· 综述 ·

慢性肾脏病患者主要心血管不良事件危险因素的临床研究与进展

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【摘要】 慢性肾脏病（chronic kidney disease，CKD）患者由于肾脏结构与功能损伤，引发全身多种并发症及多器官功能损害，降低患者生活质量，严重威胁患者生命健康，其中主要心血管不良事件（major adverse cardiovascular events，MACE）是导致患者预后不良的重要原因。然而，普通人群MACE危险因素在指导CKD临床治疗与风险评价时具有一定局限性。近年随着医学水平的进步，针对识别和评价CKD患者MACE危险因素的研究有了较大发展，多种临床指标与参数被纳入研究。本文现就此做一综述，以便为临床工作提供参考。

【关键词】 慢性肾脏病；主要心血管不良事件；危险因素；风险评价
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Clinical researchs and advances of risk factors for major cardiovascular adverse events in patients with chronic kidney diseases

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【**Abstract**】 Chronic kidney disease (CKD) patients have a variety of systemic complications and multiple organ dysfunctions due to the injuries of renal structures and functions, compromising quality-of-life and seriously threatening patient well-being. Among these CKDs, major cardiovascular adverse events (MACE) lead to adverse outcomes. However, risk factors of MACE in general population have certain limitations in guiding clinical treatments and risk evaluations of CKD patients. With recent medical advances, identifying and evaluating risk factors for MACE have made great strides in CKD patients and a large variety of clinical indicators and parameters have been adopted for researches. Here current understanding of risk factors of MACE of CKD patients was summarized to provide references for clinical practices.

【**Key words**】 Chronic kidney disease; Major adverse cardiovascular events; Risk factors; Risk assessment
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慢性肾脏病（chronic kidney disease CKD）定义为肾脏结构和功能损害至少持续三个月以上，主要表现为估算肾小球滤过率（estimated glomerular filtration rate，eGFR）＜60 mL·min^{-1}·（1. 73 m^2）$^{-1}$减低，伴或不伴蛋白尿症状的肾脏损害疾病[1]。数据显示，全球约15％成年人口患有CKD，截至2016年，每年新增超过2100万CKD病例，年直接死亡人数近120万[2-3]。中国目前有超过1亿CKD患者，且呈逐年上升趋势[4]。在CKD死亡患者中，约三分之一死于主要心血管不良事件（major adverse cardiovascular events，MACE）相关心血管并发症，心血管风险已成为CKD患者主要疾病负担，给患者临床治疗与生存预后带来诸多风险[5-7]。美国FDA建议，在针对心血管不良事件的研究中，应对包括心肌梗死、心源性死亡、心力衰竭等，MACE以及其他可能的终点事件进行观察[8]。

鉴于CKD患者病理机制的复杂性，普通人群中的心血管危险因素在指导其临床干预和风险评价时具有一定局限性。明确CKD患者MACE危险因素，有利于早期干预、改善及判断患者临床预后，为临床决策提供更多帮助。近年

来，随着诊疗技术进步及对病情认识的深入，CKD 患者 MACE 危险因素的识别和应用有了较大发展。本文通过查阅文献，对 CKD 患者部分 MACE 危险因素进行归纳与小结，以期为临床治疗与风险评价研究提供更多信息与帮助。

一、CKD 患者主要心血管不良事件危险因素

1. eGFR、蛋白尿与心血管不良事件　高血压与糖尿病是导致 CKD 的常见病因，既往认为患者 MACE 风险增加是其基础疾病所致。晚近研究发现，心血管疾病发生与肾脏功能损伤及蛋白尿程度有关。eGFR 与蛋白尿是衡量肾脏功能的经典指标，应被视为独立于高血压与糖尿病的 MACE 危险因素[9-10]。有研究显示，CKD 患者 MACE 风险随 eGFR 降低逐渐升高，其中 CKD5 期患者风险比（hazard ratio，HR）显著升高[11-12]。此外，蛋白尿的增加也与 CKD 患者心肌梗死的发生高度相关[13]。一项荟萃分析发现，eGFR≤75 mL·（min·1.73 m^2）$^{-1}$时，患者发生 MACE 风险呈线性上升，其中 CKD3-4 期患者心血管死亡率分别是正常人群的两倍和三倍；同时蛋白尿＞30 mg/g 患者 MACE 风险为正常个体两倍以上，并随蛋白尿量增加逐渐升高，提示即使蛋白尿微量增加也需引起临床注意。

