

狼疮性肾炎复发的相关生物标志物

韩 雪, 李 秋*

重庆医科大学附属儿童医院肾脏内科, 国家儿童健康与疾病临床医学研究中心, 儿童发育疾病研究教育部重点实验室, 儿童代谢与炎症性疾病重庆市重点实验室, 重庆

收稿日期: 2025年3月18日; 录用日期: 2025年4月11日; 发布日期: 2025年4月22日

摘 要

狼疮性肾炎(LN)是系统性红斑狼疮(SLE)的常见并发症之一。LN复发是慢性肾脏疾病进展甚至最终达到终末期肾病的重要危险因素, 严重影响患者的预后及生存质量。目前传统的临床指标如尿蛋白定量、血清肌酐、尿沉渣、抗dsDNA抗体、抗C1q抗体、补体水平以及肾活检对于提示LN的早期复发不够敏感或特异。因此, 长期以来一直寻找能够更好的监测LN疾病活动和识别LN复发的生物标志物。本文总结了与LN复发有关的传统的和新型生物标志物的研究现状以指导LN的临床管理。

关键词

狼疮性肾炎, 生物标志物, 复发, 早期预警

Biomarkers of Relapses of Lupus Nephritis

Xue Han, Qiu Li*

Department of Nephrology, Children's Hospital of Chongqing Medical University, National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing Key Laboratory of Pediatric Metabolism and Inflammatory Diseases, Chongqing

Received: Mar. 18th, 2025; accepted: Apr. 11th, 2025; published: Apr. 22nd, 2025

Abstract

Lupus Nephritis (LN) is one of the common complications of systemic lupus erythematosus (SLE). LN relapse is an important risk factor for the progression to chronic kidney disease and even end-stage renal disease, which seriously affects the prognosis and quality of life of patients. Currently, traditional clinical markers such as urine protein quantification, serum creatinine, urinary sediment, anti-dsDNA antibody, anti-C1q antibody, complement level, and renal biopsy are not sensitive or specific enough to identify early relapse of LN. Therefore, biomarkers that can better monitor LN

*通讯作者。

文章引用: 韩雪, 李秋. 狼疮性肾炎复发的相关生物标志物[J]. 临床医学进展, 2025, 15(4): 2391-2399.
DOI: 10.12677/acm.2025.1541192

disease activity and recognize LN relapse have long been sought. The current status of research on traditional and novel biomarkers associated with LN relapses are summarized in this article to guide the clinical management of LN.

Keywords

Lupus Nephritis, Biomarkers, Relapse, Early Warning

Copyright © 2025 by author(s) and Hans Publishers Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

1. 引言

系统性红斑狼疮(Systemic Lupus Erythematosus, SLE)是一种复杂的自身免疫性疾病,其临床表现极为多样。狼疮性肾炎(Lupus Nephritis, LN)是 SLE 最常见、最严重的临床表现之一,其发病率和死亡率均较高[1][2],严重影响了患者的预后。尽管 LN 患者的疗效总体上有所改善, LN 的 5 年和 10 年肾脏存活率有所增加,但 LN 复发率仍较高。LN 复发是慢性肾脏疾病进展甚至最终达到终末期肾病的重要危险因素,并且额外的免疫抑制治疗可能导致更多的治疗相关并发症,从而增加发病率和死亡率,并且导致更沉重的医疗负担[3]-[5]。肾脏复发往往预示着长期肾脏预后不良,因此,识别 LN 复发风险更高的患者,进行早期诊断并早期治疗至关重要。

既往研究发现了与 LN 有关的多种传统实验室生物学标志物包括血清和肾脏疾病相关指标,但是大多数研究是单中心研究,队列、样本量存在显著差异,导致结果不确切,并且对于预测 LN 复发的作用有限。迄今为止,没有单一生物标志物被证实为对 LN 复发的预测敏感和有效[6]。随着蛋白质组学和代谢组学的发展, LN 复发相关生物标志物的研究取得一定进展,因此本文旨在总结与 LN 复发有关的传统的和新型生物标志物的研究现状以寻找可靠有效的生物学指标以指导 LN 的临床管理。

2. 传统生物标志物

2.1. 尿蛋白定量

肾脏复发包括肾病性复发和肾炎性复发,肾病性复发指的是 LN 完全缓解后尿蛋白水平上升>1 g 或部分缓解后蛋白尿水平较前增加 2 倍以上;肾炎性复发是指 LN 缓解后血肌酐水平增加大于等于基础值的 25%,伴有或不伴有尿蛋白的增加[7]。因此尿蛋白定量正常并不能排除患者复发的可能性。同时由于感染等情况也可以引起尿蛋白定量增加,所以用尿蛋白定量增加来判断肾脏复发时应综合考虑[8]。

2.2. 血清肌酐

血清肌酐水平增加往往提示肾脏损害加重,预示着发生了肾炎性复发,但是对于 LN 肾脏复发的早期识别作用有限。并且当肾病性复发时,血清肌酐水平无明显升高,所以无法仅通过这一个指标来判断是否发生了肾脏复发。

2.3. 活动性尿沉渣

尿中管型、红细胞数量增加有助于提示 LN 病情活动,但是活动性尿沉渣不具有疾病特异性,标本污染或尿路感染时也可不同程度地出现此改变[9]。因此在判断 LN 是否出现肾脏复发时,应考虑有无尿

