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DIABETIC STATUS AND THE PERFORMANCES OF CREATININE- AND CYSTATIN C–BASED EGFR EQUATIONS

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KEYWORDS: creatinine, cystatin C, glomerular filtration rate

ABSTRACT

Background. The estimation of glomerular filtration rate (GFR) is one tool to detect renal disease. The most used biomarker remains serum creatinine and the European Kidney Function Consortium ($EKFC_{crea}$) equation is the most validated in Europe. More recently, cystatin C has been proposed as a biomarker. We studied the performances of the EKFC equations in a large cohort of subjects according to their diabetic status.

Methods. Four cohorts from the EKFC dataset were retrospectively considered in which the diabetic status was available. GFR was measured by plasma clearances (mGFR; iohexol or chromium 51-ethylenediaminetetraacetic acid). The performance of the equations was assessed by calculating bias, precision [interquartile range (IQR)] and P30 (percentage of eGFR values within ±30% of mGFR).

Results. In the whole population (*N* = 6158), the median age was 61 years (IQR 47-72) and 45.8% were women. The mean mGFR was 60 ml/min/1.73 m^2 (IQR 39-82). Compared with non-diabetic individuals (*n* = 5124), diabetic patients (*n* = 1034) were older, more frequently male, heavier and had

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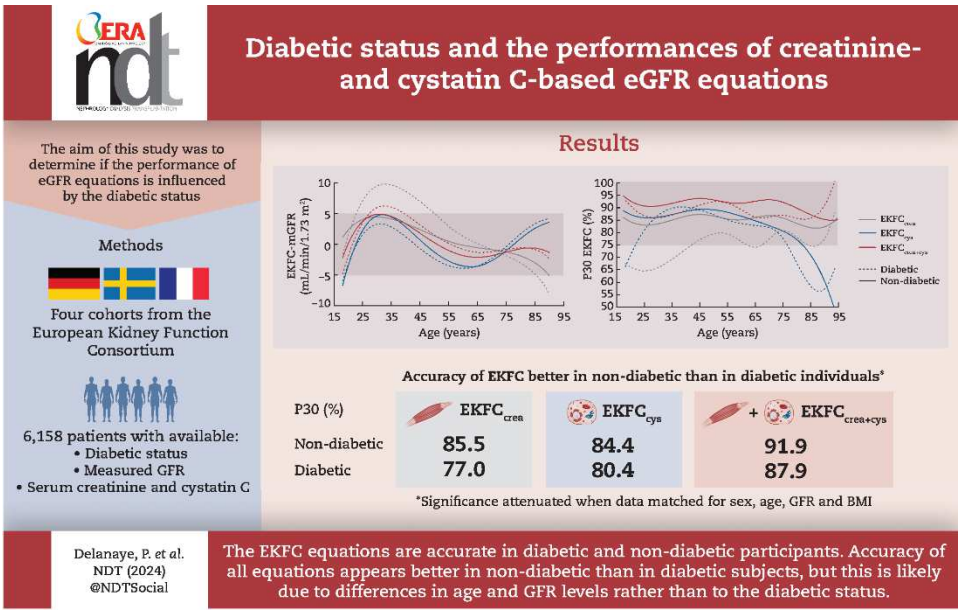
lower mGFR. The performance of the $EKFC_{cys}$ equation was similar to that of the $EKFC_{crea}$ equation, but the $EKFC_{crea+cys}$ equation had a better P30 than the single-biomarker equations. P30 values were substantially lower in diabetic patients than in non-diabetic patients, but according to a matched analysis, this is mainly explained by the difference in GFR levels between the two populations, not by diabetic status.

Conclusion. We showed that the equation combining creatinine and cystatin C performed better. If the accuracy of equations seems better in non-diabetic than in diabetic individuals, it is more likely due to differences in GFR levels rather than diabetic status.

GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Estimated glomerular filtration rate (eGFR) is a key parameter in diabetic patients.

