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# The Frequency of Bk Polyomavirus Viruria in A Sample of Iraqi Children with Acute Lymphoblastic Leukemia

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## Abstract

**Background** BK Polyoma virus (BKPyV) is a ubiquitous virus and infect children at early age and becomes latent and it has been found as the main cause of hemorrhagic cystitis in hematopoietic stem cell transplantation patients, due to immunosuppression regimen that led to the activation of the virus from the latency status and lead to increased viral shedding in urine.

**Objective** To find the frequency of BKPyV-DNA in urine (viruria) among acute lymphoblastic leukemia (ALL) patients as compared to healthy controls and compare it with age, sex, relapse and leukocytes level.

**Methods** Urine samples were collected from 60 ALL patients, and 60 apparently healthy age and sex-matched children who were taken as a control group. The BKPyV-DNA in urine (viruria) was detected using real time polymerase chain reaction and Pap-stained urine cytology smears were checked to identify the presence of decoy cells (DCs).

**Results** The BKPyV-DNA was detected in the urine of all patients (100.0%) and in 55.0% of control group (P <0.001) and all the patients were DCs negative. There was no significant effect of the positivity of viruria on neither leukocytes level nor on the occurrence of relapse in leukemia patients.

**Conclusion** The very high frequency of BKPyV-DNA in urine (viruria) indicates the importance of reactivation of this virus in ALL patients with and without chemotherapy.

**Keywords** Acute lymphoblastic leukemia, BK Polyoma virus, real time-PCR.

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**List of abbreviations:** ALL = Acute lymphoblastic leukemia, BKPyV = BK Polyoma Virus, BKPyVAN = BK Polyoma virus associated nephropathy, BKPyV-HC = BK Polyoma virus hemorrhagic cystitis, DCs = Decoy Cells, JCPyV = JC Polyoma virus, qPCR = Quantitative polymerase chain reaction, q-RT-PCR = Quantitative real time polymerase chain reaction, T Ag = Large tumor t antigen, t Ag = Small tumor antigen

## Introduction

Polyomavirus BK virus (BKPyV), a small, non-enveloped, double-stranded DNA virus that is ubiquitous and species specific. It is a member of the polyomaviridae family [(1)]. Based to reports, between the ages of 5 and 10 years old, up to 90% of the normal individuals might become seropositive for BKPyV [(2)]. The BK virus infects the renal epithelium and stays latent until immunosuppression causes reactivation. By using techniques now used in the clinical laboratory, BKPyV can be detected in the urine after reactivation. The occurrence of renal diseases such hemorrhagic cystitis (HC),

ureteral stenosis and nephropathy can be related to BKPyV viruria [3]. When the immune system is compromised, such as after solid organ or bone marrow transplantation or when taking immunosuppressive drugs, latent BKPyV infection may become active. HC is more likely to develop in patients who have had bone marrow transplants than kidney transplant recipients, which are more likely to develop renal failure [1].

In children with acute lymphoblastic leukemia (ALL), an aggressive form of cancer, an excessive number of immature lymphocytes (a type of white blood cell) are produced by the bone marrow. A healthy child's bone marrow generates blood stem cells, which are immature cells that eventually develop into mature blood cells. An excessive amount of stem cells that develop into lymphoblasts, B lymphocytes, or T lymphocytes are present in a child with ALL. These cells are also known as leukemia cells. These leukemia cells function differently than healthy lymphocytes and are not as effective in fighting off infection [4].

In immunocompromised patients, this virus is known to develop decoy cells (DCs), which may be detected in a urine sample utilizing Papanicolaou staining [5]. Clinically significant DCs can be employed as a prognostic marker for pathologies such BKPyV-induced nephropathy and HC in any circumstance when immunosuppression is present [5,6].

Given the scarcity of data about the prevalence of BKPyV infection in children with ALL [7], this study was made with the objectives to investigate the frequency of BKPyV excretion in the urine of children with children with ALL with and without chemotherapy and compare it with control group.

## Methods

A case-control study was conducted from December 2021 to May 2022. Urine samples were collected from a total of 60 ALL children (20 children newly diagnosed with ALL group 1, and from 40 children on chemotherapy for ALL group 2) in Central Pediatrics Hospital in Baghdad. Sixty apparently healthy age and sex-matched children (from colleagues' and relatives' children) were enrolled in this study as a control group (group 3).

An informed consent was obtained from the parents of all the patients and control group enrolled in this study. This study was approved by the Institute of Review Board of the College of Medicine, Al-Nahrain University number ٢٢ in the 17th of November 2021. The study was conducted in the Microbiology Department at the College of Medicine, Al-Nahrain University.

