




Comparison of creatinine-based methods for estimating glomerular filtration rate in patients with heart failure

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Abstract

Aims Glomerular filtration rate is an important factor in management of heart failure (HF). Our objective was to validate eight creatinine-based equations for estimating glomerular filtration rate (eGFR) in an HF population against measured glomerular filtration rate.

Methods and results One hundred forty-six HF patients (mean age 68 ± 13 years, mean left ventricular ejection fraction $45\% \pm 15$) within a single-centre hospital that underwent ⁵¹Cr-EDTA clearance between 2010 and 2018 were included in this retrospective study. eGFR was estimated by means of Cockcroft–Gault ideal and actual weight, the Modification of Diet in Renal Disease Study (MDRD), simplified MDRD with isotope dilution mass spectroscopy traceable calibration, the Chronic Kidney Disease Epidemiology Collaboration, revised Lund–Malmö, full age spectrum, and the Berlin Initiative Study 1. Mean measured glomerular filtration rate was 42 mL/min/1.73 m². Pearson's correlation coefficient (*r*) had the highest precision for MDRD (*r* = 0.9), followed by revised Lund–Malmö (*r* = 0.88). All equations except MDRD (mean difference –4.8%) resulted in an overestimation of the renal function. The accuracy was below 75% for all equations except MDRD.

Conclusions None of the exclusively creatinine-based methods was accurate in predicting eGFR in HF patients. Our findings suggest that more accurate methods are needed for determining eGFR in patients with HF.

Keywords Heart failure; Renal function; Estimated glomerular filtration rate; Creatinine

Received: 24 October 2019; Revised: 1 January 2020; Accepted: 22 January 2020

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Introduction

Impaired renal function is common in heart failure (HF).¹ It is a major cause for withdrawal of treatment, prevents the initiation of pharmacological therapy in HF, and is associated with higher morbidity and mortality.^{2,3} Several creatinine-based equations have been developed for estimating glomerular filtration rate (eGFR) in patients with chronic kidney disease (CKD) and/or for the general population. However, a majority of these equations have not been validated for patients with HF. In HF, several factors are influencing the precision and accuracy of creatinine-based eGFR equations. Loss of muscle mass due to inactivity causes low creatinine

levels, and fluid excess causes weight gain without an increase in lean body mass.

The cornerstones in treating HF with reduced ejection fraction are renin–angiotensin–aldosterone system inhibitors (RAAS-I), including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, as well as beta-blockers and mineralocorticoid receptor antagonists (MRAs). If a patient still has symptomatic HF and ejection fraction <35%, angiotensin receptor–neprilysin inhibitor should replace the RAAS-I.⁴ However, registry studies have shown that patients with HF fail to receive full treatment.² RAAS-I and beta-blockers are prescribed to a high extent, but MRA treatment is underutilized, and one of the most common causes of

contraindication is impaired renal function.⁵ According to the European guidelines, an eGFR below 25 or 30 mL/min/1.73 m² should cause dose reduction of RAAS-I and MRA, respectively, if on treatment.⁴ In clinical practice and randomized controlled trials, such as EMPHASIS and RALES, an eGFR below 30 mL/min/1.73 m² and serum creatinine (s-creatinine) over 221 µmol/L respectively is an exclusion criterion for initiating MRA. Hence, estimating GFR correctly within the range of 20–40 mL/min/1.73 m² is important because it can decide whether or not a patient with HF will be treated with RAAS-I and MRA.

Measurements of GFR by means of quantitative methods require plasma clearance of an exogenous marker. Plasma clearance of chromium-51-ethylenediaminetetraacetic acid (⁵¹Cr-EDTA) is comparable with other gold standard methods.⁶ However, because this method for measured GFR (mGFR) is complex, expensive, and time-consuming to conduct on a routine basis in a large number of patients, eGFR based on creatinine or cystatin C is preferred in clinical practice. Creatinine-based eGFR is the most widely used method because of its lower costs but requires adjustment for demographic and anthropometric data that alter creatinine such as sex, age, and weight.

Various equations for eGFR have been developed in order to make these adjustments. Currently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), the Modification of Diet in Renal Disease Study (MDRD), and the revised Lund–Malmö (LM-rev) are recommended in international guidelines and national assessments.^{7,8} MDRD was developed for patients with CKD and requires serum-urea (s-urea) and serum-albumin (s-albumin).⁹ The simplified MDRD isotope dilution mass spectroscopy traceable calibration (sMDRD-IDMS) excludes s-urea and s-albumin, in order to make the equation more generalizable and has been re-expressed for standardized s-creatinine as sMDRD-IDMS.¹⁰ CKD-EPI was developed for patients with GFR above 60 mL/min/1.73 m² and has better accuracy than MDRD for patients without CKD.¹¹ Three of the most recently developed equations are the LM-rev, the Berlin Initiative Study 1 (BIS1), and full age spectrum (FAS).^{12–14} LM-rev was developed in a Swedish cohort with a wide range of age, body mass index, and GFR levels. BIS1 is the only equation validated in an elderly population (70 years or older), while FAS is the only equation that has a continuity with aging, overcoming the problem of eGFR changes when otherwise switching between age-specific equations. Compared with these modern equations that were developed based on gold standard methods for mGFR, the Cockcroft–Gault actual weight (CG-AW) equation is based on creatinine clearance, and the CG and MDRD are the only equations not calibrated to a standardized IDMS-traceable s-creatinine method.¹⁵ CG ideal weight (CG-IW) is recommended by Cockcroft and Gault to be used on patients with potential volume overload.¹⁵

The overall aim of this study was to assess the accuracy of these different equations for eGFR in patients with HF by comparing the predicted eGFR with ⁵¹Cr-EDTA measurements. By identifying the most accurate equation, we hope to optimize pharmacological treatment for patients with HF.

