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Different Risk Factor Profiles Distinguish Early-onset from Late-onset BKV-Replications

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INTRODUCTION

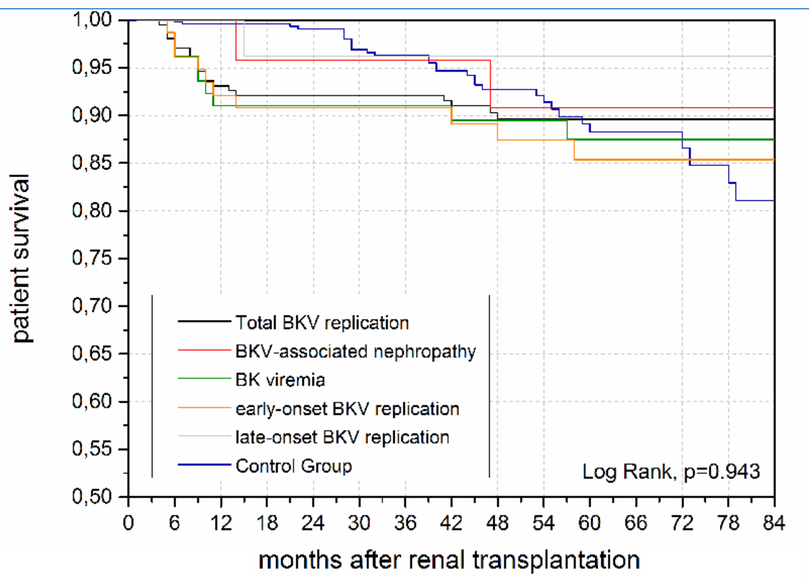
BKV-associated nephropathy (BKVN) remains one of the most challenging infectious complications after renal transplantation. BKV is known to persist in tubular epithelial cells of kidney, ureter, and bladder with intermittent reactivation and low-level viruria in up to 50% of KTRs. Reactivation of BKV from the persistent subclinical state is monitored using quantitative urine and plasma PCR. Progression to BKVN occurs in 1 to 10% of KTRs with varying degrees of allograft dysfunction and increasing serum creatinine concentrations over weeks. The gold standard for the diagnosis of BKVN is a tissue biopsy of the allograft kidney, not only to identify BKVN, but also drug toxicity, recurrence of the underlying disease and acute cellular rejection. Since both BKV-replication and concomitant cellular rejection may contribute to allograft damage, the approach to interstitial inflammation by anti-rejection treatment during and after BKV-replication needs to be discussed on an individual basis. Potent immunosuppressive drug regimens containing tacrolimus and/or MMF have been suggested to stimulate BKV-replication. BKVN, however, has been reported to occur in a large variety of immunosuppression protocols suggesting that the intensity of the immunosuppression is the key risk factor.

PATIENTS AND METHODS

We followed up 701 kidney transplant recipients with regards to BK viremia. Despite a rising number of studies addressing risk factors of BK viremia and BKVN, a clear differentiation between KTRs developing early-onset BK viremia (<6 months after renal transplantation) and KTRs developing late-onset BK viremia (>6 months after renal transplantation) has not been performed. Therefore we attempted to address following open questions: (1) Are there differences in risk factors between early-onset and late-onset BK viremia? (2) Are there differences in outcome between early-onset and late-onset BK viremia? (3) Are there differences in severity and viral kinetics between early-onset and late-onset BK viremia?

	BKV Group (n=103)	Early-onset BKV (n=67)	Late-onset BKV (n=36)	*P Value*
Age, yr	54 (18-76)	52 (18-76)	55 (24-76)	*0.950*
Male sex, n (%)	71 (69)	47 (70)	24 (67)	*0.824*
Cadaveric donation, n (%)	76 (74)	47 (70)	29 (81)	*0.348*
First kidney allograft, n (%)	85 (83)	62 (93)	23 (64)	*<0.001**
Cold ischemia time, hr:min	11:09 (4:00-29:10)	10:22 (4:00-29:10)	11:45 (6:55-22:43)	*0.756*
Time on dialysis, mo	59 (0-164)	56 (0-158)	64 (0-164)	*0.203*
CMV viremia, n (%)	57 (55)	36 (54)	16 (58)	*0.412*
Concomitant CMV viremia, n (%)	31 (30)	28 (42)	3 (8)	*<0.001**
BK nephropathy, n (%)	24 (23)	16 (24)	8 (22)	*1*
EBV viremia, n (%)	18 (17)	12 (18)	6 (17)	*1*
Delayed Graf Function, n (%)	28 (27)	19 (28)	9 (25)	*0.818*
Immunosuppression, n (%)				
Cyclosporine	21 (20)	16 (24)	5 (14)	*0.308*
Tacrolimus	82 (80)	51 (76)	31 (86)	*0.308*
Mycophenolate mofetil	95 (92)	63 (94)	32 (89)	*0.446*
Steroids	98 (95)	65 (97)	33 (92)	*0.340*
Induction with IL-2R antagonist, n (%)	83 (81)	52 (78)	31 (86)	*0.434*
Lymphocyte-depleting induction, n (%)	20 (19)	15 (22)	5 (14)	
Acute rejection, n (%)	59 (57)	39 (58)	20 (56)	*0.837*
Borderline/IA/IB	46 (45)	31 (46)	15 (42)	*0.679*
IIA/IIB/III	13 (13)	8 (12)	5 (14)	*0.765*
Concomitant acute rejection, n (%)	36 (35)	32 (48)	4 (11)	*<0.001**
Total HLA mismatch, n (%)				
4-6 HLA mismatch	42 (41)	33 (49)	9 (25)	*0.021**
PRA, n (%)				
>10%	8 (8)	2 (3)	6 (17)	*0.021**
Donor age, yr	53 (13-85)	53 (13-85)	48 (19-78)	*0.187*

