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Rapid Communication

IFN-λ3 and CCL17 as predictors of disease progression in patients with mild to moderate COVID-19: A cohort study in a real-world setting

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has overwhelmed hospitals worldwide. In Japan, serum interferon lambda 3 (IFN-λ3) and C–C motif ligand (CCL) 17 levels have been used as predictive markers for disease progression to severe COVID-19. However, the relationship between these predictive markers and the disease progression of COVID-19 has not been well evaluated. We retrospectively evaluated the patient characteristics, serum IFN-λ3 and CCL17 levels, and comorbidities of 92 patients with mild (n = 20) and moderate (n = 72) COVID-19 who were hospitalized in our institution. The results of the multivariable analysis showed that the positive rates of IFN-λ3, CCL17, and the combination of these markers were significantly elevated in patients with progressed COVID-19. Furthermore, patients who were negative for both markers did not experience disease progression. This study illustrates the importance of measuring these markers to predict disease severity and progression in patients with COVID-19.

Abbreviations: CCL, C–C motif ligand; CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio; IFN-λ3, interferon lambda 3.

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1. Introduction

Since early 2020, the coronavirus disease 2019 (COVID-19) pandemic has overwhelmed the world. Patients with mild or moderate COVID-19 sometimes experience rapid progression requiring oxygen supplementation and additional treatment, including dexamethasone. Therefore, identifying patients at risk for disease progression to severe COVID-19 is essential for the appropriate allocation of medical resources. Interferon lambda 3 (IFN-λ3) and C–C motif ligand (CCL) 17, also known as thymus and activation-regulated chemokine, are commercially utilized as predictive markers of disease progression in patients with mild to moderate COVID-19, and their testing is covered by medical insurance in Japan. However, the efficaciousness of both predictive markers was reported only in one study, which used a very small group of patients with mild to severe COVID-19 (n = 29) [1]. Thus, in clinical practice, the positive rate of each marker and the relationship between these markers and the clinical course of patients with COVID-19 remains uncertain. Therefore, we analyzed the positive rates of IFN-λ3 and CCL17 as well as disease progression in patients with mild to moderate COVID-19 in our hospital.

2. Patients and methods

We retrospectively evaluated the patient characteristics, serum IFN-λ3 and CCL17 levels, and known comorbidities as risk factors for progression and severity in patients with mild to moderate COVID-19 who were hospitalized in our institution between July 1 and September 30, 2021. The diagnosis of COVID-19 was confirmed by polymerase chain reaction for the detection of SARS-CoV-2, and the severity was based on consensus guidelines in Japan [2]. Patients with no evidence of pneumonia on computed tomography or chest radiography were defined as having mild disease, while those with evidence of pneumonia but not requiring oxygenation were defined as having moderate disease. Disease progression was defined as mild or moderate aggravating to severe (requiring oxygenation and additional treatment, including dexamethasone) or critical (requiring therapeutic management in the intensive care unit with positive pressure ventilation). We utilized an automatic immunoassay instrument, HISCL-5000 (Sysmex, Kobe, Japan), and commercially available examination kits for the measurement of serum IFN-λ3 and CCL17 levels. Based on data from a previous report [1], IFN-λ3 and CCL17 levels ≥13.6 pg/mL and ≤95.1 pg/mL, respectively, were defined as positive risk factors for disease progression. Comorbidities known to be risk factors for progression include chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, hypertension, collagen vascular disease, cancer, and smoking history.

2.1. Statistical analyses

The results are expressed as means ± standard deviations or numbers and ratios (%). Continuous variables were compared using an unpaired *t*-test. Categorical variables were compared using the Chi-square test. Highly relevant clinical variables related to the severity of patients with COVID-19 were determined using a multivariate logistic regression model. The IFN-λ3 and CCL17 levels and a combination of both were transcribed into each multivariate logistic regression model. A p-value <0.05 was considered statistically significant.

