Title:
Discrepancies in the RIFLE classification are due to the method used to assess the level of derangement of kidney function.

Short title:
Creatinine clearance is a more suitable estimator than serum creatinine.

Authors:
Manuel E. Herrera-Gutiérrez, PhD
Gemma Seller-Pérez, PhD
Esther Banderas-Bravo
Cesar Aragón-Gonzalez
Rebeca Olalla-Sánchez
Rosario Lozano-Sáez

Critical Care and Emergency Unit. University Hospital Carlos Haya, Malaga, Spain.

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CORRESPONDING AUTHOR:

Manuel E Herrera-Gutiérrez, PhD.
ICU Hospital Carlos Haya
Avd Carlos Haya s/n
29010, Málaga, Spain
Fax: +34951291143
Phone: +34951291142
mehguci@gmail.com

ABSTRACT

Purpose: We hypothesised that RIFLE based on creatinine clearance (CrCl) is superior to that based on serum cretinine (sCr) or Cockroft-Gault (C-G) because it is an earlier marker of kidney dysfunction.

Materials and Methods: At day three of admission we compared the RIFLE based on sCr, C-G and CrCl with 28-day mortality and development of RIFLE F during ICU stay.

Results: Percentages in the RIFLE levels were similar for the three estimates, but the patients included in each level were different; with CrCl as the reference, Kappa statistic was 0.29 (95% CI, 0.15 – 0.43) for sCr and 0.21 (0.07 – 0.36) for C-G.

Mortality at day 28 was 19.3%, with percentages of mortality increasing with RIFLE based in CrCl but not sCr or C-G (AUC 0.57 [45-72] for C-G, 0.57 [44-72] for sCr, and 0.64 [52-79] for CrCl). Logistic regression only showed an independent relationship with mortality for RIFLE measured with CrCl.

Conclusions: RIFLE classification using sCr or C-G at the third day of admission predicts outcome less accurately than with the use of CrCl. Due to the delay in the rise of sCr following a sudden GFR decrease, RIFLE based in CrCl may represent an advantage in terms of precocity.

KEYWORDS

Acute kidney injury. Cockroft-Gault. Creatinine clearance. Outcome. RIFLE.

INTRODUCTION

Acute kidney injury (AKI) is a common complication in the Intensive Care Unit (ICU) [1]. Recent years have witnessed an increase in our understanding of AKI and we no longer assume that is just one component of the multiple organ dysfunction syndrome (MODS) [2] and accept that is associated with attributable mortality [3,4].

These findings have led to a change in AKI definition [5] with emphasis in the early detection [6] and in the stratification with the RIFLE or AKIN systems [7-9], based in small changes in diuresis or the glomerular filtration rate (GFR). Even though equations aimed to estimate GFR and based in serum creatinine (sCr) were initially designed to be used in patients with a steady renal function they are now widely used in the ICU setting to evaluate renal function and the RIFLE system contemplates the possibility of include creatinine clearance (CrCl) as GFR estimate, but both RIFLE and AKIN systems rest mainly in changes in sCr and, therefore, share the same strengths and weaknesses. The fact that sCr levels experience a delay in their rise after sudden deterioration of the GFR suggested that the cases classified by this estimate will undergo the same delay. Different results would be shown by RIFLE stratification using sCr or by CrCl [10]. We hypothesised that the use of the CrCl may represent an advantage in terms of precocity.

SUBJECTS AND METHODS

Post-hoc analysis of a prospective study designed to validate CrCl measured with a 2-hour urine sample against the standard 24-hour procedure [11] in 307 adult ICU patients. Because we needed to calculate CrCl, anuric (but not oliguric) patients were excluded. The database included basal sCr (medical records or estimated with the MDRD tables), age, gender, weight, height and diagnosis at admission. During follow-up daily sCr, day of detection of RIFLE F stage during ICU stay, need for RRT, date of discharge from the ICU and outcome were recorded [11].

From this registry we selected those patients with known (not estimated) basal sCr at admission and with more than three days of ICU stay (because the two-hours CrCl calculated between 48-72 hours of admission was needed for the study) and excluded those with a previous history of

chronic renal failure (basal CrCl below 60 mL/min/1.73m^2 estimated with basal sCr and the Cockroft-Gault (C-G) equation). The final study sample comprised 114 cases.

