

Original Article

## The MDRD formula does not reflect GFR in ESRD patients

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### Abstract

**Background.** The Modification of Diet in Renal Disease (MDRD) equation is widely used for the estimation of glomerular filtration rate (GFR) from plasma creatinine. It has been well validated in patients with various degrees of impaired kidney function, but not in patients with end-stage renal disease (ESRD). Plasma creatinine is determined by GFR and muscle mass. Importance of the latter may increase at low GFR. Our aim was to firstly compare estimated GFR (eGFR by MDRD equation) with measured GFR (mGFR, mean of creatinine and urea clearance) just before the start of dialysis. Secondly, the relationship of eGFR and mGFR with mortality and muscle mass was analysed.

**Methods.** ESRD patients with 24-h urine collections and a plasma sample available at the start of dialysis [ $n = 569$ , 61% male, mean (standard deviation) age 58 (15) years] were selected from the Netherlands Cooperative Study on the Adequacy of Dialysis. Incident dialysis patients were followed until death, transplantation or end of study.

**Results.** mGFR was 6.0 (2.6) and eGFR was 6.8 (2.4) mL/min/1.73 m<sup>2</sup>. Although eGFR overestimated mGFR with only 0.8 mL/min/1.73 m<sup>2</sup>, limits of agreement ranged from -4.1 to +5.6 mL/min/1.73 m<sup>2</sup>. The highest eGFR values were associated with the highest mortality rates [adjusted hazard ratio 1.4 (1.0, 1.9)]. eGFR but not mGFR was associated with muscle mass ( $P = 0.001$ ).

**Conclusions.** These data imply that estimation of GFR by equations using plasma creatinine in the denominator cannot be used for this purpose in patients with ESRD because the effect of GFR on plasma creatinine is overruled by that of muscle mass.

**Keywords:** end-stage renal disease (ESRD) patients; glomerular filtration rate (GFR); Modification of Diet in Renal Disease (MDRD); mortality; plasma creatinine

### Introduction

The presence and magnitude of residual renal function are important determinants for the survival of dialysis patients [1–5]. Yet, accurate measurements of the residual glomerular filtration rate (rGFR) are difficult to obtain because these require timed urine collections. To avoid timed urine collections, attempts have been made to estimate GFR from plasma clearances using the plasma disappearance rate of an injected solute (whole body clearance) or from steady state plasma concentrations of endogenous solutes. Plasma clearances after a bolus injection of <sup>99m</sup>Tc-DTPA or <sup>31</sup>Cr-EDTA overestimate GFR by almost 100% in patients who start dialysis [6] probably due to extrarenal elimination.

The plasma creatinine concentration during steady state conditions is the most often used endogenous solute to estimate GFR. It is not only dependent on glomerular filtration and tubular secretion but also on muscle mass and consequently on age and gender. Therefore, equations have been developed to correct for these variables (reviewed in [7]). The Modification of Diet in Renal Disease (MDRD) equation is the most widely used. It has been well validated in patients with various degrees of renal impairment, but not in patients at the start of dialysis [8]. This may be relevant because the reciprocal value of plasma creatinine is used in the MDRD. It implies that MDRD estimations of GFR could be influenced by the patient's muscle mass. Furthermore, although estimating GFR in ESRD patients should not be used in the decision of starting renal replace-

ment therapy, such estimation has been performed in several studies investigating the association between estimated GFR at the start of dialysis and mortality during subsequent follow-up [9–12]. Interestingly, these studies showed that a high rather than a low kidney function is associated with poor survival. The aim of the present study was to firstly investigate the usefulness of the MDRD equation to estimate kidney function in patients just before the start of chronic dialysis treatment. To that end, the agreement between GFR as assessed by the four-variable MDRD equation and GFR measured as the mean of creatinine and urea clearance in 24-h urine collections was determined. Secondly, to further assess the usefulness of the MDRD equation for the estimation of kidney function, its relationship with mortality was examined and compared with that of measured renal function, also after correction for possible confounders. Finally, the role of muscle mass was examined in the assessment of kidney function by measured GFR and by MDRD.

