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Biomarkers

Juan Carlos Ruiz-Rodríguez
Intensive Care Department
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Shock, Organ Dysfunction and Resuscitation Research Group
Vall d'Hebron Research Institute (VHIR)
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Barcelona, Spain
juancarlos.ruiz@vallhebron.cat

Luis Chiscano-Camón
Intensive Care Department
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Shock, Organ Dysfunction and Resuscitation Research Group
Vall d'Hebron Research Institute (VHIR)
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Barcelona, Spain

Adolf Ruiz-Sanmartin
Intensive Care Department
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Shock, Organ Dysfunction and Resuscitation Research Group
Vall d'Hebron Research Institute (VHIR)
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Barcelona, Spain

Laura Martin
Intensive Care Department
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Shock, Organ Dysfunction and Resuscitation Research Group
Vall d'Hebron Research Institute (VHIR)
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Barcelona, Spain

Biomarkers in Sepsis Present and Future

A biomarker defines a measurable indicator of a patient's medical situation that can be measured precisely and accurately. Biomarkers provide value for diagnosis, prognosis, early disease detection, risk stratification, suitable treatment (theragnostic), and trial improvement for patients with sepsis or presumed sepsis.

Introduction

Sepsis is characterised by a dysregulated immune response that leads to organ dysfunction (Arina and Singer 2021). Host response biomarkers take part in a critical role in diagnosis, early detection of organ dysfunction, risk stratification, prognosis, and patient managing, including antibiotic stewardship (Huang and Ramirez 2020). Biomarkers may also be useful for trial improvement to recognise suitable patients and/or risk categorisation for an intervention.

An extensive range of biomarkers, measured by a host of different technologies, are being explored to distinguish a systemic inflammatory response syndrome (SIRS) rapidly, which is a disproportionate defensive body's response to a damaging stressor (for example, infection, trauma, surgery, acute inflammation, ischaemia or reperfusion, or cancer) (Chakraborty and Burns 2022) or prompt detection of infection-triggered organ failure (sepsis).

These biomarkers embrace measurement of acute-phase proteins, cytokines, chemokines, damage-associated molecular patterns (DAMPs), endothelial cell markers, leukocyte surface markers, non-coding RNAs, micro-RNA, and soluble receptors, as well as metabolites and alterations in gene expression (transcriptomics). Biomarkers may assist in stratifying septic patients into biological phenotypes, for example, hyperinflammatory versus immunosuppressive.

Lately, the advancement of biomarkers in the intensive care unit (ICU) has been vast. However, only a few are commonly used in clinical procedure: procalcitonin (PCT), and, newly, Mid-region fragment of pro-adrenomedullin (MR-proADM). Others are under investigation with encouraging results: pancreatic stone protein (PSP), soluble Triggering Receptor Expressed on Myeloid Cells (sTREM), and presepsin (**Table 1**).

Procalcitonin

PCT has been extensively investigated as a decision-making aid in critically ill patients with sepsis. PCT, a 116-amino acid precursor hormone of calcitonin, is the most analysed biomarker in sepsis. Its production is caused by systemic inflammation due to severe infection in response to various pro-inflammatory signals (Becker et al. 2008). The Research Committee of the Surviving Sepsis Campaign (SSC) believes research in biomarkers in sepsis as a priority for future years (Coopersmith et al. 2018) and the 2021 SSC guidelines suggest the measurement of PCT levels to help shortening the duration of antimicrobial treatment (Evans et al.2021).

PCT and diagnosis

PCT had similar performance in guessing positive sepsis results with AUROC values of 0.75 and 0.73, respectively (Mihajlovic et al .2017). A cut-off value of 1.1 ng/ml [sensitivity of 77% and specificity of 79%; area under the receiver operating characteristic curve of 0.85 (95% CI 0·81–0·88)] could be used for diagnosis of sepsis, depending on pre-test probability (Wacker et al. 2013). Another study gave

Ivan Bajaña
Intensive Care Department
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Shock, Organ Dysfunction and Resuscitation Research Group
Vall d'Hebron Research Institute (VHIR)
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Barcelona, Spain

