Editorial

KIDNEY RESEARCH AND **CLINICAL PRACTICE**

Using the Mayo Imaging Classification to predict renal outcomes in Korean autosomal dominant polycystic kidney disease patients

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cystic kidney disease, characterized by the development of renal cysts and a variety of extrarenal manifestations [1]. It was a disease that was accepted as a fate even if dialysis treatment was started at a relatively young age. Currently, the treatment goal of ADPKD is not to accept it as a fate, but to delay the time of kidney failure as much as possible through active renal protection.

In 2006, CRISP (Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease) investigators reported that kidney function decreased as the volume of the kidney increased [2]. Based on evidence that vasopressin antagonists could inhibit the progression of kidney volume, tolvaptan has been tested in clinical trials in ADPKD. In the TEMPO (Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes) 3:4 trial, tolvaptan decreased kidney growth by about 49% and slowed the rate of decline in kidney function by about 1.2 mL/min per year [3]. In 2017, the U.S. Food and Drug Administration

(FDA) approved the total kidney volume (TKV) as a biomarker of disease progression in ADPKD. In 2018, the U.S. FDA approved tolvaptan as the first drug treatment to slow kidney function decline in adult ADPKD patients who are at risk of rapidly progressive disease.

With the development of disease-modifying drugs for ADPKD, rapid and reliable tools are needed to identify patients who will benefit from an effective therapy. Irazabal et al. [4] have developed a predictive tool that uses the age-adjusted TKV as represented by the Mayo Imaging Classification (MIC). The MIC allows clinicians to estimate each patient's unique rate of kidney growth and also to identify patients with rapidly progressive disease who are likely to benefit from effective therapy [4]. In clinical practice, nephrologists can estimate the TKV growth rate and prognosis of patients by using only one TKV measurement and age. It is commonly used in stratifying and finding rapid progressors with ADPKD in Korean clinics. However, two questions have been raised in the clinical application of MIC findings in Korean ADPKD patients. One is whether the MIC, whose cohort consists mostly of Caucasians, is applicable to Koreans. The second question is whether it is better to apply the Higashihara equation which has

shown stable results of the height-adjusted TKV (HtTKV) – estimated annual growth rate (% per year, termed eHTKV-α), is calculated by the equation [HtTKV at age t] = K (1 + α/100)$^{(t–A)}$ over years, instead of the original MIC.

In this issue of *Kidney Research and Clinical Practice*, Park et al. [5] validated the MIC for predicting the renal outcome among a Korean ADPKD prospective cohort and evaluated the clinical parameters associated with rapid disease progression. A comparison of Irazabal's original equation from the MIC (A = 0 and K = 150) and a modified equation from the Higashihara group (A = 0 and K = 130) [6] showed that while the Higashihara equation showed more stable prediction ability over the years, the change in the MIC at an individual level did not differ between the original and modified equations. However, the Higashihara MIC tended to overestimate MIC subclasses compared to the original MIC in this study. Therefore, people classified as slow progressors by the original MIC might actually now be considered rapid progressors. Moreover, the Higashihara equation did not predict the renal outcome according to the MIC. Being a rapid progressor as defined by the original MIC equation was an independent predictor of the renal outcome (doubling of serum creatinine, 50% decline of estimated glomerular filtration rate (eGFR), initiation of renal replacement therapy, hazard ratio of 4.086) together with the presence of macroalbuminuria and the baseline eGFR. Rapid progressors as defined by the original MIC also demonstrated a greater annual percent change of HtTKVs (mHTKV-α) and a greater annual decline rate of the eGFR (mGFR-α) compared to slow progressors. If the eHTKV-α is stable in untreated patients, then any change in the eHTKV-α from baseline can be used to estimate individual treatment effects on the HtTKV. The Higashihara equation, which shows a more stable eHTKV-α, might be useful for estimating treatment effects. However, it could not be used for predicting renal outcomes or the mHTKV-α of Korean ADPKD patients in this study.

