

疫情常态化防控期间不规律随访对肾移植术后BK病毒再激活时的病毒载量及受者预后影响

吴周庭 王於尘 曾文利 夏仁飞 邓文锋 徐健 苗芸

【摘要】 目的 探讨在新型冠状病毒肺炎疫情常态化防控期间不规律随访对肾移植受者术后BK病毒(BKV)再激活情况及预后的影响。方法 回顾性分析363例肾移植受者的临床资料,按随访时间分为疫情前随访组与疫情期间随访组,随访期限为1年。比较疫情前随访组和疫情期间随访组的随访时间间隔,分析两组BKV感染情况,分析BKV感染进程与移植肾功能的相关性。结果 疫情前随访共计1790例次,疫情期间随访共计2680例次。与疫情期间随访组比较,疫情前随访组术后3个月内、3~6个月、7~12个月的随访时间间隔较短,差异均有统计学意义(均为 $P<0.05$)。在肾移植术后1年内,疫情前随访组35例(32%)检出BKV尿症、3例(3%)检出BKV血症、1例(1%)检出BKV相关肾病(BKVAN),疫情期间随访组53例(25%)检出BKV尿症、3例(1%)检出BKV血症、1例(1%)检出BKVAN,差异均无统计学意义(均为 $P>0.05$)。疫情前随访组术后首次检出BKV尿症时间长于疫情期间随访组,首次再激活尿BKV载量小于疫情期间随访组,差异均有统计学意义(均为 $P<0.05$)。首次再激活尿BKV载量与尿BKV载量峰值, BKV再激活后第1、3个月血清肌酐与基线血清肌酐差值呈正相关(均为 $P<0.05$)。结论 肾移植术后不规律随访可导致BKV再激活时间提前、首次尿BKV载量检出值更高,以及延迟诊断和干预,并造成不良预后。亟待建立远程随访体系以满足发生公共卫生事件时肾移植受者的随访需求。

【关键词】 肾移植; BK病毒; 术后随访; 新型冠状病毒; 疫情常态化; BK病毒血症; BK病毒尿症; BK病毒相关肾病

【中图分类号】 R617, R373 **【文献标志码】** A **【文章编号】** 1674-7445(2024)03-0014-06

Effect of irregular follow-up during normalized prevention and control of epidemic on viral load upon BK virus reactivation and prognosis of kidney transplant recipients Wu Zhouting, Wang Yuchen, Zeng Wenli, Xia Renfei, Deng Wenfeng, Xu Jian, Miao Yun. Department of Organ Transplantation, Nanfang Hospital of Southern Medical University, Guangzhou 510515, China
Corresponding author: Miao Yun, Email: miaoyunecho@126.com

【Abstract】 Objective To evaluate the effect of irregular follow-up during normalized prevention and control of novel coronavirus pneumonia (COVID-19) epidemic on BK virus (BKV) reactivation and clinical prognosis of kidney transplant recipients. **Methods** Clinical data of 363 kidney transplant recipients were retrospectively analyzed, and they were divided into the pre-epidemic follow-up group and during-epidemic follow-up group according to the follow-up time. All patients were followed up for 1 year. The follow-up interval was compared between two groups. The infection of BKV and the correlation between the infection process of BKV and renal graft function were analyzed in two groups. **Results** A total of 1790 pre-epidemic follow-up times and 2680 during-epidemic follow-up times were recorded. Compared with the during-epidemic follow-up group, the follow-up interval of the pre-epidemic follow-up group was shorter within 3 months, 3-6 months, and 7-12 months after transplantation, and the differences were statistically significant ($P<0.05$). Within 1 year after transplantation, 35 cases (32%) of BKV urinary infection, 3 cases (3%) of BKV blood infection, and 1 case (1%) of BKV-related kidney disease (BKVAN) were detected in the pre-epidemic follow-up group, while 53 cases (25%) of BKV urinary infection, 3 cases (1%) of BKV blood infection, and 1 case (1%) of BKVAN were detected in the during-epidemic follow-up group, and the differences were not statistically significant ($P>0.05$). The time to first detection of BKV urinary infection after transplantation was longer in the pre-epidemic follow-up group than in the during-epidemic follow-up group, and the first reactivation urinary BKV load was lower in the pre-epidemic follow-up group than in the during-epidemic follow-up group, and the differences were statistically significant ($P<0.05$). The first reactivation urinary BKV load was positively correlated with the peak urinary BKV load, and the difference in serum creatinine between the first and third months after reactivation was positively correlated with the difference in baseline serum creatinine ($P<0.05$). **Conclusion** Irregular follow-up after kidney transplantation can lead to earlier BKV reactivation, higher detection values of urinary BKV load, and delayed diagnosis and intervention, resulting in poor prognosis. It is urgent to establish a remote follow-up system to meet the follow-up needs of kidney transplant recipients during public health events.

