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Research paper

A study of clinicopathological features and selected laboratory parameters in a cohort of Sri Lankan patients with lupus nephritis

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Abstract

Introduction: Lupus nephritis (LN) is a complication of systemic lupus erythematosus that results in significant morbidity and mortality. Several studies have shown an association between certain pathological lesions and laboratory parameters in LN.

Objective: The objectives were to describe the clinicopathological features and laboratory parameters in a cohort of Sri Lankan patients with biopsy-proven LN and determine the associations between the pathological features and laboratory parameters.

Method: This was a retrospective, cross-sectional study of all renal biopsies of LN reported at the Department of Pathology, Faculty of Medicine, University of Colombo from January 2017 to December 2021.

Results: Eighty cases were identified. The majority were females (95%, 76/80). The mean age at biopsy was 27 ± 10.71 years. Subnephrotic range proteinuria (43.8%, 35/80) was the commonest presentation. The most frequent histological type was class IV (66.3%, 53/80) followed by class II (15%, 12/80) and class III (10%, 8/80). Serum creatinine showed a significant association with both activity and chronicity indices. Glomerulosclerosis showed an association with serum creatinine levels while cellular/fibrocellular crescents were associated with both serum creatinine levels and red cells in urine.

Conclusion: In this cohort of Sri Lankan patients with LN, the serum creatinine level showed an association with activity/chronicity indices and the presence of glomerulosclerosis and crescents in the renal biopsy. The presence of red cells in urine showed an association with crescents.

Keywords: lupus nephritis, laboratory parameters, activity index, chronicity index

Introduction

Lupus nephritis (LN) is the renal manifestation of systemic lupus erythematosus (SLE) and a critical complication which results in increased morbidity and mortality. Despite current treatments, about 17% of LN patients progress to end-stage renal disease within a decade (1,2).

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The primary pathogenic mechanism of LN involves immune complex mediated microvascular injury initiated by circulating double-stranded DNA polynucleotide antigen/anti-DNA antibody complexes, leading to inflammatory changes (3,4,5).

Although some patients may not show symptoms of kidney disease, the American College of Rheumatologists recommends regular screening of patients with SLE to look

for new-onset and recurrent renal involvement (6).

Renal biopsy is the gold standard investigation to diagnose LN (7,8). The histopathological changes of a renal biopsy in LN comprise a spectrum of tubulointerstitial, vascular and glomerular changes. The modified National Institute of Health (NIH) activity index (AI) score and chronicity index (CI) score aid in accurately assessing renal damage and improving therapeutic outcomes (9,10). Numerous studies worldwide have explored the pathological features of LN and their clinical significance (11-21).

This study aimed to describe the clinical features, blood and urinary test parameters and histopathological features in a cohort of Sri Lankan patients with LN evaluated with renal biopsy.

Additionally, this study aimed to identify associations between the blood and urinary test parameters and specific histological features in renal biopsies, which are used to calculate AI and CI.

Methods

This was a descriptive cross-sectional study of all renal biopsies of patients with LN reported at the Department of Pathology, Faculty of Medicine, University of Colombo during the five years from 1st January 2017 to 31st December 2021. This cohort included patients with a clinical diagnosis of SLE who underwent renal biopsy at the Nephrology Units of the National Hospital of Sri Lanka, Lady Ridgeway Hospital for Children and the National Institute of Nephrology Dialysis and Transplantation.

Biopsies with a minimum of seven glomeruli were included in the study. Post-transplant renal biopsies of patients with LN, patients diagnosed with other comorbidities affecting renal outcomes such as diabetes mellitus and cases with incomplete clinical data, untraceable slides/tissue blocks and faded/damaged slides, which could not be re-stained, were excluded. Ethical approval for the study was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Colombo (EC-21-044).

The selected demographic features (age, sex), laboratory parameters (serum creatinine, 24-hour urinary protein excretion, urinary protein/creatinine ratio, red cells in urine), and clinical data were obtained from the request forms. Based on the clinical information provided on the request form, the clinical presentation was categorised as subnephrotic range proteinuria, nephrotic and nephritic mixed picture, nephrotic range proteinuria / nephrotic syndrome, isolated rising serum creatinine and isolated haematuria. The serum creatinine level, 24-hour urinary protein excretion and urinary protein/creatinine ratio were documented.