This study adds:

- We contribute to the current debate in the literature regarding whether the performance of eGFR equations is different in diabetic and non-diabetic patients.
- We found that the European Kidney Function Consortium (EKFC) equation combining creatinine and cystatin C perform better than equations based on a single biomarker. Moreover, the performance of the equations is similar in diabetic and non-diabetic individuals.

Potential impact:

- The EKFC equations are accurate to estimate GFR in individuals with and without diabetes.

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Introduction

Diabetes is the main cause of chronic kidney disease (CKD) worldwide. The assessment of kidney function should be systematic in every diabetic patient according to international recommendations. Indeed, kidney function assessment is the first step before prevention or treatment of diabetic nephropathy [1, 2]. In addition to measurement of the urine albumin:creatinine ratio (UACR), estimation of glomerular filtration rate (GFR) is the main tool to assess kidney function and detect CKD. In clinical practice, GFR is estimated with biomarkers that are used in equations that also include age and sex variables. The most used biomarker remains serum creatinine, but different estimated GFR (eGFR) equations have been proposed [3–6, 7]. Among them, the European Kidney Function Consortium creatinine ($EKFC_{crea}$) equation [7] has been widely validated in Europe and has been shown to be applicable worldwide [8–10]. More recently, another renal biomarker, cystatin C, has been proposed [11] and is promoted by several guidelines, notably because its concentration is less dependent on race and sex [2]. Also, the EKFC has developed a cystatin C–based equation ($EKFC_{cys}$) [12]. In general cohorts, the cystatin C– and creatinine-based equations have similar performances, but the equation combining both biomarkers ($EKFC_{crea+cys}$, actually the mean of $EKFC_{crea}$ and $EKFC_{cys}$) has a substantially better performance, and this is also true for other combined equations [5, 12–14]. Whatever the biomarker and/or the equation considered, there is still no consensus whether equations have similar or worse performance in diabetic patients [15–23]. Moreover, the real added value of cystatin C in diabetic patients is unknown [24–30] and most of current publications are based on relatively small samples. It has to be emphasized that age and the level of GFR influence the performance of GFR equations the most. Accordingly, these factors have to be taken into consideration when comparing the accuracy and precision of such equations between diabetic and non-diabetic individuals. In the current analysis, our aim was to compare the performances of the EKFC equations (based on creatinine and/or cystatin C) in a large cohort of subjects according to their diabetic status.

MATERIALS AND METHODS

Four cohorts from the EKFC dataset with available diabetic status were included in the current analysis. These four cohorts were from Lund, Sweden (n = 2780), Berlin, Germany (n = 654), Créteil, France (n = 466) and Paris, France (n = 2258). Individuals from Paris and Créteil were referred to measure GFR in a clinical context [8, 12]. The Lund cohort includes individuals from Lund, Japan and The Netherlands used in generating the Caucasian, Asian, Pediatric and Adult (CAPA) equation [14], but no paediatric or Japanese individuals were included in the present investigation. Individuals from Berlin participated in the Berlin Initiative Study (BIS) [14, 31]. In the BIS cohort, only individuals ≥70 years of age were included [31]. In all cohorts, age, gender, height and weight were available. Diabetic status was defined in each cohort as follows: use of antidiabetic medication and/or haemoglobin A1c (HbA1c) >6.5% in the BIS data, use of antidiabetic medication or HbA1c >6.5% or

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fasting blood glucose >7 mmol/L in the Paris data and medical records in the Lund and Créteil data. Serum creatinine was measured with assays traceable to the gold standard isotope dilution mass spectrometry method and cystatin C was measured with assays calibrated to the international standard, as previously described [12]. GFR was measured by plasma clearance with recognized reference methods, as described elsewhere [7, 8, 12]. Briefly, GFR was measured by iohexol plasma clearance in Lund (single-sample method), Berlin and Créteil (multiple-sample method) and by chromium 51–ethylenediaminetetraacetic acid (^{51}Cr-EDTA) plasma clearance (multiple-sample method) in Paris [12, 32–34]. Unfortunately, the number of Black Europeans with diabetes was too low (n = 12 in Créteil and n = 217 in Paris). Moreover, we had to limit the factors potentially impacting the association between serum creatinine and GFR, and we limited the analysis to self-identified White individuals.

