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Estimation of serum Interleukin-6 level as a Predictor of Respiratory Failure in COVID-19 Patients in tertiary care hospital of central india

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Abstract

Introduction-All Patients of coronavirus disease 2019 develop respiratory failure within a short period during the clinical course. It is important to predict respiratory failure in the short term. We tried to find out the use of inflammatory markers to predict respiratory distress within three days from their analysis in COVID-19 patients.**2- Material and methods:** This retrospective observational study included 81 patients admitted with COVID-19. Patients were divided into two groups according to whether the maximum fraction of inspired oxygen (FiO_2) for three days from the blood marker measurements was ≥0.4 (high FiO_2 group; HFG) or <0.4 (low FiO_2 group; LFG). Interleukin-6 (IL-6) levels were compared between the two groups **.3-Conclusion:** The levels of markers were significantly higher in HFG patients. Areas under the receiver operating characteristic curve of IL-6 was high values of 0.85. The odds ratio of IL-6 which was crude and adjusted for dexamethasone administration initiated before laboratory measurement, showed the high value of 30.1 (5.6–295.6) and 63.9 (4.5–3242.8), respectively. IL-6 can be used as a reliable marker for predicting respiratory illness within three days after assessment.

Keywords: inflammatory marker; interleukin-6; novel coronavirus disease; respiratory failure,crp,ldh,d-dimer,ARDS,RTPCR

Introduction

Coronavirus disease 2019 was first reported in Wuhan, China, in December 2019, and WHO declared it a pandemic in January 2020 [1].The clinical signs of COVID-19 are manifold, from asymptomatic to severe viral pneumonia such as acute respiratory distress syndrome . It is important to identify patients who at risk to develop severe conditions as early as possible. Some studies have shown that several blood markers could predict respiratory failure in COVID-19 patients [2,3].It has been reported that some inflammatory cytokines could differentiate disease severity in COVID-19 [4]. Therefore, it is of high priority to identify reliable blood markers which could predict respiratory illness in the short term duration.This study aimed to investigate the predictive ability of IL-6 as a markers for respiratory failure within the short term in COVID-19 patients.

1. Materials and Methods

It was a single-center, retrospective observational study was approved from ethics committee of Gandhi medical college and hamidia hospital Bhopal. A total of 164 patients who tested positive for severe SARS-CoV-2 by RTPCR from the nasopharyngeal swab were admitted to our hospital from 5 November 2020 to 26 june 2021. Data on demographic characteristics, underlying co- morbidities, details of the treatment,

time from symptom onset to admission, and the first measurement of blood specimens, and outcomes, were collected for all patients in this study. The laboratory values measured after admission included interleukin-6 (IL-6), C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, white blood cell (WBC), and creatinine (Cr) levels. Additionally, for 3 days from laboratory measurement, the fraction of inspired oxygen (FiO_2) and the percutaneous oxygen saturation (SpO_2) as a respiratory condition were checked for all patients. For patients without invasive mechanical ventilation, the conversion of the inspired oxygen (O_2) amount [liter (L)/minute (M)] to O_2 concentration (FiO_2 0.25 to O_2 1 L/M, FiO_2 0.28 to O_2 2 L/M, FiO_2 0.32 to O_2 3 L/M, FiO_2

0.36 to O_2 4 L/M, FiO_2 0.4 to O_2 5 L/M) was used.

Laboratory Analysis of Blood Specimens

Serum and plasma samples were separated by centrifugation at 4000 rpm for 5 min. The levels of IL-6 were measured on a Cobas 8000 specimen form (Roche Diagnostics, Basel, Switzerland) by electrochemiluminescence immunoassay. LDH, Cr, and CRP levels were measured using a TBA-FX8 instrument (Canon Medical Systems, Tochigi, Japan) by an enzymatic reaction for LDH and Cr and latex turbidimetric reaction for CRP. WBC counts were performed using a DXH 900 hematology analyzer (Beckman Coulter, Tokyo, Japan). D-dimer levels were determined using a CS2100i automatic coagulation analyzer (Sysmex, Kobe, Japan) by a latex-enhanced photometric immunoassay.

