Review Article

Extracellular Vesicle Biomarkers in Systemic Lupus Erythematosus and Lupus Nephritis: Emerging Roles in Pathogenesis, Biomarker Development, and Clinical Translation

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ABSTRACT

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease characterized by loss of immune tolerance, autoantibody production, immune-complex deposition, and persistent inflammation. Lupus nephritis (LN) is a serious manifestation of SLE, affecting approximately 40–60% of patients and contributing substantially to morbidity and mortality. Conventional biomarkers, including anti-double-stranded DNA antibodies, complement C3/C4, proteinuria, and serum creatinine, incompletely reflect molecular disease activity, while renal biopsy, although the gold standard, is invasive and unsuitable for frequent longitudinal assessment. Extracellular vesicles (EVs) are membrane-enclosed particles that can transport proteins, lipids, messenger RNAs, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs) and DNA. Their cargo reflects the state of parent cells and participates in immune activation, type I interferon signaling, complement dysregulation, endothelial injury, and renal inflammation. This review synthesizes evidence on EV biology and immunopathogenesis in SLE/LN and critically evaluates EV-associated proteins, miRNAs, and emerging non-coding RNAs as biomarkers. Proteomic and multi-omics approaches increasingly support multi-analyte signatures rather than single biomarkers. Major barriers to translation include heterogeneous isolation methods, incomplete vesicle characterization, small cohorts, variable analytical workflows, limited external validation, and lack of standardized normalization. Future clinical utility will depend on MISEV-aligned workflows, prospective multicentre validation, comparison with established biomarkers, and integration of EV-associated molecular profiles with clinical data and artificial intelligence. EVs therefore represent a promising liquid-biopsy platform, but clinical adoption requires rigorous standardization and demonstration of incremental value over existing tools.

Keywords: *Extracellular vesicles; small extracellular vesicles; systemic lupus erythematosus; lupus nephritis; biomarkers.*

1. INTRODUCTION

SLE is a multisystem autoimmune disease driven by loss of immune tolerance, pathogenic autoantibodies, immune-complex deposition, and sustained innate and adaptive immune activation [1–3]. Lupus nephritis (LN) affects approximately 40–60% of patients and contributes substantially to chronic kidney disease and mortality [4, 5]. Renal biopsy remains the reference standard for classification and histopathological assessment, but its invasiveness and sampling limitations restrict repeated monitoring [4, 5].

Anti-dsDNA antibodies, complement C3/C4, proteinuria and serum creatinine provide useful clinical information but may not capture early molecular changes or distinguish active inflammation from established damage [3–5]. This creates a need for minimally invasive markers of disease activity, organ-specific injury and treatment response. EVs, including operationally defined sEVs, are attractive because their lipid bilayer protects cargo and

their molecular content can retain information about parent cells and tissues [6].

In SLE/LN, EVs can transport nucleic acids, cytokines, autoantigens, complement-associated proteins and regulatory molecules between immune and renal cells, contributing to interferon signaling, inflammation, endothelial dysfunction and tissue injury [7–9]. This dual role—as mediators of disease biology and indicators of the cellular environment-provides the rationale for their investigation as liquid-biopsy biomarkers.

This article is a narrative and critical review rather than a quantitative systematic synthesis. It follows a translational framework linking EV biology and cellular origin → molecular cargo → disease mechanisms and phenotypes → biomarker discovery and performance → comparison with established measures → clinical utility and future monitoring applications. The primary objective is to assess evidence from human SLE/LN cohorts and distinguish biological plausibility, reproducible associations and clinically validated performance.

Evidence is interpreted by maturity: established findings supported by multiple human studies; preliminary/emerging observations from exploratory or incompletely validated cohorts; and future hypotheses requiring prospective testing. This distinction is used throughout to avoid equating biological plausibility or association with clinical validation.

In accordance with current International Society for Extracellular Vesicles (ISEV) recommendations, the term extracellular vesicle (EV) is used as the default descriptor, while operational terms such as small EVs (sEVs) are used when supported by the isolation and characterization strategy. The term ‘exosome’ is retained only when the original study used this terminology or when an endosomal origin was demonstrated. Recent ISEV guidance has emphasized continued updating of MISEV recommendations to improve methodological consistency, reporting and reproducibility in EV research [10].

