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Survey of BK Virus in Renal Transplant Recipients in Iran: A Systematic Review and Meta-Analysis

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Keywords
BK virus · Renal transplantation · Meta-analysis · Systematic review · Epidemiology · Infectious disease · Virology

Abstract
Introduction: BK virus (BKV) infection in renal transplant (RT) recipients can cause hemorrhagic cystitis, transient renal dysfunction, and BKV nephropathy (BKVN). The prevalence and significance of BKV in RT recipients remain to be clarified in the Iranian population. The purpose of this review is to summarize the overall prevalence of BKV infection in RT recipients from previously published studies in Iran. ***Methods:*** We systematically reviewed articles through a comprehensive search of the main electronic and Persian national databases up to November 2019. ***Results:*** The overall pooled prevalence of BKV infection among the Iranian population was 23% (95% CI; 15–33%). Comparing these studies revealed that the prevalence of BKV in plasma samples ranges from 3 to 40%, in renal biopsies 1–13%, and in urine samples 10–49%. Due to substantial heterogeneity among reported studies ($I^2 = 93\%$, $p < 0.01$), random-effect meta-analysis was performed. BKV infection rate was slightly higher in women than men (16%, $p = 0.04$ vs. 14%, $p < 0.01$, respectively). The majority of the studies employed real-time PCR (24%, $I^2 = 93$, $p < 0.01$) and analyzed plasma samples alone or in combination with other types of specimens. BKV prevalence from 5 cities among the Iranian population showed a higher prevalence rate in Guilan. ***Conclusion:*** Our analysis provides a preliminary estimate of the epidemiology of BKV infection in RT recipients in Iran. These results arouse a need for more epidemiological studies of BKV infection in different unanalyzed regions in Iran. Early detection of BKV in RT recipients helps timely nephropathy diagnosis and prevents graft loss.

Introduction

BK virus (BKV) is a ubiquitous, small, and nonenveloped DNA virus that belongs to the *polyomaviridae* family [1]. BKV infects the majority of the population in the first decade of life and usually is asymptomatic or associated with fever and mild upper respiratory symptoms [2]. After primary infection, BKV enters a latent state and resides in the renal tubular and uroepithelial cells, where its intermittent reactivation leading to asymptomatic viruria in 7–15% of healthy subjects [3]. Reactivation of BKV ap-

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pears to cause clinical disease only in individuals with relative or absolute immunodeficiency such as pregnancy, cancer, HIV infection, those receiving chemotherapy, bone marrow, and solid organ transplant recipients [4]. Among solid organ transplant recipients, BKV infection is mostly limited to renal transplantations that results in viruria in 30–50% and viremia in 13–22% of cases [5]. BKV infection in renal allograft recipients can cause hemorrhagic cystitis, tubulointerstitial nephritis, ureteric stenosis, transient renal dysfunction, and BKV nephropathy (BKVN) [6]. BKVN occurs in about 5% of renal transplant (RT) recipients with irreversible graft failure developing in 45% of affected patients [7, 8]. Many risk factors for the development of BKVN have been proposed, including older recipient age, male gender, rejection episodes, degree of human leukocyte antigen mismatching, and BKV serostatus [9]. Detection of BKV DNA in plasma by noninvasive PCR assay has been suggested as a surrogate marker of BKVN [10]. Current recommendations for screening BK viral load in the plasma are largely opinion-based but in general suggest monthly for the first 6 months of kidney transplantation then every 3 months for the first 2 years following the transplantation [1, 11]. The prevalence and significance of BKV in RT recipients remain to be clarified in the Iranian population. The purpose of this review is to summarize the available published literature to estimate pooled prevalence of BKV infection in RT recipients from a number of studies conducted in Iran.

