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Serial monitoring of pancreatic stone protein for the detection of sepsis in intensive care unit patients with complicated abdominal surgery: A prospective, longitudinal cohort study

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ABSTRACT

Purpose: The objective of this study was to assess the performance of pancreatic stone protein (PSP) monitoring for the detection of sepsis, prediction of outcome and distinction between bacterial and fungal infections in intensive care unit (ICU) patients with complicated abdominal surgery.
Materials and methods: In this prospective multicenter cohort study, patients with complicated abdominal surgery had serial PSP measurements during their ICU stay. Infectious episodes were classified as bacterial, fungal or mixed. PSPmax (maximal PSP value within 48 h of the diagnosis of infection) and ΔPSP (difference between PSPmax and the preceding PSP value) were used for analyses.
Results: PSPmax was obtained for 118 infectious episodes (68 patients). ΔPSP was available for 73 episodes (48 patients). Both PSPmax and ΔPSP were significantly higher in patients with sepsis and in patients with a fatal outcome. A PSPmax ≥124 ng/ml and a ΔPSP ≥34 ng/ml could detect sepsis with a sensitivity/specificity of 84%/54% and 69%/76%, respectively. There was no significant difference of PSPmax or ΔPSP between patients with bacterial/mixed versus fungal infections.
Conclusions: Serial PSP monitoring may be an additional tool for the early detection of sepsis in patients with complicated abdominal surgery who are at high risk of severe infections.

1. Introduction

Intensive care unit (ICU) patients with complicated abdominal surgery (e.g. recurrent gastrointestinal tract perforation or anastomotic leakage) or acute necrotizing pancreatitis often present severe infections with septic shock in about one third of cases and an overall mortality rate of 30–40% [1]. Early antimicrobial therapy and source control are crucial for the outcome of these infections. However, their diagnosis is often delayed because of the paucity and non-specificity of clinical signs [1]. Therefore, there is a need for non-invasive rapid tests for the early recognition of sepsis in ICU patients with complicated abdominal surgery. Non-specific markers of inflammation, such as the white blood cell

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count (WBC), C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6) and pancreatic stone protein (PSP) have been used as indicators of sepsis in ICU [2,3]. PSP is a glycoprotein secreted in the pancreatic juice in response to systemic stress [2]. When compared to other biomarkers, PSP showed better accuracy for the early detection of infection and sepsis [2,4,5]. In one study in ICU patients with post-operative peritonitis, PSP was the best predictor of infection severity and death compared to WBC, CRP, PCT and IL-6 [6]. Because ICU patients with intra-abdominal infections often undergo multiple abdominal surgeries and/or have concomitant pancreatitis, which may affect PSP levels [2,7], the utility of PSP monitoring for the early detection of sepsis may be questioned in this setting. Moreover, there is no data about possible distinct PSP kinetics between patients with bacterial or fungal infections, such as *Candida* infections, which represent as many as 10–20% cases of post-operative peritonitis [1,8].

The objective of this study was to assess the performance of PSP for the detection of sepsis, prediction of outcome, and distinction between bacterial and fungal infections in ICU patients with complicated abdominal surgery.

2. Materials and methods

2.1. Study design and setting

We used data from a prospective cohort study of the Fungal Infection Network of Switzerland (FUNGINOS) [9]. Consecutive ICU patients with complicated abdominal surgery (i.e. anastomotic leakage, ischemic necrosis, recurrent gastrointestinal surgery or perforation, acute necrotizing pancreatitis) and a PSP value within 48 h from an infectious episode were included. No specific exclusion criteria were applied. Demographic, clinical and microbiological data were collected. Serial serum PSP measurements were realized every 48 h from inclusion and until two weeks after ICU discharge. PSP measurements were performed using an enzyme-linked immunosorbent assay, according to a method previously described [10].

This study was approved by the Institutional Ethical Committees of each participating center and written informed consent was obtained from the patients or their legal representatives. Study design and analyses were performed according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (http://www.strobe-statement.org).

2.2. Definitions

An infectious episode was defined as a clinically and/or microbiologically documented infection. The latter was defined as the isolation of bacterial or fungal pathogens by culture of fluid or tissue samples obtained by surgery or radiological drainage. Infectious episodes were classified as bacterial (mono- or polymicrobial bacterial growth), fungal (monomicrobial growth of *Candida* spp.) or mixed infections (concomitant growth of bacteria and *Candida* spp. in the same sample or in samples drawn at ≤48 h interval). The severity of infection was assessed according to the SEPSIS-3 definitions as sepsis (including septic shock) or no sepsis [11].