Novelty and contribution. Previous reviews have summarized EV involvement in SLE/LN pathogenesis and biomarker development [11]. This review adds a translational critical framework linking EV cargo with disease activity, renal involvement and histopathology, while explicitly assessing incremental value beyond anti-dsDNA, C3/C4, proteinuria and eGFR, treatment-related heterogeneity, and requirements for external validation and clinical implementation.

2. MATERIALS AND METHODS

This article was prepared as a narrative and critical literature review. PubMed, Scopus, Web of Science and Google Scholar were searched primarily for publications from 2011–2026, with earlier landmark studies retained for foundational EV biology. Search terms combined SLE, LN, EV/exosome terminology, miRNA, proteomics, transcriptomics and biomarkers using Boolean operators.

Original research, reviews and evidence syntheses were purposively selected for biological rationale, representative biomarker findings, methodological considerations and translational relevance rather than according to a formal systematic-review protocol.

Extracted information included population, specimen, EV isolation/enrichment, characterization, analytical platform, cargo/signature, clinical phenotype and diagnostic, prognostic or monitoring relevance. Methodological heterogeneity, cohort size, normalization, external validation and comparison with established biomarkers were specifically considered.

Evidence was synthesized thematically across EV biology, molecular cargo, immunopathogenesis, biomarker performance, disease activity/renal involvement, multi-omics, comparison with conventional measures and clinical validation requirements.

Evidence maturity was classified as established, preliminary/emerging or future hypothesis. Established evidence required multiple human SLE/LN studies and/or established biological/clinical support; preliminary/emerging evidence mainly reflected small, cross-sectional or incompletely validated

cohorts; future hypotheses remained to be prospectively tested.

2.1 EV nomenclature and methodological framework

EV terminology followed MISEV2023 [6]. Reported "exosome" findings were interpreted cautiously unless endosomal origin was demonstrated, because common enrichment procedures may recover heterogeneous EVs and non-vesicular particles. Interpretation also considered EV source, pre-analytical handling, separation, characterization, normalization and analytical platform.

MISEV2023 was the principal methodological reference; a 2026 ISEV Board editorial on future MISEV updating was considered during the final literature update but was not treated as a replacement guideline.

3. RESULTS AND DISCUSSION

3.1 Extracellular Vesicles and Operational EV Subtypes

EVs are membrane-enclosed particles released by cells and involved in intercellular communication. MISEV2023 supports EV as the default term because common isolation procedures rarely establish a specific biogenesis pathway; sEV denotes an operationally defined small population [6].

EV stability in plasma, serum and urine and their ability to carry cell-associated molecular information make them attractive for liquid biopsy. Methodological differences in isolation and characterization can substantially alter the molecular profile attributed to EVs, so biomarker findings require cautious interpretation [6].

3.2 Molecular Cargo and Biological Functions

EV cargo is selectively enriched and includes proteins, miRNAs, lncRNAs, circRNAs, DNA, lipids and metabolites. These components can act as effectors or regulators of immune, interferon, complement, endothelial and renal pathways, providing a molecular snapshot of disease processes [7, 12].

Figure 1. EV biology and translational evidence framework in SLE and LN

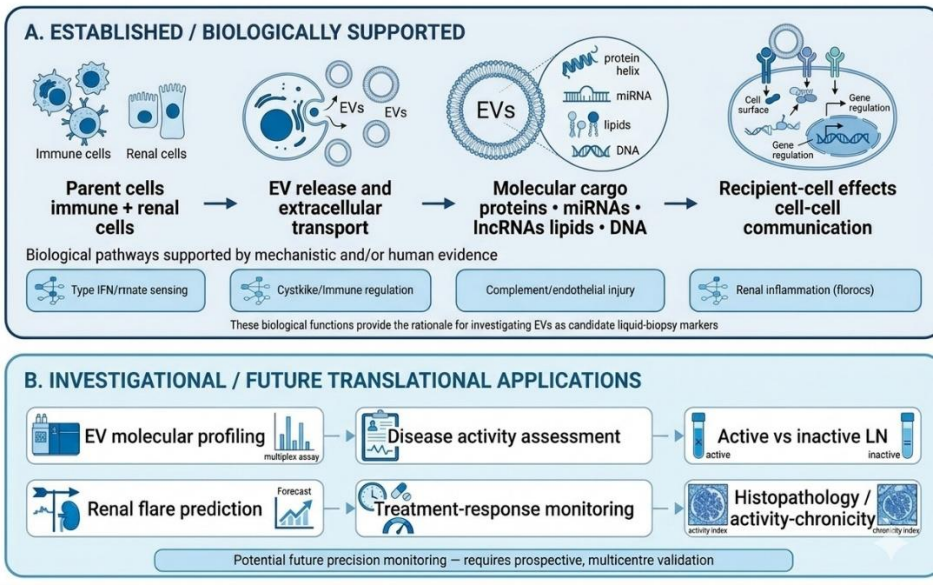


Figure 1. Biogenesis, molecular cargo, biological functions, and clinical applications of EVs in SLE and LN.

