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Impact and consequences of the error of estimated GFR in patients with heart failure

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Heart failure is a highly prevalent disease, which courses with frequent readmissions, mainly by Acute Heart Failure (AHF). Reduced renal function is associated with increased mortality in patients with HF. Therefore, an accurate and precise evaluation of renal function in patients with HF is crucial. The error of estimated GFR (eGFR) is wide and common, showing a ± 30% variability compared to measured GFR (mGFR). However, there is no evidence on the error of formulas in reflecting real renal function and particularly the consequences of this error in patients with AHF. This is a prospective study comparing the impact of mGFR versus eGFR in the onset of cardiovascular (CV) outcomes in patients with AHF. This was tested with cox survival analysis. Measured GFR was determined by the plasma clearance of iohexol-dbs and eGFR by Cockroft-Gould, MDRD, CKD-EPI creatinine, CKD-EPI cystatin-C and CKD-EPI creatinine + cystatin-C equations formulas. Also the agreement between mGFR and eGFR was analyzed. A total of 90 patients were included. Average age was 66 (± 12 years) and 52 (58%) were male. Of them 53 patients (59%) had a cardiovascular event during follow-up, 22 fatal (41%). The agreement between mGFR and eGFR indicated moderate precision and accuracy (concordance correlation coefficient of 0.77; CI = 0.73–0.82). In multiple cox survival analysis, mGFR was significantly associated with cardiovascular events together with NTproBNP, BMI, LVEF and previous coronary artery disease (p = 0.037; HR = 0.98, 95% CI = 0.95–0.99). Estimated GFR by formulas was not significant. In patients with AHF the error of formulas is large, frequent and random, also, mGFR and not eGFR predicted future CV events. The error of eGFR may have clinical consequences in specific subpopulations.

Keywords Acute heart failure, Glomerular filtration rate, Renal function, Cardiovascular outcomes

Heart failure (HF) is a frequent clinical syndrome affecting 1–2% of the adult population in Europe[1]. The diagnosis of HF portends a 20% risk for mortality at 1 year[2] which increases up to 60%[3,4] at 5 years. The disease is marked by frequent readmissions, mainly due to acute heart failure (AHF)[5,6]. These admissions are a major public health problem, causing patient disability and increasing economic costs[7]. Thus, understanding the pathogenesis and risk factors of HF may help improve clinical management and survival in this population.

Risk factors for AHF include age[8], diabetes, atrial fibrillation, obesity, poorly controlled hypertension, chronic obstructive pulmonary disease, iron deficiency or anaemia[9,10] and chronic kidney disease (CKD)[11]. The latter is a major factor for morbidity and mortality in patients with HF[12,13]. Reduced Glomerular Filtration Rate (GFR) could be as relevant as a low left ventricular ejection fraction in the evolution of HF [14]. Moreover, this picture is complicated by the fact that around 50% of the HF patients have CKD[15,16] with 29% of them having moderate to severe renal impairment[12]. Several meta-analyses observed that worsening renal function is associated with increased mortality in patients with HF[12,13,17,18]. All these aspects make an accurate and precise assessment of renal function a crucial aspect of the clinical evaluation of patients with HF.

In clinical practice, renal function is estimated by serum creatinine, cystatin-C or formulas that use these markers. More than 70 formulas have been published to estimate GFR using serum creatinine and/or cystatin-C.

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However, the reliability of these formulas has been widely questioned. The error of estimated GFR (eGFR) is wide and common, showing a ± 30% of variability compared to measured GFR (mGFR). This has been found in different populations, such as CKD[19,20], type 2 diabetes mellitus [21,22], renal and no-renal transplantation [23–25], cancer patients [26,27] and chronic liver disease [28–30]. Evidence on the variability of eGFR by formulas in patients with HF is scarce. Two studies showed that formulas either overestimated or underestimated renal function in patients with CHF [31,32]. However, in patients with AHF there is no definitive evidence on the magnitude and frequency of the error of formulas and particularly the clinical consequences of this error, being these the main objectives of this study.

Methods

In this prospective study we analyzed the error of formulas that estimate GFR and the impact of this error in the evaluation of the association between GFR and long-term cardiovascular (CV) events in patients with AHF. We evaluated a group of patients with AHF who underwent the plasma clearance of iohexol, a gold-standard method to measure renal function. At the same time eGFR was assessed by a group of creatinine- and cystatin-C–based equations. During follow-up major CV events were recorded. The protocol follows the Helsinki declaration and was approved by the Ethic Committee of the Hospital Universitario de Canarias.

Patients

We evaluated a group of patients with AHF admitted in the Acute Cardiovascular Care Unit of the Cardiology Department of the Hospital Universitario de Canarias (Tenerife, Spain). Inclusion criteria were: age > 18 years; AHF requiring admission based on the European clinical guidelines[33]; clinical stability at least 48 h following admission, defined as an amelioration of the signs of congestion i.e. stable or lowering diuretic dose, oxygen requirement, no need of inotropes/vasopressor and a SBP ≥ 90 mmHg with no evidence of blood pressure fluctuation. Also no signs of clinical hypoperfusion were allowed, including lactate level when required. Exclusion criteria were: clinical instability at inclusion defined as the presence of cardiogenic shock; need for invasive mechanical ventilation, mechanical circulatory support or concomitant active infectious disease; allergy to iodine or a history of adverse reactions to contrast media; active malignancy; acute kidney injury needing dialysis; severe psychiatric disease; pregnancy and lactation; anorexia nervosa or any other cause of cachexia and hypercatabolic states i. e. severe hyperthyroidism. Informed consent was obtained from all subjects.

