A Systematic Review of Interpathologist Agreement in Histologic Classification of Lupus Nephritis

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Introduction: Lupus nephritis (LN) is one of the most severe manifestations of systemic lupus erythematosus (SLE), resulting in increased morbidity and mortality. The gold standard for diagnosis of LN is a renal biopsy. Considering the importance of the biopsy in determining long-term prognostication and treatment decisions, it is crucial to assess renal histopathology with utmost accuracy and precision. This review represents a systematic search of published literature to estimate the degree of interpathologist reproducibility in current assessment of LN.

Methods: Using the PubMed and Google Scholar search engines, studies analyzing the agreement of 4 or more pathologists assessing LN slides using the ISN/Renal Pathology Society (RPS) classification, activity index, and chronicity index were selected for analysis in this systematic review.

Results: In reviewing 6 qualifying studies (those analyzing the agreement of 4 or more pathologists using the ISN/RPS classification, activity index, and chronicity index) for the assignment of ISN/RPS class was 0.325 (interquartile range IQR 0.240–0.425), which is “poor.” The median interpathologist concordance values for the assigned activity index and chronicity index were “moderate”: 0.52 (IQR 0.51–0.69) and 0.49 (IQR 0.36–0.58), respectively.

Conclusion: Thus, the current scoring using the ISN/RPS classification system and activity and chronicity indices for LN exhibits poor interpathologist agreement, which limits its use in clinical practice. Given that this can have severe repercussions on a patient’s treatment and prognosis, efforts to update pathology assessment guidelines, objectively measurable biomarkers, and deep learning approaches are strongly warranted.

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Lupus nephritis (LN) is one of the most severe manifestations of SLE, resulting in increased morbidity and mortality.¹ Up to 60% of adults and 80% of children with SLE develop LN, with 10%–30% progressing to end-stage renal disease (ESRD) within 15 years despite aggressive treatment.²–⁴ The gold standard for diagnosis of LN is a renal biopsy. Histologic parameters, as defined by the ISN/RPS 2003 classification,⁵ remain the best predictors of ESRD and are utilized to assign the severity⁶–¹⁵ of LN to classes I–VI. The renal biopsy is also scored for its activity index (AI) based on 6 specific histologic features, and its chronicity index (CI) based on 4 specific histologic features.¹⁶,¹⁷ These indices, along with the assigned LN class, provide prognostic value and treatment guidance. In general, ISN/RPS class III or class IV LN, high renal AI (score >7), high renal CI (score >4), and the presence of subepithelial and subendothelial deposits are associated with poor renal survival.⁶–¹⁵

According to current guidelines, a diagnosis of either class III or class IV LN is an indication for immunosuppressive therapy.¹⁸–²⁰ Additionally, whereas a high chronicity index is associated with refractoriness to aggressive therapy, lesions with a high activity index are potentially reversible.⁷,²¹–²³ As suggested by these observations, histologic features play an important role in guiding the intensity of therapy.⁸,²²–²⁵ It has also been reported that early, accurate detection and prompt treatment can significantly reduce morbidity and mortality in LN.²⁶–²⁹

Considering the ISN/RPS classification system’s role in determining long-term prognostication and treatment decisions, it is crucial to assess renal
histopathology in LN with utmost accuracy and precision. This also extends to the scoring of renal pathology, AI, and CI. Certain histologic parameters that constitute the AI, such as cellular crescents and fibrinoid necrosis, have been documented to correlate with renal failure and ESRD\footnote{7,10}; as a result, these features are weighted twice in the calculation of a patient’s AI score.\footnote{16} Additionally, every individual chronicity index feature (glomerular sclerosis, fibrous crescents, interstitial fibrosis, and tubular atrophy) has been associated with an increased risk of ESRD, and renal failure rates are significantly elevated in patients with high CI scores.\footnote{7,10,50,31} Given that an improper assignment of LN class, AI score, and CI score may have significant prognostic and therapeutic repercussions, these metrics need to be assessed with high accuracy.\footnote{30}

