Original Paper

Correlation between Clinical Manifestations for Patients with Lupus Nephritis and Pathological Activity or Chronicity Indices.

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Abstract

Background: Systemic lupus erythematosus is a disorder of the immune system with many clinical manifestations.
Aims of this study: is to find the correlations between the clinical manifestations of lupus nephritis and the pathological activity and chronicity indices.
Patients and methods: This is a random cross-sectional study that took a period of two years started from 2015 to 2017, we collected kidney biopsy specimens from thirty patients with systemic lupus erythematosus, 28 were females and 2 were males. All patients were diagnosed as systemic lupus erythematosus if fulfilled ≥4 American college of rheumatology criteria for systemic lupus erythematosus. The activity and chronicity scoring indices are based on the percentage of glomeruli with each feature in the biopsy on a 0 to 3 scale, with a score of 0 = not present, 1 = <25% glomeruli, 2 = 25-50% glomeruli, and 3 indicating >50% glomeruli.
Results: the chronicity index score increased with disease duration. The incidence of anemia increases with presence of high scores of chronicity index. With more than 40 percent of patients with lupus nephritis have glomeruli fibrosis percentage between 25-50%. Malar rash has significant correlation with both activity and chronicity indices.
Conclusion: There was no significant correlation between gender, arthritis, edema, with both activity and chronicity indices.
Key word: lupus nephritis, activity index, chronicity index.

Introduction

Systemic lupus erythematosus (SLE) is a disorder of the immune system with many clinical manifestations [(1)]. Lupus nephritis (LN) is a significant and most severe SLE finding that results in increased morbidity and mortality among SLE patients [(1)]. Recognition of associations between prognostic factors may help identification of patients who are at high risk, which allows earlier beginning of management strategies[(2)].Clinical features suggesting the activity and severity of nephritis, the time span of immunologically induced kidney injury, and the involvement of hypertension have been shown to correlate to prognosis assessments in a variety of research populations [(3)].

In a prospective study of 50 patients with LN, it was found that increased risk of chronic renal failure or death was associated with hypertension, elevated serum Creatinine concentration and higher chronicity index (CI) scores [(4)].

At renal biopsy, a highe r microscopic hematuria, impaired glomerular filtration rate (GFR), proteinuria, anemia, hypoalbuminemia, hypertension, and the presence of positive anti- deoxyribonucleic acid (DNA) antibody were all associated with the worst class, that is, class IV. These parameters were also correlated with high renal pathological activity, and/or chronicity indices in patients with LN [(5-7)].

One of the studies analyzing Iranian

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patients with LN shows that patients with higher activity index (AI) scores suffered more frequently from hematuria, whereas those with high CI scores primarily suffered from hypertension and renal failure [6-8].

Patients and methods

Over a period of two years started from 2015 to 2017, we collected kidney biopsy specimens from thirty patients with SLA, 28 were females and 2 were males. All of the patients were collected in AL-Kafeel center for nephrology and kidney transplantation, Karbala holy, Iraq. All patients were diagnosed as SLE if fulfilled ≥4 American college of rheumatology (ACR) criteria for SLE[7, 8]. Seven patients were excluded from the study due to the following exclusion criteria: two of them did not complete the investigations required for the study, three patients the biopsy not stained by the immunofluorescence stains, and two patients did not agree to do the kidney biopsy. For all patients
; detailed history and physical examination were done. All patients underwent routine and specific investigations for LN.

