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Estimating urine albumin to creatinine ratio from protein to creatinine ratio using same day measurement: validation of equations

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Abstract

Objectives: Severity of chronic kidney disease is defined by glomerular filtration rate (GFR) and albuminuria (ACR) by the KDIGO and are related to cardiovascular outcomes and end-stage-kidney-failure. However, proteinuria (PCR) is more often available than ACR in records. Recently, equations were developed to estimate ACR from PCR. We investigated their performances in our population.

Methods: In the academic medical hospital of Liège, we retrospectively analysed same day measurement of ACR and PCR and staged them according to the KDIGO A1-A2-A3 categories. Analyser Roche Cobas (R) gathered 2,633 urinalysis (May 2018-May 2019) and analyser Abbott Alinity (A) 2,386 urinalysis (May 2019-March 2020). We compared the KDIGO staging of mACR and eACR obtained from Weaver's and Sumida's equations.

Results: Median age was 63 [52;71]/64 [53;72] years old, 43/42% were female; 78/74% had diabetes; proportion of mACR-A1 was 65.6%/64.2%, A2 was 25.5%/25.5% and A3 was 8.8%/10.3% (Method R/A, respectively). Both equations gave similar distribution of KDIGO staging of eACR. Overall agreements were higher than 88% regardless of the analyser or of the equation. Performances in between equations were equivalent according to the multi-level AUC (multinomial logistic regression model).

Conclusions: Good concordance was observed between mACR and eACR regardless of the equation or of the analyser. No patient with an A3-measured ACR was estimated within the KDIGO A1 category. Though ACR should be measured when clinically needed, it may be reasonably estimated from the PCR through these equations, for epidemiologic retrospective studies or research purposes.

Keywords: albuminuria; chronic kidney disease; proteinuria.

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Introduction

According to the "Kidney Disease: Improving Global Outcomes" (KDIGO) guidelines, chronic kidney disease (CKD) is mostly defined by glomerular filtration rate (GFR) and albuminuria [1]. These variables may also help to foresee cardiovascular risk and need for renal replacement therapy [2, 3]. Albuminuria is not always available in the medical records whereas proteinuria is [3–5]. This is partly explained by cheaper cost of proteinuria measurement. Recently, equations have been developed to estimate the urinary albumin to creatinine ratio (ACR) when only urinary protein to creatinine ratio (PCR) was available [6, 7]. Approaching the ACR from the PCR is interesting for epidemiologic retrospective clinical studies or research purposes. This article aims at the evaluation of the performance of these equations in our population.

Materials and methods

This is a retrospective, observational, single centre study, only based on laboratory data.

We retrospectively analysed ACR and PCR measurements from the same sample between May 2018 and March 2020 at ULiège Academic Hospital in Liège, Belgium. All consecutive patients were

included who were eligible for reimbursement. Enrolled patients were a mixture of in and outpatients.

Two different analysers were used to measure urine albumin, urine creatinine and urine protein (Roche Cobas from May 2018 to May 2019 and Abbott Alinity from May 2019 to March 2020). Both analysers have the same measurement method for urine protein (benzethonium chloride, turbidimetric method), urine albumin (turbidimetry) and urine creatinine (Jaffe). The Roche Total Protein Urine/CSF kit (Gen.3) and the Abbott Alinity Urine/CSF Protein reagent kit have been calibrated with the National Institute of Standards & Technology (NIST) Reference Material SRM-927c using the biuret method for the quantification of protein. Of note, this standard is a reference material for serum proteins and the dilutions of this material to calibrate urine proteins has not been proven to be commutable, leading to potential biases [8, 9]. The method based on benzethonium chloride gives a stable turbidity and is rather not influenced by temperature, but its cross-reactivity with immunoglobulins is less important than for albumin, even if this has been disputed [10, 11]. Tamm-Horsfall is not significantly detected by the benzethonium chloride precipitation due to its mucin-like consistence, which renders it resistant to precipitation [12]. More generally, all turbidimetric or colorimetric methods aiming at the quantification of total proteinuria are all inaccurate for the measurement of monoclonal free light chains [13].

The Cobas Tina-quant Albumin (Gen.2) and Abbott Alinity "microalbumin" reagent have been standardized against the certified reference material in human serum of the IRMM (Institute for Reference Material and Measurements) ERM-DA470k/IFCC. However, despite using the same reference material, transferability may be limited by the use of different preparation and value transfer protocols [14].