The EKFC equations based on creatinine and cystatin C are presented in Supplementary Table S1. The EKFC creatinine-based equation has previously been shown to have a similar performance as the Lund–Malmö equations (LMR) and both EKFC and LMR equations have better performance than the corresponding Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations in Europe and the USA [7, 8, 13]. The recently re-expressed LMR equation (r-LMR) for use with rescaled biomarkers [35] has a performance similar to that of the EKFC, and both performed better with respect to precision and bias than the CKD-EPI equations in this analysis in both diabetic and non-diabetics patients (Supplementary Table S2).

The EKFC analysis was approved by the Regional Ethical Board in Lund, Sweden (registration no. 2018/220, with amendment 2021-04177 approved by the Swedish Ethical Review Authority) [7]. The data from Lund was approved by the local ethics committee (permissions LU 2015/860 and 2016/169). In Berlin, the BIS was approved by the ethics committee of Charité Universitätsmedizin (EA/009/08). In Paris, the study was approved by the institutional review board (IRB) of Assistance-Publique Hôpitaux de Paris and Paris 7 University (IRB 00006477, study 14-051). In Créteil, the study was approved by the IRB of Mondor (IRB-00011558/2021-103)

STATISTICS

All analyses and calculations were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and MedCalc (MedCalc Software, Ostend, Belgium). Data were presented as mean ± standard deviation (SD) when the distribution was normal and as median [interquartile range (IQR)] when not. Normality was assessed using the Shapiro–Wilk test. Characteristics of diabetic and non-diabetic patients were compared with the Mann–Whitney test. The performance of GFR equations was compared with the usual metrics: median bias (i.e. eGFR − mGFR) with 95% confidence intervals (CIs), imprecision (IQR), as well as P30 and P20 accuracy (percentage of eGFR values within ±30% or 20% of mGFR) with 95% CIs. The target for bias was zero, but an absolute bias of at most 5 ml/min/1.73 m^2 might be considered reasonable. Imprecision should be as low as possible [36]. The goal for P30 was 100%, yet P30 >75% has been considered as 'sufficient for good clinical decision making' by Kidney Disease Outcomes Quality Initiative, although their goal was to reach a P30 >90% [37]. To test if an equation is better than another equation in the same population, we did not use

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statistical tests, thus avoiding numerous *P*-value calculations, but we considered an equation as better when the 95% CI between equations was not overlapping, which is a more stringent criterion. To compare P20/P30 between diabetic and non-diabetic populations, we used the chi-squared test. The median bias across the age and GFR spectrum was graphically presented using median quantile regression with fourth-degree polynomials. Likewise, the accuracy of P30 (%) was graphically presented across the age spectrum using cubic splines (third-degree polynomial) with three free knots.

Analyses were also stratified according to diabetic status, GFR levels (<30, 30–60, 60–90 and ≥90 ml/min/1.73 m^2), age (18–40, 40–65 and ≥65 years), sex (male and female) and body mass index (BMI) (<18, 18–25, 25–30 and ≥30 kg/m^2).

As the characteristics of diabetic patients were different in comparison to non-diabetics in terms of age, sex, measured GFR, and body mass index (BMI), we matched diabetic and non-diabetic patients from the four cohorts using the following matching criteria: age (±3 years), sex (equal), mGFR (±3 $mL/min/1.73m^2$), and BMI (±2.5 kg/m^2). Matching was done based on a SAS macro and the code is available on request [38]. We then investigated whether there were differences in serum creatinine or cystatin C in these matching cohorts. We also studied the performance of the EKFC equations in both the matched non-diabetic and matched diabetic cohorts

Finally, we performed a logistic regression analysis (odds ratio with 95% CI) with P30 as the dependent variable (1 = accurate, 0 = inaccurate) and age, sex, BMI, mGFR and diabetic status as independent variables.

