

## ORIGINAL ARTICLE

## Title

**Histopathology Interstitial Severity Index Associated with Glomerular and Tubular Severity Index in Nephrotic Syndrome Patients**

## Authors:

Reny Setya Pratiwi Duarsa<sup>1</sup>, Ni Wayan Winarti<sup>2</sup>, and I Gde Raka Widianana<sup>1</sup>

1. Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine Universitas Udayana/Sanglah Hospital, Bali, Indonesia

2. Department of Pathology, Faculty of Medicine Universitas Udayana/Sanglah Hospital, Bali, Indonesia

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Wim van Biesen

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**Abstract**

**Background:** Nephrotic syndrome is characterized by massive proteinuria due to leakage of glomerular basal membrane, and subsequent process in tubular and interstitial tissue. It should be elucidated whether the severity of histopathological lesions in compartments of kidney tissue play a role and whether lesion in those compartments associated one to another.

**Aim:** The study aims to correlate severity histopathologic lesions among compartments in kidney tissue.

**Method:** All patients with nephrotic syndrome were biopsied and the cores were stained with Hematoxylin-Eosin, PAS, Masson's Trichrome to look at glomerular, tubular, interstitial and vascular involvements. Glomerular abnormalities including mesangial hypercellularity, endocapillary hypercellularity, membranous; tubular, interstitial, and vascular severities were scored according to type, activity, severity and distribution in histopathologic features.

**Results:** This study included 46 patients consisted of 16 (34.8%) males and 30 (65.2%) females, aged  $26 \pm 10$  years, SBP  $121.7 \pm 13.10$  and DBP  $78.21 \pm 7.80$  mmHg, diagnosed with 14 lupus and 32 non-lupus nephrotic syndrome. Histopathologic abnormalities showed glomerular index was  $4.26 \pm 2.34$ , tubular index was  $3.09 \pm 1.90$ , interstitial index was

$3.02 \pm 1.48$ , vascular index was 0-3, pathologic index was  $10.56 \pm 4.54$ . There was significant correlation of severity index between interstitial and glomerular lesions ( $R=0.49$ ,  $P=0.001$ ), and between interstitial and tubular lesions ( $R=0.45$ ,  $P=0.002$ ). However, there were no significant correlations of severity index between interstitial and vascular lesions, and glomerular and tubular lesions.

**Conclusion:** There are significant correlations of severity index between: interstitial and glomerular lesions; interstitial and tubular lesions. It may implicate that histopathological process in the interstitial tissue plays a central role in the pathogenesis of proteinuria in nephrotic syndrome.

**Keywords:** Severity Index, Interstitial, Tubular, Glomerular, Nephrotic Syndrome.

Corresponding author: Reny Prasetya Duarsa; e-mail: [reny.duarsa@kih.co.id](mailto:reny.duarsa@kih.co.id)

## Background

Proteinuria is a main component of nephrotic syndrome that could affect glomerular and extraglomerular compartments of a nephron. Urinary protein may initiate pro-inflammatory and pro-fibrotic process that may originate within glomeruli or may contribute directly to chronic tubular and interstitial damage. This proteinuria could give pictures of injury severity to the glomerular basement membrane, as well as to the extraglomerular compartments such as tubulus, interstitial and vascular. Duration of proteinuria finally could impact the total damage with outcome of a decline in the glomerular filtration rate (GFR).

Although renal interstitium is also affected by proteinuria, this renal compartment was previously understood as an inactive segment of a nephron. Currently, the role of this compartment related to kidney function had grown to be more prominent than glomerular compartment from studies at the 1970s by Bohle et al. The studies repeatedly revealed strong correlations between relative interstitial volume and serum creatinine.<sup>1,2</sup> As the renal interstitial plays an important role in kidney function, it impacts lifespan of diseased kidneys. This interstitial in a normal state is not visible because the relative volume taken up by this compartment is not more than 5%–10%. Though, it is growing to 60% of kidney tissue in unhealthy kidneys.<sup>2</sup> In chronic kidney injury, there is changes of the interstitial compartment referred to as interstitial fibrosis. However, knowledge is limited on how this badly-behaved interstitial compartment has robust connections to other compartments of the kidneys. This study aims to correlate severity of histopathologic lesions among compartments in kidney tissues.