Methods

Study population

All patients who had at least one contact with the Heart Centre or Department of Internal Medicine at Umeå University Hospital, Sweden, between 2010 and 2018 and had received a diagnosis of HF (International Classification of Diseases codes I50.X, I42.0, I42.6, I42.7, I42.9, I11.0, I13.0, and I13.2) were examined for inclusion in this retrospective study. Of these, all patients who underwent plasma clearance with ⁵¹Cr-EDTA between 2010 and 2018 were identified. Additional data required for the equations were collected from the medical records. Values of s-creatinine, s-urea, and s-albumin were recorded as close as possible to the time of the ⁵¹Cr-EDTA measurements. Data for length and weight were collected from the ⁵¹Cr-EDTA measurements.

Measurement of renal function with ⁵¹Cr-EDTA

Plasma clearance of ⁵¹Cr-EDTA was measured for all patients at Umeå University Hospital. A pretest blood sample of 5 mL was drawn, and the activity of any radioactively substance was controlled. A single injection of 3.6 mL (1.03 MBq/mL of ⁵¹Cr-EDTA) was given. After attaining stable plasma levels, series of 8 mL blood samples were taken 180, 210, 240, and 270 min after the primary injection. An additional blood sample was taken after 24 h if s-creatinine exceeded 200 µmol/L or if GFR was calculated below 30 mL/min/1.73 m². This method has an intra-individual day-to-day variance of 4 mL/min/1.73 m² (coefficient of variance 6.25%). mGFR was corrected for body surface area (BSA) according to Haycock *et al.* ($BSA = 0.024265 \times \text{Weight}^{0.5378} \times \text{Height}^{0.3964}$). ⁵¹Cr-EDTA plasma clearance was calculated according to Bröchner–Mortensen by final slope.

Creatinine-based estimated glomerular filtration rate equations

Plasma creatinine (µmol/L) was analysed consecutively with the IDMS-traceable Roche enzymatic method CREP2 on Cobas c701 analysers in the ISO 15189 accredited laboratory at Umeå University Hospital.

Eight equations were used for creatinine-based eGFR:

- (1) CG-AW (mL/min/1.73 m²) normalized to BSA 1.73m² = (Male) 1.23 × [(140 – age) × weight/Scr] × (1.73/BSA)
(Female) 1.04 × [(140 – age) × weight/Scr] × (1.73/BSA)
BSA = body surface area
= weight^{0.425} × height^{0.725} × 0.007184.
- (2) CG-IW (mL/min/1.73 m²) see Equation (1) where weight is IW except if actual body weight was lower than IW.
IW = (male) 51.65 + (1.85 × (height – 60))
(female) 48.67 + (1.65 × (height – 60))
- (3) MDRD (mL/min/1.73 m²) = 170 × (Scr/88.4)^{–0.999} × (age)^{–0.176} × (s-urea × 18 016^{*})^{–0.170} × (s-albumin/10^{**})^{+0.318} × 0.76 (if female).
*Multiplied by 18 016 to convert mmol/L to mg/dL
**Divided by 10 to convert g/L to g/dL
- (4) sMDRD-IDMS (mL/min/1.73 m²) = 175 × (Scr/88.4)^{–1.154} × (age)^{–0.203} × 0.742 (if female)
- (5) CKD-EPI for Caucasians (mL/min/1.73 m²) = (Female and Scr ≤ 62) 144 × [Scr/(0.7 × 88.4)]^{–0.329} × 0.993^{age}
(Female and Scr > 62) 144 × [Scr/(0.7 × 88.4)]^{–1.209} × 0.993^{age}
(Male and Scr ≤ 80) 141 × [Scr/(0.9 × 88.4)]^{–0.411} × 0.993^{age}
(Male and Scr > 80) 141 × [Scr/(0.9 × 88.4)]^{–1.209} × 0.993^{age}
- (6) LM-rev (mL/min/1.73 m²) = e^{X – 0.0158} × age + 0.438 × ln (age)
Male and Scr < 180 mmol/L: X = 2.56 + 0.00968 × (180 – Scr)
Male and Scr ≥ 180 mmol/L: X = 2.56 – 0.926 × ln (Scr/180)
Female and Scr < 150 mmol/L: X = 2.50 + 0.0121 × (150 – Scr)
Female and Scr ≥ 150 mmol/L: X = 2.50 – 0.926 × ln (Scr/150)
- (7) FAS (mL/min/1.73 m²) = (Age 2 to ≤40 years) 107.3/(Scr/Q)
(Age >40 years) 107.3/(Scr/Q) × 0.988^(age – 40)
Q = male 18 years: 75, male ≥20 years: 80, female 18 years: 61, female ≥20 years: 62
- (8) BIS1 (mL/min/1.73 m²) = 3736 × (Scr/88.4)^{–0.87} × age^{–0.95} × 0.82 (if female)