All renal biopsies were serially sectioned into 2-3 micrometre thick paraffin sections and stained with haematoxylin and eosin, periodic acid-Schiff, silver methenamine and Masson's trichrome stains. These were reviewed and each case was assessed and reclassified according to the revised ISN/RPS classification for LN (10). The investigators were blinded to the patient's clinical and laboratory parameters, and class and scores of activity and chronicity indices mentioned in the original report when assessing the biopsy. A consensus was obtained by reviewing the slides at a conference microscope for the biopsies which had discrepancies with respect to the class of LN and the AI and CI.

The data was analysed using Statistical Package for Social Sciences software (version 23). The laboratory parameters were converted to categorical variables for the analysis. 24-hour urinary protein excretion was categorised as nephrotic (>=3.5g/day) and non-nephrotic (<3.5g/day). Urinary protein/ creatinine ratio was categorised as nephrotic range (>=2.0g/gCr) and non-nephrotic range (<2.0g/gCr). Serum creatinine level was categorised as normal and elevated. Red cells in urine were categorised as present/absent. The chi-square test and Fisher-exact test were used to determine the associations between categorical variables. Mann–Whitney U test and Friedman test were used to compare the

differences in AI and CI in groups categorised based on the presence of elevated serum creatinine, red cells in the urine and nephrotic range proteinuria (based on 24-hour urinary protein excretion and urinary protein creatinine ratios). An Independent sample T-test was used to assess the relationship between mean serum creatinine levels and each histopathological feature studied. P-value <0.05 was considered statistically significant.

Results

Ninety-six renal biopsies of LN were reported during the study period. Eighty renal biopsies that met the inclusion and exclusion criteria were included and reviewed for this study.

Demographic features and clinical presentation of patients with LN in this study

The mean age of the patients in the study was 27 ± 10.71 years. Seventy-six (76/80,95%) were women and the female-to-male ratio was 19:1). At the time of renal biopsy, the majority (35/80, 43.8%) had subnephrotic range proteinuria. A nephrotic/nephritic mixed picture was present in 33.8% (27/80) (Table 1).

Distribution of laboratory parameters

The results of serum creatinine, 24-hour urinary protein excretion, urinary protein/creatinine ratio and urinalysis were available in 64, 27, 28 and 69 patients respectively. The median serum creatinine level was 57 µmol/L (38-98). The median 24-hour urinary protein excretion was 4 g/day (2.43-15.37). The median urinary protein/creatinine ratio was 1.23 mg/mgCr (0.66-3.65). At the time of biopsy, 79.1% of patients had red cells in the urine.

Pathological features at renal biopsy according to NIH activity and chronicity indices

The most frequent LN class in this study was class IV (66.3%) followed by class II (15%) and class III (10%) (Table 2). The most common histological feature contributing to the AI in both class III and class IV was endocapillary hypercellularity. The commonest histological feature contributing to the CI in class III was tubular atrophy and in class IV it was interstitial fibrosis (Table 3) (Figure 1).

Fibrointimal thickening of blood vessel walls was seen in five (6.25%) patients and three of these patients had hypertension.

Clinical presentation at renal biopsy	**Frequency n, (%) (N=80)**
Subnephrotic range proteinuria	35 (43.8)
Nephrotic and nephritic mixed picture	27 (33.8)
Nephrotic range proteinuria / nephrotic syndrome	7 (8.8)
Isolated rising serum creatinine	6 (7.5)
Isolated haematuria	5 (6.3)

Table 1: Clinical presentation at renal biopsy

LN Classification	Frequency n, (%) (N= 80)
Class I	4 (5.0)
Class II	12 (15.0)
Class III	8 (10.0)
Class IV	53 (66.3)
Class VI	1 (1.3)
Class IV+V	1 (1.3)
Class V+III	1 (1.3)

