Predictive prognostic biomarkers in patients with COVID-19 infection

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Abstract. The present study aimed to identify useful biomarkers to predict deterioration in patients with coronavirus disease 2019 (COVID-19). A total of 201 COVID-19 patients were classified according to their disease severity into non-severe (n=125) and severe (n=76) groups, and the behavior of laboratory biomarkers was examined according to the prognosis. Neutrophil count, aspartate aminotransferase (AST), alanine aminotransferase, lactate dehydrogenase (LDH), C-reactive protein (CRP), sialylated carbohydrate antigen KL-6 (KL-6), procalcitonin (PCT), presepsin (PSP) and D-dimer levels were significantly higher, and lymphocyte count and platelet count were significantly lower in the non-severe group compared with the severe group. In the non-severe group, ROC analysis demonstrated that only four biomarkers, CRP, PSP, AST and LDH were useful for differentiating the prognosis between improvement and deterioration subgroups. No strong correlation was revealed for any of the markers. Multivariate analysis identified CRP as a significant prognostic factor in non-severe cases (odds ratio, 41.45; 95% confidence interval, 4.91-349.24; P<0.001). However, there were no blood biomarkers that could predict the outcome of patients in the severe group. Overall, several blood markers changed significantly according to disease severity in the course of COVID-19 infection. Among them, CRP, PSP, LDH and AST were the most reliable markers for predicting the patient's prognosis in non-severe COVID-19 cases.

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Introduction

Since the outbreak of coronavirus disease 2019 (COVID-19) in China (1), COVID-19 infection has spread worldwide, resulting in a pandemic. The mortality rate of COVID-19 is, however, decreasing globally (2-4). Although COVID-19 infection causes systemic multi-organ damage, the main cause of death in COVID-19 is considered to be acute respiratory failure due to alveolar macrophage activation and inflammation (5). Patients with COVID-19 can be classified into three types: mild, requiring no oxygen administration; moderate, requiring oxygen administration; and severe, requiring artificial respiration. It is estimated that patients with severe disease-account for just under 10% of the total number of cases of infection (2,6).

Therefore, it is extremely important to identify risk factors for severe disease, so that those who are most likely to develop severe disease can be treated with potent antiviral or immunosuppressive therapies (3,7). The risk factors for severe disease status reported to date include advanced age, chronic obstructive pulmonary disease, diabetes, dyslipidemia, hypertension, chronic kidney disease, malignancy, obesity, smoking, and immunosuppression (8-11). Furthermore, many studies have revealed that blood biomarkers, including white blood cell (WBC) count, lymphocyte count, platelet (Plt) count, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, ferritin, interleukin-6, procalcitonin (PCT) levels, and prothrombin time (PT) are closely related with disease severity in patients with COVID-19 (12-25). We previously examined COVID-19 disease severity and specific biomarkers, and reported that these markers, especially CRP, ferritin, PCT, albumin, and LDH are useful for predicting the severity of the disease (26). We also showed that hemostatic abnormalities are frequently observed in patients with severe disease stage (26).

However, there is no clear blood biomarker that predicts deterioration from non-severe to severe disease. Therefore, we

investigated the prognostic biomarkers of COVID-19 infection at certain time points and focused on identifying markers that might be predictors of disease deterioration from among the commonly available blood biomarkers. We believe such markers will help improve prognosis by allowing earlier intervention.

Materials and methods

Subjects. The subjects of this retrospective observational study were 255 patients who were admitted to Mie General Medical Center between April 2019 and September 2021 with COVID-19 infection. A section of the patients in the present study were evaluated in a previous study (26). Of the 255 patients, 54 patients were excluded because of the need for oxygen administration due to underlying diseases or an unknown clinical course due to their early transfer to other hospitals. The diagnosis of COVID-19 infection was based on positive results of real-time PCR (RT-PCR) or antigen quantification tests using nasopharyngeal swabs.

We classified patients into two groups: those who need oxygen therapy at the time of admission as the severe group, and those who did not need oxygen as the non-severe group. Each group was further subdivided into an improved group and a deteriorated group. The study endpoint was defined as exacerbation before discharge from the hospital, defined as the appearance of oxygen demand in the non-severe group, and conversion to a high-flow system or death in the severe group.