Methods

Search Strategy

An extensive literature review for all published studies up to November 2019 with no specified start date was carried out. Databases such as PubMed, Web of Science, Scopus, Science Direct, Google Scholar, Embase, and Persian national databases (Magiran [www.Magiran.com], Scientific Information Database [SID] [www.sid.ir], IranMedex, and Iran Doc) were used to conduct a comprehensive search of studies in the field of BKV infection in RT patients. To this purpose, we used and combined several search terms of BKV. The following search keyword combination was used (polyomavirus, BK or polyomavirus hominis 1 or BK polyomavirus or human polyomavirus BK or polyomavirus BK) and (prevalence or seroprevalence or epidemiological study or immunity or antibody or seroepidemiology or frequency) and (Iran or Persia or "I.R. Iran" or "I R. Iran" or Islamic Republic of Iran) and (renal transplantation or renal transplantations or transplantations, renal or transplantation, renal or grafting, kidney or kidney grafting or transplantation, kidney or kidney transplantations or transplantations, kidney).

Study Selection

All studies which aimed at the detection of BKV infection in the RT recipients in the Iranian population were included. Of the total publications, irrelevant data, duplicate, and similar ones were identified and excluded based on title and abstract. Publications with the same data but in both English and Persian languages were removed in the next step. Full-length articles, short articles, and conference abstracts were allowed. Full-texts of the relevant studies were then cross-checked by researchers independently and reached a consensus on all items.

Data Extraction

The following details and information were obtained from each included article: first author, year of publication, sample size, gender, city, BK detection methods, and overall BK prevalence.

Inclusion/Exclusion Criteria

Apparently, original articles presenting data on the prevalence of BKV infection in the RT recipients in Iran were considered. Some studies were excluded from the analysis due to the following reasons: study that considered RT candidates and those which considered hemodialysis patients. Furthermore, review articles, letters, prospective studies, and case reports were excluded.

Quality Assessment

The 2 reviewers checked the quality of included studies. All included studies for this meta-analysis were critically appraised using the AXIS tool [12]. The checklist composed of 20 questions covering different methodological perspectives, which the reviewers answered 18 questions to select eligible studies to include in the main meta-analysis. Two questions about nonresponders which were not related to the chosen studies were not answered. Indeed, the "Yes" answer to each question got the point.

Statistical Analysis

The proportion of BKV in RT recipients was pooled using the inverse variance approach, based on a random-effect model (DerSimonian-Laird weights method) [13]. A logit transformation was used to stabilize the variation of proportions. The Clopper-Pearson method was used to calculate the confidence interval for individual studies [14]. Continuity correction of 0.5 was applied in studies with 0 cell frequencies statistical heterogeneity was measured using the I^2 test. The meta-analysis was performed with the R version 3.4.2 (September 28, 2017) [15], package "meta" [16].

Results

Search Results

A flowchart of the literature search and study selection is shown in Figure 1. Following careful article evaluation and the described exclusion/inclusion process, 14 relevant records with 1,578 subjects remained within protocol eligibility criteria, and their information was summarized in Table 1. These 14 articles evaluated 1,660 specimens for the presence of BKV.

