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ORIGINAL RESEARCH

BK Polyomavirus Prevalence in Renal Diseases: Associations with Immunosuppressants and Lymphocyte Subsets

Ziran Wang[1,*], Jiawei Zhao[2,*], Lingjun Kong[1], Cun Liu[3], Zhou Lv[4], Yanhong Wang[2], Yaling Dou[1], Xin You[5]

[1]Department of Clinical Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, People's Republic of China; [2]Department of Geriatric I, Aerospace Center Hospital, Peking University Aerospace School of Clinical Medicine, Beijing, People's Republic of China; [3]Department of Clinical Laboratory, The Affiliated Qingdao Third People's Hospital of Qingdao University, Qingdao, Shandong, People's Republic of China; [4]Department of Clinical Laboratory, Huangshi Aikang Hospital, Huangshi, Hubei, People's Republic of China; [5]Department of Rheumatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yaling Dou, Department of Clinical Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, 100730, People's Republic of China, Email douyl@pumch.cn; Xin You, Department of Rheumatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, People's Republic of China, Email youxin@pumch.cn

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Background: BK polyomavirus (BKV), a latent pathogen in immunocompromised individuals, poses significant risks in renal-associated diseases (RD).
Methods: This study recruited 88 healthy control (HC) individuals and 271 patients with RD, including 96 connective tissue diseases with renal involvement (CTD-RI), 90 chronic kidney disease (CKD), 66 urological tumors (UT), 19 kidney transplantation (KT), at Peking Union Medical College Hospital from January 2020 to September 2021. The BKV-DNA qPCR detection kit was evaluated in terms of lowest detection limit, linear range, accuracy, precision, analytical specificity. Urine, serum, and plasma specimens from 17 UT patients were detected simultaneously to evaluate the detection sensitivity of various sample types. The positive rates and loads of BKV-DNA were compared among the various groups. The difference in immunosuppressants use between BKV-DNA positive and negative groups was compared in patients with CTD-RI. Furthermore, the correlations between BKV-DNA loads and the counts of lymphocyte subsets were explored in the CTD-RI group.
Results: The BKV-DNA qPCR detection kit has satisfactory sensitivity, linear range, reproducibility, accuracy, and specificity to detect the presence and loads of BKV-DNA. Urine specimens are more sensitive for BKV-DNA detection than serum and plasma. The CTD-RI and UT groups had higher BKV-DNA positive rates (49.0% and 31.8%, respectively) and loads (median: 5.69 log10 copies/mL and 6.03 log10 copies/mL, respectively) compared to the HC group (positive rate 12.5%, load median 3.96 log10 copies/mL). Multivariate logistic regression analysis indicated that the use of mycophenolate mofetil (MMF) was associated with a reduced risk of BKV (odds ratio and 95% confidence interval: 0.27 (0.09–0.78), P=0.015). The trends toward negative correlations between the BKV-DNA loads and the counts of CD19+ B cells, CD4+CD28+ T cells, CD45RA+CD4+ T cells, and naive CD4+ T cells were observed.
Conclusion: These findings support monitoring BKV-DNA in high-risk RD patients to guide immunosuppressant use and mitigate renal injury. Future long-term follow-up and multicenter large-scale cohort studies are necessary to further clarify the role of BKV in RD.
Keywords: BK polyomavirus, renal associated diseases, immunosuppressant, immune cells

Introduction

BK polyomavirus (BKV) was first isolated from the urine sample of a kidney transplant patient and was named after the patient's initials in 1971 and has been a major challenge in kidney transplant recipients.[1,2] BKV is a non-enveloped, closed circular double-stranded DNA virus containing approximately 5300 base pairs. The viral shell has an icosahedral crystal structure formed by the arrangement of pentamers of VP1 structural protein, with a diameter of 40–45nm. Its genome can be divided into three different functional areas: an early coding region, a late coding region, and a non-coding regulatory region

