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Multicenter, prospective observational study to identify and validate a composite of urinary exosomal biomarkers for kidney allograft tubulointerstitial fibrosis

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Introduction: The severity of kidney allograft fibrosis is one of the most important factors affecting long-term graft survival after deceased-donor kidney transplantation. In this study, we tried to identify and validate urinary exosomal miRNA biomarkers which may reflect the grade of interstitial fibrosis and tubular atrophy (IFTA).

Methods: We collected urine samples from 109 deceased donors at the time of solid organs recovery from May 2019 to June 2021, and a zero-day biopsy was performed before transplantation at five medical centers in Korea. Among 109 specimens, 34 showed no IFTA on zero-day biopsy (No IFTA group) and the other 75 allografts showed IFTA score 1 or more than 1 on zero-day biopsy (IFTA group). Urinary exosomes were isolated by ultracentrifugation and the levels of miRNAs were quantified by qRT-PCR.

Results: After reviewing previous reports and electronic databases, a total of six miRNAs (miR-19, miR-21, miR-29c, miR-150, miR-200b, and miR-205) were chosen as potential biomarker candidates for IFTA. miR-16-5p was used as an endogenous control. Among the six candidates, relative expression levels of miR-21, miR-29c, miR-150, and miR-205 were significantly higher in the IFTA group whereas miR-19 expression level was significantly lower in the IFTA group compared with the No IFTA group. ROC analysis of miR-21 (AUC, 0.762; 95% CI, 0.6580.846; $p<0.001$) and miR-29c (AUC, 0.825; 95% CI, 0.7270.898; $p<0.001$) showed good diagnostic accuracy for predicting IFTA. Although there were no differences in patient survival, graft survival, and rejection between two groups, the eGFR level of No IFTA group at 1week post-transplant was higher than IFTA group (41.34 vs. 28.65, p-value=0.012) and the improvement patterns of eGFR over time showed significant difference (Time*Group p-value=0.031).

Conclusion: In conclusion, urinary exosomal miRNAs are potent biomarker candidates to determine the IFTA severity of kidney allograft before recovery.