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Fung, W.W.-S., Szeto, C.-C., Chow, K.-M. et al. (2026) The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease.

Kidney360. ISSN: 2641-7650

<https://doi.org/10.34067/kid.0000001126>

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Kidney360

The Relationship of Osmolality and Kidney Outcomes in Patients with Autosomal Dominant Polycystic Kidney Disease --Manuscript Draft--

Manuscript Number:	K360-2025-001216R1
Full Title:	The Relationship of Osmolality and Kidney Outcomes in Patients with Autosomal Dominant Polycystic Kidney Disease
Short Title:	Osmolality and Kidney Outcomes of ADPKD Patients
Article Type:	Original Research
Section/Category:	Cystic Kidney Disease
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Manuscript Classifications:	15: ADPKD; 317: Osmolality; 319: Outcomes; 338: Polycystic Kidney Disease
Abstract:	<p>Background. Current treatment of autosomal dominant polycystic kidney disease (ADPKD) is mainly focused on inhibiting cystogenesis through arginine vasopressin suppression and there have been interests in achieving similar vasopressin suppression by reduction of osmolality with increased water intake. However, the causal relationship between serum osmolality and kidney outcome remained unclear in ADPKD patients. We aim to evaluate the relationship of serum osmolality and its effect on kidney outcome in ADPKD patients.</p> <p>Methods. Three hundred and eleven tolvaptan treatment-naïve ADPKD patients were recruited prospectively from the CysticHK cohort, a territory-wide ADPKD registry across twelve tertiary hospitals in Hong Kong. Beside clinical data, serial measurement of serum and urinary osmolality were obtained every six months over five years. All participants were treated according to the standard of clinical care. The primary outcome was the 40% decline from baseline eGFR.</p> <p>Results. Patients with a high serum osmolality have a worse kidney outcome, as shown by the Kaplan-Meier plots (log-rank $p < 0.001$) and the Cox regression model that showed a 5.91 times higher risk of reaching 40% eGFR decline compared to the top with bottom quartiles of osmolality ($p = 0.018$). In contrast, there is an inverse relationship for urine osmolality. A ROC analysis to assess the predictive efficacy of osmolality for identifying those at high risk of kidney decline also showed a good performance for serum osmolality (AUC 0.81, 95%CI, 0.73-0.89; $p < 0.001$). The urinary osmolality did not show a clinical meaningful predictive efficacy (AUC 0.35, 95%CI 0.28-0.43; $p = 0.003$).</p> <p>Conclusions. Serum osmolality may be a possible surrogate marker for the clinical monitoring of ADPKD patients, especially when access to copeptin level is limited; and high serum osmolality conveys possible detrimental effect on the kidney outcomes.</p>

Funding Information:	Chinese University of Hong Kong (6905134)	Dr Winston Wing-Shing Fung
	Chinese University of Hong Kong (7101215)	Dr Winston Wing-Shing Fung
	Drs Richard Charles and Esther Yewpick Lee Charitable Foundation	Dr Winston Wing-Shing Fung
	Hong Kong Society of Nephrology (35th Anniversary Research Grant)	Dr Winston Wing-Shing Fung
Additional Information:		
Question	Response	
Is this a Basic Science or Clinical Science topic?	Clinical Research	
Clinical Trial Registration My study was a clinical trial and is registered in one of the registries recommended by the International Committee of Medical Journal Editors (ICMJE) .	N/A because this is not a clinical trial	
Institutional Review Board or Ethics Committee Oversight For all clinical experimentation described in this manuscript, I received approval by an Institutional Review Board or equivalent Ethics Committee and responded regarding patient consent, or I provided the reason for the exemption.	Yes	
Please select a response: as follow-up to "Institutional Review Board or Ethics Committee Oversight For all clinical experimentation described in this manuscript, I received approval by an Institutional Review Board or equivalent Ethics Committee and responded regarding patient consent, or I provided the reason for the exemption."	This study includes clinical experimentation and received Institutional Review Board or Ethics Committee approval. All patients provided written informed consent.	
Declaration of Helsinki For all clinical experimentation described in the manuscript, I adhered to the Declaration of Helsinki and indicated my response below accordingly.	This study includes clinical experimentation and complies with the Declaration of Helsinki.	
Declaration of Istanbul My study is related to clinical organ transplantation, and the clinical and research activities being reported are	N/A	

<p>consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.</p>	
<p>Animal Experimentation</p> <p>Animal experimentation is discussed in this manuscript, and I have adhered to the NIH Guide for the Care and Use of Laboratory Animals or the equivalent.</p>	N/A
<p>Preprint Server</p> <p>Posting of unrefereed manuscripts to a community preprint server by the author will not be considered prior publication provided that the conditions included within the Instructions for Authors are met. Has this paper already been posted on a preprint server such as arXiv or bioRxiv?</p>	This research was not posted on a preprint server.
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<p>Key point #2:</p> <p>as follow-up to "Key Points: Please state the 2-3 key points of the article. The responses included here will be included with your final published paper. The key points should be complete statements and not duplications of your keywords or index terms. At least two key points are required."</p>	Serum osmolality may be a possible surrogate marker for the clinical monitoring of ADPKD patients, especially when access to copeptin level is limited
<p>Key point #3:</p> <p>as follow-up to "Key Points: Please state the 2-3 key points of the article. The</p>	High serum osmolality conveys possible detrimental effect on the kidney outcomes.

