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Predictive factors of developing lupus nephritis in systemic lupus erythematosus

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Renal involvement is common in systemic lupus erythematosus (SLE), and even without elevated serum creatinine, there is a high proportion of abnormal urine analysis in these patients. Lupus nephritis (LN) develops early in the course of the disease in 50% of SLE patients, and end stage renal disease (ESRD) occurs in 4.3-10.1%. We performed a keyword-based literature search and included 31 articles published from 2004 to 2023. Ethnic and racial differences may affect LN, including higher incidence of LN in Black, Hispanic and Asian compared with white patients. In addition, male sex, longer disease duration, smoking, low albumin globulin ratio, low complement, anti-double stranded DNA, high anti-Sm is associated with disease progression to LN. High serum creatinine (>1.5 mg/dL) at disease onset is the most commonly reported independent clinical laboratory predictor for ESRD in patients with SLE. Other factors indicating an increased risk for ESRD are higher chronicity index, high systolic blood pressure, black race, male sex, hypocomplementemia, class of LN (III, IV and V) and older age.

Keywords: *predictive factors; systemic lupus erythematosus; lupus nephritis; end stage renal disease*

Introduction

Systemic lupus erythematosus (SLE) frequently affects the kidneys and the impairment of renal function results from glomerular, vascular lesions and tubule interstitial involvement [1]. Lupus nephritis (LN) often occurs within 5 years of SLE diagnosis and progresses to end-stage renal disease (ESRD) in 4.3–10.1% [2]. LN is characterized by renal inflammation, glomerular deposition of immune complexes [3] and the gold standard for its diagnosis and classification is renal biopsy [4]. LN presents with increased levels of anti-complement C1q (anti-C1q) and flares [3,5]. LN patients are classified into one of six histologic categories established by the World Health Organization (WHO) and later updated by the International Society of Nephrology/Society of Renal Pathology (ISN/ RPS) [6-8]. The most advanced stage of LN is class VI, in which patients may require kidney transplantation or dialysis [7,8]. Renal function and 24 h-urine protein may be within the normal range. Clinical presentation may be silent on urinalysis [9]. LN can be characterized by leukocyturia, hematuria,

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mild proteinuria, cellular casts and or more overt presentations including acute nephritic syndrome nephrotic syndrome or rapidly progressive renal failure [10]. Ethnic and racial differences may affect LN, including higher incidence of LN in Black, Hispanic and Asian compared with white patients, and higher proteinuria, severe underlying histopathology, higher serum creatinine in black & Hispanic [11]. LN is associated with a higher risk for progressive renal disease in males, frequent relapse, childhood onset, African or Hispanic race, incomplete remission and proteinuria > 4 g/day at diagnosis [12].

Standard treatment for LN includes the use of glucocorticoids and antimetabolite/immune-suppressive drugs (cyclophosphamide, myco-phenolate mofetil). In order to maintain a complete remission, after the maintenance phase, in addition to the standard treatment, add on therapies can be used. The European Medicines Agency (EMA) allows three add-on therapies targeting the BAFF/Bley's (belimumab), type I IFN receptor (anifrolumab), or the non-nephrotic calcineurin inhibitor voclosporin [13]. Ongoing trials further support deplete insular B cells ± plasmacytes (CAR T cells and obinutuzumab instead of rituximab), or to deplete CD38-positive plasmacytes (daratumab) or target the type I/I IFN JAK/STAT pathway (tofacitinib) in refractory SLE/LN [13].

Predictive factors of LN

In the study of Galindo-Inquired et al., the risk of developing LN was significantly higher in men than in women [14]. In another study higher Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) value, low albumin globulin ratio (AGR), anti nucleosome and positivity of immune-fluorescence in skin were associated with LN [15]. The AGR below one was the greatest predictor of appearance of LN, together with low levels of C3 and high levels of anti-double stranded DNA (anti-ds DNA) (Table 1) [15]. In a study in Seoul among 284 patients, 37 patients developed LN [16]. Young age, low C3, low C4, high anti-ds DNA, anti-Sm [hazard ratio (HR) 2.097] and low AGR were associated with higher risk of LN [16]. This study reaffirms the usefulness of AGR value at disease onset as a predictor of risk for developing LN during the course of SLE [16]. A value less than one has a higher predictive role for the development of LN [16]. The low AGR is explained by the higher level of globulins in total proteins, which is caused by various autoantibodies. For every 100 IU/mL increase in anti-ds DNA, the risk of subsequent LN increased by 1.29-fold [16]. High anti-ds DNA and erythrocyte sedimentation rate (ESR) during follow-up were risk factors for subsequent LN in SLE [16].