For DCs screening, urine (10 ml) was centrifuged in white cap tubes at 3000 rpm for 10 min. The supernatant was discarded and the sediment was re-suspended in the remaining urine.

Two slides were made for each patient; one was immediately fixed with absolute ethanol for 20 min, after which it was stored to be stained using the Papanicolaou method and examined under a light microscope at 10 and 40 X, and the other was immediately fixed with absolute ethanol for 20 min, after which it was stored at -20°C unstained for possible diagnosis confirmation. DCs, shedding cells from the superficial transitional cell layer that are viral inclusion-bearing epithelial cells with a ground-glass appearance and an enlarged nucleus filled with a basophilic inclusion surrounded by chromatin, were found to be replicating polyomaviruses [8,9]. For the quantification of DCs, a threshold of 10 DCs/slide is considered as a decoy positive [10].

Viral DNA was extracted from 200 µl of urine using EasyPure ® Viral DNA/RNA Extraction Kit (Beijing, China), viral DNA Extraction Spin Kit according to the manufacturer's protocol which is based on silica membrane column separation method and then was eluted from the column with 50 µl of RNAse free-water.

The Quantitative Real Time PCR (qRT–PCR) was carried out using the QIAGEN Rotor gene Q Real-time PCR System (Germany). The level of BKPyV was assessed using the TransStart® Top Green qPCR Super Mix kit and measuring the threshold cycle (Ct). A real-time PCR test

determines a positive reaction by accumulating a fluorescent signal. The levels and fold changes of BKPyV were assessed by measuring the Ct using the Trans Start® Top Green qPCR Super Mix kit components. A Ct number refers to the number of amplification cycles needed to attain a specific background level of fluorescence at which the real-time PCR diagnostic result switches from negative (not detectable) to positive (detectable) (i.e exceeds background level). The Ct values are inversely associated with the amount of target nucleic acid present in the sample (i.e. the lower the Ct level the greater the amount of target nucleic acid in the sample). Also melting curve analysis was performed based on the separation characteristics of double stranded DNA during cycles with increasing denaturation temperature.

**Statistical analysis**

Statistical package for social sciences (SPSS) 20.0 and Microsoft Excel 2016 were used for the statistical analysis of this case-controlled prospective study. The median and 5-95$^{th}$ percentile were used to characterize the numerical data. Count and percentage are two ways to describe categorical data. Chi-square test used to estimate the association between variables. While Mann Whitney U test and Kruskal Wallis tests used for comparison of numerical data between 2 groups or three groups respectively. The lower level of accepted statistically significant difference is bellow or equal to 0.05 [11,12].

## Results

Results of the current study showed that all leukemia patients were positive BKPyV viruria (100.0%) while only (55.0%) of control were positive (P <0.001) as shown in table (1) while table (2) shows significantly higher median for log viral load in ALL patients as compared to control (P <0.001).

**Table 1. Detection of BKPyV in study groups**

| BKPyV | Study groups | | P value |
|---|---|---|---|
| | Leukemia | Control | |
| Positive | 60<br>100.0% | 33<br>55.0% | <0.001 |
| Negative | 0<br>0.0% | 27<br>45.0% | |
| Total | 60<br>100.0% | 60<br>100.0% | |

P value by Chi-square test

**Table 2. Determination of BKPyV viral load among study groups**

| LogBKPyV viral load | Control | Patients with ALL | |
|---|---|---|---|
| | | On Chemotherapy | Without Chemotherapy |
| Median | 2.65 | 4.40 | 5.02 |
| Percentile 05 | 0.00 | 4.15 | 4.25 |
| Percentile 95 | 5.35 | 5.60 | 5.60 |
| P value | | <0.001 | |

P value by Kruskal Wallis test

Results of the current study also showed significantly higher number of positive BKPyV log viral load in urine off ALL patients who were under the age of 9 years (P <0.001) (Table 3) and who were males ALL patients (P <0.001) (Table 4).

**Table 3. The relation between BKPyV log viral load and age of the study group**

| Age groups | | | Leukemia | Control | Total | P value |
|---|---|---|---|---|---|---|
| < 9 years | BKPyV PCR | Positive | 52<br>100.00% | 26<br>52.00% | 78<br>76.50% | <0.001 |
| | | Negative | 0<br>0.00% | 24<br>48.00% | 24<br>23.50% | |
| | Total | | 52<br>100.00% | 50<br>100.00% | 102<br>100.00% | |
| ≥ 9 years | BKPyV PCR | Positive | 8<br>100.00% | 7<br>70.00% | 15<br>83.30% | 0.147 |
| | | Negative | 0<br>0.00% | 3<br>30.00% | 3<br>16.70% | |
| | Total | | 8<br>100.00% | 10<br>100.00% | 18<br>100.00% | |

