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ORIGINAL ARTICLE

Proteinuria, measured or estimated albuminuria for risk prediction in patients with chronic kidney disease?

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ABSTRACT

Background. Although albuminuria is the gold standard for defining chronic kidney disease (CKD), total proteinuria has also been widely used in real-world clinical practice. Moreover, the superiority of the prognostic performance of albuminuria over proteinuria in patients with CKD remains inconclusive. Therefore, we aimed to compare the predictive performances of albuminuria and proteinuria in these patients.

Methods. From the Korean Cohort Study for Outcome in Patients with CKD we included 2099 patients diagnosed with CKD grades 1–5 who did not require kidney replacement therapy. We measured the spot urine albumin:creatinine ratio (mACR) and protein:creatinine ratio (PCR) and estimated the ACR (eACR) using the PCR. Kidney failure risk equation (KFRE) scores were calculated using the mACR, PCR and eACR. The primary outcome was the 5-year risk of kidney failure with replacement therapy (KFRT).

Results. The eACR significantly underestimated mACR in patients with low albuminuria levels. The time-dependent area under the receiver operating characteristics curve showed excellent predictive performance for all KFRE scores from the mACR, PCR and eACR. However, eACR was inferior to mACR based on the continuous net reclassification index (cNRI) and integrated discrimination improvement index (IDI) in all CKD cause groups, except for the group with an unclassified aetiology. Moreover, the cNRI and IDI statistics indicated that both eACR and PCR were inferior to mACR in patients with low albuminuria (<30 mg/g). Conversely, the predictive performance of PCR was superior in severe albuminuria and nephrotic-range proteinuria, in which the IDI and cNRI of the PCR were greater than those of the mACR.

Conclusions. The mACR, eACR and PCR showed excellent performance in predicting KFRT in patients with CKD. However, eACR was inferior to mACR in patients with low albuminuria, indicating that measuring rather than estimating albuminuria is preferred for these patients.

Keywords: albuminuria, chronic kidney disease, kidney failure with replacement therapy, prediction, proteinuria

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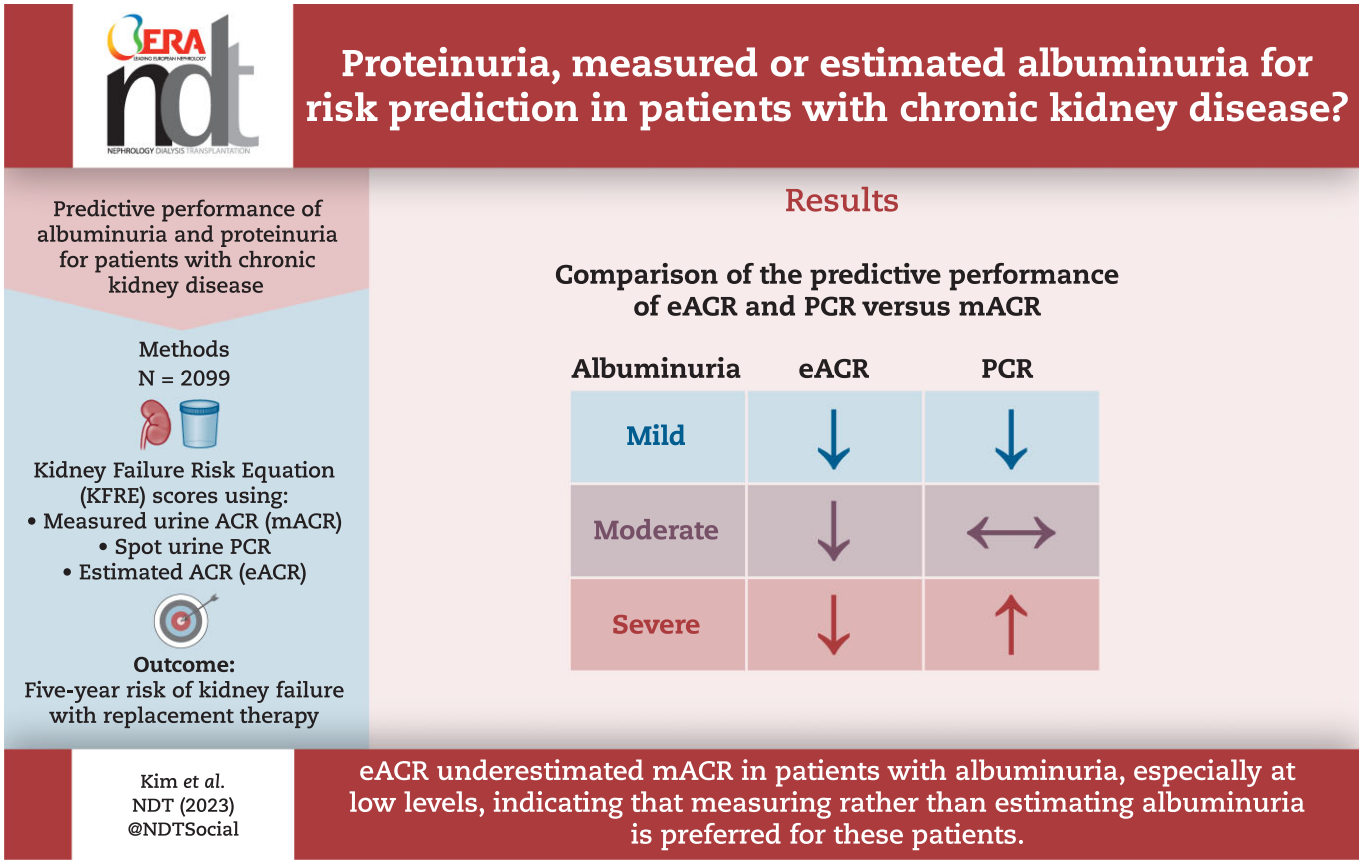
GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Although albuminuria is a gold standard to define chronic kidney disease, proteinuria is still widely used in real-world clinical practice. Some studies suggest equations for estimating albuminuria from proteinuria. However, to date, the superiority of albuminuria over proteinuria is inconclusive.

This study adds:

- Both the albumin:creatinine ratio (ACR) and protein:creatinine ratio (PCR) showed good predictive performance for the risk of kidney failure with replacement therapy. However, estimated ACR calculated from the PCR showed inferiority, especially in patients with low albuminuria.

Potential impact:

- This study indicates that predictive performance of albuminuria and proteinuria can vary according to the degree of albuminuria. Therefore, measuring albuminuria should be preferred to estimating albuminuria in patients with low albuminuria.