Procedures

Treatment of AHF

All patients after admission were treated with standard therapy according to current AHF guidelines[33], which includes diuretics, oxygen and/or vasodilators. In special cases, inotropes, vasopressors or non-invasive mechanical ventilation were used.

Measured GFR—Plasma clearance of iohexol

At inclusion all patients underwent the plasma clearance of iohexol in conditions of clinical stability as defined in the inclusion criteria. The GFR was determined by plasma clearance of iohexol as previously described[34]. Briefly, 5 mL of the iohexol solution (Omnipaque 300, GE Healthcare) was injected intravenously during 2 min. Blood samples were then taken at 120, 180, 240, 300, 360, 420, and 480 min for patients with eGFR (aMDRD) of 40 mL/min or less; and at 120, 150, 180, 210, and 240 min for those with eGFR greater than 40 mL/min. Iohexol was measured in plasma or dried blood spots (DBS)[18]. Both methods (plasma or DBS) are interchangeable[18]. Iohexol was measured by HPLC–UV at the Laboratory of Renal Function of the ULL (http://lfr.ecihucan.es/). The clearance of iohexol was calculated according to a 1 compartment model (CL1) by the formula: CL1 = Dose/AUC, where AUC is the area under the plasma concentration time curve from time equal zero to infinity. The plasma clearances were then corrected using the Bröchner-Mortensen equation[35].

Estimated GFR by formulas

Creatinine (mg/dL) was measured by isotopic dilution mass spectrometry–traceable creatinine (enzymatic assay) using the cobas c711 module (Roche Diagnostics). cystatin-C levels were determined by immunonephelometry (BN II System, Siemens Healthcare), calibrated with ERM-DA471/IFCC.

Estimated GFR was evaluated by the following equations: Cockroft Gault[36], MDRD[37], CKD-EPI creatinine[38], CKD-EPI cystatin-C[39] and CKD-EPI creatinine + cystatin-C[39]. These formulas were selected since they are the most used equations available in 2023. The agreement between formulas and measured GFR was evaluated with the formulas adjusted and unadjusted for body surface area (BSA). When estimated GFR was already adjusted, we reversed the adjustment of the result, that is, MDRD and CKD-EPI by applying the following formula GFR unadjusted = GFR adjusted × BSA/1.73[40].

Clinical variables and laboratory analysis

The following variables were collected: age, gender, weight (kg), height (cm), body mass index (BMI), hypertension, dyslipidemia, diabetes mellitus, previous cardiovascular disease, chronic kidney disease defined (eGFR < 60 mL/min) and smoker status. Laboratory variables were recorded simultaneously within the plasma clearance of iohexol and included serum creatinine, cystatin-C, hemoglobin, Quick-Time, Prothrombin activity, sodium, potassium, NT-proBNP, troponin and C- reactive protein. The highest NT-proBNP value before patient inclusion was recorded.

Specific heart failure-related variables

Etiology, duration and triggering causes of HF were recorded, as well as ejection fraction, diastolic function (E/a; E/é), presence of atrial fibrillation, left bundle branch block, pacemaker stimulation, etc. Also previous treatments were collected: aspirin, betablockers, ACEi/ARAII, furosemide dose, other diuretics (thiazide, chlorthalidone), aldactone, eplerenone and statins. Echocardiographic variables were recorded at the time of patient inclusion and include: telediastolic diameter of the LV, left ventricular ejection fraction (measured using the Simpson biplane method), left ventricle outflow tract VTI, presence and degree of mitral regurgitation and estimation of systolic pulmonary pressure. Congestion was not evaluated from echocardiography or lung ultrasound point of view, but we included data about diastolic function, NTproBNP—a marker of congestion and myocardial stress-.

Statistical analysis

Agreement analysis between estimated and measured GFR

The error of formulas was evaluated by specific statistics for continuous data, including the concordance correlation coefficient (CCC), total deviation index (TDI), coverage probability (CP)[41]. The CCC varies from 0 to 1 and combines meaningful components of accuracy and precision. A CCC of 0.90 reflects optimal concordance between measurements. The TDI captures a large proportion of data within a boundary for allowed differences between 2 measurements. Empirical TDI was calculated for a theoretical TDI of 10% and a CP of 90%. We defined a priori that acceptable bias between eGFR and mGFR should be at least 10%, and that 90% of the estimations should be included within these limits. This is based on previous reports and the reproducibility of measured GFR considering different methods[42]. Coverage probability varies from 0 to 1 and estimates whether a given TDI is less than a pre-specified fixed percentage.