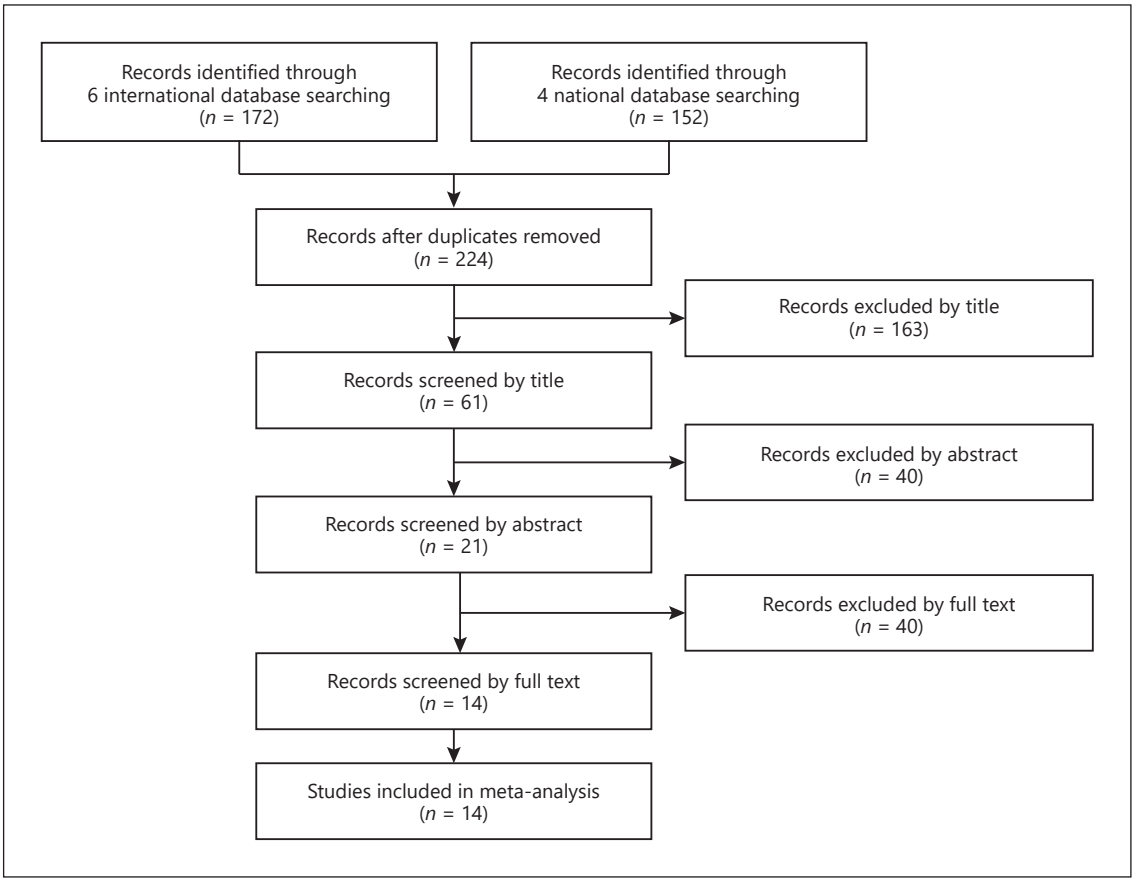

Fig. 1. Flowchart of selection process. The course of the systematic literature review on BKV prevalence in RT recipients in Iran. RT, renal transplant; BKV, BK virus.

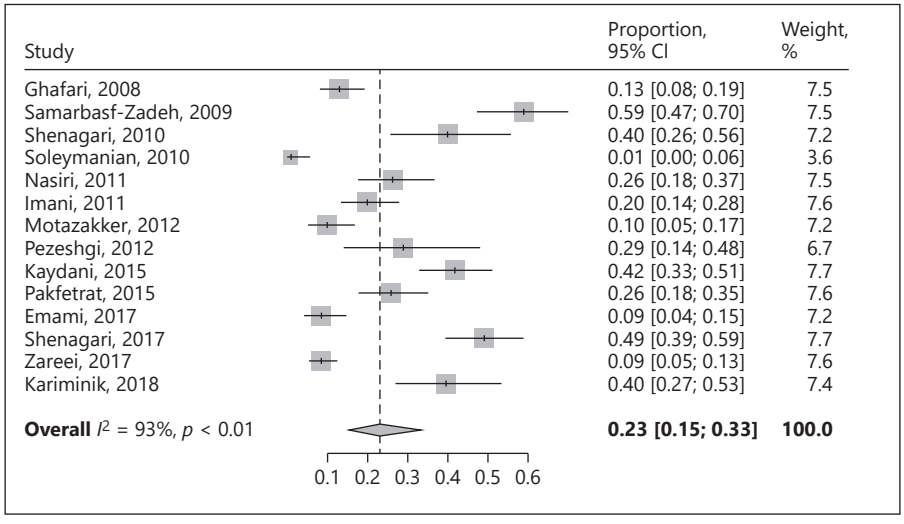

Fig. 2. Forest plot diagram of 14 studies showing positivity rate of BKV infection in RT recipient patients in Iranian population (first author and year of publication). RT, renal transplant; BKV, BK virus; CI, confidence interval.

