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LETTER

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Interferon lambda 3 in the early phase of coronavirus disease-19 can predict oxygen requirement

1 | INTRODUCTION

Since the coronavirus disease 2019 (COVID-19) pandemic started, various medications and vaccinations have been developed. However, the healthcare capacity was still exceeded during the period of rapid increase in COVID-19 cases, which hinderered timely and appropriate treatment, leading to the deterioration of patient outcomes.[1,2] Healthcare stakeholders have faced difficulties in deciding which cases should be prioritized to receive the limited but essential inpatient care.

In Japan, local public health centers and specialized facilities manage patient placement and admit patients with a high risk of disease progression or those who have already developed respiratory failure, to appropriate medical institutions. However, because COVID-19 can suddenly become severe,[3] over- or under- triage can often happen. Some patients are admitted to tertiary medical institutions despite not requiring oxygen supplementation, while other cases become seriously ill at home or in isolation facilities. Although some scoring systems have been published to estimate the risk of severe disease in patients with COVID-19,[4–6] an objective and simple index that predicts disease progression as early as possible (before critical illness) is needed.

We comprehensively investigated a total 71 humoral factors as predictive markers of COVID-19, and discovered that chemokine ligand 17 (CCL17), interferon lambda 3 (IFNλ3), interleukine 6 (IL-6), interferon-inducible protein 10 (IP-10), and C-X-C motif chemokine ligand 9 (CXCL9) potentially signal disease progression.[7]Among these biomarkers, CCL17 and IFNλ 3 are already approved and covered by the national health insurance in Japan. Therefore, these examinations can be widely available at general medical institutions. However, it is still unclear if these markes can predict oxygen demand and disease progression in the early phase of COVID-19 in the clinical setting. In this study, we attempted to determine whether these and some other markers can accurately predict the subsequent oxgen demand and progression of disease in patients with early-stage COVID-19 who do not require supplemental oxygen.

2 | METHODS

2.1 | Study design, setting, and population

Of the patients with confirmed COVID-19 admitted to our hospital between January 1, 2020 and September 30, 2021, only those who were treated or handled by the infectious disease department were enrolled in this retrospective cohort study. Of these, patients with stored sera collected within 7 days of disease onset and who did not require oxygen supplementation at the time of specimen collection were included. The day of disease onset was set as day 0 and for asymptomatic patients the day when the positive specimen was collected was set as day 0. All patients were diagnosed with COVID-19 using antigen or nucleic acid amplification tests approved in Japan. This study was approved by the ethics committee of the National Center for Global Health and Medicine (Approval No. NCGM-G-003647). Individual consent for this study was not obtained from each patient, and opt-outs were set up. Reporting of the study conforms to broad EQUATOR guidelines.[8]

2.2 | Data collection

Epidemiological, demographic, and relevant clinical data were extracted by chart review of eligible patients who met the inclusion criteria. We measured IFNλ3 and CCL17 using stored sera collected within 7 days of disease onset when there was no supplemental oxygen demand. We also evaluated C-reactive protein (CRP), lactate dehydrogenase (LDH), and lymphocyte fraction because of

a previous report[9] and the feasibility in clinical settings. These values were extracted from the clinical data measured on the same day as the date of collection of the stored sera.

Patients with higher disease severity were defined as those who needed high-flow nasal cannula (HFNC) oxygen therapy, non-invasive positive pressure ventilation, invasive respiratory ventilator, or extracorporeal membrane oxygenation (ECMO), or those who were deceased.

2.3 | Statistical analysis

Continuous variables are expressed as medians and interquartile ranges, and categorical variables as numbers and percentages. The performance of the aforementioned blood markers from days 0 to 7 in predicting the subsequent oxygen supplementation and HFNC oxygen therapy, or higher severity during hospitalization, was evaluated by receiver operating characteristic (ROC) curves and compared using the area under the curve (AUC). The cut-off values were determined using the unweighted Youden index. To further investigate the appropriate timing of measuring these markers, we divided the patients into two subgroups, namely days 0–4 and days 5–7 after disease onset, and conducted the same analyses in each group. Each marker was considered useful if the AUC was greater than 0.75.[10]

Based on the previous studies,[4,11,12] we assumed that the event of supplemental oxygen demand would occur in 20% of all patients, and the AUC of the test would be approximately 0.85. Furthermore, the event of HFNC or higher severity would occur in 2% of all patients, and the AUC of the test would be approximately 0.9. We set $\alpha = 0.05$, $1-\beta = 0.9$. Finally, we set the target number of participants for this study as 10 cases and 30 controls for predicting supplemental oxygen demand, and 10 cases and 180 controls for predicting HFNC oxygen therapy or higher severity.

