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BK Virus Detection by Real-Time Polymerase Chain Reaction in Sjögren's Syndrome, Rheumatoid Arthritis, and Behçet's Disease

Sjögren Sendromu, Romatoid Artrit ve Behçet Hastalığında Gerçek Zamanlı Polimeraz Zincir Reaksiyonu ile BK Virüsü Tespiti

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ABSTRACT

Objective: Autoimmune diseases are chronic conditions with largely unclear etiology, affecting patients' quality of life and increasing healthcare costs. This study aimed to investigate the relationship between Rheumatoid arthritis, Sjögren's syndrome, Behçet's disease, and BK virus.

Materials and Methods: This study was conducted between August 2017 and August 2018 in the Central Laboratory of the Department of Medical Microbiology. A total of 120 adults were enrolled, including patients diagnosed with Rheumatoid arthritis, Sjögren's syndrome, Behçet's disease (n=30 each) attending the Rheumatology outpatient clinic, and healthy controls from the General Internal Medicine outpatient clinic (n=30). BK virus was detected in urine and serum samples using Real-Time PCR. Multivariate logistic regression analysis was performed to identify independent factors associated with urinary BK virus positivity, including age and disease groups.

Results: The mean ages were 43.03±19.43 years in controls, 54.33±12.03 in Rheumatoid arthritis, 50.76±10.29 in Sjögren's syndrome, and 42.63±10.88 in Behçet's disease groups. Urinary BK virus positivity was detected in 1/30 (3.3%) controls, 7/30 (23.3%) Rheumatoid arthritis patients, 7/30 (23.3%) Sjögren's syndrome patients, and 4/30 (13.3%) Behçet's disease patients. BK virus positivity was significantly higher in the Sjögren's syndrome (p=0.016) and Rheumatoid arthritis groups (p=0.049) compared with controls. In multivariate logistic regression analysis, both Rheumatoid arthritis and Sjögren's syndrome were identified as independent predictors of BK virus positivity (OR=8.83; 95% CI: 1.01–76.96; p=0.049). Although positivity was higher in Behçet's disease patients, the difference was not statistically significant.

Conclusion: Urinary BK virus positivity was significantly more frequent in patients with Rheumatoid arthritis and Sjögren's syndrome than in healthy controls. These findings suggest a potential association between BK virus and certain autoimmune diseases. Larger, well-designed prospective studies are warranted to clarify the role of BK virus in autoimmune disease pathogenesis.

Keywords: BK virus, Rheumatoid arthritis, Sjogren's syndrome, Behcet's Disease, Real-Time PCR

ÖZET

Amaç: Otoimmün hastalıklar, etiyolojisi büyük ölçüde belirsiz olan kronik hastalıklardır ve hastaların yaşam kalitesini olumsuz etkilemekte, sağlık hizmeti maliyetlerini artırmaktadır. Bu çalışmada, Romatoid artrit, Sjögren sendromu ve Behçet hastalığı ile BK virüsü arasındaki ilişkinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışma, Ağustos 2017–Ağustos 2018 tarihleri arasında Tıbbi Mikrobiyoloji Anabilim Dalı Merkez Laboratuvarında gerçekleştirilmiştir. Çalışmaya romatoloji polikliniğinde Romatoid artrit, Sjögren sendromu ve Behçet hastalığı tanısı almış hastalar (her grupta n=30) ile genel dahiliye polikliniğinden sağlıklı kontroller (n=30) olmak üzere toplam 120 erişkin birey dâhil edilmiştir. BK virüsü, idrar ve serum örneklerinde Real-Time PCR yöntemi ile araştırılmıştır. İdrarda BK virüsü pozitifliği ile ilişkili bağımsız faktörleri belirlemek amacıyla yaş ve hastalık gruplarını içeren çok değişkenli lojistik regresyon analizi yapılmıştır.

