Low-Level Proteinuria in Systemic Lupus Erythematosus

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Introduction: In patients with systemic lupus erythematosus (SLE) without concurrent active urinary sediment or unexplained acute kidney injury (AKI), current guidelines recommend performing a kidney biopsy in those with at least 500 mg/24-hour (European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association [EULAR/ERA-EDTA]) or 1000 mg/24-hour (American College of Rheumatology [ACR]) proteinuria. To evaluate the relevance of these indications, we studied histopathologic findings in patients with SLE with proteinuria below these cutoffs.

Methods: We retrospectively reviewed the clinical, laboratory and histological characteristics of patients with SLE with <1000 mg/24-hour proteinuria (or mg/g urinary protein-to-creatinine ratio [UPCR]) who underwent their first kidney biopsy between 2003 and 2018.

Results: We identified 87 patients with SLE with proteinuria less than 1000 mg/24-hour (or mg/g UPCR); 52 of 87 (60%) with isolated proteinuria, that is, without AKI or active urinary sediment (hematuria). Histologic evidence of lupus nephritis (LN) was present in 40 of 52 (76%). Of the 40 patients with LN, 12 had class I or II, 14 had class III or IV, 8 had class V, 6 had a combined proliferative and membranous LN. Non-lupus diagnoses included focal segmental glomerulosclerosis, acute interstitial nephritis, and others. Patient’s age, low C3, low C4, and positivity for anti-double-stranded DNA (anti-dsDNA) antibodies predicted the histological diagnosis of LN on univariate logistic regression; however, a multivariate model including these parameters as independent covariates failed to predict LN.

Conclusions: Patients with SLE with low-level proteinuria may have significant lupus- or non–lupus-related kidney disease with management implications. There was a significant burden of severe forms of LN. The presence of LN was not predicted by laboratory abnormalities. Based on our findings, we suggest current guidelines be revised to expand kidney biopsy indications to include isolated proteinuria of any grade.

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Among patients with SLE, LN is a common complication. In a large multiethnic inception cohort of patients with SLE followed annually after the diagnosis of SLE (the Systemic Lupus International Collaborating Clinics inception cohort), LN occurred in 38.3% of patients; 80.9% at diagnosis and the rest during follow-up (mean duration 4.6 years).¹ The penetrance of LN in SLE populations, however, varies widely, for example with racial diversity (i.e., Black [69%], Asian [40%–82%], Hispanic [61%], and White [29%]).¹,³

The clinical presentation and histopathologic patterns of kidney involvement are highly variable. The focal and diffuse forms of LN (class III and IV, respectively) generally present with nephritic urine sediments and may have progressive renal failure. By contrast, mesangial (class II) and membranous LN (class V) typically present with varying ranges of proteinuria. Several studies, however, have illustrated the poor reliability of diagnoses rendered on the basis of clinical features alone.⁴–⁷ Thus, kidney biopsy is an important tool in assessing patients with LN and is essential for a definitive diagnosis of histopathological subtype and direction of proper treatment.
According to ACR and EULAR/ERA-EDTA guidelines for the management of LN, the choice of the appropriate immunosuppressive regimen is based on the histopathologic International Society of Nephrology and the Renal Pathology Society classification. Both organizations confine the use of immunosuppressive agents (i.e., cyclophosphamide or mycophenolate mofetil) to proliferative, membranous, and mixed proliferative/membranous classes.6,9 Indications for performing a kidney biopsy differ slightly between the two guidelines.