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<p>If yes, please provide a list of study group(s) and members that have contributed to or participated in the submitted work in some way. as follow-up to "Study Group:</p> <p>Does your paper include study group(s)? If yes, please provide a list of study group(s) and members that have contributed to or participated in the submitted work in some way. This list may contain either a collaboration of individuals (e.g., investigators) and/or the name of an organization (e.g., a laboratory, educational institution, corporation, or department) and its members"</p>	<p>*Collaborators of the CysticHK cohort: Ho-Kwan SIN, MBChB, FHKAM, Associate Consultant; Elaine HO, MBChB, FHKAM, Consultant; Lorraine Pui-Yuen KWAN, MBBS, FHKAM, Associate Consultant; Sing-Leung LUI, MD, FHKAM, Consultant; Koon-Ming CHAN, MBBS, FHKAM, Associate Consultant; Gary Tung-Sen SHUM, MBBS, FHKAM, Associate Consultant; Samuel Ka-Shun FUNG, MBBS, FHKAM, Consultant; Ka-Lok CHAN, MBBS, FHKAM, Associate Consultant; Sunny WONG, MBBS, FHKAM, Consultant; Anthony Kai-Ching HAU, MBBS, FHKAM, Consultant; Ronald Chi-Chun LIN, MBBS, FHKAM, Associate Consultant; Sze-Kit YUEN, MBChB, FHKAM, Consultant; Lap-Ming KWOK, MBBS, FHKAM, Associate Consultant</p>
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<p>Data Availability (<i>select all that apply</i>)*Additional information: Original data generated for the study will be made available upon reasonable request to the corresponding author: This is not recommended for large datasets but</p>	<p>All original data, including deidentified patient-level data or individual laboratory data measurements, are included in the manuscript and/or supplemental material.</p>

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Kidney360 Publish Ahead of Print

DOI: 10.34067/KID.0000001126

The Relationship of Osmolality and Kidney Outcomes in Patients with Autosomal Dominant Polycystic Kidney Disease

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ABSTRACT

Background. Current treatment of autosomal dominant polycystic kidney disease (ADPKD) is mainly focused on inhibiting cystogenesis through arginine vasopressin suppression and there have been interests in achieving similar vasopressin suppression by reduction of osmolality with increased water intake. However, the causal relationship between serum osmolality and kidney outcome remained unclear in ADPKD patients. We aim to evaluate the relationship of serum osmolality and its effect on kidney outcome in ADPKD patients.

Methods. Three hundred and eleven tolvaptan treatment-naïve ADPKD patients were recruited prospectively from the CysticHK cohort, a territory-wide ADPKD registry across twelve tertiary hospitals in Hong Kong. Beside clinical data, serial measurement of serum and urinary osmolality were obtained every six months over five years. All participants were treated according to the standard of clinical care. The primary outcome was the 40% decline from baseline eGFR.

Results. Patients with a high serum osmolality have a worse kidney outcome, as shown by the Kaplan-Meier plots (log-rank $p < 0.001$) and the Cox regression model that showed a 5.91 times higher risk of reaching 40% eGFR decline compared to the top with bottom quartiles of osmolality ($p = 0.018$). In contrast, there is an inverse relationship for urine osmolality. A ROC analysis to assess the predictive efficacy of osmolality for identifying those at high risk of kidney decline also showed a good performance for serum osmolality (AUC 0.81, 95%CI, 0.73-0.89; $p < 0.001$). The urinary osmolality did not show a clinical meaningful predictive efficacy (AUC 0.35, 95%CI 0.28-0.43; $p = 0.003$).

Conclusions. Serum osmolality may be a possible surrogate marker for the clinical monitoring of ADPKD patients, especially when access to copeptin level is limited; and high serum osmolality conveys possible detrimental effect on the kidney outcomes.

Supplemental Digital Content: <http://links.lww.com/KN9/B537>

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, accounting for about 10% of prevalent patients with kidney failure [1]. It is characterized by the development of multiple progressively enlarging kidney cysts which eventually replace healthy tissue, leading to kidney failure [2]. There have been considerable advances in the field regarding prognostication and treatment recently. In particular, the advent of effective disease-modifying agents (with tolvaptan as the first approved agent) has transformed the management paradigm of ADPKD and there is now important drive to diagnose the disease early, such that treatment can be started promptly and proactively [3].

Indeed, two major trials have demonstrated the efficacy of the first disease-modifying agent tolvaptan [4,5]. Despite evidence of clear efficacy in delaying disease progression, the uptake of Tolvaptan remains limited in many regions due to significant side effects and prohibitive reasons such as cost [6,7]. There have been interests in achieving similar arginine vasopressin (AVP) suppression through increased water intake, but trials have yet to demonstrate its benefit [8]. One challenge in the study design is to ensure patient's tolerance and compliance to increased water intake, but there are no effective surrogate markers to monitor whether patients have achieved adequate hydration status. Serum copeptin has been proposed as a possible biomarker, but it is largely limited to research

settings [9]. Urinary osmolality (uOSM) has also been shown to be a useful surrogate marker [10], but association of serum osmolality (sOSM) with kidney outcome is unclear [11,12].

In this study, we aim to evaluate the relationship of osmolality and its effect on kidney outcome in patients with ADPKD using the CysticHK cohort, a territory-wide registry of involving 300 Chinese patients with ADPKD across twelve major public hospitals in Hong Kong. By defining the causal relationship of osmolality and kidney outcomes in ADPKD patients, it will help guide management, especially where effective disease-modifying agents such as tolvaptan and serum copeptin testing are limited.

METHODS

This is a multi-centre prospective study ([Supplemental Figure 1](#)). Unrelated adult patients with clinical diagnosis of ADPKD based on imaging [13] and family history were recruited from the CysticHK cohort. This is a territory-wide registry of Chinese patients with ADPKD across twelve major public hospitals in Hong Kong. Patients with an estimated glomerular filtration rate (eGFR) less than 30ml/min/1.73m² (CKD-EPI formula) or already on kidney replacement therapy were excluded. Patients already on tolvaptan are also excluded for this study and these are patients who are either not indicated for tolvaptan following assessment or have declined the medication.

