Autoimmunity Reviews 24 (2025) 103810

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Lupus nephritis trials network (LNTN) repeat kidney biopsy-based definitions of treatment response: A systematic literature review-based proposal

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ARTICLE INFO

Keywords:
Systemic lupus erythematosus
Lupus nephritis
Kidney biopsy
Rheumatology
Autoimmunity

ABSTRACT

Within the frame of the Lupus Nephritis Trials Network (LNTN), we conducted a systematic literature review (SLR) to propose kidney tissue-based definitions of treatment outcomes in lupus nephritis (LN). Given the limitations of clinical markers like proteinuria in predicting immunological, histological, and long-term outcomes, our work emphasises the importance of repeat kidney biopsies. Such biopsies help identify discordance between clinical and histological response, which has implications for long-term kidney outcomes. The research objectives of this SLR focused on defining repeat biopsy-based treatment response and histological remission, and their associations with long-term outcomes. The SLR reviewed studies published from 2000 to 2022, identifying 20 eligible works. Histological response was commonly defined by changes in the National Institutes of Health (NIH) Activity Index (AI), with response indicated by a decrease of $\geq$50 % and to $\leq$3. Remission was most commonly defined as an AI score of 0. These benchmarks were associated with improved long-term renal outcomes, such as reduced flare rates and preserved kidney function. Conversely, NIH AI scores $\geq$4 and NIH Chronicity Index (CI)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AI, Activity Index; CI, Chronicity Index; CKD, chronic kidney disease; EM, electron microscopy; IC, immune complex; IF, immunofluorescence; Ig, immunoglobulins; ISN/RPS, International Society of Nephrology/Renal Pathology Society; LN, lupus nephritis; LoA, level of agreement; LNTN, Lupus Nephritis Trials Network; MLN, membranous lupus nephritis; NIH, National Institutes of Health; PLN, proliferative lupus nephritis; RCT, randomised controlled trial; RTX, rituximab; sCr, serum creatinine; SGLT2, sodium-glucose cotransporter-2; SLE, systemic lupus erythematosus; SLR, systematic literature review.

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https://doi.org/10.1016/j.autrev.2025.103810
Received 10 January 2025; Received in revised form 27 March 2025; Accepted 31 March 2025
Available online 1 April 2025

scores ≥4 were associated with poor prognosis, highlighting their predictive utility. Consensus definitions were established through expert panel deliberation, setting a foundation for standardising LN treatment evaluation in clinical trials and observational studies. These definitions are not intended for routine clinical decisions but aim to enhance uniformity and comparability in research, especially when repeat kidney biopsies are performed, an approach strongly advocated by our work. Further validation through ongoing initiatives and molecular characterisation efforts will refine these criteria, fostering advances in LN management and patient outcomes.

1. Introduction

Systemic lupus erythematosus (SLE) leads to kidney involvement in up to 65 % of the patients, most commonly in an immune complex (IC)-mediated fashion, a manifestation known as lupus nephritis (LN) [1]. Since LN potentially results in severe kidney damage [2], especially when it has not been adequately treated, it should always be considered a severe condition that necessitates prompt commencement of therapy. When affecting children, LN often has a more aggressive presentation, resulting to a greater extent in kidney dysfunction [3,4]. Recent advancements in LN treatment with the introduction of add-on belimumab [5], voclosporin [6] in combinatory regimens hold promise for patients with LN [7–9]. Moreover, although not yet approved for LN, obinutuzumab demonstrated promising efficacy in the phase II NOBILITY [10] and the phase III REGENCY [11] trials. However, the proportion of complete clinical responders in these trials did not exceed 50 % raising doubts about the proteinuria as a sufficient predictor of immunological remission, in particular in patients with risk factors for non-immune causes of proteinuria, such as chronic damage due to repeated episodes of LN, obesity, and salty diet, among other causes [12]. Furthermore, inconsistencies in primary endpoints across trials make it challenging to compare the effectiveness of new therapies, underscoring the critical need for standardised definitions of an immunological treatment response.

Kidney biopsies play a pivotal role in diagnosing LN and guiding therapeutic decisions. In recent years, it has also been suggested that per-protocol repeat kidney biopsies are vital for accurately assessing treatment response and guiding further intensity of immunosuppression [13,14]. This is owing to accumulating evidence that shows a substantial discordance between treatment response based on routine clinical parameters and histopathological findings in post-treatment kidney biopsies. Notably, almost 30 % of complete clinical responders have treatable inflammatory kidney lesions, which would have gone undetected without per-protocol repeat biopsies [15–19]. Of course, kidney biopsy is an invasive procedure with potential untoward complications. Even though such complications are infrequent [20], this highlights the need for reliable biomarkers of kidney histology in peripheral blood or urine, the so-called liquid biopsy. However, until biomarkers that accurately reflect kidney inflammation and damage are established, repeat kidney biopsies remain crucial for evaluating treatment effectiveness and for informing appropriate adjustments to treatment.

While per-protocol repeat kidney biopsy gains attention, the strength of evidence in such efforts is limited by the lack of universally accepted tissue-based definitions of treatment outcome, particularly short-term outcome that is linked to long-term prognosis. To address this need, an international task force was formed under the auspices of the Lupus Nephritis Trials Network (LNTN) with the goal of proposing evidence-based histological definitions of treatment outcome in LN, according to information gleaned from repeat kidney biopsies. Towards this goal, the conduct of a systematic literature review (SLR) preceded and served as the evidence informing the definitions. The objectives of the SLR are summarised in Table 1. It is important to mention that these definitions are not intended to guide therapeutic decisions in routine clinical practice, but rather be used in the design of clinical trials and observational studies of repeat kidney biopsies.

2. Methods

2.1. Objectives of research

With the purpose of proposing kidney tissue-based definitions of renal outcome in LN, an international task force comprising fourteen investigators was assembled in 2022 within the frame of LNTN. The task force included rheumatologists, nephrologists, and renal pathologists. It was convened by IP and FH, and the steering committee also comprised two experts acting methodologists (JM and MT).

Three research objectives were agreed upon by the members of the task force, which formed the basis for the SLR. The objectives concerned the identification of kidney tissue-based definitions of (i) treatment response or failure, (ii) histological remission, both based on repeat kidney biopsies, as well as (iii) associations between those definitions and long-term renal outcomes, in adult and/or paediatric patients with a biopsy-proven LN (population), to inform the definitions proposed by the task force (Table 1). To this end, it is important to stress on the distinction between response and remission, with remission denoting absence of treatable lesions of active inflammation while response denotes a continuum from no response (no change or worsening regarding modifiable tissue injury) to partial response (improvement of tissue injury, yet no achievement of remission) or complete response (improvement to remission or near-remission states, which are coupled with favourable long-term outcome).

