International Journal of Advance Research in Medical Surgical Nursing

E-ISSN: 2663-2268
P-ISSN: 2663-225X
www.surgicalnursingjournal.com
IJARMSN 2025; 7(2): 116-119
Received: 20-07-2025
Accepted: 25-08-2025

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BK polyomavirus and inflammatory cytokine IL-6 in renal transplant patients in Iraq

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DOI: https://www.doi.org/10.33545/surgicalnursing.2025.v7.i2b.276

Abstract

Background: BK virus (BKV) infection remains a major post-transplant complication in renal transplant recipients, potentially contributing to graft dysfunction. Interleukin-6 (IL-6) is a pro-inflammatory cytokine that plays a central role in immune regulation and transplant rejection. This study aimed to evaluate the relationship between BKV infection and IL-6 levels in renal transplant patients.

Methods: A case-control study was conducted involving 105 renal transplant recipients and 30 apparently healthy individuals as a control group were included in this study. Plasma samples were analyzed for BKV DNA using polymerase chain reaction (PCR), and IL-6 concentrations were measured by enzyme-linked immunosorbent assay (ELISA; USCH-SEA079Hu). The distribution of BKV infection was assessed according to demographic and clinical factors.

Results: Bk virus infection was detected in 7 out of 105 patients (6.67%). Interleukin-6 levels were highest in BKV-positive patients (2.22±1.40 pg/mL), followed by BKV-negative patients (0.79±0.61 pg/mL), and the lowest in control group (0.36±0.16 pg/mL). However, IL-6 level in all groups remained within the normal range (normal range of IL-6 is less than 7 pg/mL). possibly due to the immunosuppressive therapy administered to transplant recipients.

Conclusion: While BK virus infection occurred in a small proportion of renal transplant patients, IL-6 levels did not show inflammatory response, likely due to the immunosuppressive treatment. These findings suggest that IL-6 may not serve as a reliable biomarker for detecting BKV-associated inflammation in this patient population. Further studies with larger cohorts and longitudinal monitoring are recommended.

Keywords: BK virus, interleukin-6, renal transplantation, PCR, ELISA

Introduction

BK polyomavirus (BKV) is a member of the Polyomaviridae family and is a well-recognized opportunistic pathogen in immunocompromised individuals, particularly renal transplant recipients (RTRs) [1, 2]. The virus remains latent in the uroepithelium and renal tubular epithelial cells of most adults, following an often-asymptomatic primary infection during childhood [3]. Reactivation of BKV in transplant patients, often due to potent immunosuppressive therapy, can lead to BK virus-associated nephropathy (BKVAN), a major cause of graft dysfunction and potential loss in kidney transplant recipients [4, 5].

BK virus-associated nephropathy is characterized by active viral replication within renal tissues, resulting in intranuclear inclusion bodies, tubular cell lysis, and interstitial inflammation [6]. The risk of BK virus reactivation increases significantly with the use of modern immunosuppressive agents such as tacrolimus and mycophenolate mofetil [5]. Despite the clinical significance, there are currently no specific antiviral therapies for BKV infection, and management typically involves reducing immunosuppression a strategy that carries its own risks [4, 7].

Interleukin-6 (IL-6) has garnered attention as a key inflammatory cytokine involved in viral infections and immune-mediated tissue injury [8, 9]. Interleukin-6 is a multifunctional cytokine produced by immune cells such as macrophages and T cells, as well as by non-immune cells like fibroblasts, adipocytes, and endothelial cells [10, 11]. It plays a crucial role in acute-phase responses, B-cell differentiation, inhibition of regulatory T cells, and modulation of immune cell function [12, 13].

Elevated IL-6 levels are associated with various inflammatory and autoimmune diseases, and its dysregulation is implicated in transplant rejection and viral reactivation [9, 4].

Emerging evidence suggests that IL-6 may be upregulated during BK virus reactivation, reflecting the host's inflammatory response to viral replication and tissue damage [15, 16].

Therefore, the present study aimed to investigate the association between BK virus infection and serum IL-6 levels in renal transplant recipients in Iraq. This may help clarify the potential utility of IL-6 as a biomarker of BK virus reactivation and guide future diagnostic or therapeutic strategies in transplant settings.