INTRODUCTION

Chronic kidney disease (CKD) is a major health concern, affecting approximately 1 in 10 people worldwide [1]. As a decrease in kidney function is associated with a substantial increase in the risk of cardiovascular disease (CVD) and mortality [2, 3], accurate prediction of prognosis and early intervention of risk factors are important therapeutic strategies for CKD.

Albumin is a predominant urinary protein and its presence can be indicative of kidney damage, which may lead to the development of CKD. Measuring albuminuria is more sensitive and accurate than measuring total proteinuria for the early detection of kidney disease, particularly at low levels of proteinuria [4]. Moreover, clinical practice guidelines for the screening and management of CKD recommend using glomerular filtration rate (GFR) and albuminuria to diagnose CKD [5]. Therefore, measurement of albuminuria is essential for the initial diagnosis of CKD. Moreover, albuminuria is a well-established prognostic factor of CKD [2] and recent predictive tools for CKD include albuminuria in their equations [6, 7]. Formulas have also been proposed for converting the urine protein:creatinine ratio (PCR) into an estimated urine albumin:creatinine ratio (eACR) [8]. Nevertheless, many physicians

still measure urine total protein because it is less expensive and more customary or because measuring urine albumin is sometimes not available in real-world clinical practice. In addition, in some diseases, such as glomerulonephritis, proteinuria is still used to determine disease severity and treatment goals [9]. In addition, there remains uncertainty regarding the superiority of albuminuria over proteinuria in predicting the risk of kidney failure with replacement therapy (KFRT) [10, 11], and there is no agreement on whether PCR should be converted if ACR is not accessible. Therefore, it is necessary to clarify whether the predictive performances of albuminuria and proteinuria differ for various CKD aetiologies.

The Korean Cohort Study for Outcome in Patients with CKD (KNOW-CKD) is a prospective cohort study that included patients already diagnosed with CKD grades 1–5 with various aetiologies. This study aimed to compare the predictive performance of the measured spot urine ACR (mACR), PCR and eACR converted from the PCR for the risk of KFRT.

MATARIALS AND METHODS

Study population

The KNOW-CKD is a multicentre prospective cohort study launched in 2011. The detailed design and methods have been described previously (NCT01630486; http://www.clinicaltrials.gov) [12]. Briefly, KNOW-CKD recruited patients 20–75 years of age who were diagnosed with various causes of CKD at tertiary hospitals in Korea. A total of 2238 patients were initially recruited. For this study, we excluded 123 patients for whom ACR and PCR were not measured and 12 patients for whom PCR was measured to be less than the ACR. In addition, we further excluded four patients who were lost to follow-up after baseline. Finally, 2099 patients were included in this study. This study was performed in accordance with the Declaration of Helsinki and the study protocol was approved by the institutional review boards of the participating centres.

Data collection

Baseline demographic information, anthropometric measurements and medical histories were collected using a standard questionnaire administered by trained healthcare providers. These data were extracted from the electronic data management system of the KNOW-CKD. All blood and urine samples were collected after overnight fasting and sent to the KNOW-CKD central laboratory (Lab Genomics, Seongnam, Korea). Serum and urine creatinine levels were measured using the Jaffe method traceable to isotope dilution mass spectrometry using an ADVIA Chemistry XPT analyser (Siemens Healthcare, Erlangen, Germany) with Siemens Chemistry Calibrators (REF 09784096) and ADVIA Chemistry Creatinine_2 (CREA_2) Reagents (REF 03039070). The estimated GFR (eGFR) was calculated based on the 2009 Chronic Kidney Disease Epidemiology Collaboration equation [13]. Urine protein was measured using a pyrogallol red/molybdate protein dye-binding assay with ADVIA Chemistry Total Protein_2 (Urine) Reagents (REF 05000171) and ADVIA Chemistry Urine Total Protein Calibrators (REF 07889923). Urine albumin was measured using an immunoturbidimetric assay with ADVIA Chemistry Microalbumin_2 Reagents (REF 03051194) and ADVIA Chemistry Microalbumin_2 Calibrators (REF 06487733). Urine protein and albumin were measured on an ADVIA Chemistry XPT analyser (Siemens Healthcare) using the same samples in the central laboratory.

Main exposures

The kidney failure risk equation (KFRE) score was the primary exposure of interest. We calculated the risk of KFRT using a previously published non-North American four-variable KFRE [6], including age, sex, eGFR and albuminuria. We used spot urine mACR values for albuminuria to calculate the KFRE scores. To compare the predictive performance of each model, we used eACR or measured spot urine PCR values instead of mACR. The eACR was calculated from PCR using a previously proposed conversion equation [8]. The model used in this study was: $eACR = \exp(5.392 + 0.3072 \times \log(\min(PCR/50, 1)) + 1.5793 \times \log(\max(\min(PCR/500, 1), 0.1)) + 1.1266 \times \log(\max(PCR/500, 1)))$.

Outcome assessment

The primary outcome was the 5-year KFRT risk. KFRT was defined as dialysis (haemodialysis or peritoneal dialysis) for 3 months or kidney transplantation during the follow-up period. The secondary outcome was the 2-year KFRT risk.

Statistical analysis

Continuous variables are expressed as means and standard deviations (SDs) and compared using one-way analysis of variance. Categorical variables are expressed as numbers and percentages. Linear-by-linear associations between groups were examined and presented as *P* for trend. Skewed variables are expressed as medians and interquartile ranges (IQRs) and compared using the Jonckheere–Terpstra test. The agreement between mACR and eACR was visualized using a difference plot. The predictive performance of the KFRE score was evaluated using the time-dependent area under the receiver operating characteristics curve (AUROC) with mortality as a competing risk. The continuous net reclassification index (cNRI) and integrated discrimination improvement index (IDI) were used. We considered a significant difference in predictability when at least two of the three methods showed statistical significance. We compared the performances of the predictors in subgroups of CKD causes, including glomerulonephritis, diabetic nephropathy, hypertensive nephropathy, polycystic kidney disease (PKD) and unclassified CKD. Additionally, we performed a subgroup analysis based on the amount of mACR [normal–mild (<30 mg/g), moderately increased (30–300 mg/g) and severely increased (≥300 mg/g)] and PCR (<1000, 1000–3500, ≥3500 mg/g). For sensitivity analysis, we used follow-up urinalysis (mACR and PCR) after 1 year. After excluding patients without follow-up urinalysis measurements and those who reached the KFRT outcome during the 1-year follow-up, 1413 patients were included in the sensitivity analysis (Supplementary Fig. S1). All statistical analyses were performed using SPSS Statistics for Windows (version 21.0; IBM, Armonk, NY, USA) and R (version 3.6.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

The baseline characteristics of the patients according to the albuminuria categories are presented in Table 1. There were no significant differences in the age and sex distribution of the patients based on different levels of albuminuria. However, patients with high albuminuria levels had more comorbidities, such as diabetes, hypertension and peripheral vascular disease. In addition, glomerulonephritis and diabetic nephropathy were the most common underlying causes of CKD in patients with high

Table 1: Baseline characteristics of patients according to albuminuria categories.