2.2. Search strategy and study selection

The search strategy was designed in collaboration with expert librarians from Karolinska Institutet. The MEDLINE, EMBASE, and Web of Science databases were searched for studies published between January 1st, 2000, and November 18th, 2022. Details regarding the search strategy are provided in the online Supplementary Methods and Supplementary Table S1–S3. Additional articles published within the aforementioned timeframe were added by hand searching. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram [21] was used to synthetise the key points of the selection process and is presented in Fig. 1. The studies should have included and made use of at least one clear kidney tissue-based definition of one of the aforementioned objectives in patients with a biopsy-proven LN, adult or paediatric. Study participants should have undergone a per-protocol repeat kidney biopsy for disease and/or treatment evaluation, and/or decision of the subsequent therapy, including intensification or tapering of the immunosuppressive therapy. If the decision for the repeat biopsy was not per-protocol, one of the above reasons for performing the biopsy should have been clearly

Table 1
Summary of research objectives for the systematic literature review.

#	Research objectives
1	To identify kidney tissue-based definitions of treatment response or failure
2	To identify kidney tissue-based definitions of histological remission
3	To identify tissue-based determinants of long-term renal outcome

For all objectives, the population of interest was adult or paediatric patients with a biopsy-proven lupus nephritis who underwent a repeat kidney biopsy for treatment or disease evaluation, and/or for guidance in decision-making regarding subsequent immunosuppression.

indicated in the study.

The studies were screened by two independent investigators (NC, LP). Disagreements were solved through consensus, together with one of the lead investigators (IP).

2.3. Data extraction

Two independent investigators (NC, LP) extracted information from full publication texts, including authors, year of publication, country, study design, number of study participants, demographics and clinical characteristics of study participants, intervention, kidney tissue-based definitions of renal outcome, reported use of the definition including clinical outcomes coupled with the tissue-based definitions, and time between the first and the repeat kidney biopsy. Discrepancies were discussed among the two investigators until consensus was reached, and another investigator (IP) was consulted to solve disagreements.

The findings are detailed as reported by the authors in Tables 2–4.

2.4. Risk of bias assessment

Risk of bias (RoB) of all included studies was assessed by two independent investigators (NC, LP) under the supervision of another investigator (IP), using the Joanna Briggs Institute critical appraisal tools (checklists) [22], which was accompanied by evaluation of the Level of Evidence (LoE) using the Oxford Centre for Evidence-Based Medicine [23]. Detailed information on the RoB procedure and the critical appraisal for each study is provided in the Supplementary Methods and Supplementary Table S4. As previously suggested [24], a study was rated as robust if it clearly fulfilled at least 70 % of the checklist criteria, intermediate if it fulfilled 50–70 % of the checklist criteria, and weak if fewer than 50 % of the checklist criteria were fulfilled.

3. Results

3.1. Study selection

Of 1475 initial hits and 1481 hits after hand searching, 78 studies were selected for full-text evaluation, and 21 studies (19 articles and 2 conference abstracts) were deemed eligible for data extraction (Fig. 1). These comprised 19 cohort studies and two post-hoc analyses of RCTs. Sixteen studies were assessed as robust in critical appraisal, five were assessed as intermediate, and one was assessed as weak. Tables 2–4 show the extracted data from all included studies, sorted by research objective.

3.2. Kidney tissue-based definitions of treatment response or failure in LN (objective 1)

Sixteen studies containing a histological definition of treatment response or treatment failure were retrieved [15–17,19,25–36]. Of these, thirteen studies reported a definition of treatment response [16,25–36], and six reported a definition of treatment failure [15–17,19,33,36]. Detailed information is provided in Table 2.

3.2.1. Kidney tissue-based definitions of treatment response in LN

3.2.1.1. Decrease in activity index scores. Nine studies i.e., two post-hoc analyses of an RCT [29,36] and five cohort studies assessed as robust in

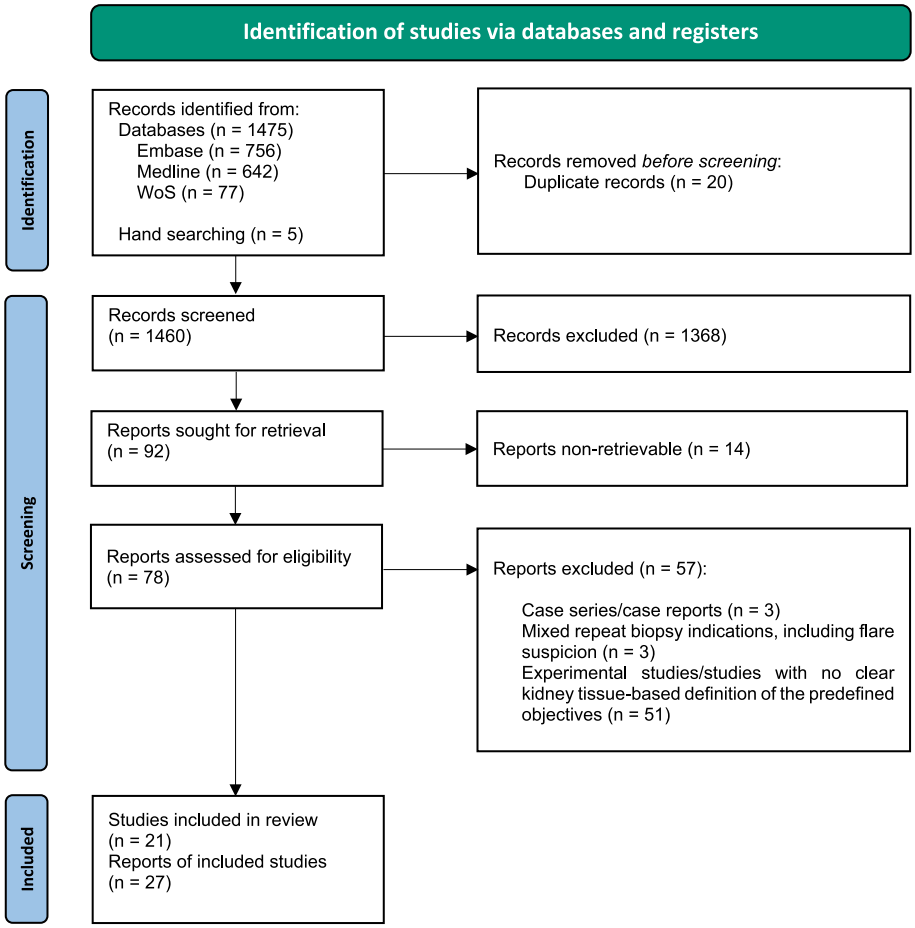

Fig. 1. PRISMA 2020 flow diagram illustrating the identification and eligibility evaluation of studies included in the systematic literature review.

Table 2
Objective 1: kidney tissue-based definitions of treatment response or failure in LN.

