Predicting Kidney Survival in Lupus Nephritis by Adding Clinical Data to Pathologic Features

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In this issue of Kidney 360, Moroni et al. report that including activity and chronicity indexes to the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) lupus nephritis (LN) classification improves the prognostic value of the kidney biopsy (1). Furthermore, adding clinical features to the histologic characteristics provides the best model to predict kidney function impairment (KFI) at the time of kidney biopsy.

LN constitutes one of the major organ manifestations that considerably alters the course and prognosis of systemic lupus erythematosus (SLE) (2). As many as 60% of adult patients with SLE develop LN during the disease course (3). Over the past few decades, there has been a substantial increase in the knowledge of the complex genetic factors and molecular mechanisms underlying the pathogenesis of LN. Likewise, novel treatment options have emerged that have changed the landscape of contemporary LN management. However, despite exponential increase in the knowledge and improved treatment options, LN remains a major cause of morbidity and death among patients with SLE (3,4). Despite treatment, 5%–20% of patients with LN progress to kidney failure within 10 years. Moreover, 35%–40% of patients who initially respond to the treatment may experience flares that are associated with higher morbidity and decreased kidney survival (5,6).

The major goal of LN treatment is to minimize kidney scarring by achieving rapid resolution of acute inflammation and attaining complete remission of the active disease. Consequently, an early and accurate diagnosis and prompt treatment of LN are paramount to improve kidney survival and outcomes at large. Conversely, a delay in the diagnosis or treatment of LN can result in inadequate response to treatment, irreversible kidney damage, progression of kidney disease, and overall abysmal outcomes.

Patients with LN present with a wide spectrum of clinical features, ranging from asymptomatic urinary abnormalities to nephrotic syndrome, acute nephritic syndrome, rapidly progressive kidney disease, or advanced kidney disease (2). Moreover, several features such as proteinuria, hematuria, and elevated serum creatinine are nonspecific, and can be present in both active and chronic LN or denote a kidney injury not related to SLE. Therefore, a precise diagnosis of LN cannot be made on the basis of clinical symptoms and laboratory data alone. Kidney biopsy remains the gold standard for making an accurate diagnosis of LN.

Given the heterogeneity of pathologic lesions, LN is histologically classified into six distinct classes potentially to distinguish subgroups of patients with different prognoses. The current 2003 ISN/RPS classification is based on the original 1974 World Health Organization (WHO) classification with several subsequent modifications (7,8). All LN classifications thus far have mainly focused on glomerular pathology. However, glomerular-based measures do not perform well in identifying LN patients at high risk for kidney failure (9). It is becoming increasingly evident that the long-term prognosis of LN is largely influenced by the degree of tubulointerstitial inflammation, fibrosis, and atrophy (9,10). The 2003 ISN/RPS classification recognized that an accurate description of tubulointerstitial and vascular lesions is needed and explicitly stated that concurrent interstitial fibrosis, tubular atrophy, and vascular lesions should be narrated in the biopsy report, and A, C, and A/C designations should be provided for active, chronic, and concomitant active and chronic lesions, respectively (8).

The concept of active versus chronic lesions has been known for decades. A system of semiquantitative scores for activity and chronicity, described as the Activity Index (AI) and Chronicity Index (CI), was introduced by the investigators at the National Institute of Health (NIH) (11), and these indexes have frequently been used as an adjunct to the WHO or the 2003 ISN/RPS LN classifications. Although concerns have been raised about their reproducibility (12), high scores on the AI and CI have been associated with an unfavorable kidney prognosis (13). Unfortunately, despite these efforts, very little improvement has occurred in determining long-term kidney outcomes by examining histology alone.