2.3. Statistical analysis

For the analyses, the maximal PSP value (PSPmax) obtained within +/− 48 h of each infectious episode was recorded. The kinetics of PSP increase (ΔPSP) was also assessed by calculating the difference between the PSPmax and the preceding 48 h PSP value. PSPmax and ΔPSP values were compared between patients with sepsis versus (vs) no sepsis criteria, survival at end of hospital stay vs in-hospital death, and bacterial or mixed vs fungal infections. Receiver operating characteristic (ROC) curves were assessed using different PSPmax and ΔPSP cut-off values with expression of the area under the curve (AUC). The Youden index was used to define the optimal cut-off value and performance was expressed in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

All analyses were performed using the R software version 4.3.1 (2023) (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/). Descriptive results were expressed as proportions (percentages) or as medians with interquartile range (IQR). The Wilcoxon Rank-Sum test was used to compare continuous variables between groups. Differences between groups were considered as significant for a *P* value ≤0.05.

2.4. Ethical approval statement

The ethics committee of the Canton of Vaud approved this prospective cohort study of FUNGINOS (study protocol number 214/05, 14th November 2005). The original French title upon approval was "Etude prospective multicentrique chez des patients à haut risque hospitalisés aux soins intensifs chirurgicaux sur l'utilité de nouveaux tests de laboratoire pour le diagnostic précoce et le suivi de la candidose invasive et sur le rôle des polymorphismes de gènes impliqués dans l'immunité innée pour la susceptibilité à ce type d'infection sévère". All procedures were followed in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1975.

3. Results

3.1. Characteristics of patients and infections

A total of 118 infectious episodes were analyzed in 68 patients (Fig. 1), of which 83/118 (70.3%) were bacterial, 10/118 (8.5%) fungal and 25/118 (21.2%) mixed infections. The localization of infection was intra-abdominal in 85/118 (72%), pulmonary in 14/118 (11.9%) and other in 19/118 (16.1%) cases. Criteria of sepsis (including septic shock) were present in 62/118 (52.5%) infectious episodes. Sepsis was present in 46/83 (55.4%), 2/10 (20%) and 14/25 (56%) bacterial, fungal and mixed infections, respectively. All-cause in-hospital mortality was 11/

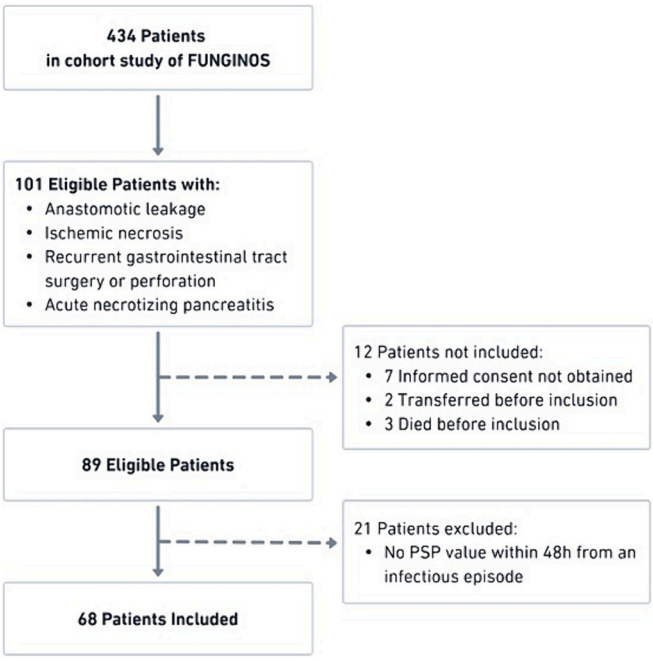

Fig. 1. Flowchart of included patients.
Abbreviations: FUNGINOS, Fungal Infection Network of Switzerland; PSP, pancreatic stone protein.

68 (16.2%) in the entire patient population and 7/53 (13.2%) in patients with intra-abdominal infections. Patient demographics and clinical characteristics are shown in Table 1.

