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Short communication

Pancreatic Stone Protein in patients with liver failure: A prospective pilot cohort study

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ABSTRACT

Background: Pancreatic Stone Protein (PSP) seems to have higher accuracy for sepsis detection compared to other biomarkers. As PSP has never been studied in patients with liver failure (LF), our purpose was to assess its accuracy for diagnosis of infection and prognosis in this population.
Methods: We conducted a prospective pilot cohort study on patients with LF consecutively admitted to the Intensive Care Unit of a liver transplant center in 2021–2023. Ongoing overt infection was an exclusion criterion. Daily measurements of biomarkers were performed until discharge, death, or for 21 days. Analysis was performed by adjusting the baseline for the first infection episode (median on D3), which was the reference for those non-infected.
Results: Sixteen patients were included, 7 with acute and 9 with acute-on-chronic LF. Median age was 54 (interquartile range 42–64) years, half were female, with admission SOFA score of 10 (IQR 8–12). Hospital mortality was 43.8% (n = 7). An infection was observed in 8 patients, who presented non-significantly higher levels of PSP than non-infected ones during follow-up. Levels were higher in non-survivors than survivors ($p < 0.05$ from D4 on and since the day of infection considering only infected patients). Similarly, patients under renal replacement therapy had higher PSP levels than others ($p < 0.05$, D2 to D7 after admission).
Conclusion: This pilot study provides early insights into PSP kinetics, suggesting a potential role for prognosis in patients with LF. PSP rises in both ALF and ACLF to levels sustainably higher than those expected for healthy adults. Further research is needed to reassess its diagnostic accuracy for infection and redefine cut-offs in this population.

Introduction

Patients with acute liver failure (ALF) are at high risk of infection, which occurs in nearly half of patients [1]. Likewise, infection is a frequent complication of cirrhosis which often precipitates the development of acute-on-chronic liver failure (ACLF), being an independent risk to mortality [2–4].

The usefulness of commonly used biomarkers in infection diagnosis is limited in liver failure (LF) [1]. High levels of C-reactive protein (CRP) are found in cirrhosis without infection [5], significantly higher in ACLF [2], and increasing with the number of precipitants [3]. In ALF, CRP is poorly synthetized therefore, blood levels are frequently low. Moreover, procalcitonin (PCT) blood levels may rise due to hepatic necrosis, irrespective of

Abbreviations: ACLF, acute-on-chronic liver failure; ALF, acute liver failure; CRP, C-reactive protein; LF, liver failure; PCT, procalcitonin; PSP, Pancreatic Stone Protein; RRT, renal replacement therapy.

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infection, particularly in acetaminophen toxicity [6]. PCT blood levels also vary with acute kidney injury, a common complication of LF.

Pancreatic Stone Protein (PSP) is a 16 kDa glycoprotein secreted by the gastrointestinal tract that discriminates well between sterile inflammation and infection [7,8].

Further research on biomarkers to distinguish infection from inflammation and to help predict clinical deterioration is warranted as per the latest European ALF guidelines [1]. To the best of our knowledge, there is a lack of data on PSP utility in patients with liver failure (LF), either ALF or ACLF.

Methods

We conducted a prospective cohort study on adult patients with ALF or ACLF consecutively admitted to the Intensive Care Unit of a liver transplant center in Lisbon (Portugal) from December 2021 to May 2023. The exclusion criteria were ongoing overt infection or antimicrobial therapy with a therapeutic purpose (not prophylactic) at ICU admission or during the 3 days before, late screening (5 days after admission), participation refusal, or hospitalization shorter than 48 h.

Informed consent was obtained from patients or their next of kin. The local ethics committee approved the study protocol (n° 1116/2021). This study abided by the principles of the Declaration of Helsinki.

Daily measurements of C-reactive protein (CRP), Procalcitonin (PCT), and Pancreatic Stone Protein (PSP) were performed from ICU admission (Day 1) and for 21 days, until hospital discharge or death. Patients were followed up until discharge or death if hospitalization was longer than 21 days.

PSP levels were determined with the point-of-care device abioSCOPE® (Abionic SA, Switzerland), measuring levels between 20 and 600 ng/mL. According to internal data, the normal range in healthy adults is 27–61 ng/mL (5^{th} and 95^{th} percentiles, median 41.7 ng/mL). CRP and PCT measurements were performed by a central laboratory using cobas® 8000 device (Roche Diagnostics) (normal range of 5 mg/L and 0.05 ng/mL, respectively). As PSP is secreted mostly by the pancreas, lipase and amylase were monitored daily for control.

ALF and ALCF were defined according to the most recent European Association for the Study of the Liver definitions and infections according to previously used definitions [9].

