Estimated GFR in stable older kidney transplant recipients – are present algorithms valid? A national cross-sectional cohort study.

Corresponding author:
Kristian Heldal; MD, PhD
Clinic of Internal Medicine, Telemark Hospital Trust, Skien, Norway
Box 2900 Kjørbekk
3710 Skien, Norway
e-mail: hkri@sthf.no
phone: +47 900 18 417

and University of Oslo, Faculty of Medicine, Institute of Clinical Medicine
and Department of Transplantation, Section of Nephrology, Oslo University Hospital
Contribution: Research idea and study design. Data interpretation. Statistical analysis. Wrote manuscript.

Karsten Midtvedt; MD, PhD
Department of Transplantation, Section of Nephrology, Oslo University Hospital
Contribution: Research idea and study design. Data interpretation. Supervision. Revision of manuscript

Anders Hartmann, MD, PhD
Department of Transplantation, Section of Nephrology, Oslo University Hospital
and University of Oslo, Faculty of Medicine, Institute of Clinical Medicine
Contribution: Research idea and study design. Data interpretation. Revision of manuscript

Anna Varberg Reisæter, MD, PhD
Department of Transplantation, Section of Nephrology, Oslo University Hospital
Contribution: Data interpretation. Revision of manuscript

Torbjørn Fossum Heldal, medical student
Department of Transplantation, Section of Nephrology, Oslo University Hospital
and University of Oslo, Faculty of Medicine
Contribution: Data interpretation. Revision of manuscript

Stein Bergan, PhD
Department of Pharmacology, Oslo University Hospital
and University of Oslo, School of Pharmacy, Department of Pharmaceutical Biosciences
Contribution: Iohexol measurements. Data interpretation. Revision of manuscript

Cathrin Lytomt Salvador, MD
Department of Medical Biochemistry, Oslo University Hospital
and University of Oslo, Faculty of Medicine, Institute of Clinical Medicine
Contribution: Data interpretation. Revision of manuscript

Anders Åsberg, PhD
Department of Transplantation Medicine, Section of Nephrology, Oslo University Hospital
University of Oslo, School of Pharmacy, Department of Pharmaceutical Biosciences
Contribution: Research idea and study design. Data acquisition. Data interpretation. Supervision. Revision of manuscript

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Abstract

Several equations have been developed for estimated glomerular filtration rate (eGFR) in patients with chronic kidney disease (CKD), but none were developed based on data from elderly kidney transplant recipients (KTR). The primary aim of this study was to evaluate different creatinine based equations in stable elderly KTR. A national cross-sectional study was performed using data from 263 consecutive kidney transplant recipients 60 years or older who performed a routine GFR measurement one year after engraftment. GFR was measured by iohexol clearance calculation based on two samples. eGFR was calculated from a range of different creatinine based equations using information obtained at the time of GFR measurement. Bias, precision, and accuracy were evaluated for each equation. All equations apart from Nankivell had accuracy > 80%. The BIS1, FAS, LMR_{CR} and Cockcroft & Gault equations in recipients older than 70 years and the FAS, LMR_{CR} and MDRD in recipients 60-69 years old had non-significant bias. The CKD-EPI had significant bias in both groups. If one should choose a single equation for follow-up of individual CKD progression in all recipients ≥ 60 years, the FAS or LMR_{CR} equations are probably the best alternatives.

Introduction

Glomerular filtration rate (GFR) is a measure of kidney function used for diagnostic and research purposes. It can be measured by several methods and the gold standard has been inulin clearance [1]. However, inulin clearance measurement is an inconvenient procedure in routine clinical practice as it requires continuous intravenous infusion of inulin and urine sampling [2]. As a consequence, other methods using X-ray contrast (iohexol and iothalamate) [3] or radiolabelled substances such as ^{51}Cr-EDTA [4] and ^{99}Tc-DTPA have been developed. In everyday clinical practice, there is however a need for a simple and reliable method for estimation of GFR.

Several equations have been developed to estimate GFR based on readily available variables; age, gender, ethnicity and laboratory data like serum creatinine or cystatin C. In addition, the Cockcroft & Gault (C&G) equation [5], which estimates creatinine clearance, includes weight while the Nankivell equation [6] includes weight, height and serum urea, but not age. According to the KDIGO 2012 guidelines [7], the Chronic Kidney Disease EPIdemiology collaboration (CKD-EPI) equation [8] should be preferred unless another equation has been shown to improve accuracy of GFR estimates compared to the CKD-EPI equation.

The equations were developed based on data from different populations, but until the Berlin Initiative study (BIS1) equation was published in 2012 [9], none of them were developed from individuals predominantly older than 70 years. The Lund-Malmö revised (LMR_{CR}) equation was developed from a Swedish cohort including 850 individuals aging 18-95 years (median 95 years) [10] and the full age spectrum (FAS)

equation has been presented as an equation representative for all ages [11]. In a recent paper, Björk et al conclude that the LMR_{CR} and FAS_{CR} seem to be attractive alternatives to CKD-EPI_{CR} in estimating GFR by creatinine-based equations in older Europeans [12].