3.2. PSP for the detection of sepsis

PSPmax values displayed important inter-individual variations (12.3–5560 ng/ml) and were significantly higher for infectious episodes occurring during the ICU stay in comparison to those occurring after ICU discharge (median 318.8 vs 73.4 ng/ml, $p < 0.0001$). Higher PSPmax and ΔPSP values were observed in episodes with sepsis vs no sepsis (respectively; median 349.6 vs 118.3 ng/ml, $p < 0.0001$, and 67.5 vs 13.9 ng/ml, $p = 0.005$) (Fig. 2a & 3a). These differences were mainly driven by episodes with septic shock both for PSPmax (423 ng/ml, IQR: 181.6–751) and ΔPSP (83 ng/ml, IQR: 20.9–156.7). ROC analyses of the performance of PSPmax and ΔPSP to predict the severity of infection (sepsis vs no sepsis) showed an AUC of 0.71 (95% confidence interval: 0.62–0.81) and 0.69 (0.56–0.82), respectively (Fig. 4a). The optimal cut-off values were a PSPmax of 123.8 ng/ml (sensitivity 83.9%, specificity 53.6%, PPV 66.7%, NPV 75%) and a ΔPSP of 33.9 ng/ml (sensitivity 68.8%, specificity 75.6%, PPV 68.8%, NPV 75.6%). When the analysis was limited to the episodes of intra-abdominal infections, these differences remained statistically significant for PSPmax (85 episodes, 57 patients; 399.5 vs 116.3 ng/ml, $p = 0.0008$ for sepsis vs no sepsis) and for ΔPSP (46 episodes, 33 patients; 57.2 vs −17.4 ng/ml, $p = 0.036$ for sepsis vs no sepsis). These differences were mainly driven by episodes with septic shock both for PSPmax (453 ng/ml, IQR: 193.3–751) and ΔPSP (100 ng/ml, IQR: 27–153). ROC analyses of the performance of PSPmax and ΔPSP to predict the severity of infection (sepsis vs no sepsis) in intra-abdominal infections showed an AUC of 0.71 (95% confidence interval: 0.6–0.83) and 0.68 (0.51–0.85), respectively (Fig. 4b). The optimal cut-off values were a PSPmax of 123.8 ng/ml (sensitivity 85.4%, specificity 54.1%, PPV 70.7%, NPV 74.1%) and a ΔPSP of 33.9 ng/ml (sensitivity 60.9%, specificity 82.6%, PPV 77.8%, NPV 67.9%).

Table 1
Patient demographics and clinical characteristics.

	$n = 68$
Age (years), median (IQR)	63.5 (51–74)
Female sex	21 (30.9)
Primary diagnosis at ICU admission	
Intraabdominal tumor	22 (32.4)
Acute necrotizing pancreatitis	9 (13.2)
Gastrointestinal perforation	9 (13.2)
Ileus	8 (11.8)
Intestinal ischemic disorder	6 (8.8)
Gastrointestinal bleeding	5 (7.4)
Others	9 (13.2)
Abdominal surgery during study	68 (100)
Number of surgical interventions, median (IQR)	4 (2–5)
Sites of abdominal surgery during study (≥1 site/patient)	
Small intestine	33 (48.5)
Colon	33 (48.5)
Biliary tract	16 (23.5)
Pancreas	15 (22.1)
Stomach	4 (5.9)
Esophagus	2 (2.9)
Infectious episodes ($n = 118$)	
Bacterial	83 (70.3)
Fungal	10 (8.5)
Mixed	25 (21.2)
Severity	
APACHE-II score (at inclusion), median (IQR)	21 (14–26)
SAPS-II score (at inclusion), median (IQR)	51 (40–58)
Sepsis (during hospitalization)	62 (52.5)
Outcome	
Length of hospital stay (days), median (IQR)	52.5 (31–78)
Length of ICU stay (days), median (IQR)	16 (9–30)
In-hospital mortality	11 (16.2)

Data are median (interquartile range, IQR) or number of cases (%).
Abbreviations: ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score.