路感染等因素的混杂。

2.4. 抗双链 DNA 抗体

既往研究表明, 血清抗 dsDNA 抗体的增加通常先于狼疮复发。此外, 在抗 dsDNA 抗体水平升高后对患者进行预防性治疗可降低后续肾脏复发可能性[9]-[11]。但也有研究表明抗 dsDNA 抗体的预测效能欠佳[12], 这可能与抗 dsDNA 特异性不高有关, 如肝炎、感染、其他风湿性疾病也可引起抗 dsDNA 阳性, 因此临床实际应用价值有限。

2.5. 血清补体

补体系统与 SLE 密切相关[13], 初次诊断时 C3/C4 降低与预后不良相关[14]。然而一些研究表明, C3/C4 预测 LN 或肾脏复发作用有限[15] [16]。总体而言, C3 (75%/71%)和 C4 (48%/71%)用于识别肾脏复发的灵敏度/特异性较低[9], 并且由于其指标在患者取得临床缓解后很长时间内一直处于比较稳定的水平, 因此不适宜用于 LN 肾脏复发的早期识别。

2.6. 抗 C1q 抗体

C1q 是补体激活经典途径的第一组分和识别蛋白, 它在清除凋亡细胞和维持免疫耐受中发挥了至关重要的作用。抗 C1q 抗体对 SLE 无特异性, 可存在于其他自身免疫性疾病和与狼疮疾病无关的肾脏疾病中, 如低补体血症性荨麻疹性血管炎综合征(HUVS)和硬皮病[17] [18]。多数研究发现 SLE 患者中抗 C1q 抗体的存在与 LN 有关[19] [20]。大多数作者认为抗 C1q 抗体阴性可以排除活动性肾脏疾病[21] [22], 且有研究表明抗 C1q 抗体滴度可能有助于预测 LN 复发[21]。

2.7. 肾活检

肾活检是确诊、评估 LN 活动度的金标准, 但由于是有创性检查, 在缓解期的患者很少接受重复肾活检。因此, 通过早期重复肾活检在组织学上识别 LN 肾脏复发十分困难, 而且对于复发后的 LN 患者, 也可因患者病情严重或主观不愿意接受肾活检使重复肾活检的实施受到限制。综上其对于早期判断肾脏复发的作用有限。

3. 新型生物标志物

3.1. 尿液生物标志物

LN 患者的尿液是生物标志物的潜在丰富来源。许多参与 LN 自身免疫反应的相关分子通过尿液的形式从受损的肾脏中排出, 因此可以直接反映肾脏的受损情况。

3.1.1. 肿瘤坏死因子样凋亡微弱诱导剂(TNF-Like Weak Inducer of Apoptosis, TWEAK)

主要由单核细胞和巨噬细胞产生, 作为促炎症细胞因子起作用。几种与疾病活动相关的尿细胞因子/趋化因子, 如 IL-6、MCP-1 和 IP 10, 受 TWEAK 调节[23] [24]。一些横断面研究发现与非活动性肾炎和慢性稳定性肾炎的 SLE 患者相比, 活动性 LN 患者和肾脏复发患者中的 uTWEAK 显著更高[25] [26]。TWEAK 在尿中的水平似乎在 LN 的活动期显著升高, 并在缓解期下降[27]-[29]。uTWEAK 有望成为一个 LN 复发的预测指标。

3.1.2. 尿脂联素(Urinary Adiponectin)

脂联素是一种脂肪细胞来源的细胞因子, 除了在代谢和葡萄糖调节中的核心作用外, 还能调节炎症[30]-[32]并诱导 MCP-1 的产生[33]。脂联素在 LN 患者的尿液中显著升高[34] [35], 且与非活动性肾炎的

SLE 患者、其他非狼疮性肾病患者以及健康对照相比, LN 肾脏复发期间尿脂联素显著升高[30]。纵向研究显示在肾脏复发的 2 个月前尿脂联素就开始升高, 并与蛋白尿和血清肌酐相关[30]。

3.1.3. 尿中性粒细胞明胶酶相关载脂蛋白(Urinary Neutrophil Gelatinase-Associated Lipocalin, uNGAL)

uNGAL 是一种可溶性蛋白, 是脂质运载蛋白家族的成员。Brunner 等人[36]比较了儿童期发病的 SLE 与 JIA 对照病例的尿 NGAL (uNGAL)水平, 发现活检证实为 LN 的 SLE 患者的 NGAL 水平显著高于对照组, 但未发现无肾炎的 SLE 患者的 NGAL 水平升高。此外, NGAL 与疾病活动的临床评分和肾组织病理学活动评分密切相关, 但与慢性评分或肾损害指数无关, 这突出表明尿 NGAL 是 SLE 肾脏复发的潜在生物标志物[36]。在进一步的研究中, 尽管 pSLE 患者的血浆和尿 NGAL 水平均显著升高, 但只有 uNGAL 水平随着全身或肾脏疾病活动性的恶化而显著升高[37]。RUBINSTEIN 等人[37]在研究中发现尿 NGAL 水平在 LN 复发前 3~6 个月开始升高, 在复发预警方面较血清抗 dsDNA 抗体滴度更优。

3.1.4. 尿粘附分子

细胞间粘附分子-1 (ICAM-1)和血管细胞粘附分子-1 (VCAM-1)是迄今为止在 LN 患者中研究的最常见的粘附分子[26] [38] [39]。Pizarro 等人[40]发现活动期 SLE 患者的尿 VCAM-1 水平高于非活动期 SLE 患者, 血清 VCAM-1 水平与总体疾病活动性相关。活动性肾患者的尿 VCAM-1 水平高于血清 VCAM-1 水平, 尿 VCAM-1 水平与蛋白尿及 SLEDAI 密切相关[40]。