Statistical Analysis

Categorical variables were presented as proportions or frequencies (%), and the χ^2 test or Fisher's exact test was used to compare the prevalence between the 2 groups. Normal and non-normally distributed continuous variables were presented as mean standard deviation and median (interquartile range) and were analyzed by variance analysis and Mann–Whitney U-test, respectively. Statistical significance was set at $p < 0.05$. The predictive value was evaluated by measuring the area under the curve (AUC). The optimal cutoff value was obtained by calculating the Youden index. Several cutoff values of each marker were obtained from different coordinates of the ROC curve to compare the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of these cutoff values. The odds ratio (OR) estimation was performed by using Fisher's exact test. The correlation coefficients were obtained by the Spearman correlation analysis. Statistical analyses were performed using R software package (version 4.0.3, R Core Team. R: A language and environment for statistical computing.

2. Results

Patient Characteristics

Among the 164 eligible patients, those lacking laboratory data (n = 74) and those younger than 18 years (n = 8) were excluded.

A total of 81 adult patients were included in the study (Figure 1). These patients were divided into a FiO_2> 0.4 group (high FiO_2 group (HFG) and a FiO_2 < 0.4 group (low FiO_2 group; LFG) according to the maximum FiO_2 for three days from the measurement of laboratory markers. A total of 16 patients were assigned to the HFG group, and 65 patients were allocated to the LFG group (Figure 1).

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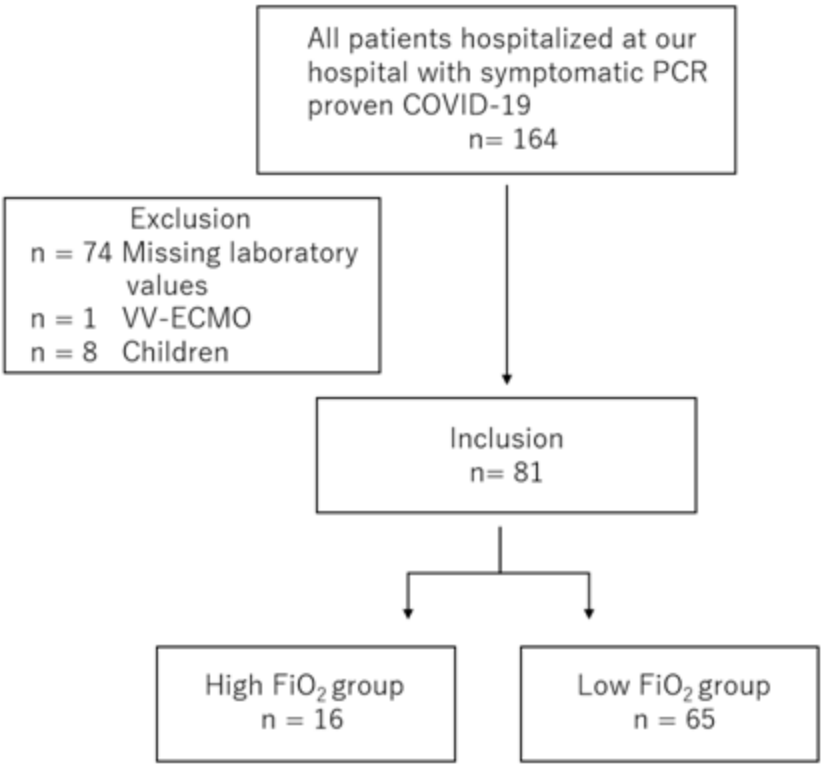

Figure 1. Study flow.

Among all patients, 50 patients (61.7%) were male, the mean age was 62.0 16.3 years, and the mean body mass index (BMI) was 25.0 4.5 kg/m^2. There were no significant differences in sex, age, or BMI between the two groups. The number of comorbidities was significantly higher in the HFG patients. The most common comorbidity was hypertension (43.2%; Table 1). Most HFG patients (81.2%) received invasive mechanical ventilation, and all HFG patients were prescribed dexamethasone 6 mg daily (Table 1). The median times from symptom onset to admission and to the first measurement of each marker in the HFG patients were longer than those in the LFG patients.

Table 1. Clinical characteristics between the two groups.