Another characteristic of Korean ADPKD patients in this study was their faster enlargement of the mHTKV-α with a similar mGFR-α according to MIC classes compared with previous studies of the TEMPO 3:4 and HALT-PKD groups [3,7]. The mGFR-α was in rapid progressors (–3.58 mL/min per year in 1C, –3.7 in 1D, and –4.52 in 1E), and the mHTKV-α was in rapid progressors (5.3% per year in 1C, 9.4% in 1D, and 11.7% in 1E). Another study showed that the average age at which Koreans reach kidney failure is seven years later than that of a Caucasian population [8]. These differences are highly likely to be related to ethnicity or a genetic predisposition. There is a need to study whether
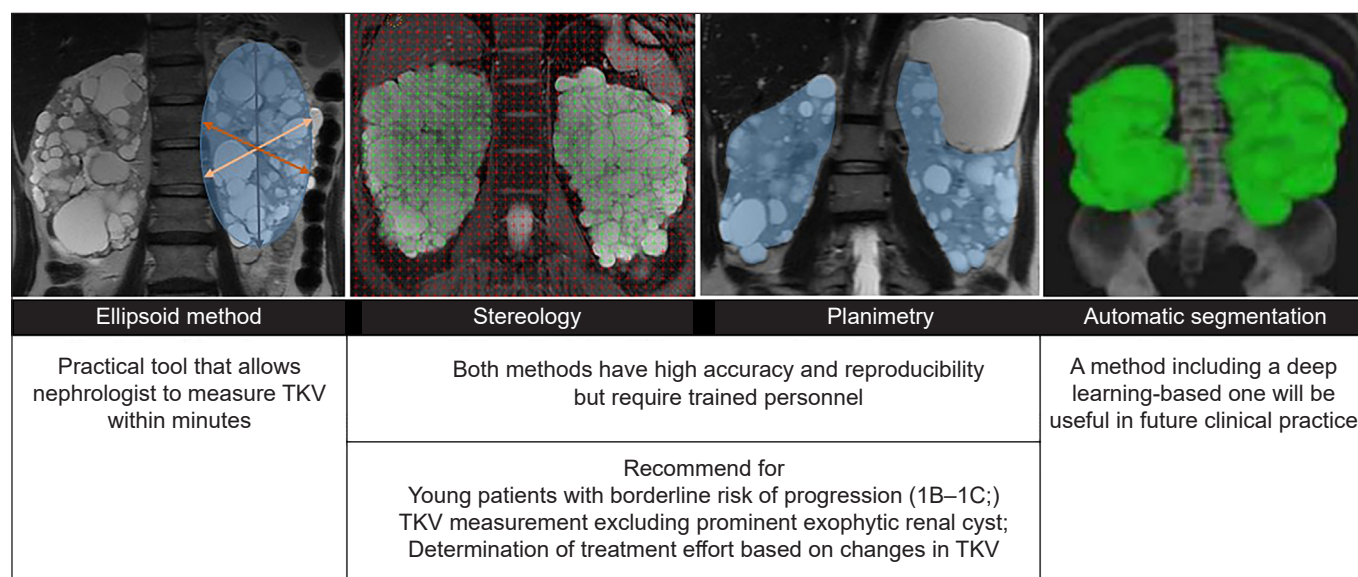

Ellipsoid method	Stereology	Planimetry	Automatic segmentation
Practical tool that allows nephrologist to measure TKV within minutes	Both methods have high accuracy and reproducibility but require trained personnel		A method including a deep learning-based one will be useful in future clinical practice
	Recommend for Young patients with borderline risk of progression (1B–1C;) TKV measurement excluding prominent exophytic renal cyst; Determination of treatment effort based on changes in TKV		

Figure 1. Imaging techniques for measuring kidney volume to predict autosomal dominant polycystic kidney disease progression.
TKV, total kidney volume.

there are differences in the clinical course or prognosis and treatment response using a large number of patients with varying ethnicities.

This study showed that MIC classes could change over time in some individuals. In particular, patients whose MIC classes changed overtime were younger than those whose MIC classes were stable. Younger age is also important because it is a risk factor that is associated with rapid progression, along with male sex, high blood pressure, higher body mass index, higher serum uric acid, and lower eGFR. Although this study confirmed a strong correlation of TKV by ellipsoid with TKV by stereology, more accurate methods (such as stereology and planimetry) are needed to measure the TKV in younger patients with borderline 1B/1C classification because even a small miscalculation in the TKV might change the MIC subclass, such as between class 1B and 1C [9]. An expanded imaging classification can recalculate the TKVs by excluding prominent exophytic cysts in both class 2Ae and class 1 patients with prominent exophytic cysts, leading to improved predictions for developing chronic kidney disease (CKD) stage 3 and eGFR trajectories [10]. Volumetry using stereology and planimetry is useful for excluding prominent exophytic cysts. It is also useful for determining treatment effects based on changes in the TKV (Fig. 1).

This study showed that MIC classes could change overtime in some individuals. Especially, patients whose MIC classes changed overtime were younger than those whose MIC classes were stationary. Younger age is also important because it is a risk factor along with male sex, high blood pressure, higher body mass index, higher serum uric acid, and lower eGFR associated with rapid progressors. Although this study confirmed the strong correlation of TKV by ellipsoid with TKV by stereology, more accurate methods such as stereology and planimetry are needed to measure TKV for younger patients with borderline class 1B/1C because even small miscalculation of TKV might change the subclass of MIC such as class 1B and 1C [9]. An expanded imaging classification can recalculate TKVs by excluding prominent exophytic cysts in both class 2Ae and class 1 patients with prominent exophytic cysts, leading to improved predictions for developing CKD stage 3 and eGFR trajectories [10]. Volumetry using stereology and planimetry is useful for excluding prominent exophytic cysts. It is also useful for determining treatment effects based on changes in TKV (Fig. 1).

In summary, the original MIC can be useful for predicting renal outcomes and effectively defining rapid progressors among Korean ADPKD patients. A nephrologist can easily measure the TKV using the ellipsoid method to determine kidney volume, and the results can be applied to the MIC. More accurate volumetry (such as stereology and planimetry) should also be considered in younger patients, who are at higher risk for rapid progression.

Conflicts of interest

The author has no conflicts of interest to declare.

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