At the initial clinic visit after recruitment, baseline specified clinical data and biochemical parameters were collected. An MRI were also performed after the first visit. The protocol of the MRI acquisition has been adapted from that used by the EuroCYST consortium [14]. Patients were then followed routinely every six months as per our protocol or earlier if clinically indicated (such as rapidly worsening in kidney function). The clinical data and biochemical parameters were collected at each follow-up visit. These include blood tests and eGFR measurement. In particular, morning sOSM and uOSM (as suggested by the current KIDGO guideline for ADPKD [3]) were also routinely measured at each follow-up visit with a time-averaged osmolality calculated for analysis at the end of the whole study period. All participants were treated according to the standard of care in routine clinical practice and they were encouraged to increase water intake according to thirst by the treating physician. The primary outcome was an assessment of kidney disease progression as defined by the slope of eGFR decline or a 40% decline from baseline eGFR. We calculated the slope of eGFR for each patient using a linear mixed model with random intercept and slope to account for the subject variability. Comparative analysis was done according to quartiles of osmolality. Further details of the protocol are presented in our previous paper [15].

Statistical analysis was performed by SPSS software version 29.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics was used to describe the baseline characteristics of patients. Data are presented as mean \pm standard deviation (SD) or median (inter-quartile range [IQR]) as appropriate. Difference between groups were compared by ANOVA test as appropriate. Correlations between

parameters were analysed with Pearson's rank correlation coefficients. Kaplan-Meier survival analysis and the Cox regression analysis were performed to assess the longitudinal association between the primary kidney event (i.e., 40% decline from baseline eGFR, dialysis, or death) and the different osmolality quartiles. Differences between Kaplan-Meier curves were tested using the log-rank test. Receiver-operating characteristic (ROC) curves were constructed by standard methods. The ability of osmolality target to identify those at high risk of reaching 40% eGFR decline was analysed using the area under the curve (AUC). Because osmolality may be affected by diuretics, a sensitivity analysis was conducted using the same methodology, but patients on diuretics were excluded. P values < 0.05 were considered statistically significant. All probabilities were two-tailed.

The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong (CREC Ref. No. 2018.421) and the study was performed in compliance with the Declaration of Helsinki.

RESULTS

Three hundred and eleven patients with ADPKD recruited were available for analysis. Their baseline characteristics are summarized in [Table 1](#). The mean age in the cohort is 53.1 ± 13.7 years old and there was a female preponderance (1.57 to 1). The mean age at diagnosis was 36.2 ± 15.1 years old. Two hundred and forty-four patients (78.5%) had a positive family history. The baseline biochemical parameters are shown in [Table 2](#). The mean creatinine was 95.83 ± 38.45 $\mu\text{mol/l}$, while

the mean time-averaged sOSM and uOSM was 293.95 ± 6.03 and 415.74 ± 133.31 mOsm/Kg respectively. We then compared the characteristics according to quartiles of sOSM (Table 3) or uOSM (Table 4) respectively. Those with high sOSM tended to be older diagnosed at a later age, and had a higher systolic blood pressure. They also had a significantly bigger height adjusted total kidney volume (HtTKV) with worse kidney function and slope of eGFR decline as compared to those with a low sOSM. In contrast, there is an inverse relationship for uOSM (Table 4).

We also performed a Pearson's correlation analysis for sOSM. There is a significant strong correlation with creatinine and a modest correlation with slope of eGFR decline ($r = 0.646$, $p < 0.001$; $r = -0.227$, $p < 0.001$ respectively). There is also a modest correlation between sOSM and Ht-TKV ($r = 0.397$, $p < 0.001$). As for uOSM, there is a significant but modest correlation with creatinine and slope of eGFR decline and Ht-TKV ($r = -0.142$, $p = 0.021$; $r = 0.200$, $p < 0.001$; $r = -0.298$, $p < 0.001$).

Kaplan-Meier plots were done to compare the risk of reaching 40% eGFR decline between those with high sOSM/uOSM values to those with low values, respectively. Those with a higher sOSM throughout the follow up period had a significantly worse kidney function decline (log-rank $p = < 0.001$) (Figure 1). Again, there was an inverse relationship in kidney outcome in those with a high uOSM (log-rank $p = 0.009$) (Figure 2). Univariate and multivariate Cox regression model were also done to assess the risk of 40% eGFR decline (Table 5). In the multivariate model, those with highest sOSM quartiles have a 5.914 (95% confidence interval 1.364 to 25.644, $p = 0.018$) times higher risk

to reach 40% eGFR decline as compared to those with the lowest sOSM quartiles. In contrast, there is an inverse relationship among the uOSM quartiles as compared to the sOSM quartiles.

A sensitivity analysis was performed with the exclusion of those on diuretics, and otherwise conducted using the same procedures as for the original analysis. Sixteen patients were excluded and their baseline characteristics were similar to the original cohort (Supplemental Table 1 and Supplemental Table 2). The sensitivity analysis showed that the significant effect of sOSM on kidney outcome diminished slightly in the multivariate Cox regression model (Supplemental Table 3).

Finally, we performed a ROC curves analysis to assess the predictive efficacy of osmolality for identifying those at high risk of kidney decline (Figure 3). The AUC for sOSM was 0.81 (95%CI, 0.73-0.89; $p < 0.001$), showing a good performance. Based on the ROC curve, we tested our target for sOSM > 290 mOsm/kg. At this value, the sensitivity and the specificity are 92.3% and 33.2%. Although statistically significant, the uOSM did not show a clinical meaningful predictive efficacy (AUC, 0.35, 95%CI 0.28-0.43; $p = 0.003$).

DISCUSSION

Our results showed that there is a significant correlation and causal relationship between sOSM and kidney outcomes in adult patients with ADPKD. This is suggested by the Kaplan-Meier survival plots and the multivariate Cox regression analysis showing a 5.914 times higher risk to reach 40% eGFR decline comparing those with the highest sOSM to those with the lowest sOSM quartiles. The

AUC in our ROC curves analysis for sOSM was shown to be 0.81, suggesting that this may be a useful marker in the monitoring for kidney decline. Indeed, sOSM has been previously shown to be an independent risk factor for kidney function decline and the risk of chronic kidney disease in healthy individuals [16,17]. However, the relationship of sOSM and kidney function decline is less definitive in patients with ADPKD, and this study provides some evidence for this relationship.

