Commentary

The two sides of creatinine: both as bad as each other?

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Acute and chronic kidney diseases are major public health problems, and even relatively small rises in serum creatinine have been found to be associated with an increased risk of morbidity and mortality (1-4). In contrast, the relevance of serum creatinine levels below the normal range is appreciated far less in clinical practice.

A recent paper published in Critical Care Medicine alluded to the fact that a low serum creatinine is an important risk factor for poor outcome (5). Using the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation database, Udy *et al*. retrospectively analyzed the data of >1 million adult patients admitted to ICU between 2000–2013 and evaluated the association between peak serum creatinine concentration in the first 24 hours of ICU admission and hospital mortality (5). Patients on chronic dialysis, re-admissions, and renal transplant recipients were excluded. The key findings were:

- A peak serum creatinine concentration <60 µmol/L in the first 24 hours after ICU admission was independently associated with an increased risk of mortality;
- In patients with a serum creatinine <30 µmol/L (which accounted for 0.6% of the total cohort), the adjusted odds of dying in hospital were over 2-fold higher than the reference range (70–79 µmol/L), and exceeded the risk implied with a serum creatinine >180 µmol/L.

These findings were consistent across medical, surgical, trauma and infection-related admission types and independent of gender, age, and admission year. Weight and height data to calculate the body mass index (BMI) were available for 9% of patients, and analysis of this cohort showed that the relationship between low serum creatinine and hospital mortality was consistent across all BMI categories. Although neither the aetiology of low creatinine levels nor the causes of death were available, these results may have very important repercussions for clinical practice.

Firstly, the paper serves as a reminder that serum creatinine is more than a marker of renal function. Creatinine is a metabolite of creatine and as such a by-product of muscle metabolism. Creatine is initially synthesized from the amino acids glycine and arginine in liver and kidneys and then transported to the skeletal muscle cells. A proportion of creatine also stems from dietary meat intake. Following conversion to phosphocreatine, it serves as a rapidly mobilizable reserve of high-energy phosphates in muscle. The total amount of creatinine generated from creatine is determined by muscle function, meat intake and *de novo* generation of creatine. In health, creatinine is produced at a constant rate, but rapid, substantial and sustained falls in production have been demonstrated during critical illness. Therefore, the concentration of creatinine measured in the serum represents the balance between creatinine production and creatinine clearance.

Because creatinine is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney (although tubular secretion does occur), it serves as a marker of renal function in clinical practice. However, serum creatinine has important limitations: it can take 24–36 hours to rise after a definite renal insult, it may overestimate renal function as a result of secretion in the proximal tubule and it can increase following administration of medications that inhibit tubular secretion despite no change in renal function. In addition, creatinine is distributed in total body water and measured as a concentration and may, therefore,

be affected by variations in volume status.

The causes of a low serum creatinine concentration are generally well known and include reduced muscle bulk, liver disease, significant fluid overload and poor nutritional status but also augmented renal clearance as seen in pregnancy. Although previous studies have described the association of increased mortality with lower creatinine levels in patients on chronic dialysis, in those commencing renal support in the ICU and in older patients (6-9), the implications of a low serum creatinine in critically ill patients are less well known. The study by Udy *et al*. with data of >1 million patients is undoubtedly the largest in the literature. Cartin-Ceba *et al*. previously performed a retrospective analysis of 11,291 critically ill patients admitted to three ICUs over a 47-month period and like Udy *et al*. showed that both a high and low serum creatinine were risk factors for poor outcome (10). A low baseline serum creatinine was independently associated with increased hospital mortality in a concentration-dependent fashion. Adjusted stay in ICU was also longer in this cohort.

The question is what mechanisms could underlie these observations. The studies by Udy *et al*. and Cartin-Ceba *et al*. do not provide any definitive mechanistic insights (5,10). Without detailed data about the underlying causes, it is certainly possible that a low serum creatinine was simply an indicator of underlying chronic liver disease, reduced muscle mass, and poor nutritional state. Both studies focused on creatinine concentrations in the first 24 hours of ICU admission. One potential explanation given by the authors is that the results may have been confounded by chronic fluid overload or excessive fluid administration pre-ICU.

It is likely that the relationship between low serum creatinine levels and mortality is more complex than assumed at first glance. For instance, serum creatinine can overestimate renal function, and a proportion of patients with a serum creatinine level below the normal range may have had significantly impaired renal function. Udy *et al*. also showed that the adjusted hospital mortality of patients with a serum creatinine <50 μmol/L in the first 24 hours of admission increased with rising admission albumin levels and was highest in those with a plasma albumin ≥45 g/L (5). The authors argue that a low serum creatinine in the setting of adequate albumin levels may imply marked physical deconditioning or muscle wasting (5,11). Although this is possible, it remains unproven. Using a large database, the authors obviously were unable to provide data on detailed muscle function. Instead, they analyzed the impact of serum creatinine in different BMI groups and showed that the association between low serum creatinine and mortality was independent of BMI. However, BMI is a poor marker of muscle mass (11).

What are the practical implications of these results? With data of >1 million ICU patients from an ethnically diverse population, the study by Udy *et al*. has external validity. Clearly, further studies are needed, especially to provide mechanistic insights that could lead to potential therapeutic interventions. In the meantime, the presence of a low baseline serum creatinine level should alert clinicians to the high-risk potential of individual patients. Interestingly, the APACHE II score includes a low creatinine value as a risk factor and assigns two points to the severity score if the most extreme serum creatinine level during the first 24 hours is <0.6 mg/dL (53 μmol/L). However, other risk prediction scores like the Simplified Acute Physiology Score II and Sequential Organ Failure Assessment (SOFA) score do not take into account low creatinine levels. We already know that high creatinine levels are associated with poor outcomes, and now we know that low levels may be just as bad whatever the exact cause.

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Footnote

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