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INVITED COMMENTARY

Unlocking the Role of Biomarkers in Febrile Neutropenia

Gauri Kapoor[1] · **Payal Malhotra**[1]

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Mid-regional proadrenomedullin (MR-proADM) has emerged as a promising biomarker in the early identification of high-risk patients with sepsis and as a predictor of mortality in critically ill patients [1]. Several meta-analyses have found ProADM to be a robust predictor of short-term complications and mortality in children and adults with community-acquired pneumonia, better than C-reactive protein and procalcitonin (PCT) in most cases [2, 3]. It has also been shown to determine the risk of mortality in children with sepsis presenting to the emergency department [4].

Febrile neutropenia (FN) is a common complication of chemotherapy in children with cancer and one of the most important causes of morbidity and mortality in them. Fever is often the only sign of infection in patients with chemotherapy-induced neutropenia, while the source of infection is often difficult to identify. The early detection of bacteremia and rapid therapeutic intervention are crucial to successful outcome in this immunocompromised group [5].

Blood culture, considered as the gold standard for diagnosing bacteremia, has a turnaround time of 48 h and is usually positive in only a third of the patients. Hence, Meena et al. in their study published in the current issue of *Indian Pediatrics* have attempted to study the role of ProADM in diagnosing clinically documented infections (CDI)/microbiologically documented infections (MDI)/fever without focus in children with cancer having FN, to aid clinical decision-making and avoid unnecessary use of antimicrobial therapy [6].

As a stable precursor of the bioactive peptide adrenomedullin, ProADM plays a key role in the regulation of inflammation, vascular tone, and immune response. MR-proADM is released in response to hyper-permeability in the microcirculation and capillary leakage. It acts as a counter-regulator for tissue ischemia, tissue damage, and deranged microcirculation [7]. The proposed ability of the biomarker to differentiate between infection and non-infectious causes of fever, as well as its association with poor clinical outcomes such as prolonged fever or need for intensive care, underscores its potential as an early diagnostic and prognostic tool. Importantly, proADM may facilitate early initiation of targeted antimicrobial therapy, potentially reducing the overuse of broad-spectrum antibiotics and aiding in timely intervention [8]. Considering these facts, the present study appears to be based on the rationale that as a marker if ProADM rises early in response to infection, even in the absence of overt clinical signs, it holds the promise of improving the management and outcomes of febrile neutropenic episodes in children with cancer.

The authors have also attempted to compare prognostic utility of ProADM with another well-established biomarker PCT in identifying adverse clinical outcome [6]. Following a stimulus of bacterial endotoxins, extrathyroid PCT synthesis occurs from liver and neuroendocrine cells in the lungs. PCT shows a favorable kinetic profile as a biomarker for infections with a rapid rise peaking after 6 h, a plateau phase up to 24 h and normalizing within 2–3 days. In the past few decades, PCT has emerged as a promising marker of infection with a proposed higher sensitivity and specificity than traditional markers such as C-reactive protein [8].

In the present study, the authors observed that ProADM could not differentiate between MDI and CDI. On multivariate analysis, the day-7 PCT was a significant independent predictor of day-30 mortality outcome, while ProADM was not. Both PCT and ProADM on day-1 were unable to predict the need for second-line antibiotics. Furthermore, no significant reduction in median ProADM levels were seen after antibiotic administration [6].

Similar results were observed by Agnello et al. [9] in a study carried out in a pediatric onco-hematology unit in Italy. They reported on 37 FN episodes and did not observe

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✉ Gauri Kapoor
kapoor.gauri@rgcirc.org

[1] Department of Pediatric Hematology-Oncology and Bone Marrow Transplant, Rajiv Gandhi Cancer Institute and Research Centre, Sector 5, Rohini, New Delhi, Delhi 110085, India

any significant difference in ProADM levels between the FN patients with and without bacteremia. In their analysis, receiver operating characteristic curve revealed that ProADM levels had low diagnostic accuracy for blood culture positivity [6]. Lack of severe complications in their population was cited as one of the reasons that the prognostic significance of this biomarker could not be properly evaluated. While in another study of FN in children receiving chemotherapy for solid cancers, Kesik et al. [10] reported that the day-1 plasma ADM levels significantly predicted the presence of culture positivity and high-risk patients with neutropenic fever ($p = 0.016$). Interestingly, they observed culture positivity in 30% high-risk and none of the low-risk FN patients.

There may be multiple reasons for the discordance between these studies, the most important being heterogeneity in patient population in terms of primary disease, chemotherapy protocol, and phase of treatment. Other factors include small sample size, type of assay used for ProADM estimation, identification of high-risk patients, and severity of infection. Most data on the utility of ProADM as an infection biomarker has been documented in neonatal or pediatric intensive care unit (PICU) settings, although data are limited for its use in pediatric oncology. In the same study, it was observed that MR-proADM may be helpful as a prognostic biomarker to stratify the mortality risk in cases of sepsis and septic shock with different degrees of organ damage.

As therapeutic decisions to escalate or de-escalate may be more reliably done based on the patient's general condition rather than results of biomarkers, many investigators have incorporated clinical severity scores such as Pediatric Early Warning Score (PEWS), Pediatric Index of Mortality, and Risk of Early Admission to PICU to better predict clinical severity and likelihood of deterioration [2, 11]. Large sample size of the present study with 66 out of 345 children requiring ICU admission, offers an opportunity to assess the performance of biomarkers and clinical severity scores in this subset. However, it is imperative to understand that these biomarkers may fail their utility to judge severity in viral or fungal infections, though may help differentiate them from bacterial infections.

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Declarations

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