

BK Virus Infection in Adult Renal Transplant Recipients; Risk Factors and their Impact on Allograft Survival

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Abstract

Background: Since the discovery of BK Virus (BKV) in 1971, it became a growing challenge in the renal transplant field. Many hypotheses over the latest years have been made to justify the increased risk of acquiring BKV infection post-renal transplantation. Excessive immunosuppression remains the primary risk factor. Risk factors such as older recipients, male gender, prolonged cold ischemia time, ureteric stent insertion, degree of HLA mismatching and others have all been linked as additional risks for acquiring BKV infection. Nevertheless, the current literature on risk factors are inconclusive and no single identifiable risk factor can determine recipients who at risk.

Objective: The objective of this review is to delineate and contemplate the potential risk factors published in the literature and leads to BKV nephropathy.

Methodology: For this review, a variety of sources were utilised including EMBASE, Scopus, PubMed/Medline database and Google Scholar for observational studies on probable risk factors predisposing to BK viremia and/or nephropathy.

Results: almost 22 distinctive risk factors were identified.

Discussion: Over immunosuppression remains the major risk factor for acquiring BKV infection post-renal transplant, though it is uncertain whether the occurrence of BKVN (BKV Nephropathy) is owing to quantitative and/or qualitative differences in immune suppressants.

Besides immunosuppression, other probable risk factors for BKV infection were recognized. Whilst some of them were reproducible in many of these studies, they were denied by others. For instance, ureteric stents, recipient's age, race, deceased-donor type and acute rejection episodes, were inconsistently recognised as significant risk factors for BKV infection.

Conclusions: Over immunosuppression remained the reproducible risk factor for BKV infection in all studies, never the less published data on other risks factors varies. This may mirror the patient's geographical area, genetic vulnerability and probably a different BK gene variant with different risk susceptibility, these warrant further investigation.

Introduction

In 1971, Gardner and colleagues were the first to isolate polyomavirus BK (BKV) from both urine and ureteral epithelial cells of a Sudanese renal transplant recipient, presented with ureteral stenosis and renal failure [1]. They named the virus "BK" after the initials of this patient. Numerous large cells with intra-nuclear inclusions were present in the urine, named later as "decoy cells" because they resembled malignant cells [1-3]. Since then, numerous reports on various aspects of BKV in renal transplant recipients have been published [4-8]. Though human polyomaviruses, BK virus (BKV) were discovered in 1971, yet, the understanding of its negative impact was limited till 3 decades later when BKV was identified as a significant reason for interstitial nephritis and allograft failure in renal transplant recipients [9,10]. Factors that precipitated its higher occurrence over the latest years and its pathogenesis remain poorly comprehended. Increased awareness, the ability of clinicians to recognize BK infection at an earlier stage, and the accessibility of better diagnostic tools may all add to the high frequency of BKV infection [11,12].

Polyomaviridae (PyV) viruses

The human BKV belongs to the Polyomaviridae (PyV) virions, a subgroup of papovaviruses, which includes BKV, JC virus, and simian virus 40 (SV-40). It is a family of small, non-enveloped DNA viruses with icosahedral capsid of 40- 45nm in diameter, and can withstand heat up to 50°C for 30 min with little effect on infectivity. BKV has a circular double-stranded DNA genome of approximately 5000 base pairs [2,13-17]. Twelve additional human polyomaviruses have been isolated lately between the years 2007- 2017. These new

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Polyomaviruses were named based on the site of discovery, the land/territories, the diseases they may cause, or the order of discovery: MWPyV (Malawi), WUPyV (Washington University), and KIPyV (Karolinska Institute) or Human polyomavirus-3, MCPyV (Merkel cell carcinoma), TSPyV (trichodysplasia spinulosa); HPyV6, HPyV7, HPyV9 and HPyV12 (human polyomaviruses 6,7, 9 and 12), STLPyV (Saint Louis polyomavirus) or Human polyomavirus-11, New Jersey polyomavirus (NJPyV, also famous as polyomavirus-13), Lyon IARC polyomavirus (LIPyV or Human polyomavirus-14) [18-22].

BKV genetic variants

BKV can be categorised into four genotypes/subtypes according to the DNA sequence variations in the genomic region of VP1 [23-25]. Genotype I is the predominant subtype of all circulating viruses, accounting for greater than 80% worldwide, followed by genotype IV which is the second most frequent genotype, found approximately in 15% of the normal human population. Alternatively, genotypes II and III are relatively rare and infect only a minority of people [25,26].