DOI: 10.3969/j.issn.1674-7445.2023231

基金项目: 国家自然科学基金(82270784、82070770); 广东省基础与应用基础研究基金(2023A1515012276); 广东省学位与研究生教育创新计划项目(2022JDXM031)

作者单位: 510515 广州, 南方医科大学南方医院器官移植科

作者简介: 吴周庭 (ORCID 0009-0003-7304-6720), 硕士研究生, 研究方向为肾移植, Email: wuzhout@163.com

通信作者: 苗芸 (ORCID 0000-0003-3592-4695), 博士, 主任医师, 研究方向为肾移植, Email: miaoyunecho@126.com

Compared with the during-epidemic follow-up group, the follow-up intervals within 3, 3-6 and 7-12 months after kidney transplantation were shorter in the pre-epidemic follow-up group, and the differences were statistically significant (all $P < 0.05$). Within 1 year after kidney transplantation, 35 cases (32%) were diagnosed with BKV viremia, 3 cases (3%) of BKV viremia and 1 case (1%) of BKV-associated nephropathy (BKVAN) in the pre-epidemic follow-up group, and 53 (25%), 3 (1%) and 1 (1%) in the during-epidemic follow-up group, with no statistical significance (all $P > 0.05$). In the pre-epidemic follow-up group, the time for the initial diagnosis of BKV viremia was longer and the viral load of the first urinary BKV reactivation was smaller than those in the during-epidemic follow-up group, with statistical significance (both $P < 0.05$). The load of the first urinary BKV reactivation was positively correlated with the peak load of urinary BKV, and the differences between the baseline and serum creatinine levels at 1 and 3 months after BKV reactivation (all $P < 0.05$). **Conclusions** Irregular follow-up after kidney transplantation may lead to early BKV reactivation and higher detection value of the first viral load of urinary BKV, delay diagnosis and interventions, and lead to poor prognosis. It is urgent to establish a remote follow-up system to meet the follow-up requirements of kidney transplant recipients when public health incidents occur.

【 Key words 】 Kidney transplantation; BK virus; Follow-up; Novel coronavirus; Normalization of epidemic; BK viremia; BK viremia; BK virus-associated nephropathy

BK 病毒 (BK virus, BKV) 属多瘤病毒科多瘤病毒属, 全世界 70% 以上的普通人群有感染过 BK 病毒的血清学证据^[1-3]。BKV 感染通常发生在儿童时期, 但健康人群没有特定的症状^[4-6]。BKV 在原发感染后潜伏在肾小管及尿路上皮细胞中, 当宿主免疫功能低下时, 可导致 BKV 再激活^[1,4,7-8]。BKV 相关肾病 (BKV-associated nephropathy, BKVAN) 是肾移植受者中 BKV 再激活引起的严重并发症之一, 发生在 1%~10% 的肾移植受者中, 是导致移植术失败的重要原因^[9-14]。早期发现病毒复制对于预防 BKVAN 至关重要, 建议所有肾移植受者应定期筛查尿液或血浆中 BKV 复制水平, 以确定 BKVAN 风险增加的受者^[14-16]。自 2020 年初新型冠状病毒肺炎疫情暴发以来, 疫情常态化防控机制可能影响肾移植受者的随访规律, 给术后随访管理工作带来全新的挑战。本文通过对比疫情发生前后肾移植受者的随访和临床资料, 分析疫情常态化防控对 BKV 相关疾病的预防以及全程管理的影响, 为今后可能发生的类似公共卫生事件提供经验和参考。