Materials and Methods

Study Design and Setting: This case-control study was conducted at Rizgary Teaching Hospital, Erbil, Iraq, in collaboration with the Technical Research Center of the Northern Technical University. Blood samples were collected from participants between October 1, 2024, and January 15, 2025.

Study Population: The study included 105 renal transplant patients and 30 control group. Inclusion criteria for renal transplant recipients included being over 18 years old, having received a kidney transplant at least one month prior to participation, upper limit less than 2 years and having no active autoimmune disease or concurrent infection. The control group consisted of healthy individuals with no history of renal disease or immunosuppressive therapy.

Ethical approval: This study was approved by the Scientific Research Ethics Committee at Tikrit University, College of Medicine. Ethical approval for the project titled "Detection of BK Virus and its Relation with Some Immunological Factors in Renal Transplant Patients in Iraq" was granted under approval date 22/6/2025. The principal investigator was Muhammad Haydar Ali Naqi. Written informed consent was obtained from all participants prior to enrollment in the study, and all procedures were conducted in accordance with the ethical standards of the institutional research committee.

Sample Collection: About five milliliters of the patients' venous blood were taken and controls group under sterilized condition using sterile disposable syringe and placing 2 milliliters in EDTA tube and mix to prevent blood clotting for estimation of hemoglobin level. Placing the remaining 3 milliliters of blood in gel tube and allow at room temperature for 10-20 minutes to clot. The tube then centrifuged 3000 rpm for 10 min. then transfer the clear serum into clear dry two Eppendorf's tubes and kept at -20 °C in a deep freezer until analysis.

Detection of BK Virus by PCR: BK virus DNA was extracted from plasma using a standard viral DNA extraction kit. PCR amplification targeted the large T antigen *Tag2* gene using the following primers [17].

- **Forward primer:** 5′-AGCAGGCAAGGGTTCTATTACTAAAT-3′
- **Reverse primer:** 5′-GAAGCAACAGCAGATTCTCAACA-3′

These primers amplify a 732 bp fragment. PCR was performed under the following conditions: initial denaturation at 95 °C for 5 min, followed by 45 cycles of 94 °C for 30 s, annealing at 56 °C for 30 s, and extension at 72 °C for 30 s with a final extension at 72 °C for 5 min. PCR products were visualized on 1.5% agarose gel stained with ethidium bromide.

Measurement of Interleukin-6 (IL-6): Serum IL-6 level were measured using an enzyme-linked immunosorbent assay (ELISA) kit (USCN Life Science Inc., Wuhan, China; Catalogue No. USCH-SEA079Hu), following the manufacturer's instructions. Absorbance was read at 450 nm using a microplate reader. Each sample was tested in duplicate, and the average value was recorded.

Statistical Analysis: Data were analyzed using IBM SPSS version 25. Continuous variables are expressed as mean ± Standard deviation (SD).

Results

A total of 105 renal transplant patients (RTPs) and 30 control group were included in this study. Among the RTPs, 7 patients (6.67%) tested positive for BK virus (BKV) by PCR.

The level of serum IL-6 was 2.22±1.40 pg/mL in renal transplant patients (RTPs) with BK virus infection, 0.79±0.61 pg/mL in RTPs without BKV infection, and 0.363±0.161 pg/mL in the control group. The difference between the groups was statistically significant ($p < 0.001$), indicating that IL-6 levels were markedly higher in patients with BK virus infection compared to the other groups (Table 1).

Table 1: Serum IL-6 levels among study groups

The study groups	Level of IL-6 (pg/mL) (Mean ± SD)
Patients with BKV infection	2.22±1.40
Patients without BKV infection	0.79±0.61
Control group	0.363±0.161
P value	< 0.001

In the present study, BKV was detected in 7 out of 105 (6.67%) renal transplant patients. The rate of infection in males was slightly higher in males than that in females (6.76% and 6.45% respectively). The highest rate of BK virus infection was recorded in the 20-30 years group (11.11%), followed by the 31-40 years group (10.00%) and the 41-50 years group (3.45%), while no positive cases were detected in the 51-60 years category.