RESULTS

POPULATION

The characteristics of the patients in the entire population (*N* = 6158) and in each cohort are described in Supplementary Table S3. The median age was 61 years (IQR 47–72) and 45.8% were women. The median mGFR was 60 ml/min/1.73 m^2 (IQR 39–82). The percentage of diabetic patients in each cohort ranged from 8.8 to 26.5%. In Supplementary Table S4, we describe the characteristics in diabetic (n = 1034) and non-diabetic patients (n = 5124). Compared with non-diabetic individuals, diabetic patients were significantly older (median age 67 versus 59 years; $P < .0001$) and more frequently male (62.6 versus 52.5%; $P < .0001$). They also had a higher BMI (28.3 versus 25.5 kg/m^2; $P < .0001$), lower mGFR (45 versus 64 ml/min/1.73 m^2; $P < .0001$) and higher creatinine (1.44 versus 1.06 mg/dl; $P < .0001$) and cystatin C (1.67 versus 1.20 mg/l; $P < .0001$) concentrations.

COMPARISON OF CREATININE- AND CYSTATIN C–BASED EQUATIONS

The performance of the $EKFC_{cys}$ was similar to that of $EKFC_{crea}$, except for some metrics in the whole population, notably the absolute bias (Table 1). Indeed, both $EKFC_{crea}$ and $EKFC_{crea+cys}$ were unbiased,

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whereas $EKFC_{cys}$ slightly underestimated GFR, and this was observed in both diabetic and non-diabetic participants. For the combined equations, we observed a better P20 and P30 compared with the equations with one biomarker in both diabetic and non-diabetic individuals.

Table 1: *Comparison of the performance of creatinine versus cystatin C versus the combined EKFC equations.*

Population	$EKFC_{crea}$	$EKFC_{cys}$	$EKFC_{crea+cys}$
Whole population (*N* = 6158)			
Bias (ml/min/1.73 m^2), median (95%	0.15 (-0.19-0.45)[a]	-0.86 (-1.17 to -0.57)	0.11 (-0.19-0.33)[a]
IQR (ml/min/1.73 m^2) (Q1-Q3)	14.2 (-6.7-7.5)	14.7 (-8.7-6.0)	11.1 (-5.8-5.3)
P30, % (95% CI)	84.1 (83.2-85.0)	83.7 (82.8-84.6)	91.2 (90.5-92.0)[b]
P20, % (95% CI)	68.3 (67.1-69.5)[a]	65.4 (64.2-66.6)	78.5 (77.5-79.5)[b]
Non-diabetic population (*n* = 5124)			
Bias (ml/min/1.73 m^2), median (95% CI)	0.14 (-0.22-0.47)[a]	-0.77 (-1.10 to -0.44)	0.14 (-0.16-0.38)[a]
IQR (ml/min/1.73 m^2) (Q1-Q3)	14.3 (-6.7-7.6)	15.3 (-8.9-6.3)	11.5 (-5.9-5.6)
P30, % (95% CI)	85.5 (84.5-86.5)	84.4 (83.4-85.4)	91.9 (91.2-92.7)[b]
P20, % (95% CI)	70.3 (69.1-71.6)[a]	66.1 (64.8-67.4)	79.7 (78.6-80.8)[b]
Diabetic population (n = 1034)			
Bias (ml/min/1.73 m^2), median (95%	0.21 (-0.51-0.91)[a]	-1.24 (-2.03 to -0.58)	-0.12 (-0.74-0.57)[a]
IQR (ml/min/1.73 m^2) (Q1-Q3)	13.8 (-6.8-7.0)	11.9 (-7.6-4.3)	9.5 (-5.3-4.2)
P30, % (95% CI)	77.0 (74.4-79.5)	80.4 (77.9-82.8)	87.9 (85.9-89.9)[b]
P20, % (95% CI)	58.3 (55.3-61.3)	61.8 (58.8-64.8)	72.5 (69.8-75.3)[b]

Q1: quartile 1; Q3: quartile 3.