Clara Palmada
Intensive Care Department
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Shock, Organ Dysfunction and Resuscitation Research Group
Vall d'Hebron Research Institute (VHIR)
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Barcelona, Spain

Cristina Martin
Intensive Care Department
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Shock, Organ Dysfunction and Resuscitation Research Group
Vall d'Hebron Research Institute (VHIR)
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Barcelona, Spain

Ricard Ferrer
Intensive Care Department
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Shock, Organ Dysfunction and Resuscitation Research Group
Vall d'Hebron Research Institute (VHIR)
Vall d'Hebron University Hospital
Vall d'Hebron Barcelona Hospital Campus
Barcelona, Spain

AUROC values of 0.87 for PCT in predicting bacteraemia (Leli et al. 2016). Plasma concentrations of PCT were gradually higher in sepsis and septic shock than in non-septic patients. PCT was slightly superior to presepsin in one more study of septic patients admitted to intensive care (Enguix-Armada et al. 2016).

PCT and prognosis

In patients with septic shock and multiorgan dysfunction, a sustained high concentration of PCT is associated with significantly lower survival. PCT clearance could be a useful tool for monitoring the clinical evolution of the patients and the prognosis can be assessed by PCT clearance at 48h (Ruiz-Rodríguez et al. 2012).

Procalcitonin-guided antimicrobial stewardship in sepsis helps individual assessments on the duration of antibiotics, treatment approaches, and diagnostic interventions (Saeed et al. 2019). In earlier studies, procalcitonin assistance in the intensive care unit improved clinical results and diminished the length of stay, with no associated problems (Iankova et al. 2018; Balk et al. 2017). Adding up, studies are describing the mortality advantages of procalcitonin guidance. In a prior meta-analysis (Lam et al. 2018) the positive effects of a procalcitonin-guided strategy for de-escalation in decreasing the threat of death were found. Also, in another study, procalcitonin-guided therapy in patients with sepsis reduced mortality (Wirz et al.2018).

PCT guided therapy

Changes in PCT plasma concentrations have been helpful to distinguish patients with a reasonable response to antimicrobial treatment and have their therapy de-escalated. A decrease to levels < 0.5 ng/ml or by at least 80-90% of the peak in combination with clinical progress can be applied to support the clinical decision to lessen antimicrobial coverage, thus escaping from antibiotic-related adverse effects (de Jong et al. 2016).

PCT-guided de-escalation

PCT-guided de-escalation algorithms rely on the early evidence demonstrating that patients with positive progress and satisfactory reaction to antibiotic treatment have a rapid decline in PCT concentrations (Harbarth et al. 2001). In at least three meta-analyses, PCT-guided algorithms have been efficient and secure to de-escalate antibiotics in sepsis and septic shock, with no side effects on patient results (Wirz et al. 2018; Lam et al. 2018).

Previous studies revealed patients with lower respiratory tract infections can often be de-escalated when PCT concentrations are low, provided that medical assessment supplements biomarker measurements. A patient-level meta-analysis of 2,910 patients demonstrated that PCT guidance reduced antibiotic treatment period to 5.7 days from 6.2 days in controls ($p < 0.0001$) (Wacker et al. 2021). In another randomised study of 1,546 ICU patients, PCT guidance lessened the duration of antibiotic therapy. It improved the number of antibiotic-free days matched to control, though the number of ventilator-associated pneumonia (VAP) patients was not specified (Kim et al. 2019). Numerous observational studies have shown the absence of utility of PCT measurements in VAP diagnosis. The primary reason for explaining these conclusions was that another non-infectious diseases or infections out of the lung can raise PCT concentrations in patients on mechanical ventilation. The recent ERS/ESICM/ESCMID/ALAT guidelines (Gibot et al. 2012) suggest that PCT can be helpful to guide treatment duration or extend it in several circumstances, such as inappropriate antibiotic treatments, infections caused by multidrug-resistant or extensively drug-resistant microorganisms.

Some analyses do not promote the use of PCT-guided de-escalation in sepsis. However, these studies have incorporated in non-septic or non-critically ill patients with lower respiratory tract diseases (Huang et al. 2018).