All statistical analyses were performed with EZR version 1.41 (Saitama Medical Center, Jichi Medical University), a graphical interface for R version 3.6.1.[13] Statistical significance was set at $p < .05$.

3 | RESULTS

A total of 188 patients (median age: 49 years; men: 64.4%) met the inclusion criteria and were included in this study. Of the these, 41 (21.8%) needed oxygen supplementation, and 5 (2.7%) required HFNC oxygen therapy or had higher severity. In 110 and 78 patients, sera were collected on days 0–4 and days 5–7 of disease onset, respectively. The overall patient characteristics and subgroups are presented in Table 1.

The performances of IFNλ3, CRP, CCL17, LDH, and lymphocyte fraction in predicting the subsequent severity of COVID-19 are shown in Table 2. Regarding the prediction of supplemental oxygen demand, IFNλ3 on days 0–7 after disease onset showed relatively good test characteristics with a cut-off value of 7.6 pg/ml, AUC of 0.833 (95% confidence interval [CI], 0.763–0.903). In particular, on days 5–7 after disease onset, IFNλ3 showed even better test characteristics with a cut-off value of 7.6 pg/ml, AUC of 0.908 (95% CI, 0.841–0.975). The ROC curve of IFNλ3 for predicting the subsequent oxygen supplementation is shown in Figure 1. In contrast, all other blood markers had an AUC < 0.75 for predicting oxygen supplementation on days 0–7. When limited to days 5–7, CRP (cut-off value, 3.02 mg/dl) and LDH (cut-off value, 236 U/L) showed relatively good performance with AUC > 0.75. The predictive performance of IFNλ3 was significantly better than that of CRP on days 0–7 ($p = .022$, Figure 2). The sensitivity and specificity at representative thresholds of IFNλ3 and CRP are shown in Tables S1-S2.

For the prediction of HFNC or higher severity, the AUC of IFNλ3 (cut-off value 7.6 pg/ml) was 0.928 (95% CI, 0.831–1.0) when collected on days 0–7 after disease onset and 0.984 (95% CI, 0.951–1.0) on days 0–4 (cut-off value, 15.3 pg/ml). CRP (cut-off value, 3.69 mg/dl), LDH (cut-off value, 214 U/L), and lymphocyte fraction (cut-off value, ≤20.0%) showed good results, with AUC > 0.75 on days 0–7 of disease onset. However, CCL17 showed opposite results between days 0–4 and days 5–7, and performance on days 5–7 was very good, with a cut-off value of 19.1% or less and an AUC of 0.984 (95% CI, 0.946–1.0). The ROC curves for IFNλ3, CRP, CCL17, LDH, and lymphocyte fractions are shown in Figures S1-S5.

4 | DISCUSSION

We showed that IFNλ3 predicted subsequent oxygen demand better than CRP in patients in the early phase of COVID-19 without supplemental oxygen demand. IFNλ3 may effectively predict whether a patient with COVID-19 will require medical intervention, such as oxygen supplementation, at an earlier point before the patient presents with respiratory failure. In particular, the performance of IFNλ3 on days 5–7 after disease onset was particularly good. This is the time when patients with COVID-19 can become critically ill.[14] IFNλs are antiviral cytokines which affect against viral infection at the epithelial tissue. IFNλ3 is induced by various microbial ligands and can exacerbate antimicrobial responses. In COVID-19 pathogenesis, IFN lambdas may be exacerbating factors in relation to

