

COVID-19相关性肾损伤研究进展

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摘要

自2019年12月发现新型冠状病毒肺炎(Corona Virus Disease 2019, COVID-19)以来, 该病以其高传染性、高致病率, 成为威胁全球的突发公共卫生事件。COVID-19造成的相关性肾损伤已在临床上受到广泛关注, 为此我们通过对COVID-19相关性肾损伤的流行病学特征、致病机制、临床防治处理等方面进行阐述, 以供临床研究决策, 改善患者临床预后。

关键词

新型冠状病毒肺炎, 肾损伤, 治疗与预防

The Research Progress of COVID-19 Related Kidney Injury

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Abstract

Since the discovery of COVID-19 (corona virus disease 2019, COVID-19) in December 2019, the disease has become a public health emergency threatening with high infectivity and high morbidity. The correlation of kidney injury caused by COVID-19 has received wide clinical attention. For this reason, we expounded the epidemiological characteristics, pathogenic mechanisms and clinical prevention and treatment of COVID-19 related kidney injury, in order to provide decisions for

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clinical research, and improve the clinical prognosis of patients.

Keywords

COVID-19, Kidney Injury, Treatment and Prevention

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1. 引言

新型冠状病毒肺炎(corona virus disease 2019, COVID-19)是由严重急性呼吸综合征冠状病毒 2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2)感染引起的传染性疾病。截止目前, 该病已造成全球感染人数超过 6.4 亿, 累计死亡人数超 600 万, 给人类的生命健康带来巨大威胁[1] [2]。

COVID-19 虽然最初损害肺部, 但也影响包括肾脏在内的许多其他器官, 病情越严重, 肾脏受累的风险越大[3] [4]。患者可出现急性肾损伤(acute kidney injury, AKI)、急性肾功能衰竭(acute renal failure, ARF), 甚至死亡。既往患有慢性肾脏疾病(chronic kidney disease, CKD)、透析及肾移植的 COVID-19 患者则拥有更高的死亡风险[5] [6]。

COVID-19 引起的相关性肾损伤已在临床上受到广泛重视和讨论, 在此我们将探讨 SARS-CoV-2 诱导肾功能损害的流行病学特征、发病机制、临床防治处理, 以提供临床研究决策。

2. 流行病学及临床特点

通过对 COVID-19 患者进行回顾性分析, 约有 40%~60% 的患者普遍存在蛋白尿、血尿和血清肌酐(SCr)升高为主要表现的肾脏损伤[7] [8] [9]。进展为 AKI 的发病率在 0.5%~80% 之间不等, 这种差异可能与各地区医疗水平、人口环境的不同有关[8] [10]。ICU 患者中 AKI 的发病率为 19%~90% 之间, 大多数患者需要肾脏替代治疗及机械通气支持治疗, 部分患者可进展为 ARF [11]。

对于出现基线 SCr 升高、基线 BUN 升高、蛋白尿、血尿和 AKI 等相关症状的 COVID-19 住院患者, 则有更高的 CKD 发生风险及死亡风险[12] [13]。老年人、男性、肥胖人群、患有基础疾病如合并 CKD、高血压、冠心病、糖尿病患者, 治疗过程中需要机械通气患者均更容易发生 AKI [14] [15] [16]。AKI 的发生预示着预后更差, 死亡风险更高。

COVID-19 相关性肾损患者病理学检查可见急性肾小管损伤、急性间质性肾炎、新发肾小球疾病等。包括刷状缘消失、液泡变性、管腔扩张、局灶节段性肾小球硬化、肾脏微血栓形成等[17] [18] [19] [20]。其肾脏 CT 检查可见不同程度密度减低、肾脏实质缺损、皮质和髓质变薄等表现[21] [22]。部分患者血管 CT 造影可显示肾动脉充盈缺损, 提示血栓形成[23] [24]。