Definition of treatment response	Population	Time between diagnostic and per-protocol repeat biopsy	Use of the definition	Link of definition to long-term renal outcome	SD; OA*	Reference
Kidney tissue-based definitions of treatment response						
Decrease in AI scores	77 adult patients with LN	12–18 months	The median AI score decreased by 50 % (from 2.0 to 1.0) in patients with CRR (proteinuria <0.3 g/day and sCr ≤ 125 μmol/L), and by 25 % (from 4.0 to 3.0) in non-responders	No	5; R	Alsuwaida, 2012 [35]
Decrease in AI scores	39 adult patients with PLN	24 months	Decrease in AI scores was inversely associated with renal relapse ($HR_{adj} = 0.73$; $p = 0.039$)	No	5; I	Arends, 2012 [29]
Decrease in AI scores	30 adult patients with PLN	24 months	The median AI score decreased by 80 % (from 10.0 to 2.0) in patients treated with CYC/AZA and by 59 % (from 8.5 to 3.5) in patients treated with CYC/MMF	No	5; R	Stoenoiu, 2012 [36]
Decrease in AI scores by ≥50 %			Decrease in AI scores by ≥50 % at 3rd biopsy correlated with improvement in sCr from baseline to the 3rd biopsy ($R^2 = 0.31$; $p = 0.005$)	No		
Decrease in AI scores	25 adult patients with LN	6 months (2nd biopsy); 42 months (3rd biopsy)	Compared to MMF, CYC yielded more prominent AI decrease at 3rd biopsy in multivariable regression adjusting for change in C4 ($B = -3.55$; $p = 0.013$) or change in sCr (i = −3.81; $p = 0.007$); the AI was decreased by a mean of 11.0 points in the CYC group versus 5.2 points in the MMF group ($p = 0.003$)	No	5; I	Alvarado, 2014 [30]
Decrease in AI scores	40 adult patients with LN	6 months	The mean AI score decreased by 56 % (from 4.7 to 2.1) in patients with CRR (proteinuria <0.3 g/day, inactive urinary sediment, normal serum albumin, sCr ≤ 15 % above baseline levels), and by 63 % (from 6.6 to 2.5) in clinical non-responders	No	5; I	Singh, 2014 [31]
2003 ISN/RPS class improvement Decrease in AI scores	16 adult patients with LN	12 months	In 11/16 (69 %) patients, repeat biopsy showed transition to more favourable 2003 ISN/RPS class, consistent with response to RTX Decrease in median AI score by 56 % (from 8.0 to 3.5) following RTX therapy	No	5; R	Tsanyan, 2014 [28]
2003 ISN/RPS class I, II, or III/IV (C) at repeat biopsy	67 adult patients with active LN (PLN or MLN)	8 months	19/35 (54 %) clinical responders (proteinuria <0.5 g/day, inactive urinary sediment, normal/stable eGFR), were histological responders at repeat biopsy	No	5; R	Zickert, 2014 [16]
Decrease in AI scores by ≥50 %	63 adult patients with active LN (PLN or MLN)	8 months	Of a total of 26 patients with clinical response (≥ 50 % decrease in proteinuria, inactive urinary sediment, normal/improved eGFR), 14 (54 %) were histological responders at repeat biopsy	No	5; R	Parodis, 2015 [25]
2003 ISN/RPS class I, II, or III/IV(C) at repeat biopsy	56 adult patients with active LN (PLN or MLN)	7 months	Histological responders showed lower serum IFN-λ levels after treatment at the time of repeat biopsy ($p = 0.010$); this was not the case for patients with CRR (proteinuria <0.2 g/day, inactive urinary sediment, normal/stable eGFR)	No	5; R	Zickert, 2016 [33]
AI ≤3 at repeat biopsy	19 adult patients with PLN	6–12 months	Kappa = 0.47–0.53 between histological and clinical response (≥ 50 % reduction in proteinuria, inactive urinary sediment, normal or improved eGFR) at repeat biopsy	No	5; W	Campos, 2017 [32]
Decrease in AI scores by ≥50 %	63 adult patients with active LN	8 months	Baseline serum sTNFR2 predicted histological response at repeat biopsy (AUC = 0.90; sens.: 83 %; spec.: 80 %; cut-off: 9.0 ng/mL) in patients with MLN	No	5; R	Parodis, 2017 [26]
Decrease in AI scores by ≥50 %	64 adult patients with active LN	8 months	Serum Axl decreased after treatment in patients who achieved histological response ($p < 0.001$); higher baseline Axl levels (≥ 36.6 ng/mL) predicted histological response (OR = 5.5; $p = 0.029$; $OR_{adj} = 9.3$; $p = 0.020$)	No	5; R	Parodis, 2019 [27]
Resorption of IC deposits	24 adult patients with MLN	10 months	Greater resorption of IC deposits at repeat biopsy in clinical responders (≥ 50 % reduction in proteinuria, normal or improved eGFR) versus non-responders ($p = 0.022$) to RTX	No	5; I	Zickert, 2021 [34]
Kidney tissue-based definitions of treatment failure						
Persistence of 2003 ISN/RPS class III/IV (A) or III/IV (A/C) or V, or transformation into class V	67 adult patients with PLN	8 months	16/39 (41 %) histological non-responders were clinical responders (proteinuria <0.5 g/day, inactive urinary sediment, normal/stable eGFR)	No	5; R	Zickert, 2014 [16]
Persistence of 2003 ISN/RPS class III/IV (A) or III/IV (A/C)	56 adult patients with PLN	7 months	Persistently elevated serum IFN-λ levels were associated with unfavourable histological	No	5; R	Zickert, 2016 [33]

(continued on next page)

Table 2 (*continued*)

Definition of treatment response	Population	Time between diagnostic and per-protocol repeat biopsy	Use of the definition	Link of definition to long-term renal outcome	SD; OA*	Reference
or V, or transformation into class V			response, whereas no clear association was seen with clinical response at repeat biopsy			
AI ≥4 at repeat biopsy	69 adult patients with PLN	6 months	14/28 (50 %) patients with CRR (proteinuria <500 mg/day, normal/improved sCr) still had AI ≥4 at repeat biopsy	No	5; R	Malvar, 2017 [15]
AI scores at repeat biopsy	36 adult patients with PLN	36 months	High AI scores at repeat biopsy were associated with flare (proteinuria >0.5 g/day or increase in sCr by ≥0.3 mg/dL) during a follow-up of 24 months (OR = 1.7; $p < 0.001$)	Yes; refer to Table 4	5; R	De Rosa, 2018 [17]
AI ≥1 at repeat biopsy			AI scores ≥1 at repeat biopsy were associated with renal flare during a follow-up of 24 months (OR = 31.7; $p < 0.001$)	Yes; refer to Table 4		
AI scores at repeat biopsy	42 adult patients with PLN	24 months	High AI scores at repeat biopsy were associated with impending renal relapse (UPCR >1 g/g) (HR = 1.2; $p = 0.007$) within a median follow-up of 108 months	Yes; refer to Table 4	5; R	Parodis, 2020 [19]
AI ≥4 at repeat biopsy			AI ≥4 at repeat biopsy were associated with impending renal relapse (HR = 4.8; $p = 0.014$) within a median follow-up of 108 months	Yes; refer to Table 4		

Study design: 1: Analytical cross-sectional study; 2: Case-control study; 3: Case report; 4: Case series; 5: Cohort study; 6: Diagnostic test accuracy study; 7: Economic evaluation; 8: Prevalence study; 9: Qualitative research; 10: Quasi-experimental study; 11: Randomised controlled trial; 12: Meta-analysis, with or without systematic review.