High serum creatinine (>1.5 mg/dL) at disease onset is the most commonly reported independent clinical laboratory predictor for ESRD in patients with SLE alone or LN [14, 17-20]. Other factors indicating an increased risk for ESRD are: higher chronicity index, high systolic blood pressure, black race, male sex, hypocomplementemia, class of LN (III, IV and V) and older age [14, 17-20].

Discussion

According to the American College of Rheumatology (ACR) criteria, the presence of ≥ 4 of 11 serological and/or clinical criteria is required for SLE calcification. The Systemic Lupus International Collaborating Clinics (SLICC) research group introduced a new set of classification criteria where ≥ 4 of 17 criteria need to be met. An observational study demonstrated the superiority of the SLICC criteria over the ACR by showing that the SLICC criteria allow SLE to be classified at an earlier stage of the disease [21]. Despite aggressive treatment, approximately 60% of patients with LN do not achieve complete remission, and these patients have poor long-term outcomes [22-25]. Furthermore, 27-66% of patients with LN that is in remission have subsequent flares [26].

A retrospective cohort study in 2008-2018 on 48 SLE patients, 20 patients developed LN [27]. There was no difference in the percentage of primary manifestations except for more discoid rash in the group without LN [27]. Predictors of subsequent LN were increased mean anti-ds DNA, high mean ESR and low mean serum complement [27]. In a big cohort of SLE patients in Latin America (COLOMBIA) LN developed in 39% of patients [28]. Being male (OR 1.98), long disease duration (>10 years) (OR 1.48), positive

Table1: Predictors of developing LN

Factor	OR	95%CI	P
positive anti-ds DNA	8.58	1.06-1.47	≤ 0.001
Low C3	36.50	13.52-81.91	≤ 0.001
AGR ≤ 1	47.58	11.85-79.17	≤ 0.001
Male	1.27	1.04-1.55	≤ 0.001
Duration of SLE ≥ 10 years	1.37	1.08-1.74	≤ 0.001
Positive anti-SM	1.46	1.10-1.95	≤ 0.001
Smoker	1.66	1.22-2.25	≤ 0.001
Non-Smoker	0.56	0.41-0.77	≤ 0.001

LN, lupus nephritis; anti-ds DNA, anti-double stranded DNA; C3, complement component 3; AGR: albumin globulin ratio; SLE, systemic lupus erythematosus, anti-SM: anti-smooth muscle antibody

anti-ds DNA (OR 1.34), positive anti-Sm (OR 1.45) and smoking (OR 1.66) were significantly associated with LN [28]. In another study, LN with pleuritis In a big cohort of SLE patients in Latin America (COLOMBIA) LN developed in 39% of patients [28]. Being male (OR 1.98), long disease duration (>10 years) (OR 1.48), positive anti-ds DNA (OR 1.34), positive anti-Sm (OR 1.45) and smoking (OR 1.66) were significantly associated with LN [28]. In another study, LN with pleuritis (OR=2.44), pericarditis (OR=1.62), younger age (OR=0.97), anti-Sm (OR=1.70), anti-ds DNA, (OR=2.22), low complement level (OR=1.37), low AGR and absence of apL were related [29]. In one cohort of 1827 patient newly diagnosis SLE nephritis occurred in 38% in a mean year of 4.6 year [30]. LN was associated with threefold increased risk of death [30]. In a study in Tunisia Age ≤ 34 years was the only independent predictor of LN in multivariate regression analysis [31].

Conclusion

According to our literature review in patients with SLE, male sex, longer disease duration, smoking, low AGR, low complement, anti-dsDNA, high anti-SM is associated with disease progression to LN.

