Prognostic and Diagnostic Values of Novel Serum and Urine Biomarkers in Lupus Nephritis: A Systematic Review

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Keywords

Lupus nephritis · Systemic lupus erythematosus · Biomarker · Urinary · Serological · Systematic review

Abstract

Introduction: While renal biopsy remains the gold standard for diagnosing lupus nephritis (LN), the prognostic and diagnostic role of non-invasive biomarkers for LN is currently debated. **Methods:** Available studies published in last 5 years (2015–2020) assessing the diagnostic and prognostic value of urinary and/or serological biomarkers in subjects with LN were analyzed in this systematic review. **Results:** Eighty-five studies were included (comprehending 13,496 patients with systemic lupus erythematosus [SLE], 8,872 LN, 487 pediatric LN, 3,977 SLE but no LN, 160 pediatric SLE but no LN and 7,679 controls). Most of the studies were cross-sectional (62; 73%), while 14 (17%) were prospective. In sixty studies (71%), the diagnosis of LN was biopsy-confirmed. Forty-four out of 85 (52%) investigated only serological biomarkers, 29 studies (34%) tested their population only with urinary biomarkers, and 12 (14%) investigated the presence of both. Outcome measures to assess the clinical utility of the analyzed biomarkers were heterogeneous, including up to 21 differ-

ent activity scores, with the SLEDAI (in 60%) being the most used. Despite some heterogeneity, promising results have been shown for biomarkers such as urinary monocyte chemoattractant protein, urinary adiponectin, and urinary vascular cell adhesion protein 1. **Discussion/Conclusion:** While serum and urine biomarkers have the potential to improve diagnostic and prognostic pathways in patients with LN, the vast heterogeneity across studies severely limits their applicability in current clinical practice. With the kidney biopsy still representing the gold standard, future efforts should focus on harmonizing study inclusion criteria and outcomes, particularly in clinical trials, in order to improve comparability and facilitate the implementations of available biomarkers into the daily practice.

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Significance Statement

While kidney biopsy is crucial for lupus nephritis (LN) diagnosis, the identification of one or more non-invasive biomarkers (serological or urinary) is highly needed. Potentially, the study of novel biomarkers may be useful to provide further information on LN: mainly the degree of

disease activity, early recognition of renal flares, guide treatment selection, and responsiveness to the therapy. In this systematic review, we analyzed 85 studies comprehending 13,496 patients with systemic lupus erythematosus (SLE) and 8,872 with LN. Despite some heterogeneity, promising results have been shown for biomarkers such as urinary monocyte chemoattractant protein, urinary adiponectin, and urinary vascular cell adhesion protein 1. This could pave the way to a new era of precision medicine in the treatment and management of LN, ultimately improving the prognosis of patients.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of autoantibodies directed against nuclear components (e.g., anti-dsDNA, anti-SSA/Ro, anti-SSB/La, anti-Sm, and anti-RNP) and soluble mediators. The binding of these autoantibodies to their antigens generates immune complexes that can be deposited and can damage different organs, causing a wide variety of clinical manifestations [1]. The kidney is one of the main organs affected (50–80% of SLE patients), and its involvement, LN, represents a major cause of morbidity and mortality in SLE patients [2, 3]. Several events, such as complement activation, aberrant apoptosis, and genetic predisposition, concur in the loss of self-tolerance that leads to these autoantibody production and immune complex deposition, thus supporting LN development and progression [4–6].

Despite the presence of guidelines regarding diagnosis and management, standard-of-care immunosuppression can fail and LN can progress to end-stage renal disease within 5 years after the onset [7].

Renal biopsy, an invasive procedure, is the gold standard for the diagnosis of LN and to determine the degree of glomerular, tubular, vascular, and interstitial involvement [8]. Similarly, its utility in guiding the choice of one immunosuppressive therapy over another is still limited [9]. This is made more difficult by the high degree of heterogeneity existing among patients with SLE. Alterations in specific pathways, and in this case in immune pathways, can contribute more than others to the development and progression of the disease in a certain patient. The use of biomarkers seems to be a valuable approach to overcome these issues.

Biomarkers represent biological characteristics that can be evaluated as indicators of physiological processes, pathological processes, or responsiveness to therapy [10]. The

conventional prognostic and diagnostic biomarkers for LN include primarily proteinuria [11], as well as elevated levels of serum creatinine, hematuria, urinary cellular casts, anti-double-stranded DNA, and complement levels.

Recently, we have experienced a growing body of evidence investigating the potential prognostic and diagnostic role of genetic polymorphisms and protein detectable in serum and/or urine samples to guide the management of LN [12]. Among the latter ones, there are proteins involved in the immune response, such as cytokines, chemokines, and complement factors and other proteins highly expressed by the glomerular and tubular injured cells, such as adhesion molecules and growth factors [13, 14].

Thus, while a kidney biopsy is crucial for LN diagnosis, the identification of one or more biomarkers would be useful to provide further information on the degree of disease activity, early recognition of renal flares, guide treatment selection, and responsiveness to the therapy. Ideally, the future goal would be the development of specific approaches for each patient as we are experiencing in the field of oncology in the era of precision medicine. The aim of this systematic review was to study the clinical utility of serological and urinary biomarkers that have been investigated in the field of LN in the last 5 years.

