



Review Article

Prevalence of BK Virus among Iranian Renal Transplant Recipients: A Systematic Review and Meta-Analysis

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ABSTRACT

Background and objectives: BK virus (BKV) reactivation is a major challenge for renal transplant recipients. The purpose of this study was to summarize current knowledge on the status of BKV in Iranian renal transplant recipients.

Methods: Specific terms, including “BKV” and “Renal Transplantation” were used to search the online databases. I² and Cochran’s Q-value were tested for heterogeneity. The incidence rate was determined at 95% confidence interval. Publication bias was also investigated using funnel plot, the Egger’s and Begg’s statistics.

Results: Twelve studies were included in the study. The random model's overall evidence rate was 0.347 (CI 95%, 0.225-0.493, p-value=0.04).

Conclusions: In Iran, the estimated prevalence of BKV among renal transplant recipients is 34.7% (~10-60%), which is higher than the rate reported from other parts of the world. Therefore, it is recommended to screen organ donors for BKV in Iran.

Keywords: Bk Virus; Systematic Review; Meta-Analysis; Renal Transplantation

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population sample, Motazakker et al. have

INTRODUCTION

Kidney transplantation is the last-line treatment for end-stage renal disease (ESRD). In this regard, there are major concerns regarding graft rejection due to immunity and a variety of viral infections. BK virus (BKV), a member of the Polyomaviridae family, is involved in the rejection of renal transplants. It is known that > 60% of healthy adults are seropositive to Polyomaviridae that may become active under immunosuppression (1). Reactivation of polyomaviruses in renal and bone marrow transplant recipients is related to the use of immunosuppressive drugs and immunodeficiency (2,3). Therefore, it is important to examine the prevalence of these viruses in transplant recipients in order to assess the impact of the virus on graft rejection (4).

BKV is a human polyomavirus that was first isolated from the urine of an immunocompromised renal transplant patient in 1971 (5). Primary respiratory tract infection contributes to asymptomatic latent BKV infection, which results in a high rate of seropositivity in humans (6). The use of immunosuppressive drugs in transplant recipients increases the risk of BKV infection (7–10). BKV may be reactivated following renal transplantation, leading to nephropathy accompanied with renal graft rejection. BKV may be transmitted via respiratory and oral routes, and has 82% seroprevalence in adults (6). In a previous research in Iran, BKV was detected in 13.1% of biopsy samples from renal transplant patients (11). Samarbasf-Zadeh et al. demonstrated a 3-fold increase in BKV reactivation within four months of renal transplantation (12). BKV strains have also been reported to be associated with BK viremia in liver transplant recipients (13).

BKV is classified into four serotypes (I-IV). Within the world's population, serotype I is the most common (80%), followed by serotype IV (15%) (6). In a small

shown that BKV serotype I is prevalent in Iranian-Turkish renal transplant recipients (14). In a relatively larger study in Iran, BKV serotype I (94.11%) was found to be predominant serotype compared to serotype IV (5.89%) (15).

Given the clinical significance of BKV examination of renal transplant recipients, particularly immunocompromised patients, this systematic review and meta-analysis was performed to summarize the latest knowledge on BKV incidence in Iranian renal transplant recipients.

MATERIALS AND METHODS

Search strategy

We performed this systematic review and meta-analysis according to the Meta-Analysis of Observational Studies in Epidemiology consensus statement and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PubMed, Google Scholar and Iranian medical repositories have been screened for reports on BKV prevalence in Iran. For PubMed, the following keywords were used: "BK virus" OR "BKV" in title AND "renal transplantation" OR "kidney transplantation" in title/abstract, AND "Iran" in affiliation. The findings were filtered into "Epidemiology". Last adjustment was rendered by the transfer of data on the human subject/species. For Google Scholar, the exact phrase "BK virus" And "BKV" plus "Iran" plus "renal transplantation" OR "kidney transplantation" were searched. All data published until the end of 2018 were included in the study.

Inclusion and exclusion criteria

Abstract/full manuscripts in English or Persian were included. Accordingly, researches describing BKV experiments in countries other than Iran were excluded. In addition, review papers were not included in the analysis. Studies on BKV incidence in

immunocompromised patients, rather than renal transplant recipients, were also excluded. Grey studies or unpublished papers were included. There was only one report from our department that has not yet been published.