AVP is known to be produced and stored in neurons within the hypothalamus, and these neurons express osmoreceptors that are exquisitely responsive to sOSM [18, 19]. High sOSM is a significant physiological stimulant of AVP and copeptin secretion. Studies in non-ADPKD patients have suggested that the sOSM level are directly proportional to those of copeptin, a surrogate marker for AVP [20,21]. There have also been studies reporting an association between sOSM and copeptin levels in patients with ADPKD [22]. Overall, this forms the basis and rationale for increased water intake and a low osmolar diet to maintain a low sOSM to delay disease progression through reduced release of AVP, with the latest KDIGO guideline suggesting that patients with ADPKD adapt to a water intake of 2–3 litres per day, spread throughout the day [3].

However, several studies on ADPKD patients have also suggested that the relationship between sOSM and AVP levels, obtained after water deprivation, was severely blunted [21,23]. These findings suggested that there is possibly a central defect altering the release of AVP in response to increased osmolality [24]. Further study delineating the pathophysiology of possible central osmoregulation defects in patients with ADPKD would be needed. Unfortunately, we do not have the AVP or

copeptin level to assess this relationship in our study at present. Our data clearly demonstrated a correlation between sOSM and Ht-TKV, suggesting a possible link between the degree of sOSM with the severity of ADPKD based on the Mayo classification. Regardless, our prospective data with a long follow up period of five years showed that high sOSM is evidently associated with a worse kidney outcome, although it may be partially driven by diuretics as noted from the sensitivity analysis showing a diminished hazard ratio following exclusion of those on diuretics.

Our results also showed that there is an inverse relationship of uOSM, which is in keeping with previous studies [10]. Results from the TEMPO 3:4 trial showed that a lower baseline uOSM is independently associated with presence of hypertension, lower eGFR, higher Ht-TKV and higher age [10]. These data suggest that patients with ADPKD have defects in urine concentrating capacity and these defects are thought to be the cause of increased AVP secretion [22,25,26]. Indeed, findings of a decreased urine concentrating capacity in an early phase of ADPKD, before kidney impairment occurs, strengthen this hypothesis [27]. Given uOSM is closely related to disease severity, the inverse relationship seen here for uOSM may simply reflect a reverse causality, reflecting the ability of urine concentrating capacity decreases as the disease progresses.

There are also other biomarkers being investigated currently, with HtTKV being an established gold standard [9]. For example, our previous study suggested that differences in MRI morphology pattern may confer varying prognostic values similar to Mayo classification [15]. However, sOSM and uOsm may offer a relatively cheaper and easily accessible options. A combined assessment of

these surrogate markers together may be very useful in providing a more accurate prognostic assessment.

Whether copeptin levels are available or not, sOSM and other biochemical and clinical parameters would increase the strength of these surrogate biomarkers and biochemical and clinical correlates would provide the nephrologist with a stronger database with which to guide treatment. These data will provide an estimate of time to renal failure. With this estimate, preparations can begin for preparation of either transplant, preferred, or type of dialysis and the required surgery for the choice. The decision to pursue transplantation is time-sensitive, and the use of multiple surrogate markers of the shape of decline in slope to renal failure will determine if a patient remains in a favourable position to receive a transplant. As age advances, together with the probability of new co-morbidities, transplantation may become a less viable choice.

The strength of our study is that this is a territory-wide database involving 311 ADPKD patients across multiple tertiary centres in Hong Kong with serial data and a long follow up of about five years. This will provide long term longitudinal information and allow analysis at a population-based level. Additionally, our data are taken from the CysticHK registry in a real-world setting, which closely reflects clinical effects in real-life. Furthermore, this particular cohort of patients are tolvaptan treatment naïve, which could truly reflect the effects of the sOSM and uOSM without the influence of tolvaptan.

However, our study has several limitations. As mentioned, we do not have a corresponding copeptin level for correlation and comparative analysis. Although copeptin has been suggested as a better and more reliable marker than sOSM [28], it is important to note that this measurement is currently not readily available with access limited to only a few places. Unlike the TEMPO study cohort which restricted use of diuretics, and included dietary and standard fluid ingestion recommendations [10], we did not control the patient's dietary intake or have detailed information on salt intake in our study, which may affect the overall serum and urine osmolality. Some patients may also be on medications that may affect the uOSM, which we did not exclude in our cohort. This have affected the urine concentrating ability and could confound the overall results. However, the sensitivity analysis excluding patients on diuretics showed the effect of sOSM and uOSM on kidney outcome remained significant. Our study is not a randomised controlled trial and thus its correlation between sOSM and kidney outcomes is only observational and may not be definitive, especially with respect to reverse causality. Finally, our cohort is mostly comprised of Chinese patients, and our results may not be generalisable to other ethnicities.

Nevertheless, our study showed that sOSM may be a possible surrogate marker for the monitoring of patients with ADPKD, especially when access to copeptin level is limited, and high sOSM level appears to convey a detrimental effect on the kidney outcomes. Further studies would be needed to confirm these finding, which may allow sOSM to be a new surrogate marker for monitoring in clinical practices as well as a potential target for research trials.

Acknowledgement

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACCEPTED

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Figure Legend

Figure 1. Kaplan-Meier curves showing 40% eGFR decline against sOSM quartiles over a period of 5 years

- Those with a high average sOSM have a significant higher risk of kidney decline leading to a 40% drop of eGFR (log rank = <0.001).

