RESEARCH ARTICLE

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Evaluation of the Prognostic Value of Proteinuria Severity in Predicting the Development of Lupus Nephritis in Patients with Systemic Lupus Erythematosus

Sistemik Lupus Eritematozuslu Hastalarda Lupus Nefriti Gelişimini Tahmin Etmede Proteinüri Şiddetinin Prognostik Değerinin Değerlendirilmesi

ABSTRACT

Objective

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease where lupus nephritis (LN) remains a leading cause of morbidity. Proteinuria is a hallmark of renal involvement, but the prognostic value of lower thresholds (<500 mg/day) for predicting LN remains understudied. This study aims to evaluate whether proteinuria >300 mg/day at diagnosis predicts LN development in patients with SLE and to identify associated clinical and serological risk factors.

Materials and Methods

This retrospective single-center study analyzed 140 SLE patients (90% female; mean age 43.8 ± 11.8 years) diagnosed at a tertiary rheumatology clinic. Data on demographics, organ involvement, serological markers (ANA, anti-dsDNA, C3/C4), SLE Disease Activity Index (SLEDAI), and 24-hour proteinuria were collected. Patients were stratified by proteinuria levels (≤300 vs. >300 mg/day) and followed for LN development. Logistic regression identified predictors of renal involvement.

Results

Of 140 patients, 33 (23.6%) developed LN during follow-up. Patients with proteinuria >300 mg/day at baseline had significantly higher SLEDAI scores (21.7 vs. 8.3, p<0.001), anti-dsDNA positivity (57% vs. 23%, p=0.001), and renal involvement (79% vs. 10%, p<0.001), alongside lower C3 (p=0.002) and haemoglobin (p=0.001). Eleven patients without initial renal involvement developed LN during follow-up, exhibiting higher baseline proteinuria (p=0.004) and lower C3/C4 (p<0.01). Logistic regression confirmed proteinuria >300 mg/day independently predicted LN (OR=1.008, 95% CI=1.001–1.014, p=0.021).

Conclusion

Proteinuria >300 mg/day at SLE diagnosis is a robust predictor of LN, associated with higher disease activity, hypocomplementemia, and anti-dsDNA positivity. This threshold may improve early risk stratification compared to the conventional 500 mg/day cutoff.

Key Words

Systemic lupus erythematosus, Lupus nephritis, Proteinuria, Prognosis, Disease activity

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ÖZ

Amaç

Sistemik lupus eritematozus (SLE), çoklu organ tutulumu olan otoimmün bir hastalıktır ve lupus nefriti (LN) morbiditenin önde gelen nedenlerinden biridir. Proteinüri renal tutulumun temel göstergesi olmakla birlikte, LN'i öngörmede daha düşük eşiklerin (<500 mg/gün) prognostik değeri yeterince araştırılmamıştır. Bu çalışma, tanı anında proteinürinin >300 mg/gün olmasının SLE hastalarında LN gelişimini öngörüp öngörmediğini ve ilişkili klinik/serolojik risk faktörlerini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler

Bu retrospektif, tek merkezli çalışmada, üçüncü basamak romatoloji kliniğinde tanı alan 140 SLE hastası (%90 kadın; ortalama yaş 43,8 ± 11,8 yıl) incelendi. Demografik veriler, organ tutulumları, serolojik belirteçler (ANA, anti-dsDNA, C3/C4), SLE Hastalık Aktivite İndeksi (SLEDAI) ve 24 saatlik proteinüri kaydedildi. Hastalar proteinüri düzeyine göre (≤300 ve >300 mg/gün) sınıflandırıldı ve LN gelişimi açısından izlendi. Renal tutulumun belirleyicilerini saptamak için lojistik regresyon kullanıldı.

