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Comprehensive Laboratory Data Analysis to Predict the Clinical Severity of Coronavirus Disease 2019 in 1,952 Patients in Daegu, Korea

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Background: Laboratory parameter abnormalities are commonly observed in COVID-19 patients; however, their clinical significance remains controversial. We assessed the prevalence, characteristics, and clinical impact of laboratory parameters in COVID-19 patients hospitalized in Daegu, Korea.

Methods: We investigated the clinical and laboratory parameters of 1,952 COVID-19 patients on admission in nine hospitals in Daegu, Korea. The average patient age was 58.1 years, and 700 (35.9%) patients were men. The patients were classified into mild (N = 1,612), moderate (N = 294), and severe (N = 46) disease groups based on clinical severity scores. We used chi-square test, multiple comparison analysis, and multinomial logistic regression to evaluate the correlation between laboratory parameters and disease severity.

Results: Laboratory parameters on admission in the three disease groups were significantly different in terms of hematologic (Hb, Hct, white blood cell count, lymphocyte%, and platelet count), coagulation (prothrombin time and activated partial thromboplastin time), biochemical (albumin, aspartate aminotransferase, alanine aminotransferase, lactate, blood urea nitrogen, creatinine, and electrolytes), inflammatory (C-reactive protein and procalcitonin), cardiac (creatinine kinase MB isoenzyme and troponin I), and molecular virologic (Ct value of SARS-CoV-2 *RdRP* gene) parameters. Relative lymphopenia, prothrombin time prolongation, and hypoalbuminemia were significant indicators of COVID-19 severity. Patients with both hypoalbuminemia and lymphopenia had a higher risk of severe COVID-19.

Conclusions: Laboratory parameter abnormalities on admission are common, are significantly associated with clinical severity, and can serve as independent predictors of COVID-19 severity. Monitoring the laboratory parameters, including albumin and lymphocyte count, is crucial for timely treatment of COVID-19.

Key Words: Hypoalbuminemia, Lymphopenia, Prothrombin time, Coronavirus disease 2019, Severity, Laboratory parameters

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INTRODUCTION

Daegu, South Korea, was host to the first coronavirus disease 2019 (COVID-19) outbreak outside of China. Since February 18, 2020, the number of infected patients increased exponentially, and by August 5, 2020, more than 6,943 confirmed cases (48.03% of the total cases in South Korea) and 191 deaths were reported in Daegu [1, 2].

The initial clinical characteristics of COVID-19 are non-specific, and the clinical spectrum varies widely from asymptomatic, mild respiratory symptoms, and pneumonia to acute respiratory distress syndrome [3-5]. An exponential increase in the number of COVID-19 patients led to a shortage of hospital beds, healthcare supplies, and medical personnel. By early March, more than 2,000 patients were waiting for hospital beds, and three patients died at home in Daegu. Therefore, while the number of confirmed cases increases, rapid and strategic patient allocation according to clinical severity and proper treatment are critical to lower the mortality rate.

The Korean government has classified COVID-19 cases by severity to prioritize the treatment of more severe cases at hospitals, while asymptomatic patients and those with mild symptoms receive medical treatment and monitoring at community treatment centers. Depending on their condition, patients with more severe disease are admitted to infectious disease hospitals or nationally designated treatment facilities for immediate treatment [6]. Severity-based classification involves several indicators, such as consciousness level, body temperature, presence of pneumonia, age, and comorbidities in confirmed cases [7]. The clinical and laboratory parameters of COVID-19 have been analyzed to identify risk factors that can predict severity. Laboratory parameters may be more objective than clinical parameters for assessing patient condition. Several studies have attempted to identify laboratory parameters correlated with disease severity [8–10]. Abnormal results of laboratory parameters, such as C-reactive protein (CRP), lactate dehydrogenase (LD), neutrophil: lymphocyte ratio, fibrinogen, D-dimer, interleukin (IL)-6, platelet count, and lymphocyte count, are reportedly related to COVID-19 severity [8]. However, most of these results are from other countries or races and are based on meta-analysis. Thus, there is a need to identify predictive laboratory parameters in Korean CO-VID-19 patients.

To manage the next wave of the pandemic, complimentary strategies should be established for efficient epidemic management and patient care. We comprehensively analyzed laboratory parameters of COVID-19 patients in Daegu and determined their correlation with clinical disease severity to provide a basis for the development of improved treatment strategies.

MATERIALS AND METHODS

Patients

All hospitals providing COVID-19 treatment in Daegu were requested to submit clinical and laboratory data to the Korea Disease Control and Prevention Agency database, Internet-based Clinical Research and Trial (iCReaT). In total, 1,952 patients hospitalized at nine general hospitals in Daegu between February 17, 2020 and April 12, 2020 were enrolled retrospectively. Most patients were Korean (1,932; 99.0%), fourteen were Korean-Chinese, and six were of other nationalities. All patients were confirmed of having COVID-19 using the real-time reverse transcription (RT) PCR testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using upper and/or lower respiratory tract (URT/LRT) specimens.

Clinical severity was assessed on admission based on an eight-category WHO ordinal scale modified by the Korea National Committee for Clinical Management of COVID-19: (1) no limitation in performing daily activities; (2) limitation in performing daily activities, but no need for supplemental oxygen therapy; (3) need for supplemental oxygen therapy via a nasal cannula; (4) need for supplemental oxygen therapy via facial mask; (5) need for high-flow supplemental oxygen therapy or noninvasive mechanical ventilation; (6) need for invasive mechanical ventilation; (7) multi-organ failure or the need for extracorporeal membrane oxygenation (ECMO) therapy; and (8) death [11]. On admission, the clinical severity scores for the patients were 1–2 (mild), 3–4 (moderate), and 5–8 (severe) in 1,612 (82.6%), 294 (15.1%), and 46 (2.4%) patients, respectively. The 294 patients in the moderate group were treated with supplemental oxygen therapy via a nasal cannula (N=223) or facial mask (N=71). Of the 46 patients in the severe group, 37 were treated with either high-flow oxygen/noninvasive mechanical ventilation (N=21), mechanical ventilation (N=15), or ECMO (N=1), while nine patients died on the day of admission. This study was approved by the Daegu Joint Institutional Review Board (2020-07-001) in agreement with the World Medical Association Declaration of Helsinki.