Study screening and data extraction

After retrieval, the abstracts of each study were screened and checked for eligibility. Then full-texts were read by two researchers. Any disagreement between the two researchers was resolved through discussion with a third researcher. Data regarding names of authors, year of publication, number of patients and control subjects, gender, mean age, sample size and BKV detection method(s) in both case (renal transplant recipients) and/or control (healthy volunteers) groups were collected.

Data analysis

Meta-analysis was conducted using the Comprehensive Meta-Analysis Software V2 (16). Study type was specified as "Estimate of means, proportions of rates in one category at a time-point". Effect size data entry was set as two dichotomous formats, representing non-events and sample sizes in each group. This helped determine the incidence rate of BKV among renal transplant recipients. I² and Cochran's Q-

value were used for heterogeneity. I² value of more than 25% indicated heterogeneity. The incidence rate was evaluated at 95% confidence interval (CI). Publication bias was also double-checked by funnel plot and Egger's and Begg's methods. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

Literature review and data extraction

Overall, 12 studies as well as a study performed in our department were eligible for inclusion in the analysis. Data were collected for BKV detection in different types of samples. In this respect, the research was extended to 15 studies (Figure 1). For example, results from two urine and plasma samples were obtained in one study and analyzed separately (12). Similar data were collected from two additional studies performed by Shenagari et al. (urine and plasma) and Pakfetrat et al. (plasma and biopsy) (17,18). More data were collected for the study of subgroups. As a result, four groups of BKV detection were derived from the included experiments, including real-time PCR (7/15), PCR (5/15), double PCR and semi-nested PCR (2/15), and light microscopy (1/15)

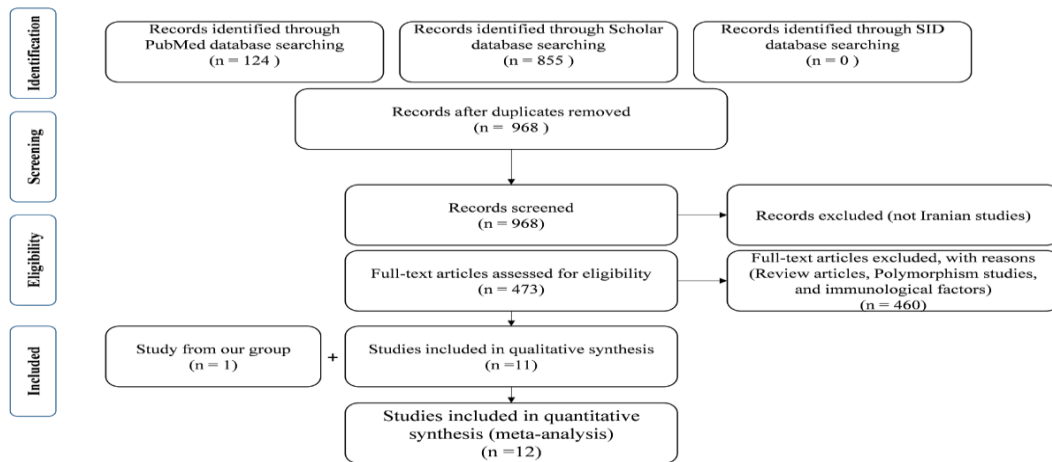


Figure 1 PRISMA of database search and number of included studies.

Meta-analysis report and statistics

Heterogeneity was found in the studies ($Q = 293.737$, $df(14)$, $I^2 = 95.234$, $\text{tau-squared}=1.295$, $p\text{-value} = 0.0001$). This was further investigated using a randomized model (Figure 2). As shown, the prevalence of BKV was higher in the Pakfetrat et al. study with a sample size of 82 cases (0.89 CI 95%, 0.8-0.94). The lowest rate was found in the Jozpanahi et al. study (9.8E-3 CI 95%, 6.11E-4-0.138) with 50 subjects. The overall incidence rate of BKV in the random model was 0.347 (CI 95%, 0.225-0.493, $p\text{-value} = 0.04$).