TABLE 1 Baseline characteristics of the patients

	No. of available data in overall population	Overall, $n = 188$	Onset to sampling in day 0–4, $n = 110$	Onset to sampling in day 5–7, $n = 78$
Onset to sampling day	188	4.0 [3.0–6.0]	3.0 [2.0–4.0]	6.0 [5.0–7.0]
Age	188	49.0 [36.0–63.3]	49.5 [34.3–65.0]	49.0 [36.0–61.5]
Male sex	188	121 (64.4)	70 (63.6)	51 (65.4)
BMI, kg/m^2	180	23.7 [20.9–26.5]	23.4 [20.9–26.8]	23.9 [20.9–25.7]
Vaccination	128			
0 time		124 (66.0)	64 (58.2)	60 (76.9)
1 time		2 (1.1)	2 (1.8)	0
2 times		2 (1.1)	1 (0.9)	1 (1.3)
Any allergy	180	55 (30.6)	28 (25.5)	27 (34.6)
Comorbidities				
Diabetes	188	33 (17.6)	22 (20.0)	11 (14.1)
Hypertension	188	40 (21.3)	31 (28.2)	9 (11.5)
Asthma	188	18 (9.6)	12 (10.9)	6 (7.7)
Atopic dermatitis	188	11 (5.9)	8 (7.3)	3 (3.8)
Dialysis	188	3 (1.6)	3 (2.7)	0
Pregnancy	188	7 (3.7)	5 (4.5)	2 (2.6)
Malignancy	188	1 (0.5)	0	1 (1.3)
Usual systemic corticosteroid	188	4 (2.1)	2 (1.8)	2 (2.6)
Usual immunosuppressant	188	1 (0.5)	1 (0.9)	0
Treatment before sampling	188			
Remdesivir		3 (1.6)	2 (1.8)	1 (1.3)
Systemic corticosteroid		2 (1.1)	0	2 (2.6)
Casirivimab/Imdevimab		0	0	0
Laboratory data at sampling				
White blood cell, /μl	182	4660 [3680–5680]	4620 [3770–5680]	4850 [3470–5670]
Lymphocyte, %	179	25.0 [18.7–30.3]	23.4 [16.0–30.0]	26.2 [19.4–31.2]
Lactate dehydrogenase, U/L	180	197 [163–264]	180 [160–247]	223 [180–273]
C-reactive protein, mg/dl	183	1.36 [0.35–3.87]	0.89 [0.25–3.19]	2.18 [0.47–4.28]
CCL17, pg/ml	188	153.7 [101.1–229.1]	152.5 [106.4–237.6]	158.8 [93.8–223.9]
IFNλ3, pg/ml	188	3.8 [2.9–8.3]	3.4 [2.9–7.5]	4.5 [2.9–8.6]
Oxygen supp. During COVID-19	188	41 (21.8)	21 (19.1)	20 (25.6)
HFNC or higher severity	188	5 (2.7)	3 (2.7)	2 (2.6)

Note: Data are indicated as median [IQR] or number (%). Each denominator is fixed to number of patients in each group.

neutrophil chemotaxis and the complement/coagulation cascade.[15] IFNλ3 surged and then dropped suddenly before the development of severe disease requiring oxygen support.[7] Therefore, IFNλ3 may be useful in making decisions regarding appropriate patient placement.

Although previous studies have suggested the usefulness of CRP as a prognostic marker for patients with COVID-19,[11,16] IFNλ3 showed better predictive performance than CRP in the present study. A comparison of the results of the previous study and the present results is shown in Table 3. The median value of CRP in the present study was lower than that reported in previous studies. The median time from disease onset to specimen collection in this study was 4 days, which was shorter than that

TABLE 2 Characteristics of each examination to predict the outcome in COVID-19 patients without oxygen supplementation at sampling