The primary endpoint was the association between PSP levels and infection occurrence during the study follow-up. The secondary endpoint was the association between PSP levels and hospital all-cause mortality.

Based on previous literature, to detect a difference of at least 30% (from 50% to 20%) in infection prevalence, with a power of 0.80 and a significance level of 0.05, we would require an overall sample of 16–18 patients [10]. Fisher exact, Mann-Whitney, and Spearman's correlation tests were used for statistics. Analysis of PSP according to survival was performed by comparing levels since admission. Regarding infection analysis, patients were allocated to the "infection" group or not according to the occurrence of an infection during the first 21 days after admission. In the infection group, the event day was set on the day of diagnosis of the first episode of infection. The "event" reference day in the "no infection" group was set to Day 3, which was the median day of infection in the "infection" group. A similar analysis was performed regarding renal replacement therapy (RRT), set to Day 1 (median of RRT start). Analyses were conducted on EZR®, version 1.61, and IBM® SPSS® Statistics software, version 29.

Results

During the study period, a total of 16 patients with ALF and 43 with ACLF were identified, and 16 were included in the final analysis, 7 with ALF (all non-acetaminophen related) and 9 with ACLF. Baseline characteristics including demographics, organ support, acuity (SOFA or CLIF-SOFA scores), and clinical outcomes (liver transplantation and mortality) were similar between infected and non-infected patients (Table 1). At least one episode of infection occurred in 8 patients during follow-up, at a median (interquartile range) of 3 (1–5) days post-admission. Primary bloodstream infections and pneumonia were the most frequent sources (n = 3). On admission 4 patients had ongoing prophylactic antimicrobial treatment.

Overall, 216 PSP blood measurements were performed (18 (8–19) per patient). The highest median levels were observed on D+2 (345 (192−600) ng/mL), falling gradually until D+11 and remaining above 120 ng/mL during the last days. During follow-up, pancreatic enzyme levels remained within normal range.

Since the day before infection diagnosis, infected patients showed persistent non-significantly higher levels of PSP compared with non-infected ones (Fig. 1a), independently of the clinical course. In the infection group, PSP median levels were frequently above 300 ng/mL, with the highest on D+1 (600 (317–600) ng/mL). The late peak observed is due to a second episode of infection that occurred in two patients. In the non-infected group, the highest median levels were observed on D-1 (315 (197–531) ng/mL), remaining mainly below 200 ng/mL after D+3.

PCT levels were significantly higher in infected patients than others on the day of infection (Table 1) and CRP levels on D-1 (48.5 (29.6–95.0) *vs.* 19.0 (5.6–19.0) mg/L, $p = 0.048$).

Median PSP levels were higher in non-survivors than survivors ($p < 0.05$ from Day 4 after admission), contrary to other biomarkers (Fig. 1b). Considering only infected patients, levels were significantly higher in non-survivors since the day of infection diagnosis (Fig. 1d). Patients under RRT had constantly higher values of PSP than the remaining ones (Fig. 1c). No difference was present between patients with ALF vs. ACLF.

Overall, PSP and SOFA scores strongly correlated from D+2 to D+5 after infection diagnosis ($p < 0.05$, $0.7 \leq r < 0.8$, $0.5 < R^2 < 0.6$).

Discussion

In this pilot study, we observed that, despite liver failure, median PSP levels were higher in infected patients than in non-infected ones without a statistically significant difference. This might be explained by the following factors: the low number of included patients; the point-of-care test's upper limit of detection of 600 ng/mL; and clinical confounders such as sterile inflammation in LF, possible non-diagnosed infections, RRT, use of prophylactic antimicrobials, or immunomodulatory and transplant-related medications. Concerning the previously described PSP earliness on infection detection, we were not able to reproduce it [7]. On the one hand, the median day of infection was premature, and on the other hand, an intra-individual variability of PSP levels was observed during serial measurements.

In our cohort, we showed PSP blood levels rise in both ALF and ACLF to levels sustainably higher than those expected for healthy adults. Particularly in ALF, this is an advantage compared to CRP which behaves as a false-negative during infection due to lack of production. Increased PSP levels have been described in patients with cirrhosis, but not with acute or chronic hepatitis [11]. As PSP is not found in hepatocytes, a decrease in clearance due to a reduction in hepatic uptake and portal-systemic shunt has been

Table 1
Baseline characteristics, prognostic scores, severity scores, organ support, and outcomes according to the presence of infection.