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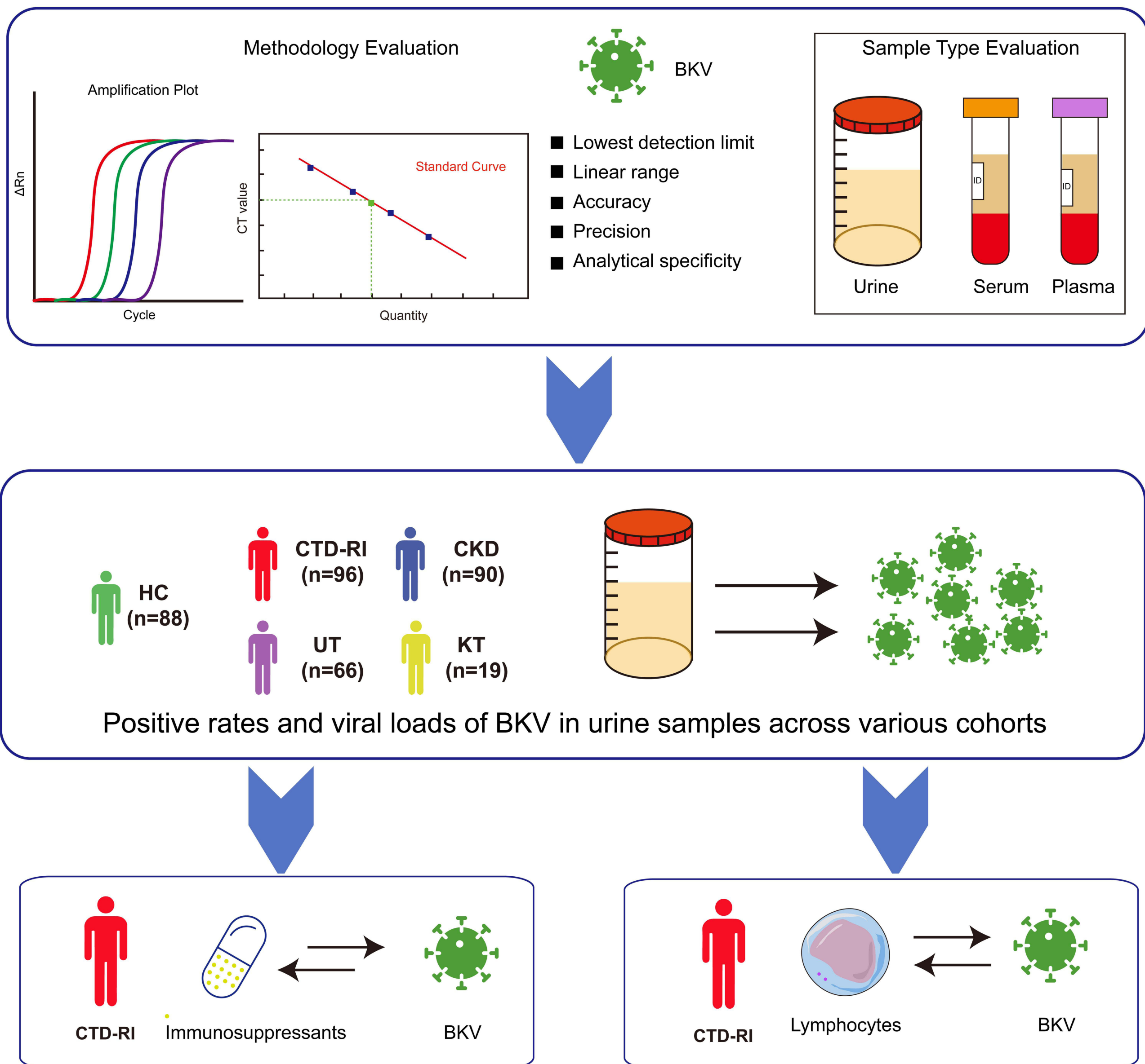
Graphical Abstract



(NCCR).[3] BKV is hypothesized to be transmitted by the respiratory tract, the fecal-oral route and direct human-to-human contact.[4] Notably, BKV is prevalent in the populations. It is estimated that more than 80% of adults are seropositive for BKV, but it is not usually pathogenic in healthy individuals.[5] However, for individuals with immune dysregulation, BKV infection has been reported to be associated with a variety of diseases such as autoimmune disorders, haemorrhagic cystitis, vasculopathy, kidney disease, and even cancer.[6,7]

Generally, after the primary infection in childhood, BKV can remain latent persistently in renal tubular epithelial cells or urinary epithelial cells. Nevertheless, when the body's immune balance is impaired, BKV may be reactivated. Reactivation is implied by the fact that the virus is disrupting normal cell cycle regulation and the natural immune response, thereby leading to necrosis flaking.[4] It is worth noting that the pathogenicity of BKV depends on a several determinants (host, organ, virus) and modulators (infection, antivirals, immune dysfunction).[6,8] The individual effects of

BKV may be influenced by a combination of these factors as well as complex interactions between them. Thus, detection of the virus does not indicate onset of disease, but monitoring changes in viral loads in high-risk populations can help in the treatment management and prognostic evaluation.

Connective tissue diseases (CTD) are a heterogeneous group of diseases based on immune-mediated chronic inflammation, which can often lead to tissue damage, collagen deposition and even severe loss of target organ function.[9] There are diverse degrees of renal involvement (RI) often observed in CTD and complicate the progression of the condition, especially in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren syndrome, systemic scleroderma (SSc) as well as auto-immune myopathies.[10] Reactivation of BKV also may trigger the production of autoantibodies, contributing to the onset and progression of SLE.[11] Chronic kidney disease (CKD) is defined as the presence of abnormalities in the structure or function of the kidneys for more than 3 months with certain clinical consequences.[12] In 2017, the global prevalence of CKD was reported to be 9.1%, with approximately 700 million cases.[13] The persistence of low-grade inflammation is recognized as a driver of CKD and is strongly associated with increased mortality and cardiovascular events.[14] Urological tumors (UT), including kidney, prostate and bladder cancers, not only pose a huge threat to patients' life, but also contribute to the enormous burden of healthcare. It has been shown that HLA class I molecules play an important role in immune escape for UT, suggesting that immune factors may have an influential impact on the advancement of UT.[15] BKV is also considered a potential agent and precondition for the development of UT. Kidney transplantation (KT) is one of the effective treatments for chronic renal failure. In immunocompromised individuals, such as KT, BKV may reactivate and proliferate with high levels of replication, which can lead to severe disease or graft failure. Notably, immunosuppression may also increase the risk of infection, leading to graft failure or other adverse outcomes. Some studies suggested immunosuppressants, such as mycophenolate mofetil (MMF), could increase the risk of BKV, while others reported the antiviral effects-highlighting the need for further investigation.[16–18] Since BKV is usually latent in the kidneys or urinary tract and its reactivation can cause severe complications in immune-dysregulated conditions, it is necessary to monitor BKV-DNA loads in patients with renal associated diseases (RD).

Given BKV's tropism for renal tissue and reliance on immune suppression for reactivation, we hypothesized that distinct renal disease populations exhibit varying BKV prevalence and immune correlates. In this study, we aimed to (1) validate a qPCR method for BKV-DNA detection, (2) compare BKV prevalence/viral loads across renal diseases, and (3) assess associations between BKV, immunosuppressants, and lymphocyte subsets in CTD with renal involvement (CTD-RI) patients.