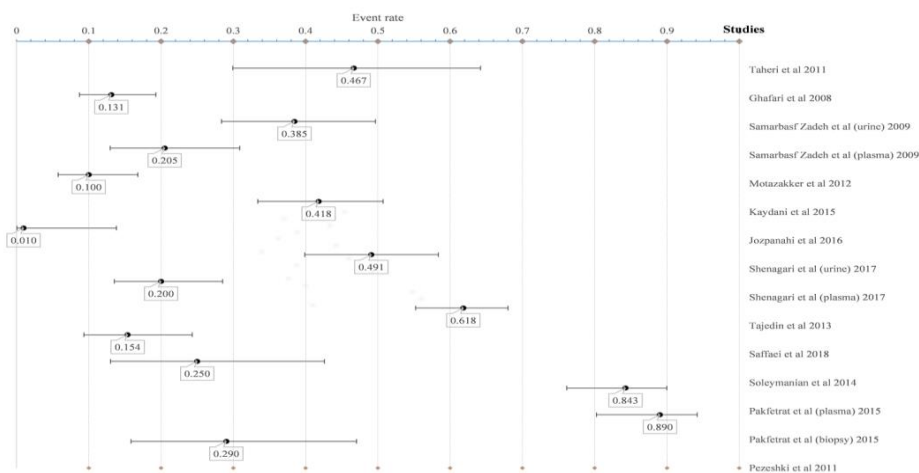


Figure 2 Forest plot reveals the frequency of BKV prevalence among renal transplant recipients. Data are not gathered and dispersed around the plot, which suggests that there are heterogeneities

in the studies.

As shown in the funnel plot (Figure 3), the data is well distributed in a low standard error axis. Furthermore Begg's and Egger's regression results were not significant (3.93, df(13), $p > 0.05$).

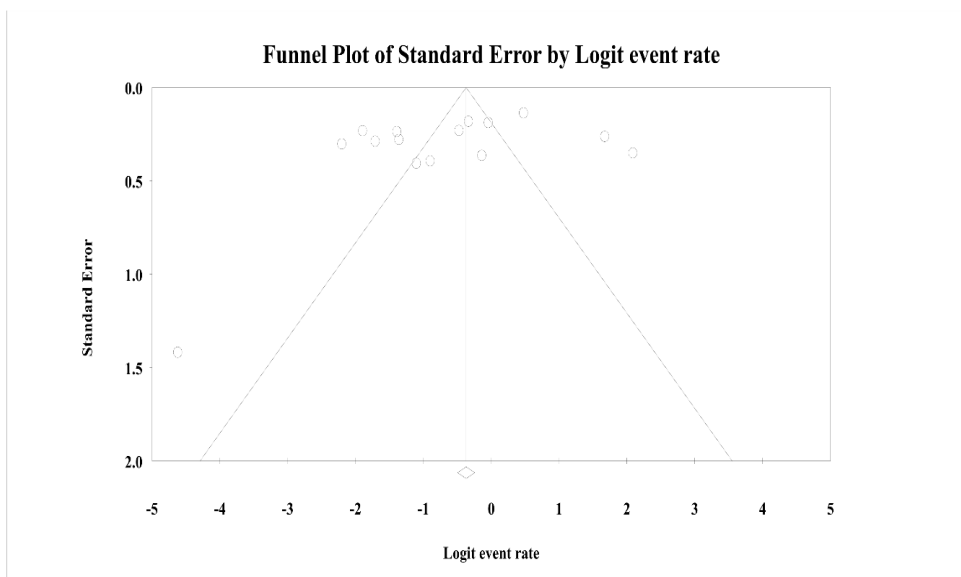


Figure 3 Funnel plot of standard error by logit event rate.

Sub-group analysis

In order to find heterogeneity in the studies, we looked deeply into the methodological analysis in the patient group (Table 1 and Figure 4). Data included heterogeneity within all forms of methodologies. Whereas, heterogeneity in the double PCR group was slightly low.

The total random incidence rate for the double PCR method was 0.287 (6.96E-2-0.685, p -value > 0.05). The overall evidence rate for light microscopy was 0.131 (0.014-0.618, p -value > 0.05). In comparison, the random event rates for PCR and real-time PCR subgroups were 0.287 (0.121-0.54, p -value > 0.05) and 0.465 (0.252-0.692, p -value > 0.05), respectively. Two real-time PCR studies showed higher evidence rates (0.84 and 0.89) within the random model. The mean standard error for the subgroup analysis was 0.1 ± 0.044 (0.052-0.18).

