EDITORIAL

Will my patient survive? Look for creatinine in the urine!

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The ability to risk stratify critically ill patients and target intensive care unit resources to those who benefit the most is appealing and has resulted in a growing interest in the search for novel risk factors [1, 2]. Performance status has gained significant attention recently [3, 4]. In the same line, poor nutritional status, often judged by a low body mass index (BMI), is a prominent factor associated with poor short- and long-term outcomes [5, 6]. Several assessments of nutritional status and muscle mass have been evaluated and validated, such as albumin and prealbumin levels, anthropometric measurements, skeletal muscle mass or fat infiltration measured by imaging studies, various scores or multicomponent scales, fat-free mass or the sarcopenia index [7–9]. Some of these parameters have been reported to be associated with outcome in ICU patients [7–9].

In the steady state, creatinine is produced by skeletal muscle cells and excreted in the urine at a relatively constant rate. Timed measurement of urinary creatinine excretion (UCE) could be, therefore, a valid reflection of muscle mass and has been associated with survival in patients with coronary artery disease [10–12]. In an article recently published in *Intensive Care Medicine*, Hessels et al. reported the performance of 24 h UCE in the prediction of short- and long-term outcome in ICU patients [13]. This retrospective cohort study included patients ≥ 15 years old, admitted to a single center between 2002 and 2015, and in whom 24 h urinary creatinine was measured during the first 3 days of admission. The study outcomes included the hospital and 5-year mortality rates. Among the 37 283 patients admitted

during the study period, 6151 met the eligibility criteria. UCE in 24 h, before and after adjustment for confounders [i.e., age, BMI, estimated glomerular filtration rate (eGFR), illness severity and trauma] and stratified for gender, was found to be an independent predictor of outcome (i.e., low urinary creatinine excretion was associated with higher short- and long-term mortality). Several subgroups and sensitivity analyses performed on patients according to age, gender, BMI, underlying acute kidney injury, and trauma as a reason for ICU admission or presence of rhabdomyolysis, confirmed the main findings.

The authors have to be congratulated for this interesting study. It confirms that a simple and non-expensive measurement of urine creatinine excretion, as a surrogate of muscle mass, provides important prognostic information and may add to the existing prognostic scores.

There are also several limitations to this study which need to be underlined. First, creatinine excretion only reflects production (muscle mass) when GFR is in steady state. This assumption is probably not valid in ICU patients during the first 3 days. In addition, the authors used eGFR by the CKF-EPI equation to adjust for kidney function, which, in view of the delay of serum creatinine in detecting changes in GFR and the variability in serum creatinine due to factors unrelated to kidney function (such as fluid overload, decreased creatinine production related to low muscle mass or sepsis), is an imperfect reflection of true GFR [14, 15]. Hence, the assumption that urinary creatinine excretion solely reflects muscle creatinine production is not verifiable. More importantly, the reported finding that urinary creatinine excretion was associated with the clinical outcome could be related to the influence of underlying AKI which could lower urinary creatinine excretion per se. Lastly, serum creatinine is not sensitive enough to detect small day-by-day changes in GFR. The authors partially addressed this limitation by excluding patients with stage 3 AKI and

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by using the median UCE over the first 3 days for each patient. In addition, mean UCE was similar on day 1 and 3, and the results were similar with estimated UCE accounting for the change in serum creatinine. The effect was observed in patients with and without AKI, and the adjustment for kidney function yielded similar results with the eGFR or measured creatinine clearance (a better reflection of true GFR).

Second, the findings are not externally validated, and; hence, the results may not be generalizable. The vast majority of patients admitted during the study period were excluded for ICU stay less than 24 h or missing creatinine excretion. This study was performed in a single center, and factors such as overall BMI or overall nutritional status may reflect factors specific to the study center [16]. Ethnicity, another determinant of muscle mass, was not reported. The adjustment also does not account for comorbidities and frailty. Although sarcopenia, frailty, and comorbidities are partly correlated, these three preexisting conditions are distinct events, and each of them may be associated with outcome [17].

And finally, even though this study gives reliable clues suggesting that creatinine excretion might be independently associated with outcome, its relevance to the clinical practice is debatable. Optimal nutrition strategies in ICU remain controversial, the influence of early mobilization is likely to extend across nutritional strata, and significance of the findings at an individual patient versus population level is uncertain.

Despite these limitations, the study by Hessels et al. certainly raises several hypotheses requiring additional

studies. Validation of these findings in larger multicenter studies, ideally across several countries and continents, may increase its generalizability. These subsequent studies should ideally include an adequate adjustment for real-time changes in renal function to better discriminate the role of GFR changes from the role of sarcopenia. Ideally, multiple techniques to assess nutritional status/sarcopenia should be compared, with a clear description of the test diagnostic or prognostic performance, including the rate of misclassification and predictive model calibration. Such studies will also help in delineating the ideal measure of nutritional status at the bedside while taking into account confounders both at patient and population levels (Fig. 1).

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