2. 矿物质代谢紊乱与心血管不良事件　CKD 可导致患者全身矿物质和骨代谢紊乱。临床可表现为血钙、血磷及相关调节激素紊乱，骨转换、矿化、体积及线性生长或强度异常，血管或其他软组织钙化[14]，可引起代谢性骨病与心血管疾病的发生，KDIGO（Kidney Disease：Improving Global outcomes）指南将其定义为慢性肾脏病-矿物质骨代谢异常（chronic kidney disease-mineral and bone disorder，CKD-MBD）。

血液中的磷主要以无机磷酸盐形式存在，其稳态是肾脏、骨骼、肠道及甲状旁腺之间相互协调作用的结果。参与其调控的激素主要包括：甲状旁腺激素（parathyroid hormone，PTH）、骨化三醇及成纤维生长因子 23（fibroblast growth factor 23，FGF23）。大量研究表明，磷酸盐稳态失衡会给 CKD 患者带来严重的临床后果，同患者 MACE 和全因死亡风险显著相关[15-19]。Moon 等[20]研究发现，在代偿期 CKD 患者中，高磷酸血症会增加其进展为终末期肾病（end stage renal disease，ESRD）与发生死亡的风险。此外，血清磷酸盐水平升高也同移植患者 MACE 与死亡有关[19]。对于维持性血液透析患者，血清磷酸盐水平的稳定则有利于其 MACE 与死亡风险的降低[21]，因此在临床诊疗中对于不同阶段 CKD 患者的血清磷酸盐浓度应当给予一定重视。

血液中磷酸盐水平升高还可诱发 FGF23、PTH 合成分泌增加、骨化三醇减少等改变。其中 FGF23 合成分泌增加可导致 CKD 患者心室肥厚，进一步增加其死亡风险[22-23]。大量研究表明，FGF23 是 CKD 患者 MACE 及全因死亡的重要危险因素，其浓度升高不仅增加代偿期 CKD 患者 MACE 风险，也与 ESRD 进展有关[24-26]。对于 CKD-MBD 透析患者，FGF23 水平同 MACE 和死亡风险显著相关。最近研究还发现[27]，FGF23 显著介导了 CKD 患者与缺铁有关的死亡和心力衰竭。但在健康人群中，FGF23 与心血管病变没有显示出明显相关性[28]。

骨化三醇是调节血钙的重要活性物质，其合成分泌减少可诱发继发性甲状旁腺功能亢进（secondary hyperparathyroidism，SHPT），引起 PTH 合成分泌增多。有研究表明 SHPT 使 CKD 患者死亡风险增加 1.3 倍、MACE 风险增加 2.2 倍，显著影响 CKD 病情进展并增加患者骨折风险[29]。此外，Ginsberg 等[30]研究显示，CKD3 期以上患者 PTH 浓度增高与 MACE 及全因死亡显著相关。有研究者分析发现，在未进行透析治疗的 CKD4-5 期患者中，PTH 与血清磷酸盐水平升高同患者死亡风险相关，风险临界值分别为 70 pg/mL 与 3.8 mg/dL[31]。在进行血液透析的 ESRD 患者中，PTH 水平升高与心肌损害的发生密切相关[32]。另有研究发现，低 PTH 血液透析患者发生 MACE 与死亡的风险高于 SHPT 血液透析患者，这表明过高或过低的 PTH 浓度都可能增加患者预后不良风险[33]。

体内矿物质间吸收与排泄存在相互影响，除钙磷代谢紊乱外，CKD 患者还存在血镁浓度异常。有荟萃研究分析发现，血清中镁离子浓度同 CKD 患者 MACE 与全因死亡相关[34]。高镁血症同代偿期 CKD 患者和 ESRD 患者的心血管死亡（*HR*=0.71，95%*CI*：0.53～0.97，*P*=0.03）与全因死亡风险负相关（*HR*=0.86，95%*CI*：0.79～0.94，*P*=0.001），亚组分析显示，血液透析患者全因死亡风险的增加与低镁血症相关（*HR*=1.29，95%*CI*：1.12～1.50，*P*=0.0005）。此外有研究发现，低镁血症与肾移植患者 MACE 发生有关[35]。最近研究显示，24 小时尿液中镁离子浓度同 CKD1-4 期患者 MACE 有关（*HR*=1.612，95%*CI*：1.056～2.460）[36]。