Only the Nankivell equation was developed on basis of data from kidney transplant recipients (KTR) [6]. Consequently none of the development populations for the existing GFR equations were representative for older KTR. The equations are, with a few exceptions [12-15], not evaluated in an elderly population of KTR and as far as we know, no studies have evaluated eGFR equations in KTR older than 70 years. Masson et al [16] compared the CKD-EPI with the Modification of Diet in Renal Diseases (MDRD) [17] equation in KTR and found that the CKD-EPI did not offer a better prediction of GFR. In a recently published study from our center, the MDRD equation was found to have the best performance among creatinine based equations in adult KTR [18].

The primary aim of the present study was to evaluate the most commonly used creatinine based eGFR equations (Table 1) in a population of KTR older than 60 years. Each equation was evaluated against measured GFR (mGFR) and the results were compared between recipients 60-69 years and those older than 70 years.

Materials and Methods

All Norwegian KTR are offered a measurement of GFR one year after engraftment at the national transplant center as part of the regular post transplant follow-up. In the present study we included all patients who performed a valid one-year post-transplantation mGFR investigation at an age of 60 years or older between November

2013 and June 2017. KTR were classified as senior (60-69 years) or elderly (70 years or older).

We used iohexol clearance to determine mGFR according to the Bröchner-Mortensen method as previously described [19] with two samples; at 2 hours for all patients and, respectively, 5 or 8 hours after iohexol (Omnipaque^{TM}, 300 mg iodine/mL, GE Healthcare) administration depending on whether eGFR (CKD-EPI) was above or below 40 mL/min/1.73m^2. Serum iohexol concentrations were measured utilizing a high performance liquid chromatography (HPLC) system and the between series coefficient of variation was <6%. The results are reported normalized for body surface area (BSA) as mL/min/1.73m^2.

In order to evaluate different eGFR equations with regards to their applicability in diagnosing and staging of chronic kidney disease (CKD) as well as for clinical follow-up, the following creatinine based equations were tested with normalization to 1.73 m^2 body surface area: BIS1 [9], FAS [11], LMR_{CR} [10], MDRD-4 [17], CKD-EPI [8], C&G [5] and Nankivell [6]. Serum creatinine concentrations were measured by an enzymatic calorimetric method, (reagents from Roche Diagnostics®, Rotkreutz, Switzerland) IDMS traceable. The coefficient of variation was ≤ 3.7%.

Data included in this quality study were retrieved from the transplantation database at our center and analyses were performed on de-identified data. All patients who are included in the database have given written consent for saving their clinical data and to use them in research and quality assessment studies. In accordance with national guidelines there was consequently no need for ethics approval for quality analyses.

The study was performed in accordance with the Declaration of Helsinki 2000. The clinical and research activities being reported are consistent with the principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Statistics

Each equation was evaluated against mGFR with respect to bias, precision and accuracy according to the 2002 K/DOQI clinical guidelines on evaluation, classification and stratification of chronic kidney disease [20].

Bias was expressed as the systematic deviation from the mGFR given by mean difference between the eGFR and mGFR (eGFR – mGFR). Precision describes the variability of eGFR around mGFR and was expressed as the standard deviation of the bias. Bias was evaluated using paired sample T-test.

Accuracy was expressed as the proportion of estimates within ±15% (P15) and ±30% (P30) of the mGFR and compared using the McNemar test.

Patient characteristics were compared using t-test for continuous data and Fishers exact test for categorical data. All reported p-values were two-sided. All statistical analyses were performed using the IBM SPSS statistics version 24.

Results

In the investigation period, more than 40% of patients in our center were older than 60 years at time of transplantation. Of the 329 patients above 60 years, alive with a functioning graft at the 1-year control, 274 underwent an mGFR investigation. Data from 11 recipients were excluded because the second iohexol sample was obtained too early according to their eGFR. Data from the remaining 263 KTR (60-69 years, n= 166, >70 years, n=97) were included in the analyses, representing 78% and 84% of the patients alive with a functioning graft.

Demographic characteristics at time of investigation are presented in Table 2. No recipients received trimethoprim, cimetidine or other drugs known to interfere with creatinine secretion in the kidney.

Bias and precision are presented in Table 3. Precision was comparable for all equations. In KTR older than 70, the BIS1, FAS, LMR_{CR} and C&G equations had absolute mean bias < 2 mL/min/1.73m^2 not significantly different from zero. Among recipients aging 60-69 years, the FAS, LMR_{CR} and MDRD equations had non-significant absolute mean bias < 2 mL/min/1.73m^2.

Regarding accuracy, both age groups had P30 above 80 % for all equations apart from the Nankivell equation and C&G (P30: 79.5% in 60-69). Only Nankivell in the 70+ group ($p < 0.001$) and CKD-EPI ($p = 0.02$), C&G ($p < 0.001$) and Nankivell ($p < 0.001$) in the 60-69 group had significant different P30 accuracy compared with the reference. In the 60-69 group, the FAS, LMR_{CR} and MDRD all showed P30 accuracy above 90%. Complete data are presented in Table 4.