## Materials and methods

### Patients

Patients with end-stage renal disease (ESRD) starting dialysis treatment in 38 dialysis centres in The Netherlands were invited to participate in the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study. Inclusion criteria were age  $\geq 18$  years and starting renal replacement therapy for the first time. Additional criteria for the present analysis were the presence of a 24-h urine collection and a plasma sample available within 4 weeks prior to the start of dialysis. The study was approved by the medical ethics committees of all participating hospitals and conducted according to the declaration of Helsinki [13]. All patients gave written informed consent.

### Design

NECOSAD is a large multicentre prospective follow-up study of incident ESRD patients starting dialysis treatment. Recruitment of patients was between January 1997 and January 2005. At the start of dialysis, data regarding clinical and demographic characteristics, including gender, age, smoking status, primary kidney disease and co-morbidity, were collected. Furthermore, patients were asked to collect a 24-h urine sample, and blood was drawn. Skin folds were measured at 3 months after the start of dialysis. Patients were followed at 3 and 6 months after the start of dialysis treatment. Thereafter follow-up was done at 6-monthly intervals until time of death, transplantation, transfer to a non-participating hospital, recovery of renal function or end of study (1 January 2007). Follow-up was censored to a maximum of 5 years.

### Data collection

Creatinine (uncalibrated) and urea were measured in blood and 24-h urine samples mainly using the alkaline picrate method at the local laboratories. Primary kidney disease was defined according to the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) [14]. Co-morbidity risk score was assessed as recommended by Khan *et al.* [15]. The triceps skin fold (TSF) measurements were made in 3-fold at the site of the body, opposite to the vascular access using a skin fold caliper. The mean of three measurements was used for further calculations. The mid-upper arm circumference (MUAC) was measured with a millimetered tape at the midpoint of the same arm, between the olecranon and acromion. As an estimate of muscle mass, arm muscle area (AMA) was calculated by the following equations for men:  $[(MUAC - \pi \times TSF)^2 / 4\pi] - 10$ , and for women:  $[(MUAC - \pi \times TSF)^2 / 4\pi] - 6.5$  [16]. Causes of death were determined using the ERA-EDTA codes [14].

### GFR

GFR was measured as the mean of urea and creatinine clearance, calculated from 24-h urine collections (mGFR) and indexed for body surface area. The abbreviated MDRD equation was used to estimate GFR (eGFR)

**Table 1.** Patient characteristics of the study population at the start of dialysis ( $n = 569$ )

Age, year	58.5 (15.3)
Gender, % male	61
BMI, kg/m <sup>2</sup>	25.0 (4.0)
Ethnicity, % Caucasian	92
Primary kidney disease, %	15
Diabetes	12
Glomerulonephritis	16
Renal vascular disease	57
Other or unknown	
Dialysis modality, % HD	49
Khan co-morbidity score, %	
Low	45
Medium	32
High	24

Data are presented as mean (SD) or %. BMI, body mass index; HD, haemodialysis.

as  $186 * [\text{plasma creatinine}^{-1.154}] * (\text{age})^{-0.203} * (0.742 \text{ if female}) * (1.210 \text{ if African-American})$  [8].

### Statistical analysis

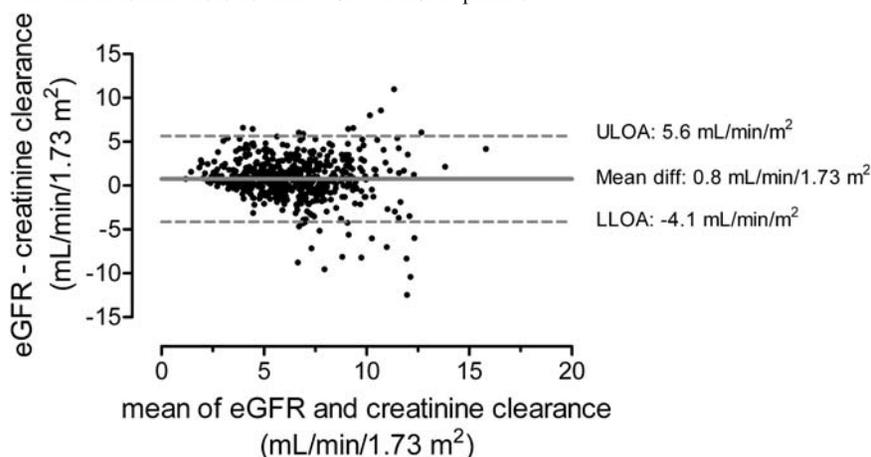
Continuous variables were described as mean with standard deviation (SD) and categorical variables as proportions. Comparisons between patient groups were made by using the chi-square or independent sample *t*-test, as appropriate. Correlation between variables was assessed by Pearson test. Agreement between the two methods for obtaining GFR (mGFR and eGFR) was assessed using analysis of variance followed by calculation of the intraclass correlation coefficient (ICC). In order to correct for systematic differences between the two methods, ICC was also calculated by variance components. The ICC can have a maximum value of 1, indicating perfect agreement between the two methods. Bland–Altman analysis was performed to assess the mean difference together with the limits of agreement between the two methods [17]. As a measure of accuracy, an agreement plot was made to judge the clinical relevance of the agreement between mGFR and eGFR [18]. Finally, the percentage of estimates falling within 30 and 50% above or below the measured GFR was calculated and presented as measure of accuracy.