(*n* = 81)		Yes (*n* = 16)	No (*n* = 65)	
Mean age, y (±SD)	62.0 ±16.3	68.1 ± 13.9	60.6 ± 16.5	0.090
Male sex, *n* (%)	50 (61.7%)	12 (75.0%)	38 (58.5%)	0.260
Mean BMI, kg/m^2 (±SD)	25.0 ±4.5	25.7 ± 4.4	24.9 ± 4.5	0.500
Hypertension, *n* (%)	35 (43.2%)	10 (62.5%)	25 (38.5%)	0.007
Coronary artery disease, *n* (%)	8 (9.9%)	2 (12.5%)	6 (9.2%)	0.100
Diabetes mellitus, *n* (%)	18 (22.2%)	5 (31.2%)	13 (20.0%)	0.650
Chronic obstructive pulmonary disease, *n* (%)	7 (8.6%)	2 (12.5%)	5 (7.7%)	0.330
Bronchial asthma, *n* (%)	6 (7.4%)	0 (0%)	6 (9.2%)	0.590
Sleep apnea syndrome, *n* (%)	8 (9.9%)	2 (12.5%)	6 (9.2%)	0.650
Chronic kidney disease, *n* (%)	6 (7.4%)	3 (18.8%)	3 (4.6%)	0.088
Bacterial superinfection, *n* (%)	2 (2.5%)	1 (6.2%)	1 (1.5%)	0.360
Laboratory parameters				
Median CRP level, mg/dL (IQR)	3.0 (1.1–7.9)	8.7 (7.0–12.1)	2.3 (0.9–5.7)	<0.001
Median LDH level, IU/L (IQR)	249 (203–329)	335 (285–484)	236 (193–300)	<0.001
Median WBC count, ×10^3/mm^3 (IQR)	5.6 (4.2–7.8)	8.3 (5.3–11.2)	5.1 (3.9–7.3)	0.003
Median Cr level, mg/dL (IQR)	0.8 (0.7–1.1)	0.9 (0.8–2.0)	0.5 (0.2–1.4)	0.048

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Treatments				
Invasive mechanical ventilation, *n* (%)		14 (17.3%)	13 (81.2%)	1 (1.5%) <0.001
Supplemental oxygen, *n* (%)	25 (30.9%)		3 (18.8%)	22 (33.8%) 0.370
Dexamethasone, *n* (%)	63 (77.8%)		16 (100%)	47 (72.3%) 0.017
Favipiravir, *n* (%)	53 (65.4%)		9 (56.2%)	44 (67.7%) 0.400
Median time from symptom onset to		4 (2–7)	7 (5–7)	4 (2–6) 0.020
Median time from symptom onset to the first		6 (4–9)	7 (6–10)	5 (3–9) 0.030
Prognosis				
Survivors, *n* (%)		76 (93.8%)	13 (81.2%)	63 (96.9%) 0.050
Non-survivors, *n* (%)		5 (6.2%)	3 (18.8%)	2 (3.1%)

FiO_2, fraction of inspiratory oxygen; BMI, body mass index; SD, standard deviation; IQR, interquartile range; IL-6, interleukin-6; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell; Cr, creatinine.

The 63 patients who received dexamethasone 6 mg daily were divided into 2 subgroups based on whether dexamethasone administration was initiated before or after the laboratory values were measured. A total of 28 patients received dexamethasone before the laboratory values were measured (preceding group). The remaining 35 patients were administered dexamethasone after the laboratory values were assessed (followed group). There were 10 and 6 patients assigned to the HFG in the preceding and followed groups, respectively. More patients in the HFG group received invasive mechanical ventilation in both the preceding and followed groups. No significant difference in the median time from symptom onset to dexamethasone therapy was found between the HFG and LFG groups (Table 2).

Table 2. Clinical characteristics between the two groups in the patients who received dexamethasone before or after measurement of blood markers.

	Preceding Dexamethasone			**Following Dexamethasone**		
	Maximum FiO_2 ≥0.4		***p*-Value**	**Maximum FiO_2 ≥0.4**		***p*-Value**
	Yes (*n* = 10)	**No (*n* = 18)**		**Yes (*n* = 6)**	**No (*n* = 29)**	
Median IL-6 level, pg/mL (IQR)	97.3 (58.1–144.0)	13.6 (4.9–27.3)	<0.001	79.2 (48.5–106.5)	31.7 (17.2–45.0)	0.054
Median CRP level, mg/dL (IQR)	7.4 (6.8–12.5)	2.7 (1.6–7.4)	0.018	9.9 (8.3–11.4)	3.0 (1.1–5.7)	0.023
Median LDH level, IU/L (IQR)	325 (263–455)	267 (210–349)	0.084	408 (301–585)	234 (199–270)	0.003
Median WBC count, $\times 10^3/mm^3$ (IQR)	10.5 (6.1–12.6)	7.5 (6.4–9.9)	0.204	6.2 (4.7–8.3)	4.9 (4.0–6.3)	0.220
Median D-dimer level, μg/mL (IQR)						

