Critical Care

CORRESPONDENCE

Open Access

Pancreatic stone protein as a biomarker of sepsis

Diogo Lopes[1*], Beatriz Chumbinho[2], João Pedro Bandovas[2], Pedro Faria[1], Catarina Espírito Santo[1], Bernardo Ferreira[1], Luis Val-Flores[1], Rui Pereira[1], Nuno Germano[1] and Luís Bento[3,4]

Dear Editor,

Regarding the extensive review published in *Critical Care* on biomarkers for sepsis by Dr. Barichello and coworkers [1], we would like to add a comment concerning an absent biomarker. *Do biomarkers in patients with sepsis or septic shock predict mortality, MODS, or organ dysfunction?* was the question addressed and after analysing around sixty biomarkers, they concluded that *significant work is needed to identify the optimal combinations of biomarkers that can augment diagnosis, treatment, and good patient outcomes*. Surprisingly, they do not mention a quite studied biomarker: the Pancreatic Stone Protein (PSP).

PSP is a 16 kDs C-type lectin protein produced mostly by the pancreas and the intestine. Originally described in 1990 as a protein secreted by pancreatic acinar cells to inhibit growth and nucleation of calcium carbonate crystals in the pancreatic juice, subsequent preclinical studies have shown that PSP is actually a damage-associated molecular patterns (DAMPs) produced as a response to sepsis.

PSP has been the subject of 13 clinical studies with 1674 unhealthy patients until 2019. Overall, comparing to routine biomarkers, namely C-reactive protein (CRP) and procalcitonin (PCT), PSP has shown to be more specific and sensitive on infection and sepsis diagnosis in different clinical settings (adults, pediatrics, post-operative, trauma, emergency and intensive care departments).

In 2020, a prospective study in 90 severely burned patients showed that PSP rises significantly earlier (up to 72 h) than the onset of clinical signs of sepsis [2]. PSP accuracy was superior to PCT on sepsis prediction with an area under the curve (AUC) in receiver operating characteristic (ROC) analysis of 0.89—95%CI 0.81–0.97 vs. 0.86—95% CI 0.77–0.94, respectively, and even higher (0.90 to 0.92) if both combined. Early identification of sepsis was confirmed by a prospective multicenter study with 243 critically ill patients from 14 centers that was published in 2021 in *Critical Care* [3], where PSP preceded clinical diagnosis even earlier (5 days), comparing to PCT and CRP (3 and 2 days, respectively). A contemporary meta-analysis (5 studies and 631 patients) [4] concluded that PSP is "a promising biomarker to diagnose infections in hospitalized patients", outperforming CRP or PCT on discriminating infection from non-infection.

Furthermore, on patients admitted for sepsis, the value of PSP at admission correlates with SOFA score (severity of sepsis) and predicts ICU mortality. In COVID-19 patients PSP revealed a potential role as triage tool in emergency department due to its excellent negative predictive value for 7-day mortality [5].

Lastly, knowing that early recognition of sepsis is essential and a major determinant of the outcome, point-of-care testing as the one available for PSP is very appealing, as it provides results at bedside in less than 10 min.

For all these reasons, as in previous reviews, we consider PSP must be included in any manuscript regarding sepsis diagnosis.

This comment refers to the article available online at https://doi.org/10.1186/s13054-021-03862-5.

*Correspondence: diogo.lopes@chlc.min-saude.pt
[1] Department of Intensive Care Medicine (Unidade de Cuidados Intensivos Polivalente), Curry Cabral Hospital, Central Lisbon University Hospital, Lisbon, Portugal
Full list of author information is available at the end of the article