Treatment. All treatments basically followed the best treatment at the moment. Both, patients with suspected or confirmed mild disease without evidence of hypoxia or pneumonia as well as asymptomatic patients, were treated symptomatically. The antiviral agent, favipiravir, remdesivir, was administered to patients with pneumonia. In severe cases, general symptom management and supportive care with standard thromboprophylaxis were performed, and patients who continued to deteriorate despite standard oxygen therapy were given advanced respiratory therapy, such as high-flow therapy or artificial oxygen/ventilatory support. Systemic corticosteroid therapy, an IL-6 inhibitor and/or a Janus kinase (JAK) inhibitor, was used according to the patient's status (3,4).

Methods. Basically, blood biomarkers were examined as early as possible after admission in all the subjects. Biomarkers included WBC count, neutrophil count, lymphocyte count, hemoglobin (Hb), Plt count, AST, ALT, LDH, creatinine, CRP, PCT, KL-6, Presepsin (PSP), and D-dimer. WBC count, Hb, neutrophil count, and lymphocyte count were measured using a fully automated blood cell counter XN-3000 (Sysmex Co., Kobe, Japan). AST, ALT, LDH, creatinine, and CRP were measured using LaboFit AST, LaboFit ALT, CicaFit LD-IFCC (Kanto Chemical Co., Inc., Tokyo, Japan), Signasu-auto CRE (Shino-Test Co., Tokyo, Japan, and CRP-LT, Japan) and CRP-Latex X2 (Denka Co., Niigata, Japan) using Labospect006 (Hitachi High-Tech Co., Tokyo, Japan), respectively. PCT was measured by Elecsys® BRAHMS PCT (Roche Diagnostics K.K., Tokyo, Japan) using a Cobas 8000 e602 (Roche Diagnostics K.K., Tokyo, Japan). KL-6 was measured by Lumipulse Presto II using Lumipulse Presto KL-6 (Sekisui Medical Co., Ltd., Tokyo, Japan); PSP was measured by STACIA CLEIA Presepsin (LSI Medience Co., Tokyo, Japan). D-dimer was measured by an automatic coagulation analyzer CS-5100 (Sysmex Co., Kobe, Japan) with LIAS AUTO D-dimer Neo (Sysmex Co., Kobe, Japan). The result of each test was considered 0 if it was less than the sensitivity level of the test.

Statistical analysis. Data are expressed as medians. An unpaired t-test was used to evaluate differences in biomarkers in each group. In addition, correlation coefficient analysis was performed; ROC analysis was used to calculate the threshold to discriminate between the improved subgroup and deteriorated subgroup, and cutoff values were calculated. Multivariate analysis was also performed by logistic regression analyses. Covariates for multivariate regression were selected according to a significance level of less than 0.2 in the univariate model using a stepwise method. Values of $P<0.05$ were considered to indicate statistical significance. All statistical analyses were performed using BellCurve for Excel (version 3.23; Social Survey Research Information Co., Ltd.).

The study was conducted with the approval of the Mie General Medical Center Ethics Committee (No 2020-44). All study procedures were performed in accordance with the 1975 Declaration of Helsinki (revised in 1983) on human rights and experimentation.

Results

Comparison of biomarker levels between the non-severe and severe groups. A total of 201 patients (median age 48 years, 105 males and 96 females) were included in the analysis. Of these, 125 were in the non-severe group and 76 in the severe group. The patients in the severe group were significantly older than those in the non-severe group (54 vs. 44 years, $P<0.05$) and included a higher proportion of males (M/F; 53/23 vs. 52/73, $P<0.05$). In terms of blood biomarkers, neutrophil count ($P<0.001$), AST ($P<0.001$), ALT ($P=0.005$), LDH ($P<0.001$), Cre ($P=0.002$), CRP ($P<0.001$), KL-6 ($P<0.001$), PCT ($P<0.001$), PSP ($P<0.001$), and D-dimer levels ($P=0.024$) were significantly higher in the severe group, while lymphocyte ($P<0.001$) and Plt count ($P=0.013$) were significantly lower than those in the non-severe group, although WBC ($P=0.061$) count and Hb level ($P=0.223$) were not different (Fig. 1A-N).