Phylogenetic analysis has further identified four subgroups, sub-cloned of subtype I (I/a, I/b-1, I/b-2 and I/c), and six subgroups of subtype IV (IV/a-1, IV/a-2, IV/b-1, IV/b-2, IV/c-1 and IV/c-2). As with subtype-I subgroups, each of the subtype four subgroups may reflect different geographical and the migration pattern of the human population [14,25-27]. The subgroup of subtype-I (I/b-2) has been noticed mostly in American and European populations, whereas subgroup I/c dominate in Asians. Among subtype IV isolates, subgroup IV/c-2 is predominant amongst Americans and Europeans, whereas the other subgroups are more common in Asian populations [15,28]. Apart from the genotypic variations of VP1 region, additional two other forms of BKV present secondary to variations in the NCCR, namely, rearranged (rr) and archetype (ww) variants. Persistent and continuous replication of the viral genome during the reactivation process can result in deletion and duplication in the NCCR sequences with subsequent generation of variant viruses. The clinical and immunological consequences of these genotypes on clinical perspective and the course of the disease are still undefined [26,29]. In a recent study, Korth, *et al.* 2019 had linked allograft failure with BK genotype II and IV compared to genotype 1 & III ($P=0.007$) [30].

Epidemiology, pathogenesis and clinical manifestations

Studies revealed as much as 60%-85% of the general population is seropositive for BKV [28,31-40]. Primary infection prevalently happens during early childhood; subsequently, the virus stays dormant throughout life in immune-competent people [2,11,26]. In the setting of immunosuppressive therapy, the virus activates and begins to proliferate inside the interstitium and crosses into the peritubular capillaries, creating a sequence of events that begins with tubular cells lysis and viruria. The outcome relies upon the degree of damage, inflammation and fibrosis [2,3].

In renal allograft recipients, BKV has been correlated with different clinical manifestations, among which are the BKV Nephropathy (BKVN), ureteric stenosis and late-onset haemorrhagic cystitis [2,9,41,42]. Outside renal transplantation, BKV is commonly encountered in patients with Hematopoietic Stem Cell Transplant recipients (HSCT) as haemorrhagic and non-haemorrhagic cystitis [43,44], while in HIV infected patients, BKV may disseminate leading to severe viremia with multi-organ involvement such as meningoencephalitis, Guillain-Barré syndrome, progressive multifocal leukoencephalopathy, vasculopathy, bilateral atypical retinitis and severe interstitial pneumonitis, and eventually lead to death [45-51].

Aim of the study

This systematically structured review aims to identify and stratify potential risk factors published in the literature and can predispose to BK nephropathy. Recognizing risk factors can help in laying strategic policy and recommendations for monitoring, screening and initiating early treatment for high-risk patients based on data analysis, which may reflect positively on allograft survival and improve patient's quality of life.

Methodology and Research Design

PICOS

This analysis will use the following PICOS parameters:

- **Population:** kidney transplant recipients.
- **Intervention:** identification of statistically significant risk factors, predisposing to BKV reactivation in kidney transplant recipients.
- **Comparison:** patients who developed BKV viremia/viruria and/or nephropathy post-renal transplant, versus who did not.
- **Outcomes:** BKV viremia/viruria and/or nephropathy
- **Studies:** studies based on prospective/ or retrospective analysis with at least 12-24 months of follow-up.

Inclusion and exclusion criteria

Inclusion Criteria: this research intended to define risk factors for BK viremia/nephropathy in adult recipients, hence all analyses accomplished for adults renal transplant recipients with BK viruria/viremia/and nephropathy; published in English were included. However, a few paediatric studies are also pertinent to this research and are also incorporated.

Exclusion Criteria: studies that lack diagnosis/criteria for BK viremia/nephropathy.

Significance of the Research

BKV remains an evolving challenge for renal transplant physicians since it was discovered in 1971. Different theories were generated to explain the increased risk for acquiring BK infection post-transplantation, yet no single clinical risk factor can determine the recipients who will develop BKV nephropathy. Additionally, the results in the current literature are conflicting, and a risk factor may appear as significant in one study while it looks irrelevant in another. We hope from our study to discover out definite risk factors and to identify any possible modifiable factors that favour infection with a view toward BK prevention and to support in laying strategic plan and recommendations for risk factors monitoring, screening and treatment of high-risk patients based on data analysis.

