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Biomarkers of Lupus Nephritis Histopathology: Where Do We Stand?

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Objective. Lupus nephritis (LN) is characterized by a variable disease course, necessitating continuous monitoring. There is an urgent need to identify noninvasive biomarkers. By reviewing and critically assessing the quality of existing studies on LN biomarkers correlating with histopathology, we here explore the challenges in promoting their use in clinical practice and identify promising candidates for future validation.

Methods. A systematic literature search was conducted, including studies on adult patients with biopsy-proven LN published between 2012 and 2024. The search focused on studies demonstrating correlations between biomarkers and histologic findings, particularly the National Institutes of Health activity and chronicity indices, the International Society of Nephrology/Renal Pathology Society histologic classes, and specific active and chronic lesions. The quality of selected articles was assessed by a multidisciplinary panel of experts using a standardized scoring system.

Results. Ninety-three articles investigating the potential utility of >100 biomarkers were selected. In quality assessment, 68% of the articles were weak or very weak (score <5, scale 2–9). From the remaining articles (adequate or robust) we identified five biomarkers with a potential for implementation in clinical practice: transforming growth factor β1, pentraxin-3, (soluble) CD163, CD11b, and interleukin-16.

Conclusion. The methodologic heterogeneity across studies and the overall moderate score of the quality of the articles represent obstacles to the implementation of new biomarkers into clinical practice. The LN working group advocates further research on selected biomarkers that demonstrated good capacity to reflect specific histopathologic features outperforming traditional tests. At present, the choice of biomarkers that perform to these standards is very limited.

INTRODUCTION

Given the complexity and variable course of systemic lupus erythematosus (SLE), in combination with potential adverse effects of therapy, continuous clinical and laboratory assessments are required to predict and evaluate organ involvement, response to treatment, and disease progression.[1] In current clinical practice, kidney biopsy, in combination with the assessment of well-known serum and urinary parameters reflecting the severity of kidney involvement in SLE, are used to monitor patients affected by lupus nephritis (LN). However, it is known that these routine clinical biomarkers do not adequately mirror the evolving lesions that we know occur in due course in the kidneys of patients with LN.[2] Many new biomarkers have been suggested to hold promise for additional clinical value above those of traditional tests.

Searching MEDLINE for "biomarkers" and "lupus nephritis" through PubMed yields nearly 2,000 results over a period of 48 years, with the most hits in recent years.[3] New biomarkers

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have been proposed to be easily measured and valuable for disease monitoring. These biomarkers aim to serve a variety of purposes, such as aiding in diagnosis, indicating disease severity and prognosis, guiding treatment decisions, and helping to identify flares. No single biomarker is likely to address all these aspects; most probably only a panel of multiple biomarkers, with complementary predictive value, could help to improve current clinical practice, and the challenge lies in determining the perfect combination of biomarkers that could serve to do so.

Certain biomarkers correlate with histologic findings, offering the potential to supplement kidney biopsy in monitoring disease activity. Although the kidney biopsy provides a wealth of information regarding the pattern of injury at a specific point in time, its use for longitudinal assessment, with repeat biopsies, is cumbersome. In contrast, a "liquid biopsy," based on biomarkers derived primarily from blood or urine, may offer a noninvasive, rapid, highly specific, and sensitive assessment of LN activity and damage.[4] Ideally, such biomarkers should faithfully recapitulate kidney biopsy findings, and we here set out a search to identify them.

Despite several LN biomarkers identified using omics approaches,[5,6] none has been integrated into clinical practice yet. Biomarkers are often tested in cross-sectional studies and the results are rarely validated in independent cohorts. Most importantly, only a few studies examine how biomarkers and histopathology change over time although it seems evident that this is what they are primarily needed for. The longitudinal correlation of a biomarker with histopathology must be established to qualify a biomarker for clinical use. Furthermore, a qualified biomarker should outperform or offer significantly added value compared with existing clinical markers used for LN management.

We conducted a systematic analysis of the recent literature on potential noninvasive biomarkers that specifically associate with histologic findings detected in kidney biopsies to gain insights into which biomarkers could eventually be helpful in representing tissue findings in LN. Furthermore, we provide an assessment of the quality of the studies and address why qualification of biomarkers is cumbersome. Lastly, we identify which biomarkers appear to be of most interest for future validation.