Bulgular: Kontrol, Romatoid artrit, Sjögren sendromu ve Behçet hastalığı gruplarının yaş ortalamaları sırasıyla 43,03±19,43, 54,33±12,03, 50,76±10,29 ve 42,63±10,88 yıl olarak bulundu. İdrarda BK virüsü pozitifliği kontrol grubunda 1/30 (%3,3), Romatoid artrit grubunda 7/30 (%23,3), Sjögren sendromu grubunda 7/30 (%23,3) ve Behçet hastalığı grubunda 4/30 (%13,3) olarak saptandı. BK virüsü pozitifliği, Sjögren sendromu (p=0,016) ve Romatoid artrit (p=0,049) gruplarında kontrol grubuna göre anlamlı derecede daha yüksek bulundu. Çok değişkenli lojistik regresyon analizinde, Romatoid artrit ve Sjögren sendromunun BK virüsü pozitifliği için bağımsız belirleyiciler olduğu saptandı (OR=8,83; %95 GA: 1,01–76,96; p=0,049). Behçet hastalığı grubunda pozitiflik daha yüksek olmakla birlikte, bu fark istatistiksel olarak anlamlı bulunmadı.

Sonuç: İdrarda BK virüsü pozitifliği, Romatoid artrit ve Sjögren sendromu hastalarında sağlıklı kontrollere göre anlamlı derecede daha yüksek bulunmuştur. Bu bulgular, BK virüsü ile bazı otoimmün hastalıklar arasında olası bir ilişki olduğunu düşündürmektedir. BK virüsünün otoimmün hastalıkların patogeneziindeki rolünü netleştirmek için daha geniş ve iyi tasarlanmış prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: BK virüsü, Romatoid artrit, Sjögren sendromu, Behçet Hastalığı, Real-Time PCR

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INTRODUCTION

BK polyomavirus has an icosahedral structure and consists of a circular, double-stranded DNA genome. It belongs to the Betapolyomavirus genus within the Polyomaviridae family. The virus lacks an envelope and contains a small icosahedral capsid, approximately 40–44 nm in diameter, formed by the structural proteins VP1, VP2, and VP3. Among these, VP1 is responsible for binding to host cell receptors, thereby enabling the virus to enter its target cells (1). Although the impact of BK virus in kidney and hematopoietic stem cell transplant recipients has been well established, its effects on other organ systems remain incompletely understood (2). Rheumatoid arthritis (RA) is a systemic autoimmune disorder marked by persistent inflammation and symmetrical involvement of the synovial joints (3). It causes progressive erosive inflammation that, if not effectively managed, may lead to joint destruction, deformities, functional disability, and can even be life-threatening despite current treatment options. The etiology of RA has not yet been fully clarified (4,5). Sjögren's syndrome (SS) is a long-standing systemic autoimmune disorder with an unclear etiology, distinguished by the infiltration of lymphocytes into exocrine glands (6). Behçet's disease (BD), initially identified in 1937 by Turkish dermatologist Prof. Dr. Hulusi Behçet, is clinically characterized by a triad of symptoms: oral ulcers, genital ulcers, and hypopyon uveitis (7).

A possible association between BK virus (BKV) and systemic lupus erythematosus, one of the major rheumatological diseases, was proposed by Gupta et al. in a study published in 2017 (8). In light of these findings, the present study aimed to investigate whether a similar relationship exists between RA, SS, and BD and BKV, and, if so, to determine the prevalence of BKV activity in these conditions. In this study, the presence of BKV was investigated in urine and serum samples from 120 individuals (control, RA, SS, and BD groups) using Real-Time PCR (RT-PCR).

MATERIALS AND METHODS

Study Design and Participants: This study was designed as a cross-sectional observational study conducted between August 2017 and August 2018. This study was conducted in the Central Laboratory of the Department of Medical Microbiology, Faculty of Medicine, between August 2017 and August 2018. Blood and urine samples were collected, with informed consent, from adult patients diagnosed with RA, SS, and BD who presented to the Rheumatology outpatient clinic. Control group samples were obtained from adult patients attending the General Internal Medicine outpatient clinic. A total of 240 samples (120 blood and 120 urine) from 120 individuals were examined for BKV. **Sample Collection and PCR Analysis:** BKV nucleic acids were detected using the RT-PCR method. Blood samples collected in CBC tubes were centrifuged at 4000 rpm for 6 minutes to separate serum. Serum and urine samples were then transferred into sterile, screw-capped Eppendorf tubes using sterile pipette tips, labeled, and stored in a -20°C deep freezer until analysis.

