Identification of novel biomarkers in critically ill patients

Impact paragraph

Diagnostic and prognostic implications

To date, it has not been possible to identify a biomarker that can reliably distinguish infection or sepsis from sterile, non-infectious inflammation. Currently, most frequently used biomarkers for this purpose are procalcitonin (PCT) and C-reactive protein (CRP).

PCT has been proven as an useful biomarker for early diagnosis of sepsis in critically ill patients[13]. More important than a single absolute value is the kinetics of PCT. When procalcitonin decreased by at least 80%, the negative predictive value for ICU/in-hospital mortality was reported with 90%. Stagnation of PCT levels or even increase was associated with an unfavorable prognosis, with respective positive predictive values for mortality of approximately 50%[165]. Moreover, PCT is of great importance with regard to guide the duration of an anti-infective therapy in critically ill patients[8,166].

CRP is an acute phase protein, that is secreted by hepatocytes in response to inflammation, infection and tissue damages. The accuracy of determination of CRP levels for the diagnosis of bacterial infection have been shown inferior to PCT, most likely due to a delayed rise (6 to 10 hours after infection) and a prolonged half-life (up to 48h) in comparison to PCT (increase 2h after infection, half-life 4 to 6h)[167].

In the intensive care setting, biomarkers are not only used to confirm the diagnosis of the underlying disease, for instance sepsis, but also to differentiate from other critical clinical conditions, monitor the effectiveness of therapeutic interventions and to predict prognosis. In a recently published systematic review, prognostic associations of routine blood measurements in the intensive care unit have been examined. A total of 128 studies in adult critical care investigating associations between parameters measured routinely in whole blood, plasma or serum, and outcome parameters such as length of stay or mortality have been identified[168].

Interestingly, for the majority of examined biomarkers the certainty of evidence for associations with outcome was low or moderate. Only increased red cell distribution width, low platelet count, increased neutrophil-to-lymphocyte ratio and decreased serum albumin have been demonstrated to be consistently associated with mortality, whereas data on CRP were inconsistent.

The studies we performed and the results that are presented in this thesis aimed at improving the understanding of the regulation and pathophysiological role of the investigated biomarkers in critical illness and sepsis and to demonstrate their potential as novel diagnostic and prognostic biomarkers.

We identified calprotectin as predictive for poor 180- and 365-days outcome in septic patients, with increasing calprotectin during the course of critical illness indicates an improved overall survival (**chapter 2**). Circulating M30 was closely associated with disease severity and mortality, supporting the utility of circulating levels of the apoptosis-related keratin fragment M30 as a prognostic biomarker at ICU admission (**chapter 3**). Visfatin was strongly associated with disease severity and organ failure and we demonstrated the validity and performance of visfatin as a biomarker for the prediction of ICU or overall survival in critically ill patients (**chapter 5**). Low CTRP3 plasma concentrations at ICU admission predicted the overall mortality in critically ill patients (**chapter 7**). Elevated copeptin levels at ICU admission predicted short-term and long-term mortality (**chapter 9**). High MR-proANP plasma concentrations indicated organ dysfunction, sepsis, disease severity and mortality risk in ICU patients (**chapter 10**).

An ideal biomarker has a high sensitivity and specificity and is suitable for clinical application in terms of diagnosis, staging, prognosis, and treatment of disease. Currently, there are just a few routinely clinically used biomarkers which meet these criteria in the setting of intensive care medicine. Nevertheless, laboratory values are widely used in daily clinical practice on the ICU and generate high healthcare costs.

A profound understanding of causative biological mechanisms and ongoing (biomarker) research in critical disease will a) allow to identify novel molecules as biomarkers, b) define biomarker thresholds and c) specify the adequate timepoint of assessment for implementation in clinical practice and by this improving patient care[169]. Humbly, we hope to have contributed a modest part to the large and steadily growing field of clinical biomarker research with our work.

Socio-economic implications

The identification, validation and integration of novel biomarkers into clinical routine is most likely associated with an increase in health care expenditure. Therefore, biomarker development is not only a matter of the clinical benefit of a specific tool, but also of monetary benefits.

Yet, cost-effectiveness and cost-utility studies are uncommon in the economic assessment of new clinical laboratory tests. However, it must first be noted, that a new biomarker will never make economic sense without clinical benefit[170]. Cost-utility studies can evaluate the ratio between the cost of a clinical test and the resulting benefit, displayed as the numbers of clinical events (e.g., early diagnosis of sepsis, prevention of cardiovascular events) or the amount of money gained per quality adjusted life year (QALY). According to the definition of the British National Institute for Health and Care Excellence (NICE), QALY is “a measure of the state of health of a person

or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health"[171].

Generally, a threshold for financial expenditure of 50.000 US Dollar (USD) per QALY gained is considered as cost-effective[170].

As an example, in the US, early treatment of chronic left-ventricular heart failure with ACE inhibitors has been demonstrated as cost-effective with approximately 5600 USD per QALY. Screening (all patients >55 years) for asymptomatic left ventricular dysfunction by echocardiography has been proven to be not cost effective. Importantly, screening with BNP testing and performing echocardiography if the BNP is abnormal has been found to be is cost-effective in all populations over 55 years at USD 19.000 per QALY compared to no screening[172].

However, cost-effectiveness studies not common for clinical laboratory tests and very rarely in the critically ill patients. A recent meta-analysis revealed just a few publications on health economic evaluations in critically ill patients, comprising, with regard to laboratory biomarkers, PCT-guided antibiotic therapy and lactate testing[173].

With respect to the high economic and social burden of critical diseases, high quality economic studies in cooperation of scientists, economists and clinicians are urged, to improve understanding of cost-effectiveness in the complex setting of intensive care medicine[174].

References are given in the References section of the Addendum