

原发性膜性肾病预后生物标志物的研究进展

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摘要

膜性肾病(Membranous Nephropathy, MN)是成人肾病综合征(Nephrotic Syndrome, NS)的主要病因, 预后因个体化具有差异性。部分患者可能在10年内发展至终末期肾病(End-stage renal disease, ESRD)。因此迫切需要无创且可靠的生物标志物来早期识别中高危患者, 延缓疾病进展和改善预后。本文将对原发性膜性肾病(Primary membranous nephropathy, PMN)的预后生物标志物进行叙述, 旨在为膜性肾病的病情评估、早期干预及预后改善提供参考。

关键词

原发性膜性肾病, 预后, 标志物

Research Advances in Prognostic Biomarkers of Primary Membranous Nephropathy

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Abstract

Membranous Nephropathy (MN) is a leading cause of Nephrotic Syndrome (NS) in adults, and its prognosis varies considerably among individuals. Some patients may progress to end-stage renal

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disease (ESRD) within 10 years. Therefore, there is an urgent need for non-invasive and reliable biomarkers to early identify patients at intermediate to high risk, in order to delay disease progression and improve outcomes. This article reviews prognostic biomarkers for primary membranous nephropathy (PMN), aiming to provide references for disease assessment, early intervention, and prognosis improvement in MN.

Keywords

Membranous Nephropathy, Prognosis, Biomarkers

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1. 引言

膜性肾病(Membranous Nephropathy, MN)是成人肾病综合征(Nephrotic Syndrome, NS)最常见原因,多见于老年人,尤其是男性。约80%的病例为原发性膜性肾病(Primary membranous nephropathy, PMN)。由于多种因素影响,不同患者的预后存在显著差异。据统计[1],约有三分之一的患者在10年内会发展至终末期肾病。早期诊断和治疗是延缓或防止膜性肾病进展的最佳策略。虽然肾活检是肾病确诊的金标准,但其有创性和难以重复性限制了其应用。因此迫切需要无创且可靠的生物标志物,帮助评估病情、指导治疗,从而改善预后[2]。近年来,随着科研的进步,部分生物标志物已被发现,在原发性膜性肾病的预后预测中展示了较传统标志物更大的潜力。

2. 免疫学生物标志物

2.1. 抗体

PLA2R 是 PMN 最常见的靶抗原,其与自身抗体结合形成上皮下沉积物,导致足细胞损伤且形成蛋白尿[3]。抗 PLA2R 抗体在 PMN 中具有复发预测和预后判断的作用。低基线和降低的抗 PLA2R 抗体水平强烈预测自发缓解,抗体水平变化往往先于临床症状。抗 PLA2R 抗体滴度变化可预测治疗反应,也可预测长期结局。一项研究[4]指出,血清抗 PLA2R 抗体滴度 ≥ 150 RU/ml 时,其在疾病预后中起主要作用,滴度升高,临床缓解时间延长。相对抗体阳性患者而言,血清 PLA2R 抗体阴性患者的自发缓解率更高[5]。有前瞻性多中心研究表明[6],抗 PLA2R1 抗体水平是 PMN 患者长期预后的预测因素。

临床中通常通过检测血清抗 PLA2R-IgG 来分析抗 PLA2R 抗体,PLA2R-IgG4 在 PMN 的病理损害机制中占主导地位。PLA2R-IgG4 是 PMN 预后评估的有效生物标志物[7],同时在治疗效果分析方面也有效[8]。研究证实[9]血清 PLA2R-IgG4 和 PLA2R-IgG4/IgG 与肾小球 PLA2R 抗原的相关性比 PLA2R-IgG 更强,高 PLA2R-IgG4 和 PLA2R-IgG4/IgG 水平是 PMN 缓解的高风险因素。有学者提出,初诊时抗 CysR-IgG4、抗 CTLD1-IgG4 和抗 CTLD6-7-8-IgG4 的低浓度水平预示着治疗后病情的快速缓解。结合不同表位特异性 IgG4 抗体的水平、估算肾小球滤过率(eGFR)和尿蛋白水平,可以更准确地预测 PMN 的预后[10]。因此,临床医生可以结合 PLA2R 相关生物标志物,为患者制定更有效的治疗方案。