Variables	Total	Albuminuria categories			*P* for trend
		Normal–mildly increased (<30 mg/g)	Moderately increased (30–300 mg/g)	Severely increased (≥300 mg/g)	
Participants, *n*	2099	335	637	1127	
Age (years), mean ± SD	53.6 ± 12.2	53.0 ± 13.3	53.4 ± 11.9	54.0 ± 12.1	.163
Male, *n* (%)	1283 (61.1)	223 (66.3)	380 (59.7)	680 (60.3)	.103
Current smoker, *n* (%)	331 (15.8)	61 (18.3)	92 (14.5)	178 (15.8)	.505
DM, *n* (%)	709 (33.8)	55 (16.4)	166 (26.1)	488 (43.3)	<.001
HTN, *n* (%)	2016 (96.0)	294 (87.8)	609 (95.6)	1113 (98.8)	<.001
CVD history, *n* (%)					
Coronary heart disease	129 (6.1)	17 (5.1)	28 (4.4)	84 (7.5)	.054
Cerebrovascular disease	127 (6.1)	21 (6.3)	34 (5.3)	72 (6.4)	.705
Peripheral vascular disease	75 (3.6)	6 (1.8)	19 (3.0)	50 (4.4)	.013
Congestive heart failure	33 (1.6)	3 (0.9)	6 (0.9)	24 (2.1)	.044
Charlson comorbidity index, mean ± SD	2.3 ± 1.6	1.5 ± 1.6	2.1 ± 1.5	2.7 ± 1.6	<.001
Cause of CKD, *n* (%)					
Glomerulonephritis	749 (35.7)	43 (12.8)	213 (33.4)	493 (43.7)	
Diabetic nephropathy	488 (23.2)	21 (6.3)	99 (15.5)	368 (32.7)	
Hypertensive nephropathy	385 (18.3)	102 (30.4)	126 (19.8)	157 (13.9)	<.001
Polycystic kidney disease	351 (16.6)	150 (44.8)	169 (26.5)	32 (2.8)	
Unclassified	126 (6.0)	19 (5.7)	30 (4.7)	77 (6.8)	
BMI (kg/m^2), mean ± SD	24.6 ± 3.4	24.1 ± 3.3	24.3 ± 3.3	24.9 ± 3.5	<.001
SBP (mmHg), mean ± SD	127.9 ± 16.3	125.0 ± 15.7	125.7 ± 14.6	130.0 ± 17.1	<.001
DBP (mmHg), mean ± SD	77.1 ± 11.2	77.3 ± 11.7	76.5 ± 10.3	77.2 ± 11.5	.593
Creatinine (mg/dl), mean ± SD	1.8 ± 1.2	1.3 ± 0.7	1.6 ± 0.8	2.1 ± 1.3	<.001
eGFR (ml/min/1.73 m^2), mean ± SD	53.0 ± 30.7	72.2 ± 30.0	55.9 ± 29.2	45.7 ± 29.1	<.001
Haemoglobin (g/dl), mean ± SD	12.8 ± 2.0	13.8 ± 1.7	13.1 ± 1.9	12.4 ± 2.1	<.001
Calcium (mg/dl), mean ± SD	9.1 ± 0.5	9.3 ± 0.4	9.2 ± 0.5	9.0 ± 0.6	<.001
Phosphate (mg/dl), mean ± SD	3.7 ± 0.7	3.5 ± 0.5	3.5 ± 0.6	3.8 ± 0.7	<.001
Albumin (g/dl), mean ± SD	4.1 ± 0.4	4.4 ± 0.3	4.3 ± 0.3	4.0 ± 0.5	<.001
Total cholesterol (mg/dl), mean ± SD	174.2 ± 38.9	174.5 ± 33.5	169.5 ± 35.2	176.7 ± 42.2	.029
Triglyceride (mg/dl), mean ± SD	157.8 ± 99.4	133.6 ± 77.4	143.2 ± 84.9	173.4 ± 109.8	<.001
hs-CRP (mg/l), median (IQR)	1.0 (0.0–2.0)	0.0 (0.0–1.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	.079
PTH (pg/ml), median (IQR)	51.0 (32.0–84.0)	38.0 (28.0–56.0)	48.0 (30.0–74.0)	59.0 (36.0–105.0)	<.001
mACR (mg/g), median (IQR)	353.3 (77.9–1099.8)	10.3 (5.8–17.4)	120.9 (67.9–207.9)	998.0 (525.8–1972.6)	<.001
eACR (mg/g), median (IQR)	214.0 (30.4–764.6)	5.6 (4.9–10.3)	55.0 (23.1–98.5)	680.9 (324.0–1532.8)	<.001
PCR (mg/g), median (IQR)	493.0 (143.0–1513.0)	46.0 (30.0–72.0)	208.0 (120.0–301.0)	1365.0 (706.0–2805.0)	<.001
RAS blocker, *n* (%)	1798 (85.7)	257 (76.9)	542 (85.1)	999 (88.6)	<.001
Statin, *n* (%)	1088 (51.9)	121 (36.2)	280 (44.0)	687 (61.0)	<.001

Median (IQR) data compared by Jonckheere–Terpstra test.
DM: diabetes mellitus; HTN: hypertension; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; hs-CRP: high-sensitivity C-reactive protein; PTH: parathyroid hormone.

albuminuria levels, whereas hypertensive nephropathy and PKD were less common. The mean eGFR was 53.1 ml/min/1.73 m^2 and tended to decrease in patients with high albuminuria. A total of 1809 (85.7%) patients were taking a renin–angiotensin system (RAS) blocker and the proportion of patients taking an RAS blocker increased with increasing albuminuria. Baseline characteristics according to the cause of CKD are presented in Supplementary Table S1.