Search strategy

For this analysis, various sources were used through searching PubMed/Medline database, Scopus, EMBASE, EBSCO, Google Scholar, Cochrane Database of Systematic Reviews (CDSR), directory of open access journals (DOAJ) and conference proceedings. The search was conducted, using the following keywords; transplant, kidney transplantation, nephropathy, BK Virus, BKV-associated nephropathy; risk factors, BK viremia and BK viruria. English articles, full articles on BK risk factors, articles in kidney transplant, combined kidney with other organ transplant were then selected. More than 1000 articles were identified. Articles were then analysed for their applicability to clinical practice, a duplicate was removed, and articles in English were selected. Further references were selected from the citation section of individual papers.

Results and data analysis

More than 80 observational studies on risk factors were identified and critically appraised, using PRISMA/CAPS Guidelines. Most of these studies were done retrospectively while few were prospective. The viremic patients were compared to non-viremic to analyse the different potential risk factors. Studies with statistically significant risk factors were analysed and illustrated in the following tables, where Table 1 summarises the predictive risk factors for biopsy-proven BKVN, while Table 2 summarises the most detectable risk factors for BK viremia. Some of the risk factors were statistically significant in some studies while not in others, which will be elaborated further in the discussion. Other risk factors identified by this process will also be reviewed. The significant BK-risk factors can be categorised into three areas; transplant-related, donor-related and recipient-related factors.

Main Discussion

Risk factors

Several risk factors might attribute to the occurrence of BKVN. Generally, all published risk factors can be organised into three categories (Table 3):

- A. Transplant-related risk factors
- B. Donor-related risk factors
- C. Recipient-related risk factors

(A). Transplant-related risk factors

Immunosuppression

Induction, as well as maintenance immunosuppression, appears to impact the BKVN risk.

BK Association with induction therapy: BK nephropathy was identified before the era of induction therapy [80]. However, potent therapeutics used for induction was thought to add further risk in activating BKV. Polyclonal anti-thymocyte globulin induction therapy had significantly increased the risk of BKVN in 2 different retrospective analyses (P-value of 0.0003 and 0.0005) [52,53]. This was further supported in a broader analysis of USA Organ Procurement and Transplantation Network (OPTN) of 48,000 kidney transplants performed between 2003 to 2006 [81].

Further international studies had confirmed this finding [82-84]. This is not surprising given the immunosuppressive effects of this agent as a lymphocyte depleting drug, leading to impaired cell-mediated immunity against BKV infection. However, others did not find any association of BK with anti-thymocyte therapy [54,55,57,61]. On the other hand, induction with a humanised monoclonal antibody alemtuzumab and Basiliximab failed to demonstrate the increased incidence of BKVN in different retrospective cohort studies, though it induces pan-T cell depletion, leading to impairment in the cellular immune system [57,85-88].

BK Association with maintenance immunosuppressant therapy: Immunosuppression appears as the primary risk for BKV infection. There is some supportive evidence to propose an increased risk of specific immunosuppressive regimens, such as tacrolimus compared with cyclosporine; and mycophenolate-mofetil (MMF) compared to azathioprine, though prospective data are necessary to confirm these findings [83,88-92]. Tacrolimus, compared to sirolimus or cyclosporine, activates BKV proliferation through a mechanism involving FK-binding protein (BP-12) [93]. Furthermore, Thölking, *et al.* suggested a fast Tacrolimus metabolic rate (a low C/D ratio of <1.05 ng/mL*1/mg) to be an independent risk for BKVN and CNV nephrotoxicity, however, patients with BKVN in that analysis were low in number, limiting

Table 1. Potential risk factors for biopsy-proven BKVN (OR: odds ratio; HR: hazard ratio)

