Editorial

Renal biomarkers for the initiation of renal replacement therapy—is this the future?

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Acute kidney injury (AKI) is a common complication in critically ill patients (1) affecting approximately 57.3% of all patients in the intensive care unit (ICU) and is associated with a high morbidity and mortality (2). Therapeutic options are still restricted to the use of renal replacement therapy (RRT). According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, this supportive option should be initiated immediately in patients with life-threatening fluid accumulation or greater disequilibrium in homeostasis (3). However, most of the critically ill patients with AKI do not have an absolute indication for RRT, they rather have a progressive decline of kidney function and here the key question is when RRT should be implemented in in these patients. Initiating RRT early may provide benefits through early elimination of uremic toxins, achieving volume and solute control, and correcting electrolyte imbalances at an early stage of the disease. The disadvantage of beginning early is that patients with AKI might spontaneously recover without requiring RRT (4). In this case, an early approach would mean an unnecessary therapy escalation exposing patients to unnecessary treatment related complications. The main question is how can we identify patients who will have a disease progression and definitely require RRT. Exactly these patients might benefit from early initiation of RRT.

Several years ago, researchers started looking for an ideal biomarker that can early detect AKI and predict the need for RRT (5-7). However, most of these new biomarkers are not available as point-of care test and are therefore not suitable for clinical use. Neutrophil gelatinase associated lipocalin (NGAL), one of the biomarkers available as point-of care test, has been shown to be a good predictor for non-recovery of AKI and for the need of RRT in patients with severe AKI (8,9). According to the renal angina concept, novel biomarkers should be measured in patients with a certain clinical risk profile, including different co-morbidities and certain clinical conditions (10), since measuring biomarkers in every patient would reduce the specificity of these tests.

Several, prospective studies have been performed over the last few years to approach the question of optimal timing of RRT (11-14). Three of these used a biomarker based approach.

The feasibility trial by Srisawat *et al.* consists of two parts: a triage and an interventional part (14). Adult patients diagnosed with AKI by Risk, Injury, Failure, Loss, End stage renal disease (RIFLE) criteria were included (15). In the triage part, patients were selected according to the level of pNGAL. Only patients with levels ≥400 ng/mL [according to (9)] were randomized in the interventional part to receive either early (within 12 h after randomization) or late initiation of RRT (when one of the following complications occurred: refractory severe acidosis, severe peripheral edema, no response to diuretics, refractory hyperkalemia, anuria or oliguria, or BUN >60 mg/dL). Of the 40 patients included in the interventional part, 10/20 (50%) of the early

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and 9/20 (45%) of the standard group died at 28 days after randomization (P=0.72).

In the ELAIN trial, patients were eligible if they had at least a moderate AKI (KDIGO stage 2: ≥2-fold increase in serum creatinine as compared to baseline and/or urine output <0.5 mL/kg/h for ≥12 h), were critically ill (severe sepsis/septic shock, use of vasopressors, refractory fluid overload or progression of non-renal organ dysfunction (non-renal SOFA score >2), and pNGAL was above 150 ng/mL [according to (8)] (11). These criteria were selected to minimize the inclusion of those patients who have a high likelihood of spontaneous recovery, as the aforementioned criteria are known to be associated with a progressive decline in renal function (16-18). Patients were assigned to receive either early (at KDIGO stage 2) or delayed (after reaching KDIGO stage 3) RRT. Of the 231 patients enrolled, mortality after 90 days was 39.9% and 54.7% in the early and late group, respectively (P=0.03).

In the STARRT-AKI pilot trial, the inclusion criteria consisted of evidence of kidney dysfunction [serum creatinine ≥100 µmol/L (female) or ≥130 µmol/L (male)], and all of the additional criteria [(I) presence of severe AKI (defined as 2-fold increase in serum creatinine from baseline, urine output <6 mL/kg ≤12 h or whole blood NGAL ≥400 ng/mL), (II) absence of urgent indications for RRT, and (III) low likelihood of volume-responsive AKI] (13). Patients were randomized to the accelerated (initiation of RRT within 12 h of the patient fulfilling eligibility) or the standard arm (initiation when serum potassium >6 mmol/L, serum bicarbonate <10 mmol/L or PaO_2/FiO_2 <200 with infiltrates compatible with pulmonary edema). The study was a feasibility trial and not powered to detect a mortality difference between the two groups. Therefore, it is not surprising that the difference in mortality at 90 days was not significant between the two groups (38% in the accelerated *vs.* 37% in the standard group, P=0.92).

When analyzing outcome differences, adequately powered randomized-controlled trials are needed to detect a difference in the two groups. The study by Srisawat *et al.*, who included only 40 patients, was underpowered and could therefore not detect a mortality difference. However, the most important point that needs to be highlighted is the trial design. When using biomarkers for interventional trials, one has to make sure that the biomarkers are properly used. For instance, troponin I is only used in patients with acute chest pain to detect an acute coronary syndrome because in other patient cohorts (e.g., sepsis) the specificity diminishes and false positive values occur (19). The same approach is required for the setting of AKI. NGAL as marker for the need of RRT, should only be used in critically ill patients with AKI and risk factors as well as a certain clinical condition. In the trial by Srisawat *et al.*, NGAL was measured in all adult patients with signs of kidney dysfunction according to the RIFLE criteria. That means that also patients with RIFLE-R and NGAL ≥400 ng/mL were potentially eligible for inclusion. However, these patients do not show any signs of a progressive decline in renal function assuming that the likelihood for needing RRT was low. High NGAL levels could be explained by other factors resulting in NGAL elevations such as sepsis and myocardial dysfunction (20-22). In a recently performed meta-analysis evaluating different biomarkers for predicting the need of RRT, the authors concluded that although heterogeneity was very high and several studies showed good predictive performance for NGAL, they could not confirm that NGAL was superior to other markers in predicting RRT (23).

Unfortunately, the paper by Srisawat *et al.* does not provide any additional information about RIFLE stage at RRT initiation and RRT data of the randomized patients. It would be interesting to know in how many patients RRT was initiated at RIFLE-R, since most of the patients were not on vasopressors and the SOFA score was relatively low in both groups, assuming that patients were not severely ill. Moreover, continuous RRT was used, but without the use of any anticoagulation. However, the KDIGO guidelines recommend the use of an anticoagulation strategy in patients without an increased bleeding risk or impaired anticoagulation to avoid filter clotting and enable an effective therapeutic performance (3). Since there is no data on the effectiveness of RRT available, it remains unknown whether the treatment in both groups, especially in the early group in which all patients were treated with RRT, was effective.

Even though the results may not be useful to permit a reliable answer to the question about optimal timing of RRT, it shows that patients with higher pNGAL values ≥400 ng/mL have a significant worse outcome (28-day mortality, ICU free days, and ventilator free days) as compared to the low pNGAL group, irrespective of the underlying cause. Further, large randomized-controlled, multicenter trials analyzing a biomarker approach for the optimal timing of RRT are urgently needed. There are two trials upcoming, the IDEAL-ICU trial (24) where recruitment was already stopped and the STARRT-AKI

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trial (25), hopefully bringing new insights to this long-lasting unresolved problem. However, both are pragmatic trials and unfortunately, they do not use an individualized approach by using biomarkers.

The current biomarkers, including NGAL, may not be ideal markers to guide decision-making process for initiating RRT in critically ill patients as they all exhibit certain limitations, but, as in other fields of medicine (e.g., oncology), we need new biomarkers to individualize the therapy.

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Footnote

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