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GFR shot by RIFLE: errors in staging acute kidney injury

Acute kidney injury is responsible for the loss of thousands of lives each year. Up to 25% of patients in the intensive care unit develop acute kidney injury, which dramatically reduces survival.[1] The RIFLE classification is a simple tool for classifying the severity of the disease. RIFLE was developed because of the need to establish a standard by which trials could be compared and to aid the determination of whether renal function is stable or getting worse or better.[2] Such a consensus was an important step forward. RIFLE uses glomerular filtration rate (GFR) as one of two alternatives for its first three categories: risk (R), injury (I), and failure (F) (table). The other criterion is urinary output.

Unfortunately, the increases in serum concentration of creatinine and the decreases in glomerular filtration rate in the definitions of R and F do not correspond. In steady-state, with no secretion of creatinine, glomerular filtration rate is inversely proportional to serum creatinine. Thus a 1·5-fold increase in serum creatinine corresponds to a one-third decrease (not 25%) in glomerular filtration rate and a three-fold increase to a two-thirds decrease in glomerular filtration rate (not 75%).

In a review of 24 studies[3] published from 2004 until June, 2007, that used RIFLE to correlate the diagnosis of acute kidney injury with prognosis (including mortality), six were identified as having used both serum creatinine and glomerular filtration rate to classify patients. None of these studies measured glomerular filtration rate, but estimated it by a formula, either the modification of diet in renal disease (MDRD) or the Cockcroft–Gault formula, which relate age, weight, race, and serum creatinine to glomerular filtration rate.[4–9] One study chose the greater of the rise in creatinine or fall in estimated glomerular filtration rate for RIFLE.[4] With the MDRD formula a 1·5-fold increase in serum creatinine corresponds to a 37% decrease in glomerular filtration rate, and a three-fold increase in serum creatinine to a 72% decrease. Thus, in a study such as that by Ostermann and Chang,[8] who estimated glomerular filtration rate, the number of patients classified as R was probably overestimated and the number in F slightly underestimated. In any case, calculated glomerular filtration rates (ie, estimated) are only valid when plasma creatinine is in equilibrium, which is not the case in acute kidney injury.

In view of this possible error in RIFLE, we urge caution in interpreting results. RIFLE has recently been modified by the Acute Kidney Injury Network (AKIN) and now does not include glomerular filtration rate itself, only serum creatinine, in the three AKIN stages that map, at least partly, to R, I, and F[10] (table). Urinary output criteria are still included. Contrary to a recent comment[11] in *The Lancet*, the RIFLE and AKIN criteria are not for all practical purposes the same and particular attention must be made to the methodology used to classify each patient into R, I, or F. Both RIFLE and AKIN have been used as outcome measures in clinical trials and in epidemiological studies that compared the incidence of acute kidney injury in the intensive care unit and hospital populations. However, they have yet to be validated in the community population with acute renal failure.

RIFLE stage	RIFLE criteria	AKIN stage	AKIN criteria
R (risk)	≥150% increase in serum creatinine, or >25% decrease in GFR	I	≥150% or ≥0·3 mg/dL increase in serum creatinine
I (injury)	>200% increase in serum creatinine, or >50% GFR decrease	II	>200% increase in serum creatinine
F (failure)	>300% increase in serum creatinine, or serum creatinine of ≥4 mg/dL in setting of an increase of ≥0·5 mg/dL, or >75% decrease in GFR	III	>300% increase in serum creatinine, or serum creatinine of ≥4 mg/dL in the setting of an increase of ≥0·5 mg/dL

GFR=glomerular filtration rate. Serum creatinine increases are all relative to baseline value for individual patient.

Table: **RIFLE and AKIN serum creatinine and glomerular filtration rate criteria for severity of acute kidney injury**

The confusion over how glomerular filtration rate should be used highlights the potential misclassification of severity when an estimate is used. Changes in plasma creatinine, and hence of estimated glomerular filtration rate, are a consequence of the altered true rate, and not vice versa.[12,13] The removal of glomerular filtration rate from the AKIN staging will reduce the chance of misclassification. However, AKIN has noted that current research on biomarkers of injury and glomerular filtration rate may lead to their use in future diagnostic criteria.[10] Biomarkers of injury will complement rather than replace measured glomerular filtration rate (not the estimated rate), so that injury and functional change can be identified as separate but related events, analogous to enzyme release and change in ejection fraction after myocardial infarction.[13]

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Public disclosure of clinical research

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The issue of publication bias in clinical research has been debated in the medical and scientific community for many years,[1,2] and concerns remain that studies that are not published alter the collective understanding of the results of clinical trials. There are also concerns that the content of publications may not reflect the results in an accurate and balanced manner.[3]

It is of crucial importance that the results of all studies which evaluate a particular medical intervention are in the public domain and reported accurately, so that the evidence base that is used to help inform medical judgment and advance medical science is complete. Traditionally, results have been publicly disclosed by seeking publication in peer-reviewed scientific literature, but there are well recognised limitations. First, how do we know whether completed studies are published? Second, what happens when it is not possible to publish a study in a peer-reviewed journal?

The registration of protocol summaries when studies are started helps to address the first question because it enables all studies to be tracked to publication.[4,5] Studies that have been registered but for which the results are not publicly disclosed can be identified and researchers called to account. Protocol registration also enables journal editors and peer reviewers to assess the submitted manuscript against the protocol summary (eg, ensuring that results from the appropriate population are reported, that all the primary outcomes and relevant secondary outcomes are included, and a balanced account is rendered). Evaluation of the manuscript can be augmented by reviewing the protocol and any amendments which the researchers can provide.

When it is not possible to publish studies in a peer-reviewed journal, putting results summaries on internet-based registers is a partial solution and ensures that results are in the public domain whether or not they are accepted for publication. Another venue is publication and presentation at scientific or medical congresses, which remain the most expeditious routes to disclose results to the relevant scientific and medical communities. However, congresses are often limited to those who attend the congress or who have access to congress