[a]Better than one equation (cr or cys or cr + cys).

[b]Better than the two equations with a single biomarker (cr + cys versus cr and cys)

P20 and P30 were substantially worse in diabetic patients than in non-diabetic patients. P30 for $EKFC_{crea}$, $EKFC_{cys}$ and $EKFC_{crea+cys}$ in diabetic and non-diabetic patients was 77.0% versus 85.5% (P < .0001), 80.4% versus 84.4% (P = .0015) and 87.9% versus 91.2% (P < .0009), respectively.

SENSITIVITY ANALYSES ACCORDING TO AGE, SEX, BMI AND MGFR

In Supplementary Table S5, the performance of the three EFKC equations was compared stratified by age in both diabetic and non-diabetic populations. Figure 1 illustrate the bias and P30 for the three equations according to age in non-diabetic and diabetic populations. In both populations, the P30 for $EKFC_{crea+cys}$ was better than the P30 for $EKFC_{crea}$ and $EKFC_{cys}$, except in young patients, for whom the $EKFC_{crea+cys}$ was only better than $EKFC_{crea}$, but equal to $EKFC_{cys}$ (n = 64). The bias was higher in diabetic patients compared with non-diabetic patients for the $EKFC_{crea}$ and in young people for all three equations. P20 and P30 were worse in diabetic patients than in non-diabetic patients for the $EKFC_{crea}$ equation.

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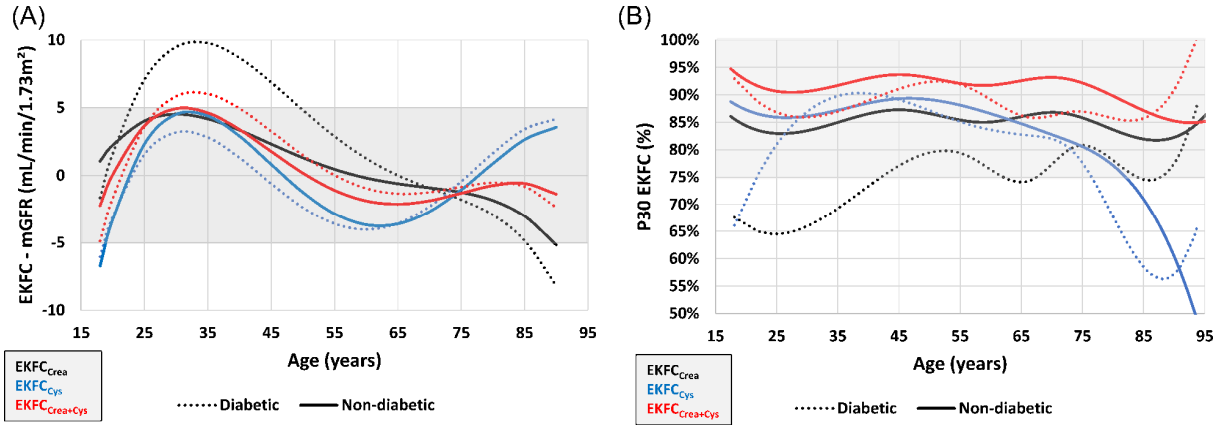
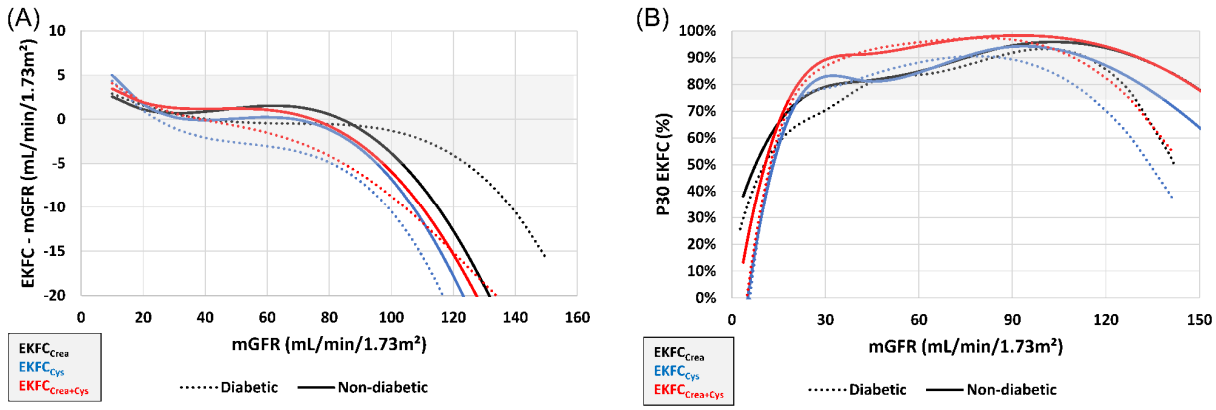
Figure 1: *(**A**) Bias and (**B**) accuracy within 30% of the EKFC equations (with creatinine, cystatin C or combination) in diabetic and non-diabetic populations according to age.*