Clinical and laboratory parameters

We collected demographic and clinical information on age, sex, initial symptoms, comorbidities, and final outcomes (discharge, hospitalized, or death). On admission, we analyzed the following laboratory parameters: complete blood counts (CBC) [hemoglo-

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bin (Hb), hematocrit (Hct), lymphocyte (LYM)%, white blood cell (WBC) count, platelet (PLT) count], coagulation profile [activated partial thromboplastin time (aPTT) and prothrombin time (PT) international normalized ratio (INR)], biochemical parameters [albumin, total bilirubin (T-BIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine (Cr), CRP, glucose (Glu), sodium (Na), chloride (Cl), potassium (K), lactate (Lac), LD, procalcitonin (PCT)], cardiac markers [creatinine kinase MB isoenzyme (CK-MB), troponin I (TnI), troponin T (TnT)], and molecular marker for SARS-CoV-2 [Ct values of RNA-dependent RNA polymerase (*RdRP*) gene of SARS-CoV-2 RT-PCR]. We compared the clinical characteristics and laboratory parameters according to the clinical severity determined on admission.

Statistical analysis

Continuous variables are expressed as mean±standard deviation, while categorical variables are presented as frequencies and percentages. Groups of variables were compared using Chi-square test or one-way ANOVA. Multiple comparison analysis was performed using Scheffé's method [12]. Multinomial logistic regression analysis was used to evaluate the correlations between laboratory parameters and clinical severity on admission in COVID-19 patients. Two types of multinomial logistic regression analysis were used: one using the independent variables, i.e., the laboratory parameters, as quantitative variables and the other using the independent variables as qualitative variables, categorizing them as normal or abnormal based on their respective reference range.

Among the 26 laboratory parameters, albumin and LYM% showed abnormality most frequently among the groups according to clinical severity, with approximately 80% of patients in the severe group showing abnormal results. Therefore, we also analyzed the correlations of hypoalbuminemia (albumin <3.5 g/dL), lymphopenia (LYM% <21%), and combined hypoalbuminemia and lymphopenia with clinical severity. Odds ratios (ORs) with

Table 1. Baseline clinical characteristics of 1,952 COVID-19 patients in Daegu, Korea

Variable		All patients (N=1,952)	Mild (N=1,612)	Moderate (N=294)	Severe (N=46)	P
Age (yr)		58.1±19.9	55.3±20.0	71.7±12.6	70.1±14.5	<0.001
Male, N (%)		700 (35.9)	536 (33.3)	137 (46.6)	27 (58.7)	<0.001
Symptoms, N (%)	Fever	422 (21.6)	294 (18.2)	108 (36.8)	20 (43.5)	<0.001
	Cough	874 (44.8)	714 (44.3)	145 (49.3)	15 (32.6)	<0.001
	Sputum	677 (34.7)	555 (34.4)	111 (37.8)	11 (23.9)	<0.001
	Sore throat	242 (12.4)	215 (13.3)	24 (8.2)	3 (6.5)	<0.001
	Rhinorrhea	193 (9.9)	167 (10.4)	25 (8.5)	1 (2.2)	<0.001
	Myalgia	392 (20.1)	331 (20.5)	53 (18.0)	8 (17.4)	<0.001
	Dyspnea	402 (20.6)	213 (13.2)	158 (53.7)	31 (67.4)	<0.001
	Headache	389 (19.9)	348 (21.6)	39 (13.3)	2 (4.4)	<0.001
	Diarrhea	257 (13.2)	213 (13.2)	41 (14.0)	3 (6.5)	<0.001
Comorbidities, N (%)	Diabetes	368 (18.9)	257 (15.9)	97 (33.0)	14 (30.4)	<0.001
	Hypertension	619 (31.7)	443 (27.5)	151 (51.4)	25 (54.4)	<0.001
	Asthma	67 (3.4)	51 (3.2)	12 (4.1)	4 (8.7)	<0.001
	COPD	27 (1.4)	18 (1.1)	9 (3.1)	0 (0)	<0.001
	CKD	38 (1.9)	21 (1.3)	13 (4.4)	4 (8.7)	<0.001
	CLD	33 (1.7)	24 (1.5)	8 (2.7)	1 (2.2)	<0.001
	Malignancy	86 (4.4)	64 (3.97)	16 (5.44)	6 (13.0)	<0.001
Final outcomes, N (%)	Discharged	1,490 (76.3)	1,337 (82.9)	146 (49.7)	7 (15.2)	<0.001
	Hospitalized	298 (15.3)	223 (13.8)	65 (22.1)	10 (21.7)	
	Death	164 (8.4)	52 (3.2)	83 (28.2)	29 (63.0)	

Data are presented as the mean±SD or N (%).
Abbreviations: CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease.

95% confidence intervals (CIs) were calculated to examine the significance of correlations. The optimal cut-off values for albumin and LYM% in predicting severity were evaluated using receiver operating characteristic (ROC) curve analysis. Data were analyzed using the SPSS Statistics 19.0 software (IBM corporation, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline clinical characteristics