2.2. 补体

补体系统在 PMN 发病机制中起重要作用,甘露糖结合凝集素途径(Mannose-binding lectin pathway, LP)是补体系统激活主要途径之一。Pal 等人研究发现[11]甘露糖结合凝集素(Mannose-bound lectins, MBL)

与 PLA2R-IgG4 共同沉积在 PMN 患者上皮细胞下, 形成膜攻击复合物, 损伤足细胞导致蛋白尿。肾小球 MBL 阳性组表现出更严重的间质纤维化和更差的临床结局, 高 MBL 是蛋白尿和肾功能缓解的不利预测因子[12]。然而, 有研究表明[13] MBL 沉积的患者比无 MBL 沉积的患者更快地达到不完全缓解, MBL 沉积是 PMN 患者蛋白尿缓解的有利预测因子。这种差异可能源于研究设计不同, 包括随访时间、患者基线特征(如年龄、肾功能状态)、以及缓解标准的定义等。我们提出假说: MBL 可能在疾病早期通过激活补体途径加重损伤, 而在治疗干预或疾病后期, 其免疫调节功能可能促进炎症消退。这一假说仍需通过前瞻性、多中心、分层研究进一步验证。在 PMN 患者中, 血清 C3 ≤ 93.4 mg/dl 预测不良肾脏结局, 即 C3 沉积越大, 血清 C3 水平越低, 意味着长期肾功能不良[14]。此外, 补体因子 B (Complement factor B, CFB) 水平与 PMN 的疾病活动性和进展密切相关, 高基线血清 CFB 水平可作为不良预后和肾功能衰退的预测因子[15]。

2.3. 细胞因子

生长分化因子-15 (Growth differentiation factor-15, GDF-15) 与抗炎途径相关, 与炎症、心血管及肺部疾病、癌症等病理机制的抗炎途径相关。研究表明[16], GDF-15 是尿微量白蛋白增加的独立危险因素, 可作为一种生物标志物预测慢性肾脏病的不良预后。致癌抑制因子 2 (Suppression of tumorigenicity, ST-2) 是肾脏疾病严重程度标志物。进一步研究证实[17], GDF-15 和 ST2 是与 PMN 严重程度相关的生物标志物, 二者联合模型可有效预测 PMN 不完全缓解的危险因素, 但单独使用时均不能作为 PMN 预后的独立预测因子。

白细胞介素-8 (Interleukin-8, IL-8) 是由内皮细胞和巨噬细胞产生的促炎细胞因子, 可吸引中性粒细胞和淋巴细胞至炎症部位。Souto 等人发现[18], 特发性肾病综合征 (Idiopathic nephrotic syndrome, INS) 患者血清 IL-8 浓度升高, 且肾病期血清 IL-8 水平明显高于缓解期。尿 IL-8 水平升高与肾组织严重炎症反应有关, 尿 IL-8 浓度 > 61.65 pg/ml 是 PMN 患者发生不良预后的危险因素[19], 控制患者体内 IL-8 水平有利于改善预后。另一研究发现[20], 基线血清白细胞介素-35 (IL-35) 可作为预测 PMN 预后的生物标志物。IL-35 水平越低的 PMN 患者, 缓解率越低, 缓解时间越长。