Laboratory Markers in COVID-19 Patients with Respiratory Failure

The levels of IL-6, CRP, LDH, WBC, D-dimer, and Cr in blood specimens of the HFG and LFG patients were compared. As shown in Table 1, the values of IL-6, CRP, LDH, WBC, D-dimer, and Cr were significantly higher in the HFG than in the LFG≥ patients. To test the diagnostic value of these parameters for respiratory failure with maximum FiO_2 0.4 within three days from laboratory measurement, ROC analysis was performed. The AUC value of IL-6, CRP, and LDH was high value of 0.85 [0.74–0.97], 0.82 [0.71–0.92], and 0.81 [0.70–0.92] with the cutoff value of 43.9, 5.7, and 268, respectively (Table 3). Among all patients, the OR value of each marker for the optimal cutoff value was evaluated. The crude OR of IL-6, CRP, and LDH showed the high value of 30.1 [5.6–295.6], 18.9 [3.8–188.4] and 9.5 [2.3–57.4], respectively (Table 4).Among the patients who received preceding dexamethasone, the values of each laboratory marker for predicting respiratory failure were compared between HFG and LFG. IL-6 and CRP levels were significantly higher in the HFG than in the LFG (Table 2). Considering that the dexamethasone therapy will affect respiratory condition, the adjusted OR for each dexamethasone group was evaluated. The values

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of IL-6 and CRP adjusted for preceding dexamethasone were 53.9 [4.5–3242.8] and 16.1 [1.6–847.9], respectively (Table 4). The OR value of IL-6 and CRP adjusted for followed dexamethasone therapy showed the same value (Table 4).

Table 3. Diagnostic characteristics of each marker to predict respiratory failure within three days from the measurement of these marker values.

				(CI)	(CI)	(CI)	(CI)
IL-6 level (pg/mL)	0.85 (0.74–0.97)	<0.001	43.9	87.5 (61.7–98.4)	81.5 (70.0–90.1)	53.8 (33.4–73.4)	96.4 (87.5–99.6)
CRP level (mg/dL)	0.82 (0.71–0.92)	<0.001	5.7	87.5 (61.7–98.4)	73.8 (61.5–84.0)	45.2 (27.3–64.0)	96.0 (86.3–99.5)
LDH level (IU/L)	0.81 (0.70–0.92)	<0.001	268	81.2 (54.4–96.0)	69.2 (56.6–80.1)	39.4 (22.9–57.9)	93.8 (82.8–98.7)
WBC count ($\times 10^3/mm^3$)	0.74 (0.61–0.87)	<0.001	7.8	56.2 (29.9–80.2)	81.5 (70.0–90.1)	42.9 (21.8–66.0)	88.3 (77.4–95.2)
Cr level (mg/dL)	0.68 (0.54–0.82)	0.012	0.9	66.7 (41.0–86.7)	58.5 (45.6–70.6)	30.8 (17.0–47.6)	86.4 (72.6–94.8)

IL-6, interleukin-6; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell; Cr, creatinine; AUC, area under the curve; CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Table 4. The odds ratio of each marker for all patients and adjusted for preceding and followed dexamethasone therapy

					(CI		(CI)	
IL-6	29.1	(5.6–	<0.001	53.9	(4.5–	<0.0	12.1 (1.1–	0.019
CRP	18.9	(3.8–	<0.001	16.1	(1.6–	0.006	12.1 (1.1–	0.019
LDH	9.5	(2.3–	<0.001	2.3 (0.4–18.0)		0.434	∞ (2.3–∞)	<0.001
WBC	5.5	(1.5–	0.004	2.8 (0.4–22.5)		0.254	4.1 (0.3–	0.195
D-	6.0	(1.5–	0.005	5.4 (0.5–285.8)		0.194	3.6 (0.4–	0.191
Cr	2.8	(0.8–	0.068	4.4 (0.7–36.5)		0.114	3.4 (0.32–	0.377

IL-6, interleukin-6; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell; Cr, creatinine; OR, odds ratio; CI, 95% confidence interval.

because this study aimed to evaluate the predictive ability of blood markers for respiratory failure within three days from analysis of these values, the cutoff point of IL-6, CRP, and LDH at which the value of PPV was the highest was determined. The cutoff value of IL-6 showed 91.5 with the corresponding PPV of 75.0% [42.8–94.5] (Table 5). The PPV value of CRP and LDH with the cutoff point of 6.7 and 305 was 50.0% [29.9–70.1] and 42.3% [23.4–63.1], respectively (Table 5).