Association between estimated or measured GFR and major CV outcomes

The evolution of the patients enrolled was assessed by reviewing the electronic clinical charts. The main outcome was the first onset of fatal and nonfatal major cardiovascular events occurring after the first episode of AHF. These included: (a) coronary artery disease: unstable angina, acute coronary syndrome, the need of coronary revascularization either percutaneously than surgical; (b) AHF: advanced heart failure requiring admission; (c) sudden cardiac death; (d) cerebrovascular disease: stroke or transient ischemic attack; (e) peripheral vascular disease: symptoms of intermittent claudication, amputation or need of re-vascularization; (f) heart transplant or need of long-term ventricular assist device implantation. The causes of non-cardiovascular death were recorded.

The association between eGFR or mGFR and the onset of CV events was evaluated with cox-survival analysis. In the simple analysis, all possible variables with a proven or possible association with CV events were included, such as: age, sex, duration of heart failure syndrome, LVEF, smoking, diabetes mellitus type 2, dyslipidemia, previous history of cardiovascular events, body mass index, serum creatinine, cystatin-C, eGFR, mGFR, treatments (diuretics, betablockers or ACE inhibitors), NT-proBNP and us-Trop T levels and renal function, estimated or measured.

For the multiple cox analysis models, all the significant variables tested in the simple analysis were included. Also, other confounders with proven association with cardiovascular events were included irrespective of the results of simple cox analysis, such as NTproBNP and LVEF. One covariate was included every 8 events.

Three different multiple cox survival models were created. i) the main model including mGFR; ii) the second model replacing mGFR by serum creatinine or by cystatin-C; iii) the third model with eGFR replacing mGFR either by creatinine based-formulas (MDRD, EPI-CKD, CG) or cystatin-C-based-formulas (EPI-cys; EPIcys-Cr). The comparison between groups of qualitative variables was made using the χ^2 test or Fisher's exact test, as appropriate, and the study of quantitative variables, with the Student's t test in case they followed a normal distribution or the Mann–Whitney test in another case. A value of $p < 0.05$ was considered statistically significant. We estimate the discriminative accuracy of mGFR and of each estimated formula for predicting adverse events using receiver operating curves (ROC) including 95% confidence intervals. We have also calculated the C-statistics. The C-statistics (equivalent to the area under the receiver operating characteristic curve) is a standard measure of the predictive accuracy of the logistic regression models. The variables used in logistic cox survival models were BMI, LVEF, previous coronary artery disease and NT-proBNP and each of the estimated or measured GFR. Statistical analysis was carried out with SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY) and MedCalc Statistical Software version 22.016 (MedCalc Software Ltd, Ostend, Belgium).

Data collection

A web-based online platform was designed for data collection before starting the inclusion.

Results

Patients

Ninety patients were included. Average age was 66 ± 12 years, 52 patients (58%) were male and 27 (30%) have past history of CHF (Table 1). Previous coronary artery disease was present in 35 subjects (39%), and ischemic disease was the most prevalent etiology of HF (38; 35%) followed by valvular disease (24; 27%). Most patients had diabetes (54; 60%), hypertension (68; 76%) or dyslipidemia (63; 70%). About one third of the patients had atrial fibrillation (34%) and mean LVEF was 41% ± 14.54 (Table 1). Average measured GFR was 59.7 ± 26 mL/min, whereas estimated GFR by formulas was 70.2 ± 32 mL/min (MDRD), 70.2 ± 30 mL/min (CKD-EPI), 74.8 ± 38 (Cockroft-Gault), 61.2 ± 29 (EPI-Cys) and 65.3 ± 28 (EPI-Cys_Cr) (Table 2). Cystatin-C determination was available in 60 patients with a mean value of 1.46 ± 0.69 mL/min. No differences were shown in the group with and