RESULTS



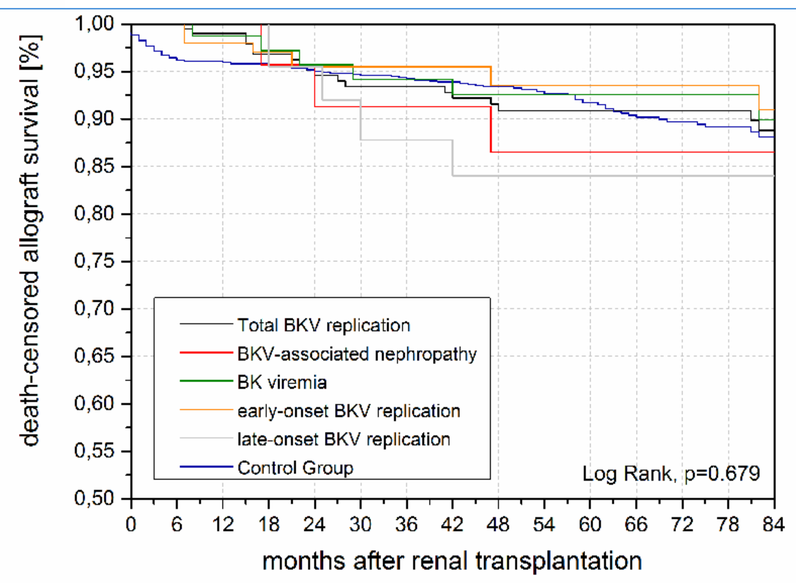


Figure 1AB: 1A Kaplan-Meier plot of patient survival by BKV-replication after renal transplantation. No differences were observed between KTRs with BKVN, KTRs with BK viremia only, early-onset, late-onset BKV-replication, and the control group (Log Rank, p=0.943). **1B Kaplan-Meier plot of death-censored graft survival by BKV-replication after renal transplantation.** No differences were observed between KTRs with BKVN, KTRs with BK viremia only, early-onset, late-onset BKV-replication, and the control group (Log Rank, p=0.979).

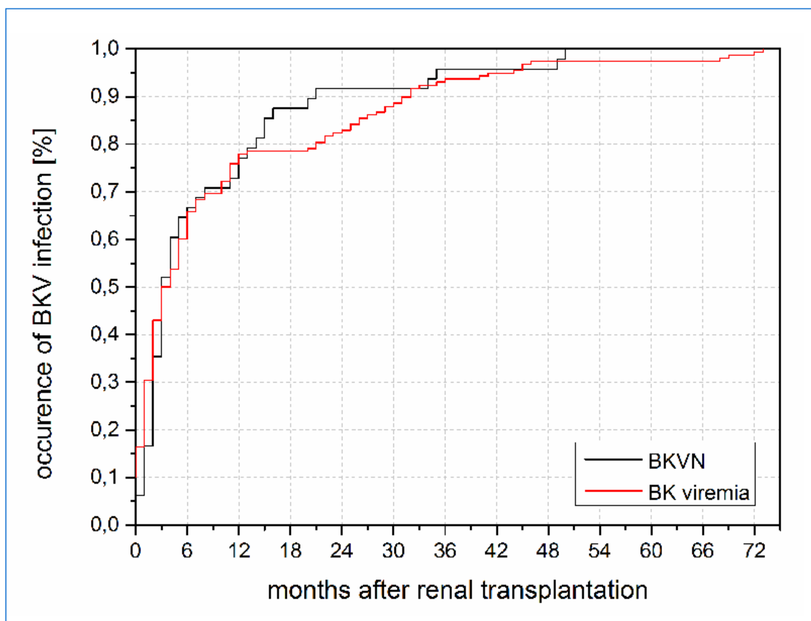
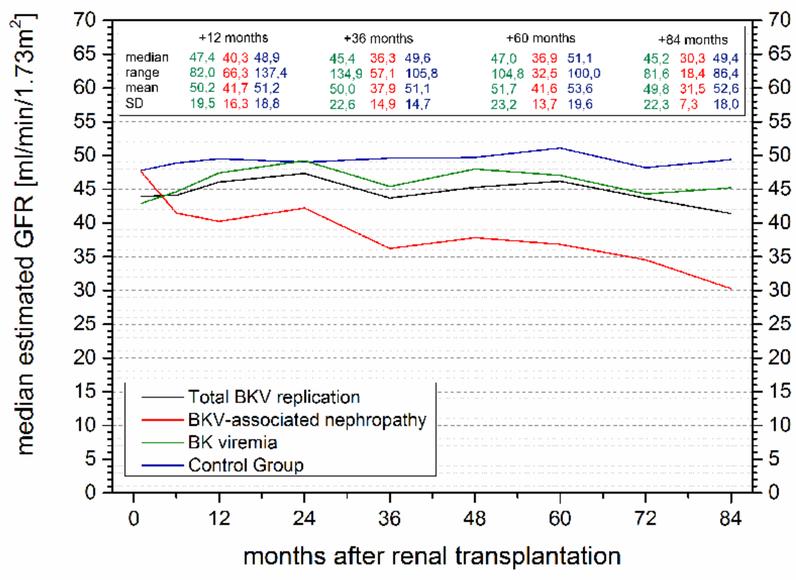