Klotho 蛋白是 CKD 矿物质代谢的关键调节因子，klotho 蛋白能够协同 FGF 受体（fibroblast growth factor receptor，FGFR）结合 FGF23，具有保护肾脏功能、抗纤维化与抗血管钙化等多种功能。既往研究发现，可溶性 klotho 蛋白减少与患者肾脏功能减退、心血管系统病变有关[37-38]。Memmos 等[39]研究显示，在血液透析患者中，低 klotho 组（≤745 pg/mL）生存曲线显著低于高 klotho 组。多因素分析结果发现，低 klotho 组发生 MACE 和全因死亡的 *HR* 为 2.759（95%*CI*：1.223～6.224，*P*=0.014）。

3. 肠道微生物代谢物与心血管不良事件　肠道微生物群在人体代谢、生理和免疫过程中发挥重要作用。CKD 患者由于肾脏生理功能损伤，引起了代谢毒物排泄障碍，导致肠道菌群失调与肠道屏障功能受损，进而加重慢性内毒素堆积。其中多种肠道微生物代谢物同 CKD 患者的病情进展、心血管风险增加、尿毒症毒性和炎症有关[40]。氧化三甲胺（trimethylamine-N-oxide，TMAO）是肠道微生物与肝脏对胆碱等物质代谢所生成的一种小分子化合物[41]。作为一种已知的尿毒症毒素，TMAO 与 CKD、动脉粥样硬化、结直肠癌和 MACE 有关。有研究认为，TMAO 相关代谢产物浓度的升高与血液透析患者心源性死亡、猝死、首次心血管不良事件发生以及全因死亡有关[42]。系统评价表明，包括 CKD 患者在内，血液中高浓度 TMAO 患者有更高的 MACE 风险（*RR*=1.62，95% *CI*：1.45～1.80）与全因死亡风险（*RR*=1.63，95% *CI*：1.36～1.95），TMAO 前体物

质浓度升高会使患者MACE风险增加1.3～1.4倍[43]。最近研究显示，腹膜透析患者中，血清TMAO浓度与高血压和糖尿病的发生正相关，高浓度TMAO组与MACE风险独立相关（*HR*=2.27，95%*CI*：1.02～5.05）[44]。Zhang等[45]发现，TMAO浓度与血液透析患者MACE风险增加有关，TAMO＞4.73 mg/mL患者可能有更高风险。

硫酸对甲酚（p-cresol sulfate，PCS）与硫酸吲哚酚（indoxyl sulfate，IS）属于肠源性的蛋白质结合类尿毒症毒素（protein-bound uremic toxins，PBUTs）。PCS来源于肠道厌氧菌对苯丙氨酸和酪氨酸的分解，经肠道吸收后主要由肾小管分泌、经尿液排出。PCS可诱导白细胞生成自由基引起血管损伤，并通过激活NADPH氧化酶促进心肌细胞凋亡[46-47]。既往研究表明，PCS是老年血液透析患者全因死亡与MACE的独立危险因素，另一项研究的亚组分析显示，在血清白蛋白较低的血液透析患者中，PCS与IS水平较高的患者心源性死亡和心源性猝死风险较高[48-49]。最近研究还发现，PCS与血液透析患者主动脉硬化相关（*OR*=1.067，95%*CI*：1.002～1.136），最佳预测临界值为18.99 mg/L（AUC：0.661，95%*CI*：0.568～0.746）。IS主要由肠道细菌分解色氨酸形成的吲哚经过肝脏代谢后生成，经肾小管分泌、随尿液排泄[50]。IS可通过NF-κB信号通路、氧化应激等作用促进血管与心肌损伤[51]。Fan等[52]发现，IS

