

The role of pancreatic stone protein as a prognostic factor for COVID-19 patients

M. LAGADINO^{1,2}, T. PARASKEVAS¹, D. VELISSARIS¹, C. MICHAILIDES¹,
G. ELEFThERAKIS¹, F. SAMPSONAS³, G. SIAKALLIS⁴,
S.F. ASSIMAKOPOULOS^{1,2}, M. MARANGOS^{1,2}

¹Department of Internal Medicine, ²Division of Infectious Diseases, ³Respiratory Medicine Department, University Hospital of Patras, Patras, Greece

⁴Department of Basic and Clinical Sciences, Medical School University of Nicosia, Nicosia, Cyprus

Abstract. – OBJECTIVE: The outbreak of Severe Acute Respiratory Syndrome-CoronaVirus 2 (SARS-CoV-2) has rapidly spread throughout the world straining health care systems. Several biomarkers indicate the presence of hyper-inflammation and evaluate the severity of the disease. Our aim was to investigate the prognostic value of pancreatic stone protein plasma concentration in patients with SARS-CoV-2 pneumonia.

PATIENTS AND METHODS: We prospectively studied 55 patients with acute SARS-CoV-2 pneumonia admitted to our tertiary hospital. Sepsis biomarkers, including pancreatic stone protein (PSP), were measured on admission. The role of these biomarkers in the prediction of in-hospital mortality (28 day) and length of hospital stay was investigated.

RESULTS: Although Pancreatic stone protein did not have significant prognostic value for in-hospital mortality, there was a moderate accuracy for prolonged length of stay. The optimal cut-off value for prolonged hospital stay was 51 ng/dL (Sensitivity: 0.65, Specificity: 0.913).

CONCLUSIONS: Pancreatic Stone Protein on admission could accurately identify patients requiring prolonged hospitalization. The results of this study can serve as a strong early basis for future validation studies of such an innovative approach.

Key Words:

Pancreatic stone protein, SARS-CoV-2 infection, Hospitalization, Disease severity.

Introduction

The outbreak of Severe Acute Respiratory Syndrome-CoronaVirus 2 (SARS-CoV-2) has rapidly spread throughout the world straining health care systems¹. Both epidemiological and clinical features of patients with COVID-19 lead

to clusters of severe respiratory illness with increased intensive care unit (ICU) admissions and high mortality rates².

Several biomarkers indicating the presence and degree of inflammation evaluate the severity of the disease. Since therapeutic strategies should be adapted to each individual patient, the identification of patients who are at high risk of death and who might benefit most from aggressive treatment represent a step towards such a tailored management. The ideal biomarker for sepsis is still warranted and should be the one with the best accuracy in the early identification of sepsis and increased prediction capability. Pancreatic stone protein (PSP), a pro-inflammatory mediator that binds to polymorphonuclear cells and triggers their activation *in vitro*, is a novel biomarker with promising results in various clinical settings. It can be used to diagnose and evaluate patients with sepsis, characterize the severity of infection, and predict the outcome of patients with sepsis requiring ICU management³.

We aimed to investigate the prognostic value of PSP in a group of hospitalized patients with lung infection due to COVID-19.

Patients and Methods

Adult patients with confirmed SARS-CoV-2 infection and respiratory tract symptoms who needed hospitalization were enrolled in this prospective study. All patients were treated in the COVID-19 Units of the Department of Internal Medicine of Patras University Hospital, Greece, from November 2021 to December 31, 2021. We excluded patients with age < 18 years, those who had any pre-existent infection (for the past 2 we-

eks) and any known chronic disease that affected the lungs. Written informed consent was obtained from all patients enrolled in the study. The Ethics Institutional Board of the Hospital approved the study protocol.

White blood cells (WBC), absolute lymphocytes count (ALC), Neutrophil to Lymphocytes ratio (NLR), absolute monocyte count, d-dimers, fibrinogen, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, highly sensitive troponin I (hs-TnI) on admission day for each patient were recorded. We measured Pancreatic Stone Protein plasma levels on admission using a diagnostic capsule for quantitative measurement with a desktop spectrophotometer diagnostic device (*abioSCOPE*). Final outcome (death or discharge) for each patient was recorded. Length of hospital stay (LOHS) was treated as a categorical outcome for ROC analysis, and LOHS>10 days was considered as prolonged hospitalization. Patients' data were extracted from the Hospital's electronic medical records.

