ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2016 January 28; 22(4): 1331-1728

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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World Journal of Gastroenterology is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, Digital Object Identifier, and Directory of Open Access Journals. According to the 2014 Journal Citation Reports® released by Thomson Reuters (ISI), the 2014 impact factor for *WJG* is 2.369, ranking 41 among 76 journals in gastroenterology and hepatology, quartile in category Q2.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

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Pleasanton, CA 94588, USA
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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
January 28, 2016

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1007-9327/g_info_20100315215714.htm

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DOI: 10.3748/wjg.v22.i4.1532

World J Gastroenterol 2016 January 28; 22(4): 1532-1540
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

2016 Liver Transplantation: Global view

Different behaviour of BK-virus infection in liver transplant recipients

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Author contributions: Umbro I wrote the paper; Tinti F performed the literature search; Muiesan P and Mitterhofer AP designed the research.

Supported by Italian Society of Nephrology.

Conflict-of-interest statement: The authors have no conflict of interest to report.

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Received: May 29, 2015
Peer-review started: June 2, 2015
First decision: September 11, 2015
Revised: October 10, 2015
Accepted: November 24, 2015
Article in press: November 24, 2015
Published online: January 28, 2016

Abstract

Polyomavirus BK (BKV) infects up to 90% of the general population. After primary infection, occurring early during childhood, a state of non-replicative infection is established in the reno-urinary tract, without complications for immunocompetent hosts. In immunocompromised individuals, particularly transplanted patients, asymptomatic BKV viremia and/or viruria can be observed. Renal grafts may also be sources of infection as BKV prefers kidneys rather than other solid organs for transplantation such as the liver. The mechanism behind the higher incidence of BKV infection in kidney transplant patients, compared to liver or heart transplantation, is unclear and the prevalence of BKV infection in non-renal solid organ transplants has not been yet thoroughly investigated. We evaluated the prevalence of Polyomavirus BK infection among liver transplant recipients. A PubMed search was conducted using the terms BKV infection AND liver transplant recipients; BKV AND non-renal solid organ transplant*; BKV infection AND immunosuppression; the search was limited to title/abstract and English-language articles published from 2000, to March 2015. Eleven relevant studies suggest that the prevalence of BKV viruria and/or viremia among liver transplant recipients is less than that reported in kidney or heart transplant recipients, except when chronic kidney disease (CKD) is present at the same time. Data also suggest that viruric and viremic patients have higher levels of serum creatinine than BKV negative patients. Moreover, no specific immunosuppressive drugs are associated with the onset of BKV nephropathy. The comorbidity of transplantation and CKD could play a major role in promoting BKV replication.

Key words: BK virus; Polyomavirus BK infection; Liver transplantation; Liver transplant recipients

Core tip: The prevalence of polyomavirus BK (BKV) infection among non-renal solid organ transplant recipients has been insufficiently investigated. Our review suggests that BKV viruria and/or viremia in liver transplantation is less prevalent than what has been reported in kidney or heart transplants, except when renal dysfunction is present. In general, viruric and viremic liver transplant patients have higher levels of serum creatinine. Therefore, renal dysfunction in liver transplantation may be an additional factor causing immunologic dysfunction that could make patients more susceptible to BKV infection.

Umbro I, Tinti F, Muiesan P, Mitterhofer AP. Different behaviour of BK-virus infection in liver transplant recipients. *World J Gastroenterol* 2016; 22(4): 1532-1540 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i4/1532.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i4.1532

INTRODUCTION

Polyomaviruses are widespread among vertebrates. Man is the natural host for BK virus (BKV) also known as Polyomavirus hominis 1. The human Polyomavirus BK was first isolated in the 1970s[1,2] from the urine of a renal transplant patient with ureteric stenosis, shedding cytopathically altered cells with atypical nuclear morphology[2]. This patient's initials gave the name to the virus.

BKV GENOME

BKV and JCV are species of Polyomavirus of the family *Polyomaviridae*, which are characterized by a typical morphology of non-enveloped virions with icosahedral capsids of 45 μm diameter. These capsids enclose the viral genome, a small circular double-stranded DNA genome of 5300 base pairs coated by host-cell histones. The BKV genome shares an overall homology of 75% with JCV and can be divided into regulatory, early, and late regions[3].