To examine the relationship between mGFR versus eGFR at the start of dialysis and mortality risk, the study group was categorized according to tertiles of mGFR and tertiles of eGFR. Kaplan–Meier curves were plotted, and mortality rates were calculated for the different tertile groups. Crude and adjusted hazard ratios for the different tertile groups of mGFR and eGFR were obtained using Cox regression analyses. Analyses were performed with the Statistical Package for Social Sciences (SPSS for Windows 14.0; SPSS Inc., Chicago, IL).

## Results

### Patient flow

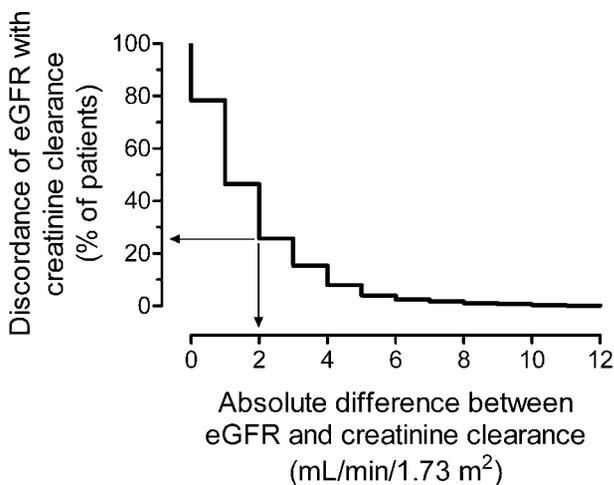
A total of 1952 incident dialysis patients were included in the NECOSAD. Of these, 831 were excluded because of missing mGFR data at the start of dialysis. Furthermore, patients who had no data on plasma creatinine ( $n = 3$ ), ethnicity ( $n = 35$ ), follow-up time ( $n = 1$ ) or a blood ( $n = 489$ ) or urine ( $n = 24$ ) sample within 4 weeks prior to the start of dialysis were excluded. Therefore, 569 patients were included in the present analysis. Data on muscle mass were available in 500 of these patients. Of the patients, 61% were men, and renal vascular disease was the most common primary cause of kidney disease (Table 1).



**Fig. 1.** Bland and Altman plot comparing measured GFR (mGFR) and estimated GFR (eGFR) in ESRD patients at the start of dialysis. The solid lines represent the mean difference between measured and estimated GFR; the dashed lines represent the upper and lower limits of agreement between measured and estimated GFR. ULOA, upper limit of agreement; mean diff, mean difference; LLOA, lower limit of agreement.

#### Agreement between mGFR and eGFR

The mean (SD) mGFR was 6.0 (2.6) mL/min/1.73 m<sup>2</sup> with a mean eGFR of 6.8 (2.4) mL/min/1.73 m<sup>2</sup> for the complete group. The correlation between mGFR and eGFR was moderate ( $r = 0.52$ ,  $P < 0.001$ ). The ICC for the two GFR measurement methods was 0.45, which improved to 0.51 after correction for methodologic differences. eGFR overestimated mGFR by 0.8 mL/min/1.73 m<sup>2</sup> (limits of agreement  $-4.1$  and  $5.6$  mL/min/1.73 m<sup>2</sup>), as assessed by Bland–Altman analysis (Figure 1). Figure 2 presents the percentage of patients having a larger difference from mGFR than indicated, at each given level of (absolute) difference between estimated GFR and mGFR. For example, ~22% of GFRs estimated by the MDRD equation were in disagreement with mGFR, resulting in an agreement of 78%, when 2 mL/min/1.73 m<sup>2</sup> was considered an acceptable difference between the two measures of kidney function (Figure 2). Finally, the percentage of estimates falling within 30 and 50% above or below the measured GFR (p30 and p50, respectively) was 61 and 77%, respectively.