Comparison of biomarker levels between the improved and deteriorated groups. To examine the predictors of disease severity in each group, each group was further divided into improved and deteriorated groups (Table I). There were no significant differences in age, sex, or BMI between the improved and deteriorated subgroups of either the non-severe or severe group. In the non-severe group, CRP ($P=0.002$) and LDH ($P=0.002$) were significantly higher in the deteriorated subgroup than in the improved subgroup. In the severe group, WBC count ($P=0.047$), neutrophil count ($P=0.039$) and PSP ($P=0.035$) were significantly higher in the deteriorated subgroup, and Plt count ($P=0.044$) was significantly lower than in the improved subgroup (Table II).

Next, the ability of each marker to predict between improvement and deterioration was examined using ROC

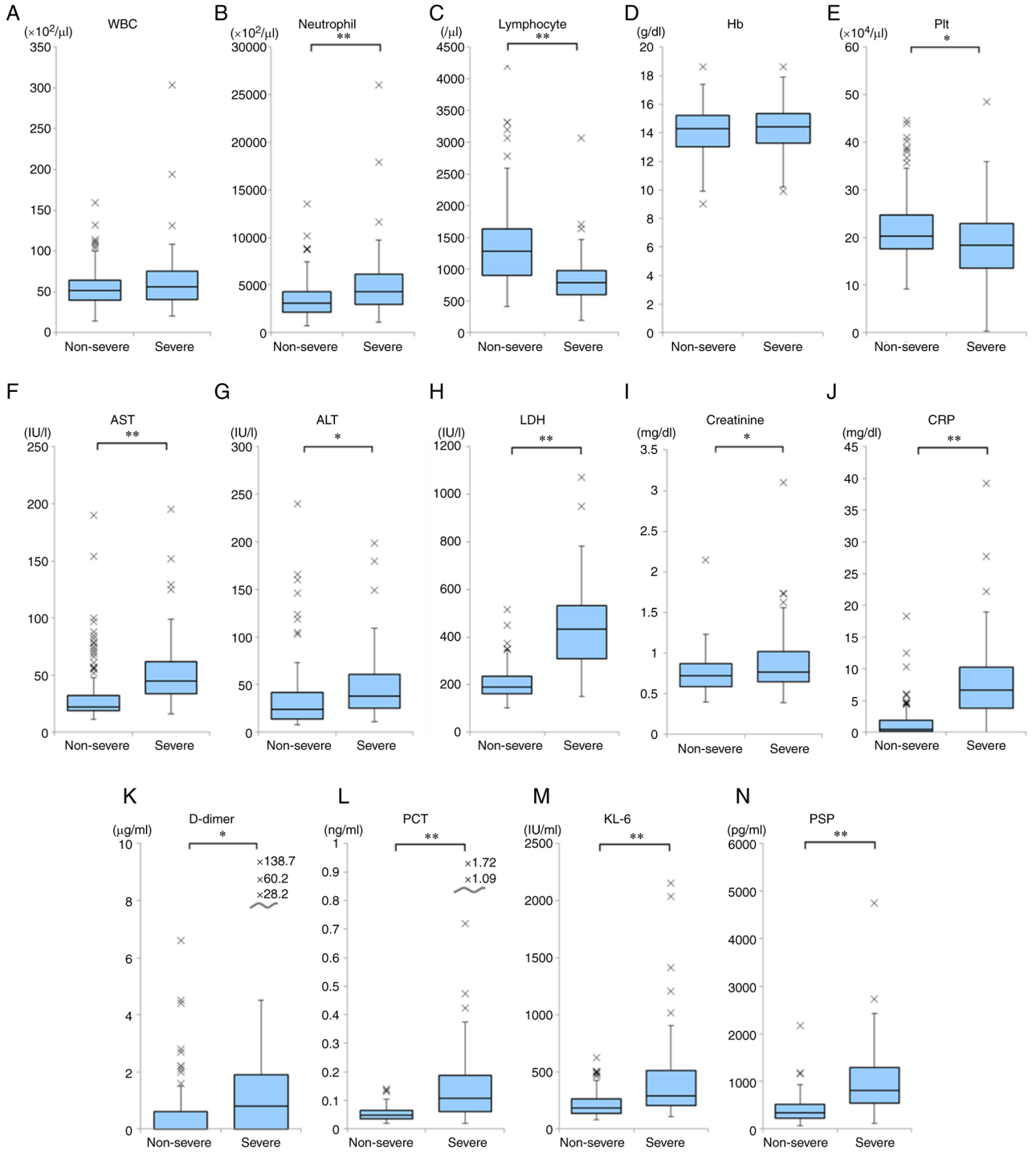

Figure 1. Distribution of each biomarkers in severe and non-severe groups. (A) WBC, (B) neutrophil, (C) lymphocyte, (D) Hb, (E) platelet, (F) AST, (G) ALT, (H) LDH, (I) creatinine, (J) CRP, (K) D-dimer, (L) PCT, (M) KL-6 and (N) PSP are shown in severe and non-severe groups. *P<0.05, **P<0.001. WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, procalcitonin; KL-6, sialylated carbohydrate antigen KL-6; PSP, presepsin.

analysis. ROC analysis revealed that CRP (AUC=0.830), LDH (AUC=0.761), AST (AUC=0.709), PCT (AUC=0.696), PSP (AUC=0.674), and ALT (AUC=0.640) had relatively good discriminatory ability in the non-severe group. Lymphocyte count (AUC=0.589), D-dimer (AUC=0.510), and KL-6 (AUC=0.547) were not good predictive markers of severe disease (Table III; Fig. 2A and B).

Statistical superiority in predicting prognosis was observed only for CRP (P<0.001), LDH (P<0.001), AST (P=0.002), and PSP (P=0.028). Spearman's rank correlation coefficient showed a weak correlation between AST and LDH and between LDH and PSP (Fig. 3). Stepwise logistic regression analysis of the non-severe group identified only CRP as a significant predictor of disease severity (odds ratio 41.45, 95% confidence interval: 4.91-349.24, P<0.001).

