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Prognostic factors of lupus nephritis in an Iranian population

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Several studies have been done on Lupus Nephritis (LN) and the related outcomes, but there are limited data about the outcome of the disease in Iranian patients. Our aim of this study was to determine predictive factors of poor prognosis of LN amongst an Iranian population. This retrospective study included 111 LN patients, which were followed at least for one complete year according to their medical records. Data such as age, gender, geographical region, classification of renal biopsy, serum creatinine, blood pressure, complement levels, proteinuria, anti-dsDNA level, hemoglobin, Glomerular Filtration Rate (GFR) and serum albumin were collected. The short-term outcome was considered as complete remission, partial remission or non-remission; possible factors affecting the occurrence of these outcomes were evaluated. Pearson Chi-Square test and logistic regression were used for data analysis. A P value of less than 0.05 was considered statistically significant. Female: male ratio was 9.1:1 and the mean age of patients was 26.86±7 years. Low albumin, low GFR, low hemoglobin, high systolic and diastolic blood pressure, high serum creatinine, proteinuria and biopsy class IV at baseline were significantly associated with no remission or partial remission. There was no relationship between the mentioned outcomes and age, gender and geographic region of the subjects. All variables associated with the risk of non-remission should be considered in determining the prognosis and treatment plan. Of all the factors mentioned above, systolic blood pressure and low C3 levels had the highest correlation with the failure of remission.

Keywords: lupus nephritis, prognosis, remission

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory autoimmune connective tissue disease that can affect many organs, which in the presence of antibodies and formation of immune complexes may cause tissue damage, due to an unknown reason [1, 2]. Renal involvement, as a consequence of Lupus Nephritis (LN), was first described by William Osler [3, 4]. It is estimated that lupus nephritis occurs in one-third of patients with SLE and this frequency varies from 29% to 54% in different studies [3].

Although the management of lupus nephritishas has improved in the recent years, 10%-15% of patients remain at risk of developing End-Stage Renal Disease (ESRD) [1]. Hence, it would be beneficial to identify histological and clinical characteristics related to disease outcome and patient's survival rate [5]. Being armed with prognostic factors that may affect the outcome of LN can be helpful for choosing an appropriate therapeutic regimen for SLE patients with various degrees of renal involvement. Furthermore, the complications of cytotoxic drugs, such as infertility and increased risk of cancer, can be prevented, in cases without the need for high-dose prescriptions [6].

Among the numerous studies conducted in the recent years, a few studies have determined the LN prognostic factors in Asian populations. For example, Dhir et al. in 2012 reported low levels of complement component 3 (C3), hypertension, hematuria, high levels of creatinine, lack of remission and occurrence of major infections, as factors affecting poor outcome of LN in Asian-Indians patients [7]. Yokayamain (2004) suggested baseline class IV renal biopsy as the most important prognostic factor associated with renal failure in Japanese population [8].

Due to data shortage from Iranian adult patients with LN, as well as insufficient knowledge about their prognostic factors, this study aimed to evaluate the clinical and laboratory characteristics impressing the prognosis and remission occurrence in these patients.

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Methods and Materials

Patients

This was a retrospective study of 111 patients with LN referred to the nephrology and rheumatology clinics of Shahid Sadoughi hospital, Yazd, between January 2002 to December 2012. Diagnosis of SLE was performed based on the American college of rheumatology criteria. Through the inclusion criteria, 15-45 year-old patients with LN, which were followed by rheumatologist for longer than one complete year (from the diagnosis of their disease until data collection time), were included. Baseline information such as age, gender, geographical region (Yazd or southern provinces such as Hormozgan and Kerman), classification of renal biopsy, serum creatinine, blood pressure, complement levels, proteinuria, anti-dsDNA level, hemoglobin, GFR and serum albumin were collected from patient's records. Incomplete data, overlapping syndromes, less than two examinations per year, and not receiving standard therapy [6] (methyl prednisolone sodium succinate plus cyclophosphamide) were considered as the exclusion criteria.

Measurements

Based on the average of two seated blood pressure readings, systolic blood pressure below 120 and diastolic below 80 mmHg was considered normal. Systolic values of 120 to 139 and diastolic values of 80 to 89 were considered as pre-hypertension. Hypertension was defined as higher values [9]. Hemoglobin levels equal or greater than 11 g/dL for women and 14 for men were considered normal and lower values were defined as anemia [10]. Measured by Jaffe colorimetric-kinetic method, baseline serum creatinine higher than 1.4 mg/dL was considered abnormal [11]. A GFR greater than 90 mL/min/1.73 m^2 was considered a natural parameter and less than 90 was considered abnormal. In classification of Chronic Kidney Disease (CKD), the term chronic renal failure was typically defined by CKD stages higher than 3, in which GFR is considered below 60. As a result, abnormal GFR amounts of 60-89 and less than 60 were reported as two subgroups [12].

