Clinico-Pathological Correlation of Severe Tubulointerstitial Fibrosis in Glomerular Diseases

Nuttasith Larpparisuth MD*,
Duangrat Tanratananon MD*, Bunyarit Cheunsuchon MD**, Paisan Parichatikanon MD**, Somkiat Vasuvattakul MD*

* Division of Nephrology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
** Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Renal histopathology is the best method available to assess chronicity of glomerular diseases. However, renal biopsy is an invasive procedure and is available only in medical schools or tertiary-care hospitals in Thailand. Clinical predictors that discriminate the chronicity index of renal pathology may be valuable for the best timing of biopsy. The authors conducted this study to identify the clinical parameters of severe fibrosis in glomerular diseases.

Material and Method: The authors retrospective analyzed all consecutive patients with glomerular diseases who underwent ultrasound-guided renal biopsy in Siriraj Hospital between 2008 and 2010. The patients were stratified according to degree of tubulointerstitial fibrosis (IF) into mild to moderate group (IF <50%) and severe group (IF ≥50%). Data of clinical and radiological parameters which relate to severe fibrosis were obtained. Formula for prediction of advanced IF was also developed by backward stepwise logistic regression analysis. The authors also validated the model by application to the patients who underwent kidney biopsy in our center between 2011 and 2012.

Results: Of a total 682 patients, 169 patients (24.8%) were classified as a severe IF group. In the multivariate model, higher serum creatinine, lower mean length of both kidneys and systolic blood pressure (SBP) of more than 140 mmHg were significantly related to severe IF. All three factors were incorporated into a predictive model: ex/(1+ex) while x = 1.3+(0.6 x serum Cr in mg/dl)–(0.4 x mean length of both kidneys in cm)+(0.7 x 1 if SBP ≥140 mmHg or 0 if <140 mmHg). The formula had AUROC of 0.82 and if calculated probability of fibrosis is higher than 0.37, it yields 90% specificity and 44% sensitivity for the prediction of severe fibrosis. When applied to 523 patients who underwent renal biopsy in 2011 and 2012, the sensitivity was 65.6% while specificity was 87.8%.

Conclusion: High serum creatinine, presence of HT and decreased mean length of both kidneys are important clinical markers to predict renal fibrosis. The model constructed from these factors could be used in clinical practice for appropriate decision making.

Keywords: Tubulointerstitial fibrosis, Chronicity index, Renal pathology, Renal ultrasonography, Glomerular diseases

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Glomerular disease is the major cause of chronic kidney disease, which has a high rate of treatability. One of the most important factors for unsuccessful management is the chronicity degree of renal pathology. Clinical and pathological studies have revealed that degree of tubulointerstitial damage correlates well with deterioration of renal function and worse renal survival[1,2]. However, renal biopsy, the only procedure to obtain kidney tissue, is an invasive procedure and is available only in medical schools or tertiary centers in Thailand. In addition, if histological findings are consistent with severe tubular atrophy and interstitial fibrosis, further aggressive treatment with immunosuppression is not beneficial. From our data, the major complication rate of renal biopsy in the patients with serum creatinine ≥4.0 mg/dl was nearly 10 fold higher than for the population with less serum creatinine[3].

Many non-invasive clinical parameters were used to predict the severity of renal fibrosis such as serum creatinine, kidney size, echogenicity, and hematocrit. Unfortunately, no specific parameters can exactly prognosticate the chronicity of renal pathology. Serum creatinine is the standard measurement of renal function in clinical practice but it could not distinguish between acute kidney injury and chronic kidney disease. Ultrasonographic evaluation of kidney is also a well-known non-invasive method. Both kidney size
and echogenicity have been the salient factors employed to determine the proper management. Many studies revealed good correlation between echogenicity and tubulointerstitial fibrosis in renal biopsy specimens\(^3\), but the results of some reports have not been found to yield such relationship\(^5\). Therefore, the use of ultrasonographic parameters alone might be insufficient for nephrologists to decide whether the patient should undergo kidney biopsy.

Despite advancing technology, there is no promising laboratory marker to predict tubulointerstitial fibrosis exactly. The clinical indexes that discriminate the chronicity of renal pathology in glomerular diseases might be valuable for the best timing of biopsy in clinical practice. Therefore, the objective of this study was to address the clinical predictors of severe renal fibrosis based on demographic data, laboratory results and radiological evaluation. The authors developed a model from these significant markers, which may be helpful to determine the management plan. This model was also validated in another group of patients.

