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# THE EFFECTS OF VALACYCLOVIR ON POLYOMAVIRUS INFECTION (BKV) IN KIDNEY TRANSPLANT RECIPIENTS

Samad i K. [a],

Ghorbansabbagh M. [b],

Raesi V. [c],

Marouzi P. [b],

Sharifipour F. [b],

Jalambadani Z. [a]

[a] Sabzevar University of Medical Sciences,Sabzevar, Iran.

[b] Mashhad University of Medical Sciences, Mashhad, Iran.

[c] Birjand University of Medical Sciences, Birjand, Iran.


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# ВЛИЯНИЕ ВАЛАЦИКЛОВИРА НА ПОЛИОМАВИРУСНУЮ ИНФЕКЦИЮ (ПВИ) У РЕЦИИЕНТОВ ТРАНСПЛАНТАЦИИ ПОЧЕК

Самади К. [1],

Горбансаббах М. [2],

Раези В. [3],

Марузи П. [2],

Шарифипур Ф. [2],

Джаламбадани З. [1]

[1] Университет медицинских наук Сабзевар, Сабзевар, Иран.

[2] Университет Мешхеда медицинских наук, Мешхед, Иран.

[3] Бирджандский университет медицинских наук, Бирджанд, Иран.


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**Abstract**

Polyomavirus-associated nephropathy (PVAN) is one of the most serious infectious complications in allograft recipients, with the BK virus (BKV) being the primary etiologic agent. This study was conducted to investigate the efficacy of valacyclovir on BK virus (BKV) infection and viremia control in infected patients in Iran.

This quasi-experimental study involved 21Iranian patients. All kidney transplant recipients with a confirmed diagnosis of BKV infection based on renal biopsy and PCR were administered standard therapy (reduced doses of immunosuppressive drugs) with or without valacyclovir at a one-gram dose twice daily for one month. After collecting the data, the data was analyzed using SPSS 23. The K-S test confirmed the normality of the quantitative data. Chi-square for trend, independent-t, and Fisher's exact tests were used to examine group homogeneity in terms of socio-demographic characteristics. Before the intervention, a t-test was used to compare mean scores among the groups; and repeated measures independent sample test, pair sample test, chi square test and ANOVA. The significance level of $P < 0.05$ was considered for all tests.

The mean creatinine level, mean GFR(Glomerular Filtration Rate **)** level, and median viral load in the serum were not significantly different between the two groups at the time of graft rejection diagnosis. One month after treatment, the serum viral load decreased in 90.9% of patients in the intervention group and 50% of patients in the control group, with the difference being statistically significant(p=0.038). Also, in the two-month review, the results showed that the reduction of the virus serum load level was observed in 81.8% of patients in the intervention group and 40% of patients in the control group, and this difference was statistically significant (p=0.049). Mean age, body mass index, and transplant duration were comparable between the two groups. Neither creatinine nor GFR

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levels differed significantly between the two groups after the intervention (P=0.557 and P=0.387).

Valacyclovir can effectively reduce the serum viral load in BKV-infected kidney transplant recipients. This reduction, however, is not accompanied by an improvement in renal function or prevention of rejection.

**Keywords:** Kidney transplant, polyomavirus infection, valacyclovir.


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**Резюме**

Нефропатия, ассоциированная с полиомавирусом (ПВАН), является одним из самых серьезных инфекционных осложнений у реципиентов аллотрансплантата, причем основным этиологическим агентом является вирус BK (BKV). Настоящее исследование было проведено для изучения эффективности валацикловира на BKV-инфекцию и контроль виремии у инфицированных пациентов в Иране.

В поведенном квазиэкспериментальном исследовании приняли участие 21 пациент из Ирана. Всем реципиентам почечного трансплантата с подтвержденным диагнозом инфекции BKV на основе биопсии почки и ПЦР назначалась стандартная терапия (сниженные дозы иммунодепрессантов) с валацикловиром или без него в дозе один грамм два раза в день в течение одного месяца. После сбора данных они были проанализированы с помощью программы SPSS 23. Тест K-S подтвердил нормальность количественных распределения данных. Для изучения однородности группы по социально-демографическим характеристикам использовались методы хи-квадрат для тренда, независимый t-критерии и точный метод Фишера. Перед вмешательством использовался t-тест для сравнения средних баллов среди групп; повторные измерения независимого выборочного теста, парного выборочного теста, критерия хи-квадрат и дисперсионного анализа. Для всех тестов уровень достоверности был установлен $P < 0,05$.