Overall appraisal: R: Robust; I: Intermediate; W: weak.

Abbreviations: AI: National Institutes of Health (NIH) Activity Index; AUC: Area Under the Curve; AZA: Azathioprine; *B*: Beta coefficient in multivariate linear regression; BAFF: B-cell activating factor; CI: National Institutes of Health (NIH) Chronicity Index; CRR: Complete Renal Response; CYC: Cyclophosphamide; C4: Complement component 4; dPLN: diffuse Proliferative Lupus Nephritis; eGFR: estimated Glomerular Filtration Rate; HR: Hazard Ratio; HR_{adj}: Hazard Ratio adjusted; IC: Immune Complex; IFN-λ: Interferon lambda; 2003 ISN/RPS: 2003 International Society of Nephrology/Renal Pathology Society classification; LN: Lupus Nephritis; MLN: Membranous Lupus Nephritis; MMF: Mycophenolate Mofetil; OR: Odds Ratio; OR_{adj}: Odds Ratio adjusted; PLN: Proliferative Lupus Nephritis; R^2: R squared coefficient; RTX: Rituximab; sCr: serum Creatinine; sens.: sensitivity; spec.: specificity; sTNFR2: soluble Tumor Necrosis Factor Receptor 2; UPCR: Urinary Protein/Creatinine Ratio;

* Study design and overall appraisal (adapted from the Joanna Briggs Institute Manual for Evidence Synthesis [22]).

critical appraisal [25–28,35], and two cohort studies [30,31] assessed as intermediate in critical appraisal, defined histological response to treatment as a decrease in National Institutes of Health (NIH) Activity Index (AI) scores. Data from these studies are detailed in Table 2 and comprehensively discussed in the Supplementary Results.

3.2.1.2. Improvement based on 2003 ISN/RPS classification. In two studies by Zickert et al. comprising patients with active LN, both assessed as robust in critical appraisal, histological response was defined as a change in the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification from class III/IV (A) or (A/C) and/or class V to class I–II or III/IV (C) at repeat kidney biopsy (data are detailed in Table 2 and in Supplementary Results) [16,33].

3.2.1.3. Resorption of sub-epithelial immune complex deposits in repeat biopsy. Sub-epithelial immune deposits of immunoglobulins (Ig), C3, and C1q represent a well-known histological hallmark of membranous LN (MLN), and can be observed by means of immunofluorescence (IF) and/or electron microscopy (EM) [37]. In a study by Zickert et al. assessed as robust in critical appraisal, samples from kidney biopsy performed at baseline and after a median time of 8 months on 24 adult patients with MLN were studied using EM [34]. The study found that proportionally more patients among those who achieved clinical response to RTX therapy, defined as ≥50 % reduction in proteinuria to levels ≤2 g/day and normal renal function, compared to patients who did not, showed resorption of sub-epithelial IC deposits in the repeat kidney biopsy ($p = 0.022$), based on an arbitrary semiquantitative grading system evaluating resorption phenomena and podocyte fusion in electron micrographs from the diagnostic and repeat biopsies.

3.2.2. Kidney tissue-based definitions of treatment failure in LN

3.2.2.1. Activity Index scores in repeat biopsy. Three studies, all assessed as robust in critical appraisal, showed that persistent activity in the repeat kidney biopsy denoted treatment failure or failure of the treatment strategy (Table 2) [15,17,19]. In one study by De Rosa et al., 36 patients with PLN in complete clinical renal remission were followed-up prospectively for 24 months after a per-protocol kidney biopsy [17]. The authors reported that residual activity in the repeat biopsy was associated with a LN flare during the subsequent 2-year follow-up (AUC = 0.91; OR = 1.7; $p < 0.001$), with endocapillary hypercellularity (AUC: 0.94; OR: 5.3; $p < 0.001$) and subendothelial deposits (AUC: 0.90; OR: 3.7; $p < 0.001$) being the elements that mainly drove this association. In the same study, setting the AI cut-off at 1 predicted a LN flare with a sensitivity of 91 % and a specificity of 76 % [17].

In a study by Parodis et al., 42 adult patients with a biopsy-proven PLN underwent per-protocol kidney biopsy for disease evaluation after a median time of 24 months from the baseline biopsy [19]. In this study, increasing AI scores in the repeat kidney biopsy were associated with impending renal flare defined as repeated urinary protein to creatinine ratio (UPCR) > 1 g/g after a previous disease quiescence in response to the initial therapy (HR: 1.2; 95 % C.I.: 1.1–1.7; $p = 0.007$) [19]. In the same study, AI scores ≥4 in the repeat kidney biopsy were associated with a nearly five times increased hazard of renal flare occurrence (HR: 4.8; 95 % C.I.: 1.4–16.7; $p = 0.014$) [19].

In another study by Malvar et al., which compared frequencies of clinical and histological remission after 6 months of initial therapy in patients with PLN, patients who achieved early clinical remission (defined as normal or improved sCr and proteinuria <0.5 g/day) were stratified into those having an AI score ≤ 3 and those having an AI score ≥ 4 [15]. Notably, 14/28 (50 %) of patients who were in clinical remission still had an AI score ≥ 4, and 8/28 (29 %) still had an AI score

Table 3
Objective 2: kidney tissue-based definitions of histological remission in LN.