In order to align histology better to treatment response and prognosis, a revision of the 2003 ISN/RPS classification has been proposed by the working group for LN classification (14). The new classification redefines several histopathological lesions and incorporates a modified version of the NIH AI and CI in

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the LN classification. However, the revised classification has not yet been officially endorsed by the ISN/RPS and is awaiting validation studies from well-characterized LN cohorts. Umeda et al. reevaluated kidney biopsies from 170 LN patients and demonstrated that the revised 2018 ISN/RPS classification was significantly better than the 2003 ISN/RPS classification in predicting renal prognosis, defined as a 30% decline in eGFR over a median follow-up of 50 months (15). Similarly, in a cohort of 101 Chinese LN patients followed for 10 years, the revised NIH CI and its individual components used in the 2018 ISN/RPS classification were found to be independent risk factors for the composite renal outcome, comprising a 30% decline in eGFR, ESKD, and death (16).

The current study by Moroni et al. includes a cohort of 203 patients with biopsy-proven LN enrolled over a period of 36 years (1984–2019), closely followed over a median of 14 years (1). Modified NIH AI and CI, as used in the 2018 ISN/RPS classification, were applied to reevaluate the kidney biopsies. The study compared various histologic features, including individual components of the AI and CI, with the outcomes using univariate and multivariate analysis. They observed a strong association between a CI score ≥2 and all individual components of CI with KFI, defined as a ≥30% decrease in creatinine clearance from baseline. On the contrary, the composite AI score was not associated with KFI. Interestingly, the only component of AI that was associated with KFI on univariate analysis was interstitial inflammation. However, when analyzed separately in patients with or without concurrent interstitial fibrosis, the correlation was maintained only in the presence of tubular atrophy/interstitial fibrosis and was lost in cases where interstitial inflammation was present solely in the normal cortex, further underscoring the importance of chronic lesions in the long-term renal prognosis. Among clinical indicators, an increase in serum creatinine and arterial hypertension were independent predictors of KFI. Although these findings are not novel, they add to the growing body of evidence that chronic changes on kidney biopsy that epitomize irreversible kidney damage and clinically manifest as elevated serum creatinine portend poor outcomes in LN patients. Importantly, the key message conveyed by the study is the demonstration of a significant correlation of time interval between the onset of clinical signs and kidney biopsy with CI and KFI. It is noteworthy that Moroni et al. observed a median CI score of 2 at the time of kidney biopsy. In other words, by the time a pathology diagnosis was established, half of the patients already had significant irreversible scarring, suggesting a significant delay in the diagnosis of LN. Indeed, a significantly higher CI was detected in patients whose renal symptoms had persisted for more than 3 months before kidney biopsy was performed. Accordingly, this correlation suggests a causal relationship between the diagnostic delay and the occurrence of chronic kidney lesions and ensuing poor renal outcomes.

Although the current guidelines recommend kidney biopsy in SLE patients with any sign of kidney involvement (glomerular hematuria and/or cellular casts, proteinuria >0.5 g/24 hours, unexplained decrease in GFR) (17), clinicians may be hesitant in performing kidney biopsies in patients with minor renal abnormalities. However, significant kidney disease has been observed in some patients with SLE, even with no clinical signs of kidney disease (silent LN) (2). Clearly, better biomarkers are needed that closely parallel renal pathology and aid in the early diagnosis of LN. Although recent insights into the genetic and molecular basis of LN have paved the way for the development of new therapies, early diagnosis remains of utmost importance for the novel therapies to be instituted promptly and to be successful in preventing irreversible kidney damage.

The data from Moroni et al. eloquently show that a delay between the onset of clinical manifestations of kidney disease and kidney biopsy constitutes an important, independent risk factor of poor renal outcomes. From a clinical standpoint, these findings underscore the need for close monitoring of patients with SLE to detect urinary abnormalities and to perform kidney biopsy promptly as soon as clinical signs of kidney disease become evident. Early detection of kidney involvement in SLE and prompt management can have a significant effect on disease outcome.

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Author Contributions
R. Saxena conceptualized, wrote the original draft, reviewed, and edited the manuscript.

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