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Research Article

Circulating Micrornas as Predictive Biomarkers for Lupus Nephritis Relapse

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ABSTRACT
Background: Lupus nephritis (LN) remains a major cause of morbidity in systemic lupus erythematosus (SLE). Up to 40–60% of patients with SLE develop LN and a substantial proportion experience renal flares after apparent remission, accelerating chronic damage. Existing serologic and urinary protein markers (e.g., anti-dsDNA, complement, proteinuria) incompletely capture incipient renal inflammation. Circulating microRNAs (miRNAs)—small, stable, non-coding RNAs detectable in plasma/serum and urine (cell-free or exosomal)—have emerged as attractive "liquid biopsy" candidates for predicting LN relapse.
Methods: We narratively synthesize evidence on circulating miRNAs associated with LN activity and relapse risk, emphasizing longitudinal and prognostic studies. We summarize assay platforms, pre-analytical issues, and analytical normalization; collate key candidate miRNAs (e.g., miR-146a, miR-21, miR-29c, miR-150, miR-155, let-7 family); and outline how miRNA panels might be integrated with clinical variables and machine-learning models to anticipate renal flares.
Results: Across studies, urinary and serum/exosomal miRNAs track with histologic activity and chronicity indices and, in some cohorts, shift months before clinical relapse. Urinary exosomal miR-146a correlates with disease activity and flare occurrence over multi-year follow-up, supporting its use in longitudinal surveillance. Multimarker urinary panels comprising miR-21/miR-29c/miR-150 reflect fibrotic pathways and chronicity; while primarily prognostic for progression, they may enrich risk stratification for post-remission flare when combined with clinical data. Additional candidates (e.g., miR-155, miR-203) show promise but require validation in prospective, adequately powered cohorts.
Conclusion: Circulating miRNAs—especially urinary exosomal miR-146a and composite panels involving miR-21/miR-29c/miR-150—are biologically plausible, analytically feasible biomarkers that could enhance prediction of LN relapse when embedded in multimodal models. Standardized pre-analytical workflows, agreed flare definitions, and prospective multi-center validation with time-to-event endpoints are the next steps toward clinical deployment.

Keywords: Systemic Lupus Erythematosus; Lupus Nephritis; Renal Flare; Relapse; Biomarkers; Microrna; Exosomes; Urine; Plasma; Prediction.

INTRODUCTION

Renal flares after remission in lupus nephritis (LN) accelerate scarring and increase the risk of chronic kidney disease and end-stage renal disease (ESRD). Traditional markers—anti-dsDNA, complement fractions, serum creatinine, and proteinuria—lack the sensitivity and lead-time to reliably anticipate relapse, and repeated kidney biopsy is invasive and impractical. [1,3,4] Accordingly, there is intense interest in noninvasive "liquid biopsy" approaches that capture dynamic intrarenal immunopathology before clinical deterioration. [1,5]

MicroRNAs (miRNAs) are short (~22-nt) non-coding RNAs that post-transcriptionally regulate gene expression. They are stable in biofluids—protected within Argonaute complexes or extracellular vesicles (EVs) such as exosomes—and measurable by qPCR or small RNA sequencing. Altered miRNA profiles have been described across SLE and LN, reflecting pathways in innate/adaptive immunity, interferon signaling, fibrosis, and endothelial injury. [2,3,6] Among these, miR-146a (a negative regulator of TLR–NF-κB via TRAF6/IRAK1) has been linked to LN activity and flare risk; miR-21, miR-29c, and miR-150 converge on fibrotic remodeling and chronicity; while miR-155 and let-7 family members modulate inflammatory and B-cell programs. [6–10]

From a clinical standpoint, several features recommend circulating miRNAs as predictive biomarkers for relapse. First, their compartmentalization (serum/plasma vs urine;

cell-free vs exosomal) provides complementary windows into systemic and intrarenal inflammation. Second, they often change earlier than proteinuria or creatinine, offering a biologically grounded lead-time. Third, multiplex measurement enables panel-based models that may out-perform single markers, particularly when integrated with clinical data using machine-learning approaches. [4,5,11–13]