Summary of identified risk factors for biopsy-proven BKVN					
Classification	Risk factors	BKVN cases/ Overall recipients	Relative effect (95%CI)	P-value	References
Transplant-related; Immunosuppressive regimen	Induction with Polyclonal antibody	25/542	OR 11.04 (2.94-41.52)	0.0003	52
		39/880	HR 6.6 (2.3-18.9)	0.0005	53
	Mycophenolate	39/880	HR=3.5 (1.6-7.5)	0.0013	53
	Tacrolimus	39/880	HR 3.3 (1.5-7.6)	0.0038	53
		33/99	OR 1.3 (1.02-1.7)	0.03	54
	Prednisone dose	33/99	OR 1.22 (1.04-1.4)	0.02	54
Transplant-related; graft-related factors	Cold ischemia timing	9/227	HR 1.18 (1.04-1.35)	0.009	55
	Ureteral Stents	20/66	OR 4.71(1.22- 18.18)	0.003	56
		31/666	HR 3.18 (1.42-7.12)	0.005	57
	Acute rejection	9/227	HR 4.05 (0.99-16.53)	0.051	55
		40/404	OR 2.1	0.0001	58
	39/880	HR 5.1 (1.8-14.6)	0.0021	53	
Donor/recipient-related	CMV infection	39/327	OR 2.6 (1.29-5.26)	0.006	59
		31/666	HR 2.72 (1.19-6.24)	<0.001	57
	Donor BKV seropositive	12/407	HR 2.89 (1.33-6.29)	0.007	60
	ABO-incompatibility	11/ 62	OR 2.32 (NR)	0.04	59
	Afro-American recipients	31/666	HR 2.89 (1.36-6.14)	0.006	57
	Recipients age	31/666	HR 1.04 (1-1.07)	0.048	57
	HLA-DR mismatch	25/542	OR 7.31 (2.58-20.71)	0.0003	52
		31/666	HR 1.45 (1.12-1.88)	0.006	57
	Donor source (deceased)	9/226	not reported	0.005	55
		39/327	OR 2.2 (1.1-4.43)	0.024	61

Table 2. Summary of predictive risk factors for BK viremia (OR: odds ratio; HR: hazards ratio, NR: not recorded)

Classification	Risk factors	The occurrence of BKV viremia (viremic patients/ total recipients)	Patients with BK Viremia subjected to risk factor	Relative effect (95%CI)	p-value	Reference
Transplant-related	Immunosuppressive regimen (tacrolimus vs cyclosporine)	102/998	64/102	HR 0.68 (0.44-1.07)	0.094	62
		22/265	NR (not recorded)	OR 5.27 (1.2-23.16)	0.027	63
		38/229	32/38	HR 2.9 (1.1-8.1)	0.032	64
		71/251	49/71	OR 0.99 (0.91-1.25)	0.19	65
		41/553	32/41	OR 0.71 (0.24-2.05)	0.53	66
		111/407	84/111	HR 0.76 (0.48-1.23)	0.264	60
		29/183	10/29	OR 3.65 (1.42-9.39)	<0.0-01	67
	History of previous transplant	48/352	9/48	OR 2.74 (1.05-7.15)	0.039	68
		71/251	20/71	OR 1.53 (0.62-4.42)	0.07	65
	ureteral stent	23/198	10/ 23	HR 3 (NR)	0.018	69
		93/600	NR	OR 1.65 (1.05-2.6)	0.0315	70
		171/1318	76/171	HR 1.36 (1.05-2.6)	0.024	71
		89/403	44/89	OR 1.92 (1.04-3.74)	0.044	72
		71/251	24/71	OR 0.737 (0.49- 1.09)	0.129	65
	Acute rejection	163/609	21/163	HR 2.01 (1.096- 3.685)	0.02	73
		48/352	11/ 48	OR 3.79 (1.5-9.58)	0.005	68
		102/998	44/102	HR 0.96 (0.58- 1.56)	0.89	62
		71/251	50/71	OR 0.92 (0.85-1.02)	0.02	65
		80/412	36/80	NR	<0.001	57
	16/30	5/16	NR	0.021	74	
	Cold ischemic time (min)	102/998	NR	NR	0.30	62
warm ischemic time (min)	57/194	53/57	Not recorded	0.019	75	
Donor and recipient characteristics	HLA mismatch (4–6)	102/998		HR 0.77 (0.49–1.24)	0.28	62
	HLA-A2 match	102/998	21/102	HR 0.51 (0.28–0.8)	0.011	62
	B44 match	102/998	3/102	HR 0.31 (0.076–0.85)	0.019	62
	C6 match	102/998	0/102	HR 0.24 (0.013–1.12)	0.075	62
	DQ7 match	102/998	18/102	HR 1.63 (0.91–2.78)	0.097	62
	DR7 match	102/998	3/102	HR 0.49 (0.12–1.36)	0.19	62
	DR15 match	102/998	3/102	HR 0.35 (0.084–0.93)	0.034	62
	Mean Lymphocyte percentage (%)	16/52	Not recorded/16	HR 0.878 (0.783–0.984)	0.026	76
		16/268	16/16	AUC 0.77 (0.589–0.951)	0.012	77
	57/194	44/57	Not mentioned	0.006	75	
	GCSF use	80/666	42/80	HR 1.76 (0.87–3.57)	0.0006	57
	CMV infection	80/666	17/80		0.001	57
	Panel-reactive antibody test > 50%	60/629	18/60	OR 3.352 (1.737-6.338)	< 0.001	78
	Afro-Caribbean ethnicity	60/629	20/60	OR 2.882 (1.549-5.259)	0.0024	78
	Male Recipient	102/998	78/102	HR 2.38 (1.46-4.09)	<0.001	62
		42/487	35/42	OR 2.49 (1.05-5.89)	0.038	79
		71/251	64/71	OR 1.42 (0.99-1.98)	0.033	65
		41/553	30/41	OR 1.77 (0.79-3.85)	0.24	66
		111/407	73/111	HR 1.04 (0.68-1.6)	0.842	62
	20/174	15/20	OR 3.47 (1.11-10.86)	0.03	67	