3. Results

The patient characteristics and comparison of the clinical data are presented in Table 1. We analyzed 92 patients with COVID-19, of whom 20 and 72 had mild and moderate disease, respectively. Disease progression was observed in 14 patients, of whom one patient, who was an 85-year-old female with chronic kidney disease, died due to respiratory failure. Three of the 20 patients in the mild group were positive for CCL17, while none were positive for IFN-λ3. In the moderate group, 17 patients tested positive for both IFN-λ3 and CCL17. Among them, seven (41.1%) experienced progression; 26 were positive for only IFN-λ3, of whom six (23.1%) developed severe COVID-19; and eight were positive for only CCL17, of whom one (12.5%) experienced disease progression. The remaining 20 patients in the moderate group were negative for both IFN-λ3 and CCL17, and none experienced progression. No patients received any treatment for COVID-19 before hospitalization. Among the patients with moderate COVID-19, 60 (83.3%) received remdesivir. All patients who tested positive for either CCL-17 or IFN-λ3 received remdesivir, except for one patient who could not receive this medication owing to hepatic dysfunction. Among those with mild COVID-19, only one was administered casirivimab/imdevimab. All 14 patients who experienced disease progression originally belonged to the moderate group and had already received remdesivir. All patients who experienced progression received corticosteroids and temporarily received oxygen.

A comparison of the clinical data and patient characteristics showed that the body mass index (p = 0.047), severity (p = 0.032), duration from onset to hospitalization (p = 0.029), IFN-λ3 (p = 0.001), and CCL17 (p = 0.033) were significantly higher in patients who experienced progression than in those who did not. Among those who showed progression, a significantly greater number of patients received remdesivir (p = 0.002). No significant differences were found among comorbidities. We performed multivariable logistic regression analysis according to the result of the univariate analysis (Table 2). Severity could not be analyzed because no patient in the mild group experienced progression. We conducted a multivariable logistic regression analysis in the three models, and the results showed that IFN-λ3 (odds ratio [OR]: 7.95; 95% confidence interval [CI]: 1.5–41.7), CCL17 (OR: 4.32; 95% CI: 1.13–16.5), and their combination (OR: 3.99; 95% CI: 1.04–15.3) were significantly higher in patients who experienced progression. The duration from onset to hospitalization was significantly longer in Models 2 (OR: 1.33; 95% CI: 1.03–1.73) and 3 (OR: 1.30; 95% CI: 1.01–1.67); however, the ORs were lower than those of previously shown markers.

Table 1 – Characteristics and comparison of the clinical data in patients with and without progression.

Variable	All patients (N = 92)	Without progression (n = 78)	With progression (n = 14)	p-value
Age at presentation (years) Mean ± SD	46.8 ± 16.1	45.9 ± 16.2	51.9 ± 15.0	p = 0.481
Male	60 (65.2%)	48 (61.6%)	12 (85.7%)	p = 0.080
Height (cm)	166.1 ± 8.0	166.0 ± 7.9	166.7 ± 8.7	p = 0.497
Weight (kg)	69.8 ± 16.2	68.7 ± 16.5	76.0 ± 13.0	p = 0.090
Body mass index (kg/m^2)	25.2 ± 5.1	24.8 ± 5.2	27.2 ± 3.6	p = 0.047*
Severity				p = 0.032*
Moderate	72 (78.3%)	58 (74.3%)	14 (100%)	
Mild	20 (21.7%)	20 (25.7%)	0 (0%)	
Duration from onset to hospitalization	5.85 ± 2.8	5.60 ± 2.9	7.2 ± 2.2	p = 0.029*
Positive for IFN-λ3	43 (46.7%)	31 (39.7%)	12 (85.7%)	p = 0.001*
Positive for CCL17	30 (32.6%)	22 (28.2%)	8 (57.1%)	p = 0.033*
History of vaccination	6 (6.5%)	5 (6.4%)	1 (7.1%)	p = 0.919
Comorbidity				
COPD	1 (1.1%)	1 (1.3%)	0 (0%)	p = 0.670
CKD	7 (7.6%)	6 (7.7%)	1 (7.1%)	p = 0.943
DM	15 (16.3%)	12 (15.4%)	3 (21.4%)	p = 0.573
HT	13 (14.1%)	11 (14.1%)	2 (14.3%)	p = 0.986
CVD	5 (5.4%)	4 (5.1%)	1 (7.1%)	p = 0.760
Smoking history	31 (33.7%)	28 (35.9%)	3 (21.4%)	p = 0.290
Cancer	3 (3.3%)	3 (3.8%)	0 (0%)	p = 0.456
Treatment after hospitalization				
Remdesivir	60 (65.2%)	46 (59.0%)	14 (100%)	p = 0.002*
Corticosteroids	14 (15.2%)	0 (0%)	14 (100%)	NS
Casirivimab/imdevimab	1 (1.1%)	1 (1.3%)	0 (0%)	NS
Mortality	1 (1.1%)	0 (0%)	1 (7.1%)	NS

*p < 0.05.
Abbreviations: COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; DM, diabetes mellitus; HT, hypertension; CVD, collagen vascular disease

Table 2 – Multivariate logistic regression analysis.