The baseline characteristics of the COVID-19 patients hospitalized in Daegu are summarized in Table 1. The mean age of the study population was 58.1 ± 19.9 years, and 700 (35.9%) patients were men. The mean patient age in the mild group was
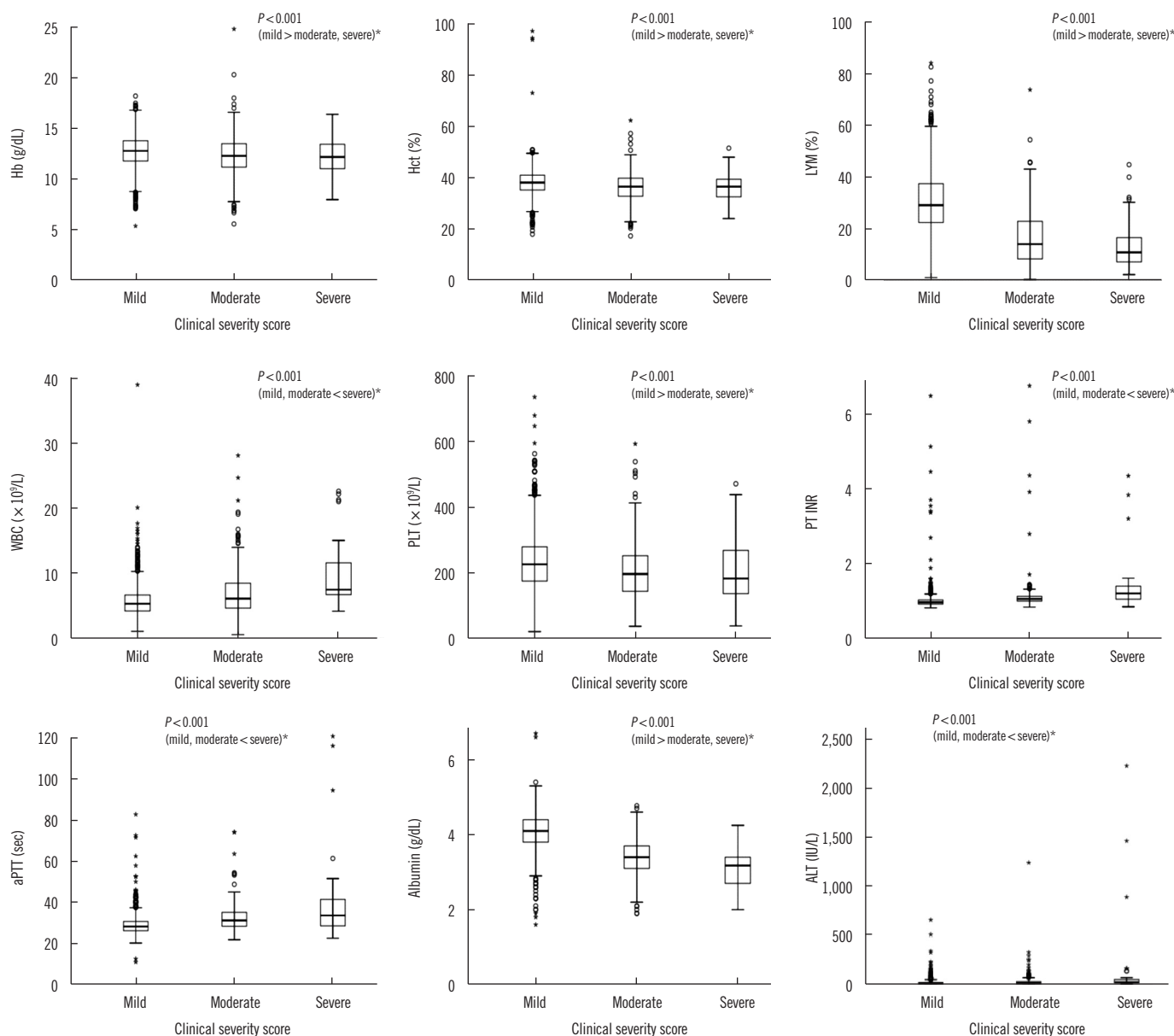

Fig. 1. Comparison of laboratory parameters based on clinical severity. *Multiple comparison result using Scheffé's method.

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK-MB, creatinine kinase MB isoenzyme; Cl, chloride; Cr, creatinine; CRP, C-reactive protein; Ct, cyclic threshold; Glu, glucose; K, potassium; Lac, lactate; LD, lactate dehydrogenase; LRT, lower respiratory tract; LYM, lymphocyte; Na, sodium; PCT, procalcitonin; PLT, platelet; PT INR, prothrombin time international normalized ratio; *RdRP*, RNA-dependent RNA polymerase gene; T-BIL, total bilirubin; TnI, troponin I; TnT, troponin T; URT, upper respiratory tract; WBC, white blood cell.
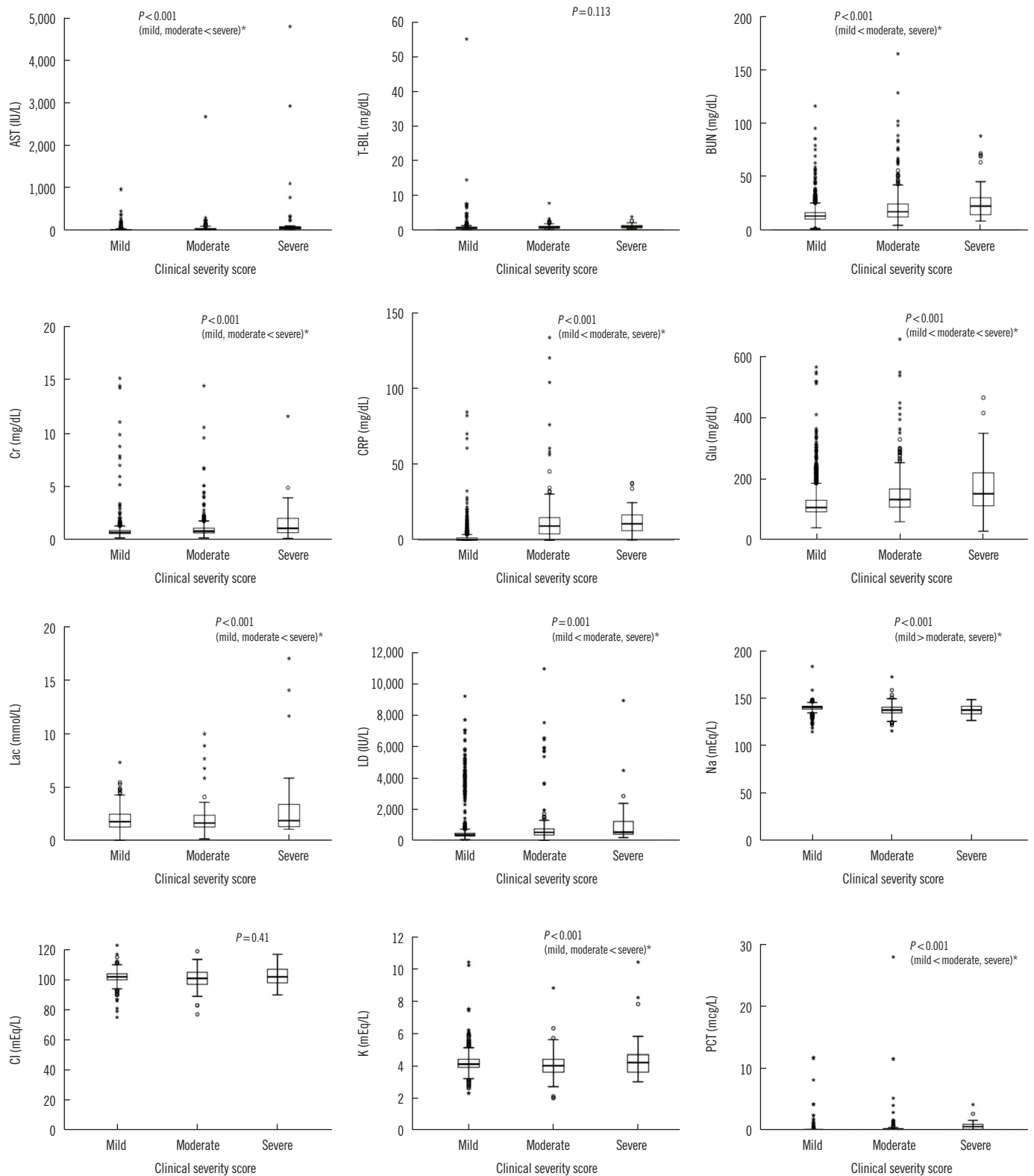
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Fig. 1. Continued.

