

SUPPLEMENTAL MATERIAL

Supplemental Table 1. Baseline characteristics of the patients with and without serum KL-6 measurement on admission.

Variables	KL-6 (-) (n=899)	KL-6 (+) (n=2,226)	P-value
Age, years	55.1 ± 18.6	56.3 ± 17.0	0.086
Gender, male	579 (64.4)	1529 (58.7)	0.023
BMI, kg/m ²	24.7 ± 5.0	24.8 ± 4.8	0.872
Current smoker	123 (15.4)	328 (15.7)	0.909
Smoking history	347 (43.9)	982 (47.2)	0.251
Onset to hospitalization, days	5.64 ± 4.00	7.03 ± 4.50	<0.001
Comorbidities			
Hypertension	291 (32.8)	741 (33.7)	0.673
Diabetes mellitus	174 (19.6)	467 (21.2)	0.327
Cardiovascular disease	86 (9.7)	214 (9.7)	0.976
Autoimmune disease	32 (3.6)	90 (4.1)	0.528
COPD	35 (4.0)	85 (3.9)	0.918
Asthma	69 (7.9)	150 (6.9)	0.354
Hyperuricemia	81 (9.2)	231 (10.5)	0.321
Chronic liver disease	27 (3.1)	99 (4.6)	0.070
Chronic kidney disease	45 (5.2)	159 (7.5)	0.030
Critical Outcome	114 (12.7)	434 (19.5)	<0.001
High Flow Oxygen Therapy	26 (3.3)	104 (4.7)	0.125
IPPV	81 (9.0)	317 (14.2)	<0.001
ECMO	11 (1.3)	52 (2.4)	0.049
Mortality	17 (2.0)	77 (3.5)	0.027
Severity			
Asymptomatic	33 (3.7)	50 (2.3)	0.036
Mild	458 (50.1)	1073 (48.2)	0.167
Severe	292 (32.5)	671 (30.1)	0.200
Most Severe	116 (12.9)	432 (19.4)	<0.001

Data are presented as the mean ± SD or No. (%) of patients. Differences in variables with and without critical events were compared using unpaired *t*-tests or chi-square tests.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; IPPV, invasive positive-pressure ventilation.

Supplemental Table 2. Comparison between serum KL-6-high and -low patients without critical outcomes on admission.

Variables	KL-6 < 304 U/mL (n=1,417)	KL-6 ≥ 304 U/mL (n=665)	P-value
Age, years	52.4 ± 17.4	63.2 ± 14.2	<0.001
Gender, male	930 (65.6)	490 (73.7)	<0.001
BMI, kg/m²	24.4 ± 4.6	25.1 ± 4.5	0.014
Critical Outcome	112 (7.9)	178 (26.8)	<0.001
High Flow Oxygen Therapy	39 (2.8)	54 (8.1)	<0.001
IPPV	67 (4.7)	116 (17.4)	0.769
ECMO	6 (0.4)	13 (2.0)	<0.001
Mortality	19 (1.3)	32 (4.8)	<0.001
Severity			
Asymptomatic	33 (2.3)	17 (2.6)	0.760
Mild	854 (60.3)	219 (32.9)	<0.001
Severe	416 (29.4)	254 (38.2)	<0.001
Most Severe	114 (8.1)	175 (13.9)	<0.001

Data are presented as the mean ± SD or No. (%) of patients. Differences in variables with and without critical events were compared using unpaired *t*-tests or chi-square tests. **Abbreviations:** ECMO, extracorporeal membrane oxygenation; IPPV, invasive positive pressure ventilation.

Supplemental Table 3. Comparison of the clinical characteristics of patients with high and low serum KL-6 levels.