Scr = serum creatinine. Weight was measured in kilograms, height in centimetres, and age in years. Ethnicity was not recorded in this database, and all patients were assumed to be non-Black. Creatinine was divided by 88.4 for use with μmol/L. BSA was calculated with Du Bois method and ideal weight with Lemmens formula.

Statistical analysis

For patient characteristic data, categorical variables are presented with frequencies and percentage and analysed with Pearson's χ^2 test. Continuous variables without normal distribution are presented as medians with inter-quartile range and analysed with Mann–Whitney *U* test. Continuous variables are presented as means with standard deviations and analysed with Student's *t*-test. A *P* value less than 0.05 was considered statistically significant.

Tests for agreement were performed on eight different equations for eGFR. Pearson's correlation coefficient (*r*) and Bland–Altman plots evaluated precision and bias respectively between measured GFR and each method for eGFR. The precision was considered acceptable if *r* > 0.8. The accuracy was defined as the percentage of patients with estimated GFR within ±30% of measured GFR (P30), calculated [eGFR–mGFR] – 100/mGFR, and considered acceptable if ≥75% of the eGFR was within ±30% of mGFR. McNemar test was performed for all equations to compare proportion of patients that were falsely divided into wrong eGFR group compared with mGFR, when sorted into groups of under or above GFR 30 mL/min/1.73 m². All analyses were performed in SPSS Version 25.

Ethics

This study complies with the Declaration of Helsinki. The Regional Ethical Review Board in Umeå, Sweden, has approved the study (Registration Number 2015/419-31).

Results

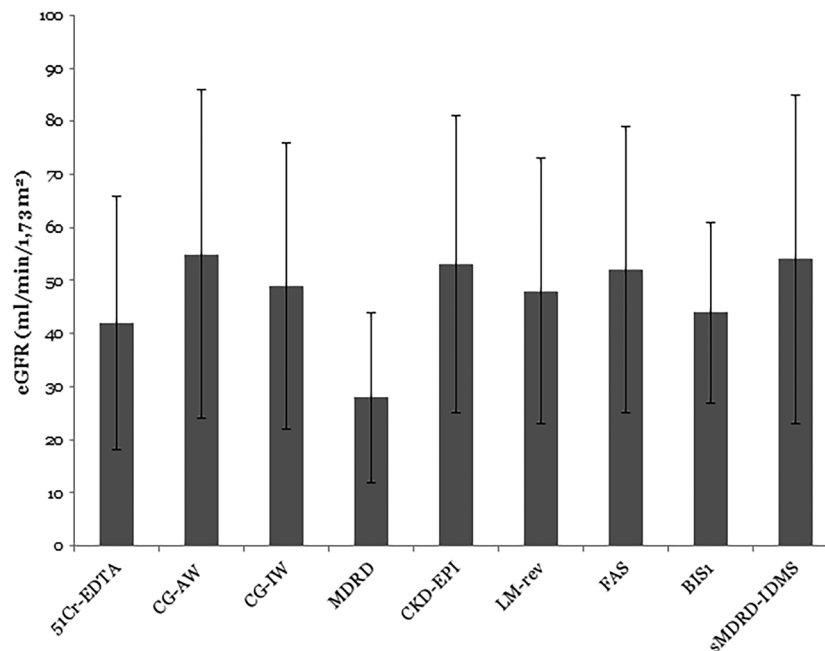
Out of 4450 patients in the total HF population, 146 patients (3%) had undergone a ⁵¹Cr-EDTA measurement. Among included patients, the mean left ventricular ejection fraction (±SD) was 47% ± 14, the mean age was 70 ± 14 years, and 57% were male; 33% of these had HF with reduced ejection fraction, 20% with mid-range ejection fraction (HFmrEF), and 47% with preserved ejection fraction (HFpEF). Comparing the patient characteristics of the study group with the total HF population, the study group was younger but had a similar left ventricular ejection fraction, while N-terminal pro-B-type natriuretic peptide was significantly higher. Furthermore, diabetes was more common, and s-creatinine was higher in the study group (Table 1).