PMN 以足细胞膜抗原特异性为特征, 足细胞损伤可引发蛋白尿。1 型肾母细胞瘤 (Wilms tumor type 1, WT1) 作为足细胞标志蛋白 (Podocalyxin, PODXL) 的调节因子, 可防止足突粘连, 维持足细胞的正常结构。miR-193a 高表达会促进足突的广泛消失, 其对肾病的促进作用依赖于对 WT1 的抑制。研究发现, miR-193a 联合 WT1 和 PODXL 可评估 PMN 预后, 且能区分不同阶段的预后。但目前尚不清楚 miR-193a/WT1/PODXL 轴在 PMN 病因学中的作用, 且该研究的结果可能不适用于非华裔 PMN 患者[21]。

2.4. 细胞亚节

全身免疫炎症指数 (Systemic immune inflammatory index, SII) 和泛免疫炎症值 (Pan-immune inflammation value, PIV) 被认为是预测中低危 PMN 患者不缓解的可靠标志物[22]。一项回顾性研究显示[14], 中性粒细胞与淋巴细胞比值 (Neutrophil-to-lymphocyte ratio, NLR) 能预测 PMN 患者的预后, $NLR > 3.34$ 提示不良肾脏结局。NLR 是 PMN 蛋白尿未缓解的独立危险因素, 对于 24 小时蛋白尿 ≥ 1 g 和 CKD3-4 期的高 NLR 患者应予以更多关注[23]。此外, 较高的单核细胞-淋巴细胞比值 (Monocyte-lymphocyte ratio, MLR) 与较差的肾脏结局相关, 可能可用于预测 PMN 患者预后, 但需要更大规模和更长时间的研究进一步证实[24]。B 细胞活化因子 (B-cell activation factor, BAFF) 是 TNF 细胞因子超家族的跨膜蛋白, 高血清 BAFF 水平提示 PMN 患者病情严重、疾病进展不良[25]。

B 淋巴细胞库可以反映 MN 的 B 细胞免疫状态, 既往的研究结果显示免疫球蛋白重链 (Immunoglobulin

heavy chain, IGH)库是预测 PMN 预后的潜在生物标志物[2]。部分研究发现 MN 的发病机制与 T 细胞密切相关, T 细胞受体 β 链(T-cell receptor beta chain, TCR β)库具有潜力作为非侵入性生物标志物预测 PMN 患者预后,但仍需要更多队列研究进一步验证[26]。

3. 蛋白尿生物标志物

研究表明[27],肾活检时的 24 小时蛋白尿水平是不良预后的独立预测因子。基线蛋白尿水平越高,预后越差[28]。初始蛋白尿(疗程中前 6 个月的平均蛋白尿水平)是肾脏病结局或肾病性蛋白尿进展的独立预测因子。相比基线蛋白尿,其能避免单次检测的偏倚和不稳定性,还可反映蛋白尿初始治疗反应。初始血尿也是肾病性蛋白尿进展的独立危险因素,动态检测和有效管理蛋白尿、血尿有助于改善 PMN 患者预后[7]。与 24 小时尿蛋白相比,尿白蛋白与肌酐比值(Urine albumin to creatinine ratio, UACR)昼夜变化是预测 PMN 预后的更简便方法,能更精准地识别需进一步全面评估的患者[29]。

4. 病理生物标志物

严重慢性肾小管间质损伤是肾脏不良预后的危险因素。老年 PMN 患者肾小球硬化和肾小管间质损伤与蛋白尿严重程度呈正相关,早期初始免疫抑制治疗可获益[30]。研究证实[31],单独或联合评估局灶节段性硬化症(Focal segmental sclerosis, FSGS)、肾小管萎缩(Tubular atrophy, TA)、血管透明质瘤病(Vascular hyalinosis, VH)和间质纤维化(Interstitial fibrosis, IF)这 4 项组织学指标的存在和程度,可预测肾功能结局。PMN 伴肾小球硬化和肾小管间质损伤的患者可从免疫抑制治疗中获益。因此, Maria J Stangou 等提出的综合评分 FSTIV 可以帮助评估疾病严重程度,指导治疗方案制定。