After completing the investigations each SLE patient in this study was considered as a case of LN if have one of the following ACR criteria [7,8]: Proteinuria persistent 0.5 gm. per day or greater than 3+by dipstick, And /or cellular casts comprising red blood cells casts, granular, tubular or mixed casts. Active urinary sediment ≥5 RBCs/high-power field [HPF], ≥5 WBCs/HPF in the absence of infection. In this study LN patients were divided into three groups according to the duration of SLE: less than two years, two to four years, more than four years. 20 out of 30 patients have chronic kidney disease at presentation and they were mainly in stage 3 CKD classified according to Kidney Disease Improving Global Outcomes guideline [9]. All patients were informed about the indications, method used and possible complications of kidney biopsy procedure beforehand, and informed consents were signed. The procedure was done according to the standard guideline by Kerstin Amann [10]. Three cores were taken from either the right or left kidney under ultrasound guidance, with assistance of trained interventional radiologist. One core was kept in 5% formalin contained tube, two cores were kept in 0.9% isotonic saline contained tube, and all the specimens were sent immediately after the procedure to the laboratory for Immunofluorescence and light microscopic studies. The following reagents were applied for all the biopsies: Hematoxylin and eosin stain, Periodic acid –Schiff (PAS) stain, trichrome stain, Methenamine silver stain, and Congo red stain, IF protein stains. Each specimen was studied by two different pathologists and specimen should contain more than or equal to ten glomeruli for LM study, and >fife glomeruli for IF study [10]. Lupus nephritis disease activity can be assessed on a renal biopsy using the modified National Institutes of Health activity and chronicity indices. Indicators of disease AI include endocapillary hypercellularity, neutrophils or karyorrhexis within glomerular capillary loops, fibrinoid necrosis, hyaline deposits, cellular or fibro cellular crescents, and interstitial inflammation. Indicators of disease CI include the total percentage of global glomerulosclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis. The scoring is based on the percentage of glomeruli with each feature in the biopsy on a 0 to 3 scale, with a score of 0 = not present, 1 = <25% glomeruli, 2 = 25-50% glomeruli, and 3 indicating >50% glomeruli [11].

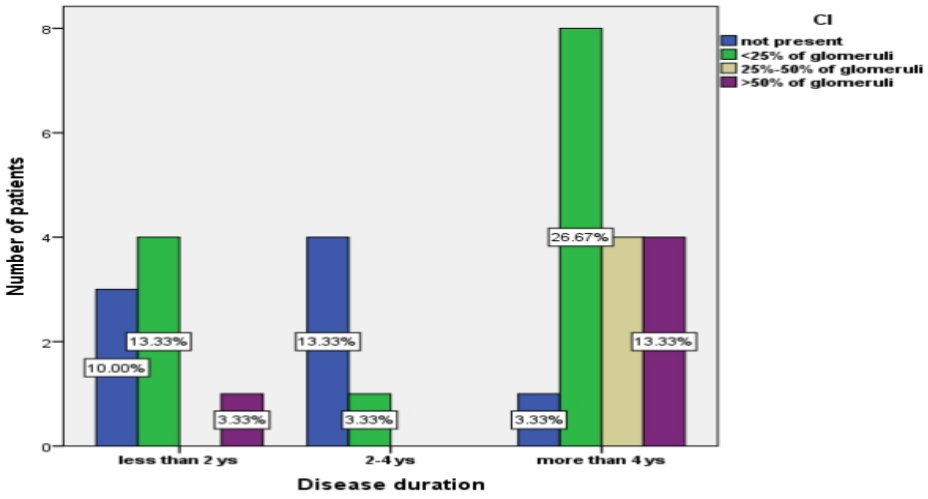
We use Statistical package for social sciences (SPSS) version 24 computer program by choosing chi square test, Pearson correlation, and single table student “T” test. P values <0.05 was considered statistically significant. The sample size was calculated according to Minitab.G*power software [12].

Results

The CI score increased with disease duration with more than 55 percent of patient have the highest degree of fibrosis when the disease duration more than 4 years and it was statistically significant at a p value < 0.05, see figure1.