Variable	KL-6 < 304 U/mL (n = 773)	KL-6 ≥ 304 U/mL (n = 1,453)	P-value
Demographics			
Age, years	52.6 (51.8–53.5)	63.1 (62.1–64.1)	<0.001
Male, n (%)	957 (65.9)	572 (74.0)	<0.001
BMI, kg/m ²	24.5 (24.2–24.8)	25.3 (24.8–25.7)	0.005
Comorbidities			
Hypertension, n (%)	389 (27.2)	352 (45.8)	<0.001
Diabetes mellitus, n (%)	227 (15.8)	240 (31.3)	<0.001
Cardiovascular disease, n (%)	113 (7.9)	101 (13.13)	<0.001
Autoimmune disease, n (%)	62 (4.3)	28 (3.7)	0.456
COPD, n (%)	39 (2.72)	46 (6.01)	0.003

Asthma, n (%)	105 (7.4)	45 (5.94)	0.194
Hyperuricemia, n (%)	139 (9.70)	92 (11.96)	0.098
Chronic liver disease, n (%)	59 (4.2)	40 (5.3)	0.247
Chronic kidney disease, n (%)	77 (5.56)	82 (11.0)	<0.001
Symptoms			
Cough, n (%)	907 (63.3)	507 (68.15)	0.003
Sputum, n (%)	409 (28.54)	209 (28.7)	0.95
Sore throat, n (%)	399 (28.1)	147 (20.2)	<0.001
Rhinorrhea, n (%)	236 (16.6)	77 (10.53)	0.001
Dysgeusia, n (%)	306 (21.6)	104 (14.2)	<0.001
Olfactory disorder, n (%)	271 (19.1)	75 (10.23)	<0.001
Shortness of breath, n (%)	458 (32.4)	391 (53.0)	<0.001
Abdominal pain, n (%)	51 (3.6)	27 (3.7)	0.904
Abdominal distension, n (%)	10 (0.7)	7 (0.96)	0.531
Hematochezia, n (%)	10 (0.7)	4 (0.6)	0.673
Diarrhea, n (%)	310 (21.7)	108 (14.8)	0.001
Nausea, n (%)	148 (10.5)	61 (8.4)	0.129
Fatigue, n (%)	794 (55.5)	445 (60.1)	0.04
Signs			
Unconsciousness, n (%)	30 (2.1)	57 (7.63)	<0.001
Fever (≥ 37.5 °C), n (%)	1225 (84.8)	613 (80.6)	0.011
Laboratory findings			
White blood cells, $\times 10^3/\mu\text{L}$	5.44 (5.30–5.59)	6.71 (6.50–6.91)	<0.001
Neutrophils, $\times 10^3/\mu\text{L}$	3.83 (3.69–3.97)	5.08 (4.89–5.28)	<0.001
Lymphocytes, $\times 10^3/\mu\text{L}$	1.07 (1.04–1.10)	0.94 (0.90–0.97)	<0.001
Eos, $/\mu\text{L}$	40.5 (35.8–45.2)	29.5 (23.1–35.9)	<0.001
Hb, g/dL	14.3 (14.2–14.4)	14.3 (14.1–14.4)	0.578
Plt, $\times 10^4/\mu\text{L}$	20.2 (19.7–20.7)	20.0 (19.3–20.7)	0.739
Alb, g/dL	3.83 (3.80–3.86)	3.39 (3.35–3.44)	<0.001
T-Bil, mg/dL	0.65 (0.63–0.67)	0.70 (0.67–0.73)	0.007
AST, IU/L	40.1 (37.3–42.9)	49.6 (45.8–53.5)	<0.001
ALT, IU/L	38.2 (36.1–40.3)	43.0 (40.1–45.9)	0.01
ALP, IU/L	152 (146–158)	157 (149–166)	0.315
γ -GTP, IU/L	67.8 (63.0–72.5)	77.0 (70.5–83.6)	0.025
BUN, mg/dL	14.9 (14.4–15.5)	21.1 (20.4–21.9)	<0.001

Cre, mg/dL	1.02 (0.95–1.09)	1.19 (1.09–1.29)	0.005
LDH, IU/L	258 (250–266)	380 (370–290)	<0.001
UA, mg/dL	4.70 (4.60–4.79)	5.07 (4.94–5.19)	<0.001
CK, IU/L	156 (128–183)	231 (193–268)	0.002
BNP, pg/mL	36.5 (15.4–57.5)	97.6 (69.7–125.6)	0.001
Ferritin, ng/mL	512 (474–551)	922 (869–976)	<0.001
HbA1c, %	6.13 (6.06–6.20)	6.76 (6.67–6.85)	<0.001
Fibrinogen, mg/dL	481 (472–490)	524 (513–534)	<0.001
D-dimer, µg/mL	1.30 (0.88–1.72)	4.17 (3.60–4.74)	<0.001
CRP, mg/dL	4.40 (2.68–6.10)	9.33 (6.99–11.67)	0.001
PCT, n (%)	0.20 (0.12–0.28)	0.38 (0.28–0.49)	0.007