The creatinine reagents from both companies are IDMS traceable.

Limit of quantification (LOQ) of urinary albumin was 3 and 0.72 mg/L; LOQ of urinary protein was 39.96 and 26 mg/L; and LOQ of urinary creatinine was 0.05 and 0.03 g/L for Roche Cobas and Abbott Alinity, respectively.

Data extraction gathered the following items: age, gender, urinary proteins, urinary albumin, urinary creatinine, glycosuria, glycaemia, glycated haemoglobin (HbA_{1c}). Patients were considered as diabetic according to the following criteria: randomly measured glycaemia > 200 mg/dl, presence of glycosuria, HbA_{1c} > 6% or if the prescriber was a diabetologist. We only considered one sample (the first one available) per patient. Patients were then classified by ACR according to the KDIGO classification: A1 <30 mg/g; A2 between 30 and 300 mg/g; A3 > 300 mg/g (Supplementary Table 1). We then used Weaver et al. [6] and Sumida et al. [7] equations to estimate ACR from the PCR (Table 1). Estimated ACR (eACR) were also ranked according to the KDIGO classification.

Data distribution was defined as normal or non-normal by the Shapiro-Wilk test [15]. The distribution of the main data was non normal and results were then expressed as medians [P25; P75]. We compared the KDIGO rankings (in %) between eACR and measured ACR (mACR). Concordance between eACR and mACR was assessed by calculation of overall agreement (number of true positives + true negatives divided by the total), sensitivity, specificity, positive predictive value and negative predictive value using the KDIGO threshold: A1 vs. A2/A3 (threshold ACR 30 mg/g) or A1/A2 vs. A3 (threshold ACR 300 mg/g). We designed the ROC curves (receiver operating characteristic) according to these thresholds as performed in Weaver's original papers. Youden's index (Y) appreciate the precision of a statistic method and depends on the test's sensitivity and specificity. It does not depend on the prevalence of the disease (Y = Se + Sp-1). Y index defined new thresholds of ACR that give the best balance for sensitivity and specificity in our population. Statistical analyses were performed on Microsoft Excel and MedCalc (Ostende, Belgium) for ROC curves processing (non-parametric AUCs) and Y index. Difference between ROC curves was appreciated by the test of Hanley & McNeil [16].

We also performed ordinal logistic regression with the KDIGO ACR categories (<30 mg/g, 30–300 mg/g, >300 mg/g) as the dependent variable and the estimated ACR from Weaver or Sumida as independent variable (continuous variable, not categorized). The multi-level AUC is an overall area under the ROC curve, calculated from the multinomial logistic regression model. The pairwise AUCs are area under the curve for the pairwise comparisons of categories (levels). The pairwise and multi-level AUCs were calculated with the MultiAUC macro in SAS 9.4. Since our population is mainly diabetic patients, we performed a sub analysis according to diabetes, applying the Bonferroni correction to claim significant difference (alpha level of 0.05/8 = 0.00625).

Table 1: Equations to estimate median ACR according to sex.

Method	PCR, mg/g	Equations eACR = (mg/g)
Sumida [7]		Exp (5.3920 + 0.3072 × ln (min (PCR/50, 1)) + 1.5793 × ln (max (min (PCR/500, 1), 0.1)) + 1.1266 × ln (max (PCR/500, 1)))
Weaver [6]	Women:	
	<40	Exp (1.7060 − 0.0572 × ln(PCR))
	40 to <60	Exp (0.2183 + 0.3460 × ln(PCR))
	60 to <250	Exp (−6.2539 + 1.9269 × ln(PCR))
	250 to <1,000	Exp (−4.4287 + 1.5963 × ln(PCR))
	≥1,000	Exp (0.0445 + 0.9488 × ln(PCR))
	Men:	
	<40	Exp (0.7373 + 0.1697 × ln(PCR))
	40 to <60	Exp (−2.7625 + 1.1184 × ln(PCR))
	60 to <250	Exp (−6.9212 + 2.1342 × ln(PCR))
	250 to <1,000	Exp (−1.9690 + 1.2372 × ln(PCR))
	≥1,000	Exp (−0.1522 + 0.9742 × ln(PCR))

PCR, urinary protein to creatinine ratio; ACR, urinary albumin to creatinine ratio; ln, neperian logarithm.