表1　MACE部分危险因素与效能

研究者	类别	MACE危险因素	CKD阶段	效能（*HR*/*OR*，95%*CI*）
Currie[12]	eGFR与蛋白尿	eGFR（45～59）		3.65（3.13～4.35）
		eGFR（30～45）		4.01（3.40～4.74）
		eGFR（15～29）		5.78（4.70～7.10）
		eGFR（＜15）		9.0（5.71～14.18）
Chickera[13]		蛋白尿	1-5	4.53（3.30～6.21）
Merhi[19]	矿物质代谢物	磷酸盐	移植后	1.14（1.00～1.31）
Moon[20]		磷酸盐	1-5	1.35（1.22～1.49）
Block[24]		FGF23	HD	1.09（1.03～1.16）
Xue[25]		FGF23	1-5	1.37（1.15～1.63）
Ginsberg[30]		PTH	3-5	1.29（1.06～1.57）
Memmos[39]		Klotho（≤745 pg/mL）	HD	2.76（1.22～6.22）
Xiong[34]		低镁	HD	1.29（1.12～1.50）
Yuan[36]		24 h尿镁	1-4	1.612（1.056～2.460）
Chang[44]	肠道微生物代谢物	TMAO	PD	2.27（1.02～5.05）
Zhang[45]		TMAO	HD	1.18（1.07～1.29）
Wu[48]		PCS	HD	1.088（1.003～1.179）
Fan[52]		IS	1-5	1.45（1.02～2.06）
Lee[60]	炎症相关物质	hs-CRP（1.0～2.99 mg/L）	1-5	1.33（0.87～2.03）
		hs-CRP（＞3.0 mg/L）		2.08（1.30～3.33）
Steinhagen[64]		IL-6	HD	1.53（1.03～2.28）
Krzanowski[69]		PTX3	5	1.18（1.02～1.37）
Amdur[65]	血浆脂蛋白	TNF-α	3-5	1.10（1.06～1.40）
Lee[71]	其他生物标志物	LDL-C（≥159 mg/dL）	3-5	1.26（1.15～1.39）
Tada[76]		LP（a）	3-5	1.11（1.06～1.16）
Forne[77]		MMP-9	3-5	1.24（1.07～1.42）
		OPN（log^2）		12.3（3.39～44.6）
		OPG（log^2）		1.33（1.07～1.66）
		VEGF		1.27（1.06～1.53）
Bae[80]		cTNFR1	1-5	2.51（1.19～5.29）
		cTNFR2		4.16（1.91～9.03）
Zoccali[79]		神经肽-Y	2-5	1.25（1.09～1.44）
Feldreich[81]		KIM-1	5	2.12（1.43～3.16）
高玉伟[78]		miR-126	2-4	0.35（0.19～0.64）

注：CKD为慢性肾脏病；MACE为主要心血管不良事件；eGFR为估算肾小球滤过率；FGF23为成纤维生长因子23；PTH为甲状旁腺激素；TMAO为氧化三甲胺；PCS为硫酸对甲酚；IS为硫酸吲哚酚；hs-CRP为高敏C反应蛋白；IL-6为白介素-6；PTX3为正五聚蛋白；TNF-α为肿瘤坏死因子-α；LDL-C：低密度脂蛋白胆固醇，LP（a）为脂蛋白a；MMP-9为基质金属蛋白酶-9；OPN为骨桥蛋白；OPG为骨保护素；VEGF为血管内皮生长因子；cTNFR为循环肿瘤坏死因子受体；KIM-1为肾损伤分子-1；HD为血液透析；PD为腹膜透析。

与CKD1-5期患者MACE风险独立相关，最佳预测临界值为 1.61 mg/100 mL（AUC=0.78，95%*CI*：0.618～0.798）。Lin等[53]研究显示，IS与血液透析患者外周动脉疾病发生有关，但与MACE没有明显关联，Gelder等[54]研究也得出相同结果。此外研究中还发现，经过6个月治疗，高通量血液滤过患者IS降低8%，血液透析患者IS增加11.9%，残余肾功能与多种PBUTs水平负相关。