**Fig. 2.** Percentage of patients with discordance between measured GFR (mGFR) and estimated GFR (eGFR).

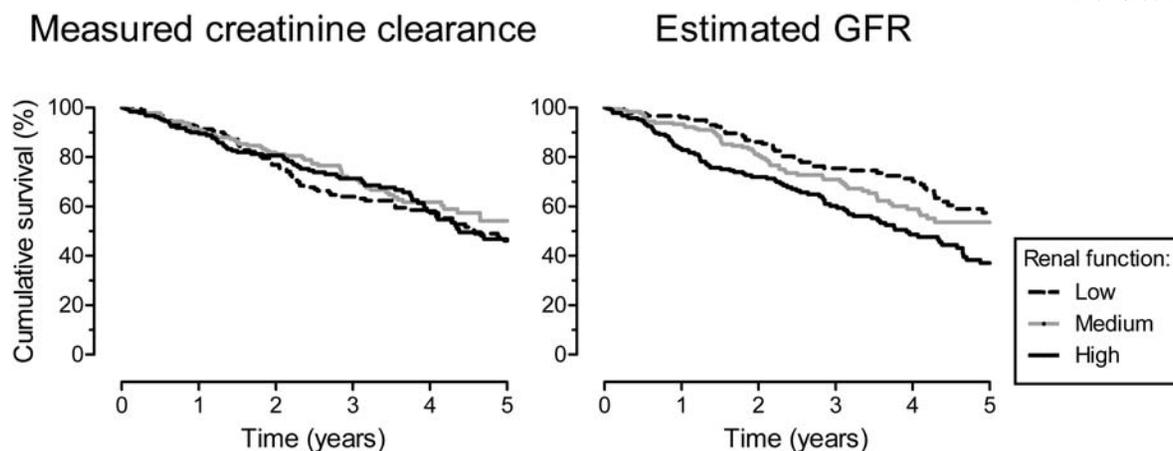
#### Association with mortality

During the 5-year follow-up, 198 patients (35%) died. Furthermore, a total of 256 patients (45%) were censored in the survival analysis for reasons of transplantation ( $n = 170$ ), patient or centre stopped participation ( $n = 69$ ), transfer of the patient to another dialysis centre which did not participate in the study ( $n = 6$ ), recovery of renal function ( $n = 2$ ) and others ( $n = 9$ ). The 5-year mortality rate was 13.0/100 patient-years. Mortality rates stratified by either mGFR or eGFR are shown in Table 2. The measured GFR at the start of dialysis was not significantly associated with mortality during subsequent follow-up (Figure 3), although the mortality rate was highest in the lowest tertile (Table 2). In contrast, patients with the highest eGFR at the start of dialysis were at increased mortality risk compared to patients with the lowest eGFR at the start of dialysis (Figure 3 and Table 2). Patients with the best kidney function had a crude HR (95% CI) of 0.9 (0.7, 1.3) when mGFR was used, whereas this was 1.9 (1.4, 2.8) for the eGFR (Table 3). Adjustment for primary kidney disease, dialysis modality and Khan co-morbidity score attenuated the discrepancy between mGFR and MDRD in their association with mortality to some extent (Table 3).

**Table 2.** Five-year mortality rates in ESRD patients by tertiles of renal function, as assessed either as measured GFR from 24-h urine collections or estimated GFR by MDRD formula

Renal function	Low	Medium	High
<b>Measured GFR, mL/min/1.73 m<sup>2a</sup></b>	3.4 (1.1)	5.8 (0.5)	8.8 (2.0)
Deaths, $n$	73	58	67
Patient-years	518	506	503
MR/100 py	14	11	13
<b>Estimated GFR, mL/min/1.73 m<sup>2a</sup></b>	4.5 (0.9)	6.4 (0.5)	9.4 (1.9)
Deaths, $n$	50	60	88
Patient-years	535	504	488
MR/100 py	9	12	18

<sup>a</sup>Data are mean (SD). MR, 5-year mortality rate.