Bulgular

Toplam 140 hastanın 33'ünde (%23,6) takip sürecinde LN gelişti. Başlangıçta proteinürisi >300 mg/gün olan hastalarda SLEDAI skorları anlamlı derecede yüksekti (21,7'ye karşı 8,3; p<0,001), anti-dsDNA pozitifliği daha sıktı (%57'ye karşı %23; p=0,001) ve renal tutulum oranı daha yüksekti (%79'a karşı %10; p<0,001); ayrıca C3 (p=0,002) ve hemoglobin düzeyleri daha düşüktü (p=0,001). Başlangıçta renal tutulumu olmayan 11 hastada izlemde LN gelişti; bu hastalarda başlangıç proteinürisi daha yüksek (p=0,004) ve C3/C4 düzeyleri daha düşüktü (p<0,01). Lojistik regresyon analizi, proteinürinin >300 mg/gün olmasının LN'ini bağımsız olarak öngördüğünü doğruladı (OR=1,008; %95 GA=1,001–1,014; p=0,021).

Sonuç

SLE tanısında günde >300 mg proteinüri, LN için güçlü bir prediktör olup; daha yüksek hastalık aktivitesi, hipokomplementemi ve anti-dsDNA pozitifliği ile ilişkilidir. Bu 300 mg/gün eşik değeri, geleneksel 500 mg/gün değerine kıyasla erken bir LN risk sınıflandırmasını sağlayabilir.

Anahtar Kelimeler

Sistemik lupus eritematozus, Lupus nefriti, Proteinüri, Prognoz, Hastalık aktivitesi

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease in which immune complexes and autoantibodies accumulate in organ capillaries, leading to multi-organ involvement (1, 2).

SLE features wide clinical variation due to multi-organ involvement, primarily in the integumentary, musculoskeletal, cardiopulmonary, neurological, haematological, gastrointestinal, and renal systems. Most SLE patients experience exacerbations between relatively benign periods, while complete remission is rare.

The primary risk factors for morbidity and mortality in SLE patients are ethnicity, age at disease onset, disease severity, and socioeconomic status. Signs of severe disease, such as renal and central nervous system involvement, vasculitis, thrombosis, and infection, have been associated with early deaths, and disease-induced damage, such as myocardial infarction and cerebrovascular event, and treatment toxicity have been associated with late deaths (3). Of these factors, lupus nephritis (LN) and infection are the leading causes of death associated with SLE in the first decade of the disease. In light of this information, this study was conducted to evaluate the prognostic value of various risk factors, particularly protein levels, in predicting the development of LN in patients with SLE.

MATERIALS and METHODS

The sample of this retrospective single-center study consisted of 140 patients over the age of 18 diagnosed with SLE at the Internal Medicine Rheumatology Outpatient Clinic 1 of Akdeniz University Medical Faculty Hospital. The study protocol was approved by the Local Ethics Committee of Antalya Training and Research Hospital (Date: 04.04.2013, Decision No: 17/3). The present study is based on M. N. Internal Medicine specialty thesis entitled The 10 Years Clinical, Treatment and Progression Evaluation of the Systemic Lupus Erythematosus Patients Followed-Up Between the Years 2003–2013, which was completed in 2014 under the supervision of Prof. Dr. Mustafa Ender Terzioglu.

Patients' data, including demographic (age and gender), clinical ((organ involvement, SLE Disease Activity Index (SLE-DAI) scores assessed at diagnosis or first presentation at the outpatient clinic, findings at the last follow-up visit), genetic and biochemical ((antinuclear antibody (ANA) titer, autoantibody profile, renal biopsy), treatment (drugs used in treatment, changes in treatment, and response to treatment)) characteristics were obtained from the MediHasta ® records, the monitoring program of Akdeniz University Medical Faculty Hospital. Patients with LN were divided into groups based on treatment response: complete response, partial response, no response, or relapse. Accordingly, patients with protein levels ≤300 mg in 24-hour urine analysis and stable renal function (serum creatinine levels within the normal range or increased by

15% from baseline) were included in the complete response group, those with protein levels between 300 mg and 2.9 g in 24-hour urine analysis but decreased by 50% and stable renal function were included in the partial response group, those with protein levels >0.5 g in 24-hour urine analysis and a 50% increase in creatinine levels after remission induction or maintenance therapy were included in the no response group, and those with protein levels >0.5 g in 24-hour urine analysis and a 50% increase in creatinine levels after a complete response achieved during or after completion of immunosuppressive therapy were included in the relapse group.

