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Novel Biomarkers of SLE with Renal and Neuropsychiatry Complications

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ABSTRACT

SLE is a complex multi-organ autoimmune disease exhibiting renal, dermatological, neuropsychiatric, and cardiovascular symptoms. In this autoantibodies attack their own organs and immune complex formation occurs as well and ultimately leads to death. Its causes are relatively unknown but complex environmental, genetic, hormonal, and immunological factors are involved in it. This review article summarizes the insights of the past 5 years of research about biomarkers, including activity, monitoring, prognosis, diagnosis, genetic, complement, and traditional biomarkers of SLE with Lupus and neuropsychiatric complications. Our initial search for articles was based on a search from NCBI and PubMed, along with journals from Frontier, Nature Science, and PNAS. Novel Biomarkers in SLE that showed complication with LN and NPSLE are IL-6, IL-16, IL-10, IL-18, IL-1ra, and IL-1b, (cytokine biomarker), Osteopontin (serum biomarker), Lipocalin-2 (NGAL), M-CSF (CSF-1, and M-CSF), Anti-ribosomal P+, VCAM-1, TNF-a, Serum Uric Acid (SUA), Ceruloplasmin, C3 complement components were involved both in NPSLE and LN disease activity of the patients. Also, biomarkers like Angiostatin have shown excellent sensitivity (88%) but poorer specificity (44%) with an AUC value of 0.65 in NPSLE while NLR and PLR showed high sensitivity (90%, 95%) and specificity of (50%, 50%) in LN. We opted for tools that can diagnose, assess disease activity, and predict flares more accurately without conducting an unhealthy process like Biopsy. So this review article is focused on finding the Biomarkers from Blood, Urine, and CSF, with diagnosis, prognosis, and predictive value (Though not clinically validated). It also discusses its use in developing Diagnostics and disease monitoring panels which could further improve SLE diagnosis and assessment of D.A. thus improving the overall patient's condition. However, more thorough research is required due to the general absence of confirmation research among different groups.

INTRODUCTION

A biomarker is an objective measurement that tells us about the condition of cells, tissues, or an organ. It tells us if our cells or organs operate normally, physically, genetically, biochemically, or, biologically. They act as a warning for our cells about anything abnormal. We can use them as reference points to relate to abnormal conditions of the body (1). Biomarkers should show changes associated with the pathological features or presentation of a disease, offering diagnostic or prognostic value. They are pivotal in personalized medicine (2). An ideal biomarker should have a high specificity and sensitivity, be obtainable non-invasively (e.g., blood, urine, or other bodily fluids), and involve affordable and reproducible lab tests. Examples include clinical measurements like blood pressure and body weight, lab tests for urine or cerebrospinal fluid (CSF), and molecular or cellular changes.(1) In systemic lupus erythematosus (SLE), biomarkers such as interleukins, cytokines, proteins, immune pathways, and genetic mutations play a significant role. SLE is a chronic, multisystem inflammatory disease characterized by autoantibodies targeting self-regulatory antigens, immune complex formation, and immune dysregulation. It can damage nearly any organ, with the kidneys, lungs, skin, joints, blood components, and central nervous system being the most commonly affected. The disease involves upregulation of the innate and adaptive immune systems, complement activation, and inflammatory responses in tissues. (3) Diagnosing and managing SLE is challenging due to variability in clinical manifestations and treatment responses among patients. SLE is more prevalent in women, with a female-to-male ratio of 8:1 to 15:1, likely due to hormonal factors like estrogen, which is involved in autoimmunity, which explains its predominance in females (4). This ratio decreases to 3:1 when hormonal levels are similar (4). The disease duration is also generally longer in females (5). Although its exact cause is unknown, genetic,

environmental, immunological, hormonal, and epigenetic factors are implicated. While SLE cannot be cured, early diagnosis can help manage the condition effectively.

The European Alliance of Associations for Rheumatology (EULAR)-American College of Rheumatology (ACR) criteria are used for SLE classification. Patients must first test positive for anti-nuclear antibodies (ANA), followed by evaluation against additive clinical (e.g., constitutional, hematological, neuropsychiatric) and immunological (e.g., antiphospholipid antibodies, complement proteins) criteria. A total score of 10 or more points classifies a patient as having SLE. These criteria have demonstrated a sensitivity of 96.1% and specificity of 93.4%, outperforming previous classification systems.(6) However, challenges remain due to the suboptimal performance of many biomarkers. For example, ANA has high sensitivity (97.8%) but a specificity of 74.7% (7)(8)and is present in 5–10% of healthy controls.(9) Anti-dsDNA shows variable specificity (94–96%) and moderate sensitivity (52.4%), while Anti-Sm DNA has very high specificity (94–99%) but extremely low sensitivity (5–20%).(10)

The variation in sensitivity and specificity among biomarkers significantly impacts SLE management. Robust and efficient biomarkers with high sensitivity and specificity are essential for accurate diagnosis, prognosis, disease progression assessment, and drug response evaluation. This review highlights recent findings on novel biomarkers that could improve SLE diagnosis, prognosis, and management, particularly for lupus nephritis (LN) and neuropsychiatric SLE (NPSLE). Importantly, many biomarkers can be obtained through non-invasive methods, such as blood or urine tests, facilitating disease monitoring and treatment strategies.

METHODS

We conducted a thorough search for Research articles by using the PubMed database. We selected those articles ranging from 2019 to 2024 which is also our inclusion criteria for this review article. Our methods include a brief introduction of biomarkers in SLE in general and later specifically towards its types and manifestation in lupus nephritis and neuropsychiatric SLE.

Biomarker in SLE

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of autoantibodies and the deposition of immune complexes, affecting a wide range of organs. Genetic factors, environmental factors, and hormonal factors are believed to contribute to the occurrence of SLE (11) diagnosis continues to be a challenge in modern days due to its multiorgan involvement and the usage of non-specific biomarkers. Sometimes SLE coincides with the symptoms of other diseases making it more complex. Other times patients have a set of symptoms and clinical manifestations making it easy along with lab tests but if the signs are isolated it can be very demanding. (12)

EULAR/ACR 2019 classification criterion has high sensitivity and specificity of 96.1% and 93.4%. (6) Although its specificity and sensitivity are relatively high the immunological biomarker (ANA (7) AntidsDNA (9) have specificity and sensitivity which are not enough to optimally determine SLE exactly. Even though it has been relatively good, false negatives and positive impacts its sensitivity and specificity. Therefore, the tests need to be standardized to achieve better outcomes. (13) There is a need for optimum biomarkers which can diagnose and predict the disease.

Activity Biomarkers

These are used to assess the activity of the disease. Whenever they are present at an abnormal amount, it indicates that SLE is active.