Средний уровень креатинина, средний уровень СКФ (скорость клубочковой фильтрации) и медианная вирусная нагрузка в сыворотке существенно не отличались между двумя группами на момент постановки диагноза отторжения трансплантата. Через месяц после лечения вирусная нагрузка в сыворотке статистически достоверно снизилась у 90,9% пациентов в группе вмешательства и у 50% пациентов в контрольной группе ($p = 0,038$). Кроме того, в ходе двухмесячного мониторинга показано, что достоверное

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снижение уровня вирусной нагрузки в сыворотке наблюдалось у 81,8% пациентов в группе вмешательства и у 40% пациентов в контрольной группе (p = 0,049). Средний возраст, индекс массы тела и продолжительность трансплантации были сопоставимы между двумя группами. Уровни креатинина и уровни СКФ не различались существенно между двумя группами после вмешательства (P=0,557 и P=0,387).

Валацикловир может эффективно снижать вирусную нагрузку в сыворотке у реципиентов почечного трансплантата, инфицированных BKV. Однако это снижение не сопровождается улучшением функции почек или предотвращением отторжения.

**Ключевые слова:** Трансплантация почки, полиомавирусная инфекция, валацикловир.

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## 1 Introduction

BK polyomavirus is a circular, double-stranded DNA virus from the polyomavirus family. Based on DNA sequence variations, BK polyomavirus can be divided into six subtypes or genotypes. Genotype I is the most frequent worldwide (80%), followed by Genotype IV (15%). BK polyomavirus is ubiquitous in the population, with >80% of adults being seropositive, with infection typically being acquired during childhood[1].

Polyomavirus-associated nephropathy (PVAN) is one of the most serious infectious complications in allograft recipients, with the BK virus (BKV) being the primary etiologic agent. It is characterized by cytopathic changes in epithelial and glomerular cells in the transplanted kidney [1,8,12,15,23,24,27,31]. Approximately 30-50% of transplant recipients develop BKV nephropathy due to the reactivation of latent polyomaviruses in the urinary tract [14,15,27].

The common characteristics of early events in the pathogenesis of BKV nephropathy and the severe clinical overlap necessitate preventive treatment strategies to impede disease progression and obvious renal damage, even before the diagnosis is confirmed by biopsy. Validated protocols for patient screening and preventive therapies are now included in the recommendations for graft management following renal transplantation [4,11,13,15,19,25,35,36].

There are too many clinical indications for renal biopsy leading to a histological diagnosis of definitive PVAN, which are contingent on the standard of each medical facility, the set of treatment measures, and the availability of resources. Some kidney transplant facilities typically perform a biopsy on patients with viremia or possible PVAN to ensure the diagnosis of PVAN. Additionally, renal biopsy allows for the determination of the severity of acute and chronic kidney tissue damage, as well as the evaluation of other kidney diseases that may affect allograft functionality and patient management [13,15,26].


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The biopsy is especially important when we consider that quantitative PCR tests are not standard for evaluating BK viremia and that BK viremia titers only predict the degree of viral kidney damage in a limited way and thus cannot provide diagnostic certainty [2,21,23,27,38].

In the vast majority of cases, kidney allograft biopsies are performed to diagnose unexplained and unspecified clinical disorders in the functioning of transplanted kidneys, which can be caused by underlying BK nephropathy. Definitive PVAN may also be found unexpectedly in surveillance biopsies of patients with stable grafts [5,23,34].

Indeed, biopsies of kidney allografts are performed under various clinical conditions and for various indications, during which morphological evidence of PVAN may be observed. In developed countries, the incidence of biopsy-proven PVAN ranges between 5% and 6%, although its prevalence varies considerably between institutions [2,38].