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Table 1. Characteristics of included studies evaluating the prevalence of BKV in RT recipients in Iran

First author	Study region	Total individuals	Total positive	Age range, year	Male (positive)	Female (positive)	Sample type	Method	Quality
Ghafari et al. [24]	Urmia	160	21	9–59 mean 35.5±11.6	107 (15)	53 (6)	Renal biopsies	Immune histochemistry	17
Samarbafzadeh et al. [29]	Ahvaz	78	Urine (30)/plasma (16)	16–60 mean (34.87)	51	27	Urine/plasma	Nested-PCR	17
Shenagari et al. [30]	Tehran	45	Viruria (18)/viremia (12)	12–59	25	20	Serum/urine	Nested-PCR	10
Soleymanian et al. [25]	Tehran	96	1	13–74 years mean (36.48±14.10)	54 (1)	42 (0)	Renal biopsies	Immune histochemistry	17
Nasiri et al. [17]	Tehran	91	Urine (24)/plasma (3)	19–76 mean (43.58±13.02)	57 (urine: 16, plasma: 2)	34 (urine: 8, plasma: 1)	Urine/plasma	Quantitative PCR	16
Imani et al. [26]	Urmia	130	26	8–74 mean (42.18)	80 (16)	50 (8)	Urine	PCR	15
Pezeshgi etal. [18]	Tehran	31	Urine (9)/plasma (?)	17–59 mean (38.3±12.8)	21	10	Urine/plasma	Quantitative PCR	11
Motazakker et al. [27]	Urmia	120	12				Urine	PCR	15
Kaydani et al. [28]	Ahvaz	122	51	13–86 mean (38.6)	76	46	Urine/plasma	PCR	15
Pakfetrat et al. [19]	Shiraz	108 plasma/ 82 tissue	Plasma 17/tissue 11	15–68 mean (40)	65 (6 plasma)	43 (11 plasma)	Plasma/tissue	Real-time PCR	17
Emami et al. [20]	Shiraz	129	11	15–68 mean (38.0±0.89)	76 (6)	53 (5)	Plasma	Real-time PCR	17
Shenagari et al. [21]	Guilan	110	Urine (54)/plasma (22)	(18–77) mean 43.9	66 (urine: 30, plasma: 17)	44 (urine: 24, plasma: 5)	Urine/plasma	Real-time PCR	18
Zareei et al. [22]	Shiraz	270	23				Plasma	Real-time PCR	Not available
Kariminik et al. [23]	Shiraz	98	23				Plasma	Real-time PCR	17

RT, renal transplant; BKV, BK virus.