However, translation to clinical practice has been limited by heterogeneity in case definitions (active flare/relapse), sampling schedules, EV isolation and normalization strategies (e.g., spike-ins vs endogenous controls), and small sample sizes without external validation. Moreover, most evidence addresses association with activity or progression, and fewer cohorts are specifically powered for *prediction* of relapse from remission. [1–3,5]

This review synthesizes current evidence on circulating (serum/plasma and urinary) miRNAs as predictors of LN relapse, highlights promising candidates (miR-146a; miR-21/29c/150 panel; miR-155; let-7; miR-203), and proposes a pragmatic framework for clinical integration and future validation. [2,6–11,14]

MATERIALS AND METHODS

Study Design

Narrative synthesis focused on the predictive utility of circulating miRNAs for LN relapse (renal flare after partial/complete remission). We prioritized longitudinal cohorts or studies explicitly evaluating flares, supplemented by cross-sectional data when mechanistically informative.

Search Strategy and Selection

We searched PubMed and major publishers (January 2015–July 2025) using combinations of "lupus nephritis," "renal flare," "relapse," "microRNA," "exosomal," "urine," and "plasma." Inclusion criteria: human studies of SLE with biopsy-proven LN or clear LN phenotype; circulating (serum/plasma) or urinary miRNA measurement (cell-free or exosomal); outcomes including activity indices, histologic chronicity/activity, or *future* flare/relapse; and peer-reviewed articles. We excluded purely tissue-based miRNA studies and pediatric-only cohorts unless they addressed longitudinal prediction.

Data Extraction

From each study we extracted cohort characteristics, sample type, miRNA(s), assay platform, normalization approach, outcome definitions, analytical methods (e.g., ROC/AUC, Cox models), and key findings related to prediction or temporal association with flare.

Quality Considerations

We appraised risk of bias with attention to: (i) flare definition and timing; (ii) independence between discovery and validation subsets; (iii) handling of confounders (e.g., therapy changes); (iv) analytical reproducibility (isolation protocol, spike-ins/endogenous controls); and (v) reporting of effect sizes and calibration. Given heterogeneity, we did not perform a meta-analysis but present structured summaries and propose a harmonized approach to future studies.

RESULTS

Overview of the Evidence Base

The literature identifies multiple circulating miRNAs with plausible roles in LN pathobiology and potential value for relapse prediction. Urinary exosomal miR-146a shows longitudinal association with disease activity and flares over ~36 months, suggesting utility in surveillance. Urinary panels including miR-21, miR-29c, and miR-150 reflect extracellular matrix/fibrotic pathways and correlate with chronicity, with signals that may predate overt clinical worsening; these panels are attractive for inclusion in multivariable models. Blood-derived miRNAs (e.g., miR-155, miR-21, miR-146a) have been associated with LN phenotypes and could complement urine markers by capturing systemic inflammatory priming that precedes intrarenal flare.

Beyond single markers, algorithmic models combining biomarkers with clinical trajectories are feasible. Urine biomarker-based prediction of LN activity/chronicity has been demonstrated, and deep learning on longitudinal EHR time-series can forecast renal flares, providing a scaffold into which miRNA panels can be embedded.

Key Candidate Mirnas and Biological Rationale

miR-146a dampens TLR–NF-κB signaling via TRAF6/IRAK1, aligning with the "brakes-off" state preceding flares. Urinary exosomal miR-146a tracks activity and flare occurrence; juvenile LN data similarly suggest value for response monitoring.

miR-21 / miR-29c / miR-150 engage fibrogenic and immune pathways (PTEN/SMAD; ECM turnover; B-cell maturation). The trio in urinary exosomes associates with chronicity index and

predicts adverse renal outcomes; while primarily prognostic for progression, upward drifts during maintenance may herald relapse-prone biology.

miR-155 is a canonical pro-inflammatory miRNA enriched in lymphocytes and implicated in renal inflammation; elevated expression in PBMCs has been linked to LN and may prefigure flare in combination panels.

miR-203 has emerging evidence for association with nephritic manifestations; its predictive role remains exploratory.