Statistical Analysis

Statistical analysis of data was performed using SPSS-26 statistical software (IBM, Armonk, NY, USA). Continuous variables were expressed as median (IQR). The level of statistical significance, *p*-value, was set at 0.05.

The Mann-Whitney U test was used to compare continuous variables between survivors and non-survivors. Chi-square test was used for categorical variables. Receiver operating characteristic (ROC) curve analysis was used to assess the prognostic value of LDH, NLR, Fibrinogen, PSP, CRP,

Ferritin and hs-TnI in the enrolled patients. Youden Index was used to find the cut-off point for PSP.

Results

A total number of 55 consecutive adult patients (≥18 years old) with laboratory-confirmed SARS-CoV-2 infection *via* PCR technique were finally enrolled. Median age of the patients was 68.8±14 years. 51.9% were men. Median length of hospitalization was 10.9 ± 5 days.

Differences between demographic characteristics and laboratory values are presented in Table I.

Prediction of In-Hospital Mortality and Prolonged Hospitalization by Biomarkers: ROC Curves

To determine the prognostic value of acute phase proteins in patients with COVID-19, Receiver Operating Characteristic (ROC) curve analysis was performed. Regarding in-hospital mortality, AUC values of PSP and hs-troponin I were 0.588 and 0.671, respectively. Further, AUC values of ferritin, fibrinogen and CRP were 0.755, 0.519, and 0.600 respectively (Figure 1).

Regarding the length of hospitalization, AUC values for PSP, hs-troponin, NLR, CRP, and Ferritin were as follows: 0.800, 0.643, 0,500, 0,491, and 0,490, respectively (Figure 2).

Furthermore, we performed a secondary exploratory analysis for the predictive value in the survivor's subgroup which showed a similar, but lower AUC (0.706).

Table I. Plasma levels of the studied biomarkers in patients who died during hospitalization vs. those who survived.

Parameter	COVID-19 patients who died(n=19)	COVID-19 patients who survived (n=36)	<i>p</i> -value
Age (years)	75.08 (13)	71.09 (18)	<i>p</i> : 0.138
Sex (F/M)	8/8	18/18	<i>p</i> : 0.295
Length of Hospitalization (LOHS)	11.3 (9.5)	10.8 (9)	<i>p</i> : 0.309
Polymorphonuclear total number (K/μL)	9812.1 (8589)	4691.7 (4250)	<i>p</i>: 0.012
Lymphocytes total number (K/μL)	2903.8 (620)	1145.6 (670)	<i>p</i>: 0.05
Monocytetotal number (K/μL)	530.4 (260)	553.8 (335.4)	<i>p</i> : 0.544
NLR	14.8 (9)	6.87 (6)	<i>p</i>: 0.004
LDH (U/l)	429.9 (307)	296.4 (200)	<i>p</i>: 0.007
Ferritin (mg/dL)	3064.8 (1262)	636.6(767)	<i>p</i>: 0.003
CRP (mg/dL)	8.1 (9)	4.52 (7)	<i>p</i> : 0.157
PSP (ng/dL)	107.5(130)	57.7 (55)	<i>p</i> : 0.409
Fibrinogen	550 (383)	550 (217)	<i>p</i> : 0.936
Hs-TnI (pg/ml)	215.25 (48)	105 (22)	<i>p</i>: 0.003