Analysis of comparison variable within study

Table 1. Random model for different sub-groups within study analysis.

Groups	No. Studies	Event rate (lower-upper limit)	Q-value (df)	I-squared	p-Value
Double PCR	2	0.287 (0.07-0.685)	5.892 (1)	83.027	0.015
Light microscopy	1	0.131 (0.014-0.618)	0 (0)	0	1.0
PCR	5	0.287 (0.121-0.539)	96.259 (4)	95.845	0
Real-time PCR	7	0.465 (0.252-0.692)	126.826 (6)	95.269	0
Grand Total	15	0.327 (0.176-0.526)			0.087

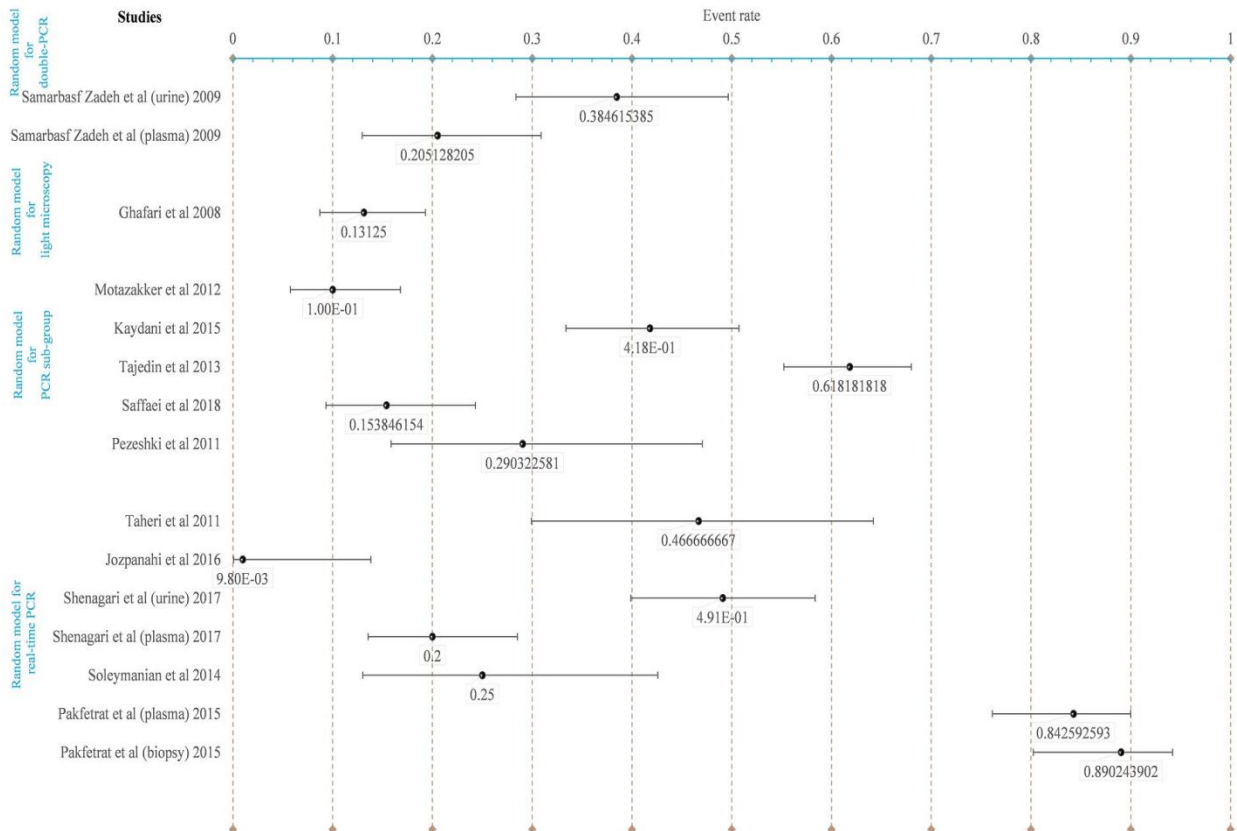


Figure 4 Forest plot. The incident rates for each sub-group are shown. As shown, most data are accumulated on the left side of the forest plot with an event rate of < 0.6.