The ACR guidelines recommend performing a kidney biopsy in patients with SLE for (i) an otherwise unexplained decrease in renal function, (ii) proteinuria of at least 1 g/24 hours (or UPCR of at least 1 g/g), or (iii) proteinuria of at least 500 mg/24 hours (or UPCR 500 mg/g) in association with either microscopic hematuria (≥5 red blood cells/high-power field on urinalysis), cellular casts, or both.9 By contrast, the EULAR/ERA-EDTA guidelines are less strict, with the recommendation to biopsy for “any sign of renal involvement,” particularly proteinuria ≥500 mg/24 hours with or without glomerular hematuria and/or cellular casts.6 Both guidelines do not recommend a kidney biopsy for patients with isolated proteinuria of less than 500 mg/24 hours (or UPCR 500 mg/g); however, patients with no urinary findings or isolated proteinuria might have “silent” LN. A limited body of studies has explored this particular population, showing that a meaningful subset of patients with absent or isolated low-level proteinuria do indeed have class III, IV, III/IV plus V, or V on kidney biopsy, which would require immunosuppressive agents (proliferative and mixed proliferative and membranous classes) or at least zealous clinical surveillance (pure class V) as per current ACR and EULAR/ERA-EDTA guidelines.

In this 2-center retrospective study, we explored the clinical and histological characteristics of patients with SLE with low-level proteinuria (less than 1 g/24 hours or UPCR 1 g/g), with a strong emphasis on the subset of patients with isolated low-level proteinuria (who under current guidelines may not be offered a kidney biopsy).

### MATERIAL AND METHODS

Among patients with SLE who underwent a native kidney biopsy at Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center between June 2003 and September 2018, we reviewed the biopsies of patients with less than 1000 mg/24 hours proteinuria (or less than 1000 mg/g UPCR when 24-hour urinary collections were not available). We only included in our study patients having their first kidney biopsy with an already established diagnosis of SLE according to the ACR classification criteria21 without history of LN. Patients younger than 21 years were excluded.

Baseline data, including age at biopsy, ethnicity, and laboratory values comprising serum creatinine, complement levels, anti-dsDNA positivity status, urinalysis, and proteinuria (either from 24-hour collections or UPCR), were collected from electronic medical records. Low-level proteinuria was defined as <1000 mg/24 hours proteinuria or mg/g UPCR. Microscopic hematuria of at least 5 red blood cells/high-power field on urinalysis was used as a surrogate for active urinary sediment in all cases. AKI was defined as an increase in creatinine of at least 0.3 mg/dl from baseline as per Kidney Disease Improving Global Outcomes definition.22 Estimated glomerular filtration rate was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation.23

Histology slides were retrieved for all cases and reevaluated by an experienced renal pathologist. Biopsies showing LN were reclassified according to the International Society of Nephrology and The Renal Pathology Society classification of LN.24 The biopsies that showed proliferative LN (i.e., classes III, IV, and either III or IV plus V, according to the International Society of Nephrology and the Renal Pathology Society classification) were also scored with the National Institutes of Health activity and chronicity indices.25

The study was approved by the Johns Hopkins Medicine Institutional Review Board and undertaken in accordance with the principles of the Declaration of Helsinki. The Institutional Review Board waived the requirement for informed consent of this study.

Differences in continuous variables were assessed using Student’s t-tests and in categorical variables using χ² and Fisher’s exact tests, where appropriate. Univariate logistic regression analysis was used to assess the impact of various clinical elements (sex, age, ethnicity, hypocomplementemia, and anti-dsDNA positivity) on the probability of LN at kidney biopsy in the subset of patients with isolated low-level proteinuria and no prior histological evidence of LN. Odds ratios (ORs), expressed by the values of exp (B), were reported with their respective 95% confidence intervals (CIs) and statistical significance. All independent variables that showed statistical significance on univariate analysis were entered in a multivariate logistic regression model. A 2-sided P value ≤ 0.05 was the chosen level of statistical significance. All data analyses were performed using IBM SPSS, version 25 (IBM Corp., Armonk, NY).

### RESULTS

We identified 87 cases that met our inclusion criteria (Figure 1). The patients’ baseline characteristics are...
summarized in Table 1. Fifty-two (60%) patients had isolated low-level proteinuria; the remaining 35 (40%) had low-level proteinuria plus AKI \((n=17)\), hematuria \((n=11)\), or both \((n=7)\).