The Polyomavirus genome architecture is conserved and encodes only 6 proteins. It consists of the non-coding control region (NCCR) that contains the origin of DNA replication and bidirectional promoters. The two early gene proteins, the small and the large tumour antigen (LTag), are encoded by the early genes. The four late gene proteins, including the three viral capsid proteins and the agnoprotein, are encoded by the late genes. The LTag is a conserved multifunctional regulator of transcription and replication of polyomavirus. Rearrangements of the NCCR occur with persisting BKV replication increasing replication capacity[4,5]. The LTag interacts with proteins of the host cell and disrupts its division, collecting factors to promote viral DNA replication[6].

After production of proteins constituting the viral capsid, the virion is assembled in the nucleus with subsequent lysis of the host cell and discharge of the viral progeny. As viral antigens are released in the host's circulation a reactive nonspecific inflammatory response mounts, followed by a specific immune response[1].

BKV EPIDEMIOLOGY

Polyomavirus hominis 1 infects up to 90% of the general population[1,7,8]. Primary BKV infection occurs early during childhood, in the first decade of life, more often at an age of 4-5 years[9]. During the first 10 years of life, the sero-prevalence reaches 50% of the individuals whilst in the adult population it is recorded as more than 70% worldwide with exception of isolated populations of Asia and South America[7]. Immunosuppression, as in the elderly and pregnant women, is a known risk factor for an increased prevalence of BKV infection.

Natural BKV transmission is likely to occur *via* the respiratory or oro-pharyngeal tracts[1]. The primary route of transmission is likely to be *via* fomites or aerosol given the association of primary infection with upper respiratory infections[10,11]. Further possible routes of BKV transmission are related to semen, blood products transfusions and transplantation of organs, in particular of the kidney[7,12-15].

After primary infection, BKV colonizes the reno-urinary tract, most likely, *via* a primary viremia[1,16]. Latency is a state of silent infection which is localised in urothelial cells and in the tubular epithelium, without known complications for the immunocompetent host. Other sides of detection of BKV genomes include prostatic tissue, ureteric and bladder urothelial, renal cortex and medulla[12,16].

Reactivation and asymptomatic shedding in the urine of healthy BKV sero-positive immunocompetent individuals ranges from 0%-62%[8,17,18]. About 5% of healthy individuals intermittently reactivate BKV replication with low detectable level of asymptomatic viruria[1,13].

In individuals with impaired immune functions, particularly after solid organ transplantation (SOT) or hematopoietic stem cell transplant (HSCT), asymptomatic high-level urinary BKV replication is observed with appearance of "decoy cells" in urine cytology and virus particles detectable by direct negative staining electron microscopy[19-21].

BKV REACTIVATION

High prevalence, latent infection, and asymptomatic reactivation of BKV interfere with a straightforward knowledge/comprehension of the pathogenic role of this virus. Therefore, BKV infection, BKV replication

and BKV disease were defined as stated in a previous review by Hirsch *et al*[1]: (1) BKV infection is diagnosed by serological evidence of replicative and non-replicative virus exposure (latency); (2) BKV replication is confirmed by demonstration of active or lytic infection with multiple modalities. Primary infection is diagnosed by isolation of viral genes or products in sero-negative individuals. When the BKV replicates in sero-positive individuals, this is defined as secondary infection. Reinfection is defined by diagnosis of a new subtype and reactivation by detection of replication of a latent virus; and (3) BKV disease occurs when the replicating BKV leads to organ dysfunction and failure as shown by tissue disease together with viral replication.

BKV DISEASES

Major symptoms are uncommon and restricted to patients with an impairment of immune system. The Polyomavirus BK is closely linked to two major complications in transplant recipients, polyomavirus associated nephropathy (PVAN) in 1%-10% of kidney transplant (KT) patients[22-25] and polyomavirus-associated haemorrhagic cystitis in 5%-15% of HSCT patients[26-28]. Both diseases occur only sporadically in patients with non-renal SOT (NRSOT) or with inherited, acquired or drug-induced immunodeficiency[1,29]. Besides these major problems, BKV has been associated with other pathologies such as tubulo-interstitial nephritis, ureteral stenosis, vasculopathies, pneumonia, hepatitis, encephalitis, retinitis, as well as multi-organ failure, autoimmune disease and cancer[1,30-33].