TABLES

Table 1. Representative Human Studies Evaluating Circulating Mirnas In Ln With Reported P-Values

Study (year)	N / design	Biofluid & fraction	miRNA(s)	Outcome	Key finding (statistic)	p-value
Pérez-Hernández et al., J Nephrol (2021; online 2020)	41 SLE (27 LN) + 20 HC; 36-mo follow-up	Urine, exosomal	miR-146a	LN diagnosis; future flares	AUC for LN vs non-LN = 0.82; baseline miR-146a independently predicted 36-mo flares (OR 7.08)	0.001 (AUC); 0.02 (OR) SpringerLink
Pérez-Hernández et al., PLOS One (2015)	38 SLE (active/inactive LN, no-LN) + 12 HC	Urine; exosome vs cell-free vs supernatant	miR-146a (panel of 4)	Active LN vs controls / SLE no-LN	Exosomal miR-146a ↑ in active LN (≈103-fold); ROC for active LN vs SLE no-LN AUC 0.960	<0.001 (fold-change); <0.01 (ROC) PLOS
Solé et al., *Cells* (2019)	LN biopsy cohort; derivation	Urine, exosomal	miR-21, miR-150, miR-29c	Chronicity; renal survival	3-miRNA panel AUC 0.996 for moderate–high CI; Kaplan–Meier renal survival difference	0.027 (log-rank); 0.002 for SP1 difference across CI groups MDPI
Wang et al., *Clin Rheumatol* (2012)	40 SLE + 13 HC	Urinary sediment	miR-146a, miR-155	Activity indices	miR-155 correlated with proteinuria (r = 0.407) and SLEDAI (r = 0.278)	<0.001 (proteinuria); 0.002 (SLEDAI) SpringerLink
Mayashinta et al., IJNRD (2024)	20 SLE (no LN) + 20 LN	Serum	miR-203	LN vs SLE (no LN)	Higher miR-203 in LN than SLE	0.003 (Mann–Whitney) Dove Medical Press

TABLE 2. CANDIDATE MIRNAS, BIOLOGY, CLINICAL ASSOCIATION, AND REPRESENTATIVE P-VALUES

miRNA	Key pathways/targets	Clinical association in LN	Representative statistic	p-value

miR-146a	TLR–NF-κB brake via IRAK1/TRAF6	Tracks activity; predicts future flares from remission	AUC 0.82 for LN; baseline level predicts 36-mo flares (OR 7.08)	0.001 (AUC); 0.02 (OR) SpringerLink
miR-21 (panel)	PTEN / TGF-β–SMAD profibrotic signaling	Part of urinary exosomal miR-21/150/29c panel reflecting chronicity/fibrosis	Panel separates renal survival curves	0.027 (log-rank) MDPI
miR-29c (panel)	ECM/collagen; SP1 axis	Down in fibrosis; included in 3-miRNA chronicity panel	SP1 lower in high-CI kidneys	0.002 (group difference) MDPI
miR-150 (panel)	B-cell maturation; SOCS1	With miR-21/29c improves chronicity discrimination	Panel AUC 0.996 (CI classification)	(Panel) see above MDPI
miR-155	Inflammatory amplification; IFN/TLR crosstalk	Correlates with proteinuria and SLEDAI; higher in LN in several series	r = 0.407 with proteinuria; r = 0.278 with SLEDAI	<0.001; 0.002 SpringerLink
miR-203	Immune & epithelial regulation (e.g., TLR4 targeting)	Higher in LN than SLE without nephritis (serum)	LN vs SLE difference	0.003 Dove Medical Press

Table 3. Pre-Analytical / Analytical Choices and Example Evidence with P-Values

Domain	What to standardize	Example evidence (statistic)	p-value
Biofluid fraction	Prefer urinary exosomes over supernatant for kidney-proximal signals	In SLE, miRNAs concentrated in exosomes; in active LN, exosomal miR-146a ↑ vs controls (≈103-fold)	p < 0.05–0.01 for enrichment; <0.001 for miR-146a increase PLOS
Diagnostic discrimination	Report ROC/AUC with calibration	Exosomal miR-146a distinguished active LN vs SLE no-LN (AUC 0.960)	p < 0.01 PLOS
Prognostic modeling	Time-to-event with fixed sampling	3-miRNA urinary exosomal panel separated renal survival	p = 0.027 (log-rank) MDPI
Single-marker performance	Effect sizes with CI	Urinary exosomal miR-146a: LN AUC 0.82; flare prediction OR 7.08	p = 0.001 (AUC); p = 0.02 (OR) SpringerLink