	Onset-sampling	Oxygen demand			HFNC or more severe condition		
		Day 0–7	(Day 0–4)	(Day 5–7)	Day 0–7	(Day 0–4)	(Day 5–7)
IFNλ3, pg/ml	Cut-off value	7.6	3.9	7.6	7.6	15.3	7.6
	AUC	0.833[a]	0.767[a]	0.908[a]	0.928[a]	0.984[a]	0.842[a]
	95% CI	0.763–0.903	0.652–0.882	0.841–0.975	0.831–1.000	0.951–1.000	0.553–1.000
	Sensitivity (%)	70.7	85.7	85.0	100	100	100
	Specificity (%)	84.4	66.3	86.2	74.3	95.3	69.7
CRP, mg/dl	Cut-off value	3.02	1.92	3.02	3.69	3.69	3.86
	AUC	0.726	0.679	0.783[a]	0.874[a]	0.910[a]	0.812[a]
	95% CI	0.633–0.819	0.552–0.806	0.652–0.914	0.77–0.977	0.803–1.000	0.519–1.000
	Sensitivity (%)	65.0	61.9	78.9	100	100	100
	Specificity (%)	75.5	69.3	70.9	75.3	81.1	66.7
CCL17, pg/ml	Cut-off value	88.9 (or less)	43.8 (or less)	151.8 (or less)	47.7 (or less)	388.7 (or less)	47.7 (or less)
	AUC	0.573	0.443	0.714	0.501	0.185	0.984[a]
	95% CI	0.462–0.684	0.295–0.59	0.564–0.863	0.096–0.905	0.000–0.401	0.946–1.000
	Sensitivity (%)	34.1	9.5	80.0	40.0	100	100
	Specificity (%)	84.4	98.9	62.1	96.7	5.6	96.1
LDH, U/L	Cut-off value	186	188	236	214	227	214
	AUC	0.685	0.608	0.785[a]	0.807[a]	0.894[a]	0.641
	95% CI	0.593–0.778	0.475–0.741	0.674–0.897	0.639–0.976	0.720–1.000	0.285–0.997
	Sensitivity (%)	81.6	65.0	77.8	100	100	100
	Specificity (%)	50.0	58.6	67.3	57.7	72.1	46.5
Lymphocyte, %	Cut-off value	27.0 (or less)	24.8 (or less)	27.0 (or less)	20.0 (or less)	20.0 (or less)	19.1 (or less)
	AUC	0.598	0.589	0.629	0.827[a]	0.824[a]	0.84[a]
	95% CI	0.498–0.698	0.447–0.731	0.482–0.775	0.721–0.933	0.638–1.000	0.697–0.984
	Sensitivity (%)	77.5	76.2	78.9	100	100	100
	Specificity (%)	41.0	48.8	49.1	70.1	66.7	77.8

[a]AUC > 0.75.

in a previous study.[16] CRP peaks 48 hours after initiation of the inflammatory reaction.[17] Thus, CRP levels at an earlier phase of the disease may have influenced the results. In fact, in our study, the median CRP was higher on days 5–7 than on days 0–4, and the predictive performance also seemed better on days 5–7. However, CRP is not a disease-specific marker and can be influenced by various conditions. In contrast, IFNλ3 can be a more accurate marker than CRP, although its disease specificity requires further investigation.

In addition to IFNλ3, CRP, LDH, and lymphocyte fraction also showed good predictive performance for HFNC oxygen therapy or higher severity. A previous scoring system[4] that predicts the risk of subsequent severe disease based on the findings of COVID-19 patients at admission, has already been reported. This study was limited to patients in the early stage of disease with no supplemental oxygen demand at sampling, and showed good predictive performance of a single blood marker, IFNλ3. In clinical practice, simple and easy tests for COVID-19 severity are warranted. However, the sample size for the analysis of HFNC oxygen therapy or higher severity in this study was insufficient because the number of patients with severe disease was small. Therefore, these results should be interpreted with caution.

The performance of CCL17 in predicting HFNC oxygen therapy or higher severity was poor. In patients with severe COVID-19, CCL17 levels were reported to be low,[7] but the detailed mechanism is not clear. Considering that the results were completely opposite on days 0–4 and 5–7, CCL17 may fluctuate dynamically in the early phase of COVID-19. Nevertheless, CCL17 may be a helpful marker

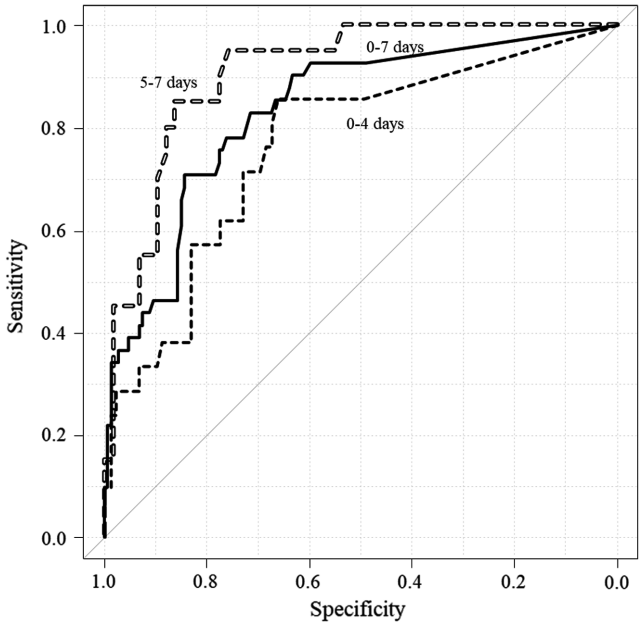

FIGURE 1 ROC curve of IFNλ3 to predict oxygen demand in COVID-19 patients without oxygen supplementation at sampling