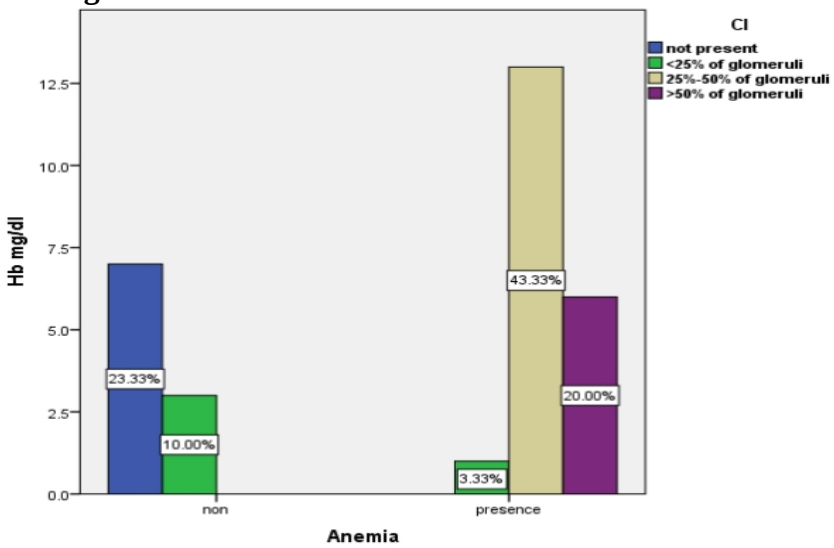
Figure 2 shows the incidence of anemia increases with presence of high scores of CI. With more than 40 percent of patients with LN they have glomeruli fibrosis percentage between 25-50% while more than 20 percent of patients, glomerular fibrosis constitute more than 50% this was statistically significant P value < 0.05.

The number of LN patients who presented with CKD have high CI on kidney biopsy and constitute more than 60% while those who don't have CKD at presentation have low CI and constitute less than 35% and this correlation has p value <0.05. This study found that more than half of patients with LN with malar rash have high AI score on their kidney biopsies tissue with p value <0.05, figure 4, 5.



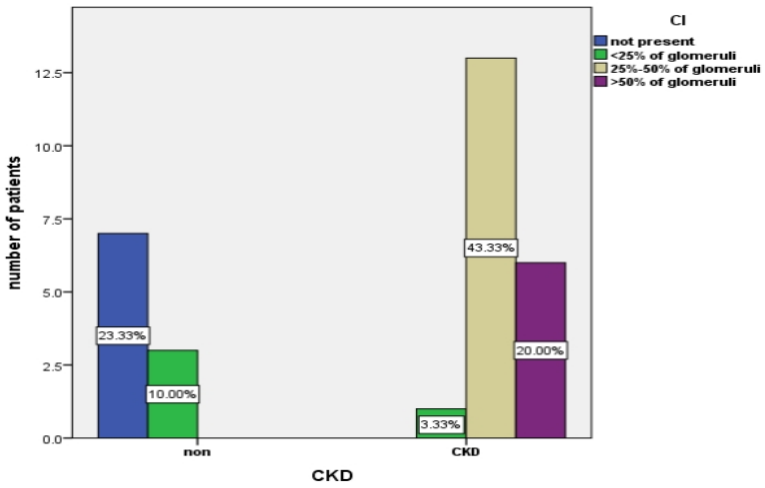
CI: chronicity index.

Figure 1. the correlation between disease duration and CI



Hb: hemoglobin, CI: chronicity index.

Figure 2. the correlation between anemia and CI



CKD: chronic kidney disease, CI: chronicity index.