ICAM-1 在免疫介导的肾脏疾病(包括 LN)中具有重要作用, 其可能是通过促进白细胞与肾实质的粘附来发挥作用[41] [42]。许多研究发现 ICAM-1 在鼠和人 LN 中的表达增加[43] [44]。总体而言, 粘附分子 VCAM-1 和 ICAM-1 似乎在 LN 中具有生物标志物的潜力。

3.1.5. 尿肾损伤分子(uKim-1)

Kim-1 是一种跨膜蛋白, 在肾小管间质炎症和纤维化中起作用, 其表达上调可见于急性肾缺血、多囊肾、慢性肾病和 LN 患者中[45]-[48]。一项研究[49]显示与非活动性 LN 患者相比, 活动性 LN 患者的 uKim-1 水平显著升高。此外, 在活动性 LN 组中 uKim-1 水平与蛋白尿和肾小管损伤相关, 这提示 uKim-1 在评估 LN 活动性中有潜在价值。但能否用于 LN 复发的早期预警尚需要临床的验证和证实。

3.1.6. 尿单核细胞趋化蛋白-1 (uMCP-1)

MCP-1 主要由活化的单核-巨噬细胞、T 细胞和自然杀伤细胞表达, 能吸引血液中的单核细胞向炎症部位和肿瘤部位募集。许多研究发现 LN 患者的 uMCP-1 显著升高, 并且与 SLE 疾病活动性以及肾脏组织学疾病活动性相关[50] [51]。在一些纵向研究中 uMCP-1 似乎早在肾脏复发的前 2~4 个月就开始升高, 并随着类固醇治疗所达到临床缓解而降低, 而在难治性患者中 uMCP-1 仍然很高, 这增加了使用 uMCP-1 进行疾病监测或预测肾复发的可能性[52] [53]。

3.1.7. 转化生长因子- β (TGF- β)

TGF- β 在炎症调节和肾纤维化的进展中起重要作用[54] [55], 它通过刺激血管内皮生长因子(VEGF)的表达[56]使血管通透性增高从而导致蛋白尿。尿 TGF- β mRNA 的表达与临床疾病活动、SLEDAI 评分和组织学活动指数相关[52]。研究发现活动性 LN 患者中 TGF- β 的血浆水平降低和尿排泄增加[57]。因此 TGF- β 可作为一个潜在的生物标志物用于预测 LN 的疾病复发和慢性化。

3.1.8. 微小 RNA (microRNA, miRNA)

miRNAs 是一种短的非编码 RNA, 通过调节靶基因的表达而发挥作用。在先前的一项研究中, 与健康对照组相比, 活动性 LN 患者尿沉渣中 miR-146a 和 miR-155 的水平较高[58]。另一项研究发现, 活动性 LN 患者的尿 miR-200a、miR-200c、miR-141、miR-429 和 miR-192 水平低于健康对照组[59]。上述研

研究表明尿沉渣 miRNA 水平可能是有用的生物标志物, 应考虑进一步验证其有效性。

3.1.9. 尿液生物标志物联合诊断 LN

BRUNNER 等人[35]基于 6 种尿生物标志物浓度的测量构建了一个组合以评估 LN 的活动性, 称为 LN 活动性指标(Renal Activity Index for Lupus, RAIL), 包括 NGAL、肾损伤因子-1 (KIM-1)、铜蓝蛋白、脂联素、血红素结合蛋白和 MCP-1。RAIL 包含的 6 种生物标志物除 MCP-1 之外, 其余 5 种在保护肾脏免受炎症损伤方面均有很强的生物学作用。研究显示 RAIL 组合预测 LN 活动的灵敏度高达 92%; 此外, 其能够在治疗 3 个月内预测疗效, 可以作为 LN 活动性以及治疗反应的预测因素[60]。该指标综合了多个生物标志物, 每种标志物均提供独立的信息, 联合几种生物标志物综合评估可以在一定程度上更早期识别 LN 复发。但由于该研究的样本数量有限, 未来该结果需要在其他人群中进行大规模的研究以验证其性能。

3.2. 血清生物标志物

3.2.1. 白介素(IL)

目前研究发现 IL-6、17 与 LN 疾病活动相关[61] [62], IL-17 可诱导产生细胞因子和趋化因子, 从而募集炎症细胞损伤靶器官。IL-6 可促进 Th2 和 Th17 辅助淋巴细胞适应性反应以及 B 细胞的增殖、分化产生抗体。研究发现活动性 LN 患者的血清 IL-6 和 IL-17 水平明显高于非活动性 LN 患者[63], 且待病情稳定后血清 IL-17 水平出现明显下降[64]。因此我们可以通过监测 IL-6 和 IL-17 的水平早期识别 LN 复发。

3.2.2. 补体 C3b

2016 年的一项研究[65]进一步解释了补体 C3b 对 LN 的预测作用, 其研究结果显示与抗补体 C1q IgG 相比, 抗补体 C3b IgG 对 LN 的敏感性较低, 但特异性更强。LN 复发时, 抗补体 C3b IgG 水平呈上升趋势, 提示抗补体 C3b IgG 对识别 LN 复发有较强的特异性, 但其敏感性低, 未来需要更大样本量研究来证实。