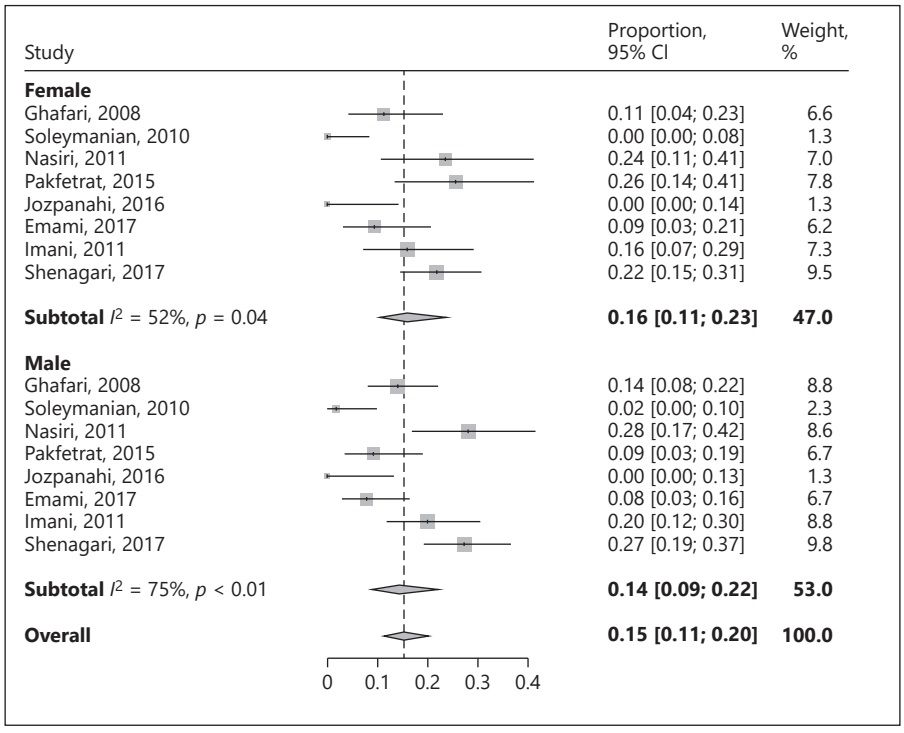

Fig. 3. Forest plots of BKV prevalence in RT patients in the males and females population. RT, renal transplant; BKV, BK virus; CI, confidence interval.

Prevalence of BKV

A total of 383 individuals out of 1,660 were BKV positive. Due to substantial heterogeneity among reported studies (I^2 = 93%, p < 0.01), random-effect meta-analysis (REM) was performed. The overall pooled prevalence of BKV infection among the Iranian population was 23% (95% CI; 15–33%). It should be noted that the prevalence of BKV in plasma samples ranges from 3 to 40%, in renal biopsies ranges from 1 to 13%, and in urine samples ranges from 10 to 49% in these studies. The forest plot in Figure 2 suggests a high heterogeneity between the studies.

Subgroup Analysis

This study analyzed pooled prevalence of BKV based on gender, method of detection, city, and sample type. Classification of participants according to gender shows high prevalence of BKV among females (16%, I^2 = 52, p = 0.04 vs. 14%, I^2 = 75%, p < 0.01, respectively) (Fig. 3). Seven studies employed real-time PCR (24%, I^2 = 93, p < 0.01) [17–23], 2 immunohistochemistry (5%, I^2 = 85, p < 0.01) [24, 25], 3 PCR (22%, I^2 = 94%, p < 0.01) [26–28], and 2 nested-PCR methods (50%, I^2 = 75, p = 0.04) [29, 30] (Fig. 4). Pooled prevalence of BKV from 5 cities among Iranian population was as follows: 4 studies from Tehran (22%, I^2 = 81%, p < 0.01) [17, 18, 25, 30], 4 studies from Shiraz (18%, I^2 = 93%, p < 0.01) [19, 20, 22, 23], 1 study from Ahvaz (42%) [28], 3 studies from Urmia (14%, I^2 = 62%, p = 0.07) [24, 26, 27], and 1 study from Guilan (49%) [21] (Fig. 5). Since the study by Samarbafzadeh et al. [29] examined samples from Tehran, Shiraz, and Ahvaz, this study excluded from the city subgroup analysis. The majority of articles analyzed plasma sample alone or in combination with other type of specimens. Two studies solely used biopsy tissues [24, 25], 2 studies solely used plasma [20, 22, 23], 5 studies used a combination of plasma and urine [17, 18, 21, 28, 29], 1 study used plasma plus biopsy tissue [19], 1 study used serum plus urine [30], and 2 study used urine alone [26, 27]. Overall, the prevalence of BKV in plasma was (16%, I^2 = 86%, p < 0.01), in renal biopsies was (10%, I^2 = 71%, p = 0.03) [19, 24, 25], and in urine was (29%, I^2 = 88%, p < 0.01) [17, 18, 21, 26, 27, 29, 30] (Fig. 6).

