A clinical predictor index for renal survival

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ABSTRACT

Introduction: A clinical index that discriminates disease progression independent of histopathologic features may be valuable in the best timing of biopsy. **Objective:** This study addresses the question if a clinical index based on cortical echogenicity, renal length to body height ratio (KL/H), and serum creatinine levels predicts renal survival. **Methods:** The study enrolled 154 patients. Biopsy specimens were graded for chronic (glomerular obsolescence, segmental glomerular sclerosis, tubular atrophy and interstitial fibrosis) and acute (mesangial proliferation, leucocyte permeation, crescent and fibrinoid necrosis and interstital infiltrate) index by the sum of scored lesions. A chronic clinical index was created by the sum of scored cortical echogenicity relative to liver or spleen, creatinine serum levels and KL/H. The study end point was start on dialisis. **Results:** Higher grade of chronic clinical and biopsy indices were associated with poorer long-term renal survival. Five out of six patients with serum creatinine levels > 2.5mg/dL, highest cortical echogenicity and KL/H < 0.60, before biopsy, startet on dialysis and one increased creatinine levels up to 4.5 mg/dL. The chronic clinical index correlates well with chronic biopsy index. **Conclusions:** The chronic clinical index could be useful to predict a clinical setting in which a renal biopsy will show advanced chronic and irreversible lesion. In patients with highest grade of clinical parameters renal biopsy can be obviate. As a chronicity of illness index for groups of patients with renal medical diseases, the system could be useful in outcome comparisons and evaluation of therapeutic efficacy.

Keywords: needle biopsy, chronic kidney failure, interventional ultrasonography, measures of association, exposure, risk or outcome, severity of illness index.

INTRODUCTION

Renal biopsy is, nowadays, a widely used approach to patients with renal disease. If the kidneys are small the risk factor is increased and the histological diagnosis is thought to be negligible to the patient management.[1,2] Therefore, in this situation patients should not be referred for renal biopsy. However, there is no consensus on renal length value below which the biopsy should not be performed.[3,4,5] Since the kidney length to body height ratio better represents kidney size than absolute renal length[6], its use in a biopsy series would be valuable.

Serum creatinine is the most commonly used measure of renal function in clinical practice today, however, isolated serum creatinine could not differentiate acute from chronic kidney failure. A clinical parameter that could help us to differentiate acute from chronic kidney failure at early stage is lacking.

Ultrasonography is now a well-known non-invasive method of evaluating kidneys with various medical disorders. The assessment of relative hepatorenal echogenicity has been used as an important parameter in renal parenchymal evaluation. In addition to its value in parenchymal assessment, sonography is the method of choice to determine location of the puncture site in renal biopsy.

Many reports tried to find a relationship between sonographic features and the histopathological lesions in kidney biopsy.[4,7,8,9,10,11] Some prospective[7,11,12] and retrospective[4,8,9,10,13] reports found a good correlation between renal cortical echogenicity and tubulointerstitial abnormality seen in biopsy specimens. Moreover, it was considered of prognostic value for cortical echogenicity in childhood nephrotic syndrome[13] and hemolytic uremic syndrome.[14]

Curiously, in the medical literature,[15] the decision to perform a biopsy does not take into account renal cortical echogenicity.

Renal biopsy indications based on current criteria have yielded many reports that found an incidence of predominantly chronic lesions up to 17.2 % of the biopsies[1]. Therefore, a clinical index that discriminates disease progression independent of histopathological features may be valuable in the best timing of renal biopsy.

This prospective study was designed to address the feasibility of a clinical index based on cortical echogenicity, renal length to body height ratio, and serum creatinine levels as a predictor factor for renal survival.

Material and Methods

This study is a prospective clinicopathological analysis of 154 patients who were submitted to renal sonographic examination before percutaneous biopsy. The patients ranged in age from 13 to 88 years at the time of biopsy (mean age 37.59 ± 15.97 years); there were 82 females and 72 males.

The variables included in the evaluation of the ultrasound images were kidney length (KL) and cortical echogenicity. Because of the well-known individual variation in kidney size according to the height, sex and age of subjects we calculated the relative kidney length by dividing the absolute renal length (in milimeters) by the subject body height (in centimeters) (KL/H).[6]

Sonograms were graded by degree of cortical echogenicity relative to liver/spleen parenchyma in the following manner: echogenicity of the cortex of the kidney less than that of the liver or spleen (grade 0), echogenicity of the cortex of the kidney equal to that of the liver or spleen (grade 1), echogenicity of the cortex of the kidney greater than that of the liver or spleen (grade 2). The echogenicity of the cortex of the right kidney was preferred in all cases but in cases of highly echogenic liver, with or without distal attenuation, the echogenicity of the left kidney was considered. Cortical echogenicity grade 0 was assumed as normal.