Legend: Evidence framework for extracellular vesicle biology and translational applications in SLE and LN**.** EVs are released by multiple cellular pathways and contain proteins, miRNAs, lncRNAs, circRNAs, DNA and lipids that may participate in intercellular communication and immune or renal processes. Panel A summarizes biological pathways supported by mechanistic and/or human evidence. Panel B illustrates investigational applications, including disease-activity assessment, differentiation of active versus inactive LN, renal flare prediction, treatment-response monitoring and potential integration with renal histopathology. These latter applications remain investigational and require prospective, multicenter validation.

The major classes of EV cargo and their potential relevance to SLE and LN are summarized in Table 1.

Table 1. EV cargo classes, biological relevance and biomarker development status in SLE/LN References [7, 8, 9, 12-15, 17-21, 23, 24]

Cargo	**Representative molecules**	Biological Function/ Pathway	**Potential SLE/LN Phenotype**	**Potential Biomarker Application**	**Evidence Maturity**	**Major Limitations**
Proteins	CD9/CD63/CD81, ALIX/TSG101; cytokines; complement and adhesion proteins	Immune activation, complement/ endothelial injury; diagnosis and monitoring	SLE activity; renal involvement; tissue injury	Disease activity and renal monitoring	Preliminary / emerging for biomarker use	EV heterogeneity; protein abundance influenced by cellular origin and isolation efficiency; limited external validation
miRNAs	miR-21, miR-146a, miR-155, miR-29c, miR-451a	Immune regulation, inflammation, fibrosis; disease activity/LN	SLE activity; LN/renal injury	Activity assessment and renal monitoring	Preliminary / emerging	Normalization variability; cohort heterogeneity; inconsistent findings; lack of validated thresholds
lncRNAs/ circRNAs	NEAT1, MALAT1; selected circRNAs	Transcriptional regulation and miRNA sponging; emerging biomarkers	Potential inflammatory/ immune phenotype	Candidate biomarkers	Emerging	Limited SLE/LN evidence; predominantly exploratory studies; uncertain reproducibility
DNA	Genomic and mitochondrial DNA	TLR9/cGAS-STING activation; interferon and inflammation	IFN/ inflammatory activation	Potential disease-mechanism	Emerging	EV specificity and biological attribution remain challenging; limited clinical biomarker validation
Lipids/ metabolites	Ceramides, phospholipids, sphingolipids	Membrane signaling, metabolism and inflammatory phenotyping	Metabolic/ inflammatory phenotypes	Molecular phenotyping	Emerging	Limited SLE/LN-specific clinical evidence; analytical standardization required

EVs mediate communication among immune, endothelial and renal cells. In SLE, disease-associated vesicles may transport self-derived nucleic acids and inflammatory mediators to pDCs and other immune cells, promoting type I interferon and chronic inflammation [9, 17, 24, 25]. In LN, vesicles from podocytes, tubular epithelial, mesangial and immune cells may contribute to renal injury, while urinary EVs provide a potential route for sampling renal molecular changes [26–29].

3.3 EV-mediated Immunopathogenesis

3.3.1 Innate and Adaptive Immunity

Innate immune dysregulation provides a mechanistic bridge between EV biology and lupus. EVs containing DNA, RNA, nucleoproteins or immune-complex-associated material can activate TLR7/TLR9–MyD88–IRF7 signaling and IFN-α production [9, 17, 25]. Macrophage- and NET-associated vesicles may reinforce inflammatory polarization,

complement activation and endothelial injury [20, 24, 30].

EVs also influence adaptive immunity through antigen presentation, co-stimulatory signaling and regulatory RNAs [16]. B-cell-derived vesicles can carry autoantigens and immunoglobulins, linking EV-associated cargo with autoreactive T- and B-cell responses [7, 9, 18]. These mechanisms provide a rationale for multi-analyte rather than isolated biomarkers.