In the study group, the mean mGFR was 42 mL/min/1.73 m², while mean eGFR was 30–59 mL/min/1.73 m² for all equations except MDRD (Figure 1). The reasons for conducting ⁵¹Cr-EDTA were CKD (33%), heart/lung/renal transplantation (29%), and malignancy (37%). All mGFR was

Table 1 Baseline characteristics of the study group and the total HF population

Baseline characteristics	Study group (n = 146)	Total HF population (n = 4450)	P
Male sex (%)	83 (57)	2348 (54)	0.481
Age (years)	70 ± 14	81 ± 13	<0.001
LVEF (%)	47 ± 14	46 ± 12	0.640
HFpEF (%)	68 (47)	1728 (44)	0.213
HFmrEF (%)	29 (20)	1162 (30)	0.031
HFrEF (%)	48 (33)	1044 (27)	0.407
Diabetes (%)	56 (39)	1077 (25)	<0.001
Hypertension (%)	108 (74)	3066 (71)	0.366
Coronary artery disease (%)	72 (49)	1830 (42)	0.676
Heart rate (b.p.m.)	81 ± 21	80 ± 20	0.385
Systolic BP (mmHg)	129 ± 22	127 ± 22	0.247
Diastolic BP (mmHg)	72 ± 13	72 ± 13	0.809
Height (cm)	170 ± 10	168 ± 11	0.055
Body weight (kg)	80 ± 21	77 ± 26	0.166
NT-proBNP (ng/L) [median (IQR)]	2438 (839–6100)	1776 (608–5209)	0.036
Serum creatinine (μmol/L) [median (IQR)]	116 (85–186)	97 (77–129)	<0.001
RAAS inhibition	114 (78)	3465 (80)	0.549
Beta-blocker	131 (90)	3655 (84)	0.084
Mineralocorticoid receptor antagonist	53 (36)	1543 (36)	0.875
Loop diuretics	112 (86)	3188 (83)	0.404

BP, blood pressure; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, inter-quartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAAS inhibitor, renin–angiotensin–aldosterone system inhibitor. All values were reported as mean ± standard deviation unless otherwise indicated.

Figure 1 Mean glomerular filtration rate (±1 SD) mL/min/1.73 m². For details, see Supporting Information, Table S1.

conducted before start-up of cytostatic drugs. Seven patients conducted mGFR before the transplantation, and among the renal transplanted, all patients had conducted mGFR after transplantation. Mean mGFR for the renal transplanted was 29 mL/min/1.73 m², and the majority have their transplantation performed several years before conducting

mGFR, why the values were relatively stable. MDRD included 69 patients (47%) with a mean eGFR of 28 mL/min/1.73 m², as s-urea and s-albumin were mainly available for patients with impaired renal function. BIS1 was applied on patients 70 years or older and included 71 patients (49%).

Eighty-five per cent of the s-creatinine values and 81% of the s-albumin and s-urea values were measured within ± 14 days from the ^{51}Cr -EDTA measurement, and 96% of the s-creatinine values were measured within ± 30 days.

The equation with the highest precision was MDRD. LM-rev showed almost as high precision as MDRD (*Figure 2*). Bland–Altman plots showed that MDRD was the only equation to underestimate the renal function while all remaining equations overestimated the eGFR (*Figure 3*). Furthermore, MDRD had superior accuracy as 80% had an eGFR within $\pm 30\%$ of measured GFR, while all the remaining equations fell under the 75% cut-off (*Figure 4*). Among the creatinine-based equations, LM-rev and CG-IW both had the lowest overestimation, with a mean difference of 18%, but LM-rev showed higher accuracy. One of the most commonly used equation, CKD-EPI, showed a wide variation of eGFR values in HF patients with low precision and accuracy. All equations except the MDRD falsely categorize patients that have an actual GFR under 30 mL/min/1.73 m² into GFR over 30 mL/min/1.73 m², thus overestimating GFR when compared with mGFR (*Figure 2*).

Mean age was comparable when categorizing the study group into subgroups, but in the HFpEF group, a majority of the patients were female and had higher creatinine levels compared with the other groups (Supporting Information, *Table S1*). Furthermore, CG-IW was more accurate in patients with HF with reduced ejection fraction and HFmrEF than the whole study group. BIS1 had slightly better results in patients with HFpEF, and LM-rev showed better results in patients with HFmrEF and HFpEF compared with the whole study group, while MDRD had consistently good results in all subgroups (*Table 2*).

Discussion

A majority of HF patients suffer from impaired renal function,¹⁶ and while many attempts have been made to find the best creatinine-based equation to estimate GFR, most of the equations have not been validated before in an HF population. In this study, we evaluated bias, precision, and accuracy of eight creatinine-based equations for eGFR in a wide range of HF patients, with both reduced and preserved ejection fraction. In subgroup analyses of the different HF classes, the result was consistent with the whole study group. The results indicate that none of the exclusively creatinine-based methods had a high accuracy or precision in predicting GFR. Nevertheless, even with mGFR, there are methodological issues and imprecisions, and results from EDTA measurements and inulin clearance, which is the historical gold standard, may differ considerably.

Revised Lund–Malmö, BIS1, FAS, and sMDRD-IDMS have to our knowledge not previously been externally validated in HF patients.^{16–20} In this study, none of the exclusively creatinine-

based eGFR equations met the criteria of accuracy, precision, and a non-significant McNemar test. Furthermore, all creatinine-based eGFR equations led to an overestimation of the renal function. Therefore, we concluded that none of the exclusively creatinine-based equations for eGFR were accurate for estimating GFR in this population of HF patients. In accordance with our findings, previous studies comparing creatinine-based equations in HF have shown an overestimation of eGFR at lower GFR values.^{18,19} In this study, MDRD was the only equation that did not overestimate GFR under 30 mL/min/1.73 m².