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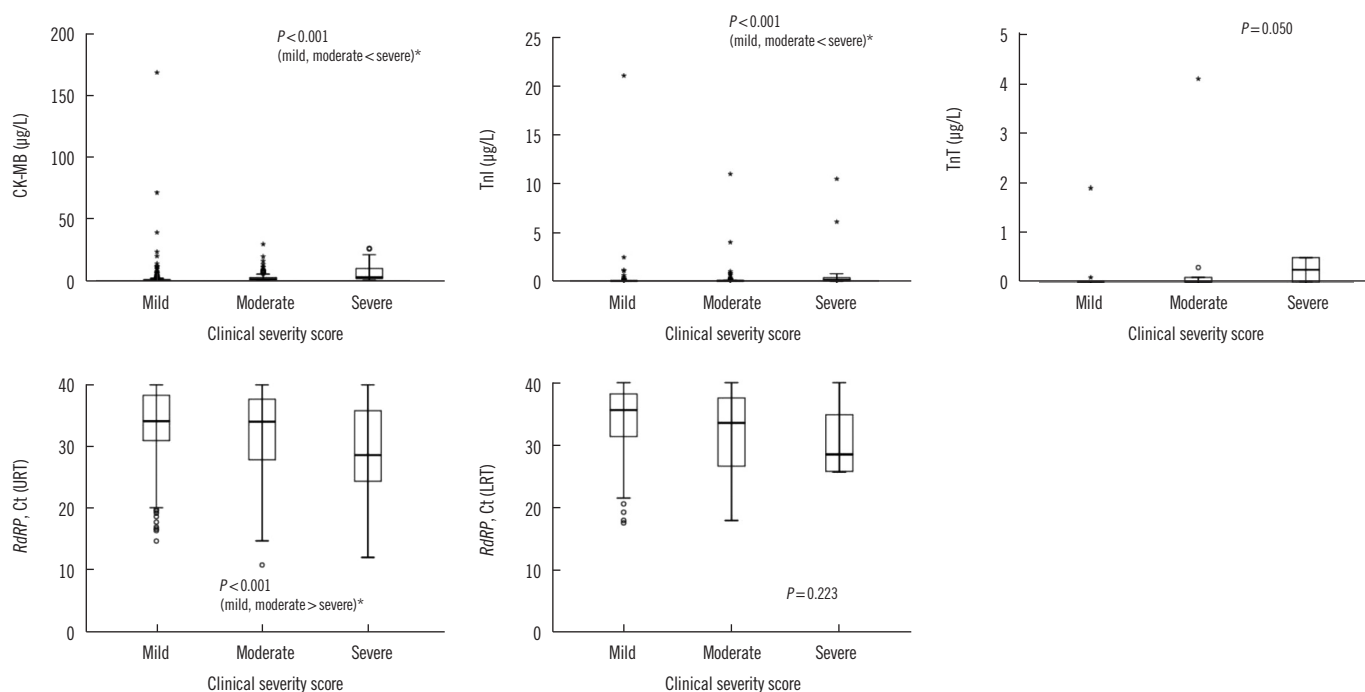
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Fig. 1. Continued.

lower than that in the other groups. The most common symptom on admission was cough (874 patients, 44.8%), followed by sputum (677 patients, 34.7%), fever (422 patients, 21.6%), and dyspnea (402 patients, 20.6%). Fever and dyspnea were more common in the severe and moderate groups than in the mild group ($P<0.001$). The most common comorbidity was hypertension (619 patients, 31.7%), followed by diabetes (368 patients, 18.9%) and malignancy (86 patients, 4.4%). At the time of epidemiological data collection, 1,490 (76.3%) of the 1,952 patients had been discharged, and 164 (8.4%) patients had died. The proportions of outcomes significantly differed among the three groups ($P<0.001$).

Laboratory parameters according to clinical severity on admission

The laboratory parameters of the patients in each group are shown in Fig. 1. The coagulation profiles and levels of hematologic parameters, biochemical markers, inflammation markers, cardiac markers, and a molecular marker significantly differed according to clinical severity. Hb, Hct, LYM% levels and PLT counts were lower in the moderate and severe groups than in the mild group ($P<0.001$). WBC count, aPTT, PT INR, ALT, AST, Cr, K, Lac, CK-MB, and TnI levels were significantly higher in the severe group than in the mild and moderate groups ($P<0.001$). The Glu level increased with clinical severity ($P<0.001$). In contrast, albumin and Na levels were significantly lower in the moderate and severe groups than in the mild group ($P<0.001$). T-BIL, Cl, and TnT levels and Ct values of RdRP in LRT specimens were not associated with clinical severity.