5. 基因生物标志物

PMN 的易感性与遗传因素密切相关,其中 HLA 等位基因控制 PLA2R 抗体的产生,与 PMN 结局相关。研究发现[32], DRB1 *1501 和 DRB1 *0301 是危险等位基因。还有研究表明,携带 HLA 等位基因 DRB1 *13:01、DQB1 *06:03、DRB1 *04:05 和 DQB1 *03:02 中的任何一种,均与中国 PLA2R 相关 PMN 患者的不良预后独立相关[33]。

6. 代谢相关生物标志物

基线时高浓度血清胆固醇(Total cholesterol, TC)和非高密度脂蛋白胆固醇(Non-high-density lipoprotein cholesterol, non-HDL-C)是 PMN 患者蛋白尿不缓解的独立危险因素[34]。PLA2R 抗原及抗 PLA2R 抗体是预测 PMN 疾病预后的有效生化指标,高 TC、non-HDL-C 和低密度脂蛋白胆固醇(Low-density lipoprotein cholesterol, LDL-C)可以独立预测抗 PLA2R 阳性[35]。使用他汀类药物可让 PMN 患者获益。一项队列研究发现[36],基线血清尿酸(Uric acid, UA)是 PMN 患者肾脏预后不良的独立预测因子。高 UA 还是 PMN 患者发生急性肾损伤(Acute kidney injury, AKI)的独立预测因素,AKI 增加 PMN 预后不良风险[37]。因此,早期干预 UA 有利于 PMN 患者预后。

7. 小结与展望

上述标志物在可靠性、安全性及便捷性方面有一定的优势,但有些生物标志物(如 MBL)仍存在争议,需更多设计严谨、大规模、长期随访的研究来明确其临床意义,以推进临床实践进展。值得注意的是,多数生物标志物并非孤立存在,而是嵌入在 PMN 复杂的免疫炎症网络中。PLA2R 抗体通过激活补体经典途径和凝集素途径(可能涉及 MBL),并可能进一步招募和活化替代途径(如通过 CFB),导致足细胞损伤和蛋白尿;补体活化产物(如 C3a、C5a)进一步招募炎症细胞,释放 IL-8、GDF-15 等细胞因子,放大炎

症反应;同时,B细胞和T细胞的活化与调控异常(如BAFF升高、TCR β 库)维持了自身免疫反应;最终,持续的免疫炎症导致肾小球硬化和间质纤维化,表现为eGFR下降和蛋白尿持续。因此,未来的研究应致力于将多个标志物(包括CFB等补体成分)整合进统一的病理生理框架中,构建多指标联合预测模型。此外,遗传背景(如HLA基因型)和代谢因素(如脂质代谢异常、高尿酸血症)可能通过调控免疫反应和炎症状态,影响生物标志物的表达和预后价值,提示我们在评估预后时需综合考虑。

当前PMN预后生物标志物的研究仍处于快速发展阶段,虽已有多个潜在标志物显示出临床价值,但其标准化检测方法、临界值界定以及多中心验证仍需进一步完善。尤其是对于存在争议的标志物(如MBL),应开展设计严谨、长期随访的研究以明确其临床意义。未来的研究方向应包括:1、开展大规模前瞻性队列研究,验证现有标志物的预后价值,并建立多指标联合预测模型;2、深入探索标志物之间的相互作用及其在PMN病理生理通路中的具体机制;3、结合组学技术(如蛋白质组、转录组、单细胞测序)发现新的标志物,并探索其与临床表型的关联;4、关注特殊人群(如老年患者、合并甲状腺功能障碍者[38])的生物标志物特征,实现更精细的风险分层;5、推动生物标志物指导下的个体化治疗策略,如基于抗PLA2R抗体滴度或补体水平调整免疫抑制方案。

总之,生物标志物的发展有望为实现PMN的早期干预、动态监测和精准治疗提供有力工具。通过整合多维度信息,构建可靠的预后评估体系,将有助于改善患者长期肾脏结局。

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