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Prediction of mortality using quantification of renal function in acute heart failure☆

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ABSTRACT

Background: Renal function, as quantified by the estimated glomerular filtration rate (eGFR), is a predictor of death in acute heart failure (AHF). It is unknown whether one of the clinically-available serum creatinine-based formulas to calculate eGFR is superior to the others for predicting mortality.

Methods and results: We quantified renal function using five different formulas (Cockroft–Gault, MDRD-4, MDRD-6, CKD-EPI in patients < 70 years, and BIS-1 in patients ≥ 70 years) in 1104 unselected AHF patients presenting to the emergency department and enrolled in a multicenter study. Two independent cardiologists adjudicated the diagnosis of AHF. The primary endpoint was the accuracy of the five eGFR equations to predict death as quantified by the time-dependent area under the receiver-operating characteristics curve (AUC). The secondary endpoint was the accuracy to predict all-cause readmissions and readmissions due to AHF. In a median follow-up of 374-days (IQR: 221 to 687 days), 445 patients (40.3%) died. eGFR as calculated by all equations was an independent predictor of mortality. The Cockcroft–Gault formula showed the highest prognostic accuracy (AUC 0.70 versus 0.65 for MDRD-4, 0.55 for MDRD-6, and 0.67 for the combined formula CKD-EPI/BIS-1, $p < 0.05$). These findings were confirmed in patients with varying degrees of renal function and in three vulnerable subgroups: women, patients with severe left ventricular dysfunction, and the elderly. The prognostic accuracy for readmission was poor for all equations, with an AUC around 0.5.

Conclusions: Calculating eGFR using the Cockcroft–Gault formula assesses the risk of mortality in patients with AHF more accurately than other commonly used formulas.

1. Introduction

Acute heart failure (AHF) is a current worldwide pandemic with unacceptably high morbidity and mortality [1–3]. The intense interference and crosstalk between cardiac and renal function in AHF, including its potential modification by novel therapies, have attained increasing recognition [1–6]. Therefore, current clinical practice guidelines universally recommend the use of the estimated glomerular filtration rate (eGFR) to quantify renal function in AHF patients.

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Four serum creatinine-based formulas, initially derived and validated in patients with chronic kidney disease (CKD), are currently applied in patients with AHF: the Cockroft–Gault formula [7], the Modification of Diet in Renal Disease (MDRD) 6 formula [8], the simplified MDRD-4 formula [9], and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [10]. These formulas incorporate factors such as age, gender, race, and weight and allow a reasonably accurate estimation of eGFR [11]. A less commonly used creatinine-based equation, the Berlin Initiative Study 1 (BIS-1) formula, seems to be more accurate than the CKD-EPI to estimate GFR in persons aged 70 years or older [12].

While it has been consistently shown that impaired renal function is common in AHF and associated with a higher rate of death, it is largely unknown whether one of the clinically-available serum creatinine-based formulas to calculate eGFR is superior to the others to predict death. Recent pilot studies (two in AHF and three in chronic heart failure (CHF)) have begun to shed light on the relevance of the method used to calculate eGFR [13–17].

Based on the observations made in CHF [15], we hypothesized that eGFR, as calculated by the Cockroft–Gault formula, predicts post-discharge outcomes in AHF more precisely than MDRD-4, MDRD-6, CKD-EPI or BIS-1. We aimed to test this hypothesis in a large, international multicenter study.

2. Methods

2.1. Setting and study population

We prospectively analyzed unselected patients presenting with AHF at the emergency department (ED) of one of four participating centers in two countries, Switzerland (Basel, Luzern and S. Gallen), and Brazil (Sao Paolo). The diagnosis of AHF was adjudicated by two independent cardiologists based on available medical records and according to the current guidelines of the European Society of Cardiology [1]. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. All patients provided written informed consent to participate.

For inclusion in these analyses, patients were required to have serum creatinine quantification and information on body weight at presentation to the ED. We excluded patients with endstage kidney disease requiring dialysis.

2.2. Clinical assessment

We prospectively recorded medical history, physical exam, electrocardiography, blood tests, radiographies, echocardiograms and other studies performed during hospital admission. We collected blood samples for serum creatinine at presentation to the ED. All samples were analyzed in the respective central laboratory. Serum creatinine was measured using the enzymatic method (COBAS INTEGRA®, Roche Diagnostics GmbH, at 37 °C, calibrated to IDMS standard).

2.3. Quantification and interpretation of renal function

We calculated eGFR using: 1) the Cockroft–Gault equation [7], ((140 − Age in years) ∗ weight at admission in kg / (72 ∗ serum creatinine (sCr) in mg/dl) ∗ 0.85 (if female)). In a secondary analysis, we adjusted the same equation for body surface area (BSA) according to the Mosteller formula (Height in cm ∗ Weight in kg / 3600)$^{1/2}$; 2) MDRD-4 equation [18] (186.3 ∗ sCr$^{-1.154}$ ∗ Age$^{-0.203}$ ∗ 0.742 (if female)); 3) MDRD-6 equation [8], (170 ∗ sCr$^{-0.999}$ ∗ Age$^{-0.176}$ ∗ 0.762 (if female) ∗ serum urea nitrogen in mg/dl$^{-0.170}$ ∗ Albumin in g/dl$^{0.318}$; 4) CKD-EPI creatinine equation [10], 141 min(sCr/κ, 1)$^{\alpha}$ max(sCr/κ, 1)$^{-1.209}$ ∗ 0.993^{Age} ∗ 1.018 (if female), where κ is 0.7 for female and 0.9 for male, α is −0.329 for female and −0.411 for male, min is the minimum of serum creatinine/κ or 1, and max is the maximum of serum creatinine/κ or 1; and 5) BIS-1 equation [12], 3637 ∗ sCr in mg/dl$^{-0.87}$ ∗ Age in years$^{-0.95}$ ∗ 0.82 (if female).