Basal CrCl was estimated with C-G (based on the basal sCr recorded at admission). CrCl on the third day was measured from a 2-hour urine collection and also estimated with C-G from the sCr obtained in this 2-hours. We calculated RIFLE stage at the third day of ICU stay with these three approaches (RIFLE-sCr, RIFLE-CG and RIFLE-CrCl).

Results of statistical tests are presented as the mean and 95% confidence interval for the mean or number of cases (percentage). Variables related to time are presented as medians (interquartile range). The Chi-square test was used for univariate comparisons. Agreement was evaluated with Kappa statistics. Two outcomes were analysed, mortality at 28 days after ICU admission and development of RIFLE-F during the first week of ICU stay, using the Area under the ROC curves (AUC). A logistic regression analysis was performed for each one of the three calculated RIFLE used in this study, with 28-day mortality as the dependent variable. SPSS for Windows 11.0 ® was used for calculations.

RESULTS

Mean age was 53.7 (50.2 – 57.2) years, and 76 (66.7%) were males. Thirty (26.3%) were septic, 24 (21.1%) were admitted after trauma, 33 (37.7%) after surgery and 9 (7.9%) after liver transplantation. The basal sCr was 76.9 (71.6 – 80.4) µmol/L and the basal GFR was 112.2 (103.3 – 108.6) mL/min/1.73m^2. Median ICU stay was 6.5 days (4 – 14.25).

At the third day in ICU 32, 43 and 44 cases of AKI were detected using RIFLE-sCr, RIFLE-CG and RIFLE-CrCl respectively. At this time only 1 AKI-F was detected with RIFLE-sCr, none with RIFLE-CG and 8 with RIFLE-CrCl (see table 1). Eighteen patients (15.8%) reached RIFLE level F during their stay, with a median delay of 10 (7 – 20.75) days; 7 (38.9%) required RRT and 12 (66.7%) died.

When comparing RIFLE-CrCl with RIFLE-sCr or RIFLE-CG, there were significant differences in these measures ($p<0.05$) (Table 1) and the agreement was poor: Kappa 0.29 (95% CI, 0.15 – 0.43) for RIFLE-sCr and Kappa 0.21 (0.07 – 0.36) for RIFLE-CG.

The ICU mortality was 20.2% (23 cases), 22 (19.3%) during the first 28 days. We calculated a ROC curve for RIFLE level against development of RIFLE F during ICU stay and the AUC of was 0.64 (95% CI 0.48-0.76) for RIFLE-CG, 0.68 (0.53-0.80) for RIFLE-sCr and 0.77 (0.63-

0.91) for RIFLE-CrCl. For mortality the AUC was 0.57 (95% CI 0.45-0.72) for RIFLE-CG, 0.57 (0.44-0.72) for RIFLE-sCr and 0.64 (0.52-0.79) for RIFLE-CrCl.

In order to define the relationship of RIFLE with mortality we performed three logistic regression analyses (one for each RIFLE estimator), with 28-day mortality as the dependent variable and age, sex, basal CrCl (estimated with the C-G equation), need for RRT, and RIFLE as independent variables. Of the three estimates only RIFLE-CrCl was related to mortality (p 0.016, OR 5.5 [95% CI 1.4-21.6] for R against no risk).

DISCUSSION

Our results show significant differences in the RIFLE classification based in sCr or CrCl and we hypothesise that this difference is due to the gap between CrCl fall and posterior sCr increments at the initiation of AKI. Although this inconvenience can be avoided using sCr with 48 hours intervals in the case of AKIN or to one week in the case of RIFLE [7], we should aim for an earlier detection and suggest, based in our findings, that RIFLE based in CrCl measured over a short period of time may represent a significant advantage in terms of precocity.

AKI is a common problem in critical patients and one associated with a worse prognosis [1,12,13]. Early AKI detection needs of a marker easy to measure and feasible for all laboratories and we know that small rises in creatinine concentrations have prognostic repercussions [14,15]. These facts make sCr a good candidate but on the other side its level do not depend only on its production and renal tubular secretion; other influential variables, such as muscle mass, sex, age, diet or race, must also be taken into account.

A potential problem of the RIFLE classification is equating changes in CrCl to changes in sCr, a problem that was pointed out by Englberger et al [16] and which our results seem to confirm. Our data show that the patients classified in each group differed significantly for each estimated used. Like in some studies with long follow-up periods [17-19], we did detect higher mortality with worsening renal function, but in our series it was only evident when we used RIFLE-CrCl (for RIFLE-sCr or RIFLE-CG patients in stage R experienced higher mortality than those in stage I) [20]. According to the kinetics of renal damage, the initial insult is followed by a period during which sCr has still not risen whereas the renal damage continues worsening [21], thus

we believe that cases in stage R according to RIFLE-sCr do, in fact, correspond to stages I or F for RIFLE-CrCl.