Ethics

Remnant samples only were used in this study. No specific approval was requested to the CHU de Liège Institutional Review Board as a leaflet including the following statement is given to all admitted patients: "According to the law of the December 19, 2008, any left-over of biological material collected from patients for their standard medical management and normally destroyed when all diagnostic analysis have been performed, can be used for validation of methods." The law authorizes such use except if the patient expressed an opposition when still alive (presumed consent). Written informed consent for participation was not required for this study in accordance with the Belgian national legislation and the Institutional requirements.

Results

We analysed 2,633 results with Roche Cobas and 2,386 results with Abbott Alinity. Characteristics of the population are detailed in Table 2. Briefly, median age was 63 [52;71] and 64 [53;72] years old, 43 and 42% were women, and 78 and 74% had diabetes, in Roche Cobas and Abbott Alinity cohorts, respectively.

Staging according to KDIGO for mACR was the following: 65.6% were staged A1, 25.5% were A2; and 8.8% were A3 with Roche Cobas. With Abbott Alinity, 64.2% were staged A1; 25.5% were A2; and 10.3% were A3.

Based on the Weaver equation, the proportion of patients with eACR A1 was 64;7%; A2 was 25;7%; and A3 was 9;6% with Roche Cobas. For Abbott Alinity, the proportion of eACR A1 was 62.5%; A2 was 25.7%; and A3 was 11.7% (Table 3).

Considering the A1-A2 (30 mg/g) threshold, sensitivity of eACR to approach mACR was 85 and 89%, with a specificity of 91 and 92%; the positive predictive value was 83 and 85%, the negative predictive value was 92 and 94%, and overall agreement was 89 and 91% for Roche Cobas and Abbott Alinity analysers, respectively (Table 4). The corresponding area under the curve was 0.958 ($p < 0.0001$) and 0.970 ($p < 0.0001$) (Supplementary Material: Figures 1 and 2). The Youden index was 26 mg/g and 24 mg/g for Roche Cobas and Abbott Alinity, respectively.

Table 3: Distribution of mACR and eACR [6,7].

	A1	A2	A3
mACR			
Roche Cobas	65.6%	25.5%	8.8%
Abbott Alinity	64.2%	25.5%	10.3%
Weaver eACR			
Roche Cobas	64.7%	25.7%	9.6%
Abbott Alinity	62.5%	25.7%	11.7%
Sumida eACR			
Roche Cobas	65.9%	25.0%	9.0%
Abbott Alinity	64.8%	24.1%	11.1%

mACR, measured urinary albumin to creatinine ratio; eACR, estimated urinary albumin to creatinine ratio.

Table 2: Patient's characteristics.

	Roche Cobas	Abbott Alinity
n =	2,633	2,386
Duration	365 days (May 2018 - May 2019)	306 days (May 2019 - March 2020)
Men/women	57/43% 1,500/1,133	58/42% 1,402/984
Diabetes	78%	74%
Age, years, median [P25; P75]	63 [52; 71]	64 [53; 72]
mACR median, mg/g	14	15
mACR [P25; P75], mg/g	[5; 59]	[7; 61]
mACR min, mg/g	0.97	0.32
mACR max, mg/g	10,239	17,833
Creatininuria median, g/L	1.02	0.9
Creatininuria [P25; P75], g/L	[0.65; 1.55]	[0.58; 1.44]
Creatininuria min, g/L	0.05	0.06
Creatininuria max, g/L	5.47	76.53
PCRm median, mg/g	99	101
PCRm [P25;P75], mg/g	[66; 187]	[66; 196]
PCRm min, mg/g	32	1
PCRm max, mg/g	12,390	27,168
KDIGO PCRm		
P1 (<150 mg/g)	68.1% (1792)	66.7% (1,591)
P2 (150–500 mg/g)	21.9% (576)	21.3% (509)
P3 (>500 mg/g)	10.1% (265)	12% (286)
KDIGO mACR		
A1 (<30 mg/g)	65.6% (1728)	64.2% (1,532)
A2 (30–300 mg/g)	25.5% (672)	25.5% (608)
A3 (>300 mg/g)	8.8% (233)	10.3% (246)

PCR, urinary protein to creatinine ratio; ACR, urinary albumin to creatinine ratio; m, measured.

Table 4: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the ROC curve (AUC) and overall agreement for threshold A1-A2 (30 mg/g) and A2-A3 (300 mg/g) with Roche Cobas et Abbott Alinity analysers, according to Weaver et al.'s equation [6]. Sub analysis according to diabetes status.