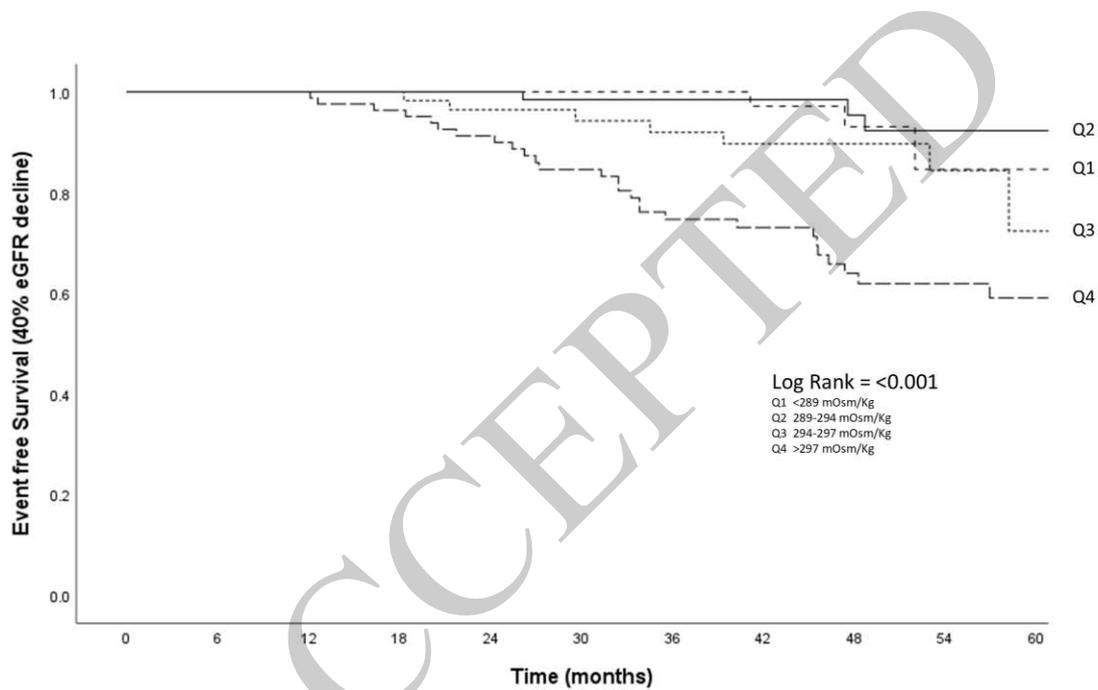


Figure 2. Kaplan-Meier curves showing 40% eGFR decline against uOSM quartiles over a period of 5 years

- Those with a high average uOSM have a significant lower risk of kidney decline leading to a 40% drop of eGFR ((log rank = 0.009).

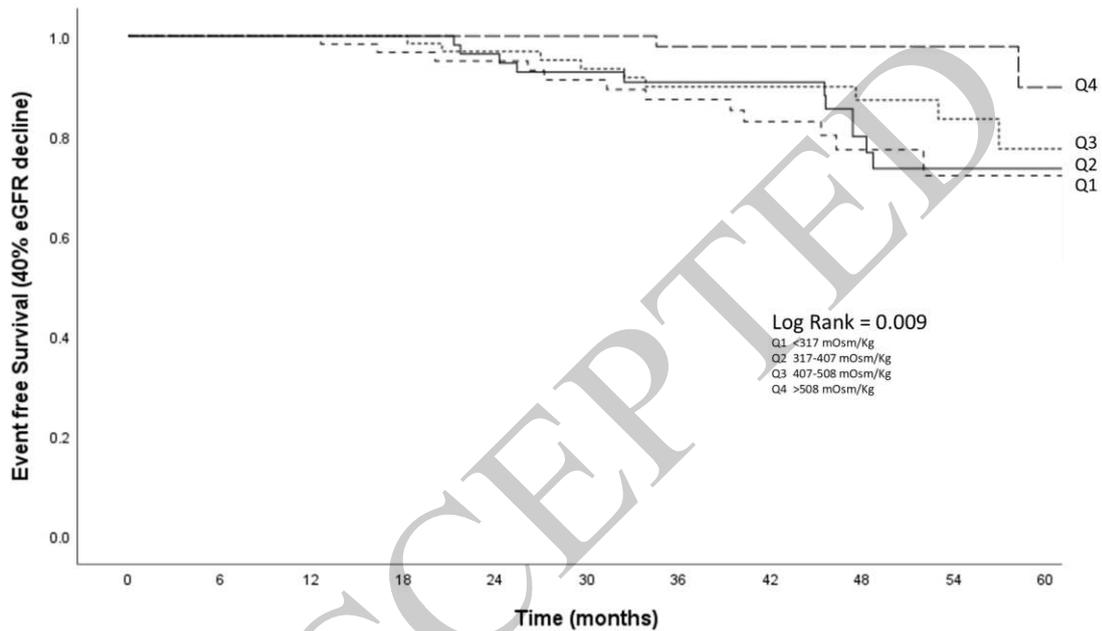
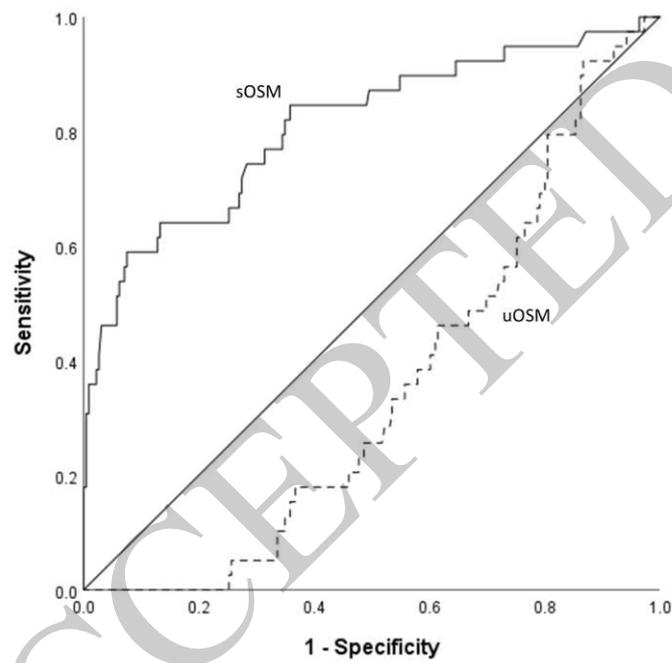


Figure 3. ROC curve of sOSM and uOSM for predicting risk to 40% eGFR decline from baseline.