	Overall	With Events	Without events	*p-value*
N	90	53 (59)	37 (41)	
Age (year)	66 ± 12	67 ± 13	65.7 ± 12	0.5
Gender: men—n (%)	52 (58)	34 (64)	18 (48%)	0.14
Body mass index kg/m^2	29 ± 5	30 ± 5	27 ± 5	0.01
Comorbidities				
Diabetes mellitus—n(%)	54 (60)	34 (64)	20 (54)	0.33
Hypertension—n(%)	68 (76)	42 (79)	26 (70)	0.33
Current smoker—n(%)	20 (22)	11 (21)	9 (24)	0.7
Dyslipidemia—n(%)	63 (70)	38 (72)	25 (68)	0.67
Coronary artery disease—n(%)	35 (39)	28 (53)	7 (19)	0.001
Cerebrovascular diseases—n(%)	12 (13)	9 (17)	3 (8)	0.23
CKD (GFR < 60 mL/min)—n(%)	31 (34)	24 (45)	7 (19)	0.009
Heart failure (HF)				
De novo HF -n(%)	63 (70)	31 (58)	32 (86)	0.004
Previous history of HF	27 (30)	22 (37)	5 (12)	0.006
Etiology of HF				
Ischemic—n(%)	38 (35)	30 (59)	8 (23%)	0.001
Idiopathic—n(%)	16 (18)	9 (18)	7 (21)	0.73
Restrictive—n(%)	2 (2)	1 (1)	1 (3)	0.77
Hypertensive—n(%)	5 (6%)	3 (6)	2 (6)	1
Valvular—n(%)	24 (27%)	8 (15)	16 (47)	0.002
Known duration of HF year	1.7 (0–30)	2.7 (0–30)	0.2 (0–4)	0.005
Left ventricular diameter mm	57 ± 8	59 ± 9	55 ± 7	0.017
E/é ratio	17 ± 6.5	17 ± 6	17 ± 6	0.54
LVOT–VTI cm	14 ± 5	14 ± 5	14 ± 4	0.90
SPAP > 50 mmHg	18 (20)	10 (19)	8 (22)	0.73
LVEF %	41 ± 14.5	38 ± 14	43 ± 14	0.04
Medications				
Aspirin—n(%)	44 (49)	30 (57)	14 (38)	0.08
ACEi/ARAii—n(%)	52 (61)	32 (61)	20 (38)	0.34
Betablockers—n(%)	54 (60)	34 (64)	20 (54)	0.34
Furosemide—n(%)	52 (58)	40 (75)	12 (32)	< 0.0001
Statins (n-%)	60 (67)	41 (77)	19 (51)	0.10
Mineralocorticoid receptor antagonists (n-%)	21 (24)	17 (33)	4 (11)	0.02
Laboratory				
Hemoglobin gr/dL	12 ± 2	12 ± 2	12.8 ± 2	0.09
HbA1c %	6.9 ± 1.8	7.1 ± 1.9	6.5 ± 1.5	0.14
Triglycerides mg/dL	119 ± 50	118 ± 50	121 ± 49	0.77
LDL-cholesterol mg/dL	78 ± 34	65 ± 28	95 ± 32	0.0001
Troponin T us pg/mL	208 ± 353	245 ± 372	156 ± 321	0.25
NT-proBNP pg/mL	8745 ± 8349	8238 ± 7949	9470 ± 8954	0.45
Heart Rate bpm	97 ± 23	92 ± 18	106 ± 26	0.002
Systolic BP mmHg	132 ± 29	127 ± 25	139 ± 32	0.06
Diastolic BP mmHg	75 ± 16.4	72 ± 13	78 ± 20	0.06
Follow-up time year	3 ± 2	2 ± 2	4 ± 1.5	p < 0.001

Table 1. Baseline characteristics. previous treatments and laboratory variables. SBP, systolic blood pressure; DBP, diastolic blood pressure; LVOT-VTI, left ventricular outflow tract—velocity/time integral; SPAP, systolic pulmonary arterial pressure; LVEF, left ventricular ejection fraction; CKD, chronic kidney disease.

without cystatin-C except NTproBNP level (Table 2_Supplementary material). All the patients received intravenous diuretics and doses during the first three days were recorded (Fig. 1_Supplementary material).

Baseline characteristics in patients with and without primary end-point

A total of 53 patients (59%) had a cardiovascular event during follow-up (Table 3). In 22 cases (41.5%) the event was fatal: advanced HF in 18 (82%), acute myocardial infarction in 3 cases (14%) and 1 (4.5%) fatal-stroke. Non-fatal events were observed in 31 patients (58.5%): hospitalizations due to AHF in 26 (83.8%); coronary artery

	Overall	With events	Without events	p value
N	90	53 (59)	37 (41)	
Creatinine (mg/dL)	1.2 ± 0.52	1.3 ± 0.5	1 ± 0.4	0.01
mGFR (mL/min)	59.74 ± 26	55.55 ± 22	65.64 ± 28	0.06
MDRD (mL/min)	70.18 ± 32	63.83 ± 28	79.10 ± 35	0.02
CKD-EPI (mL/min)	70.21 ± 30	66.85 ± 31	75.16 ± 28	0.20
CG (mL/min)	74.75 ± 38	71.96 ± 40	78.86 ± 36	0.41
Cystatin-C (mL/min) *(n = 60)	1.46 ± 0.69	1.52 ± 0.74	1.38 ± 0.63	0.46
CKD-EPI-cys (mL/min)	61.19 ± 29	60.25 ± 29	62.6 ± 29	0.76
CKD-EPI-Cr-cys (mL/min)	65.34 ± 28	63.5 ± 29	68.1 ± 29	0.54
Bun/Cr ratio	26.88 ± 15	25.47 ± 13	28.91 ± 17	0.28

Table 2. Renal function. mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate; CG, Cocroft-Gault.

Events	n = 53
Coronary artery disease	
Unstable Angina	0
Acute Coronary Syndrome	6
New revascularization	2
Heart Failure	43
Cerebrovascular disease	
Stroke	1
Transient ischemic attack	0
Peripheral Vascular disease	
Acute ischemic event	1
Amputation	1
Revascularization	0
Fatal events	22
Non-fatal events	31
Non-cardiovascular events	17
Sepsis	9
Oncology	5
Bleeding	1
COVID	1
COPD	1

Table 3. Patients with first-onset fatal or nonfatal major cardiovascular events (primary endpoint). COPD, chronic obstructive pulmonary disease.

disease in 3 (9.6%) and peripheral vascular disease in 2 (6.4%) cases. Non-cardiovascular fatal events occurred in 17 patients (19%): 9 sepsis and 5 oncological diseases, 1 severe intracranial bleeding, 1 due to COVID-19 and another related to advanced COPD (Table 3). During a median follow-up of 3 ± 1.9 years, 39 (43%) patients died, 22 of cardiovascular causes.

