Time to Recovery From Proteinuria and Its Related Factors in Patients With Lupus Nephritis

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Abstract- Lupus nephritis (LN) is a severe form of systemic lupus erythematosus (SLE) with renal involvement. It affects the kidneys in about 50% of SLE patients. The aim of this study was to assess the evaluation of proteinuria recovery time and its related factors associated with lupus nephritis patients in Urmia-Northwest of Iran. A retrospective cohort study was carried out, in which medical records of 80 patients with systemic lupus nephritis referred to Imam Khomeini university hospital were reviewed. According to these records, the biopsy-proven renal disease has been progressed from September 2009 to September 2013. Proteinuria, less than 0.5 g/24h, was defined as proteinuria recovery. The time elapsed from the diagnosis of proteinuria to its recovery is considered as the duration of proteinuria recovery (month). The findings were analyzed by STATA11 statistical software. The mean age at diagnosis of lupus nephritis was 26.50±8.10 years (14-51 years). The mean creatinine level at the start of treatment was 1.20±0.61 mg/dl (0.5-2.80). Proteinuria recovery time was four months for 25% of patients, six months for 50% of patients (median time), and 12 months for 75% of them. The higher class of LN had a trend toward 31 % lower risk of proteinuria recovery (HR: 0.73, 95% CI 0.56-0.96; *P*=0.02), the expected risk is 1.94 times greater in women as compared with men (HR: 1.94, 95% CI 1.1-3.48; *P*=0.02). The patients in this study population respond to treatment in less time, and in comparison with other studies, their proteinuria recovers earlier. Class of lupus nephritis (negative) and gender (positive) were predictive factors of proteinuria recovery among LN patients.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory and autoimmune disease, commonly known as lupus. This disease causes the body's immune system to attack its own cells and tissues. According to four COPCORD studies, SLE was detected in 0.06% of the Iranian population (1). Lupus nephritis (LN), with the sign of renal involvement, is one of the most common and serious manifestations of SLE (2). It affects the kidneys in about 50% of SLE patients (3). Among the Iranian population, LN occurred at a young age and mostly in females (4).

Among LN patients, being free from renal flares was associated with attaining Complete Remission (CR) at 12 months after induction therapy (5). According to the Hopkins lupus cohort study, renal remission status at 24 months following LN diagnosis is a significant predictor of long-term renal survival (6).

Although potent anti-inflammatory and immunosuppressive therapies end in CKD or ESRD in many patients (3), LN is considered as a poor prognosis indicator and an important risk factor for morbidity and mortality in SLE (3). Approximately 30% of patients will progress to end-stage renal disease (ESRD) despite immunosuppressive therapy (7).

The level of proteinuria at the baseline visit predicted the time for improvement. (8) The ability of Proteinuria

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to change faster at 12 months makes it a favorable endpoint for clinical trials and research studies (9). Proteinuria does not have a significant effect on short-term outcomes (complete or partial or not remission) among the Iranian population (10). According to Hopkins lupus cohort data, proteinuria alone was not predictive of ESRD or mortality but was associated with long-term outcomes. Proteinuria mostly predicts long-term renal outcomes in lupus nephritis (11).

The main aim of the study was to assess the Evaluation of proteinuria recovery time and its related factors in lupus nephritis patients in Urmia Northwest of Iran.

Materials and Methods

This retrospective cohort study evaluating of proteinuria recovery time and its related factors associated with lupus nephritis patients in Urmia-Northwest of Iran.

After approval of the ethics committee Urmia University of Medical Sciences (No: IR: UMSU.res.1393.207) and obtaining written informed consent, a total number of 80 patients were studied. Medical records of patients with systemic lupus erythematosus were reviewed. According to these records, the biopsy-proven renal disease has been progressed from September 2009 to September 2013. To be included in the study, patients were required to be diagnosed with lupus nephritis. Exclusion criteria were any other disease that accompanies similar proteinuria diabetes. Their process of medical treatment was registered using data recorded in terms of proteinuria.