Table 5. The cutoff value of three inflammatory markers with the highest positive predictive value

Variable		Cuto	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
IL-6	level	91.5	56.2 (29.9–80.2)	95.4 (87.1–99.0)	75.0 (42.8–	89.9 (80.2–
CRP	level	6.7	81.2 (54.4–96.0)	80.0 (68.2–88.9)	50.0 (29.9–	94.5 (84.9–
LDH	level	305	68.8 (41.3–89.0)	76.9 (64.8–86.5)	42.3 (23.4–	90.0 (80.0–

IL-6, interleukin-6; CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value

As SpO_2/FiO_2 ratio would decrease by respiratory deterioration, the minimum value of SpO_2/FiO_2 ratio within three days from laboratory measurement was selected for the correlation analysis. Among the whole patients, the correlation coefficient value of CRP was higher than that of IL-6. For the preceding dexamethasone group, that value was higher in IL-6 than CRP (Figure 2).

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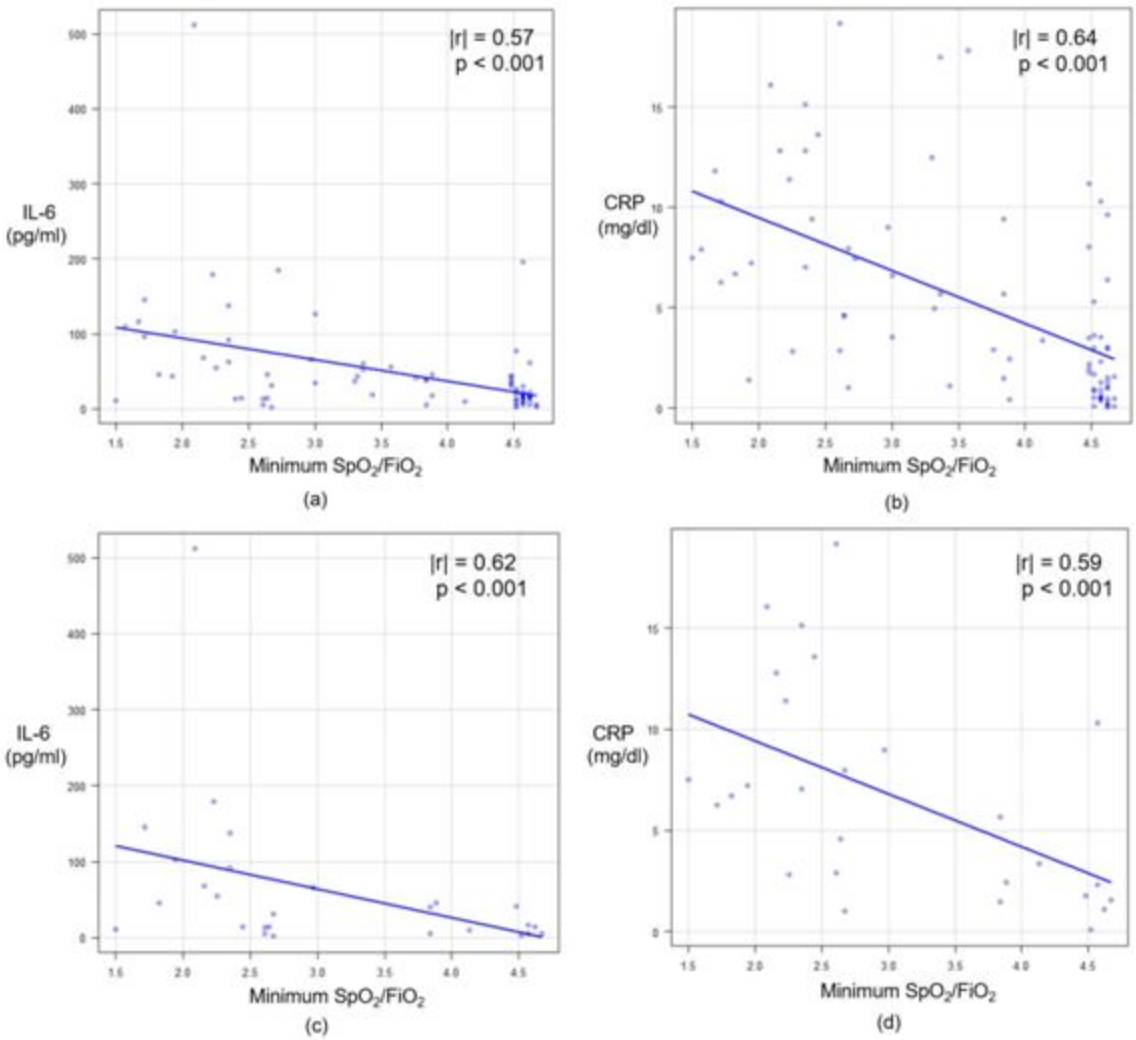