1 资料与方法

1.1 研究对象

回顾性收集南方医科大学南方医院 2017 年 1 月至 2021 年 12 月行肾移植术且术后规律随访 1 年以上的受者, 根据纳入和排除标准, 最终纳入 363 例, 其中男 245 例, 女 118 例, 年龄 (43±13) 岁。

排除标准: (1) 手术时年龄 > 70 岁; (2) 术前

群体反应性抗体 (panel reactive antibody, PRA) 阳性; (3) 术前或术后 2 周内 BKV 阳性; (4) 非首次肾移植或多器官联合移植; (5) 术后 1 年内移植肾失功。本研究经南方医科大学南方医院伦理委员会批准 (批号: NFEC-2020-044)。

1.2 BKV 感染的监测

通过实时荧光定量聚合酶链反应 (real-time quantitative polymerase chain reaction, RT-qPCR) 检测受者尿液、血液的 BKV 载量水平, 可快速有效了解感染情况及进行病毒载量监控^[17-18]。本中心检测受者尿液和外周血中 BKV 载量的临界值为 5×10^3 copies/mL, 当尿液或血液 RT-qPCR 结果高于此数值时, 则认为病毒激活, 即受者处于 BKV 尿症或 BKV 血症状态。诊断 BKVAN 的金标准仍然是移植肾活组织检查 (活检), 由经验丰富的病理科医师根据移植肾穿刺活检结果并结合标准化评分判定^[1,18-20]。观察终点为术后满 1 年或 BKV 再激活。

1.3 分组

将 2020 年 1 月至 2023 年 1 月视为疫情常态化防控期, 以 2020 年 1 月 1 日为界分为疫情前随访组和疫情期间随访组。跨 2020 年 1 月 1 日随访的受者共 48 例, 其中 BKV 再激活的阳性事件 6 例, 此部分受者仅纳入随访问隔比较及病毒感染进程与移植肾功能的相关性分析。疫情前随访组 108 例, 男 74 例, 女 34 例, 年龄 (44±11) 岁, 99 例使用抗胸腺细胞球蛋白诱导, 12 例发生排斥反应; 疫情期间随访组 207 例, 男 136 例, 女 71 例, 年龄 (43±13) 岁,

185例使用抗胸腺细胞球蛋白诱导, 26例发生排斥反应。两组一般资料比较差异均无统计学意义(均为 $P>0.05$)。随访频率相关数据按随访例次计, 疫情前的随访例次归于疫情前随访问隔的计算, 疫情期间的随访例次归于疫情期间随访问隔的计算。

1.4 研究内容

收集受者的人口学资料、移植病史和术后随访资料。比较疫情前随访组和疫情期间随访组的随访时间间隔, 分析两组BKV感染情况, 分析BKV感染进程与移植肾功能的相关性。

1.5 统计学方法

采用SPSS 25.0软件进行统计学分析, 近似正态分布计量资料用均数±标准差表示, 比较采用 t 检验; 非正态分布的计量资料以中位数(下四分位数, 上四分位数)表示, 比较采用秩和检验; 计数资料以率表示, 比较采用 χ^2 检验或Fisher精确检验。采用一元线性回归分析首次再激活尿BKV载量与尿蛋白、尿白细胞、尿红细胞、血清肌酐等的关系。统计检验均采用双侧检验, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 随访时间间隔的比较

疫情前随访共计1790例次, 疫情期间随访共计2680例次。与疫情期间随访组比较, 疫情前随访组术后3个月内、3~6个月、7~12个月的随访时间间隔较短, 差异均有统计学意义(均为 $P<0.05$, 表1)。

表1 术后12个月内疫情前随访组与疫情期间随访组随访间隔的比较($\bar{x}\pm s, d$)

Table 1 Comparison of follow-up intervals between the pre-epidemic follow-up group and the during-epidemic follow-up group within 12 months after surgery

分组	例次	术后随访问隔		
		3个月内	3~6个月	7~12个月
疫情前随访组	1 790	10±5	23±9	30±12
疫情期间随访组	2 680	11±6	24±10	32±16
<i>P</i> 值		0.010	0.028	0.048