Among the 52 patients with isolated low-level proteinuria, 40 (76%) had LN and 12 (24%) had non–lupus-related kidney disease (Table 1). Nine (90%) of 10 patients with isolated 24-hour proteinuria <500 mg (or 500 mg/g UPCR) had LN. By contrast, in the group with proteinuria plus hematuria and/or AKI, 29 (82%) and 6 (18%) had LN and non–lupus-related kidney disease, respectively.

No significant differences were noted in demographic (age, gender, ethnicity), laboratory (hypocomplementemia and anti-dsDNA antibodies positivity), pathology (presence of LN and frequency of LN classes, National Institutes of Health activity and chronicity indices), or treatment regimens between those with isolated low-level proteinuria and the rest of the cohort, both when considering them as a whole and when comparing only the respective subsets with LN.

There were significant differences in creatinine levels, estimated glomerular filtration rate, presence of hematuria, or AKI between the 2 groups, as expected by selection criteria. As for proteinuria, a minimal, albeit statistically significant, difference was observed.

There were no significant differences between patients with isolated proteinuria <500 mg/24 hours (or mg/g UPCR) and those with isolated proteinuria between 500 and 1000 mg/24 hours (or mg/g UPCR) in aforementioned parameters, both when considering them in aggregate and when comparing only the respective subsets with LN, with the exception of proteinuria, once again as expected by selection criteria (Table 2).

Comparing those with and without LN in the isolated low-level proteinuria group, patients with LN were significantly younger, with lower serum C3 levels and higher estimated glomerular filtration rate, and more frequently had low C3, low C4, and positive anti-dsDNA antibodies, than patients who did not have LN.

In patients with isolated low-level proteinuria, age (OR: 0.92; 95% CI: 0.87–0.98; \(P=0.005\)), low C3 (OR: 6.88; 95% CI: 1.32–35.77; \(P=0.022\)), low C4 (OR: 12.83; 95% CI: 1.51–109.27; \(P=0.020\)), and positivity for anti-dsDNA antibodies (OR: 8.33; 95% CI: 1.60–43.29 ; \(P=0.012\)) predicted LN on univariate logistic regression (Table 3). These parameters were therefore included as independent variables in a multivariate logistic regression model, which showed none of them held predictive value when considered together (Table 4).

**DISCUSSION**

Albeit with the inherent limitations of a retrospective study, we found a disproportionate fraction of patients with SLE with low-level proteinuria who indeed had...
LN in our series. Moreover, a relevant proportion of cases had either proliferative or membranous LN, warranting treatment with immunosuppressive agents in the former and at least close clinical surveillance in the latter.

In an early study from our institution that retrospectively evaluated 21 patients with SLE with low-level proteinuria <1000 mg/24 hours who underwent kidney biopsy between 1995 and May 2003 for new-onset proteinuria, worsening proteinuria, or hematuria, 16 of 21 had LN, 10 of 21 with proliferative LN class III and 2 of 21 with class IV. Six patients had mixed classes. Seven patients had isolated low-level proteinuria without hematuria, 4 (57%) had class III, IV, or V. One patient without hematuria and <500 mg proteinuria had class III LN. None of these patients were included in the current study. Because current guidelines do recommend (i) performing a kidney biopsy for low-level proteinuria when there is concurrent active urinary sediment and/or AKI, and (ii) repeating a kidney biopsy when clinically warranted, for example, when there is refractoriness to therapy, partial