MATERIALS AND METHODS

Search strategy and selection criteria. We performed a systematic literature search on biomarkers in LN, following up on that by Palazzo et al of 2022,[3] but restricting our search to studies with a histologic focus. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating the selection process is shown in Figure 1. We selected studies in English published between January 1, 2012, and August 22, 2024, using terms including but not limited to "lupus nephritis," "systemic lupus erythematosus," "biomarker," "urine," "serum," "kidney," "tissue," "antibody," "antigen," "cytokine," "protein," "RNA," "peptide," and "receptor" (detailed in Supplementary Table S1). We included studies conducted on adult patients (aged ≥18 years) with biopsy-proven LN that highlighted a correlation between one or more biomarkers and histologic findings, with a focus on the National Institutes of Health (NIH) activity index (AI) and chronicity index (CI), the International Society of Nephrology/Renal Pathology Society (ISN/RPS) histologic classes (I–VI), and specific active or chronic lesions in the glomerular, tubulointerstitial, and vascular compartments. We excluded case reports, case series, reviews, animal studies, and studies on pediatric patients. We also subsequently conducted a manual search covering the same timeframe and inclusion criteria; this involved analyzing the references of the previously selected articles and searching the MEDLINE through PubMed for individual biomarkers already identified.

Data analysis. Considering the mixed design of many studies included in this review, the risk of bias (RoB) was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies or the JBI Critical Appraisal Checklist for Cohort Studies (Supplementary Tables S2 and S3), based on the main design of the study and the methodology used to explore biomarker-histopathologic correlations. We assembled a multidisciplinary group of experts and researchers in the field of LN—one nephrologist (DRWJ), one rheumatologist (IP), one pathologist (IMB), and two junior researchers (VQ and LP)—and asked them to provide their opinion about the quality of each article, based on the grading system of Guyatt et al. This system classifies the quality of evidence in four levels—high, moderate, low and very low—according to the likelihood that future research will change the confidence in the estimated effect, namely the performance of the biomarker.[7] A score of 2 was for "very low quality," 5 was for "low quality," 7 was for "moderate quality," and 9 was for "high quality." We then calculated the average score for each article. Finally, we calculated the score for each biomarker based on the average of the quality evaluations from the various articles reviewed (one or multiple, depending on the biomarker).

RESULTS

Different categories of biomarkers reflect a broad spectrum of histopathologic lesions. From the systematic search, we extracted 74 publications and through a manual search we ultimately selected 19 additional articles. We investigated the potential utility of >100 biomarkers, dividing them into categories and describing their associations with histopathologic features (Supplementary Table S4). The biomarkers' categories included autoantibodies (n = 8); complement factors (n = 5); cytokines, chemokines, and growth factors (n = 26); cell adhesion molecules and cell surface molecules (n = 7); immune cells (n = 8); markers of kidney damage (n = 17); micro-RNA (n ≈ 12); and others (n ≈ 29). The histopathologic parameters included solitary or combined lesions from the cell level to combined