Further, in the severe group, ROC analysis of laboratory values showed relatively high accuracy for creatinine (AUC=0.646), PCT (AUC=0.644), Plt (AUC=0.630), and PSP

Table I. Demographic characteristics of non-severe improved group, non-severe deteriorated group, severe improved group and severe deteriorated group.

Characteristic	Non-severe improved group	Non-severe deteriorated group	Severe improved group	Severe deteriorated group
n	111	14	54	22
Male, n	46	6	38	15
Female, n	65	8	16	7
Age, years (range)	43 (14-88)	56 (27-85)	51 (29-82)	60 (22-91)
BMI, kg/m^2 (range)	23.4 (13.7-42.1)	25.7 (13.1-36.3)	27.6 (19.6-48)	25.2 (17.8-42)

Table II. Initial laboratory findings of patients with COVID-19.

Variable	Non-severe improved group	Non-severe deteriorated group	Severe improved group	Severe deteriorated group
WBC (x10^2/μl)	54.3 (14-159)	62.2 (31-132)	57.9 (20-131)	77.5[a] (27-304)
Neutrophil (/μl)	3,408.7 (727-13,499)	4,419.4 (1,603-10,158)	4,581.0 (1,094-11,659)	6,471.8[a] (1,685-26,022)
Lymphocyte (/μl)	1,393.7 (416-4,275)	1,226.1 (482-3,313)	814.7 (192-1,711)	867.1 (200-3,070)
Hb (g/dl)	14.1 (9.0-18.6)	13.9 (10.8-17.4)	14.4 (10.2-18.6)	14.2 (9.9-17.9)
Plt (x10^4/μl)	21.9 (9.2-43.9)	21.8 (10.4-44.6)	20.3 (3.5-48.5)	16.3[a] (0.3-28.4)
AST (IU/l)	31.1 (11-190)	40.6 (16-97)	47.6 (17-152)	60.5 (16-195)
ALT (IU/l)	33.1 (8-240)	44.9 (9-160)	48.9 (11-180)	49.5 (13-199)
LDH (IU/l)	202.3 (102-517)	265.6[b] (162-451)	428.6 (174-949)	491.0 (150-1,071)
Creatinine (mg/dl)	0.74 (0.4-2.15)	0.77 (0.51-1.08)	0.83 (0.42-3.10)	1.00 (0.39-1.74)
CRP (mg/dl)	1.19 (0.01-18.283)	3.59[b] (0.083-12.458)	7.83 (0.038-27.756)	8.84 (1.046-39.193)
D-dimer (μg/ml)	0.51 (0-6.6)	0.47 (0-2.2)	2.77 (0-60.2)	8.71 (0-138.7)
PCT (ng/ml)	0.05 (0.00-0.13)	0.07 (0.02-0.10)	0.15 (0.02-1.09)	0.25 (0.03-1.72)
KL-6 (IU/ml)	213.5 (96-627)	262.2 (79-501)	419.9 (124-2,154)	442.0 (105-2,036)
PSP (pg/ml)	395.8 (78-2,171)	519.9 (73-830)	872.9 (117-2,421)	1,240.7[a] (373-4,752)