According to Godsell et al. Serum IL-10 is at higher levels in SLE patients compared to HC and is involved actively in the disease activity. Its presence is high in active patients in comparison to inactive ($p < 0.01$). The data suggests the involvement of IL-10 in organ diseases esp. musculoskeletal activity, renal disease, serositis, and serological activity. (14) According to Ruacho et al. CSF-1 in serum and urine, calprotectin in saliva and urine, as well as TNF- α, IP-10, and MCP-1 in urine were elevated in the SLE patients in comparison with HCs and are involved in the disease activity. ($p<0.05$). (15) According to Sawada et al. Serum PS-PLA1 were present in higher level in untreated SLE patients compared with healthy individuals and patients with RA, SSc, and SS. It also positively correlated with SLEDAI. (16) Systemic Lupus Erythematosus (SLE) disease activity biomarkers include TNF-α and IL-17. Elevated levels correlate with high disease activity (SLEDAI score). TNF-α has dual immunosuppressive and proinflammatory roles, while IL-17 promotes inflammation with IL-23. Increased cytokine titers are found in lupus patients. Therapeutic targeting is promising, but TNF-α inhibition risks ATIL, whereas IL-17 inhibition requires further investigation. According to kim et al. ratio of blood iC3b to serum C3 concentrations correlates with the extent of SLE disease activity and with clinically meaningful changes in disease activity in patients with SLE; also iC3b: C3 differentiates among active SLE and inactive SLE. (17) According to M.Soliman et al. NLR and PLR were both present in elevated SLE patients in comparison to control.(Although PLR showed a non-significant value of 0.275 and NLR 0.00). Both are edisease activity markers showed significantly increased values in active SLE patients. NLR and PLR were

positively correlated with SLEDAI, ESR, and CRP and negatively correlated with C4.(18) According to Emad el din et al. Anti-C1q was much more common in patients with SLE and is associated with disease activity. Those with positive Anti-C1q showed a very high SLEDAI in comparison to negative patients. (19) According to Patyna et al. Sphingosine levels such as chain length specific ceramides, C16cer, C18Cer, and C24:1Cer were present in higher amounts in the plasma and serum of SLE. (20) cGAS and IFI16 are significantly higher in PBMCs and act as disease activity biomarkers. IFN-B can also act as a diagnostic biomarker (89.1% & 89.2%). (21)

Serum Cytokines

According to Jin et al. Levels of serum cytokines such as IL-6, IL-10, and TNF-alpha are at a much higher level in SLE with severe disease activity and mild disease activity in comparison with mild disease or low disease activity, according to Mathian et al. Serum IFN-alpha are better activity biomarker than the Farr test and can distinguish active patients or flare from inactive patients. Serum IFN-alpha positively correlates with SLE disease activity. It has the 83% sensitivity and 92% specificity. (22) **Cytokine IL-6** is higher in SLE in comparison to healthy. (5)(23)(24)(25)(Mean the above three researches have already proved IL-6 potency) **IL-10** is higher in SLE in comparison to HC. (5) In our study, we observed higher serum IL-10 levels in SLE patients compared to controls, which is consistent with previous findings by other authors (13, 6, 9, 14, 15) **Interleukin 18** are statistically high amounts in SLE in comparison to HC. (26) **Fucosylation of IGs** can be used as SLE diagnostic tool (In the present study, we found that core fucosylation on IgG was significantly upregulated in SLE serum. (27) **cGAS** and **IFI16** are significantly higher in PBMCs and act as disease activity biomarkers. IFN-B can also act as a diagnostic biomarker (89.1% & 89.2%). (28) **Galectin:** According to Matsuoka et al. Galectin level correlated positively with disease activity. Its levels significantly were very high but dropped after treatment. Its presence was also positively correlated with IFN-alpha. (29) **IL-26:** it is present in significant levels in the SLE patients in comparison to controls. It was significantly higher in active than inactive SLE disease. And have a positive correlation with SLEDAI and urine protein to creatinine (uPCR), Anti-DNA antibody levels. It can be used for active disease identification. (30)

Genetic Biomarker

Recent studies have shown that a lot of genetic markers are included in the pathogenesis of SLE, and thus can be used as Biomarkers to diagnose and assess disease activity or treatment response. We will discuss some of the novel genetic-related biomarkers including LnRNA, circular RNA, miRNA, etc.

MiRNA: MicroRNAs (miRNAs) are a large family of endogenous, single-stranded, small (~22 nucleotides), nonprotein-coding RNA molecules that regulate gene expression at the post-transcriptional level. (15) They have an important role in gene expression regulation in plants as uwell as animals. (16) Their altered expression profile led to the loss of function and thus exhibited associations with multiple autoimmune-related disorders. (31) Judging from the importance of it, it should have a very important role in the SLE. So, a lot of studies were dedicated to finding the role of the miRNA in SLE and related complications. Recent studies find that indeed it is involved in SLE up to an extent. In PBMCs, the level of miRNA-146a level was significantly elevated compared to HCs. (32) In miR-146a rs2910164 C/G, an elevated level of miR-146a was observed in SLE patients with CG and GG genotypes in comparison to the CC genotype, showing a possible relation with the G genotype. (32) In another study, conducted by Li et al, Exosomal miR-21 and miR-155 were at a high level in comparison to HC with a p-value of <0.01. While the level of exosomal miR-146a was very much low in comparison. (33) SLE patients displayed significantly increased plasma sCD14, TNF-α, and IFN-α levels in comparison to healthy controls. The prevalence of mutant genotypes (CT and TT) and minor allele (T) of CD14 (C-159T) polymorphism was significantly higher in SLE cases compared to HC. **sCD14 polymorphism** causes pre-disposition to SLE. (34) **Hsa_circ_0006689** may be a useful circRNA biomarker for SLE diagnosis and prognosis. (35) ***CD226* gene:** rs763361 polymorphism in the *CD226* gene may be a potential genetic susceptibility factor; can't be said to be a biomarker but increases the likelihood of SLE onset. (Meta-analysis) **TCONS 00483150:** TCONS 00483150 as diagnostic Biomarker and potential therapeutic target. (36) Polymorphisms in the **BLK allele**s rs13277113 A/G, rs2736340 T/C, and rs2248932 T/C are associated with susceptibility to SLE (meta-analysis) 2017. **tRF-His's-GTG-1:** tRF-His's-GTG-1 was upregulated in patients of SLE than controls. We analyzed tsRNA signatures in SLE serum and identified that tRF-His-GTG-1 was significantly elevated in SLE serum. tRF-His-GTG-1 and the anti-dsDNA panel could act as potential diagnostic Biomarkers with a high AUC. (36) **Nine-protein combination:** Nine-protein combination (PHACTR2, GOT2, L-selectin, CMC4, MAP2K1, CMPK2, ECPAS, SRA1, and STAT2) showed a robust performance in assessing disease exacerbation (prognostic biomarker); TOMMO40, STAT1, STAT2------>genetic biomarker for their involvement in the genetic pathway. (37) The CDC27 gene has a role in diagnosing SLE. (38)

Complement Biomarker

They are a group of proteins present in blood plasma responsible for providing immunity, and protection from

harmful microbes and have a role in the modulation of inflammation. They are very commonly employed in clinical practices for diagnosis, prognosis and to find the disease activity status. (39)Traditionally complement biomarkers are employed in clinical practices. They have a role in the diagnosis, prognosis, and disease activity-related functions. They can be used to diagnose, prognosis, and asses the disease activity of SLE.