Furthermore, MDRD was the most precise equation with the highest accuracy and lowest bias, but because both s-urea and s-albumin are required, the results in this study should only be generalizable to patients with both HF and CKD as all patients included in this group had a mean eGFR under 30 mL/min/1.73 m² because s-urea and s-albumin only were available for patients with known CKD. Overestimation of eGFR in patients with HF could be due to a haemodynamically driven renal impairment.²¹ Reduced renal perfusion causes reduced filtration rate in the nephron, but the tubuli were still intact and able to secrete creatinine. Hence, creatinine levels are not built up in the blood as compared with primary renal disease where there is a loss of both glomeruli and corresponding tubuli. With the MDRD equation, it is possible that s-urea and s-albumin correct for the low creatinine levels in HF. Another factor contributing to overestimated GFR in HF is lower s-creatinine due to physical inactivity leading to reduced muscle mass in this group of patients, causing cardiac cachexia.²² Impaired renal function is a known risk factor for morbidity and mortality in HF, implying that patients with impaired renal function to a further extent have more severe HF, thus more exaggerated muscle mass waste.

Among the exclusively creatinine-based equation, LM-rev was the most accurate equation. It had almost as high precision as MDRD but overestimated eGFR compared with mGFR and did not meet the criteria for significant accuracy. LM-rev was developed on a Swedish population with a substantial variability in mGFR, body mass index, and age, which could explain the better results when applied in our study group with similar demographic characteristics. Furthermore, LM-rev is based on an IDMS-traceable s-creatinine analysis. Only LM-rev, CKD-EPI, FAS, BIS1, and sMDRD-IDMS are based on the standardized IDMS-traceable methods as recommended.²³ The commonly used CKD-EPI equation showed very low accuracy in this study. CKD-EPI was developed on patient with a higher mean mGFR than our study population. In this study, 80% of all included patients had an eGFR under 60 mL/min/1.73 m² and more than a third had diabetes as well, implying that CKD-EPI was not suitable in this group of patients.

Cockcroft–Gault ideal weight had almost comparable results with LM-rev. CG-IW and CG actual weight were the only equations to include weight. When comparing the two methods to calculate CG, calculating the ideal body weight

Figure 2 Pearson's correlation coefficient (r). For details, see *Table 2*. McNemar test with glomerular filtration rate 30 mL/min/1.73 m² limits (green lines): $P < 0.001$ for all tests except MDRD ($P = 0.727$).