Methods

A detailed literature search has been developed a priori to identify articles that reported findings from clinical and laboratory studies that analyzed the prognostic role, diagnostic role, and the role in the evaluation of the therapy response of biomarkers (either urinary of serological) in patients with SLE and LN. Keywords and subject terms included (“lupus nephritis” [MeSH Terms] OR (“lupus” [All Fields] AND “nephritis” [All Fields]) OR “lupus nephritis” [All Fields]) AND (“biomarkers” [MeSH Terms] OR “biomarkers” [All Fields]) AND (“April 25, 2015” [PDat]: “April 22, 2020” [PDat])). The search strategy was applied to Ovid MEDLINE, In-Process and Other Non-Indexed Citation and Ovid MEDLINE for the last 5 years (from July 2015 to 2020). Abstracts from EULAR and ACR/ARHP Annual Meetings (2015–2020) were screened and included in the analysis when meeting the inclusion criteria and not replicating studies published elsewhere.

Inclusion criteria of the studies were as follows:

1. Studies that included at least 50 SLE patients of which at least 25 were LN sufferers.
2. Urinary and/or serological testing of novel* biomarkers.

Studies that met the inclusion criteria were systematically analyzed by 2 independent reviewers (M.R. and P.M.). Disagreements were resolved by consensus; if consensus could not be achieved, a third party (S.S.) would provide an assessment of eligibility. As the data on eligibility were dichotomous (eligible: yes/no), agreement

Table 1. Report of the studies included in the systematic review (for list of references, see online suppl. material)

Year	First author	Design	LN patients, <i>n</i>	Activity scores used	Controls, <i>n</i>	Biomarker tested	Urinary/serological	Response/prognosis/diagnosis
2020	Mejia-Vilet et al. [S1]	LG + CS	249 (CS); 116 (LG) (active)	ACR criteria	101	Soluble CD163	Urinary	Response/prognosis
2020	Fasano et al. [S2]	PR + CS	61 (total); 8 patients with renal flare at FU, 33 patients with previous LN	ACR criteria, SLEDAI	0	VCAM-1; ICAM-1; MCP-1; NGAL; LPGDS	Urinary	Response/prognosis
2020	Zhang et al. [S3]	CC	109 (35 active, 58 inactive)	UK	74	miR-203	Serological	Diagnosis/prognosis
2020	Bedair et al. [S4]	CS	27	SLEDAI, SLICC/ACR DI, SLICC RAS	43	Uromodulin	Urinary	Diagnosis/prognosis
2020	Dierckx et al. [S5]	CC	36	SLEDAI 2K, urinary protein/creatinine ratio	149	Glycoproteinacetylation	Serological	Response/prognosis
2019	Bona et al. [S6]	CS	65 (34 active, 31 inactive)	SLEDAI	20	Oxidative stress biomarkers	Serological and urinary	Response/prognosis
2019	Fayed et al. [S7]	CC	50	SLICC/ACR DI, SLEDAI, AI + CI	100	Sclerostin	Serological	Response/prognosis
2019	Abediazar et al. [S8]	CC	25 (23 active)	SLEDAI, AI	64	CXCL10 and vitamin D	Serological	Response/prognosis
2019	Parodis et al. [S9]	CS	30 (11 active)	Renal BILAG, SLEDAI 2K, SLICC/ACR DI	178	ALCAM and VCAM-1	Urinary	Response/prognosis
2019	Torres-Salido et al. [S10]	CS	70 (active)	SLEDAI 2K, AI + CI	75	Urinary neutrophilin-1	Urinary	Response/prognosis
2019	Zhao et al. [S11]	CS	33	rSLEDAI, SLEDAI	147	Galectin-3	Serological	Response
2019	Qin et al. [S12]	CS	113 (89 active, 24 inactive)	rSLEDAI, SLEDAI, SLICC RAS	86	d-dimer, plasmin, TF, and TFPI	Urinary	Prognosis
2019	Nordin et al. [S13]	CS	85 (29 active)	SLEDAI 2K, BILAG 2004	35	IL-17A	Serological and urinary	Prognosis
2019	Stutthet et al. [S14]	PR + CS	110 (active)	SLEDAI 2K, AI + CI	0	TWEAK	Urinary	Response
2019	Lee et al. [S15]	CS	39 (42)	SLEDAI 2K, BAI, BCI	30	Immunoglobulin binding protein 1	Urinary	Diagnosis/response
2019	Adhya et al. [S16]	CS	67 (21 active, 46 inactive)	SLEDAI	20	MCP-1; RANTES; sTNF-R1; IP-10 MIP-1a; VEGF; MIP-1a	Serological and urinary	Prognosis
2019	El-Ghoneimy et al. [S17]	CS	35 pLN	SLEDAI, rSLEDAI, SLICC/ACR DI	65	NETs; Nox2	Serological	Diagnosis/prognosis
2019	Dedong et al. [S18]	PR + CS	80 (37 active, 43 inactive)	SLEDAI, AI + CI	20	IL17, IL23	Serological	Response/prognosis
2019	Hossny et al. [S19]	CS	37 (29 active) pLN	SLEDAI	63	HMGB-1	Serological	Diagnosis
2019	Huang et al. [S20]	CS	29	SLEDAI 2K	185	Anti-ENO1 combined with β 2 microglobulin	Serological	Diagnosis
2019	Kang et al. [S21]	CS	79	SLEDAI 2K, AI + CI	0	Anti-ribosomal P antibody	Serological	Prognosis
2019	Garcia-Vives et al. [S22]	CS	98 (active)	SLEDAI 2K, rSLEDAI, SLICC/ACR DI, AI + CI	160	a-PLA2R	Serological	Prognosis
2019	Parodis et al. [S23]	CS	52 (active)	SLEDAI 2K, AI + CI	20	Axl	Serological	Response
2019	Kitagawa et al. [S24]	CS	118 (active)	SLEDAI, rSLEDAI, BAI	154	CD11b and CD16b	Urinary	Prognosis
2019	Wirestam et al. [S25]	PR + CS	75	SLEDAI 2K, clinical SLEDAI, SLICC/ACR DI	269	Osteopontin	Serological	Prognosis
2019	Li et al. [S26]	PR + CS	54	UK	36	Polyomavirus BK, BKV microRNA, and NGAL	Urinary	Prognosis

