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CORRESPONDENCE

Biomarker cruises in sepsis: who is the CAPTAIN? Discussion on "Circulating biomarkers may be unable to detect infection at the early phase of sepsis in ICU patients: the CAPTAIN prospective multicenter cohort study"

George Briassoulis[1*], Panagiotis Briassoulis[1], Marianna Miliaraki[1], Stavroula Ilia[1], Marianna Parlato[2], François Philippart[3,4], Alexandra Rouquette[5,6], Virginie Moucadel[7], Jean-Marc Cavaillon[8], Benoît Misset[9] and Combined Approach for The eArly diagnosis of INfection in sepsis (CAPTAIN) study group

Initial correspondence from Dr. Briassoulis et al.

Dear Editor,

With great interest, we have read the article by Parlato et al. assessing the accuracy of circulating biomarkers to discriminate between sepsis and non-septic SIRS [1]. In their multicenter study (CAPTAIN), the authors showed that only eight biomarkers had an area under the receiver-operating curve (ROC-AUC) > 0.6. Although these are important findings, some limitations to this assessment need to be addressed. First of all, the authors used the 2003 Sepsis-2 criteria (in the "Methods" section), although they defined sepsis by the 2016 Sepsis-3 definition ("Introduction"–"Discussion"). Using updated definitions, their conclusion that the circulating biomarkers tested discriminate poorly between sepsis and SIRS and that no combination performs better than CRP might be misleading. Second, only patients with SIRS, performing poorly on discriminant validity and convergent validity in sepsis, were eligible, as soon as the physician considered antibiotic therapy (sepsis 87.3%; SIRS 67.0%). Only 13.3% of septic patients had septic shock, 15.4% had cancer, and lower lactate compared to SIRS. Excluding cancer patients, using the Sepsis-3 definition, including trauma-SIRS only, it was recently shown [2] that resistin and extracellular heat-shock protein (eHSP)-90α (ROC-AUC > 0.85) could discriminate sepsis (82.6% septic shock) from SIRS ($p < 0.001$) better than CRP or lactate in adults. In children, eHSP-72, eHSP-90α, and lactate were all strong discriminators of sepsis (94.4% septic shock; ROC-AUC > 0.85) ($p < 0.001$) compared with CRP or resistin (ROC-AUC > 0.75) [2]. An independent (captain) diagnostics model augmenting the discriminatory ability of Sepsis-3 novel biomarkers should be explored across heterogeneous populations in extensive validation studies.

Reply from Dr. Parlato et al.

As indicated by Dr. Briassoulis, we used the 2003 definitions to include patients as our study started before the publication of the 2016 consensus. We aimed to help clinicians to discriminate between intensive care unit (ICU) patients with actual infection from patients without. This could only be done by using a definition of acute inflammation such as SIRS, a term that no longer appears in the 2016 consensus, but still appropriately defines the status of many critically ill patients without infection. According to the 2016 consensus, "suspicion" of infection is part of the syndrome. Therefore, it remains useful to attempt

*Correspondence: ggbriass@otenet.gr
[1] Pediatric Intensive Care Unit, Faculty of Medicine, University Hospital, University of Crete, 71110 Heraklion, Crete, Greece
Full author information is available at the end of the article

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to distinguish "actual" from "suspected" infections (in our study by assessing patients' evolution in the days following inclusion) in order to prompt antibiotic therapy only for those patients with confirmed infection [3].

Dr. Briassoulis pointed out that only 13.3% of our septic patients had shock at ICU admission. However, at inclusion in the study, based on the use of vasopressor drugs, this percentage was higher (40.9%) and consistent with the severity and the mortality of our patients. Discriminant levels of CRP, heat shock proteins, or lactates between septic and SIRS children have been reported by the Briassoulis group [2, 4]. Before these publications, not enough accumulative proofs justified the selection of HSPs among the long list of biomarkers of interest [5], although we had also observed increased HSP-70 among sepsis patients [6]. We found opposite results for CRP and lactates, which may reflect similar severity between our septic and non-septic SIRS patients while their non-septic SIRS patients had low severity [2]. Those biomarkers may rather be markers of severity than of infection [7].

Author details
[1] Pediatric Intensive Care Unit, Faculty of Medicine, University Hospital, University of Crete, 71110 Heraklion, Crete, Greece. [2] Laboratory of Intestinal Immunity and Institut Imagine, INSERM, UMR1163, Paris, France. [3] Service de Médecine Intensive et Réanimation, Groupe Hospitalier Paris Saint-Joseph, Paris, France. [4] Unité Endotoxines Structures et Réponse de l'hôte, Département de Microbiologie, Institut de Biologie Intégrative de la Cellule, Université Paris-Saclay, Saclay, France. [5] Service de Santé Publique et d'Épidémiologie, Hôpital du Kremlin-Bicêtre, CHU de Bicêtre, Assistance Publique, Hôpitaux de Paris, Bicêtre, France. [6] CESP, INSERM, Université Paris-Sud, UVSQ, Université Paris-Saclay, Paris, France. [7] Medical Diagnostic Discovery Department, BioMérieux SA, Lyon, France. [8] Experimental Neuropathology Unit, Institut Pasteur, Paris, France. [9] Service de Réanimation Médicale, Hôpital Charles Nicolle and Groupe de Recherche sur l'Adaptation Microbienne, Université de Rouen Normandie, EA 2656, Rouen, France.

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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflict of interest.

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