Traditional Complement Markers in SLE Diagnosis

According to SLICC and EULAR/ACR criteria, Hypocomplementemia is decreased in the C3, C4, or CH450; Low C3 or C4 levels are based on these two criteria respectively. They are in the diagnosis of SLE. (40)(6)

Traditional Complement Markers in the Assessment of SLE Activity

The systemic lupus erythematosus disease activity index (SLEDAI), the validated activity index frequently used for assessing global SLE activity, includes the presence of low complements that is, the decrease in CH50, C3, or C4 in qualitative assessment. (41)

Traditional Complement Markers in Predicting SLE Prognosis

In SLE management it is really important to prevent flare. To accomplish this goal it is very important to look out for the signs that indicate the onset of flare. We have to keep looking for risk factors which include low complement levels and anti-dsDNA. (42) In Lupus Nephritis low level of C3 and C4 serum level is a predictor of flare. (43)

Autoantibodies

According to a study by Hantao. et al, 46 antibodies were examined from lupus nephritis patients. It was found that only the pone subset binds to NETs, promoting inflammation. The Crithidia luciliae test detected anti-dsDNA antibodies with high specificity. Results showed significant differences in DNA binding scores (p=0.03)."Autoantibody-dependent amplification of inflammation in SLE. (44)

REAP effectively identified autoantibodies in 106 SLE patients and 20 healthy controls. It confirmed known autoantigens and discovered new ones, with predictive capability (AUC=0.785). Severe SLE patients had more autoantibodies, with specific reactivities linked to distinct symptoms, such as kidney damage. (45)

In SLE patients, DNASE1L3 activity was significantly lower in those with kidney damage (median 69%). 43% of renal SLE patients had anti-DNASE1L3 autoantibodies, which specifically targeted DNASE1L3 and inhibited its activity by 30%. (46)

A study evaluating 74 proteins for autoantibody detection found significant differences between patient groups. IgG autoantibodies were higher in ILE (19.1%) and SLE (26%) patients, while IgM levels were higher in ILE (17.2%) patients. Seven IgG clusters were identified, and the IgG: IgM ratio increased from healthy controls to SLE patients. (47)

A study of 107 new-onset SLE patients found that 42% were ANCA-positive, with 88.9% being MPO-ANCA-positive. ANCA-positive patients had higher rates of ILD (55.6% vs 24.2%), renal involvement, and other symptoms. Active SLE was more common in ANCA-positive patients (71.1% vs 32.3%, P<0.05). The study suggests that ANCA may be useful in diagnosing new-onset SLE and predicting ILD involvement. (48)

The BEAT-LUPUS study (2017-2019) analyzed 44 patients with lupus. At 52 weeks, 48% of patients receiving belimumab had a major clinical response, compared to 35% in the placebo group, with a 13% between-group difference (95% CI -15 to 38). Elevated baseline IgA2 anti-dsDNA antibodies predicted a better response to belimumab, with a 48% difference (95% CI 10 to 70) and an AUROC of 0.88. (49)

A one-year study of 115 inactive SLE patients found that 40% experienced a relapse, with 17% having a renal relapse. Baseline anti-nucleosome antibody (anti-NCS) positivity, seen in 16% of patients, was significantly linked to renal relapse (39% vs. 14%, p=0.02). Immunosuppressive therapy reduced renal relapse risk (HR: 0.28), while anti-NCS positivity increased this risk at 6 and 12 months (RR: 3.85 and 2.90). (50)

Out of 11,014 samples tested for ANA, 23.99% were positive and 0.23% were anti-PCNA positive. The majority of patients (83%) were female, with a mean age of 51.5 years. Half of the patients had SLE, while others had Antiphospholipid Syndrome (33%), Systemic Sclerosis (17%), or Behçet Disease (17%). Common symptoms included cutaneous manifestations (83%), articular symptoms (50%), and neurological symptoms (50%). The study found that anti-PCNA antibodies are not exclusive to SLE and can be present in other autoimmune diseases. (51)

Diagnostic Biomarkers

According to Sandholm et al, Plasma C1q was lower in SLE patients than matched controls (p<0.001). C1q also showed an association with SLEDAI. (52) IGRA-NL/MT is a useful indicator of active SLE, particularly when used in combination with C3.TB-IGRA test may be a useful biomarker in SLE, as well as a diagnostic aid for other diseases associated with IFN-γ activation. Elevated SIR appears to be associated with a limited number of disease processes, including SLE. (53) IL-40 as a diagnostics biomarker for SLE severity. (54) C3dg: C3dg is a diagnostic marker that can differentiate between HC and SLE patients. uNGAL and uKIM-1: uNGAL and uKIM-1 levels before treatment compared to control are high, they can act as diagnostic biomarkers for SLE. (55) Six-protein combination: The six-protein combination (IFIT3, MX1, TOMM40, STAT1, STAT2,

and OAS3) exhibited good performance for SLE disease diagnosis from HC and R.A.

Table 1
Biomarkers in Lupus Nephritis

Biomarkers	Sensitivity/Specificity	Metrics	References
ALCAM, calpastatin, hemopexin, peroxiredoxin 6 (PRDX6), platelet factor 4 (PF4), properdin, TFPI and VCAM-1	Calpastatin FE 100%, PF4 FE 100% ,(PRDX6) FE 100% ,Properdin FE 100%		S. A. Soliman, et al.,2022.(56)
hsa_circ_0044235 , hsa_circ_0068367	Validation Cohort (23 SLE, 21 HCs) Specificity: 0.619 External Validation Cohort Specificity: 1.0	AUC (0.731-0.730) values	Guo G, et al; 2019 (57)
Adiponectin, MCP-1, sVCAM-1, PF4, IL-15, vWF			Whittall-Garcia L, et al;2022 (58)
hsa_circ_0044235, hsa_circ_0068367, hsa-miRNA-892a, Anti-double-stranded DNA (anti-dsDNA) antibodies, Anti-ribosomal protein P antibodies			Luo, et al; 2019 (59)
IFI44, IFI44L, EIF2AK2, IFIT3, IFITM3, ZBP1, TRIM22, PRIC285, XAF1, PARP9			Jiang Z, et al; 2022 (60)
T cell IgM	96% specificity, 85% sensitivity.		Colucci M, et al;2020 (61)
CSF-1, TNF-α, IP-10, MCP-1, Calprotectin, IL-34, MIP-1α	CSF-1: 73.1% - 74.1% TNF-α: 75.9% - 80.6% IP-10: 82.8% - 85.7% MCP-1: 81.5% - 84.8% Calprotectin: 67.9% - 78.6% IL-34: 63.2% - 71.4% MIP-1α/β: 60.7% -73.8%		Ruacho G,et al; 2022 (63)
Serum Uric Acid (SUA)	Sensitivity: 67% (0.67) and Specificity: 89% (0.89)	(p=0.02), 76% ROC accuracy.	Ugolini-Lopes MR,et al ;2019 (64)
NPT, IFN-α			Labouret M, et al; 2023 (65)
Linc8986, Linc0597	Linc8986: Sensitivity: 85.7% and Specificity: 87.5% Linc0597: Sensitivity: 82.9% and Specificity: 85.7%		Rong C, et al; 2021 (66)
Metabolomic biomarkers: Glycocholic acid, Cholic acid, Deoxycholic acid, LysoPC, LysoPC, Ceramide Lipidomic biomarkers: PC, PE, PI, PS	Metabolomic Biomarkers: Average specificity: 84.2% Sensitivity: 83.3% Lipidomic Biomarkers: Average specificity: 86.8% Sensitivity: 86.7%		Li Y, et al 2019 (67)
PS-PLA 1	Sensitivity: 85.7% And Specificity: 91.7%		Sawada T, et al;2022 (68)
serum creatininehypocomplementaeia, high chronicity and systolic B.P (prognostic indicators)			Mahajan, A.et al; 2020 (69)
Serum Osteopontin			Spinelli, et al; 2019.(70)
sMCP_1(diagnostic) uMCP-1 (prognostic, Disease activity.			Abozaid,et al;2020. (71)
STNF-R1 and linc0597 (diagnostic biomarker, disease activity)			Zheng, et al; 2020. (72)
Urine L-selectin (diagnostic marker, prognostic biomarker, disease activity)			Shen, Y.(73)
uNGAL, uKIM, uNGAL/Creat ratio, and uKIM/Creat ratio (disease activity, predictor			Ibrahim, et al;2024 (55)
tRF-His-GTG-1	Specificity: 96 % and Sensitivity: 66%		Yang.et al;2021(74)
C3dg and MAC	Specificity: 100% sensitivity: 75%.		Shi. et al;2023 (75)
NLR	Specificity: 54% and sensitivity: 83%		M.Soliman. et al;2018 (18)
Anti-C1q			Emad el din.et al;2022 (19)
anti-P (Disease activity)	Specificity: 99% and sensitivity: 31 %		Wang.et al;2020 (76)