Table 1 (continued)

Year	First author	Design	LN patients, <i>n</i>	Activity scores used	Controls, <i>n</i>	Biomarker tested	Urinary/serological	Response/prognosis/diagnosis
2018	Gong et al. [S27]	CS	68	SLEDAI, AI + CI	54	sMer, sAxl, and GAS6	Serological	Prognosis
2018	Pacheco-Lugo et al. [S28]	CS	80	SLEDAI, rSLEDAI	40	39 cytokines using Luminex xMAP technology	Serological	Diagnosis
2018	Khoshmirisafa et al. [S29]	CS	30 (15 active, 15 inactive)	SLEDAI 2K, ACR criteria	55	miR family	Serological	Diagnosis/prognosis
2018	Vincent et al. [S30]	CS	31 (18 active, 13 inactive)	SLEDAI 2K, rSLEDAI, SLICC/ACR DI	153	BAFF	Urinary	Diagnosis
2018	Ouyang et al. [S31]	CS	30	SLEDAI 2K, rSLEDAI	82	Expression of circRNAs	Serological	Diagnosis
2018	Brunner et al. [S32]	PR + CS	89 (14 active) pLN	SLEDAI 2K, rSLEDAI, SLICC/ACR DI, AI + CI	0	AdipoQ, ceruloplasmin, KIM-1, NGAL, osteopontin, TGF- β , Vit-BP, LfABP, transferrin	Urinary	Prognosis
2018	Ding et al. [S33]	CS	109	SLEDAI, AI + CI	50	KIM-1; NGAL; MCP-1	Urinary	Prognosis
2018	Go et al. [S34]	CS	62 (21 active)	SLEDAI	59	Vit-BP, TTR, RBP4, PTGDS	Urinary	Prognosis
2018	Wang et al. [S35]	CS	156 (125 active, 31 inactive)	ACR criteria, AI	91	Acnp30; sICAM-1; NCAM-1; CD26	Urinary	Prognosis
2018	Mende et al. [S36]	CS	58	SLEDAI 2K, rSLEDAI	178	IL-1 β and IL-18	Serological	Diagnostic/prognostic
2018	Zhang et al. [S37]	CS	101	SLEDAI	100	microRNA-200 family	Serological	Diagnostic/prognostic
2018	Ren et al. [S38]	PR + CS	44	SLEDAI	30	HE4	Serological	Diagnostic
2018	Dong et al. [S39]	CS	39	SLEDAI, rSLEDAI	30	MCP-1; TWEAK	Urinal	Prognosis
2018	Pedersen et al. [S40]	CS	34 (30 active)	UK	24	Renal DNase I	Urinary	Prognosis
2018	He et al. [S41]	CS	80 (45 active and 35 inactive) 80 (45 active and 35 inactive)	SLEDAI 2K	40	IL-35	Serological	Diagnosis
2018	El Shahawy et al. [S42]	CS	50 (active)	ACR criteria, rSLEDAI, AI + CI	40	NGAL	Urinary	Prognosis
2018	Wu et al. [S43]	CS	60 (55 active) pLN	SLEDAI 2K, AI + CI + GI + TI	51	β 2M; KIM-1; MCP-1; IL 18; NGAL; TFF3; osteopontin; GST- π	Urinary	Diagnosis/prognosis
2018	Hardt et al. [S44]	CS	148 (41 active) LN	SLEDAI 2K, SLAM, SLICC/ACR DI, BILAG	563	Anti-MDA Ab	Serological	Diagnosis/prognosis
2018	Zhang et al. [S45]	LG + CS	34 (baseline); 40/81 (after FU)	SLEDAI	165 (baseline)/ 133 (after FU)	CD25	Serological	Prognosis
2018	Dong et al. [S46]	CS	48 (active)	SLEDAI, rSLEDAI, BAL, BCI	42	MCP-1; TWEAK	Urinary	Prognosis
2018	Mok et al. [S47]	CS	80 (active)	SELENA-SLEDAI, rSLEDAI, PGA	200	Angiostatin; CXCL4; VCAM-1	Urinary	Diagnosis/prognosis
2017	Martin et al. [S48]	LG + CS	45 (CS); 69 (LG)	SLEDAI, SLEDAI 2K	130 (CS); 112 (LG)	C4d	Serological	Prognosis
2017	Živković et al. [S49]	CS	27 (5 active)	SLEDAI, ACR criteria	75	MCP-1	Serological and urinary	Diagnosis/prognosis
2017	Soliman et al. [S50]	CS	54 (active)	SLEDAI, BAL, BCI	N	Angiostatin; VCAM-1	Urinary	Prognosis
2017	Turnier et al. [S51]	LG serum LG urine CS serum CS urine	47 cLN 39 cLN 41 active cLN 52 active cLN	SLEDAI 2K, rSLEDAI	103	S100 proteins	Serological and urinary	Prognosis