	N = 16	Infection (n = 8)	No Infection (n = 8)	*p*-value
Age, years (IQR)	54 (42–64)	54 (40–64)	53 (45–61)	0.916
Gender female, n (%)	8 (50.0)	3 (37.5)	5 (62.5)	0.619
Charlson comorbity index, (IQR)	4 (2–5)	4 (2–6)	4 (3–4)	0.958
SAPS II score, (IQR)	57 (49–67)	57 (53–67)	55 (46–70)	0.721
ALF, n (%)	7 (43.8)	4 (50.0)	3 (42.9)	1.0
ACLF, n (%)	9 (56.2)	4 (50.0)	5 (62.5)	1.0
grade II, n (%)	5 (56)	2 (25.0)	3 (37.5)	1.0
grade III, n (%)	4 (44)	2 (25.0)	2 (25.0)	1.0
CLIF-C ACLF score, (IQR)	50 (46–62)	53 (49–58)	47 (46–62)	0.806
MELDNa, (IQR)	30 (27–34)	34 (29–37)	27 (25–33)	0.219
SOFA score (admission), (IQR)	10 (8–12)	9 (8–12)	11 (8–13)	0.557
CLIF-SOFA score (admission), (IQR)	13 (11–16)	12 (10–15)	14 (11–18)	0.399
Vasopressors, n (%)	14 (87.5)	6 (75)	8 (100)	0.467
IMV, n (%)	15 (93.8)	8 (100)	7 (87.5)	1.0
RRT, n (%)	11 (68.8)	7 (87.5)	4 (50)	0.282
HVPE, n (%)	3 (18.8)	2 (25)	1 (12.5)	1.0
Urgent liver transplant, n (%)	8 (50.0)	4 (50)	4 (50)	1.0
Day of liver transplant, days (IQR)	5 (3–7)	4 (2–6)	6 (4–8)	0.343
ICU LOS, days (IQR)	8 (6–48)	11 (8–16)	8 (6–10)	0.370
Hospital LOS, days (IQR)	26 (8–56)	33 (10–47)	18 (7–73)	0.958
Hospital mortality, n (%)	7 (43.8)	4 (50)	3 (37.5)	1.0
Hospital day of death, days (IQR)	8 (4–10)	10 (7–21)	5 (4–7)	0.368
1-year mortality, n (%)	10 (62.5)	5 (62.5)	5 (62.5)	1.0
Blood biomarkers on day of infection diagnosis, (IQR)				
PSP levels (ng/mL)	289 (134–575)	398 (145–600)	259 (140–438)	0.433
CRP levels (mg/L)	24.5 (9.6–72.2)	43.8 (21.0–86.7)	11.7 (6.2–28.2)	0.232
PCT (ng/mL)	0.62 (0.27–1.45)	1.02 (0.72–2.07)	0.25 (0.23–0.55)	0.037

Abbreviations: ALF, acute liver failure; ACLF, acute-on-chronic liver failure; CLIF-C, chronic liver failure-consortium; CRP, C-reactive protein; ICU, Intensive Care Unit; HVPE, high-volume plasma exchange; IQR, interquartile range; IMV, invasive mechanical ventilation; LOS, length of stay; MELDNa - Model for End-Stage Liver Disease sodium; PCT, procalcitonin; PSP, Pancreatic Stone Protein; RRT, renal replacement therapy; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