the efficacy of this test [94]. Brennan [69] prospectively assessed the changes in viruria and viremia with the three immunosuppressive combination therapies. He reported higher incidences of viruria with the tacrolimus-MMF therapy (46%) compared with the cyclosporine-MMF combination (13%, P=0.002). However, he did not find any difference in viremia or BK-nephritis related to either of calcineurin inhibitors or other adjuvant immunosuppression.

On the other hand, tacrolimus therapy was only classified as a risk factor for BK viremia in 7 multivariate analyses [62–68] (Table 2) and a risk factor for BKVN in other two multivariate analyses [53,54]. The rest of studies which correlated tacrolimus with BK viremia and showed clearance of viremia upon reducing or withdrawing tacrolimus had small sample size (11 to 60 patients) and did not have control groups [95-98]. Besides being retrospective analyses, the protocol of lessening immunosuppression was heterogeneous in these studies and includes

either drawing of one agent (MMF or the calcineurin inhibitor), or reducing the dose of both agents without removing any drug, which creates a few confounders in their data analysis. Further retrospective analyses found that BKV nephropathy is correlated with a combination of tacrolimus in higher doses (levels >8 ng/ml) and MMF (dosages 1.5-2g/d)/or mycophenolic-acid (> 1g/d) [54,83,99,100]. mTOR-inhibitors (sirolimus or everolimus) on the other hand, may have an inhibitory effect on BKV replication in the urothelial cells [101,102]. Sirolimus can inhibit the expression of BKV LT-antigen in both primary human renal tubular cells and immortalised human renal cells [103]. Moreover, mTOR inhibitors control the differentiation of memory CD8 T-cells. Thus, it improves the immune reaction against BKV infection [102].

Of particular interest, BKVN has been reported in recipients getting almost every immunosuppressive drug or combination of drugs, including calcineurin-free triple-drugs [104,105], dual therapy

Table 3. Potential Risk factors associated with an increased risk of post-transplant BKV re-activation

Transplant-related:	Donor-related:	Recipient-related:
Immunosuppression <ul style="list-style-type: none"> • Induction therapy (ATG) • Type and degree of immunosuppression Graft-related <ul style="list-style-type: none"> • Prior treatment of acute rejection • Prolonged cold/warm ischemia timing • Delayed graft function • Ureteric stent placement • Renal injury (immune related,.. etc.) 	<ul style="list-style-type: none"> • Older donor age • Donor BK virus seropositivity • Degree of HLA matching • ABO-Incompatibility • Absence of HLA-C7 • Donor status (deceased versus living donor) 	<ul style="list-style-type: none"> • Older recipient Age>50 • Gender (male recipient) • Recipient race • Obesity (BMI>30 kg/m²) • Previous graft loss due to BK nephropathy • Diabetes mellitus • BK seronegativity • HLA mismatching, Absence of HLA-C7, certain HLA alleles • High PRA titres • Genetic factors • Lymphocytes mean percentage (%) • G-CSF use • Dialysis Modality pre-transplantation • CMV status

with a calcineurin inhibitor and sirolimus [106-108], mycophenolic acid [61] and tacrolimus monotherapy [109]. Additionally, the analysis of USA Organ Procurement registry data has suggested an influence of maintenance steroids on the development of BKV, although the hazard ratio with steroid therapy was modest (HR 1.16, 95% CI 1.02-1.31) [110]. Taken altogether, it appears that the overall status of immunosuppression is responsible for the development of BKV infection rather than a particular drug. Indeed, some considered BKV replication to be an indicator of excess immunosuppression [111].