		Sensitivity	Specificity	PPV	NPV	AUC	Overall agreement
mACR/eACR A1-A2 (Roche Cobas)	**Global**	**84.9%**	**90.6%**	**82.6%**	**92.0%**	**0.958**	**88.6%**
	Diabetes	83.7%	91.9%	83.5%	92.0%	0.960	89.2%
	Non diabetes	89.1%	84.5%	79.6%	91.9%	0.952	86.4%
mACR/eACR A1-A2 (Abbott Alinity)	**Global**	**89.5%**	**91.5%**	**85.5%**	**94.0%**	**0.970**	**90.8%**
	Diabetes	89.3%	93.1%	87.3%	94.2%	0.975	91.8%
	Non diabetes	89.8%	86.5%	80.5%	93.2%	0.958	87.8%
mACR/eACR A2-A3 (Roche Cobas)	**Global**	**93.1%**	**98.5%**	**85.8%**	**99.3%**	**0.996**	**98.0%**
	Diabetes	93.1%	99.0%	89.0%	99.4%	0.997	98.5%
	Non diabetes	93.2%	96.4%	77.5%	99.1%	0.992	96.0%
mACR/eACR A2-A3 (Abbott Alinity)	**Global**	**98.4%**	**98.3%**	**86.7%**	**99.8%**	**0.996**	**98.3%**
	Diabetes	97.6%	98.7%	88.5%	99.8%	0.997	98.6%
	Non diabetes	100.0%	96.9%	83.3%	100.0%	0.992	97.3%

mACR, measured urinary albumin to creatinine ratio; eACR, estimated urinary albumin to creatinine ratio.

Regarding the A2-A3 threshold (300 mg/g), sensitivity was 93 and 98% and specificity was 98% for both analysers. The positive predictive value was 86 and 87%, the negative predictive value was 99 and 100%, and overall agreement was 98 and 98% for the Roche Cobas and Abbott Alinity analysers, respectively (Table 4). The area under the curve was 0.996 ($p < 0.0001$) (Supplementary Material: Figures 1 and 2). The Youden index was 249 mg/g and 287 mg/g for Roche Cobas and Abbott Alinity, respectively. The multi-level AUC calculated from the multinomial logistic regression model was 0.95 and 0.96 for the Roche Cobas and Abbott Alinity analysers, respectively (Figures 1 and 2). The pairwise AUC for A1 vs. A2 was 0.93 and 0.94, A1 vs. A3 was 0.999 and 1 and A2 vs. A3 was 0.93 and 0.93 for the Roche Cobas and Abbott Alinity analysers, respectively.

Of importance, none of the mACR A3 was estimated as A1 by the equation with both assays.

The sub-analysis according to diabetes status found a multi-level AUC calculated from the multinomial logistic regression model of 0.96 (diabetics) and 0.94 (non diabetics) for the Roche Cobas and of 0.97 (diabetics) and 0.93 (non diabetics) for the Abbott Alinity analyser, respectively.

Based on the Sumida equation, the proportion of patients with eACR A1 was 65.9%, A2 was 25%, and A3 was 9% with the Roche Cobas. For Abbott Alinity, the proportion of eACR A1 was 64.8%; A2 was 24.1%, and A3 was 11.1% (Table 3).

Regarding the A1-A2 threshold (30 mg/g), sensitivity was 83 and 86%, with a specificity of 91 and 93%; the positive predictive value was 83 and 87%, the negative predictive value was 91 and 92%, and overall agreement was 88 and 90% for the Roche Cobas and Abbott Alinity analysers, respectively (Table 5). The area under the curve was 0.954 ($p < 0.0001$) and 0.969 ($p < 0.0001$) (Supplementary Material: Figures 1 and 2). The Youden index was 23 mg/g and 24 mg/g for Roche Cobas and Abbott Alinity, respectively.