Difference between mACR and eACR

Median mACR and PCR values were 354 and 490 mg/g, respectively. The median value of eACR was 213 mg/g, which was lower than that of mACR. The median difference between mACR and eACR was 139.0 mg/g, and this difference tended to increase with increasing mACR (Fig. 1A). However, when we examined the eACR:mACR ratio, eACR significantly underestimated mACR in patients with low mACR, but the ratio tended to approach 1.0 with increasing mACR (Fig. 1B).

mACR:PCR ratio

The median values of the mACR:PCR ratio were 0.23, 0.67, and 0.72, respectively, across the albuminuria categories (Fig. 1C). These values increased with increasing mACR. Patients were classified into proteinuria categories (<1000, 1000–3500 and ≥3500 mg/g) and the median ratios were 0.68, 0.72 and 0.67, respectively. The ratio was significantly lower in patients with nephrotic-range proteinuria than in those with proteinuria between 1000 and 3500 mg/g (Fig. 1D).

Predictive performance of mACR, eACR and PCR for 5-year risk of KFRT

We compared the predictive performances of mACR, eACR and PCR for the 5-year risk of KFRT using the time-dependent AUROC. All KFRE scores using these three metrics generally showed excellent predictive performance, with AUROC values >0.9 for the 5-year risk of KFRT across all types of CKD causes (Fig. 2). In addition, there were no statistically significant differences in the

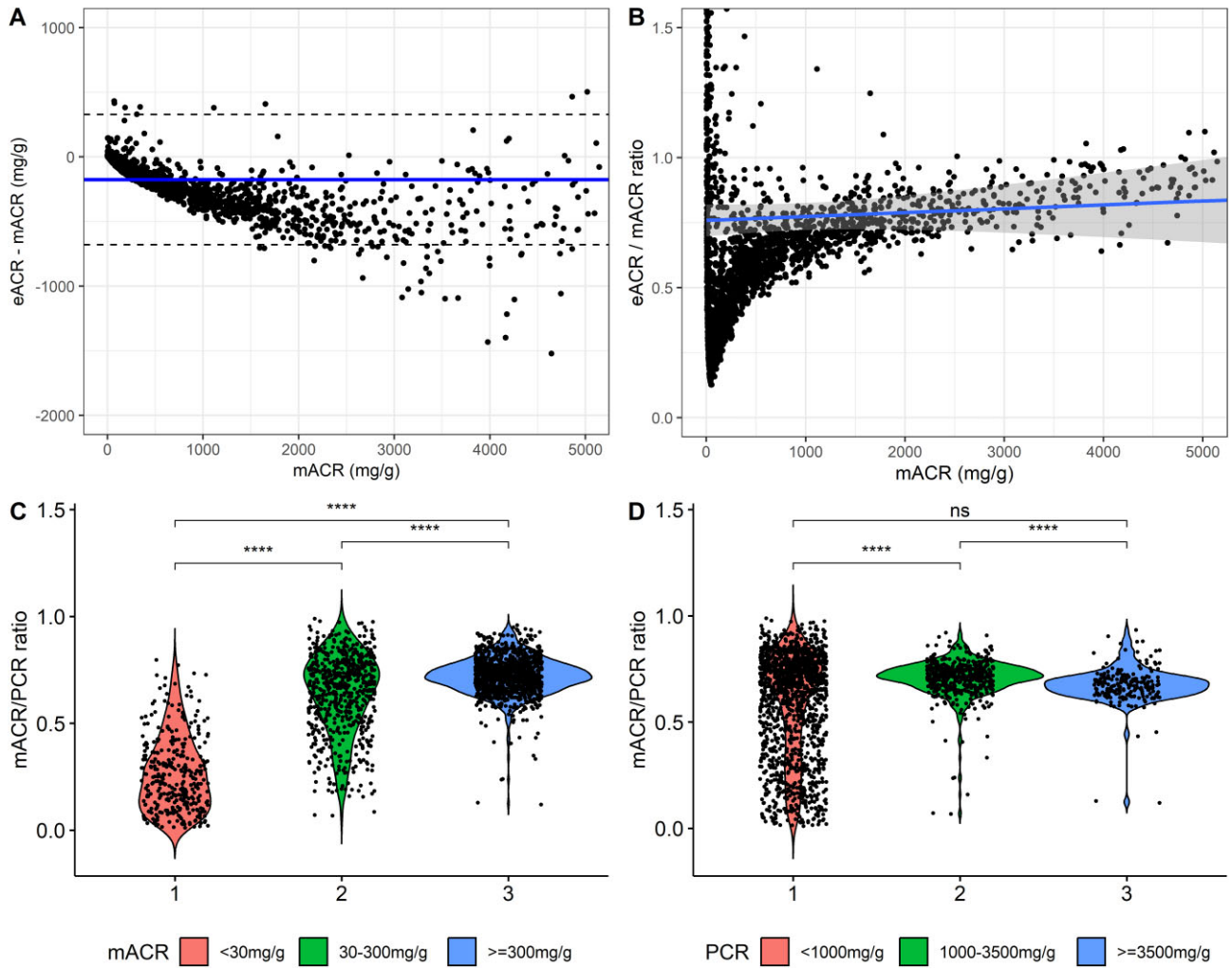


Figure 1: Difference between mACR and eACR and mACR:PCR ratio. **(A)** Difference plot for agreement between mACR and eACR. Blue solid line and dashed lines represent mean and SDs of difference between mACR and eACR. **(B)** Scatter plot for the mACR and the eACR:mACR ratio. Blue line and grey area represent linear association and 95% CIs between mACR and eACR:mACR ratio. **(C)** Violin plot for the mACR:PCR ratio according to mACR category. **(D)** Violin plot for the mACR:PCR ratio according to PCR category.

AUROCs of the eACR and PCR compared with those of mACR. However, the IDI and cNRI statistics showed that eACR had inferior discrimination and reclassification abilities compared with mACR for various CKD causes, except for the group with an unclassified aetiology (Table 2). Meanwhile, the PCR exhibited discrimination and reclassification performances similar to those of the mACR. Notably, in patients with PKD, the PCR showed significantly higher IDI and cNRI values than the mACR.