Discussion

This systematic review of 14 published studies from various geographical regions in Iran allowed us to estimate the prevalence of BKV infection in RT recipients. Our analysis revealed the overall pooled BKV positivity rate of 23%. This regional estimate was derived using very

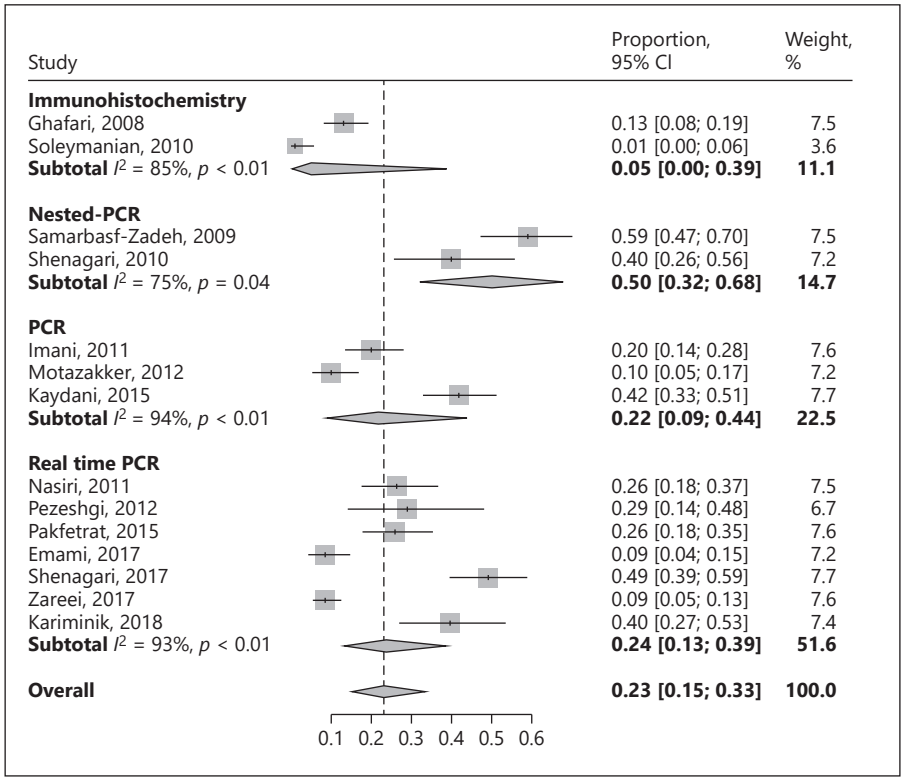

Fig. 4. Forest plots of BKV prevalence in RT patients by method of detection. RT, renal transplant; BKV, BK virus; CI, confidence interval.

