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LETTER

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Interleukin-6 is upregulated and may be associated with myocardial injury in some patients who have recovered from COVID-19

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Abstract: Coronavirus disease (COVID-19) causes myocardial injury by inducing a cytokine storm in severe cases. Studies have reported that myocardial injury persists for a prolonged period during COVID-19 recovery, and cardiac troponin is a useful indicator of myocardial injury. The interleukin-6 (IL-6) level is known to be associated with the morbidity and mortality of COVID-19, but this association has not been studied during recovery. The current study examined the association between IL-6 levels and myocardial damage during COVID-19 recovery. Four of 209 patients (1.9%) who recovered from COVID-19 had elevated IL-6 levels. All 4 patients tested positive for high-sensitivity troponin T, and 3 patients had subclinical left ventricular (LV) dysfunction according to echocardiography. Positivity for IL-6 during COVID-19 recovery suggests ongoing myocardial damage due to inflammation.

***Keywords*:** COVID-19, interleukin-6, cardiac troponin, myocardial damage, echocardiography

Coronavirus disease (COVID-19) continues to be prevalent worldwide, and in severe cases, it induces a cytokine storm that causes myocardial damage. In addition, studies have reported that myocardial damage is prolonged even during the recovery period as a result of elevated troponin levels and abnormalities in cardiac imaging studies (*1,2*). However, no studies have reported an association between cytokines and myocardial injury in patients who have recovered from COVID-19. The current study examined the relationship between the level of interleukin-6 (IL-6) and myocardial damage during COVID-19 recovery.

Subjects were patients who participated in the COVIPLA study of convalescent plasma therapy in Japan from April to September 2020 (*3*). Patients who had recovered from COVID-19 underwent blood tests and echocardiography at least 3 weeks after the onset of infection. All data were retrospectively collected at the National Center for Global Health and Medicine. IL-6 and high-sensitivity troponin T (hsTnT) were measured in stored frozen serum. An IL-6 level ≥ 8 pg/mL and a hsTnT level ≥ 0.003 ng/mL were considered to be a positive result (Roche Diagnostics, Tokyo, Japan).

Echocardiography was performed using Canon Artida, and standard guidelines were used as a reference for abnormal values of left and right ventricular function (*4*). Tricuspid annular plane systolic excursion (TAPSE) of 17 mm or more was regarded as normal. Left ventricular global longitudinal strain (LVGLS) was determined from the average of the 4-chamber, 3-chamber, and 2-chamber views, and LVGLS was analyzed using TOMTEC. A LVGLS value of < -20 was regarded as abnormal (*5*).

This study complied with the Declaration of Helsinki and was approved by the Hospital Ethics Committee. Informed consent was obtained in an opt-out format.

Subjects were 209 patients from the COVIPLA registry who underwent echocardiography and blood tests between April and September 2020. IL-6 could not be measured in 3 patients due to insufficient sample volume. The mean age (± standard deviation) was 44 ± 12 years (range: 36-55 years), and the proportion of males was 51%. Of 74 patients (35.4%) with hsTnT below the limit of detection, all had an IL-6 level below the limit of detection. hsTnT levels were above the limit of detection (> 0.003 ng/mL) in 135 patients (64.6%), and the IL-6 level exceeded the sensitivity threshold in 4 patients (3.0%). Those 4 patients had high peak CRP levels of 10.03 mg/dL, 18.91 mg/dL, 17.24 mg/dL, and 8.99 mg/dL during their hospitalization for COVID-19 (Table 1).

Of the IL-6-positive patients, all 4 had no history of hypertension, diabetes, or cardiovascular disease, and their echocardiographic ejection fraction was greater than 50%. Patient 1 received oxygen therapy during hospitalization, with slightly reduced left ventricular function (LVGLS -19.3%) and normal right ventricular function (TAPSE 23.1 mm). Patient 2 did not need oxygen therapy and had slight left ventricular and right ventricular dysfunction (LVGLS -18.9%, TAPSE 16.7

Table 1. Patient characteristics including myocardial troponin T and echocardiographic data for IL-6-positive patients

Patients No.	Age (years)	Sex	BMI (kg/m^2)	Period from onset to testing (days)	COVID-19 severity during hospitalization	Medication for COVID-19	Peak CRP during infection (mg/dL)	CRP during recovery (mg/dL)	IL-6 (pg/mL)	hsTnT (ng/mL)	Left ventricular function LVGLS	Right ventricular function TAPSE
1	57	Male	21.5	65	Oxygen required	Remdesivir, steroid	10.03	0.02	14	0.004	-19.3%	23.1 mm
2	42	Male	27.2	27	No oxygen therapy	Remdesivir	18.91	0.06	14	0.004	-18.9%	16.7 mm
3	53	Male	28.9	28	Oxygen required	Remdesivir, steroid, Tocilizumab	17.24	0.04	103	0.005	-17.7%	14.2 mm
4	46	Male	29	24	Intubation	Remdesivir, steroid	9.0	0.43	12	0.004	-20.0%	18.4 mm

BMI: body mass index; IL-6: interleukin-6; hsTnT: high-sensitivity troponin T; LVGLS: left ventricular global longitudinal strain; TAPSE: tricuspid annular plane systolic excursion.

mm). Patient 3 required oxygen and had the highest IL-6 level (103 pg/mL) during recovery. The patient had marked left ventricular and right ventricular dysfunction (LVGLS -17.7%, TAPSE 14.2 mm). Patient 4 had previously been on mechanical ventilation but had no left ventricular or right ventricular hypofunction (LVGLS -20.0%, TAPSE 18.4 mm). All 4 patients with elevated IL-6 during COVID-19 recovery were positive for hsTnT. Of the 4, 3 had impaired left ventricular function, 2 had impaired right ventricular function, and 2 had both impaired left and right ventricular function.

Previous studies have reported the presence of subclinical myocardial damage with positive hsTnT in about 70% of patients recovering from COVID-19 (*1*). A recent study in Japan reported that 65% of patients who recovered from COVID-19 had a hsTnT level exceeding the limit of detection (*6*), and another study reported that a hsTnT level is associated with decreased LVGLS (*7*).

In the current study, all 4 patients who were positive for IL-6 were also positive for hsTnT, and all of the CRP tests performed during recovery were negative, suggesting that myocardial injury due to different inflammatory mechanisms may occur during COVID-19 recovery.

A recent study found that significantly elevated IL-6 levels in patients hospitalized for COVID-19 were associated with worse clinical outcomes such as ICU admission and death (*8*). In an analysis of risk factors for ARDS and death by Wu *et al.* (*9*), IL-6 was significantly elevated in patients with COVID-19 who developed ARDS (median 7.4 pg/mL, IQR 5.6-10.9 *vs.* median 6.3 pg/mL, IQR 5.4-7.8, $p = 0.03$). Ruan *et al.* (*10*) found that IL-6 levels were significantly higher in patients who died of COVID-19 compared to those who survived (11.4 ± 8.5 pg/mL *vs.* 6.8 ± 3.6 pg/mL, $p < 0.001$).

Among the patients with elevated IL-6 who recovered from COVID-19, 3 had impaired left and right ventricular function, suggesting that cytokine-induced inflammatory mechanisms persist and may contribute to impaired cardiac function even during COVID-19 recovery. Patients positive for IL-6 and with impaired cardiac function should be carefully monitored for a further decline in cardiac function. Two limitations of this study were the lack of data on cytokine levels and the lack of echocardiography images during hospitalization.

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