In Supplementary Table S6, the performance of the three EKFC equations was compared according to mGFR in both diabetic and non-diabetic populations. Figure 2 illustrates the bias and P30 of the three equations according to mGFR in non-diabetic and diabetic populations. In both populations, the three equations performed similarly (and poorly) when mGFR is <30 ml/min/1.73 m^2. In both populations, the P30 for $EKFC_{crea+cys}$ was better than for $EKFC_{crea}$ and $EKFC_{cys}$ when mGFR was 30–90 ml/min/1.73 m^2. In patients with an mGFR >90 ml/min/1.73 m^2, no difference was observed between the three equations in the 44 diabetic patients and the $EKFC_{crea+cys}$ was better than the $EKFC_{cys}$ in the 987 non-diabetics.

Figure 2: *(**A**) Bias and (**B**) accuracy within 30% of the EKFC equations (with creatinine, cystatin C or combination) in diabetic and non-diabetic populations according to mGFR.*



P30 results were similar between diabetic and non-diabetic populations according to the mGFR level.

In the analysis stratified by sex (Supplementary Table S7), the conclusions are similar as in the global population. We observed a better P20 and P30 for $EKFC_{crea+cys}$ than for the equations with one

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biomarker in both diabetic and non-diabetic individuals. Moreover, P20 and P30 were worse in diabetic patients than in non-diabetic patients.

In the analysis stratified by BMI (Supplementary Table S8), assuming that the sample size of individuals with a BMI <18 kg/m² was too low to be considered, we observed a better P20 and P30 for $EKFC_{crea+cys}$ than for the equations with one biomarker in both diabetic and non-diabetic individuals. In patients with diabetes and BMI between 18 and 25, the better accuracy for $EKFC_{crea+cys}$ was only in comparison with $EKFC_{crea}$.

P20 and P30 were worse in diabetic individuals for the $EKFC_{crea}$ equation.

MATCHING ANALYSES

Now the criteria are described in the "Methods", we could match data for 289 females and 546 males. Results of the matching analysis are shown in Supplementary Table S9. In men and women, when mGFR, BMI and age are identical, we showed that cystatin C and creatinine concentrations were very similar. The performance of the three equations in the matched population is shown in Table 2. The results in the matched cohorts were very similar between diabetic and non-diabetic individuals, and this was true for every biomarker and every equation. The only exception was a lower P20 result for $EKFC_{crea}$ in the whole diabetic population.

