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Measurement of AKI biomarkers in the ICU: still striving for appropriate clinical indications

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Compared to other organ systems, diagnostic criteria for acute kidney injury (AKI) using serum creatinine and urine output are well established [1]. Despite this, there is little evidence to support any specific interventions to improve outcomes after AKI diagnosis. Delayed and imprecise identification of early AKI by conventional diagnostic criteria may explain these failures. Consequently, numerous plasma and urinary biomarkers for renal injury or renal dysfunction have been the subject of intense study for well over 10 years with the aim of earlier and more precise recognition of incipient AKI [2]. Despite this activity, only a few AKI biomarkers have been commercially marketed for clinical use. The most well-known plasma or urinary neutrophil gelatinase-associated lipocalin (NGAL) [3] has been available for

over 5 years, but has failed to demonstrate clear clinical utility [4–6] or gain widespread uptake in the ICU. More recently, a promising combination of two cell cycle arrest markers (TIMP-2 and IGFBP-7) [7, 8] has been licenced for the early detection of AKI; however, it is as yet uncertain what clinical impact this assay will have. Importantly, while proving a statistical association with the development of AKI is relatively easy, demonstrating that a biomarker measurement meaningfully alters practice, let alone clinical outcomes, is much trickier [9]. AKI complicating critical illness is highly heterogeneous in severity, aetiology and timing [10], all of which may variably affect biomarker results. In turn, candidate biomarkers are judged by their ability to predict later AKI defined by serum creatinine—the imperfect diagnostic test that we are trying to improve. Thus, defining the appropriate timing and frequency of biomarker measurement and interpreting these results in individual patients are extremely difficult. As a consequence there are, as yet, no positive prospective randomised studies of biomarker-driven interventions for AKI, nor have any novel biomarkers been considered ready for incorporation into AKI diagnostic systems [11]. Importantly, one of the key features of successful clinical introduction of biomarkers for other clinical conditions (such as venous thromboembolism or coronary thrombosis) has been to restrict measurement to patients with a reasonable pre-test probability of the specific disease. Thus, in order to establish a role for AKI biomarkers we may need to better identify clinical indications for their measurement.

In their recent article in *Intensive Care Medicine* [6], Legrand and colleagues report on measurement of novel and conventional makers of tubular injury, tubular function, glomerular filtration and systemic neurohormonal stress responses in a group of mixed critically ill patients selected by the presence of >6 h of oliguria (urine output <0.5 ml/kg/h). Persistence or development of creatinine-defined AKI over 7 days occurred in 43 of 111

patients; importantly, this was associated with increased mortality, underlining the importance of prognostication in this group. Several biomarkers showed a significant association with the biochemical renal outcome; however, none were statistically superior to the absolute serum creatinine value at the time of biomarker assessment. In a further analysis the authors considered a risk prediction model including creatinine, age, illness severity and sepsis and assessed whether individual biomarkers could significantly improve this model. Only plasma NGAL significantly improved prediction on receiver-operating characteristic (ROC) analysis although other biomarkers appeared to improve the model when assessed using the continuous Net Reclassification Index (NRI) [12]. One should be wary of overinterpreting analyses of combinations of variables in small data sets, however. Multiple comparisons of biomarkers in a small population raise the likelihood of chance associations, while as a marker of positive combinations the continuous NRI can be over-sensitive and give a misleading impression of practical improvement in model prediction [13]. Overall, as the authors acknowledge, their study failed to demonstrate that the panel of biomarkers provided meaningful prognostic information in critically ill patients with oliguria over and above serum creatinine at the time of oliguria.

Despite these apparent negative conclusions, several points can be learnt from the approach taken. First, the consideration of a subset of patients defined by oliguria has much to commend it. Oliguria is a sensitive, but non-specific predictor of biochemical AKI [14] that often presents the clinician with a therapeutic dilemma between, on one hand, continued resuscitation to reverse incipient organ dysfunction and, on the other, avoidance of fluid overload in the face of impaired urinary excretion in AKI. Oliguria-indicated biomarker measurement could thus constitute a consistent time point for biomarker assessment (aiding between-patient comparison) at a point in the clinical course when knowledge of the renal prognosis could provide useful therapeutic guidance. Second, the assessment of the AKI biomarkers against clinical and conventional biochemical information is appropriate as it is difficult to justify a novel marker that fails to improve on available diagnostic information.

Combining biomarkers together or with other clinical data is an attractive way to refine diagnostic ability and assess true biomarker utility. Unfortunately the more predictive variables considered, the more data are required to develop and validate reliable statistical models. Furthermore, refining the prediction of models beyond a level of prediction associated with a good biomarker in isolation is limited by the non-availability of an adequate gold standard for AKI diagnosis. This makes the predictive

Fig. 1 Effect of an imperfect “gold standard” (sensitivity 0.9, specificity 0.8) on the assessment of a biomarker perfectly predictive of true underlying AKI (sensitivity 1, specificity 1) at different population prevalences of disease (assuming conditional independence of the biomarker and gold-standard test). Identification of a population with reasonable pre-test disease prevalence is essential to biomarker assessment when the gold standard is imperfect. However, even then, an upper limit of the apparent ROC-AUC to predict the imperfect gold standard may preclude detection of increased predictive ability for underlying AKI from individual biomarkers or from combining biomarkers and clinical data in risk-prediction models. Adapted from [15]

performance required to confidently predict AKI in individuals difficult to achieve [15]. Effectively, beyond a certain level, the diagnostic ability of a biomarker or model will be limited not by its own relationship with the underlying AKI, but by the performance of the gold standard, so that improvement of diagnostic performance beyond a certain level is impossible (Fig. 1). Importantly, with an imperfect gold standard an adequate prevalence of disease in the population is essential to demonstrate even reasonable diagnostic performance, emphasising the importance of some form of patient selection prior to biomarker testing (Fig. 1).

Future efforts in this field should probably concentrate on assessing the best current biomarkers in well-defined groups with high pre-test probability for AKI and in contexts where biomarkers can alter clinical decision-making; early oliguria might be such a setting. Finally, given the intrinsic limitation of conventional AKI diagnosis as a gold standard, prospective studies comparing outcomes from biomarker-directed care against conventional clinical and biochemical-directed intervention may be the only way to truly establish the clinical value of novel diagnostics.

Conflicts of interest Dr Prowle has no relevant conflicts of interest to declare.

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