Table 2: Frequency of LN class in the study population

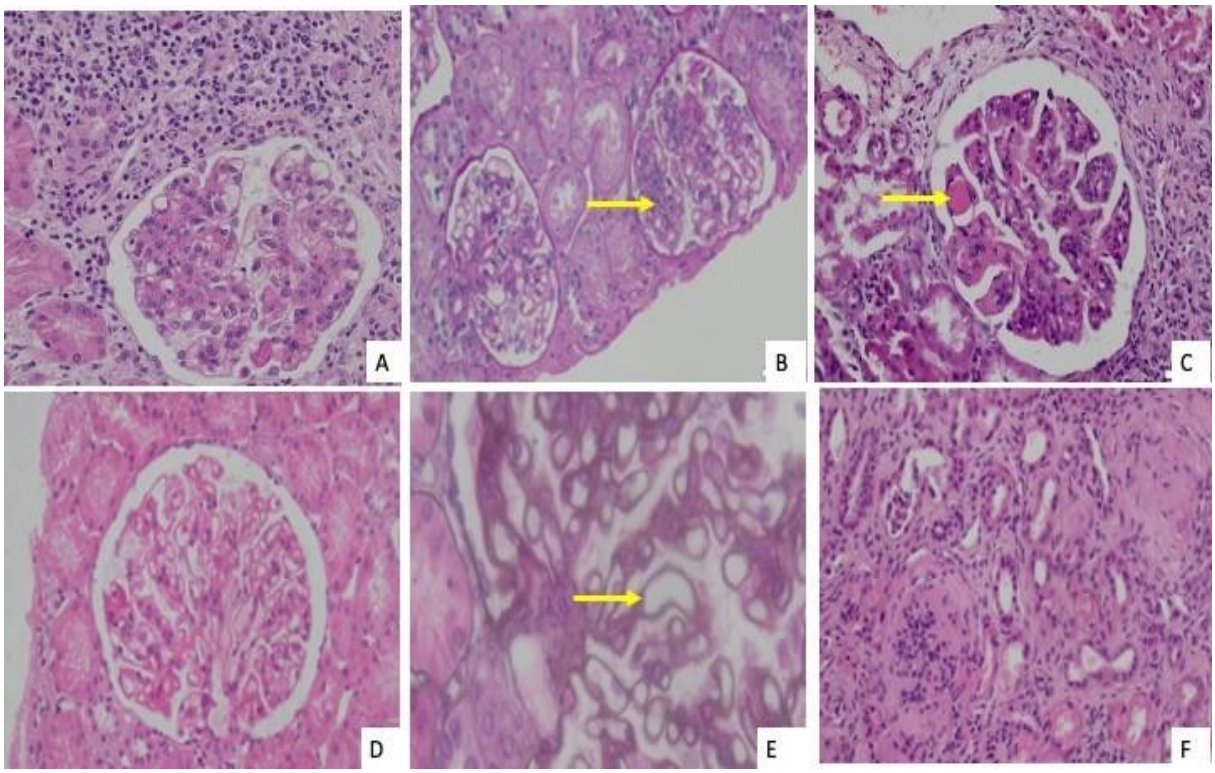

Figure 1: A. Class II - Glomeruli show mesangial matrix expansion and mesangial hypercellularity (H&E x400) **B**. Class III - <50% of glomeruli show proliferative glomerular lesions, and other glomeruli are histologically normal. One glomerulus shows endocapillary proliferation and other glomerulus is histologically normal (arrow, H&E x200) **C.** Class IV - >50% of glomeruli show proliferative glomerulonephritis. Features include endocapillary proliferation, karyorrhexis and leukocyte infiltration and hyaline thrombi in glomerular capillaries (arrow, H&E x400) **D.** Class V - Most of the glomeruli show glomerular capillary basement membrane thickening (H&E x400) **E.** Class V - Spikes formation in silver methenamine stain (arrow x400) **F.** Class VI - All glomeruli are partially or globally sclerosed with moderate to severe tubular atrophy and interstitial fibrosis (H&E x400)