Definition of histological remission	Population	Time between diagnostic and per-protocol repeat biopsy	Use of the definition	Link of definition to long-term renal outcome	SD; OA*	Reference
WHO class I/II at repeat biopsy	18 adult patients with PLN	6 months	Transformation into WHO class I or II was associated with low-grade albuminuria (< 0.5 g/day) at repeat biopsy ($p = 0.001$)	No	5; I	Gunnarsson, 2002 [38]
AI = 0 at repeat biopsy	77 adult patients with LN	12–18 months	Renal survival at 10 years was 100 % in patients with AI = 0 at repeat biopsy ($p < 0.001$); all patients whose sCr doubled had AI ≥1	Yes; refer to Table 4	5; R	Alsuwaida, 2012 [35]
AI = 0 at repeat biopsy	69 adult patients with PLN	6 months	8/13 (62 %) of the patients who had AI = 0 at repeat biopsy had proteinuria >0.5 g/day	No	5; R	Malvar, 2017 [15]
AI = 0 at repeat biopsy	36 adult patients with PLN	36 months	No patient with median AI = 0 at repeat biopsy developed renal flare (proteinuria >0.5 g/day or increase in sCr by ≥0.3 mg/dL) during a follow-up of 24 months compared to patients with median AI = 3 at repeat biopsy who flared ($p < 0.001$)	Yes; refer to Table 4	5; R	De Rosa, 2018 [17]
AI = 0 at repeat biopsy	76 adult patients with PLN	12 months (2nd biopsy); 42 months (3rd biopsy)	Biopsy-informed management of maintenance therapy (tapering off if AI = 0) resulted in a lower flare rate (0.01 flares per patient-year) compared to usual practice during a median follow-up of 96 months	Yes; refer to Table 4	5; R	Malvar, 2020 [40]
AI = 0 and absence of IF patterns at repeat biopsy	89 adult patients with PLN	42 months	No patient with AI = 0 and absence of IF patterns (IgA, IgG, IgM, C1q, C3) at repeat biopsy developed a LN flare during a median follow-up of 44 months	Yes; refer to Table 4	5; I	Malvar, 2020 [41]
AI = 0 at repeat biopsy	29 adult patients with PLN	36 months	16/16 (100 %) patients with CRR (proteinuria <0.5 g/day, inactive urinary sediment, normal or reduction ≥50 % in sCr from baseline, serum albumin >3.5 g/dL) for >48 months versus 11/13 (85 %) patients with CRR for 24–48 months had achieved histological remission ($p = 0.050$)	No	5; R	Das, 2021 [39]

Study design: 1: Analytical cross-sectional study; 2: Case-control study; 3: Case report; 4: Case series; 5: Cohort study; 6: Diagnostic test accuracy study; 7: Economic evaluation; 8: Prevalence study; 9: Qualitative research; 10: Quasi-experimental study; 11: Randomised controlled trial; 12: Meta-analysis, with or without systematic review.
Overall appraisal: R: Robust; I: Intermediate; W: weak.
Abbreviations: AI: National Institutes of Health (NIH) Activity Index; CI: National Institutes of Health (NIH) Chronicity Index; CRR: Complete Renal Response; C1q: Complement component 1q; C3: Complement component 3; IF: immunofluorescence; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; LN: Lupus Nephritis; PLN: Proliferative Lupus Nephritis; sCr: serum Creatinine; WHO: World Health Organization.
* Study design and overall appraisal (adapted from the Joanna Briggs Institute Manual for Evidence Synthesis [22]).

≥ 5, providing evidence that clinical and histological findings do not always align in patients with LN [15].

3.3. Kidney tissue-based definitions of remission in LN (objective 2)

A total of seven studies containing a histological definition of remission were retrieved [15,17,35,38–41]. Apart from one study, which defined histological remission as a change in World Health Organization (WHO) class I or II at repeat kidney biopsy, assessed as intermediate in critical appraisal [38], all other studies that were identified made use of the NIH AI score to define histological remission. A summary of the studies is provided in Table 3.

In six studies, five of them assessed as robust [15,17,35,39,40] and one assessed as intermediate [41] in critical appraisal, an AI score of 0 at the time of the repeat kidney biopsy was considered histological remission (Table 3). The studies are comprehensively discussed in the Supplementary Results.

3.4. Kidney tissue-based determinants of long-term outcome (objective 3)

To further determine the predictive properties and thus robustness of the tissue-based definitions mentioned above, we checked the selected articles for whether attainment or non-attainment of those definitions had been coupled with long-term kidney outcomes i.e., outcomes evaluated after at least 24 months of follow-up from the time of the repeat kidney biopsy (deterioration of the renal function or proxies, such as recurrence of LN activity). We identified eight studies in total reporting such linkage [15–17,19,35,40–42]. A detailed description of kidney tissue-based determinants of poor or favourable long-term outcome based on these studies is provided in Table 4.

3.4.1. Kidney tissue-based determinants of favourable long-term outcome in LN

3.4.1.1. Activity Index = 0 in repeat biopsy. In three studies, an NIH AI score of zero in the repeat kidney biopsy was associated with favourable long-term renal outcomes. In one study, no patient with a zero NIH AI score in the repeat biopsy experienced a doubling of serum creatinine over a 10-year follow-up [35], while two other studies reported a reduced risk of subsequent renal flares [17,40]. As recurrent flares are known to contribute to cumulative kidney damage over time, their occurrence may serve as a proxy for long-term kidney function deterioration. Collectively, these findings consolidate the potential utility of this definition to signify histological remission (Table 4) [17,35,40]. The studies are discussed in the Supplementary Results.

3.4.1.2. Resorption of immune-complex deposits in repeat biopsy. The concept of immunological remission has gained some traction for the evaluation of kidney biopsy in LN [15,34]. One study by Malvar et al. examined the IF patterns (presence of IgG, IgA, IgM, C1q, C3 deposits) in consecutive kidney biopsies, performed on 89 adult patients with PLN treated with initial immunosuppressive therapy for six months, followed by maintenance regimens [41]. In this study, lower IC deposits were found in patients who had an AI score of 0 in the repeat kidney biopsy compared with patients who had an AI score ≥ 1 [41].

In addition, the authors compared repeat kidney biopsy findings in patients who developed a LN flare and patients who did not; none of the patients who flared had demonstrated a complete resolution of the IF

Table 4
Objective 3: kidney tissue-based definitions of short-term outcomes linked to long-term renal outcome in LN.