Materials and Methods

Study Population

This study recruited 88 healthy control (HC) individuals and 271 patients with RD (96 CTD-RI, 90 CKD, 66 UT, 19 KT) at Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences from January 2020 to September 2021. HC individuals were defined as individuals who had no abnormal results on routine physical examination routines at our hospital and had normal renal function. The CTD-RI group included 65 cases of SLE, 9 cases of vasculitis, 4 cases of polymyositis, 8 cases of primary Sjögren's syndrome, and 10 cases of other connective tissue diseases. The UT group included 28 cases of kidney tumors and 38 cases of urinary tract tumors. All patients with RD were diagnosed according to current guidelines and clinical practice. RD patients who met the diagnostic criteria and had complete clinical information were included in the study, while patients whose samples were unavailable or who had concurrent infections were excluded. For HC group, the subjects were selected from individuals undergoing routine physical examinations, whilst subjects with kidney involvement or concurrent infections were further excluded. General characteristics, laboratory test results, diagnosis and treatment information of all subjects were obtained through the hospital information system (HIS) or laboratory information system (LIS). This study was performed in compliance with Declaration of Helsinki and approved by the Ethics Committee of Peking Union Medical College Hospital (No. HS2019104).

Samples Collection

For urine specimens, about 2 mL of mid-morning urine was retained in a sterile container and sent to the laboratory within 2 h. For blood specimens, 4 mL of whole blood was collected using EDTA anticoagulated or procoagulant blood collection tubes and sent to the laboratory within 2h. Whole blood was centrifuged at 1600 rpm/min for 10 min at room temperature and then serum or

plasma was transferred and stored in sterile centrifuge tubes. Specimens that cannot be tested promptly can be stored at 2~8 °C for 72 h or −20 °C for up to 12 months.

BKV-DNA Detection

Nucleic acid extraction (magnetic bead method) reagent (Beijing Applied Biological Technologies Co., Ltd) was used to extract nucleic acids from all specimens. Subsequently, the extracted DNA was detected using the BKV-DNA real-time fluorescent probe qPCR kit (Beijing Applied Biological Technologies Co., Ltd). The specific PCR reaction conditions were: pre-reaction, 50 °C for 2 min, 95 °C for 5 min, 1 cycle; denaturation, 95 °C for 15 s, 55 °C for 45 s, 45 cycles; cooling: 12 °C for 1 min. Negative and positive quality controls (QC) and standards were detected along with the specimens. PCR reactions and data analysis were performed in the Applied Biosystems (ABI) 7500 Real-time System (ABI Inc. CA, United States) instrument and matching software. BKV-DNA was detected using the FAM channel and internal control (IC) gene was detected using the VIC channel. For positive QC, the FAM channel Ct value should be 27 ± 3 while negative QC should have no amplification. All standards should have amplification in the FAM channel, and a standard curve is fitted based on the concentrations and Ct values of all standards. The linear coefficient of the fit should satisfy the condition: $|r| \geq 0.98$. All samples, negative and positive QCs as well as standards should have amplification in VIC channel. When all the above criteria were fulfilled, the sample detection results were analyzed and the BKV-DNA loads was determined according to the standard curve.

Performance Evaluation of BKV-DNA qPCR Detection Kits

The performance of BKV-DNA qPCR detection kits was evaluated according to the document of nucleic acid amplification test reagents (kits) (YY/T 1182–2010) issued by National Medical Products Administration (NMPA). Performance evaluation includes the following aspects: lowest detection limit, linear range, accuracy, precision and analytical specificity.

Statistical Analysis

Data were collected and managed using Excel 2019 software (Microsoft, USA) while data statistical analyses were performed using R Project (version 4.4.2) and RStudio (Open-Source Edition) software. Considering the large variability in BKV-DNA loads, the log10 transformation was performed when using BKV-DNA loads for inter-group comparisons and correlation analyses. For qualitative data, the chi-square test or Fisher's exact probability method was applied; for quantitative data, the *t*-test or Wilcoxon test was used. Multivariate logistic regression analysis was used to explore the relationship between BKV and immunosuppressant use. The Spearman correlation analysis was utilized to calculate the correlation between BKV-DNA loads and lymphocyte subsets. $P<0.05$ was considered statistically significant.

Results

Performance Evaluation of BKV-DNA qPCR Detection Kits

After evaluation, the lowest detection limit of the BKV-DNA qPCR detection kit was 1×10^3 copies/mL. The linear range of the kit was determined to be 1×10^3 copies/mL − 2×10^{10} copies/mL, and the recovery rate of the quantitative assay ranged from 85% to 115%. The results of the precision experiments showed that the coefficients of variation (CVs) of the kit were less than 5% for intra-batch, inter-batch and inter-day. For specificity assessment, the kit does not amplify common similar pathogens including human cytomegalovirus (CMV), JC polyomavirus (JCV), EB virus (EBV), varicella zoster virus (VZV), and adenovirus (ADV). In addition, the kit is resistant to the effects of certain concentrations of endogenous (bilirubin 300 μmol/L, hemoglobin 50 mg/L triglycerides 5 mmol/L, IgG 40 g/L) interfering substances and exogenous interfering substances (α-interferon 1×10^6 U/L, sodium foscarnet 2×10^6 U/L, ganciclovir 66 μmol/L). Overall, the BKV-DNA qPCR detection kit has satisfactory sensitivity, linear range, reproducibility, accuracy, and specificity to detect the presence and loads of BKV-DNA in samples efficiently and accurately. Furthermore, on the basis of the lowest detection limit of the kits, we used 1×10^3 copies/mL as the cut-off value to determine negative and positive for BKV-DNA.