Table 2: *Performance of the EKFC equations for eGFR in the matched cohorts.*

Variables	$EKFC_{crea}$	$EKFC_{cys}$	$EKFC_{crea+cys}$
Non-diabetic (n = 835)			
Bias (ml/min/1.73 m²), median (95% CI)	0.24 (-0.51-0.96)	-0.59 (-1.01-0.22)	0.38 (-0.22-0.84)
IQR (ml/min/1.73 m²) (Q1-Q3)	12.2 (-5.1-7.1)	12.2 (-6.6-5.6)	9.0 (-4.1-4.9)
P30, % (95% CI)	82.4 (79.8-85.0)	82.5 (79.9-85.1)	90.2 (88.2-92.2)
P20, % (95% CI)	66.6 (63.4-69.8)	63.5 (60.2-66.7)	77.4 (74.5-80.2)
Females (n = 289)			
Bias (ml/min/1.73 m²), median (95% CI)	-0.12 (-1.05-1.62)	1.80 (0.03-2.85)	0.92 (-0.07-2.43)
IQR (ml/min/1.73 m²) (Q1-Q3)	13.2 (-5.8-7.4)	13.9 (-5.1-8.8)	10.6 (-3.8-6.7)
P30, % (95% CI)	78.2 (73.4-83.0)	76.5 (71.6-81.4)	86.9 (82.9-90.8)
P20, % (95% CI)	63.7 (58.1-69.3)	56.4 (50.7-62.2)	74.1 (69.0-79.1)
Males (n = 546)			
Bias (ml/min/1.73 m²), median (95% CI)	0.35 (-0.57-1.50)	-1.17 (-2.08 to -0.51)	0.02 (-0.62-0.65)
IQR (ml/min/1.73 m²) (Q1-Q3)	11.5 (-4.6-7.0)	11.7 (-7.6-4.1)	8.5 (-4.4-4.2)
P30, % (95% CI)	84.6 (81.6-87.7)	85.7 (82.8-88.7)	91.9 (89.7-94.2)
P20, % (95% CI)	68.1 (64.2-72.1)	67.2 (63.3-71.2)	79.1 (75.7-82.5)
Diabetic (n = 835)			
Bias (ml/min/1.73 m²), median (95% CI)	0.66 (-0.31-1.38)	-1.10 (-1.92 to -0.30)	0.05 (-0.57-0.68)
IQR (ml/min/1.73 m²) (Q1-Q3)	13.7 (-6.3-7.4)	11.7 (-7.5-4.2)	9.3 (-5.0-4.3)
P30, % (95% CI)	78.2 (75.4-81.0)	81.9 (79.3-84.5)	89.2 (87.1-91.3)
P20, % (95% CI)	59.8 (56.4-63.1)	63.5 (60.2-66.8)	74.7 (71.8-77.7)
Females (n = 289)			
Bias (ml/min/1.73 m²), median (95% CI)	-0.32 (-1.46-1.19)	0.66 (-0.74-1.79)	0.46 (-0.66-1.52)
IQR (ml/min/1.73 m²) (Q1-Q3)	14.1 (-7.6-6.5)	12.8 (-6.5-6.3)	8.6 (-4.3-4.4)
P30, % (95% CI)	75.4 (70.4-80.4)	78.2 (73.4-83.0)	88.6 (84.9-92.3)
P20, % (95% CI)	56.1 (50.3-61.8)	59.2 (53.5-64.9)	75.1 (70.1-80.1)
Males (n = 546)			
Bias (ml/min/1.73 m²), median (95% CI)	1.08 (0.13-1.71)	-2.06 (-3.30 to -1.07)	-0.17 (-1.06-0.71)
IQR (ml/min/1.73 m²) (Q1-Q3)	13.5 (-5.7-7.8)	11.4 (-7.8-3.5)	9.4 (-5.2-4.1)
P30, % (95% CI)	79.7 (76.3-83.1)	83.9 (80.8-87.0)	89.6 (87.0-92.1)
P20, % (95% CI)	61.7 (57.6-65.8)	65.8 (61.8-69.7)	74.5 (70.9-78.2)

Q1: quartile 1; Q3: quartile 3.

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LOGISTIC REGRESSION

The variables studied, and notably the diabetic status, were not associated with bias in any of the three EKFC equations (Supplementary Table S10). By far, mGFR was the variable most importantly associated with accuracy (all $P < .0001$). P10, P20 and P30 accuracy were associated with diabetes status only for $EKFC_{crea}$.

