بسم الله الرحمن الرحيم

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صدق الله العظيم

سورة البقرة ﴿32﴾

Introduction

Over the last few decades, more than 35 different definitions have been used to define acute kidney injury (AKI). Multiple definitions for AKI have obviously led to a great disparity in the reported incidence of AKI making it difficult or even impossible to compare the various published studies focusing on AKI ***(Lopes & Jorge, 2013).***

AKI formerly known as "acute renal failure," has been traditionally described as a rapid (ranging from hours to weeks, to less than 3 months) decrease in kidney function as measured by increases in serum creatinine. The Acute Kidney Injury Network (AKIN) defined it more precisely as "An abrupt (within 48 hours) reduction in kidney function," and offered specific laboratory and clinical values to guide diagnosis ***(Bonventre &Yang, 2011).***

While recent advances in renal replacement therapy (RRT) and critical therapy have led to improved AKI-related outcomes, the incidence of AKI continues to rise, possibly explained by an aging population with multiple co morbidities and an increase in sepsis-related hospitalizations ***(Yong et al., 2011).***

AKI continues to be associated with significant mortality, hospital length of stay and economic costs, particularly in the

context of critically ill patients in the intensive care setting ***(Yong et al., 2011).***

In a report of 9210 patients, it was found that a minor change in creatinine (0.5mg/dL) from baseline was associated with a 6.5-fold increased risk of death (95% CI 5.0–8.5) ***(Chertow et al., 2005).***

Reports of the incidence of AKI in the community ranged from 2,147 to 4,085 per million populations per year in developed world. Recent hospital studies in the developed world report AKI in 3.2-9.6% of admissions, with overall in-hospital mortality around 20%, and up to 50% in ICU patients. AKI requiring renal replacement therapy occurs in 5-6% of ICU patients, with an extremely high in-hospital mortality rate of 60% ***(Li et al., 2013).***

AKI is responsible for approximately 2 million deaths annually worldwide ***(Chawla&Kimmel , 2012).***

There are chronic consequences even if the patients survive their acute illness, with a high risk of developing or exacerbating chronic kidney disease and hastened development of end stage renal disease ***(Bonventre &Yang , 2011)***

It was found that an episode of dialysis-requiring AKI was associated with a 28-fold increased risk of developing advanced

CKD, and a 2-fold increase in mortality ***(Chawla & Kimmel, 2012).***

Hypothesized mechanisms underlying CKD progression include effects of systemic and intrarenal hypertension and hyperfiltration, tubular hypertrophy, and hypertension resulting in arteriosclerosis, tubulointerstitial fibrosis, and glomerulosclerosis, ***(Chawla & Kimmel, 2012).***

There is also evidence that AKI impairs innate immunity and is associated with higher infection rates ***(Lopes, 2013).*** Although the incidence of AKI continues to rise, the optimum management of AKI remains uncertain with no uniform standard of care, as reflected by wide disparity in clinical practice. While multiple studies have addressed the issue of optimal RRT modality and/or RRT dose in critical AKI, the initiation and duration of RRT in critical AKI remains unclear ***(Yong et al., 2011).***

AKI is a recognized complication of cardiac surgery with cardiopulmonary bypass and is associated with increased morbidity and mortality (15-30%) with approximately 1% of all the affected patients requiring dialysis. Early detection of AKI would enable intervention before occurrence of irreversible injury and might minimize the morbidity and mortality. Recently developed biomarkers of AKI facilitate its earlier discovery and

help assessment of its severity and prognosis ***(Gude & Jha, 2012).***

The traditional clinical biomarkers for the detection of AKI are creatinine, urea, and urine output. All have serious limitations as early detectors of AKI. In response to these limitations, innovative technologies such as functional genomics and proteomics have facilitated the detection of several potential earlier biomarkers of AKI ***(Moore et al., 2010).***

Kidney injury molecule-1 (KIM-1), a recently discovered transmembrane tubular protein, is undetectable in normal kidneys, but it is markedly induced in renal injury including AKI and CKD ***(Huo et al., 2010).***

KIM is markedly increased in ischemic and nephrotoxic proximal tubule epithelial cell injury and was found to be elevated in cases of AKI after pediatric cardiac surgery ***(Zheng et al., 2013).***

A substantial increase in KIM-1 excretion with urine occurs a few hours after cardiosurgical procedures. Increased excretion of KIM-1 with urine is more specific for ischemic kidney injury and is practically independent of the type of chronic kidney disease or urinary tract infection ***(Lisowska-Myjak , 2010).***

AIM OF THE WORK:

This study aims to identify risk factors of AKI post cardiac surgery, early diagnosis, and predicting outcome of AKI post cardiac surgery using KIM-1as a novel biomarker of AKI.