### Table 1. Characteristics of patients with isolated and nonisolated low-level proteinuria

| Patients’ characteristics                      | Isolated low-level proteinuria | Low-level proteinuria with AKI and/or microscopic hematuria | P value |
|-----------------------------------------------|--------------------------------|-----------------------------------------------------------|--------|
| Patients, n (%)                               | 52 (100)                       | 35 (100)                                                  |        |
| Female, n (%)                                 | 48 (92)                        | 31 (89)                                                   | NS     |
| Age, y, mean (± SD)                           | 39 (± 13)                      | 39 (± 16)                                                  | NS     |
| Ethnicity, n (%)                              |                                |                                                           |        |
| African American                              | 31 (59)                        | 21 (60)                                                   | NS     |
| White                                          | 13 (25)                        | 12 (24)                                                   | NS     |
| Asian                                          | 5 (10)                         | 2 (6)                                                     | NS     |
| Hispanic                                       | 3 (6)                          | 0 (0)                                                     | NS     |
| Laboratory/clinical features                  |                                |                                                           |        |
| Creatinine, mean (± SD) mg/dl                 | 0.78 (± 0.2)                   | 1.56 (± 1.1)                                              | <0.0001|
| eGFR, mean (± SD) mL/min per 1.73 m²          | 111.3 (± 28.4)                 | 67.9 (± 38.7)                                             | <0.0001|
| Proteinuria, mean (± SD) mg/dl or g/24-h      | 0.655 (± 0.209)                | 0.525 (± 0.287)                                           | 0.0166 |
| C3, mean (± SD) mg/dl (normal >81)            | 82.06 (±31.21)                 | 79.24 (±38.24)                                            | 0.6996 |
| C4, mean (± SD) mg/dl (normal >13)            | 17.22 (±13.9)                  | 14.64 (±18.53)                                            | NS     |
| Low C3, n (%)                                 | 24 (46)                        | 22 (63)                                                   | NS     |
| Low C4, n (%)                                 | 22 (42)                        | 20 (57)                                                   | NS     |
| Positive anti-dsDNA, n (%)                    | 27 (52)                        | 25 (71)                                                   | NS     |
| AKI, n (%)                                     | 0 (0)                          | 23 (66)                                                   | <.00001|
| Microhematuria, n (%)                         | 0 (0)                          | 18 (51)                                                   | <.00001|
| Drugs                                         |                                |                                                           |        |
| Glucocorticoids, n (%)                        | 27 (52)                        | 19 (54)                                                   | NS     |
| Immunosuppressive agents, n (%)               | 17 (33)                        | 7 (20)                                                    | NS     |
| RAAS inhibitors, n (%)                        | 20 (38)                        | 10 (29)                                                   | NS     |
| Pathology                                     |                                |                                                           |        |
| Non-LN, n (%)                                 | 12 (24)                        | 6 (18)                                                    | NS     |
| FSGS, n (%)                                   | 2 (4)                          | 1 (3)                                                     |        |
| AIN, n (%)                                     | 2 (4)                          | 0 (0)                                                     |        |
| ATN, n (%)                                     | 0 (0)                          | 1 (3)                                                     |        |
| Chronic tubulointerstitial inflammation, n (%)| 0 (0)                          | 0 (0)                                                     |        |
| Diabetic nephropathy, n (%)                   | 1 (2)                          | 0 (0)                                                     |        |
| IgG4-positive plasma cell-rich interstitial inflammation, n (%)| 1 (2)                          | 0 (0)                                                     |        |
| Immune complex-mediated GN, n (%)             | 2 (4)                          | 1 (3)                                                     |        |
| IgM nephropathy, n (%)                        | 1 (2)                          | 0 (0)                                                     |        |
| Nonspecific lymphoplasmyocytic interstitial inflammation, n (%)| 1 (2)                          | 0 (0)                                                     |        |
| Unremarkable kidney, n (%)                    | 2 (4)                          | 1 (3)                                                     |        |
| Thin basement membrane disease, n (%)         | 0 (0)                          | 1 (3)                                                     |        |
| LN, n (%)                                      | 40 (76)                        | 29 (82)                                                   | NS     |
| Class I or II, n (%)                          | 12 (23)                        | 7 (20)                                                    | NS     |
| Class III or IV or III/IV plus V, n (%)       | 20 (38)                        | 17 (49)                                                   | NS     |
| NIH activity index, score (± SD) units        | 4.53 (± 2.17)                  | 5.5 (± 2.44)                                              | NS     |
| NIH chronicity index, score (± SD) units      | 2.71 (± 2.54)                  | 2.07 (± 2.43)                                             | NS     |
| Class V, n (%)                                 | 8 (15)                         | 5 (13)                                                    | NS     |