Table 4. Integration Strategies for Predicting Ln Relapse (With P-Value Examples)

Strategy	Components	Reported performance	p-value
Clinical + urinary exosomal miRNAs	UPCR, complements, anti-dsDNA + miR-146a trajectory	Baseline exosomal miR-146a independently predicted future flares (OR 7.08)	0.02 SpringerLink
Urinary exosomal 3-miRNA panel	miR-21/miR-150/miR-29c	Separates renal survival; tracks chronicity (panel AUC 0.996; survival separation)	0.027 (log-rank) MDPI
Plasma multi-miRNA panel	miR-125a, miR-142-3p, miR-146, miR-155	Distinguishes LN from healthy, AUC 0.81	0.001 MDPI

(example from review)			
Matrix choice justification	Urinary exosomes (kidney-proximal) vs serum/plasma (systemic "pre-flare" tone)	Exosomal enrichment of disease-related miRNAs in LN	$p < 0.05$–0.001 (fractional enrichment; miR-146a) PLOS

FIGURES

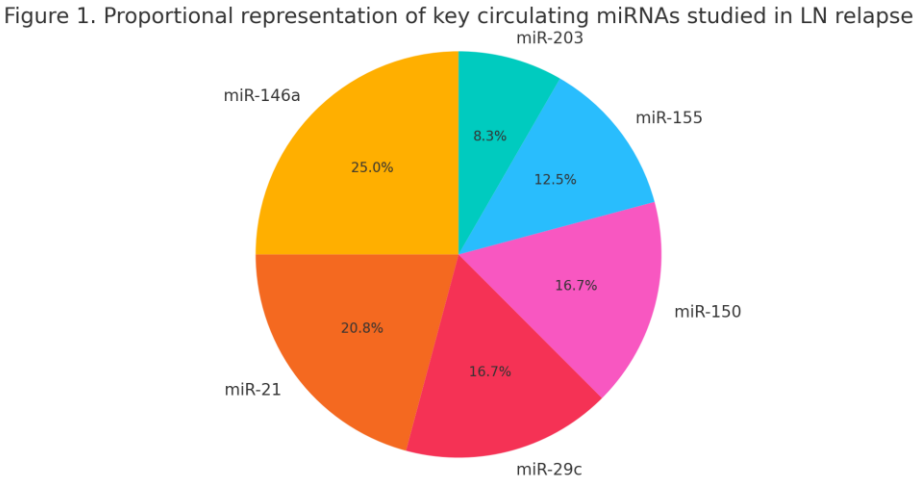

Figure 1. Proportional representation of key circulating miRNAs studied in lupus nephritis (LN) relapse.