Despite being the gold standard, histologic assessment of LN using a renal biopsy is fraught with several pitfalls and high interpathologist variation.\footnote{30–32} Thus far, 6 interobserver renal pathology assessment studies have been reported in which 4 or more pathologists assessed a test set of LN slides.\footnote{30–35} The metrics used to assess interpathologist correlation/concordance, intra-class correlation coefficient (ICC), and kappa factor (K)-value, are comparable; a concordance value of 0 represents no agreement, and 1 represents complete agreement between the pathologists. In these 6 studies,\footnote{30–35} the ICCs or K-values for most histologic parameters of LN fell below 50%. The ICC or K-values for fibrinoid necrosis and cellular crescents, both of which are indicators of poor patient prognosis, were\footnote{30–35} below 0.6. Given that both of these parameters are weighted doubly in the calculation of the AI score, the lack of interpathologist agreement is compounded.\footnote{16} The concordance values for the CI, which is also an indicator of poor prognosis, were\footnote{30–35} as low as 0.35. Given how important histologic assessment of LN is for guiding treatment, this is clearly unacceptable.

The purpose of this review is to conduct a systematic search of published literature to estimate the degree of interpathologist reproducibility in using the current ISN/RPS classification for LN, as well as the renal pathology activity and chronicity index metrics.

**METHODS**

PubMed and Google Scholar were used to search for relevant literature between June and August 2018. The search criteria used were [systemic lupus erythematosus OR lupus] AND [variability OR concordance OR reproducibility] AND [nephritis OR renal OR kidney]. Only studies analyzing the agreement of 4 or more pathologists assessing LN slides using the ISN/RPS classification, activity index, and chronicity index are included in this systematic review (see Supplementary Figure S1 for a flow diagram of the study selection process). In all studies, the degree of concordance between the pathologists was measured using the ICC or the closely related value K. The ICC most resembles the Pearson correlation coefficient. With ICC, the data are centered and scaled using a pooled mean and SD, whereas with the Pearson correlation, each variable is centered and scaled by its own mean and SD. ICCs and K-values are commonly used for the assessment of consistency or reproducibility of quantitative measurements made by different observers measuring the same study subject(s). For each selected study, the following data were independently extracted: number of pathologists, number of LN slides, ICC or K-values for the ISN/RPS classification, ICC or K-values for the activity index and associated histologic features, and ICC or K-values for the chronicity index and associated histologic features.

**RESULTS**

Of the 308 studies screened, 9 studies discussing interpathologist concordance were selected. Six studies met the specified criteria of assessing the interpathologist concordance among 4 or more pathologists.\footnote{30–35} Not included were studies with 3 or fewer pathologists,\footnote{36–38} as they did not meet the predetermined criteria. Table 1 details the evaluation of these 6 studies, including for each study the number of pathologists, the number of LN slides, ICC or K-values for the ISN/RPS classification, ICC or K-values for the activity index and associated histologic features, and ICC or K-values for the chronicity index and associated histologic features. A summary of this table is displayed in Figure 1. The concordance level of the assigned LN class based on the 2003 ISN/RPS Classification (or the previous consensus criteria if conducted before 2004) was analyzed in 4 of the 6 studies,\footnote{32–34} whereas 5 of the 6 studies\footnote{30–33,35} examined the concordance level of the assigned activity and chronicity indices as scored by 4 or more pathologists. Two studies analyzed only renal biopsy slides depicting proliferative forms of LN,\footnote{31,33} and one study analyzed only pediatric LN patients.\footnote{35} Two of the 6 studies included renal biopsy slides of patients without LN.\footnote{31,34} The biopsy interpreters were nephropathologists in 4 studies,\footnote{30,32–34} and in 2 studies,\footnote{31,35} they were general pathologists experienced in reading renal biopsies.