Comparison of BKV-DNA Detection Results in Urine, Serum, and Plasma Specimens

To compare the detection sensitivity of various specimen types, we performed BKV-DNA detection on urine, serum and plasma specimens simultaneously from 17 UT patients. The results showed that 15 patients were all negative for BKV-DNA in urine, serum and plasma. However, for patient UT2 and patient UT3, BKV-DNA was detected in urine with loads of 11660 copies/mL and 29496 copies/mL, respectively, whereas it was not detected in serum and plasma (Table 1). The preliminary results suggested that urine specimens were more sensitive for BKV-DNA detection than serum and plasma. Considering the comparability of results among individuals, we chose to use urine specimens for the detection of BKV-DNA in subsequent studies.

BKV-DNA in HC and RD Groups

To understand the prevalence profile of BKV in the HC and RD groups, we first compared the difference in the positive rates of BKV-DNA between these two groups. As shown in Figure 1A, the positive rate of BKV-DNA in RD group was 32.1% which was significantly higher than that in HC group (12.5%, $P<0.001$). Furthermore, when the RD groups were subdivided, the Figure 1B showed that the positive rate of BKV-DNA was higher in CTD-RI group (49.0%) and UT group (31.8%) than in HC group, while there was no significant difference in the positive rate between CKD (15.6%) and HC groups. Notably, the KT group (26.3%) had a higher positive rate of BKV-DNA compared to the HC group, but the difference was not statistically significant. Additionally, we compared the differences in viral loads of BKV-DNA positive individuals and observed similar results. Figure 1C illustrated that the RD group (median: 5.67 log10 copies/mL) had higher BKV viral loads compared to the HC group (median: 3.96 log10 copies/mL, $P=0.002$). RD patients with >5.67 log10 copies/mL had 1.2-fold higher creatinine than patients with ≤5.67 log10 copies/mL, which may imply that BKV infection may indicate renal impairment. Additionally, the CTD-RI group (median: 5.69 log10 copies/mL, $P=0.02$) and UT group (median: 6.03 log10 copies/mL, $P=0.002$) had higher viral loads whereas there was no significant difference between the CKD (median: 3.92 log10 copies/mL) and HC groups (Figure 1D). It is worth noting that the KT group had the highest median viral loads (median: 6.64 log10 copies/mL), but was not significantly different from the HC group.

Table 1 Comparison of BKV DNA Detection Results in Urine, Serum, and Plasma Specimens

Sample ID	BKV DNA (Urine)	BKV DNA (Serum)	BKV DNA (Plasma)
UT1	Negative	Negative	Negative
UT2	Positive, 11660 copies/mL	Negative	Negative
UT3	Positive, 29496 copies/mL	Negative	Negative
UT4	Negative	Negative	Negative
UT5	Negative	Negative	Negative
UT6	Negative	Negative	Negative
UT7	Negative	Negative	Negative
UT8	Negative	Negative	Negative
UT9	Negative	Negative	Negative
UT10	Negative	Negative	Negative
UT11	Negative	Negative	Negative
UT12	Negative	Negative	Negative
UT13	Negative	Negative	Negative
UT14	Negative	Negative	Negative
UT15	Negative	Negative	Negative
UT16	Negative	Negative	Negative
UT17	Negative	Negative	Negative

Abbreviation: UT, urological tumors.