Definitions of AKI: RIFLE and AKIN

Definitions for AKI vary widely between studies, ranging from absolute or relative increases in serum creatinine (SCr) from baseline to the requirement for RRT ***(Mehta et al., 2007).***

The lack of a uniform definition may explain the large differences in reported incidence and outcomes of AKI in the literature, and as a consequence in 2004, a consensus on the definition of acute renal failure known as the Risk-Injury-Failure-Loss-End stage renal disease (RIFLE) classification was reached by a group of international experts ***(Bellomo et al., 2004).***

The RIFLE classification is based on SCr and urine output (UO) determinants, and considers three severity classes of AKI (Risk, Injury and Failure), according to the variations in SCr and/or UO, and two outcome classes (loss of kidney function and end-stage kidney disease). **(Table 1)**

The patient should be classified using the criteria (SCr and/or UO) which lead to the worst classification (maximum RIFLE) ***(Lopes & Jorge, 2013).***

The temporal pattern of the SCr and/or UO variation is also relevant for defining AKI: the deterioration of renal function must be sudden (1–7 days) and sustained (persisting >24 h) ***(Lopes & Jorge, 2013).***

The RIFLE classification was modified by the Acute Kidney Injury Network (AKIN) to include (1) re-categorization of the original RIFLE into AKIN stage 1, 2, and 3, (2) addition of an absolute increase in creatinine ≥26μmol/L (0.3mg/dL) to stage 1 criteria, and (3) automatic classification of patients starting RRT as stage 3, regardless of serum creatinine or urine output **(*Yong et al., 2011*).**

These modifications were based on the cumulative evidence that even small increases in SCr are associated with a poor outcome, and in the extreme variability of resources and of the indications to start RRT exhibited in different countries and hospitals ***(Lassnigg et al., 2004).***

Table 1: Comparison of the old RIFLE and modified AKIN classification (*Yong et al., 2011*).

RIFLE			AKIN		
Category	**SCr/GFR**	**UO**	**Stage**	**SCr**	**UO**
Risk	Cr increase by x1.5 times or GFR decrease by ≥25%	UO ≤ 0.5mL/kg/hr for 6hrs	**Stage 1**	Cr increase by x1.5 times or ≥ 26μmol/L(0.3 mg/dL)	UO ≤ 0.5mL/kg/hr for 6hrs
Injury	Cr increase by x2 times or GFR decrease by ≥50%	UO ≤ 0.5mL/kg/hr for 12hrs	**Stage 2**	Cr increase by x2	UO ≤ 0.5mL/kg/hr for 12hrs
Failure	Cr increase by x3 times or GFR decrease by ≥75% or Cr ≥ 354μmol/L (with acute rise ≥ 44μmol/L)	UO ≤ 0.3mL/kg/hr for 24hrs or anuria for 12hrs	**Stage 3**	Cr increase by x3 or Cr ≥ 354μmol/L (with acute rise 44μmol/L) or RRT	UO ≤ 0.3mL/kg/hr for 24hrs or anuria for 12hrs
Loss (outcome)	Persistent ARF = complete loss of renal function > 4 weeks (but ≤3 months)	N/A	**Nil**		
ESRD (outcome)	Complete loss of renal function > 3 months	N/A	**Nil**		

Strengths and limitations of the RIFLE classification

Strengths of the RIFLE classification:

RIFLE has been largely validated in terms of determining the incidence of AKI and its prognostic stratification in several settings of hospitalized patients. In these studies, RIFLE facilitated the identification of a large proportion of AKI patients and there was an independent and stepwise increase in mortality as AKI severity increased; RIFLE also exhibited a good prognostic accuracy in terms of mortality ***(Lopes & Jorge, 2013).***

Furthermore, it has been shown that the RIFLE enables monitoring of the progression of AKI severity during hospitalization and RIFLE classes are strongly associated with increased lengths of stay, RRT requirement, renal function recovery and discharge from hospital to a care facility ***(Ostermann & Chang, 2007).***

Originally, the RIFLE criteria were established to standardize the definition and stratification of AKI severity. Several studies, however, have determined the ability of the RIFLE in predicting mortality using the area under the receiver operating characteristic (AUROC) curve, and some of them have inclusively compared it with other general or specific scoring systems ***(Lopes & Jorge, 2013).***

