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Presepsin as a predictive biomarker of severity in COVID-19: a case series

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To the editor

Guidelines for the diagnosis and treatment of the novel coronavirus disease 2019 (COVID-19) present clear criteria, including respiratory rate, hemoglobin oxygen saturation (SaO_2), and oxygenation indicator (PaO_2/FiO_2)[1]. However, these criteria are susceptible to subjective and objective interpretation, which may lead to an extended delay in diagnosis and the possibility of misdiagnosis in severe COVID-19.

Presepsin (P-SEP) is a soluble CD14 subtype with a truncated N-terminal and is reported to be a novel biomarker in sepsis. Several studies have shown that P-SEP is not only useful for the diagnosis of sepsis but could also be predictive of the severity and mortality of disease[2-4]. Recently, it was also reported that elevated P-SEP could be a biomarker in the prognostic assessment of patients with COVID-19[5]. In this case series, we retrospectively compared the clinical features and serum biochemical markers of disease including P-SEP between mild and severe COVID-19 patients and investigated the utility of P-SEP for evaluating the severity of COVID-19.

This case series included 6 patients confirmed to have COVID-19 by detecting SARS-CoV-2 RNA using nasopharyngeal swabs specimens, in accordance with national recommendations in Japan[4], at Saitama Medical

University Hospital from February to March 2020. Disease severity was classified according to the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th Edition)[6]. The 6 patients were at different stages and had different severity of infection. Three had moderate disease on admission that was later determined to be severe COVID-19 (the moderate-to-severe group), in whom secondary worsening resulted in invasive mechanical ventilation (Cases 1-3); 1 of these intubated patients ultimately died of COVID-19 pneumonia (Case 1). The other 3 patients (Cases 4-6) were diagnosed as having mild COVID-19 (mild group). The Supplementary Table 1 shows the baseline clinical laboratory findings. The initial clinical laboratory workup included a complete blood count and the inflammatory biomarker profiles for C-reactive protein (CRP), P-SEP, procalcitonin (PCT), and Krebs von den Lungen-6 (KL-6). The Figure 1 shows clinical course of each patient in terms of changes in laboratory findings and in treatment outcome until discharge alive, transfer from infectious disease ward, or death. P-SEP levels were measured using the STACIA® clinical assay system (LSI Medience Corporation, Tokyo, Japan) based on a chemiluminescent enzyme immunoassay, which has a normal reference range of 59-250 pg/mL.

The majority of serum biochemical markers, including white blood cell, lymphocyte, and platelet counts, showed no differences between the mild and severe COVID-19 groups. P-SEP and CRP were higher on admission in the moderate-to-severe group than in those in the mild group, although PCT was slightly higher in the moderate-to-severe group. Baseline KL-6 levels for both groups were within normal limits (Supplementary Table 1). The Figure 1 shows the

clinical course in relation to CRP, P-SEP, and KL-6 levels. P-SEP increased immediately following elevation of CRP in the moderate-to-severe group, resulting in invasive mechanical ventilation with exacerbation of COVID-19 pneumonia. In Cases 2 and 3, P-SEP levels remained higher than those in the mild group but eventually decreased along with improvement in their lung disease. In Case 1, P-SEP levels did not correlate with CRP levels, with further increases in P-SEP prior to increases in KL-6 elevation and eventually death. These findings suggest that P-SEP may correlate with lung damage caused by COVID-19 pneumonia and may be useful as a prognostic biomarker for severe COVID-19. In this case series, PCT levels were constant in all patients throughout the clinical course and none of the patients had renal dysfunction during the observation period.

In the moderate-to severe COVID-19 group (Cases 1-3), CRP peaked during the course of treatment with invasive mechanical ventilation and was not directly correlated with severity in Case 1, who eventually died of severe COVID-19 pneumonia. However, P-SEP levels characteristically increased early before KL-6 levels increased, demonstrating its potential as a good predictor of severity in moderate-to-severe cases of COVID-19. Although the detailed mechanism of P-SEP elevation in COVID-19 pneumonia is not known, several reports have shown that P-SEP could be a strong prognostic marker for short-term mortality in ARDS[7].

Our findings have relevant clinical implications and strengths: because P-SEP can predict aggravation of ARDS based on laboratory tests on admission, this enables clinicians to identify high-risk COVID-19 patients and determine treatment

strategies at an early stage. Further studies are warranted to confirm our findings with a large number of participants in a multicenter setting. Nevertheless, our findings show that P-SEP has potential as a biomarker for severe COVID-19 pneumonia.

Conflict of Interests

The authors declare that there were no conflict of interests.

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Ethical Statement

This study was approved by the Ethics Committee of Saitama Medical University (Approval No. 19136).

References

1. N.H.C.o.t.P.s.R.o. China., The notice of launching guideline on diagnosis and treatment of the novel coronavirus pneumonia (NCP). Revised version of the 5th edition., (2020).

2. Endo. S, Suzuki. Y, Takahashi. G, et al., Usefulness of presepsin in the diagnosis of sepsis in a multicenter prospective study, J Infect Chemother. 18 (2012) 891-897.

3. Masson. S, Caironi. P, Spanuth. E, et al., Presepsin (Soluble CD14 Subtype) and Procalcitonin Levels for Mortality Prediction in Sepsis: Data from the Albumin Italian Outcome Sepsis Trial, Crit Care. 18 (2014) R6.

4. National Institute of Infectious Diseases, Japan. Manual for the Detection of Pathogen 2019-nCoV Ver.2.6. https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/2484-idsc/9403-labo-manual.html.

5. Zaninotto. M, Mion. M. M, Cosma. C, et al., Presepsin in risk stratification of SARS-CoV-2 patients, Clin Chim Acta. 507 (2020) 161-163.

6. China National Health Commission. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition). [http://kjfy.meetingchina.org/msite/news/show/cn/3337.html] (Accessed on May 2, 2020)

7. Zhang. S, Lin. Q-H, Shen. L-H, et. al., Diagnostic value and prognostic evaluation of presepsin for acute respiratory distress syndrome (ARDS), Fudan Univ J Med Sci. 46 (2019) 357-365.

Figure 1. Presepsin (P-SEP), C-reactive protein (CRP), and KL-6 levels on consecutive days (n=6)

Daily changes in P-SEP (solid circles), CRP (open circles), and KL-6 (solid square). X-axis: days from admission. Left Y-axis: P-SEP level. Right Y-axis: CRP and KL-6 levels. Horizontal bar indicates the duration of invasive mechanical ventilation (Cases 1-3); Case 1 died of COVID-19 pneumonia on hospital day 17.