[a]P<0.05 and [b]P<0.01 in comparison with improved group. WBC, white blood cell; Hb, hemoglobin; Plt, platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, procalcitonin; KL-6, sialylated carbohydrate antigen KL-6; PSP, presepsin. The values in parenthesis indicate the range.

(AUC=0.604), although the values did not reach statistical significance. Lymphocyte count (AUC=0.510), D-dimer (AUC=0.531), and KL-6 (AUC=0.516) at the time of admission were not predictive markers of deterioration adequately in the severe group (Table IV).

Discussion

Identification of clinical and laboratory predictors of disease progression toward severe or critical status is extremely important for clinicians to be able to treat patients appropriately and save their lives. In this study, we found several biomarkers related to hematology, sepsis, inflammation, blood coagulation, hepatic function, and renal function that were significantly different between the non-severe and severe groups. These results were consistent with previous reports. Several meta-analyses have shown that many biomarkers are involved in severe patients, including neutrophil, lymphocyte, monocyte, and eosinophil counts, Hb, Plt count, albumin, serum sodium, AST, ALT, blood urea nitrogen (BUN), creatinine, CRP, PCT, LDH, D-dimer, glucose levels, and have demonstrated significantly different levels of these markers between non-severe and severe patients, suggesting that systemic disorders or organ failure, in addition to respiratory failure and coagulation abnormalities, are prominent in the severe stage of this infection (12,15-20,27).

We previously reported that patients' backgrounds, including their median age and sex, hypertension, hyperlipidemia, and diabetes mellitus are related to the severity of COVID-19 infection. We also reported that levels of CRP, ferritin, PCT, albumin, HbA1c, and LDH are useful markers of severity, and that hemostatic abnormalities are frequently observed in patients in a severe disease stage (26).

In fact, these markers are critically important for evaluating the patient's condition, including the occurrence of complications and disease severity. However, it is not well elucidated whether these biomarkers can predict the prognosis of patients. Therefore, we divided patients in both the severe and non-severe groups into two further groups each, the improved and deteriorated subgroups. We found that in

Table III. ROC curve of non-severe improved group vs. non-severe deteriorated group.

Variable	Cutoff value	Sensitivity (%)	Odds ratio	AUC	P-value
WBC	71x10^2/μl	35.7	2.381	0.517	0.858
Neutrophil	4,941.6 /μl	35.7	3.299	0.572	0.404
Lymphocyte	1,165.5 /μl	57.1	1.687	0.589	0.253
Hb	13.2 g/dl	42.9	2.025	0.519	0.845
Plt	18.6x10^4/μl	57.1	2.895	0.549	0.569
AST	27 IU/l	71.4	5.000	0.709	0.002
ALT	26 IU/l	64.3	2.640	0.640	0.078
LDH	216 IU/l	75.0	7.714	0.761	<0.001
Creatinine	0.85 mg/dl	50.0	2.581	0.576	0.361
CRP	1.61 mg/dl	85.7	22.957	0.830	<0.001
D-dimer	0 mg/dl	66.7	1.176	0.510	0.917
PCT	0.062 ng/ml	75.0	9.000	0.696	0.085
KL-6	220 IU/ml	50.0	1.816	0.547	0.647
PSP	369 pg/ml	71.4	3.404	0.674	0.028

WBC, white blood cell; Hb, hemoglobin; Plt, platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, procalcitonin; KL-6, sialylated carbohydrate antigen KL-6; PSP, presepsin.