	Class III (n=8)	**Class IV (n=53)**
Activity index	2.875 ± 3.28	7 ±4..5
Endocapillary hypercellularity	7 (87.5%)	52 (98.11%)
Neutrophils/karyorrhexis	3 (37.5%)	33 (62.26%)
Fibrinoid necrosis	0(0%)	7 (13.20%)
Hyaline deposits	2 (25%)	36 (67.92%)
Cellular/fibrocellular crescent	1 (12.5%)	25 (47.16%)
Interstitial inflammation	5 (62.5%)	45 (84.9%)
Chronicity index	2 ± 2.6	2.45 ± 3.06
Total glomerulosclerosis score	4 (50%)	6 (11.32%)
Fibrous crescents	0 (0%)	6 (11.32%)
Tubular atrophy	7 (87.5%)	10 (18.86%)
Interstitial fibrosis	4 (50%)	32 (60.37%)

Table 3: Individual histological features contributing to AI and CI in class III and IV

Comparison of AI and CI based on abnormalities in laboratory parameters

Mann-Whitney U test was used to compare the activity and chronicity indices based on the presence of an abnormality in each of the laboratory parameters assessed. Only elevated serum creatinine showed a significant association with AI ($p<0.001$) and CI ($p<0.001$) indices. The presence of red cells in the urine and nephrotic range proteinuria on 24-hour urinary protein analysis and urine protein: creatinine ratio showed no significant association with AI and CI.

Association of individual histological features of NIH with activity and chronicity indices at renal biopsy with laboratory parameters

Analysis of associations between individual histological features of AI and CI and the presence of red cells in the urine, elevated 24-hour urinary protein excretion and elevated urinary protein: creatinine ratio showed that cellular and fibrocellular crescents had a significant association with the presence of red cells in urine. Mean serum creatinine values were compared with each of the histological features assessed, and cellular and fibrocellular crescents and glomerulosclerosis showed a significant association with elevated serum creatinine values (Table 4).

Discussion

This retrospective study describes the clinical presentation, serum and urinary laboratory parameters and histological features in a cohort of Sri Lankan patients with LN.

Demographic features of patients with LN

The young age of onset of LN and female preponderance in our study is comparable to previous studies carried out in Sri Lanka and other countries (Table 5). The difference in the incidence of LN between sexes may stem from immune, genetic and hormonal factors, in addition to geographic and racial variations (24).

Histological findings	**Laboratory parameters**										
	Urinary red cells		P-value	24 hours urinary protein excretion (g/day)		P-value	Urinary protein/ creatinine ratio (g/gCr)		P-value	**Serum creatinine (micromol/L)**	P-value
	Presence (n=53)	Absence (n=14)		Less than 3.5 (n=13)	= or more than 3.5 (n=14)		Less than 2 (n=11)	= or more than 2 (n=17)			
Endocapillary proliferation											
Presence	42(79.2)	10(71.4)	0.533	12(92.3)	10(71.4)	0.326†	8(72.7)	12(70.6)	0.903	125.45±126.057	0.089
Absence	11(20.8)	4(28.6)		1(7.7)	4(28.6)		3(27.3)	5(29.4)		86.68±97.643	
Fibrinoid necrosis											
Presence	5(9.4)	1(7.1)	1.000†	2(15.4)	1(7.1)	0.596†	1(9.1)	2(11.8)	1.000†	69.16±24.894	0.653
Absence	48(90.6)	13(92.9)		11(84.6)	13(92.9)		10(90.9)	15(88.2)		122.59±126.06	
Cellular / fibrocellular crescents											
Presence	23(43.4)	1(7.1)	**0.013**	5(38.5)	5(35.7)	0.883	3(27.3)	5(29.4)	1.000†	155.32±150.29	**0.007**
Absence	30(56.6)	13(92.9)		8(61.5)	9(64.3)		8(72.7)	12(70.6)		91.75±89.658	
Interstitial inflammation											
Presence	37(69.8)	9(64.3)	0.692	9(69.2)	13(92.9)	0.165†	7(63.6)	10(58.8)	1.000†	130.86±131.04	0.063
Absence	16(30.2)	5(35.7)		4(30.8)	1(7.1)		4(36.4)	7(41.2)		83.63±85.036	
Glomerulosclerosis											
Presence	30(56.6)	7(50.0)	0.659	8(61.5)	8(57.1)	0.816	4(36.4)	10(58.8)	0.440†	142.05±143.15	**0.027**
Absence	23(43.4)	7(50.0)		5(38.5)	6(42.9)		7(63.6)	7(41.2)		86.11±76.487	
Interstitial fibrosis											
Presence	31(58.5)	7(50.0)	0.568	7(53.8)	8(57.1)	0.863	5(45.5)	8(47.1)	0.934	137.38±142.01	0.083
Absence	22(41.5)	7(50.0)		6(46.2)	6(42.9)		6(54.5)	9(52.9)		90.45±79.435	

