

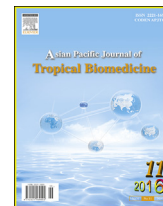
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## Procalcitonin and mid-regional pro-adrenomedullin as promising markers for sepsis diagnosis and prognosis



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To the Editor,

We read with great interest the recent review by Limongi *et al.* on sepsis biomarkers [1]. Recently, the combined use of two biomarkers, procalcitonin (PCT) and mid-regional pro-adrenomedullin (MR-proADM) has been reported in sepsis diagnosis and prognosis. PCT is a polypeptide produced as a precursor of calcitonin by thyroid C cells normally not detectable in healthy individuals, but increased during bacterial infections. For this characteristic, PCT demonstrated high reliability in the early diagnosis of sepsis compared to other biomarkers, such as C-reactive protein [2].

Adrenomedullin is a vasodilatory peptide expressed by many different tissues. Increased levels of adrenomedullin and its prohormone MR-proADM are found in many diseases, such as heart failure, cancer and infections and are associated with disease severity [3]. This biomarker is showed to play a role during host defense against bacterial infections, in fact it can induce hyperdynamic circulation during the early stages of sepsis and the progression to septic shock [4,5]. Recently, MR-proADM has been proposed as a useful biomarker to predict the severity and outcome of sepsis [6].

In the last years, many articles have been published on the role of PCT and MR-proADM in the diagnosis and prognosis of bacterial infections in different settings. Angeletti *et al.* showed that MR-proADM differentiates sepsis from non-infectious systemic inflammatory response syndrome with high specificity and that the simultaneous measurement of MR-proADM and PCT in septic patients increases the post-test diagnostic probability compared to the independent determination of individual markers [7]. Furthermore, in a recent study, PCT and MR-proADM were described as promising markers in

the management of febrile patients with hematological malignancies [8].

Recently, the measurement of PCT, MR-proADM, compared to a panel of 12 cytokines, potentially involved in bacterial systemic infections response, was reported. The receiver operating characteristic curve analysis suggested that PCT, MR-proADM, tumor necrosis factor (TNF)- $\alpha$  were useful markers for sepsis diagnosis. The best post-test probability was found with the combination of PCT with MR-proADM or PCT with TNF- $\alpha$  compared to the single marker determination. Authors, interestingly proposed a composite score derived from PCT, MR-proADM, and TNF- $\alpha$  values showing high reliability in the early diagnosis of sepsis [9].

A score derived from the combination of PCT and MR-proADM has been recently proposed as a useful clinical tool to provide rapid diagnosis as well as suggest prognosis of bacterial infections. The combined score, calculated on the basis of defined score assigned for each PCT and MR-proADM value, can predict bacterial infections and differentiate localized infections from systemic infections, as suggested by receiver operating characteristic curve analysis. On the basis of the score values, localized infections could be differentiated from systemic infections and the severity of the infectious disease can be predicted [10].

For this reason, the use of the combined score was further recommended with serial measurement in the days following the diagnosis of bacterial infections. This evaluation could evidence the worsening of the clinical condition or the absence of response to the antimicrobial therapy.

The importance of the use of this multi-marker approach in the diagnosis and prognosis of sepsis is more evident since the publication of the new definition of sepsis that has been updated

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assigned an important role to the organ dysfunction. A task force represented by experts gathered by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine produced new recommendations and established that “Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the sequential (sepsis-related) organ failure assessment score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L (> 18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%” [11–13].

In conclusion, upon this new definition of sepsis, the use of a multi-marker approach based on PCT and MR-proADM combination represents a valid tool to identify and define a systemic bacterial infection that is evolving and producing an organ dysfunction.

### Conflict of interest statement

We declare that we have no conflict of interest.

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