Prolyl 3-hydroxylase 1 (P3H1), phosphatase and actin regulator 4 (PHACTR4), and regulator of G-protein signaling 12 (RGS12) ICx		(AUC) values of 0.82, 0.99, and 0.90	Tang.et al;2022 (77)
CD14, CD34, cystatin A, myocyte enhancer factor 2C (MEF2C), RGS12, and ubiquitin C (UBC) ICx		AUC value of 0.85	Tang.et al;2022 (77)
(serum +plasma) C16ceramide (Cer), C18Cer, C20Cer and C24:1Cer, Sphinganine concentrations			Patyna.et al;2019 (20)
sCD14, TNF-α, and IFN-α		ROC, AUC of 0.98, 0.86, 0.93 and 0.90	PAnda. et al;2020 (34)
VCAM-1 and ICAM-1		Seropositivity rate 93.10% and 37.93% ROC AUC of 0.98, 0.86, 0.93 and 0.90	Yu.et al; 2021 (78)
Serum ICAM-1 level		ROC AUC of 0.75 and 0.66	Yu.et al; 2021 (78)
Syndecan-1, HA and thrombomodulin		ROC: 0.98, 0.91, 0.82 and 0.95 for syndecan-1; AUC: 1.00, 0.84, 0.97 and 0.79 for thrombomodulin	Yu. et al ;2021 (79)
IL-35			He. et al; 2018 (80)
MALT-1		AUC =0.811	Wang et.al;2022(64)
UsVCAM-1, U-sALCAM		P < 0.001	Parodis.et al;2019 (81)
transferrin, AGP-1, ceruloplasmin, MCP-1 and sVCAM-1		P <0.0001), AUC 0.898	(82)
IL-10 and IL-37…IL-10			Godsell .et al; 2016 (14)
Serum HOTAIR, lncRNA-Cox2	Specificity: 100% Sensitivity: 79.3%		Mahmoud.et ai; 2022(83)
Serum and urinary Chemoattractant protein I(MCP-I)			Abozaid.et al;2020 (71)
TCONS 00483150 (diagnostic Biomarker)			Guo, et al ; 2020 (35)
uNGAL and uKIM-1 (diagnostic biomarker)			Ibrahim.et al ;2024 (57)
IFIT3, MX1, TOMM40, STAT1, STAT2, and OAS3(SLE disease diagnosis from HC and R.A) PHACTR2, GOT2, L-selectin, CMC4, MAP2K1, CMPK2, ECPAS, SRA1, and STAT2 (performance in assessing disease exacerbation) prognostic markers			Li.et al;2022 (37)
rs13277113 A/G, rs2736340 T/C, and rs2248932 T/C			Song.et al ; 2017(84)
PRO-C3 (serum) and PRO-C6 (serum and urine)			Genovese et al;2021(85)
CD226 gene (rs763361 polymorphism)			Bai.et al;(86)
IL-40 (diagnostics biomarker)	Specificity: 90.9 Sensitivity:99%		Al Rubaye.et al; 2023 (54)
Cytokine IL-6			Winikajtis-Burzyńska. et al ;2023 (5), Umare V.et al ;2014 (23) 1.Guimarães P.M.et al ;2017(24) 2.Talaat R.M.et al;2014(25)
IL-10			Winikajtis-Burzyńska. et al ;2023 (5), [13,6,9,14,15,19].
CDC27	Specificity: 94.4% Sensitivity: 82.3%		Shang.et al,;2022 (38)
Fucosylation of IGs			(27)
Uric acid	Specificity: 83.3% and sensitivity: 81%		Hafez.et al ;2021(87).
tRF-His-GTG-1	Specificity: 94.19% Sensitivity: 83.72%		Yang. et al ;2021(36)
iC3b and Serum C3			Kim.et al;2019 (17)
NLR and PLR	Specificity: 50 & Sensitivity: 90(NLR) Specificity: 50 & Sensitivity: 95 (PLR)		M. Soliman.et al ;2018(18)
IGRA-NL/MT, TB-IGRA test			Thomason. et al;2020 (53)

Interlukin 18			Mende et al.,(2018).Analysis of Serum Interleukin(26)
Anti-C1q			Emad el din.et al;2022 (19)
Sphingosine			Patyna. et al;2019 (20)
plasma sCD14, TNF-α, and IFN-α			PAnda.et al;(2020 (34)
hsa_circ_0006689 (diagnosis and prognosis)		Confidence Interval-CI (95%); AUC:0.713	Li .et al;(2022) (33)
anti-α-enolase Ab combined with β2-MG		anti-α-enolase Ab (AUC: 80.9%) or β2-MG (AUC: 84.5%)	Y Huang et al; 2019 (88)
cGAS and IFI16	Specificity: 89.1% sensitivity: 89.2%		Fu .et al;2022(89)
LPGDS, transferrin, AGP-1, ceruloplasmin, MCP-1 and sVCAM-1		P>0.0001 SLEDAI ≥15	(82)
CSF anti-UCH-L1	Specificity: 91% sensitivity: 53%		Li. et al;2019 (90)
anti-UCH58-69	Specificity: 92.3% sensitivity: 37.5%		Guo, et al ; 2022(91)
TNFSF13B (BAFF) and OAS1		0.924, 0.936 (AUC VALUES)	Wang Y.et al ;2022 (92)
EGF, Lipocalin-2/NGAL, uPA, ASC	Lipocalin-2 was 88%, with an 83% specificity. EGF, the sensitivity was 100% with a 100% specificity. upa 84% sensitivity and a 65% specificity, ASC was 63% with a 53%	EGF (AUC = 0.9935), Lipocalin-2/NGAL (0.9554), ASC (0.7666), and uPA (0.7522)	Johnson NH .et al ;2022 (93)
IgA2 anti-dsDNA ab Urinary		Belimumab+ Rituximab OR=1.07, P value= 0.038, AUROC= 0.88 AUs= 10.7 Rituximab+placebo AUROC= 0·23	(94)
Urine-soluble CD163		SLEDAI-2K scores (p < 0.0001),	(95)
IL16		(AUC) of 0.85 (p = 0.016) and 0.89 (p = 0.037)	(96)
MCP1	sensitivity of 83%, 70%, and 77% specificity of 81%, 86%, and 90%,		(97)
Serpin A3	sensitivity of 68% and specificity of 69%. (3 months) sensitivity of 85% and specificity of 70% (6 months)	(AUC) = 0.764 (3 months) AUC = 0.861 (6 months)	(98)
Ig binding protein 1		P-value of < 0.05	(99)
C3M		C3M PRO-C3= 21% were below LLOQ PRO-C6= 7%	Genovese.et al ; 2021 (85)
S100		serum S100A12 (p<0.05). urine S100A8/A9 and S100A12(p< 0.005).	(100)
LPGDS, transferrin, AGP-1, ceruloplasmin, MCP-1 + sVCAM-1		transferrin (P <0.005), AGP-1 (P <0.0001), MCP-1 (P <0.001) and sVCAM-1 (P <0.005)	(101)
exosomal miR-146a		36-month follow-up flares (OR 7.08, p = 0.02).	(102)