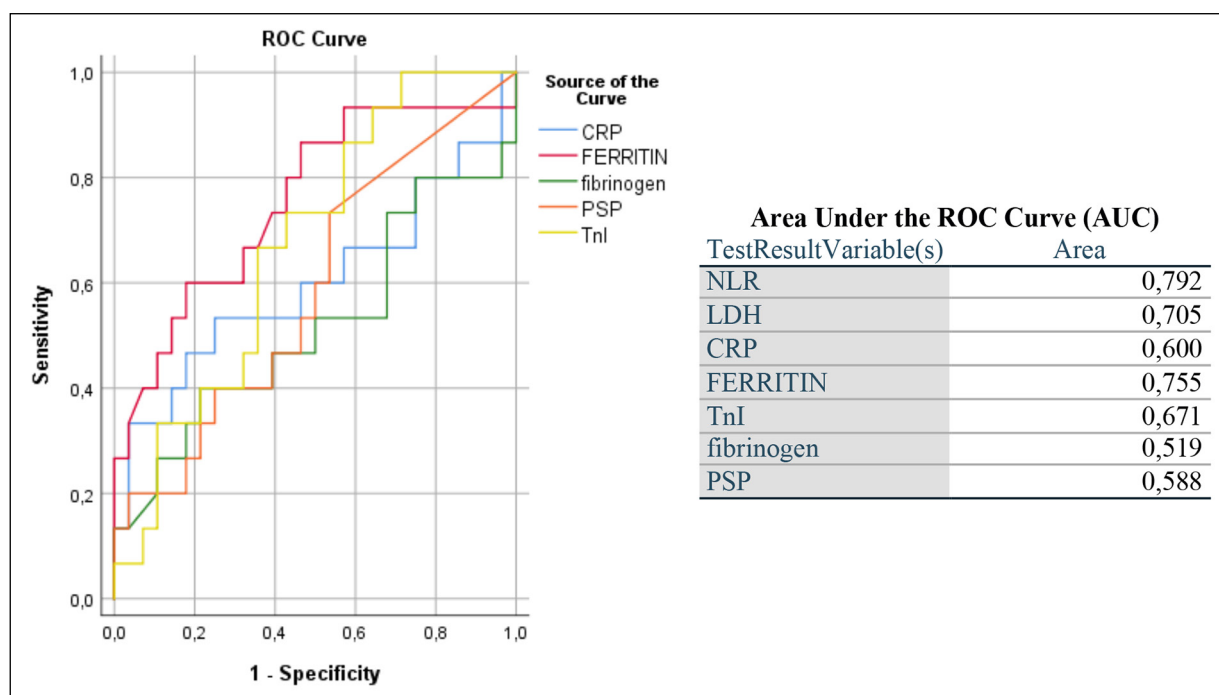


Figure 1. ROC analysis of NLR, LDH, C-reactive protein, Ferritin, Fibrinogen, hs-Troponin I and pancreatic stone protein on in-hospital mortality of patients with COVID-19.

When exploring the predictive value of PSP on the use of non-invasive mechanical ventilation we found a low AUC (0.545).

The optimal cut-off value of PSP for prolonged hospitalization using Youden Index was 51 ng/dL with a sensitivity value of 65% and a specificity value of 91.3%.

Discussion

Pancreatic stone protein belongs to the family of lectin-binding proteins and is constitutively secreted by pancreatic acinar cells into pancreatic juice along with other enzymes (zymogens). Pancreatic stone protein (PSP) regenerating protein 1-alpha (reg) is associated with inflammation, infection, and other disease-related stimuli³. PSP is a relatively novel biomarker and research related to it is of great interest^{5,6}. Particularly in sepsis patients, PSP appears to be an acceptable biomarker to exclude short term risk of death¹. PSP has been studied and compared to other biomarkers in various settings of infections and sepsis, either as a diagnostic marker of infection and/or sepsis or as a prognostic marker of outcome⁷.

The results of this study suggest that PSP measured on admission, could be used for identifi-

cation of patients with SARS-CoV-2 pneumonia at highest risk of prolonged hospitalization reflecting more severe disease and the need for intensive treatment. Remarkably, in all our patients there was no bacterial co-infection at the time of measurement so the PSP upon admission was attributed only to pneumonia due to SARS-CoV-2. That is mentioned because in regard to respiratory tract infections, Boeck et al⁷ reported that non-surviving patients with Ventilator Associated Pneumonia (VAP) had significantly elevated PSP levels. Additionally, the researchers showed that Pancreatic stone protein (PSP)/regenerating protein (reg) was associated with the SOFA score from VAP onset, reflecting the organ dysfunction failure, discriminated survivors from non-survivors and potentially stratified VAP patients with good and poor outcome⁸.