目前的研究显示, 多数患者出院时, 肾功能及尿液分析可恢复正常, 然而多达一半的 AKI 患者肌酐没有恢复到基线水平, 可能持续存在 CKD [25]。因此, 尽早对患者肾脏功能进行检测及评估, 积极干预, 是保护肾脏, 改善患者预后的重要方式及手段。

3. 发病机制

COVID-19 对肾脏的确切作用机制尚不明确, 目前认为 COVID-19 可能会直接或间接地影响肾脏。

其直接途径是通过 SARS-CoV-2 与血管紧张素转化酶 2 (angiotensin-converting enzyme 2, ACE2) 参与介导肾脏的直接损伤。其间接途径可能与肾素 - 血管紧张素 - 醛固酮系统 (renin-angiotensin-aldosterone system, RAAS) 失衡、炎症通路激活引起的细胞因子风暴和凝血系统之间的相互作用等有关, 从而参与影响 COVID-19 患者肾脏损伤。

3.1. ACE2 参与介导肾损伤

目前已经证实, SARS-CoV-2 通过 ACE2 进入宿主细胞, 肾脏足细胞及近端小管细胞为 SARS-CoV-2 入侵肾脏的主要宿主细胞[26] [27]。病毒感染入侵肾脏细胞后, 复制增殖并破坏裂解细胞, 导致肾脏滤过、重吸收功能受限, 患者出现蛋白尿、血尿、肾功能检测异常等临床表现[28]。肾脏细胞凋亡, 死亡脱落的细胞碎片, 可进一步启动肾组织炎症瀑布效应, 这也可能是造成肾损伤的原因之一[29]。

其次, ACE2 除作为介导病毒入侵宿主细胞的主要受体外, 其亦是 RASS 的重要组成部分。随 SARS-CoV-2 入侵细胞, ACE2 表达显著下调, RASS 失衡, 导致血管紧张素 II (Ang II) 水平相对升高, 进而出现机体内环境紊乱, 导致血管收缩造成血流动力学不稳定; 其次可激活凝血途径、损害肾血管内皮, 导致肾小球功能障碍; 同时可促进过度的炎症反应及组织纤维化形成、氧化应激反应增加等造成肾脏损伤[30] [31]。

3.2. 炎症反应及细胞因子风暴形成

SARS-CoV-2 入侵可导致机体 T 淋巴细胞减少及各类炎症因子(如白细胞介素、 γ 干扰素、肿瘤坏死因子- α 、粒细胞集落刺激因子等)显著增加[32] [33]。这些炎症因子可进一步诱导炎症细胞浸润, 破坏组织修复, 进而导致患者出现全身炎症应激反应、形成细胞因子风暴及造成多器官损害。目前已证实, 细胞因子风暴与患者疾病严重程度呈正相关关系, 重症患者均存在不同程度的免疫缺陷, 其炎症细胞因子水平可明显高于轻症患者[34] [35]。

大量细胞因子可以各种方式积累于肾脏, 导致肾功能损伤。Gradin 等通过检测尿液中细胞因子含量的得出, 合并肾损患者的尿液中免疫细胞因子水平显著升高, 其中 31 种细胞因子与肾脏损伤相关, 19 种细胞因子与肌酐数值变化相关[36]。有研究表明 COVID-19 患者肾组织可见补体成分(C1q、C3、C5b-9)沉积、免疫球蛋白及损伤相关分子(脾酪氨酸激酶(Syk)、粘蛋白-1 (MUC1))高表达; 提示患者补体激活, 并且加重患者肾脏组织损伤及炎症反应[37]。

3.3. 其他因素

大多数重型及危重型 COVID-19 可出现急性呼吸窘迫综合征、多器官功能障碍, 导致机体出现低氧血症、脓毒血症、横纹肌溶解等严重并发症[38] [39], 进一步诱导肾脏组织出现灌注不足、缺血缺氧、氧化应激反应等, 加重肾脏损害, 可导致 AKI 和 CKD 的发生。