Bland-Altman plots illustrating the relationship between mGFR and bias for each formula are presented in Figure 1a and Figure 1b. Figure 2a and Figure 2b compare the performance of each equation with the mGFR.

Discussion

To our knowledge, this is the first study to evaluate the most commonly used creatinine based eGFR equations, including the recently developed BIS1, LMR_{CR} and FAS equations, in KTR older than 70 years of age. Our results showed that all equations apart from the Nankivell equation were sufficiently accurate in stable older KTR with P30 > 80%. The BIS1, FAS, LMR_{CR} and C&G equations also had mean bias < 2 mL/min/1.73m^2.

The Bland-Altman plots illustrate however that the bias is not constant over all stages of kidney function. For instance, even if the mean bias of the BIS1 equation is almost zero, the plot shows that this is only the fact for patients with a mGFR around 50 mL/min/1.73m^2. In patients with mGFR in the lower range the bias is positive, whereas the bias is negative in patients in the higher mGFR-range. The same pattern was observed for all other equations, but it was less pronounced for the CKD-EPI and the MDRD equations (Figure 1a and Figure 1b). Based on results from previous publications [8, 9, 11, 15] we chose to define mean bias within ± 2 mL/min as "clinical irrelevant" and P30 accuracy > 80% as "acceptable". This definition is definitively disputable and one may argue that an acceptable P30 accuracy should be at least 90% [21]. In the 2002 guidelines from the Kidney Disease Outcomes Quality Initiative (K/DOQI), a P30 accuracy above 75% was however considered as "sufficient for good decision-making" [20]. In a paper published in 2015 [22], Luis-

Lima et al discuss the important challenge of defining acceptable boundaries of error. They argued that the boundaries most commonly used were too wide. Björk et al recently compared the performance of the LMR_{CR}, FAS and CKD-EPI and found P30 accuracy between 91.7% (CKD-EPI) and 95.8% (FAS) [23]. If we expand our definition of "clinical irrelevant" bias to ± 5 mL/min/1.73m^2, the MDRD may be considered as the best equation taking into account the more constant bias over the range of renal function as shown in the Bland-Altman plots (Figure 1a and Figure1b). On the other hand, if we increased the level for acceptable accuracy to 85%, the MDRD would not reach this level in recipients older than 70 years. Since accuracy is a combination of bias and precision, it is by many considered to be the most important variable in the evaluation of eGFR equations and in the KDIGO 2012 guidelines it is stated that if one should select a single eGFR equation, "the criteria for selection should be based on accuracy compared to measured GFR and usefulness in clinical care and public health" [7]

In an evaluation process, the estimate from each equation is compared with a gold standard. GFR can be measured using different methods with different strengths and limitations. The original gold standard, inulin clearance, is not easy to perform in a clinical setting [2]. The X-ray media iohexol and iotalamate are at present the most widely used exogenous substances for measurement of GFR and both have been shown to correlate well with inulin clearance even though it requires multiple blood samples to obtain reliable results [24, 25]. In our analyses, we have measured GFR as iohexol clearance with two samples, which is the clinical standard at our center and presents good accuracy.

In a recently published Brazilian study comparing the BIS1, MDRD, CKD-EPI and C&G equations, David-Neto et al concluded that the CKD-EPI equation was the best tool for monitoring GFR in elderly KTx recipients [13]. They validated the eGFR equations against ^{51}Cr-EDTA plasma clearance in 70 recipients older than 60 years, including a subgroup of 35 recipients older than 65 years (median 68 years). They found that CKD-EPI in the oldest subgroup had a mean bias of 0 mL/min/1.73 m^2, and an accuracy (P30) of 74%. In the total group of patients older than 60 years, the bias of CKD-EPI was 2 mL/min/1.73m^2 compared to 4 and 5 mL/min/1.73m^2 for BIS1 and MDRD, respectively. The main limitation of this study is however the low number of elderly KTR.

Buron et al validated the MDRD, CKD-EPI, C&G and Nankivell equations in 1297 recipients including a subgroup of 309 recipients older than 60 years [14]. They concluded that the MDRD equation was superior to all the other equations regardless of age and that all the other equations were overestimating GFR expressed as inulin clearance. This finding corresponds well with our findings in patients aging 60-69 years. Since neither the BIS1 nor the FAS equations were developed at the time of this publication, these equations have up to now, not been properly validated against inulin or iohexol clearance in KTR.

In a study from 2013, Koppe et al validated the MDRD, CKD-EPI and BIS1 equations in a population of 224 CKD patients against inulin clearance performed due to established or suspected renal dysfunction [15]. In this population there was also a subgroup of 41 KTR. Median biases in the KTR subgroup were 9, 6.7 and 6.1 mL/min/1.73m^2 respectively. Corresponding accuracy (P30) were 66, 66 and 78%. In

our study, the estimates were more accurate for all equations. A possible explanation is the fact that GFR measurements in Koppes study were performed on indication whereas our measurements were performed by protocol in stable KTR.