AIN, acute interstitial nephritis; AKI, acute kidney injury; ATN, acute tubular injury; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; LN, lupus nephritis; NIH, National Institutes of Health; NS, not statistically significant; RAAS, Renin-Angiotensin-Aldosterone System.
response, or suspect of class switch or of kidney disease other than LN, we separately analyzed the subset of patients with no indication for biopsy according to ACR and EULAR/ERA-EDTA recommendations. EULAR/ERA-EDTA guidelines are less restrictive, recommending a kidney biopsy for isolated proteinuria of at least 500 mg/24 hours (or mg/g UPCR). Ten of 57 with isolated proteinuria <1000 mg/24 hours (or mg/g UPCR) had less than 500 mg/24 hours proteinuria (or mg/g UPCR). Even in this group, LN was present in 9 of 10. Most of these biopsies showed proliferative or mixed proliferative and membranous lupus, or pure membranous LN (Figure 1). Silent LN has been variably defined as LN in patients with no urinary abnormalities, with isolated low-level proteinuria (less than 500 or 300 mg/24 hours or mg/g UPCR) or either <500 mg/24 hours proteinuria (or mg/g UPCR) or no urinary abnormalities at all. In the studies adopting a definition of silent LN based on the presence of isolated <500 mg/24 hours proteinuria (or mg/g UPCR) and extrapolating those who fit this definition from the study by Cavallo and colleagues, the proportion of proliferative or mixed proliferative and membranous cases varied between 17% and 38%, that is, generally lower than our series (50%).

In one study, C3 hypocomplementemia and anti-dsDNA antibody positivity predicted transition from

| Patients’ characteristics | Isolated < 0.5 g/g or g/24-h proteinuria | Isolated 0.5–1 g/g or g/24-h proteinuria | P value |
|---------------------------|-----------------------------------------|------------------------------------------|--------|
| Patients, n (%)           | 10                                      | 42                                       | NS     |
| Female, n (%)             | 9                                       | 39                                       | NS     |
| Age, y, mean (±SD)        | 36 (± 12)                               | 38 (± 12)                                | NS     |
| Ethnicity                 |                                         |                                          |        |
| 1African American, n (%)  | 6                                       | 40                                       | NS     |
| 1White, n (%)             | 2                                       | 19                                       | 27     |
| 1Asian, n (%)             | 2                                       | 6                                        | 9      |
| 1Hispanic, n (%)          | 0                                       | 5                                        | 7      |
| Labo/clinical features    |                                         |                                          |        |
| 1Creatinine, mean (± SD) mg/dl | 0.72 (± 0.17)                             | 0.76 (± 0.21)                            | NS     |
| 1eGFR, mean (± SD) ml/min per 1.73 m² | 119.9 (± 20.8)                   | 109.2 (± 29.6)                           | NS     |
| 1Proteinuria, mean (± SD) g/g or g/24-h | 0.439 (± 0.01)                     | 0.699 (± 0.159)                          | <0.0001|
| 1C3, mean (± SD) mg/dl (normal >81) | 70 (± 40.38)                            | 82.58 (± 29.04)                          | NS     |
| 1C4, mean (± SD) mg/dl (normal >13) | 22.2 (± 7.04)                           | 15.96 (± 8.78)                           | NS     |
| 1Low C3, n (%)            | 7                                       | 17                                       | 40     |
| 1Low C4, n (%)            | 5                                       | 17                                       | 40     |
| 1Positive anti-dsDNA, n (%) | 5                                       | 22                                       | 52     |
| Drugs                     |                                         |                                          |        |
| Glucocorticoids, n (%)    | 6                                       | 21                                       | 50     |
| Immunosuppressive agents, n (%) | 2                                       | 15                                       | 36     |
| RAAS inhibitors, n (%)    | 6                                       | 14                                       | 33     |
| Pathology                 |                                         |                                          |        |
| Non-LN, n (%)             | 1                                       | 11                                       | 25     |
| 1FSGS, n (%)              | 0                                       | 2                                        | 5      |
| 1AIN, n (%)               | 0                                       | 2                                        | 5      |
| 1Diabetic nephropathy, n (%) | 0                                       | 1                                        | 2      |
| 1IgG6-positive plasma cell-rich interstitial inflammation, n (%) | 0 | 1 | 2 |
| 1Immune complex-mediated GN, n (%) | 0 | 2 | 5 |
| 1IgM nephropathy, n (%)   | 0                                       | 1                                        | 2      |
| 1Nonspecific lymphoplasmacytic interstitial inflammation, n (%) | 0 | 1 | 2 |
| 1Unremarkable kidney, n (%) | 1                                       | 1                                        | 2      |
| LN, n (%)                 | 9                                       | 31                                       | 75     |
| 1Class I or II, n (%)     | 3                                       | 9                                        | 21     |
| 1Class III or IV or III/IV plus V, n (%) | 5 | 15 | 36 |
| 1NIH activity index, score (± SD) units | 3.75 (±2.28)                      | 4.17 (±2.34)                            | NS     |
| 1NIH chronicity index, score (± SD) units | 2.25 (±2.86)             | 2.1 (± 2.5)                             | NS     |
| 1Class V, n (%)           | 1                                       | 7                                        | 18     |