The highest rate of definitive PVAN is observed in kidney transplants with ABO-incompatible donors and recipients (18%) and after desensitization in highly sensitized allograft recipients (20%) [9,38].The Renal Pathology Society, the Banff Working Group on Liver Allograft Pathology, and the Nephrology Working Group of the European Society of Pathology have proposed a standard approach to classifying this disorder, which has been supported and validated by studies [28].

Approaches such as reducing the dose of suppressive drugs to the use of antiviral treatments based on the severity of viremia and the occurrence of evidence of nephropathy have been introduced [39]. Brincidofovir is a prodrug of cidofovir that has been used so far, although limited results of its success rate have been reported [29]. IVIG products containing high titers of BK virus-neutralizing antibodies have been used as adjuvant therapy and increase the virus clearance rate from serum [22,40].


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So far, there is no consensus regarding the definitive treatment of BK virus nephropathy in kidney transplant patients, and this research was conducted for the first time to investigate the effect of valacyclovir on treating BKV infection and controlling viremia in infected patients.

## 2 **Methods**

This quasi-experimental study evaluated 21 patients with a confirmed BKV infection (PCR test results) who were referred to Hospitals in Iran. The sample size was calculated using the formula for a quasi-experimental survey [41].

In this study, random allocation was not used. With a margin of error = 0.05 and = 10%, an expected power of 90%, a Z value of 1.28. The participants were 21 Iranian patients.

$$n = \frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2 (\partial_1^2 + \partial_2^2)}{(\mu_1 - \mu_2)2}$$

Evidence of BKV nephropathy and BKV viremia constituted the inclusion criteria, while exclusion criteria comprised lack of consent, a history of hypersensitivity reactions to valacyclovir, and the incidence of complications upon valacyclovir therapy.


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## Ethical Approval

Ethical approval in this study, all procedures performed on human samples were conducted following the relevant guidelines and regulations of the Helsinki Declaration. The study protocol was approved by the Research Ethics Committee (IR.MUMS.MEDICAL.REC.1399.031) in Mashhad Iran.

## Study groups

In addition to intravenous immunoglobulin (IVIG), patients received standard transplant drug dose reduction and modification in case required. The control group received the standard routine treatment, while the intervention group received one gram of valacyclovir (Abidi Company) twice daily in addition to the standard treatment. The drug dosage was modified according to creatinine clearance. PCR was reiterated one and two months after treatment initiation to assess and compare viremia levels between groups. Uniplex Real-time PCR on 21 virus DNA samples extracted from plasma based on the ISEX version of the kits JC Virus PCR and BK Virus PCR related  Vídeňská, Czech Republic( GeneProof) was performed.

There were not any adverse effects of Valacyclovir noticed during treatment. A decrease in viral load was defined as a decline in the serum level of the viral genome after treatment relative to the baseline value at the time of diagnosis. Based on the objectives of the research project, the researcher designed a checklist that included gender, age, height, weight, body mass index (BMI), cause of renal failure, duration of transplant, coinfection with CMV, polyomavirus PCR result (before treatment, one month after treatment, and two months after treatment). All kidney transplant patients were infected with BKV PCR (BKV or kidney biopsy proven at the time of study with interstitial fibrosis and tubular atrophy (IFTA <20). Serum creatinine level prior to and two months after treatment, GFR prior to and two months after treatment, and the study group.

## Data analyses


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After collecting the data, the data was analyzed using SPSS 23. The K-S test confirmed the normality of the quantitative data. Chi-square for trend, independent-t, and Fisher's exact tests were used to examine group homogeneity in terms of socio-demographic characteristics. Before the intervention, a t-test was used to compare mean scores among the groups; and repeated measures independent sample test, pair sample test,chi square test and ANOVA. The significance level of $P < 0.05$ was considered for all tests.

## 3 **Results**

A total of 21 patients were examined, 11 patients were included in the intervention group and 10 patients were included in the control group. The average age in intervention group patients was 39 ± 10.4 years and in control group patients was 32 ± 8.2 years, the observed difference was not significant (p=0.104). The average height in the intervention and control groups was 164.5 ± 7.9 and 166.9 ± 7.5 cm, respectively, and the average weight in the intervention and control groups was 63 ± 15.5 and 66 ± 10.2 kg, respectively. None of the observed differences were significant (p 0.496 and 0.612, respectively). The average body mass index in the intervention group was 24.1 ± 6.7 Kg/m2 and in the control group it was 24.7 ± 3.1 Kg/m2, so there was no significant difference between the two groups (P=0.804). Mean age, height, BMI, and weight did not differ significantly between the control and intervention groups before of intervention, as displayed in Table 1 (P> 0.05). In both groups, the median transplant duration was 12 months.