miRNA: Recent studies conducted on the potential of micro-RNA as a biomarker. They have identified certain mi-RNA which have the potential to be used as a biomarker. According to a study, expression of miRNA-21 ($p<0.01$) and miR-155($p<0.05$) was at a high level in patients of Lupus Nephritis compared to those without LN. The ROC curve analysis also shows a potential diagnostic value. (33) Judging from the importance of it, it should have a very important role in the SLE. So, a lot of studies were dedicated to finding the role of the miRNA in SLE and related complications. Recent studies find that indeed it is involved in SLE up to an extent. In PBMCs, the level of miRNA-146a level was significantly elevated compared to HCs. (103) In miR-146a rs2910164 C/G, an elevated level of miR-146a was observed in SLE patients with CG and GG genotypes in comparison to the CC genotype, showing a possible relation with the G genotype. (103) In another study,

conducted by Li et al, Exosomal miR-21 and miR-155 were at a high level in comparison to HC with a p-value of <0.01. While the level of exosomal miR-146a was very much low in comparison. (22) **LnRNA:** According to et al., Serum levels of sTNF-R1 and linc0597 were higher in comparison to SLE patients and control groups. They can be employed as a diagnostic biomarker and are positively correlated with SLEDAI, also activity biomarker. (104) **Activity Marker:** According to Ruacho et al. TNF-α, IP-10, and MCP-1 in urine and CSF-1 and IP-10 in serum were significantly higher in the active renal SLE in comparison with inactive renal SLE. (105) Serum PS-PLA$_1$ was significantly higher in SLE patients than in healthy controls, RA, and SS patients. PS-PLA$_1$ was significantly elevated in SSc and SS patients compared with healthy controls, PS-PLA$_1$ was significantly higher in untreated SLE patients than in treated SLE patients and disease control patients. Serum Gal-9 was present in significant levels in patients with active renal involvement in comparison with no active renal disease. **cGAS** and **IFI16** are significantly higher in PBMCs and act as disease activity biomarkers. Along with IFN-B can act as a diagnostic biomarker (89.1% & 89.2%). (106) **Levels of six urine (LPGDS, transferrin, AGP-1, Ceruloplasmin, MCP-1, and sVCAM-1**) proteins are high in SLE in comparison to HC but it does not act as an activity Biomarker. >0.0001(sign.) Ceruloplasmin and MCP-1 levels were significantly elevated in patients with 'high' (SLEDAI ≥15) disease activity. (107) **MCP-1:** According to Abozaid et al. sMCP_1 is diagnostic while uMCP-1 is prognostic marker for LN as well. (Also, disease activity) sMCP-1 and uMCP-1 were present in high amount in comparison to Control group could be of help in diagnosis. uMCP-1 was positively correlated with renal SLEDAI, Biopsy Index, and 24-hour Proteinuria. It can be a useful tool to distinguish between LN and non-LN and follow up. (108) **URINE L-Selectin:** According to et al. Urine L-selectin was significantly elevated in the active LN than in active non-renal Lupus. It positively correlated with SLEDAI in Chinese, US, and African patient cohorts. It also shows a surprisingly low quantity after the treatment. It acts as a diagnostic as well predictive biomarker. (73) **uKIM And uNGAL:** According to Ibrahim et al. The LN group before treatment showed higher levels of uNGAL and uKIM-1 (*P*-value < 0.001) than post-treatment. ROC analysis also shows that it has surprisingly good specificity and sensitivity. uNGAL, uKIM, uNGAL/Creat (100% sen and 97% specificity)ratio, and uKIM/Creat ratio(sen and spec 90%) can be used as a predictor and a marker of disease activity for lupus nephritis. They can be used in the panel to give us high sensitivity and specificity. (55) **tRF-His-GTG-1:** tRF-His-GTG-1 can also be used as a biomarker for differentiating btw Non-lupus SLE and Lupus SLE. It was significantly lower in the SLE patients with LN.ROC curve analysis was performed to determine diagnostic value, it has an AUC value of 0.81. It also has a role in immunity modulation .non-coding RNA. (36) **C3dg and MAC:** C3dg and MAC depositions may be potential biomarkers for disease severity and tissue injury in LN. (75) **NLR:** NLR reflects renal involvement in the SLE. (18) According to Emad el din et al. **Anti-C1q** presence in the SLE patients positively correlated with Proteinuria (0.002). This shows how it is involved with renal patients. (19) SLE patients with positive anti-P have an earlier onset age and are more prone to skin erythema, lupus nephritis as well as higher disease activity. (76) Prolyl 3-hydroxylase 1 (P3H1), phosphatase and actin regulator 4 (PHACTR4), and regulator of G-protein signaling 12 (RGS12) ICx exhibited discriminative capability in distinguishing LN from HC. CD14, CD34, cystatin A, myocyte enhancer factor 2C (MEF2C), RGS12, and ubiquitin C (UBC) ICx could distinguish active LN from inactive LN with an AUC value of 0.85. (77) According to Patyna et al., serum and plasma levels of **C16ceramide (Cer), C18Cer, C20Cer, and C24:1Cer** are elevated in patients with Renal complications. Especially **C24:1Cer** which can potentially act as a diagnostic biomarker (ROC level). (20) These cytokines (**sCD14, TNF-α, and IFN-α**) were significantly elevated in patients with lupus nephritis compared to those without kidney involvement. CD14 (C-159T) polymorphism is associated with an increased predisposition to the development of lupus nephritis: sCD14 is a promising novel biomarker for assessing disease activity and lupus nephritis. (34) The seropositivity rate for VCAM-1 and ICAM-1 was 93.10% and 37.93% respectively at the time of nephritic flare, and 44.83% and 13.79%.(Mean they were higher during nephritic Flare).**VCAM-1 distinguished active LN from healthy subjects, LN in remission, active non-renal lupus, and CKD.**(VCAM-1 acts very good when used with C3 or proteinuria in distinguishing active from remission). (78) **Serum ICAM-1** level distinguished active LN from healthy subjects and LN patients in remission, but did not distinguish between renal versus non-renal lupus. ICAM-1 level in combination with markers of endothelial cell activation (syndecan-1, hyaluronan, and thrombomodulin) was superior to proteinuria, anti-dsDNA, or C3 in distinguishing active LN from quiescent disease. (78) Syndecan-1, HA, and thrombomodulin levels were higher in LN active patients as compared to controls (non-renal SLE, HC, SLE) **Syndecan-1** and **thrombomodulin** were at a higher level 3.5 months before the Nephritic Flare and **HA** was at a high level just before the Flare. Receiver operating characteristic curve analysis showed that syndecan-1 and thrombomodulin levels distinguished patients with