Proteinuria, less than 0.5 g/24h, was defined as proteinuria recovery. The time elapsed from the diagnosis of proteinuria to its recovery is considered as the duration of proteinuria recovery (month). Demographic and Para clinic characteristics, such as age, gender, base creatinine level, the gap between diagnosis of lupus nephritis, chronicity index, and a class of lupus nephritis, were extracted.

Chronicity status was determined based on chronicity index: Glomerular chronicity indices composed of Glomerular sclerosis 0-3, Fibrous crescents 0-3, Tubulointerstitial chronicity Interstitial fibrosis 0-3, Tubular atrophy 0-3.

The World Health Organization (WHO) has divided lupus nephritis into five stages based on biopsy. Classification of lupus nephritis was determined based on the World Health Organization (WHO) recommendations as pathologic findings. This schema included normal glomeruli (class I), pure mesangial disease (class II), focal proliferative glomerulonephritis (class III), diffuse proliferative glomerulonephritis (class IV), and membranous glomerulonephritis (class V) (2). Mean±SD (Standard deviation) was calculated for continuous variables, and frequencies were measured for categorical variables. Proteinuria recovery time of patients was the primary of the study. The cumulative risk of proteinuria recovery time between two groups was studied by the Kaplan-Meier method. The survival curves of the two groups were formally compared by use of the log-rank test. In continuous predictors (age, based creatinine and Protein level, IN-chronicity status), we considered the Cox proportional hazard model with a single continuous predictor. Predictors with p-values less than the cut-off value of 0.25 (Univariate Cox regression) were considered to be included in the final cox proportional hazards regression analysis to assess the effect of studied factors on protein recovery time in patients. Schoenfeld test was used to assess the fitted Cox regression model that adequately describes the data. All of the analyses were performed by STATA 11 software.

Results

This study encompasses 80 patients with lupus nephritis. The mean age at diagnosis of lupus nephritis was 26.50±8.10 years (14-51 years). The mean creatinine level at the start of treatment was 1.20±0.61 mg/dl (0.5-2.80). The mean Protein level was 2559.31±1787.65 g/24h (600-9500). Lupus nephritis Class I was seen in 1% of patients, Class II in 28%, Class III in 3%, Class IV in 50 %, Class V in 16 %. Diffuse proliferative lupus nephritis (Class IV) was the most common type of lupus nephritis among our patients.

The percentile of survival proteinuria recovery time derives from a Kaplan-Meier survivor function. Accordingly, Proteinuria recovery time was four months for 25% of patients, six months for 50% of patients (median time), and 12 months for 75% of them (considering the 25^{th}-50- 5th percentiles seen regarding the recovery time) (Table 1).

Figure 1 shows the duration of proteinuria recovery time for the effect of sex on proteinuria recovery time (Kaplan‑Meier method) in patients with lupus nephritis. Median (Q1-Q3) duration of proteinuria recovery time was statistically higher in men than women (12; 4.19-16.48 vs. 6; 4.7-81.19, log-rank test P=0.04).

Table 2 shows Cox regression analysis for the duration of protein recovery time using univariate and

multivariate analyses. In univariate analyses (unadjusted model), creatinine at initiating treatment, high chronicity scores, and a class of LN, increasing age were associated with 36%, 12%, 28 %, and 1 % lower hazard of proteinuria recovery, respectively.

Final Cox, proportional hazards regression analysis higher class of LN, had a trend toward 31 % lower hazard of proteinuria recovery, the expected hazard is 1.94 times higher in women as compared to men.