- The sOSM and the risk to 40% eGFR decline is significantly correlated (AUC 0.81). The uOSM did not show a clinical meaningful predictive efficacy (AUC 0.35).



Supplemental Table of Contents

Supplemental Figure 1. Flow diagram of the study

Supplemental Table 1. Demographic and baseline clinical data with patients on diuretics excluded for sensitivity analysis

Supplemental Table 2. Baseline biochemical parameters with patients on diuretics excluded for sensitivity analysis

Supplemental Table 3. Univariate and multivariate Cox regression analysis on the risk of 40% eGFR decline with patients on diuretics excluded for sensitivity analysis

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TABLE 1. Demographic and baseline clinical data

Number of patients	311
Sex male : female	121 : 190
Age (years)*	53.1 ± 13.7
Duration of follow up (months)*	43.6 ± 15.8
Age at diagnosis (years)*	36.2 ± 15.1
Family history	244 (78.5%)
Smoker	37 (11.9%)
Comorbidities	
Diabetes	31 (10.0%)
Hypertension	182 (58.5%)
Hyperlipidemia	131 (42.1%)
Ischemic heart disease	8 (2.6%)
Stroke	16 (.1%)
Peripheral vascular disease	0 (0%)
Respiratory disease	29 (9.3%)
Cancer	18 (5.8%)
Clinical parameters/ arthrometries	
Height (m)*	1.64 ± 0.09
Weight (Kg)*	64.4 ± 13.1
Blood pressure (mmHg)*	133.3 ± 17.7 / 77.4 ± 11.4
Medications	
ACE inhibitors/ Angiotensin II receptor blockers	187 (60.1%)
Diuretics	16 (5.1%)
MRI parameters	
Total Kidney Volume (TKV) (ml)#	1088 (626 – 1794)
Height adjusted TKV (ml/m)#	648 (371 – 1061)
Mayo class (1A:1B:1C:1D:1E:2) %	13.5: 20.6: 25.1: 13.5: 10.3: 17.0

*Expressed as mean ± standard deviation; # Expressed as median (Interquartile range)

TABLE 2. Baseline biochemical parameters

Number of patients	311
Haemoglobin (g/dL)	12.36 ± 1.68
White blood cell (x 10 ⁹ /L)	6.35 ± 2.00
Platelet (x 10 ⁹ /L)	238.02 ± 65.62
Sodium (mmol/l)	140.00 ± 2.96
Potassium (mmol/l)	4.15 ± 0.42
Urea (mmol/l)	8.90 ± 6.31
Creatinine (μmol/l)	95.83 ± 38.45
Total protein (g/L)	73.56 ± 4.15
Albumin (g/L)	38.86 ± 3.96
Bilirubin (μmol/l)	9.36 ± 5.59
Alkaline phosphatase (IU/L)	71.81 ± 30.63
Alanine aminotransferase (IU/L)	21.88 ± 15.26
Calcium (mmol/l)	2.34 ± 0.09
Phosphate (mmol/l)	1.15 ± 0.25
Urate (mmol/l)	0.36 ± 0.11
Osmolality (mOsm/Kg)	294.03 ± 9.16
Urinary Osmolality (mOsm/Kg)	432.84 ± 174.51
Time-averaged Osmolality (mOsm/Kg)	293.95 ± 6.03
Time-averaged Urinary Osmolality (mOsm/Kg)	415.74 ± 133.31
Urinary protein/ Creat ratio (mg/mg Cr)	0.21 ± 0.33

*Data expressed as mean ± standard deviation

TABLE 3. Differences in sOSM group according to quartiles

Parameter	sOSM (mOsm/Kg)				P value
	Q1 <289	Q2 289-294	Q3 294-297	Q4 >297	
Number of patients	72	80	68	91	
Clinical*					
Age (years)	43.2±10.9	50.9±12.9	57.6±11.5	60.9±12.0	<0.001
Age at diagnosis (years)	29.5±13.0	35.1±14.9	39.8±14.3	41.7±14.8	<0.001
Systolic blood pressure (mmHg)	128.7±19.1	132.7±15.4	134.3±18.2	138.6±18.0	0.008
Diastolic blood pressure (mmHg)	76.4±12.2	78.6±10.5	75.8±11.8	78.6±11.2	0.334
Age starting antihypertensives (year)	34.5±10.4	43.4±12.4	45.8±11.2	43.8±12.1	<0.001
Blood*					
Haemoglobin (g/dL)	12.59±1.25	12.73±1.66	12.46±1.84	11.84±1.78	0.005
White blood cell (x 10 ⁹ /L)	6.27±1.57	6.20±1.71	6.26±2.00	6.62±2.53	0.544
Platelet (x 10 ⁹ /L)	263.1±51.2	234.7±65.4	240.4±68.2	220.6±69.3	0.001
Sodium (mmol/l)	138.1±2.7	139.6±2.2	140.6±1.9	141.0±3.8	<0.001
Potassium (mmol/l)	4.0±0.4	4.0±0.4	4.2±0.3	4.3±0.5	<0.001
Urea (mmol/l)	5.0±1.6	6.8±2.6	8.5±3.0	14.0±9.3	<0.001
Creatinine (µmol/l)	67.4±19.6	82.4±22.7	98.1±31.5	125.3±44.1	<0.001
Bilirubin (µmol/l)	9.1±5.1	9.1±3.9	9.6±4.9	8.8±5.7	0.789
Alkaline phosphatase (IU/L)	59.8±38.4	69.7±24.0	72.6±20.5	84.2±34.1	<0.001
Alanine aminotransferase (IU/L)	19.6±17.3	23.4±14.4	22.1±13.0	23.0±16.8	0.503
Albumin (g/L)	40.0±2.8	39.1±3.7	38.9±3.9	37.3±4.4	<0.001
Calcium (mmol/l)	2.33±0.08	2.34±0.08	2.36±0.08	2.32±0.11	0.092
Phosphate (mmol/l)	1.10±0.16	1.09±0.15	1.11±0.15	1.27±0.37	<0.001
Urate (mmol/l)	0.29±0.07	0.35±0.08	0.39±0.11	0.39±0.12	<0.001
Urinary protein/ Creat ratio (mg/mg Cr)	0.14±0.22	0.18±0.24	0.14±0.11	0.38±0.52	<0.001
MRI parameters*					
Total Kidney Volume (ml)	906±698	999±669	1408±1224	2182±1946	<0.001
HtTKV (ml/m)	560±412	609±403	852±733	1322±1190	<0.001
Primary outcome*					
Slope of eGFR decline (ml/min per 1.73m ² / year)	-2.09±3.15	-2.89±4.51	-2.99±3.48	-3.55±3.03	0.130
Event-free survival at 2 years	1.0	1.0	0.97	0.91	<0.001
Event-free survival at 5 years	0.84	0.92	0.73	0.59	<0.001