以往研究认为，饮食摄入不仅能够影响肠道微生物代谢产物，还可诱发炎症反应。有研究显示，饮食炎症指数（dietary inflammatory index，DII）升高与CKD病情进展风险有关[55]。摄入蔬菜、全谷物及鱼类等可降低DII，精制谷物、红肉等则相反。Wang等[56]研究发现，长期摄入红肉会使TMAO合成增加，肾脏排泄减少，引起TMAO水平增高。因此除临床治疗外，健康教育与患者依从性对改善CKD患者预后也具有重要意义。

4. 炎症相关物质与心血管不良事件　CKD患者通常处于慢性炎症状态，以往研究显示，炎症状态能引起CKD患者心血管系统损伤、增加患者MACE风险，部分炎症标记物与CKD患者MACE风险相关[57-58]。

高敏C反应蛋白（high-sensitive C-reactive protein，hs-CRP）是临床检测机体炎症状态的重要标志物，属短正五聚蛋白，比C反应蛋白（C-reactive protein，CRP）有更高的灵敏度与特异度，可通过激活补体、参与机体免疫应答对血管造成损伤。有学者将其浓度与冠心病危险度分为五个阶段，分别为健康人群（<0.7 mg/L）、低危险组（0.7～1.1 mg/L）、需观察组（1.2～1.9 mg/L）、高危险组（2.0～3.8 mg/L）与极高危险组（>3.9 mg/L）[59]。Lee等[60]的研究发现，hs-CRP升高与CKD1-5期患者MACE及全因死亡的发生存在关联。相比较hs-CRP<1.0 mg/L的CKD患者，hs-CRP血清浓度处于1.0-2.99 mg/L和3.0 mg/L以上患者的HR分别为1.33（95% *CI*：0.87～2.03）、2.08（95% *CI*：1.30～3.33）。

白介素-6（interleukin-6，IL-6）是炎症反应重要调节因子，广泛表达于活化淋巴细胞中。其大量分泌可导致心肌肥厚，诱导心肌纤维化、抑制心脏收缩功能；同时可促进血管内皮下巨噬细胞生成，巨噬细胞吞噬低密度脂蛋白并分泌蛋白溶解酶，引起斑块破裂，增加心血管不良事件发生风险[61-62]。Stanifer等[63]研究显示，包括IL-6在内的多种炎症标记物与老年CKD1-5期患者eGFR负相关，同全因死亡风险相关（*HR*=1.13，95%*CI*：1.03～1.25）。在针对血液透析患者的研究中，患者IL-6水平明显高于对照组，并与MACE风险增加有关[64]。有研究者利用IL-6、肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）、纤维蛋白原、血清白蛋白生成综合炎症评分系统，并预测CKD患者MACE发生概率，结果显示AUC=0.73（95% *CI*：0.71～0.76）[65]。

正五聚蛋白（pentraxin-3，PTX3）属长链五聚素，为急性炎症期反应蛋白，受炎症信号刺激后水平可显著升高，在肾近曲小管细胞和成纤维细胞处表达。PTX3主要通过血清补体q1作用，导致机体发生免疫反应，加重血管和组织损伤；同时可与纤维细胞生长因子2结合，导致纤维斑块发生破裂，进而诱发MACE发生[66-68]。在针对CKD5期患者的研究中发现，透析患者PTX3水平更高，PTX3>1.43 ng/mL患者维持透析的时间更长，生存时间更短，其浓度同IL-6，Hs-CRP等多种炎症标志物正相关，是患者MACE独立危险因素（*HR*=1.18，95%*CI*：1.02～1.37，*P*=0.026）[69]。

此外，研究发现，肿瘤坏死因子相关凋亡诱导配体（tumor necrosis factor related apoptosis-inducing ligand，TRAIL）与CKD3-5期患者动脉粥样硬化进展有关，可能是CKD患者MACE潜在危险因素[70]。

