Review Article

Estimating Kidney Function in the Critically Ill Patients

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Glomerular filtration rate (GFR) is an accepted measure for assessment of kidney function. For the critically ill patient, creatinine clearance is the method of reference for the estimation of the GFR, although this is often not measured but estimated by equations (i.e., Cockroft-Gault or MDRD) not well suited for the critically ill patient. Functional evaluation of the kidney rests in serum creatinine (Crs) that is subjected to multiple external factors, especially relevant overhydration and loss of muscle mass. The laboratory method used introduces variations in Crs, an important fact considering that small increases in Crs have serious repercussion on the prognosis of patients. Efforts directed to stratify the risk of acute kidney injury (AKI) have crystallized in the RIFLE or AKIN systems, based in sequential changes in Crs or urine flow. These systems have provided a common definition of AKI and, due to their sensitivity, have meant a considerable advantage for the clinical practice but, on the other side, have introduced an uncertainty in clinical research because of potentially overestimating AKI incidence. Another significant drawback is the unavoidable period of time needed before a patient is classified, and this is perhaps the problem to be overcome in the near future.

1. Epidemiology of Acute Kidney Injury in the ICU

Acute kidney injury (AKI) can be defined as a decrease of the glomerular filtration rate (GFR) that appears acutely, is maintained for some time, causes an accumulation of waste products from metabolism and uremic toxins, and conditions a mishandling of body fluids and a loss of the ability to maintain homeostasis of electrolytes and acid-base balance. In the intensive care setting, AKI presents with a high incidence and, once established, has an important impact in the patient and the resources [1, 2].

The reported incidence of AKI in the intensive care units (ICUs) shows a wide variability depending on the population analyzed and the criteria employed for its definition, but when this is based in the new systems for stratification, as RIFLE [3] or AKIN [4], more than 30% of ICU patients are found to present with some degree of AKI [5], and mortality rate increases according to this degree of renal dysfunction [6, 7]. These figures are a good measure of the magnitude of the problem, and even when functional recovery after AKI is good, it has been demonstrated that the development of severe AKI can lead to an increase in long-term mortality [8] with an estimation of the incidence of chronic kidney disease (CKD) after an episode of AKI as high as 7.8 per 100 patients per year [9, 10].

This scenario has put in evidence the necessity of new tools for continuous assessment of kidney function given that the classical approach of measurements of isolated determinations of serum creatinine (Crs) has proven insufficient [11].
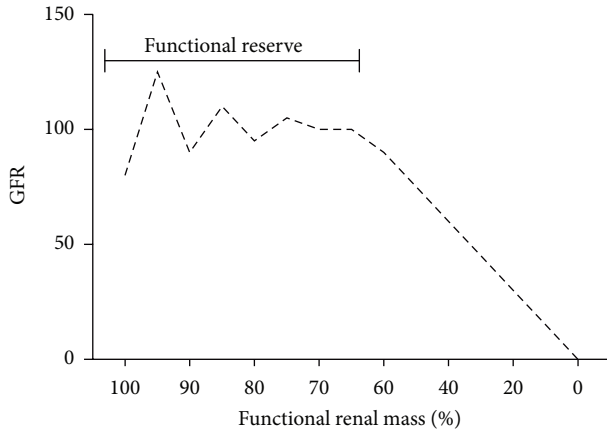
Figure 1: When enough renal mass is present, GFR changes in response to patient necessities, but when damage is severe this "renal reserve" is lost. Adapted from [12].

2. Measuring Kidney Function

2.1. Glomerular Filtration Rate. One way to evaluate renal function is studying its capability to maintain an adequate rate of filtration in the glomerulus, that is, the GFR. The GFR is a measure of the amount of blood filtered per unit of time but not necessarily of kidney damage. We must keep in mind that a direct relationship between renal mass and changes in GFR does not exist until late in the process of damage because the kidneys are able to compensate the loss of renal mass through a raise in the filtration rate in those nephrons still functioning (Figure 1) [12]. GFR can be estimated by the measurement of the rate of elimination (clearance) of different molecules that are filtered by the glomerulus but not secreted or reabsorbed by the tubule, and the use of endogenous molecules naturally producing in the organism has been proposed for this purpose, mainly Crs.

2.2. Serum Creatinine. Crs is an organic protein resulting from the degradation of creatine, produced and eliminated at a constant rate, exclusively cleared by the kidneys, and filtered at the glomerulus without significant tubular reabsorption or tubular secretion. Its main drawback is based on the fact that changes in Crs do not follow a linear relationship with changes in GFR, so that when detecting changes in its concentration we must not assume similar changes in the GFR (Figure 2) [16]. Also, Crs being an endogenous molecule, its metabolism is subjected to interpersonal variations depending on different factors [17]. Taking into consideration these aspects, Crs is still the parameter universally adopted for the diagnosis of kidney failure, but we must keep in mind that its value reflects the functionality of the kidney and not necessarily the presence of actual damage.

