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Critical research on biomarkers: what's new?

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Introduction

A biomarker may be defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". When assessing the need for a biomarker in clinical practice, a crucial aspect of its value is whether it might improve patient management. In this regard, biomarkers may provide important information regarding the presence, severity, and prognosis of specific disease processes, and may also provide important information regarding management options; such information may not be clinically obvious without biomarker measurement. As such, biomarkers are increasingly of interest for use in critical care medicine, for the early recognition of organ injury and to better understand the pathological processes leading to organ failure. Because of both the high prevalence and the poor prognosis associated with acute kidney injury (AKI) and with cardiovascular failure in the critically ill, this paper describes new findings in the critical care application of renal and cardiovascular biomarkers (Table 1).

Biomarkers of renal injury and renal dysfunction

Although very promising results were reported from initial clinical studies, later studies showed more conflicting results in the capability of biomarkers to detect and predict the occurrence of AKI. In contrast to the discovery of troponin in patients with acute myocardial infarction, the quest for a biomarker of acute tissue necrosis in the kidney remains a modestly unfulfilled exercise. Neutrophil gelatinase associated lipocalin (NGAL) is one of most studied biomarkers in this regard. Despite data suggesting that NGAL may predict the onset of AKI after cardiopulmonary bypass, diagnostic accuracy for loss of renal function is modest in septic patients and NGAL has been associated with poor prognosis in this setting [1]. Valette et al. [2] recently reported that plasma NGAL did not differ in patients with and without AKI after contrast media injection in critically ill patients. However, plasma NGAL had rather good accuracy in predicting the need for renal replacement therapy in patients with AKI on admission (area under receiver-operating characteristic curve, 0.90). In another study, although commercially available NGAL tests performed equally well in detecting AKI, discrepancies were present between their results in those with the most severe forms of AKI [3]. Also, differences exist between urine and blood NGAL levels,

Table 1 Summary of recent findings with respect to renal and cardiac biomarkers in critically ill patients

Biomarkers	Potential interest	Recent findings	Limits
Renal biomarkers			
Cystatin C	Increase in plasma cystatin C level reflects a decrease of glomerular filtration rate. Detection of urine cystatin C is a biomarker of tubular injury	Urine cystatin C increases the day of AKI, modest increase of plasma levels the day before	Poorly predictive of AKI in ICU patients
NGAL L-FABP NAG KIM-1 IL-18	Reflect renal tubular injury	Wide variations for prediction of AKI with respect to mechanism of AKI. Increase of many cases of pre-renal AKI	Large gray zone, clinical implications unclear with increase serum or urine levels in patients with preserved renal function
Serum creatinine	Marker of glomerular filtration rate (GFR), renal dysfunction	Increase serum creatinine associated with mortality	Risk of overestimating GFR (hemodilution, decrease production); delay in detecting drop of GFR
Urine sodium and urea	Marker of tubular function	Not predictive of rapid recovery from AKI	Under influence or renal and systemic hemodynamics and neuro-hormonal status
Cardiac biomarkers			
BNP–Nt-pro-BNP	Marker of heart failure and cardiac congestion	Prediction of respiratory failure after extubation. Guide diuretics treatment for weaning procedure	Large gray zone, under influence of renal function
Troponin (Tns), high-sensitivity cTns	Marker of myocardial injury	Prediction of mortality in septic patients. Rapid absolute changes suggest coronary origin in acute chest pain	Non-specific of coronary origin, clinical implications unclear in ICU patients
sST-2	Marker of cardiac mechanical stress	Associated with poor prognosis in cardiovascular failure	Non-specific for the etiology, clinical implications unclear
Chromogranin A	Marker of catecholamine release and β-adrenergic stimulation	Prediction of mortality and circulatory failure, especially in septic patients	Non-specific, clinical implication unclear

Owing to space limitations, the list of biomarkers and results of findings in not exhaustive

NGAL neutrophil gelatinase associated lipocalin, *AKI* acute kidney injury, *BNP* brain natriuretic peptide, *KIM-1* kidney injury molecule, *NAG* *N*-acetyl-β-D-glucosaminidase, *L-FABP* liver-type fatty acid binding protein, *IL-18* interleukin-18, *sST2* soluble sST2

suggesting the recognition of different isoforms. Mårtensson et al. [4] measured NGAL using two different ELISAs in 44 critically ill patients detecting a monomeric HNL/NGAL that is believed to be more specific for the kidney epithelium and a dimeric HNL/NGAL form secreted by neutrophils. Other biomarkers of renal injury include urine kidney injury molecule (KIM)-1, *N*-acetyl-β-D-glucosaminidase (NAG), liver-type fatty acid binding protein (L-FABP), alkaline phosphatase, and interleukin-18, among others. These appear promising but are less well studied [5].