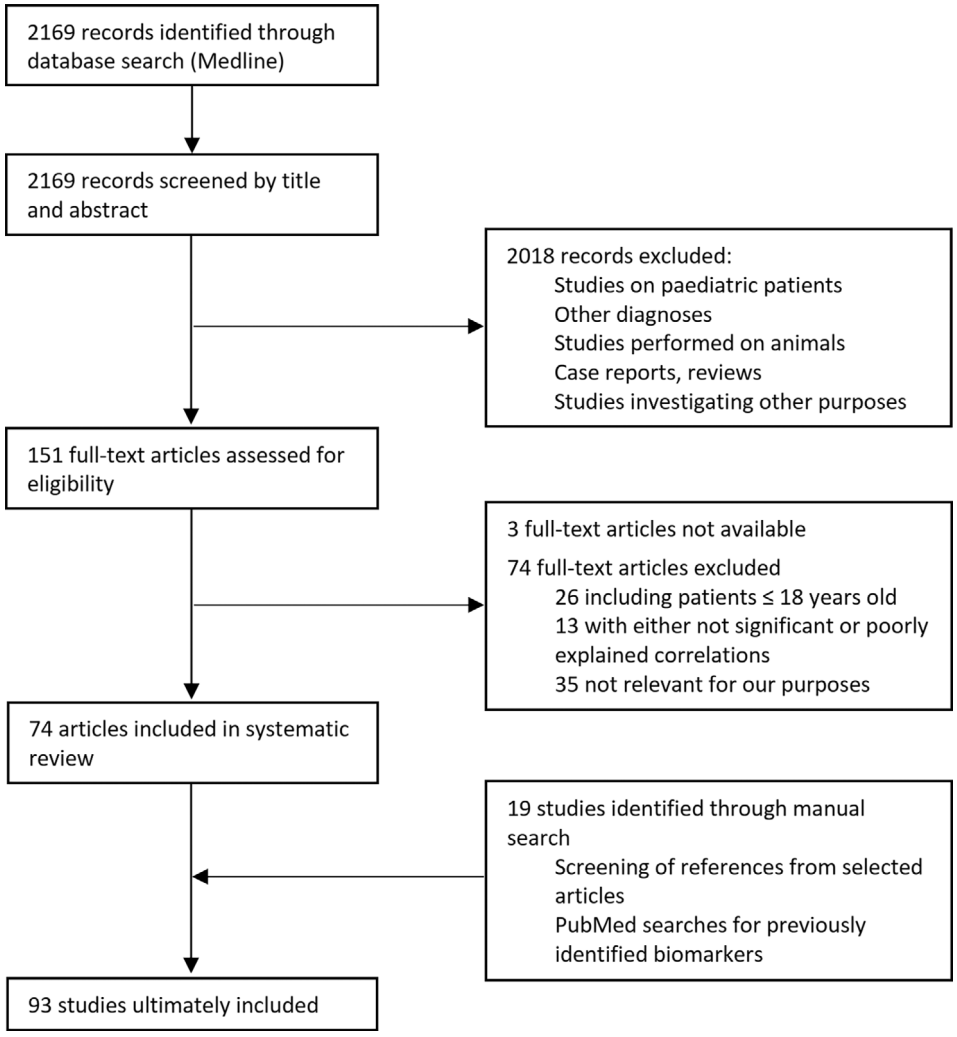

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the included studies.

measurements such as the NIH indices and ISN/RPS classes. Figure 2 shows biomarkers in relation to the histopathologic lesions, as described in the 93 publications.

A low overall quality of the articles affects the reliability of analyzed biomarkers. More than 50% of the articles received low overall scores in critical appraisal, with 18% scoring <5. One article was scored above 8, whereas the remaining 42% displayed moderate scores (Supplementary Table S5). Importantly, the RoB did not necessarily align with the overall quality of the articles, for which other aspects such as the clinical relevance, clarity of results and methodology, and applicability of findings are also important.

Approximately 10% of the biomarkers were scored within the highest score range, 10% scored within the lowest range, and several biomarkers clustered around a score of 6, the threshold above which quality is considered acceptable (Figure 3). In the next section we will primarily focus on biomarkers that obtained a good overall score (≥6).

Autoantibodies mostly reflect active kidney injury, whereas immune cells have not proven useful as biomarkers. Numerous antibodies, including anti–double-stranded DNA (anti-dsDNA) and antinucleosome antibodies, have been investigated for their usefulness in assessing activity in LN.[8–12] The study designs differed considerably and correlated antibody levels or positivity with various histologic parameters. For instance, in a study of 107 patients the positivity for anti-dsDNA and antinucleosome antibodies was associated with NIH AI scores.[10] Other studies looked more generally at the ability of various autoantibodies to distinguish "proliferative" classes III/IV from "nonproliferative" and/or membranous class V LN.[13,14] In a different approach, the absence of anti-Sjogren's-syndrome-related antigen B (anti-SSB) and anti-Smith (anti-Sm) antibodies was protective against the development of severe LN.[15] Anti-neutrophil cytoplasmic autoantibodies (ANCAs) do not have a defined role in LN with contradictory results regarding their correlation with NIH AI and CI scores or with a variety of lesions.[11,16,17] Some investigators suggested that LN that was more vasculitic in nature would also be ANCA positive,[18] but that was never verified.