**Material and Method**

**Patients**

The authors retrospectively reviewed all consecutive patients who underwent ultrasound-guided renal biopsy at Division of Nephrology, Department of Medicine, Siriraj Hospital between January 1, 2008 and December 31, 2010. In the case where a patient underwent more than one biopsy, only data from the first one was selected. The exclusion criteria were patients under 15 years old, those with incomplete renal ultrasonographic data or pathological results not compatible with glomerular diseases, and kidney transplant recipients.

**Methods**

The data were obtained from the database of Nephrology Division and Siriraj Hospital. Baseline demographic data including age, gender, blood pressure, height, weight were collected. The histopathological results, which were reported from one of two renal pathologists, were reviewed for definitive diagnosis and degree of tubulointerstitial fibrosis. The authors stratified the patients according to the degree of tubulointerstitial fibrosis (IF) into mild to moderate (IF 0-49%) and severe groups (IF ≥50%).

The data of blood chemistry that consisted of serum creatinine, blood urea nitrogen, serum albumin, hemoglobin and hematocrit were also reviewed. We also performed an urinalysis and focused on the presence of dysmorphic red blood cells (RBCs) and RBC casts. Quantitative analysis of urine protein by means of spot urine protein per creatinine ratio (UPCR) or 24-hour urine collection (if no data of UPCR) was obtained.

Before the biopsy, an ultrasound of both kidneys was routinely performed by nephrology fellows and subsequently confirmed by attending staff. All radiographic data were recorded in database of Nephrology Division. The ultrasound scanner was GE LOGIQ Book XP (China) with a 3 MHz convex transducer. Renal length was measured by the longest longitudinal section through the kidney. The authors used both the length of the biopsied kidney and mean length of both sides to determine kidney size and evaluate the relationship with renal fibrosis from histopathology. Because of individual variation in kidney size according to height, the adjusted length was also calculated from dividing the biopsied renal length by the participant’s height. Echogenicity of kidney was assessed by comparing it with the liver and then reported as increased or normal. This study was approved by Ethics Committee of Faculty of Medicine Siriraj Hospital.

**Statistical analysis**

Statistical analyses were executed with PASW version 18.0 (Chicago, USA). The baseline characteristics and demographic data were summarized as mean ± standard deviation (SD) or percentage (%). Comparison of categorical data was achieved by the Chi-square test or Fisher’s exact test. For continuous data, the independent t-test or Mann-Whitney U test was used depending on distribution of data. Predictors for severe interstitial fibrosis were examined by univariate and multivariate analysis using binary logistic regression. A formula for predicting advanced IF was developed using backward stepwise linear regression analysis. A \( p\)-value <0.05 was considered as statistically significant. Sensitivity, specificity, negative predictive value and positive predictive value were calculated when applied to the model to another group of patients.

**Results**

Six hundred eighty two patients were included in this study, 169 patients (24.8%) were classified in the severe fibrosis group. The baseline characteristics revealed 68% were female with an average age of 40 years and mean blood pressure of 138/82 mmHg. The laboratory results indicated that mean serum
Creatinine was 2±2.03 mg/dl, mean serum albumin was 2.9±0.8 g/dl, mean urine protein was 5.5±5 g/gCr and mean hematocrit was 34±3.6%. Mean length of the biopsied kidney was 9.8±0.8 cm and mean length of both kidneys was 9.7±0.8 cm. Of the total number of patients, 29.8% had an increased echogenicity of the kidney as shown in Table 1.

Among the patients, lupus nephritis (40%) was the largest population followed by minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) (16%), IgA nephropathy (15%), and membranous nephropathy (8%), as shown in Fig. 1.

According to the univariate analysis, patients with severe renal fibrosis tended to be of male and older than patients with less fibrosis. This group also had significantly higher systolic blood pressure, serum creatinine, serum albumin and urine protein. Lower hematocrit was demonstrated in advanced tubulointerstitial damage ($p<0.01$). However, the presence of urine RBCs and RBC casts were not significantly different in both groups. Renal ultrasonography revealed indifferent length of biopsied kidney ($p = 0.1$) but there was a significantly different mean length of both kidneys ($p < 0.01$). Adjusted length of kidneys with height was no more meaningful than the exact length. Increased echogenicity was more commonly found in the severe group as shown in Table 2.