AIN, acute interstitial nephritis; AKI, acute kidney injury; ATI, acute tubular injury; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; LN, lupus nephritis; NS, not statistically significant; NIH, National Institutes of Health; RAAS, Renin-Angiotensin-Aldosterone System.
silent LN to clinically overt LN, whereas other investigators\(^1\) found that low C3, CH50, and anti-Sm antibody positivity in patients with isolated low-level proteinuria predicted LN on kidney biopsy. A recent study in a Chinese population found that albuminuria and elevated Systemic Lupus Erythematosus Disease Activity Index predicted severe LN on kidney biopsy, defined as either class III, IV, or V as per International Society of Nephrology and the Renal Pathology Society classification.\(^1\)

Similarly to other studies of patients with silent LN/LN in the setting of isolated low-level proteinuria, we found that low complement levels and positive anti-dsDNA antibodies were significantly more frequent in those with isolated low-level proteinuria with LN on kidney biopsy than those with other diagnoses (Supplementary Table S1). However, when considering all the statistically significant variables on univariate logistic regression as independent covariates in a multivariate logistic regression model, the prediction was lost (Tables 3 and 4). Therefore, no clinical/laboratory finding was predictive of LN on kidney biopsy in this population, supporting the rationale for performing a kidney biopsy in patients with SLE with proteinuria of any grade.

In light of the high proportion of patients with proliferative/mixed proliferative and membranous or pure membranous LN in our series, we argue that the benefits of a kidney biopsy in these patients outweigh the risks related to the procedure. The risk of bleeding after kidney biopsy is low in the SLE population, as previously shown,\(^2\) and we did not observe any biopsy-related complication in our series of 87 patients. Two recent prospective observational cohort studies exploring the value of repeat biopsies in guiding maintenance immunosuppression in patients with proliferative LN reported virtually no biopsy-related complication.\(^2\),\(^3\)