Graft-related risk factors

Allograft Rejection

Acute rejection was an independent risk factor for BK virus activation in several studies [57,58,74,112,113]. Dharnidharka, *et al.* [110] showed that acute rejection in the initial 6-months post-transplantation might increase the risk of BKV replication. Moreover, in 5 univariate analyses, higher incidences of viremia were demonstrated in those who had at least one episode of acute rejection during the follow-up period (Table 2 and 3) [57,62,65,68,73]. The effect of allograft rejection might be related to the intense treatment of rejection with immunosuppressive medication rather than the rejection itself [74,114]. Theodoropoulos, *et al.* [57] had reported that recipients with acute rejection episodes had 17.7% higher rate of BK viruria ($P < 0.001$), 22.7% higher rate of BK viremia ($P < 0.001$) and 39% higher rate of BKVN ($P < 0.001$) and the rejection episodes had preceded the onset of clinical BKVN in 6/19 (32%) of the cases at a median time of 11 weeks. Furthermore, he noticed that cellular rejections were associated significantly with BKVN, while the humoral rejections were only correlated with viruria; an interesting finding which he could not explain [57].

Prolonged warm ischemia timing

In a single report, Steubl, *et al.* had reported a statistically significant BK viremia in patients with prolonged warm ischemia timing ($P = 0.019$) [75]. A probable explanation for this is that prolonged warm ischemia can induce renal injury and leads to a pro-inflammatory status, which may contribute to viral reactivation [115]. Nevertheless, Warm ischemia timing was not a significant factor in different studies [42,74,116].

Prolonged cold ischemia timing (CIT)

Allograft damage resulted from Ischemia-reperfusion lesions; appear experimentally to facilitate BKV replication in ischemic adult mouse kidneys [101]. Prolonged CIT was an independent risk factor for the development of viremia and BKVN [55]. However, this was not a constant finding in other studies [57,68,74,78].

Delayed graft function (DGF)

DGF was independently associated with BKV replication and development of BKVN [55,117,118], though this was not confirmed in a broader cohort analysis [58,78,114].

Ureteric stent placement

5-multivariate analyses have demonstrated an increased risk of BKV in recipients who had a ureteric stent placement with significant risk ratios ranging from 1.36 to 3 [56,69-72], proposing that these patients might benefit from an early BKV screening. Wingate, *et al.* in 2017, reported only a prolonged stent duration of >3 weeks is associated significantly with increased risk of BK Viremia compared with short stent duration <3 weeks or no stenting ($P = 0.044$) [72]. This data needs further validation before we can recommend using stents for less than three weeks based on a single centre report. Furthermore, other data had failed to show any correlation between stenting and BKV infections [18] while others did not include ureteric stenting among their data analysis [55,68,87,110], possibly because they are using stents routinely as part of their post-operative clinical practice.

(B). Donor-related risk factors

Donor age

Favi, *et al.* [78] had identified the elderly donors (≥ 60 years) as a significant predictive risk factor for BKVN in multivariate analysis ($P = 0.048$). Nevertheless, this was insignificant findings in other studies [58,68].

ABO-incompatibility

In a single study from John Hopkins Hospital, Sharif, *et al.* had demonstrated a higher BKVN incidence amongst ABO-incompatible

recipients than in HLA-incompatible recipients (17.7% vs 5.9%) even after adjusting the number of rejection episodes [59]. Nonetheless, it is not clear whether the ABO-incompatibility in itself expands the risk of BKVN or BK disease is a consequence of intensified desensitisation regimens received by ABO-incompatible individuals. T-cell depletion caused by desensitisation regimens might increase the risk of T-cell-dependent infectious diseases such as CMV, BKV infections and even severe sepsis.¹¹⁹ A study which included 26 ABO-incompatible renal transplant recipients and continued follow-up for one year post-transplantation revealed a higher risk of BKV in patients that received intensified desensitisation with r-ATG [120].

Donor source

The corresponding analyses revealed strong associations between BK-viremia/BKVN and deceased donor [55, 63-65,67,121], however, this was not observed in other analyses [57,58,78,114].