Table 1. Clinical characteristics of patients with lupus nephritis at the time of renal biopsy

Variables		N (80)
Males (%)		16(20)
Age (Mean±Sd)		26.50±8.10
Creatinine Level at Recovery Time (Mg/Dl)		1.16±0.7
Based Creatinine Level (Mg/Dl)		1.20±0.61
Proteinuria At Initiating Treatment (Mg/24h)		2559.31±1787.65
Gap Between Proteinuria and Diagnosis of Lupus Nephritis (Years)		1.92±3.62
Class Of Lupus Nephritis (%)*	**I**	1(1)
	Ii	22(28%)
	Iii	2(3)
	Iv	40(50)
	V	13(16)
Ln-Chronicity Status∞	**0**	8(10.4)
	1	11(14.3)
	2	28(36.4)
	3	14(18.2)
	4	10(13)
	5	1(1.3)
	6	4(5.2)
	9	1(1.3)

*2 patients had mixed class, ∞Chronicity Index

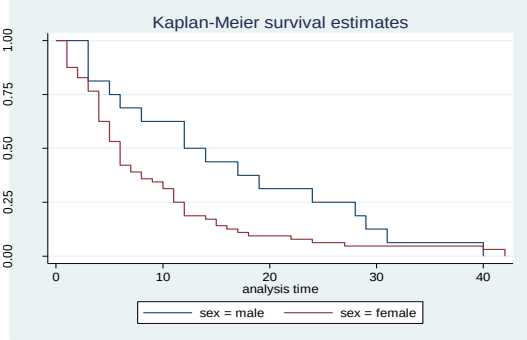

Figure 1. Kaplan-Meier method for the effect of sex on proteinuria recovery time in patients with lupus nephritis

Table 2. Cox regression analysis for the duration of protein recovery time using a univariate and multivariate model

Variables	Univariate	Multivariate∞
	Hazard ratios CI* (95%); *P*	**Hazard ratios CI (95%)**
Creatinine at initiating treatment (mg/dl)	0.64 (0.44-0.92);0.01	0.81(0.53-1.22);0.31
LN-chronicity status*	0.88(0.76-1.02);0.1	0.95(0.81-1.10);0.48
Proteinuria at initiating treatment (mg/24h)	1.00(0.99-1.0002);0.44	--
Age	0.99(0.96-1.01);0.54	--
Class of lupus nephritis	0.72(0.57-0.92); <0.01	0.73(0.56 -0.96);0.02
Sex (female)	1.71(0.97-2.98);0.06	1.94(1.1-3.48);0.02

*CI= confidence Interval, **Chronicity Index, ∞ backward selection of significant variables

Discussion

There are many factors to consider in the time to recovery from proteinuria in patients with lupus nephritis. Recovery proteinuria is one of these factors. Determining the recovery time and investigating the factors affecting

it can help patients' treatment process and follow up the response to the treatment.

In this research, most LN patients were females (1,9,11), and male sex was a risk factor of the late proteinuria recovery (8). Grade IV had the highest frequency among patients in this study which is similar to other Iranian studies (10,12). Patients in this study had a lower age average compared to other studies. This study is in the same line with other studies in which aging did not have a significant decline in proteinuria recovery.

In comparison to other studies, the patients responded to treatment in less time, and proteinuria recovery happened earlier in this study (3,7,13). Similar to our research, recovery from proteinuria was defined as proteinuria<0.5 g/24 h in the study of Touma Z in 2014 (8). Proteinuria recovery time was 52% within two years that is much later than our research, and the level of proteinuria at baseline visit predicted the time of improvement. The difference which exists between proteinuria recovery time in this study and other studies may be caused by different methods of patient inclusion such as biopsy, clinical status, and laboratory criteria as in active urine sedimentation simultaneous with proteinuria (7). All the patients in our study reached< 0.5 g proteinuria in 4 years of follow-up. Touma *et al.*, showed that 39 % (84 of 212) of patients in his study still did not get proteinuria recovery in the last visit (after 2.3±3.2 years of follow-up). The reason for this discrepancy is that the recovery time was differently accomplished between the two studies in another hand; Touma *et al.,* registered proteinuria recovery only if it happened twice respectively, whereas in our study, one-time proteinuria< 0.5 g in 24 hours was little enough to categorize patients as recovered from proteinuria. Also, in this research, the only criteria for protein loss in urine was a 24-hour urine analysis measuring proteinuria, but Touma *et al*., have used dipstick or spot ratio of urine creatinine if they did not have access to 24-hour urine samples (8). Hernandez *et al.*, showed more similar results with a study in which 69 % of patients after six months and 86 % after 12 months of treatment beginning were recovered from proteinuria (14). In another study by Chen YE *et al.*, 44 %, nearly half of patients, had achieved recovery from proteinuria through 16±14 months. The reason for the difference may be the fact that all classes of lupus nephritis were included in our study, but others had just studied patients with class IV and V of lupus nephritis (15). Furthermore, we defined proteinuria< 0.5 g/24 hours as recovery, but in this study, proteinuria≤ 0.33 g/24 hours was considered as a recovery criterion.