EULAR/ERA-EDTA and ACR guidelines both recommend major immunosuppressive agents (e.g., cyclophosphamide, mycophenolate mofetil) for proliferative or mixed proliferative and membranous LN, whereas for class V with subnephrotic proteinuria, the recommendations is to treat with renin-angiotensin-aldosterone system inhibitors and monitor closely. Because the patients included in our and similar studies have been for the most part treated according to the histological diagnosis, we do not have a sense of how the clinical course would have been without treatment. Older studies, characterized by wide variability in patient selection and treatment choice/time of initiation, suggested better survival of silent than overt LN, but the definition of silent LN in those studies relied on the actual absence of proteinuria (<150 mg/24 hours or mg/g UPCR), thus making impossible a comparison with our population.\(^1\) However, lupus-related renal disease in those patients might simply have been caught at an early, still subclinical stage, reflecting a more aggressive pursuit of kidney biopsy; the better outcome observed might therefore reflect the effect of earlier therapeutic intervention. This has been shown to be true for the general LN population: over the years, a tendency in patients to present with milder clinical presentation at onset and to have better short- and long-term outcome was observed in a large retrospective cohort of patients with LN spanning 5 decades, likely reflecting both earlier diagnosis/intervention and more aggressive/effective treatment.\(^3\)

It has been long appreciated that proliferative LN is associated with the worst renal outcome among all LN classes,\(^3\) and that a delay in performing a kidney biopsy is associated with increased risk of renal relapses\(^1\) (OR: 1.03; 95% CI: 1.01–1.05 for each month delay) and end-stage renal disease\(^3\) (OR: 4.2; 95% CI: 1.24–12.7 for more than 6 months’ delay). Moreover, creatinine at onset is a well-established predictor of outcome in LN\(^3\); patients with isolated low-level proteinuria in our and other series have higher estimated glomerular filtration rate, likely harboring a better prognosis. It is therefore reasonable to expect that earlier identification of patients requiring major immunosuppressive agents and thus early therapy initiation would lead to earlier clinical response and better short- and long-term

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**Table 3.** Univariate analysis of variables predictive of lupus nephritis in the 52 patients with isolated low-level proteinuria and no prior diagnosis of lupus nephritis

| Factors predictive of lupus nephritis - univariate logistic regression | OR (95% CI) | P value |
|---|---|---|
| Sex (female vs male) | 1.12 (0.11–11.89) | 0.924 |
| Age, y | 0.92 (0.87–0.98) | 0.005 |
| Ethnicity (African American vs others) | 1.67 (0.45–6.12) | 0.441 |
| Low C3 | 6.88 (1.32–35.77) | 0.022 |
| Low C4 | 12.83 (1.51–109.27) | 0.020 |
| Anti-dsDNA positivity | 8.33 (1.60–43.29) | 0.012 |

CI, confidence interval; dsDNA, double-stranded DNA; OR, odds ratio.

**Table 4.** Multivariate logistic regression model for the prediction of lupus nephritis in the 52 patients with isolated low-level proteinuria and no prior diagnosis of lupus nephritis

| Factors predictive of lupus nephritis - multivariate logistic regression | OR (95% CI) | P value |
|---|---|---|
| Age, y | 0.95 (0.88–1.01) | 0.100 |
| Low C3 | 1.04 (0.99–1.21) | 0.977 |
| Low C4 | 6.10 (3.68–104.59) | 0.212 |
| Anti-dsDNA positivity | 5.70 (0.92–35.34) | 0.061 |

CI, confidence interval; dsDNA, double-stranded DNA; OR, odds ratio.
outcomes, as these patients would be identified at the time they are more likely to respond to therapy (i.e., while their renal function is still preserved).

Finally, patients with low-level isolated proteinuria but no LN in our series had nonetheless significant kidney disease, including interstitial nephritis and focal segmental glomerulosclerosis (Table 1), diagnoses that, albeit not necessarily SLE-related, carry obvious implications on management, including informing treatment.

Our results add to the small but growing body of evidence showing that a relevant proportion of patients with SLE with isolated low-level proteinuria indeed have proliferative or membranous LN, requiring aggressive immunosuppressive treatment or at least close monitoring, respectively. These results suggest that it might be time to rethink current SLE recommendations and expand indications for kidney biopsy to include patients with SLE with isolated low-level proteinuria of any grade, as supported by our series.

**DISCLOSURE**

The authors declared no competing interests.

**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)

**Table S1.** Characteristics of patients with isolated low-level proteinuria with and without lupus nephritis.

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