Another aspects to be considered regard sCr measurement [22]. For example our laboratory uses the Jaffe technique, known to have variations from 5.3 to 27.4 μmol/L [23], within which lies the value that in the AKIN system classifies a patient as AKIN-1. An added problem in critically ill patients is the dilution of sCr secondary to fluid accumulation, which might result in underestimation of the severity of AKI, thereby increasing the time required to identify a 50% relative increase in sCr. These data could in part explain the poor behaviour of RIFLE-sCr as our study was done during the first three days of admission [24]. These facts add to explain as well the failure of the equations to estimate the GFR based on isolated determinations of sCr when applied to critically ill patients [25] and we agree with Cruz et al that these equations are not suitable for classifying AKI in critically-ill patients [10,21].

These questions, together with the equally important point of early detection of AKI, mean that biomarkers of renal damage are becoming a necessary alternative for the early diagnosis and possible stratification of this entity (25). Among these biomarkers, Cystatin C, used in isolated determinations in blood or else incorporated to new equations for estimating the CrCl (26,27), has been proposed as a simple method for early detection, but the results are not conclusive. Until these biomarkers prove their usefulness, RIFLE classification based in the determination of CrCl in urine over a short period of time may represent an advantage.

CrCl in a short-timed sample of urine has been challenged for a long time arguing that AKI is not a steady state and that, in this scenario, a longer recollection is needed. As we have demonstrated previously [11], when a strict protocol and a carefully timed recollection of urine is performed, this is not the case and in critically ill patients a 2-hours recollection gives equivalent results to the standard 24-hours measurement. Additionally, in this study, the use of short-time collection assures that the sCr value used for calculating RIFLE was the same for the three estimates.

The use of C-G to calculate the basal CrCl could represent a possible bias in our results but we selected this equation because has been validated in general populations and in our centre has shown a better behaviour than the MDRD equation [28]. We addressed this problem by just selecting those patients with a known basal sCr because, even when risking a selection bias,

we assured the validity of the basal CrCl estimate (a more serious problem than that derived from a selected population). This theoretical selection bias could be aggravated because we recruited only patients with more than three days of ICU stay but once more this was unavoidable in order to have at the least 48-72 hours between the basal and the reference measurement and thus obtain a clinical meaningful result. Additionally, the study was carried out at a single centre, and the results may not be applicable to other populations, though it was a general unit with a case-mix comprising the main risk groups for renal dysfunction (cardiac surgery, transplant, sepsis or trauma), which would lessen this bias. Another possible limit in our findings lays in the fact that all the analyzed patients had a "normal or near normal" basal renal function; when addressing patients with a previously impaired renal function some authors suggest that staging of AKI patients could be better done using absolute changes in sCr in patients [29]

Though we based our study on prospective data, the fact that it was a post-hoc analysis eliminates the possibility of controlling all the possible confounding variables. Nevertheless, we believe that this deficiency by no means invalidates the result, as we only detected an independent relation with mortality for the RIFLE-CrCl, but not for RIFLE-sCr or RIFLE-CG (subjected to the same deficiencies of protocol). All the variables applied had been prospectively registered in the original study [11] and were meant to calculate CrCl in 2 hour urine samples, exactly the same way these data were used in this new study.

Finally, we did not use the component of diuresis in the stratification, which reduces the sensitivity of RIFLE to predict mortality [30] but this intended omission increased the consistency of our results by comparing exactly the behaviour of the estimators in the absence of other interference. The use of diuresis would surely have resulted in less obvious a difference between the estimators potentially masking the results.

Our study supports current reports about an increase in mortality with a rise in the level of the RIFLE scale [31,32], though in our case RIFLE-CrCl appears to be a more suitable predictor of mortality than RIFLE-sCr on the lower risk levels (Risk and Injury). This result may be due to the delay in the increase of sCr following a sudden GFR decrease and in this case RIFLE-CrCl may represent an advantage in terms of precocity.

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Figure 1. Percentage of 28-day mortality for each RIFLE stage using serum creatinine (sCr), Cockroft-Gault (C-G) or Creatinine clearance (CrCl) as GFR estimators: mortality increased with the RIFLE level for the CrCl group, but was higher for level R than I when using sCr or C-G as estimators.