Table 1 (continued)

Year	First author	Design	LN patients, <i>n</i>	Activity scores used	Controls, <i>n</i>	Biomarker tested	Urinary/serological	Response/prognosis/diagnosis
2017	Collard et al. [552]	CS	36 (active)	SLEDAI	213	Anti-ficolin-2 Ab	Serological	Prognosis
2017	Diaz-Rizo et al. [553]	CS	30 (active)	SLEDAI, rSLEDAI	73	Leptin; adiponectin	Serological	Prognosis
2017	Aggarwal et al. [554]	PR + CS	44 (active)	SLEDAI, rSLEDAI	44	HAP; RBP; ACT	Serological and urinary	Diagnostic
2017	Brunner et al. [555]	PR + CS	87 (74 active) cSLE	rSLEDAI, rBILAG, AI + CI, microalbumin/creatinine ratio	0	NGAL; ceruloplasmin; KIM-1; MCP-1; adiponectin; hemoexin; AGP; cystatin C; heparin; LFGDS; LFABP; osteopontin; TGF- β ; transferrin; VDBP	Urinary	Response
2017	Cardenas-Gonzalez et al. [556]	CS	175 (active)	UK	186	365 different MIRNAs	Urinary	Prognosis
2017	Jakuszko et al. [557]	CS	74 (49 active)	SLEDAI, rSLEDAI	91	Anti-mCRP	Serological	Response/prognosis/diagnosis
2017	Satrapoj et al. [558]	CS	68 (active)	SLEDAI, rSLEDAI, AI + CI	0	NGAL	Urinary	Response
2017	Stratigou et al. [559]	CS	30 (19 active)	SLICC RAS, SLEDAI, BILAG, rBILAG	20	SLAMF; CD4; CD8	Serological	Prognosis
2017	Xue et al. [560]	CS	31 (active)	ACR criteria	150	DKK-1	Serological and urinary	Diagnostic
2017	Turner-Stoke et al. [561]	CS	254	UK	0	ANCA	Serological	Prognosis
2016	Zaixing Yang et al. [562]	CS	138	SLEDAI	177	HE4	Serological	Diagnostic
2016	Ahn Sung Soo et al. [563]	CS	149	SLEDAI	0	Anti-SM	Serological	Prognosis
2016	Ding et al. [564]	CS	85 (66 active)	SLEDAI, rSLEDAI, AI + CI	38	IGFBP-4	Serological	Prognosis
2016	Gupta et al. [565]	LG	121 (58 active)	SLEDAI, rSLEDAI	123	MCP-1	Serological and urinary	Prognosis
2016	Kitagori et al. [566]	CS	29	SLEDAI, AI + CI	77	Osteopontin	Serological and urinary	Prognosis
2016	Lan et al. [567]	PR + CS	178	SLEDAI, AI + CI	0	MCP-1; fractalkine; RAGE	Serological and urinary	Diagnosis/response
2016	Landolt et al. [568]	CS	Discovery 60 (active) Validation 66 (33 active) Discovery 60 (active) Validation 66 (33 active)	SLEDAI 2K, rSLEDAI 2K SLEDAI 2K, rSLEDAI 2K	Discovery 49 Validation 16 Discovery 49 Validation 16	128 different proteins	Urinary	Diagnosis
2016	Li et al. [569]	PR + CC	1,814	SLEDAI, AI + CI	0	ANCA	Serological	Prognosis/response
2016	Loghman et al. [570]	CS	25	SLEDAI	25	Adiponectin	Urinary	Diagnosis
2016	Ding et al. [571]	CS	187 (71 active)	SLEDAI, AI + CI	0	Albumin	Urinary	Prognosis
2016	Navarro-Quiroz et al. [572]	CS	100	SLEDAI	80	MicroRNAs	Serological	Diagnosis
2016	Jog et al. [573]	CS	32 (active)	SLEDAI, rSLEDAI, SELENA-SLEDAI	37	HMBG-1	Urinary	Prognosis
2016	Pang et al. [574]	PR + CS	210 (discovery) 130 (validation) 210 (discovery) 130 (validation)	SLEDAI, AI + CI	230	Anti-A08-C1q	Serological	Prognosis

Table 1 (continued)