active LN from healthy subjects, LN patients in remission, patients with active non-renal lupus, and patients with non-lupus chronic kidney disease. (79) **Syndecan-1** level was significantly higher in patients with active LN compared with LN patients in remission, patients with active non-renal lupus, CKD patients, or healthy subjects. (79) **Serum HA** level was significantly higher in patients with active LN compared with LN patients in remission, CKD patients, and healthy controls. (79) **Thrombomodulin** levels were significantly higher in patients with active LN compared with LN patients in remission, patients with active non-renal SLE, CKD patients, or healthy subjects. (All these can act as diagnostic biomarkers for early active LN and even we can use it to determine Flare). (79) **PRO-C3** (serum) and **PRO-C6** (serum and urine) were able to discriminate patients with LN from healthy controls. **PRO-C6 (serum),** a biomarker of interstitial collagen degradation, **C3M,** promising biomarkers reflecting histologic alterations, and possibly the degree of disease activity in LN patients. (85) **IL-35** has a role in LN in SLE. Present in every lower amount in comparison to HC, and SLE patients. (The 2018 study can be replaced by a new study). (109) **MALT-1** is higher in LN in comparison to SLE, it also determines the risk of LN {large sample study can be conducted to prove it} (prognostic marker for LN) Also acts as a distinguishing biomarker between classes of LN. (0.046)MALT-1 has a role in kidney damage through the renin-angiotensin pathway. (64) High **UsVCAM-1** appears to reflect active SLE disease. **sVCAM-1** and **U-sALCAM** showed the ability to distinguish SLE patients with active renal involvement from patients with quiescent or no prior nephritis. High U-sVCAM-1 may indicate patients at increased risk for long-term renal function loss. (110)Levels of **transferrin, AGP-1, ceruloplasmin, MCP-1, and sVCAM-1** (all P <0.0001) were higher in SLE patients with active LN when compared with patients without active LN. A combination of five urine proteins, namely **AGP_1, LPGDS, transferrin, ceruloplasmin, MCP-1, and sVCAM-1** was a good predictor of active LN (AUC 0.898). (111) Anti-α-enolase Ab combined with β2-MG for evaluating the incidence of nephritis in SLE patients had the best assessment of the effectiveness (area under the receiver operating characteristic curve (AUC): 92.7%) compared with only anti-α-enolase Ab (AUC: 80.9%) or β2-MG (AUC: 84.5%). (112) **cGAS** and **IFI16** are significantly higher in PBMCs and act as disease activity biomarkers. Along with IFN-B can act as a diagnostic biomarker (89.1% & 89.2%). (21) **Diagnostic (LN) : cGAS** and **IFI16** are significantly higher in PBMCs and act as disease activity biomarkers. Along with IFN-B can act as a diagnostic biomarker (89.1% & 89.2%).(21) **C1q:** They were found to be in lower amounts in comparison to people without nephritis with a p-value of 0.01.

Figure 1

The sensitivity and specificity of the top 10 most accurate biomarkers for lupus nephritis

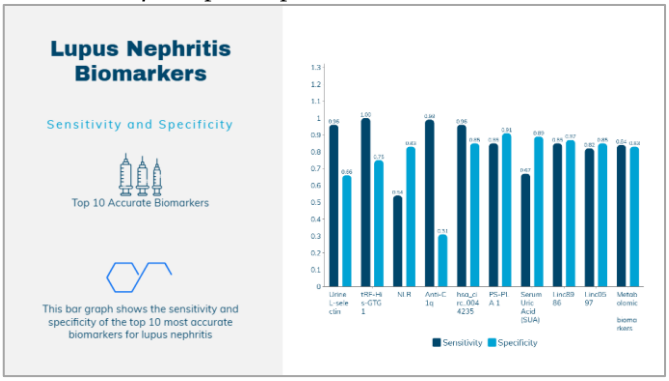


Table 2

Biomarkers in NPSLE

Biomarkers	Sensitivity/ Specificity	Metrics	References
Anti-ribosomal P+		AUC: 0.57; OR: 2.0–3.3	Huang et al., 2020 [113]
Anti-Sm (+)		OR: 1.0–3.3	Magro-Checa C et al., 2019 [114]
Anti-β2GP1 (+)		OR: 2.5–11.3	Magro-Checa C et al., 2019 [114]
Anti-GAPDH		ρ = 0.57	Sun, J.; et al., 2019 [115]
NfL		AUC: 0.65	Engel, S.; et al., 2021 [116]
HMGB1		AUC: 0.84; OR: 1.7	Huang, Q. et al., 2020 [117]
NSE		ρ = -0.37	Chen J et al., 2022 [118]
IL-6 (>74.9 pg/mL)	Sens.: 75%; Spec.: 100%	AUC: 0.89	Kitagori, K et al., 2019 [119]
ApoA1 (levels)ApoE (levels)Free T3 (levels)Free T4 (levels)HDL-C (levels)IGFBP7 (levels)		ρ = 0.21ρ = -0.21ρ = 0.19–0.32ρ = 0.28–0.42ρ = 0.05–0.08ρ = -0.22	Lu, L. et al., 2021 [120]
Osteopontin(>963.4 ng/mL)	Sens.: 70%; Spec.: 100%;	AUC: 0.88	Kitagori et al., 2019 [119]
Lipocalin 2 (",≥122 pg/mL;≥126 pg/mL;)	Sens.: 76–94%; Spec.: 80%	AUC: 0.80–0.85	Mike, E.V et al., 2019 [121]
Angiostatin(≥12 ng/mL)	Sens.: 88%; Spec.: 44%	AUC: 0.65	Vanarsa, K. et al., 2022 [122]