The C&G equation is de facto an estimate of absolute creatinine clearance and not GFR. Since creatinine is secreted in the tubuli in addition to the glomerular filtration, creatinine clearance will overestimate the GFR, especially at low renal function. According to this it is not surprising that the C&G equation has a positive bias in our analyses even though it was "clinically irrelevant" in KTR older than 70 years. The C&G equation is also difficult to use in regular clinical practice since it includes weight and consequently cannot be reported automatically from the lab. It is more surprising that the Nankivell equation, which is the only equation developed based on data from KTR, perform so poorly. The most likely explanation may be that the Nankivell equation does not include age and thus does not adjust for the effect of advanced age. Both the C&G and the Nankivell equations were developed based on serum creatinine assessed by methods that were more frequently affected by interfering substances than the currently recommended enzymatic assays [26] and neither of them were developed with serum creatinine from IDMS traceable assays.

In clinical practice, individual rate of decline in kidney function is evaluated for each patient by comparing the serum creatinine change between visits. In this setting, eGFR brings the clinician limited extra information as long as the patient is reasonably stable in the other variables that affect serum creatinine concentrations except for renal function. However, for the correct diagnosis of CKD stage and in

long-term follow-up of KTR, eGFR equations adds important information to the clinical care of these patients and should be as accurate as possible.

In clinical research, eGFR or change in eGFR is often used as a study endpoint. In these cases, an accurate estimate of GFR is needed and international consensus on which equation to use is lacking. This often makes it problematic and sometimes nearly impossible to compare studies with eGFR as primary outcome.

The strengths of this study are first of all the standardized systematic retrieval of data from all nephrology centers in Norway. All KTR were examined at one-year post engraftment. All had stable kidney function and were on a stable immunosuppression regimen without receiving trimethoprim, cimetidine or other drugs known to alter creatinine secretion. They were also transplanted within a relatively short time period representing a modern surgical and medical treatment protocol. The data should consequently be representative for most patients receiving a kidney transplant nowadays. In addition, iohexol clearance is considered to have good agreement with inulin clearance [3, 24]. Iohexol clearance was also the method of choice in the development of both the BIS1 and the FAS equations [9, 11].

The limitations include the fact that we only used two sample measurements of iohexol even though there is documentation that shows that more serum concentration measurements over a longer time period after dosing increase the accuracy of iohexol clearance estimation to a certain degree [24]. In the recent literature concerning evaluation of eGFR equations in older ESRD patients, a variety of sampling protocols have been used, including single-point [11, 12, 27], two-point [11] and multiple [9,

11, 12] sampling. Ebert et al described that measurement of iohexol clearance up to 5 hours leads to clinically relevant overestimation of GFR compared with 24 hours measurement, especially in patients with considerably reduced GFR [24]. Since we used the second sample taken at 5 hours or 8 hours depending on whether eGFR (CKD-EPI) was above or below 40 mL/min/1.73 m^2, and there were few patients with severely reduced GFR, we consider the risk of overestimation of GFR by iohexol clearance to be low. In addition, the performance of two-point iohexol clearance has to our knowledge not been specifically validated against full AUC-iohexol clearance in older KTR, and consequently we do not know if findings from older CKD patients can be extrapolated to older KTR. Secondly, we had only two recipients included with GFR < 20 mL/min/1.73 m^2. Consequently, further validations should be performed including KTR with low GFR (CKD stage (4-5). Finally, the study is performed on a single transplant center population of predominantly Caucasians, potentially making extrapolation of our findings to non-white recipients challenging.

Equations including cystatin C have shown promising results in older CKD patients [9] and may also be attractive in older KTR. Since cystatin C was not included as a routine analysis at the one-year post engraftment control, we were not able to evaluate cystatin C based equations in this study. This should definitely be performed in later studies. On the other hand, cystatin C analyses are still less available worldwide than creatinine indicating that the creatinine based equations will still be preferred at most transplant centers. In addition, Masson et al found no clinical advantage of cystatin C over creatinine-based equations in a population of KTR [28].

In the present analyses, equations were not evaluated in non-elderly adult KTR. In previous publications, the accuracy in non-elderly KTR has been described to be lower than what is reported for elderly in the present analysis [13, 14, 22]. The performance of the newer equations should consequently be further evaluated in future studies including non-elderly KTR.

In conclusion, all validated equations apart from the Nankivell showed acceptable accuracy in both age groups. The BIS1, FAS, LMR_{CR} and C&G equations in KTR older than 70, and the FAS, LMR_{CR} and MDRD equations in those aging 60-69 years had clinically irrelevant and also significantly lower bias than all other evaluated equations. Consequently we conclude that the FAS and the LMR_{CR} equation are the best tools for estimation of GFR in stable KTR older than 60 years. Taking into account that the FAS equation also is proven to be valid over the full age spectrum in non-transplanted individuals [11], the FAS equation may be recommended as the equation of choice for all individuals, including KTR. To confirm this, further studies including KTR younger than 60 years should be performed.

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Contributions:

Research idea and study design: KH, KM, AH and AÅ; data acquisition: AÅ; Data analysis/interpretation: KH, KM, AH, AVR, TFH, CLS, SB and AÅ; Statistical analysis: KH; Supervision: KM and AÅ. Each author contributed important during manuscript drafting and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Table 1

eGFR equations. Serum creatinine (s-creat) is reported in µmol/L and serum urea in mmol/L, age in years, weight in kg and height in meter.