When considering time of sample collection after transplant, BK virus infection was found in 11.11% of patients during 1-6 months after transplantation, 11.54% of patients during 6-12 months and only 1.92% of patients after 1 year.

An inverse relationship appeared between hemodialysis duration before transplantation and BK virus positivity. The highest rate was observed in patients with <6 months of hemodialysis (18.52%), decreasing to 7.69% in those with hemodialysis >6 months, and reaching 0% in those with hemodialysis for more than 12 months.

All variables are summarized in Table 2, which illustrates the distribution of BK virus infection across the analyzed subgroups.

Table 2: Demographic and clinical distribution of BK virus infection in renal transplant patients

Variable	Subgroup	No. of patients	Patients with BK Virus Infection	
			No.	%
Sex	Male	74	5	6.76
	Female	31	2	6.45
Age (year)	20-30	18	2	11.11
	31-40	40	4	10.00
	41-50	29	1	3.45
	51-60	18	0	0
Time of sample collection after transplant (month)	1-<6	27	3	11.11
	6-12	26	3	11.54
	>12	52	1	1.92
Hemodialysis duration before transplant (month)	< 6	27	5	18.52
	6-12	26	2	7.69
	> 12	51	0	0

Discussion

This study investigated the prevalence of BK virus infection among renal transplant patients and its association with demographic factors and interleukin-6 (IL-6) levels. Our findings showed a slightly higher BK virus positivity among male patients (6.76%) compared to females (6.45%), although the difference was minimal. This aligns with some previous reports suggesting no strong gender bias in BK virus infection among transplant recipients [18, 19]. Other study doing by Lorant, Male sex was identified as a significant risk factor for developing BKPyV-associated nephropathy (BKPyVAN) or high-level BKPyV DNAemia, with an odds ratio of 2.85 ($p = 0.025$), indicating a higher susceptibility in male kidney transplant recipients. The highest infection rate was observed in the younger age group of 20-30 years (11.11%), with no positive cases detected in patients aged 51-60 years. While younger recipients may be more susceptible to BK virus reactivation, the limited sample size and lack of a clear linear trend necessitate cautious interpretation [20, 21].

The infection was predominantly observed within the first year after transplantation, with similar positivity rates in the 1-6 month and 6-12-month intervals (11%). Beyond one-year post-transplant, BK virus positivity declined sharply to 1.92%. This temporal distribution corresponds with previous studies emphasizing the early post-transplant period as the critical window for viral reactivation and graft monitoring [22, 23]. Interestingly, BK virus infection rates were higher in patients with less than six months of dialysis before transplant (18.52%) compared to those with longer dialysis durations. This inverse association might reflect immune system modulation or pre-transplant viral exposure dynamics, consistent with findings reported by da Costa *et al*. and Ajeel *et al*. in dialysis populations [24, 25].

In the present study, the serum levels of interleukin-6 were assessed among three groups: virus-positive transplant recipients, virus-negative recipients, and control group. With respect to BK virus infection, the highest IL-6 concentration was detected in the BKV-positive group (2.22±1.40 pg/mL), compared to lower levels observed in the BKV-negative group (0.79±0.61 pg/mL) and the control group (0.363±0.161 pg/mL). all of them was in normal range. This observation agrees with prior research showing that immunosuppressive drugs like tacrolimus can modulate IL-6 production, thereby influencing both viral replication and graft inflammation [13, 26].

Conclusion

This study highlights the notable presence of BK virus infection among renal transplant recipients, particularly during the first post-transplant year. Although infection rates were higher among younger patients and males. Interleukin-6 levels were moderately elevated in BK virus-positive patients compared to control group; however, the levels remained within the normal range, likely due to the immunosuppressive therapy administered post-transplantation. These findings emphasize the importance of regular screening for BK virus and associated inflammatory markers to prevent graft injury. Further large-scale studies are recommended to clarify the immunological interactions and support more tailored management strategies in renal transplant patients.

Conflict of Interest

Not available.

Financial Support

Not available.

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How to Cite This Article
Al-Bayati MH, IH Saadoon, Hadi AM, Hussein AL. BK polyomavirus and inflammatory cytokine IL-6 in renal transplant patients in Iraq. International Journal of Advance Research in Medical Surgical Nursing. 2025; 7(2): 116-119.