## Methods

### Study Population

The study is a cross-sectional study of patients undergoing native kidney biopsy at Sanglah Hospital, Bali, Indonesia. These study inclusion criteria were patients from age of 12 to 60 years who underwent a clinically indicated kidney biopsy of nephrotic syndrome between October 2016 and May 2018. These patients were recruited consecutively. Patients provided blood and urine samples before kidney biopsy.

Urinary protein excretion was measured quantitatively. Exclusion criteria were the inability to provide consent, solitary kidney, hemorrhagic diathesis, uncontrolled severe hypertension, severe anemia or volume depletion, cystic kidney, hydronephrosis, acute pyelonephritis or abscess, kidney neoplasm, and End Stage Renal Disease (ESRD). The study was approved by Sanglah Hospital Research Committee.

### Histopathology Evaluation

All biopsies were examined under light microscopy and the cores were stained with Hematoxylin-Eosin, Periodic Acid-Schiff, and Masson's Trichrome. A senior renal pathologist was evaluating the cores and discussed through Clinicopathologic Conference (CPC). We developed the semiquantitative scores through CPC discussions to evaluate 4 compartments: glomerular, tubular, interstitial and vascular involvements. Glomerular involvement will be assessed for any abnormality present including activity, severity and distribution of abnormalities involved. Tubular involvement will be assessed for any abnormality present, including activity, distribution and presence of cast in tubuli. Interstitial involvement will be assessed for any abnormality present, including activity and distribution in the interstitial tissue. Vascular involvement will be assessed for the presence of endothelial injury and sclerosis.

### Outcomes

Glomerular will be scored 1 if abnormality found, and if no abnormality found will be scored of 0. Activity related to glomerulus consisted of score 0 to 3: 0 = normal, 1 = mesangial hypercellularity/mesangial matrix expansion, 2 = endocapillary hypercellularity, wireloops, 3 = membranous. Severity related to glomerulus consisted of score 0 to 3: 0 = normal, 1 = cellular crescent, 2 = fibrocellular crescent, 3 = fibrous crescent or fibrosis. Distribution related to glomerulus consisted of score 0 to 2: 0 = normal, 1 = focal, 2 = diffuse. Glomerular severity index was measured by summing abnormalities in glomerulus, glomerular activity, glomerular severity, and glomerular distribution.

Tubular abnormality will have score of 1, no abnormality

will have score of 0. Activity related to tubular consisted of score 0 to 2: 0 = normal, 1 = early course cloudy swelling, vacuolization, cell infiltration, 2 = injury: atrophy. Distribution related to tubular consisted of score 0 to 2: 0 = normal, 1 = focal, 2 = diffuse. Cast presence has score of 1, none = 0. Tubular severity index was measured by summing abnormalities in tubulus, tubular activity, tubular distribution, and tubular cast.

Interstitial abnormality will have score of 1, no abnormality will have score of 0. Activity related to interstitial consisted of score 0 to 3: 0 = normal, 1 = cell infiltration, 2 = edema, 3 = fibrosis. Distribution related to interstitial consisted of score 0 to 2: 0 = normal, 1 = focal, 2 = diffuse. Interstitial severity index was measured by summing abnormalities in interstitial, interstitial activity, and interstitial distribution.

Vascular abnormality will have score of 1, no abnormality will have score of 0. Activity related to vascular consisted of score 0 to 2: 0 = normal, 1 = endothelial injury, 2 = sclerosis. Vascular severity index was measured by summing abnormalities in vascular and vascular activity. Pathology severity index was measured by summing glomerular, tubular, interstitial, and vascular severity indexes.

Patient's information was collected including laboratory data, ultrasounds, x-rays, and biopsy reports. These study data were collected by electronic data system at Sanglah Hospital.