Year	First author	Design	LN patients, <i>n</i>	Activity scores used	Controls, <i>n</i>	Biomarker tested	Urinary/serological	Response/prognosis/diagnosis
2016	Pang et al. [575]	CS	213 (discovery) 75 active (validation) 213 (discovery) 75 active (validation)	SLEDAI, AI + CI	163	Pentraxin 3	Serological and urinary	Prognosis
2016	Parodis et al. [576]	PR + CS	64 LN	SLEDAI 2K, AI + CI	314	sTNFR2	Serological	Prognosis
2016	Plawewski et al. [577]	CS	36 (active)	SLEDAI, AI	177	Anti-ficolin-3 Ab	Serological	Diagnosis
2016	Tyden et al. [578]	CS	35 (active)	SLEDAI 2K, ACR criteria	165	S100 family	Serological	Diagnosis
2016	Vadasz et al. [579]	CS	57 (35 active)	SLEDAI, AI + CI	242	sCD72	Serological	Diagnosis/prognosis
2016	Wu et al. [580]	CS	86 (68 active)	SLEDAI, rSLEDAI, AI + CI	43	IGFBP-4	Serological	Prognosis
2016	Wu et al. [581]	CS	154 (76 active)	SLEDAI, rSLEDAI, AI + CI	71	PGRN	Serological and urinary	Diagnosis/prognosis
2015	Pesickova et al. [582]	PR + CS	57 (46 active)	SLEDAI, AI	112	Anti-CRP-Ab	Serological	Prognosis
2015	Qi et al. [583]	CS	67 (32 active)	SLEDAI 2K, rSLEDAI	35	Renalase	Serological	Prognosis
2015	Chi et al. [584]	CS	35	SLEDAI, ACR criteria	74	Anti-Clq	Serological	Diagnosis/prognosis
2015	Cheng et al. [585]	PR + CS	40	SLEDAI, AI + CI	156	HNP	Serological	Diagnosis

Design: LN, lupus nephritis; pLN, pediatric LN; CS, cross-sectional; CC, case-control; PR, prospective; LG, longitudinal. Activity scores: SLEDAI, systemic lupus erythematosus activity index; rSLEDAI, renal SLEDAI; renal SLEDAI, ACR, American College of Rheumatology; AI, activity index; CI, chronicity index; GI, glomerular index; TI, tubulointerstitial index; SLICC, Systemic Lupus International Collaborating Clinics; SLICC RAS, Systemic Lupus International Collaborating Clinics Renal Activity Score; ESSDAI, The European League Against Rheumatism SS disease activity index; SLAM, systemic lupus activity measure; SELNA, Safety of Estrogens in Lupus Erythematosus National Assessment; PGA, physician's global assessment; RAIL, renal activity index in lupus. Biomarkers: a-A08-Clq ab, anti-A08-Clq antibodies; ACT, alpha-1 anti-chymotrypsin; AdipoQ, adiponectin; AGP, alpha-1-acid glycoprotein; a-mCRP, antibodies against monomeric C-reactive protein; anti-CRP-Ab, autoantibodies against monomeric C-reactive protein; anti-ENO1, anti-endothelial nitric oxide synthase; aFCN1, anti-ficolin-2 autoantibodies; BAFF, B-cell activating factor; BK virus, human polyomavirus; ICST3, cystatin C; CP, ceruloplasmin; Gal-3, galectin-3; GAS6, growth arrest-specific protein 6; GlycA, glycoprotein acylation; GST- π , glutathione S-transferase π ; HAP, haptoglobin; HE4, human epididymis protein 4; HMGB-1, high-mobility group box-1; HNP1-3, human neutrophil peptides 1–3; IGBP-1, immunoglobulin-binding protein 1; IgG anti-MDA, IgG anti-malondialdehyde protein; IGFBP-2, insulin-like growth factor-binding protein-2; LEP, leptin; LF-ABP, liver fatty acid-binding protein; LFGDS, lipocalin-type prostaglandin D synthase; MCP-1, monocyte chemoattractant protein 1; NETs, neutrophil extracellular traps assay; Nox2, NADPH oxidase; NR1P1, neuropilin-1; OPN, osteopontin; OFN-N, N-terminal fragment of the osteopontin; PGDS, prostaglandin D synthase; PGRN, progranulin; PTX3, pentraxin 3; RAGE, receptor for advanced glycation end products; RBP4, retinol binding protein 4; SLAM, signaling lymphocyte activation molecule; sICAM-1, soluble intercellular cell adhesion molecule; SOD, superoxide dismutase; SOST, sclerostin; sTNFR2, soluble tumor necrosis factor receptor-2; TF, tissue factor; TFF3, trefoil factor 3; TFP1, tissue factor pathway inhibitor; TTR, transthyretin; TWEAK, TNF-like weak inducer of apoptosis; UMOD, uromodulin; Vit-D BP, Vit-D binding protein; VCAM-1, vascular cell adhesion protein 1.