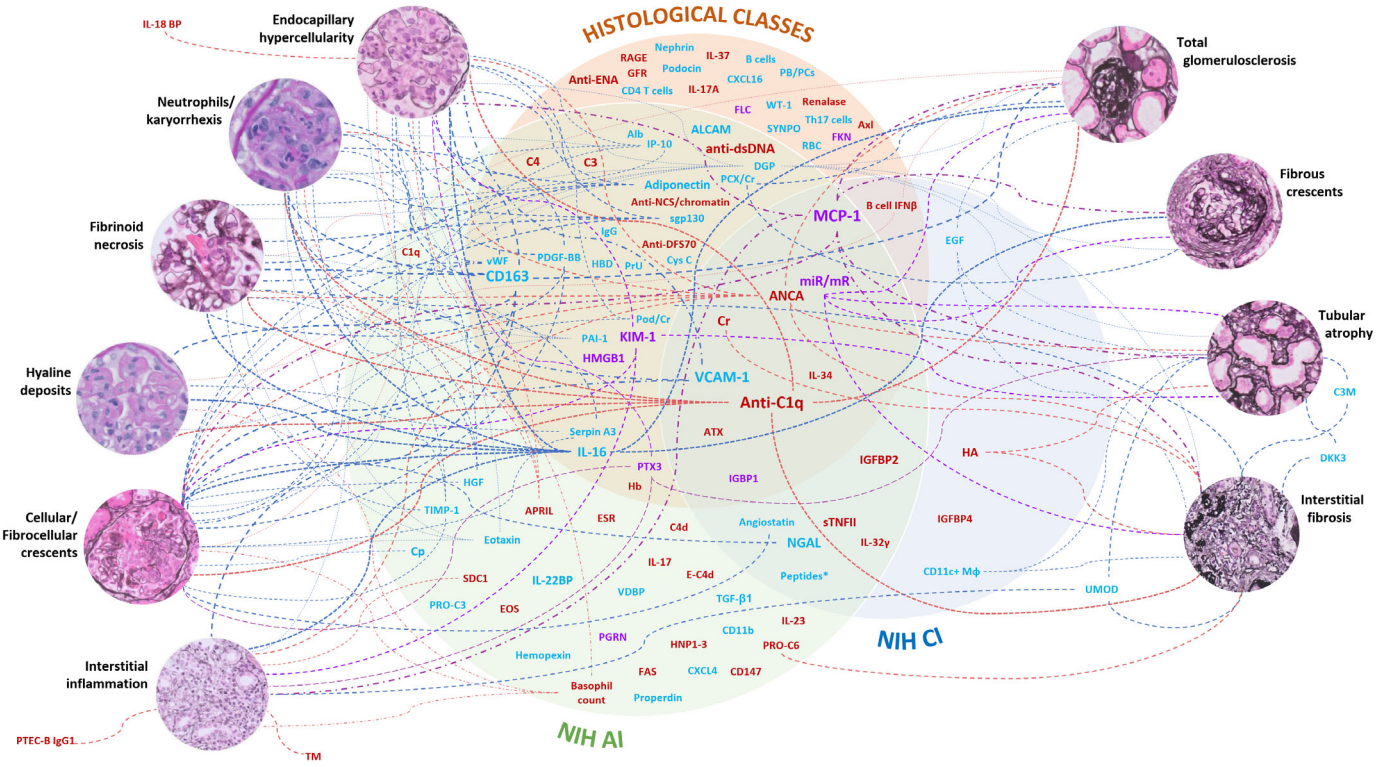

Figure 2. All biomarkers measured in serum (in red), urine (in blue), or both (in purple) that have shown a significant correlation with one or more histologic features identifiable in renal biopsy, particularly the NIH AI (green circle), the NIH CI (blue circle), the histologic classes (orange circle), and the active and chronic lesions that determine the indices (smaller outer circles with histologic pictures). The arrows indicate the correlations with the active and chronic lesions. Only biomarkers extensively described in the articles are included. The biomarkers and arrows are displayed in varying font sizes and thicknesses, respectively, based on the number of published articles on each of them. *A total of 137 peptides correlate with AI and 7 with CI. AI, activity index; Alb, albumin; ANCA, antineutrophil cytoplasmic antibody; anti-C1q, anticomplement component 1q antibody; anti-dsDNA, anti–double-stranded DNA; anti-ENA, antiextractable nuclear antigen antibody; APRIL, A proliferation-inducing ligand; BP, binding protein; C3, complement component 3; C4d, complement component 4d; CI, chronicity index; Cp, ceruloplasmin; Cr, creatinine; CXCL4, chemokine ligand 4; Cys C, cystatin C; DGP, granulocytes degranulation product; DKK3, Dickkopf 3; EOS, eosinophil count; ESR, erythrocyte sedimentation rate; FAS, fas cell surface death receptor; FKN, fractalkine; GFR, glomerular filtration rate; HA, hyaluronan; Hb, hemoglobin; HMGB1, high mobility group box 1; HNP1-3, human neutrophil peptides 1-3; IGFBP4, insulin-like growth factor binding protein 4; IL, interleukin; IP-10, interferon-γ inducible protein 10; KIM-1, kidney injury molecule 1; MCP-1, monocyte chemoattractant protein-1; miR, micro-RNA; mR, messenger RNA; Mϕ, macrophage; NIH, National Institutes of Health; PAI-1, plasminogen activator inhibitor type 1; PGRN, progranulin; Pod, podocyte; PTEC, proximal kidney tubular epithelial cell; PTX3, pentraxin 3; RAGE, receptor for advanced glycation end-products; RBC, red blood cell; SDC1, syndecan-1; sTNFRII, soluble tumor necrosis factor receptor II; TGF-β1, transforming growth factor β1; TIMP-1, tissue inhibitor of metalloproteinase-1; TM, thrombomodulin; VDBP, vitamin D binding protein; vWF, Von Willebrand factor.