Measurement of albumin amounts was carried out using the BCG (albumin reagent) method. An albumin excretion rate greater than 300 mg in a 24-hour urine was defined as proteinuria [13] and values between 300-3500 mg/m^2 were considered as macro-albuminuria. Albumin excretion rate greater than 3500 mg/m^2 was considered in the nephritic range [14]. Results of renal biopsy were recorded on the base of World Health Organization (WHO) classification [15]. Moreover, a serum albumin level below 4.1 g/dL was considered abnormal.

Serum C3 and C4 levels, depending on the normal values reported by the laboratory, were recorded as either normal or less than normal. Anti-dsDNA, evaluated by enzyme linked immunosorbent assay (ELISA), was recorded as normal and above normal values.

All data was relative to the baseline and each visit was extracted from patient's records. It should be noted that short-term outcomes in this study were considered as follows: Complete Remission (CR), which is defined as the presence of normal levels of serum creatinine and albumin and urine protein level of less than 300 mg per day. Partial Remission (PR) was defined as the presence of proteinuria of 300 to 500 mg per day with stable plasma creatinine level. According to the collected data in the first year and by using the previously mentioned definitions of short-term outcomes, patients were divided to three groups: complete remission, partial remission and Non-Remission (NR).

Statistical analysis

All data analysis was performed using the SPSS v.16 software. Pearson Chi-Square test was used for comparison between groups. Using logistic regression analysis, odds ratios were calculated for variables associated with nonremission occurrence. A P value of less than 0.05 was considered statistically significant.

Results

Of the 111 patients with LN, there were 100 women and 11 men, with a mean age of 26.86±7 (a range between 14 and 45 years). It should be mentioned that selected patients in this study had been followed for an average of 4.4 years (1.5 to 10 years) and at the end of the first year, the occurrence of remission was investigated in all patients. The number of patients with complete remission, partial remission and with no remission were 44 (39.64%), 27 (24.32%) and 40 (36.04%), respectively.

There was no significant relationship between the occurrence of these short-term outcomes and demographic characteristics such as age, gender and geographical location (Table 1).

Baseline systolic and diastolic blood pressure, proteinuria, serum albumin, creatinine, GFR, hemoglobin and C3 levels were significantly associated with the occurrence of the remission during the first year of disease. Normal amounts of these variables recorded in the complete remission group were more than other groups and abnormal amounts were more frequent in the non-remission group in comparison with the other two groups (Tables 2 and 3). In contrast, such a relationship

was not observed between C4 (P value = 0.12) and anti-dsDNA (P value = 0.165) with three different short-term outcomes (Table 3). Pathologic results showed a significant association with the short-term outcomes of the disease. The frequency of stage IV in the non-remission group was more than the other groups and stage II abundance in the complete remission group was more than the two other groups (P value = 0.001). Pathologic stage of IV was more frequent in patients (Table 4).

Odds ratio was calculated for all variables with adverse effect on remission by logistic regression test and accordingly, the most important factors were high systolic blood pressure and low C3, respectively (Table 5).

Table 1. The Association between demographic data and short-term outcomes

Group	Age at diagnosis				Sex		Geographical region	
	20>	20-29	30-39	40 & over	Female	Male	Persian Gulf	Others
CR	7(31.8%)	13(31.31%)	22(55%)	2(28.6%)	39(39%)	5(45.5%)	12(40%)	32(39.5%)
PR	5(22.7%)	15(35.07%)	5(12.5%)	2(28.6%)	26(26%)	1(9.1%)	8(26.7%)	19(23.5%)
NR	10(45.5%)	14(33.03%)	13(32.5%)	3(42.9%)	35(35%)	5(45.5%)	10(33.3%)	30(37%)
***P* value**	0.162				0.456		0.915	
S/NS	NS				NS		NS	

Abbreviations: CR: Complete Remission; NR: No Remission; NS: Non-Significant; PR: Partial Remission; S: Significant

Table 2. The association between systolic and diastolic pressure and short-term outcomes

Baseline blood pressure	Subtypes	CR(44 patients)	PR(27 patients)	NR(40 patients)	*P*value	S/NS
Systolic pressure	120>	42(95.5)	23(85.2%)	5(12.5%)	< 0.001	S
	120-139*	0(0%)	3(11.01%)	11(27.5%)		
	140≤**	2(4.5%)	1(3.7%)	24(60%)		
Diastolic pressure	80	42(95.5%)	25(92.6%)	18(45%)	< 0.001	S
	80-89*	0(0%)	0(0%)	3(7.5%)		
	90≤**	2(4.5%)	2(7.4%)	19(47.5%)		

