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Biomarkers as Prognostic Predictors and Guide in Critically Ill Patients

An overview of promising biomarkers in critical care, characteristics a biomarker should have and how to ensure their usefulness in clinical practice.

Introduction

Precision medicine is a medical approach that tailors treatments based on individual patient characteristics and their unique response to therapies for a particular disease. The goal of precision medicine is to achieve accuracy in both diagnosis and treatment using innovative clinical and laboratory tools (Collins and Varmus 2015).

Biomarkers play a crucial role in precision medicine as they enable personalised treatment based on a patient's specific needs (von Groote and Meersch-Dini 2022). Biomarkers can be objectively, systematically, and accurately measured in a biological sample. Their levels can indicate whether a biological process is normal or pathological. An ideal biomarker should be easy and cost-effective to measure while having high sensitivity and specificity. Additionally, it should provide clinical assessments with supplementary information (Moons 2010).

Six steps have been proposed to progressively evaluate new biomarkers before their integration into clinical practice (Hlatky et al. 2009). These include:

1. Proof of concept: Is there a significant difference in levels of the new biomarker between subjects with different perioperative outcomes?
2. Prospective validation: Can the new biomarker predict the likelihood of certain outcomes in prospective studies?
3. Incremental value demonstration: Does the new biomarker provide additional predictive information to standard risk markers?
4. Clinical utility: Can modifying the levels of the new biomarker predict risk when changing the recommended therapy?
5. Improved clinical outcome: Does the new biomarker lead to improved clinical outcomes?
6. Cost-effectiveness: Is the use of the new biomarker cost-effective, given the improvement in clinical outcomes?

Promising Biomarkers in Intensive Care

Many biomarkers are potentially interesting, some already integrated into clinical practice, while others require more validation.

C-Reactive Protein (CRP) is a widely used clinical marker to detect infection and sepsis. It is used to diagnose intra-abdominal infections (Kørner et al. 2009), pneumonia, and tracheal infections. It can also aid in differentiating bacterial infection from viral. Elevated CRP levels have been linked to an increased risk of organ failure and mortality in critical patients (Travlos et al. 2022). CRP concentrations have been used as a biomarker of infection in septic patients with community-acquired pneumonia or ventilator-associated pneumonia and to monitor bacterial load and appropriate antibiotic therapy. However, compared to other biomarkers, CRP rises late, takes time to recover normal values and can also increase in non-infectious processes.

Interleukins are cytokines that modulate and originate an immune response by carrying signals to neighbouring cells. Interleukin-6 (IL-6) is a biomarker with pro-inflammatory and anti-inflammatory activity, and its levels rise after surgery, trauma, or critical illness. Elevated IL-6 levels have been linked to adverse outcomes, and thresholds vary between systemic inflammatory response syndrome, sepsis, and septic shock. In addition, IL-6 levels can be used to stratify patients for therapeutic intervention (Jawa et al. 2011). IL-6 is also used as a biomarker of COVID-19 severity, and its levels have been used to decide on the administration of immunosuppressive treatment for cytokine storms (Kavanaugh 2008).

The urokinase-like soluble plasminogen activator receptor (suPAR) is a biomarker associated with cancer and infections, and its level reflects the degree of immune activation in the patient. Studies have shown that suPAR levels are associated with higher mortality in critical patients with sepsis and serious infectious pathology. However, suPAR is elevated in patients with other diseases and cannot discriminate sepsis from other pathologies, making its interpretation nonspecific (Huang et al. 2020).

Presepsin is a soluble subtype of the CD14 glycoprotein expressed on the surface of monocytes and macrophages. CD14 is the receptor of protein-bound lipopolysaccharide complexes, which translates signals of endotoxins released by gram-negative bacteria, leading to the release of cytokines (Zou et al. 2014). Its elevation implies the activation of monocytes and macrophages by an inflammatory or infectious stimulus, with elevated levels in the early stages of sepsis. Elevated presepsin has also been associated with major cardiovascular and perioperative cerebrovascular complications in high-risk patients undergoing noncardiac surgery (Handke et al. 2019) and proposed as a biomarker for predicting mortality in cardiac surgery (Clementi et al. 2019).