BKV INFECTION IN LIVER TRANSPLANT RECIPIENTS

Polyomavirus BK-associated nephropathy represents the most important cause of graft dysfunction after KT. Risk factors for PVAN are related to donor, graft, virus, recipient characteristics and immunosuppressive regimens.

Renal grafts may also be sources of infection as BKV prefers kidneys rather than other solid organs for transplantation such as the liver[34]. As suggested in literature, BKV is known for its tropism for renal epithelial cells. The mechanism by which BKV infection incidence is greater in KT compared to heart transplant (HT) and liver transplantation (LT) is not clear. It is plausible that different viral genome may be passed from donors into susceptible recipients with the transplanted kidney as a new infection[35-37]. Such mechanism would not be open to transplantation of different solid organs. Therefore, BKV-specific cytotoxic T-lymphocytes would be impotent in eliminating viral genome which is thus able to escape the immune system causing PVAN[34,36,38]. On the contrary, it seems that BKV genome is not able to resist in cells from liver and heart, therefore it is unlikely that it could be transmitted by these organs.

BKV reactivation may be allowed by some factors, such as inflammation. This could be showed by the greater association between BKV infection and KT from deceased donors compared to living donor KT, probably due to the longer cold ischaemia time[35]. Moreover, BKV replication in KT could be related to ischaemic injury which occurs during the surgical procedure or to kidney graft rejections.

The immunosuppressive regimens have also been suggested to play a key role. Although immunosuppressive therapy is administered to all SOT patients, induction therapy is more often used in renal transplantation and steroids are typically administered for longer time in KT compared to LT[37]. The role of steroids in the reduction of immune reaction has been demonstrated. They may cause T-cells apoptosis and granzyme B downregulation. The latter has a pivotal role in granule exocytosis used by natural killer and cytotoxic T-cells[39]. Furthermore they are able to prevent production and normal activity of dendritic cells[40,41]. The impaired function of natural killer, dendritic and T-cells related to the use of steroids may be associated with the major predilection of PVAN for KT patients. Nevertheless, immunodepression on its own, could not clarify the elevated BKV incidence in KT, since renal transplant recipients do not seem to be significantly more immunosuppressed than LT and HT recipients[35,42-44].

Chronic kidney disease (CKD) occurs in up to half cases of NRSOT in the long-term follow-up[45-48] and it is associated with a worse prognosis compared to patients without CKD[45]. In particular, CKD is very common after LT and its cause is often multifactorial, though calcineurin-inhibitor nephrotoxicity plays a pivotal role. Therefore, among LT patients, pre-transplant renal function, hepatitis-C virus infection, diabetes and older age have been identified as risk factors for CKD[45]. In this context, the role of BKV infection in the occurrence of CKD has not been systematically studied. As renal biopsies are not performed in a routine way after NRSOT, unrecognized factors such as PVAN could also play a role[49].

RESEARCH

A PubMed search was conducted using the terms BKV infection AND liver transplant recipients; BKV AND non-renal solid organ transplant*; BKV infection AND immunosuppression. Results were limited to title/abstract and English-language articles published from 2000, to March 2015. From this search, relevant articles presenting clinical data on the prevalence of BKV infection among liver transplant recipients were identified. The PubMed search retrieved 125 articles, and these abstracts were screened for relevance. Case reports, case series, review articles, and editorials were not considered.

Studies on children and renal transplantation only

were removed from the list. Of the remaining 19 articles, 11 studies were identified that specifically evaluated the prevalence of BKV infection among adult liver transplant recipients. The relevant studies involved 490 liver, 498 kidney, 121 heart, 51 lung, 11 kidney-heart, 8 kidney-pancreas, 5 kidney-liver, 1 heart-lung and 1 kidney-heart-liver transplant recipients.