The proportions of patients with abnormal laboratory parameter results were determined according to the reference values for the parameters (Table 2). The proportions of patients with abnormal LYM%, albumin, AST, and CRP levels were significantly higher in the moderate and severe groups than in the mild group. There was no difference in the proportions of patients with abnormal Lac ($P=0.226$), LD ($P=0.590$), and TnT ($P=0.279$) according to clinical severity.

Correlation between laboratory parameters and clinical severity

Multinomial regression analyses showed significant changes in the OR for each laboratory parameter with clinical severity in hospitalized COVID-19 patients (Table 3). For every unit increase in WBC, PT INR, PCT, CRP, and Cr levels, the risk of being in the moderate group was 1.189, 2.384, 1.417, 1.225, and 1.306 times higher, respectively, than the chance of being in the mild group. For every unit increase in WBC, PT INR, PCT, CRP, Cr, K, Lac, and TnI, the risk of being in the severe group was 1.332, 3.127, 1.462, 1.227, 1.433, 1.589, 1.519, and 1.320 times higher, respectively, than the chance of being in the mild group.

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Table 2. Comparison of abnormal proportions of laboratory parameters based on clinical severity

Variable	Reference range	Abnormal proportion according to clinical severity on admission, N / total N (%)			P
		Mild (N=1,612)	Moderate (N=294)	Severe (N=46)	
Hb (g/dL)	M 12.9–16.9 F 11.5–15.5	427/1,608 (26.6)	125/294 (42.5)	20/43 (46.5)	<0.001
Hct (%)	M 37.9–49.1 F 32–43	344/1,609 (21.4)	114/293 (38.9)	24/43 (55.8)	<0.001
LYM (%)	21–51	410/1,606 (25.5)	208/291 (71.5)	34/41 (82.9)	<0.001
PLT (×10⁹/L)	140–380	232/1,609 (14.4)	85/294 (28.9)	16/42 (38.1)	<0.001
WBC (×10⁹/L)	3.6–9.6	289/1,609 (18.0)	87/294 (29.6)	17/42 (40.5)	<0.001
aPTT (sec)	28–45	467/895 (52.2)	150/202 (74.3)	20/34 (58.8)	<0.001
PT INR	0.8–1.2	44/902 (4.9)	31/205 (15.1)	17/34 (50.0)	<0.001
Albumin (g/dL)	3.5–5.1	146/1,596 (9.2)	147/279 (52.7)	32/41 (78.1)	<0.001
ALT (IU/L)	<40	212/1,607 (13.2)	69/291 (23.7)	17/41 (41.5)	<0.001
AST (IU/L)	<35	313/1,608 (19.5)	176/292 (60.3)	33/41 (80.5)	<0.001
T-BIL (mg/dL)	<1.2	64/1,601 (4.0)	40/277 (14.4)	8/41 (19.5)	<0.001
BUN (mg/dL)	8.0–23.0	243/1,608 (15.1)	105/294 (35.7)	20/42 (47.6)	<0.001
Cr (mg/dL)	0.5–1.2	160/1,605 (10.0)	76/293 (25.9)	20/42 (47.6)	<0.001
CRP (mg/dL)	<0.5	654/1,579 (41.0)	273/286 (95.5)	38/41 (92.7)	<0.001
Glu (mg/dL)	74–109	728/1,506 (48.3)	196/271 (72.3)	28/33 (84.9)	<0.001
Lac (mmol/L)	0.7–2.1	237/525 (45.1)	48/130 (37.0)	9/19 (47.4)	0.226
LD (IU/L)	<250	1,376/1,458 (94.4)	216/232 (93.1)	32/33 (97.0)	0.590
Na (mEq/L)	135–148	103/1,601 (6.4)	94/289 (32.5)	14/41 (34.2)	<0.001
Cl (mEq/L)	98–110	127/1,077 (11.8)	68/229 (29.7)	8/33 (24.2)	<0.001
K (mEq/L)	3.5–5.1	153/1,598 (9.6)	70/288 (24.3)	15/41 (36.6)	<0.001
PCT (mcg/L)	<0.5	17/639 (2.7)	23/158 (14.6)	11/22 (50.0)	<0.001
CK-MB (μg/L)	<3.6	29/653 (4.4)	33/184 (17.9)	13/28 (46.4)	<0.001
TnI (μg/L)	<0.3	6/641 (0.9)	7/162 (4.3)	9/28 (32.1)	<0.001
TnT (μg/L)	<0.1	2/18 (11.1)	6/22 (27.3)	1/2 (50.0)	0.279

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK-MB, creatinine kinase MB isoenzyme; Cl, chloride; Cr, creatinine; CRP, C-reactive protein; F, female; Glu, glucose; K, potassium; Lac, lactate; LD, lactate dehydrogenase; LYM, lymphocyte; M, male: Na, sodium; PCT, procalcitonin; PLT, platelet; PT INR, prothrombin time international normalized ratio; T-BIL, total bilirubin; TnI, troponin I; TnT, troponin T; WBC, white blood cell.

In contrast, for every unit increase in the levels of Hb, LYM%, albumin, K, and Na, the risk of being in the moderate group was 0.855, 0.880, 0.084, 0.656, and 0.860 times lower, respectively, than the chance of being in the mild group. For every unit increase in the LYM%, albumin, Na, and Ct values of the *RdRP* gene in URT specimens, the risk of being in the severe group was 0.849, 0.036, 0.868, and 0.883 times lower, respectively, than the chance of being in the mild group. Prolonged PT (*P*<0.001), hypoalbuminemia (*P*<0.001), and abnormal K levels (*P*=0.003) were significantly correlated with severe disease.