## Statistical Analysis

Descriptive statistics were summarized as mean  $\pm$  SD, minimum and maximum. We used Pearson correlation test to determine the associations among histopathologic severity scores. Linear association was considered significant if probability less than 0.05.

## Results

In this cross-sectional study of patients undergoing native kidney biopsy at Sanglah Hospital, we found that female was dominant than male at 65.2% and 34.8% respectively. Minimum age was 12 and maximum age was 48 with mean

26  $\pm$  10.38. Urine 24 hour was from 600 to 6100 cc per 24 hours. Serum creatinine ranged from 0.36 to 7.3 mg/dL.

Most individuals came with glomerular abnormalities (89.1%), tubular abnormalities (80.4%), interstitial abnormalities (84.8 %), but a very low number of vascular abnormalities (6.5%).

At the glomerular level, we grouped abnormalities based on activity, severity and distribution. Based on glomerular activity, most lesions we found were endocapillary hypercellularity (43.5%), followed by mesangial hypercellularity (34.8%). Based on glomerular severity, most of the glomeruli were normal (71.7%), followed by fibrous crescent/fibrosis findings (17.4%). Based on distribution, lesions found were mostly with focal distribution (45.7%).

At the tubular level, we grouped abnormalities based on activity, distribution, and cast. Based on tubular activity, we had a higher number of normal pattern (37%), followed by tubular atrophy (34.8%). Cast was found mostly in our study (58.7%). At the level of interstitial, an area that cannot be separated from tubulus as the inflammation in progress, found that infiltration of inflammation cells was very high (65.2%) compared to edema or fibrosis. Last compartment, at the vascular level, we found 93.5 % without vascular abnormalities.

## Study Population Characteristics

This study included 46 individuals consisted of 16 (34.8%) males and 30 (65.2%) females, aged 26  $\pm$  10.38 years, SBP 121.7  $\pm$  13.10 and DBP 78.21  $\pm$  7.80 mmHg, diagnosed with 14 lupus and 32 non-lupus nephrotic syndrome.

**Table 1. Baseline clinical characteristics of Sanglah Hospital Kidney Biopsy**

Characteristics	N = 46	Min.	Max.	Mean	SD
Age (years)		12	48	26	10.38
Systolic BP (mmHg)		110	160	121.68	13.10
Diastolic BP (mmHg)		70	96	78.21	7.80
Urine 24 hour (ml)		600	6100	1895	1151.47
Hematuria		0	3	1.30	0.73
Proteinuria		0	4	2.54	1.26
Serum creatinine (mg/dL)		0.36	7.3	1.73	2.8

## Patterns of Histopathology

We were grouping histopathology pictures based on abnormalities found in 4 compartments: glomerulus, tubulus, interstitial, and vascular. These abnormalities were scored, added up to index of glomerulus, tubulus, interstitial, and vascular.

### Glomerular Lesions

We found 89.1% with glomerular abnormalities. Activities were divided into score 0 to 3, score 0 with normal pictures of glomerulus was found 5 out of 46 individuals (10.9%). Score 1 with mesangial hypercellularity was found in 16 out of 46 individuals (34.8%). Score 2 with endocapillary hypercellularity was found in 20 out of 46 individuals (43.5%). Score 3 with membranous pattern was found in 5 out of 46 individuals (10.9%).

Glomerulus severity were divided into the same score of 0 to 3. Score 0 with no severity was found in 33 out of 46 individuals (71.7%). Score 1 with cellular crescent picture was found in 3 out of 46 individuals (6.5%). Score 2 with fibrocellular crescent was found in 2 out of 46 individuals (4.3%). Score 3 with fibrous crescent/fibrosis was found in 8 out of 46 individuals (17.4%).

Glomerulus abnormality distribution was divided into score 0 to 2, score 0 with none of focal nor diffuse was found in 9 out of 46 individuals (19.6%). Score 1 with focal picture was found in 21 out of 46 individuals (45.7%). Score 2 with diffuse picture was found in 16 out of 46 individuals (34.8%).

Glomerular severity index equals to the total sum of glomerular abnormality, glomerular activity, glomerular severity, and glomerular distribution score.