Figure 3: Onset of BK viremia and BKVN after renal transplantation. 65% of KTRs showed early-onset BK viremia within the first 6 months posttransplantation.



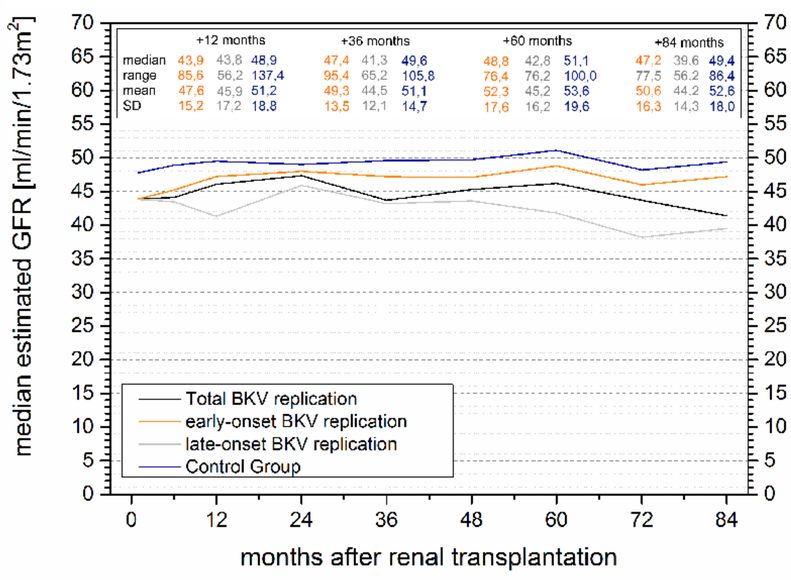


Figure 2AB: 2A Decreased median eGFR in patients with BKVN (p<0.05). KTRs developing BKV-replication showed significantly worse renal function compared to the control group starting at +72 months posttransplantation (p=0.015). KTRs with BKVN showed significantly worse renal function compared to KTRs with BK viremia only starting at +60 months (p<0.05). **2B Decreased median eGFR in patients with late-onset BKV-replication (p<0.05).** KTRs developing late-onset BKV-replication showed significantly worse renal function compared to the control group starting at +48 months posttransplantation (p=0.015). KTRs with late-onset BKV-replication showed significantly worse renal function compared to KTRs with early-onset BKV-replication starting at +12 months (p<0.05).

CONCLUSIONS

1. Our results suggest concomitant CMV-reactivation and acute cellular rejection as risk factors for early-onset BKV-replication. These observations support previous works suggesting, that the intensity of immunosuppression is the key issue in the pathogenesis of BKV-replication in the early period. Here, previous studies suggest an association between lymphocyte-depleting induction and higher incidences of early-onset BKV-replication. However, our data didn't show a difference for lymphocyte-depleting induction between KTRs with early-onset and late-onset BKV-replication and therefore question this association. This finding suggests that other factors than lymphocyte-depleting induction may contribute to the increased risk of BK viremia in presensitized KTRs. These factors may include presensitization due to retransplantation with an increased risk of acute cellular rejection, PRA, and higher CNI trough levels.
2. Our data show, that KTRs developing late-onset BKV-replication are more likely to undergo renal retransplantation with the presence of preformed PRA. Since BKV-replication appears to be a complication affecting almost exclusively recipients of renal transplantation, the intensity of immunosuppression itself cannot be responsible alone. Therefore, inflammation within the graft as a result of previous episodes of acute rejections predisposing to allosensitization and a chronic inflammatory state in the presence of DSA can be considered as important risk factors.
3. Our data show no differences in patient survival and allograft survival between KTRs developing BKV-replication, BKVN, and the control group. Interestingly, however, KTRs with BK viremia showed impaired allograft function in long-term follow-up. This finding may be at least in part explained by cases of undiagnosed BKVN in the cohort of KTRs with BK viremia. In addition, this observation may be related to the very recently suggested association of BKV-replication with allosensitization in terms of development of de novo donor-specific antibodies. This hypothesis is further strengthened by our observations, that KTRs with late-onset BKV-replication show inferior allograft function compared to KTRs with early-onset BKV-replication.

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