Taking into account that the RIFLE relies only on renal function it would be conceivable that the RIFLE prognostic capacity was inferior to that of other general scores (i.e. Acute Physiology and Chronic Health Evaluation, Simplified Acute Pathophysiology Score). However, RIFLE has proven to be an important tool in predicting patient outcome and, furthermore, seems to have increased the prognostic ability of those general scores usually employed in the intensive care unit (ICU) ***(Lopes & Jorge, 2013).***

Limitations of the RIFLE classification:

Despite its clinical use, the RIFLE classification has a number of important limitations:

- **First:** baseline SCr is necessary to define and classify AKI; this baseline value is frequently unknown in clinical practice. In this situation, the Acute Dialysis Quality Initiative (ADQI) work group ***(Bellomo et al., 2004)*** propose estimating the baseline SCr using the MDRD equation ***(Manjunath et al., 2001),*** assuming a baseline GFR of 75 mL/min/1.73m².

  In CKD patients, baseline SCr determined assuming a GFR of 75 mL/min/1.73 m². has a low correlation with the

real value of SCr and results in an overestimation of AKI incidence ***(Bagshaw et al., 2009)***.

- **Second:** the MDRD formula has been validated in CKD patients with stable renal function, not in AKI patients. ***(Lopes & Jorge, 2013).***

- **Third:** in several of the studies done before, only SCr was used to define and stage AKI ***(Ostermann & Chang, 2007).***In CKD patients, compared with patients with previously normal renal function, the percentage increase in SCr used to define AKI generally occurs later and, thus, defining AKI using only the SCr criteria could diminish the sensitivity of AKI diagnosis in CKD patients ***(Waikar & Bonventre, 2009).***

Moreover, determination of renal function using SCr has several other limitations as listed below: ***(Lopes& Jorge, 2013).***

I. The endogenous production and serum release of Cr are variable, and it is influenced by multiple factors, namely age, gender, diet, and muscle mass.

II. Ten to forty % of Cr elimination is performed by tubular secretion and this mechanism is amplified as the GFR diminishes, thus, overestimating renal function in AKI patients.

III. Many medications inhibit tubular secretion of Cr (i.e. trimethoprim, cimetidine), causing a temporary increase in SCr.

IV. Various factors can interfere with SCr determination (i.e. acetoacetate accumulated in diabetic ketoacidosis can interfere with the alkaline picrate method), causing a false elevation in SCr.

V. SCr is a marker of renal function, and not of renal lesion.

- **Fourth:** decrease in the UO is sensitive and frequent in AKI; however, it also has some important limitations in defining and staging AKI: ***(Hoste & Kellum, 2006).***

I. Sensitivity and specificity of UO can be significantly changed by the use of diuretics, and this issue is not specifically considered in the RIFLE classification.

II. The UO can only be determined in patients with a bladder catheter in place, which, despite being common in ICU patients, is not frequent in other hospitalized patients.

It is possible that the predictive ability of UO could be inferior to that of SCr, which can explain the difference in terms

of mortality between the same classes defined by each one of those criteria, observed in studies that utilized both criteria to define and classify AKI .The capacity of the RIFLE (using both criteria) to predict mortality can be more stable than the ability of this classification employing only SCr ***(Cruz et al., 2007)***.

- **Fifth:** the etiology of AKI and the requirement for RRT are not considered in the RIFLE classification. In two studies that evaluated ICU patients with AKI requiring continuous RRT, the RIFLE classification showed less acuity in predicting mortality. One possible explanation for this phenomenon is that in both studies, the clinical severity of patients was so high that it could not allow RIFLE to discriminate mortality according to AKI severity (i.e. between the three classes) ***(Lopes & Jorge, 2013).***

- **Finally**, the RIFLE classification does not provide any information regarding the origin of the renal lesion (i.e.cellular or subcellular levels), as opposed to several biomarkers of AKI recently identified and studied ***(Lopes & Jorge, 2013).***

The AKIN CLASSIFICATION

The AKIN classification was published in March 2007 in Critical Care ***(Mehta et al., 2007)***, and it is a later version of the

RIFLE classification with some modifications: ***(Lopes & Jorge, 2013).***

- The diagnosis of AKI is only considered after achieving an adequate status of hydration and after excluding urinary obstruction.
- The AKIN classification only relies on SCr and not on GFR changes.
- Baseline SCr is not necessary in the AKIN classification.
- It requires at least two values of SCr obtained within a period of 48 h.
- The two outcome classes (loss of kidney function and end-stage kidney disease) were removed from the classification.

It has been shown that the AKIN classification, like the RIFLE classification, allowed the identification and stratification of AKI in a large proportion of hospitalized patients and was independently associated with the outcome ***(Barrantes et al., 2008).***

The AKIN classification could theoretically improve the RIFLE criteria sensitivity and specificity, although the advantages