Variable	Odds ratio (95% CI)		
	Model 1	Model 2	Model 3
Age	1.02 (0.98–1.07)	1.04 (0.99–1.09)	1.03 (0.99–1.07)
Sex	0.25 (0.04–1.41)	0.24 (0.04–1.37)	0.28 (0.05–1.51)
Body mass index (kg/m^2)	1.10 (0.95–1.28)	1.11 (0.96–1.28)	1.10 (0.96–1.26)
Duration from onset to hospitalization	1.32 (0.99–1.77)	1.33 (1.03–1.73) *	1.30 (1.01–1.67) *
Positive for IFN-λ3	7.95 (1.5–41.7) *	–	–
Positive for CCL17	–	4.32 (1.13–16.5) *	–
Positive for both markers	–	–	3.99 (1.04–15.3) *

CI, confidence interval.
Model 1: adjusted for age, sex, body mass index, duration from onset to hospitalization, and positivity for IFN-λ3.
Model 2: adjusted for age, sex, body mass index, duration from onset to hospitalization, and CCL17 positivity.
Model 3: adjusted for age, sex, body mass index, duration from onset to hospitalization, and positivity for both markers (IFN-λ3 and CCL17).
*p < 0.05.

4. Discussion

IFN-λ3 and CCL17 showed a high tendency (OR, 3.99–7.95) of predicting COVID-19 progression. Based on the statistical examination findings, we believe that IFN-λ3 is a better predictor of disease progression than CCL17. Moreover, all patients who were negative for both IFN-λ3 and CCL17 did not experience progression. Therefore, it is important to consider both predictive markers. Almost all patients who were positive for at least one marker were administered remdesivir. Therefore, the effect of treatment on the positivity of those markers was almost irrelevant. In the health insurance policies of Japan, the IFN-λ3 level is measured more than once in patients with mild or moderate COVID-19. For instance, four patients presented negative serum IFN-λ3 upon admission but had positive serum IFN-λ3 on the second test. CCL17 is an activation-regulated chemokine and a well-known biomarker of allergic diseases, including atopic dermatitis [3] and asthma [4]. In COVID-19, a specific

immune response occurs during the early phase of infection in patients with severe to critical COVID-19 [1]. However, the mechanism that suppresses serum CCL17 in patients with COVID-19 is unknown. IFN-λ3 is an initial molecule released from immune cells against pathogens [5,6] and a key molecule for the development of severe or critical symptoms [1]. Furthermore, IFN-λ is present in the lower, but not upper, airways of patients with COVID-19 [7]. The association between IFN-λ3 and SARS-CoV-2 infection is similar to that of chronic hepatitis C, possibly because the hepatitis C virus is a ribonucleic acid virus [8].

To the best of our knowledge, this is the first report to describe the correlation between IFN-λ3, CCL17, comorbidities, and progression in patients with mild to moderate COVID-19 in a real-world setting. However, this study has several limitations. First, the study design was retrospective, and the number of participants was relatively small. Second, the study was conducted between July and September 2021, wherein a different dominant variant of SARS-CoV-2 was affecting the world. However, the dominant variant of SARS-CoV-2 was different in a previous study [1]. Nevertheless, we think that these predictive markers may still be useful even if the dominant variant of SARS-CoV-2 changes. Third, only a few vaccinated patients were included in this study. Moreover, IFN-λ3 is a predictive marker of active hepatitis; however, some patients were not checked for the presence of hepatitis B and C viruses. Vaccination against COVID-19 is widely performed globally; however, some people remain unvaccinated and have a high tendency of progression if diagnosed with COVID-19. In such cases, checking the serum IFN-λ3 and CCL17 levels to predict the possibility of disease progression may be valuable.

5. Conclusions

In this study, serum IFN-λ3 and CCL17 levels exhibited efficacy as predictive markers for progression in patients with mild to moderate COVID-19 with high sensitivity. Further studies are needed to validate these markers in people vaccinated against COVID-19.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of Saitama Saiseikai Kawaguchi General Hospital (IRB No. 2021–36) on October 25, 2021, and the requirement for patient consent was waived.

Availability of data and materials

All data generated and/or analyzed in the current study are included in this paper.

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Authors' contributions

Study design: YS and MS; Data analysis: YS, MS, SN, and YN; Collection of patient data: YS, HE, YM, MT, and KN; Manuscript writing: YS, MS, and KT; Final preparation of the entire manuscript: YS and MS; All authors have read and approved the final manuscript.

Conflict of interest

The authors have no conflict of interest to disclose.

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