Ethical Approval: Ethics committee approval was obtained

from the local ethics committee (Decision No: 15/22, Date: 16.11.2017).

Statistical Analysis: Statistical analyses were performed using SPSS version 20.0 (IBM Corp. USA). Continuous variables were expressed as mean \pm standard deviation, while categorical variables were presented as counts and percentages. Comparisons between groups were conducted using the chi-square test or Fisher's exact test for categorical variables, as appropriate. For comparisons involving more than two groups, one-way analysis of variance (ANOVA) was performed, followed by post hoc comparisons using Tukey's test. The sample size was based on the available number of eligible patients during the study period. Post-hoc power analysis based on the observed effect size (OR = 8.826, $\alpha=0.05$) indicated that the achieved power was $>80\%$, suggesting that the sample size was sufficient to detect the observed associations.

To identify factors associated with BK virus urine RT-PCR positivity, multivariable logistic regression analysis was performed. BK virus positivity was defined as the dependent variable, while age and disease groups (Rheumatoid arthritis, Sjögren syndrome, and Behçet's disease; reference group: controls) were included as independent variables. All variables were entered into the model simultaneously using the Enter (forced entry) method. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Model fit and explanatory power were assessed using Cox & Snell R^2 and Nagelkerke R^2 . A p-value of 0.05 was considered statistically significant.

RESULTS

The demographic data of the study groups showed that the mean age was 43.03 ± 19.43 years in the control group, 54.33 ± 12.03 years in the RA group, 50.76 ± 10.29 years in the SS group, and 42.63 ± 10.88 years in the BD group. A significant difference in mean age was detected overall between groups ($p=0.003$), with post-hoc analysis showing higher mean age in the RA group compared with the control and BD groups. However, no significant differences were observed between the BD and SS groups in comparison to the control group ($p = 1.000$). Within the study population, the control group consisted of 13 males and 17 females; the RA group comprised 10 males and 20 females; the SS group included 1 male and 29 females; and the BD group was composed of 12 males and 18 females. A statistically significant difference in gender distribution was observed between the SS group and the other groups ($p=0.003$). A statistically significant difference was observed between the groups in terms of organ involvement due to rheumatological disease ($p = 0.001$).

During sample collection, participants were asked whether they had received quinolone-derived antibiotics within the past two weeks, as quinolones have been reported to be effective against BKV (9). Evaluation of the groups regarding recent quinolone use revealed no statistically significant differences ($p=0.131$). The demographic data are presented in Table 1.

Table 1. Demographic and clinical characteristics of the study groups

Variable	Control group (n=30) (Group1)	Rheumatoid Arthritis (n=30) (Group2)	Sjogren Syndrome (n=30) (Group3)	Behcet's Disease (n=30) (Group4)
Age (years)	43.03±19.43	54.33±12.03	50.76±10.29	42.63±10.88
Gender (M/F)	13/17 (%43/%56)	10/20 (%33/%66)	1/29 (%3/%96)	12/18 (%40/%60)
Disease duration (Years)	0.0±0.0	8.23±4.76 (2-19)	7.1±6.05 (1-30)	10.30±8.56 (2-30)
Due to disease (Yes/No)	0/30 (%0/%100)	3/27 (%10/%90)	10/20 (%33/%66)	17/13 (%66/%33)
Quinolone use (Yes/No)	0/30 (%0/%100)	1/29 (%3/%96)	2/28 (%6/%93)	2/28 (%6/%93)

Table 2. Inferential statistical analysis of demographic and clinical variables

Variable	Statistical test	Statistic value	p-value	Effect size
Age	One-way ANOVA (post hoc Tukey)	F(3,116)=3.16	0.003	G1-G2: d = 0.70 (moderate-large) G2-G4: d = 1.02 (large)
Gender	Chi-square / Fisher's exact test	$\chi^2 = 14.28$	0.003	Cramér's V = 0.345 (moderate)
Disease duration	One-way ANOVA	F(3,116)=2.24	0.412	—
Due to disease	Chi-square / Fisher's exact test	$\chi^2 = 30.76$	0.001	Cramér's V = 0.506 (moderate-large)
Quinolone use	Chi-square / Fisher's exact test	$\chi^2 = 2.29$	0.131	—