RESULTS

Splendiani *et al*[50] conducted a single-centre prospective analysis among 118 consecutive ambulatory patients (37 LT and 81 KT) evaluating the prevalence of BKV infection activity and potential associations with renal dysfunction. They looked for BKV genome by urinary PCR. In positive patients, they repeated PCR on plasma. Furthermore they considered hepatitis-C infection in order to highlight associations with renal dysfunction. Mycophenolate mofetil (MMF), tacrolimus (TAC), and sirolimus (SRL) were the most commonly used immunosuppressive agents. Among KT, transplant mean age was 7 years, mean serum creatinine level was 1.4 mg/dL, BUN 57 mg/dL, GOT 18 UI/L, GPT 16 UI/L; 5 recipients showed hepatitis C virus (HCV)-positivity. Eleven patients were BKV positive on urine and 7 also on plasma; all patients were HCV-negative. Among LT, transplant mean age was 4 years, mean sCr level was 1.2 mg/dL, BUN 55 mg/dL, GOT 36 UI/L, GPT 46 UI/L; 13 recipients were HCV-positive. Five patients had BKV in their urine and only one had BKV viremia. Three of these were also HCV-positive. Considering only BKV-positivity, 16 patients had BKV viruria (5 among liver and 11 among kidney recipients) and 8 had BKV viremia as well (1 and 7 in liver and kidney recipients respectively). All LT recipients with BKV viruria had normal renal function whereas viruric KT patients had renal dysfunction, more severe in case of BKV viremia.

In another single-centre prospective study Muñoz *et al*[51], investigated the prevalence of BKV replication and the association between BKV replication and renal function among 156 non-selected recipients of a SOT (49 KT, 43 HT and 64 LT). Urine and plasma samples, collected about 559 d after transplantation, were analysed for BKV by qualitative PCR. Mycophenolate acid and TAC were the most commonly used immunosuppressive agents. Renal dysfunction (defined as sCr level of 1.5 mg/dL) was present in 42% of recipients, BKV viruria and viremia in 19% and 6% of transplant patients, respectively. Incidence of BKV viruria and viremia was significantly higher in KT and HT compared to LT patients. Among 9 viremic patients (6 KT and 3 HT), 1 heart transplant and all KT recipients had elevated levels of sCr at the time of detection of viremia. Interestingly when the authors investigated the association between BKV replication and renal function, they found mean sCr of 1.3 mg/dL in BKV-negative patients, 1.9 mg/dL in patients with BKV viruria, and 3.5 mg/dL in patients with BKV viremia. The authors also showed that the association between BKV replication and renal function was significant in HT patients but not in LT or KT patients. Independent factors associated to renal dysfunction were renal transplantation, BKV replication, and MMF therapy.

In a cross-sectional study by Randhawa *et al*[52], BKV viral load among 103 KT at risk for viral nephropathy and 44 LT patients were compared with BKV viral load among 23 non-immunosuppressed subjects with suspected urinary tract infection. Immunosuppression consisted primarily of pre-transplant induction with anti-CD52 antibody and maintenance on TAC, prednisone and MMF. In the KT group, BK viruria was found in 36 recipients (34.9%), whereas BK viremia was showed in 8/103 (7.7%) recipients. Plasma viral load was significantly less than urine load in the corresponding patients. In LT patients, BKV viruria was observed in 7 (15.9%) recipients. No cases of BKV viremia were observed in LT recipients. Among 23 non-immunosuppressed patients, BKV viruria was found in 2 (8.7%). Mean BKV urinary viral load in KT patients was greater than in LT recipients. Moreover, BKV viruria was more common in KT recipients than in non-immunosuppressed individuals. The 2 KT recipients showing high urinary BKV load had viral interstitial nephritis; plasma viral load was available for only one of these. In the other cases, renal dysfunction was associated to acute cellular rejection, calcineurin inhibitors (CNI) toxicity and chronic allograft nephropathy.