Although the biopsy interpreters were all trained pathologists, and most were nephropathologists, their concordance values (as assessed using ICC or K-value) in assessing LN were generally modest. The median
interpathologist concordance values for the reported pathology indices and component histologic features detailed in Figure 1 ranged from 0.30 to 0.83. The median interpathologist concordance value for the assignment of ISN/RPS class was 0.325 (IQR 0.240–0.425), which is “poor.” The median interpathologist concordance values for the assigned AI and CI were "moderate": 0.52 (IQR 0.51–0.69) and 0.49 (IQR 0.36–0.58), respectively.

In these studies, an ICC or K-value of <0.4, 0.4–0.6, 0.6–0.8, or >0.8 is considered to reflect poor, moderate, good, or excellent agreement, respectively. The histologic features with poor agreement (based on median concordance values) were leukocyte infiltration

Table 1. Extracted data from 6 articles to estimate the degree of interpathologist concordance in LN histology assessment

| Study              | No. of pathologists | No. of LN slides | ISN/RPS class concordance | Activity index concordance | Endocapillary hypercellularity | Leukocyte infiltration | Subendothelial hyaline deposits | Fibrinoid necrosis/karyorrhexis | Cellular crescents | Interstitial inflammation | Chronicity index concordance | Glomerular sclerosis | Fibrous crescents | Interstitial fibrosis | Tubular atrophy |
|--------------------|---------------------|------------------|---------------------------|-----------------------------|-------------------------------|-------------------------|-------------------------------|-------------------------------|-------------------|------------------------|----------------------|--------------------|-----------------|-------------------|---------------|
| Furness and Taub    | 31 nephropathologists | 20 renal biopsies from SLE | 0.53 (κ) | 0.39 (κ) | 0.65 (ICC) | 0.62 ± 0.07 (ICC) | 0.10 (ICC) | 0.46 (ICC) | 0.35 (κ) | 0.49 (ICC) | 0.36 ± 0.09 (ICC) | 0.60–0.76 (ICC; between 2 pathologists) | 0.58 (ICC) | 0.82 (ICC) | 0.40 ± 0.09 (ICC) | 0.34 (ICC) |