In a prospective cohort study of COVID-19 patients in the emergency department (ED) of a Swiss tertiary center, the accuracy of bedside clinical severity scores (qSOFA score and CRB-65), PSP and CRP, were evaluated on admission for the 7-day mortality and ICU admission. The results of the study showed that CRB-65, CRP and PSP in the ED had excellent accuracy to rule out early mortality in COVID-19 patients. The com-

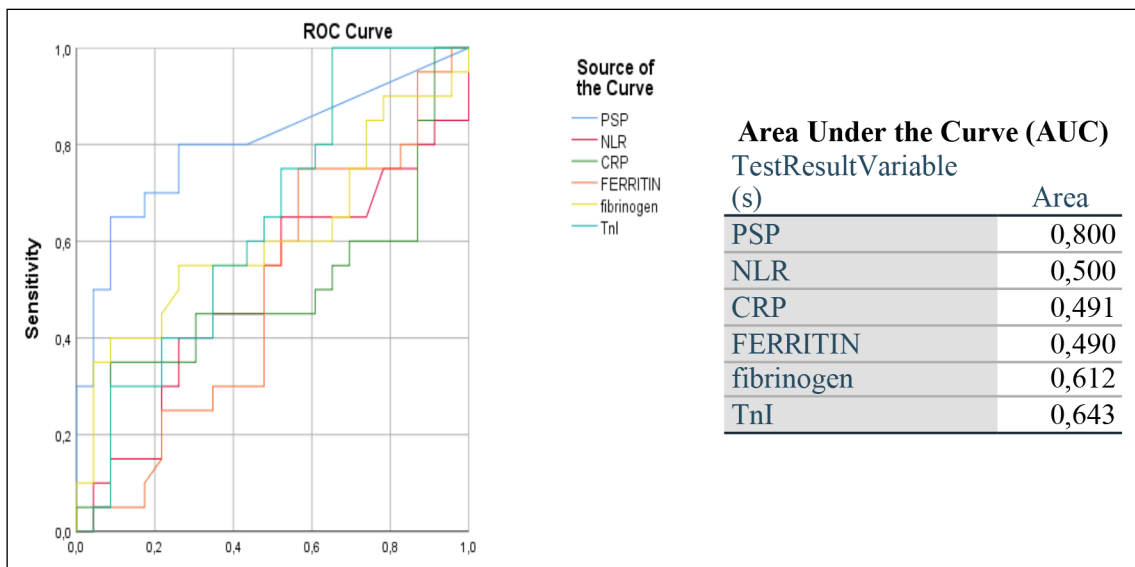


Figure 2. ROC analysis of NLR, LDH, C-reactive protein, Ferritin, Fibrinogen, hs-Troponin I and pancreatic stone protein on length of hospitalization of patients with COVID-19.

combination of CRP-65 and either biomarker improved the prognostic accuracy. PSP was showed to be a good biomarker to exclude short term risk of death but could not exclude ICU admission for these patients¹.

In our study, regarding length of hospitalization PSP performed best among the measured acute phase proteins given the rather moderate AUC. Using PSP, maybe we will be able to create a triage based on an easily measured biomarker in order to manage resources and early establish proper treatment⁹. That will in turn improve the outcome and reduce the hospital stay.

Moreover, Coparli et al¹⁰ reported that routine blood parameters, such as d-Dimers, urea, and Alanine Liver Transferase (ALT) are significant in predicting mortality in COVID-19 patients hospitalized in the Intensive Care Units. The combination of PSP and such simple parameters could be an important research field in the future.

Our study has some limitations. At first, it is a single-center study with a small number of patients. Secondly, the assessed plasma parameters were referring only to the hospital admitted patients, which may impact upon inflammatory markers due to the disease severity. More multi-center studies are warranted for the extraction of safer conclusions in regards to the predictive role of the PSP in COVID-19. Additionally, the impact of different co-morbidities on PSP levels at baseline remains unclear. In future trials, a major focus

should be put on the impact of potential clinical co-morbidities on the distribution of PSP levels.

Conclusions

Pancreatic Stone Protein seems to be a promising biomarker and a useful tool for risk stratification of COVID-19 patients admitted to hospital. The potential for the use of PSP alone or in combination with other biomarkers used for the severity and prognosis of COVID-19, is promising thus more clinical studies are needed.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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