Razonable *et al*[53] conducted a longitudinal surveillance study considering epidemiology and clinical consequences of BKV infection in 263 SOT patients (121 LT, 92 KT, 45 HT and 5 kidney-pancreas transplants) at high risk of Cytomegalovirus (CMV) disease. BKV viremia was found in 32/263 (12.2%) at the median time of 100 d after transplantation and 24 of them (75%) were KT recipients. Thus, among 92 KT patients, BKV viremia incidence was 26%. In most cases BKV DNA positivity in the blood was subclinical whereas coexisted with clinical or biopsy-proven acute kidney rejection in 6 patients (25%). Three out of 32 (25%) patients with BKV DNAemia were HT (6.7%) and 5 were LT (4.1%) recipients. All HT recipients and 1 LT recipient had BKV DNAemia after treatment for acute graft rejection. Notably none of these patients had renal dysfunction within a month before or 1 mo and 1 year after BKV DNAemia. Seventeen of 32 (53%) BKV DNAemic patients developed CMV viremia, 10 of whom (32%) had CMV disease, compared to 16% of BKV DNAemic recipients.

In the prospective, single-centre, cross-sectional study conducted by Barton *et al*[54], 34 recipients of lung, liver, heart, or heart-lung transplants with CKD of unknown aetiology were enrolled with the purpose of defining the prevalence of BK-related viruria/viremia, and risk factors associated with BK infection.

Immunosuppressive therapy included cyclosporine, TAC, azathioprine, MMF, SRL and prednisone. Five out of 34 patients (15%) had BK viruria, but viremia was not detected in any patient and no renal biopsy was performed during the study period. Polyomavirus BK viruria was significantly associated to CMV disease, MMF and cyclosporine, and inversely associated to TAC. No associations with episodes of rejection were found.

Puliyanda *et al*[37] investigated the predisposition to BKV infection by plasma PCR analysis in 173 KT, 11 kidney-heart, 5 kidney-liver, 3 kidney-pancreas, 1 kidney-heart-liver, 24 heart and 37 LT patients between 3 and 18 mo after transplantation. Among KT, immunosuppressive therapy included induction with interleukin-2 receptor blockers or Thymoglobulin and maintenance with TAC or cyclosporine, MMF and prednisone. Antiviral CMV prophylaxis was based on ganciclovir or valganciclovir for donor-positive/recipient-negative patients and acyclovir for others. Among HT, induction therapy was based on Thymoglobulin or OKT3 while maintenance therapies included cyclosporine or TAC, MMF and prednisone. Among LT, induction therapy was not often used while maintenance therapy was based on TAC and prednisone. Four percent of KT, 9.1% of kidney-heart, 20% of kidney-liver and 2.7% of LT patients showed BKV viremia. Nine out of 10 (90%) recipients who were BKV positive on plasma were on MMF compared to 166/244 (65%) recipients who were BKV plasma negative. No significant differences were found between cyclosporine or TAC-based immunosuppression regimens among patients with or without BKV viremia.

In the single-centre, prospective longitudinal study by Doucette *et al*[49], BKV infection and its association with renal dysfunction were analysed in 60 patients (7 HT, 25 LT, 28 lung transplant recipients). They evaluated BKV on urine by quantitative PCR while plasma was analysed only if urine was positive. Patients with (n = 9) and without (n = 51) BK viruria were not significantly different in their baseline characteristics. Immunosuppressive therapy was also similar in the two groups with about half of the patients receiving TAC. In BKV viruric patients baseline glomerular filtration rate (GFR) was not significantly less than in patients without viruria. In both groups, baseline renal dysfunction was mainly related to hepatorenal syndrome, diuretic therapy and low cardiac output, altogether conditions which could potential improve after transplantation. Five out of 9 patients with BKV viruria had only one episode of documented viruria; 1/9 and 3/9 had BK viruria in two and three occasions, respectively. The trend of GFR was similar in those with and without BKV viruria from baseline to 9 mo after transplantation. BKV viruria was found in 15% (9/60) of recipients. No patient had BKV viremia and no association was found between BKV viruria and renal function.