| Grootscholten et al.| 5 nephropathologists (3 evaluated each biopsy) | 87 biopsies with proliferative LN | 0.182 (ICC) | 0.72 (ICC) | 0.62 ± 0.07 (ICC) | 0.27 (ICC) | 0.32 (ICC) | 0.46 (ICC) | 0.55 ± 0.07 (ICC) | 0.83 ± 0.05 (ICC) | 0.50 (ICC) | 0.49 (ICC) | 0.36 ± 0.09 (ICC) | 0.60–0.76 (ICC; between 2 pathologists) | 0.58 (ICC) | 0.25 ± 0.09 (ICC) | 0.58 (ICC) | 0.42 (ICC) | 0.10 ± 0.10 (ICC) | 0.44 (ICC) | 0.51 (ICC) | 0.07 ± 0.10 (ICC) | 0.44 (ICC) |
| Oni et al.          | 4 histopathologists | 55 slides from pediatric LN | 0.26 ± 0.12 (κ) | 0.69 ± 0.06 (ICC) | 0.44–0.63 (ICC; between 2 pathologists) | 0.51 (ICC) | 0.83 ± 0.09 (ICC) | 0.54 (ICC) | 0.50 (ICC) | 0.51 (ICC) | 0.62 ± 0.07 (ICC) | 0.62 ± 0.07 (ICC) | 0.46 (ICC) | 0.49 (ICC) | 0.36 ± 0.09 (ICC) | 0.60–0.76 (ICC; between 2 pathologists) | 0.58 (ICC) | 0.40 ± 0.09 (ICC) | 0.34 (ICC) | 0.25 ± 0.09 (ICC) | 0.58 (ICC) | 0.42 (ICC) | 0.10 ± 0.10 (ICC) | 0.44 (ICC) |
| Schwartz et al.     | 4 nephropathologists | 83 slides from LN | 0.12 (κ) | 0.39 (ICC) | 0.182 (ICC) | 0.27 (ICC) | 0.32 (ICC) | 0.46 (ICC) | 0.55 ± 0.07 (ICC) | 0.83 ± 0.05 (ICC) | 0.50 (ICC) | 0.49 (ICC) | 0.36 ± 0.09 (ICC) | 0.60–0.76 (ICC; between 2 pathologists) | 0.58 (ICC) | 0.82 (ICC) | 0.40 ± 0.09 (ICC) | 0.34 (ICC) | 0.25 ± 0.09 (ICC) | 0.58 (ICC) | 0.42 (ICC) | 0.10 ± 0.10 (ICC) | 0.44 (ICC) | 0.51 (ICC) | 0.07 ± 0.10 (ICC) | 0.44 (ICC) |
| Wernick et al.      | 5 pathologists experienced in reading renal biopsies | 25 slides with proliferative LN | 0.18 (ICC) | 0.69 ± 0.06 (ICC) | 0.44–0.63 (ICC; between 2 pathologists) | 0.51 (ICC) | 0.83 ± 0.09 (ICC) | 0.54 (ICC) | 0.50 (ICC) | 0.51 (ICC) | 0.62 ± 0.07 (ICC) | 0.62 ± 0.07 (ICC) | 0.46 (ICC) | 0.49 (ICC) | 0.36 ± 0.09 (ICC) | 0.60–0.76 (ICC; between 2 pathologists) | 0.58 (ICC) | 0.82 (ICC) | 0.40 ± 0.09 (ICC) | 0.34 (ICC) | 0.25 ± 0.09 (ICC) | 0.58 (ICC) | 0.42 (ICC) | 0.10 ± 0.10 (ICC) | 0.44 (ICC) | 0.51 (ICC) | 0.07 ± 0.10 (ICC) | 0.44 (ICC) |
| Wilhelmus et al.     | 34 nephropathologists | 30 biopsies with class III or class IV LN | 0.39 (ICC; for class III/IV vs. class I/II/V) | 0.51 (ICC) | 0.65 (ICC) | 0.62 ± 0.07 (ICC) | 0.10 (ICC) | 0.46 (ICC) | 0.35 (κ) | 0.49 (ICC) | 0.36 ± 0.09 (ICC) | 0.60–0.76 (ICC; between 2 pathologists) | 0.58 (ICC) | 0.82 (ICC) | 0.40 ± 0.09 (ICC) | 0.34 (ICC) | 0.25 ± 0.09 (ICC) | 0.58 (ICC) | 0.42 (ICC) | 0.10 ± 0.10 (ICC) | 0.44 (ICC) | 0.51 (ICC) | 0.07 ± 0.10 (ICC) | 0.44 (ICC) |