Patients with CV events during follow-up were more obese, had more previous coronary artery and chronic kidney disease before admission compared with patients without events (Table 1). The presence of ischemic etiology of the HF was the most prevalent in the group with events (30% vs 8%, p 0.001), LV were more dilated and they had lower LVEF. Regarding renal function, patients with events had higher creatinine levels (1.3 vs 1 mg/dl, $p = 0.012$) on admission compared with the group without events, but no differences in estimated or measured GFR were observed.

Agreement between measured GFR and estimated GFR

For all the formulas evaluated, TDI averaged 73%, ranging from 54 to 81% for the CKD-EPI (creatinine + cystatin-C) and Cockcroft-Gault equations, respectively (Table 4). For example, the aMDRD formula had a TDI of 76%, meaning that 90% of estimations erred from − 76 to 76 of measured GFR. A similar TDI was observed for the other CKD-EPI formulas. CCC averaged 0.77, reflecting moderate precision and accuracy, ranging from 0.73 to 0.82, for the Cockcroft-Gault and CKD-EPI (creatinine + cystatin-C) formulas, respectively (Table 4) Finally, cp averaged 22, indicating that more than 80% of the estimations had an error greater than ± 10% (Table 4).

	CCC	TDI	CP
CockcroftGault	0.73 (0.64)	81.21 (95.40)	0.20 (0.17)
aMDRD	0.74 (0.67)	75.79 (89.23)	0.21 (0.19)
CKD_EPI	0.76 (0.68)	72.46 (85.12)	0.22 (0.19)
CKD_EPI_cisc	0.69 (0.58)	80.60 (98.95)	0.20 (0.18)
CKD_EPI_crecisc	0.82 (0.74)	54.07 (65.46)	0.29 (0.24)

Table 4. Agreement between Measured GFR and Estimated GFR. The agreement between estimated by 5 creatinine and/or cystatin-C formulas and measured GFR was evaluated by specific statistics for continuous data, including the concordance correlation coefficient (CCC), total deviation index (TDI), coverage probability (CP) [X]. The CCC varies from 0 to 1 and combines meaningful components of accuracy and precision. A CCC > 0.90 reflects optimal concordance between measurements. The TDI captures a large proportion of data within a boundary for allowed differences between 2 measurements. Empirical TDI was calculated for a theoretical TDI of 10% and a CP of 90%. We defined a priori that acceptable bias between eGFR and mGFR should be at least 10%, and that 90% of the estimations should be included within these limits. This is based on previous reports and the reproducibility of measured GFR considering different methods [X]. Coverage probability varies from 0 to 1 and estimates whether a given TDI is less than a prespecified fixed percentage.

Low concordance between mGFR and eGFR

Single values of mGFR were associated with an ample range of estimations (Fig. 1). For example, in subjects with 27 mL/min of mGFR, CKD-EPI-creatinine estimated GFR from 19 to 53 mL/min (Fig. 1-A). Similar results were observed for the CKD-EPI-cystatin-C, CKD-EPI-cr-cy and MDRD equations (Fig. 1).

Association between estimated or measured GFR and major CV outcomes

Simple cox survival analysis

The following variables were associated with the onset of cardiovascular events: BMI, previous coronary artery disease, chronic kidney disease and the presence of chronic heart failure, the use of furosemide and statins, creatinine, total and LDL cholesterol, LVEF, LV end-diastolic diameter (Table 5). Measured GFR or eGFR were not associated with the primary endpoint. The discriminative accuracy (AUC) of mGFR for predicting adverse events in terms of simple analysis were 0.736 for mGFR (95% Confidence interval 0.632 to 0.824). AUC of the estimated formulas are shown in Table 4 and Fig. 2_Supplementary material.

Multiple cox survival analysis

Model 1: renal function evaluated by mGFR

The variables significantly associated with cardiovascular events were mGFR, BMI, LVEF and previous coronary artery disease. Higher levels of mGFR were associated with a lower risk for CV events. When previous coronary artery disease was replaced by previous history of chronic heart failure no major changes were observed in the model (Table 6).

Model 2: mGFR replaced by creatinine or cystatin-C

Model 3: mGFR replaced by eGFR

None of the formulas: CKD-EPI-creatinine, CKD-EPI-cystatin-C, CKD-EPIcr-cys, MDRD or Cockrof-Gould were significantly associated with the primary endpoint (Table 6). The C-statistic of the multiple analysis model shows an AUC of 0.73 (CI 0.59–0.84) for the model with mGFR, AUC of the estimated formulas are shown in Table 5_Supplementary material.

Discussion

We analyzed the error of formulas that estimate GFR and the impact of this error in the evaluation of the association between GFR and long-term CV events in 90 patients with AHF. The main finding of this study was that mGFR outperformed eGFR in the prediction of long-term CV events in patients with AHF.

In patients with AHF, the error of formulas that estimate GFR was frequent and wide. Also, we observed that this error limited the correct evaluation of the impact of renal function as a risk factor for cardiovascular events in patients with AHF. In fact, mGFR and not eGFR was associated with the incidence of cardiovascular events.