Crs is a functional parameter and its role in the diagnosis of renal injury is closely related to what we can address as "renal reserve." When a patient initially presenting a normal Crs concentration surpasses 2 mg/dL, he or she may have lost approximately 50% of the functioning renal mass [12, 14], but
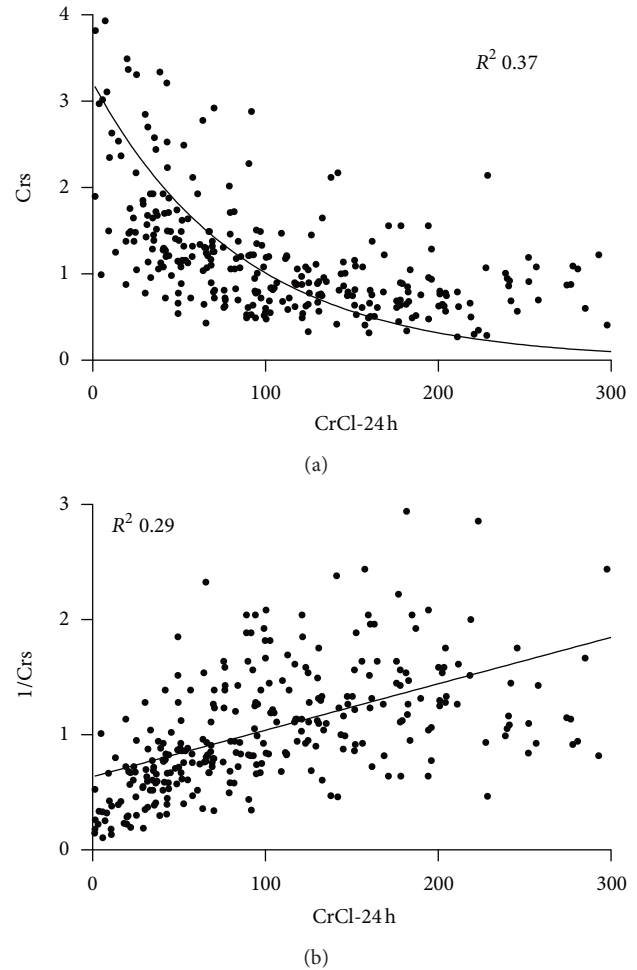

(a)

(b)

Figure 2: Relationship between serum creatinine and creatinine clearance. Data from the authors, adapted from [13].

on the other hand, changes in Crs after a serious renal insult depend largely on the basal figures as well, so that 24 hours after a 90% fall in the creatinine clearance (CrCl), the increase of Crs might be up to 246% when kidney function is normal but only 174% when the patient already featured a dysfunction in stage 2 of the KDIGO guidelines [18] or as low as 74% when the patient was in stage 4, for a virtually identical absolute increase in the Crs (between 1.8 and 2 mg/dL). For this reason, some authors have advocated for a definition of AKI based upon changes of Crs levels for a given period (between 24 and 48 hours) instead of absolute serum levels [19]. This approach palliates the problem derived from the delayed raise in Crs (more than 48 hours) following a change in GFR (Figure 3) [14, 15, 18, 19].

2.3. Fluids and Crs. Another key point when assessing serial changes in Crs is the repercussion of the balance of fluids. In those situations when aggressive hydration has been necessary and water balance is positive, the relative serum

concentration of Crs decreases and therefore underestimates the real value [20–23].

2.4. Crs Assay. The method described by Jaffé for the assay of Crs has been the cornerstone for the diagnosis of the renal failure until recently but shows variations for a range from 0.06 to 0.31 mg/dL, a range previously considered safe but is now considered to be of potential prognostic value [24, 25]. This fact has favored its displacement by the enzymatic assay [26].