Table 2. EV-associated pathways linking SLE/LN pathogenesis with potential biomarker relevance

Cell/source	Representative cargo/process	Pathogenic Function	Associated Clinical Phenotype	Potential Biomarker Meaning	Evidence Maturity	Major Limitations	References
pDCs	DNA/RNA; TLR7/TLR9 activation	Activation of innate nucleic-acid sensing and type I IFN responses	SLE inflammatory activity	Potential indicator of IFN-related inflammatory activity	Biological evidence relatively established; biomarker evidence emerging	EV-specific contribution difficult to isolate from broader nucleic-acid sensing	[9, 25]
Macrophages /monocytes	Cytokines, inflammatory proteins, miRNAs	Inflammatory activation and tissue injury	Systemic inflammation /tissue injury	Potential Inflammatory molecular signature	Preliminary / emerging	Cellular source may be heterogeneous; association does not establish EV-specific causality	[8, 9]
Neutrophils	NET-associated DNA, histones and inflammatory cargo	Vascular/endothelial injury and amplification of inflammatory and complement pathways	Vascular injury and LN-associated inflammation	Potential marker of inflammatory /vascular injury	Preliminary / emerging	Difficult to distinguish pathogenic cargo from secondary products of inflammation; limited clinical validation	[20, 24, 30]
Dendritic cells/T cells	MHC, co-stimulatory proteins, regulatory RNAs	Antigen presentation and modulation of adaptive immune activation	Autoimmune immune activation	Potential indicator of adaptive immune activity	Emerging	Mechanistic rationale exceeds clinical biomarker evidence	[8, 9]
B/plasma cells	Autoantigens, immunoglobulins, miRNAs	Autoantigen/immune-complex-associated immune activation and humoral responses	Autoantibody /immune-complex activity	Potential indicator of humoral immune activation	Emerging	Limited EV-specific clinical validation; cellular origin and specificity remain challenging	[8, 9, 18]

3.3.2 Inflammatory, Complement and Endothelial Pathways

Persistent SLE inflammation involves interconnected interferon, cytokine, complement, endothelial and renal pathways. EV-associated nucleic acids and regulatory RNAs can sustain IFN-I signaling, while protein/RNA cargo may influence TNF-α, IL-6, IL-1β, IL-17 and BAFF pathways [7, 9, 25]. Complement-associated and endothelial-derived EVs may amplify tissue injury [19-21].

An EV molecular signature may integrate several pathological processes, but association with disease activity does not establish EV-specific causality. A molecule may drive disease, reflect inflammation or represent secondary tissue

injury; causal inference requires longitudinal and mechanistic evidence [6, 9].

Biological function and clinical utility should therefore be assessed separately. Clinical biomarker development requires reproducible measurement, a clinically meaningful phenotype, comparison with established markers, external validation & demonstrated incremental utility [6].

3.4 EV-associated Protein Biomarkers and Proteomics

EV-associated proteins are attractive candidates because they are relatively stable and close to functional processes. LC–MS/MS, DIA-MS, proximity extension and multiplex platforms have identified altered proteins linked to inflammation, complement, coagulation, leukocyte migration, endothelial injury and renal involvement [21–23].

The field is shifting from single candidates toward coordinated signatures that may capture multiple pathways and distinguish SLE from controls or renal from non-renal disease [21,23]. However, differences in cohorts, EV preparation, platforms, normalization and statistics limit comparison, and few candidates have independent external validation.

Table 3. Analytical approaches for EV-associated protein biomarker discovery in SLE and LN