### Tubular Lesions

We found 80.4% with tubular abnormalities. Activities in tubulus were divided into score 0 to 2, score 0 with normal picture of tubulus was found 17 out of 46 individuals (37%). Score 1 with early course picture such as cloudy swelling, vacuolization, infiltration of inflammation cells was found

in 13 out of 46 individuals (28.3%). Score 2 with injury atrophy was found in 16 out of 46 individuals (34.8%).

Tubular abnormality distribution was divided into score 0 to 2, score 0 with none of focal nor diffuse was found in 16 out of 46 individuals (34.8%). Score 1 with focal picture was found in 27 out of 46 individuals (58.7%). Score 2 with diffuse picture was found in 3 out of 46 individuals (6.5%).

Tubular cast was divided into score 0 to score 1, score 0 with no cast was found in 19 out of 46 individuals (41.3%). Score 1 with cast was found in 27 out of 46 individuals (58.7%).

Tubular severity index equals to the total sum of tubular abnormality, tubular activity, tubular distribution, and tubular cast score.

### Interstitial Lesions

We found 84.8 % with interstitial abnormalities. Interstitial activity was divided into score 0 to 3, score 0 with normal picture of interstitial was found 7 out of 46 individuals (15.2%). Score 1 with infiltration of inflammation cells was found in 30 out of 46 individuals (65.2%). Score 2 with edema was found in 5 out of 46 individuals (10.9%). Score 3 with fibrosis was found in 4 out of 46 individuals (8.7%).

Interstitial abnormality distribution was divided into score 0 to 2, score 0 with none of focal nor diffuse was found in 7 out of 46 individuals (15.2%). Score 1 with focal picture was found in 30 out of 46 individuals (65.2%). Score 2 with diffuse picture was found in 9 out of 46 individuals (19.6%).

Interstitial severity index equals to the total sum of interstitial abnormality, interstitial activity, and interstitial distribution.

### Vascular Lesions

We found 93.5 % without vascular abnormalities. Activities in vascular were divided into score 0 to 2, score 0



with normal picture of vascular was found 43 out of 46 individuals (93.5%). Score 1 with endothelial injury was none. Score 2 with sclerosis was found in 3 out of 46 individuals (6.5%). Vascular severity index equals to the total sum of vascular abnormality and vascular activity.

### Correlations among Histopathology Parameters

Histopathologic abnormalities showed glomerular severity index was  $4.26 \pm 2.34$ , tubular severity index was  $3.09 \pm 1.90$ , interstitial severity index was  $3.02 \pm 1.48$ , vascular severity index was 0-3, pathologic severity index was  $10.57 \pm 4.55$ .

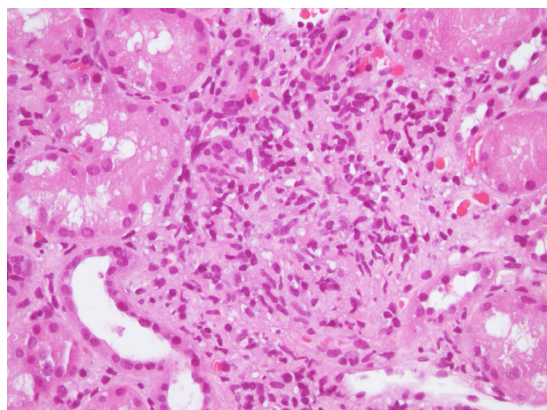
There was significant correlation between glomerular severity index and interstitial severity index ( $R=0.49$ ,

$P=0.001$ ), see figure 2. Also, there was a significant association between tubular severity index and interstitial severity index ( $R=0.45$ ,  $P=0.002$ ), see figure 3. However, there were no significant correlations of severity index between interstitial and vascular lesions, glomerular and tubular lesions.