Table 2. Summary of the activity scores used in the studies included in the systematic review (for list of references, see online suppl. material)

Score	Full name	Reference	Studies using the score, <i>n</i> (%)
SLEDAI	Systemic lupus erythematosus disease activity index	[S86]	51 (60)
AI	Activity index	[S87]	31 (36.47)
rSLEDAI	Renal systemic lupus erythematosus disease activity index	[S64]	27 (31.76)
CI	Chronicity index	[S87]	26 (30.58)
SLEDAI 2K	Systemic lupus erythematosus disease activity index 2000	[S88]	25 (29.41)
ACR criteria	American College of Rheumatology criteria	[S89]	9 (10.58)
SLICC/ACR DI	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Criteria Damage Index	[S90]	9 (10.58)
UK	Unknown		5 (5.88)
BAI	Biopsy activity index	[S91]	4 (4.70)
BCI	Biopsy chronicity index	[S91]	3 (3.53)
rBILAG	Renal British Isles Lupus Assessment Group	[S9]	3 (3.53)
SLICC RAS	The Systemic Lupus International Collaborating Clinics Renal Activity Score	[S92]	3 (3.53)
BILAG	British Isles Lupus Assessment Group	[S93]	2 (2.35)
SELENA-SLEDAI	Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLEDAI	[S94]	2 (2.35)
GI	Glomerular index	[S87]	1 (1.17)
TI	Tubulointerstitial index	[S87]	1 (1.17)
BILAG 2004	British Isles Lupus Assessment Group 2004	[S95]	1 (1.17)
SLAM	Systemic lupus activity measure	[S96]	1 (1.17)
PGA	Physician's global assessment		1 (1.17)
Urinary protein/creatinine ratio			1 (1.17)
Microalbumin/creatinine ratio			1 (1.17)

at both the title and abstract review and the full article review stages was determined by calculation of Cohen's kappa coefficient ($k = 0.9$). The literature search strategy is shown in online suppl. Fig. 1S (see www.karger.com/doi/10.1159/000517852 for all online suppl. material).

The present study has been performed according to PRISMA guidelines [15]. Studies that tested only the presence of serological or urinary biomarkers that are recommended in the current guidelines [16, 17] for LN were excluded.

Results

Data from 13,496 SLE patients included in 85 retrieved studies were analyzed (references of the included studies are available in the online suppl. material as "online suppl. references"). The retrieved studies had different designs and varying sample sizes. Table 1 displays the main characteristics of the studies included in the analysis, the enrolled populations, study design, activity scores used, studied biomarker, and the role of the latter.

When considering the populations included in the studies that met the inclusion criteria of the systematic review, a total of 8,872 patients with SLE and LN (1,573 patients with active LN, 2,906 with inactive LN, and

4,393 cases in which the activity of LN was not addressed in the study) and a total of 487 pediatric patients with SLE and LN were analyzed. As controls, a total of 3,977 patients with SLE but no LN were included, as well as 160 pediatric patients with SLE and without renal involvement. Totally, the studies included 7,679 controls, comprehending 2,457 healthy donors, 268 patients with glomerulopathies but not LN, 154 patients with autoimmune conditions but not SLE, and 34 patients with diabetic nephropathy.

When focusing on study design, 62 studies used a cross-sectional approach, 14 studies were prospective, 4 studies were case-control, 4 studies were longitudinal and cross-sectional, and 1 study was longitudinal. Considering the definition of LN, renal biopsy was used as a gold standard in 60 studies (71%), while in 9 studies (11%), histological confirmation was not performed, in 9 studies (11%), the information on renal biopsy could not be retrieved [18–25], and in 7 studies (8%), renal biopsy was performed only in a subgroup of the investigated SLE patients included in the analysis.

When focusing on the tool used to assess activity of LN, 21 different activity scores have been used in the analyzed studies, as summarized in Table 2. In particular,

Table 3. Combinations of activity scores used in the studies included in the systematic review.

Scores used, <i>n</i>	Type of scores primarily used	Studies, <i>n</i> (%)	
1	SLEDAI	12 (75)	16 (18.82)
	ACR criteria	2 (12.5)	
	SLEDAI 2K	2 (12.5)	
2	SLEDAI + rSLEDAI	7 (29.17)	24 (28.23)
	SLEDAI 2K + rSLEDAI	5 (20.83)	
	SLEDAI + AI	3 (12.5)	
	SLEDAI + ACR criteria	3 (12.5)	
	Other combinations	6 (25)	
3	SLEDAI + AI + CI	11 (40.74)	27 (31.77)
	SLEDAI 2K + AI + CI	5 (18.52)	
	Other combinations	11 (40.74)	
4	9 different combinations	9 (10.6)	
5	4 different combinations	4 (4.7)	
UK	UK	5 (5.88)	

SLEDAI, systemic lupus erythematosus activity index; rSLEDAI, renal SLEDAI; SLEDAI 2K, SLEDAI 2000; ACR, American College of Rheumatology; AI, activity index; CI, chronicity index.

the most used resulted to be systemic lupus erythematosus activity index – SLEDAI (51 studies out of 85 = 60%), activity index – AI (31 out of 85 = 36.47%), renal Systemic Lupus Erythematosus Activity Index – rSLEDAI (27 out of 85 = 31.76%), chronicity index – CI (26 out of 85 = 30.58%), and Systemic Lupus Erythematosus Activity Index 2000 – SLEDAI 2K (25 out of 85 = 29.41%). Moreover, the majority of the studies (69 out of 85 = 81.18%) combined the use of >1 score. More details about their combination are shown in Table 3.