Figure 3. the correlation between CKD and CI

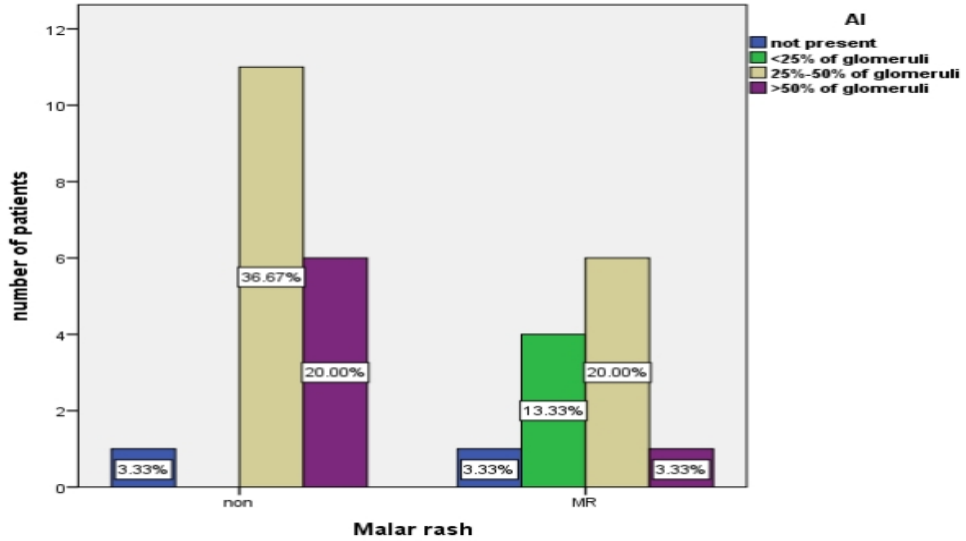
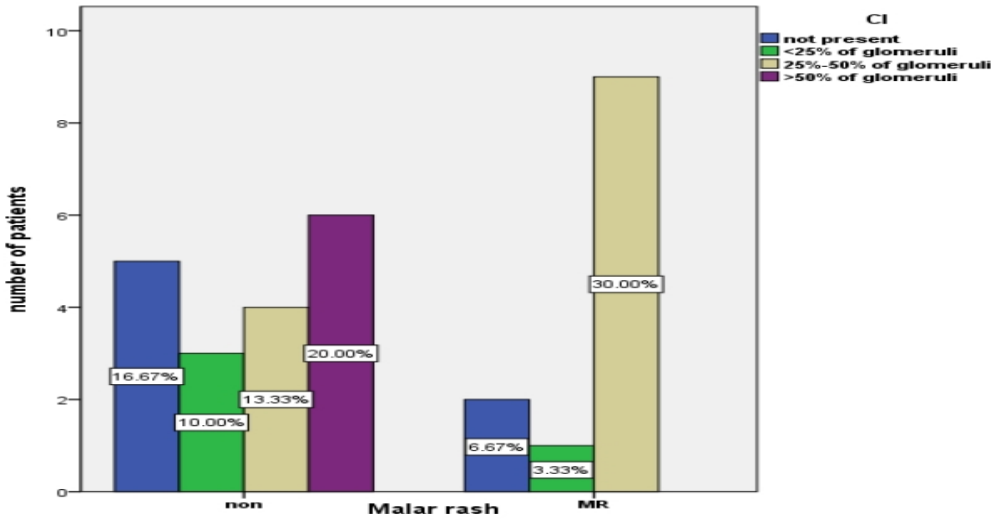


Figure 4. the correlation between malar rash and AI



AI: activity index.

Figure 5. the correlation between malar rash and CI

There was no statistically significant correlation between joint pains and either activity or chronicity indices see table 1.
The correlation between edema and either activity or chronicity indices was not significant see table 2.
There was no statistically significant correlation between gender and either AI or CI see table 3&4.

Table 1. Correlation between joint pain and AI.

	Value	df	P value
Pearson Chi-Square	3.845a	3	**.279**
Likelihood Ratio	4.619	3	.202

AI: activity index, DF: degree of freedom.

Table 2. correlation between edema and AI.

	Value	DF	P value
Pearson Chi-Square	2.952	3	**.399**
Likelihood Ratio	2.893	3	.408

AI: activity index, DF: degree of freedom.

Table 3. correlation between gender and AI. Font type should be the same

	Value	DF	P value
Pearson Chi-Square	2.820[a]	3	.420
Likelihood Ratio	2.591	3	.459

AI: activity index, DF: degree of freedom.

Table 4. correlation between gender and CI.