† **Fisher exact value**

Table 4: Association between individual histological features in AI and CI with laboratory parameters

Study	Year	Country/ number of patients	Mean age (years)	Females (n,%)	Clinical presentation (n, %)	Laboratory parameters				LN Class					
						SCr (mg/dL)	24-hour UPE (g/day)	UPCR(g/g Cr)	MH N (%)	I	II	III	IV	V	VI
Ranatunga et al.	2022	Sri Lanka n=80	27 ± 10.713	76 (95%)	Sub-nephrotic range proteinuria (35, 43.8%) Nephrotic and nephritic mixed picture (27, 33.8%) Nephrotic range proteinuria /nephrotic syndrome (7, 8.8%)	1.33 ± 1.37	4.33 ± 3.682	3.84 ± 4.181	53 (79.1%)	4 5%	12 15.0%	8 10.0%	53 66.3%	2† 2.6%	1 1.3%
Perera et al.[13]	2015	Sri Lanka n=75	27	66 (88%)	Asymptomatic sub-nephrotic range proteinuria (35, 47%) Nephrotic syndrome (16, 21%) Hypertension (13, 17%)					0	10 13%	3 4%	59 79%	0	-
Herath et al.[15]	2017	Sri Lanka n=72	28	64 (89%)	Sub-nephrotic range proteinuria (56, 78%) Nephrotic syndrome (16, 22%) Rising serum creatinine > 1.3mg/dl (20, 28%)					0	10 13%	3 4%	59 79%	0	-
Katsuyama et al.[16]	2020	China n=158	45	124 (79%)		0.87 ± 0.51	-	3.00 ± 2.78	52 (44%)	-	-	20 17%	84 71%	24‡ 31%	-
Shariati-Sarabi et al. [17]	2013	Iran n=71	24	65 (91.5%)	Hypertension (38, 53.5%) Nephrotic syndrome (6, 8.5%) Renal failure (24, 33.8%)	1.6 ± 1.5	1.8 ± 1.3	-	60 (84.5%)	-	-	15 21.1%	37 52.1%	14 19.7%	5 7.1%
Farah RI et al.[19]	2019	Jordan n=79	29.95 ± 12.16	68 (86.1%)	Hypertension (59, 74.7%) Proteinuria (78, 98.8%)	1.0987 ± 0.76	-	-	34 (43.1%)	2 2.5 %	5 6.3 %	10 12.7 %	37 46.8 %	15 19 %	1 1.3 %
Satirapoj et al.[20]	2015	Thailand n=244	34.0 ± 12.0	219 (89.8%)	Hypertension 1(163, 66.8%) Nephrotic range proteinuria (125, 51.2%) Nephrotic syndrome (74, 30.3%)	1.3 ± 1	-	4.4 ± 3.2	157 (64.3%)	-	7 2.86%	38 15.57%	156 63.9%	43 17.6%	-
Velásquez-Franco et al. [11]	2017	Colombia n=132	24	110 (83%)	Nephritic syndrome (61, 46%) Nephrotic syndrome (50, 38%) Acute renal failure (22, 17%)	0.9 (0.7-1.3)	2.450 (0.813-4.995)	-	85 (64%)	-	-	-	71 82.6%	-	-
Neumann et al.[22]	1995	USA n=107	29	NA	NA	NA	NA	NA	NA	0.9%	9.3%	15.0%	47.7%	12.1%	4.7%
Huong et al. [23]	1999	France n=158	28	NA	NA	NA	NA	NA	NA	1.9%	21.5%	21.5%	27.8%	20.3%	1.3%
Siso et al. [24]	2010	Spain n=190	28.8	170 89.5%	Elevated SCr	NA	NA	NA	NA	4.2%	17.4%	24.2%	37.9%	14.7%	1.6%