eGFR, estimated glomerular filtration rate; HtTKV, Height adjusted Total Kidney Volume.

*Data expressed as mean ± standard deviation

TABLE 4. Differences uOSM group according to quartiles

Parameter	uOSM (mOsm/Kg)				P value
	Q1 <317	Q2 317-407	Q3 407-508	Q4 >508	
Number of patients	83	76	77	75	
Clinical*					
Age (years)	55.2±12.8	58.6±13.7	51.9±12.0	48.7±14.5	<0.001
Age at diagnosis (years)	37.7±13.2	41.2±15.7	34.4±14.4	33.4±15.0	0.010
Systolic blood pressure (mmHg)	135.1±17.5	138.4±20.9	130.4±15.9	132.1±16.1	0.052
Diastolic blood pressure (mmHg)	77.9±11.4	76.4±11.1	77.3±9.8	78.3±12.4	0.765
Age starting antihypertensives (year)	42.5±12.8	45.3±11.2	40.6±9.1	42.6±15.6	0.276
Blood*					
Haemoglobin (g/dL)	11.65±1.67	12.11±1.68	12.54±1.68	13.18±1.37	<0.001
White blood cell (x 10 ⁹ /L)	6.90±2.65	6.18±1.71	6.20±2.20	6.16±1.21	0.114
Platelet (x 10 ⁹ /L)	243.3±67.3	226.3±58.3	230.1±67.4	252.6±64.4	0.084
Sodium (mmol/l)	138.9±3.7	139.8±2.2	140.6±3.5	140.4±2.3	0.006
Potassium (mmol/l)	4.2±0.5	4.1±0.4	4.2±0.4	4.1±0.4	0.632
Urea (mmol/l)	10.4±8.9	9.3±6.3	8.5±4.2	6.6±2.1	0.003
Creatinine (µmol/l)	101.1±41.7	98.1±43.0	93.0±35.1	81.6±23.6	0.014
Bilirubin (µmol/l)	7.8±3.4	8.8±3.6	10.5±7.5	9.0±4.0	0.023
Alkaline phosphatase (IU/L)	77.5±25.6	79.0±48.0	69.8±26.8	65.9±19.6	0.061
Alanine aminotransferase (IU/L)	21.3±15.6	21.8±15.0	23.1±18.6	21.9±12.1	0.918
Albumin (g/L)	38.0±4.3	38.1±3.8	38.2±4.1	40.2±2.9	0.002
Calcium (mmol/l)	2.34±0.11	2.34±0.10	2.32±0.07	2.34±0.07	0.608
Phosphate (mmol/l)	1.24±0.33	1.19±0.25	1.10±0.21	1.06±0.16	<0.001
Urate (mmol/l)	0.36±0.10	0.36±0.12	0.38±0.11	0.34±0.09	0.141
Urinary protein/ Creat ratio (mg/mg Cr)	0.32±0.52	0.21±0.31	0.23±0.31	0.13±0.11	0.022
MRI parameters*					
Total Kidney Volume (ml)	1618±1203	1426±1214	1841±2073	769±474	0.002
HtTKV (ml/m)	986±708	871±770	1129±1265	464±274	0.002
Primary outcome*					
Slope of eGFR decline (ml/min per 1.73m ² / year)	-3.80±3.81	-2.88±4.38	-3.06±2.95	-1.87±3.04	0.027
Event-free survival at 2 years	0.95	0.96	0.97	1.0	0.009
Event-free survival at 5 years	0.72	0.74	0.78	0.90	0.009

eGFR, estimated glomerular filtration rate; HtTKV, Height adjusted Total Kidney Volume.

*Data expressed as mean ± standard deviation

TABLE 5. Univariate and multivariate Cox regression analysis on the risk of 40%**eGFR decline**

Clinical factors	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Hypertensive	2.497 (1.279 – 4.874)	0.007	1.434 (0.700 – 2.934)	0.324
Male	2.042 (1.129 – 3.696)	0.018	1.441 (0.737 – 2.817)	0.285
Quartiles of sOSM				
Q1 <289 mOsm/kg	Reference		Reference	
Q2 289-294 mOsm/kg	0.997 (0.223 – 4.462)	0.997	1.362 (0.248 – 7.465)	0.722
Q3 294-297 mOsm/kg	2.670 (0.707 – 10.085)	0.148	3.163 (0.661 – 15.139)	0.149
Q4 >297 mOsm/kg	4.263 (1.900 – 20.648)	0.003	5.914 (1.364 – 25.644)	0.018
Quartiles of uOSM				
Q1 <317 mOsm/kg	Reference		Reference	
Q2 317-407 mOsm/kg	0.840 (0.393 – 1.794)	0.652	0.666 (0.309 – 1.435)	0.299
Q3 407-508 mOsm/kg	0.484 (0.207 – 1.128)	0.093	0.410 (0.174 – 0.969)	0.042
Q4 >508 mOsm/kg	0.128 (0.029 – 0.565)	0.007	0.129 (0.029 – 0.582)	0.008

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Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: January 7, 2026

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Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

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Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

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Disclosure Updated Date: December 23, 2025

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Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

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W. Chu reports the following:

Employer: The Chinese University of Hong Kong

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Winnie Cw Chu

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: December 8, 2025

Disclosure Updated Date: December 8, 2025

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

O. Devuyst reports the following:

Employer: University of Zurich; Consultancy: Sanofi, Vertex; and Advisory or Leadership Role: Editorial board: Kidney International, Nephrology Dialysis Transplantation, Pflügers Archiv, CJASN.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Olivier Devuyst

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease.