When analyzing the novel biomarkers, 44 out of 85 (52%) investigated only serological biomarkers, while 29 studies (34%) tested their population only with urinary biomarkers. Moreover, 12 studies (14%) investigated the presence of novel biomarkers in both urine and blood. Interestingly, 5 studies (6%) tested the investigated biomarkers (serological or urinary) also on the renal biopsy specimens. Last, regarding the clinical utility of the biomarker, 59 studies tested the biomarkers to evaluate the activity and long-term prognosis/renal outcome of LN, 36 studies tested the biomarkers during the diagnostic process, and 14 studies tested the biomarkers in correlation with response to therapy.

Table 4 resumes the serological and urinary biomarkers investigated in the studies included in the systematic review. The most researched biomarkers are discussed separately.

Monocyte Chemoattractant Protein-1 (MCP-1)

MCP-1 has been used as biomarker in 18 (21%) of the included studies. In particular, in 13 studies (15%), it has been analyzed in urine samples, and in 5 studies (6%), it has been analyzed in serum samples. MCP-1 belongs to the C-C chemokine family. Even if it is produced by many cell types, it is mainly expressed by activated monocytes/macrophages, T cells, and natural killer cells and takes part in leukocyte infiltration to the kidney [26]. This and the observation that its antagonist can ameliorate the induction and progression of LN in transgenic mouse model [27], make it one of the most used biomarkers when considering LN. As shown in online suppl. Table 1S, while 7 out of 13 studies found a potential diagnostic or prognostic role for this marker in the context of LN, still a certain level of disagreement exists. In fact, 5 studies out of 13 reported an association between the presence of the increased level of this biomarkers and LN. When looking at its prognostic role using renal disease activity as an outcome, 3 studies showed a negative correlation with MCP-1 and 8 demonstrated a positive correlation (2 studies did not investigate upon this aspect). Further prospective analyses are needed to the additional value, ideally as both diagnostic and prognostic perspectives.

Table 4. Serological and urinary biomarkers investigated in the studies included in the systematic review (for list of references, see online suppl. material)

Urinary Vascular Cell Adhesion Protein 1 (VCAM-1)

VCAM-1 has been used as a urinary biomarker in 5 of the analyzed studies (6%). It represents an adhesion molecule that is involved in the recruitment of inflammatory cells by its interaction with infiltrating leukocytes. Its soluble levels appear elevated in autoimmune disease, such as SLE and rheumatoid arthritis. Moreover, when considering SLE patients, it has been demonstrated an even more pronounced increase of urinary VCAM-1 in patients with LN [28]. Details are shown in Table 3. When compared to other biomarkers, albeit limited in numbers, available studies seem to show a good level of consistency in supporting its role as a potential marker in LN.

Urinary Adiponectin (AdipoQ)

AdipoQ has been used as a urinary biomarker in 5 of the analyzed studies (6%). It is a small adipocytokine presenting both anti- and pro-inflammatory functions. When considering patients suffering from LN, and in particular active LN, adiponectin results to be highly expressed in glomeruli and renal tubules and shows an increase of its urinary levels, not found in SLE patients without renal involvement [29, 30].

Urinary Kidney Injury Molecule-1 (Kim-1)

Kim-1 has been used as a urinary biomarker in 5 of the included studies (6%). It is a transmembrane protein of proximal tubule cells whose expression is strongly upregulated during tubule damage. Recent studies highlighted an increase of Kim-1 urinary levels in the presence of active LN and then a new decline during the remission phase [31].

Urinary TNF-Like Weak Inducer of Apoptosis (TWEAK)

Urinary levels of TWEAK have been analyzed in 5 of the included studies (6%). This protein belongs to the TNF receptor superfamily. It plays a role in chronic inflammation and, in particular, shows a close correlation with renal inflammation. Also in this case, its urinary levels seem to be markedly elevated during the active phase of LN and to undergo a decrease during the remission phase [26].

Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL has been used as a urinary biomarker in 8 of the analyzed studies (9.5%). It is a soluble protein secreted during conditions of stress and inflammation by leukocytes and tubular epithelial cells. Several studies high-

lighted how NGAL can help predicting acute kidney injury and that high urinary levels can be detected among SLE patients suffering from LN [21]. However, 3 out of 8 retrieved studies analyzing the clinical accuracy of NGAL did not report any conclusive results.

Discussion/Conclusion

To date, the gold standard for diagnosing LN remains renal biopsy. The histological findings not only are fundamental for diagnosis but also guide treatment options [32]. From this perspective, some considerations are worth noting. First, kidney biopsy is overall a safe procedure if performed in experienced centers, even in patients with autoimmune diseases [8]. Second, the use of protocolized repeated biopsy is currently debated, and an international study is currently ongoing [33]. Available evidence is suggesting that the per-protocol repeating of kidney biopsy might provide the treating physicians with critical information to further guide the management (e.g., by assessing the degree of glomerular sclerosis and/or histological features of response to treatment [9, 34, 35]. To date, the question if kidney biopsy should be repeated per-protocol or performed “on demand” in case of clinical changes remains to date open. The challenge for the future is to implement our ability to management LN by using noninvasive biomarkers [36, 37]. Tests able to improve our abilities to accurately predict future renal flares are highly needed. Similarly, biomarkers allowing the identification of ongoing LN earlier than currently available tools (e.g., proteinuria, hematuria, and increased serum creatinine levels) have the potential to improve our diagnosis accuracy [38].