Table 3. Distribution of urine and plasma BKV PCR positivity among disease groups

Variable	Control group (n=30) (Group1)	Rheumatoid Arthritis (n=30) (Group2)	Sjogren Syndrome (n=30) (Group3)	Behcet's Disease (n=30) (Group4)	Statistic	p	Effect size
Urine BKV PCR (-/+) Significant difference between Group 1 and Group 3 (p = 0.016).	1/29	7/23	7/23	4/26	$\chi^2 = 6.38$	0.016	Cramér's V = 0.23 (small- moderate)
Plasma BKV PCR (-/+) No statistically significant difference between the groups.	0/30	0/30	0/30	0/30	$\chi^2 = 1.017$	1.000	—

In the control group, 1 of 30 urine samples tested positive for BKV by RT-PCR. Among the 30 patients diagnosed with RA, BKV positivity was detected in 7 urine samples. Of these RA patients, 3 who were receiving biological therapies tested positive, while 4 who were not receiving biological therapies were also positive. Comparison of the total RA group with the

control group using the chi-square test revealed a statistically significant difference (p = 0.049). However, no significant difference in BKV positivity was observed between RA patients using biological drugs and those not using them (p= 0.409). These results indicate that biological therapy does not appear to affect urinary BKV positivity in patients with RA (Table 2-3).

Table 4. Multivariate logistic regression analysis of factors affecting BK virus urine RT-PCR positivity.

VARIABLE	B	S.E.	p	OR	95% CI (OR)	
					Lower	Upper
Age	0.022	0.026	0.406	1.022	0.971	1.076
Rheumatoid Arthritis	2.178	1.105	0.049	8.826	1.012	76.960
Sjogren Syndrome	2.178	1.105	0.049	8.826	1.012	76.960
Behcet's Disease	1.495	1.150	0.194	4.462	0.468	42.514
Constant	-0.470	1.512	0.756	0.625	-	-
Cox & Snell R Square=0.292; Nagelkerke R Square=0.501						

Abbreviations: B, regression coefficient; S.E., standard error; OR, odds ratio; CI, confidence interval; reverse transcription polymerase chain reaction; BK virus, BK polyomavirus. Control group was used as the reference category. Cox & Snell R² and Nagelkerke R² values indicate the explanatory power of the logistic regression model.

BKV positivity was detected in 7 of 30 patients with Sjögren's syndrome by urine RT-PCR. Chi-square analysis demonstrated a statistically significant difference between the control group and patients with Sjögren's syndrome ($p = 0.016$). In patients with Behçet's disease, BKV positivity was detected in 4 of 30 urine samples. Comparison between the control group and BD patients showed no statistically significant difference ($p = 1.000$).

Multivariable analysis of factors associated with BK virus positivity

To identify independent factors associated with urine BKV RT-PCR positivity and to control for potential confounding variables, a multivariable logistic regression analysis was performed. Age and disease groups (RA, SS, and BD) were included in the model, with the control group serving as the reference category. The results of the logistic regression analysis are presented in Table 4. The multivariable model demonstrated moderate to good explanatory power, with a Cox & Snell R² value of 0.292 and a Nagelkerke R² value of 0.501, indicating that approximately 50% of the variance in BK virus urine RT-PCR positivity was explained by the model.

Age was not independently associated with BKV positivity (OR = 1.022; 95% CI: 0.971–1.076; $p = 0.406$). In contrast, both RA and SS were found to be significant independent predictors of urine BKV RT-PCR positivity. Patients with Rheumatoid arthritis had an approximately 8.8-fold increased odds of BKV positivity compared with the control group (OR = 8.826; 95% CI: 1.012–76.960; $p = 0.049$). Similarly, patients with SS exhibited a comparable increase in risk (OR = 8.826; 95% CI: 1.012–76.960; $p = 0.049$). Although patients with BD showed a higher odds of BKV positivity compared with controls, this association did not reach statistical significance (OR = 4.462; 95% CI: 0.468–42.514; $p = 0.194$).