**Fig. 3.** Cumulative survival for different tertile groups of measured GFR (left panel) and estimated GFR (right panel).

#### Role of muscle mass

To explore further the discrepancy of the association of both measures of kidney function with mortality, we examined the role of muscle mass. Muscle mass, as assessed from AMA, was significantly and inversely associated with eGFR ( $r = -0.15$ ,  $P < 0.001$ ) but not with mGFR ( $r = -0.031$ ,  $P = 0.5$ ) (Figure 4).

#### Post hoc sensitivity analyses

Several post hoc sensitivity analyses were performed to test the robustness of our results. First, a similar assessment was performed for the six-variable MDRD equation in order to investigate whether the inclusion of urea and albumin in serum in the estimation of eGFR attenuates the effect of creatinine. The mean (SD) eGFR by six-variable MDRD equation (6v-eGFR) could be calculated in 559 patients and was 6.8 (2.2) mL/min/1.73 m<sup>2</sup>. The correlation with mGFR and ICC was similar to that of the four-variable eGFR ( $r = 0.55$  and  $r = 0.51$ , respectively). The 6v-eGFR overestimated mGFR by 0.75 (2.33) mL/min/1.73 m<sup>2</sup> (limits of agreement -3.91, 5.41 mL/min/1.73 m<sup>2</sup>). The p30 and p50 were 62 and 76% respectively. Associations of 6v-eGFR with mortality were also similar to those of the four-variable MDRD equation [crude HR (95% CI) medium 6v-eGFR 1.2 (0.9, 1.8), high 6v-eGFR 1.8 (1.2, 2.5)]. Adjustment for primary kidney disease, dialysis modality and Khan co-

morbidity score attenuated the mortality risks to some extent [adjusted HR medium 6v-eGFR 1.1 (0.7, 1.5), high 6v-eGFR 1.2 (0.9, 1.7)]. eGFR as assessed by six-variable MDRD equation was significantly associated with muscle mass ( $r = -0.14$ ,  $P = 0.003$ ).

Second, since patients with diabetes generally start dialysis at higher levels of estimated GFR, we explored whether the association of the two measures of kidney function with muscle mass is different between patients with and without diabetes. A total of 115 patients (20%) had diabetes mellitus, either as primary cause of kidney disease or as a co-morbid condition. The mean (SD) difference between eGFR and mGFR was significantly greater in patients with diabetes [1.4 (3.0) mL/min/1.73 m<sup>2</sup>] than in patients without diabetes [0.6 (2.3) mL/min/1.73 m<sup>2</sup>,  $P = 0.013$ ]. The association of eGFR with muscle mass was stronger in patients with diabetes ( $r = -0.24$ ,  $P = 0.015$ ) than in those without diabetes ( $r = -0.13$ ,  $P = 0.011$ ). In contrast, mGFR was not associated with muscle mass in either patient group ( $r = 0.027$ ,  $P = 0.8$  in patients with diabetes,  $r = -0.06$ ,  $P = 0.2$  in patients without diabetes). Finally, the association of both measures of kidney function with mortality was not different between patients with and without diabetes.

## Discussion

The results of the present analysis show that the MDRD equation is not suitable for the estimation of GFR in ESRD patients at the start of dialysis. This is for two reasons. First, the limits of agreement with the measured values range from -4.1 to +5.6 mL/min. Second, plasma creatinine is in the denominator of the MDRD equation. In the presence of a low GFR, the muscle mass of a patient will be a relatively more important determinant of plasma creatinine than the GFR. Therefore, patients with a large muscle mass will by definition have a low value for eGFR, while in those with a small muscle mass higher values for eGFR will be obtained. The purpose of the present study was to investigate further the above assumption by analysing the relationships of measured and estimated kidney function with mortality and muscle mass.