Beyond biomarkers of renal injury, biomarkers that sensitively assess renal function may be of use for predicting the onset of AKI. Among these are cystatin C (CyC) and β trace protein (BTP). The advantage of both markers is their ability to identify renal dysfunction in milder states of reduced glomerular filtration, when compared to serum creatinine. As impaired baseline renal function is thought to be a risk factor for AKI, this more refined ability to detect mild renal dysfunction may be important. CyC is a 13-kDa protein produced at a constant rate by all nucleated cells. It is filtered and then catabolized by tubular cells. In a recent multicenter cohort of 151 patients, the area under the curve (AUC) of plasma CyC was 0.72 for the prediction of AKI 2 days before its occurrence but was (surprisingly) poor the day before onset. Although urine CyC increased on the day of AKI, it could not predict it [6]. BTP has been recently investigated in this setting but additional studies are required to explore potential advantages oven serum creatinine or CyC [7].

Clearly, more information and experience in this area are important as our understanding evolves regarding the pathophysiology of AKI. For example, although loss of function appears to be associated with no or modest rises of injury biomarkers in patients with heart failure [8], many septic patients without subsequent AKI had major increases of biomarkers of injury [9]. Similarly, it is likely that many episodes of pre-renal azotemia identified using standard biomarkers of renal function are in fact associated with tissue injury [10]. These data reinforce our view

that a continuum exists in the AKI process and that the relationship between function and injury is highly complex and influenced by (1) the nature of renal injury (i.e., heart failure vs. sepsis), (2) the underling renal structure (i.e., chronic renal damage), and (3) management (i.e., resuscitation strategy). Therefore, the clinical scores (e.g., AKIN or RIFLE classification) as a gold standard to assess the performance of biomarkers of injury has been challenged. The concept of pre- or subclinical AKI has emerged, illustrating ongoing organ damage without detected loss of function. Importantly, except histology, no gold standard for renal tissue injury exists so far [11]. Finally, how biomarkers could modify our therapeutic strategies and improve outcome is unknown and requires investigation.

Cardiovascular biomarkers

High-sensitivity cardiac troponin (hsTn) assays are available worldwide. An advantage of hsTn methods is that they are able to detect and resolve even small concentrations of the biomarker in normal subjects. A major advantage of hsTn is the much shorter delay to detect acute myocardial infarction. Indeed, among patients presenting with acute chest pain, using absolute changes of hsTn over 1 h could accurately differentiate those with acute myocardial infarction from patients with non-coronary mechanisms of cardiac injury (such as hypertensive emergency, myocarditis, pericarditis, Takotsubo cardiomyopathy etc.) [12]. However, the role of hsTn in ICU patients is still a matter of debate. It is well known that a high proportion of ICU patients, including septic patients, have "detectable" and elevated troponin (61 % of septic patients in a recent review) with an association with mortality in septic patients (RR 1.91; CI 1.63–2.24) as well as development of sepsis-mediated ventricular dysfunction [13]. Importantly, elevations in troponin are independent of acute myocardial infarction, implying direct injury of the cardiomyocyte by acute illness. It is expected that with hsTn use, a higher incidence of cardiomyocyte necrosis in the acutely ill patient will be observed.

Besides hsTn, the natriuretic peptides are cardiac biomarkers with potential promise for the evaluation and management of critically ill patients. Besides being elevated in a prognostic manner in patients with a broad array of cardiopulmonary disorders such as heart failure, pulmonary hypertension, myocardial infarction, and pulmonary embolism, there are other potential roles for B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP). For example, natriuretic peptides are independently prognostic in patients with sepsis as well as acute respiratory distress syndrome; they are predictive of the onset of sepsis-mediated ventricular dysfunction and may also predict the likelihood for weaning failure/success from mechanical ventilation. Ouanes-Besbes et al. [14] found that NT-proBNP was an independent predictor of the occurrence of post-extubation respiratory distress in a prospective observational study of 143 patients who were