3.3. PSP for outcome prediction

We observed a significantly higher PSPmax value and a higher ΔPSP in patients with a fatal in-hospital outcome compared to those who were alive at hospital discharge (respectively; median 841 vs 223.1 ng/ml, $p = 0.008$ and median 164.1 vs 18 ng/ml, $p = 0.007$) (Fig. 2b & 3b). ROC analyses of the performance of PSPmax and ΔPSP to predict the outcome (in-hospital death vs survival at hospital discharge) showed an AUC of 0.75 (0.56–0.94) and 0.79 (0.59–0.99), respectively (Fig. 4c). The optimal cut-off values were a PSPmax of 754.5 ng/ml (sensitivity 63.6%, specificity 89.5%, PPV 53.8%, NPV 92.7%) and a ΔPSP of 82.9 ng/ml (sensitivity 77.8%, specificity 79.5%, PPV 46.7%, NPV 93.9%). When the analysis was limited to the episodes of intra-abdominal infections, these differences remained statistically significant for PSPmax (841 vs 211.1 ng/ml, $p = 0.021$ for death vs survival), but not for ΔPSP (164.1 vs 3 ng/ml, $p = 0.12$ for death vs survival). ROC analyses of the performance of PSPmax and ΔPSP to predict the outcome (in-hospital death vs survival at hospital discharge) in intra-abdominal infections showed an AUC of 0.81 (0.62–1) and 0.79 (0.52–1), respectively (Fig. 4d). The optimal cut-off values were a PSPmax of 744 ng/ml (sensitivity 71.4%, specificity 89.1%, PPV 50%, NPV 95.3%) and a ΔPSP of 121.5 ng/ml (sensitivity 83.3%, specificity 81%, PPV 55.6%, NPV 94.4%).

3.4. PSP for the distinction of bacterial and fungal infections

We did not observe any significant difference of PSPmax or ΔPSP between fungal and bacterial or mixed infections neither in the entire patient population (respectively, 212.9 vs 178.3 ng/ml, $p = 0.58$, and 0.9 vs 24 ng/ml, $p = 0.2$) nor in patients with intra-abdominal infections only (351.6 vs 223.4 ng/ml, $p = 0.64$, and 0.6 vs 17.1 ng/ml, $p = 0.58$). Because pancreatitis has been associated with high PSP values [7], we compared PSPmax and ΔPSP between patients with and without acute necrotizing pancreatitis, and did not find a significant difference (169.9 vs 238.1 ng/ml, $p = 0.5$ and 23.9 vs 20.8 ng/ml, $p = 0.87$ respectively).

4. Discussion

In this longitudinal cohort study, we showed that PSP was a predictor of the severity of infection and in-hospital death in a specific subset of ICU patients with complicated abdominal surgery or acute necrotizing pancreatitis. Previous studies performed in other ICU settings, such as patients with trauma, cardiac surgery or ventilator-associated pneumonia, also supported the association of high PSP levels with infection/sepsis and their outcomes [10,12,13]. However, the optimal positivity cut-off may vary according to the studied populations [14]. Indeed, patients with post-operative peritonitis seem to have higher median PSP compared to those with post-trauma or post-cardiac surgery infections [6,10,13,14]. We also observed a significant variability of PSP values between infectious episodes occurring in the ICU vs outside of the ICU in our cohort. In a large multicenter study conducted in a general ICU population, Pugin et al. reported a 72% sensitivity and 69% specificity of PSP to discriminate the presence versus absence of sepsis at a cut-off of 290 ng/ml [4]. In the present study limited to the specific subset of patients with complicated abdominal surgery or acute necrotizing pancreatitis, we found an optimal performance (84% sensitivity and 54% specificity) at a lower cut-off (123.8 ng/ml). In a similar patient setting, Gukasjan et al. found that PSP could predict fatal outcome with a 78% sensitivity and 62% specificity using a 130 ng/ml cut-off [6], while our results suggested a higher optimal cut-off for the prediction of in-hospital death (754.5 ng/ml).

The large variability of PSP levels across studies and patient subsets makes that it is difficult to define an optimal cut-off. Because PSP is a