Equation	Group	Formula
BIS1	Male	$3736 * (\text{s-creat}/88.4)^{-0.87} * \text{age}^{-0.95}$
	Female	$3736 * (\text{s-creat}/88.4)^{-0.87} * \text{age}^{-0.95} * 0.82$
FAS	Male > 40 years	$(107.3/(\text{s-creat}/80)) * 0.988^{(\text{age}-40)}$
	Female > 40 years	$(107.3/(\text{s-creat}/62)) * 0.988^{(\text{age}-40)}$
LMR_{CR}		$e^{X-0.0158*\text{Age}+0.438*\ln(\text{Age})}$
	Female s-creat < 150	$x = 2.50+0.0121 * (150-\text{s-creat})$
	Female s-creat ≥ 150	$x = 2.50-0.926 * \ln(\text{s-creat}/150)$
	Male s-creat < 180	$x = 2.56+0.00968 * (180-\text{s-creat})$
	Male s-creat ≥ 180	$x = 2.56-0.926 * \ln(\text{s-creat}/180)$
MDRD	Male	$175* (\text{s-creat}/88.4)^{-1.154} * \text{age}^{-0.203}$
	Female	$175* (\text{s-creat}/88.4)^{-1.154} * \text{age}^{-0.203} * 0.742$
CKD-EPI	Male, s-creat ≤ 80	$141* (\text{s-creat}/80)^{-0.411} * 0.993^{\text{age}}$
	Male, s-creat > 80	$141* (\text{s-creat}/80)^{-1.209} * 0.993^{\text{age}}$
	Female, s-creat ≤ 62	$144* (\text{s-creat}/62)^{-0.329} * 0.993^{\text{age}}$
	Female, s-creat > 62	$144* (\text{s-creat}/62)^{-1.209} * 0.993^{\text{age}}$
C&G	Male	$((140-\text{age}) * \text{weight})/(72*\text{s-creat}/88.4)$
	Female	$((140-\text{age}) * \text{weight})/(72*\text{s-creat}/88.4)*0.85$
Nankivell	Male	$(6700/\text{s-creat}) + (0.25*\text{weight}) - (0.5*\text{s-urea}) - 100/(\text{height})^2 + 35$
	Female	$(6700/\text{s-creat}) + (0.25*\text{weight}) - (0.5*\text{s-urea}) - 100/(\text{height})^2 + 25$

BIS: Berlin initiative study, FAS: Full age spectrum, LMR_{CR}: Lund-Malmö revised, MDRD: Modification in renal disease, CKD-EPI: Chronic kidney disease epidemiology collaboration, C&G: Cockcroft and Gault

Table 2
Patient characteristics at time of investigation. Continuous variables are presented as mean ± SD. Categorical variables are presented as N (%). Concentrations of immunosuppressive drugs are presented as trough values (C_0).

	70+ (N=97)	60-69 (N=166)	P-value
Age (years)	74.0 ± 3.0	64.7 ± 2.7	< 0.001
Male gender	70 (72%)	123 (74%)	0.77
Living donor	15 (16%)	45 (27%)	0.03
Donor age (years)	63.5 ± 12.0	57.8 ± 13.6	< 0.001
Male donor	44 (45%)	91 (55%)	0.16
mGFR (mL/min/1.73m^2)	46.6 ± 14.0	53.0 ± 14.7	< 0.001
mGFR > 60 mL/min/1.73m^2	15 (16%)	52 (31%)	0.005
Weight (kg)	79.4 ± 13.9	81.6 ± 15.6	0.25
Height (meter)	1.73 ± 0.10	1.74 ± 0.10	0.23
BMI (kg/m^2)	26.5 ± 4.0	26.7 ± 4.4	0.71
S-creatinine (µmol/L)	123.4 ± 38.1	118.2 ± 34.8	0.27
S-urea (mmol/L)	10.0 ± 4.0	8.8 ± 3.2	0.01
Tacrolimus (N)	94 (97%)	155 (93%)	0.27
Tacrolimus conc. (µg/L)	6.0 ± 1.3	6.1 ± 1.7	0.63
Cyclosporine (N)	3 (3%)	6(4%)	1.00
Cyclosporine conc. (µg/L)	113 ± 53	160 ± 49	0.27
Everolimus (N)	1 (1%)	5 (3%)	0.42
Everolimus conc. (µg/L)	7.6	7.9 ± 1.5	NA
Prednisolone (N)	97 (100%)	162 (98%)	0.30
Prednisolone dose (mg/day)	5.3 ± 1.1	5.2 ± 1.0	0.51

Table 3

Bias and precision (SD of Bias) for different equations validated in a population of KTR older than 70 years (N=97) and 60-69 years (N=166) kidney transplant recipients. P-value (paired sample T-test) tests if the bias is different from zero.