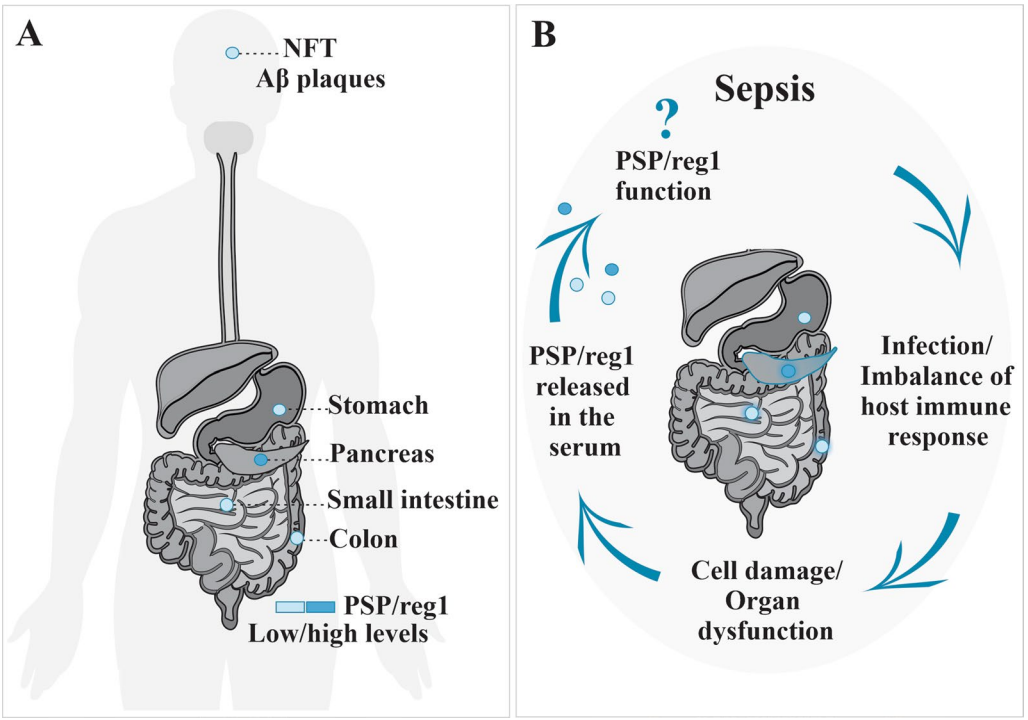

Fig. 1 PSP/reg1 and sepsis. **A** Distribution of PSP/reg1 in a healthy human digestive system and the deposition in the brain of Alzheimer's disease patients. **B** Hypothetical model of PSP's involvement in sepsis. Sepsis triggers an imbalance of the host immune response triggering cell or organ dysfunction, increasing the PSP/reg 1 in the serum of the septic patients. Amyloid-beta (Aβ), neurofibrillary tangles (NFL), pancreatic stone protein (PSP)

Is pancreatic stone protein (PSP) a biomarker for sepsis?

Tatiana Barichello[5,6*], Mervyn Singer[7] and Felipe Dal-Pizzol[6]

*Correspondence: Tatiana.Barichello@uth.tmc.edu
[5]Faillace Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), 1941 East Road, Suite 3140, Houston, TX 77054, USA. [6]Laboratory of Experimental Pathophysiology, Graduate Program in Health Sciences, University of Southern Santa Catarina (UNESC), Criciúma, SC, Brazil. [7]Bloomsbury Institute of Intensive Care Medicine, University College London, London, UK.

We thank Dr. Lopes and colleagues for their letter and for providing new publications that post-dated our literature search [1]. We do readily acknowledge that pancreatic stone protein (PSP), among others, could also have been included as biomarkers of interest in our narrative review [1] but such a review is, by definition, not intended to be all-inclusive. We are uncertain as to the underlying mechanism by which serum PSP levels rise in septic patients. In Fig. 1, we offer some speculative thoughts, suggesting that sepsis triggers an imbalance in the host's immune response mechanisms triggering cell or organ dysfunction and a resulting increase in serum PSP/reg 1 levels. We would also highlight issues relating to specificity as Dr. Lopes and colleagues did not mention that PSP also rises in acute and chronic pancreatitis, pancreatic and gastric cancers, pediatric acute osteomyelitis, type 2 diabetes mellitus, chronic renal failure [6], and in postoperative patients with secondary peritonitis admitted to the intensive care unit (ICU) [7]. Notably, the recent systematic review by Prazak et al. [4] suggests a PSP cut-off value of 44.2 ng/ml in patients diagnosed with an infection in the emergency department or ICU, while Pugin et al. [3] identified a cut-off value of 290.5 ng/ml in patients developing sepsis while in the ICU with non-septic patients having levels exceeding 150 ng/ml throughout their ICU stay. Clearly, a better understanding of what a PSP level represents in specific patient populations is needed. Crucially, like every proposed sepsis biomarker, PSP must also pass the acid test of being able to direct definitively change patient management and improve outcomes.

Acknowledgements
Not applicable.

Authors' contributions
DL wrote the original draft. BC, JPB, PF, CES, BF, LVF, RP, NG and LB revised the manuscript. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
We give our consent for the publication of this letter, as well as our personal information.

Competing interests
We are currently conducting an observational prospective trial using this biomarker, without any financial funding from PSP developer (Abionic®).

Author details
[1]Department of Intensive Care Medicine (Unidade de Cuidados Intensivos Polivalente), Curry Cabral Hospital, Central Lisbon University Hospital, Lisbon, Portugal. [2]Department of General Surgery, Curry Cabral Hospital, Central Lisbon University Hospital, Lisbon, Portugal. [3]Department of Intensive Care Medicine (Unidade de Urgência Médica), São José Hospital, Central Lisbon University Hospital, Lisbon, Portugal. [4]NOVA Medical School, Universidade Nova de Lisboa, Lisboa, Portugal.

Received: 24 February 2022 Accepted: 26 February 2022
Published online: 08 April 2022

References

1. Barichello T, Generoso J, Singer M, Dal-Pizzol F. Biomarkers for sepsis: more than just fever and leukocytosis—a narrative review. Crit Care. 2022;26:14. https://doi.org/10.1186/s13054-021-03862-5.
2. Klein H, Niggemann P, Buehler P, et al. Pancreatic stone protein predicts sepsis in severely burned patients irrespective of trauma severity. Ann Surg. 2021;274(6):e1179–86. https://doi.org/10.1097/SLA.0000000000003784.
3. Pugin J, Daix T, Pagani JL, et al. Serial measurement of pancreatic stone protein for the early detection of sepsis in intensive care unit patients: a prospective multicentric study. Crit Care. 2021;25:151. https://doi.org/10.1186/s13054-021-03576-8.
4. Prazak J, Irincheeva I, Llewelyn M, et al. Accuracy of pancreatic stone protein for the diagnosis of infection in hospitalized adults: a systematic review and individual patient level meta-analysis. Crit Care. 2021;25:182. https://doi.org/10.1186/s13054-021-03609-2.
5. Van Singer M, Brahier T, Brochu Vez MJ, et al. Pancreatic stone protein for early mortality prediction in COVID-19 patients. Crit Care. 2021;25:267. https://doi.org/10.1186/s13054-021-03704-4.
6. Li L, et al. Elevated serum level of pancreatic stone protein/regenerating protein (PSP/reg) is observed in diabetic kidney disease. Oncotarget. 2017;8(24):38145–51.
7. Gukasjan R, et al. Pancreatic stone protein predicts outcome in patients with peritonitis in the ICU. Crit Care Med. 2013;41(4):1027–36.

Publisher's Note