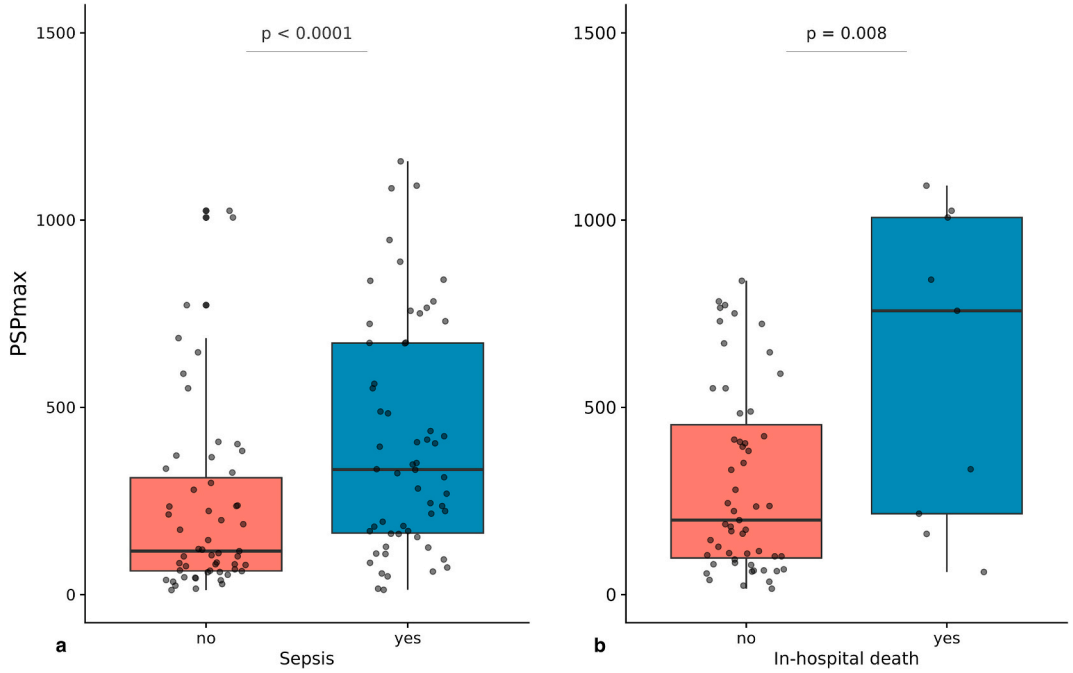

Fig. 2. Distribution of PSPmax values per infectious episode by severity of infection (no sepsis vs sepsis), **2a**), and clinical outcome (survival at hospital discharge vs in-hospital death), **2b**). For visualization purposes, the outliers with PSPmax values of 1592, 2251, 2512, 3029 and 5560 ng/ml were hidden in the plot but included in the statistical comparison.
Abbreviations: PSP, pancreatic stone protein; PSPmax, maximal PSP value obtained within +/− 48 h of each infectious episode.