Mid-Region Fragment of Pro-adrenomedullin

Mid-region fragment of proadrenomedullin (MR-proADM) quickly suggests concentrations of adrenomedullin, a potent vasodilator agent with immune-modulating and metabolic properties that rises in sepsis. MR-proADM is synthesised in different tissues, including the adrenal cortex, kidney, lung, blood vessels, and heart. It has biological assets, including vasodilating, inotropic, diuretic, natriuretic, and bronchodilating. In one study, mid-regional pro adrenomedullin (MR-proADM) was an independent prognosticator of five different organ dysfunctions (respiratory, coagulation, cardiovascular, neurological, and renal), compared to lactate which predicted three (coagulation, cardiovascular and neurological), PCT two (cardiovascular and renal) and C-Reactive protein (CRP) none (Martín-Fernández et al. 2021).

MR-proADM most precisely recognised patients with a high likelihood of further disease progression compared to other biomarkers and clinical scores (Schuetz 2015). A total of 1089 individuals with either sepsis (142) or septic shock (977) were included in a randomised controlled study. The MR-proADM level within the first 24 h after sepsis diagnosis was associated with 7-day mortality (AUROC 0.72, $p < 0.001$)and 90-day mortality (AUROC 0.7, $p < 0.001$). Patients with declining PCT levels but persistently high MR-proADM levels on day-1 or day-4 had a substantially higher mortality risk of 19.1 (8.0–45.9) and 43.1 (10.1–184.0), respectively; MR-proADM identifies disease severity and treatment response more accurately than established biomarkers and scores, adding additional information to facilitate rapid clinical decision-making and improve personalised sepsis treatment (Elke et al.2018). Adult patients hospitalised in ICU had their bioactive-MR-proADM levels measured in this retrospective observational study. This study comprised a total of 1867 patients, 632 septic patients, and 267 septic shock patients. The median bioactive-ADM was 74 pg/mL in sepsis patients, 107 pg/ mL in septic shock, and 29 pg/mL in non-septic patients. The association of elevated bioactive-ADM and mortality in sepsis patients and the ICU population resulted in O.R.s of 1.23 and 1.22, respectively (Lundberg et al. 2020).

Newly, the association has been reported between a higher clearance of MR-proADM levels during ICU stay and favourable outcomes, with survivors displaying a blood plasma concentration fall to 1.65 nmol/L 48 hours after admission and lower levels on day five compared to non-survivors. The role of MR-proADM in the early identification of severe cases at higher risk of organ dysfunction has been evaluated, irrespective of the location of the infection source. Furthermore, MR-proADM is used to aid clinical decisions regarding the use of hospital and ICU resources, having the highest predictive value for mortality compared to PCT, CRP, Sequential Organ Failure Assessment (SOFA) scores, and lactate (Baldirà et al. 2020).

In conclusion, MR-proADM is a good applicant in the prompt identification of sepsis patients with moderate illness severity but at threat of mortality and is a reliable marker of mortality danger and disease severity along time in sepsis (Andaluz-Ojeda et al. 2017).

Biomarker	Utility
Presepsin	Initial diagnosis and sepsis risk stratification
	Potential marker to distinguish Gram (+) and Gram (-) bacterial infection
sTREM-1	Sepsis indicator
	An early distinction between sepsis and SIRS
	Septic shock prediction
	Theragnostics, Precision Medicine
PCT	PCT clearance for monitoring clinical evolution and prognosis
	Measurement of PCT levels to support shortening the duration of antimicrobial therapy
	Guided de-escalation
	Mortality benefits of procalcitonin guidance
PSP	Identification of sepsis
	Prognostic tool
MR-proADM	Discrimination of survivors and non-survivors
	Identified patients with a high likelihood of further disease progression
	Higher clearance of MR-proADM levels during ICU stay and favourable outcomes
	Organ dysfunction biomarker

Table 1. Relationship of biomarkers and clinical utility
MR-proADM: Mid-region fragment of pro-adrenomedullin; PSP: Pancreatic Stone Protein; PCT: procalcitonin; sTREM-1: soluble TREM-1