在 COVID-19 患者治疗用药中, 仍有部分药物被证实可能造成肾脏损伤。有研究证实 COVID-19 患者在接受洛匹那韦/利托那韦和羟氯喹治疗后, 出现 AKI 的高发病率。在非 ICU 患者中, 接受洛匹那韦/利托那韦和羟氯喹三联疗法后 AKI 的发病率显著增加(三联治疗: 90.5%, 对照组: 21.4%, $p = 0.002$), 接受三联疗法治疗的患者表现出更多尿或无尿性肾损伤的趋势[40]。Grein 等人的一项关于对 61 例 COVID-19 患者使用瑞德西韦的研究中报道, 12 例患者出现了严重的并发症, 包括脓毒性休克、多器官功能障碍综合征、急性肾损伤[41]。在另一项研究中, COVID-19 患者开始使用万古霉素后血肌酐和尿素浓度升高, 停用万古霉素后一些患者的血肌酐和尿素指标恢复正常[42]。其余用于 COVID-19 的治疗用药如阿兹夫定片、奈玛特韦片/利托那韦片(Paxlovid)、莫努匹拉韦、阿奇霉素等, 虽然目前尚未有其关于肾

脏不良反应的报道，但是在对患者使用该类药物时，应随时关注药物的肾毒性风险，对于肾功能不全患者应谨慎使用。

4. 治疗及预防

目前，针对 COVID-19 相关性肾损伤患者的治疗策略，仍以对症支持治疗为主。早期发现的肾功能异常患者，可积极干预，减轻肾脏负担。危重型患者可发生 AKI，则要积极查找病因，在纠正病因的同时，注意维持内环境平衡。必要时可给予连续性肾替代治疗(CRRT)或血液净化治疗。促进患者预后，降低病死率。

4.1. 抗病毒药物及抗生素药物

到目前为止，多种抗病毒及抗生素药物已经用于治疗 COVID-19。包括阿兹夫定片、奈玛特韦片/利托那韦片(Paxlovid)、瑞德西韦、莫努匹拉韦、伊维菌素、阿奇霉素等[43] [44] [45] [46]。上述药物能明显改善患者部分症状，但其同时也会导致不同程度的不良反应。大多数用于治疗 COVID-19 的药物经肾脏代谢，可能对肾损伤具有协同作用，因此需斟酌使用，尤其是多种药物联合使用时，应及时监测不良反应，以尽量减小药物对肾脏的造成损害。

4.2. 糖皮质激素

糖皮质激素具有强大的免疫抑制和调节多种生理功能的作用[47]。糖皮质激素能维持肾素、改善组织缺血再灌注的损伤、可直接保护足细胞功能并减轻肾小球组织学改变[48] [49] [50]。然而糖皮质激素使用不当时，可能会过度抑制免疫反应、延缓机体对病毒的清除、增加继发感染和其他并发症等风险[51]。因此糖皮质激素更适用于短期内治疗免疫系统过度激活的危重症 COVID-19 患者。在临床应用过程中，应准确判断窗口期，结合病情特点，足量、快速、高效、及时地对患者进行干预。注意监测不良反应，以提高危重患者治愈率，降低病死率。

4.3. 免疫治疗

目前针对于病情进展较快的 COVID-19 高危患者，多采用 COVID-19 感染者恢复期血清(convalescent plasma, CP)输注治疗、静注人免疫球蛋白(human immunoglobulin for intravenous injection, IVIG)以及托珠单抗进行免疫治疗。

CP 治疗与静注 IVIG 输注治疗两者来源及制备工艺虽有所不同，但是其目的均是为人体被动补充抗体，以促进 SARS-CoV-2 病毒清除，抑制其感染细胞。同时可抑制机体过度激活的免疫系统，来阻止细胞因子风暴形成，以减轻肺部及其他组织器官损伤。CP 治疗与静注 IVIG 输注治疗更适用于重型和危重型 COVID-19 患者，应在疾病早期干预性使用高水平抗体治疗，可降低患者病情恶化风险，降低患者的医疗资源需求及死亡风险[52] [53] [54]。

