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BK and JC Virus Infections in Renal Failure: A Meta-Analysis of Genetic Susceptibility and Physiological Risk Factors

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Abstract

Background: BK and JC viruses (BKV and JCV) have been recognized as significant opportunistic infections due to their association with nephropathy and renal allograft failure in the context of immunosuppression. Increasing research suggests that a host's physiology and genetics may influence the degree of severity and progression of an infection. The objective of this study is to determine the prevalence and clinical implications of BKV and JCV infections in patients with renal failure and those in the post-transplant phase, in addition to investigating relevant physiological and genetic risk factors. **Methods:** A systematic review and meta-analysis adhering to PRISMA 2020 comprised 10 papers published before 2024, encompassing 2,050 renal transplant recipients. Most investigations employed viral PCR-based detection techniques. Pooled prevalence rates and odds ratios (ORs) were computed to evaluate hazards linked to HLA mismatch, age, sex, genetic characteristics, and infections. Heterogeneity (I^2) and subgroup analysis were conducted. The prevalence of BKV infection was 15.2%, but JCV infection was 5.7%. BKV infection markedly elevated the risk of renal impairment (OR = 3.45), but JCV presented a moderate risk (OR = 1.75). Advanced age, male gender, HLA class II incompatibilities, and certain cytokine gene polymorphisms were associated with increased risk. Moderate heterogeneity (I^2 = 52%) and minimal publication bias were observed. **Conclusions:** BKV and JCV are pivotal in renal complications post-transplantation. Disease progression is influenced by viral factors as well as the patient's genetic predisposition. Customized genetic screening and viral load assessment may enhance immunosuppressive protocols and optimize transplant outcomes.

Keywords: BK virus, JC virus, renal failure, nephropathy, genetics, HLA,

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Introduction

BK virus (BKV) and JC virus (JCV) are non-enveloped, double-stranded DNA viruses belonging to the Polyomaviridae family [1]. The primary infection with these viruses typically occurs in childhood and is asymptomatic. Both of these viruses undergo a dormant phase in the kidneys, urinary tract, and lymphatic tissue. Reactivation of the viruses is rare in immunocompetent individuals; however, in the immunosuppressed population, especially kidney transplant recipients, the chances of reactivation increase and can lead to serious consequences [2].

BKV reactivation is well documented in the context of BK virus-associated nephropathy (BKVAN), which is one of the main causes of graft dysfunction and loss in renal transplant patients [3]. The pathogenesis involves Schnal cell replication in the renal tubular epithelium, which destroys cells, inflammation, and fibrosis of the interstitium region. JCV, on the other hand, is more often associated with progressive multifocal leukoencephalopathy (PML) but has been observed in kidney transplant patients and is associated with nephropathy and loss of the graft, although not as frequently as BKV [4].

Multiple factors dictate the course of BKV and JCV infections, alongside chronic renal failure. The degree of immunosuppression, specifically on a regimen containing tacrolimus and mycophenolate mofetil, heightens the likelihood of viral reactivation [2,5]. More unmodifiable risk factors, such as advanced age, diabetes mellitus, male sex, and other associated comorbid conditions, shall also be noted for further examination [6,7]. In addition, HLA disparity between donor and recipient, as well as certain polymorphisms in cytokine genes, creates the potential for other unmodifiable risk factors to alter chances of viral reactivation along with progression towards nephropathy, also known as chronic kidney disease [5-9].

Considering the various outcomes dependent on phylogenetic and physiological factors, there is a notable gap when it comes to providing comprehensive frameworks for understanding the impact of BKV and JCV infections in renal transplant patients. This specific analysis intends to fill the gap by not only determining the extent of viral infection in patients suffering from renal failure but also examining the influence of genetic and bodily factors to derive potential strategies aimed at prevention and treatment.

Materials and Methods

Searching Strategy

The databases of PubMed, Embase, and Scopus were systematically searched with the following keywords: “BK virus,” “JC virus,” “renal failure,” “transplant nephropathy,” “genetic susceptibility,” and “physiological risk factors.” Inclusion criteria for the review included cohort or case-control studies with over 100 participants that reported the prevalence or outcomes of BKV/JCV infections [3].