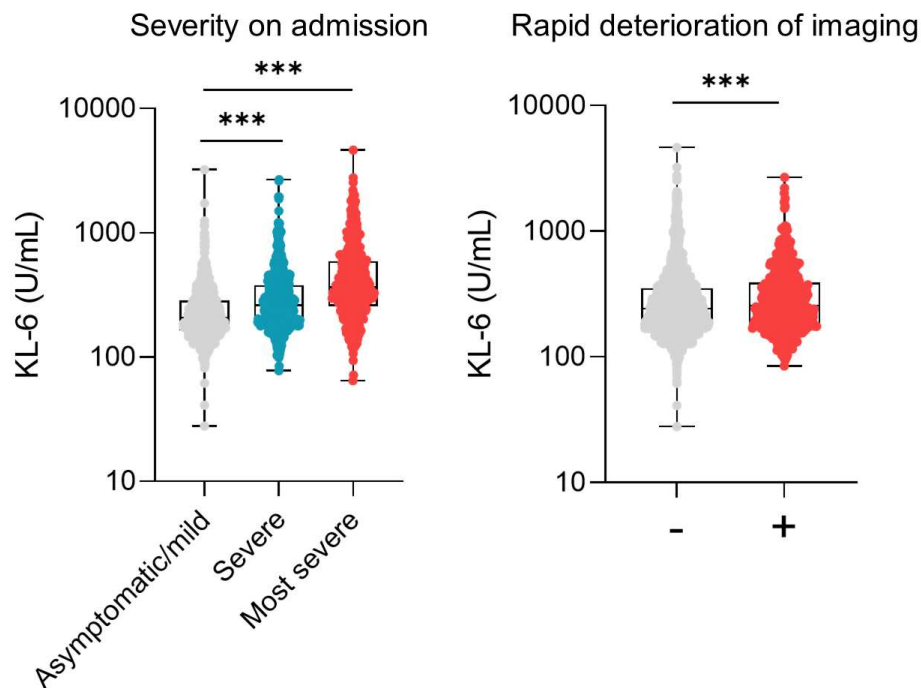
Data are presented as the median (interquartile range) or number (%). Differences between values in patients with high or low serum KL-6 levels were compared using unpaired *t*-tests or the Wilcoxon rank sum test for continuous variables, or the chi-square tests or Fisher's exact test for categorical variables.

Supplemental Table 4. Correlation between serum KL-6 and other serological biomarkers with the severity of COVID-19.

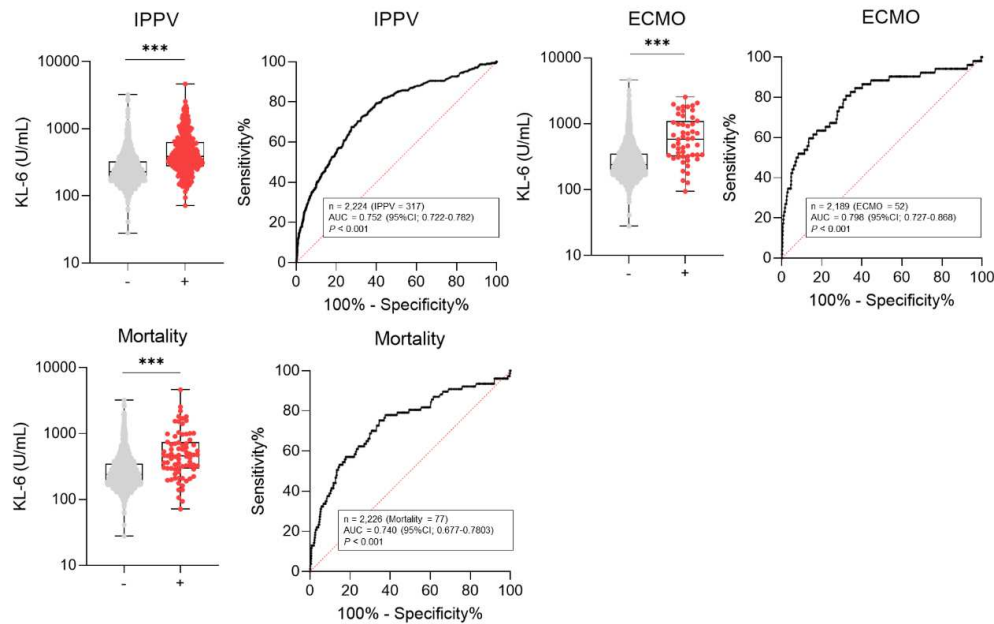
Parameter	Correlation coefficient (r)	<i>P</i> value
CRP	0.05	0.028
Ferritin	0.31	<0.001
D-dimer	0.27	<0.001