2.2 BKV感染情况分析

在肾移植术后1年内, 疫情前随访组35例检出BKV尿症(32%)、3例检出BKV血症(3%)、1例检出BKVAN(1%), 疫情期间随访组53例检

出BKV尿症(25%)、3例检出BKV血症(1%)、1例检出BKVAN(1%), 两组差异均无统计学意义(均为 $P>0.05$)。

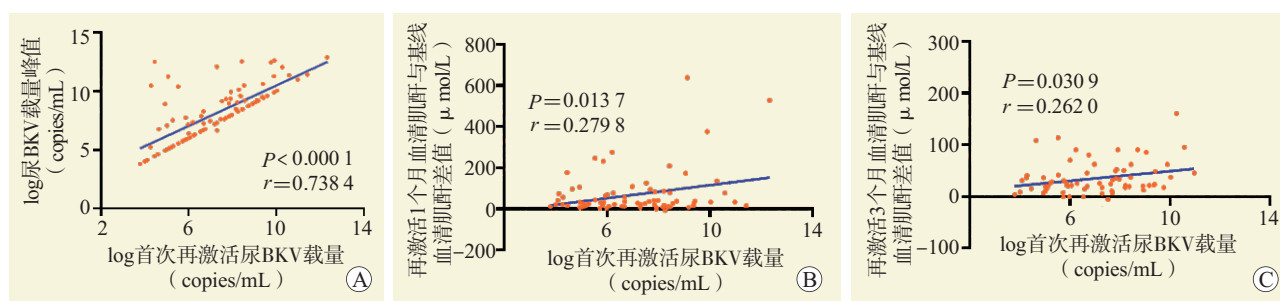
疫情前随访组术后首次BKV尿症检出时间为152(99, 223)d, 疫情期间随访组为110(70, 171)d, 差异有统计学意义($P=0.021$)。疫情前随访组首次再激活尿BKV载量 1.99×10^7 (1.31×10^5 , 2.17×10^8)copies/mL, 疫情期间随访组为 7.38×10^7 (2.73×10^6 , 1.41×10^9)copies/mL, 差异有统计学意义($P=0.030$)。疫情前随访组与疫情期间随访组首次再激活血BKV载量 $[1.12\times 10^5$ (8.38×10^4 , 1.94×10^5)copies/mL比 9.37×10^4 (1.66×10^4 , 1.90×10^6)copies/mL]、尿BKV载量峰值 $[2.91\times 10^8$ (4.59×10^6 , 1.33×10^{10})copies/mL比 7.53×10^7 (1.61×10^6 , 3.22×10^9)copies/mL]、血BKV载量峰值 $[1.12\times 10^5$ (8.38×10^4 , 3.42×10^6)copies/mL比 7.09×10^5 (9.37×10^4 , 2.72×10^6)copies/mL], 差异均无统计学意义(均为 $P>0.05$)。

2.3 病毒感染进程与移植肾功能的相关性分析

首次再激活尿BKV载量与尿BKV载量峰值, BKV再激活后第1、3个月血清肌酐与基线血清肌酐差值呈正相关($P<0.05$, 图1)。而BKV再激活后第1、3、6、9、12个月尿蛋白、尿白细胞及尿红细胞定量与首次再激活尿BKV载量的相关性无统计学意义(均为 $P>0.05$)。

3 讨论

肾移植受者术后需规律复查, 定期评估移植肾功能、监测血药浓度和评估各类并发症的发生风险, 以保证受者及移植物的长期存活。根据《中国实体器官移植受者BK病毒感染临床诊疗指南(2016版)》推荐意见, 应在术后3个月内每2周检测1次尿Decoy细胞, 6个月内每个月检测1次, 2年内每3个月检测1次^[21]; 2009年改善全球肾脏病预后组织(Kidney Disease:Improving Global Outcomes, KDIGO)的建议为肾移植术后3~6个月内, 每个月检测1次血浆BKV定量, 6~12个月内每3个月检测一次血浆BKV定量^[22]; 2013年美国移植学会的意见为移植术后2年内每3个月检测1次病毒定量^[9]。我中心实施的随访要求与上述推荐随访频率基本一致。疫情暴发和疫情常态化防控措施可使肾移植受者出行受限或主动监测意识下降, 不可避免地导致随访问隔