Dipeptidyl peptidases (DPPs) are a class of enzymes involved in various cellular activities and physiological functions. DPP3 is an enzyme that inactivates angiotensin II, a hormone crucial in haemodynamic balance and heart function. The release of DPP3 into the blood leads to haemodynamic instability and cardiac dysfunction. High levels of circulating DPP3 are associated with reduced cardiac output, multi-organ failure, and circulatory shock (Ye et al. 2022). Elevated blood levels of DPP3 are observed in septic shock, and low or decreasing levels of DPP3 in the first 24 hours of ICU admission predict improved organ function and better outcomes. DPP3 is considered a promising biomarker for shock diagnosis and stratification and for guiding haemodynamic and shock therapy (Takagi et al. 2020).

Pancreatic Stone Protein

Pancreatic stone protein (PSP) was initially identified as a molecule that inhibits the growth of calcium carbonate crystals in pancreatic juice. PSP has also been associated with pathological changes in the pancreas during inflammation (Eggimann et al. 2019). In experiments with rats, PSP was found to be an indicator of systemic stress, which numerous studies have since confirmed. The pancreas responds to remote organ damage and systemic stress by secreting PSP, particularly in cases of serious infectious complications and sepsis, as PSP may activate neutrophils and promote bacterial aggregation (Reding et al. 2017). The normal levels of PSP in healthy individuals are 10.4 ng/mL (7.5–12.3). PSP is a promising biomarker for early diagnosis of infections in hospitalised patients, using a cut-off value of 44.18 ng/L (Prazak et al. 2021). PSP values can be obtained through the point-of-care Platform Abioscope®. Elevated PSP levels have predicted the onset of sepsis before clinical manifestation in several scenarios, including trauma and cardiac surgery (Pugin et al. 2021). Additionally, PSP can aid in patient stratification based on severity (Lopes et al. 2022).

Future Outlook

The positioning of numerous biomarkers will require validation (Pierrakos et al. 2020; Vincent et al. 2020). In critical and perioperative medicine, as in oncology, precision medicine aims to personalise and improve the precision of treatments to enhance outcomes (Ware 2017). To achieve this goal, panels of biomarkers, biomarker scaling, point-of-care biomarker testing, therapies tailored to control biomarkers with specific biological effects that impact outcomes, and the development of systems biology and genomics will all improve the accuracy, speed, and efficiency of patient care.

Point of Care (PoC) devices are becoming increasingly common in perioperative and ICU settings. These devices typically include equipment for blood gas, haematimetry, basic biochemistry, and coagulation tests. There is growing interest in developing cost-effective biomarkers in PoC that can provide quick results and can be easily obtained by clinicians when needed. A successful PoC biomarker should be affordable, sensitive, specific, easy to use, fast, robust, and effective (Rhee and Kahn 2010). A reliable PoC biomarker in surgical and ICU settings would provide valuable information about high-risk patients and could supplement the information provided by standard clinical, monitoring, and analytical variables (Vincent et al. 2020).

Biomarkers play a key role in implementing precision medicine in the ICU, but their precise role may be more fully defined in the coming years (Póvoa et al. 2023). Developing biomarkers alongside clinical phenotyping, systems biology, artificial intelligence, and big data analysis are future challenges that must be addressed to advance precision medicine (Seymour et al. 2017). It is important to acknowledge that biomarkers are useful in infection and congestion in critically ill patients and perioperative risk stratification. In the future, therapies associated with deficits of specific biomarkers will be available, and biomarkers will describe phenotypes associated with prognosis and the usefulness of specific therapies. Clinicians must understand the advantages and limitations of biomarkers for rational and effective use. The development of more specific biomarkers, point-of-care biomarkers, and panels of biomarkers, along with clinical or genetic data, will shape prognosis in intensive and perioperative care in the future (Méndez Hernández and Ramasco Rueda 2023).

Key Points

- Biomarkers play a crucial role in precision medicine as they enable personalised treatment based on a patient's specific need.
- Six steps have been proposed to progressively evaluate new biomarkers: proof of concept, prospective validation, incremental value demonstration, clinical utility, improved clinical outcome and cost-effectiveness.
- Pancreatic Stone Protein (PSP) is a promising biomarker for early diagnosis of infections in hospitalised patients.
- Elevated PSP levels have predicted the onset of sepsis before clinical manifestation in several scenarios, including trauma and cardiac surgery.
- PSP values can be obtained through the point-of-care Platform Abioscope®.

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References

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