We evaluated a group of patients with AHF defined by current European Society of Cardiology HF guidelines[33]. GFR was measured with a gold standard method (iohexol) and estimated with a group of formulas, the most commonly used in clinical practice. To avoid the interaction of acute haemodynamic changes with renal function, the evaluation of GFR was performed only in a clinical stable situation at least 48 h following admission. Stable diuretic doses and no inotropic or vasopressor were required, always with a SBP > 90 mmHg.

Our main finding was that eGFR was not associated with future major cardiovascular outcomes in patients admitted with AHF. The explanation of this phenomenon is not simple. Clearly, it may be considered a consequence of the error of eGFR in reflecting real GFR. Formulas that estimate renal function proved to have low precision and accuracy in the estimation of real GFR. The average variability of eGFR in our population was about ± 30%, indicating that relevant overestimation or underestimation of GFR by formulas are more frequent than expected. In general, for the creatinine-based equations, we found a 10 mL/min higher GFR than

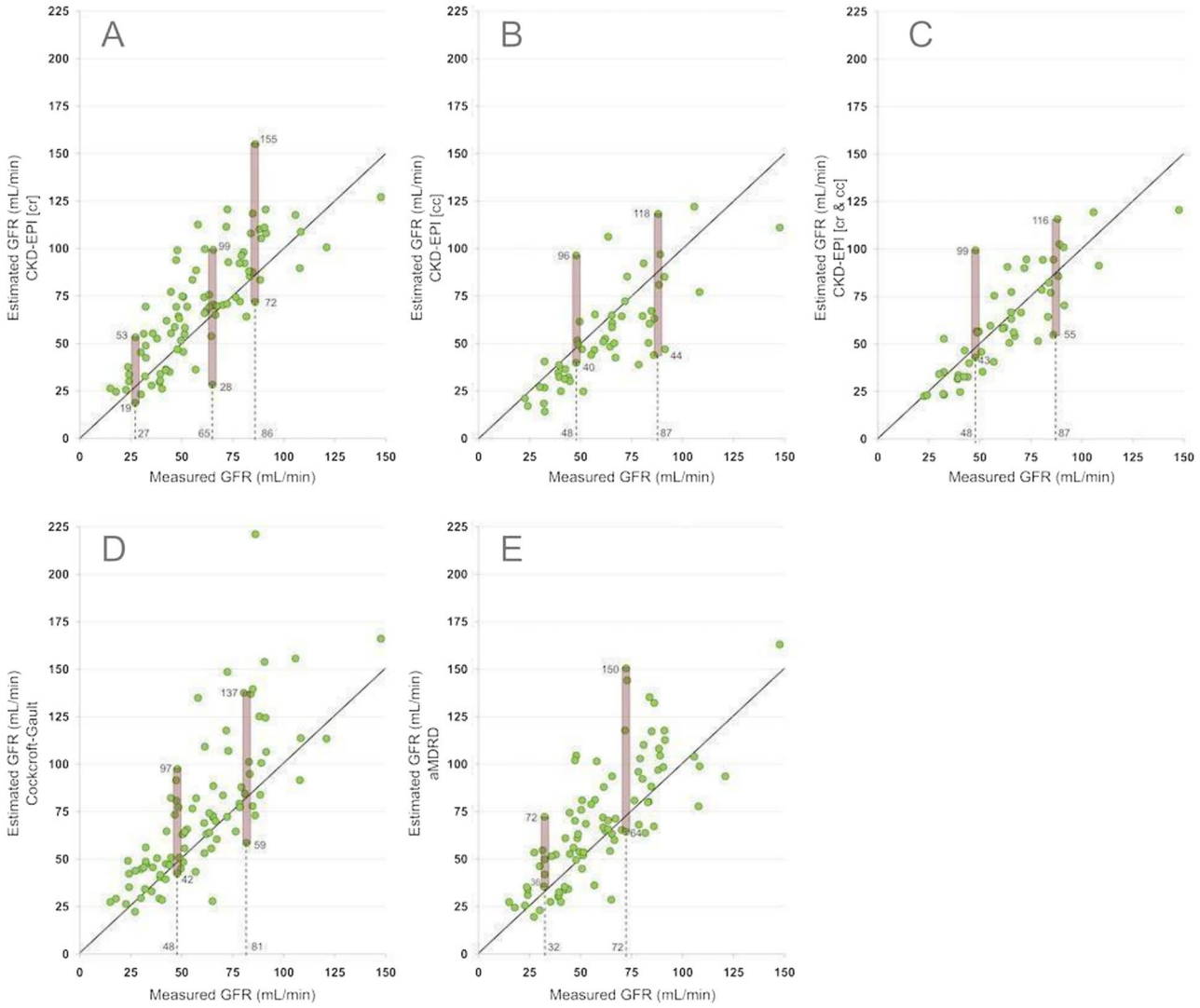

Fig. 1. Plot between measured GFR and estimated GFR by five equations CKD-EPI based on creatinine (**A**) CKD-EPI based on cystatin-C (**B**), CKD-EPI based on creatinine-cystatin-C (**C**) or Cockroft-Gault (**D**); and MDRD (**E**).

mGFR. This overestimation may falsely alter the association between eGFR and events. Previous studies comparing creatinine-based equations in HF have shown an overestimation of eGFR at lower GFR values[43,44]. Others observed that eGFR differed widely from mGFR in this population. However, these studies did not compare with mGFR. Smilde et al.[45] showed that in CHF, eGFR equations using CG, MDRD and CrCl overestimated in the lower ranges and underestimated in the upper ranges of renal function when it was compared with mGFR with ^{125}I-iothalamate clearance. Another study in heart transplant patients demonstrated that the level of agreement between eGFR and mGFR by iohexol was very low for creatinine-based equations (CG, MDRD, CKD-EPI), with percentage errors ranging from 93 to 157%[46].