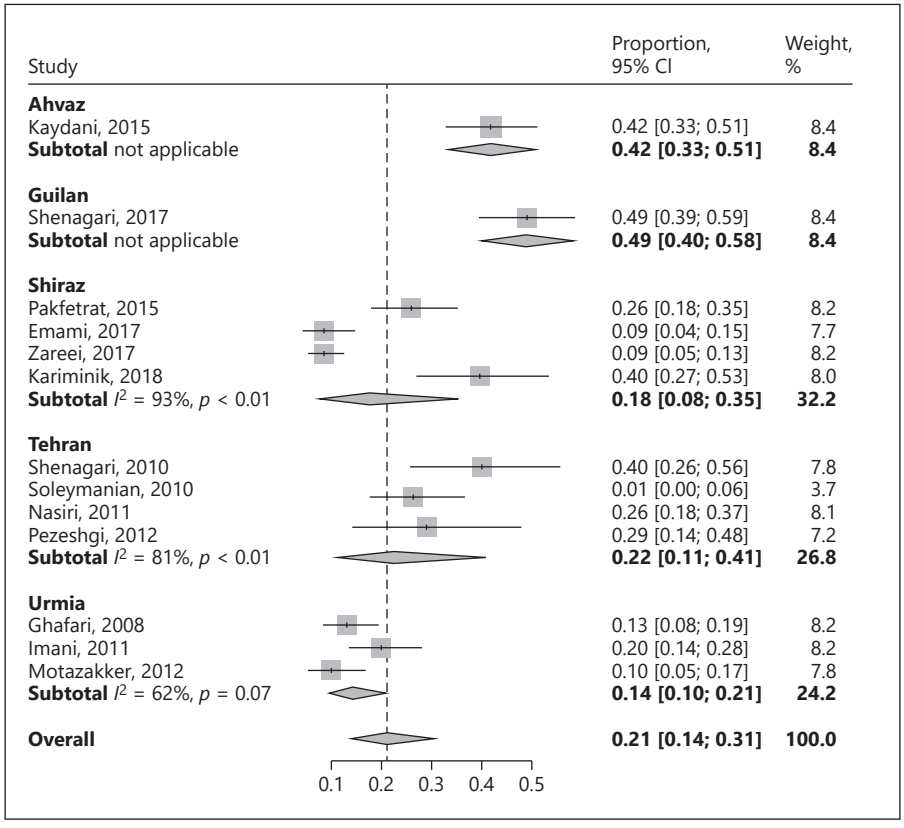

Fig. 5. Forest plots of BKV prevalence in RT patients in different cities of Iran. RT, renal transplant; BKV, BK virus; CI, confidence interval.

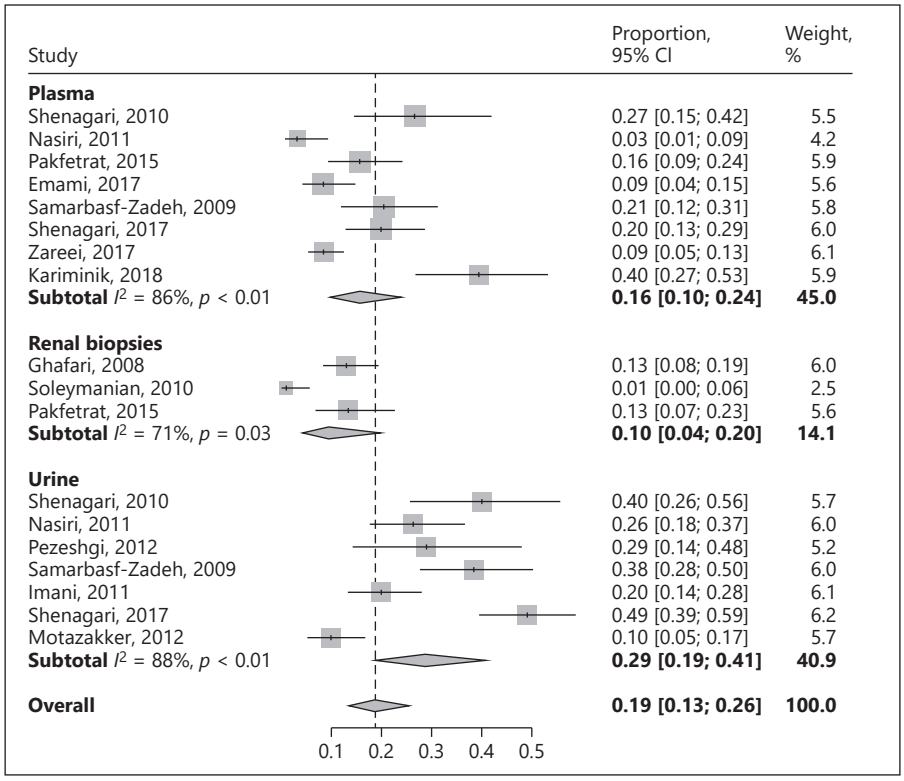

Fig. 6. Forest plots analysis of BKV prevalence in RT patients by sample type. RT, renal transplant; BKV, BK virus; CI, confidence interval.

heterogeneous sets of studies in terms of various sources (I^2 > 75% in many analyses). Comparing these studies revealed that the prevalence of BKV in plasma samples ranges from 3 to 40%, in renal biopsies 1–13%, and in urine samples 10–49%. This variability in the reported prevalence of infection may reflect differences in study methods used, several technical aspects (sensitivity of the assays and quality of the DNA), and type of sample examined (urine, serum, plasma, and tissue biopsy). Given this heterogeneity, random-effect models were adopted to ensure valid estimation with the available information. The prevalence of BKV was found to be different based on geographic regions in Iran. This may reflect real regional differences in the BKV detection rate but may also be related to variations in research design, sample size, and type of samples as BKV more detected among plasma samples than histological samples. More investigations are needed in many unanalyzed regions of Iran to estimate the prevalence of BKV in Iranian RT recipients reliably.