### Table 1. Baseline characteristic of all included patients

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>n (%) or mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender (n, %)</td>
<td>465 (68.2%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40±15</td>
</tr>
<tr>
<td>Systolic blood pressure (SBP) (mmHg)</td>
<td>136±18</td>
</tr>
<tr>
<td>Diastolic blood pressure (DBP) (mmHg)</td>
<td>82±12</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>2.00±2.03</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>2.9±0.8</td>
</tr>
<tr>
<td>Urine protein (g/gCr or g/day)</td>
<td>5.5±5.0</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>34±6</td>
</tr>
<tr>
<td>Length of biopsied kidney (cm)</td>
<td>9.8±0.8</td>
</tr>
<tr>
<td>Mean length of both kidneys (cm)</td>
<td>9.7±0.8</td>
</tr>
<tr>
<td>Increased echogenicity (%)</td>
<td>203 (29.8%)</td>
</tr>
</tbody>
</table>

### Table 2. Univariate analysis of parameters associated with severe tubulointerstitial fibrosis

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Patients with tubulointerstitial fibrosis &lt;50% (n = 413)</th>
<th>Patients with tubulointerstitial fibrosis ≥50% (n = 169)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender (%)</td>
<td>78.5</td>
<td>20.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.0±15.0</td>
<td>43.7±16.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135±18</td>
<td>141±18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82±12</td>
<td>83±12</td>
<td>0.83</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.5±1.3</td>
<td>3.6±2.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>2.9±0.8</td>
<td>3.1±0.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urine protein (g/gCr or g/day)</td>
<td>5.0±4.9</td>
<td>5.9±5.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>35±6</td>
<td>32±6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Length of biopsied kidney (cm)</td>
<td>9.80±0.83</td>
<td>9.74±0.91</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean length of both kidneys (cm)</td>
<td>9.84±0.72</td>
<td>9.60±0.93</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Increased echogenicity (%)</td>
<td>22.6</td>
<td>51.5</td>
<td>&lt;0.01</td>
</tr>
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</table>
From the multivariate analysis, only three parameters correlated with severe fibrosis, including serum creatinine, mean length of both kidneys, and systolic blood pressure $\geq 140$ mmHg ($p<0.01$ for all factors). The backward stepwise logistic regression analysis yielded the following equation,

$$\text{Probability of fibrosis} = \frac{e^{1.3+(0.6 \times \text{Cr})-(0.4 \times \text{mean length of both kidney})+(0.7 \times \text{HT})}}{1+e^{1.3+(0.6 \times \text{Cr})-(0.4 \times \text{mean length of both kidney})+(0.7 \times \text{HT})}}$$

where, Cr is serum creatinine in mg/dl, mean length of both kidneys in cm, and HT is 1 if SBP $\geq 140$ mmHg otherwise HT = 0.

A Receiving Operating Characteristic (ROC) curve of the model was performed and the area under the curve was 0.82. For the application of this formula in routine medical practice, we required high specificity. If a specificity of 0.9 was selected, it corresponded to a sensitivity of 0.44 at the probability of fibrosis of more than 0.37 as shown in Fig. 2. The positive predictive value (PPV) and negative value (NPV) were found to be 59% and 82%, with 25% of the prevalence of fibrosis in glomerular disease.

The authors validated the model in all consecutive patients who underwent renal biopsy at our center between January 1, 2011 and December 31, 2012. Total of 523 patients, 128 patients (24.5%) had severe tubulointerstitial fibrosis. When applied to these patients, the sensitivity and specificity of this model were 65.6% (95% CI = 57.4-73.9%) and 87.9% (95% CI = 84.1-90.8%), respectively. PPV was 63.6% (95% CI = 55.4-71.8%) while NPV was 88.8% (95% CI = 85.1-91.6%).

**Discussion**

The extent of tubulointerstitial damage was not only correlated with impairment of glomerular filtration rate, but also with progressive renal failure$^{6,7}$. Lack of clinical markers to evaluate chronicity of renal pathology has led to dispensable renal biopsies. The authors designed this study to evaluate the relationships between clinical parameters and severe renal fibrosis. Such clinical markers or the model derived from them might be used to prognosticate the chronicity, especially in the settings within which renal biopsy cannot be easily performed.