P value by Chi-square test

**Table 4. The relation between BKPyV log viral load and sex of the study group**

| Sex | | | Leukemia | Control | Total | P value |
|---|---|---|---|---|---|---|
| Females | BKPyV PCR | Positive | 16<br>100.00% | 9<br>56.20% | 25<br>78.10% | 0.003 |
| | | Negative | 0<br>0.00% | 7<br>43.80% | 7<br>21.90% | |
| | Total | | 16<br>100.00% | 16<br>100.00% | 32<br>100.00% | |
| Males | BKPyV PCR | Positive | 44<br>100.00% | 24<br>54.50% | 68<br>77.30% | <0.001 |
| | | Negative | 0<br>0.00% | 20<br>45.50% | 20<br>22.70% | |
| | Total | | 44<br>100.00% | 44<br>100.00% | 88<br>100.00% | |

P value by Chi-square test

This study showed that relapse occurrence in the second group had no significant difference in the median of the negative and positive cases of urine Log BKPyV viral load (P = 0.524) (Table 5). Finally, results of this study demonstrated that BKPyV log viral load in urine positivity had no significant effect on leukocyte levels of the patients (Table 6). Figure 1 shows the melting curve for some of the positive samples in the study in qPCR that evaluates the

features of double-stranded DNA's dissociation after heating.

**Table 5. Median Log BKPyV viral load and relapse occurrence**

| Log BKPyV viral load | Relapse | | P value |
|---|---|---|---|
| | No | Yes | |
| Median | 4.30 | 4.50 | |
| Percentile 05 | 4.20 | 4.10 | 0.524 |
| Percentile 95 | 5.50 | 5.70 | |

P value by Mann Whitney U test

**Table 6. Relation of BKPyV log viral load in urine with leukocyte levels**

| Patients with ALL and BKPyV | Leukocyte Level | | | Total |
|---|---|---|---|---|
| | Leukopenia | Normal | Leukocytosis | |
| | 26 | 8 | 26 | 60 |
| | 100.00% | 100.00% | 100.00% | 100.00% |

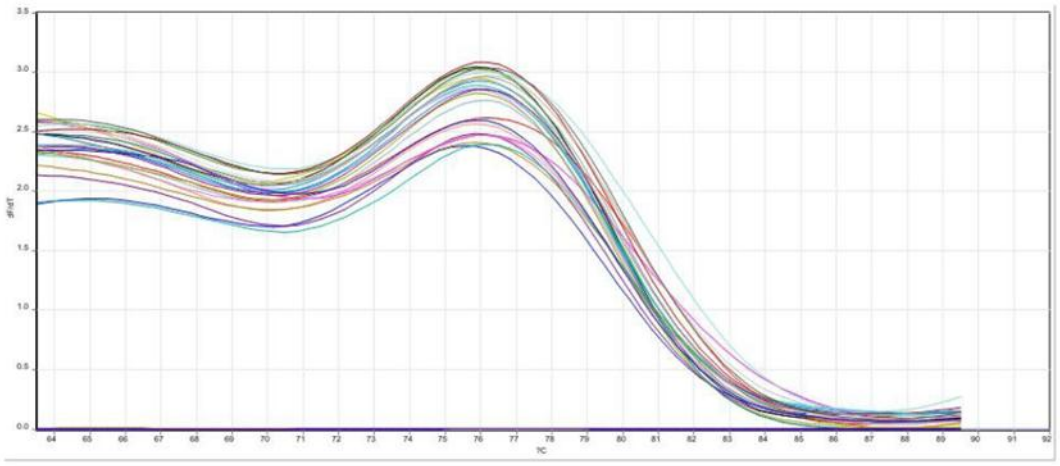

**Figure 1. Melting curve analysis of BKV positive samples by qPCR**

## Discussion

The urogenital tract gets infected by the polyomavirus known as BKPyV, which then remains there as a latent infection. The seroprevalence of BKPyV in the first 10 years of life is 90% or higher suggesting that infancy is the time when most primary infections actually occur. Reactivation of a latent infection as hemorrhagic cystitis or BK virus nephropathy commonly occurs in immunocompromised persons [13-16].

This is, as far as we are aware, the first research to evaluate urinary BKPyV excretion in Iraqi children with newly diagnosed ALL and whom are on chemotherapy.

In Pap-stained urine cytology smears the detection of viral pathological effect on the urothelial cells (DCs) all of the patients and control subjects came negative, this could be

explained by the fact that all the patients included in the study didn't have any symptomatic BKPyV infection, neither HC (macroscopic or microscopic hematuria) nor nephritis, in such pathological conditions there is virally infected-urothelial cells shedding presented as decoy cells, while in a symptomatic children there will be only virus particles shedding without cell shedding, which is the condition in these patients and also in the control group. If the patient had HC the virus would excrete intracellularly, as 10 DCs/slide or more is considered as decoy positive for DCs quantification, and it means the beginning of pathological effect of the virus [10].

