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The early increase of urinary exosomal BK virus microRNA as a predictive marker for BK virus nephropathy: a prospective kidney transplantation cohort

WON HEE CHO[1], SU WOONG JUNG[1], JUNG WOO SEO[1], KYUNG HWAN JEONG[2], JIN SUG KIM[2], CHAN DUCK KIM[3], BYUNG HA CHUNG[4], JAE BERM PARK[5], YEONG HOON KIM[6], SANG HO LEE[1]
[1]Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, Kyung Hee University Medical Center, Korea, Republic of
[3]Department of Internal Medicine-Nephrology, Kyungpook National University Hospital, Korea, Republic of
[4]Department of Internal Medicine-Nephrology, The Catholic University of Korea, Seoul St. Mary's Hospital, Korea, Republic of
[5]Department of Surgery-Transplantation, Samsung Medical Center, Korea, Republic of
[6]Department of Internal Medicine-Nephrology, Inje University Busan Paik Hospital, Korea, Republic of

Objectives: BK virus-encoded microRNAs are present in urinary exosomes obtained from patients with BK virus nephropathy (BKVN). Previously, urinary exosomal bkv-miR-B1-5p was found to be significantly associated with BKVN in a cross-sectional study. However, its posttransplant time-dependent changes and its predictive value for BKVN have not been investigated in a prospective study.

Methods: In a prospective multicenter cohort of 422 kidney transplant recipients, urinary exosomal bkv-miR-B1-5p were examined at 0.5, 3, 6, and 12 months after kidney transplantation. All enrolled patients were reviewed to identify the patients diagnosed with BKVN histologically (definitive BKVN) and those with presumptive BKVN (plasma BK virus DNA load > 4 $\log_{10}$ copies/ml). The patients without biopsy-proven and presumptive BKVN were designated as No BKVN. Urinary exosomal miR was quantified using real-time PCR.

Results: The median time (interquartile range) to biopsy-proven BKVN was 3.9 (2.8-5.4) months. In patients with biopsy-proven and presumptive BKVN, urinary exosomal bkv-miR-B1-5p level and plasma BKV DNA load showed a similar time-dependent change as shown by being highest at 3 months posttransplant and thereafter decreasing. However, at 2 weeks posttransplant, the urinary exosomal bkv-miR-B1-5p level in patients with biopsy-proven BKVN was significantly higher than that of No BKVN, whereas plasma BKV DNA load was nearly undetectable in both groups. This finding indicates that an increase in urinary exosomal bkv-miR-B1-5p level is an earlier event to BKVN than BK viremia. In cox regression, urinary exosomal bkv-miR-B1-5p levels at 2 weeks and 3 months posttransplant independently predicted subsequent BKVN development.

Conclusions: The high level of urinary exosomal bkv-miR-B1-5p during the early period of kidney transplantation may be served as a predictive marker for BKVN, enabling early intervention.

Figure 2. Time course of urine exosomal bkv-miR-B1-5p and plasma BK virus DNA load after kidney transplantation

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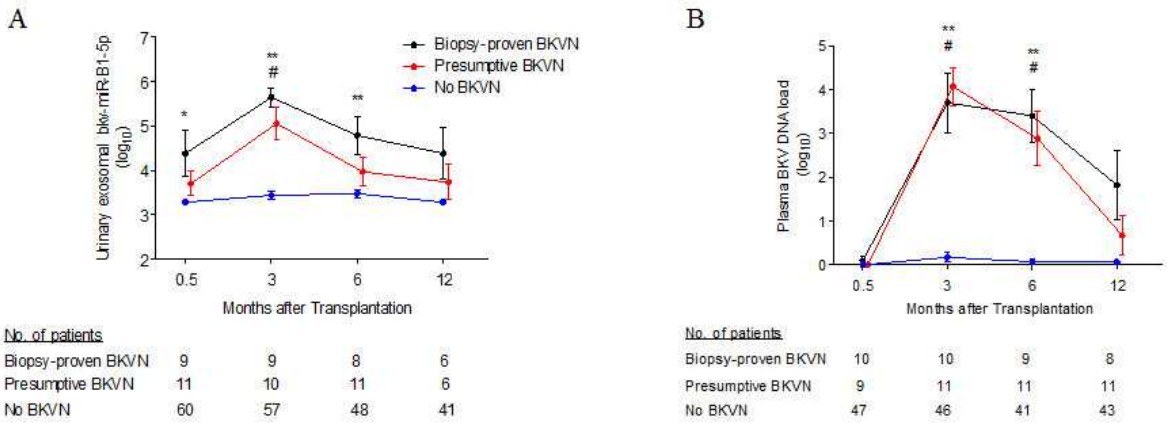

No. of patients				
Biopsy-proven BKVN	9	9	8	6
Presumptive BKVN	11	10	11	6
No BKVN	60	57	48	41

No. of patients				
Biopsy-proven BKVN	10	10	9	8
Presumptive BKVN	9	11	11	11
No BKVN	47	46	41	43

*P<0.01 biopsy-proven BKVN versus No BKVN.

**P<0.001 biopsy-proven BKVN versus No BKVN.

#P<0.01 presumptive BKVN versus No BKVN.

Kruskal-Wallis test with bonferroni correction

Kruskal-Wallis test with bonferroni correction

Cox proportional hazards models for development of biopsy-proven BKVN

Table 2. Cox proportional hazards models for development of biopsy-proven BKVN

A. urine exosomal bkv-miR-B1-5p at 2 weeks

Model	continuous variable			categorical variable (>5.1)		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Unadjusted	2.3	1.5 to 3.6	<0.001	10.7	2.2 to 52.5	0.004
Model 1	2.8	1.5 to 5.3	0.002	20.4	2.1 to 194.5	0.009
Model 2	2.8	1.3 to 6.0	0.008	17.2	1.4 to 207.1	0.03

B. urine exosomal bkv-miR-B1-5p at 3 months

Model	continuous variable			categorical variable (>5.5)		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Unadjusted	4.2	1.9 to 9.7	<0.001	10.5	2.3 to 47.7	0.002
Model 1	4.4	1.8 to 10.5	<0.001	10.5	2.2 to 50.4	0.003
Model 2	9.3	1.4 to 59.3	0.02	13.9	2.1 to 89.8	0.006

Model 1: adjusted for recipient's factors including age, gender, body mass index, diabetes, and the use of ATG (versus basiliximab).

Model 2: adjusted for recipient's factors in model 1 plus donor age and type of donor (deceased or living donor).