The lack of association between cystatin-C based equations and CV events may be due to factors different from the overestimation of GFR as observed for creatinine-based equations. The agreement between cystatin-C-based equations and mGFR was weak and comparable to that of creatinine-based equations. Clearly the variability was not due to the overestimation of GFR but of scatter variability. The poor agreement between formulas based on cystatin-C and mGFR has been described before. Valente et. al showed that in CHF patients with mild impairment of renal function that cystatin-C-based eGFR showed the lowest bias (− 3 ± 14 mL/min/1.73) and were more precise than creatinine-based GFR compared with measured GFR with iothalamate[47].

Some studies have evaluated the capacity of diverse formulas in the prediction of future CV events following an episode of AHF. In stable and ambulatory CHF the Cockroft-Gault formula was more accurate compared with MDRD and CKD-EPI eGFR formulas to improve the risk stratification for death[48]. Iokfai et al.[49] published that eGFR-EPI-Cys improved mortality prediction over creatinine-based, creatinine/cystatin-C-based and MDRD equations. Moreover, other studies have shown that eGFR-MDRD was an independent predictor of long-term mortality after discharge among patients with AHF treated in the coronary care unit[50]. On the other side, Weidmann et al.[51] in a multicenter study demonstrated that the prognostic accuracy for readmission was poor for

First onset composite event					
				95% CI	
Comorbidities	B	p-value	HR	Lower	Upper
Age year	0.01	0.52	1.01	0.98	1.05
Gender men	− 0.64	0.14	0.53	0.22	1.24
Body mass index kg/m^2	0.11	0.02	1.12	1.02	1.23
Diabetes Mellitus	0.42	0.34	1.52	0.65	3.58
Hypertension	0.48	0.33	1.61	0.61	4.25
Current smoker	− 0.20	0.69	0.81	0.29	2.22
Dyslipidemia	0.17	0.67	1.22	0.49	3.03
Previous cardiovascular disease					
Coronary artery disease	1.57	0.002	4.8	1.79	12.84
Cerebrovascular diseases	0.84	0.23	2.32	0.58	9.22
Chronic Kidney Disease	1.27	0.01	3.55	1.32	9.45
Heart Failure variables					
"De novo" Heart Failure	1.46	0.009	0.2	0.07	0.068
Duration of Heart Failure	0.59	0.02	1.8	1.09	2.99
Previous treatments					
Aspirin	0.76	0.08	2.14	0.91	5.05
BB	0.42	0.34	1.52	0.65	3.58
Furosemide	1.86	< 0.001	6.41	2.53	16.25
Statins	1.17	0.01	3.24	1.30	8.05
Aldactone	− 0.08	0.92	0.92	0.19	4.4
Eplerenone	2.56	0.02	12.92	1.62	103.31
Laboratory values					
Hematocrit	− 0.07	0.09	0.93	0.86	1.01
Hemoglobin	− 0.18	0.09	0.83	0.67	1.03
HbA1c	0.21	0.15	1.24	0.92	1.66
Uric Acid	0.19	0.06	1.21	0.99	1.47
Creatinine	1.17	0.02	3.23	1.23	8.46
mGFR	− 0.02	0.06	0.98	0.97	1.00
eGFR MDRD	− 0.01	0.1	0.99	0.97	1.00
eGFR CKD_EPI	− 0.01	0.19	0.99	0.98	1.00
Cystatin	0.31	0.45	1.36	0.60	3.08
eGFR CKD_EPI_cys	− 0.003	0.76	0.99	0.98	1.01
eGFR CKD_EPI_Cr_cys	− 0.006	0.54	0.99	0.98	1.01
BUN/Cr ratio	− 0.016	0.20	0.9	0.95	1.01
Troponin T us	0.001	0.25	1.001	0.99	1.00
BUN	0.02	0.18	1.02	0.99	1.04
Total Cholesterol	− 0.02	0.001	0.98	0.97	0.99
Triglycerides	− 0.001	0.76	0.99	0.99	1.01
LDL	− 0.03	0.01	0.97	0.95	0.98
HDL	− 0.006	0.69	0.99	0.97	1.02
logNT-proBNP	− 0.32	0.57	0.72	0.24	2.2
HR	− 0.03	0.004	0.97	0.98	0.99
Systolic blood pressure	− 0.01	0.06	0.98	0.97	1
Diastolic blood pressure	− 0.02	0.07	0.98	0.95	1
Atrial Fibrillation	− 0.19	0.67	0.82	0.34	1.98
LV end-diastolic diameter	0.07	0.02	1.07	1.01	1.1
E/é ratio	− 0.02	0.54	0.98	0.92	1.04
LVOT-VTI	− 0.005	0.90	0.99	0.91	1.09
Left ventricular ejection fraction (LVEF)	− 0.03	0.048	0.97	0.94	0.99

Table 5. Simple Cox survival analysis—First onset composite event. Univariable regression analysis. variables associated with the first onset of a composite event. LVOT—VTI, left ventricular outflow tract volume-time interval; CKD, chronic kidney disease.