Predictive performance of mACR, eACR and PCR according to degree of albuminuria and proteinuria

When we categorized patients into different levels of albuminuria (normal–mild, moderate and severe), we found that the mACR, PCR and eACR had comparable predictive powers based on the AUROC (Table 3). However, the eACR showed significantly lower IDI and cNRI values than the mACR for all albuminuria categories. In contrast, PCR yielded varying results for different degrees of albuminuria. In patients with normal–mild albuminuria (mACR <30 mg/g), the PCR had significantly lower IDI {−0.168 [95% confidence interval (CI) −0.404 to −0.035], $P < .001$} and cNRI [−0.442 (95% CI −0.820 to −0.048), $P < .001$) values than mACR. However, the values were comparable in patients with moderate albuminuria (mACR 30–300 mg/g) and were higher for the IDI [0.009 (95% CI 0.002–0.016), $P = .007$] and cNRI [0.292 (95% CI 0.167–0.390), $P = .007$] in patients with severe albuminuria (mACR ≥300 mg/g). When we further categorized patients into the degree of proteinuria, inferior discrimination and reclassification of eACR were found in patients with subnephrotic proteinuria (<3500 mg/g) but not in those with nephrotic proteinuria (≥3500 mg/g). Meanwhile, the IDI difference between the ACR and PCR for participants with nephrotic-range PCR was 0.019.

Predictive performance of mACR, eACR and PCR according to CKD grade

We further categorized patients according to their CKD grades. Generally, eACR and PCR showed similar predictive performances to mACR from CKD G1 to G3 (Table 4). However, all AUROC, IDI and cNRI values indicated that eACR was inferior to mACR in patients with CKD G4–5. PCR had a significantly lower AUROC than mACR for CKD G4–5, but the IDI and cNRI values were comparable.

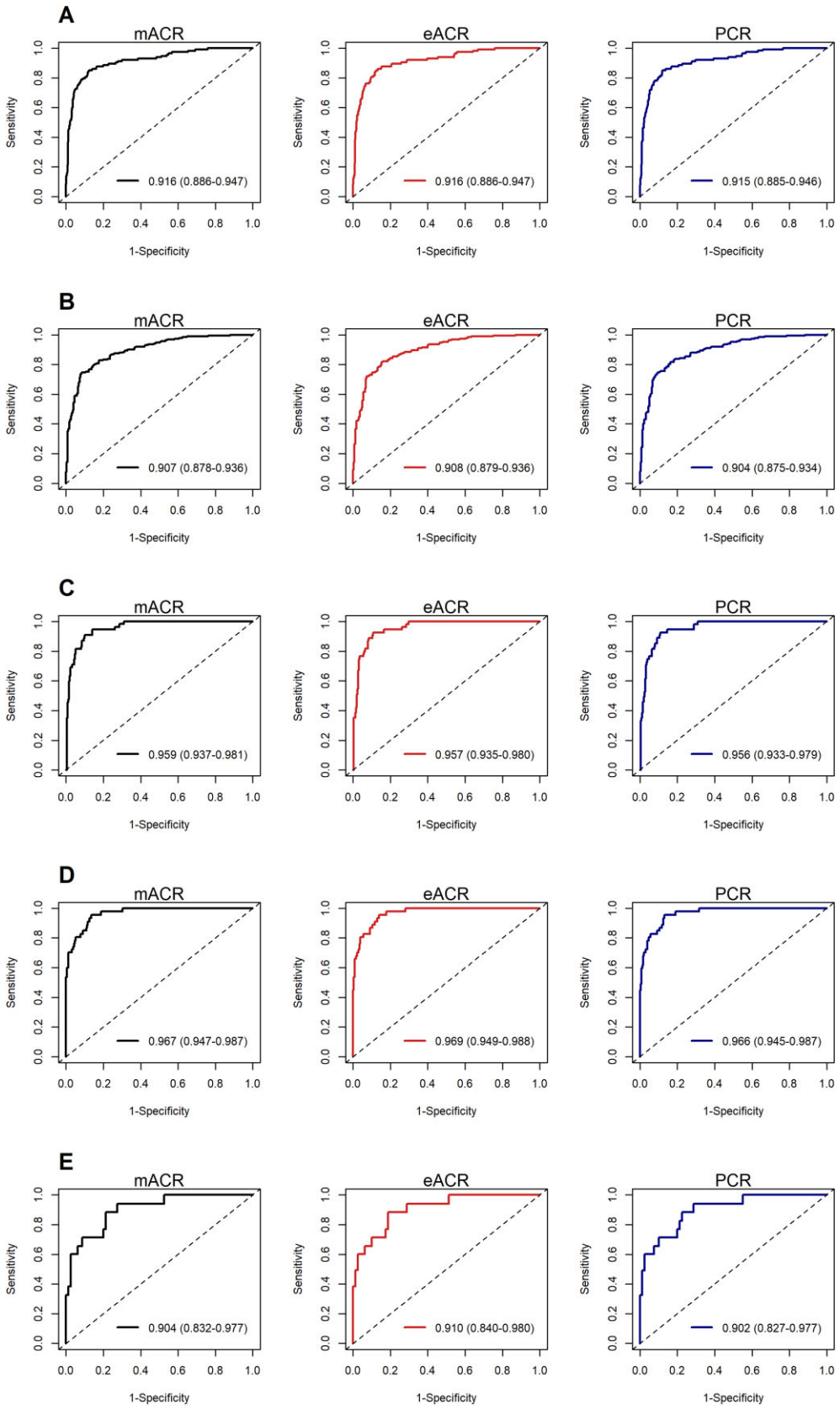


Figure 2: Predictive performance of mACR, eACR and PCR for the 5-year risk of KFRT according to the cause of CKD: **(A)** glomerulonephritis, **(B)** diabetic nephropathy, **(C)** hypertensive nephropathy, **(D)** polycystic kidney disease, **(E)** unclassified. Predictive performance was examined by time-dependent AUROC.

Table 2: Predictive performance of eACR and PCR for 5-year risk of KFRT according to cause of CKD.

Cause of CKD	Events, *n*		IDI (95% CI)	P-value	Continuous NRI (95% CI)	P-value
GN (*n* = 749)	117	mACR	Ref.	–	Ref.	–
		eACR	−0.019 (−0.032 to −0.007)	<.001	−0.467 (−0.590 to −0.353)	<.001
		PCR	0.011 (−0.005–0.027)	.140	0.340 (0.162–0.530)	<.001
DN (*n* = 488)	202	mACR	Ref.	–	Ref.	–
		eACR	−0.015 (−0.028 to −0.007)	<.001	−0.262 (−0.609 to −0.105)	<.001
		PCR	0.001 (−0.013–0.011)	.777	0.081 (−0.508–0.251)	.571
HTN (*n* = 385)	57	mACR	Ref.	–	Ref.	–
		eACR	−0.036 (−0.059 to −0.012)	<.001	−0.581 (−0.781 to −0.396)	<.001
		PCR	−0.002 (−0.044–0.041)	.997	0.181 (−0.687–0.642)	.578
PKD (*n* = 351)	49	mACR	Ref.	–	Ref.	–
		eACR	−0.044 (−0.070 to −0.024)	.020	−0.637 (−0.789 to −0.432)	<.001
		PCR	0.031 (0.007–0.056)	.020	0.441 (0.216–0.653)	<.001
Unclassified (*n* = 126)	18	mACR	Ref.	–	Ref.	–
		eACR	0.006 (−0.013–0.028)	.512	−0.171 (−0.411–0.616)	.698
		PCR	0.003 (−0.030–0.044)	.844	0.214 (−0.390–0.480)	.352

GN: glomerulonephritis; DN: diabetic nephropathy; HTN: hypertensive nephropathy.