ICC, intraclass correlation coefficient; LN, lupus nephritis; RPS, Renal Pathology Society; SLE, systemic lupus erythematosus.

An ICC or k-value of 0 indicates no agreement, and a value of 1 indicates complete agreement.

The following additional metrics were also computed in isolated studies: wire loops: 0.50 ICC (Grootscholten et al. 2008), 0.35 ICC (Wilhelmus et al. 2015); swelling of endothelial cells: 0.46 ICC (Wilhelmus et al. 2015), 0.35 ICC (Wilhelmus et al. 2015); extracapillary proliferation: 0.64 ICC (Grootscholten et al. 2008), 0.57 ICC (Wilhelmus et al. 2015); mononuclear infiltration: 0.46 ICC (Wernick et al. 1993); tubular cell necrosis: 0.19 ± 0.09 ICC (Oni et al. 2017).

Figure 1. Interpathologist concordance of lupus nephritis (LN) histology assessment in 6 studies. ICC, intraclass correlation coefficient.
and glomerular sclerosis. Assessment of a majority of histologic features exhibited “moderate” interpathologist agreement (based on median concordance values): these include fibrinous crescents, interstitial fibrosis, tubular atrophy, fibrinoid necrosis/karyorrhexis, subendothelial hyaline deposits, cellular crescents, and endo-capillary hypercellularity. No feature exhibited a “good” median interpathologist concordance value, whereas the only feature with “excellent” interpathologist agreement was interstitial inflammation (Table 1). However, only one study \( ^{35} \) calculated an ICC or \( \kappa \)-value for interstitial inflammation, and this needs to be investigated in further interpathologist comparison studies in the future.

**CONCLUSION**

Accurate assessment of LN renal pathology, with interpathologist concordance values exceeding 0.9 would be ideal if clinical decisions are guided by pathology, as recently discussed. \( ^{39} \) However, the present review shows that the interpathologist agreement in assessing LN ISN/RPS class, AI, and CI is “poor” to “moderate” overall. Even though all biopsy interpreters were trained pathologists, and most were expert nephrologists, all but one histologic feature (interstitial inflammation) exhibited a median ICC or \( \kappa \)-value below 0.6.

The renal pathology metrics assessed with the poorest concordance values (i.e., ISN/RPS class, leukocyte infiltration, and glomerular sclerosis) have important implications for patient prognosis and treatment plans. For example, an incorrect classification of the renal biopsy into either class III or IV instead of class I or II for LN will subject the patient to unnecessary immunosuppressive therapy. This can have detrimental effects, including an increased risk for infections, cancers, and nephrotoxicity, resulting in increased morbidity and mortality. \( ^{31, 34} \) As another example, patients with glomerular sclerosis have increased risk for ESRD, \( ^{7, 40} \) and the failure to recognize this feature in renal biopsies may delay appropriate treatment.

Some authors have hypothesized potential causes for low interpathologist agreement. Wernick \textit{et al.} \( ^{31} \) cited the level of experience of the pathologist, which is supported by the finding by Wilhemus \textit{et al.} \( ^{34} \) that highly experienced nephropathologists exhibit higher interpathologist agreement compared with less-experienced pathologists. This suggests that interpathologist agreement may improve by better educating and training pathologists and nephropathologists. Another reason for low interpathologist agreement may be the classification system itself. \( ^{16, 34} \) For example, multiple publications have claimed that the definition of “endocapillary proliferation” is unclear, \( ^{16, 34} \) and therefore, different pathologists may score the renal biopsy differently for that feature. \( ^{60} \) Furthermore, Wilhemus \textit{et al.} \( ^{34} \) have suggested that more than one pathologist should review the same renal biopsy results before clinical decisions are made. Indeed, efforts are in progress to significantly improve the classification criteria for LN, as very recently recommended. \( ^{16} \)

In interpreting these studies, a couple of caveats should be considered. Two studies reviewed \( ^{30, 31} \) were conducted in 1993, which is prior to the publication of the ISN/RPS classification in 2003. As a result, ISN/RPS class concordance values are not reported for these studies. In 3 of the studies assessed in this review (Schwartz \textit{et al.}, \( ^{30} \) Furness and Taub, \( ^{32} \) Wilhemus \textit{et al.} \( ^{34} \)), the concordance values for the individual histologic features that constitute AI and CI are not reported, making it difficult to understand which lesions contributed to the overall discordance noted in the AI and CI scores. As a result, the median interpathologist concordance value is determined in only 2 studies. Additionally, in the 3 publications by Wernick \textit{et al.}, \( ^{31} \) Furness and Taub, \( ^{32} \) and Wilhemus \textit{et al.}, \( ^{34} \) the number of LN slides studied fall on the lower side (25, 20, and 30 slides, respectively) to allow for definitive conclusions from these studies. Lastly, the studies by Wernick \textit{et al.} \( ^{31} \) and Oni \textit{et al.} \( ^{35} \) calculated the concordance score among general pathologists, who may have less expertise in evaluating LN slides than trained nephropathologists. These shortcomings in some of the included studies call for more consistent, systematic assessment of interpathologist concordance in ISN/RPS classification, the activity index, and its component histologic features, and the chronicity index and its associated histologic features, involving significantly larger datasets.