托珠单抗是一种重组人源化抗人白介素 6 (IL-6)受体单克隆抗体，可阻断 IL-6 信号介导的抗炎作用[55]。但是目前托珠单抗治疗 COVID-19 的有效性存在争议，且该药存在严重的副作用，应极度谨慎地使用该药。

4.4. 肾脏替代治疗及血液净化治疗

国家卫健委发布的《新型冠状病毒肺炎诊疗方案(试行第九版)》及中华医学会肾脏病学专家共识均认同了肾脏替代治疗(renal alternative therapy, RRT)及血液净化治疗对于危重型 COVID-19 患者的救治[2] [56]。

对于高钾血症、严重酸中毒、利尿剂无效的肺水肿或水负荷过多以及多器官功能不全时的患者，可使用连续性肾脏替代(CRRT)治疗，也可以选择血液净化治疗。通过消除炎症因子和阻断“细胞因子风暴”，从而缓解炎症反应给人体造成的损伤。发挥“肾脏支持”和“内环境支持”作用，维持水液、电解质、酸碱稳定，进而阻止或延缓病情[57] [58] [59]。

在治疗过程中可同时出现人体微量元素丢失、血药浓度下降、导管相关性感染以及其他相关并发症。目前临床上针对这些问题多是采用对症辅助治疗，所以，在开展对 COVID-19 患者的临床救治工作中，应注意根据病人的客观治疗要求，慎重实施。

4.5. 中医中药防治

中医中药在我国抗击疫情期间展现出了卓越的效果。在短时间内可做到缓解症状，控制疾病发展，减轻并发症等显著疗效。除国家诊疗方案中的三药三方作为中医药治疗选择外。各地结合当地病情、气候特点、人群体质差异等情况，因地制宜，对患者进行辨证论治。尤其是以六经辨证为核心的《伤寒论》用方在临床使用过程中疗效显著，如葛根汤、桂枝加厚朴杏子汤、子龙宣白承气汤、葛根芩连汤、竹叶石膏汤等[60]。对于感染 COVID-19 患者，应当灵活运用《伤寒论》中的理法方药，遵循病情传变规律，在疾病不同时期进行中医药干预治疗，起到截断病势，以防传变的功效。同时，也要遵循祛邪务尽，培补正气以愈病的治疗原则。为保护肾脏功能，避免肾脏损伤做好保障。同时，针灸、推拿、中国传统功法、刮痧、熏蒸等方法也在 COVID-19 的诊治预防工作中起到重要的辅助治疗作用[61] [62] [63]。

4.6. SARS-CoV-2 新变种及预防

最近，SARS-CoV-2 毒株已出现多种变异，目前主要流行变异株为奥密克戎 BA.5、BQ.1、BF.7、BA.2.75 [64]。新毒株显示出更高的传染性和免疫逃逸能力[65] [66]，然而目前尚不清楚它们对肾脏的影响是否与原始毒株不同，仍需要对其进行临床研究及随访。

疫苗仍是目前有效的预防措施。然而，随着 SARS-CoV-2 疫苗在世界各地的广泛使用，已有少数病例报告患者接种后出现肾脏损伤为表现的副作用。表现为肉眼血尿、IgA 肾病、肾小管间质损伤和血栓性微血管病变等不良反应。SARS-CoV-2 疫苗可能会刺激 IgA 肾病复发[67] [68] [69]。因此，对于肾脏疾病患者应对其病情进行评估，对于适合接种病人应尽早进行接种，同时接种后需进行密切监测，避免患者出现不良反应。

5. 小结与展望

COVID-19 并发肾损伤目前仍是临床上需要引起积极关注研究的重要问题，其发生发展往往关系患者的预后生存。早筛查发现、早治疗干预、尽早保护患者肾功能，有望大大减少疾病发展为危重症或者慢性疾病的风险。采取中西医结合治疗，未病先防，谨防传变。面对疫情反复，应当鼓励有条件患者积极接种疫苗，加强肾病患者的防控意识。

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