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

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 (SaO₂), and oxygenation indicator (PaO₂/FiO₂). 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. Recently, it was also reported that elevated P-SEP could be a biomarker in the prognostic assessment of patients with COVID-19. In this case series, we retrospectively compared the clinical features and serum biochemical markers of disease including P-SEP between patients with mild and severe COVID-19 and investigated the utility of P-SEP for evaluating the severity of COVID-19.

This case series included six patients confirmed to have COVID-19 by detecting severe acute respiratory syndrome coronavirus 2 RNA using nasopharyngeal swabs specimens, in accordance with national recommendations in Japan, 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). The six 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 (case 1-3); one of these intubated patients ultimately died of COVID-19 pneumonia (case 1). The other three patients (case 4-6) were diagnosed as having mild COVID-19 (mild group). The Table S1 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 to 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 (Table S1). 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 before 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 (case 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.

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 patients with COVID-19 and determine treatment strategies at an
**FIGURE 1**  Presepsin (P-SEP), C-reactive protein (CRP), and Krebs von den Lungen-6 (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 (case 1-3); case 1 died of coronavirus disease 2019 (COVID-19) pneumonia on hospital day 17.
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 are no conflict of interests.

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

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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