Pancreatic Stone Protein

Pancreatic stone protein (PSP) is a 14 kDa insoluble polypeptide encoded by a single transcript of the reg gene, resulting in a 144-amino acid length glycoprotein, structurally similar to C-type lectin-like proteins (Jin et al. 2011) which are calcium-dependent glycan-binding proteins involved in the process of cell to cell and host-cell interaction, including adhesion and signalling receptors in homeostasis and innate immunity as well leukocyte and platelet trafficking in inflammatory responses (Varki et al. 2009). The role of PSP in the immune and inflammatory response to infection prompted its identification as a potential biomarker of infection and sepsis since a pivotal observation was accidently made in

rat experiments by the group of Rolf Graf in which PSP was found to be an indicator of systemic stress (Graf et al. 2002).

PSP as a diagnostic tool for sepsis

PSP demonstrates a significant interaction between time and presence of sepsis suggesting that besides a fixed cut-off value (as in standard ROC curve analysis) the time-related kinetics of PSP has a crucial role in the identification of sepsis when considering the time-dependency of the infectious/septic event (Pugin et al. 2021). In a meta-analysis, the results of PSP were better than CRP or PCT for the diagnosis of community acquired infections in the emergency department and surgical infections after cardiac surgery (Prazak et al. 2021).

In a multicentric international prospective observational clinical study conducted in 14 ICUs in France, Switzerland, Italy, and the United Kingdom where adult patients at risk of nosocomial sepsis were included, clinical sepsis diagnosis was associated with an increase in biomarkers value over the 3 days preceding this diagnosis [PSP ($p = 0.003$), PCT ($p = 0.025$) and CRP ($p = 0.009$)] , of note that PSP started to increase 5 days before the clinical diagnosis of sepsis. So, serial PSP measurement demonstrated an increase of this marker the days preceding the onset of signs necessary to clinical diagnose sepsis (Pugin et al. 2021).

PSP as a prognostic tool

PSP has shown good performance in the prognosis of septic patients. PSP was evaluated in a cohort of 101 patients with VAP; the highest values were obtained in non-survivors (Boeck et al.2011). In another study, PSP was the only biomarker significantly increased in non-survivors (Que et al. 2012). In patients with septic shock, PSP was substantially higher in non-survivors in the first six hours after diagnosis and on the second day of admission to the ICU (Guadiana-Romualdo et al. 2019). In another study performed in 249 septic patients, higher PSP values were linked with clinical severity and non-survivors (Que et al. 2015).

Presepsin

Presepsin is a biomarker to identify sepsis, but its prognostic value has not been exhaustively reviewed. Known as soluble CD14 subtype, is a 13-kDa glycoprotein cleavage N-terminal fragment of CD14, released into circulation after activation of a pro-inflammatory signal cascade on contact with infectious agents (Wright et al. 1990). The diagnostic accuracy of presepsin in sepsis was established by a meta-analysis (Zhang et al. 2015) where eleven studies fulfilled the inclusion criteria; the overall diagnostic sensitivity of presepsin for sepsis was 0.83 (95% CI: 0.77–0.88), and specificity was 0.78 (95% CI: 0.72–0.83) but the major design deficits of the included studies were lack of prespecified thresholds and patient selection bias. Another meta-analysis (Yang et al. 2018) encompassed a total of 10 studies and 1617 patients were involved. Presepsin levels in the first sampling (within 24 hours) were considerably lower among survivors as matched with non-survivors: the pooled SMD between survivors and non-survivors was 0.92 (95% CI: 0.62–1.22) in the random effects model ($I2 = 79\%$, $P< 0.01$). In subgroups, separated by the sepsis severity or study site, pooled SMD was consistently noting higher presepsin levels in non-survivals. A meta-analysis with 19 studies included (19 observational studies and no randomised controlled trials) that had enrolled 3012 patients, showed that the diagnostic accuracy of procalcitonin and presepsin in identifying infection was similar and that both were useful for early diagnosis of sepsis and subsequent reduction of mortality in critically ill adult patients (Kondo et al. 2015). Presepsin also has been demonstrated to have predictive value for circumstances other than sepsis such as cardiac surgery (Bomberg et al. 2017), haemophagocytic syndrome (Nanno et al. 2016), or renal failure (Nagata et al. 2015).