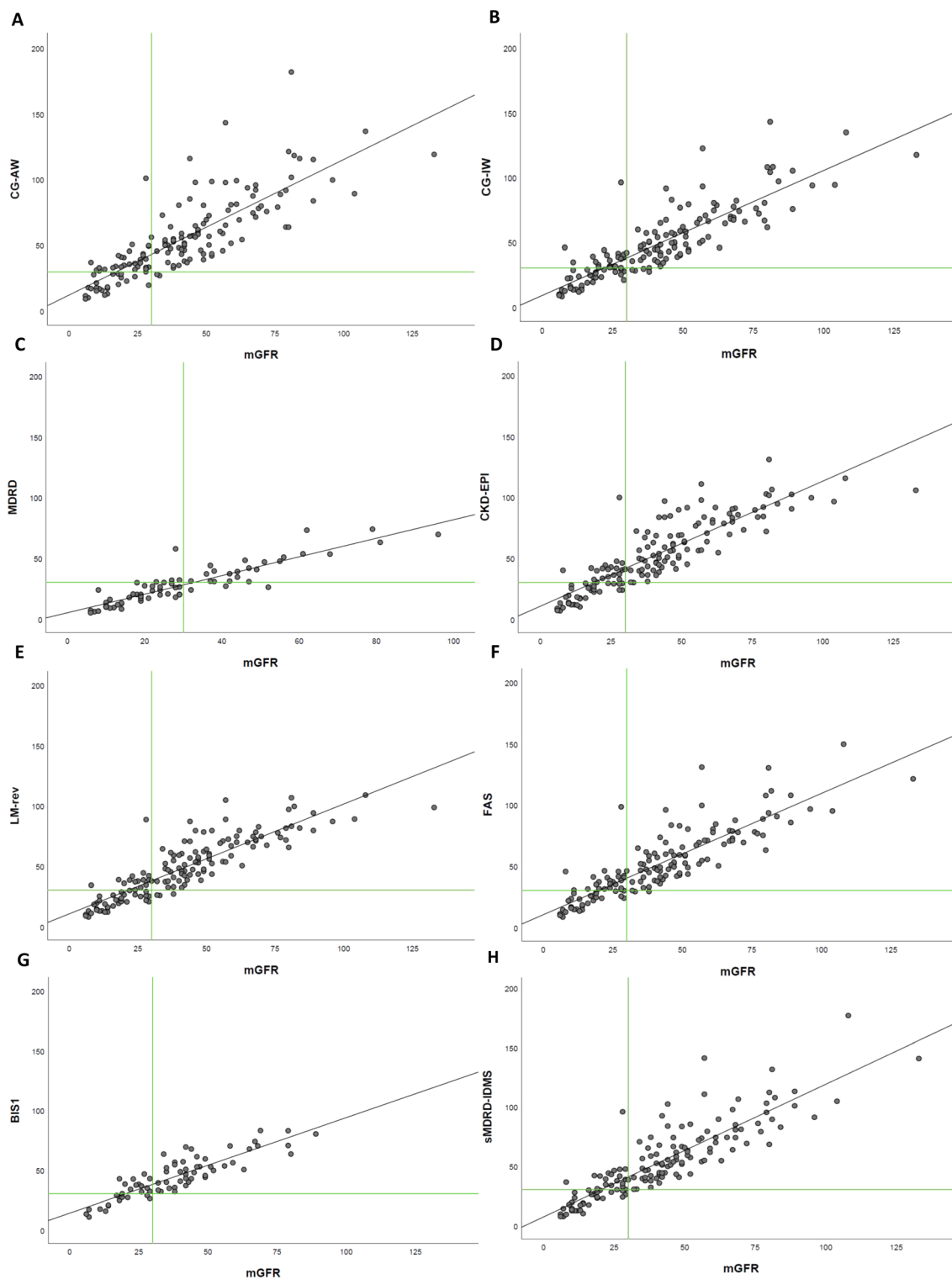
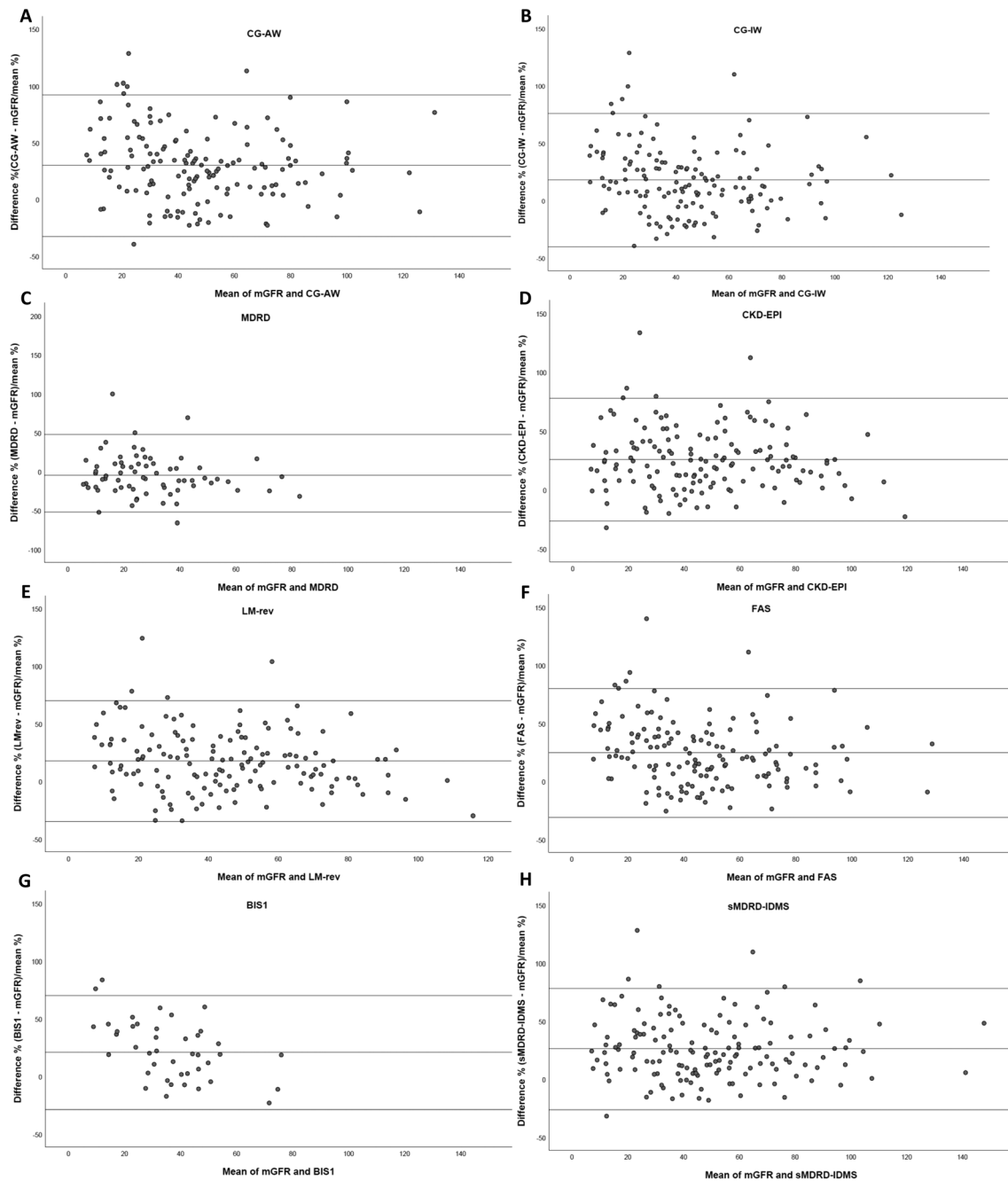