**Table 3.** Crude and adjusted hazard ratios of renal function for mortality (95% CI) in ESRD patients, as assessed by measured or estimated GFR

Renal function	Low	Medium	High
<b>Measured GFR</b>			
1. Crude	1.0	0.8 (0.6, 1.2)	0.9 (0.7, 1.3)
2. 1 + PKD	1.0	1.0 (0.7, 1.5)	1.0 (0.7, 1.4)
3. 2 + dialysis modality	1.0	1.0 (0.7, 1.5)	1.0 (0.7, 1.4)
4. 3 + Khan score	1.0	1.0 (0.7, 1.5)	1.0 (0.7, 1.3)
<b>Estimated GFR</b>			
1. Crude	1.0	1.3 (0.9, 1.9)	1.9 (1.4, 2.8)
2. 1 + PKD	1.0	1.3 (0.9, 1.9)	1.6 (1.1, 2.3)
3. 2 + dialysis modality	1.0	1.2 (0.9, 1.8)	1.6 (1.2, 2.3)
4. 3 + Khan score	1.0	1.2 (0.8, 1.8)	1.4 (1.0, 1.9)

PKD, primary kidney disease.

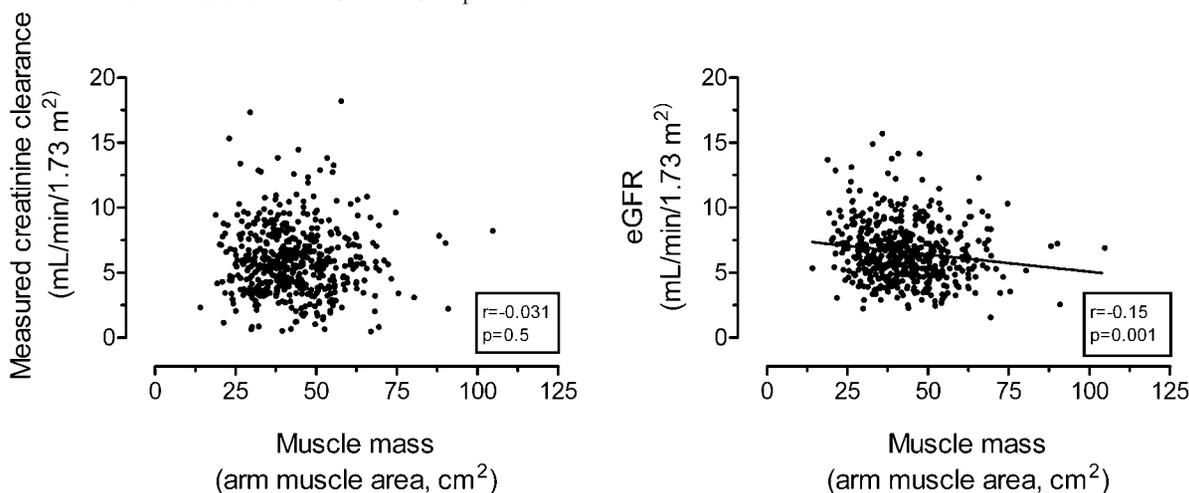


Fig. 4. Association between muscle mass as assessed by arm muscle area and measured GFR (left panel) and estimated GFR (right panel).

This study showed that a high eGFR as assessed by the four-variable MDRD formula is associated with increased mortality even after adjustment for important confounders, which is not the case for measured GFR. This trend sustained even after inclusion of urea and albumin in the (six variable) MDRD equation. Furthermore, eGFR but not mGFR is inversely associated with muscle mass, which may explain the discrepancies of the two kidney function measures in their relationship with mortality. Among patients with diabetes, overestimation of mGFR by eGFR was more pronounced and the association of eGFR with muscle mass was stronger. A number of studies on measured GFR in dialysis patients have shown a beneficial effect of preservation of residual renal function on patient survival [1–5]. However, this was not found in the present study in stage 5 chronic kidney disease patients. This could in part be explained by the fact that in the present study, patients were strictly selected on having data available in the 4 weeks prior to the start of dialysis, in order to exclude an influence of dialysis on the performance of the MDRD prediction equation. A study from the USA also reported no effect of measured creatinine clearance at the start of dialysis on survival [9]. An explanation could be that dialysis is often started at a higher GFR in patients with marked co-morbidity compared to those without. The studies showing a beneficial effect of measured kidney function on patient survival were performed in patients who were already treated with dialysis [1–5]. However, correction for age, co-morbidity, primary kidney disease and dialysis modality in the present study did not change the hazard ratios for mortality. Furthermore, start of dialysis may also have been guided by symptoms of uraemia, fluid overload and complications in individual patients rather than by precise level of GFR. Alternatively, effects of lead time bias [19] and/or the limited sample size cannot be excluded with certainty and may explain discrepancies between studies. The importance of clinical signs and symptoms is supported by the results of a randomized controlled trial comparing an early initiation of dialysis with a late start [20]. It showed that many patients from the late start group did not reach their target eGFR and began dialysis earlier because of clinical reasons.