DISCUSSION

Together with measuring UACR, eGFR is the key parameter in a strategy of CKD screening and prevention [2]. In the current analysis, we first confirm the fact that equations combining both biomarkers have a better performance than equations based on a single biomarker, which holds true in patients with and without diabetes. Cystatin C–based eGFR has no added value compared with creatinine-based eGFR in the main analysis [5, 12, 13].

Regarding the performances of the equations in diabetic versus non-diabetic populations, several points need to be further discussed. At first glance, it could be concluded that the EKFC equations perform worse in diabetic than in non-diabetic patients (especially creatinine-based equations), but it must be kept in mind that diabetic patients in our cohort were also older and had lower GFR values, two factors known to greatly influence the performance of the equations [12, 13]. The importance of the mGFR level in the performance of equations is confirmed in the regression analysis, where mGFR is by far the variable most tightly associated with accuracy. The differences according to diabetic status also disappeared in the subanalysis according to mGFR. The matched pairs analysis confirms that the EKFC equations perform equally well in diabetic and non-diabetic patients. These results suggest that age and, to a greater extent, the level of GFR has a greater influence on the performances of eGFR equations than the diabetic status, even if the diabetic status could slightly influence the performance of the $EKFC_{crea}$ equation.

This analysis must be read in light of its limitations. First, only White Europeans were included, and our results need to be validated in other populations. Second, the number of young diabetic patients was small ($n = 64$) and the results in this subpopulation must be interpreted with caution. Along the same line, the number of diabetic patients with high GFR levels (≥90 ml/min/1.73 m^2) was particularly low ($n = 44$). Accordingly, no strong conclusion can be drawn for diabetic patients with hyperfiltration. However, it is very likely that all equations have a low performance in estimating GFR and/or detecting hyperfiltration in such patients [39]. Hyperfiltration is a recognized pathological entity for which measuring GFR by plasma clearances can also be more difficult [40, 41]. Finally, we could not test the potential effect of anti-diabetic therapies; the severity, type (type 1 versus type 2) or the duration of diabetes; or the presence of pathological albuminuria on the performances of the equations.

In conclusion, in a large dataset, we showed that the EKFC equations are as accurate in diabetic as in non-diabetic patients. This is particularly true for the cystatin C–based or combined equations. Diabetes status could still slightly influence the performance of the creatinine-based equation, but

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its impact is limited compared with age or mGFR level. As in the general population, combining the creatinine- and cystatin C–based equations results in a more accurate estimate of GFR compared with the single-biomarker EKFC equations.

SUPPLEMENTARY DATA

Supplementary data are available at *Nephrology Dialysis Transplantation* online.

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AUTHORS' CONTRIBUTIONS

P.D. and H.P. collected data, contributed to the discussion and wrote the first draft of the manuscript. J.B., E.V.P., M.F., N.E., E.S., A.G., A.C., A.A., U.N. and T.S. researched and reviewed data, contributed to the discussion and edited the manuscript. All authors approved the final version of the manuscript. P.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

A short protocol is available to interested readers by contacting P.D. (pdelanaye@chuliege.be). Statistical codes (SAS) are available for interested readers by contacting H.P. (hans.pottel@kuleuven.be). The EKFC dataset used in the present study is hosted by the Lund University Population Research Platform. Legal and ethical restrictions prevent public sharing of the dataset. Data may be made available to interested researchers for collaboration upon request but would generally require a new ethical permission and the permission of each of the data owners. Contact information for the data host can be found at www.lupop.lu.se. The data from Paris and Créteil are not publicly available due to the confidential nature of patient information obtained for clinical care. Legal and ethical restrictions prevent public sharing of the dataset. Data can be made available for collaborations upon request to interested researchers but would generally require a new ethical permission and the permission of each of the data owners.

CONFLICT OF INTEREST STATEMENT

P.D. is consultant for Nephrolyx. E.S. and N.E. received grants from Bayer AG. E.S. received funding from the National Kidney Foundation. The other authors declare no conflicts of interest.

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