CR: Complete Remission; PR: Partial Remission; NR: No Remission; S: Significant; NS: Non-Significant
*Pre-hypertension; ** Hypertension

Table 3. The association between laboratory parameters and short-term outcomes

Baseline variables	Subtypes	CR	PR	NR	P values	S/NS
Creatinine	1.4>	42(95.45%)	26(96.29)	31(77.5%)	0.012	S
	>1.4	2(4.55%)	1(3.71%)	9(22.5%)		
Albumin	4.1>	29(65.91%)	24(88.88%)	38(95%)	0.001	S
	4.1<	15(34.09%)	3(11.11%)	2(5%)		
Hemoglobin	Normal	33(75%)	14(51.86%)	12(30%)	< 0.001	S
	Abnormal	11(25%)	13(48.14%)	28(70%)		
Anti-ds DNA	Normal	13(29.55%)	6(22.23%)	5(12.5%)	0.165	NS
	Abnormal	31(70.45%)	21(77.77%)	35(87.5%)		
C3	Normal	38(86.37%)	18(66.66%)	16(40%)	< 0.001	S
	Low	6(13.63%)	9(33.34%)	24(60%)		
C4	Normal	23(52.28%)	9(33.34%)	11(27.5%)	0.120	NS
	Low	21(47.72%)	18(66.66%)	29(72.5%)		
GFR	90≤	38(86.36%)	12(44.44%)	14(35.89%)	< 0.001	S
	60-89	4(9.09%)	13(48.14%)	12(30.76%)		
	<60	2(4.55%)	2(7.42%)	13(33.35%)		
Proteinuria	300-3500	44(100%)	27(100%)	29(72.5%)	< 0.001	S
	3500<*	0(0%)	0(0%)	11(27.5%)		

CR: Complete Remission; PR: Partial Remission; NR: No Remission; C3: complement component 3; C4: complement component 4; GFR: Glomerular Filtration Rate; S: Significant; NS: Non-Significant
* Nephritic range

Table 4. The association between pathology stages and short-term outcomes

Subgroups	Pathology stage at baseline					
	II	III	IV	IV+V	V	VI
CR	5(11.36%)	11(25%)	28(63.46%)	0(0%)	0(0%)	0(0%)
PR	0(0%)	7(25.92%)	20(74.07)	0(0%)	0(0%)	0(0%)
NR	0(0%)	0(0%)	31(77.5%)	6(15%)	3(7.5%)	0(0%)
P value			< 0.001*			

CR: Complete Remission; PR: Partial Remission; NR: No Remission

* *P* value<0.05 was considered significant

Table 5. The Risk factors leading to a poor short-term outcome by univariate logistic regression

Variables	Odds Ratio (95% CI)	*P* value	S/NS
Low C3	3.9(0.96 -16.2)	0.056	S
Creatinine	2.6(0.14 – 4.7)	0.37	NS
Albumin	0.7(0.4-2.9)	0.3	NS
Diastolic hypertension(80mmHg<)	1.0 (0.129 -7.9)	0.88	NS
Systolic hypertension(120mmHg<)	23.8(9.1-36.7)	0.000	S
Proteinuria	1.0(0.5-2.3)	0.43	NS
Hemoglobin	1.6(0.14-3.2)	0.781	NS
GFR	1.3(0.14-3.7)	0.87	NS

C3: complement component 3; GFR: Glomerular Filtration Rate; S: Significant; NS: Non-Significant

Discussion

The female to male ratio in this study was 9.1:1 (90.1% female and 9.9% male). Among Iranian studies, in a study conducted on the correlation of clinical and pathological findings in patients with lupus nephritisin from Shiraz, this ratio was 5.57:1 [16], and in a study about the epidemiology of lupus nephritis at Imam Khomeini Hospital of Tehran, this ratio was reported as 6.4:1 [2]. In another study conducted in Mashhad, this ratio was 16:1 [3].

The mean age of the patients in the present study was 26.86±7 (range 14 to 45 years). In the first Iranian study mentioned above, the age range was 2 to 63 years [16]. According to the difference in the prognosis of the disease at early ages, we avoided such a wide range. Mean age in three studies from Shiraz, Tehran and Mashhad were 25.6±10.3, 21.5±6 and 25.12±12.05, respectively [2, 3, 16].

This study and other Iranian studies indicate that lupus nephritis is often found at a young age and mostly in females.