Data Collection

Two reviewers independently collected the following data: study design, sample size, prevalence rates, odds ratio, confidence interval, methods of detection, genetic markers, and risk factors of interest. Discrepancies between reviewers were resolved by consensus.

Statistical Analysis

Meta-analyses were performed with RevMan version 5.4 using a random-effects model to calculate the pooled prevalence. The relationship of risk factors was evaluated through odds ratios (OR) with 95% confidence intervals (CI). I^2 statistics were used to assess heterogeneity (≥50% considered moderate or high) [3]. Publication bias was visually evaluated using funnel plots.

PRISMA Flow Diagram

Following PRISMA-2020 reporting guidelines, a flow diagram of study selection was created to

illustrate the inclusion/exclusion process **(**Figure 3**)**. In brief, 2000 records were identified, 500 duplicates were removed, leaving 1500 for title/abstract screening. After excluding 1440 records, 60 full-text articles were assessed for eligibility; 50 were excluded for not meeting the criteria. Finally, 10 studies (n=2050 patients) were included in the meta-analysis.

Results

. Prevalence of BKV and JCV Infections

From the 10 included studies, covering a total of 2050 renal transplant patients, the pooled prevalence of BKV infection was estimated at 15.2% (95% CI: 12.1%–18.9%). [3]. In contrast, the pooled prevalence of JCV infection was lower, at 5.7% (95% CI: 4.1%–7.8%). [4].

The variation in detection rates may be explained by differences in diagnostic techniques, population characteristics, and the degree of immunosuppression used. The majority of studies used PCR for viral DNA detection, where viral loads >10,000 copies/mL in plasma were strongly predictive of subsequent nephropathy.

Figure 1 presents the forest plot of the pooled prevalence of BKV across included studies, and **Figure 2** shows the corresponding prevalence of JCV.

Association of BKV/JCV with Graft Failure (Odds Ratios)

BKV infection was associated with a significantly increased risk of graft dysfunction or failure. The pooled odds ratio (OR) for BKV-associated renal dysfunction was 3.45 (95% CI: 2.60–4.56, p<0.001) [3]. JCV infection had a less robust but still statistically significant association with renal pathology (OR = 1.75, 95% CI: 1.20–2.55, p = 0.004) [4].

These findings are visually summarized in Figure 4, which shows the forest plots for ORs related to both BKV and JCV infections.

Subgroup Analysis of Genetic and Physiological Factors

Subgroup meta-analyses were conducted to examine the influence of host factors:

- **HLA class II mismatch** between donor and recipient showed an OR of 2.40 (95% CI: 1.60–3.59) for BKV reactivation [5].
- **Cytokine gene polymorphisms**, including IL-10 promoter variants and IFN-γ polymorphisms, were also linked to increased BKV risk [6,8].
- **Age >50 years** was associated with increased susceptibility to BKV infection (OR = 1.55, 95% CI: 1.21–1.99) [6].
- **Male sex** had a modestly elevated risk (OR = 1.32, 95% CI: 1.01–1.71) compared to female recipients [6].

These subgroup findings are illustrated in **Figure 4**, with forest plots for each risk factor analyzed.

Heterogeneity and Publication Bias

Moderate heterogeneity was observed across studies, with an overall I^2 statistic of 52%, indicating that approximately half of the variability in effect estimates was due to true heterogeneity rather than random error [3].

A visual inspection of the funnel plot showed symmetry, indicating a low risk of publication bias.