Predictive performance of mACR, eACR and PCR for 2-year risk of KFRT

Next we compared the ability of the KFRE scores to predict the risk of the 2-year KFRT. As expected, all scores using the mACR, PCR and eACR performed better for predicting the 2-year KFRT risk than the 5-year risk (Supplementary Table S2). However, the difference in predictability between the scores was less pronounced for 2-year risk than for 5-year risk. Nonetheless, based on IDI and cNRI analyses, eACR was found to be inferior and PCR was superior to mACR in predicting the 2-year risk of KFRT in patients with hypertensive nephropathy. When stratified by albuminuria category, PCR and eACR showed no difference in performance for the 2-year KFRT risk across at least two statistical methods (Supplementary Table S3). However, superior discrimination and reclassification using the PCR have been observed in patients with nephrotic-range proteinuria. No predictor showed significantly different performances using at least two statistical methods across the CKD grade categories (Supplementary Table S4).

Sensitivity analysis

For the sensitivity analysis, we examined the performance of the KFRE scores in patients with diabetic nephropathy based on the albuminuria category and in patients with glomerulonephritis based on the proteinuria category (Supplementary Table S5). In patients with diabetic nephropathy, the inferiority of the eACR to the mACR was observed in the subgroup with mACR <300 mg/g based on the IDI and cNRI; however, PCR was not superior to mACR. In patients with glomerulonephritis, inferiority of eACR and superiority of PCR were observed only in the subgroup with a PCR of 1000–3500 mg/g based on the IDI and cNRI, and no predictor showed significant differences by at least two statistical methods in the other subgroups. Finally, we analysed follow-up urinalysis data collected after 1 year (Supplementary Fig. S1) and similar results were observed in a subgroup of 1413 patients who underwent urinalysis at 1 year and did not reach KFRT during the 1-year follow-up. In the subgroups of CKD causes, we found that eACR was inferior to mACR in patients with diabetic nephropathy and PKD based on the IDI and cNRI (Supplementary Table S6). In addition, the inferiority of the eACR was also observed in the subgroup of mACR 30–300 mg/g in the albuminuria category and in PCR <1000 mg/g in the proteinuria category (Supplementary Table S7). The superiority of the PCR was observed in the mACR ≥300 mg/g and PCR 1000–3500 mg/g subgroups.

DISCUSSION

In this study we examined the predictive performance of mACR, eACR and PCR for KFRT risk in patients with CKD. We calculated the KFRE scores using these metrics and found that all scores showed excellent predictive performance for the risks of the 5-year and 2-year KFRT. However, the eACR showed inferior discrimination and reclassification abilities compared with the mACR for various causes of CKD. In addition, when patients were classified according to the degree of albuminuria, the inferiority of the eACR to the mACR was more pronounced in patients with albuminuria <30 mg/g. Similar results were observed in the various sensitivity analyses.

Albuminuria is one of the most important prognostic factors for CKD and is included in the diagnostic criteria [5]. Therefore, many well-performing clinical prediction models for KFRT have included albuminuria as a predictor [6, 7, 14–17]. Furthermore, as even higher albuminuria within the normal–mild albuminuria category (<30 mg/g) is significantly associated with an increased risk of adverse clinical outcomes [18], it should be measured at the initial diagnosis of CKD. Nevertheless, in clinical practice, measuring albuminuria and predicting CKD risk may not always be feasible, particularly in low- to middle-income countries [19]. Moreover, urine albumin measurement is more expensive than total urine protein measurement [20]. In Korea, the cost of mACR is approximately seven times higher than that of PCR. Therefore, depending on the socio-economic conditions and health policies of each country, PCR measurements may be preferred over ACR measurements. Several equations have been proposed to predict ACR using PCR [8, 21, 22]. Therefore, we tested whether eACR and PCR were as effective as mACR alone in predicting the risk of KFRT.

Despite the overall good performance of the eACR and PCR, the IDI and cNRI statistics showed that the eACR was inferior to the mACR in patients with various causes of CKD. Notably, the inferiority of the eACR was more prominent in patients with a low

Table 3: Predictive performance of mACR, eACR and PCR for 5-year risk of KFRT according to degree of albuminuria and proteinuria.

Degree	Events, *n*		AUROC (95% CI)	*P*-value	IDI (95% CI)	*P*-value	Continuous NRI (95% CI)	*P*-value
mACR								
Normal–mild (<30 mg/g) (*n* = 335)	6	mACR	0.887 (0.754–1.000)	–	Ref.	–	Ref.	–
		eACR	0.878 (0.750–1.000)	.244	−0.168 (−0.404 to −0.035)	<.001	−0.442 (−0.820 to −0.048)	<.001
		PCR	0.880 (0.754–1.000)	.326	−0.144 (−0.308 to −0.021)	<.001	−0.454 (−0.824 to −0.025)	.007
Moderate (30–300 mg/g) (*n* = 637)	65	mACR	0.896 (0.860–0.931)	–	Ref.	–	Ref.	–
		eACR	0.893 (0.857–0.928)	.370	−0.060 (−0.094 to −0.025)	.007	−0.509 (−0.647 to −0.379)	<.001
		PCR	0.893 (0.858–0.929)	.422	−0.008 (−0.039–0.021)	.678	0.076 (−0.544–0.346)	.930
Severe (≥300 mg/g) (*n* = 1127)	372	mACR	0.909 (0.889–0.929)	–	Ref.	–	Ref.	–
		eACR	0.910 (0.890–0.930)	.090	−0.013 (−0.019 to −0.008)	<.001	−0.285 (−0.359 to −0.190)	<.001
		PCR	0.909 (0.889–0.928)	.737	0.009 (0.002–0.016)	.007	0.292 (0.167–0.390)	.007
PCR								
<1000 mg/g (*n* = 1392)	144	mACR	0.917 (0.893–0.940)	–	Ref.	–	Ref.	–
		eACR	0.914 (0.890–0.938)	.029	−0.033 (−0.050 to −0.017)	<.001	−0.518 (−0.621 to −0.435)	<.001
		PCR	0.911 (0.888–0.936)	.016	0.009 (−0.011–0.031)	.219	0.236 (−0.439–0.409)	.113
1000–3500 mg/g (*n* = 494)	173	mACR	0.866 (0.828–0.903)	–	Ref.	–	Ref.	–
		eACR	0.863 (0.825–0.900)	.272	−0.021 (−0.033 to −0.012)	<.001	−0.478 (−0.625 to −0.347)	<.001
		PCR	0.862 (0.824–0.900)	.166	−0.006 (−0.016–0.009)	.791	0.118 (−0.030–0.334)	.100
≥3500 mg/g (*n* = 213)	126	mACR	0.933 (0.898–0.969)	–	Ref.	–	Ref.	–
		eACR	0.937 (0.902–0.971)	.048	0.001(−0.005–0.007)	.784	0.021 (−0.232–0.201)	.857
		PCR	0.936 (0.902–0.970)	.060	0.019 (0.010–0.029)	<.001	0.311 (0.138–0.473)	<.001

