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Cover Story

Smart Diagnostics

Improved Patient Assessment with MR-proADM

Interviewee: Professor Carlo Tascini | Head of Infectious Diseases Clinic | Udine University Hospital | Italy

Prof. Carlo Tascini is Head of Infectious Diseases Clinic at Udine University Hospital. Prior to that, he was the Head of First Division of Infectious Diseases Unit at Cotugno Hospital. His field of interests include endocarditis, meningitis, sepsis, MDR bacterial infection and fungal infections. HealthManagement.org spoke to Prof. Tascini about the clinical benefits of MR-proADM.

Key Points

- Biomarkers, as standalone markers, might function as early indicators of microvasculature and endothelial damage.
- MR-proADM may help facilitate safe discharge of patients in the emergency department.
- It can also help in identifying critical patients that require further diagnostic work-up.
- MR-proADM can help guide antibiotic and sepsis-driven adjunctive therapy.
- In COVID-19, it may help identify dysfunction of microvascular and endothelial cells, before the onset of respiratory failure.

What is mid-regional proadrenomedullin (MR-proADM) and what role does it play in risk assessment in the emergency department and ICU?

Adrenomedullin plays a significant role in vascular permeability, endothelial barrier regulation, and stabilisation of the microcirculation all of which contribute to the development of organ dysfunction and failure in sepsis and septic shock. This biomarker may be induced by bacteria, fungi or viruses. The increase of adrenomedullin is an indicator of organ dysfunction. The incorporation of MR-proADM into an early sepsis management protocol may therefore help guide early diagnostic interventions and facilitate more intensive treatment in these patient groups before development of any further organ dysfunction.

In the ICU, MR-proADM levels can be used to improve risk stratification. Elevated values (>2.5 nmol/L) are indicative of treatment failure & poor outcomes. As such, high MR-proADM values can help guide an escalation in antibiotic and resuscitation therapy in patients at risk of deterioration. Alternatively, low or declining levels of MR-proADM may facilitate early discharge.

Are there any large scale clinical trials that have demonstrated how MR-proADM can help in safe discharge of low risk patients?

A multinational observational study has demonstrated that MR-proADM can be used to identify patients with low disease severity, who may benefit from early discharge from the ED. Early discharge is essential in maintaining an efficient bed management workflow and may have an overall clinical benefit. Low MR-proADM values can identify patients with low microcirculatory and vascular damage, where additional diagnostic or interventional procedures are not necessary. MR-proADM is able to identify uncomplicated infections with low risk of further progression and therefore might improve in the emergency department (ED) the rate of hospitalisation and out-patient treatment.

A recent multinational observational study by Saeed et al. (2019) indicates that using this biomarker in ED can increase out-patient treatment decisions without increasing subsequent mortality and re-hospitalisation rates. MR-proADM as a standalone marker might be beneficial in high-risk patient settings such as ED, to improve the use of the scarce resources and save costs by increasing outpatient treatment. This needs to be validated in further large studies.

Can MR-proADM be used in COVID-19 patients to assess the risk of disease progression?

The pathological mechanisms of organ damage in COVID-19 patients remain poorly understood. The multiple organ failure described in COVID-19 suggests involvement of multiple pathway. Endothelial cells (EC) dysfunction could be one of the explanations for organ failures and edema as endotheliitis might be an important, although still underrecognised characteristic of COVID-19 severe disease. SARS-CoV-2 causes vascular barrier breach in the lungs, leading to increased content of fluids and edema, endotheliitis, activation of coagulation, further leading to disseminated intravascular coagulation (DIC) and dysregulation of inflammatory cells. ECs in the lungs have a role in Acute Respiratory Distress Syndrome (ARDS), a major complication in COVID-19. Adrenomedullin (ADM), is essential in maintaining endothelial stability, therefore it is a good biomarker to understand the EC damage.

Montrucchio et al. (2020) demonstrated in a small cohort of COVID-19 patients admitted to ICU, that a higher mortality was found in patients with MR-proADM values higher than 1.8 nmol/L. The logistic regression model revealed that, with an odds ratio equal to 10.2 this biomarker had the best predictive ability for mortality compared to age, gender, procalcitonin (PCT), pC-reactive protein (CRP), presence of diabetes or cardiovascular diseases.

At Udine hospital, analysis of 112 COVID-19 patients admitted to ICU and ID department, an initial value of MR-proADM > 1 nmol/L was associated with reduced PaO2/FiO2 ratio values, less than 250 and increased mortality *(C. Tascini personal experience)*.

What are the cut-off points and conclusions that can be drawn from the results?

Saeed et al. (2019) have studied MR-proADM in the ED. This study found two uses for this biomarker: 1) identify patients with values >1.5 nmol/L that have the potential for further progression of the disease and would benefit from an early escalation of antibiotic and resuscitation treatment and these patients should therefore be treated in the hospital. 2) a reduction of hospitalisation for ED patients without endothelial damage reflected by values < 0.87 nmol/L.

In the first case, the authors were able to identify a subset of patients with increased length of stay, ICU admission and mortality, thus these findings facilitated rapid intervention such as escalation of antibiotics, infusion of fluids, the use of other sepsis therapies and additional diagnostic tests. Particularly high mortality risk was seen for patients with MR-proADM > than 2.5 nmol/L therefore these patients may benefit from immediate admission to a high dependent unit or to the intensive care unit to initiate a more aggressive diagnostic and therapeutical approach. Several studies have demonstrated that in patients with high MR-proADM, mortality is around 30%.

What benefit can MR-proADM provide in terms of allocation of scarce resources?