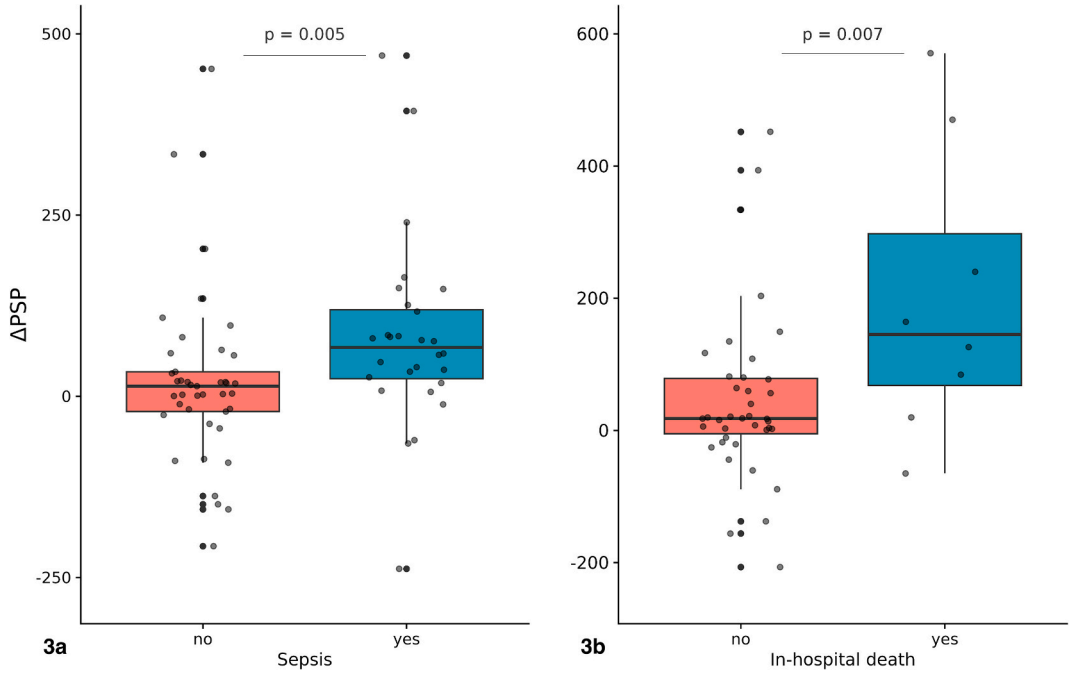

Fig. 3. Distribution of ΔPSP values per infectious episode by severity of infection (no sepsis vs sepsis), **3a**), and clinical outcome (survival at hospital discharge vs in-hospital death), **3b**). For visualization purposes, outliers with ΔPSP values of −1583, −517, 570.6 and 2050 ng/ml were hidden in the plot but included in the statistical comparison.
Abbreviations: PSP, pancreatic stone protein; ΔPSP, difference between the PSPmax and the preceding PSP value.

non-specific inflammatory marker, it can be influenced by non-infectious stress conditions that are often present among ICU patients with post-operative peritonitis [2]. In particular, recent surgery and chronic pancreatitis were shown to increase PSP levels [7,13]. Although PSP is secreted by the pancreas, our analysis did not find significant differences of PSP values between patients with presence or absence of acute necrotizing pancreatitis. However, because we observed a wide range of PSPmax values in our study cohort, we also analyzed the kinetics of PSP to see if a significant PSP rise would represent a better marker of sepsis rather than an absolute PSP value. We observed that a PSP increase of ≥34 ng/ml (ΔPSP) over 48 h was also an indicator of severe infection and bad prognosis. While PSPmax had a better