Most studies investigating biomarkers based on the presence of inflammatory cells in urine and serum did not obtain a good score in the quality assessment. Of note is a study that identified that a urinary count exceeding 800 CD4 T cells/mL exhibited a remarkable sensitivity and specificity (area under the curve = 0.9969) for identifying proliferative forms of LN.[19]

Urinary interleukin-16, (soluble)CD163, transforming growth factor β1, and CD11b are promising biomarkers of LN activity. Cytokines are more commonly tested in the urine from patients with LN because of their presumed greater specificity in reflecting kidney injury or damage. Several studies investigated their correlation with histopathologic findings and study designs usually aimed to distinguish between proliferative and nonproliferative LN[20–22] or to correlate the biomarker levels with the NIH AI and CI scores.[23–28] Only a few high-quality studies also described correlations with specific histopathologic lesions.[23,29–32]

In a discovery study, urinary levels of interleukin (IL)-16, macrophage surface molecule CD163, and transforming growth factor β1 (TGF-β1) were postulated as biomarkers correlating best with the NIH AI scores.[6] Interestingly, there was abundant glomerular and interstitial IL-16 expression in proliferative forms of LN and an association between urinary levels of IL-16 and the number of IL-16$^+$ cells in the kidney. This suggests that urinary IL-16 levels are likely derived from the kidney and, in agreement with previous studies,[21,29] could potentially serve as a good biomarker of active forms of LN.[6] In a subsequent study involving