Statistical Analysis

The statistical analyses of the collected data were conducted using SPSS 16.0 (Statistical Package for the Social Sciences for Windows, Version 16.0, SPSS Inc., Chicago, IL, US, 2007). The results of the statistical analyses were expressed using descriptive statistics, i.e., mean ± standard deviation for continuous variables and counts (n) and percentages (%) for categorical variables. The chi-square test was used to compare the categorical data between groups. Additionally, in comparing the differences in numerical variables between two independent groups, the student's t-test was used for numerical variables determined to conform to the normal distribution, and the Mann-Whitney U test was used for numerical variables determined not to conform to the normal distribution. Logistic regression analysis was used to determine the factors that significantly predict renal involvement in patients with SLE. All hypotheses were constructed as two-way hypotheses. In all statistical analyses, probability (p) statistics of ≤ 0.05 were deemed to indicate statistical significance.

RESULTS

Patients' demographic, clinical, and genetic characteristics are shown in Table I.

Table I. Clinical and Immunological Features of SLE Patients (N=140)

Characteristics	n (%)
Sex	
Female	126 (90.0)
Male	14 (10.0)
Age, *years*	43.8 ± 11.8 [21-72]
Organ Involvement	
Musculoskeletal	132 (94.3)
Cutaneous	52 (37.1)
Renal	33 (23.6)
Hematological	28 (20.0)
Pulmonary	11 (7.9)
Antiphospholipid syndrome	10 (7.1)
Neurological	5 (3.6)
Gastrointestinal	1 (0.7)
ANA Pattern	
Homogeneous	83 (59.3)
Speckled	37 (26.4)
Nucleolar	8 (5.7)
Negative	12 (8.6)
ANA Titer	
1:1000	62 (44.3)
1:100	37 (26.4)
1:320	16 (11.4)
1:640	13 (9.3)
Negative	12 (8.6)

Note: Data are presented as n (%) or mean ± SD [range]. ANA: Antinuclear antibody; SLE: Systemic lupus erythematosus; SD: Standard deviation.

The distribution of SLE patients' demographic, clinical, genetic, and biochemical characteristics between patient groups with protein levels >300 mg/day and ≤ 300 mg/day at presentation is shown in Table II. The groups significantly differed in skin and renal involvements, hemoglobin, complement component 3 (C3), and C-reactive protein (CRP) levels, anti-double-stranded-deoxyribonucleic (anti-ds DNA) positivity, erythrocyte sedimentation rate (ESR) values, and SLE-DAI scores. Accordingly, skin involvement, C3 and hemoglobin levels were significantly lower, whereas renal involvement, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, SLE-DAI scores, and anti-double stranded-deoxyribonucleic (anti-ds DNA)-positivity were significantly higher in SLE patients with protein levels >300 mg/day than in SLE patients with protein levels ≤300 mg/day at first presentation. On the other hand, C3 and C4 levels were significantly lower, whereas protein levels were significantly higher in 11 patients who had no renal involvement by the time of diagnosis but developed LN during the follow-up period than those of 107 patients who never had renal involvement (p=0.011, p=0.003, and p=0.004, respectively). Among these 11 patients, 8 had proteinuria ≤300 mg/day at diagnosis, whereas 3 patients had proteinuria between 300 and 500 mg/day (305 mg/day, 313 mg/day, and 400 mg/day, respectively).

Logistic regression analyses, including univariate and multivariate models, revealed protein levels >300 mg/dl at diagnosis independently predicted renal involvement in SLE patients (p=0.021, Odds Ratio (OR)=1.008, 95% Confidence Interval (CI)=1.001-1.014)).

Table II. Clinical and Laboratory Parameters Stratified by Proteinuria Level in SLE Patients