Biomarker/Analytical Approach	Sample Type	SLE/LN Phenotype Evaluated	Direction/ Output	Biological Information	Supporting Studies	Evidence Maturity Level	Major Limitations
LC–MS/MS proteomics	Plasma /serum/EV preparations	SLE and LN-associated molecular signatures	Differential protein abundance	Broad inflammatory, complement, coagulation, endothelial and tissue-injury pathways	Fan *et al.*, [21]; Schey et al. [22]	Preliminary / emerging	Discovery-oriented; heterogeneous EV preparations; relatively small cohorts; potential batch effects; limited external validation
DIA-MS	EV preparations	Comparative EV molecular signatures	Quantitative multi-protein profiles	Broad pathway-level characterization	Fan *et al.*, [21]	Preliminary / emerging	Platform and preprocessing differences; requires standardized normalization; clinical utility remains unestablished
PEA/multiplex protein assays	Plasma /serum/EV-associated material	Inflammatory and disease-associated phenotypes	Targeted protein signatures	High-sensitivity measurement of predefined inflammatory proteins	Chatzopoulos *et al.*, [23]	Preliminary / emerging	Restricted to selected targets; platform-specific effects; EV specificity may vary; limited independent validation
Pathway/omics integration	EV proteomic datasets ± clinical data	SLE/LN molecular phenotypes	Multi-protein/ pathway signatures	Integration of inflammatory, complement, endothelial and renal pathways	Fan *et al.*, [21]; Chatzopoulos *et a.*, [23]	Preliminary / emerging	High-dimensional data increase overfitting risk; biological association does not establish causality; clinical interpretability and reproducibility remain uncertain
Multi-analyte EV protein panels	Plasma /serum/urine EVs	SLE vs controls; renal vs non-renal disease	Composite molecular signature	Potential simultaneous representation of several disease pathways	Fan *et al.*, [21]; Chatzopoulos *et al.*, [23]	Preliminary / emerging	Few independently validated panels; heterogeneous populations and methods; incremental value over conventional biomarkers not adequately established

Complement- and endothelial-associated proteins are of particular interest because they relate to clinically relevant SLE/LN pathways. Their likely role is complementary to anti-dsDNA, C3/C4, proteinuria and histopathology rather than replacement; prospective studies must establish incremental value [19–22].

3.5 EV-associated microRNA Biomarkers

EV-associated miRNAs are 18-25-nucleotide regulators whose encapsulation protects them from degradation in serum, plasma and urine [7, 20, 26]. They influence TLR/NF-κB, type I interferon, cytokine, lymphocyte and fibrotic pathways [11, 17, 31–33]. Biological relevance is clear, but cohort and normalization variability limits translation into standardized assays.

Table 4. Critical appraisal of EV-associated miRNA candidates investigated as biomarkers in SLE and LN

Biomarker	Supporting studies	Sample Type	SLE/LN Phenotype	Direction of Change	Biological Pathway	Evidence Maturity Level	Major Limitations
miR-21	[7]	Serum/plasma EVs; urinary EVs	Increased in circulating EVs; increased in urinary EVs in association with renal chronicity/fibrosis	Direction may vary with disease state and treatment.	Immune activation; SP1/Smad3–TGF-β signaling; extracellular-matrix remodeling and fibrosis	Preliminary / emerging	Direction and magnitude may vary between cohorts; heterogeneous EV isolation and normalization; limited external validation; association with disease does not establish causality or clinical utility
miR-146a	[7, 31]	Serum/plasma EVs; urinary EVs	SLE; immune dysregulation and disease activity	Dysregulated	NF-κB and type I IFN regulation; IRAK1/TRAF6 signaling; negative-feedback control of innate inflammatio	Preliminary / emerging	Biological role is better established than its value as an EV biomarker; expression may depend on disease state and cellular source; lack of standardized clinical threshold and prospective validation
miR-155	[7, 32]	EVs/immune-cell-derived vesicles	Autoimmune inflammation; SLE-related immune activation	Often increased/pro-inflammatory	T-cell and macrophage activation; inflammatory signaling	Preliminary / emerging	Much of the evidence is mechanistic or disease-association based; limited evidence for EV-specific diagnostic performance; insufficient independent validation
miR-29c	[7, 33]	Urinary EVs	LN/renal injury; renal fibrosis	Reduced/dysregulated	TGF-β/Smad3 signaling; extracellular-matrix remodeling and renal fibrosis	Preliminary / emerging	Evidence is particularly dependent on renal context; normalization and urine concentration are important confounders; limited longitudinal and biopsy-linked validation
miR-451a	[7, 9]	Serum/plasma EVs	SLE disease activity and renal involvement	Reduced/dysregulated	Inflammatory and immune-regulatory pathways	Preliminary / emerging	Relatively limited independent evidence; inconsistent directionality across studies; unclear incremental value over conventional biomarkers
Multiple EV-miRNA signatures	[7, 17, 27, 29, 23]	Serum/plasma/urine EVs	SLE activity, LN and treatment/clinical response	Multiple dysregulated miRNAs	Association with IFN, TLR/NF-κB, cytokine, fibrosis and immune-regulatory pathways	Preliminary / emerging	Small and heterogeneous cohorts; differences in EV enrichment, RNA extraction and normalization; risk of overfitting; limited external validation; absence of standardized clinical cut-offs

miR-21, miR-146a, miR-155 and miR-29-family alterations illustrate the field: they are linked to immune activation, interferon regulation, inflammatory responses and renal fibrosis [7, 29, 31–33]. Most evidence remains associative, and no single EV-associated miRNA has consistently

demonstrated validated performance sufficient to replace conventional biomarkers.