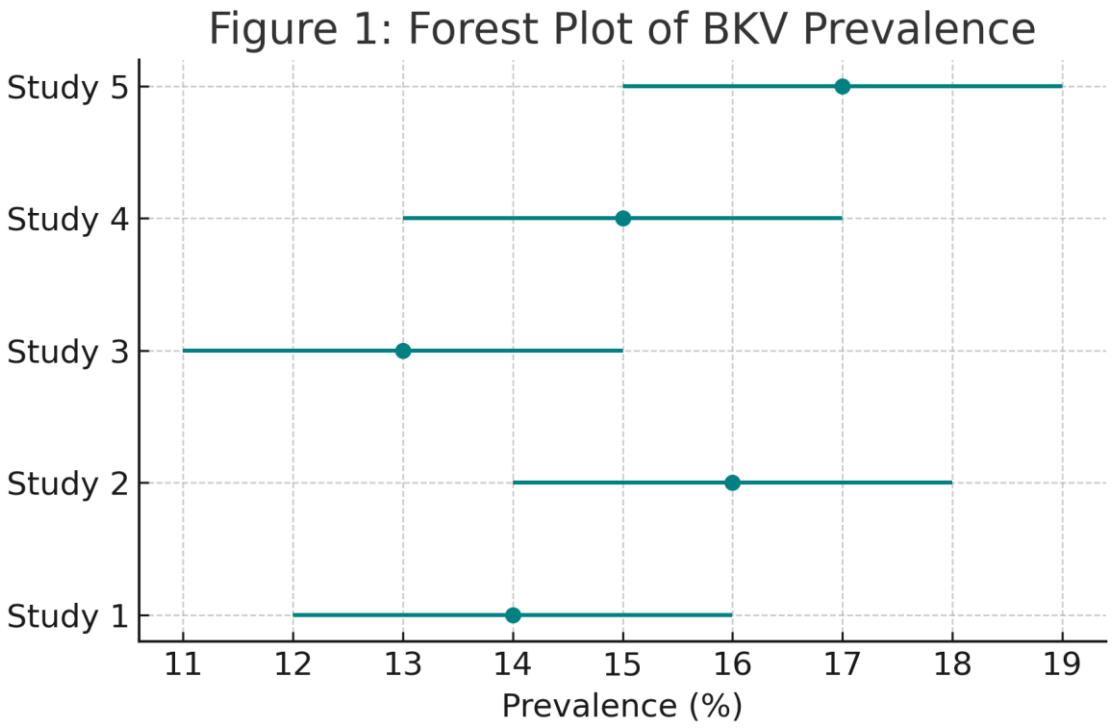
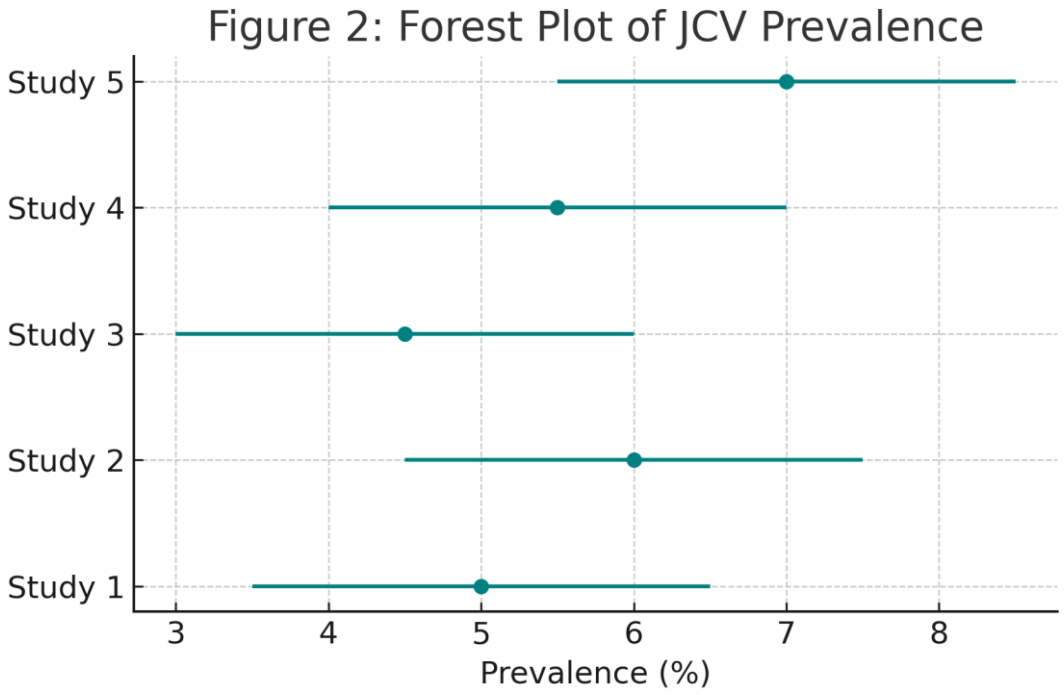