SCr – Serum creatinine, UPE – urinary protein excretion, UPCR – urine protein creatinine ratio, MH – microscopic haematuria, LN – lupus nephritis, NA - Not applicable, †Class IV + V – (1.3%), Class III + V – 1 (1.3%) ‡Class V – 15 (13%,), Class III+V - 2 (10%), Class IV+V - 7 (8%)

Table 5: Comparison of demographic features, clinical presentation, laboratory parameters and LN

	Ranatunga et al.	Katsuyama et al. [16]	Satirapoj et al. [20]	Nasri et al. [19]	Velásquez-Franco et al. [11]	Shariati-Sarabi et al.[17]
Laboratory parameter	**Histological parameters which have shown significant association with laboratory parameters**					
Serum creatinine	Activity index Chronicity index Glomerulosclerosis Cellular / fibrocellular crescents	Glomerulosclerosis	Activity index Chronicity index	Activity index Chronicity index Proportion of glomeruli with crescents	Activity index	Chronicity index
Microscopic haematuria	Cellular/ fibrocellular crescents		Activity index Chronicity index			Activity index
Urinary protein levels	-	Wire loops (did not show correlation with endocapillary proliferation or crescents)	Activity index Chronicity index			
Urinary protein/creatinine ratio (UPCR)			Activity index Chronicity index			
Estimated glomerular filtration rate (EGFR)			Activity index Chronicity index			

Table 6: Association of AI, CI and individual histology features at renal biopsy and laboratory parameters in previous studies

The mean age of the study population was 27 years. Younger age at presentation of LN in SLE is known to be associated with severe forms of the disease, poor outcomes and earlier mortality (24). Studies have shown a higher prevalence of renal damage in Asian patients with SLE residing in Western countries compared to white patients (23). The geographical variation in the outcome of patients with LN depends not only on ethnicity but also on socioeconomic factors, poverty, educational level, cultural factors and access to health care (23).

Clinical presentation at the time of renal biopsy

In this study, the most common clinical presentation at the time of renal biopsy was subnephrotic range proteinuria (43.8%), a finding consistent with previous research conducted in Sri Lanka and data from the Spanish Registry of Glomerulonephritis from 2008 and 2019 (13,15,25). Conversely, studies from Thailand, Jordan, and Iran have reported hypertension as the predominant clinical presentation at biopsy (17,19,20). In the present study, only 10 patients (12.5%) exhibited high blood pressure. A study conducted in Colombia identified nephritic syndrome as the most common clinical presentation (11) (Table 5).

Distribution of laboratory parameters

The present study showed higher values of serum creatinine and 24-hour urinary protein excretion than studies carried out in Colombia, China, Thailand and Iran (11,16,17,19). In this study mean serum creatinine was 1.33 ± 1.37 mg/dL. Studies carried out by Katsuyama et al. and Velásquez-Franco et al. showed mean serum creatinine values of 0.87 ± 0.51 mg/dL and 0.9 (0.7- 1.3) mg/dL, respectively (11,16). The mean 24-hour urinary protein excretion in this study was 4.33 ± 3.682 g/day. Studies carried out by Velásquez-Franco et al. and Shariati-Sarabi et al. showed mean 24-hour urinary protein excretion values of 2.450 g/day (0.813-4.995) and 1.8 ± 1.3 g/day, respectively (11,17) (Table 5).