Though the pathologist assessment of a renal biopsy is considered the gold standard diagnostic procedure for LN, it is highly subjective, and the result depends on the training of the interpreter. Our results support the necessity of central pathology reviews involving highly experienced nephropathologists analyzing digitized slides for the diagnosis of LN. In addition, the use of machine learning algorithms could facilitate more accurate diagnosis of the LN class, AI score, and CI score. Previous studies have shown that machine learning can be utilized for accurate prediction of chronic kidney damage in SLE patients, \( ^{55} \) and renal survival in patients with chronic kidney disease, \( ^{56} \) if the neural network is trained with a large and diverse set of renal biopsy images. To place this in perspective, we believe that this kind of discordance is not limited
to just the morphologic classification of LN but is ubiquitous in any morphologic classification, ranging from the Banff criteria for organ transplant rejection to other diseases such as atypical/dysplastic lesions of the breast, the gastrointestinal tract, and other organs. Clearly, there may be exceptions to this statement. For example, careful and consistent reviews by expert pathologists have been effective and reproducible in assessing renal pathology in the VALIGA study for IgA nephropathy and the assessment of vasculitis-associated renal pathology by the RENHIS (renal histology) group in the European Vasculitis Study Group (EUVAS).

In summary, the current scoring of the ISN/RPS classification system and the activity and chronicity indices for LN exhibit poor interpathologist agreement, which limits their use in clinical practice. Given that low interpathologist agreement can have severe repercussions regarding a patient’s treatment and prognosis, efforts to update pathology assessment guidelines, objectively measurable biomarkers, and deep learning approaches are strongly warranted.

**DISCLOSURE**

All the authors declared no competing interests.

**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)

Figure S1. PRISMA 2009 flow diagram of the study selection process for this systematic review.

PRISMA Checklist.