Given that the BIS-1 formula seems to be superior to the CKD-EPI to estimate GFR in elderly patients, for the purpose of the study, we combined the CKD-EPI and BIS-1 formulas in a single equation, hereafter referred to as CKD-EPI/BIS-1, using CKD-EPI in patients < 70 years and BIS-1 in patients ≥ 70 years.

Renal dysfunction was defined as a GFR < 60 ml/min/1.73 m^2. eGFR was categorized into five groups based on the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) stages [19]: ≥90 ml/min/1.73 m^2; 89 to 60 ml/min/1.73 m^2; 59 to 30 ml/min/1.73 m^2; 29 to 15 ml/min/1.73 m^2 and <15 ml/min/1.73 m^2. Categories 4 and 5 were combined given the small number of patients.

A clinical history of CKD was determined by interview or examination of clinical reports.

2.4. Follow-up and endpoints

The primary endpoint was all-cause mortality. Secondary end-points were all-cause rehospitalization and rehospitalization due to AHF. Clinical follow-up data were obtained by telephone interview with the patient or with the referring physician at 3, 6, 12 and 24 months after presentation at the ED, and from hospital-based reports and administrative databases.

2.5. Statistical analysis

Continuous variables are reported as mean (standard deviation [SD]) or median (interquartile range [IQR]), according to their distribution; categorical variables are expressed as numbers and percentages. Continuous variables were compared using the independent Student's t-test or the Wilcoxon–Mann–Whitney U-test and categorical variables using Pearson's chi-square test. The Wilcoxon signed-rank test was used for pairwise comparisons. Spearman's rank-correlation coefficients and a Bland–Altman method with 95% limits of agreement (LoA) were used to describe the pairwise agreement between eGFR calculated with the various formulas.

Cohen's Kappa was used to compare agreement in classification into the four defined stages of the NKF K/DIGO or as a dichotomized variable (impaired versus preserved renal function). We compared Spearman's rank correlation coefficient and Cohen's kappa values between pairing methods using a bootstrap method with 500 replicates. The predictive performance of the eGFR equations was calculated constructing a time-dependent receiver operating characteristic (ROC) curve, as proposed by Haegerty [20], comparing the areas under the curve (AUC) with a Wilcoxon test. Prognostic accuracy between predefined subgroups was evaluated constructing a ROC curve and calculating the AUC in a standard fashion, and comparisons were made using a DeLong test. Survival was calculated using Kaplan–Meier analysis and differences between the curves were evaluated using Log-Rank statistics. Cox proportional hazards regression modeling was performed to assess time-to-event associations with mortality. Variables with <10% missing values and a p-value < 0.1 at univariate analysis were entered into the multivariate model using a forward stepwise selection. Covariates with p > 0.1 in a univariate analysis but with theoretically clinical relevance were also included in the model. The improvement in predictive accuracy for the Cockroft–Gault equation over the other equations was tested using the net reclassification improvement (NRI) as continuous NRI, as proposed by Pencina et al. [21]. Significance was defined as two-tailed p value < 0.05. Analyses were performed with IBM SPSS Statistics version 21.0 (SPSS, Chicago, Illinois), R software version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and MedCalc version 14.8.1 (MedCalc Software, Ostend, Belgium).

3. Results

3.1. Baseline characteristics of the cohort

A cohort of 1104 patients with AHF was included in the analysis (Table 1): 45% of patients were female, median age was 79 years and the prevalence of comorbidities was high. The most common cause of chronic heart failure was ischemic heart disease and the median left ventricular ejection fraction was 45% (IQR: 30–58%). A history of CKD was present in 43.3% of patients.

3.2. Renal function

Fig. 1 shows the estimates of GFR using the four formulas, and Table 2 shows their categorization in four groups across the NKF/DOQI classification. The quantitative distribution (p < 0.01 using a Wilcoxon signed-rank test) and the prevalence of renal insufficiency differed significantly according to the four formulas: 69.4% using the Cockroft–Gault, 56.7% with the MDRD-4, 40.8% with the MDRD-6, and 75.7% with the CKD-EPI/BIS-1 (p < 0.05 using Pearson's χ^2).

3.3. Agreement of measurements

The four formulas correlated significantly when evaluated using the Spearman correlation test, with r-values between 0.92 and 0.99 (Table 3, online supplement). However, when assessed as a categorical variable using Cohen's Kappa, the correlation was overall poorer (between 0.18 and 0.68 when values were divided into four categories according to the KDIGO classification, and 0.36 and 0.77 when values were divided into two categories according to the presence or absence of renal dysfunction). The correlation analysis using a scatterplot and Bland–Altman method (Fig. 2) showed a good agreement between the