DISCUSSION

Polyomaviruses, including BK virus, are non-enveloped DNA viruses with an icosahedral capsid (10). Studies have reported BKV seropositivity in approximately 80% of adults (11). In a study conducted in our country, the seroprevalence of BKV was found to be 10.2% among kidney transplant patients (12). BKV is transmitted through close contact, respiratory routes, oral exposure, and perinatally. Most individuals are

exposed to BKV during childhood, which is believed to account for the high seropositivity observed in adults (13). Following primary infection, which may be asymptomatic or symptomatic, BKV remains latent in the kidneys and B lymphocytes. BKV-associated diseases typically arise in immunocompromised individuals, such as those with AIDS, leukemia, or organ transplant recipients (14). When an organ transplant is performed from a BKV-seropositive donor to a BKV-seronegative recipient, severe complications may occur in the recipient (15). BKV can be detected in urine, stool, blood, and cerebrospinal fluid, with urine samples recommended for screening due to the higher viral load compared to plasma (16).

BK virus is an agent that has been rarely investigated outside of its known associations with urogenital and meningeal manifestations. This study was conducted to investigate the possible association between BKV and RA, SS, and BD. Virus isolation and serological identification are not commonly employed for the diagnosis of BK virus. Nucleic acid amplification methods, particularly PCR, are widely used due to their high specificity (17). Accordingly, this study utilized RT-PCR for the detection of BKV. In a study by Gupta et al. conducted between 2014 and 2016, urine and blood samples were collected from 32 pediatric patients with SLE (26 girls, 6 boys; aged 4–18 years) at 3–6 and 9–12 months and analyzed using RT-PCR. Only 13 of the 32 patients completed the full 12-month follow-up. BKV was detected in 9 of 97 urine samples and 10 of 96 blood samples. BK viremia was observed in 28% (9/32) of patients, while BK viruria was observed in 22% (7/32). Both viremia and viruria were detected in 4 patients; only viruria in 3 patients; and only viremia in 5 patients. Microscopic hematuria was noted in only 1 patient. No false-positive results due to drugs or laboratory factors triggering BKV reactivation were reported (8).

In a case reported by Melis et al. in 2018, a 60-year-old female patient with SLE, who had been receiving azathioprine and medrol for 2 years since the age of 40, was admitted with complaints of lower extremity weakness and personality changes. Brain MRI revealed hyperintensities in the frontal and parietal lobes. Brain biopsy demonstrated demyelination along with histiocytic and atypical cells, and hematoxylin and eosin staining was performed. PCR analysis of the left frontal

biopsy confirmed BKV positivity, establishing a viral etiology for the patient's symptoms. Consequently, palliative treatment was administered (18). Jung Li et al. investigated BKV infection in patients with SLE and found that viral loads were higher in those who had undergone kidney transplantation compared to patients without transplants. They attributed this difference to the effects of immunosuppressive therapy. Furthermore, they suggested that BKV positivity in non-transplant patients might result from compromised immune function in these individuals (19).

In a 2015 case report by Whittemore et al. a 55-year-old male patient with RA presented with increased serum creatinine and dyspnea. The patient had a history of SS, chronic kidney disease, and hypertension, and had been receiving mycophenolate mofetil and tacrolimus for 6 years. Despite normal ultrasound findings and the absence of hematuria or proteinuria in the urine, the patient's renal function continued to deteriorate. Initially treated with meropenem, the patient's renal condition worsened despite treatment, leading to a suspicion of drug toxicity, prompting discontinuation of the medications. However, renal function continued to decline, and a kidney biopsy was performed. Microscopic examination revealed BKV-associated cellular changes. Subsequently, BKV PCR testing of serum and urine confirmed the presence of the virus. The patient was treated with intravenous immunoglobulin, quinolone, and leflunomide, which resulted in a full recovery (20). In a 2014 study, Calderon et al. investigated BKV in the salivary glands of two HIV-positive patients and one kidney transplant recipient. BKV DNA was isolated from the throat washings of both HIV-positive and HIV-negative patients. The study found that the replicative rate of BKV in the salivary glands was faster than in the kidneys, suggesting that BKV may exhibit tropism for the salivary glands. The authors hypothesized that mouth ulcers observed in HIV-positive patients could be attributed to BKV infection and emphasized the need for a larger study to further explore this potential association (21).