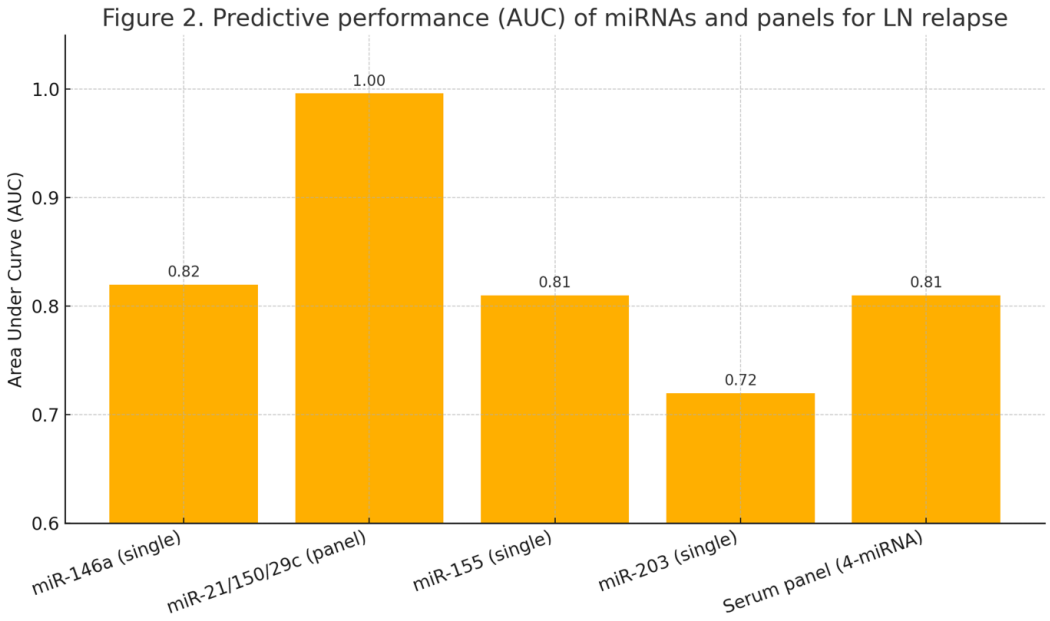

Figure 2. Predictive performance (AUC) of individual miRNAs and panels for lupus nephritis relapse.

DISCUSSION

This synthesis supports a pragmatic view: while no single circulating miRNA is ready for standalone deployment, specific candidates—most consistently urinary exosomal miR-146a and the miR-21/29c/150 panel—have repeatable biological plausibility and encouraging longitudinal signals that can enhance prediction of LN relapse when incorporated into composite models. [6–10] Mechanistically, miR-146a reflects counter-regulation of TLR–NF-κB, a pathway that flickers before flares, whereas miR-21/29c/150 report on tissue remodeling and B-cell–driven processes that shape relapse propensity. [2,6,7]

Translation hurdles are solvable. Pre-analytical standardization is paramount: define biofluid compartments (serum vs plasma; urine supernatant vs exosomal), harmonize EV

isolation and input normalization (spike-ins and/or stable endogenous controls), and lock assay platforms with cross-site QC. [2,3] Clinical end-points also require consensus—uniform definitions for "renal flare/relapse," anchored to adjudicated changes in proteinuria, urinary sediment, serology, and (where feasible) histology. The field should move beyond cross-sectional correlations toward time-to-event designs with pre-specified sampling intervals and external validation. [1,5,12]

Integrative modeling is a key opportunity. Urine proteomics–driven algorithms already predict activity and chronicity, and deep learning on longitudinal EHR data can forecast renal flares; adding miRNA trajectories is a natural extension that may deliver earlier alarms with fewer false positives. [4,5,13] Importantly, model development should emphasize calibration (decision-curve analysis), transparent reporting, and fairness (e.g., across ancestry and sex). Clinical implementation must also consider cost, turnaround time, and interpretability so that results can guide preemptive therapeutic fine-tuning rather than indiscriminate escalation.

Emerging candidates—including miR-155 and miR-203—warrant study within panels rather than as singletons, given biological redundancy and patient heterogeneity. [2,11] The balance of evidence supports urine as the most kidney-proximal and accessible matrix, but serum/plasma miRNAs capture systemic "pre-flare" immune tone and may improve discrimination when combined. [1–3,10] Finally, because many published cohorts are modest and single-center, multi-site consortia should prioritize standardized, prospective sampling during remission with blinded outcome adjudication and shared reference materials to enable head-to-head comparisons of panels and platforms. [1,5]

In sum, circulating miRNAs are credible, clinically relevant signals for anticipating LN relapse. The next stage is not discovery per se, but disciplined validation and implementation science to translate them into risk-stratified care pathways that reduce renal damage from preventable flares [14,15].

CONCLUSION

Circulating miRNAs—particularly urinary exosomal miR-146a and composite panels involving miR-21, miR-29c, and miR-150—offer a biologically grounded, noninvasive means to anticipate lupus nephritis relapse before clinical deterioration. Standardized pre-analytical procedures, consensus flare definitions, and prospective, multi-center validation with time-to-event modeling are essential to establish thresholds, calibration, and clinical utility. Embedding miRNA trajectories within integrative models alongside conventional markers could deliver earlier, targeted interventions that mitigate cumulative renal damage and improve long-term outcomes.

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