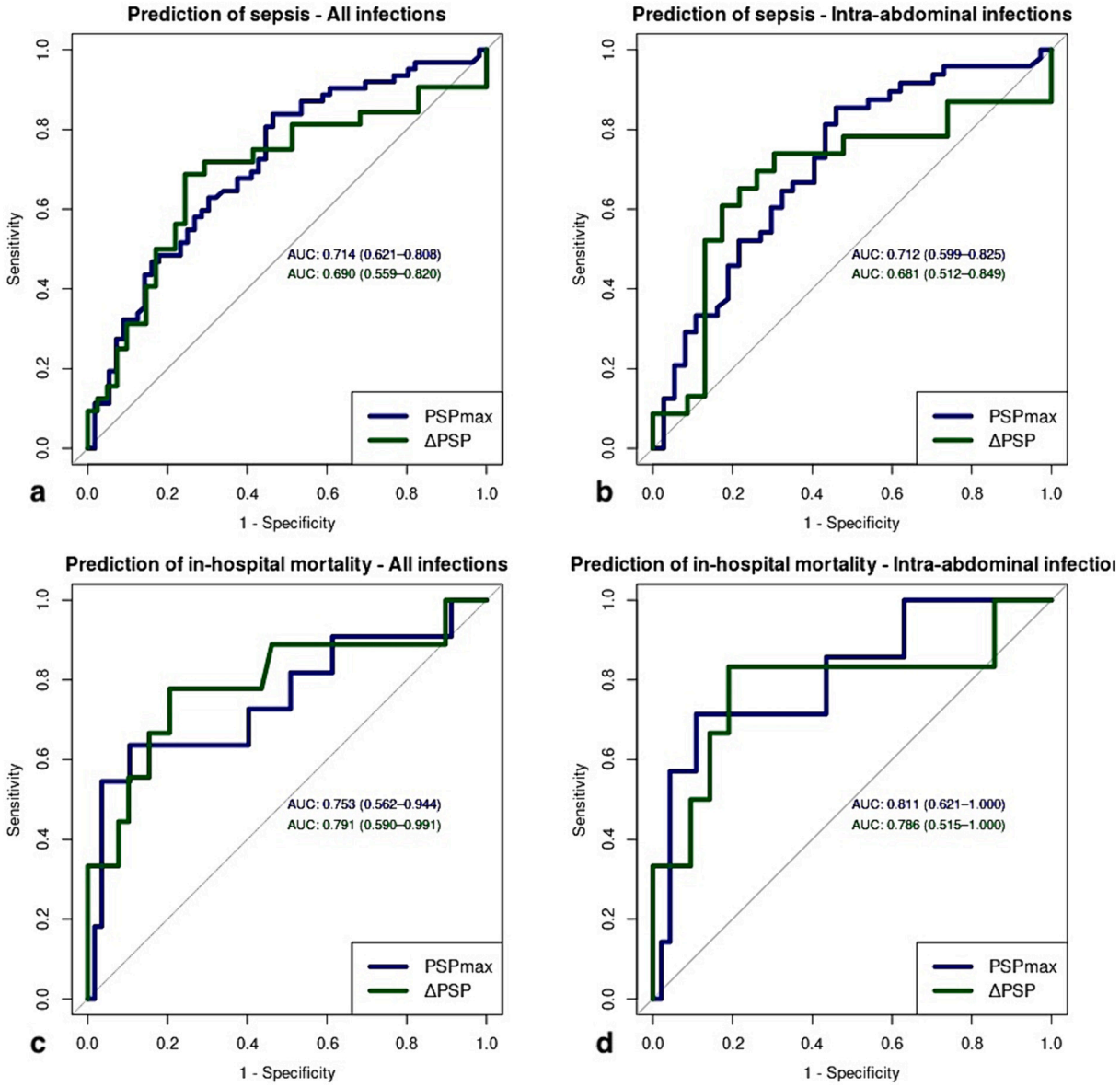

Fig. 4. Receiver operating characteristic (ROC) curves of the performance of PSPmax and ΔPSP for the prediction of sepsis in all patients (**4a**), in-hospital mortality in all patients (**4b**), sepsis in patients with intra-abdominal infections only (**4c**), and in-hospital mortality in patients with intra-abdominal infections only (**4d**). 95% confidence intervals are shown in parenthesis near each AUC value.
Abbreviations: PSP, pancreatic stone protein; PSPmax, maximal PSP value obtained within +/− 48 h of each infectious episode; ΔPSP, difference between the PSPmax and the preceding PSP value; AUC, area under the curve.

sensitivity than ΔPSP for sepsis detection (84% vs 69%), the ΔPSP had a better specificity than PSPmax (76% vs 54%).

Overall, these results suggest that monitoring of PSP might be helpful to identify patients who would benefit from a prompt initiation of antimicrobial therapy. However, the question whether a PSP shift could anticipate clinical signs of sepsis and improve clinical outcome remains open. Indeed, because the majority of infectious episodes occurred within a short time window after study inclusion or frequently overlapped, we could not systematically examine PSP kinetics over a longer period. For the same reasons, we could not make conclusions about the utility of PSP values in follow-up to assess the response to therapy. Nonetheless, some previous studies suggested that PSP increase preceded the clinical signs of sepsis and the rise of other inflammatory biomarkers [2,4,5,10].

Although PSP is a non-specific marker, we investigated its potential utility to distinguish bacterial from fungal infections. Intra-abdominal candidiasis, caused by *Candida* spp., may affect 10 to 20% of patients with complicated abdominal surgery and the question whether to start empirical antifungal therapy in case of sepsis remains a matter of debate [9]. We compared PSPmax and ΔPSP between fungal vs bacterial/mixed infections and did not find a statistically significant difference. Although this analysis was limited by the very small number of pure fungal infections, our study is the first to investigate the value of this marker for the diagnosis of fungal infection.

While it would be interesting to compare PSP with other inflammatory markers, such measurements were not included in our prospective sample collection, thereby precluding comparisons between different biomarkers. In their study, Gukasjan et al. found that PSP outperformed WBC, CRP, PCT and IL-6 for the prediction of the severity and prognosis of infection [6]. Pugin et al. have also showed that PSP predicted sepsis in a more timely manner than CRP and PCT [4]. Additionally, besides the analysis of intra-abdominal infections only, we also performed an analysis both intra- and extra-abdominal infectious episodes. In fact, in the "real life" clinical setting, patients hospitalized in the ICU with

severe intra-abdominal complications often suffer from extra-abdominal infections, which are equally crucial to diagnose in the same way as intra-abdominal infections. The higher mortality rate among patients with all types of infections (16.2%) compared to those with intra-abdominal infections only (13.2%) further supports this fact.