DAN(≥21,457 pg/mL)	Sens.: 76%; Spec.: 63%;	AUC: 0.75	Vanarsa, K. et al., 2022 [122]
Fibronectin(≥3539 pg/mL)	Sens.: 67%; Spec.: 85%;	AUC: 0.81	Vanarsa, K. et al., 2022 [122]
HCC-1(≥3665 pg/mL)	Sens.: 52%; Spec.: 85%;	AUC: 0.69	Vanarsa, K. et al., 2022 [122]
M-CSF(≥41 pg/mL,≥95 pg/mL)	Sens.: 47–80%; Spec.: 94–100%	AUC: 0.71–0.91	Vanarsa, K. et al., 2022 [122]
SERPING1(≥415 ng/mL)	Sens.: 70–100%; Spec.:89–100%	AUC:0.78–0.95	Vanarsa, K. et al., 2022 [122]
PD-1 (FC)		ρ = 0.24	Bassiouni, S.A et al., 2021 [123]
miR-23a (FC ≥ 0.1;FC ≥ 7.3)	Sens.: 90–100%; Spec.:96–100%	AUC:0.95–0.98	Sharaf-Eldin, W et al., 2020 [124]
miR-155 (FC ≥ 0.1;FC ≥ 7.3)	Sens.: 60–90%; Spec.:88–90%	AUC:0.76–0.92	Sharaf-Eldin, W et al., 2020 [124]
miR-572 (FC ≥ 4.5)	Sens.: 90%; Spec.: 68%;	AUC: 0.80	Sharaf-Eldin, W et al., 2020 [124]
IL-17		OR: 1.21 p = 0.029	Xiang M et al., 2022 [125]
IL-13		OR: 1.06	Xiang M et al., 2022 [125]
IL-16		OR: 0.97	Xiang M et al., 2022 [125]
IL-18		OR: 1.10	Xiang M et al., 2022 [125]
IL-1b		OR: 1.04	Xiang M et al., 2022 [125]
IL-1ra		OR: 1.15	Xiang M et al., 2022 [125]
IL-2		OR: 1.16	Xiang M et al., 2022 [125]
IL2ra		OR: 1.01	Xiang M et al., 2022 [125]
IL-4		OR: 0.95	Xiang M et al., 2022 [125]
IL-5		OR: 0.94	Xiang M et al., 2022 [125]
IL-6		OR: 0.81	Xiang M et al., 2022 [125]
IL-8		OR: 1.04	Xiang M et al., 2022 [125]

There is no standard by which the classification of NPSLE is possible. It cannot even be differentiated from other nervous system-related complications. Diagnosing it is a bit of a challenge as this manifestation of SLE has not been researched like LN. Diagnostic tests are also not available to find this disease. Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple organ systems. Neuropsychiatric (NP) involvement is one of the most serious disorders in SLE and is usually associated with a poor prognosis (126). Neuropsychiatric (NP) manifestations occur in 40–90% of patients, with symptoms ranging from anxiety, depression, and cognitive impairment to psychosis, which are collectively referred to as neuropsychiatric lupus (NPSLE) or central nervous system (CNS) lupus and remain a major cause of mortality in SLE population (127). NPSLE may be among the earliest signs of SLE, but NP-SLE manifestations lack correlation with systemic disease flare. As neuropsychiatric symptoms are non-specific and clinically validated biomarkers for diagnosis are nonexistent, primary NPSLE diagnosis is routinely documented by ruling out secondary causes and in some cases may even go undiagnosed. NP-SLE can be subdivided into focal or diffuse syndromes. Focal NP-SLE presents as focal seizures, strokes, movement disorders, and/or migraine or cluster headache and may involve a predominant ischemic-vascular pathway. Patients with diffuse NP-SLE present with symptoms including psychosis, mood disorder, cognitive dysfunction, acute confusional states, and headaches other than migraine, or cluster headaches and/or anxiety disorders. Despite the devastating impact of both focal and diffuse NP-SLE on health-related quality of life, underlying disease mechanisms remain largely unknown, often leading to palliative rather than therapeutic protocols (128).

Recently, much focus has been on finding Novel Biomarkers that have the potential to help in the diagnosis of complex disorders. According to et al. level of Gal-9 was significantly elevated in CSF in NPSLE Patients in comparison with non-SLE with a p-value of 0.093. (103). According to et al. Among SLE patients those with LN have significant levels of sMer, sAXL, and GAS6 levels than patients without LN. High sMer, sAXL and GAS6 levels of LN tended to suffer from proliferative glomerulonephritis. Furthermore, the sAXL and GAS6 levels had also a strong positive correlation with Activity Index in LN patients. (17) A significantly increased expression of lncRNA-Cox2 was reported in SLE patients with neurological manifestations (P = 0.007). There was a marked increase in the serum expression level of HOTAIR in SLE patients with the presence of cutaneous manifestations, photosensitivity, and anti-cardiolipin antibodies IgG and IgM.CSF anti-UCH-L1 diagnostics potential with 91% specificity,

organ involvement; CSF UCH-L1 with SLEDAI.(90) Serum levels of anti-UCH58-69 can be used non-invasive diagnostic biomarker; associated with SLEDAI. (91)

Perspective on NPSLE

Several potential biomarkers for NPSLE diagnosis, evaluation, and treatment have been identified. CSF α-Klotho, miR-23a, serum IL-6, miR-155, M-CSF, CSF lipocalin-2, and IgM have demonstrated the possibility for diagnosis. CSF IL-8, IL-13, and G-CSF may predict therapy response, while serum IFN-α and NSE are promising biomarkers for evaluating disease activity. Despite progress, there are still many obstacles to overcome in the knowledge of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE). The therapeutic utility of diagnostic biomarkers is limited, and the underlying mechanisms of NPSLE remain insufficiently understood. Additionally, research on prognosis is limited. To overcome these constraints, future studies should investigate CSF biomarkers, improve classification schemes, and make use of cutting-edge technologies like as proteomics and genomics. International cooperation is necessary to carry out extensive research and enhance progress in this area.

Figure 2

The sensitivity and specificity of the top 10 most accurate biomarkers for neuropsychiatric SLE (NPSLE)

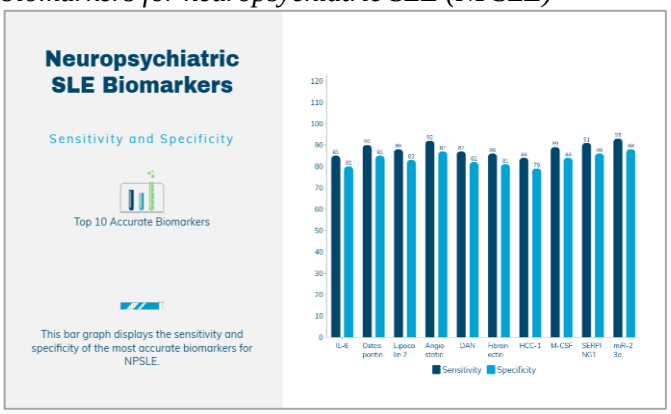
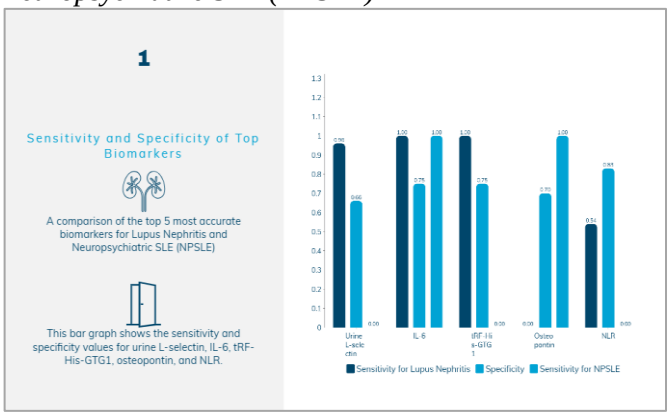


Figure 3

The Sensitivity and Specificity of the Top 5 Most Accurate Biomarkers for both Lupus Nephritis and Neuropsychiatric SLE (NPSLE)



RESULT

We found 211 relevant articles. After further analysis, we selected up to 128 articles and used them in our study. We found a lot of biomarkers that can help in diagnosis, prognosis D.A, and even drug response assessment.