Characteristics	Proteinuria >300mg/day (n=28)	Proteinuria ≤300mg/day (n=112)	p-values
Demographics			
Age *(years)*	39.9 ± 11.5	44.8 ± 11.8	0.053
Laboratory Parameters			
Hemoglobin *(g/dL)*	10.9 ± 2.4	12.2 ± 1.7	**0.001**
Leukocyte *(cells/μL)*	5864 ± 2772	6447 ± 2451	0.277
Neutrophil *(cells/μL)*	3839 ± 1915	4001 ± 2010	0.702
Lymphocyte *(cells/μL)*	1423 ± 892	1718 ± 913	0.127
Platelet *(×10³/μL)*	228107 ± 90048	235973 ± 92522	0.687
Creatinine *(mg/dL)*	0.98 ± 1.0	0.75 ± 0.53	0.093
C3 *(mg/dL)*	77.9 ± 34.0	98.5 ± 29.9	**0.002**
C4 *(mg/dL)*	14.1 ± 9.6	15.2 ± 8.3	0.559
ESR *(mm/hr)*	48.5 ± 26.9	32.5 ± 23.9	**0.003**
CRP *(mg/L)*	1.9 ± 3.8	0.6 ± 1.0	**0.002**
ALT *(U/L)*	19.3 ± 8.0	21.9 ± 13.3	0.308
SLEDAI	21.7 ± 14.2	8.3 ± 5.9	**<0.001**
Clinical Features *(%))*			
Musculoskeletal	100	92	0.359
Cutaneous	14	44	**0.004**
Renal	79	10	**<0.001**
Hematological	14	21	0.443
Pulmonary	7	8	1.000
APAS	10	6	0.424
Neurological	10	1	0.570
Gastrointestinal	0	0.9	1.000
Immunological Features *(%))*			
Anti-dsDNA positive	57	23	**0.001**

Note: Data are presented as mean ± SD or percentage. Significant p-values (<0.05) are in **bold**. ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ALT: Alanine transaminase; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; APAS: Antiphospholipid antibody syndrome; C3/C4: Complement components 3 and 4; Anti-dsDNA: Anti-double stranded DNA antibodies.

DISCUSSION

Renal involvement is critical in the clinical follow-up of SLE patients in terms of LN development. Kidney disease and end-stage renal disease occur at higher rates and at younger ages in people of African descent compared to Caucasians (4). In our study of 140 patients over a 120-month follow-up period, 33 patients (23.6%) developed lupus nephritis, which is lower than both the 38.1% rate reported in another Turkish study (5) and the 30-50% prevalence observed in the literature (6).

Importantly, recent guideline recommendations emphasize that clinically relevant renal involvement in SLE may be present even at proteinuria levels below traditionally accepted thresholds, and that low-grade proteinuria should not exclude further diagnostic evaluation for lupus nephritis, particularly in the appropriate clinical and serological context (7). The KDIGO 2024 Lupus Nephritis Guideline identifies proteinuria ≥0.5 g/24 h as a critical level warranting close reassessment and consideration of renal biopsy, particularly when proteinuria is persistent or accompanied by other markers of disease activity (8). Similarly, the EULAR 2025 updated recommendations emphasize that persistent proteinuria at or above this threshold represents a key indicator of renal involvement requiring further diagnostic evaluation (7). In our cohort, lupus nephritis developed in 11 patients who had no evidence of nephritis at baseline, three of whom exhibited initial proteinuria levels within the 300–500 mg/day range, highlighting that renal involvement may evolve even in patients with borderline proteinuria. Taken together, these findings support current guideline perspectives and underscore the importance of careful monitoring and timely evaluation of SLE patients presenting with low-grade proteinuria.

LN can be effectively treated in the earlier stages just before scar formation , fibrosis and athrophy. In another study, a diagnostic biopsy revealed LN in 16 of 21 patients with low-severity proteinuria (<1 g/day) (9). It has been reported that planning treatment of patients with similar renal characteristics, the presence of low proteinuria should be taken into consideration in terms of the classification of LN (10). Among 33 patients with lupus nephritis, treatment analysis was conducted on 30 patients, as one patient underwent renal transplantation and two patients refused treatment. All analysed patients (100%) received oral steroids, and 85% received hydroxychloroquine treatment.

As the first remission induction therapy, intravenous (IV) cyclophosphamide (CYC) was administered to 60% of our patients, azathioprine (AZA) to 23.3%, and mycophenolate mofetil (MMF) to 16.7%. No significant difference regarding efficacy was detected among AZA, CYC, or MMF treatment groups administered to SLE patients with class 3, class 4, or class 5 LN as first-remission induction therapy.