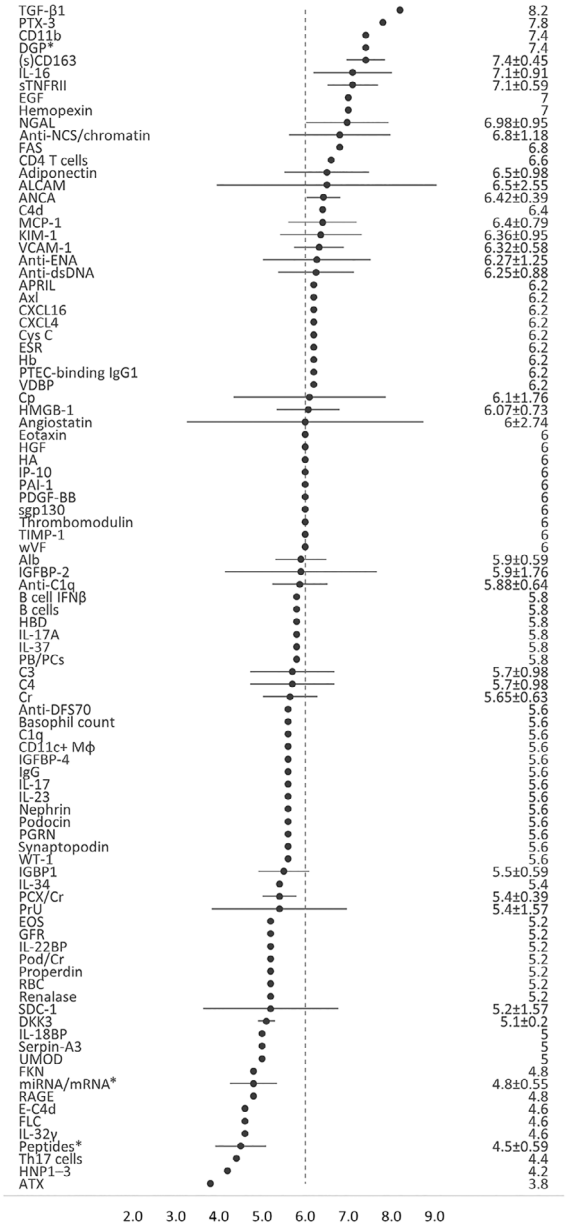

Figure 3. Forest plot showing the mean score and the 95% confidence interval for each biomarker according to the quality evaluation of the articles by the expert panel. Only biomarkers extensively described in the articles are included. *These categories encompass numerous biomarkers; peptides include both collagen and noncollagen types (details for each biomarker can be found in the corresponding articles listed in Supplementary Table S4). Alb, albumin; ALCAM, activated leukocyte cell adhesion molecule; ANCA, antineutrophil cytoplasmic antibody; anti-C1q, anticomplement component 1q antibody; anti-DFS70, antidense fine speckled 70-kDa MW antibody; anti-dsDNA, anti–double-stranded DNA; anti-ENA, antiextractable nuclear antigen antibody; anti-NCS, antinucleosome antibody; APRIL, A proliferation-inducing ligand; ATX, autotaxin; Axl, axl receptor tyrosine kinase; C3, complement component 3; C4, complement component 4; C4d, complement component 4d; CI, chronicity index; Cp, ceruloplasmin; Cr, creatinine; CXCL4, chemokine ligand 4; CXCL16, chemokine ligand 16; Cys C, cystatin C; DGP, granulocytes degranulation product; DKK3, Dickkopf 3; E-C4d, endothelial complement component 4d; EGF, epidermal growth factor; EOS, eosinophil count; ESR, erythrocyte sedimentation rate; FAS, fas cell surface death receptor; FKN, fractalkine; FLC, free light chains; GFR, glomerular filtration rate; HA, hyaluronan; Hb, hemoglobin; HBD, hemoglobin subunit delta; HGF, hepatocyte growth factor; HMGB1, high mobility group box 1; HNP1-3, human neutrophil peptides 1-3; IFNβ, interferon β; IGBP1, Ig binding protein 1; IGFBP2, insulin-like growth factor binding protein 2; IGFBP4, insulin-like growth factor binding protein 4; IL, interleukin; IP-10, interferon-γ inducible protein 10; KIM-1, kidney injury molecule 1; MCP-1, monocyte chemoattractant protein-1; miRNA, micro-RNA; mRNA, messenger RNA; NGAL, neutrophil gelatinase-associated lipocalin; PAI-1, plasminogen activator inhibitor type 1; PB, plasmablast; PC, plasma cell; PCX, podocalyxin; PDGF-BB, platelet-derived growth factor subunit B; PGRN, progranulin; Pod, podocyte; PrU, proteinuria; PTEC, proximal kidney tubular epithelial cell; PTX3, pentraxin 3; RAGE, receptor for advanced glycation end-products; RBC, red blood cell; SDC-1, syndecan-1; sgp130, soluble gp130; sTNFRII, soluble tumor necrosis factor receptor II; TGF-β1, transforming growth factor β1; TIMP-1, tissue inhibitor of metalloproteinase-1; UMOD, uromodulin; VCAM-1, vascular cell adhesion molecule 1; VDBP, vitamin D binding protein; vWF, Von Willebrand factor; WT-1, Wilms tumor 1.

225 patients, the proliferative LN signature was predominantly characterized by elevated urinary levels of CD163 and IL-16, in addition to many granulocyte degranulation products.[32] Previous high-quality studies had already reported the ability of CD163 and its soluble form (sCD163) to predict activity in LN, correlating both with the NIH AI scores and proliferative classes.[24,33,34] Specifically, an analysis of a limited cohort of repeat biopsies showed that levels of urinary CD163 could help distinguish even minimal degrees of activity (AI > 1) from quiescent biopsies (AI = 0).[33] Importantly, CD163 outperformed proteinuria in reflecting histologic activity.[32,33] In another study, urinary levels of the leukocyte surface molecule CD11b were significantly increased and related to histologic activity, and this marker was superior to CD163 in predicting proliferative forms of LN.[35] Consistently, urinary levels of CD11b were also correlated with the number of CD11b+ cells in glomeruli and, to a lesser extent, in the interstitium.[35] These studies suggest that IL-16, CD163, TGF-β1, and CD11b are some of the most promising biomarkers for inclusion in a hypothetical liquid biopsy panel.

Other potential biomarkers need further investigation to define their specific role in LN. Some cytokines, such as the soluble form of tumor necrosis factor receptor II (sTNFRII) or the monocyte chemoattractant protein-1 (MCP-1), exhibit dual correlations with both the NIH AI and CI scores.[24–27,31,36] This makes them difficult to use as biomarkers, unless they are combined with other potential candidates, such as urinary neutrophil gelatinase-associated lipocalin (NGAL), a well-known marker of more acute kidney injury that demonstrated a correlation with the NIH AI scores and, to a lesser extent, the NIH CI scores.[26,37,38] The combination of urinary MCP-1 with NGAL and kidney injury molecule 1 (KIM-1), enhanced the ability to predict active and chronic tubulointerstitial lesions in patients with LN.[30] Serum levels of sTNFRII were particularly effective in detecting chronic rather than active damage, associating with long-term estimated glomerular filtration rate deterioration.[25] Similarly, urinary levels of a molecule normally expressed by kidney tubules, epidermal growth factor, were negatively correlated with the NIH CI score and most of its components and appeared to reflect the onset of chronic damage before creatinine levels rose.[39]

Numerous studies have demonstrated the utility of adhesion molecules as biomarkers to detect activity in LN.[28,40–43] In a cohort of 96 patients, urinary levels of activated leukocyte cell adhesion molecule correlated positively with NIH AI scores and performed well in discriminating proliferative LN from membranous LN exceeding the ability of traditional markers such as C3, anti-dsDNA, and 24-h urine protein to indicate disease activity.[43] Urinary levels of vascular cell adhesion molecule 1 (VCAM-1), which plays a role in inflammatory cell trafficking, were positively correlated with NIH AI scores and active lesions.[28,40–42] In a large study involving 154 patients, the combination of urinary VCAM-1 with cystatin C and KIM-1 appeared to be more effective than VCAM-1 alone in differentiating proliferative from membranous LN, reaching a sensitivity of 94.7% and improving overall diagnostic performance.[42] In the same cohort, urinary VCAM-1 levels also demonstrated a positive correlation with the NIH CI scores[42]; however, this aspect has not been demonstrated in previous studies. Therefore, further investigation is required to confirm the specificity of VCAM-1 as a biomarker of histologic activity.