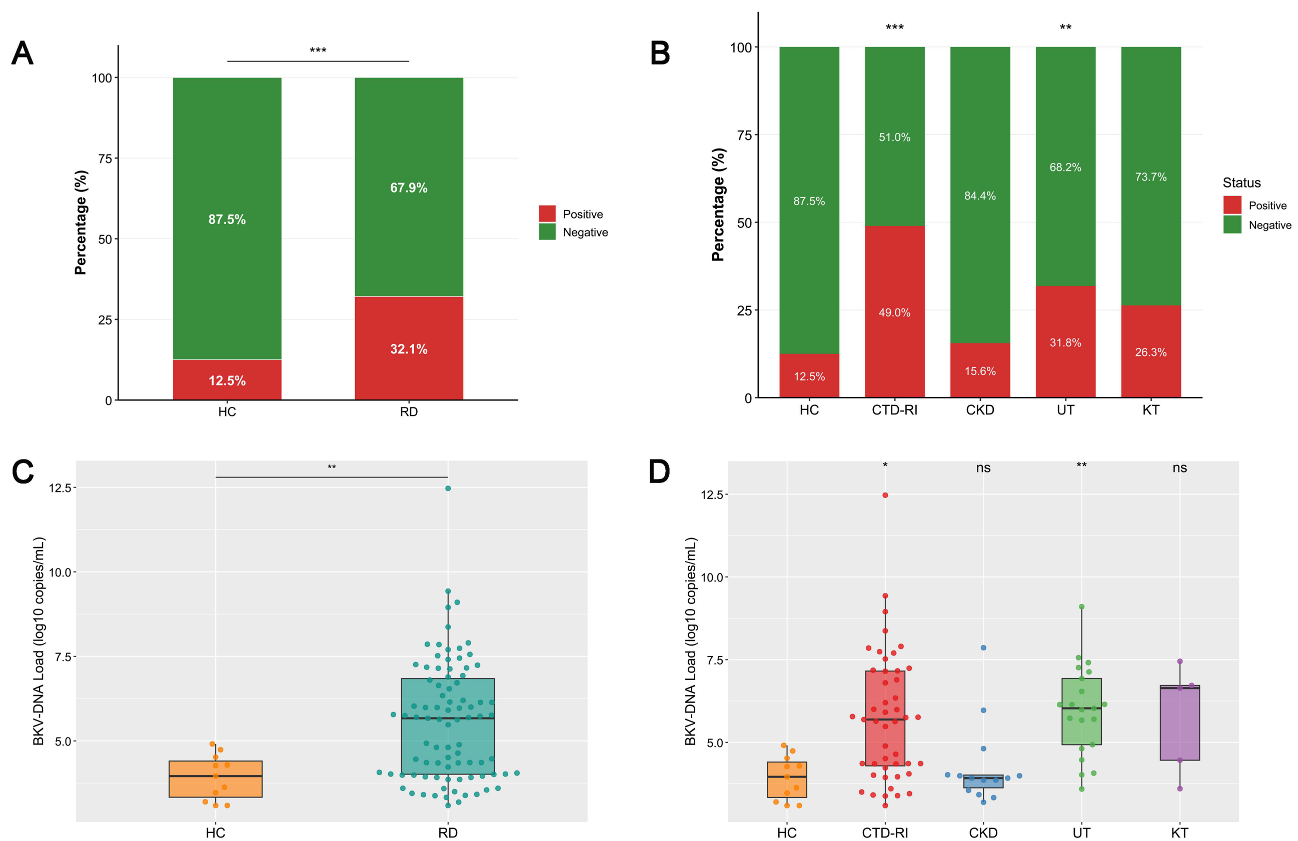


Figure 1 BKV-DNA in HC and RD groups. (**A**), BKV-DNA positive rates in HC and RD groups; (**B**), BKV-DNA positive rates in HC, CTD-RI, CKD, UT and KT groups; (**C**), BKV-DNA loads in HC and RD groups; (**D**), BKV-DNA loads in HC, CTD-RI, CKD, UT and KT groups. Given that BKV-DNA loads distributions span multiple orders of magnitude, we applied $\log_{10}$ transformation to the original load values to enhance data comparability across study groups. The HC group served as the control group, *P<0.05; **P < 0.01; ***P<0.001; ns, no significance.

Abbreviations: HC, healthy control; RD, renal associated diseases; CTD-RI, connective tissue diseases with renal involvement; CKD, chronic kidney disease; UT, urological tumors; KT, kidney transplantation.

The Association Between Immunosuppressant Use and BKV in CTD-RI Group

Based on the fact that nearly half of the patients in the CTD-RI group were BKV-DNA positive and that most patients in this group would use immunosuppressants, we further investigated the association between BKV and immunosuppressants use. Table 2 demonstrated the difference in immunosuppressant use between BKV-DNA positive and negative patients in the CTD-RI group. It can be observed that a lower proportion of patients in the BKV-DNA positive group used hydroxychloroquine (HCQ) (P=0.042) and MMF (P=0.008) compared to the BKV-DNA negative group. Multivariate logistic regression analysis indicated that the use of MMF was associated with a reduced risk of BKV (Figure 2, odds ratio and 95% confidence interval: 0.27 (0.09–0.78), P=0.015).

Correlation Analysis of BKV-DNA Loads with Lymphocyte Subsets in CTD-RI Group

Given the crucial role of immune dysregulation in CTD-RI progression and BKV reactivation, we further analyzed the correlation between BKV-DNA loads and the amounts of lymphocyte subsets. We first found a positive correlation between the BKV-DNA loads and the serum creatinine of patients (R=0.45, P=0.0023), indicating that higher BKV-DNA loads may be associated with renal function impairment in patients with CTD-RI (Figure 3). We also observed the negative correlation trends between the BKV-DNA loads and the counts of CD19+ B cells (R=−0.33, P=0.079), CD4+CD28+ T cells (R=−0.36, P=0.086), CD45RA+CD4+ T cells (R=−0.46, P=0.063), and naive CD4+ T cells (R=−0.45, P=0.071) (Figure 3).

Table 2 The Difference in Immunosuppressant Use Between BKV-DNA Positive and Negative Patients in the CTD-RI Group

Variables	BKV-DNA Negative (n = 49)	BKV-DNA Positive (n = 47)	*P* Value
Sex, n (%)			0.377
F	42 (85.7)	36 (76.6)	
M	7 (14.3)	11 (23.4)	
Age, Median (Q1, Q3)	38 (25, 53)	52 (36, 57)	0.117
GC, n (%)			0.108
No	1 (2)	5 (10.6)	
Yes	48 (98)	42 (89.4)	
MTX, n (%)			0.054
No	49 (100)	43 (91.5)	
Yes	0 (0)	4 (8.5)	
CTX, n (%)			0.919
No	40 (81.6)	37 (78.7)	
Yes	9 (18.4)	10 (21.3)	
HCQ, n (%)			**0.042**
No	18 (36.7)	28 (59.6)	
Yes	31 (63.3)	19 (40.4)	
MMF, n (%)			**0.008**
No	30 (61.2)	41 (87.2)	
Yes	19 (38.8)	6 (12.8)	
TAC, n (%)			0.925
No	41 (83.7)	38 (80.9)	
Yes	8 (16.3)	9 (19.1)	
RAP, n (%)			0.495
No	47 (95.9)	47 (100)	
Yes	2 (4.1)	0 (0)	
LEF, n (%)			0.715
No	44 (89.8)	44 (93.6)	
Yes	5 (10.2)	3 (6.4)	
CsA, n (%)			1
No	44 (89.8)	43 (91.5)	
Yes	5 (10.2)	4 (8.5)	
BEL, n (%)			0.056
No	44 (89.8)	47 (100)	
Yes	5 (10.2)	0 (0)	
RTX, n (%)			1
No	47 (95.9)	45 (95.7)	
Yes	2 (4.1)	2 (4.3)	

Note: Bold text indicates $P<0.05$.