3.2.3. 血清集落刺激因子-1 (CSF-1)

狼疮性肾炎发病时肾小管会表达 CSF-1, 随着病情发展, CSF-1 的表达增加。研究发现血清 CSF-1 的升高预示着 LN 的发生, 而血清或尿液中 CSF-1 的升高则预示着 LN 的复发, 甚至在有其他 SLE 表现的患者中, CSF-1 的升高也早于肾小球功能障碍的临床证据和常规血清学指标[66] [67]。这些研究结果表明连续监测 SLE 患者血清或尿液中 CSF-1 水平可反映肾脏组织病理学, 并且能预测 LN 的发生及复发。

3.2.4. 趋化因子

LN 的发病过程中有趋化因子的参与, 它通过介导免疫细胞的激活和募集淋巴细胞到炎症部位起作用。既往研究[68]发现许多血清趋化因子与 SLE 疾病活动密切相关, 且 CXCL 11、CXCL 13、CXCL 10 (IP-10)和 CCL 3 (MIP 1a)与 LN 相关性较强。另一研究也发现[69], 活动性 LN 患者的血清 CCL 5 (RANTES)、CCL 2 (MCP-1)、CCL 19、IFN- γ 诱导的单核因子(IFN- α)、IP-10、CXCL 11 和 IL-8 (构成趋化因子评分)显著高于非活动性和非肾性狼疮患者。此外也发现趋化因子 CCL 2、CCL 3、CCL 5、CXCL 10、CXCL 12 和 CXCL 13 的水平在活动性 LN 患者的血清和尿液中均升高[70] [71]。需要进一步的纵向研究来确定这些趋化因子在预测肾脏复发中的效用, 并评估它们与肾脏组织病理学的相关性。

4. 总结

LN 的发病机制很复杂, 病情迁延。LN 患者有较高的病死率, 反复的肾脏复发会加重肾脏损害, 严

重影响患儿的预后。因此早期预测患儿复发在改善患儿远期预后方面尤为重要。尽管目前已经发现了大量用于预测和评估 LN 复发的新型生物学指标, 但目前大部分指标的有效性还有待进一步验证。到目前为止, 这些新的生物标志物尚未被标准化用于日常临床实践, 或者取代用于监测疾病进展和预测肾脏复发的传统生物标志物。仅靠单一生物标志物来预测 LN 复发的作用有限, 未来 LN 生物标志物研究的方向应集中于联合几种生物标志物综合评估, 这可能更有助于早期预测 LN 复发并及时干预。

参考文献

- [1] Yap, D.Y.H. and Lai, K.N. (2010) Cytokines and Their Roles in the Pathogenesis of Systemic Lupus Erythematosus: From Basics to Recent Advances. *Journal of Biomedicine and Biotechnology*, **2010**, Article ID: 365083. <https://doi.org/10.1155/2010/365083>
- [2] Mok, C.C. (2010) Biomarkers for Lupus Nephritis: A Critical Appraisal. *Journal of Biomedicine and Biotechnology*, **2010**, Article ID: 638413. <https://doi.org/10.1155/2010/638413>
- [3] Andrade, S.d.O., Julio, P.R., Nunes de Paula Ferreira, D. and Appenzeller, S. (2021) Predicting Lupus Flares: Epidemiological and Disease Related Risk Factors. *Expert Review of Clinical Immunology*, **17**, 143-153. <https://doi.org/10.1080/1744666x.2020.1865156>
- [4] Parikh, S.V., Nagaraja, H.N., Hebert, L. and Rovin, B.H. (2014) Renal Flare as a Predictor of Incident and Progressive CKD in Patients with Lupus Nephritis. *Clinical Journal of the American Society of Nephrology*, **9**, 279-284. <https://doi.org/10.2215/cjn.05040513>
- [5] Tamirou, F. and Houssiau, F.A. (2021) Management of Lupus Nephritis. *Journal of Clinical Medicine*, **10**, Article No. 670. <https://doi.org/10.3390/jcm10040670>
- [6] Gensous, N., Marti, A., Barnetche, T., Blanco, P., Lazaro, E., Seneschal, J., *et al.* (2017) Predictive Biological Markers of Systemic Lupus Erythematosus Flares: A Systematic Literature Review. *Arthritis Research & Therapy*, **19**, Article No. 238. <https://doi.org/10.1186/s13075-017-1442-6>
- [7] Bertsias, G.K., Tektonidou, M., Amoura, Z., Aringer, M., Bajema, I., Berden, J.H.M., *et al.* (2012) Joint European League against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) Recommendations for the Management of Adult and Paediatric Lupus Nephritis. *Annals of the Rheumatic Diseases*, **71**, 1771-1782. <https://doi.org/10.1136/annrheumdis-2012-201940>