Renal tissue was obtained by percutaneous biopsy using a disposable gun needle. After a report for diagnosis purposes, the following histological features were evaluated for gradation: glomerular obsolescence (GO), mesangial proliferation (MP), leukocyte permeation (LP), crescent and fibrinoid necrosis (CFN), segmental glomerular sclerosis (SGS), tubular atrophy (TA), interstitial fibrosis (IF) and interstitial infiltrate (II). The histological findings were graded according to extension and severity in 0 (0%, no change), 1 (< 25% of the sample), 2 (≥ 25% ≤ 50% of the sample), and 3 (>50% of the sample).

In accordance with chronicity and activity indices for lupus nephritis lesions, MP, LP, CNF and mononuclear II were classified as acute lesions and GO, SGS, TA and IF as chronic[16]. Patients were assigned a biopsy chronicity index based on the the sum of grade of GO, SGS, TA, and IF. Likewise, a biopsy acute index was assigned based on the sum of the grade of MP, LP, CFN and II. A clinical index of renal chronicity was created by scoring cortical echogenicity grade (grade 0: 0; grade 1: 1; grade 2: 2), serum creatinine levels (≤ 1.4 mg/dL: 0; > 1.4 < 2.5 mg/dL: 1; ≥ 2.5 mg/dL: 2) and right kidney length to height ratio (KL/H) (< 0.60: 1; ≥ 0.60: 0).

The chronic clinical index, chronic and acute biopsy indices were then further grouped to facilitate statistical analysis as follows: I, for sum ranging from 0 to 2; II, for sum ranging from 3 to 5 and III, for sum equal or more than 6 to create both chronic and acute biopsy indices. If serum creatinine level was equal to or less than 1.4 mg/dL the chronic clinical index was 0. If serum creatinine level was greater than 1.4 mg/dL, the value of the chronic clinical index was the sum of the assigned weights for all measurements recorded: I, for sum ranging from 0 to 1; II, for sum ranging from 2 to 3 and III, for sum ranging from 4 to 5.

The pathological and sonographic data were analyzed blindly, respective to sonogram and histological findings, and independently by two different corresponding specialists. Both had knowledge of clinical information.

The study end point was start of dialysis. For patients who did not reach the outcome the assessment of renal function was made at least one year later.

The decision to treat with steroids or immunosuppressive drugs was based solely on patient physician discretion.

The association between indices was done using Spearman correlation test.

Comparison of survival was done by Kaplan-Meier method, with differences in survival curves evaluated by log rank sum testing.

The influence of the indices on the risk of a specific outcome was investigated by the Cox proportional hazards regression model. The level of significance $p < 0.05$ was used to indicate a statistical difference.

Results

Besides kidney size clinical and laboratory data are shown in Table 1. The mean serum creatinine level was 2.09 mg/dL (ranging from 0.5 to 11.7 mg/dL). 71 patients had impaired renal function (serum creatinine > 1.4 mg/dL). Ten biopsies out of 154 yielded less than five glomeruli and were ruled out of the study. Table 2 lists the histological diagnosis in the 144 patients based on the results of light microscopy and immunofluorescence.

Table 1	Distribution of continuous clinical and laboratory data and kidney size.							
	Age	Disease duration	Creatinine	Albumin	Proteinuria	Hematocrit	KL	KL/H
	years	years	mg/dL	g/dL	mg/24h	%	mm	
mean	37.59	3.52	2.09	2.97	5972	35.85	109.7	0.67
SD	15.97	10.22	1.94	1.07	5673	7.44	10.56	0.06

SD - standard deviation; KL - kidney length; KL/H - kidney length/ height.

Table 2	Histological diagnosis
FSG	26
SLE	22
MGN	13
Minimal change disease	12
IgAN	12
MPGN	8
Sclerosing GN	6
Hypertension	6
Collapsing FSG	4
Amyloidosis	4
HIV	4
TI Nephritis	3
DM	3
Postinfectious GN	3
Proliferative GN	2
Indeterminate	2
IgMN	2
HCV	2
Thrombotic microangiopathy	2
Miscelaneous	8

FSG – focal segmental glomerulosclerosis; MGN – membranous glomerulonephritis; IgAN – immunoglobulin A nephropathy; IgMN – immunoglobulin M nephropathy; MPGN – membrano-proliferative glomerulonephritis; TI – tubulointerstitial; SLE – systemic lupus erythematosus; DM – *diabetes mellitus*; HCV – hepatitis C virus.

Cortical echogenicity was graded 0 in 53 patients (37.6%), 1 in 52 patients (36.9%), and 2 in 36 patients (25.5%). In three patients with both hepatic and splenic disease the cortical echogenicity was not evaluated. KL/H was equal to or more than 0.60 in 124 patients and less than 0.60 in 19. In one bedridden patient the height could not be measured.