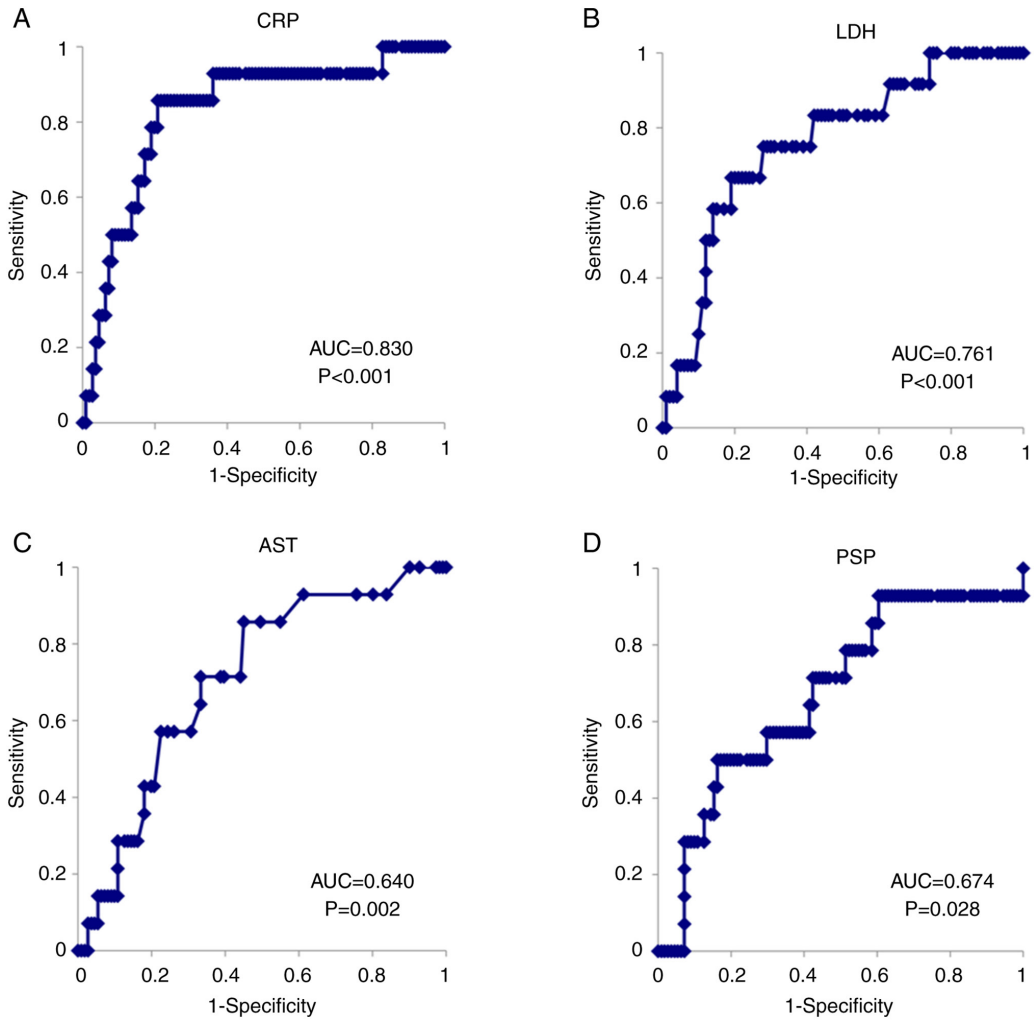

Figure 2. Correlation between each parameter and deterioration of non-severe COVID-19 patients. Receiver operating characteristics curve of (A) CRP (AUC=0.830; P<0.001), (B) LDH (AUC=0.761; P<0.001), (C) AST (AUC=0.709; P=0.002) and (D) PSP (AUC=0.674; P=0.028) for the diagnosis of deteriorated non-severe COVID-19 patients. LDH, lactate dehydrogenase; CRP, C-reactive protein; AST, aspartate aminotransferase; PSP, presepsin; AUC, area under the curve.