- [8] Fine, D.M., Ziegenbein, M., Petri, M., Han, E.C., McKinley, A.M., Chellini, J.W., *et al.* (2009) A Prospective Study of Protein Excretion Using Short-Interval Timed Urine Collections in Patients with Lupus Nephritis. *Kidney International*, **76**, 1284-1288. <https://doi.org/10.1038/ki.2009.344>
- [9] Birmingham, D., Irshaid, F., Nagaraja, H., Zou, X., Tsao, B., Wu, H., *et al.* (2010) The Complex Nature of Serum C3 and C4 as Biomarkers of Lupus Renal Flare. *Lupus*, **19**, 1272-1280. <https://doi.org/10.1177/0961203310371154>
- [10] Bootsma, H., Spronk, P., de Boer, G., Limburg, P., Kallenberg, C., Derksen, R., *et al.* (1995) Prevention of Relapses in Systemic Lupus Erythematosus. *The Lancet*, **345**, 1595-1599. [https://doi.org/10.1016/s0140-6736\(95\)90114-0](https://doi.org/10.1016/s0140-6736(95)90114-0)
- [11] Ho, A., Magder, L.S., Barr, S.G. and Petri, M. (2001) Decreases in Anti-Double-Stranded DNA Levels Are Associated with Concurrent Flares in Patients with Systemic Lupus Erythematosus. *Arthritis & Rheumatism*, **44**, 2342-2349. [https://doi.org/10.1002/1529-0131\(200110\)44:10<2342::aid-art397>3.0.co;2-8](https://doi.org/10.1002/1529-0131(200110)44:10<2342::aid-art397>3.0.co;2-8)
- [12] Pan, N., Amigues, I., Lyman, S., Duculan, R., Aziz, F., Crow, M., *et al.* (2013) A Surge in Anti-dsDNA Titer Predicts a Severe Lupus Flare within Six Months. *Lupus*, **23**, 293-298. <https://doi.org/10.1177/0961203313515763>
- [13] Binder, E. and Edelbauer, M. (2013) Use of Biomarkers in the Management of Children with Lupus. *Current Rheumatology Reports*, **15**, Article No. 312. <https://doi.org/10.1007/s11926-012-0312-0>
- [14] Watson, L. and Beresford, M.W. (2012) Urine Biomarkers in Juvenile-Onset SLE Nephritis. *Pediatric Nephrology*, **28**, 363-374. <https://doi.org/10.1007/s00467-012-2184-y>
- [15] Welch, T.R. and Blystone, L.W. (2009) Renal Disease Associated with Inherited Disorders of the Complement System. *Pediatric Nephrology*, **24**, 1439-1444. <https://doi.org/10.1007/s00467-008-1027-3>
- [16] Moroni, G., Quaglini, S., Radice, A., Trezzi, B., Raffiotta, F., Messa, P., *et al.* (2015) The Value of a Panel of Autoantibodies for Predicting the Activity of Lupus Nephritis at Time of Renal Biopsy. *Journal of Immunology Research*, **2015**, Article ID: 106904. <https://doi.org/10.1155/2015/106904>
- [17] Orbai, A., Truedsson, L., Sturfelt, G., Nived, O., Fang, H., Alarcón, G.S., *et al.* (2014) Anti-c1q Antibodies in Systemic Lupus Erythematosus. *Lupus*, **24**, 42-49. <https://doi.org/10.1177/0961203314547791>
- [18] Norsworthy, P. and Davies, K.A. (2003) Complement Components and Their Autoantibodies. *Molecular Biotechnology*,