We performed qualitative multinomial logistic regression analyses of the laboratory parameters (classified as normal vs. ab-

normal according to the reference values) (Table 4). Abnormal laboratory parameters results showed significant correlations with disease severity. Abnormal levels of LYM%, PT INR, albumin, AST, and PCT were associated with a 7.310, 3.474, 11.060, 6.277, and 6.234 times increased risk of moderate disease severity, respectively, as compared to the mild group. Abnormal levels of LYM%, PT INR, albumin, AST, and PCT levels were associated with a 14.169, 19.500, 35.312, 17.037, and 36.588 times increased risk of severe disease, respectively, as compared to the mild group. Abnormal CRP values were more often observed in the moderate group than in the mild group (OR 30.280, 95% CI: 17.205–53.289, *P*<0.001). Abnormal CK-MB and TnI lev-

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Table 3. Multinomial logistic regression analysis of laboratory parameters for clinical severity

Variable	Mild vs. moderate		Mild vs. severe	
	OR (95% CI)	P	OR (95% CI)	P
Hb (g/dL)	0.855 (0.797–0.917)	<0.001	0.858 (0.725–1.014)	0.073
Hct (%)	0.934 (0.911–0.957)	<0.001	0.943 (0.889–1.000)	0.049
LYM (%)	0.880 (0.866–0.894)	<0.001	0.849 (0.816–0.884)	<0.001
PLT ($\times 10^9$/L)	0.996 (0.995–0.998)	<0.001	0.996 (0.992–1.000)	0.058
WBC ($\times 10^9$/L)	1.189 (1.138–1.243)	<0.001	1.332 (1.244–1.428)	<0.001
aPTT (sec)	1.100 (1.071–1.13)	<0.001	1.141 (1.104–1.18)	<0.001
PT INR	2.384 (1.543–3.684)	<0.001	3.127 (1.897–5.156)	<0.001
Albumin (g/dL)	0.084 (0.062–0.113)	<0.001	0.036 (0.02–0.064)	<0.001
ALT (IU/L)	1.007 (1.003–1.01)	<0.001	1.009 (1.005–1.012)	<0.001
AST (IU/L)	1.020 (1.015–1.025)	<0.001	1.021 (1.017–1.026)	<0.001
BUN (mg/dL)	1.058 (1.046–1.071)	<0.001	1.068 (1.051–1.085)	<0.001
Cl (mEq/L)	0.960 (0.93–0.992)	0.014	1.016 (0.935–1.104)	0.713
Cr (mg/dL)	1.306 (1.157–1.473)	<0.001	1.433 (1.230–1.670)	<0.001
CRP (mg/dL)	1.225 (1.195–1.255)	<0.001	1.227 (1.191–1.263)	<0.001
Glu (mg/dL)	1.007 (1.006–1.009)	<0.001	1.010 (1.007–1.013)	<0.001
K (mEq/L)	0.656 (0.517–0.833)	0.001	1.589 (1.173–2.153)	0.003
Lac (mmol/L)	1.096 (0.935–1.284)	0.258	1.519 (1.253–1.842)	<0.001
LD (IU/L)	1.000 (1.000–1.000)	0.006	1.000 (1.000–1.000)	0.006
Na (mEq/L)	0.860 (0.833–0.887)	<0.001	0.868 (0.811–0.929)	<0.001
PCT (mcg/L)	1.417 (1.115–1.802)	0.004	1.462 (1.119–1.909)	0.005
T-BIL (mg/dL)	1.058 (0.97–1.153)	0.204	1.076 (0.967–1.197)	0.177
CK-MB (µg/L)	1.048 (1.006–1.092)	0.023	1.065 (1.018–1.113)	0.006
TnI (µg/L)	1.163 (0.929–1.455)	0.188	1.320 (1.043–1.669)	0.021
TnT (µg/L)	1.298 (0.446–3.777)	0.633	1.358 (0.204–9.028)	0.752
RdRP, Ct (URT)	0.955 (0.925–0.986)	0.005	0.883 (0.83–0.939)	<0.001
RdRP, Ct (LRT)	0.951 (0.892–1.013)	0.120	0.936 (0.822–1.065)	0.315

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CI, confidence interval; CK-MB, creatinine kinase MB isoenzyme; Cl, chloride; Cr, creatinine; CRP, C-reactive protein; Ct, cyclic threshold; Glu, glucose; K, potassium; Lac, lactate; LD, lactate dehydrogenase; LRT, lower respiratory tract; LYM, lymphocyte; Na, sodium; OR, odds ratio; PCT, procalcitonin; PLT, platelet; PT INR, prothrombin time international normalized ratio; *RdRP*, RNA-dependent RNA polymerase gene; T-BIL, total bilirubin; TnI, troponin I; TnT, troponin T; URT, upper respiratory tract; WBC, white blood cell.

els indicated severe disease more significantly than mild disease (OR, 18.648, 95% CI: 8.125–42.8, $P<0.001$ and OR, 44.561, 95% CI: 14.072–141.11, $P<0.001$, respectively).

Hypoalbuminemia and lymphopenia are associated with severe COVID-19

The frequencies of hypoalbuminemia and relative lymphopenia are shown in Table 5. In the severe group, 39 (95%) patients had either hypoalbuminemia or relative lymphopenia. The ORs of combined lymphopenia and hypoalbuminemia were 15.228

(95% CI: 10.988–21.104, $P<0.001$) and 36.474 (95% CI: 18.413–72.251, $P<0.001$) in the moderate and severe groups, respectively. In the ROC curves, the area under the curve (AUC) for albumin was 0.877 (95% CI: 0.831–0.922, $P<0.001$), with a sensitivity of 78.0% and a specificity of 84.8%, and that for LYM% was 0.824 (95% CI: 0.752–0.896, $P<0.001$), with a sensitivity of 73.2% and a specificity of 85.8%. The optimal cut-off levels of albumin and LYM% to predict severe COVID-19 were 3.44 g/dL and 14.8%, respectively.