The frequency of BKPyV viruria in patients with ALL in both first and second group was significantly higher compared to control group (P <0.001). This is supported by the observation of having a BKPyV urine viral load peak is significantly higher in ALL patients than in the control group [17,18]. As in the control group (third group) levels of BKPyV loads are detected in 33 subjects (55.0%), this is supported by the fact that it is widespread in the general population with a seropositivity rate of >90% by early school-age years [19]. Also, in otherwise healthy individuals, HPyVs can reactivate and cause asymptomatic viruria [20,21]. Urban sewage thus typically becomes contaminated and provides higher virus titers [22].

Both healthy and immunocompromised individuals may develop asymptomatic viruria, with incidence rates of 5% in the healthy population and about 60% in immunocompromised patients [23,24]. In order to consider the viral excretion in urine as a BKPyV viuria there is cutoff of ≥7 log10 /ml [25]. In this study, the maximum viral load in each patients group was 4 log10 /ml this also supports that there is no pathological effect of the virus but there is increase shedding of the whole virus in patients with leukemia significantly higher than those in healthy control subjects, so viuria is significantly higher in patients with acute leukemia newly diagnosed and on chemotherapy than in the control group which means that the effect of leukocytosis or leukopenia causes a type of immune-suppression in those children and make them more prone for BKPyV viuria, which is mainly a reactivation of the virus as the virus is normally excreted at low levels in children as most of the children are generally acutely infected by the virus early in life [26].

On the other hand, both leukocytosis or leukopenia are now considered as risk factors to increase BKPyV viuria as viral shedding in urine is more common for immunocompromised patients than for healthy subjects [27]. In one case report study of acute lymphoblastic leukemia in a child with tubulointerstitial nephritis caused by the BKPyV, the immunodeficiency induced by chemotherapy made the primary BKPyV infection worse as BKPyV DNA was detected in her urine 8.1 log10 /ml as the virus had caused pathological effect [29].

Since BKPyV viruria detected in the urine of newly diagnosed ALL children more than that in the control group (P <0.001) it could be that the virus is one of the viruses triggering ALL, BKPyV was investigated for its potential role to trigger cancer in 2012 in a study conducted on people by the International Agency for Research Cancer (IARC), BKPyV was found to really be "possibly carcinogenic to humans" [29]. Moreover, Polyoma BK was the most often found virus (51.2%) in research that included 43 children with acute lymphoblastic leukemia who were hospitalized to the pediatric oncology department in Egypt [30].

As the products of the two viral oncoproteins the large T-antigen (TAg) and the small t-antigen (tAg) can alter the normal cell cycle, which eventually results in cell immortalization and neoplastic transformation [31]. In vitro and in neonatal hamsters, rats, and mice, the oncoprotein Tag is assumed to be the motivating factor behind the transformation of BKPyV laboratory infection, resulting in carcinogenesis or transformation [32-34]. Of the known HPyV members (other than MCPyV), only BKPyV and JCPyV are recognized as being likely to induce human malignancies and are classified as 2B carcinogens (possibly carcinogenic to humans). Understanding the molecular processes underlying viral oncogenic

activity and identifying a virus as the etiological agent clearly require much research [35]. BK virus has been associated in several case studies for bone and brain cancer, Kaposi sarcoma, and bladder and prostrate carcinomas [36-39].

Or the virus could be resulting as a consequence of ALL immune suppression follows as the virus has been seen in the urine of both ALL children without/with chemotherapy more than that in the control group (P <0.001) and the viral load is significantly higher than normal controls so the virus activation could be a result of the disease development as ALL patients are Immunocompromised or with disturbed immunity that cause the reactivation of the virus and its shedding in urine [40,41]. Since BKPyV nephropathy often affects people with impaired immune systems. The immune system may be suppressed by chemotherapy. There has been a reported case of native kidney BK virus nephropathy in a child with ALL without any type of transplant, similar to the most recent case in an adult with CLL, which was the first case of native kidney BK virus nephropathy to be described [42].

In Conclusions, BKPyV viruria (viral DNA in urine) was found among ALL patients and quantitatively was higher than control group indicating that viral activation occurs among ALL patients, which could be a risk on the urothelium.

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## Author contribution

Ali: performed the sample collection and laboratory works and wrote the draft of this paper. Dr. Al-Obaidi: designed supervised and interpreted the results of this work. Dr. Ali and Dr. Abbas contributed in clinical aspects. The final version of this manuscript was read and approved by all the authors.

## Conflict of interest

The authors declare that they have no conflict of interest.

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