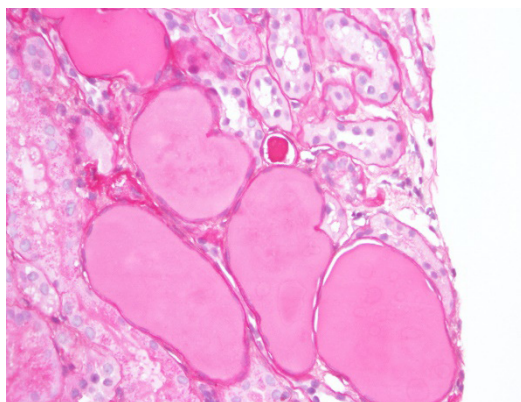
### Discussion

The main findings were significant correlation of severity index between interstitial and glomerular lesions ( $R=0.49$ ,  $P=0.001$ ), between interstitial and tubular lesions ( $R=0.45$ ,  $P=0.002$ ) in our nephrotic syndrome patients. Proteinuria as a fundamental part in nephrotic syndrome, is at the same time as a severity picture of the glomerular capillary wall changes and its permeability. Proteinuria can be a good marker of the overall severity of glomerular damage. Fur-

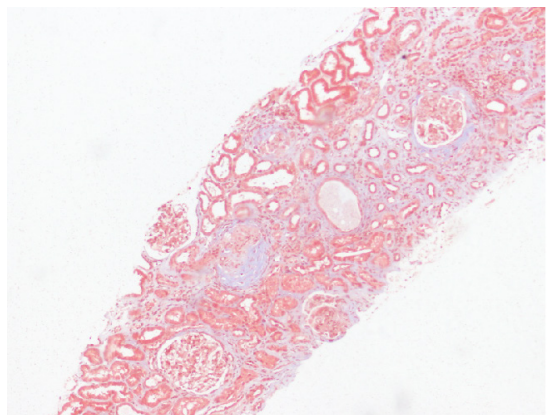
**Figure 1a-1d. Histopathologic pictures of Sanglah Hospital Kidney Biopsy.**



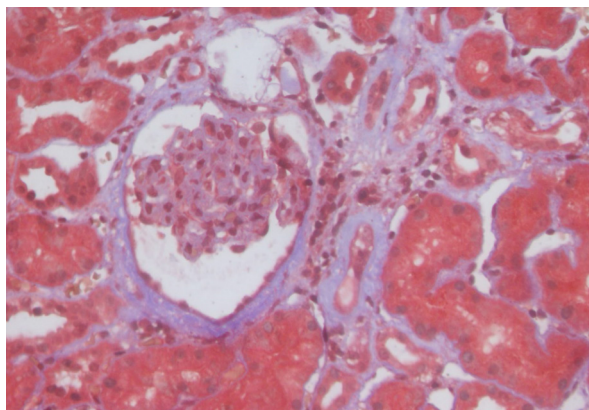
**1a.** Interstitial infiltration of lymphocyte. H&E 400X



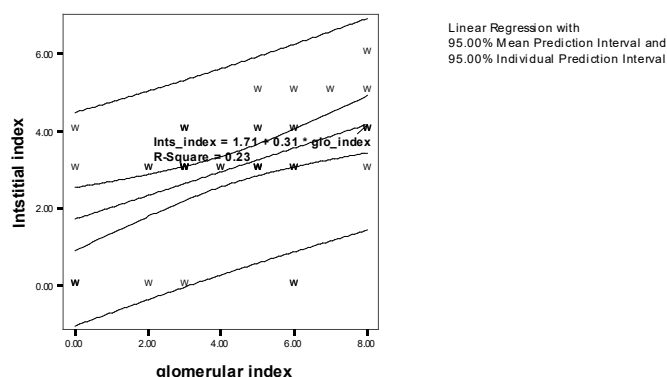
**1b.** Tubules thyroidization, characterized by enlarged round tubules with markedly flattened epithelium and intratubular casts. PAS 400X



