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Clinica Chimica Acta 507 (2020) 161–163

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Presepsin in risk stratification of SARS-CoV-2 patients

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ARTICLE INFO

Keywords:
SARS-CoV-2 patients
Biomarkers
Presepsin
Prognosis

ABSTRACT

Background: A severe form of pneumonia, is the leading complication of the respiratory Coronavirus disease 2019 (COVID-19), recently renamed SARS-CoV-2. Soluble cluster of differentiation (CD)14 subtype (sCD14-ST also termed presepsin PSP) is a regulatory factor that modulates immune responses by interacting with T and B cells, useful for early diagnosis, prognosis and risk stratification prediction.

Methods: In 75 consecutive patients suffering from COVID-19 microbiology proven infection, admitted to intensive care unit (ICU, n = 21, 28%) and/or in infectious disease ward (IW, n = 54, 72%), PSP (Pathfast, Mitsubishi, Japan) has been measured in addition to routine laboratory tests performed during the period of hospitalization (from January to March 2020).

Results: PSP demonstrates: -statistically significant higher values (Mann-Whitney test) in 6 patients died (median, IQR = 1046, 763–1240; *vs* 417, 281–678 ng/L, $p < 0.05$); -statistically significant but poor correlations with CRP ($r = 0.59$, $p < 0.001$), LDH ($r = 0.52$, $p < 0.001$) and PCT ($r = 0.72$, $p < 0.001$) measured at the same day; -a significant relationship between concentrations and ICU stay. In fact patients showing PSP values higher than 250 ng/L (cut-off for risk stratification) did stay in ICU for a significantly longer time (median 17 days, IQR 12–31; $p < 0.001$) than those exhibiting lower values (median 10 days, IQR 7–18).

Conclusions: The data obtained seems to demonstrate the role of PSP in providing prognostic information in COVID-19 patients, allowing to identify, during the early phase of the monitoring, the patients suffering from a more severe disease which will be hospitalized for a more long time.

To the Editor,

A severe form of pneumonia, potentially evolving towards acute respiratory distress syndrome (ARDS) and occasionally associated with multiorgan failure, is the leading complication of the respiratory virus now producing an outbreak of pandemic proportions, the Coronavirus disease 2019 (COVID-19), recently renamed SARS-CoV-2 [1,2].

Soluble cluster of differentiation (CD) 14 subtype (sCD14-ST; 64 amino acids, 13 kDa), also termed presepsin (PSP), a small soluble peptide generated from soluble CD14, is known to function as a regulatory factor that can modulates immune responses by interacting with T and B cells [3]. Currently, the results of many clinical studies indicated that PSP is a useful biomarker not only for early diagnosis, but also for risk stratification, and prognosis prediction in sepsis patients as well in patients suffering from pneumonia [4–7]. In order to verify the potential usefulness of this biomarker in risk stratification of patients (n = 75) suffering from COVID-19 microbiology proven infection (Table 1), PSP measurement in lithium-heparin plasma samples using a chemiluminescent enzyme immunoassay (CLEIA) (Pathfast, Chemical Medience Corporation, Tokyo, Japan), was carried out in addition to routine laboratory tests performed during the period of hospitalization (from January to March 2020) in the intensive care unit (ICU, n = 21, 28%) and/or in infectious disease ward (IW, n = 54, 72%). The biochemical parameters were measured using Cobas 8000 system (Roche Diagnostics, GmbH, Mannheim, Germany) with the exception of Procalcitonin (PCT) (Liaison Brahms PCT II gen, Diasorin SpA, Saluggia, Italy) and C reactive protein (CRP) (Dimension Vista, Siemens Healthcare Diagnostics Inc, Tarrytown USA) while hematological data were obtained using Sysmex XE 2100 (Sysmex, Kobe, Japan). The CT scans performed at the time of admission, revealed abnormal results in 86.2% of patients being the ground-glass opacity (56.4%) and bilateral patchy shadowing (51.8%) the most common patterns. According to the severity and the evolution of the disease, n = 39 patients (52%) admitted to IW were moved after few days in ICU, while n = 6 (8%) died. In the population studied, the results of some relevant routine laboratory tests that may provide prognostic information, as suggested by other studies [8–10] showed (Table 1): lymphocytopenia (lymphocytes $< 1.50 \times 10^9$/L) and thrombocytopenia (platelets $< 150 \times 10^9$/L) in

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https://doi.org/10.1016/j.cca.2020.04.020
Received 15 April 2020; Received in revised form 17 April 2020; Accepted 17 April 2020
Available online 22 April 2020

Table 1
Demographic, Clinical Characteristics (A), and Laboratory Findings (B) of the Study patients (IQR, Interquartile Range; y, years).

Demographic and Clinical Characteristics (A)	
Sex	
Males, n (%); Females, n (%)	56 (75); 19 (25)
Age	
Median, IQR (years)	67, 56–76
Enrollment period	From 5 to 7 March 2020
Time from hospital presentation-admission to presepsin measurement n (%)	
Median, IQR (days)	5, 2–7
Hospital stay	
Median, IQR (days)	17, 9–26
Clinical outcomes	
Discharged n (%); dead n (%)	n = 69 (92%); n = 6 (8%)