Figure 2. The correlation between minimum SpO2/FiO2 ratio and each blood marker: (**a**) IL-6 and (**b**) CRP among all patients; (**c**) IL-6 and (**d**) CRP in the preceding dexamethasone group. SpO2, percutaneous oxygen saturation; FiO2, fraction of inspired oxygen; IL-6, interleukin-6; CRP, C-reactive protein.

4.

Discussion

This study showed that IL-6 levels were associated with the severity of COVID-19 infection within three days, which were significantly elevated in HFG compared with that in LFG. In the context of critical COVID-19 infection as multiple organ disease caused by cytokine response. Terpos et al. mentioned that high D-dimer levels might be associated with lethal disseminated intravas- cular coagulation (DIC)-related complications other than ARDS [5]. This study revealed the high correlation coefficients of the serum level of IL-6 and CRP to minimum SpO2/FiO2 ratio, demonstrating that increase of the two markers indicates respiratory failure within three days after laboratory measurement. To find out the practical cutoff of these markers for respiratory failure, we set the outcome of this study on oxygen requirement with maximum FiO2 0.4. The ROC analysis showed the high AUC and OR value of both IL-6 and CRP in the whole group. IL-6 level would be most useful with the highest value of AUC

and the significant value of OR.The dexamethasone therapy itself will not influence IL-6 level, which is supported by an analysis of the transcriptomic data that indicates the therapeutic mechanism of dexamethasone in severe COVID-19 patients does

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not involve IL-6 pathway [6]. The OR value of IL-6 adjusted for preceding dexamethasone administration showed a high value, indicating that IL-6 levels might reflect an ongoing respiratory deterioration in COVID-19 patients even under the dexamethasone therapy. On the contrary, previous reports have demonstrated that IL-6 receptor inhibitor therapy, such as tocilizumab, could prompt IL-6 synthesis to spike by receptor blockage [7]. Herold et al. demonstrated that elevated IL-6 levels predicted the need for mechanical ventilation [8].

Our results suggest that IL-6, which is the key cytokine located upstream of the inflam- matory cytokine cascade, increases prior to ARDS in critical COVID-19 patients, followed by an increase in acute-phase protein levels, such as CRP [9,10]. SARS-CoV-2 can rapidly activate pathogenic Th1 cells to secrete pro-inflammatory cytokines such as granulocyte- macrophage colony-stimulating factor (GM-CSF) and IL-6 [11].

A cytokine storm causing critical respiratory distress in COVID-19 is an immune disease characterized by high-level activation of immune cells and excessive production of massive inflammatory cytokines and chemical mediators [12]. In clinical settings, many anti-inflammatory drugs, such as corticosteroids and IL-6 receptor inhibitors, are candidates for therapeutic strategies against COVID-19.The optimal timing for the administration of these drugs remains unclear. Too early administration can adversely lead to a decrease in viral clearance [13]. The use of corticosteroids has detrimental effects on the survival of patients not requiring oxygen [14]. IL-6 plays an important role in lung repair responses following viral insults, which means that the timing of administration of IL-6 receptor inhibitors could affect proper tissue remodeling [15]. Recently, in Japan, out-of-hospital sudden death during home recuperation owing to COVID-19 pandemic is an emerging problem. The analysis for the COVID-19 patients dying at home or in a hotel for recuperation showed that the duration from COVID-19 diagnosis to death was 1–10 days (mean four days, median three days) [16].This study had several limitations.This study was a single-center, retrospective observational study; thus, the number of cases was small, and other confounding factors might not have been considered.

5. Conclusions

The serum level of IL-6 is highly predictive of respiratory failure within three days in COVID-19 patients. Further studies are needed to investigate the validity of this inflammatory marker for predicting respiratory illness associated with COVID-19.

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