Biomarkers can indicate the onset of microvascular and endothelial damage earlier than the appearance of clear clinical symptoms. As such, they can be used to help rapidly guide the most appropriate diagnostic and therapeutic approach, leading to a better allocation of resources.

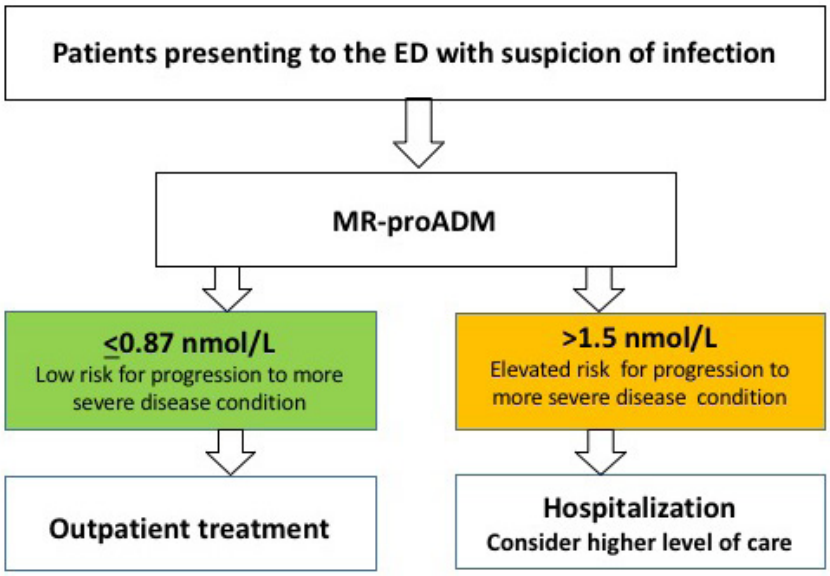
How does MR-proADM compare to other clinical scores such as SOFA, APACHE, etc.?

Clinical scores such as the Sequential Organ Failure Assessment (SOFA) score and Acute Physiological and Chronic Health Evaluation (APACHE) II score have been developed to assess severity of critical patients. These scores are not able to capture individual organ system dysfunction and they might be too complex to be used in daily routine. A biomarker, if effective, might be more useful than scores, in predicting severity of patients.

MR-proADM was studied by Elke et al. (2018) in a secondary analysis of a large randomised controlled trial on sepsis. The ROC curve and multivariate cox regression identified MR-proADM as the strongest factor, with respect to SOFA and APACHE II, associated with 28-day mortality in total population. They found that initial use of MR-proADM within the first 24 h after sepsis diagnosis resulted in the strongest association with short-term, mid-term and long-term mortality compared to all other biomarkers or clinical scores (including SOFA and APACHE). The addition of MR-proADM increased the accuracy of all other biomarkers and scores. Viaggi et al. (2018) demonstrated that MR-proADM, at least in a single neurointensive ICU, might predict the deterioration of organ dysfunction in infected patients, 24 hours before the SOFA score.

How is MR-proADM performed?

Mid-regional proadrenomedullin (MR-proADM) is a reliable and stable surrogate biomarker directly reflecting blood concentrations of highly unstable adrenomedullin. ADM is a peptide produced under stress conditions by a variety of tissues and especially by ECs. ADM may have multiple biological functions included diuretic, vasodilatory activities and more important immunomodulatory and microbicidal activities. An automated fluoroimmunoassay is commercially available (B·R·A·H·M·S MR-proADM KRYPTOR, Thermo Fisher Scientific, Hennigsdorf, Germany). EDTA plasma MR-proADM concentrations were measured using the fully automated fluoroimmunoassay on the KRYPTOR platform, with an assay range of 0.05–100 nmol/L.



Can it facilitate and/or improve clinical decision making?

MR-proADM is a standalone biomarker that may help in facilitating early discharge of patients from ED and ICU and it might be used to escalate antibiotic and fluidic therapies, to make a decision in performing surgery and source control and to apply other therapies used in organ dysfunction such as continuous filtration and other therapies used in organ dysfunction including continuous filtration.

Can MR-proADM also help guide antibiotic treatment?

As yet, no data is available that directly demonstrates using MR-proADM for antibiotic stewardship. However, it can be used to assess the overall risk for therapeutic failure and poor outcome. Thus, Elke al. (2018) have demonstrated in their randomised trial about sepsis, that an increasing value of MR-proADM or a continuous elevated value, despite decreasing PCT concentration is associated with subsequent failure of therapy and a poor outcome. In cancer patients with fever, MR-proADM concentration was increased in patients who did not respond to antibiotic therapy. In these cases antibiotic escalation might be useful. On the other hand, in the case of bacterial meningitis, the use of non bacteriolytic antibiotic, might be associated with better outcome, due to the fact that these antibiotics (e.g. rifampicin) are able to kill bacteria without releasing inflammation mediators. In this subset of patients with high MR-proADM concentration and bacterial meningitis, the early use of non bacteriolytic agents might be associated with increased survival.

Overall, what would you say are the key clinical benefits offered by MR-proADM?

MR-proADM may help in early discharge of patients from ED with values lower than 0.87 nmol/L and, on the other hand, hospitalisation of patients with values higher than 1.5 nmol/L. Furthermore, it may help to identify critical patients with values > 2.5 nmol/L that deserve further diagnostic work-up and intensify antibiotic and sepsis-driven adjunctive therapy. In COVID-19 it might help to identify patients with microvasculature and ECs dysfunction before that respiratory failure may happen. ■

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