2.5. Creatinine Clearance. This method does in effect show a lineal relationship with GFR and is less affected by the delayed changes of Crs after GFR decrement but shares all the other problems of the Crs already mentioned. In routine ICU clinical practice, CrCl measured with diuresis of 24 hours is not operational, and different investigators have sought alternatives more adapted to the ICU environment. An approach is the measurement of CrCl with samples of urine collected in shorter intervals of time, making repetitive measures more feasible, urine samples from simultaneous patients easier to handle, and (the most critical aspect) without delay for the results [27]. Different timings for collection of urine have been validated by some authors, ranging from one hour by Hoste et al. [28], two hours by Herrera-Gutiérrez et al. [13] or periods from two to twelve hours by Wilson and Soullier [29]. In addition, these studies show how among those patients with Crs in normal or near-normal range (below 1.5 mg/dL) up to 25% already had a significantly diminished CrCl and also put in evidence that equations for estimation of GFR in the ICU (Cockroft-Gault and MDRD) are not adequate [13, 28]. However, despite the scarcity of studies addressing the validity of these equations in the acute patient (and specifically in the ICU patient) and the general agreement against its use in this scenario, these equations (especially MDRD) have become the usual tool for estimation of CrCl and guiding prescription of drugs that require adjustment in the presence of renal dysfunction [30, 31]. When an exact measure is deemed necessary none of these equations replaces a measurement of CrCl [32].

2.6. Cys-C. Cys-C is a low molecular weight protein produced by all nucleated cells at a constant rate, being filtered by the glomerulus and reabsorbed and metabolized in the proximal tubule without tubular secretion and only minimal extrarenal elimination. Cys-C has shown promising results as an estimator of GFR in patients with stable renal function [33, 34].

2.7. Biomarkers of Kidney Injury. Different biomarkers of kidney injury have recently been evaluated with mixed results [35]. It is still necessary to define the kinetics of these molecules and their relationship to the development of kidney injury [36]. Another important point to emphasize is that these new biomarkers are not aimed to the assessment of renal function (do not estimate GFR) and therefore can not replace but are complementary to Crs or Cys-C.
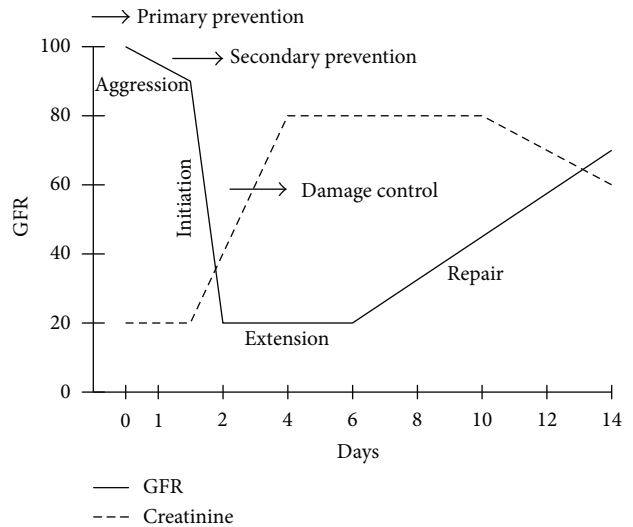

Figure 3: Relationship between glomerular filtration rate (GFR) and serum creatinine (Crs) in time. Adapted from [14, 15].

3. Stratification of AKI

From the moment the aggression occurs until the kidneys begin to show alterations and dysfunction, different mechanisms of compensation have been launched that which produce a decrease in the GFR [37] but, due to the lack of sensible methods of diagnosis, we acknowledge the presence of this renal failure once this initial phase has already been surpassed. This problem is worsened because there is not a clear definition of what we must consider AKI [38, 39] but the definition of two systems aimed to stratify acute kidney dysfunction based on sequential changes of Crs (RIFLE and AKIN) has come to fill this gap for the AKI patient (Figure 4) [3, 4].

The RIFLE (an acronym for risk, injury failure, loss, and end-stage) system made a proposal for a new definition considering AKI as a dynamic process. Another major advantage of this system was its simplicity, advocating for the use of biomarkers universally affordable (Crs and diuresis). In 2007, the AKIN (acute kidney injury network) group designed a new stratification system based on the premises of the RIFLE system but incorporating the findings from Lassnigg et al. that demonstrated how small increases in Crs carry a proportional increase in mortality [24, 40–43]. These two systems have been evaluated in large series of UCI patients and are currently consolidated as reference, but both systems present some problems [44] and their introduction has conditioned a substantial increase in the incidence of AKI published, having in fact increased on the order of 2 to 10 times [45].

The problem, shared by both systems, is the need for a minimum timeframe to proceed with the classification, which in RIFLE extends up to a week and in AKIN for 48 hours. This inevitable time window will condition a delay in the detection of AKI. Yet another problem with RIFLE arises from the possibility to choose indistinctly between CrCl or Crs, even when these values are not linearly related and do not

	RIFLE	
Crs ↑ × 1.5 or GFR ↓ 25%	Diuresis < 0.5 mL/kg/h 6 hours	Risk
Crs ↑ × 2 or GFR ↓ 50%	Diuresis < 0.5 mL/kg/h 12 hours	Injury
Crs ↑ × 3 or GFR ↓ 75% or Crs ≥ 4 mgr/dL	Diuresis < 0.3 mL/kg/h 24 hours or Anuria > 12 h	Failure