- 23, 259-270. <https://doi.org/10.1385/mb.23:3:259>
- [19] Calatroni, M., Moroni, G., Conte, E., Stella, M., Reggiani, F. and Ponticelli, C. (2024) Anti-c1q Antibodies: A Biomarker for Diagnosis and Management of Lupus Nephritis. A Narrative Review. *Frontiers in Immunology*, **15**, Article ID: 1410032. <https://doi.org/10.3389/fimmu.2024.1410032>
 - [20] Akhter, E., Burlingame, R., Seaman, A., Magder, L. and Petri, M. (2011) Anti-c1q Antibodies Have Higher Correlation with Flares of Lupus Nephritis than Other Serum Markers. *Lupus*, **20**, 1267-1274. <https://doi.org/10.1177/0961203311411597>
 - [21] Moroni, G., Trendelenburg, M., Del Papa, N., Quaglini, S., Raschi, E., Panzeri, P., *et al.* (2001) Anti-c1q Antibodies May Help in Diagnosing a Renal Flare in Lupus Nephritis. *American Journal of Kidney Diseases*, **37**, 490-498. <https://doi.org/10.1053/ajkd.2001.22071>
 - [22] Cai, X., Yang, X., Lian, F., Lin, X., Liang, M., Li, J., *et al.* (2010) Correlation between Serum Anti-C1q Antibody Levels and Renal Pathological Characteristics and Prognostic Significance of Anti-C1q Antibody in Lupus Nephritis. *The Journal of Rheumatology*, **37**, 759-765. <https://doi.org/10.3899/jrheum.090779>
 - [23] Tucci, M., Barnes, E.V., Sobel, E.S., Croker, B.P., Segal, M.S., Reeves, W.H., *et al.* (2004) Strong Association of a Functional Polymorphism in the Monocyte Chemoattractant Protein 1 Promoter Gene with Lupus Nephritis. *Arthritis & Rheumatism*, **50**, 1842-1849. <https://doi.org/10.1002/art.20266>
 - [24] Tian, S., Li, J., Wang, L., Liu, T., Liu, H., Cheng, G., *et al.* (2007) Urinary Levels of RANTES and M-CSF Are Predictors of Lupus Nephritis Flare. *Inflammation Research*, **56**, 304-310. <https://doi.org/10.1007/s00011-007-6147-x>
 - [25] Schwartz, N., Su, L., Burkly, L.C., Mackay, M., Aranow, C., Kollaros, M., *et al.* (2006) Urinary TWEAK and the Activity of Lupus Nephritis. *Journal of Autoimmunity*, **27**, 242-250. <https://doi.org/10.1016/j.jaut.2006.12.003>
 - [26] Adhya, Z., Borozdenkova, S. and Karim, M.Y. (2011) The Role of Cytokines as Biomarkers in Systemic Lupus Erythematosus and Lupus Nephritis. *Nephrology Dialysis Transplantation*, **26**, 3273-3280. <https://doi.org/10.1093/ndt/gfq860>
 - [27] Dong, X., Zheng, Z., Luo, X., Ding, J., Li, Y., Li, Z., *et al.* (2018) Combined Utilization of Untimed Single Urine of MCP-1 and TWEAK as a Potential Indicator for Proteinuria in Lupus Nephritis. *Medicine*, **97**, e0343. <https://doi.org/10.1097/md.00000000000010343>
 - [28] Moloi, M.W., Rusch, J.A., Omar, F., Ekrikpo, U., Dandara, C., Bello, A.K., *et al.* (2021) Urinary MCP-1 and TWEAK as Non-Invasive Markers of Disease Activity and Treatment Response in Patients with Lupus Nephritis in South Africa. *International Urology and Nephrology*, **53**, 1865-1873. <https://doi.org/10.1007/s11255-020-02780-9>
 - [29] Costa-Reis, P., Maurer, K., Petri, M.A., Levy Erez, D., Zhao, X., Faig, W., *et al.* (2022) Urinary HER2, TWEAK and VCAM-1 Levels Are Associated with New-Onset Proteinuria in Paediatric Lupus Nephritis. *Lupus Science & Medicine*, **9**, e000719. <https://doi.org/10.1136/lupus-2022-000719>
 - [30] Rovin, B.H., Song, H., Hebert, L.A., Nadasdy, T., Nadasdy, G., Birmingham, D.J., *et al.* (2005) Plasma, Urine, and Renal Expression of Adiponectin in Human Systemic Lupus Erythematosus. *Kidney International*, **68**, 1825-1833. <https://doi.org/10.1111/j.1523-1755.2005.00601.x>
 - [31] Wulster-Radcliffe, M.C., Ajuwon, K.M., Wang, J., Christian, J.A. and Spurlock, M.E. (2004) Adiponectin Differentially Regulates Cytokines in Porcine Macrophages. *Biochemical and Biophysical Research Communications*, **316**, 924-929. <https://doi.org/10.1016/j.bbrc.2004.02.130>
 - [32] Neumeier, M., Weigert, J., Schäffler, A., Wehrwein, G., Müller-Ladner, U., Schölmerich, J., *et al.* (2006) Different Effects of Adiponectin Isoforms in Human Monocytic Cells. *Journal of Leukocyte Biology*, **79**, 803-808. <https://doi.org/10.1189/jlb.0905521>
 - [33] Rovin, B.H. and Song, H. (2006) Chemokine Induction by the Adipocyte-Derived Cytokine Adiponectin. *Clinical Immunology*, **120**, 99-105. <https://doi.org/10.1016/j.clim.2006.01.010>
 - [34] Diaz-Rizo, V., Bonilla-Lara, D., Gonzalez-Lopez, L., Sanchez-Mosco, D., Fajardo-Robledo, N.S., Perez-Guerrero, E.E., *et al.* (2017) Serum Levels of Adiponectin and Leptin as Biomarkers of Proteinuria in Lupus Nephritis. *PLOS ONE*, **12**, e0184056. <https://doi.org/10.1371/journal.pone.0184056>
 - [35] Brunner, H.I., Gulati, G., Klein-Gitelman, M.S., Rouster-Stevens, K.A., Tucker, L., Ardoin, S.P., *et al.* (2018) Urine Biomarkers of Chronic Kidney Damage and Renal Functional Decline in Childhood-Onset Systemic Lupus Erythematosus. *Pediatric Nephrology*, **34**, 117-128. <https://doi.org/10.1007/s00467-018-4049-5>
 - [36] Brunner, H.I., Mueller, M., Rutherford, C., Passo, M.H., Witte, D., Grom, A., *et al.* (2006) Urinary Neutrophil Gelatinase-Associated Lipocalin as a Biomarker of Nephritis in Childhood-Onset Systemic Lupus Erythematosus. *Arthritis & Rheumatism*, **54**, 2577-2584. <https://doi.org/10.1002/art.22008>
 - [37] Suzuki, M., Wiers, K.M., Klein-Gitelman, M.S., Haines, K.A., Olson, J., Onel, K.B., *et al.* (2008) Neutrophil Gelatinase-Associated Lipocalin as a Biomarker of Disease Activity in Pediatric Lupus Nephritis. *Pediatric Nephrology*, **23**, 403-412. <https://doi.org/10.1007/s00467-007-0685-x>