Regarding the A2-A3 threshold (300 mg/g), sensitivity was 81 and 86% for Roche Cobas and Abbott Alinity analysers, respectively; specificity was 99% for both analysers, positive predictive value was 90% for both analysers, negative predictive value was 98%, and overall agreement was 98% for both analysers (Table 5). The area under the ROC curve was 0.996 ($p < 0.0001$) for both analysers with a cut-off value of ACR according to Youden's index at 146 mg/g ($Y = 0.9596$) and 203 mg/g ($Y = 0.9762$) for Roche Cobas and Abbott Alinity, respectively (Supplementary Material: Figures 1 and 2). The multi-level AUC calculated from the multinomial logistic regression model was 0.95 and 0.96 for the Roche Cobas and Abbott Alinity analysers, respectively (Figures 1 and 2). The pairwise AUC for A1 vs. A2 was 0.92 and 0.94, A1 vs. A3 was 0.999 and 1, and A2 vs. A3 was 0.93 and 0.94 for the Roche Cobas and Abbott Alinity analysers, respectively. Again, no mACR A3 was estimated as A1 by the equation.

The sub-analysis according to diabetes status found a multi-level AUC calculated from the multinomial logistic regression model of 0.96 (diabetics) and 0.94 (non diabetics) for the Roche Cobas and of 0.97 (diabetics) and 0.93 (non diabetics) for the Abbott Alinity analyser, respectively.

When comparing the performance of the two equations, we found no statistically significative difference between the areas under the curves. The threshold values defined by Youden index with the Weaver equation are closer to the KDIGO threshold values then those obtained with the Sumida equation.

The sub-analysis according to diabetes status is shown Tables 4 and 5. The AUC in all sub analyses were all excellent and higher than 0.9. The difference between overall agreement

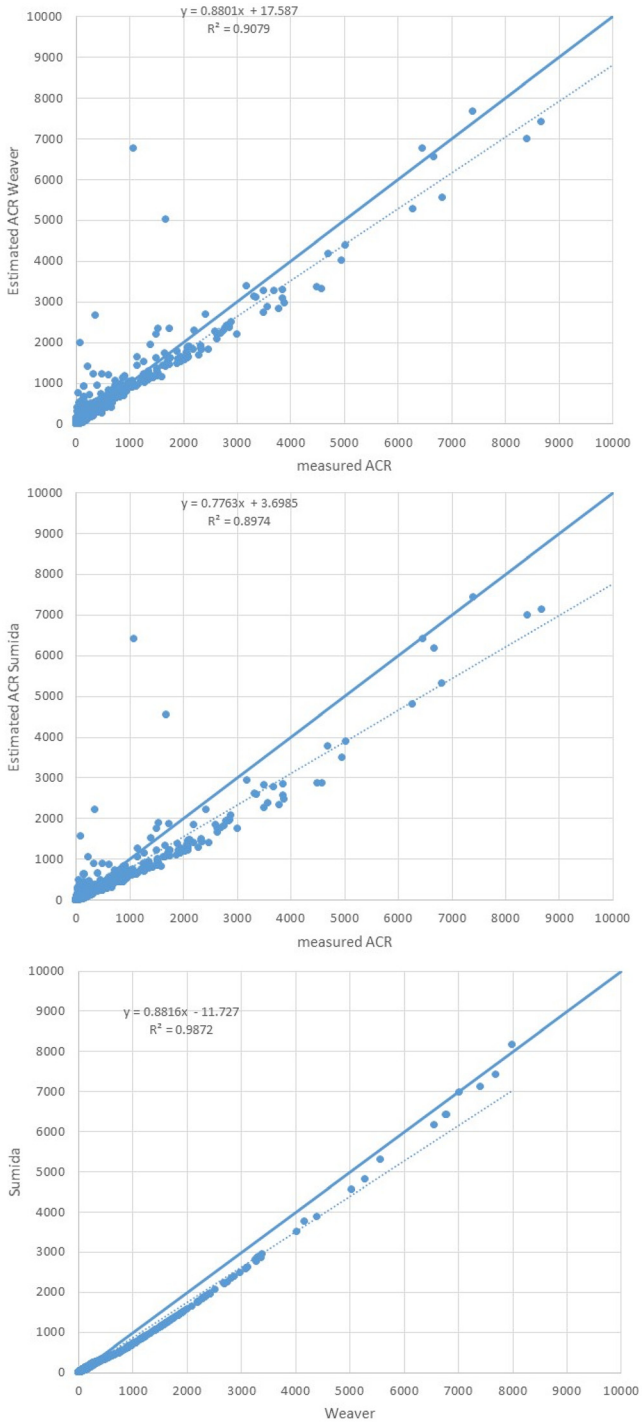

Figure 1: Estimating ACR from PCR (Roche Cobas data). Multinomial logistic regression model which generates the multi-level AUC. AUC, area under the curve; ACR, urinary albumin to creatinine ratio.

was not significant except for the Roche cohort with Weaver A2-A3: 98.5% (diabetics) vs. 96.0% (non-diabetics) ($p = 0.0002$) and the Alinity cohort with Weaver A1-A2: 91.8% (diabetics) vs. 87.8% (non diabetics) ($p = 0.0037$).