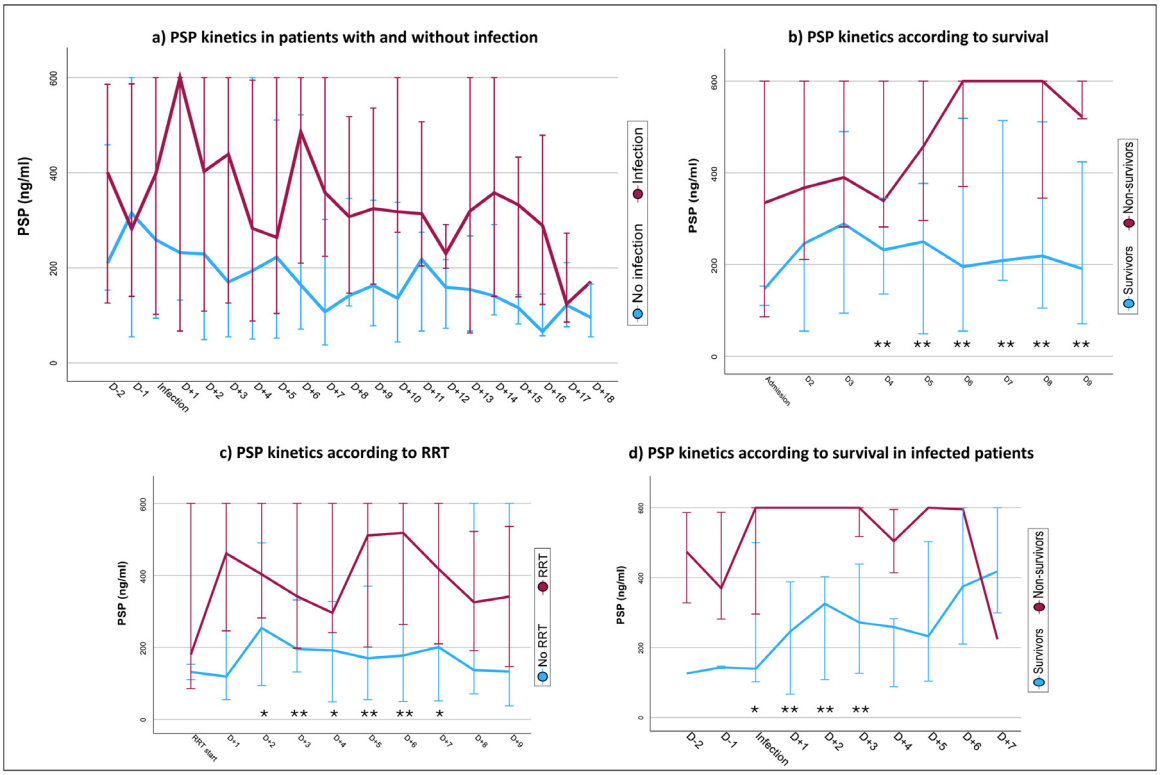

Fig. 1. Comparison of Pancreatic Stone Protein levels and kinetics between (a) patients with or without an infection[a], (b) survivors and non-survivors, (c) with and without renal replacement therapy (RRT)[b], and d) survivors and non-survivors considering only infected patients (n = 8).
[a] *p* was non-significant from D-2 to D+18.
[b] Only patients with RRT longer than 24 h were considered (median RRT duration was 5 (IQR 2–9) days).
**$p < 0.05$.
*$p < 0.10$.
Abbreviations: IQR, interquartile range; NS, not significant; PSP, Pancreatic Stone Protein; RRT, renal replacement therapy.

proposed. PSP performance by receiver operating characteristic (ROC) curve was not feasible in this small cohort, imposing further research to redefine the appropriate cut-off in patients with LF.

Moreover, non-survivors had sustained higher levels of PSP compared to survivors, thus suggesting a potential prognostic role for short-term mortality, previously described in other critically ill patients [12]. Therefore, further studies may explore the potential role of PSP as an early biomarker at bedside assessing prognosis in LF.

Regarding acuity, the correlation between PSP levels and SOFA score found in general critically ill patients was apparent in our cohort of patients with LF [8]. Compared to SOFA score, which requires 6-organ-related parameters and at least 24 h to assess, PSP point-of-care measurements, available within 6 min, may be a simpler tool to integrate into clinical practice. Further studies are needed to assess the equivalence of their prognostic role in assessing overall disease severity.

Patients with impaired renal function are known to have higher levels of PSP [11]. In our cohort, patients under RRT had significantly higher values of PSP, but RRT was also more prevalent in infected patients and non-survivors, a potential source of confounding. Up-regulation because of organ dysfunction and accumulation due to lack of renal filtration are possible mechanisms. Presently, there is a lack of studies evaluating the PSP kinetics under RRT, hemoadsorption, or plasma exchange.

No data is published on PSP kinetics according to antimicrobial treatment efficacy. A progressive decline of PSP levels was observed in all survivors, probably due to a reduction of inflammation. Still, the decline was slow, suggesting a potential practical limitation to assess response to antibiotic therapy or to consider stopping treatment in this population.

Our results need to be interpreted considering the following limitations: this was a small single-center pilot study and thus prone to selection bias; both patients with ALF and ACLF were included as LF models, however, these diseases have largely different demographics, physiopathology, and outcomes; we could not properly account for some clinical confounding factors, as mentioned earlier.

Despite these limitations, our pilot study may provide early insights into the PSP blood kinetics in patients with LF, with and without infection. Furthermore, it may inform future studies on the potential diagnostic and prognostic roles of this biomarker in patients with either ALF or ACLF.

CRediT authorship contribution statement

This study was conceptualized by DL in the context of his PhD. DL drafted the manuscript, which was reviewed by all authors. DL, JPB, BC, CES, MS, BF, LVF, RP collected patients' samples and DL collected patients' data. DL, RP, FSC and PP contributed to statistical analysis. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Consent for publication

All authors consent to the publication of this manuscript, as well as our personal information.

Ethical statement

Informed consent was obtained from patients or their next of kin. The local ethics committee approved the study protocol (n° 1116/2021). This study abided by the principles of the Declaration of Helsinki.

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Declaration of competing interest

All authors have no conflict of interest on the topic to declare.

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