Salama *et al*[55] performed a cross-sectional prevalence study in 41 unselected LT patient looking at BKV viruria/viremia prevalence and its association with renal function. Immunosuppressive therapy was based on cyclosporine, azathioprine, and prednisolone. Tacrolimus and MMF were started when more effective immunosuppressive therapy was required and CNI were decreased in recipients affected by CKD. None patients had antibody induction as standard therapy. Blood and urine specimens were collected from all recipients for BKV viremia, viruria or decoy cells recognition. Authors found 24.3% of BKV viruria positive patients without any significant difference in terms of time after transplantation, renal dysfunction and immunosuppressive therapy when compared to BKV viruria negative recipients. Decoy cells were detected in 4/41 recipients even if none of these resulted positive for BKV viruria by PCR. Furthermore, no measurable BKV viremia was found in LT patients. A condition of moderate CKD was diagnosed in 83%, whereas severe CKD was diagnosed in 7% of patients. The GFR decline in recipients with BKV viruria was not different from those without viruria. No association was found between CNI therapy and CKD, though CNI was associated with a quicker reduction in GFR after one year post-transplantation. In the multivariate analysis, pre-transplant renal function, time after transplantation, gender, hepatitis status, CNI therapy and blood levels, and BKV viruria did not interact with the annual GFR modification.

In a prospective longitudinal study, Loeches *et al*[56] described the incidence of BKV infection and its association with renal dysfunction in 62 LT patients. They analysed urine and plasma samples for BKV by qualitative and quantitative PCR. Quantitative analysis showed BKV viremia in 11 (18%) and viruria in 13 (21%) patients. The median BK viral load was 2.01×10^5 copies/mL in plasma and 7.58×10^6 in urine. The authors did not report any significant association with age, gender, race and immunosuppressive therapy between BKV-negative recipients, viruric and viremic patients. Immunosuppressive therapy consisted of TAC, MMF and corticosteroids. No differences in the rates of diabetes and HCV infection were found. Notably, a significant more frequent BKV viremia was showed in patients who experienced a rejection episode (10.6% *vs* 40%). The authors found no differences in renal function when BKV infection was present. In particular, 19 patients (30.6%) had renal dysfunction at some time during the follow-up. Viremia was found in the first month after transplant in 7 patients, in the third month in 3 and on day 270 in one recipient. No BKV viremia was identified after 1 year post-transplant.

Our group[34] first performed a study on the evaluation of BKV replication on plasma and urine samples, using quantitative PCR, in 20 patients with end stage liver disease (ESLD) and listed for LT. The assumption was that ESLD patients are

Table 1 Summary of studies evaluating the prevalence of BK virus infection among liver transplant recipients *n* (%)

Ref.	Organ	*n*	Study Design	Viruria	Viremia
Splendiani *et al*[50]	Liver	37	Single-centre	5 (13.5)	1 (2.7)
	Kidney	81	prospective	11 (13.6)	7 (8.6)
		Total 118	analysis		
Muñoz *et al*[51]	Liver	64	Prospective	5 (7.8)	0 (0)
	Kidney	49	prevalence	13 (26.5)	6 (12.2)
	Heart	43	study	11 (25.6)	3 (7.0)
		Total 156			
Randhawa *et al*[52]	Liver	44	Cross-sectional	7 (15.9)	0 (0)
	Kidney	103	study	36 (34.9)	8 (7.7)
		Total 147			
Razonable *et al*[53]	Liver	121	Longitudinal	No urine	5 (4.1)
	Kidney	92	surveillance	analysis	24 (26.1)
	Heart	45	study		3 (6.7)
	Kidney-pancreas	5			0 (0)
		Total 263			
Barton *et al*[54]	Liver	8	Prospective,	0 (0)	0 (0)
	Heart	2	single-centre,	1 (50.0)	0 (0)
	Lung	23	cross-sectional study	4 (17.4)	0 (0)
	Heart-lung	1		0 (0)	0 (0)
		Total 34			
Puliyanda *et al*[37]	Liver	37	Single centre,	No urine	1 (2.7)
	Kidney	173	prospective	analysis	7 (4.0)
	Kidney-liver	5	study		1 (20.0)
	Heart	24			0 (0)
	Kidney-heart	11			1 (9.1)
	Kidney-pancreas	3			0 (0)
	Kidney-heart-liver	1			0 (0)
		Total 254			
Doucette *et al*[49]	Liver	25	Single centre,	3 (12)	0 (0)
	Heart	7	prospective	1 (14.3)	0 (0)
	Lung	28	longitudinal	5 (17.8)	0 (0)
		Total 60	study		
Salama *et al*[55]	Liver	41	Cross-sectional point	10 (24.4)	0 (0)
		Total 41	prevalence study		
Loeches *et al*[56]	Liver	62	Prospective	13 (21.0)	11 (18.0)
		Total 62	longitudinal study		
Mitterhofer *et al*[34]	Liver	20	Single-centre	1 (5.0)	1 (5.0)
		Total 20	prospective study		
Mitterhofer *et al*[57]	Liver plus	9	Single-centre	1 (11.1)	5 (55.5)
	CKD	22	prospective	5 (23.0)	3 (13.6)
	Liver no CKD	Total 31	study		

