular atrophy and inflammatory infiltrate, but was worse than sclerosed glomeruli percentage and interstitial fibrosis. As expected, the opposite was verified in relation to specificity – table 3

We also compared cortical echogenicity performance against IF/II index (a general score developed to include significant histopathological parameters). They had very similar discriminatory capacity – table 3. Except by the better, but not statistically significant, sensitivity of the IF/II index, renal echogenicity was comparable to this histopathology index.

One of the most important parameters influencing clinical decision in this setting is the capacity to ascertain that patients with a higher cortical echogenicity most certainly have advanced and irreversible CKD; otherwise, these patients would be incorrectly excluded from renal biopsy. This capacity means a higher predictive positive value (PPV). Renal cortex echogenicity had a regular PPV, only 63.8% [50.1-76.0], but higher than that of histopathological parameters, except for inflammatory infiltrate, with a PPV of 71.4% [47.8 – 88.6] – table 3.

When analyzing only patients with eGFR less than 30 mL/min/1.73m² at the renal biopsy, the PPV increased to 92.1% [75.6 -98.7]. In fact, in this subgroup, only three patients with increased renal echogenicity did not have advanced CKD confirmed after a 6 months follow-up: two patients had an eGFR between 30-40 mL/min/1.73m² and another one had an eGFR close to 50mL/min/1.73m².

Table 3. Discriminatory capacity, sensitivity, specificity, predictive positive and negative values of each simple or combined histopathology parameter and renal echogenicity. IF/II index: composite index adding interstitial fibrosis and inflammatory infiltrate

Parameter	AuROC	Sensitivity (%)	Specificity (%)	Predictive positive value (%)	Predictive negative value (%)
Tubular atrophy	0.694 [0.593 – 0.795]	36.8 [21.8 – 54.0]	91.8 [86.0 – 95.9]	56.0 [34.9 – 75.6]	83.9 [77.0 – 89.4]
Interstitial fibrosis	0.783 [0.707 – 0.879]	82.5 [67.2 – 92.6]	70.3 [61.9 – 77.8]	44.6 [33.0 – 56.6]	93.3 [61.9 – 77.8]
Sclerosed glomeruli	0.712 [0.618 – 0.805]	70.4 [54.8 – 83.2]	49.7 [40.7 – 57.9]	30.7 [21.9 – 40.7]	83.9 [74.1 – 91.2]
Inflammatory infiltrate	0.740 [0.640 – 0.839]	39.5 [24.1 – 56.6]	95.6 [90.4 – 98.3]	71.4 [47.8 – 88.6]	85.0 [98.3 – 90.2]
IF/II index	0.797 [0.718 – 0.876]	84.6 [71.8 – 93.1]	72.7 [64.6 – 79.8]	53.0 [41.7 – 64.0]	92.8 [86.4 – 96.7]
Renal echogenicity	0.793 [0.719 – 0.867]	68.5 [54.4 – 80.5]	85.3 [78.4 – 90.7]	63.8 [50.1 – 76.0]	87.8 [81.1 – 92.7]

Table 4. Multivariate analysis with advanced chronic kidney disease after 6 months follow-up as the dependent variable

	Standardized Beta coefficient	95%CI	p
Tubular Atrophy	0.863	0.471 – 1.583	0.635
Interstitial Fibrosis	3.026	1.655 – 5.532	<0.001
Sclerosed Glomeruli	1.008	0.902 – 1.029	0.158
Inflammatory Infiltrate	2.803	1.788 – 4.396	<0.001

Renal Echogenicity, Crescent Lesions and Advanced Irreversible Chronic Kidney Disease

In the studied population, 33 (16.7%) patients had more than 20% of glomeruli with crescent lesions. In this subpopulation, 11 (33.3%) patients had advanced CKD. Again, renal echogenicity had a good discriminatory capacity to detect advanced CKD - AuROC: 0.872 [0.736 – 1.000] and a PPV of 72.7% - while IF/II index had an AuROC of 0.806 [0.660 – 0.952] and PPV of 50%.

Discussion

In the present study, for the first time, we evaluated the discriminatory capacity of renal echogenicity to identify irreversible advanced CKD in glomerular disease patients using a prospective design and eGFR as the surrogate end-point. In summary, quantitative echogenicity had a good inverse correlation with eGFR at follow-up and a good performance in identifying patients with irreversible advanced CKD. Moreover, in patients presenting with eGFR < 30 mL/min/1.73 m², renal cortex echogenicity higher than that of the liver had a good PPV in identifying irreversible advanced CKD.

In many situations, especially in glomerular disease, advanced CKD can exist with a normal kidney length, making renal biopsy necessary to assess renal prognosis. In our series, no patient had a kidney length less than 8 cm, making advanced irreversible CKD diagnosis a clinical challenge. In this scenario of normal kidney length and suspected irreversible scarring, renal echogenicity utility has been previously evaluated. Several studies have investigated whether an elevated renal cortex echogenicity can differentiate acute from chronic kidney injury [8, 9]. This potential is based on the assumption that the collagen present in interstitial fibrosis and glomerulosclerosis is responsible for increased echogenicity.