Soluble Triggering Receptor Expressed on Myeloid Cells-1

The Triggering Receptor Expressed on Myeloid Cells (TREM) family includes several isoforms that share low sequence homology with each other and have only one immunoglobulin-like domain. Engagement of TREMs triggers a signalling pathway leading to intracellular calcium mobilisation, actin cytoskeleton rearrangement and activation of transcriptional factors. TREM-1 was first detected on both human and murine myeloid cells, especially neutrophils, mature monocytes and macrophages. Its expression at the cell-surface of these effector cells is significantly enhanced in skin, biological fluids and tissues infected by Gram-positive or Gram-negative bacteria as well as by fungi (Bouchon et al. 2001). The activation of TREM-1 by its still unidentified ligand in the presence of Toll-like receptor 2 (TLR2) or TLR4 ligands amplifies the production of proinflammatory cytokines. Additionally, activation of these TLRs upregulates TREM-1 expression (Bleharski et al. 2003). Thus, TREM-1 and TLRs collaborate to produce an inflammatory response. Besides its membrane-anchored form, a soluble form of TREM-1 (sTREM-1) is released and can be measured in several body fluids.

sTREM-1 and the diagnosis of septic shock

The newest meta-analysis on sTREM-1 as a diagnostic biomarker of sepsis in adult patients was published in 2012 (Wu et al. 2012). Its assumption was that plasma sTREM-1 had a moderate diagnostic performance in distinguishing sepsis from sterile inflammatory response and was not enough for sepsis identification, especially when pre-test probability of SIRS was high.

sTREM-1 as a prognostic marker of infection

In 63 consecutive septic patients, plasma sTREM-1 concentrations were measured sequentially (Gibot et al. 2005). The baseline plasma sTREM-1 concentration was higher in survivors and was found to be an independent factor associated with good outcome. In a meta-analysis, sTREM-1 plasmatic levels had a moderate prognostic meaning in evaluating the mortality of infection in adult patients (Su et al. 2016). In a cohort of 190 septic ICU patients, sTREM-1, PCT, leucocyte surface expression of CD64 and clinical severity scores were analysed. sTREM-1 was noticed to be the best prognostic biomarker amongst those

studied (Charles et al. 2016).

sTREM-1 as a target molecule for adjuvant treatment of sepsis

Blockade of TREM-1 reduces inflammation and improves survival in animal models of bacterial sepsis. Nangibotide is a 12 amino-acid peptidic fragment derived from TREM-Like Transcript-1 (TELT-1), a receptor protein of TREM-1 family. Nangibotide can bind to TREM-1 ligand and modulate the amplification of the immune response caused by the activation of TREM-1 in sepsis.

In pre-clinical animal studies performed in peritonitis with septic shock patients, analogues of Nangibotide showed an improvement of inflammatory response and organ function, cardiovascular status, and survival (Derive et al. 2012; Derive et al. 2013). In a recent phase IIa clinical trial that investigated the safety and tolerability of three doses of Nangibotide in septic shock, Nangibotide-treated patients improved organ function biomarkers. This effect was bigger in the subgroup of patients with high circulating soluble TREM-1 (sTREM-1) levels. A phase 2b clinical trial, ASTONISH, evaluated its efficacy, safety, and tolerability in patients with septic shock, specially focused on the high sTREM-1 subgroup (ClinicalTrials.gov Identifier NCT04055909) (Francois et al. 2021). The results suggest a therapeutic potential of Nangibotide in septic shock patients with excessive activation of the TREM-1 pathway confirming also that the soluble TREM-1 biomarker predicts response to Nangibotide treatment.

Conclusion

The use of sepsis biomarkers for individualising treatments is promising. Recent progress in several areas of biomarkers research can transform the application of biomarkers as a chip at the bedside for diagnosis, predictive and prognostic enrichment in clinical studies, risk stratification, molecular phenotyping, and monitoring therapeutic response in more personalised medicine.

Statement of Ethics

We complied with the guidelines for human studies, and our research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent to publish this case was obtained and it was recorded in the medica history. Information revealing the subject's identity was avoided.

Conflict of Interest

None. ■

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