- [38] Wu, C., Yang, M., Zhou, Z., *et al.* (2015) Urinary Soluble Intercellular Adhesion Molecule-1 and Vascular Cellular Adhesion Molecule-1: Potential Biomarkers of Active Lupus Nephritis. *Journal of Southern Medical University*, **35**, 1272-1276, 1282.
- [39] Howe, H.S., Kong, K.O., Thong, B.Y., Law, W.G., Chia, F.L.A., Lian, T.Y., *et al.* (2012) Urine sVCAM-1 and sICAM-1 Levels Are Elevated in Lupus Nephritis. *International Journal of Rheumatic Diseases*, **15**, 13-16. <https://doi.org/10.1111/j.1756-185x.2012.01720.x>
- [40] Robak, E., Woźniacka, A., Sysa-Jedrzejowska, A., *et al.* (2001) Serum Levels of Angiogenic Cytokines in Systemic Lupus Erythematosus and Their Correlation with Disease Activity. *European Cytokine Network*, **12**, 445-452.
- [41] Guan, J., Wang, G., Tam, L., Kwan, B., Li, E., Chow, K., *et al.* (2012) Urinary Sediment ICAM-1 Level in Lupus Nephritis. *Lupus*, **21**, 1190-1195. <https://doi.org/10.1177/0961203312451334>
- [42] Frank, P.G. and Lisanti, M.P. (2008) ICAM-1: Role in Inflammation and in the Regulation of Vascular Permeability. *American Journal of Physiology-Heart and Circulatory Physiology*, **295**, H926-H927. <https://doi.org/10.1152/ajpheart.00779.2008>
- [43] Pallis, M., Robson, D.K., Haskard, D.O. and Powell, R.J. (1993) Distribution of Cell Adhesion Molecules in Skeletal Muscle from Patients with Systemic Lupus Erythematosus. *Annals of the Rheumatic Diseases*, **52**, 667-671. <https://doi.org/10.1136/ard.52.9.667>
- [44] Belmont, H.M., Buyon, J., Giorio, R. and Abramson, S. (1994) Up-Regulation of Endothelial Cell Adhesion Molecules Characterizes Disease Activity in Systemic Lupus Erythematosus. The Schwartzman Phenomenon Revisited. *Arthritis & Rheumatism*, **37**, 376-383. <https://doi.org/10.1002/art.1780370311>
- [45] Ichimura, T., Bonventre, J.V., Bailly, V., Wei, H., Hession, C.A., Cate, R.L., *et al.* (1998) Kidney Injury Molecule-1 (KIM-1), a Putative Epithelial Cell Adhesion Molecule Containing a Novel Immunoglobulin Domain, Is Up-Regulated in Renal Cells after Injury. *Journal of Biological Chemistry*, **273**, 4135-4142. <https://doi.org/10.1074/jbc.273.7.4135>
- [46] Han, W.K., Alinani, A., Wu, C., Michaelson, D., Loda, M., McGovern, F.J., *et al.* (2005) Human Kidney Injury Molecule-1 Is a Tissue and Urinary Tumor Marker of Renal Cell Carcinoma. *Journal of the American Society of Nephrology*, **16**, 1126-1134. <https://doi.org/10.1681/asn.2004070530>
- [47] Kuehn, E.W., Park, K.M., Somlo, S. and Bonventre, J.V. (2002) Kidney Injury Molecule-1 Expression in Murine Polycystic Kidney Disease. *American Journal of Physiology-Renal Physiology*, **283**, F1326-F1336. <https://doi.org/10.1152/ajprenal.00166.2002>
- [48] Han, W.K., Bailly, V., Abichandani, R., Thadhani, R. and Bonventre, J.V. (2002) Kidney Injury Molecule-1 (KIM-1): A Novel Biomarker for Human Renal Proximal Tubule Injury. *Kidney International*, **62**, 237-244. <https://doi.org/10.1046/j.1523-1755.2002.00433.x>
- [49] Nozaki, Y., Kinoshita, K., Yano, T., Shiga, T., Hino, S., Niki, K., *et al.* (2014) Estimation of Kidney Injury Molecule-1 (kim-1) in Patients with Lupus Nephritis. *Lupus*, **23**, 769-777. <https://doi.org/10.1177/0961203314526292>
- [50] Chan, R.W., Lai, F.M., Li, E.K., Tam, L., Wong, T.Y., Szeto, C.Y., *et al.* (2004) Expression of Chemokine and Fibrosing Factor Messenger RNA in the Urinary Sediment of Patients with Lupus Nephritis. *Arthritis & Rheumatism*, **50**, 2882-2890. <https://doi.org/10.1002/art.20471>
- [51] Rovin, B.H., Doe, N. and Tan, L.C. (1996) Monocyte Chemoattractant Protein-1 Levels in Patients with Glomerular Disease. *American Journal of Kidney Diseases*, **27**, 640-646. [https://doi.org/10.1016/s0272-6386\(96\)90097-9](https://doi.org/10.1016/s0272-6386(96)90097-9)
- [52] Torabinejad, S., Mardani, R., Habibagahi, Z., Roozbeh, J., Khajedehi, P., Pakfetrat, M., *et al.* (2012) Urinary Monocyte Chemotactic Protein-1 and Transforming Growth Factor-B in Systemic Lupus Erythematosus. *Indian Journal of Nephrology*, **22**, 5-12. <https://doi.org/10.4103/0971-4065.91179>
- [53] Marks, S.D., Shah, V., Pilkington, C. and Tullus, K. (2010) Urinary Monocyte Chemoattractant Protein-1 Correlates with Disease Activity in Lupus Nephritis. *Pediatric Nephrology*, **25**, 2283-2288. <https://doi.org/10.1007/s00467-010-1605-z>
- [54] Avihingsanon, Y., Phumesin, P., Benjachat, T., Akkasilpa, S., Kittikowit, V., Praditpornsilpa, K., *et al.* (2006) Measurement of Urinary Chemokine and Growth Factor Messenger RNAs: A Noninvasive Monitoring in Lupus Nephritis. *Kidney International*, **69**, 747-753. <https://doi.org/10.1038/sj.ki.5000132>
- [55] Lema, G.P.D., Maier, H., Nieto, E., Vielhauer, V., Luckow, B., Mampaso, F., *et al.* (2001) Chemokine Expression Precedes Inflammatory Cell Infiltration and Chemokine Receptor and Cytokine Expression during the Initiation of Murine Lupus Nephritis. *Journal of the American Society of Nephrology*, **12**, 1369-1382. <https://doi.org/10.1681/asn.v12i71369>
- [56] Kitamura, S., Maeshima, Y., Sugaya, T., Sugiyama, H., Yamasaki, Y. and Makino, H. (2004) Transforming Growth Factor-B₁ Induces Vascular Endothelial Growth Factor Expression in Murine Proximal Tubular Epithelial Cells. *Nephron Experimental Nephrology*, **95**, e79-e86. <https://doi.org/10.1159/000073675>
- [57] Hammad, A.M., Youssef, H.M. and El-Arman, M.M. (2006) Transforming Growth Factor Beta 1 in Children with Systemic Lupus Erythematosus: A Possible Relation with Clinical Presentation of Lupus Nephritis. *Lupus*, **15**, 608-612.