degree of albuminuria and proteinuria. The PCR has been known to not correlate well with the mACR in low-grade proteinuria [8, 21, 23, 24]. This may be due to inaccuracy in measuring total urine protein [4]. Because of variations in the amount and composition of urinary proteins, precise measurement of total urine protein is challenging, especially in cases of low proteinuria. Furthermore, the proportion of albumin in total urine protein can vary depending on the degree of proteinuria, making it more difficult to estimate the ACR using the PCR. In the present study, we found that the mACR:PCR ratio was low in patients with low proteinuria, which is consistent with previous studies [21, 23]. Therefore, the agreement between the mACR and eACR was poor in patients with low proteinuria, which may have contributed to the inferiority of the eACR in predicting KFRT in our study. Accordingly, this study suggests that measuring the ACR directly should be preferred over calculating the eACR using the PCR in patients with CKD who are predicted or confirmed to have mildly or moderately increased albuminuria (<300 mg/g), to ensure an accurate prediction of KFRT risk.

The KFRE score was originally designed to use the mACR; thus, in principle, the PCR cannot be used in this equation. However, albumin was the predominant urinary protein, except in cases of low proteinuria. Moreover, the mACR was applied to KFRE after using the natural logarithm, which made a small difference in the prediction score between the mACR and PCR. Thus we assumed that the PCR for KFRE would have a predictive performance similar to that of the mACR. Based on this assumption, when we categorized patients according to the degree of albuminuria and proteinuria, the PCR generally showed a predictive performance similar to that of the mACR, except in the group with normal–mild mACR (<30 mg/g). Surprisingly, the PCR showed better performance than the mACR in patients with nephrotic-range proteinuria when assessed using the IDI and cNRI. In these patients, the mACR:PCR ratio was significantly lower than that in patients with a PCR of 1000–3500 mg/g. This result may reflect the increased urinary excretion of non-albumin proteins due to severe tubular injury in patients with nephrotic-range proteinuria. Additionally, when we categorized patients according to the cause of CKD, we observed a significant superiority of the PCR over the mACR in patients with PKD, in whom tubular structural damage was the main cause of kidney injury. Therefore, although the mACR is known to be more sensitive to glomerular permeability than the PCR [25, 26], the PCR may be more sensitive to overall kidney damage with severe tubular injury, which may lead to the superior predictability of the PCR in patients with a PCR ≥3500 mg/g. Taken together, use of the PCR *per se*, not the calculated eACR, may be acceptable for predicting KFRT in patients with a PCR ≥3500 mg/g if albuminuria measurement is unavailable or if cost-effectiveness is required. However, further validation is required to confirm these findings.

This study had several limitations. First, because participants in the KNOW-CKD study were recruited and managed in tertiary hospitals in Korea, our results may not be generalizable to all primary care settings. However, it is uncommon to simultaneously measure the PCR and ACR in primary care. Therefore, efforts are needed to collect a large number of primary care patients. Second, we grouped patients as unclassified when the number of disease cases was small or difficult to categorize. This may have resulted in a mixed category of diseases, making the results inconclusive. However, using too few patients would also lead to a loss of statistical significance, therefore we grouped these patients together. Third, this study was conducted in Korean patients with CKD using the non-North American four-variable KFRE scale. Further studies using other conversion equations for different

Table 4: Predictive performance of mACR, eACR and PCR for 5-year risk of KFRT according to CKD grade.

CKD grade		AUROC (95% CI)	P-value	IDI (95% CI)	P-value	Continuous NRI (95% CI)	P-value
CKD G1–2 ($n = 736$)	mACR	0.833 (0.758–0.908)	–	Ref.	–	Ref.	–
	eACR	0.841 (0.770–0.913)	0.113	−0.001 (−0.005–0.001)	0.359	−0.330 (−0.603 to −0.018)	0.033
	PCR	0.833 (0.758–0.908)	>0.999	0.000 (−0.001–0.001)	0.472	−0.358 (−0.567–0.300)	0.299
CKD G3 ($n = 786$)	mACR	0.801 (0.759–0.844)	–	Ref.	–	Ref.	–
	eACR	0.808 (0.765–0.850)	0.061	0.004 (−0.007–0.016)	0.485	−0.115 (−0.252–0.044)	0.173
	PCR	0.802 (0.758–0.845)	0.923	0.004 (−0.003–0.011)	0.292	0.135 (0.005–0.270)	0.040
CKD G4–5 ($n = 577$)	mACR	0.854 (0.816–0.893)	–	Ref.	–	Ref.	–
	eACR	0.843 (0.803–0.883)	0.014	−0.024 (−0.037 to −0.012)	<0.001	−0.187 (−0.462 to −0.060)	<0.001
	PCR	0.842 (0.801–0.882)	0.018	−0.013 (−0.036–0.004)	0.133	−0.132 (−0.268–0.004)	0.133

ethnicities are required to validate our findings. Finally, there is currently no standardized method for measuring urine protein and albumin, therefore studies utilizing different methods may yield different results compared with our findings.