For many years, IV-CYC has been the gold standard for the treatment of LN. Since it was reported in the second half of the 2000s that the efficacy of MMF was not inferior to that of IV-CYC, MMF has been increasingly used in the treatment of LN (11). According to the most recent recommendations, both MMF and reduced-dose IV-CYC are considered appropriate first-line options for remission induction in patients with proliferative lupus nephritis (13). Low-dose CYC is preferred over high-dose CYC since it carries a lower risk of gonadotoxicity while maintaining comparable efficacy (13). Published data support the use of MMF and high-dose CYC treatments in cases of severe LN associated with an increased risk of progression to end-stage renal disease (12). LN patients in our sample were primarily administered IV-CYC, which is reimbursed by the Social Security Institution, and, secondarily, MMF, which was reimbursed in the event of unresponsiveness to IV-CYC. The most frequently used immunosuppressive treatment in our study was AZA, used as remission therapy in patients with class 2 LN and as maintenance therapy in patients with proliferative LN.

In our sample, AZA was used in 59% of patients and MMF in 37% as maintenance therapy following remission induction, consistent with the respective rates reported in the literature (12). A meta-analysis concluded that MMF or AZA therapy for LN maintenance did not significantly improve efficacy (14).

Rituximab (RTX) is typically considered a second-line therapy for LN. It is generally used in cases of relapse or lack of response to first-line treatments such as CYC and MMF (12). More recently, a post hoc analysis of the Lupus Nephritis Assessment with Rituximab (LUNAR) trial revealed that complete B-cell depletion following the treatment of LN with RTX was associated with a higher likelihood of complete response within 78 weeks (15). In comparison, remission was achieved in two of the three patients in our sample who received RTX due to refractory disease, but not in one.

Belimumab, another agent targeting B lymphocytes, became the first biological drug to receive the United States (US) Food and Drug Administration (FDA) approval for refractory LN cases after its efficacy was demonstrated (16, 17). A controlled study found that the rate of patients meeting primary and secondary endpoints was significantly higher among LN patients receiving Belimumab as standard therapy (18). None of the LN patients in our sample received Belimumab treatment.

Recent guidelines for LN recommend calcineurin inhibitors (CNIs) in combination with MMF as both remission induction and maintenance therapies (12). Of the two patients in our sample who received cyclosporine-A, a CNI, as a second remission induction therapy, one achieved a complete response, and the other did not.

In our sample, of the two patients who received a CNI, Cyclosporine-A, as a second-remission induction therapy, a complete response was achieved in one but not the other. Remission induction treatments applied to the patients in our sample resulted in complete remission in 80% of the patients and partial remission in 10%. The fact that these rates are higher than those reported in the studies in the literature may be attributed to the lack of records of patients who died during the treatment process.

In the LN mortality study conducted in Turkey, where 19 of 428 patients died, the most common cause of death was ischemic heart disease, followed by chronic renal failure and sepsis, respectively (19).

Limitations

The primary limitation of this study is that its retrospective design prevented obtaining complete information, including data on patients who were lost or died during follow-up. Therefore, large-scale prospective studies are needed in the future.

Our study found that protein levels >300 mg/day in SLE patients with LN were significantly associated with renal involvement, higher SLE-DAI scores, elevated acute-phase reactants, and hypocomplementemia, underscoring the importance of monitoring these factors during follow-up in this patient population.

CONCLUSION

In conclusion, protein levels >300 mg/day can be used to predict the development of LN during the follow-up period in patients with SLE, rather than the generally accepted threshold of >500 mg/day.

Acknowledgment

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Ethics Committee Approval

This research complies with all the relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the Local Ethics Committee of Antalya Training and Research Hospital (Date: 04.04.2013, Decision No: 17/3)

Informed Consent

Given the retrospective design of the study, the requirement for obtaining written informed consent from the participants was waived.

Author Contributions

Concept – M.E.T., M.N.; Design - M.E.T., M.N.; Supervision - M.E.T.; Resources – V.Y., M.N.; Materials - M.E.T., M.N.; Data Collection and/or Processing - M.N.; Analysis and/ or Interpretation - M.E.T., M.N.; Literature Search –F.E., M.N.; Writing Manuscript - M.N.; Critical Review - M.E.T.

Conflict of Interest

The authors have no conflict of interest to declare.

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Declaration of AI and AI-assisted technologies in the writing process

The authors declare that no generative AI or AI-assisted technologies were used in the writing and preparation of this manuscript. All content represents the original work of the authors.

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