**1c.** Periglomerular fibrosis and fibrous crescent surrounded by “not back-to-back” tubuli. MST 100X



**1d.** One glomerulus showed picture of periglomerular fibrosis. MST 400X



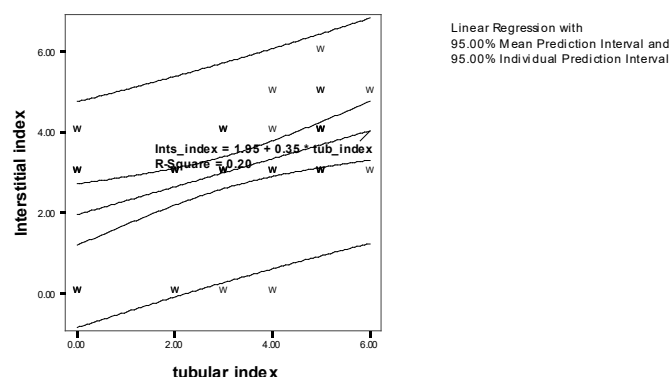
**Figure 2. Scatter plot and linear association between glomerular index and interstitial index (R=0.49; P=0.001).**

ther path of protein leakage to tubular cells compartment will involve the reabsorptive mechanisms that later can

explain the injury of the cells. Total tubulointerstitial damage has correlation to proteinuria duration and later GFR declines.<sup>3,4</sup> In all glomerular diseases, the quantity of proteinuria also has contribution to the degree of tubulointerstitial damage.<sup>3</sup>

In our study we revealed interesting facts that interstitial tissue lesions were associated with tubular lesions and glomerular lesions. It may implicate two important observations; first is the fact that proteinuria could cause extraglomerular as well as glomerular damage. Second is protein itself may produce pro-inflammatory and pro-fibrotic process that contribute to chronic tubulointerstitial damage directly.

Proteinuria could cause extraglomerular compartment damage such as in interstitial and tubular compartments. The severity of chronic extraglomerular damage such as peritubular capillary loss, tubular atrophy and interstitial fibrosis are the best representative of renal function histologically.<sup>5</sup> This renal function, in most studies are designated to serum creatinine. Series of renal morphometric studies by Bohle et al. in 1977 tried to link this serum creatinine with lesions severity in renal compartments. They found no correlation between glomerular lesions severity and serum creatinine, but there is a positive correlation between relative interstitial volume and level of serum creatinine in 40 perimem-



**Figure 3. Scatter plot and linear association between tubular index and interstitial index (R=0.45; P=0.002).**

branous glomerulonephritis patients. Serum creatinine level less than 1.2 mg/100 ml at stages I-III, renal interstitial was less expanded than serum creatinine level higher than 2 mg/100 ml.<sup>1</sup> Another glomerular disease, membranoproliferative glomerulonephritis, involving 33 patients showed that there is no certain relationship between glomerular lesions severity and serum creatinine level. But there is a significant positive correlation between the relative interstitial volume and the level of serum creatinine.<sup>6</sup> In endocapillary acute glomerulonephritis and moderately severe mesangioproliferative glomerulonephritis, are with positive correlations between relative interstitial volume and serum creatinine. These are severe glomerular lesions, but serum creatinine is around normal values in most cases where the relative interstitial volume does not increase more than 15%.<sup>7</sup> In 48 cases of renal amyloidosis and a recent study about amyloidosis, were found a statistically significant positive correlation between relative interstitial volume and serum creatinine.<sup>8</sup> The change into interstitial fibrosis seems to influence renal function, not amyloid masses. However, renal insufficiency appears to depend upon both the glomerular and the interstitial compartments, but in grades II-IV, the interstitial fibrosis is thought to be more vital for renal function.<sup>9</sup>

Both inflammatory glomerular diseases (endocapillary acute glomerulonephritis, mesangioproliferative glomerulonephritis, membranoproliferative glomerulonephritis) and non-inflammatory glomerular diseases (amyloidosis) have

significant correlation between serum creatinine level and expansion of the cortical interstitium by fibrosis.

Interstitial fibrosis could lead to these problems as follows: first is related to vessels. Narrowing of the postglomerular vessel network by interstitial fibrosis, further cause increase of resistance in the renal cortical blood flow. High resistance cause slow glomerular blood flow then may cause decrease of GFR and increase of serum creatinine.