In conclusion, all KFRE scores using the mACR, PCR and eACR converted from the PCR showed excellent predictive performance for the 5-year risk of KFRT. However, the mACR exhibited the best predictive performance in patients with an ACR <300 mg/g and thus should be used for these patients. As the PCR showed similar predictability to the mACR in patients with moderate–severe albuminuria and proteinuria, it may be alternatively used to predict the risk of KFRT in the absence of the mACR. Therefore, the choice between the PCR and ACR for predicting KFRT should be based on clinical context, availability, cost and local practices.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

H.K. and S.H.H. were responsible for the study concept and design. Y.K., Y.H.K., S.W.K., T.H.Y., K.H.O. and S.H.H. were responsible for data acquisition. H.K., Y.S.J., H.R.Y., J.K. and SHH were responsible for data analysis. All authors were responsible for data interpretation. H.K. wrote the draft manuscript. Y.K., Y.H.K., S.W.K., J.T.P., T.H.Y., S.W.K., K.H.O. and S.H.H. were responsible for manuscript review. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy and integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

DATA AVAILABILITY STATEMENT

The dataset generated and analysed during the current study is available from http://www.know-ckd.org/ckd/main/main.html.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

REFERENCES

1. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl* 2022;**12**:7–11. https://doi.org/10.1016/j.kisu.2021.11.003
2. Fox CS, Matsushita K, Woodward M *et al.* Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;**380**:1662–73. https://doi.org/10.1016/S0140-6736(12)61350-6
3. Kim KM, Oh HJ, Choi HY *et al.* Impact of chronic kidney disease on mortality: a nationwide cohort study. *Kidney Res Clin Pract* 2019;**38**:382–90. https://doi.org/10.23876/j.krcp.18.0128
4. Lamb EJ, MacKenzie F, Stevens PE. How should proteinuria be detected and measured? *Ann Clin Biochem* 2009;**46**:205–17. https://doi.org/10.1258/acb.2009.009007
5. Kidney Disease: Improving Global Outcomes CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Summary of recommendation statements. *Kidney Int Suppl* 2013;**3**:5–14.
6. Tangri N, Grams ME, Levey AS *et al.* Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *JAMA* 2016;**315**:164–74. https://doi.org/10.1001/jama.2015.18202
7. Grams ME, Sang Y, Ballew SH *et al.* Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. *Kidney Int* 2018;**93**:1442–51. https://doi.org/10.1016/j.kint.2018.01.009
8. Sumida K, Nadkarni GN, Grams ME *et al.* Conversion of urine protein–creatinine ratio or urine dipstick protein to urine albumin–creatinine ratio for use in chronic kidney disease screening and prognosis. *Ann Intern Med* 2020;**173**:426–35. https://doi.org/10.7326/M20-0529
9. Kidney Disease: Improving Global Outcomes Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int* 2021;**100**(4 Suppl):S1–S276. https://doi.org/10.1016/j.kint.2021.05.021
10. Methven S, MacGregor MS, Traynor JP *et al.* Assessing proteinuria in chronic kidney disease: protein–creatinine ratio versus albumin–creatinine ratio. *Nephrol Dial Transplant* 2010;**25**:2991–6. https://doi.org/10.1093/ndt/gfq140
11. Methven S, MacGregor MS, Traynor JP *et al.* Comparison of urinary albumin and urinary total protein as predictors of patient outcomes in CKD. *Am J Kidney Dis* 2011;**57**:21–8. https://doi.org/10.1053/j.ajkd.2010.08.009

12. Oh K-H, Park SK, Park HC *et al.* KNOW-CKD (KoreaN cohort study for Outcome in patients With Chronic Kidney Disease): design and methods. *BMC Nephrol* 2014;**15**:80. https://doi.org/10.1186/1471-2369-15-80
13. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006
14. Keane WF, Zhang Z, Lyle PA *et al.* Risk scores for predicting outcomes in patients with type 2 diabetes and nephropathy: the RENAAL Study. *Clin J Am Soc Nephrol* 2006;**1**:761–7. https://doi.org/10.2215/CJN.01381005
15. Lin C-C, Li C-I, Liu C-S *et al.* Development and validation of a risk prediction model for end-stage renal disease in patients with type 2 diabetes. *Sci Rep* 2017;**7**:10177. https://doi.org/10.1038/s41598-017-09243-9
16. Wan EYF, Fong DYT, Fung CSC *et al.* Prediction of new onset of end stage renal disease in Chinese patients with type 2 diabetes mellitus – a population-based retrospective cohort study. *BMC Nephrol* 2017;**18**:257. https://doi.org/10.1186/s12882-017-0671-x
17. Vistisen D, Andersen GS, Hulman A *et al.* A validated prediction model for end-stage kidney disease in type 1 diabetes. *Diabetes Care* 2021;**44**:901–7. https://doi.org/10.2337/dc20-2586
18. Levey AS, de Jong PE, Coresh J *et al.* The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* 2011;**80**:17–28. https://doi.org/10.1038/ki.2010.483
19. Qarni B, Osman MA, Levin A *et al.* Kidney care in low- and middle-income countries. *Clin Nephrol* 2020;**93**:21–30. https://doi.org/10.5414/CNP92S104
20. Lamb EJ, McTaggart MP, Stevens PE. Why albumin to creatinine ratio should replace protein to creatinine ratio: it is not just about nephrologists. *Ann Clin Biochem* 2013;**50**:301–5. https://doi.org/10.1177/0004563212473284
21. Weaver RG, James MT, Ravani P *et al.* Estimating urine albumin-to-creatinine ratio from protein-to-creatinine ratio: development of equations using same-day measurements. *J Am Soc Nephrol* 2020;**31**:591–601. https://doi.org/10.1681/ASN.2019060605
22. Grams ME, Li L, Greene TH *et al.* Estimating time to ESRD using kidney failure risk equations: results from the African American Study of Kidney Disease and Hypertension (AASK). *Am J Kidney Dis* 2015;**65**:394–402. https://doi.org/10.1053/j.ajkd.2014.07.026
23. Atkins RC, Briganti EM, Zimmet PZ *et al.* Association between albuminuria and proteinuria in the general population: the AusDiab Study. *Nephrol Dial Transplant* 2003;**18**:2170–4. https://doi.org/10.1093/ndt/gfg314
24. Fisher H, Hsu CY, Vittinghoff E *et al.* Comparison of associations of urine protein-creatinine ratio versus albumin-creatinine ratio with complications of CKD: a cross-sectional analysis. *Am J Kidney Dis* 2013;**62**:1102–8. https://doi.org/10.1053/j.ajkd.2013.07.013
25. Newman DJ, Thakkar H, Medcalf EA *et al.* Use of urine albumin measurement as a replacement for total protein. *Clin Nephrol* 1995;**43**:104–9.
26. Ballantyne FC, Gibbons J, O'Reilly DS. Urine albumin should replace total protein for the assessment of glomerular proteinuria. *Ann Clin Biochem* 1993;**30**:101–3. https://doi.org/10.1177/000456329303000119

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