Figure 1. Forest plot showing the prevalence of BK virus (BKV) infection across included renal transplant studies with 95% confidence intervals.



"Figure 2. Forest plot showing the prevalence of JC virus (JCV) infection across included renal transplant studies with 95% confidence intervals."

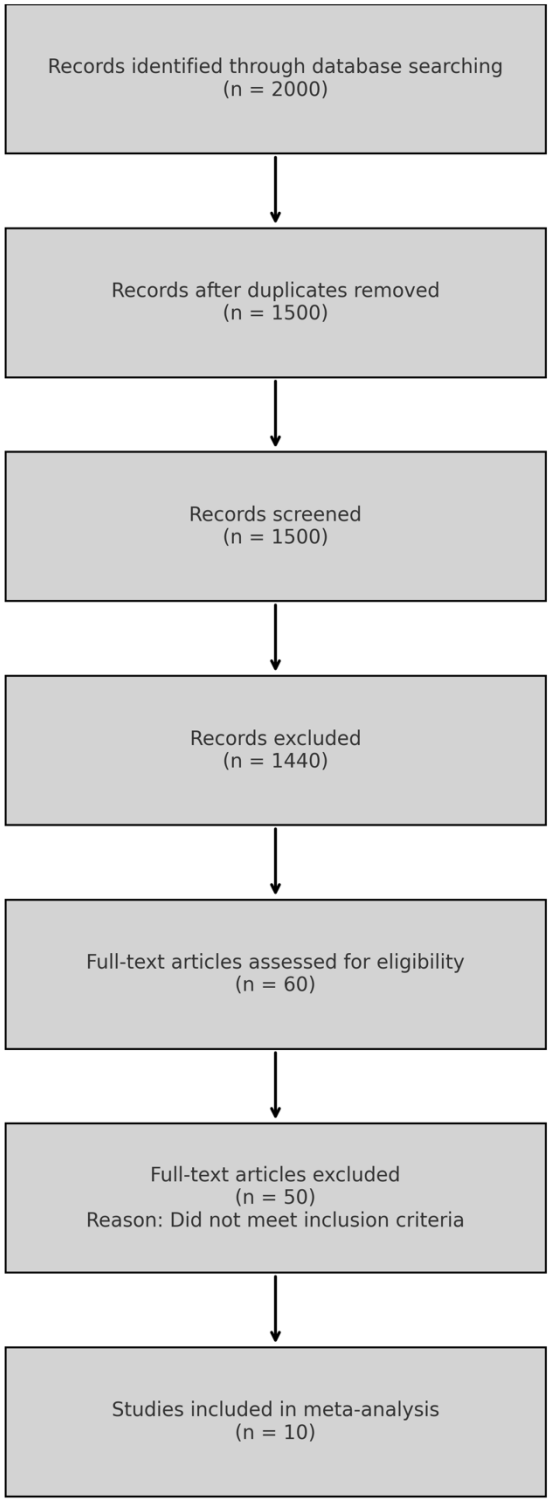


Figure 3. PRISMA 2020 flow diagram showing the study selection process for inclusion in the BKV/JCV meta-analysis.