Table 4. Multinomial logistic regression analysis of abnormal laboratory parameters for clinical severity (abnormal vs. normal)

Variable	Mild vs. moderate		Mild vs. severe	
	OR (95% CI)	P	OR (95% CI)	P
Hb (g/dL)	2.046 (1.583–2.643)	<0.001	2.405 (1.308–4.424)	0.005
Hct (%)	2.342 (1.800–3.048)	<0.001	4.645 (2.515–8.579)	<0.001
LYM (%)	7.310 (5.536–9.654)	<0.001	14.169 (6.233–32.208)	<0.001
PLT (×10^9/L)	2.414 (1.810–3.219)	<0.001	3.653 (1.930–6.914)	<0.001
WBC (×10^9/L)	1.920 (1.450–2.542)	<0.001	3.106 (1.656–5.827)	<0.001
aPTT (sec)	0.378 (0.269–0.532)	<0.001	0.764 (0.381–1.531)	0.448
PT INR	3.474 (2.133–5.657)	<0.001	19.500 (9.328–40.764)	<0.001
Albumin (g/dL)	11.060 (8.275–14.783)	<0.001	35.312 (16.533–75.419)	<0.001
ALT (IU/L)	2.045 (1.506–2.778)	<0.001	4.661 (2.463–8.821)	<0.001
AST (IU/L)	6.277 (4.816–8.181)	<0.001	17.067 (7.806–37.312)	<0.001
BUN (mg/dL)	3.121 (2.371–4.108)	<0.001	5.107 (2.745–9.500)	<0.001
Cl (mEq/L)	3.159 (2.252–4.433)	<0.001	2.394 (1.057–5.421)	0.036
Cr (mg/dL)	3.163 (2.324–4.304)	<0.001	8.210 (4.385–15.372)	<0.001
CRP (mg/dL)	30.280 (17.205–53.289)	<0.001	18.264 (5.614–59.416)	<0.001
Glu (mg/dL)	2.793 (2.101–3.713)	<0.001	5.985 (2.299–15.582)	<0.001
K (mEq/L)	3.033 (2.210–4.162)	<0.001	5.449 (2.825–10.510)	<0.001
Lac (mmol/L)	0.711 (0.479–1.056)	0.091	1.094 (0.437–2.736)	0.848
LD (IU/L)	0.805 (0.462–1.401)	0.442	1.907 (0.257–14.130)	0.528
Na (mEq/L)	7.011 (5.107–9.625)	<0.001	7.541 (3.837–14.821)	<0.001
PCT (mcg/L)	6.234 (3.241–11.988)	<0.001	36.588 (13.944–96.005)	<0.001
T-BIL (mg/dL)	4.053 (2.668–6.157)	<0.001	5.822 (2.585–13.112)	<0.001
CK-MB (μg/L)	4.702 (2.769–7.986)	<0.001	18.648 (8.125–42.800)	<0.001
TnI (μg/L)	4.780 (1.584–14.423)	0.006	44.561 (14.072–141.110)	<0.001
TnT (μg/L)	3.000 (0.525–17.159)	0.217	8.000 (0.347–184.364)	0.194
RdRP, Ct (URT)	1.791 (1.238–2.592)	0.002	2.338 (0.919–5.952)	0.075
RdRP, Ct (LRT)	3.161 (1.737–5.754)	<0.001	3.035 (0.792–11.634)	0.105

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CI, confidence interval; CK-MB, creatinine kinase MB isoenzyme; Cl, chloride; Cr, creatinine; CRP, C-reactive protein; Ct, cyclic threshold; Glu, glucose; K, potassium; Lac, lactate; LD, lactate dehydrogenase; LRT, lower respiratory tract; LYM, lymphocyte; Na, sodium; OR, odds ratio; PCT, procalcitonin; PLT, platelet; PT INR, prothrombin time international normalized ratio; *RdRP*, RNA-dependent RNA polymerase gene; T-BIL, total bilirubin; TnI, troponin I; TnT, troponin T; URT, upper respiratory tract; WBC, white blood cell.

Table 5. Hypoalbuminemia and relative lymphopenia as laboratory parameters associated with severe COVID-19

Variable	N/total N (%)			Mild vs. moderate		Mild vs. severe	
	Mild	Moderate	Severe	OR (95% CI)	P	OR (95% CI)	P
Hypoalbuminemia (<3.5 g/dL)	141/1,596 (8.8)	147/279 (52.7)	32/41 (78.1)	10.433 (7.833–13.895)	<0.001	23.846 (14.432–45.741)	<0.001
Lymphopenia (<21%)	343/1,606 (21.5)	206/291 (70.8)	34/41 (82.9)	8.924 (6.748–11.801)	<0.001	17.885 (7.860–40.697)	<0.001
Hypoalbuminemia+ lymphopenia	80/1,591 (5.0)	124/276 (44.6)	27/41 (65.9)	15.228 (10.988–21.104)	<0.001	36.474 (18.413–72.251)	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio.

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DISCUSSION

We found old age, male sex, relative lymphopenia, PT prolongation, and hypoalbuminemia to be significant indicators of CO-VID-19 severity. Patients with both hypoalbuminemia and lymphopenia showed an increased risk of severe COVID-19.

With respect to general characteristics, old age and male sex were significantly associated with severe COVID-19, in line with previous results [3, 4, 13]. Old age is often associated with compromised immune function and the presence of underlying comorbidities, which may lead to poor patient outcomes [14]. Recently, Takahashi, et al. [15] showed key differences in T-cell responses and cytokine levels during the course of COVID-19 in male and female patients. These differences may explain the higher vulnerability of men to COVID-19.