- <https://doi.org/10.1177/0961203306071873>
- [58] Szeto, C. (2014) Urine miRNA in Nephrotic Syndrome. *Clinica Chimica Acta*, **436**, 308-313. <https://doi.org/10.1016/j.cca.2014.06.016>
- [59] Wang, G., Tam, L., Li, E., Kwan, B., Chow, K., Luk, C., *et al.* (2011) Serum and Urinary Free MicroRNA Level in Patients with Systemic Lupus Erythematosus. *Lupus*, **20**, 493-500. <https://doi.org/10.1177/0961203310389841>
- [60] Aljaberi, N., Bennett, M., Brunner, H.I. and Devarajan, P. (2019) Proteomic Profiling of Urine: Implications for Lupus Nephritis. *Expert Review of Proteomics*, **16**, 303-313. <https://doi.org/10.1080/14789450.2019.1592681>
- [61] Chun, H., Chung, J., Kim, H., Yun, J., Jeon, J., Ye, Y., *et al.* (2007) Cytokine IL-6 and IL-10 as Biomarkers in Systemic Lupus Erythematosus. *Journal of Clinical Immunology*, **27**, 461-466. <https://doi.org/10.1007/s10875-007-9104-0>
- [62] Jin, W. and Dong, C. (2013) IL-17 Cytokines in Immunity and Inflammation. *Emerging Microbes & Infections*, **2**, e60. <https://doi.org/10.1038/emi.2013.58>
- [63] Abdel Galil, S.M., Ezzeldin, N. and El-Boshy, M.E. (2015) The Role of Serum IL-17 and IL-6 as Biomarkers of Disease Activity and Predictors of Remission in Patients with Lupus Nephritis. *Cytokine*, **76**, 280-287. <https://doi.org/10.1016/j.cyto.2015.05.007>
- [64] 何援军, 黄德东, 来晓维, 等. 狼疮性肾炎患者血清白细胞介素-17和白细胞介素-23表达及意义[J]. 中华临床免疫和变态反应杂志, 2016, 10(2): 117-124.
- [65] Birmingham, D.J., Bitter, J.E., Ndukwe, E.G., Dials, S., Gullo, T.R., Conroy, S., *et al.* (2016) Relationship of Circulating Anti-C3b and Anti-C1q IGG to Lupus Nephritis and Its Flare. *Clinical Journal of the American Society of Nephrology*, **11**, 47-53. <https://doi.org/10.2215/cjn.03990415>
- [66] Menke, J., Iwata, Y., Rabacal, W.A., Basu, R., Yeung, Y.G., Humphreys, B.D., *et al.* (2009) CSF-1 Signals Directly to Renal Tubular Epithelial Cells to Mediate Repair in Mice. *Journal of Clinical Investigation*, **119**, 2330-2342. <https://doi.org/10.1172/jci39087>
- [67] Menke, J., Amann, K., Cavagna, L., Blettner, M., Weinmann, A., Schwarting, A., *et al.* (2015) Colony-Stimulating Factor-1. *Journal of the American Society of Nephrology*, **26**, 379-389. <https://doi.org/10.1681/asn.2013121356>
- [68] Bauer, J.W., Baechler, E.C., Petri, M., Batliwalla, F.M., Crawford, D., Ortmann, W.A., *et al.* (2006) Elevated Serum Levels of Interferon-Regulated Chemokines Are Biomarkers for Active Human Systemic Lupus Erythematosus. *PLOS Medicine*, **3**, e491. <https://doi.org/10.1371/journal.pmed.0030491>
- [69] Fu, Q., Chen, X., Cui, H., Guo, Y., Chen, J., Shen, N., *et al.* (2008) Association of Elevated Transcript Levels of Interferon-Inducible Chemokines with Disease Activity and Organ Damage in Systemic Lupus Erythematosus Patients. *Arthritis Research & Therapy*, **10**, R112. <https://doi.org/10.1186/ar2510>
- [70] Schiffer, L., Worthmann, K., Haller, H. and Schiffer, M. (2014) CXCL13 as a New Biomarker of Systemic Lupus Erythematosus and Lupus Nephritis—From Bench to Bedside? *Clinical and Experimental Immunology*, **179**, 85-89. <https://doi.org/10.1111/cei.12439>
- [71] Kulkarni, O. and Anders, H.J. (2008) Chemokines in Lupus Nephritis. *Frontiers in Bioscience*, **13**, 3312-3320. <https://doi.org/10.2741/2927>