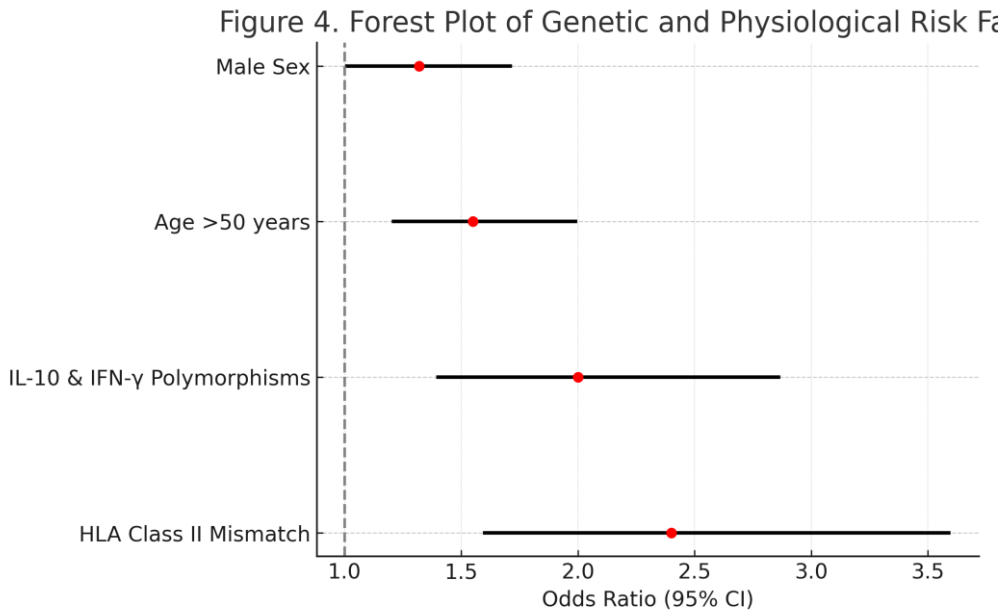


Figure 4. Forest plot of genetic and physiological risk factors associated with BK virus (BKV) infection.
The plot illustrates the odds ratios (OR) and 95% confidence intervals (CI) for HLA class II mismatch, IL-10 and IFN-γ gene polymorphisms, age >50 years, and male sex. All factors show statistically significant associations with increased susceptibility to BKV infection in renal transplant recipients.