DISCUSSION

This review integrates recent developments in the discovery and validation of new biomarkers for Systemic Lupus Erythematosus (SLE), with special emphasis on their application in the diagnosis, monitoring of disease activity, prediction of flares, and particularly tackling the intricacies of Lupus Nephritis (LN) and Neuropsychiatric SLE (NPSLE). The last five years have seen notable advances in the identification of a wide variety of potential biomarkers from blood, urine, and cerebrospinal fluid (CSF), including cytokines, serum proteins, genetic markers (such as non-coding RNAs), complement components, and autoantibodies. Our review identifies a number of promising biomarkers that provide better diagnostic and prognostic performance than conventional markers. For example, new cytokine biomarkers such as IL-6, IL-10, IL-16, IL-18, IL-1ra, and IL-1β have been found to have robust correlations with disease activity in both LN and NPSLE. Serum biomarkers Osteopontin and Lipocalin-2 (NGAL) and CSF markers M-CSF have shown promise in distinguishing disease states. The incorporation of genetic biomarkers such as certain miRNAs (e.g., miR-21, miR-155, miR-146a), lncRNAs (e.g., linc0597), and circRNAs (e.g., hsa_circ_0006689) provides novel opportunities for dec iphering SLE pathogenesis and possibly disease susceptibility and progression.

The complement system remains a vital field of biology, with classic markers such as C3 and C4 still being useful for diagnosis and tissue activity measurements. New data also indicate the efficacy of complement activation products such as iC3b and C3dg in capturing disease activity and tissue damage. Autoantibodies, outside of the established anti-dsDNA and ANA, are being further defined by the recognition of NET-binding subsets and new targets such as DNASE1L3, and they provide the potential for more specific diagnostic and prognostic uses. In particular, the predictive value of baseline IgA2 anti-dsDNA antibodies for response to belimumab highlights the significance of personalized medicine strategies in SLE.

For LN, the review highlights the major advances in the identification of urinary biomarkers like uNGAL, uKIM-1, and urine L-selectin, which hold promising sensitivity and specificity for diagnosis and monitoring

of activity with a potential decrease in the use of invasive biopsies. Mixtures of urinary proteins, such as AGP-1, LPGDS, transferrin, ceruloplasmin, MCP-1, and sVCAM-1, are even more promising in predicting active LN accurately. In addition, serum biomarkers such as VCAM-1, ICAM-1, syndecan-1, hyaluronan, and thrombomodulin provide information regarding endothelial activation and can potentially be used as early markers of nephritic flares.

The diagnostic and explanatory challenge of NPSLE continues to be relevant. NPSLE can be one of the first manifestations of SLE, but its expression is not typically correlated with systemic exacerbations of disease. Because neurological and psychiatric symptoms do not have specificities and there are no clinically proven biomarkers for diagnosis, primary NPSLE diagnosis is typically established by exclusion of secondary etiologies and in some instances may even not be diagnosed. NP-SLE can be classified into focal or diffuse syndromes. Focal NP-SLE usually manifests as focal seizures, strokes, movement disorders, and/or migraine or cluster headache and may be associated with a major ischemic-vascular pathway. Diffuse NP-SLE patients manifest with the following symptoms: psychosis, mood disorder, cognitive impairment, acute confusional states, headaches other than migraine or cluster headache, and/or anxiety disorders. In spite of the destructive effect of both focal and diffuse NP-SLE on health-related quality of life, disease mechanisms are poorly understood and in many cases result in palliative instead of therapeutic regimens. In recent years, a lot of attention has been paid to the identification of new biomarkers that could potentially be used for the diagnosis of multifactorial disorders such as NPSLE.

For example, Galectin-9 levels were significantly higher in the CSF of NPSLE patients than in non-SLE individuals. Furthermore, among SLE patients, those with LN had significantly higher levels of sMer, sAXL, and GAS6 than patients without LN, with elevated levels of these biomarkers in LN being associated with proliferative glomerulonephritis and the Activity Index in LN patients. A highly elevated expression of lncRNA-Cox2 was described in SLE patients presenting neurological manifestations. Additionally, serum HOTAIR expression levels were very high in SLE patients with cutaneous presentation, photosensitivity, and anti-cardiolipin antibodies IgG and IgM. CSF anti-UCH-L1 has diagnostic potential with very high specificity, and CSF levels of UCH-L1 relate to SLEDAI. Serum concentrations of anti-UCH58-69 can also serve as a non-invasive diagnostic biomarker and correlate with SLEDAI.

Various possible biomarkers for the diagnosis, assessment, and treatment of NPSLE have been noted. CSF α-Klotho, miR-23a, serum IL-6, miR-155, M-CSF, CSF lipocalin-2, and IgM have proved useful for diagnosis. CSF IL-8, IL-13, and G-CSF can predict response to therapy, whereas serum IFN-α and NSE are potential biomarkers for assessing disease activity. While all this has been remarkable progress, there are still numerous hurdles to clear regarding our knowledge of NPSLE. Diagnostic utility of the therapeutic biomarkers is limited, and the mechanisms of NPSLE are poorly understood. Prognostic studies are also few in number. These limitations should be addressed by exploring CSF biomarkers, enhancing classification systems, and applying advanced technology such as proteomics and genomics. Global collaborative efforts are needed to conduct a wide range of research and accelerate advancements in the difficult field of NPSLE. The convergence of multi-omics strategies, integrating genomics, transcriptomics, proteomics, and metabolomics, has vast potential to elucidate the complex pathogenesis of SLE and develop more complete and robust biomarker panels. Such panels, with biomarkers derived from various sources of biological material (blood, urine, CSF) and classes (cytokines, autoantibodies, genetic markers), might provide a more complete representation of the state of the disease, enhancing diagnostic sensitivity, disease activity measurement, and prediction of flares and treatment response.

In spite of the encouraging results discussed, some limitations and avenues for future research are worth considering. Most of the biomarkers discussed need to be validated in larger, independent cohorts from various ethnic backgrounds to establish their clinical usefulness. Standardization of assays and establishment of definite cut-off values for these biomarkers are essential for their use in clinical practice. Longitudinal studies would be required to maximize their prognostic and predictive significance, specifically in observing progression of disease as well as treatment response with passage of time.

In addition, studies should aim to determine the functional significance of these new biomarkers in the immunopathogenesis of SLE. Clarifying how these molecules lead to inflammation, autoantibody generation, and organ injury would reveal important insights into disease mechanisms and even offer potential therapeutic targets.

In summary, the past five years have provided an abundance of promising biomarkers that have the potential to enhance the diagnosis and treatment of SLE, especially its renal and neuropsychiatric manifestations. Although the results are promising, strict validation and additional mechanistic research are needed to bring these findings into clinically relevant tools that can ultimately enhance the lives of those living with SLE. The establishment of highly sensitive and specific, non-invasive, multi-biomarker panels continues to be a major focus for future investigation in this area.

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