5. 血浆脂蛋白异常与心血管不良事件　血浆脂蛋白异常是导致心血管疾病的重要原因之一，有针对性的干预血浆脂蛋白浓度一直是临床治疗和预防心血管疾病的重要手段。Lee等[71]研究显示，低密度脂蛋白胆固醇（low-density lipoprotein cholesterol，LDL-C）≥159 mg/dL的CKD3-5期患者发生MACE的*HR*=1.261（95%*CI*：1.451～1.388，*P*<0.001）；晚期CKD患者［eGFR<30 mL·（min·1.73 m^2）$^{-1}$］中，低浓度LDL-C（30～49 mg/dL）依然与MACE风险显著相关，表明关注CKD患者LDL-C浓度并尽早干预有利于改善临床预后。研究中还发现，除LDL-C以外，三酰甘油/高密度脂蛋白（TG/HDL-C）对于早期糖尿病CKD患者［eGFR≥30 mL·（min·1.73 m^2）$^{-1}$］的MACE风险具有一定预测价值。同类研究显示，在炎症状态下，HDL-C浓度与CKD1-5期患者MACE发生呈反向趋势，有研究者建议应将TG/HDL-C作为危险因素之一[72-73]。

脂蛋白（a）（LP（a））是LDL-C与载脂蛋白（a）的复合物，LP（a）可通过促进血栓形成、刺激炎症因子释放及抑制纤溶系统，诱发动脉粥样硬化发生[74]。有研究发现，CKD患者LP（a）浓度显著高于健康人群，这可能与患者脂蛋白合成增加或肾小球滤过功能减低有关[75]。最近研究显示，LP（a）浓度不仅同患者病情进展有关，也是CKD3-5期患者发生心肌梗死的危险因素之一（*OR*=1.11，95% *CI*=1.06～1.16，*P*<0.001）[76]。

6. 其他生物标志物与心脏影像学检查　在一些风险评价研究中，部分生物标志物与MACE风险也呈现出一定相关性。Forne等[77]研究发现，基质金属蛋白酶9（matrix metalloproteinase，MMP-9）、骨桥蛋白（osteopontin，OPN）、血管内皮生长因子（vascular endothelial growth factor，VEGF）及骨保护素（osteoclastogenesis inhibitory factor，OPG）均与CKD患者MACE风险相关。此外，循环TNF受体（circulation tumor necrosis factor receptors，cTNFR）、神经肽Y（neuropeptide Y）、肾损伤分子-1（Kidney injury molecule 1，KIM-1）和miR-126也在一些研究中显示出独立的风险预测价值[78-81]。

影像学技术作为一种几乎无创的检查手段，可以对心脏结构与功能进行更加直观动态的观察，美国心脏协会与美国心脏病学会基金会都建议对有多种危险因素或糖尿病的移植候选者进行无创心血管风险评价[82]。目前常用的影像学技术主要包括，CT血管造影（computed tomography angiography，CTA）评价冠状动脉钙化、单光子发射计算机断层扫

描(single photon emission tomography, SPET)进行心肌血流灌注成像、心脏核磁共振(cardiovascular magnetic resonance imaging, CMRI)特征追踪技术以及超声心动图(ultrasonic cardiogram, UCG)及其衍生出的斑点追踪技术(speckle-tracking echocardiography, STE)。

除上述实验室指标外,现已被证实同CKD患者MACE风险独立相关的影像学参数主要包括:(1)SPET累积压力评分(summed stress score, SSS)与累积差异评分(summed difference score, SDS)[83-85],(2)CTA冠状动脉钙化评分(Coronary artery calcium score, CACS)[86-87],(3)CMRI与STE左室总体纵向应变[88-89](global longitudinal strain, GLS)(4)UCG左室射血分数[90]、左室质量指数(left ventricular mass index, LVMI)计算[91]和左房应变[92](left atrial strain, LAS)等。

二、总结与展望

综上所述,除基础疾病外,肾脏功能损伤、毒素物质累积、炎症等多种病理生理改变给CKD患者带来严重的心血管疾病负担,使患者MACE与死亡风险持续上升。明确各种危险因素,有针对性的及时干预,利用高效能危险因素进行风险评价,有利于降低患者发病率与病死率。CKD患者MACE病理过程复杂,涉及多种危险因素间相互作用,在临床诊疗与风险评价时需多方面考虑。鉴于心血管并发症的严重后果,未来应更加关注CKD患者MACE的干预与预防,进一步探寻其发病机制,构建并优化风险预测模型,为患者、医生及医疗决策者提供更多帮助。

利益冲突　所有作者均声明没有利益冲突

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