New emerging biomarkers with a precise pathophysiologic localization within the kidney parenchyma demonstrated greater capacity to delineate specific aspects of damage occurring in the context of LN. For instance, KIM-1, a transmembrane glycoprotein expressed by proximal tubular cells, was not only associated with the NIH AI scores and proliferative forms of LN[26,30,42] but also showed an interesting correlation with acute and chronic tubulointerstitial damage.[30,44,45] Another insight for the possibility of detecting whether a tubulointerstitial component of damage is present and more significant comes from the study by Yap et al; patients with moderate-to-severe tubulointerstitial inflammation exhibited a higher incidence of proximal kidney tubular epithelial cell–binding IgG1 seropositivity compared with those with no or mild inflammation, suggesting also a pathogenic role of this subclass of IgG in LN tubular injury.[46] Finally, increased levels of vitamin D binding protein in urine, which is normally undetectable because of active tubular reabsorption, demonstrated a significant correlation with the NIH AI scores, suggesting a potential role in detecting even a subclinical tubular damage.[42]

Pentraxin 3 correlates with specific active lesions in LN. Elevated serum levels of a systemic inflammation indicator, pentraxin 3 (PTX3), were associated not only with the NIH AI scores but particularly with class IV LN, endocapillary hypercellularity, and leukocyte infiltration. Its urinary levels also exhibited a significant correlation with cellular crescents and interstitial inflammation, potentially making PTX3 a reliable marker of histologic activity in LN.[47] Further studies with multiple marker panels may allow integrated assessments of which combined markers allow the best understanding of disease states.

DISCUSSION

LN is a severe manifestation of SLE in the kidney, leading to considerable patient morbidity and mortality.[48] More and more studies show that in addition to the valuable role of the histologic evaluation in establishing the diagnosis of LN, repeat kidney biopsies are useful in making decisions about the management of LN patients during long-term follow-up.[2,49] However, taking a kidney biopsy always carries a certain, although often minor, risk of complications.[50] Therefore, there is a continuous call for urinary and serum biomarkers as surrogates for the kidney biopsy. To obtain insight into the current status of biomarkers related to the histopathology of LN, we critically reviewed studies published in the last

12 years that presented one or more biomarkers with a relation to the spectrum of lesions in LN. We investigated how these biomarkers could be used in making the first steps of what a liquid biopsy could look like. Our aim was to identify biomarkers of LN histopathology with strong evidence for their applicability in clinical practice to select those that should be prioritized in future feasibility studies to facilitate their advancement toward regulatory approval and clinical usage.

Our results reveal an abundance of studies describing numerous biomarkers that correlate with many different histopathologic parameters and were conducted through a variety of methodologic approaches. Only a small number of studies were graded as being of good quality according to a vigorous quality control assessment. Low- or moderate-quality studies were usually characterized by very small cohorts from different populations, a lack of robust control groups and/or specificity about the timeframe between taking the biopsy and the sample for biomarker assessment, and an oversimplification of histopathology. From the studies graded to be of good quality, we identified a role for the urinary biomarkers (s)CD163 and IL-16 as surrogate markers for active lesions in LN,[24,29,32–34] for PTX3 to be related to endocapillary hypercellularity and cellular crescents,[47] and for urinary CD11b to be correlated to infiltrating cells in the glomerular and tubulointerstitial compartments.[35] TGF-β1 was shown to have a correlation with the total score of the NIH AI.[6] Notably, the combination of these biomarkers seems to capture a broad scope of the spectrum of active lesions in LN, and it would be tempting to investigate in a future study how much of the variation within the LN biopsy profile could be predicted by the combination of these biomarkers in a new clinical test.

Despite these promising findings, it was disappointing to realize that the heterogeneity of methodologic approaches, in combination with the overall low level of quality of most of the studies, considerably limited the interpretation of >50% of the identified articles. Importantly, almost 40% of the analyzed articles did not accurately report the timing of sample collection in relation to the kidney biopsy, affecting the reliability of the results. This might constitute room for improvement in future studies. Moreover, quality was often negatively influenced by oversimplification of the complexity of histopathologic lesions. Many studies made gross generalizations by lumping together a great number of subtle lesions to demarcate, for example, "active" versus "inactive" LN or "proliferative" versus "nonproliferative" LN. Furthermore, comparisons between studies were hampered by methodologic issues, for example with regard to different cutoffs for the NIH AI used in studies to investigate how biomarkers were able to detect various levels of disease activity. It is important to underline that many studies stopped at a point at which a distinction would have been informative in the diagnostic phase, whereas the clinical interest of new biomarkers lies more in their capacity to monitor the evolution of disease over time and guide therapy accordingly, sometimes obviating the need for a kidney biopsy. Considering the difficulty in establishing standardized cutoffs for the NIH AI and CI to evaluate biomarkers and their potential usefulness, it would be more appropriate to develop panels with biomarkers that each reflect specific histologic lesions rather than the overall NIH AI or CI score.