In conclusion, the present study further supports the role of PSP as a marker of severe infection and predictor of outcome in ICU patients, including among those with other stress conditions that may affect PSP levels, such as recurrent abdominal surgery and/or acute necrotizing pancreatitis. As the performance in ROC curves (AUC around 70%) is moderate, PSP should be interpreted in conjunction with other clinical indices or biological markers of severity of infection. Serial measurement of PSP may be useful for the early detection of sepsis in this latter category of patients at high risk of severe infections.

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Financial disclosure and conflicts of interest

FL has received research funding from Gilead, MSD, Pfizer and Novartis, has participated to advisory boards of Gilead, MSD and Pfizer, and has received honoraria for conferences from Gilead and Mundipharma. All contracts were made with and fees paid to his institution (CHUV).

Other authors: no conflict of interest.

CRediT authorship contribution statement

Paraskevas Filippidis: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Leana Hovius:** Writing – review & editing, Writing – original draft, Data curation, Investigation. **Frederic Tissot:** Writing – review & editing. **Christina Orasch:** Writing – review & editing. **Ursula Flückiger:** Writing – review & editing. **Martin Siegemund:** Writing – review & editing. **Jean-Luc Pagani:** Writing – review & editing, Methodology. **Philippe Eggimann:** Writing – review & editing. **Oscar Marchetti:** Writing – review & editing. **Frederic Lamoth:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2024.154772.

References

[1] Blot S, Antonelli M, Arvaniti K, Blot K, Creagh-Brown B, de Lange D, et al. Epidemiology of intra-abdominal infection and sepsis in critically ill patients: "AbSeS", a multinational observational cohort study and ESICM Trials Group Project. Intensive Care Med 2019;45(12):1703–17.
[2] Eggimann P, Que YA, Rebeaud F. Measurement of pancreatic stone protein in the identification and management of sepsis. Biomark Med 2019;13(2):135–45.
[3] Tan WJ, Ng WQ, Sultana R, de Souza NN, Chew MH, Foo FJ, et al. Systematic review and meta-analysis of the use of serum procalcitonin levels to predict intra-abdominal infections after colorectal surgery. Int J Colorectal Dis 2018;33(2):171–80.
[4] Pugin J, Daix T, Pagani JL, Morri D, Giacomucci A, Dequin PF, 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(1):151.
[5] Que YA, Delodder F, Guessous I, Graf R, Bain M, Calandra T, et al. Pancreatic stone protein as an early biomarker predicting mortality in a prospective cohort of patients with sepsis requiring ICU management. Crit Care 2012;16(4):R114.
[6] Gukasjan R, Raptis DA, Schulz HU, Halangk W, Graf R. Pancreatic stone protein predicts outcome in patients with peritonitis in the ICU. Crit Care Med 2013;41(4):1027–36.
[7] Sarles H. Epidemiology and physiopathology of chronic pancreatitis and the role of the pancreatic stone protein. Clin Gastroenterol 1984;13(3):895–912.
[8] de Ruiter J, Weel J, Manusama E, Kingma WP, van der Voort PH. The epidemiology of intra-abdominal flora in critically ill patients with secondary and tertiary abdominal sepsis. Infection 2009;37(6):522–7.
[9] Tissot F, Lamoth F, Hauser PM, Orasch C, Fluckiger U, Siegemund M, et al. beta-glucan antigenemia anticipates diagnosis of blood culture-negative intraabdominal candidiasis. Am J Respir Crit Care Med 2013;188(9):1100–9.
[10] Keel M, Harter L, Reding T, Sun LK, Hersberger M, Seifert B, et al. Pancreatic stone protein is highly increased during posttraumatic sepsis and activates neutrophil granulocytes. Crit Care Med 2009;37(5):1642–8.
[11] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):801–10.
[12] Boeck L, Graf R, Eggimann P, Pargger H, Raptis DA, Smyrnios N, et al. Pancreatic stone protein: a marker of organ failure and outcome in ventilator-associated pneumonia. Chest 2011;140(4):925–32.
[13] Klein HJ, Csordas A, Falk V, Slankamenac K, Rudiger A, Schonrath F, et al. Pancreatic stone protein predicts postoperative infection in cardiac surgery patients irrespective of cardiopulmonary bypass or surgical technique. PLoS One 2015;10(3):e0120276.
[14] Prazak J, Irincheeva I, Llewelyn MJ, Stolz D, de Guadiana Garcia, Romualdo L, 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(1):182.