In a previous study, using this same quantitative approach, Moghazi et al [2]. correlated renal echogenicity with histopathology findings. An elevated echogenicity was independently associated with tubular atrophy and interstitial inflammation, similar to our findings. Interestingly, while renal echogenicity is closely related to tubular atrophy, interstitial fibrosis was a more powerful predictor of reduced eGFR. Moghazi et al [2]. showed that although histopathological parameters correlated with renal echogenicity, they accounted for only 20% of the variation in renal cortex echogenicity. Our data add to this knowledge, as we found a correlation between nephrotic syndrome severity and renal echogenicity.

In this same study, the authors suggested that a combined renal length less than 20 cm and renal echogenicity greater than that of the liver has a greater discriminatory capacity for the diagnosis of severe chronic kidney disease at biopsy. Our findings have an advantage in relation to this study regarding a crucial point: we used prospective evaluation of eGFR during a 6 month follow-up period to define advanced and irreversible CKD, with a similar definition adopted by recent KDIGO consensus [1]. Although renal biopsy parameters are universally accepted to assess renal prognosis, even advanced interstitial fibrosis is not necessarily associated with markedly reduced eGFR. In fact, it is used more frequently as a predictor of renal function decline. For example, in a study evaluating patients with IgA nephropathy, those patients with severe interstitial fibrosis/tubular atrophy had a mean eGFR of 48 mL/min [12]. So, it is important to evaluate quantitative echogenicity against GFR and in our study we disclosed a good inverse correlation between these parameters, which can have important clinical implications.

We evaluated the potential of quantitative renal echogenicity in identifying advanced CKD using eGFR as an end-point and, moreover, compared the non-invasive data provided by renal echogenicity with histopathological parameters. Because renal biopsy provides not only one but several parameters that can be associated to kidney disease chronicity and progression, we performed a multiple logistic regression analysis to derive a unique index representative of histopathology to identify advanced CKD. Even when compared with

this associated index, echogenicity had similar discriminatory capacity to evaluate kidney chronicity.

However, only a good discriminatory capacity determined by the ROC curve may not be sufficient to help the clinician decide whether or not to perform the renal biopsy. In the clinical setting of glomerular disease, we think the best parameter is the one with the greatest accuracy, as well as a good PPV. Considering all patients, our PPV was only 57.4%, i.e. more than 40% of patients with elevated renal echogenicity would not have advanced CKD. This low PPV can be explained because many patients with advanced CKD and reduced renal size were not included, thus decreasing its real prevalence and negatively influencing PPV. In an attempt to overcome this pitfall, we analyzed only patients with an eGFR less than 30 mL/min/1.73m² at renal biopsy: a subpopulation in whom renal cortex echogenicity can impact on the clinical decision to whether or not perform the renal biopsy. This value increased to nearly 90% in this subgroup analysis. This approach is logical in this clinical setting as no physician will refuse to perform a renal biopsy in a patient with a presently normal or near normal eGFR, so the renal echogenicity is expected to be helpful only for those patients presenting with reduced eGFR.

To explore why renal echogenicity is increased in patients with higher eGFR levels, we investigated the association with clinical parameters and found an association between renal echogenicity and nephrotic syndrome severity (24h-proteinuria and serum albumin). We suggest that in these patients, renal echogenicity can be increased due to intratubular proteinaceous debris and/or interstitial edema.

Taking the liberty of reanalyzing the abovementioned data provided by Moghazi et al., [2] we observed that renal echogenicity higher than that of the liver had an AuROC of 0.671 in identifying advanced CKD defined by histopathological parameters. According to our data, using eGFR as a surrogate endpoint, the AuROC was 0.793. We suggest this difference can be explained because the biopsy sample is not representative of the entire kidney, but just of eGFR. Also, the limited sample extracted by renal biopsy can explain why a parameter that can suffer influence from several other conditions, such as renal echogenicity, had a performance similar to that of renal histopathological analysis.

Another important clinical scenario where acute and chronic kidney disease must be differentiated is in the setting of rapidly progressive glomerulonephritis. Although we evaluated a small number of patients (n=33) with crescent lesions, our data suggest that renal echogenicity remained a useful tool in evaluating reversibility of renal function in glomerulopathies with crescent lesions. Quantitative renal echogenicity is a potential tool to be included in future studies attempting to assess glomerular disease prognosis.

Our study has several limitations: first, a single experienced nephrologist performed all renal ultrasounds. However, in a previous study, which had similar findings about the correlation between renal echogenicity and histopathological parameters, trainees performed all renal ultrasounds [2]. This exemplifies a good technique validation. Secondly, our study was limited to patients submitted to renal biopsy due to suspected glomerular lesion and must be validated in other renal disease populations such as pure tubular interstitial disease and obstructive nephropathy. Finally, although we had excluded patients with diagnosed liver disease, it is possible that some patients present fatty liver disease, affecting liver echogenicity and, consequently, the kidney/liver echogenicity ratio.

Conclusion

We demonstrated that quantitative renal echogenicity can be a useful tool in patients with glomerular disease, normal kidney size (>8 cm) and no liver disease to identify those patients with irreversible eGFR less than 30mL/min/1.73m². We expect these findings can help physicians in the decision-making process when indicating renal biopsy and immunosuppressive treatment, avoiding ineffective procedures.

Disclosure Statement

None.

Acknowledgments

ABL is recipient of a grant from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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