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Conflict of interest

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References

1. Mahajan A, Amelia J, Gary K, Kaur G, Levy RA, Roth D, Bass D. Systemic lupus erythematosus, lupus nephritis and end-stage renal disease: a pragmatic review mapping disease severity and progression. ***Lupus*** 2020; 29(9):1011-20. doi: 10.1177/0961203320932219.
2. Hanly JG, O'Keeffe AG, Su L, Urowitz MB, Romero-Diaz J, Gordon C. et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. ***Rheumatology (Oxford)*** 2016; 55(2): 252-62. doi: 10.1093/rheumatology/kev311.
3. Davidson A. What is damaging the kidney in lupus nephritis? ***Nat Rev Rheumatol*** 2016; 12(3):143-53. doi: 10.1038/nrrheum.2015.159.
4. Moroni G, Quaglini S, Radice A, Trezzi B, Raffiotta F, Messa P, Sinico RA. The value of a panel of autoantibodies for predicting the activity of lupus nephritis at time of renal biopsy. ***J Immunol Res*** 2015; 2015:106904. doi: 10.1155/2015/106904.
5. Almaani S, Meara A, Rovin BH. Update on Lupus Nephritis. Clin J Am Soc Nephrol 2017; 12(5):825-35. doi: 10.2215/cjn.05780616.
6. Kiremitci S, Ensari A. Classifying lupus nephritis: an ongoing story. ***ScientificWorld Journal***n2014:580620. doi: 10.1155/2014/580620.
7. Inderjeeth CA, Habib P, Sharma C, Nossent J. Systemic lupus erythematosus: reducing life-threatening progression. ***Med Today*** 2018; 19 (9): 31–41.
8. Lau W, Appel G. Lupus nephritis in 2017: an

update. ***ASN Kidney News*** 2017; 9:17-18.

9. Wada Y, Ito S, Ueno M, Nakano M, Arakawa M, Gejyo F. Renal outcome and predictors of clinical renal involvement in patients with silent lupus nephritis. ***Nephron Clin Pract*** 2004; 98(4):c105-11. doi: 10.1159/000081551.
10. Balow JE. Clinical presentation and monitoring of lupus nephritis. ***Lupus*** 2005; 14(1):25-30. doi: 10.1191/096120330 5lu2055 oa.
11. Parikh SV, Almani S, Brodsky S, Rovin BH. Update on Lupus Nephritis: Core Curriculum 2020. ***Am J Kidney Dis*** 2020; 76(2):265-81. doi: 10.1053/j.ajkd.2019.10.017.
12. Rovin BH, Caster DJ, Cattran DC, Gibson KL, Hogan JJ, Moeller MJ. et al. Management and treatment of glomerular diseases (part 2): conclusions from a kidney disease: Improving Global Outcomes (KDIGO) Controversies Conference. ***Kidney Int*** 2019; 95(2):281-95. doi: 10.1016/j.kint.2018.11.008.
13. Roccatello D, Fenoglio R, Caniggia I, Kamgaing J, Naretto C, Cecchi I. et al. Daratumumab monotherapy for refractory lupus nephritis. ***Nat Med*** 2023; 29(8):2041-47. doi: 10.1038/s41591-023-02479-1.
14. Galindo-Izquierdo M, Rodriguez-Almaraz E, Pego-Reigosa JM, López-Longo FJ, Calvo-Alén J, Olivé A. et al. Characterization of patients with lupus nephritis included in a large cohort from the Spanish society of rheumatology registry of patients with systemic lupus erythematosus (RELESSER). ***Medicine (Baltimore)*** 2016; 95(9): e2891. doi: 10.1097/md.000000000000 2891.
15. Estévez Del Toro M, Varela Ceballos I, Chico Capote A, Kokuina E, Sánchez Bruzón Y, Casas Figueredo N. Predictive factors for the development of lupus nephritis after diagnosis of systemic lupus erythematosus. ***Rheumatic Clin (Engl Ed)*** 2022; 18(9):513-17. doi: 10.1016/j.reumae.2021.08.003.
16. Kwon OC, Lee JS, Ghang B, Kim Y-G, Lee C-K, Yoo B, Hong S. Predicting eventual development of lupus nephritis at the time of diagnosis of systemic lupus erythematosus. ***Semin Arthritis Rheum*** 2018; 48(3):462-66. doi: 10.1016/j.semarthrit.2018.02.012
17. Sisó A, Ramos-Casals M, Bové A, Brito-Zerón P, Soria N, Nardi N. Et al. Outcomes in biopsy-proven lupus nephritis: evaluation of 190 white patients from a single center. ***Medicine (Baltimore)*** 2010; 89(5):300-07. doi: 10.1097/MD.0b013e3181f27e8f.
18. Al Arfaj AS, Khalil N, Al Saleh S. Lupus nephritis among 624 cases of systemic lupus erythematosus in Riyadh, Saudi Arabia. Rheumatol Int 2009; 29(9):1057-67. doi: 10.1007/s00296-009-0905-8.
19. Moroni G, Quaglini S, Gallelli B, Banfi G, Messa P, Ponticelli C. Progressive improvement of patient and renal survival and reduction of morbidity over time in patients with lupus nephritis (LN) followed for 20 years. ***Lupus*** 2013; 22(8):810-8. doi: 10.1177/ 0961203313492576.
20. Tang Y, Zhang X, Ji L, Mi X, Liu F, Yang L, Qin W. Clinicopathological and outcome analysis of adult lupus nephritis patients in China. ***Int Urol Nephrol*** 2015; 47(3):513-20. doi: 10.1007/s11255-014-0903-y.
21. Inês L, Silva C, Galindo M, López-Longo FJ, Terroso G, Romão VC. et al. Classification of systemic lupus erythematosus: systemic lupus international collaborating clinics versus american college of rheumatology criteria. A comparative study of 2,055 patients from a real-life, international systemic lupus erythematosus cohort. ***Arthritis Care Res (Hoboken)*** 2015; 67(8):1180-5. doi: 10.1002/ acr.22539.
22. Davidson JE, Fu Q, Ji B, Rao S, Roth D, Magder LS, Petri M. Renal Remission Status and Longterm Renal Survival in Patients with Lupus Nephritis: A Retrospective Cohort Analysis. ***J Rheumatol*** 2018; 45(5):671-77. doi: 10.3899/jrheum.161554.
23. Dall 'Era M, Cisterna's MG, Smilek DE, Straub L, Hossain FA, Cervera R, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. ***Arthritis Rheumatol*** 2015; 67(5):1305-13. doi: 10.1002/art.39026.
24. Tamirou F, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Fiehn C, et al. Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate

mofetil as maintenance therapy of lupus nephritis. ***Ann Rheum Dis*** 2016; 75(3):526-31. doi: 10.1136/annrheumdis-2014-206897.

25. Tunnicliffe DJ, Palmer SC, Henderson L, Masson P, Craig JC, Tong A, et al. Immunosuppressive treatment for proliferative lupus nephritis. ***Cochrane Database Syst Rev*** 2018; 6(6): Cd002922. doi: 10.1002/14651858.CD002922.pub4.
26. Sprangers B, Monahan M, Appel GB. Diagnosis and treatment of lupus nephritis flares--an update. ***Nat Rev Nephrol*** 2012; 8(12):709-17. doi: 10.1038/nrneph.2012.220.
27. Hsu TC, Yang YH, Wang LC, Lee JH, Yu HH, Lin YT, et al. Risk factors for subsequent lupus nephritis in patients with juvenile-onset systemic lupus erythematosus: a retrospective cohort study. ***Pediatr Rheumatol Online J*** 2023; 21(1):28. doi: 10.1186/s12969-023-00806-x.
28. Díaz-Coronado JC, Rojas-Villarraga A, Hernandez-Parra D, Betancur-Vásquez L, Lacouture-Fierro J, Gonzalez-Hurtado D, et al. Clinical and sociodemographic factors associated with lupus nephritis in Colombian patients: A cross-sectional study. ***Reumatol Clin (Engl Ed)*** 2021; 17(6):351-56. doi: 10.1016/j.reuma.2019.09.005.
29. Shin JM, Kim D, Kwon YC, Ahn GY, Lee J, Park Y, et al. Clinical and genetic risk factors associated with the presence of lupus nephritis. ***J Rheum Dis*** 2021; 28(3):150-58. doi: 10.4078/jrd.2021.28.3.150.
30. Hanley JG, Aidan G O'Keeffe 2, Li Su 3, Murray B Urowitz 4, Juanita Romero-Diaz 5, Caroline Gordon et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. ***Rheumatology (Oxford)*** 2016; 55(2):252-62. doi: 10.1093/rheumatology/kev311.
31. Somai M, Daoud F, Rachdi I, Zoubeidi H, Raies L, Aydi Z. et al. Predictive factors of the lupus nephritis in a Tunisian cohort. ***Tunis Med*** 2019; 97(12):1399-406.