	Mean Bias (95% CI)	**SD of Bias**	**P-value**
≥70 years			
BIS1	0.59 (-1.14, 2.34)	8.65	0.500
FAS	-0.45 (-2.22, 1.33)	8.80	0.617
LMR_{CR}	-1.17 (-3.02, 0.67)	9.15	0.210
MDRD	3.62 (1.60, 5.64)	10.03	0.001
CKD-EPI	3.41 (1.35, 5.48)	10.23	0.001
C&G	1.31 (-0.54, 3.17)	9.23	0.164
Nankivell	18.81 (16.64, 21.00)	10.80	<0.001
60-69 years			
BIS1	2.77 (1.40, 4.14)	8.92	< 0.001
FAS	1.00 (-0.38, 2.38)	9.00	0.153
LMR_{CR}	-0.77 (-2.2, 0.67)	9.37	0.292
MDRD	1.32 (-0.16, 2.79)	9.65	0.081
CKD-EPI	3.47 (1.91, 5.04)	10.23	< 0.001
C&G	4.68 (3.01, 6.36)	10.93	< 0.001
Nankivell	14.81 (13.20, 16.41)	10.48	< 0.001

BIS: Berlin initiative study, FAS: Full age spectrum, LMR_{CR}: Lund-Malmö revised, MDRD: Modification in renal disease, CKD-EPI: Chronic kidney disease epidemiology collaboration, C&G: Cockcroft and Gault

Table 4.
Accuracy expressed as P15 and P30 for different equations validated in a population of kidney transplant recipient older than 70 years (N=97) and 60-69 years (N=166). P-value (McNemar test) represents the difference between each equation and the reference equation having the highest accuracy.

	P15 (95% CI)	P-value	P30 (95% CI)	P-value
≥ 70 years				
BIS1	63.9 (54.2-73.7)	1.00	**88.7 (82.2-95.1)**	**Ref**
FAS	**65.0 (55.3-74.6)**	**Ref**	87.6 (81.0-94.3)	1.00
LMR_{CR}	60.8 (50.9-70.7)	0.48	88.7 (82.2-95.1)	1.00
MDRD	61.9 (52.0-71.7)	0.66	82.5 (74.8-90.2)	0.11
CKD-EPI	61.9 (52.0-71.7)	0.66	83.5 (76.0-91.0)	0.18
C&G	62.9 (53.1-72.7)	0.82	86.6 (79.7-93.5)	0.69
Nankivell	9.3 (3.4-15.2)	< 0.001	34.0 (24.4-43.6)	< 0.001
60-69 years				
BIS1	57.2 (49.6-64.8)	0.06	88.6 (83.7-93.5)	0.18
FAS	**62.7 (55.2-70.1)**	**Ref**	**91.6 (87.3-95.8)**	**Ref**
LMR_{CR}	56.6 (49.0-64.2)	0.13	91.6 (87.2-95.8)	1.00
MDRD	56.0 (48.4-63.7)	0.05	90.4 (85.8-94.9)	0.69
CKD-EPI	55.4 (47,8-63.1)	0.04	85.5 (80.1-91.0)	0.02
C&G	53.6 (46.0-61.3)	0.02	79.5 (73.3-85.7)	< 0.001
Nankivell	22.3 (15.9-28.7)	< 0.001	52.4 (44.7-60.1)	< 0.001

BIS: Berlin initiative study, FAS: Full age spectrum, LMR_{CR}: Lund-Malmö revised, MDRD: Modification in renal disease, CKD-EPI: Chronic kidney disease epidemiology collaboration, C&G: Cockcroft and Gault.

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Figure 1a:

Bland-Altman plots for KTR older than 70 years. The red horizontal line represents median bias and the dotted line represents zero bias. The other lines represent the trend-line and the borders of the individual 95% confidence interval. BIS: Berlin initiative study, FAS: Full age spectrum, LMRCR: Lund-Malmö revised, MDRD: Modification in renal disease, CKD-EPI: Chronic kidney disease epidemiology collaboration, C&G: Cockcroft and Gault