Definition	Population	Time between diagnostic and per-protocol repeat biopsy	Use of the definition	SD; OA*	Reference
Associations with favourable long-term renal outcome					
AI = 0 at repeat biopsy	77 adult patients with LN	12–18 months	Renal survival at 10 years was 100 % in patients with AI = 0 at repeat biopsy ($p < 0.001$); all patients whose sCr doubled had AI ≥1	5; R	Alsuwaida, 2012 [35]
AI = 0 at repeat biopsy	36 adult patients with PLN	36 months	No patient with median AI = 0 at repeat biopsy developed renal flare (proteinuria >0.5 g/day or increase in sCr by ≥0.3 mg/dL) during a follow-up of 24 months compared to patients with median AI = 3 at repeat biopsy who flared ($p < 0.001$)	5; R	De Rosa, 2018 [17]
AI = 0 at repeat biopsy	76 adult patients with PLN	36 months	Biopsy-informed management of maintenance therapy (tapering if AI = 0) resulted in a lower flare rate (0.01 flares per patient-year) compared to usual practice during a median follow-up of 96 months	5; R	Malvar, 2020 [40]
AI = 0 and absence of IF patterns at repeat biopsy	89 adult patients with PLN	42 months	No patient with AI = 0 and absence of IF patterns (IgA, IgG, IgM, C1q, C3) at repeat biopsy developed LN flare during a median follow-up of 44 months	5; I	Malvar, 2020 [41]
Associations with poor long-term renal outcome					
AI ≥1 at repeat biopsy	77 adult patients with LN	12–18 months	RR for doubling of sCr at 10 years was 1.4 (95 % C.I.: 1.1–1.8) for patients with AI of 1 or 2 and 1.7 (95 % C.I.: 1.3–2.2) for patients with AI ≥2 at repeat biopsy	5; R	Alsuwaida, 2012 [35]
CI scores at repeat biopsy	67 adult patients with active LN (PLN or MLN)	8 months	Higher CI scores at repeat biopsy were found in patients who developed CKD compared with patients who did not ($p = 0.003$) at a 5-year follow-up	5; R	Zickert, 2014 [16]
CI ≥ 4 at repeat biopsy	69 adult patients with PLN	6 months	CI ≥ 4 at repeat biopsy was associated with CKD development during a median follow-up of 73 months ($p = 0.019$) and independently predicted long-term doubled sCr levels ($R^2 = 0.48$; $p < 0.001$)	5; R	Malvar, 2017 [15]
AI ≥1 at repeat biopsy	36 adult patients with PLN	36 months	AI ≥1 at repeat biopsy were associated with renal flare (proteinuria >0.5 g/day or increase in sCr by ≥0.3 mg/dL) during a follow-up of 24 months (OR = 31.7; $p < 0.001$)	5; R	De Rosa, 2018 [17]
AI ≥4 at repeat biopsy	42 adult patients with PLN	24 months	AI ≥4 at repeat biopsy were associated with impending renal relapse (UPCR >1 g/g) (HR = 4.8; $p = 0.014$) within a median follow-up of 108 months	5; R	Parodis, 2020 [19]
AI scores at repeat biopsy			High AI scores at repeat biopsy were associated with impending renal relapse (HR = 1.2; $p = 0.007$) within a median follow-up of 108 months		
CI ≥ 4 at repeat biopsy			CI ≥ 4 at repeat biopsy were associated with		

(continued on next page)

Table 4 (*continued*)

Definition	Population	Time between diagnostic and per-protocol repeat biopsy	Use of the definition	SD; OA*	Reference
CI scores at repeat biopsy			poor long-term renal outcome (increase in sCr ≥ 120 % of the baseline) (HR = 12.4; p = 0.022) over a median follow-up of 108 months High CI scores at repeat biopsy were associated with poor long-term renal outcome (increase in sCr ≥ 120 % of the baseline) (HR = 1.8; p = 0.016) over a median follow-up of 108 months		
Biopsy Index scores at repeat biopsy	71 adult patients with LN	6 months	Biopsy Index scores over the mean at repeat biopsy were predictive of doubling of sCr over a 10-year follow-up (p = 0.006)	5; R	Hill, 2001 [42]

Study design: 1: Analytical cross-sectional study; 2: Case-control study; 3: Case report; 4: Case series; 5: Cohort study; 6: Diagnostic test accuracy study; 7: Economic evaluation; 8: Prevalence study; 9: Qualitative research; 10: Quasi-experimental study; 11: Randomised controlled trial; 12: Meta-analysis, with or without systematic review.

Overall appraisal: R: Robust; I: Intermediate; W: weak.

Abbreviations: AI: National Institutes of Health (NIH) Activity Index; CI: National Institutes of Health (NIH) Chronicity Index; C.I.: Confidence Interval; CKD: Chronic Kidney Disease; C1q: Complement component 1q; C3: Complement component 3; dPLN: diffuse Proliferative Lupus Nephritis; HR: Hazard Ratio; IF: Immunofluorescence; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; LN: Lupus Nephritis; MLN; Membranous Lupus Nephritis; OR: Odds Ratio; PLN: Proliferative Lupus Nephritis; RR: Relative Ratio; R^2: R squared coefficient; sCr: serum Creatinine; UPCR: Urine Protein/Creatinine Ratio.

* Study design and overall appraisal (adapted from the Joanna Briggs Institute Manual for Evidence Synthesis [22]).

findings (semi-quantitatively graded on a scale 0–3) in the repeat kidney biopsy, whereas patients who had an AI score of 0 and absence of IF findings in the repeat kidney biopsy did not suffer any LN flare during a median follow-up of 44 months [41]. This coupling of resorption of IC deposits and zero scores of AI in the repeat biopsy with favourable long-term renal prognosis supports the use of these tissue-based definitions to signify renal remission.

3.4.2. *Kidney tissue-based determinants of poor long-term outcome in LN*

In two studies, the NIH AI score in repeat kidney biopsies was coupled with long-term renal outcome measures (Table 4) [19,35]. Alsuwaida et al. explored AI scores in repeat biopsies in relation to renal function deterioration over a 10-year follow-up and found that AI scores >0 yielded an increased risk for doubling of sCr [35]. Parodis et al. studied a population of 42 patients with PLN followed-up for a median time of 108 months from the repeat biopsy and found advancing AI scores in repeat biopsies to associate with renal flare occurrence (HR = 1.2; 95 % C.I.: 1.1–1.3; $p = 0.007$), which became more prominent for AI scores ≥4 (HR = 4.8; 95 % C.I.: 1.4–16.7; $p = 0.014$) [19].

Three studies, all assessed as robust in critical appraisal, referred to the NIH Chronicity Index (CI) score in the repeat kidney biopsy as a useful predictor of poor long-term renal outcome [15,16,19], emanating scores ≥4 as a poor prognostic factor (Table 4). The study findings are discussed in the Supplementary Results. It is worth noting that in these studies, proteinuria levels measured at the time of the repeat kidney biopsy showed no clear association with long-term renal outcomes, suggesting that assessment of kidney histopathology provides a more accurate prediction of renal prognosis compared with conventional clinical and laboratory evaluation [15,16,19].

4. Proposed definitions of kidney tissue-based outcomes

Based on the systematic review of the literature detailed above and expert opinion among the task force members, definitions of kidney-tissue based short-term outcomes were formulated. It is important to mention that linkage of a definition to long-term renal outcome was considered a key element. Upon discussions regarding content and formulation, each definition underwent voting. Agreement of at least 75 % was required for adoption of the definition from the first voting round. If this was not reached, the definition was discussed and amended. Next, a second voting round was applied where agreement of at least 66 % was required for adoption of the definition. If this level of agreement was not reached, the definition was discussed and amended. Next, a third voting round was applied. In this round, agreement of at least 50 % was required for adoption of the definition. If this was not reached, the definition was discarded.