Pathological features at renal biopsy

The most prevalent LN class in this study was class IV, accounting for 66.3% of cases. This finding aligns with the previous studies conducted on diverse ethnic groups worldwide (Table 5). The second most common class observed was class II, a result similar to a study conducted in Sri Lanka by Perera et al. (13). Shariati-Sarabi et al. reported class III as the second most common class in studies conducted in Iran, whereas in studies conducted in China, Jordan, and Thailand, class V was identified as the second most common class (16, 17, 19, 20) (Table 6).

Association of AI and CI with laboratory parameters

In this study, both activity and chronicity indices were significantly associated with serum creatinine. Therefore, in the presence of elevated serum creatinine levels, it is difficult to determine whether renal impairment is due to active or chronic lesions without assessing the histological features in a renal biopsy.

Similar associations between serum creatinine and AI/CI were found in studies conducted by Satirapoj et al. in Thailand in 2015 (20) and Nasri et al. in Iran in 2014 (18). Additionally, the study by Velásquez-Franco et al. in Colombia in 2017 also revealed an association between elevated serum creatinine values and high AI (Table 6).

Association of individual histological features contributing to NIH activity and chronicity indices with laboratory parameters

In the present study, serum creatinine levels were associated with glomerulosclerosis, a finding consistent with research conducted by Katsuyama et al. in China in 2020. In the present study the presence of red cells in urine was associated with cellular and fibrocellular crescents. Shariati-Sarabi et al. and Satirapoj et al. found an association between higher AI scores and haematuria (17,20). The association between haematuria, crescents and AI can be explained by the endothelial damage caused by immune complexes, leading to the extravasation of red blood cells into the Bowman space with subsequent urinary excretion.

The present study showed no significant association between AI/CI and 24-hour urinary protein excretion and urinary protein: creatinine ratio. This contrasts with the findings of Satirapoj et al. who demonstrated a significant association between AI and urinary protein: creatinine ratio (20). Satirapoj et al. also found significant correlations between CI and estimated glomerular filtration rate, serum creatinine, presence of microscopic haematuria and UPCR on multiple regression analysis (20). Katsuyama et al. found associations between urinary protein level and wire loop lesions (16).

Fibrointimal thickening of blood vessel walls was identified in five of the patients studied, three of whom were known hypertensives. Microvascular lesions seen in LN include uncomplicated vascular immune deposits, arteriosclerosis and arteriolosclerosis, noninflammatory necrotising vasculopathy, necrotising vasculitis and thrombotic microangiopathy. These were not identified in the biopsies studied. Vascular changes in LN can also be associated with haemolytic uraemic syndrome/thrombocytopenic purpura scleroderma, mixed cognitive tissue disorders and antiphospholipid antibodies (26). Vascular lesions are critical to define renal prognosis in patients with LN. However, further evidence is needed to consider the inclusion of vascular lessons into AI and CI in future.

Limitations of this study include its relatively small sample size and retrospective nature. Since data was retrieved from request forms some clinical and laboratory data was not available. The 24-hour urinary protein and urine protein:creatinine ratio were not available in the majority of patients, which might have contributed to our inability to demonstrate an association between these parameters and activity/chronicity indices, and histopathological parameters. Immunofluorescence testing had been performed in only 22 cases; therefore, the possibility of a coincidental non-lupus renal disease cannot be completely excluded. The diagnosis of LN was made based on a combination of clinical, serological and histopathological features. Additionally, the study did not investigate the effect of treatment on laboratory and pathological parameters.

Nevertheless, the study describes the clinicopathological spectrum of LN in a local setting and underscores the predictive value of red cells in urine and serum creatinine levels for renal prognosis. Larger prospective studies comparing changes in these laboratory parameters and histological features before and after treatment may help identify potential biomarkers for monitoring treatment response and predicting the risk of early end-stage renal failure in patients with LN.

Conclusion

This study describes the clinicopathological features in a cohort of Sri Lankan patients with LN and the relationship between laboratory parameters and histopathological features in renal biopsy. Findings from this study unveiled associations between serum creatinine and AI, CI, glomerulosclerosis and cellular/fibrocellular crescents. An association between haematuria and cellular and fibrocellular crescents was also identified.

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