Laboratory Findings (B)		
Biomarker, measuring unit (Reference Interval)	Number of Patients (%)	Median (IQR)
White-cell count, 10^9/L (4.4–11)	75 (100)	8.00 (5.06–12.51)
Lymphocyte count, 10^9/L (1.1–4.8)	75 (100)	0.71 (0.53–1.10)
Monocytes count, 10^9/L (0.20–0.96)	75 (100)	0.55 (0.32–0.74)
Neutrophils count, 10^9/L (1.8–7.8)	75 (100)	6.22 (3.55–10.41)
Platelet count, 10^9/L (150–450)	75 (100)	223 (162–311)
Hemoglobin, g/L (females: 123–153; males: 140–175)	75 (100)	130 (113–139)
C-reactive protein, mg/L (0–6)	64 (85)	44 (18–91)
Procalcitonin, μg/L (0.0–0.5)	45 (60)	0.15 (0.04–0.51)
Lactate dehydrogenase, U/L (females: 135–214; males: 135–225)	45 (60)	290 (232–377)
D-dimer, μg/L (0–59 y: 0–250; 60–69 y: 0–300; 70–79 y: 0–350; > 79 y: 0–400)	61 (81)	231 (150–604)

83% and 18% of patients respectively, increased D-Dimer (> 500 μg/L) and CRP concentrations (> 10 mg/L) in 31% and 85% of patients respectively, while PCT values higher than 0.5 μg/L were observed in 24% only. The time of hospitalization ranged between 9 and 60 days (median 17 days), but the comparison between biomarkers has been carried out considering only the results available at the same day. PSP measurement during the hospitalization (from 2 to 7 days after admission) demonstrated statistically significant higher values (Mann-Whitney test) in patients who died (median, IQR = 1047, 763–1240; *vs* 417, 218–679 ng/L, $p < 0.05$) as well as in patients staying in ICU during all time of hospitalization (median, IQR = 1069, 695–2299; *vs* 408, 202–660 ng/L, $p < 0.001$). According to ROC curve analysis, the AUC of presepsin values in predicting mortality was 0.72 ($p < 0.05$). Furthermore, the study of the relationship (Spearman correlation test) between PSP and different biochemical parameters reflecting inflammation, has evidenced statistically significant but poor correlations with CRP ($r = 0.59$, $p < 0.001$), LDH ($r = 0.52$, $p < 0.001$) and stronger with PCT ($r = 0.72$, $p < 0.001$) values. Despite this correlation, PCT showed values higher than 0.5 μg/L only in 2 out of 6 died patients (33%), and in 11 out of 45 patients studied (24%) [11]. The behavior of blood cells and coagulation tests has proved to be independent from those of PSP and other biochemical parameters analyzed routinely in the COVID-19 population patients [12]. An interesting and relevant information observed in our study seems to be the association between PSP concentrations and hospitalization: 47 out of 69 patients (68%) showing values higher than cut-off suggested by the manufacturer to identify patients at high risk of poor outcome (250 ng/L), did stay in ICU for a significantly longer time (median 18 days, IQR 12–31) than those exhibiting lower values (median 10 days, IQR 7–18) (Fig. 1). The logistic regression analysis supports this finding being the OR = 1.10 (95% CI: 1.03–1.17, $p < 0.001$) for the hospitalization period in patients showing higher PSP concentrations. In addition, the sensitivity and the specificity of the proposed cut-off in relation to the median length of stay observed in our study (17 days) were 85% and 43% respectively. The data obtained seem to demonstrate the role of this biomarker in providing prognostic information also in COVID-19 patients, as already described in several different diseases [3–7], allowing to identify, during the early phase of the monitoring, the patients suffering from a more severe disease which will be hospitalized for a more long time. The elevation of PSP, resulting from a dose–response mechanism of the host-pathogen interaction, occurs in the initial phase of the pathogen recognition, and remains elevated during several days on the basis of the disease severity [13] underlining the additional value of the biomarker in the prognostic assessment of patients [5–7,13]. Our study presents some limitations, namely the unavailability of the sample at admission to measure PSP and the limited number of died patients which does not allow a reliable evaluation of the value of PSP in mortality prediction. In addition further studies are needed to better explain the mechanisms involved in PSP increase in SARS-CoV-2 patients and in particular its relation with multiorgan failure syndrome (MOFS).

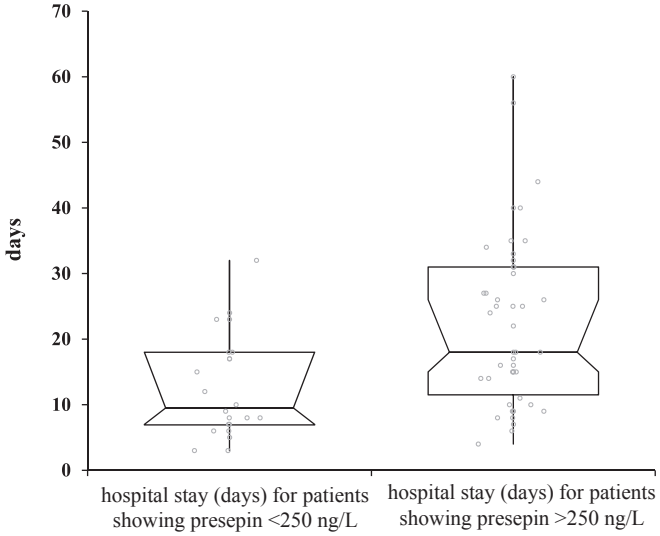

Fig. 1. Relationship between presepsin values and hospital stay.

CRediT authorship contribution statement

Martina Zaninotto: Conceptualization, Methodology, Data curation, Writing - original draft, Validation, Writing - review & editing. **Monica Maria Mion:** Conceptualization, Methodology, Data curation, Writing - original draft, Validation, Writing - review & editing. **Chiara Cosma:** Conceptualization, Methodology, Data curation, Writing - original draft, Validation, Writing - review & editing. **Daniela Rinaldi:** Conceptualization, Methodology, Data curation, Writing - original draft, Validation, Writing - review & editing. **Mario Plebani:** Conceptualization, Methodology, Data curation, Writing - original draft, Validation, Writing - review & editing.

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