According to the results of Table 2, the only symptom that led to the diagnosis of transplant rejection in both groups was an increase in serum creatinine levels (P<0.05). Besides, this study did not detect CMV coinfection in any of the examined patients in both groups (P> 0.05).

The only symptom that led to the diagnosis of transplant rejection in the patients of both groups was the increase in serum creatinine. The result of this investigation showed that the simultaneous infection with CMV was not observed in any of the

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examined patients. Also, when transplant rejection was diagnosed, there was no significant difference between the two groups in the average level of creatinine, average level of GFR and average level of viral load in serum.

The mean creatinine level, mean GFR level, and median viral load in the serum were not significantly different between the two groups at the time of graft rejection diagnosis. One month after treatment, the serum viral load decreased in 90.9% of patients in the intervention group and 50% of patients in the control group, with the difference being statistically significant (P=0.038). In addition, the two-month assessment revealed that 81.8% of patients in the intervention group and 40% in the control group experienced a reduction in serum viral load, which is statistically significant (P=0.049). Creatinine and GFR levels did not differ significantly (P=0.577 and P=0.387) between the two groups at the post-intervention examination (Table 3).

## 4 **Discussion**

According to the findings of this study, a significant decline in serum viral load was observed one month after treatment with valacyclovir along with routine treatments (90.9% in the intervention group and 50% in the control group) (P=0.038). Two months after the intervention, too, there was a significant reduction in serum viral load in the intervention group relative to the control group (81.8% in the intervention group and 40% in the control group) (P=0.049).

According to the study findings, the administration of valacyclovir in BKV-infected kidney transplant recipients can reduce the serum viral load. There is currently no consensus on the definitive treatment for BKV nephropathy in kidney transplant recipients. Approaches ranging from lowering the dose of suppressive drugs to using antiviral treatments have been utilized based on the severity of viremia and evidence of nephropathy [39].

If the number of BKV serum copies is below 10,000, a dose reduction of immunosuppressive drugs will suffice. If there are more than 10,000 copies, a

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common first step is reducing the calcineurin inhibitor dose by 25 to 50 percent. Changing prescription drugs such as tacrolimus to cyclosporine A has been associated with improved outcomes [7], although using this strategy increases the likelihood of acute transplant rejection [10]. If the number of virus copies in the serum remains elevated despite these interventions, the dose of mycophenolate mofetil should be reduced by 50 percent, or the drug should be discontinued and replaced with mTOR inhibitors [3,6] Changing the treatment from mycophenolate mofetil to leflunomide is an additional strategy with typically positive outcomes [15,16,42]. If the treatments above fail or in cases of resistance, cidofovir is the only treatment option, although its nephrotoxicity limits its administration [17,18,20]. Brincidofovir is a prodrug of cidofovir that has been used thus far, although there are only a few reports of its success rate [29].In Reischig, Tomas study Valganciclovir shows no superior efficacy in cytomegalovirus DNAemia prevention compared with valacyclovir prophylaxis. However, the risk of biopsy-proven acute rejection is higher with valacyclovir[33].

IVIG products with high BKV neutralizing antibody titers are used as an adjuvant to accelerate virus clearance from [22,32,37,40].

There is no independent evidence regarding the role of valacyclovir in BK nephropathy and viral viremia in transplant patients. Park et al. (2020) [30] investigated the effect of prophylactic valacyclovir administration on the incidence of cytomegalovirus infection in patients undergoing kidney transplantation. In this study, this disorder was diagnosed in 1 out of 46 patients in the combined treatment group and 3 out of 107 patients in the single drug treatment group; however, the observed difference was not statistically significant. Valacyclovir prophylaxis effectively decreased the occurrence of CMV infection in KTRs in their study. Therefore, they should use valacyclovir prophylaxis for 3 months in KTRs with risk factors such as old age, thymoglobulin induction, and delayed graft function.