BK Donor/recipients serostatus

Bohl, et al. [122], had recognised BK virus antibody-positive donors and recipients (BKV D+/R+) as a predictive risk for developing post-transplant BK viremia (46% BKV D+ versus 15% BKV D-). Interestingly, all of the pairs in which both donor and recipient were BK antibody-positive showed the same BK-subtypes and sequences, proposing donor origin of BK virus [122]. However, Shah recognised the seronegative recipients to have an increased risk of acquiring BKV if they got a transplant from a seropositive donor (BKV D+/R-) [123].

(C) Recipients-related risk factors

Recipient age, gender and weight

Plenty of studies had identified the importance of recipient male gender [62,65,67,68,87,124] and older recipient age [57,68,87,113] in the development of BKVN, though such findings have not been consistently observed in all analyses [55,76,114]. Similarly, Obesity (BMI over 30 kg/m²) was an independent predictor for BK viremia in a single study [125], but not in others [68,78]. In a separate analysis, presented by Mehta, et al. as a poster abstract, the advanced age was a risk factor for BK viremia among Non-Asian patients but not among East Asian or Pacific Islander descent patients [126].

Recipient race

Recipient race might be a strong predictive risk for developing BK viremia/nephropathy. African-American race has a higher rate of BKVN independent of other confounding risk factors in many analyses [57,71,87,124,127]. Similarly, Afro-Caribbean was a significant risk in a recent analysis with P-value of 0.0024 [78]. Alternatively, others had found Caucasian ethnicity to be at increased risk of BKVN rather than African American ethnicity [81,128,129]. Till date, the majority of publications which investigated ethnicity as a risk factor for BKV disease in adult's renal recipients are for USA population and only a single article was found for New Zealand [55] and an additional one for the Royal London Hospital (London, UK), where the author included Afro-Caribbean race [78]. Other than those, there are no comments on ethnicity in Asian, nor in European publications, which we feel should be addressed in future publications where a mixture of a population is present.

HLA mismatching

Presences of 4 or more mismatches are strong independent predictors of BK viremia [112,122,124]. Some had attributed this to the

increase in rejection episodes, higher occurrence of steroid-resistant rejections that necessitates treatment with lymphocyte depleting agent such as anti-thymocyte therapy [10,58]. Additionally, a relationship has been reported inconsistently between particular HLA alleles and the development of BKVN in kidney recipients [9,82]. In a retrospective cohort analysis, donor-recipient matching of HLA-A2, HLA-B44, and HLA-DR15 had a low rate of BKV infection [62], while recipient HLA-Cw4, HLA-B35 and HLA-A1 were significantly associated with post-transplant BKV infection in another study, whereas recipient HLA-Cw6 and HLA-Cw7 did not increase the risk [18]. BK risk was further increased in recipients who had both HLA B35 and Cw4 (B35/Cw4 +/-) [18]. Interestingly, in a single-centre data, HLA-C7 seemed to give a protective/defensive role against BKV, and lack of HLA-C7 allele in a donor or a recipient had raised the risk of BK-viremia by at least 3-folds [122].

Previous transplant

Previous transplantation was considered as a statistically significant predictive risk for BK viremia in 2 separate studies [68,125]. However, this factor was insignificant in different analyses [57,60,68]. Perhaps the intense immunosuppression and desensitisation therapy at pre-transplant play a role in that.

High PRA titre

Higher pre-transplant PRA level of > 50% increases the risk of BK infection. Similarly, it may owe to the desensitisation and over-immunosuppression received before transplantation [78], yet this was an insignificant factor in other analyses [58,68].

Diabetes mellitus

Pre-transplant diabetes duration was an independent factor for BKV positivity in 2 multivariate analyses; in SPK (Simultaneous pancreas and kidney transplant) recipients (P= 0.028) and renal transplant recipients (P=0.008) [61,117]. Other than these two studies, the presence of diabetes mellitus as a risk factor for BKVN/BK-viremia was suggested in isolated case reports [131-133], while unidentified in more extensive cohort studies [56,57,78,130].

Conversely, Thangaraju, et al. [113] reported a lower incidence of BK viremia in patients with diabetes as a cause of their ESRD, and he related this to lower levels of immunosuppressant used for these patients, however, we disagree with this thought since most centres do not lower immunosuppressant for diabetic patients.