Our study systematically reviewed the current literature on novel potential biomarker for diagnosing LN and monitoring renal disease activity. On the one hand, considering the stringent inclusion criteria of the included studies, one could point out that the evidence on potential novel biomarkers of interest in LN is exponentially growing, making it a dynamic research topic. On the other hand, the analysis of the included studies points out various aspects that should still be improved when investigating biomarkers in LN. First, in about a third of the studies, LN was not confirmed by kidney biopsy. Second, methodologically, there was a vast heterogeneity when evaluating together the used tools to assess the activity of the LN. Third, we observed a strong intra- and inter-assay variance in terms of laboratory testing across the analyzed studies.

One should consider that despite the mentioned level of heterogeneity, some promising results have been shown for some biomarkers such as urinary MCP-1, urinary AdipoQ, and urinary VCAM-1. Other promising biomarkers, despite not being the most frequently investigated in the included studies, are worth mentioning: the activated leukocyte cell adhesion molecule (ALCAM), the soluble marker CD163, and the B lymphocyte stimulator (BLyS). Recent studies indeed highlighted ALCAM and CD163 correlation with renal biopsy outcomes and their effectiveness in distinguishing among active and inactive LN [39–42]. When focusing on BLyS, even if it does not seem to correlate with the activity or quiescence of the disease, it resulted to be highly expressed in LN patients [43–46]. BLyS is a B-cell survival factor showing a pivotal role in B cell maturation and activation, whose expression is closely correlated with autoimmunity. These observations are in line with the recent approval of the monoclonal antibody targeting BLyS for the management of SLE. All in all, a growing body of evidence is exploring the role of ALCAM, CD136, and BLyS/BAFF to guide the different phases of the management of LN. Available evidence is still limited to a small number of studies; however, future research is highly expected to confirm the promising preliminary results. That is why the monoclonal antibody targeting BLyS (belimumab) has been recently approved for the management of SLE [47].

The role of cytokines in the pathogenesis of SLE has been largely investigated. Among others, interleukin (IL)-6, IL-17, IL-12, and transforming growth factor β (TGF- β) are the cytokines of greater interest when considering LN. A growing body of evidence is suggesting their potential role as prognostic and/or diagnostic biomarkers [48–51]. For instance, IL-6 and IL-17 levels have been observed to correlate with the disease activity and remission [48, 50]. However, to date, these results still require validation in large prospective cohorts. Besides, some technical aspects, including inter-assay variability, need to be addressed before considering this candidate as part of the clinical routine investigations. Nevertheless, the availability of therapeutic options directly targeting different cytokines is likely to further promote this area of research.

Nevertheless, while repetitive sampling to unmask the evolution of a LN and/or assess treatment response is only possible with noninvasively tools (e.g., urine-based), the “liquid biopsy” is still the Holy Grail for “lupologist” community. In fact, some pilot results have shown how urine proteomics approaches can identify an inflamma-

tory signature in the urine of patients with LN implicating monocyte and TNF- α pathways. These signatures are associated with proliferative disease, worse proteinuria, and nonresponse to treatment [52]. If confirmed, these results may pave the way for a more personalized approach to LN treatment.

This study suffers some limitations, mainly due to the heterogeneity of the studies included in the analysis. Importantly, all of the included studies were observational studies, subject to the biases inherent in such study designs, and the reproducibility of their results might suffer from it. When considering the analyzed data, the heterogeneity in the data of the studies comprehended inclusion criteria, biomarkers and assay heterogeneity, cutoff value definition, clinical details of the patients and diagnosis of LN, control groups, and definition of renal activity disease. Moreover, it was not possible to perform a meta-analysis of the studies (even when considering the biomarkers investigated in different studies due to lack of details limiting comparability).

Autoantibodies, as well as other protein biomarkers, cytokines, and chemokines, clearly play a pivotal role in SLE pathogenesis and could potentially be used as biomarkers. While the value of identifying a biomarker for the diagnosis on LN and disease monitoring would represent a cornerstone in SLE management, this could also potentially represent the basis for future therapeutic approaches.

In order to further proceed in this very promising field of research, clinical trial design in LN should be further improved and homogenized in order to be able to compare outcomes among studies and improve result interpretation. To date, kidney biopsy still represents the most accurate tool to confirm LN diagnosis and to obtain prognostic data through a proper histological evaluation.

Statement of Ethics

Due to the nature of the article (systematic review) the study did not need the approval by the local ethical committee.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

M.R., P.M., and A.B. searched the literature, assisted with the organization of the manuscript, interpreted and collected data, and wrote and edited the review. R.F., D.R., and S.S. interpreted and collected data, helped to design the figures and panel, and wrote and edited the review.

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