Figure 3 Bland–Altman scatterplots of the distribution of the true ^{51}Cr -EDTA–measured GFR (mGFR) and each creatinine-based equation for estimated glomerular filtration rate. The y axis shows the mean differences in % and the x axis the average of the mGFR and estimated glomerular filtration rate. The lines represent the mean difference in % and the upper and lower limits of agreement. For details, see *Table 2*.



rather than actual weight gave more accurate results. The difference could be explained by sodium retention leading to fluid excess and consequently falsely high weight in HF patients.²² Different methods were used to calculate BSA for CG actual weight and mGFR. BSA was already calculated according to Haycock *et al.* by the local laboratory conducting the GFR measurement. To calculate CG actual weight we

used the exact same equation from the original article by Cockcroft and Gault from 1976.¹⁵

The findings of this study imply that the choice of equation for eGFR has an impact on the categorizing of patients into whether dose adjustments should be recommended or not. A majority of creatinine-based eGFR led to an overestimation of the renal function. Dose adjustment or discontinuation of

Figure 4 P30 for each creatinine-based equation for estimated glomerular filtration rate. P30 = the percentage of patients with estimated glomerular filtration rate within +30% of measured glomerular filtration rate. The dotted line represents the 75% cut-off for acceptable accuracy. For details, see Table 2.

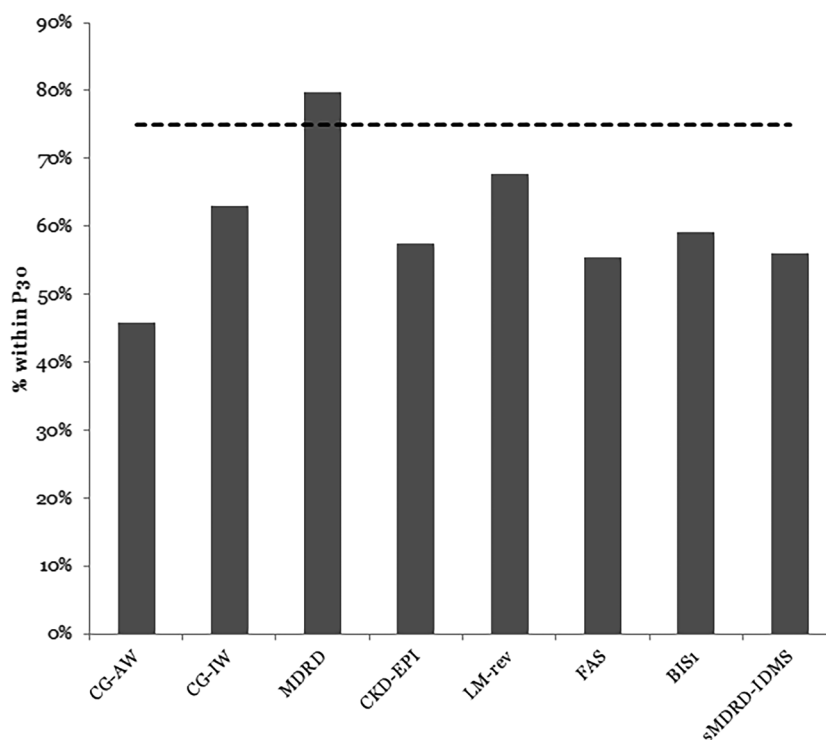


Table 2 Precision, mean difference, McNemar test, and accuracy for the study group and all subgroups

Study group	<i>r</i>	Mean difference	<i>P</i>	P30 (%)	HFmrEF	<i>r</i>	Mean difference	<i>P</i>	P30 (%)
CG-AW	0.81	30 (32)	0	46	CG-AW	0.92	27.6 (32.0)	0.06	41
CG-IW	0.85	18 (30)	0	63	CG-IW	0.92	16.4 (31.7)	0.22	62
MDRD	0.9	-4.8 (27)	0.73	80	MDRD	0.85	0.74 (38.0)	1	75
CKD-EPI	0.87	26 (27)	0	58	CKD-EPI	0.92	24.6 (31.1)	0.03	62
LM-rev	0.88	18 (27)	0	68	LM-rev	0.93	17.4 (29.3)	0.13	69
FAS	0.86	24 (28)	0	55	FAS	0.92	24.3 (30.2)	0.03	55
BIS1	0.87	21 (25)	0	59	BIS1	0.94	17.6 (20.2)	0.25	69
sMDRD-IDMS	0.87	26 (27)	0	56	sMDRD-IDMS	0.93	27.3 (29.7)	0.06	48
HFrfEF	<i>r</i>	Mean difference	<i>P</i>	P30 (%)	HFpEF	<i>r</i>	Mean difference	<i>P</i>	P30 (%)
CG-AW	0.75	32.2 (32.4)	0.12	52	CG-AW	0.8	29.0 (32.1)	0	44
CG-IW	0.8	20.6 (32.4)	0.07	71	CG-IW	0.86	16.2 (27.8)	0.11	59
MDRD	0.89	-7.6 (25.2)	0.63	77	MDRD	0.89	-5.0 (23.7)	1	83
CKD-EPI	0.8	28.5 (29.0)	0.03	56	CKD-EPI	0.9	23.8 (23.2)	0.01	57
LM-rev	0.79	19.6 (29.6)	0.13	71	LM-rev	0.91	16.3 (23.9)	0.29	65
FAS	0.79	27.1 (29.8)	0.07	58	FAS	0.89	22.5 (26.7)	0.01	54
BIS1	0.89	27.8 (25.0)	0.03	50	BIS1	0.86	17.6 (27.3)	0.13	61
sMDRD-IDMS	0.79	28.9 (29.6)	0.01	56	sMDRD-IDMS	0.9	23.4 (23.4)	0.01	59