	Value	DF	P value
Pearson Chi-Square	1.389[a]	3	.708
Likelihood Ratio	1.903	3	.593

CI: chronicity index, DF: degree of freedom.

Discussion

Systemic lupus erythematous has a wide range of clinical manifestations, as it affects almost all of the body's organ systems. Arthralgia is a common symptom that occurs in patients over 90 percent [13].
This study found that glomerular fibrosis and hence CI increases with prolonged disease duration and this reflect the progressive nature of the disease. This result is consistent with other study that included patients with disease duration more than one year [14, 15].
In this study anemia correlates with progressive kidney fibrosis and CI so it is a sign of disease chronicity when it is found with other clinical manifestation [15]. We noticed that more than two third of patients with LN in this study have stage 3 CKD, and anemia. This is due to erythropoietin deficiency become evident at this stage this study concludes that the presence of anemia at time of consultation of LN patients is a bad prognostic sign. Hematological abnormalities are common in SLE patients. Other studies found that fifty percent of anemic SLE patients have their anemia due to: anemia of chronic disease, iron deficiency anemia, autoimmune hemolytic anemia, chronic renal insufficiency and cyclophosphamide-induced bone marrow toxicity [14].
We found that patients with CKD have high CI and this indicate a worse prognosis. In retrospective study done on 82 LN patients the CI score was the highest among stage 4 CKD [5]. In comparison to our study we notice the earlier prevalence of CI score, this may be related to the delayed presentation of patients to medical care and therefore, delay in doing the kidney biopsy. On the other hand, a possible environmental pollution could have a detrimental effect on the disease progression. We recommend further studies to identify the causes of earlier onset of high CI in kidney biopsy of Iraqi patients.
The distribution of gender among patients with LN does not have clinically significant correlation in kidney biopsy. This was observed in other study done on Iranian patients [16]. On the other hand, other investigators have observed several clinical features of disease activity and severity more frequently among Black than Caucasian patients at study entry [17]. McCarty and colleagues described what may be a unique pattern of autoantibodies in Black women with LN. This included precipitating antibodies to Ro/SS-A, Smith, and nuclear ribonucleoprotein that may contribute to the development of

glomerulonephritis in these patients. It is interesting to note that this pattern of autoantibodies was not detected in Black women without LN, Black men, Asian, American Indian or Caucasian SLE patients [18]. The prevalence of autoantibodies among Iraqi population with LN may affect disease activity in both genders. Further genetic studies are recommended to identify the type and prevalence of autoantibodies in Iraqi population.

Malar rash is a significant clinical finding in SLE and LN as well this study shows a strong relationship between malar rash and disease AI, or CI scores. This may reflect that malar rash as a marker of disease activity on the top of chronic underlying pathology. Other studies found that the most common acute SLE facial lesion is a photo-sensitive, slightly raised erythema, often scaly, called "butterfly" rash, particularly on the cheeks and nose. Worsening of this rash also coincides with systemic disease flare up [17].

Although arthritis is the most clinical manifestation of SLE, it's not correlated with disease AI, nor CI scores in kidney tissue. This may be explained by the different pathogenesis underlying inflammatory arthritis in SLE [19,20].

In our study there was no significant correlation between edema and AI, or CI in LN patients. This may indicate the incidence of edema may be reduced by the use of anti-proteinuric drugs which influence the manifestation of this sign.

Conclusions:

- This study indicates that clinical findings at renal biopsy are clinically valuable in identifying AI and CI indices.
- Prolong disease duration have high CI score.
- Anemia correlates with CI score.
- Stage 3 CKD has high CI score.
- Malar rash is a sign of disease activity and can be superimposed on chronic underlying disease process.
- There is no clinically significant of gender, arthritis, edema with both AI and CI scores.

Recommendations:

- We recommend further studies to identify the causes of earlier onset of high CI in kidney biopsy of Iraqi patients.
- Further genetic studies are recommended to identify the type and prevalence of autoantibodies in Iraqi people.

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