Our retrospective study revealed that lupus nephritis is the most common pathology in our center. Primary glomerular disease is predominantly IgA nephropathy (IgAN) and focal segmental glomerulosclerosis. Compared to previous studies at our institution between 1982 and 2005, the most prevalent secondary glomerular disease is still lupus nephritis$^{8,9}$. However, in primary glomerular disease, the highest prevalence one changes from IgM nephropathy to IgAN and FSGS. The result is not different from a study in China that IgAN is the leading pathology$^{10}$. IgAN is the most common primary glomerular disease in the overall population. Explanation for quite high incidence of FSGS rather than other type of nephrotic syndrome might be that examination of renal histopathology in our country was performed only in problematic cases such as presence of HT, steroid resistance or nephrotic syndrome in advanced age.

Multivariate analysis revealed that parameters including high serum creatinine, decreased mean length of both kidneys and high systolic blood pressure were correlated with tubulointerstitial damage. Association of high serum creatinine and blood pressure with severe renal fibrosis was demonstrated in previous studies, which were performed in various types of glomerular diseases including lupus nephritis and primary nephrotic syndrome$^{2,11-14}$. There was no meaningful relationship between amount of urine protein and degree of tubulointerstitial fibrosis in our patients. This observation was consistent with previous studies, which included patients with MCD and FSGS and revealed no correlation between quantitative analysis of urine protein and the prognosis in primary nephrotic syndrome$^{12}$. Thus, the amount of proteinuria is not a good parameter for prognosticating chronicity of renal parenchyma in primary nephrotic syndrome. Presence of RBC and RBC casts in urine, which may associate with active glomerulonephritis, also did not precisely predict severity of tubulointerstitial damage.

The authors did not find any correlation between severe tubulointerstitial damage and lower
hematocrit level as in antecedent studies\(^{(2,12)}\). An explanation of this finding may be due to the high proportion of enrolled patients had lupus nephritis and who might have developed anemia from various causes, such as hemolytic anemia and anemia of chronic disease, but not directly from chronic kidney disease.

With regard to the aspect of ultrasonographic data, from multivariate analysis, we revealed that the length of the biopsied kidney and echogenicity were poorly correlated with degree of tubulointerstitial fibrosis. Even though these findings were similar to the previous studies\(^{(4,5,15,16)}\), the authors endeavored to adjust renal length with the patient’s height, body surface area and gender but failed to find any meaningful relationship. Remarkably, the mean length of both kidneys was better associated with renal fibrosis than other ultrasonographic parameters. Parameters derived from both kidneys may be more representative for overall renal function in glomerular disease. The mean length of kidneys from the present study was less than in another study of healthy participants, which reported that mean kidney length of Thai male and female was 10.34±0.7 and 10.17±0.7 cm, respectively\(^{(17)}\).

Subgroup analysis of each type of glomerular disease did not reveal any significant factors different from the overall data. In addition, the authors validated our model in another group of patients with glomerular diseases and this revealed indifferent sensitivity and specificity. However, our study had certain limitations, including being a retrospective review in nature and a single center study. The ultrasonographic evaluation had been performed by several physicians. The interpretation of pathological results was done by one of two pathologist without subsequent reassessment. The last limitation was the variety of glomerular diseases enrolled in the study, which might have exaggerated diversified clinical presentation.

This is the first report of a new model for the clinical prediction model of severe tubulointerstitial fibrosis conducted in Thai patients. The formula, which required only blood pressure, serum creatinine and kidney size, can be easily applied in every medical center, even in remote areas. The low probability score from this model encourages health care personnel to investigate extensively or refer the patients to a tertiary center. On the contrary, if probability summation is high along with clinical suspicions of chronic glomerulonephritis, the patient should not receive further invasive investigation. However, in the future, integration of new biomarkers into the model may increase its predictive value.

Conclusion

Serum creatinine, presence of HT and mean length of both kidneys are important clinical markers to predict renal fibrosis. The model constructed from these factors could be used in clinical practice for decision-making.

What is already known on this topic?

Severe chronic tubulointerstitial fibrosis is a poor prognostic factor for renal outcome in glomerular diseases. Various non-invasive clinical parameters including blood pressure, serum creatinine, hematocrit, urinalysis, renal ultrasonography data were used to predict severity of renal fibrosis.

What this study adds?

Despite advancing technology, there is no promising marker for chronic tubulointerstitial fibrosis. This study addressed the clinical and laboratory parameters which correlated with severe renal fibrosis from large renal biopsy registry. The prediction model for severe fibrosis, conducted from Thai patients, should be valuable for clinical decision of further invasive investigation.

Acknowledgment

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Potential conflicts of interest

None.