Table IV. ROC curve of severe improved group vs. severe deteriorated group.

Variable	Cutoff value	Sensitivity (%)	Odds ratio	AUC	P-value
WBC	54x10^2/μl	63.6	1.625	0.574	0.323
Neutrophil	5,715.9/μl	40.9	1.800	0.575	0.328
Lymphocyte	739.2/μl	68.2	1.990	0.510	0.892
Hb	14.6 g/dl	68.2	1.590	0.513	0.856
Plt	17.2x10^4/μl	59.1	2.270	0.630	0.057
AST	44 IU/l	59.1	1.444	0.544	0.576
ALT	32 IU/l	50.0	2.000	0.532	0.671
LDH	476 IU/l	54.5	2.471	0.580	0.334
Creatinine	0.9 mg/dl	54.5	2.850	0.646	0.055
CRP	7.039 mg/dl	63.6	2.359	0.540	0.572
D-dimer	0 mg/dl	38.9	2.430	0.531	0.717
PCT	0.149 ng/ml	68.4	6.139	0.644	0.069
KL-6	231 IU/ml	75.0	2.111	0.516	0.839
PSP	1,044 pg/ml	50.0	2.857	0.604	0.177

WBC, white blood cell; Hb, hemoglobin; Plt, platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, procalcitonin; KL-6, sialylated carbohydrate antigen KL-6; PSP, presepsin.

	AST	LDH	CRP	PSP
AST	1.0000	0.4626	0.0455	0.1197
LDH	0.4626	1.0000	0.3971	0.4326
CRP	0.0455	0.3971	1.0000	0.3885
PSP	0.1197	0.4326	0.3885	1.0000

Figure 3. Correlation coefficients of AST, LDH, CRP, and PSP in the non-severe group using Spearman's rank correlation coefficient. The intensity of the color indicates the strength of the correlation. LDH, lactate dehydrogenase; CRP, C-reactive protein; AST, aspartate aminotransferase; PSP, presepsin.

the non-severe group, four markers, CRP, LDH, AST, and PSP have significant potential as prognostic markers. Multivariate analysis demonstrated that CRP is the most useful predictive marker for prognosis among them. However, we cloud not identify potential markers of prognosis in the severe group. CRP is a type of protein produced by the liver, and its production is induced by various inflammatory cytokines, such as IL-6, and hence, it serves as an early marker of infection and inflammation (27). Many studies also suggested the usefulness of CRP in diagnosing disease severity (13,23,28-32), and the same results were obtained in this study. Our logistic regression analysis clearly demonstrated the effectiveness of CRP as a marker for diagnosing severity and predicting disease progression in non-severe COVID-19 patients, who consisted primarily of those infected with the delta variant, in Japan. Using ROC analysis in the early stage of COVID-19 infection, a previous study showed that CRP might be a valuable marker for predicting disease in non-severe COVID-19 patients (28), which is consistent with our data. Therefore, these results suggest that non-severe COVID-19 patients with high CRP levels should be adequately followed and treated for the early detection of severe manifestations and for establishing a therapeutic strategy, even if their general condition or respiratory function do not meet the standard for the severe group.

A previous study also listed PSP as a biomarker of prognostic significance (33). PSP, also known as soluble cluster of differentiation (CD) 14 subtype, is a small peptide generated from soluble CD14, and is known to be a regulatory factor that modulates immune responses through interaction with T and B cells, which is released into the blood when monocytes are activated by the recognition of lipopolysaccharides (LPS) from several infectious agents. PSP is an early marker of mortality and reportedly shows better prognostic performance than PCT. Hence, it has been proposed as a useful marker in risk stratification strategies in patients with sepsis (12,34,35). Furthermore, it was recently demonstrated that PSP plays a role as a biomarker in providing prognostic information, such as duration of hospitalization, even in COVID-19 patients. Our results, showing the high prognostic value of PSP in non-severe COVID-19 patients, suggest that PSP might be a highly sensitive indicator of immunological reactions against infectious antigens in the early stage of COVID-19 infection, and might predict subsequent disease progression. However, in our study results, since PSP showed only a weak correlation with CRP, we believe it is worthwhile to measure both PSP and CRP.

