



# The importance of early detecting high-risk patients with acute kidney injury requiring continuous kidney replacement therapy

Antonietta Gigante<sup>1</sup> · Francesca Di Mario<sup>2</sup> · Stefania Basili<sup>1</sup>

Received: 11 October 2022 / Accepted: 12 October 2022

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Acute kidney injury (AKI), defined as an abrupt and rapid decline in kidney function, represents a frequent and harmful complication in hospitalized patients, especially if critically ill [1]. Indeed, this rapidly evolving clinical condition, particularly is the most severe forms requiring kidney replacement therapy (KRT), has been associated with increased morbidity and mortality risk, increased risk of hospital readmission and subsequent development of chronic kidney disease (CKD) [2]. The reported incidence of AKI among different studies mainly varies according to the selected population and the clinical setting analyzed. AKI occurs in 20–200 per million population in the global community, in 7–18% of hospitalized patients and up to 50% of patients in the Intensive Care Unit (ICU) [3]. Among patients admitted in the ICU, the incidence of AKI is growing over time, with a need of KRT reported in 10–15% of patients and a related further increase of in-hospital mortality, reaching up to 80%. In this peculiar clinical scenario, AKI often occurs in the context of sepsis and multiorgan dysfunction, particularly in old and high-risk comorbid patients and after exposure to nephrotoxic agents [4]. Despite the pathophysiology of sepsis-associated AKI has not yet been fully clarified, it seems that kidney hypoperfusion together with an abnormal systemic inflammatory activation promotes the complex of maladaptive tissue responses, with microvascular and endothelial alterations, cells damage and dysfunction. Sepsis-induced hypoperfusion is usually revealed by acute organ failure and increase of serum lactate, secondary to insufficient oxygen delivery and exacerbated by reduced hepatic clearance [5]. Among different available dialysis modalities, continuous KRT (CKRT) is widely suggested

as the preferred extracorporeal treatment for critically ill patients with AKI, especially in those with hemodynamic instability [1]. However, even though the start of KRT is the most common intervention for AKI patients, the mortality rate remains remarkably high and often no specific treatment can reverse the progression.

Why is it important to understand the onset and the severity of AKI?

In this issue of Internal and Emergency Medicine, Zhong and colleagues presented a retrospective analysis derived from multicentric electronic-based registry, the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database, with data obtained in America between 2008 and 2019 and between July 2019 to March 2022 in Huzhou Central Hospital (China), including all adult patients with AKI undergone CKRT. The authors analyzed the association between albumin corrected anion gap (ACAG) and ICU mortality in a final cohort of 452 and 256 AKI patients requiring CKRT from America and China, respectively. The authors found that a high ACAG level ( $> 20$  mmol/L) at the initiation of CKRT was significantly associated with ICU all-cause mortality [6]. These patients had a higher ICU all-cause mortality rate (49.14% vs 21.31%,  $\chi^2 = 43.163$ ;  $P < 0.001$ ), a lower ICU cumulative survival rate (log-rank test,  $\chi^2 = 13.620$ ,  $\chi^2 = 12.460$ , both  $P < 0.001$ ) and the high ACAG at CKRT initiation was found to be an independent predictor for ICU all-cause mortality. Interestingly, these high-risk AKI patients represent those with the most severe clinical illness, as shown by the most serious alteration of acid–base balance and severe degrees of hypoalbuminemia.

Metabolic acidosis is one of the most common acid–base disorders in critically ill, often representing not only a possible complication of AKI itself, but also an independent associated life-threatening condition. The serum anion gap (AG), calculated as the difference between sodium and the sum of chloride plus bicarbonate, is commonly used to classify metabolic acidosis into elevated and normal AG metabolic acidosis. Lactic acidosis,

✉ Stefania Basili  
Stefania.basili@uniroma1.it

<sup>1</sup> Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy

<sup>2</sup> Department of Medicine and Surgery, Nephrology Unit, University of Parma, Parma, Italy

characterized by an increase of serum AG, is the most frequent form of metabolic acidosis in ICU patients [7], often occurring in course of sepsis and associated with adverse short and long-term outcomes [8]. In this regard, the occurrence of moderate/severe forms of AKI generally exacerbates the onset and progression of metabolic acidosis. Indeed, the abrupt decrease of glomerular filtration rate, particularly in the oliguric presentations of AKI, leads to the accumulation of multiple organic and inorganic acids, such as lactic, sulfuric, and phosphoric acid with a further worsening of acid base homeostasis. Moreover, ICU patients are at high risk of hypoalbuminemia, because of the impaired redistribution between the intravascular and extravascular compartments and the altered rates of synthesis and degradation of the protein [9]. As confirmed by Zhong et al. [6], the reduction of serum albumin concentrations has been widely reported as a marker of poor prognosis in critically ill, also before and after the initiation of CKRT [10]. Given the net negative charge of the albumin molecules, its serum concentration significantly affects the calculation of serum AG and the formula is usually corrected as:  $ACAG = \text{serum AG} + (2.5 \times [4.5 - \text{actual serum albumin}])$  [11]. Thus, it is interesting to consider how this clinical parameter, which has already been associated with poor outcomes in critically ill patients [12], may be a useful and quickly available tool for clinicians to identify patients with the most severe ongoing processes, also in this specific clinical context. Indeed, in patients with AKI requiring CKRT, the high ACAG may be intended as an expression of the contemporary presence of the most severe forms of AKI, metabolic acidosis, and hypoalbuminemia.

Until now, little knowledge about the risk factors for AKI delays and/or impairs good outcome in AKI patients. Indeed, as Zhong et al. underlined in their discussion [6], they showed for the first-time data about the relationship between ACAG and mortality in patients undergoing CKRT for AKI. However, this interesting study suffers from some limitations.

Unfortunately, the retrospective observational nature of the study, unspecified and unavailable underlying causes of AKI in the MIMIC-IV database and the lack of comparison between oliguric and non-oliguric patients limits the generalizability of the results. In addition, no specific data were present in patients enrolled in China during COVID-19 pandemic. Finally, it would be interesting to analyze the role of ACAG as independent mortality risk factor also after splitting AKI patients according to the presence of sepsis.

Although the significant contribution was offered by the authors in early identifying the potential mortality risk factors, more studies are needed to elucidate and confirm the obtained results. Recently, recommendations for awareness, recognition, and management of AKI have been proposed by

the American Society of Nephrology with a new initiative, AKI!Now [13], to improve the prevention and treatment of AKI.

In conclusion, the association between higher ACAG level at the initiation of CKRT and ICU all-cause mortality reported by Zhong et al. [6] sheds even more light on the early indicators of adverse outcomes in critically ill AKI patients. The early recognition and management of AKI in different setting as proposed in AKI!Now by a multidisciplinary collaboration may help clinicians to early identify and correctly stratify critically ill patients with AKI.

**Funding** This work did not receive specific funding.

## Declarations

**Conflict of interest** The authors declare that she has no conflict of interest.

**Human and animal rights statement** This research did not involve humans and/or animals.

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