Discussion

CKD is defined as abnormalities of kidney structure or function, abnormality of the urinary sediment, or presence of proteinuria or albuminuria for > 3 months [1]. GFR and urine

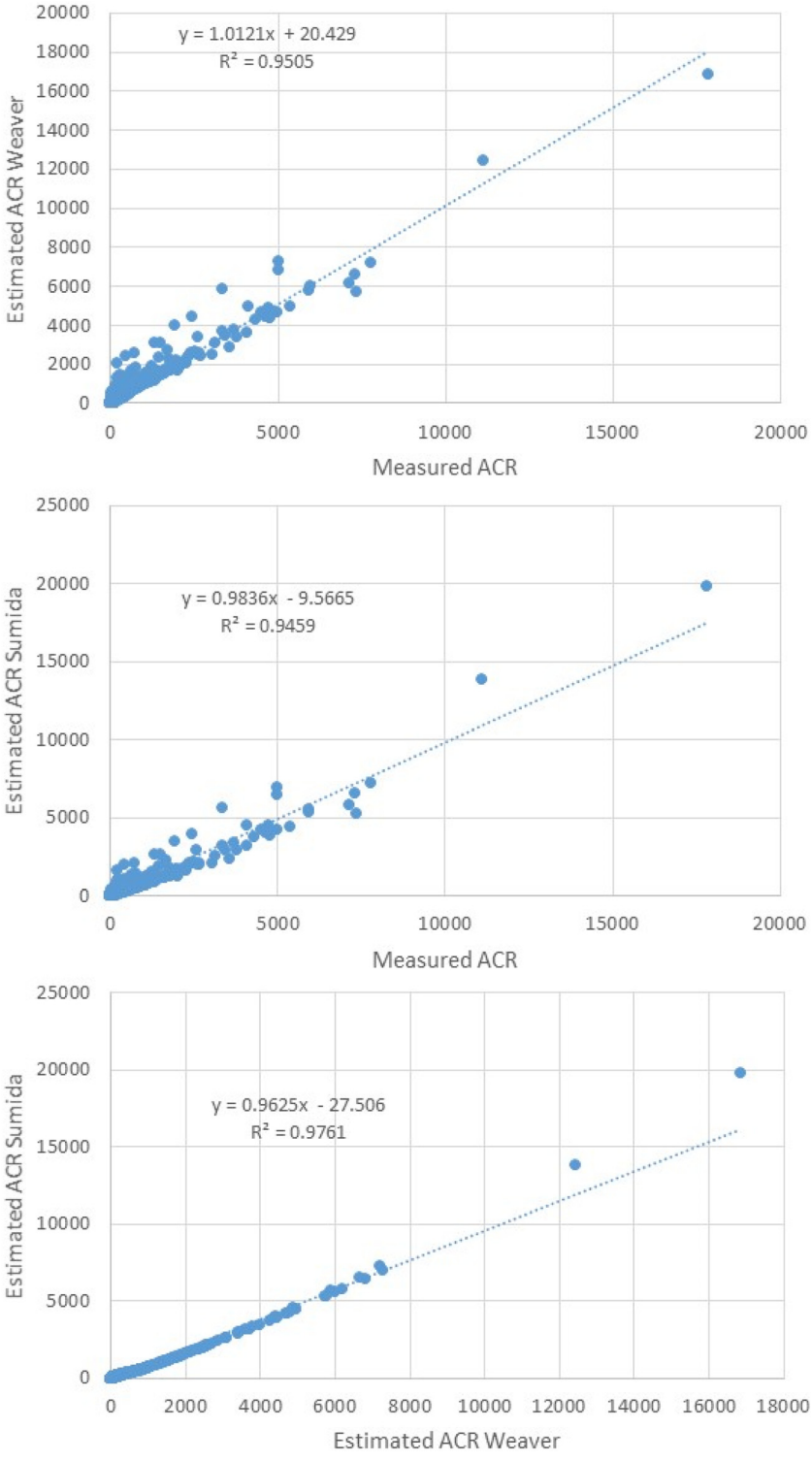

Figure 2: Estimating ACR from PCR (Abbott Alinity data). Multinomial logistic regression model which generates the multi-level AUC. AUC, area under the curve; ACR, urinary albumin to creatinine ratio.