In this study, selected patients had been followed for an average of 4.4 years (1.5 to 10 years) and at the end of the first year, the occurrence of remission was investigated in all patients. The percentage of patients with complete remission, partial remission and no remission was 39.64%, 24.32% and 36.04%, respectively. In Chen's study, 43% of patients achieved complete remission, 24% of patients reached partial remission, and 32% of patients failed to achieve remission. The remission rate reported in this study was slightly more compared with our study. One possible explanation is the five-year versus one-year period for entering the remission phase. However, the author acknowledged that after the twentieth month of the study, no significant change in the percentage of remission had occurred [17]. In Sircar's study, complete remission rate after six months was 23.3% and partial remission was 20.9% [18], which was lower than our study. After six months, Ginzler et al. reported lower complete remission rate and similar partial remission rate compared to our study [19].

There was no significant relationship between the occurrence of three short-term outcomes (complete remission, partial remission and no remission) and demographic characteristics, such as age at the baseline of the study, gender and geographical region (Yazd and southern provinces such as Hormozgan and Kerman).

In this study, we considered patients with dark skins, which had come from southern provinces to Yazd, seeking for treatment, as a separate group. Our aim for considering these two geographic areas with distinct skin pigmentation difference was creating resemblance to foreign studies in which, both white and black patients were separately examined.

In the study of Korbet et al., remission was not associated with age and gender but it occurred in white patients more than black individuals [11]. Sircar et al. also concluded that age at baseline and gender was not associated with the occurrence of remission [18].

Moroni et al. reported that remission in patients with an older average age was more frequent than those with younger average age [20], which was inconsistent with

the results of the present study. Miranda-Hernandez also found that >25 years of age at diagnosis of LN was associated with favorable response to treatment [21].

In this study, some abnormal findings at baseline such as high systolic and diastolic blood pressures, proteinuria and elevated creatinine level, low GFR and hemoglobin, low C3 and albumin, and pathologic stage IV had a significant relationship with non-remission status. In contrast, the values of C4 and anti-dsDNA did not show any relationship with remission or non-remission occurrence.

In the study of Korbet et al., only low creatinine at baseline and class IV biopsies were associated with the probability of remission [22]. Ebadi et al. [2], observed that the amount of anti-dsDNA was associated with prognosis in patients with lupus nephritis, that was inconsistent with our findings. Imam Qureyshi found that prognosis was not related to proteinuria, C3 and C4 levels, while high blood pressure and class IV biopsies at baseline were associated with lack of remission. According to this study, no remission was seen in patients with grade IV [23]. Miranda-Hernandez et al. reported that baseline creatinine clearance of less than 30 mL/minute was associated with a poor response to treatment at the end of the first year and low C3 was associated with good response to treatment in 24 months [21]. Later findings about C3 were not in accordance with the results of our study. According to Chen's study, patients with a complete remission had a lower serum creatinine compared with patients with partial or noremission [17], which was in agreement with our results.

Considering the pathological state, grade IV had the highest frequency among patients in our study, which was consistent with the results of most of the studies performed previously [3, 4, 16, 20, 23-25].

In the present study, odds ratios were calculated for all related variables with non-remission, and as a result, the most important factors that led to non-remission status were high systolic blood pressure and low C3 level. It is said that high systolic blood pressure may lead to hyper filtration glomerular hypertrophy and finally segmental sclerosis by increasing glomerular pressure. As a result of this kidney damage, blood pressure will be increased in feedback [26]. On the other hand, complement activation is thought to be involved in tissue damage associated with SLE flare. However, studies that aimed to determine whether changes in plasma levels of complement component C3 and C4 could serve as biomarkers of SLE flare, have reported conflicting results [27]. Therefore, it seems that regular control of these factors in follow-ups can be helpful in treatment success.

Among a few studies that have investigated factors influencing remission, none of them considered odds ratio for variables. Only in a study by Dhir et al., hazard ratio for End Stage Renal Disease (ESRD) and death was calculated. The study demonstrated that among all variables, lack of remission during the first year, with hazard ratio of 13.0, was a major risk factor for these two undesirable long-term outcomes [7].

Conclusion

Through an ongoing investigation, it was aimed to determine predictive factors of poor prognosis of lupus nephritis among the Iranian population. Of all factors, which should be considered in lupus nephritis prognosis determination, systolic blood pressure and low C3 level had the highest correlation with failure of remission. Obviously, further investigations such as prospective or multi central studies should be performed to evaluate factors affecting the prognosis of lupus nephritis in different populations.

Conflict of interest

The authors declare no conflict of interest.

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