Results were further examined for heterogeneity of comparative groups. As shown in table 2, heterogeneity was present in all groups.

The incidence rate was assessed for each sample using a random model (Figure 5). As shown, there was one out-group in the urine random model with an occurrence rate of 0.89 ($p < 0.0001$). The mean standard error for the comparison group was 0.082 ± 0.039 (0.009-0.167).

Table 1 Random model for comparison of different sample types.

Groups	No. Studies	Event rate (upper-lower limit)	Q-value (df)	I-squared	p-value
Biopsy	2	0.515 (0.154-0.86)	88.328 (1)	98.868	0.0001
Plasma	5	0.279 (0.106-0.557)	101.557 (4)	96.061	0.0001
Urine	8	0.343 (0.179-0.556)	98.821 (7)	92.916	0.0001
Grand Total	15	0.344 (0.215-0.502)			0.053

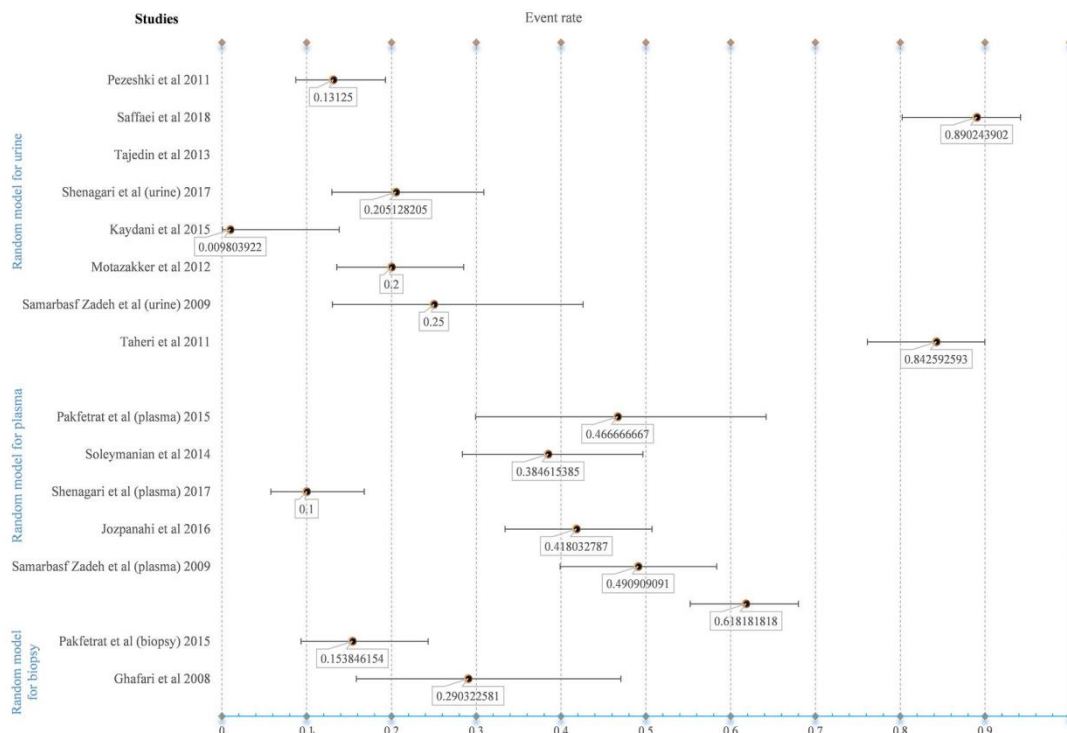


Figure 5 Forest plot of event rates for Comparison groups. 80% of data centered under event rate of 0.5.

DISCUSSION

Iran is one of the active countries in the renal transplantation services with a large number of successful transplants (19). The prevalence of ESRD in Iran is 15,000 with an annual incidence rate of 53 per one million patients (20). Viral infections are the main causes of graft rejection (21–23). As a result, BKV infection and its reactivation are major concerns in immunosuppressed renal transplant recipients. BKV-associated nephritis is a threat to the survival of renal grafts (23). This study is the first systematic review and meta-analysis on the prevalence of BKV among renal transplant recipients in Iran. A systematic review and meta-analysis research on the prevalence of BKV in colorectal cancer patients in Iran was published previously (24).