BIS1, Berlin Initiative Study 1; CG, Cockcroft–Gault; CG-AW, Cockcroft–Gault actual weight; CG-IW, Cockcroft–Gault ideal weight; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; FAS, full age spectrum; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrfEF, heart failure with reduced ejection fraction; LM-rev, revised Lund–Malmö; MDRD, Modification of Diet in Renal Disease Study; sMDRD-IDMS, simplified MDRD corrected for traceable isotope dilution mass spectrometry.

r = Pearson's correlation. Mean difference % (± 1 SD). *P* = McNemar test (*P* < 0.05 = significant). P30 = accuracy [the percentage of patients with estimated glomerular filtration rate within $\pm 30\%$ of measured glomerular filtration rate (P30)].

both RAAS-I and MRAs is recommended at eGFR below 20–30 mL/min/1.73 m²⁴ because there is a risk of exacerbated renal insufficiency if the doses exceed the therapeutic range. Previous major studies on congestive HF have used varying methods for estimation of renal function. Some studies such as SHIFT²⁴ and RALES²⁵ used a fixed exclusion cut-off s-creatinine level of more than 220 and 221 µmol/L, respectively. Calculating eGFR by the MDRD equation was used by the PARADIGM-HF²⁶ and EMPHASIS HF²⁷ trials. The CKD-EPI equation was used in the DAPA-HF²⁸ study. Creatinine clearance was estimated according to the CG formula in the EPHESUS²⁹ trial. Considering the results of this study, it is likely to conclude that dose adjustment would be needed for many HF patients if eGFR was calculated with the same equation as the original study that the recommendation is based on. Furthermore, this may imply that there is an uncertainty in the guidelines⁴ for therapeutic management of HF patients with impaired renal function, because it is based on eGFR calculated with different equations or s-creatinine.

Strengths and limitations

We compared eight established equations for eGFR, which has not been performed before in HF patients. Our study is the largest study comparing mGFR with eGFR in HF patients. Because the study group consists of patients with both preserved and reduced ejection fraction compared with previous studies,^{18,19} it should make our study more representative for real-life HF patients.

A limitation of this study is the selection of HF patients. Because the patients were selected on International Classification of Diseases coding, there may have been some cases with HFpEF that were misdiagnosed. Furthermore, this retrospective study is based on patients where a clinical decision has been made to measure GFR. However, comparing patient characteristics between the study group and all HF patients showed similarity in almost all characteristics. Nevertheless, the study group had significantly higher median s-creatinine, higher frequency of diabetes, and lower mean age. The results of this study should therefore only be generalized on patients with both HF and a mild renal dysfunction. This study also lacks data on the oldest patient group. In designing future studies, efforts should be made to include this group because the oldest patients are such a large part of the HF population. The study group also had significantly higher s-creatinine than the total HF population causing a selection bias were included patient already had a reason for conducting mGFR in the first place. Furthermore, another limitation to the study is the time interval from conducting GFR measurement and collecting s-creatinine. Because of individual fluctuation in renal function, this could cause bias in

comparing mGFR with eGFR because the difference could reflect an actual difference. However, the absolute vast majority (85%) had a maximum time interval of 14 days, and 96% had a time interval of 30 days from mGFR to s-creatinine.

Cystatin C-based equations are more accurate when estimating GFR. We were however not able to analyse these equations in this study, because we only had data available for eight patients.³⁰

Conclusions

Our findings implicate that none of the exclusively creatinine-based methods were accurate in predicting GFR in HF patients. However, MDRD was the most accurate equation for patients with both HF and renal failure. One of the most commonly used equations, CKD-EPI, was not very accurate in measuring eGFR in patients with HF. Our findings suggest that more accurate methods are needed for determining eGFR in patients with HF, as overestimation causes an unnecessary risk of serious adverse effect as well as may lead to patients not receiving an optimal drug therapy.

Acknowledgements

The authors thank all the personnel who obtained data for the study. We would like to thank Robert Lundquist, statistician at Norrbotten County Council, for his help with the statistical analysis.

Conflict of interest

None declared.

Funding

This work was supported by the Heart Foundation of Northern Sweden.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of the study group and the heart failure subgroups.

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