Curiously, 40.6% of the patients with normal serum creatinine and 34.0% with normal cortical echogenicity had mild chronic histological lesions. Moderate to severe chronic lesions figures were 7.8% to normal creatinine patients and 8.5% to normal cortical echogenicity patients.

Out of 154 patients 134 were followed-up for a mean of 40.5 months after biopsy. The duration of the follow-up from the time of biopsy was significantly shorter in patients who started on dialysis. Forty-one patients reached the outcome after a mean follow-up of 24.3 months and 93 did not require dialysis during a mean follow-up of 47.6 months. By the end of follow-up we recorded 9 deaths without start dialysis and 11 cases who abandoned treatment or did not complete one year after biopsy.

During the overall follow-up the outcome developed at some time in 12.2 % of the patients of the grade I, 38.7 % of the patients of the grade II (I vs II: p < 0.0002) and 74.1 % of the patients of the grade III (I vs III: p < 0.0001) of the chronic clinical index (p < 0.0001). Outcome was reached in 23.8 % of the patients of grade I, 55.6 % of the patients of grade II (I vs II: p = 0.0024) and 27.8 % of the patients of grade III (I vs III: p = 0.6616) of acute biopsy index (ns) and 12.2 % of grade I, 34.1 % of grade II (I vs II: p = 0.0546) and 56.3 % of grade III (I vs III: p = 0.0014) of the chronic biopsy index. Before biopsy six grade III chronic clinical index patients shared the same features: serum creatinine levels higher than 2.5 mg/dL, renal cortical echogenicity grade II and kidney length to height ratio less then 0.60. At the end of the follow-up five out of six started on dialysis and one increased serum creatinine levels to 4.5 mg/dL.

When analyzed by a life-time table, patients with a high and low grade of chronic clinical index differed significantly in renal survival (Figure 1A). Similarly, patients with a high or low chronic biopsy index differed in renal survival (Figure 1C). The outcome did not correlate well to the severity grade of the acute biopsy index (Figure 1B).

Figure 1. Renal survival according to chronic clinical index (A), acute biopsy index (B) and chronic biopsy index (C)..
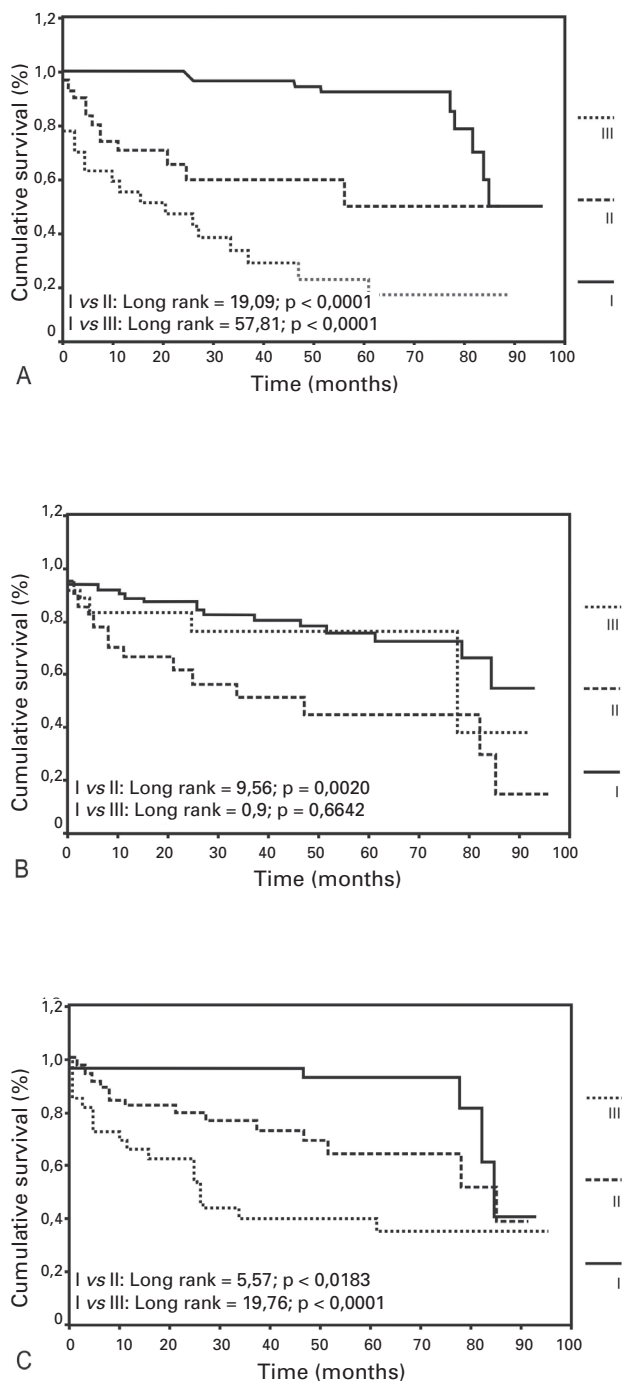
The chronic clinical index correlated well with chronic biopsy index (Spearman correlation = 0.484; p < 0.001) but not with acute biopsy index (Spearman correlation = 0.137; p = 0.131)

The Cox proportional hazards regression model showed that, independent of biopsy indices, higher chronic clinical index was associated with poorer long-term renal survival (Table 3).