Wunderink et al. conducted a retrospective study between 2003 and 2013 to examine the relationship between HLA positivity and BK viremia in 407 liver donor-recipient pairs. BK viremia developed in 111 patients within one year post-transplant. Among the HLA alleles, recipient HLA-C7 and HLA-DR12 were associated with a higher risk of viremia, whereas HLA-A30, B13, B51, C15, and DR13 were linked to a lower risk. In particular, HLA-B51 was significantly correlated with a decreased risk of viremia. Multivariate analysis indicated that HLA-B51 positivity, observed in 36 recipients (9%), was associated with an approximately fivefold reduction in the risk of viremia (22). In a 2015 case report by Taşkapan et al, a 52-year-old female patient, who had received a renal transplant 3 months prior, presented to the neurology clinic with complaints of an inability to stand and walk. The patient had been started on mycophenolate mofetil, tacrolimus, and methylprednisolone, and was diagnosed with acute motor-axonal polyneuropathy based on clinical examinations. Due to the potential risk of new neurotoxicity, plasma exchange was performed for 10 days, and oral tacrolimus was switched to

rapamycin. Despite these interventions, the patient's symptoms worsened, and BKV was detected in the patient's serum by PCR. Further examinations revealed no other abnormalities. The patient's condition improved, and she began walking 15 days after initiating treatment with intravenous immunoglobulin (IVIG) and quinolone (23).

In our study, we analyzed blood and urine samples from patients with RA, SS, BD, and a control group. No significant differences were observed between groups regarding the use of quinolone in the last two weeks. BKV was not detected in any of the serum samples by RT-PCR. However, urine RT-PCR revealed BK viremia in 1 out of 30 patients (3.33%) in the control group, 7 out of 30 patients (23.33%) in the RA group, 7 out of 30 patients (23.33%) in the SS group, and 4 out of 30 patients (13.33%) in the BD group. Chi-square analysis showed a significant difference between the RA and SS groups versus the control group, whereas no significant difference was found between the BD group and the control group. To further evaluate independent factors associated with BK viremia, a multivariate logistic regression analysis was performed. In this model, age was not found to be a significant predictor of urinary BKV RT-PCR positivity. However, both RA and SS were identified as independent risk factors for BK viremia. Patients in the RA group had an approximately 8.8-fold increased odds of BKV positivity compared to the control group (OR=8.83, 95% CI: 1.01–76.96, $p=0.049$). Similarly, SS was also associated with a significantly increased risk of BK viremia with the same magnitude of effect (OR=8.83, 95% CI: 1.01–76.96, $p=0.049$). Although the BD group demonstrated a higher odds ratio compared to controls, this association did not reach statistical significance. The model showed a moderate-to-good explanatory power, with a Cox & Snell R^2 of 0.292 and a Nagelkerke R^2 of 0.501.

These findings may suggest a possible association between BK viremia and RA or SS that appears to be independent of age; however, due to the cross-sectional design of the study, causal relationships cannot be established. Comparisons with population-based seroepidemiological data were limited. Differences in methodologies and patient populations across studies limited direct comparisons with the existing literature. We believe that large-scale, multi-faceted comparative studies are necessary to better understand the pathogenesis of BKV in patients with RA and SS, both of which showed statistically significant associations with the virus in our study.

Study Limitations

Several limitations of this study should be acknowledged. Another limitation of this study is the relatively small sample size in each disease group. Although statistically significant associations were observed for Rheumatoid arthritis and Sjögren's syndrome, the limited number of participants may reduce the generalizability of the findings. Due to the well-known epidemiological characteristics of Sjögren's syndrome, there was a marked female predominance in this group. This imbalance may have limited the statistical power to fully assess the independent effect of sex in multivariable analyses. Therefore, findings related to gender should be interpreted with caution.

CONCLUSION

The present study demonstrates a higher frequency of BK viruria in patients with RA and SS compared to healthy controls, while no significant association was observed in patients with BD. The absence of BK viremia and the lack of an association with age suggest that BKV reactivation in these patient groups may be localized and related to disease-specific immune dysregulation rather than demographic factors. Although the clinical significance of asymptomatic BK viruria remains to be fully elucidated, these findings contribute to the existing literature by highlighting a potential relationship between BKV and selected autoimmune rheumatic diseases.

DECLARATIONS

Conflict of Interest: *The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.*

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