Our finding that a higher estimated GFR is associated with a higher mortality is in line with previous studies [9–12]. All studies using estimations of creatinine clearance [12] or GFR [9–11] showed positive relationships between estimated GFR and mortality. However, none of these studies reasoned that this inverse relation might be due to the fact that plasma creatinine is present in the denominator of all equations. Apart from a minor effect of meat intake, plasma creatinine is determined by GFR and by muscle mass. In patients with normal kidney function, the effect of muscle mass is largely overruled by that of GFR, but it becomes progressively more important the lower the GFR. For instance, Lowrie and Lew reported a marked association between plasma creatinine and mortality in haemodialysis patients: a lower plasma creatinine was associated with a markedly increased risk of death and vice versa [21]. Similarly, in patients starting dialysis, quintiles of plasma creatinine were strongly and inversely associated with mortality [10]. In this line of reasoning, we analysed the effect of muscle mass on the MDRD equation. It appeared that the AMA, a measure of muscle mass, was associated with eGFR, but not with the mGFR. Similar associations were seen for eGFR with the 24-h creatinine excretion, which can be considered as an alternative marker of muscle mass, in particular within strata of mGFR (results not shown). Furthermore, the high hazard ratios for mortality of the eGFR were attenuated after additional adjustment for co-morbidity and age. Both conditions are associated with a reduction in muscle mass.

The recently proposed new formula for the prediction of GFR, the CKD-EPI formula [22], is expected to suffer the same problems as the MDRD formula in ESRD patients, since it also has plasma creatinine in the denominator. However, the CKD-EPI has been developed to improve accuracy in estimating GFR in case a GFR  $>60$  mL/min/1.73 m<sup>2</sup> is expected. Therefore, using this formula in ESRD patients beforehand would not be the best choice.

The present study has potential limitations. First, NECOSAD is a large prospective cohort study in incident ESRD patients in The Netherlands. For the present analysis, only patients who had 24-h urine collections and a matching blood sample available in the 4 weeks prior to the start

of chronic dialysis were included. The patients who were included in the present analysis were somewhat younger and had less co-morbidity than those who lacked either the 24-h urine collection and/or a matching blood sample. Although this might limit the generalizability of our results, this is unlikely given the agreement with a number of other studies. Second, GFR was assessed from the mean of 24-h urea and creatinine clearance, which can be performed in large epidemiologic studies, and not with a gold standard measurement. Although this approach yields results similar to inulin clearance [23], all these methods are dependent on accurate urine collections. However, these may have influenced the analysis based on measured clearances, but not those of the eGFR. Furthermore, the mean of 24-h urea and creatinine clearance is still accepted as useful in peritoneal dialysis patients and holds up well when compared to measured kidney function [8]. Finally, creatinine values were done in the laboratories of the participating hospitals, mainly using uncalibrated alkaline picrate methods. Therefore, we used the four-variable MDRD equation with factor 186, instead of the factor 175 recommended for calibrated methods. However, the difference between the various methods for creatinine determinations is much less for high values, as in the present study, than for values closed to the normal range.

In conclusion, the MDRD equation is not suitable for the estimation of GFR in ESRD patients at the start of dialysis. Our data imply that all estimations of GFR based on equations consisting of plasma creatinine in the denominator and demographics cannot be used in patients with ESRD. The addition of some estimation of muscle mass in the numerator may lead to better results, but such modifications require further investigations. In addition, our results provide at least a part of the explanation of the counterintuitive findings of all recent studies showing an association between a high eGFR at the start of dialysis and increased mortality.

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