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As a strength, this controlled study was conducted with two groups that were similar in basic information and included all new patients with transplant rejection, thereby eliminating selection bias.

**Limitation:**

The primary limitation of this study is the small sample size, which restricts the generalizability of its findings. Also, non-random sampling and the two-month follow-up, particularly in the absence of improvement in kidney function, limits the interpretation of the findings regarding the efficacy of this drug on transplantation's ultimate outcome (as the main goal of treating BKV infection).

## 5 **Conclusion**

Based on the findings of this study, in kidney transplant recipients with BKV infection, using valacyclovir can lower the amount of virus in the blood. However, this treatment is neither lead to better kidney function nor prevent rejection of the transplanted kidney based on the results of this study. It is suggested that future research be conducted as multicenter clinical trials with large sample sizes, longer follow-ups, and determination of the graft's outcome.

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## ТАБЛИЦЫ

**Table 1.** Characteristics of the participants in the study according to the studied groups before of intervention.

| **Parameter** | **Intervention Group Mean ± SD** | **Control Group Mean ± SD** | **P-value** |
|---|---|---|---|
| **Age (years)** | 39 ± 10.4 | 32 ± 8.2 | P=0.104 * |
| **Height (cm)** | 164.5 ± 7.9 | 166.9 ± 7.5 | P=0.496 * |
| **Weight (kg)** | 63 ± 15.5 | 66 ± 10.2 | P=0.612 * |
| **Body mass index (kg/m $^2$)** | 24.1 ± 6.7 | 24.7 ± 3.1 | P=0.804 * |
| **Transplant time (month)** | 12 | 12 | P=0.918 ** |

* The independent t-test result


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**Table 2.** Comparison of gender and etiology of kidney failure per study group before of intervention.

| **Parameter** | | **Intervention group Frequency (Percentage)** | **Control group Frequency (Percentage)** | **P-value** |
|---|---|---|---|---|
| **Gender** | Male | 5 (45.5) | 3 (30) | P*=0.659 |
| | Female | 6 (54.5) | 7 (70) | |
| **Etiology of kidney failure** | FSGS | 1 (9.1) | (0) 0 | P**=0.210 |
| | Nephrotic syndromes | 2 (18.2) | 6 (60) | |
| | DM | 2 (18.2) | 6 (60) | |
| | Hypertension | 2 (18.2) | 1 (10) | |
| | PKD | 1 (9.1) | (0) 0 | |
| | Preeclampsia | 1 (9.1) | (0) 0 | |
| | Pyelonephritis | 2 (18.2) | 1 (10) | |
| | Reflux nephropathy | 0 (0) | 2 (20) | |

DM: diabetes mellitus, FSGS: Focal segmental glomerulosclerosis, PKD: Polycystic kidney disease

** One-way Anova *Chi square


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**Table 3.** Comparing the frequency distribution of reductions in the serum viral load levels in the study groups.

| **Variables(Qualitative)** | | Intervention group Frequency (percentage) | Control Group Frequency (percentage) | P-value |
|---|---|---|---|---|
| One month after treatment | No | 1 (9.1) | 5 (50) | P=0.038 * |
| | Yes | 10 (9.90) | 5 (50) | |
| Two months after treatment | No | 2 (18.2) | 6 (60) | P=0.049 * |
| | Yes | 9 (81.8) | 4 (40) | |
| Creatinine level | | 2.2 | 2.2 | 3.2 |
| GFR level | | 29.5 | 29.5 | 24.4 |
| Serum viral load after one month | | 130,000 | 130,000 | 1,796,125 |
| Serum viral load after two months | | 4900 | 4900 | 935875 |
| **Variables(Quantitative)** | | Intervention group (Mean±standard deviation) | Control Group (Mean±standard deviation) | P-value |
| Creatinine level | | 2.1 ± 0.7 | 1.9 ± 0.5 | P=0.437 *** |
| GFR level | | 35 ± 3.11 | 42.8 ± 17.1 | P=0.231 ** |
| Serum viral load | | 479500 | 194675 | P=0.512 ** |