Although in this study, creatinine of serum and proteinuria at the initiation of treatment did not have a statistically significant effect on proteinuria recovery, similarly in various studies, higher levels of serum creatinine at the beginning of treatment were associated with decreased incidence of recovery, which is not statistically important (15,16). Ichinose *et al*., reports the protective effect of the lower level of serum creatinine on complete remission at 12 months follow-up in which duration after the renal biopsy was 51 months, which is similar to the definitions of renal remission and follow-up in this study (5). Another research in Iran reported that creatinine level, low GFR and hemoglobin, low C3 and albumin, and pathologic Class IV had a significant association with non-remission status among LN patients (10). K Ichinose *et al*., reported that CR (complete remission) attaining at 12 months had significantly lower levels of serum Cr (5). The Hopkins Lupus Cohort (>500 patients) data results showed that serum creatinine level was in the stable range between years 1 to 3 after starting the follow-up for those in CR or PR during 24 months (6). Pinto-Peñaranda LF in Colombian patients with severe proliferative lupus nephritis reports a baseline creatinine elevation and 24-h proteinuria greater than 1500 mg were statistically significant predictive factors of poor response at 12 months (13).

According to William a Fung's study, serum Cr and eGFR are fairly stable until six years after LN onset, 24H-P may be more appropriate as a biomarker due to its sensitivity to short-term change than Proteinuria in lupus nephritis (LN) patients (9). Similarly, in another study among the Iranian population in Yazd, Proteinuria does not have a significant effect on short-term outcomes (complete or partial or not remission) (10).

In this research, the high class of LN had a trend toward 31 % lower hazard of proteinuria recovery, but this trend was not statistically significant. K Ichinose *et al*., concluded that classes III and IV of lupus nephritis had less recovery time in the first 12 months of follow-up, which is not significant (5). Other studies, as in Touma *et al*., have shown a significant decline in proteinuria recovery incidence as the class of lupus nephritis gets higher (8). The decreasing effect of proteinuria recovery after an increase in the class of lupus nephritis may be due to more renal damage happening in higher classes. Membranous LN (ISN/RPS V) is seen in up to 15% of biopsied SLE patients (17), heavy proteinuria appears in many Membranous LN, and thus a longer period would be necessary to achieve renal remission (3).

In this research, a higher Chronicity index was

clinically accompanying with a lower hazard of proteinuria recovery, but it was not significant. Also, similar results were reported in other studies (4,12).

We retrospectively analyzed the complete remission rates at 12 months after induction therapy and evaluated the predictive factors for CR and their association with renal flares in patients with LN. We found that patients in our study responded to medical treatment earlier than other studies, and proteinuria recovery was achieved in less time. Class of lupus nephritis and gender had a significant effect on the incidence of proteinuria recovery.

The main strength of this study was the strict monitoring of patients. The weaknesses of this study did not evaluate partial remission of patients and Glomerular filtration rate (GFR) as one of the complete remission criteria in patients diagnosed with Lupus Nephritis.

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