We also found that the liver-related markers, AST and LDH, could predict prognosis in non-severe COVID-19 patients. Many liver-related biomarker abnormalities have been reported as being associated with COVID-19, such as total bilirubin, AST, ALT, γ-GTP, LDH, and low albumin levels. Many meta-analyses revealed that some of these biomarkers (AST/ALT, γ-GTP, LDH) exhibit significantly elevated levels in severe cases, and that high levels of AST and LDH were more likely to be observed in severe cases (17,18,20). However, since our study did not consider patients with liver disease,

further research is needed to separately evaluate patients with liver disease in greater detail.

According to previous reports, COVID-19-infected livers exhibit several pathological changes such as extensive apoptosis and binuclear hepatocytes, steatosis, lobular necrosis, inflammation of the portal area, and congestion of hepatic sinuses with micro thrombosis (36-38). Therefore, the underlying mechanisms of liver injury in COVID-19 cases might include a virus-induced cytopathic effect, immune-mediated inflammation by cytokine storm, sepsis-related liver injury, hepatic sinus congestion related to thrombosis, drug-induced liver injury, or pre-existing liver disease. Based on these considerations, liver disfunction might reflect an abnormal physiological condition in COVID-19 infection and a worse clinical course. More mechanistic understanding of liver injury with COVID-19 infection is critically important in clinical management practices for patients with hepatic injury.

Despite the potential markers of disease progression in non-severe COVID-19 cases mentioned above, our study failed to identify any biomarker that could predict the prognosis in severe cases, although mean PSP, neutrophil count and, Plt count were statistically significantly higher in the severe deteriorated subgroup than the severe improved subgroup. These results suggest that in severe cases, since various markers are already elevated due to pneumonia and multiple organ failure, it is difficult to predict the prognosis based on these markers alone.

Our results suggest that the monitoring of inflammatory markers as well as liver-related markers, might serve as an early warning system for progression to severe COVID-19. Simultaneously monitoring CRP and PSP values might allow early detection of lung disease, and might reduce over-prescription of anti-viral agents or anti-inflammatory drugs for patients who do not need them, and trigger early multidisciplinary therapy to prevent sepsis and other severe conditions.

This study has several limitations. First, although we followed the guidelines, treatment modalities changed during this study period, and in some cases the duration of treatment and the drugs used differed, even though the severity of COVID-19 was the same, which may have affected the course of the disease. Second, the retrospective study design and lack of standardization of the available documents, such as for patients' backgrounds or therapeutic interventions, could have led to selection bias. Third, the sample sizes were relatively small for an accurate assessment of risk factors. Finally, the data in this study were obtained from a single center in Japan, which could potentially limit the generalizability of the findings.

In conclusion, this analysis provides important evidence for the prediction of prognosis in non-severe COVID-19 cases based on laboratory test results at the time of admission and might facilitate efficient resource allocation in the era of scarcity of available resources, including for hospitalization.

CRP, LDH, AST, and PSP are the most reliable markers to determine the prognosis of patients with non-severe COVID-19. Future methodologically well-designed studies conducted on other populations will be needed to establish appropriate strategies for treating patients with different severities of COVID-19 infection.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HW and KS conceived the study. YI and SF designed the methodology. KI, MK, KN, KeY, SH, YS, HMik, HG, KH, YNa, HMiz, ToK, YT, SK, TaK, YNi, DS, TT, YI, IM, AY, HW and SF curated the data. SF, YI and SK confirm the authenticity of all the raw data. SF wrote the original draft preparation. KS reviewed and edited the manuscript. KI, MK, KN, KeY, SH, YS, HMik, HG, KH, YNa, HMiz, ToK, YT, SK, TaK, YNi, DS, TT, YI, IM, AY, KT, KoY, HW and SF performed the investigations. KS supervised. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was conducted with the approval of the Mie General Medical Center Ethics Committee (approval no. 2020-44). Opt-out method was performed for the participation in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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