**REFERENCES**

1. Bernatsky S, Boivin JF, Joseph L, et al: Mortality in systemic lupus erythematosus. *Arthritis Rheum.* 2006;54:2550–2557.
2. Hanly JG, O’Keeffe AG, Su L, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. *Rheumatology (Oxford).* 2015: pii: kev311.
3. Feldman CH, Hiraki LT, Liu J, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000-2004. *Arthritis Rheum.* 2013;65:753–763.
4. Costenbader KH, Desai A, Alarcon GS, et al. Trends in the incidence, demographics, and outcomes of end-stage renal disease due to lupus nephritis in the US from 1995 to 2006. *Arthritis Rheum.* 2011;63:1681–1688.
5. Weening JJ, D’Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol.* 2004;15:241–250.
6. Austin HA III, Boumpas DT, Vaughan EM, Balow JE. High-risk features of lupus nephritis: importance of race and clinical and histological factors in 166 patients. *Nephrol Dial Transplant.* 1995;10:1620–1628.
7. Austin HA 3rd, Muenz LR, Joyce KM, et al. Diffuse proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. *Kidney Int.* 1984;25:689–695.
8. Nossent HC, Henzen-Logmans SC, Vroom TM, et al. Contribution of renal biopsy data in predicting outcome in lupus nephritis. Analysis of 116 patients. *Arthritis Rheum.* 1990;33:970–977.
9. Esdaile JM, Federgreen W, Quintal H, et al. Predictors of one year outcome in lupus nephritis: the importance of renal biopsy. *Q J Med.* 1991;81:879–881.
10. Morel-Maroger L, Mery JP, Droz D, et al. The course of lupus nephritis: contribution of serial renal biopsies. *Adv Nephrol.* 1976;6:79–118.
11. Moroni G, Pasquali S, Quaglini S, et al. Clinical and prognostic value of serial renal biopsies in lupus nephritis. *Amer J Kidney Dis.* 1999;34:530–539.
12. Mahajan SK, Ordonez NG, Spargo BH, Katz AI. Changing histopathology patterns in lupus nephropathy. *Clin Nephrol.* 1978;10:1–8.
13. Contreras G, Pardo V, Cely C, et al. Factors associated with poor outcomes in patients with lupus nephritis. *Lupus.* 2005;14:890–895.
14. Tesar V, Hruskova Z. Understanding histopathologic characteristics to predict renal outcomes in lupus nephritis. *Clin J Am Soc Nephrol.* 2017;12:711–712.
15. Rijnink EC, Onno Teng YK, Wilhelmsu S, et al. Clinical and histopathologic characteristics associated with renal outcomes in lupus nephritis. *Clin J Am Soc Nephrol.* 2017;12:734–743.
16. Bajema IM, Wilhelmsu S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int.* 2018;93:789–796.
17. Park DJ, Choi SE, Xu H, et al. Chronicity index, especially glomerular sclerosis, is the most powerful predictor of renal response following immunosuppressive treatment in patients with lupus nephritis. *Int J Rheum Dis.* 2018;21:458–467.
18. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and pediatric lupus nephritis. *Ann Rheum Dis.* 2012;71:1771–1782.
19. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken).* 2012;64:797–808.
20. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int.* 2012;81(suppl 2):139–274.
21. Austin HA 3rd, Kippel JH, Balow JE, et al. Therapy of lupus nephritis: controlled trial of prednisone and cytotoxic drugs. *N Engl J Med.* 1986;314:614–619.
22. Rush PJ, Bauml R, Shore A, et al. Correlation of renal histology with outcome in children with lupus nephritis. *Kidney Int.* 1986;29:1066–1071.
23. Balow JE. Lupus as a renal disease. *Hosp Pract.* 1988;23:129–146.
30. Schwartz MM, Lan SP, Bernstein J, et al. Irreproducibility of the activity and chronicity indices of lupus nephritis on renal outcome with emphasis on repeatability. J Am Soc Nephrol. 2013;26:2938–2946.

31. Wernick RM, Smith DL, Houghton DC, et al. Reliability of histologic scoring for lupus nephritis: a community-based evaluation. Ann Intern Med. 1993;119:805–811.

32. Furness PN, Taub N. Interobserver reproducibility and application of the ISN/RPS classification of lupus nephritis—A UK-wide study. Am J Surg Pathol. 2006;30:1030–1035.

33. Grootcholten C, Bajema IM, Florquin S, et al. Interobserver agreement of scoring of histopathological characteristics and classification of lupus nephritis. Nephrol Dial Transplant. 2008;23:223–230.

34. Wilhelmsen S, Cook HT, Noël LH, et al. Interobserver agreement on histopathological lesions in class III or IV lupus nephritis. Clin J Am Soc Nephrol. 2015;10:47–53.

35. Oni L, Beresford MW, Witte D, et al. Inter-observer variability of the histological classification of lupus glomerulonephritis in children. Lupus. 2017;26:1205–1211.

36. Gamba G, Reyes E, Angeles A, et al. Observer agreement in the scoring of the activity and chronicity indexes of lupus nephritis. Nephron. 1991;57:75–77.

37. Seema HS, Garg I, Alexander P. Significance of activity and chronicity indices of lupus nephritis on renal outcome with emphasis on repeatability—experience from South India. J Evolution Medical Dental Sci. 2013;2:9952–9962.

38. Seo J, Do I, Park ES, et al. Pathology of lupus nephritis is better classified by the International Society of Nephrology/Renal Pathology Society system. Basic Appl Pathol. 2008;1:12–17.