*Based on the result of Fisher's exact test; **Based on the result of the Mann-Whitney test; ***Based on the independent t-test result


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# ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

## Блок 1. Информация об авторе ответственном за переписку

**Zeinab Jalambadani**, Assistant Professor of Health Education and Promotion, Department of Community Medicine, Faculty of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran; Assistant Professor of Health Education and Promotion, Department of Non-Communicable Diseases Research Center, Faculty of Medicine, Sabzevar University of Medical Sciences, Sabzevar, Iran;

fax: 05144018301;

telephone:05144018301;

e-mail: jalambadaniz@gmail.com / jalambadaniz@medsab.ac.ir

## Блок 2. Информация об авторах

**Katayoun Samadi,** Assistant Professor of Nephrology,Department of Internal Medicine, Faculty of Medicine, Sabzevar University of Medical Sciences,Sabzevar, Iran;

M**ahin Ghorbansabbagh,** Associate Professor of Nephrology, Department of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran;

**Vajihollah Raesi,** Assistant Professor of Nephrology,Department of Internal Medicine, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran;

**Parviz Marouzi,** Assistant Professor of Biostatistics,Department of Health Information Technology and Medical Records, School of Paramedical Sciences, Mashhad University of Medical Sciences, Mashhad, Iran;


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**Farzaneh Sharifipour**, Associate Professor of Nephrology, Department of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran;

e-mail: sharifipourf@mums.ac.ir

**Блок 3. Метаданные статьи**

THE EFFECTS OF VALACYCLOVIR ON POLYOMAVIRUS INFECTION (BKV) IN KIDNEY TRANSPLANT RECIPIENTS

**Сокращенное название статьи для верхнего колонтитула:**

POLYOMAVIRUS INFECTION (BKV) IN KIDNEY TRANSPLANT RECIPIENTS

ПОЛИОМАВИРУСНАЯ ИНФЕКЦИЯ (BKV) У РЕЦИПИЕНТОВ ПОЧЕЧНОЙ ТРАНСПЛАНТАЦИИ

**Keywords:** Kidney transplant, polyomavirus infection, valacyclovir.

**Ключевые слова:** трансплантация почки, полиомавирусная инфекция, валацикловир.

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**Блок 1. Информация об авторе ответственном за переписку**

**Зейнаб Джаламбадани,**

факс: 05144018301;

телефон:05144018301;

e-mail: jalambadaniz@gmail.com / jalambadaniz@medsab.ac.ir

**Блок 2. Информация об авторах**

**Катаюн Самади,** Доцент кафедры нефрологии, кафедра внутренней медицины, медицинский факультет, Университет медицинских наук Сабзевар, Сабзевар, Иран;

**Махин Горбансаббах,** Доцент кафедры нефрологии, кафедра внутренней медицины, медицинский факультет, Университет Мешхеда медицинских наук, Мешхед, Иран;

**Ваджихолла Раези,** Доцент кафедры нефрологии, кафедра внутренней медицины, медицинский факультет, Бирджандский университет медицинских наук, Иран;

**Парвиз Марузи,** Доцент кафедры биостатистики, кафедра медицинских информационных технологий медицинской документации, Школа парамедицинских наук, Мешхедский университет медицинских наук, Мешхед, Иран;

**Фарзане Шарифипур,** Доцент кафедры нефрологии, кафедра внутренней медицины, медицинский факультет, Университет Мешхеда медицинских наук, Мешхед, Иран;

e-mail: sharifipourf@mums.ac.ir


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**Блок 3. Метаданные статьи**

THE EFFECTS OF VALACYCLOVIR ON POLYOMAVIRUS INFECTION (BKV) IN KIDNEY TRANSPLANT RECIPIENTS

**Сокращенное название статьи для верхнего колонтитула:**

POLYOMAVIRUS INFECTION (BKV) IN KIDNEY TRANSPLANT RECIPIENTS

ПОЛИОМАВИРУСНАЯ ИНФЕКЦИЯ (BKV) У РЕЦИПИЕНТОВ ПОЧЕЧНОЙ ТРАНСПЛАНТАЦИИ


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