Second, is related to interstitial-tubular connection. Once interstitial fibrosis takes place, the nearby tubules become atrophy. This tubular atrophy could be caused by vessels related malnutrition during fibrosis.<sup>10</sup> Another important study by Bohle et al. confirmed impairment of the GFR (increase of serum creatinine) by fibrosing process at the renal cortical interstitium. The study showed significant correlations between the decrease of the proximal tubules total area, of the epithelial cells area, and both the amount of the renal cortical interstitial fibrosis and the serum creatinine level. Reduced GFR is occurred through previously explained interstitial fibrosis and impairment of resorptive capacity for NaCl from atrophy tubules, later influence GFR through tubular-glomerular feedback-mechanism of Thureau.<sup>11,12,13</sup>

Our study revealed significant correlations of severity index between interstitial and glomerular lesions. There are other pathways from glomerular to interstitial compartment. Pro-inflammatory mediators may originate within glomeruli, produced systematically or locally by inflammatory and resident glomerular cells as part of the primary nephritic process.<sup>5</sup> Glomerulonephritis activates cells of the immune system and intrinsic renal cells. The activation will produce and release pro-fibrotic cytokines and growth factors that drive the fibrotic process. It is recognized that the development of glomerular inflammation happened prior to interstitial fibrosis in glomerular diseases.<sup>14</sup> The link of mechanism of events are not clearly understood, but the role of tubular epithelial cells in intermediating this link is favored. Another alternative pathway is occurred when glomerular diseases are in acute or chronic states. In acute state is through crescentic glomerular disease where there is breaks in Bowman's capsule and allowing protein leakage into the interstitial. In chronic condition is when glomerular diseases progress and region of sclerosis of the tuft develop. These

sclerotic regions become adherent to and disrupt Bowman's capsule and cause direct leakage of the glomerular ultrafiltrate to the peritubular interstitial space.<sup>5</sup>

Urinary protein may initiate pro-inflammatory and pro-fibrotic process that contribute directly to chronic tubulointerstitial damage. Daily doses of albumin could cause overload proteinuria that consist of exogenous albumin and several endogenous plasma proteins.<sup>15</sup> This mechanism seems not related to response of immunology to albumin, but interstitial inflammation develops, and fibrosis appears right after the onset of proteinuria.

Our study revealed that no significant correlations of severity index between glomerular and tubular lesions. A study done in 1987 also confirmed that interstitial-tubular connection proved to be unrelated to severity of glomerular lesions. Severe glomerular lesions can have completely normal interstitial and tubular compartments, and vice versa.<sup>16</sup>

Our study revealed that interstitial tissue could influence other compartments, but not vascular. Biopsies results were mostly not accompanied by vascular compartments, thus less lesions were found.

Several limitations related to our study that we did not use electron microcopy or immunofluorescence because of limited facility. The data we used were from retrospective data with some data were considered as missing. Proteinuria and hematuria were determined by semiquantitative scale.

Suggestions for future studies would be to consider re-scoring the biopsies to a simpler two-phase 1-3 level activity or chronicity scale that will permit statistical parametric correlation. This severity index was not validated yet, therefore second suggestion would be to perform association between severity of proteinuria and severity of lesions in any compartments with general linear model with proteinuria in g/g creatinine as dependent, and the serum creatinine and severity scores in the different compartments as independent predictors (covariates). Third suggestion is to validate histopathology report from a single examiner to two examiners to increase data consistency in intra and inter-observation.



## Conclusions

There are significant correlations of severity index between interstitial and glomerular lesions; and between interstitial and tubular lesions. It may implicate that histopathological process in interstitial tissue plays a central role in the pathogenesis of proteinuria in nephrotic syndrome. Proteinuria could cause glomerular as well as extraglomerular damage. Protein itself may produce pro-inflammatory and pro-fibrotic process that contribute to chronic tubulointerstitial damage. Interstitial-tubular connection proved to be unrelated to severity of glomerular lesions. Various glomerular diseases could cause different pictures of severity among compartments.

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