Of note, most of the biomarker studies focus on indicators of active inflammatory lesions; almost none investigated how to predict for the membranous component of LN. One of the challenges in the clinical management of patients with LN is to determine whether ongoing proteinuria is related to class V lesions or, for instance, to chronic lesions such as segmental glomerulosclerosis. For biomarkers being used as a "liquid biopsy," this is an important area of interest that is still understudied. Extending this argument to the development of chronic lesions in general, the focus on purely active lesions alone risks neglecting the subtle, long-term damage caused by low-grade and chronic inflammation, which can progressively impair renal function.

That many of the publications included in our review had only a mediocre quality, as assessed by our scoring system, is one of the limitations of our study together with the fact that we had to rely on the published results of studies with various methodologies. Almost all the studies that obtained a higher-quality rank established associations with the NIH AI and/or CI or focused on correlations between a biomarker and single histopathologic lesions. However, practically none of them investigated whether biomarkers driven by histopathology could be used for decisions with regard to new therapies of LN. Considering the large number of drugs in development for LN that aim to target specific pathogenetic pathways such as the complement system, the interferon system, or specific inflammatory cells, it would be obvious to look for signs in the kidney tissue that capture the presence and level of activity of these drug targets, followed by the development of a biomarker that could monitor the level of activity continuously as a tool for therapy response and for renal outcome. It seems that the premises for such studies are available, and hopefully they will be performed in the very near future.

In LN trials, multiple biomarker panels could prove useful for better stratifying patients and effectively evaluating therapy response, overcoming the limitation of traditional markers, such as proteinuria. Next to that, an increasing body of research is focusing on the use of transcriptomics to detect tissue biomarkers that could serve in the diagnostic phase to tailor treatments and, thus, improve response rates. The combined use of tissue biomarkers with liquid biopsy panels could fundamentally change LN management and prognosis.

From our experience with the articles we have reviewed and analyzed here, we recommend for future studies that they adhere to several quality control parameters, which we have listed in Table 1. Standardizing validation cohorts by unifying treatment protocols and adjusting for patients' characteristics and

Table 1. Recommendations for future research on LN biomarkers that aim to reflect kidney histopathology*

Essential components of high-quality biomarker studies	Main characteristics of essential components	Other aspects to consider and further suggestions
Discovery cohort	• Representative of the spectrum of affected patients with LN • Adequate size • Kidney biopsy data available	–
Control groups	• Highest possible similarity to the cases in terms of age, sex, and ethnicity • Selected based on the research question	–
Serum/urinary sample	• Rigorous protocols for collection, processing, storage, and analysis • Collected within 2–3 weeks of the kidney biopsy (at diagnosis or flare), preferably before immunosuppressive therapy	Clinical trials should store samples for biomarker studies
Biomarker measurement	• According to manufacturer instructions • Reference to standardized cutoff values	• Evaluate confounding factors • Consider costs and ease of detection
Outcomes	• Associations with histopathologic findings, especially with specific features of activity and/or chronicity • Prediction of clinical or histopathologic outcome over time	• Centralized biopsy evaluation would mitigate interobserver variability and could thereby facilitate more structured procedures for biomarker interpretation • Biomarkers should prove superior to traditional markers in reflecting outcomes and exhibit high sensitivity and specificity
Validation process	• Standardized cohorts spanning the heterogeneity of LN • Independent prospective longitudinal studies that overcome the limitations of cross-sectional design	Centers enrolled in biomarker studies should align treatment protocols to improve interpretation of results

* LN, lupus nephritis.

comorbidities affecting outcomes should be prioritized. Furthermore, future validation processes require prospective longitudinal studies that can overcome the limitations of cross-sectional evaluations and investigate biomarker changes over time in relation to kidney histopathology.

In conclusion, there is an urgent need for closer monitoring of LN through the liquid biopsy that could prevent or predict overt reactivation of disease or clinical flares. Only by performing high-quality studies, including biomarker evaluations in clinical trials, and further investigating the clinical utility of multiple biomarkers that would reflect the complex and alternating histopathology of LN in time will we be able to add an extra dimension to the care of patients with LN.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Querin confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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