albumin-to-creatinine ratio (ACR) staging also allow to estimate CKD prognosis and cardiovascular outcomes [17–21]. Since creatinine excretion is quite constant through the day, ACR or PCR are preferred to quantify albuminuria or proteinuria alone in order to reduce the dilution variable of the spot sample. Spot urine samples are preferred since 24 h collection is more cumbersome and prone to errors. KDIGO recommends to assess albuminuria instead of proteinuria [1, 22–24]. Albumin is indeed the most prevalent urinary protein found in most chronic kidney diseases and the most

Table 5: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the ROC curve (AUC) and overall agreement for threshold A1-A2 (30 mg/g) and A2-A3 (300 mg/g) with Roche Cobas et Abbott Alinity analysers, according to Sumida et al.'s equation [7]. Sub analysis according to diabetes status.

		Sensitivity	Specificity	PPV	NPV	AUC	Overall agreement
mACR/eACR A1-A2 (Roche Cobas)	**Global**	**82.8%**	**91.3%**	**83.3%**	**91.0%**	**0.954**	**88.4%**
	Diabetes	81.4%	92.8%	84.6%	91.0%	0.957	89.0%
	Non diabetes	87.6%	84.5%	79.4%	90.9%	0.948	85.8%
mACR/eACR A1-A2 (Abbott Alinity)	**Global**	**85.7%**	**92.9%**	**87.0%**	**92.1%**	**0.969**	**90.3%**
	Diabetes	85.5%	94.3%	88.9%	92.4%	0.973	91.2%
	Non diabetes	86.2%	88.4%	82.2%	91.2%	0.959	87.6%
mACR/eACR A2-A3 (Roche Cobas)	**Global**	**80.7%**	**99.1%**	**90.0%**	**98.1%**	**0.996**	**97.5%**
	Diabetes	78.2%	99.4%	92.5%	98.1%	0.997	97.7%
	Non diabetes	88.1%	97.7%	83.9%	98.4%	0.993	96.6%
mACR/eACR A2-A3 (Abbott Alinity)	**Global**	**86.5%**	**98.9%**	**89.8%**	**98.5%**	**0.996**	**97.6%**
	Diabetes	85.5%	99.3%	92.8%	98.5%	0.997	98.0%
	Non diabetes	88.8%	97.4%	84.5%	98.2%	0.992	96.3%

mACR, measured urinary albumin to creatinine ratio; eACR, estimated urinary albumin to creatinine ratio.

important maker for rapid GFR decline. Some albuminuria assay techniques detect very low levels of ACR with great accuracy (stage A2, between 30 mg/g and 300 mg/g, formerly called "microalbuminuria"). Moreover, ACR has better sensitivity and specificity regarding changes in glomerular permeability and kidney damage than total proteinuria measurements [25]. Finally, ACR measurement assays are more reproducible than methods measuring total proteinuria since protein urinary composition and reactants are highly variable (although standardisation of methods for measuring albuminuria is still a work in progress [14, 26]). Despite these international recommendations, ACR is often overlooked in clinical practice even in diabetic patients. In a recent study including 513.165 patients with type 2 diabetes, albuminuria was measured in only half of them in the past year and in 74% in the past 3 years [27].

Measuring ACR is thus recommended in clinical practice and in epidemiological research. However, PCR is more frequently performed, namely because of a lower cost. Also, in Belgium, ACR measurement is only reimbursed in diabetic patients. Estimating the ACR from the PCR may be interesting for retrospective epidemiologic studies in order to assess the risk for cardiovascular morbidity and mortality or end stage renal disease risk, even if all limitations linked to proteinuria measurement should be kept in mind.

In our population, Weaver et al. and Sumida et al. equations estimated ACR from PCR with a good precision. The results were comparable with two different analysers. Distribution of our patients into the mACR KDIGO stages (A1-A2-A3) was quite similar to the categorization of Weaver's population. However, Sumida's distribution of patient's mACR into the KDIGO stages was not detailed in the original paper. We underline that no patient staged A3 with the measurement was staged as "healthy" A1 by the equations, regardless of the equation or the analyser.