Date of Completion: January 15, 2026

Disclosure Updated Date: January 15, 2026

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

S. Fung reports the following:

Employer: Princess Margaret Hospital, Hospital Authority; Research Funding: Research studies with Sanofi, Abbvie, GSK, Amgen, Mallinckrodt, Pfizer, NephroGenex.; Advisory or Leadership Role: Hong Kong Society Of Nephrology; The Federation Of Medical Societies Of Hong Kong; Hong Kong Kidney Foundation; Hong Kong Transplant Sport Association ; World Transplant Games Federations; and Other Interests or Relationships: Honorary Advisor Lions Kidney Educational Centre & Research Foundation ; Honorary Advisor Renal Mutual Help Association Princess Margaret Hospital ; Honorary Advisor Hong Kong Transplant Sports Association ; Honorary Advisor Alliance For Renal Patients Mutual Help Association.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Samuel K.S. Fung

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: January 14, 2026

Disclosure Updated Date: January 14, 2026

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

W. Fung reports the following:

Employer: Prince of Wales Hospital, Hospital Authority

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Winston Ws Fung

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: December 9, 2025

Disclosure Updated Date: December 9, 2025

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

K. Hau has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Kc Hau

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: January 24, 2026

Disclosure Updated Date: January 24, 2026

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

T. Ho reports the following:

Employer: Tseung Kwan O Hospital

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Tsz ling Ho

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: December 9, 2025

Disclosure Updated Date: December 9, 2025

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

P. Kwan reports the following:
Employer: Tung Wah Hospital

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Pui Yuen Lorraine Kwan

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: December 22, 2025

Disclosure Updated Date: December 22, 2025

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

L. Kwok has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Lap Ming Kwok

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: January 7, 2026

Disclosure Updated Date: January 7, 2026

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

V. Kwong reports the following:

Employer: Prince of Wales Hospital, Hong Kong

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Vickie wai ki Kwong

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: December 9, 2025

Disclosure Updated Date: December 9, 2025

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

L. Lau reports the following:

Employer: Prince of Wales Hospital

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Lik Fung Sam Lau

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: December 8, 2025

Disclosure Updated Date: December 8, 2025

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

P. Li reports the following:

Employer: Prince of Wales Hospital; Advisory or Leadership Role: President, International Association of Chinese Nephrologists; President, Hong Kong Academy of Medicine; Both unpaid; Editorial Board of KI, PDI; unpaid;; and Other Interests or Relationships: Member of ASN, ISN, ERA, ISPD.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Philip K.T. Li

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: December 9, 2025

Disclosure Updated Date: February 12, 2025

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

S. Lui reports the following:

Employer: Tung Wah Hospital; Ownership Interest: Hang Seng Bank (Hong Kong); Bank of China (Hong Kong); Tracker Fund (Hong Kong); and Research Funding: Otsuka Pharmaceutical Development & Commercialization Inc.; Bayer Healthcare Pharmaceutical Inc.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Sing-Leung Lui

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: December 9, 2025

Disclosure Updated Date: December 12, 2024

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

A. Ong reports the following:

Employer: University of Sheffield; Consultancy: Mironid; Vertex; GSK; Crinetics; Torque Bio - All moneys paid to institution; Advisory or Leadership Role: Steering committee - SAB - Mironid; All moneys paid to institution; and Other Interests or Relationships: ERA Council - unpaid; NDT Editorial Board - unpaid;

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Albert C. Ong

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: December 9, 2025

Disclosure Updated Date: January 6, 2025

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

W. Pang reports the following:

Employer: The Chinese University of Hong Kong

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Wing fai Pang

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: December 22, 2025

Disclosure Updated Date: December 22, 2025

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

L. Ronald reports the following:
Employer: Hospital Authority

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Lin Ronald

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: January 8, 2026

Disclosure Updated Date: January 8, 2026

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

T. Shum has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Tung sen Shum

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: December 10, 2025

Disclosure Updated Date: December 10, 2025

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

H. Sin reports the following:

Employer: Kwong Wah Hospital

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Ho kwan Ken Sin

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: January 14, 2026

Disclosure Updated Date: January 14, 2026

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

C. Szeto reports the following:

Employer: The Chinese University of Hong Kong; Consultancy: Baxter Healthcare; Gilead Science; Research Funding: Baxter Healthcare; Fresenius; Fibrogen Inc; Gilead; Honoraria: Baxter Healthcare; Advisory or Leadership Role: Baxter Healthcare, Gilead Science; and Other Interests or Relationships: Pfizer; AstraZeneca.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Cheuk-Chun Szeto

Manuscript ID: K360-2025-001216R1

Manuscript Title: "The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: December 9, 2025

Disclosure Updated Date: December 9, 2025

ASN Journal Disclosure Form

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S. Wong reports the following:

Employer: United Christian Hospital, Hospital Authority; Research Funding: Travers Therapeutics, Inc.; Advisory or Leadership Role: Chairman of the Hong Kong Society of Nephrology 2023-2025 (unpaid); Chairman of the Central Renal Committee of the Hospital Authority, Hong Kong since Dec 2024 (unpaid for this capacity); and Other Interests or Relationships: Chairman of the Hong Kong Society of Nephrology 2023-2025.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Sunny Sze ho Wong

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease.

Date of Completion: January 15, 2026

Disclosure Updated Date: January 15, 2026

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

S. Yuen has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Sze Kit Yuen

Manuscript ID: K360-2025-001216R1

Manuscript Title: The relationship of osmolality and kidney outcomes in patients with autosomal dominant polycystic kidney disease

Date of Completion: December 13, 2025

Disclosure Updated Date: December 13, 2025