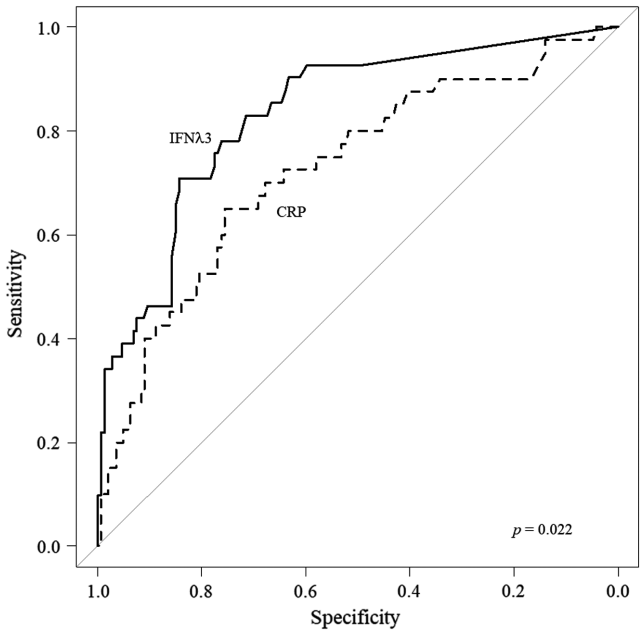

FIGURE 2 Comparisons of AUC between IFNλ3 and CRP to predict oxygen demand in COVID-19 patients without oxygen supplementation at sampling

if the timing of sample collection is optimized. Further studies are needed to determine the appropriate timing of measurement.

This study was conducted at a single institution designated for specific infectious diseases, which may have better resources for, and experience in, infectious disease treatment than general medical institutions in Japan. Therefore, our findings may not be generalizable to all medical facilities. However, compared with a large study[12] of hospitalized patients with COVID-19 in Japan, the patient backgrounds and rates of severe disease were similar, and we believe that this study reflects the general population in Japan to some extent. Moreover, this study was conducted on patients within the clinical setting, and further research is needed to determine the validity of this study for patients at home or in isolation facilities.

In addition, most patients in this study were unvaccinated against COVID-19. With most populations currently vaccinated, the clinical progression of the disease may differ from that of the unvaccinated group. Cut-off values and laboratory characteristics may change in patients who are vaccinated. Furthermore, new medications are currently under development, and those who receive such medications may show a better clinical course. Thus, the predictive performance of the blood markers discussed here is likely to change.

In summary, in patients with COVID-19 without supplemental oxygen demand for up to 7 days after disease onset, the serum IFNλ3 level predicts the occurrence of subsequent oxygen demand with high accuracy. This is important for early and easy decision-making regarding patient placement and early therapeutic intervention. In the future, IFNλ3 may be a useful tool for improving the prognosis of patients with COVID-19 while reducing the burden on medical institutions. Further research will be needed to evaluate the reliability and validity of IFNλ3 as a prognostic marker for COVID-19 in a larger population.

AUTHOR CONTRIBUTIONS

Conceptualization: TS, NI, ST, MS, MM, and NO. Sample collection: TS, NI, SA, KK, AO, GY, MI, LS, YM, and YA. Sample analysis: YO and TN. Data collection: TS, NI, YK,

TABLE 3 The comparison of CRP and IFNλ3 performance to predict oxygen demand or its equivalent status in COVID-19 patients

Author	Total patients	Patients required oxygen	Biomarkers	Cut off value	AUC	Sensitivity (%)	Specificity (%)
Wang G, et al.[10]	209	16	CRP	2.69 mg/dl	0.844	81.3	79.3
Cheng B, et al.[14]	456	251	CRP	1.085 mg/dl	0.740	61.48	78.15
This study	188	46	CRP	3.02 mg/dl	0.726	65.0	75.5
			IFNλ3	7.6 pg/ml	0.833	70.7	84.4

and MS. Data analysis: TS, NI, and ST. Original manuscript writing: TS and NI. Supervision: SS, SM, MU, KH, MS, MM, EK, and NO.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

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