Misclassifications are detailed in Table 6 (false positives and false negatives). Most of these misclassified results are values that are close to the KDIGO threshold (e.g. mACR 296 mg/g; eACR 302 mg/g). The different LOQs

Table 6: Distribution of misclassified eACR (false positives and false negatives).

Weaver		Measured A1	Measured A2	Measured A3
Roche Cobas (n=2633)	Estimated A1	x	5% (137)	0% (0)
	Estimated A2	6% (160)	X	1%(16)
	Estimated A3	0.08% (2)	1% (34)	x

		Measured A1	Measured A2	Measured A3
Abbott Alinity (n=2386)	Estimated A1	x	4% (90)	0% (0)
	Estimated A2	5% (130)	X	0.17%(4)
	Estimated A3	0% (0)	2% (37)	x

Sumida		Measured A1	Measured A2	Measured A3
Roche Cobas (n=2633)	Estimated A1	x	6% (155)	0% (0)
	Estimated A2	6% (148)	X	2%(45)
	Estimated A3	0.04% (1)	1% (20)	x

		Measured A1	Measured A2	Measured A3
Abbott Alinity (n=2386)	Estimated A1	x	5% (122)	0% (0)
	Estimated A2	5% (109)	X	1%(33)
	Estimated A3	0% (0)	1% (24)	x

black cases, false negatives; grey cases, false positives.

of albumin and total protein measurements play probably a role as well in these results.

These equations have been tested in other specific populations: Jehn et al. used Weaver equation in a cohort of 16,990 kidney transplant recipients (KTRs had been excluded by Weaver et al. for the development of the formula) and 5,304 living kidney donors [28]. In this cohort of KTRs and living donors, few ACR were estimated satisfactorily. These data are conflicting with what we found in our population. Higher prevalence of tubular proteinuria in these patients might explain the difference. Weaver et al. also applied their equation to the population of KTRs initially excluded from their study (n=2,280) in Alberta, Canada and obtained a more accurate estimation of the ACR [29]. Difference of results between Weaver's and Jehn's observations might be explained by a smaller prevalence of mACR <5 mg/g in Jehn's population. This difference might be due to a lower reporting limits for albumin concentration between laboratories or assays. Further studies are required to know the exact performance of these estimating equations in KTRs [29].

According to our results, there are no argument to favour one equation or another. Results were also similar between the two analysers, i.e. Roche Cobas and Abbott Alinity. Threshold values defined by Youden index with Weaver equation are closer to the KDIGO threshold. However, this observation is not sufficient to favour for the Weaver equations.

Our study has several strengths: the sample is large, ACR and PCR were measured on the same sample, and two different analysers were considered. The limitations include the retrospective monocentric design and the absence of concomitant urinary sediment (although an active urinary sediment might interfere in the assessment of proteinuria and albuminuria [25]). Also we had a greater proportion of patients with diabetes (75%) than in the cohorts studied by Weaver et al. (47%) or Sumida et al. (56%) [6, 7]. Also, The definition of diabetic status might be criticized, although Sumida used similar criteria.

Intuitively, these equations might perform very poorly in specific populations at risk for interstitial nephropathies (KTRs, patients with monoclonal gammopathies, …).

However, like Sumida, we found similar diagnosis performances according to diabetes status and the subanalysis between diabetic and non-diabetic patients does not modify the main conclusion.

Conclusions

We observed a very good concordance between measured and estimated ACR by the means of Weaver and Sumida equations. Importantly, no patient with an A3-ACRm was missed by the equations. ACR should definitely be measured when clinically needed but an estimated ACR can reasonably be obtained from Weaver et al. and Sumida et al. equations and may provide an acceptable performance, in the context of epidemiologic retrospective clinical research.

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Informed consent: Remnant samples only were used in this study. No specific approval was requested to the CHU de Liège Institutional Review Board as a leaflet including the following statement is given to all admitted patients: "According to the law of the December 19, 2008, any leftover of biological material collected from patients for their standard medical management and normally destroyed when all diagnostic analysis have been performed, can be used for validation of methods. The law authorizes such use except if the patient expressed an opposition when still alive (presumed consent). Written informed consent for participation was not required for this study in accordance with the Belgian national legislation and the Institutional requirements.

Ethical approval: The local Institutional Review Board deemed the study exempt from review.

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