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LETTER TO THE EDITORS

"Unconventional CD147-dependent platelet activation elicited by SARS-CoV-2 in COVID-19": Comment from Wada et al

Dear Editor,

We are very interested in the recently published report entitled "Unconventional CD147-platelet activation elicited by SARS-CoV-2 in COVID-19" by Maugeri et al.[1] Authors reported that early and intense platelet activation was reproduced *in vitro* by stimulating platelets with SARS-CoV-2, and that this was dependent on the CD147 receptor. The authors reported that platelets released soluble P-selectin and HMGB1+ extracellular vesicles and that the early accumulation of platelet HMGB+ extracellular vesicles predicted worse clinical outcomes. Although these findings were markedly important, the methodology that they used to detect platelet activation was complicated for physicians. CD147 is a receptor for SARS-CoV-2 that is well-known to play an important role in COVID-19 infection.[2]

Coronavirus disease 2019 (COVID-19), which sometimes causes acute respiratory distress syndrome, coagulopathy, and poor outcomes, has now spread worldwide. Thus, several mechanisms underlying the worsening of the condition of COVID-19 patients have been proposed.[3] Soluble C-type lectin-like receptor 2 (sCLEC-2) has been introduced as a new biomarker of platelet activation[4] and elevated plasma levels of sCLEC-2 have been reported in patients with thrombotic microangiopathy,[5] disseminated intravascular coagulation,[6] and acute cerebral infarction.[7] Elevated plasma levels of sCLEC-2 were recently reported in patients with COVID-19 infection and those were correlated with the severity of COVID-19.[8] Platelets in patients with COVID-19 infection may release large amounts of sCLEC-2 into the blood without microthrombus formation through CD147-dependent platelet activation.

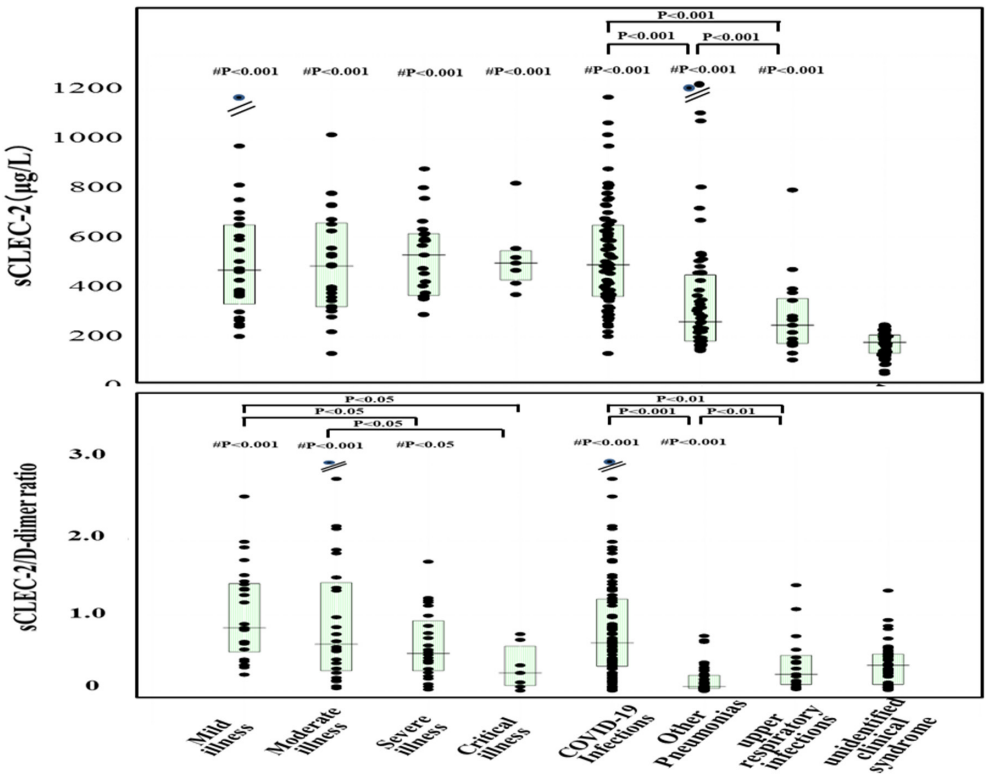

FIGURE 1 Plasma levels of sCLEC2 and sCLEC-2/D-dimer ratio in patients with COVID-19 infection and those with other infections. #$p < .001$, #$p < .01$ and #$p < .05$; $p < .001$, $p < .01$, and $p < .05$ in comparison to unidentified clinical syndrome, respectively.

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Regarding the further analysis, which included additional cases,[8] plasma sCLEC-2 levels in patients with COVID-19 infection (median 25-75th percentile, 491 μg/L; 363–651 μg/L) were significantly higher ($p < .001$, respectively) in comparison to patients with other pneumonia (276 μg/L; 183–459 μg/L), upper respiratory infection (247 μg/L; 173–355 μg/L) and unidentified clinical syndrome (178 μg/L; 134–207 μg/L) (Figure 1). There was no significant difference in the plasma sCLEC-2 levels among COVID-19 patients with mild, moderate, severe, and critical illness. These findings suggest that elevated plasma sCLEC-2 levels may not be related to pneumonia.

The platelet counts of patients with COVID-19 infection, other pneumonia, upper respiratory infection, and unidentified clinical syndrome did not differ to a statistically significant extent. Plasma D-dimer levels in patients with other pneumonia (3.4 mg/L; 1.8–8.7 mg/L) were significantly higher ($p < .001$, respectively) in comparison to patients with COVID-19 infection (0.8 μg/L; 0.4–1.5 mg/L), upper respiratory infection (1.2 mg/L; 0.6–2.2 mg/L), and unidentified clinical syndrome (0.5 mg/L; 0.4–1.6 mg/L). These findings suggest that a hypercoagulable state is more predominant in patients with other pneumonia than in patients with COVID-19 infection. The sCLEC-2/D-dimer ratio in patients with COVID-19 (650/335–1274) was significantly higher in comparison to patients with other pneumonia (61.7; 36.1–210), upper respiratory infection (224; 87.8–472), and unidentified clinical syndrome (331; 87.7–490) (all $p < .01$). The sCLEC-2/D-dimer ratio in COVID-19 patients with critical illness (241/73.5–594) was significantly lower in comparison to COVID-19 patients with mild illness (837; 519–1423) or moderate illness (660; 284–1584) (Figure 1). These findings suggest that patients with early-stage COVID-19 infection shows only platelet activation, and that severe COVID-19 infection causes hypercoagulability. Low-dose aspirin was reported to be useful for managing COVID-19 infection.[9] The administration of aspirin may be useful for patients with early-stage COVID-19.

In conclusion, the sCLEC-2 assay is an easy and rapid assay that can measure many samples, and is useful to measure platelet activation in patients with COVID-19 infection.

AUTHOR CONTRIBUTIONS

H.W. wrote the manuscript and K.S. and K.S.-I. discussed and revised the manuscript.

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CONFLICT OF INTEREST

The measurement of sCLEC-2 and D-dimer levels were partially supported by LSI Medience. The authors declare no other conflicts of interest in association with the present study.

ETHICAL APPROVAL

The study protocol (2020-S25) was approved by the Human Ethics Review committees of Mie Prefectural General Medical Center, and informed consent was obtained from each patient.

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