Recipient BK-seronegativity

Recipient BK-seronegativity might be a potential risk of BKV infection, particularly if they received a transplant from a seropositive donor (BKV D+/R-) [123].

Genetic factors and hereditary diseases

Small, preliminary studies have implicated a possible genetic predisposition to BKVN, including a lower number of recipient natural killer (NK) cell-activating receptors and donor/recipient mismatch at the MHC class I polypeptide-related sequence A (MICA) locus [111,134].

Moreover, in a single Korean centre, a higher incidence of BKVN was observed among paediatrics kidney allograft recipients with Alport syndrome, despite Alport's comprised only 6% of the study population. Nevertheless, every patient with BK viremia and Alport syndrome developed BKVN, while only 11.1% of patients with BK viremia in the

absence of Alport syndrome had progressed to BKVN in a multivariate analysis (hazard ratio 13.2, $P = 0.002$) [135].

Lymphocyte mean percentage (%)

Renal recipients with lower total lymphocytes percentage were noted in 3 multivariate analyses to increase the BKV activity (with a P -value of 0.026, 0.012, and 0.006 respectively); suggesting a reduced total lymphocyte count can be an independent predictor for preceding BK viremia [75-77]. According to Comolli [136], lymphopenia may associate with alterations in the total of BKV-specific CD4+ and/or CD8+ T cells. Additionally, lymphopenia can result from elevated MMF levels or elevated tacrolimus levels, which may elevate the MMF-AUC level via the enterohepatic circulation [75].

Granulocyte-colony stimulating factor (G-CSF) use

Theodoropoulos, *et al.* had identified the granulocyte-colony stimulating factor (G-CSF) as a risk factor for BKVN (P -value of 0.036) and BK viremia ($P=0.006$) in univariate analysis [57]. Unlike recipients of Hematopoietic Stem Cell Transplant, the use of G-CSF is limited in routine clinical practice for post-renal recipients unless the patient has severe neutropenia which again might reflect the adverse effects of immunosuppressants or severe viral infection making the interpretation of this factor difficult.

Modality of RRT pre-transplant

Hosseini-Moghaddam [18] had reported a higher incidence of BK viremia in recipients who were on haemodialysis pre-transplantation compared to PD in the univariable prospective analysis ($P=0.06$). Though the mechanism was unclear, a postulation of a chronic inflammatory response accompanying the haemodialysis process leading to chronic activation of the immune system and hypercytokinemia were anticipated [18]. Further studies had confirmed this [68,137], while others found an insignificant association of BK reactivation with the pre-transplant dialysis modalities [78].

CMV

The studies regarding CMV serostatus as a risk factor for BK reactivation is contradictory, while some had reported CMV-viremia to protect against consequent BK-viremia, possibly due to a decrease in the intensity of immunosuppression following CMV diagnosis [73], others had identified CMV infection as a potential factor for BKV replication and development of BKVN [57,68,78,124,138,139].

Conclusions

Nearly three decades of research have prompted just a minimal comprehension of BKV and its pathophysiology. This truth proves to the elusive nature of the virus and the challenge they pose to their investigators. The main objective of this review is to determine the potential risk factors for BKV infection. We believe that over immunosuppression remains the leading risk factor for acquiring BK infection post-transplant. However, it remains unclear whether the development of BKVN is attributable to quantitative and/or qualitative differences in immune suppression. In addition to immunosuppression, earlier studies showed many probable risk factors of BKV infection, including donor characteristics risk factors, recipient characteristics and transplant-related risks. Some of these factors appeared constant in many multivariate analyses with statistical significance such as ureteric stents placement, recipient's age, recipient's race, deceased donor and acute rejections episodes; however, this was not established in other

larger cohort analyses. Moreover, the diversity in published data may reflect patient's geographical area, their genetic susceptibility and probably different BK variant gene with different risk susceptibility which may explain the wide variety of risk factors that appear strongly significant in some study and irrelevant in others. With a view to prevention, it is crucial to distinguish the potentially modifiable factors that favour infection. Hence a prospective randomised cohort study with larger sample size is warranted, preferably involving many countries to eliminate any sample bias and to overcome any geographical or ethnical boundaries that may create confounding results. Additionally, it will help to readdress the immunosuppression protocol to reduce the BKV and to define the appropriate follow up period for screening those patients into consideration to reduce acute or chronic rejection episodes.

Declarations

The authors declare that they have no potential conflict of interest and no funding relevant to this article to disclose.

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