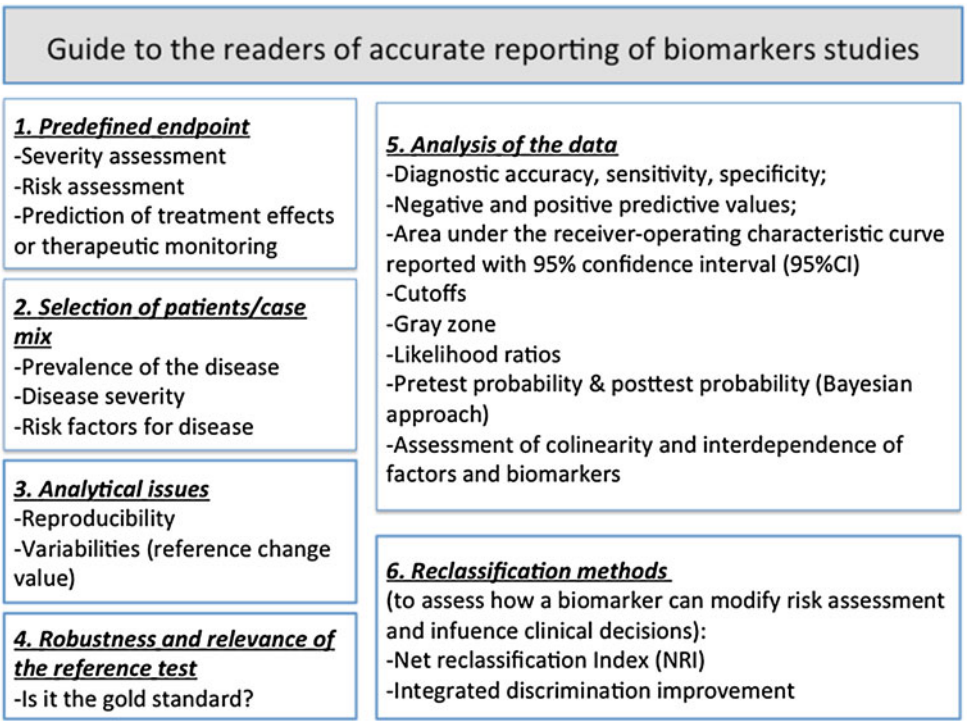

Fig. 1 Guide to accurate reporting of biomarker studies, to detect potential bias and assess the generalization of results. Usefulness of the biomarker will depend on (1) its diagnostic or prognostic accuracy, (2) how the biomarker could improve the diagnostic capability or risk stratification determined by the standard clinical and biological markers and (3) cost analysis. This should ultimately lead to diagnostic or therapeutic strategy changes compared to the standard of care

mechanically ventilated. NT-proBNP was especially accurate in ruling out post-extubation respiratory distress with a negative likelihood ratio of 0.09 for a cutoff less that 1,000 pg/ml. In a randomized controlled trial, mechanically ventilated patients were weaned with a standard strategy or a BNP-driven strategy. The BNP-driven strategy resulted in more use of diuretics, more negative fluid balance, and shorter time to weaning and increased the number of ventilator-free days [15]. Renal failure, which is associated with increased serum level of natriuretic peptides, did not influence the results of the protocol.

Other biomarkers with potential utility in critical illness include the interleukin receptor family member soluble (s)ST2, a biomarker of cardiac mechanical stress/fibrosis and chromogranin A (CgA). sST2 has been found to be a powerful prognostic biomarker in many critical care conditions, notably including acute respiratory distress syndrome, where sST2 concentrations were prognostic, particularly when measured serially [16, 17]. CgA is a granin protein co-released with catecholamines from the adrenal medulla and peripheral nerves, and is a promising biomarker. CgA levels were significantly associated with the development of septic shock and mortality in a multicenter study of critically ill patients, and the combination of SAPS II score and CgA levels reclassified risk for hospital mortality (NRI = 0.31, $P = 0.049$) [18]. These studies further enhance the major role of adrenergic tone in the course of sepsis and suggest that CgA may help in assessing this pathway in ICU patients.

A large biomarker study (ClinicalTrials.gov NCT01367093) with 2,200 ICU patients followed for a year will evaluate the importance of biomarkers to predict long-term outcome.

Conclusion

The publication of numerous original studies, reviews, and commentaries highlights the medical community's interest in biomarkers. In critically ill patients, biomarker-based assessment may provide important insights regarding tissue injury, fluid balance, inflammation, and other processes, allowing for a more refined ability to assess and manage such patients. Therefore, assessment of the diagnostic performance (and clinical usefulness) of these biomarkers requires careful consideration of appropriate methodology and avoidance of bias revealed in many previous studies (Fig. 1) [19]. Further developments will hopefully lead to patient-centered care and tailored treatments for outcome improvement.

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