Comparison of the hematologic parameters revealed significant decreases in Hb, Hct, LYM%, and PLT count in the moderate and severe groups as compared to the mild group. Patients with severe disease on admission showed a higher WBC count; this is consistent with the results of a Chinese study [16]. In particular, the ORs of LYM% differed significantly between the moderate and severe groups and the mild group in both quantitative and qualitative analyses. A previous study reported a clear correlation between lymphopenia and disease severity [17]. In a meta-analysis of 13 cases, Zhao, et al. [18] found that lymphopenia, defined as a lymphocyte count of $<1.5\times10^9$/L, was associated with a three-fold increase in severe SARS-CoV-2 infection risk and that lymphocyte count and lymphopenia may serve as biomarkers for the rapid identification of COVID-19 patients with a more severe clinical presentation. Tan, et al. [19] reported that LYM% can be used as a reliable indicator for classifying COVID-19 patients into moderate, severe, and critical disease groups. Pronounced lymphocyte depletion and persistent low lymphocyte counts may be related to critical illness and unfavorable outcomes [8-10]. Similar to SARS-CoV, SARS-CoV-2 may act mainly on lymphocytes, especially, T lymphocytes [4]. The mechanisms of action include direct infection and lymphocyte destruction, cytokine-mediated lymphocyte destruction, and the inhibition of lymphocytes by metabolites, such as Lac [19-22]. Virus particles spread through the respiratory mucosa and infect other cells, induce a cytokine storm in the body, generate a series of immune responses, and cause changes in peripheral WBCs and immune cells, such as lymphocytes.

Abnormal coagulation parameters were more frequently observed in the moderate and severe groups than in the mild group. Prominent changes in the coagulation profile, including those in aPTT and PT INR, were noted in the three study groups. Liao, et al. [23] reported that the severity of coagulopathy was associated with the severity of COVID-19 in 380 patients. Tang, et al. [24] found that increased D-dimer and fibrin degradation product levels as well as prolonged PT on admission are related to poor prognosis. In a meta-analysis of 1,105 patients, Xiong, et al. [25] reported that PT and D-dimer levels were significantly higher in patients with severe COVID-19 than in those with mild disease.

Dysfunctional coagulation is considered an important risk factor for severe disease and death [26]. Coagulation activation may be related to the sustained inflammatory response. In severe infection, coagulation activation leads to an increased risk of the excessive consumption of coagulation factors with attendant disseminated intravascular coagulation, resulting in an increased fatality rate [27]. Considerable evidence has shown that COVID-19 patients show abnormal coagulation at both clinical presentation and laboratory examination [24, 26]. COVID-19-associated lung tissue damage may induce the release of tissue factors in the circulation and promote secondary fibrinolysis via the exogenous coagulation pathway [8]. Although the specific underlying mechanisms remain unclear, COVID-19 obviously involves potentially deleterious hemostasis/coagulation and inflammation processes.

COVID-19 is a systemic disease that affects several organs, including the liver, heart, and kidneys [20, 28-30]. The incidence of liver function abnormalities in COVID-19 patients is reported to be 14%–53% [31]. In our study, hypoalbuminemia and abnormal AST levels were prominent in severe COVID-19 patients. Albumin levels were inversely correlated with COVID-19 severity, and 78.1% of the patients in the severe group showed hypoalbuminemia. Abnormal albumin level was the most frequent abnormal liver biochemical indicator on admission, and approximately 20% of all patients with acute medical admissions had reduced albumin levels [32, 33]. Decreased albumin level generally indicates depressed hepatic synthesis, poor nutritional status, or negative acute-phase reactants due to downregulation by inflammatory cytokines [34]. Studies in various clinical settings and major disease categories have shown that hypoalbuminemia is associated with increased morbidity and mortality [35, 36]. Therefore, the albumin level may be used as a clinical marker to identify patients at high risk of developing severe CO-VID-19. Although there is currently no evidence that prevention or treatment of hypoalbuminemia improves the prognosis of COVID-19 patients, a decline in the albumin level may be related to the severity of COVID-19.

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The proportion of patients with both hypoalbuminemia and relative lymphopenia was substantially higher in the severe group than in the mild group (65.9% vs. 5.0%). Although further analysis for disease progression is needed, most patients with an albumin level above 3.44 g/dL and LYM% above 14.8% on admission may not need intensive treatment. Combined hypoalbuminemia and lymphopenia may represent systemic inflammation and be associated with an increased risk of severe disease.

Although numerous studies have reported on laboratory indicators of COVID-19, most of them were meta-analyses using laboratory parameters of Chinese patients [8, 9, 32]. Meta-analysis results may be limited by the selection of an incomplete set of studies; studies lacking internal, external, construct, and statistical conclusion validity; studies with relatively small sample sizes; and heterogeneity of methods used in included studies, all of which may lead to erroneous inferences [37]. Our study included a relatively large number of patients, and the heterogeneity of the enrolled patients was relatively low.

The present study had some limitations. First, asymptomatic or minimally symptomatic patients with no concurrent disease were treated in community treatment centers and were excluded; only hospitalized patients were included. Thus, the results may be biased, with a tendency to reveal more serious consequences in terms of clinical and laboratory parameters. Second, not all tests were performed in all patients. There were differences in the laboratory tests according to the medical staff or clinical severity. Third, the 95% CIs for OR estimates were rather wide in the multinomial regression analysis using qualitative variables, including PT INR, albumin, and LYM%. This may have been due to the wide range of values for these variables and the small sample size of the severe group. Further analysis using a large dataset may be helpful. Fourth, the reagents and instruments used in the laboratories of the nine hospitals were different. However, most laboratories in Korea participate in the Korean Laboratory Accreditation Program by the Laboratory Medicine Foundation and the Korean External Quality Assessment Scheme for laboratory standardization. Thus, the differences in procedures among these laboratories are not considered significant [38].

The present study focused on laboratory parameters that could predict clinical COVID-19 severity to classify and properly treat hospitalized COVID-19 patients. Various laboratory parameters, including hematologic, coagulation, biochemical, inflammatory, and cardiac markers, can be used to predict the severity of COVID-19. Although abnormalities in these parameters are not specific to COVID-19, they can help predict clinical severity in COVID-19 patients on admission. Laboratory tests are simple and inexpensive tools to provide objective information about the severity in COVID-19 patients. thus, these test results should be closely monitored and used to take timely measures.

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AUTHOR CONTRIBUTIONS

Yoo E and Chang SH designed the study, analyzed the data, and wrote the manuscript; Song D, Lee CH, Cheong GY, Park S, Lee JH, and Lee S collected and analyzed the data; Kwak SG performed the statistical analysis; Jeon C and Song K supervised the study design and reviewed and commented on the manuscript; all authors reviewed and approved the manuscript.

CONFLICTS OF INTEREST

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