DISCUSSION

The inability of physicians to adequately measure the chronicity of kidney medical diseases has led to many unnecessary renal biopsies.[1]

Although serum creatinine is a major risk factor for renal survival, it does not fully account for the risk. Clinical markers commonly used for renal disease evaluation, including hypertension, hematuria, proteinuria, serum albumin, serum cholesterol and serum triglycerides failed to predict clinical outcome. Therefore, other risk factors must be identified in order to better evaluate the need for renal biopsy.

Ultrasound is able to outline macroscopic kidney anatomy features like location, size, contours, mobility, and to detect tumors, calculi and hydronephrosis. For renal medical disease purposes the assessment of the echogenicity of the renal compartments (cortex and medulla) are also important. Nowadays the sonographic evaluation of the kidney includes cortical echogenicity, corticomedullary definition and pyramid proeminence.

The search for a relationship between sonographic appearance of the kidney and histopathological findings was the aim of many reports in recent years. Indeed, increased cortical echogenicity correlates well with severity and chronicity of tubulointerstitial lesions.[7] From laboratory data increased serum creatinine levels correlated with enhanced cortical echogenicity.[7] Since creatinine plays a very important role when we are dealing with renal diseases, the above association strongly supports the value of renal sonogram as a sensible marker of parenchymal renal disease. Based on our findings we would like to extend the value of kidney sonography in renal medical disease.

In adjunction to other clinical and laboratory parameters cortical echogenicity could be useful to predict a clinical setting in which a renal biopsy will show advanced chronic and irreversible lesion. The chronic clinical index is reliable in predicting outcome in groups of patients and indicates chronicity of renal disease at the time of admission.

This study showed that the likelihood of progression to end-stage renal disease is most likely to occur in those patients with higher clinical chronic index. Indeed, five out of six patients with serum creatinine levels equal or higher than 2.5 mg/dL, cortical echogenicity higher than that of the liver and renal length to height ratio less than

Table 3	RISK OF OUTCOME ACCORDING TO GRADE OF INDICES		
Chronic Clinical Index			
Outcome	I	II	III
Yes	9 (12.2%)	14 (38.7%)	20 (74.1%)
No	60 (87.8%)	24 (61.3%)	7 (25.9%)
OR	-	5.44	10.60
CI 95%	-	2.21 - 13.35	4.24 - 26.54
p	-	<0.001	<0.001
Acute Biopsy Index			
Outcome	I	II	III
Yes	19 (23.8%)	15 (55.6%)	5 (27.8%)
No	61 (76.3%)	12 (44.4%)	13 (72.2%)
OR	-	3.18	1.28
CI 95%	-	1.51 - 6.70	0.42 - 3.87
p	-	0.002	0.661
Chronic Biopsy Index			
Outcome	I	II	III
Yes	6 (12.2%)	15 (34.1%)	18 (56.3%)
No	43 (87.8%)	29 (65.9%)	14 (43.8%)
OR	-	2.60	4.89
CI 95%	-	0.98 - 6.87	1.84 - 12.94
p	-	0.055	0.001

OR – odds ratio; CI – confidence interval

0.60 reached the outcome and one patient increased serum creatinine to levels higher than 4.0 mg/dL, despite treatment. For this group of patients the renal biopsy did not improve medical management, therefore biopsy can be obviated in these cases.

The strong association between biopsy chronicity and echographic-laboratory indices allows us to anticipate the chronic lesions and obviate the biopsy. These results indicate that high-risk patients can be identified by noninvasive measurements of cortical echogenicity and renal size associated with serum creatinine.

The relatively better outcome of patients with high biopsy acute index in contrast to high biopsy chronic index suggests that acute lesions, although usually dramatic, are often responsive to therapy.

The chronic clinical index uses routinely available, objective data, is quickly computed, and could be useful to obviate renal biopsy in some patients. Preliminary evaluation in this study demonstrated a strong correlation between chronic clinical index and renal survival. As a chronicity index of disease for groups of patients with renal medical diseases, the system could be useful in outcome comparisons and evaluation of therapeutic efficacy. Before it is widely used, however, multi-institutional validation is needed.

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