Urinary EV miRNAs are particularly relevant to LN because urine may contain renal-cell-derived signals. Reported associations with disease activity, treatment response and fibrosis support kidney-focused liquid biopsy, but urine concentration, pre-analytical handling, isolation and normalization remain major sources of heterogeneity [27, 29].

3.6 Emerging Non-coding RNAs and multi-omics

EV-associated lncRNAs and circRNAs remain emerging candidates in SLE/LN, with evidence less mature than for miRNAs. Their likely value may be as components of integrated signatures rather than standalone biomarkers.

Multi-omics approaches combine proteins, regulatory RNAs, lipids/metabolites and clinical variables. Machine-learning methods may improve classification or prediction, but external validation is essential and high-dimensional discovery signatures must be reduced to reproducible, interpretable panels [21, 23].

3.7 Clinical Utility and Comparative Perspective

EV biomarker relevance should be judged by incremental information beyond established measures, not merely discrimination from healthy controls. Current LN assessment relies on proteinuria and renal function, anti-dsDNA and complement, with biopsy providing histopathological information [5]. These measures capture different dimensions of disease but do not directly provide a molecular readout of renal tissue.

The key question is whether an EV marker adds clinically useful information-for example, identifying active inflammation despite stable proteinuria/eGFR, distinguishing active lesions from chronic damage, predicting renal flare, characterizing histopathology or providing an earlier treatment-response signal. Association with proteinuria, eGFR, anti-dsDNA or complement alone is insufficient.

Proteins and miRNAs may provide complementary information: proteins can reflect downstream functional injury, while miRNAs capture regulatory activity. A parsimonious EV panel integrated with anti-dsDNA, C3/C4, proteinuria and eGFR should be considered only if it improves discrimination, calibration, longitudinal prediction or clinical utility over the conventional model.

3.8 Challenges and Future Directions

Translation remains limited by methodological, analytical, clinical and regulatory barriers. Table 5 summarizes the major challenges. The principal issue is heterogeneity in collection, enrichment, characterization, cargo extraction, normalization and reporting [6, 23].

Table 5. Major barriers and priorities for clinical translation of EV-based biomarkers in SLE and LN

Challenge	Why it matters	Priority solution
EV heterogeneity and inconsistent isolation [6, 21, 22]	Different preparations yield different molecular profiles	MISEV 2023-aligned characterization and standardized isolation
Small/cross-sectional cohorts [7, 9, 23]	Limited generalizability and uncertain longitudinal value	Large prospective multicentre cohorts
Analytical and normalization variability [6, 21–23]	Poor reproducibility across platforms	Harmonized workflows and reference standards
Limited external validation [29, 23]	Uncertain clinical utility	Independent validation and direct comparator studies
High-dimensional/single-marker approaches [21, 23]	Overfitting and limited biological coverage	Validated multi-analyte panels with clinical variables
Cost/technical complexity [21–23]	Limits routine adoption	Automated, scalable assays and point-of-care platforms
Regulatory/quality requirements [6, 21, 23]	Translation requires reproducible manufacturing/testing	Defined QC, reporting and regulatory frameworks

MISEV2023-aligned workflows, reference materials, standardized normalization and transparent reporting are needed. Future studies should be prospective, longitudinal and adequately powered, with direct comparison against anti-dsDNA, complement, proteinuria, serum creatinine & renal histopathology [3–5, 29].

Treatment-related confounding is an additional concern because immunosuppressive therapy

may influence EV abundance or cargo. For example, serum EV-associated miR-451a has been reported to increase following glucocorticoid and hydroxychloroquine treatment [29]. Changes in EV signatures after therapy may reflect disease improvement, direct pharmacological effects, or both.

Future studies should record treatment type, dose, duration and recent changes; use treatment-adjusted analyses; and sample longitudinally before and after therapy. Biomarkers should demonstrate associations with disease activity after accounting for immunosuppressive exposure rather than relying on treated-versus-healthy comparisons.