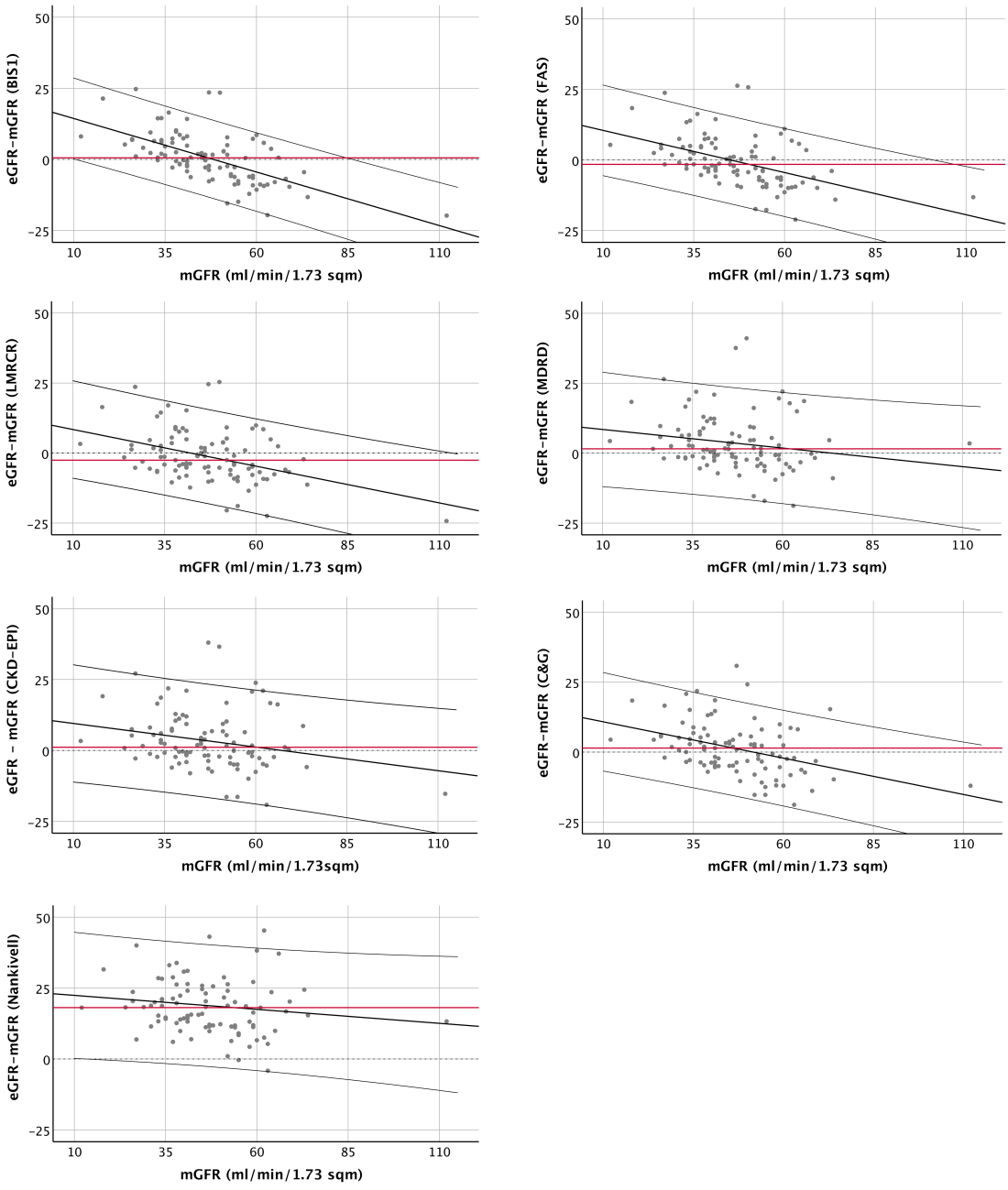

Figure 1b:

Bland-Altman plots for KTR 60-69 years. The red horizontal line represents median bias and he dotted line represents zero bias. The other lines represent the trend-line and the borders of the individual 95% confidence interval. BIS: Berlin initiative study, FAS: Full age spectrum, LMRCR: Lund-Malmö revised, MDRD: Modification in renal disease, CKD-EPI: Chronic kidney disease epidemiology collaboration, C&G: Cockcroft and Gault