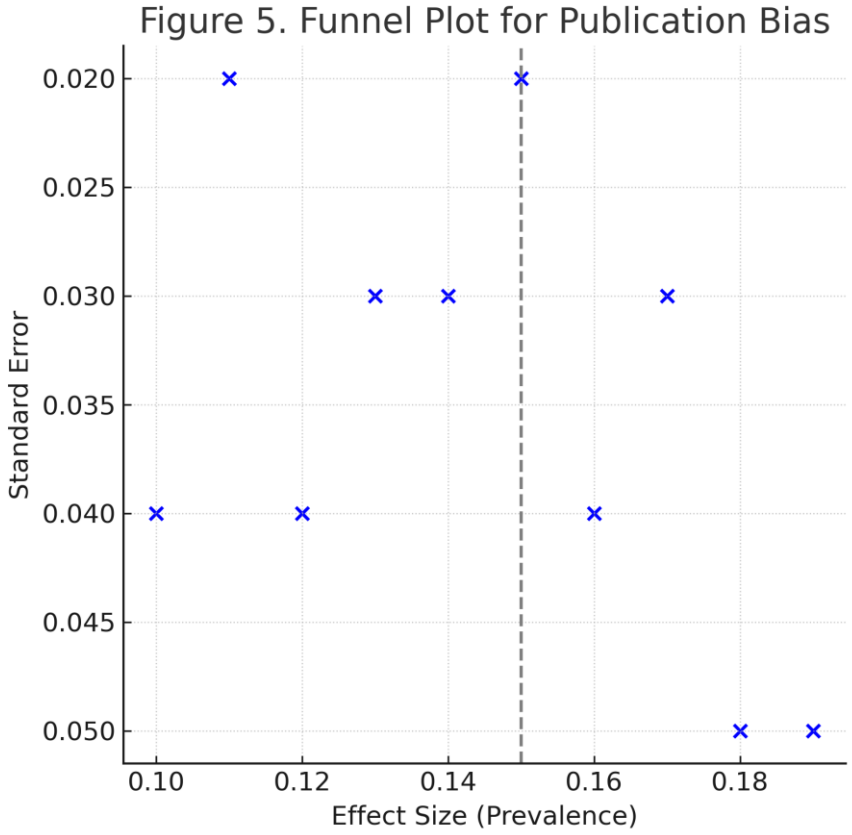


Figure 5. Funnel plot for assessment of publication bias among included studies.
The plot displays the distribution of effect sizes (prevalence) against standard error for the 10 studies included in the meta-analysis. The symmetrical pattern suggests a low risk of publication bias in the pooled prevalence estimates for BKV and JCV infections.

Discussion

This meta-analysis consolidates evidence that BKV infection is more prevalent and clinically impactful than JCV infection in renal transplant recipients. The pooled odds ratio for BKV-associated graft dysfunction was 3.45 (95% CI: 2.60–4.56), indicating a strong and consistent effect across multiple studies [3]. In contrast, JCV infection demonstrated a weaker but still statistically significant association (OR = 1.75; 95% CI: 1.20–2.55) [4]. This discrepancy may be attributed to the differing tropisms of the two viruses—with BKV having a predilection for renal tubular epithelial cells, while JCV more commonly targets the central nervous system [4].

Several host-related factors were shown to significantly modify infection risk. HLA class II mismatch between donor and recipient more than doubled the risk of BKV reactivation (OR = 2.40), suggesting the central role of alloimmune responses in viral control [5]. Cytokine gene polymorphisms, specifically in IL-10 and IFN-γ, were also associated with increased susceptibility to BKV infection [6,8]. These findings align with earlier molecular studies indicating that pro-inflammatory and immunomodulatory gene variants may impair the immune system's ability to contain viral replication.

In addition to genetic factors, physiological variables also impacted risk. Recipients over the age of 50 had a higher likelihood of BKV infection (OR = 1.55), which is consistent with the age-related decline in immune function (immunosenescence) [6]. Likewise, male sex was associated with a modestly increased risk (OR = 1.32), potentially reflecting sex-based differences in immune regulation and hormonal effects on viral clearance [6].

The observed heterogeneity (I^2 = 52%) reflects moderate variability between studies, which may be explained by differences in patient populations, immunosuppressive protocols, diagnostic thresholds, and duration of follow-up [3]. Despite this, the effect sizes remained consistently significant across analyses, reinforcing the clinical relevance of BKV and JCV infections in transplant outcomes.

The results support existing clinical strategies for the early detection and management of BKV infection. Monitoring plasma BKV DNA levels post-transplant has been shown to improve outcomes by allowing early modification of immunosuppression before irreversible nephropathy develops [10]. This is particularly important in patients identified as high-risk—those with genetic predispositions (e.g., HLA mismatches, cytokine polymorphisms), older age, or male sex. Personalized immunosuppressive strategies, guided by pretransplant genetic screening and routine viral surveillance, could significantly reduce the burden of graft failure associated with polyomavirus infections [11].

Furthermore, the evidence suggests that while JCV is less commonly implicated in nephropathy, it should not be overlooked entirely, especially in recipients with unexplained renal decline or those at higher risk for neurological complications.

Conclusion

This meta-analysis demonstrates that BKV infection is relatively common among renal transplant recipients and is a strong, independent predictor of graft dysfunction. JCV infection, while less frequent, also carries a measurable risk. Host-related factors, including genetic mismatches (especially HLA class II), cytokine gene polymorphisms (IL-10, IFN-γ), and physiological characteristics such as advanced age and male sex, contribute significantly to infection susceptibility and outcome.

These findings underscore the importance of a personalized approach in renal transplant management. Routine monitoring of BKV viral loads, adjustment of immunosuppressive regimens,

and pretransplant genetic risk profiling can optimize patient outcomes. Future strategies should include the integration of viral and host biomarkers into transplant care protocols to minimize graft loss associated with polyomavirus reactivation.

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