Emerging approaches—including single-vesicle analysis, microfluidics, nanosensors, digital immunoassays, spatial methods and AI-assisted multi-omics may improve analytical resolution. However, technological sophistication should not substitute for clinical validation; the endpoint is a reproducible assay that improves a clinical decision.

EVs link cellular origin with measurable molecular change. In SLE, vesicles carrying nucleic acids and inflammatory molecules may activate innate sensors and amplify interferon/cytokine responses; in LN, renal-cell-derived vesicles may generate more organ-focused urinary signatures [8,9,29]. Their biological breadth is an advantage, but also increases overfitting and susceptibility to population, medication, processing and platform effects [6, 23].

3.9 Renal and urinary EVs (uEVs): Specific Clinical Opportunity

LN is a key setting for EV biomarker development because urinary EVs may carry renal-cell-derived molecular signals. The clinical need is not simply LN classification, but non-invasive distinction of active versus inactive disease, reversible inflammation versus chronic damage, flare prediction and treatment response [5, 29].

Urinary EV-associated miRNAs and other RNAs have shown preliminary associations with LN activity and treatment response, but whether they distinguish active inflammation from chronic damage or predict flare before conventional markers remains unresolved.

Biopsy-linked evidence is particularly relevant. Urinary EV miR-21, miR-150 and miR-29c have been associated with renal chronicity, while urinary EV miR-146a has been associated with activity-related measures, histological features and subsequent flares [29]. These findings are promising but based on limited cohorts/subsets and do not establish a validated surrogate for renal histopathology.

Emerging urinary EV RNA studies have reported discriminatory signals between proliferative class III/IV and class V LN [27, 29]. The NIH activity index captures active inflammatory lesions, whereas the chronicity index captures irreversible features such as glomerulosclerosis, fibrous crescents, tubular atrophy and interstitial fibrosis. EV biomarkers should ideally distinguish these domains; current evidence remains preliminary.

Interstitial fibrosis/tubular atrophy are important targets because they represent chronic damage not fully captured by current inflammatory measures. Associations of urinary EV miR-21, miR-150 and miR-29c with chronicity/fibrotic phenotypes provide preliminary evidence of renal remodeling, but not independent quantification or causality.

Flare prediction and treatment monitoring are additional targets. Preliminary urinary EV miRNA findings suggest changes with renal flare and treatment response, but they do not yet demonstrate actionable lead time or improved treatment decisions. Prospective longitudinal studies with predefined endpoints are required.

Overall, urinary EVs have preliminary human evidence linking selected RNAs with disease activity, treatment response, renal chronicity and some histopathological measures, but they should not yet be regarded as surrogates for biopsy. Validation should address ISN/RPS class, NIH activity/chronicity, interstitial fibrosis/tubular atrophy, flares and treatment response, and test incremental value over proteinuria, creatinine, complement and anti-dsDNA.

A 2026 review of LN histopathology biomarkers also emphasized methodological limitations and

the limited number of candidates with evidence sufficient for potential clinical implementation [35].

3.10 Translational Roadmap

Translation can be organized into four stages: discovery of candidate signatures; targeted verification in independent samples; prospective multicentre clinical validation of discrimination, calibration, longitudinal prediction and incremental value; and implementation assessment of cost, reproducibility, regulatory requirements and clinical impact.

Standardization should accompany each stage through common EV definitions and preparation, minimum characterization, reference materials, normalization and transparent reporting. AI and high-dimensional methods should be externally validated and assessed for clinical usefulness, not accuracy alone [3,6,23].

4. CONCLUSION

EVs provide a biologically coherent link between disease mechanisms and minimally invasive biomarker discovery in SLE/LN. Proteomic and miRNA studies have identified candidate markers, and urinary EVs offer a potential kidney-focused liquid biopsy. However, no single EV biomarker has established replacement value over conventional assessment. Translation requires standardized methods, rigorous characterization, prospective multicentre validation, external replication and demonstration of incremental clinical benefit. EV-based biomarker research should therefore move from broad discovery toward validated, interpretable multi-analyte signatures that may eventually support more precise monitoring of SLE and LN.

AUTHOR CONTRIBUTIONS

Aarti Verma performed the literature search and drafted the manuscript. Jayanand contributed to conceptualization, supervision, and manuscript preparation. Vineeta Batra provided clinical interpretation and critically revised the manuscript. All authors reviewed and approved the final version.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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ETHICAL STATEMENT

This study is based solely on previously published literature and does not involve human participants or animal subjects.

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