Variables	B	p-value	HR	95% CI	
				Lower	Upper
CAD	1.72	0.003	0.18	0.06	0.55
logNT-proBNP	− 1.04	0.15	0.35	0.09	1.4
LVEF	− 0.4	0.04	0.97	0.93	0.99
BMI	0.15	0.01	1.16	1.03	1.29
mGFR	− 0.25	0.037	0.98	0.95	0.99
Model 2					
Creatinine or	0.86	0.12	2.37	0.79	7.10
Cystatin	0.16	0.74	1.17	0.45	3.02
Model 3					
MDRD or	− 0.01	0.10	0.99	0.97	1.003
CKD-EPI or	− 0.014	0.13	0.99	0.98	1.004
Cockroft-Gault or	− 0.014	0.06	0.97	0.97	1.001
CKD-EPI-Cys or	− 0.001	0.91	0.99	0.98	1.02
CKD-EPI-cc-Cr or	− 0.005	0.67	0.99	0.97	1.02

Table 6. Multiple Cox survival analysis. All the models have been evaluated with coronary artery disease, log NT-proBNP, Left ventricular ejection fraction and Body Mass Index. In the main model, model 1, with mGFR with iohexol; In model 2, mGFR was replaced either by Creatinine and Cystatin; In model 3 mGFR has been replaced by different estimation formulas used in the study (MDRD, CKD-EPI, Cockroft-Gault, CKD-EPI-Cys, CKD-EPI-cc-Cr).

all equations, with an AUC around 0.5. Also, other studies demonstrated that the eGFR-MDRD formula showed poor prognosis in predicting adverse events in AHF patients[52], although better results were demonstrated in post-cardiac transplantation[53] or diabetic patients[54]. However, all these studies did not measure GFR simultaneously with a gold-standard procedure. The studies that performed a mGFR and eGFR showed that mGFR, either with iothalamate or iohexol, was better at predicting CV events or relevant RF decline in CHF patients. The predictive value of mGFR with iothalamate for a CV event in the following 12 months showed an area under the ROC curve of 0.83. MDRD performance (0.81; P = 0.432) was comparable, but the CG formula corrected for BSA was significantly worse (0.72; P = 0.015)[45]. Measured GFR by iohexol significantly declined during a 8 months follow-up period (from 52.8 to 44.4 mL/[min × 1.73 m^2], P = 0.001) being undetected by eGFR equations (MDRD, CG and CKD-EPI). These results were found in CHF and are in line with our results in AHF[31]. In any case, considering the major role of renal dysfunction in cardiovascular disease, the poor predictive capacity of eGFR is worth investigating.

The consequences of our findings may be of clinical relevance. The error of eGFR by over or underestimation of RF might result in inappropriate continuation or discontinuation of disease-modifying heart failure therapies, such as ACEi, ARNI or MRA.

The background of the error of formulas is complex and has several causes. The serum levels of creatinine depend on several factors like meat intake, muscle mass, extra-renal clearance (gut) and particularly, renal tubular secretion and reabsorption[55]. By the other hand, CysC is considered largely independent of muscle wasting and sarcopenia, but the production of this molecule is associated with obesity, fat mass and inflammation[20–56]. Clearly, the error of these markers translates to the equations that are not able to solve the low precision and accuracy of creatinine and cystatin-C in reflecting GFR. The study was carried out on a small sample of patients and so the results must be interpreted with caution. Clearly, larger series, similar to ours, with a longer follow-up, are needed before raising definitive conclusions.

Strengths and limitations

Our study has several limitations. First, the number of patients included in the analysis may be small and so our results must be tested in larger studies; Second, cystatin-C determination was not available in all patients (n 60). Thus, this study is a generating hypothesis analysis and its results must be tested in new ad hoc designed studies. Finally, it must be considered that we worked with a sub-group of patients with AHF, excluding those unstable. Thus, our results may not apply to all subjects with AHF. Main strength is that renal function has been compared with gold-standard methods like iohexol; eGFR was determined at the same time of mGFR at 48 h of admission and in a hemodynamically stable condition.

Conclusion

In patients with AHF the error of formulas is large, frequent and random, also, mGFR and not eGFR predicted future CV events. The error of eGFR may have clinical consequences in specific subpopulations.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Author contributions

PJ and EP have contributed similarly to the design, analysis of results and revision of the manuscript. MM and MG collaborated in data collection, writing, and revision. NN and LD participated in sample determination. RP contributed to the preparation of the figures and the creation of the CRD. FG, EP, MG, FB, SL and PJ contributed to the final revision of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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