Abbreviations: F, female; M, male; GC, glucocorticoid; MTX, methotrexate; CTX, cyclophosphamide; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; TAC, tacrolimus; RAP, rapamycin; LEF, leflunomide; CsA, cyclosporine A; BEL, belimumab; RTX, rituximab.

Discussion

Detection of BKV usually involves a wide range of methods. Biopsy is valuable in defining BKV infection, but its invasive nature may limit its application. The decoy cells were observed in urine as morphological markers, which are characterized by enlarged nuclei and homogenization of nuclear chromatin under light microscopy.[19] However, it is complicated to operate and requires the practical experience for technicians. Serological testing is a classical method of detecting BKV and is commonly used in epidemiological investigations.[20] Unfortunately, the sensitivity and specificity of serological testing for BKV tend to be rather limited. In contrast, the PCR method with higher sensitivity and specificity seems to be an effective tool to detect the

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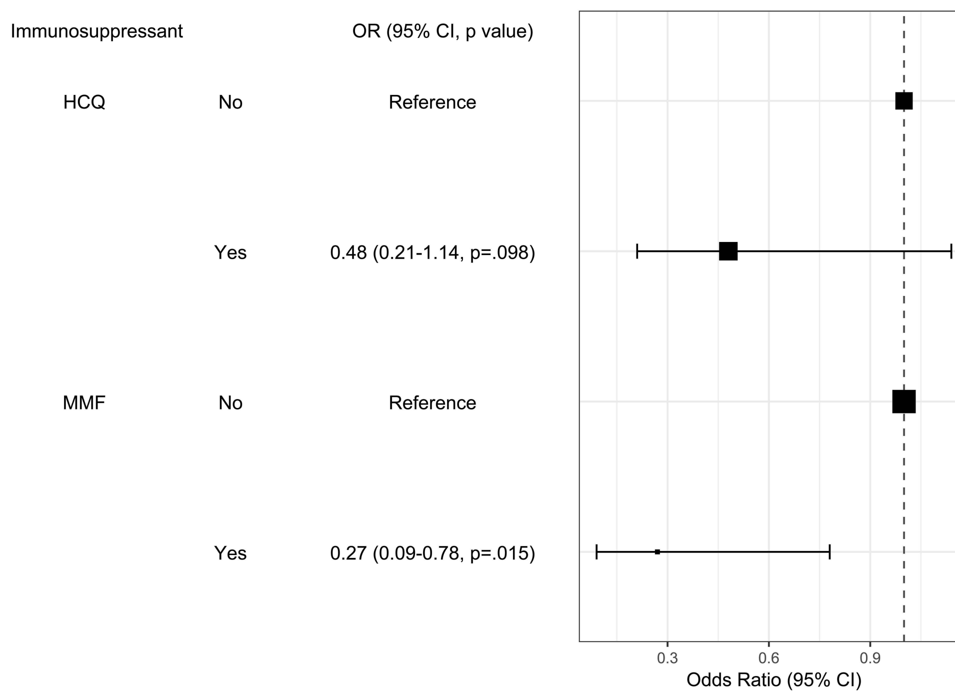

Figure 2 Multivariate logistic regression analysis of immunosuppressant use in BKV-positive and negative individuals in the CTD-RI group.
Abbreviations: HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; OR, odds ratio; CI, confidence interval.

presence of BKV.[21] In this case, the qPCR method enables monitoring of the signal generated by the fluorescent dye or probe to determine the production of reaction products, and can be compared with a standard curve to achieve the accurate quantification of the viral loads in samples.[22] It is important to note that even though the qPCR method has the above advantages, the performance of the kit still needs to be fully evaluated before testing clinical samples. In our study, we first fully evaluated the performance of the BKV-DNA qPCR detection kit according to the NMPA guideline. The results showed that the kit has satisfactory sensitivity, linear range, reproducibility, accuracy, and specificity to detect the presence and loads of BKV-DNA in samples efficiently and accurately. It can provide support and assurance for sample testing, data analysis and quality control for subsequent studies.

To determine the type of specimen for the subsequent study, we performed simultaneous detection of BKV-DNA in urine, serum and plasma from 17 patients. The results revealed that two patients were positive for BKV-DNA in urine but negative in serum and plasma. The results of a large, prospective, randomized trial found that the overall incidence of BK viruria and BK viremia was 35% and 12% respectively.[23] Similarly, in the study conducted by Babel et al, the overall prevalence of BK viruria and BK viremia was 19% and 7%, respectively.[24] Interestingly, in their study, the specificity and positive predictive values of BK viruria for BKV-associated nephropathy (BKVAN) were lower than that of BK viremia, but BK viruria preceded BK viremia by 6 weeks. This demonstrated that urinary BKV is an early and reliable marker that helps to identify high-risk patients with BKVAN, which enables early intervention to improve outcomes. Our findings are consistent with the above studies, denoting a higher sensitivity in urine than serum and plasma for BKV-DNA detection. Considering that our study population was patients with renal associated diseases, detection of BKV-DNA in urine could help to further identify the risk. Notably, we only tested the urine samples for all patients, which may result in specimen type bias. Urine was prioritized for sensitivity, but concurrent serum/plasma testing in all patients can clarify viremia-viruria discordance.