Loss of function > 4 weeks	Loss
ESRD > 3 months	Esrd

	AKIN	
Stage 1	Crs ↑ × 1.5 or ↑ > 0.3 mgr/dL	Diuresis < 0.5 mL/kg/h 6 hours
Stage 2	Crs ↑ × 2	Diuresis < 0.5 mL/kg/h 12 hours
Stage 3	Crs ↑ × 3 or Crs ≥ 4 mgr/dL	Diuresis < 0.3 mL/kg/h 24 hours or Anuria > 12 h

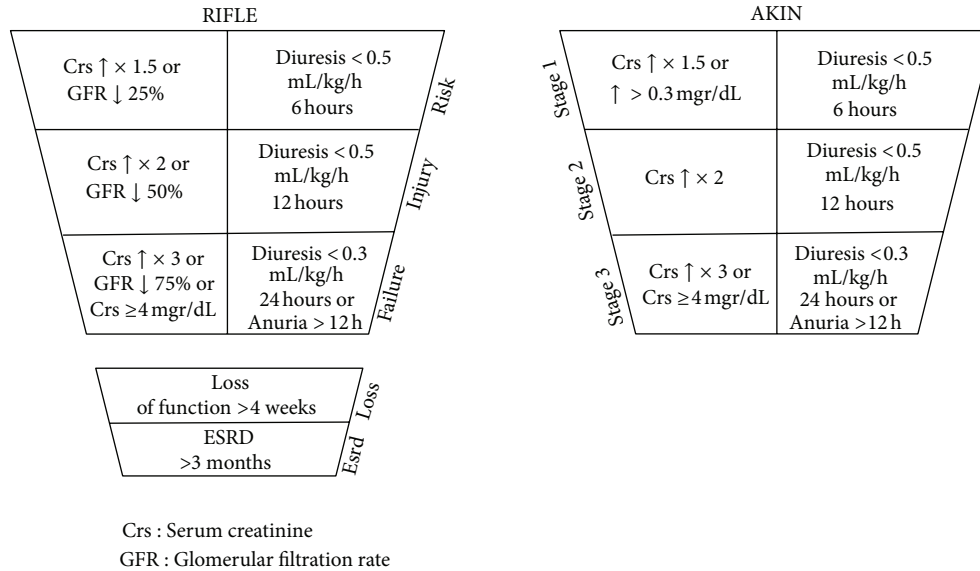Crs : Serum creatinine
GFR : Glomerular filtration rate

FIGURE 4: RIFLE and AKIN classification systems [3, 4].

change simultaneously in time [46]. Another relevant aspect and one that questions the consistency of these systems is the finding of similar outcomes for patients in the AKIN 1 and 2 levels with a significant increment for level 3 and with a similar behavior for RIFLE [47] that could be suggesting the convenience for a reappraisal of the ranges of Crs considered in each level.

4. Conclusion

A proper definition for AKI should establish the presence or absence of the disease, report on its severity and prognosis, and, perhaps more important, should be easy to understand and implement [48]. Although these assumptions have been partly met by RIFLE and AKIN, it is likely that in a near future our understanding about AKI and its impact will be modified.

It is important to stress the fact that at least 20% of hospitalized patients develop some degree of renal dysfunction, and the prognosis for these patients worsens as the degree of dysfunction increases [49] but the fact is that for those who survive, only 10% will eventually be in need for prolonged renal replacement [50]. These figures reinforce the relevance of a timely detection of impending AKI in order to apply secondary preventive measures and limit its progression, increasing the chances of recovery of our patients.

Although Crs is a parameter sensible for deciding whether a patient's kidney function remains stable, worsens, or improves, its role in the diagnosis of early renal dysfunction is more debatable, and in order to evaluate the information it provides we must understand the pathophysiology of acute renal failure and the kinetics of creatinine (be it Crs, measured CrCl or estimated by equations), and in any case, we must integrate this information in one of the stratification systems currently in use, but always acknowledging their limitations.

Serum creatinine is the key factor in the evaluation of kidney function because it is affordable, reproducible, and easy to perform, but clinicians must be aware of its limitations, among others that it is a functional marker and not a marker of injury, that changes in Crs are delayed after changes in GFR, or that fluid changes in critically ill patients can seriously difficult the capability of Crs to detect small changes in kidney function.

New trends in stratification (ADQI or AKIN) could have a significant impact in clinical practice, alerting the clinicians of the real value of small changes in Crs, and the novel biomarkers of kidney damage (in particular of tubular injury) may in the near future have a role in the diagnosis of AKI once they are included in the classification systems.

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