CKD: Chronic kidney disease.

immunocompromised and immunosuppression is a known cause of BKV reactivation. Of 20 patients one (5%) had both viremia and viruria. A second study[57] looked at the prevalence of BKV among 31 LT patients with CKD in order to assess the possible role of renal dysfunction as risk factor for BKV infection in patients with ESLD. We recognized 2 groups of patients on the basis of the presence of CKD: No CKD group (22; 71%) and CKD group (9; 29%). We did not show significant differences in the baseline characteristics of the 2 groups. The prevalence of BKV viremia and viruria was 14% (3/22) and 23% (5/22) respectively in patients without CKD whereas it was 56% (5/9) and 12.5% (1/8) respectively in recipients with CKD.

A summary of all these studies evaluating the prevalence of BKV infection among liver transplant recipients is reported in Table 1.

CONCLUSION

We identified a total of 11 relevant studies in the literature that specifically evaluated the prevalence of BKV infection among adult LT recipients. Overall these studies included 490 liver, 498 kidney, 121 heart, 51 lung, 11 kidney-heart, 8 kidney-pancreas, 5 kidney-liver, 1 heart-lung and 1 kidney-heart-liver transplant recipients. Our review suggests that the prevalence of BKV viruria and/or viremia among LT patients is less than that reported in KT or HT recipients, except when CKD is present at the same time. Data also suggest that viruric and viremic patients have higher levels of sCr than BKV-negative patients. Moreover, though KT recipients are usually exposed to higher levels of immunosuppression, the anti-rejection drugs used are similar to those prescribed in liver or heart

transplantation and no specific immunosuppressive drugs are associated with the onset of PVAN.

The higher prevalence of BKV infection among KT recipients could have other explanations. Chronic kidney disease seems to represent a risk factor for BKV replication. Immunosuppression is recognised as the major cause of BKV replication and patients affected by CKD are considered immunocompromised[57]. The immune system controlling BKV infection requires the production and the activation of specific antibody, antigen-presenting cells (APC), and cytotoxic T-cells[58]. Patients who develop CKD have disorders of acquired immunity related mainly to the function of T-lymphocytes and APC. As a result, patients may be susceptible to viral infections and show deficient responses to vaccinations. Furthermore, KT patients have disturbances of viral-specific immunity, as revealed by functional deterioration of dendritic and cytotoxic T-cells. These alterations may clarify the higher prevalence of PVAN identified in this population[57]. On the contrary, liver immunodysfunction is characterised by impairment of the antibacterial rather than antiviral immunity, with amplified apoptosis, activation of T-cells and monocytes, and macrophagic dysfunction responsible for microorganism's opsonisation and elimination[57]. In support of this different immunological mechanism no case of PVAN is reported among liver transplant patients. Nevertheless, CKD in LT could be a risk factor for BKV infection in this particular population. In fact Mitterhofer *et al*[57] showed a significant higher prevalence of BKV infection in plasma of ESLD patients with CKD prior to LT, whereas in LT recipients without CKD the prevalence was similar to normal subjects. Therefore, renal dysfunction in LT may be an additional factor causing immunologic dysfunction that could make patients more susceptible to infections. Thus, the transplant-associated comorbidity and CKD could promote BKV replication in plasma. This could represent an attractive explanation regarding the mechanisms involved in the different behaviour of BKV infection in LT recipients. Further studies will be needed to better identify the risk factors for BKV replication in NRSOT.

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P- Reviewer: Gassler N **S- Editor**: Ma YJ **L- Editor**: A
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