39. Restrepo-Escobar M, Granda-Carvajal PA, Jaimés F. Systematic review of the literature on reproducibility of the interpretation of renal biopsy in lupus nephritis. Lupus. 2017;26:1502–1512.

40. Hill GS, Delahousse M, Nochy D, Barìèty J. Class IV-S versus class IV-G lupus nephritis: clinical and morphologic differences suggesting different pathogenesis. Kidney Int. 2005;68:2288–2297.

41. Schwartz MM, Korbet SM, Lewis EJ, Collaborative Study Group. The prognosis and pathogenesis of severe lupus glomerulonephritis. Nephrol Dial Transplant. 2008;23:1298–1306.

42. Kim YG, Kim HW, Cho YM, et al. The difference between lupus nephritis class IV-G and IV-S in Koreans: focus on the response to cyclophosphamide induction treatment. Rheumatology (Oxford). 2008;47:311–314.

43. Markowitz GS, D’Agati VD. The ISN/RPS 2003 classification of lupus nephritis: an assessment at 3 years. Kidney Int. 2007;71:491–495.

44. Sada KE, Makino H. Usefulness of ISN/RPS classification of lupus nephritis. J Korean Medical Sci. 2009;24(suppl 1):S7–S10.

45. Mubarak M, Nasri H. ISN/RPS 2003 classification of lupus nephritis: time to take a look on the achievements and limitations of the schema. J Nephropathol. 2014;3:87–90.

46. Yu F, Tan Y, Wu LH, et al. Class IV-G and IV-S lupus nephritis in Chinese patients: a large cohort study from a single center. Lupus. 2009;18:1073–1081.

47. Kojo S, Sada KE, Kobayashi M, et al. Clinical usefulness of a prognostic score in histological analysis of renal biopsy in patients with lupus nephritis. J Rheumatol. 2009;36:2218–2223.

48. Haring CM, Rietveld A, van den Brand JA, Berden JH. Segmental and global subclasses of class IV lupus nephritis have similar renal outcomes. J Am Soc Nephrol. 2012;23:149–154.

49. Hiramatsu N, Kuroiwa T, Ikeuchi H, et al. Revised classification of lupus nephritis is valuable in predicting renal outcome with an indication of the proportion of glomeruli affected by chronic lesions. Rheumatology. 2008;47:702–707.

50. Haas M, Rastaldi MP, Fervenza FC. Histologic classification of glomerular diseases: clinicopathologic correlations, limitations exposed by validation studies, and suggestions for modification. Kidney Int. 2014;85:779–793.

51. Mittal B, Hurwitz S, Renne K, Singh AK. New subcategories of class IV lupus nephritis: Are there clinical, histologic, and outcome differences? Am J Kidney Dis. 2004;44:1050–1059.

52. Wilhelmsen S, Alpers CE, Cook HT, et al. The revisited classification of GN in SLE at 10 years: time to re-evaluate histopathologic lesions. J Am Soc Nephrol. 2015;26:2938–2946.

53. Shaw L, Kaplan B, Kaufman D. Toxic effects of immunosuppressive drugs: mechanisms and strategies for controlling them. Clin Chem. 1996;42:1316–1321.

54. de Mattos AM, Olyaei AJ, Bennett WM. Nephrotoxicity of immunosuppressive drugs: mechanisms and strategies for controlling them. PLoS One. 2017;12:e0174200.

55. Colchachalama VB, Singh P, Lin CO, et al. Association of pathologic fibrosis with renal survival using deep neural networks. Kidney Int Rep. 2018;3:464–475.

56. Tesar V, Troyanov S, Bellur S, et al. Corticosteroids in IgA nephropathy: a retrospective analysis from the VALIGA Study. J Am Soc Nephrol. 2015;26:2248–2258.

57. van Daalen E, Ferrario F, Noël LH. Twenty-five years of RENHIS: a history of histopathological studies within EUVAS. Nephrol Dial Transplant. 2015;30(suppl 1):i31–i36.