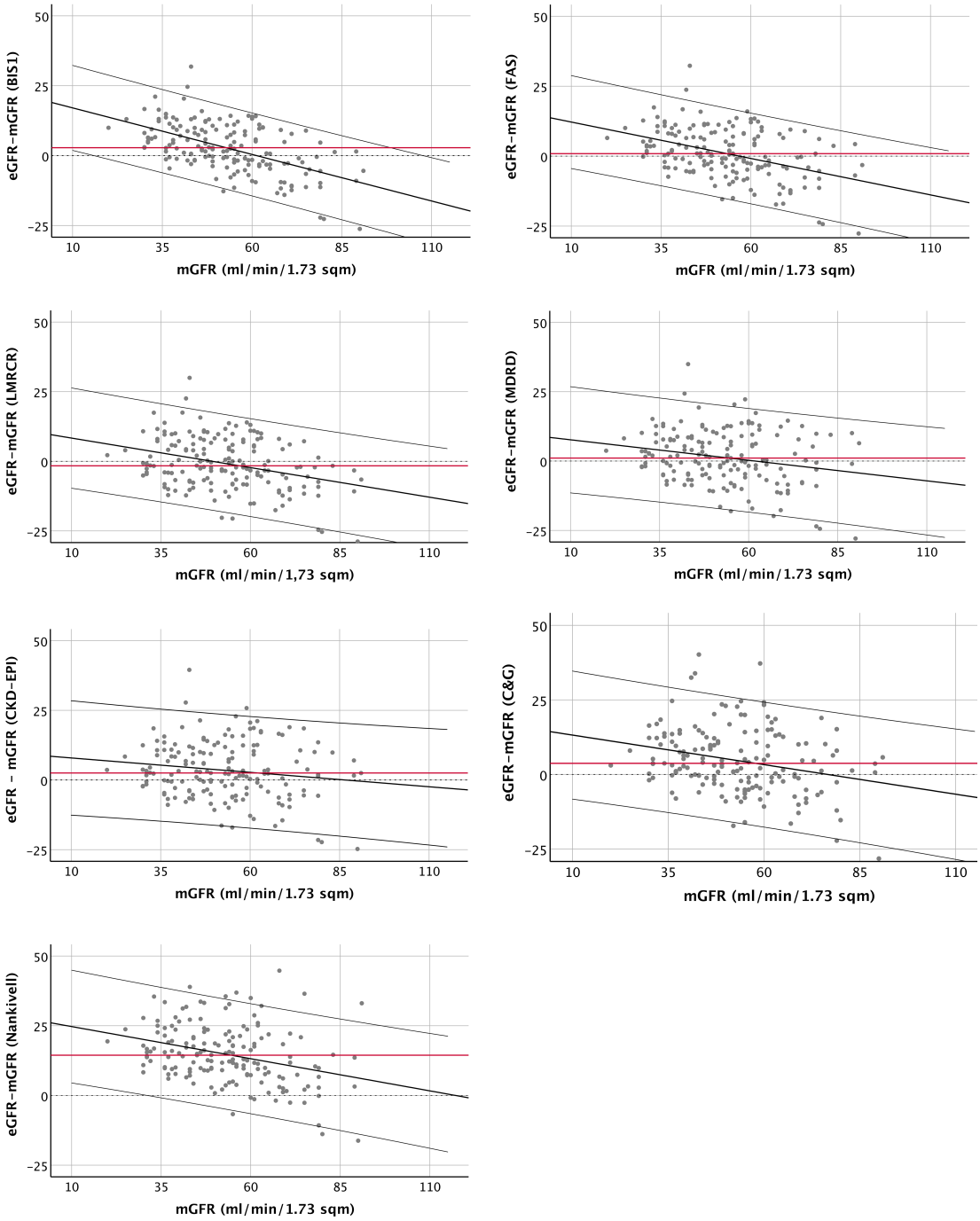

Figure 2a:

Box-plot describing the distribution of eGFR for each equation in KTR older than 70 years compared with the mGFR (to the left). The box represents median and interquartile range. Outliers are marked with a circle and extreme values with an asterix. BIS: Berlin initiative study, FAS: Full age spectrum, LMR_{CR}: Lund-Malmö revised, MDRD: Modification in renal disease, CKD-EPI: Chronic kidney disease epidemiology collaboration, C&G: Cockcroft and Gault

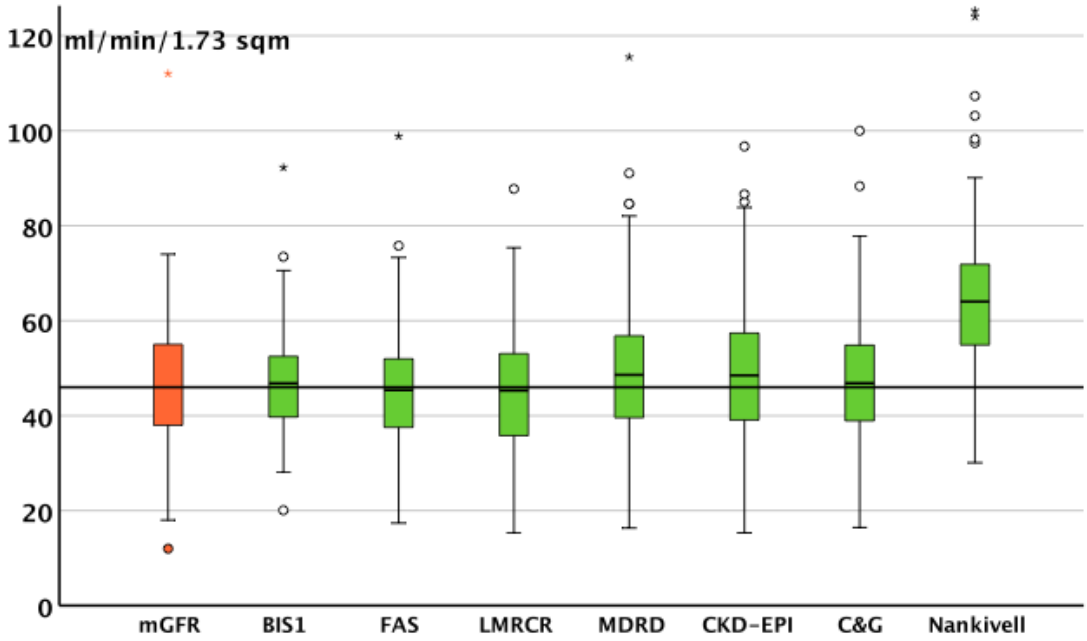

Figure 2b:

Box-plot describing the distribution of eGFR for each equation in KTR 60-69 years compared with the mGFR (to the left). The box represents median and interquartile range. Outliers are marked with a circle and extreme values with an asterix. BIS: Berlin initiative study, FAS: Full age spectrum, LMRCR: Lund-Malmö revised, MDRD: Modification in renal disease, CKD-EPI: Chronic kidney disease epidemiology collaboration, C&G: Cockcroft and Gault