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4. Rosenfield AT, Siegel NJ. Renal parenchymal
การศึกษาข้างต่างคลินิกที่มีความสัมพันธ์กับการตรวจพบพังผืดในเนื้อไตในผู้ป่วยโรคไตที่มีพยาธิสภาพเด่นที่โกลเมอรูลัส

นิสิตฯ อังวิปรีทิ, ดวงรัตน์ ตันรัตนานนท์, บุณยฤทธิ์ ชื่นสุชน, ไพศาล ปาริชาติกานนท์, สมเกียรติ วสุวัฏฏกุล

อุปสรรค: การตรวจทางพยาธิวิทยาจากชิ้นเนื้อไตเป็นวิธีมาตรฐานในการประเมินความรุนแรงของการเกิดพังผืดในเนื้อไต โดยไม่เพียงแต่การตรวจการตรวจชิ้นเนื้อไตเป็นวิธีมาตรฐานในการประเมินความรุนแรงของการเกิดพังผืดในเนื้อไต แต่การเจาะตรวจชิ้นเนื้อไตสามารถทำให้เกิดภาวะแทรกซ้อนรุนแรงได้ รวมถึงการที่ผู้ป่วยจะไม่ได้ประโยชน์ในการรักษาเฉพาะบุคคลที่มีการตรวจพบพยาธิสภาพเรื้อรังในเนื้อไต

วัสดุและวิธีการ: ผู้นิพนธ์ได้เก็บข้อมูลหลังจากผู้ป่วยที่มีพยาธิสภาพเด่นที่โกลเมอรูลัสที่ได้รับการตรวจทางพยาธิวิทยาของเนื้อไตที่โรงพยาบาลศิริราชระหว่าง พ.ศ. 2551 ถึง พ.ศ. 2553 โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม ตามความรุนแรงของการพบพังผืดในเนื้อไต ผู้นิพนธ์ได้หาสมการที่ช่วยในการพยากรณ์การพบพังผืดอย่างมาก ที่มีความสัมพันธ์กับการพบพังผืดในเนื้อไตอย่างมาก จากการวิเคราะห์แบบพหุตัวแปร

ผลการศึกษา: ผู้ป่วยทั้งหมด 682 ราย พบว่า 169 ราย (ร้อยละ 24.8) พบมีพังผืดในเนื้อไตอย่างมาก การวิเคราะห์แบบพหุตัวแปรพบว่าระดับครีแอทินินในเลือดที่สูงขึ้น การพบความดันโลหิต systolic มากกว่า 140 มิลลิเมตรปรอทและความยาวเฉลี่ยของไต 2 ข้างจากอัลตราโซนที่ลดลงนั้นสัมพันธ์กับการพบพังผืดในเนื้อไต ผู้นิพนธ์ได้สร้างสมการพยากรณ์การพบพังผืดในเนื้อไตจากข้อเบื้องต้นนี้ ด้วยสมการ ที่ค่าที่สูงขึ้น 1.3⁴+(0.6 x ระดับครีแอทินินในเลือดในหน่วยมิลลิกรัมต่อเดซิลิตร)- (0.4 x ความยาวเฉลี่ยของไต 2 ข้าง จากอัลตราโซนในหน่วยเซนติเมตร)+ (0.7 x 1 ถ้าความดันโลหิต systolic มากกว่า 140 มิลลิเมตรปรอท หรือ ถ้าความดันโลหิต systolic น้อยกว่า 140 มิลลิเมตรปรอท) ที่ค่าที่สูงขึ้น 0.82 ถ้าค่ามีได้ผลการพยากรณ์พังผืดที่มีความถูกต้องถึง 0.37 จะมีความไวร้อยละ 44 และความสามารถร้อยละ 90 ในการพยากรณ์พังผืดในเนื้อไตจากข้อเบื้องต้นนี้ การวิเคราะห์จะพบว่าผู้ป่วยมีการพบพังผืดในเนื้อไตที่สูงขึ้น 66.5 และความสามารถร้อยละ 87.8 สรุป: ระดับครีแอทินินในเลือดที่สูงขึ้น การพบความดันโลหิต systolic มากกว่า 140 มิลลิเมตรปรอท และความสามารถของไต 2 ข้างจากอัลตราโซนลดลงเป็นข้อจุดที่สำคัญในการพยากรณ์การพบพยาธิสภาพเรื้อรังอย่างมากในเนื้อไต สมการที่ค่าความจากปัจจัยเหล่านี้น่าจะมีบทบาทสำคัญในการตัดสินใจรักษาทางคลินิกต่อไป

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