After determining the robustness of the methodology and the reliability of the samples, we compared the differences in positive rates and loads of BKV-DNA among distinct groups. Unsurprisingly, BKV-DNA was positive in 12.5% of the HC group, suggesting that asymptomatic latency of BKV may exist in some healthy individuals. This point can be supported by the fact that the viral loads of the positive subjects in the HC group were not high. In contrast, nearly half of the patients in the CTD-RI group were BKV-DNA positive and had relatively high viral loads. The association between BKV and CTD-RI has been less explored at present. In previous studies, BKV infection and reactivation were frequently observed in CTD such as

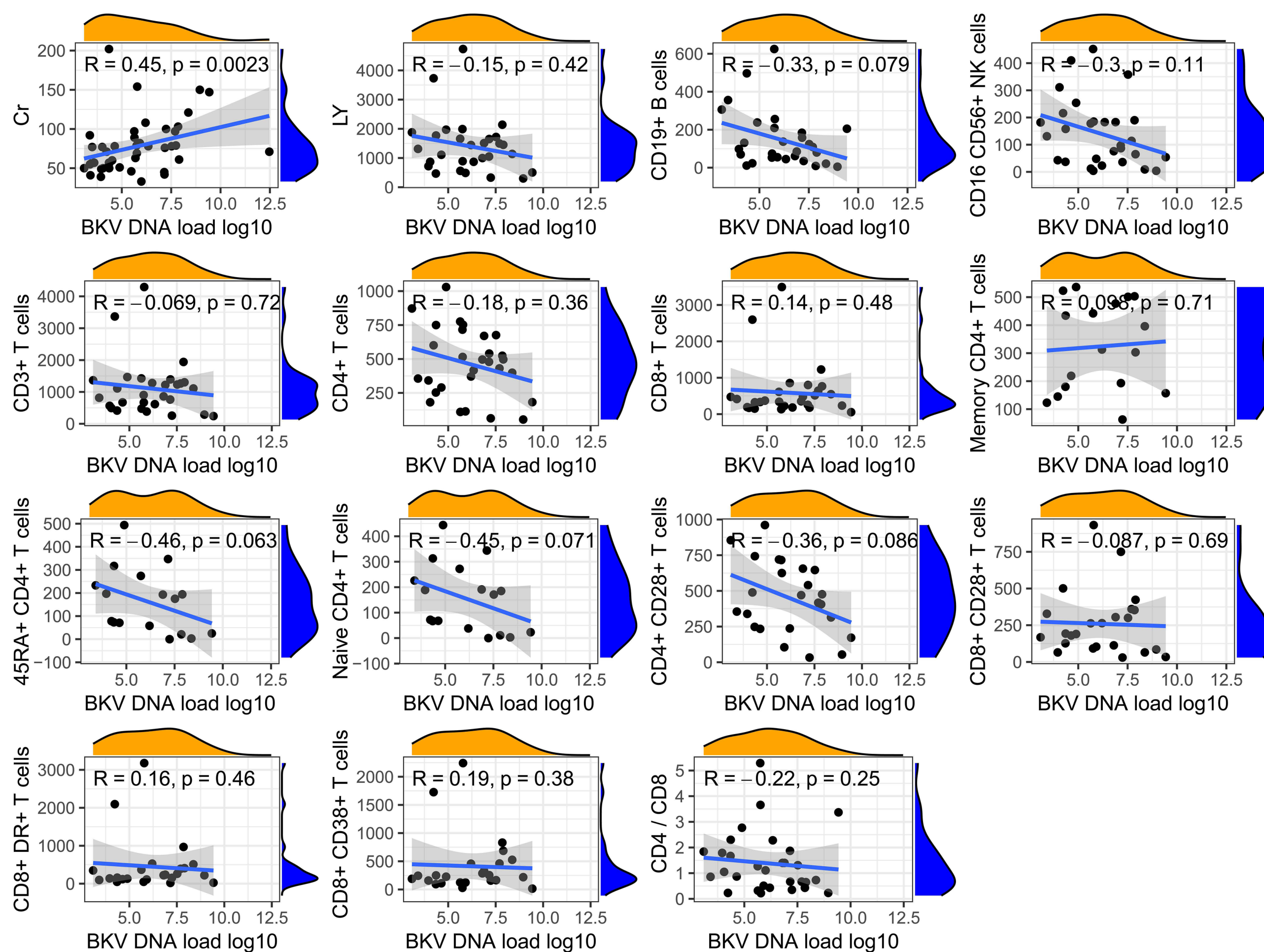

Figure 3 Correlation analysis of BKV-DNA loads with lymphocyte subsets in CTD-RI group.

SLE.[11] This may be related to the use of immunosuppressants and the immune status of the patient. Li et al reported that SLE patients with lupus nephritis (LN) had higher BKV viral loads than patients without LN.[25] This is in line with our findings, but further research is needed to verify the relationship between other CTD diseases and BKV. Similar to CTD-RI, UT group has higher positive rate for BKV-DNA and viral loads. This may provide potential clues to the interaction of BKV with tumorigenesis. Significantly, BKV has similar genetic structure with human papillomavirus (HPV), which is a well-defined human oncogene.[26] BKV is also recognized as a potential agent of urological diseases or tumors, such as bladder cancer or prostate cancer.[4] A study based on United States Transplant Cancer Match Study (2003–2013) data showed that kidney transplant recipients with BKVAN had a higher risk of UT, suggesting a potential association between BKV and urothelial carcinogenesis.[27] Mechanistically, it was reported that the oncogenic effect may be attributed to the inhibitory modulatory effect of BKV T antigen (TAg) on p53 and retinoblastoma (pRb).[28] However, in this study, no TAg or pRb data were detected to verify this hypothesis. For CKD patients, we found that their BKV-DNA positive rate and viral loads were not significantly different from the HC group. This may mean that despite the structural or functional damage to the kidney in CKD patients, the immune system still has the ability to combat or clear the virus. There have been numerous reports on the association of BKV with kidney transplantation. In our study, although the KT group appeared to have the highest viral loads among all groups, this difference was not remarkable. We speculate that this may be related to the fact that we included relatively small numbers of individuals with KT (n=19) due to recruitment challenges. The sample size of KT could be further expanded in the future to clarify the whether this non-significance reflects small sample size or true biological differences.