In the present study, the overall apparent BKV rate among renal transplant recipients was more than 34%. Furthermore, a high prevalence of BKV infection was reported in the study of Pakfetrat et al. on plasma (0.84 ± 0.26) and biopsy (0.89 ± 0.35) samples (18). The lowest BKV prevalence (0.0098 ± 1.42) was reported by Jozpanahi et al. 2016 on plasma samples. It was also noted that real-time PCR screening approaches had higher standard errors. This can be due to the poor quality of RNA or the inadequate design of primers. Comparison of BKV detection methods in renal allograft recipients was reviewed by Lee et al. (25).

Based on the results, 34.7% of Iranian renal transplant recipients have had an episode of BKV infection/reactivation. The highest frequency of BK viremia and viruria was observed within a few months after transplantation (26). Unfortunately, there was no record of sampling period in the examined studies. In addition, there was no specific screening protocol for BKV in transplant patients. One of the major risk factors for BKV infection in renal transplant recipients is infection of organ donor (4,27). In order to better understand BKB-associated renal graft loss, future studies

must provide serological data of both renal graft donors and recipients. In addition, we recommend that samples should also be obtained from patients at several intervals following renal transplantation.

After electron microscopy of urinary Haufen inclusion bodies, molecular approaches have more sensitivity and specificity than cytology. Real-time PCR using BK viral protein 1 (VP1) mRNA extracted from urinary cells was identified as a BKV-associated nephritis biomarker (28). In addition, amplification of the viral genome in biopsy, blood and urine using standard PCR is the preferred screening approach (29–32). Here, the evidence rate of BKV by different methods including double-PCR, light microscopy, PCR, and real-time PCR has been evaluated in Iranian studies. The evidence rate for BKV in the Real-Time PCR group was 0.465 (0.252–0.692) and was higher than that for PCR (0.287 [0.121–0.539]), double PCR (0.287 [0.07–0.685]) and light microscopy (0.134 [0.014–0.618]). In a study conducted by Pakfetrat et al., the prevalence of BKV was found to be 11% among renal transplant recipients using real-time PCR (18). In other studies, the prevalence of BKV was reported to be 15.7% among plasma samples (47/300) (17,18,33,34). Nevertheless, the prevalence of BKV was observed to be as high as 48.7% (68/140) in studies performed by Taheri et al. and Shenagari et al. on urine sample using real-time PCR. It simply represents an association between the form of sample and the detection method.

Diagnosis of BKV-associated diseases is dependent on virus detection in urine, blood and biopsy samples (23). Renal biopsy is the gold standard for diagnosis of BKV (35). In the present study, frequency of BKV was different in different types of samples. The evidence rate of BKV in biopsy samples (0.515 [0.154–0.86]) was shown to be higher than in urine (0.343 [0.179–0.556]) and in plasma (0.279 [0.106–0.557]). Therefore, the

clinical source of the extracted viral genome can affect the sensitivity and specificity of the screening methods. The defined sample types for BKV screening have been described previously (36).

We observed heterogeneity in the studies and subgroup studies. This implies the involvement of other risk factors for BKV, including immunosuppression (36) and immunosuppressive drugs (37), male sex, older recipient age, rejection episodes, degree of human leukocyte antigen mismatching, prolonged cold ischemia, BK sero-status and ureteral stent placement (36). Limitations of the present study included the low quality of reports in Iran, the lack of sufficient patient clinical data and the existence of out-of-group data as observed in the Funnel plot. Such limitations may have contributed to the design phases of the research and experimental procedures. Therefore, the effect of the contributing factor(s) of patients

as a prognosis for BKV infection could not be determined.

CONCLUSION

BKV is a common post-transplant opportunistic viral infection affecting 15% of renal transplant recipients in the first post-transplant year. Unlike other parts of the world, we found that the incidence of BKV among Iranian renal transplant recipients is high. Organ donors need to be screened for BKV infection using both molecular and serological approaches before transplantation. For the evaluation of BKV activation, it is recommended to further investigate BKV infection at certain post-transplant intervals using biopsy samples.

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DECLARATIONS

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Ethics approvals and consent to participate

Not applicable.

Conflict of interest

The authors declare that there is no conflict of interest.

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