Subsequently, the task force members were asked to provide their level of agreement (LoA) with each definition, using a score ranging from 0, denoting complete disagreement, to 10, denoting complete agreement. For the kidney tissue-based definition of response to treatment, the task force proposed an NIH AI score decrease of ≥50 % and/or to a score ≤ 3 in per-protocol repeat kidney biopsy, desirably performed around 12 months from treatment commencement. This definition yielded a mean LoA of 9.43 ± a standard deviation of 0.94. For the kidney tissue-based definition of remission, the task force proposed an NIH AI score of zero. This definition yielded an LoA of 9.71 ± 1.07. While the SLR included the objective of kidney tissue-based definitions of treatment failure, no distinct definition was proposed for treatment failure, since this was considered to be non-attainment of the definition of treatment response. Nevertheless, the SLR information for that objective contributed to the formulation of the histology-based definition of response. Lastly, the task force proposed that an NIH CI score ≥ 4 is a prognostic factor of poor long-term renal outcome. This definition yielded an LoA of 9.79 ± 0.43. The proposed definitions are summarised in Table 5.

Importantly, the experts agreed that more research is needed for the refinement of the definitions. In this respect, a key ongoing endeavour is the multinational investigator-initiated study "Per-protocol **re**peat kidney **bio**psy in incident cases of **lup**us nephritis", or, in short, ReBioLup (https://rebiolup.com), which aims to assess repeat kidney biopsies performed in a standardised manner at month 12 from LN onset and their value in guiding treatment refinement towards short-term and long-term renal benefit [13,43]. New insights and data from recently completed and ongoing clinical trials are also anticipated to shed light in the same directions, as is a newly started initiative for the reclassification of LN [44]. An important aspect to account for will be the molecular characterisation of LN based on multilevel omics, e.g., tissue proteomics [45], which new technologies have facilitated in recent years.

Table 5
Summary of proposed definitions of kidney tissue-based outcomes in LN[a].

	Definition[b]	LoA
Tissue-based definition of response to treatment based on repeat kidney biopsy	NIH AI score decrease by ≥50 % by 12 ± 3 months, resulting in a score ≤ 3 in the repeat kidney biopsy[c]	9.43 ± 0.94
Tissue-based definition of remission based on repeat kidney biopsy	NIH AI score = 0 in the repeat kidney biopsy	9.71 ± 1.07
Tissue-based prognostic factors of poor long-term renal outcome[d]	NIH AI scores ≥4 in the repeat kidney biopsy and/or NIH CI score ≥ 4 in the diagnostic or repeat kidney biopsy	9.79 ± 0.43

Level of agreement is presented as the mean (± standard deviation).
Abbreviations: AI: Activity Index; CI: Chronicity Index; LoA: level of agreement; NIH: National Institutes of Health.

[a] These definitions are not intended to guide therapeutic decisions in routine clinical practice, but rather be used in the design of clinical trials and observational studies of repeat kidney biopsies, towards homogenisation of tissue-based outcomes in LN.

[b] The definitions apply to proliferative LN, with or without membranous patterns.

[c] Note that both conditions (NIH AI score decrease by ≥50 % and an NIH AI score in the repeat kidney biopsy of ≤3) must be met to be classified as a responder.

[d] This definition refers to overall prognostic factors, immunological and non-immunological, to account for the multifactorial contribution to chronic changes in the lupus kidney tissue, including non-lupus causes.

5. Discussion

The need for standardised definitions of kidney tissue-based short-term outcomes in LN arises from the increasing attention around the concept of per-protocol repeat kidney biopsies for a reliable evaluation of treatment efficacy and current inflammatory status, as well as for guidance of the subsequent degree of immunosuppression and adjunct therapy [43]. The multi-centre randomised trial ReBioLup is an international effort driven by the hypothesis that tissue-based evaluation is expected to contribute to better long-term outcomes for patients with LN [13]. Similar to the need for uniform clinical definitions to serve as trial endpoints, there emerges a need for uniform kidney tissue-based definitions of treatment response and remission. To address this need, an international task force was formed under LNTN to propose evidence-based kidney tissue-based definitions of short-term outcomes in LN. The three primary objectives of this work were to identify kidney tissue-based definitions of (i) treatment response or failure, (ii) histological remission, and (iii) associations between these definitions and long-term renal outcomes in people with LN. Importantly, these definitions are not intended to guide therapeutic decisions in routine clinical practice, but be used in clinical trial and observational study design, towards homogenisation of tissue-based outcomes in LN.

Following a stringent methodology in resemblance with the EULAR standard operating procedures for the derivation of recommendations, the task force proposed that the kidney tissue-based definition of response to treatment should be determined by a decrease of ≥50 % in the NIH AI score, resulting in an NIH AI score of 3 or less in the per-protocol repeat kidney biopsy. This is supported by numerous studies demonstrating that achieving these outcomes is associated with favourable disease evolution, while failure to attain them is linked to poor outcomes [19,40]. For clarity, in cases where the diagnostic biopsy shows an NIH AI score ≤ 3, response to treatment is defined as a ≥ 50 % reduction in the NIH AI score in the per-protocol repeat kidney biopsy. Accordingly, failure to attain this definition should be considered treatment failure. Whether this should prompt intensification of the immunosuppressive therapy warrants investigation. While no firm recommendation can be made regarding the optimal timing of repeat kidney biopsy, current literature suggests that biopsies performed earlier than 9 months from treatment commencement may be too early to capture sufficient tissue recovery, whereas biopsies performed later than 15–18 months may be informative but too late to guide important therapeutic decisions, which could prevent nephron loss and improve outcomes if made earlier. It is unlikely that a single optimal timing exists for all evaluation purposes. Rather, timing should be tailored to the clinical objective: early repeat biopsies may be valuable for assessing initial treatment response and guiding subsequent treatment adjustments, whereas later biopsies may better inform modifications to maintenance therapy, including possible withdrawal. A timeframe around 12 months post-baseline may provide a reasonable balance for evaluating the initial treatment response and informing subsequent treatment.

Similarly, the task force defined kidney tissue-based remission as an NIH AI score of zero. Both definitions were supported by multiple studies which not only used these definitions in cohort studies, but also documented associations between attainment of these definitions and prevention of renal relapse and/or deterioration of the kidney function over a longer term. Along the same lines, an NIH CI score of 4 or more in the repeat kidney biopsy was highly predictive of poor long-term renal prognosis. Hence, the task force proposed this NIH CI threshold as an important indicator of the risk for renal function loss to a level of CKD stage 3–5, thus pointing to levels above this threshold being indicative of patients who need attentive surveillance and, depending on the degree of active inflammation in kidney tissue, the extra-renal disease activity, and the comorbidities, in some cases intensified immunosuppressive and/or adjunct therapy. To this end, while it is important to emphasise that the individual NIH CI items may be more indicative than the total score, an NIH CI score of 4 or more should prompt immediate consideration for action to control potential residual inflammation and spare kidney mass, and consideration of enhanced protective measures to preserve kidney function beyond angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), such as aldosterone antagonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors.