BKV infection represents a potential threat to long-term kidney transplant success, and progression to BKVN may result in graft loss [31, 32]. It should be mentioned that in the current analysis, a few proportions of recipients experienced BKVN. Ghafari et al. [24] reported BKVN among 21 (13.1%) out of 160 patients, and graft loss occurred in 57.1% of BKVN versus 12.2% of non-BKVN subjects. Additionally, a low prevalence of BKVN reported in Soleymanian et al. [25] study (1 [1.04%] out of 96 recipients). It is unclear whether BKV originates from the allograft or reactivated by immunosuppression in the recipient. Of specific interest is the recent report that suggested the donor origin of BKV infection in RT recipients [33].

Historically, BKV particles can be identified in both blood and urine. Biopsy should be performed for either evidence of BKV alone or in the setting of renal dysfunction in the presence of concomitant BKV viruria or viremia [34]. Viral load quantitation by PCR in the plasma or urine is the standard clinical tool for monitoring BKV reactivation [35]. In the current systematic review, there was no uniform detection method used in these studies, thus, raising the possibility of underestimation in prevalence investigation.

This systematic review also suggests that the BKV infection rate was slightly higher in women than men (16%, p = 0.04 vs. 14%, p < 0.01, respectively). Since the study populations are unequally distributed in terms of gender,

high numbers of infected women may lead to false positivity rates in women. Although immunosuppression is the most consistent risk factor for the development of BKVN, male gender, and older recipient age are the other hypothesized risk factors in this regard [36]. Additionally, BKV genotype-specific neutralizing antibody titer was recently discovered as an important risk factor for BKVN prediction [37]. Another recent study introduced BKV-genotyping as an additional method for risk assessment for BKVN [38].

BKVs are classified into 4 subtypes, and subtype I is the most commonly identified 1 worldwide with a prevalence range of 46–82% [39]. BKV subtype IV is found primarily in East Asia and Europe and makes up 15% of BKV infections. Subtypes II and III are occurring less frequently throughout the world [40, 41]. Little information is available on BKV subtypes in RT recipients in Iran. Only 2 studies from Iran reported data on BKV subtypes. In 2012, Motazakker et al. [27] published the first data on BKV subtypes reporting subtype I the most frequently detected in RT recipients. In another study in 2015 by Kaydani et al. [28], subtype I was the most common (94.11%), and subtype IV was second in frequency (5.89%). The much higher prevalence estimate of BKV serotype I is supported by the previous studies [42], which show that BKV infection is associated with this subtype. A better knowledge of viral subtypes is essential for tracing infection trails in epidemiologic investigations [41]. Future studies are needed in order to determine the causative roles of BKV subtypes in the development of clinical syndromes and nephropathy.

Due to the lack of detailed reporting of the study results by age-groups, subgroup analysis by age could not be performed. In this regard, we were not able to examine whether BKV presence varied by age as these data were limited in included studies. As mentioned before, older recipient age is hypothesized as a risk factor for the development of BKVN but has not uniformly observed in all studies.

Conclusion

In summary, BKV infection remains a major cause of graft loss and an important clinical problem following renal transplantation. Our analysis provides a preliminary estimate of the epidemiology of BKV infection in RT recipients in Iran. We believe these results stimulate a strong need for large, methodologically rigorous epidemiological studies of BKV infection in different unanalyzed regions in Iran. Early detection of BKV in RT recipients helps timely nephropathy diagnosis and prevents graft loss. There is room for research regarding the detection of other viruses causing coinfection with BKV or having the same clinical presentation. Moreover, assessing the correlations between the presence of different viral subtypes and the severity and course of clinical infection deserve further investigation.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors report no conflicts of interest.

Funding Source

As this is a meta-analysis, there has been no financial support.

Author Contributions

Somayeh Shatizadeh Malekshahi contributed in design of the study and writing the paper, Mohammad Farahmand performed the data extraction and analyses of the data, Horieh Soleimanjahi reviewed the paper, and comments were included, Fariba Dorostkar and Vahid salami co-worked on data extraction.

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