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Considering the key contribution of immunosuppressants and individual immune function in CTD-RI, we further analyzed the association between them and BKV-DNA. Univariate and multivariate logistic regression analyses conclusively identified MMF as a protective factor for BKV-DNA positivity in patients with CTD-RI. There is controversy regarding the link between MMF and BKV risk. As an inhibitor of inosine-5'-monophosphate dehydrogenase (IMPDH), MMF can specifically suppress the function of T cells and B cells. MMF has been reported to have antiviral activity, including against influenza A, SARS-CoV-2, Zika virus, and MERS-CoV.[29] Based on existing research, the potential antiviral mechanisms primarily include the suppression of IMPDH activity, the upregulation of interferon-stimulated genes (ISGs) expression, and the blockade of autophagic processes.[29] The comprehensive effect of MMF depends on the balance between the benefits it brings in terms of immunosuppression and antimicrobial activity, and the increased risk of infection.[30] A German study has shown that among 638 patients who received renal allografts, 7 cases developed polyomavirus-nephropathy. Among these 7 cases, 4 patients were using both tacrolimus and MMF. Moreover, the patients using this regimen had a 13-fold increased risk of developing polyomavirus-nephropathy compared with the control group.[31] Conversely, Acott et al confirmed through in vitro cell experiments that mycophenolic acid (MPA) may have protective and antiviral effects on renal tubular cells infected by BKV.[32] Our study is in line with the latter. More recently, a clinical trial showed that the use of MMF in kidney transplant recipients resulted in a higher proportion of patients clearing BKV at 6 months.[17] However, our research supports advocated for MMF's protective role but does not address conflicting literature (eg, MMF-associated BKVAN in transplant patients). We speculate that possible reasons for the varied conclusions may include: the sample size of the studies included, the underlying immune status of the patients, the disease state of the patients, the dose of the immunosuppressants as well as their interaction.

We found a positive correlation between BKV-DNA loads and serum creatinine in patients with CTD-RI, reflecting higher BKV-DNA loads maybe associated with renal impairment. While BKV loads correlated with creatinine, implications for long-term outcomes (eg, dialysis, graft loss) remain unexplored and warrant further study. Furthermore, we explored the correlations between BKV-DNA loads and the counts of lymphocyte subsets in BKV-DNA positive CTD-RI patients. CD19+ B cells, CD4+CD28+ T cells, CD45RA+CD4+ T cells and naive CD4+ T cells were observed to have negative correlation trends with BKV-DNA loads (although the P value was > 0.05), which may imply that higher BKV viral loads have a certain inhibitory effect on immune cells. As part of adaptive immunity, humoral immunity based on B cells and antibodies has a pivotal function in the defense against a variety of pathogens.[33] A low level of CD4+CD28+ T cells has been reported to be an independent predictor of high mortality in patients infected with human immunodeficiency virus (HIV).[34] CD45RA+CD4+ T cells, predominantly representing naïve CD4+ T cells, are frequently decreased in patients with SLE, RA, and lupus nephritis.[35] This reduction holds pathogenic significance as it correlates with increased disease activity. Thus, our study provides a preliminary insight into the correlations between high BKV-DNA loads and abnormal amounts of immune cells in individuals with CTD-RI. Remarkably, due to the exploratory nature of this marginal findings, further validation is required in larger cohorts.

Inevitably, there are some limitations in this study. First of all, due to the reduced statistical power caused by the small sample size and the marginal significance in the correlation analysis, our conclusions should be interpreted with caution. In the future, more patients with renal associated diseases can be included to fully explore the role of BKV in these diseases. Secondly, the study population was not followed up for a long term. Consequently, it remains unclear how the presence and viral loads of BKV influence the ultimate outcome of the patients. Future studies should track BKV loads over time to assess clinical outcomes. Thirdly, causality cannot be inferred in this study: BKV may be a marker, not a driver of disease. Besides, there may be confounding factors related to immunosuppressants: the dosage and unmeasured variables (eg, drug combinations, adherence) may influence results. Large-scale, multicenter, and prospective studies may be considered in the future to elucidate the role of BKV in disease progression and prognosis.

Overall, our study comprehensively evaluated the BKV-DNA qPCR detection kit and compared BKV-DNA loads in various renal associated diseases with healthy individuals. We have also found that in CTD-RI group, MMF serves as a protective factor, and higher BKV-DNA loads may be associated with renal impairment and immune dysfunction (although the causal relationship between BKV and renal injury could not be established in this study). Our findings support the individualized use of MMF based on clinical profiles may not increase the risk of BKV. However, treatment duration and dosage require careful consideration to ensure safety. For patients with CTD-RI, urine BKV testing can be performed based on the patient's comprehensive condition to assess potential risk. These findings might provide new insights into the effect of

BKV in renal associated disease. Future long-term follow-up and multicenter large-scale cohort studies are necessary to further clarify the role of BKV in RD.

Data Sharing Statement

The de-identified data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval Statement

This study was approved by the Ethics Committee of the Peking Union Medical College Hospital (No. HS2019104). The Ethics Committee agreed to waive the informed consent in this clinical study. The reason for the waiver is that this study would not interfere with the diagnosis or treatments of the patients. All kidneys were donated voluntarily with written informed consent, and that these were conducted in accordance with the Declaration of Istanbul. All data involving patients in this study are strictly confidential in accordance with the national legislation and the institutional requirements.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests for this work.

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