This work had some limitations, such as the potential bias introduced by selecting studies published in English and the variations in study designs and patient populations. A major limitation was the lack of literature supporting the connection between percentage change in NIH AI scores and long-term outcomes stratified by the baseline level of activity, and a dearth of data on specific NIH AI items with ability to prognosticate. For example, starting from an NIH AI score of 18 and improving to a score of 9 certainly denotes some response, but not an adequate outcome. On the other hand, starting from a score of 4 and improving to a score of 3 cannot be considered a sufficient degree of response, although the post-treatment value represents a cut-off that has been coupled with favourable prognosis in literature. While our definition of response aspired to incorporate the concepts of activity dynamics and achievement of a desirable state, it must be acknowledged that this still represents ill-defined science. Moreover, the different items of the NIH AI likely carry differential predictive value, but current literature does not allow implementation of such detail in the proposed definitions. Importantly, all studies identified were observational cohort studies, thus yielding an overall moderate level of evidence. Additionally, most studies lacked sufficiently long follow-up after the repeat kidney biopsy to robustly assess the relationship between biopsy findings and long-term renal outcomes. While these definitions provide valuable guidance, they may require further validation in large cohorts and diverse populations.

Despite these limitations, this work represents a significant step towards establishing standardised kidney tissue-based definitions for LN outcomes, addressing the critical need for uniform endpoints in LN research. While not intended to guide decisions in routine clinical practice, these definitions may facilitate more effective comparisons of treatment outcomes across future studies, thus help enhance our understanding of LN evolution. Further research and validation efforts are warranted to refine and expand upon these definitions, ultimately

improving the management and outcomes for people living with LN.

Funding

IP has received grants from the Swedish Rheumatism Association (R-995882), King Gustaf V's 80-year Foundation (FAI-2023-1055), Swedish Society of Medicine (SLS-974449), Nyckelfonden (OLL-1000881), Professor Nanna Svartz Foundation (2021-00436), Ulla and Roland Gustafsson Foundation (2024-43), Region Stockholm (FoUI-1004114), and Karolinska Institutet.

Author contributor

IP, MT, and FH were involved in the conceptualisation and design of the study. IP, NC, LP, JM and MT were involved in methodology. IP, NC, and LP were involved in data curation. IP and LP were involved in manuscript drafting. All authors were involved in interpretation of results, critical review of manuscript drafts, and approval of the final draft prior to submission.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Ioannis Parodis reports financial support was provided by Swedish Rheumatism Association. Ioannis Parodis reports financial support was provided by Karolinska Institute. Ioannis Parodis reports financial support was provided by Region Stockholm. Ioannis Parodis reports financial support was provided by Foundation King Gustaf V 80-årsfond. Ioannis Parodis reports financial support was provided by Swedish Society of Medicine. Ioannis Parodis reports financial support was provided by Professor Nanna Svartz Foundation. Ioannis Parodis reports financial support was provided by Nyckelfonden. Ioannis Parodis reports financial support was provided by Ulla and Roland Gustafsson Foundation. Ioannis Parodis reports a relationship with Amgen Inc. that includes: funding grants. Ioannis Parodis reports a relationship with Janssen Pharmaceuticals Inc. that includes: funding grants. Ioannis Parodis reports a relationship with Roche that includes: funding grants. Ioannis Parodis reports a relationship with Aurinia Pharmaceuticals Inc. that includes: consulting or advisory. Ioannis Parodis reports a relationship with BMS that includes: consulting or advisory. Ioannis Parodis reports a relationship with AstraZeneca Pharmaceuticals LP that includes: funding grants. Ioannis Parodis reports a relationship with Aurinia Pharma U.S., Inc. that includes: funding grants. Ioannis Parodis reports a relationship with Eli Lilly and Company that includes: funding grants. Ioannis Parodis reports a relationship with GSK that includes: funding grants. Ioannis Parodis reports a relationship with Novartis that includes: funding grants. Ioannis Parodis reports a relationship with Gilead that includes: funding grants. Hans-Joachim Anders reports a relationship with AstraZeneca Pharmaceuticals LP that includes: funding grants. Hans-Joachim Anders reports a relationship with GSK that includes: consulting or advisory. Hans-Joachim Anders reports a relationship with Novartis that includes: funding grants. Hans-Joachim Anders reports a relationship with Roche that includes: funding grants. Hans-Joachim Anders reports a relationship with Sobi Inc. that includes: funding grants. Hans-Joachim Anders reports a relationship with Vifor Pharma Switzerland SA that includes: funding grants. Hans-Joachim Anders reports a relationship with Boehringer Ingelheim Corp USA that includes: funding grants. Brad H. Rovin reports a relationship with Biogen that includes: consulting or advisory and funding grants. Brad H. Rovin reports a relationship with Alexion Pharmaceuticals Inc. that includes: consulting or advisory. Brad H. Rovin reports a relationship with Roche that includes: consulting or advisory. Brad H. Rovin reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Brad H. Rovin reports a relationship with GSK that includes: consulting or advisory. Brad H. Rovin reports a relationship with Kyverna Therapeutics that includes: consulting or advisory. Brad H. Rovin reports a relationship with Artiva Biotherapeutics Inc. that includes: consulting or advisory. Brad H. Rovin reports a relationship with Aurinia Pharma U.S., Inc. that includes: consulting or advisory. Brad H. Rovin reports a relationship with Novartis that includes: consulting or advisory. Brad H. Rovin reports a relationship with Sana that includes: consulting or advisory. Brad H. Rovin reports a relationship with Otsuka Pharmaceutical Co Ltd. that includes: consulting or advisory. Ming-Hui Zhao reports a relationship with Bayer that includes: consulting or advisory. Ming-Hui Zhao reports a relationship with BeiGene Ltd. that includes: consulting or advisory. Ming-Hui Zhao reports a relationship with Novartis Pharmaceuticals Corporation that includes: consulting or advisory. Ming-Hui Zhao reports a relationship with GSK that includes: consulting or advisory. Ming-Hui Zhao reports a relationship with Roche that includes: consulting or advisory. Ming-Hui Zhao reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Brad H Rovin reports a relationship with Kezar Life Sciences Inc. that includes: consulting or advisory. Brad H Rovin reports a relationship with Hibio, Inc. that includes: consulting or advisory. IP has received research funding and/or honoraria from Amgen, AstraZeneca, Aurinia, BMS, Elli Lilly, Gilead, GSK, Janssen, Novartis, and Roche. HJA has received research funding and/or honoraria from AstraZeneca, GSK, Novartis, Roche, Sobi, Boehringer-Ingelheim, and Vifor. BR has received funding from Biogen and consultancy fees from Alexion, Vera, Roche/Genentech, AstraZeneca, GSK, Kyverna, Artiva, Aurinia, Novartis, Biogen, Sana, Otsuka, Kezar, and HiBio. MZ has been a consultant or advisory board member for GSK, AstraZeneca, Roche, Novartis, Bayer, and BeiGene. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank the librarians Love Strandberg and Emma Lotta Säätelä from the Karolinska Institutet library for their assistance with the construction of the search strategy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2025.103810.

Data availability

No data was used for the research described in the article.

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