注：A 图为尿 BKV 载量峰值与首次再激活尿 BKV 载量的相关性；B 图为 BKV 再激活后第 1 个月血清肌酐与基线血清肌酐差值与首次再激活尿 BKV 载量的相关性；C 图为 BKV 再激活后第 3 个月血清肌酐与基线血清肌酐差值与首次再激活尿 BKV 载量的相关性。

图 1 首次再激活时尿 BKV 载量与移植肾功能的相关性分析

Figure 1 Correlation analysis between urinary BKV load at first reactivation and transplant kidney function

延长和规律性降低。我中心的随访人群分布较广，术后 1 年内的随访受影响较为明显。

在肾移植术后 1 年内随访期间，疫情前随访组与疫情期间随访组比较，BKV 尿症检出率、BKV 血症检出率差异无统计学意义，提示疫情防控措施并未直接影响 BKV 再激活率和检出率。但疫情期间随访组首次 BKV 检出时间较疫情前随访组早，首次尿 BKV 载量检出值较疫情前随访组更高，可能是因为肾移植术后不规律随访导致免疫抑制药浓度调节不及时，BKV 再激活时间提前，诊断和干预延迟。

本研究发现首次再激活尿 BKV 载量与尿 BKV 载量峰值、BKV 再激活后第 1、3 个月时血清肌酐升高值存在显著正相关。目前尚无针对 BKV 的特效抗病毒药物，降低免疫抑制强度是治疗 BKV 相关疾病的基本策略^[4,10,23-25]。较早的干预时间和降低病毒载量是控制 BKV 尿症或血症、改善受者预后的关键因素^[4,23,26-28]。但长时间和大幅度地降低免疫抑制强度以应对持续高载量的 BKV 尿症或血症也将带来更高的排斥反应风险^[15,23,29-30]。因此，早期监测 BKV 和及时干预对于防止肾功能损伤和随后的移植物丢失至关重要^[12,31-32]。目前对于 BKV 再激活时间的研究多为单中心研究，BKV 尿症或血症发生的中位时间在 2~6 个月不等^[1,14,33]。多中心的前瞻性研究将有助于进一步精确 BKV 再激活的高峰区间，指导更有效的随访和监测方案。

但本研究为单中心回顾性分析，随访数据有限，还需后续多中心、大样本及前瞻性研究明确不规律随访对 BKV 再激活的影响，其次，无法获取受者在当地医院随访记录以及部分受者失访可能导致结果偏

差。即时检测是一种检测成本低、检测速度快、准确度高、能自我采样获得临床诊断结果的新型诊断技术，有望应用于居家或适用于基层医疗机构的 BKV 再激活监测。用于 BKV 检测的代表性方法包括有环介导等温扩增方法和便携式集成数字聚合酶链反应（polymerase chain reaction, PCR）^[34-37]。其中便携式集成数字 PCR 仪体积小，重量轻，系统的定量结果与商用数字 PCR 仪的结果一致性高，可以直接从原始尿液样本中定量 BKV，采用简单的“样品到数字结果”操作流程，无需复杂的核酸提取和纯化步骤，为在诸如疫情等突发公共卫生事件或居家自我检测等资源有限的环境中用于监测 BKV 再激活提供了一个平台^[35]。然而，成熟的即时检测设备在技术研究领域与产品商业化方面仍然面临着诸多挑战，期待相关产品能够获得突破。此外，还可借助专业的第三方 APP 随访软件，为肾移植受者设计个体化随访方案，建立受者的个人随访数据库，并根据个体化随访要求提供随访提醒、诊疗预约等服务，并通过受者自行上传原始数据、医院信息系统数据对接等方式为医患双方提供随访数据采集服务，医师可以更加准确和及时地评估受者的病情，制定更加科学的治疗方案，同时也可以提高医疗服务的质量和效率，更好地满足受者的医疗需求^[38]。

综上，肾移植术后不规律随访可直接导致 BKV 再激活的延迟诊断和延迟干预，并造成不可逆的移植肾功能下降等不良预后。亟待建立远程随访体系以满足公共卫生事件时肾移植受者的随访需求，改善受者和移植肾的长期存活。

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(收稿日期: 2023-12-18)

(本文编辑: 方引超 吴秋玲)