Data are presented as the Pearson correlation coefficients (r) of CRP, ferritin, and D-dimer against serum KL-6. **Abbreviations:** CRP, C-reactive protein.

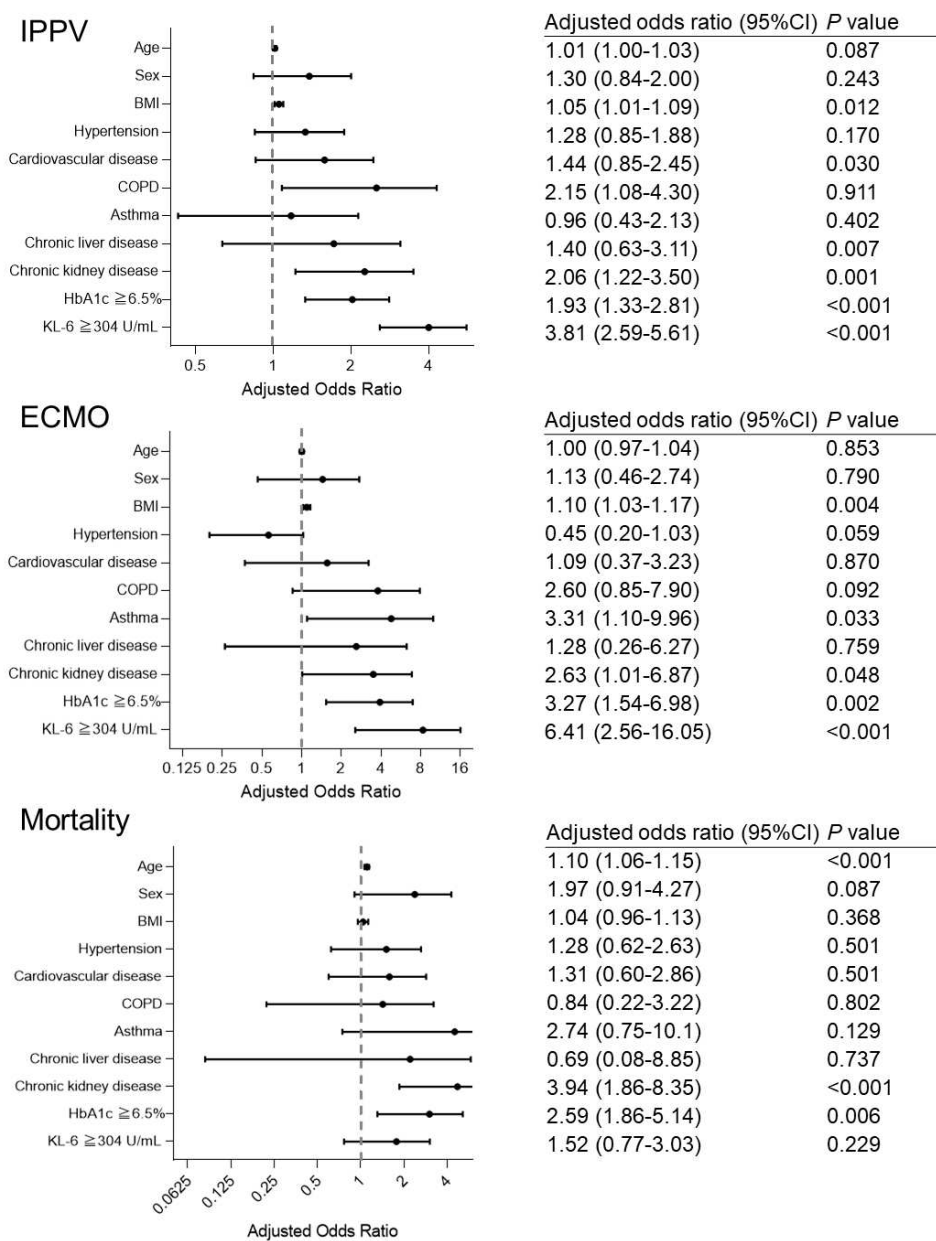
SUPPLEMENTAL FIGURES



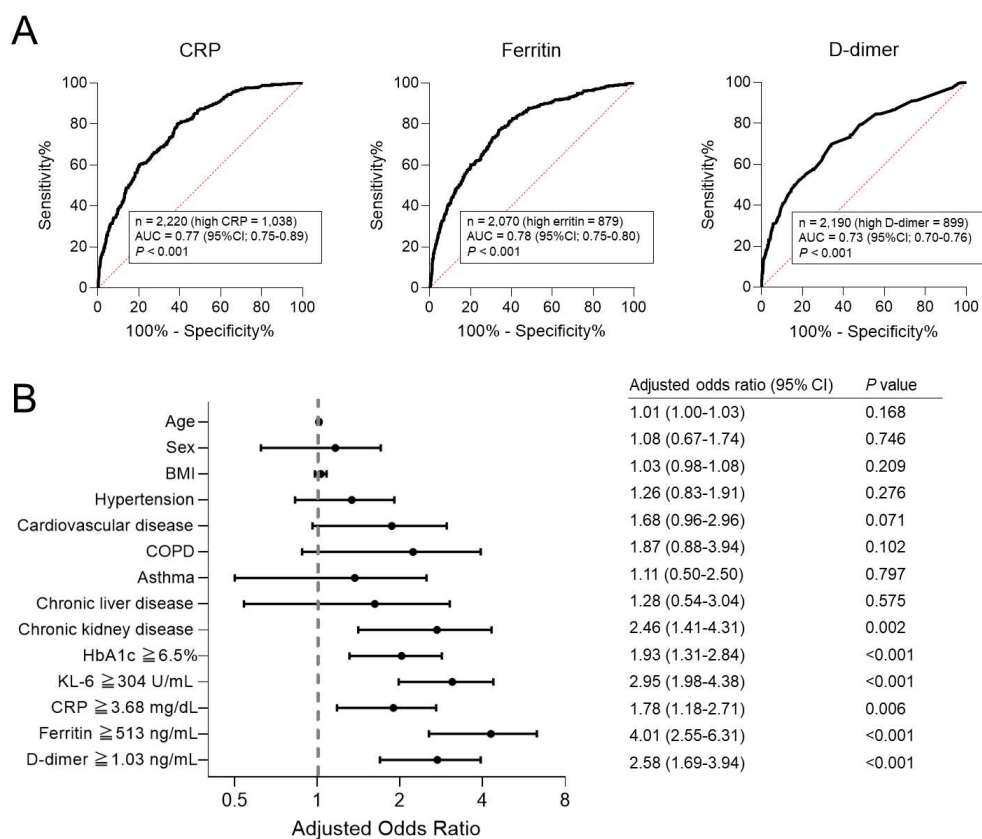
Supplemental Figure 1. Differences in serum KL-6 levels according to disease severity on admission and rapid deterioration of imaging within 48 hours of hospitalization. Group comparisons were conducted using unpaired t-tests and Dunnett's multiple comparisons tests. *** $P < 0.001$. CXR: chest X-ray.



Supplemental Figure 2. Receiver operating characteristic curves for the outcomes of COVID-19 based on the serum levels of KL-6. **Abbreviations:** AUC, area under the curve; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; IPPV, Invasive positive pressure ventilation.



Supplemental Figure 3. Multivariable logistic regression analysis for the relationship between IPPV or mortality and serum KL-6 levels and known risk factors of COVID-19. The forest plot shows the adjusted odds ratios, 95% confidence intervals, and *P*-values of the parameters of the analysis. **Abbreviations:** CI, confidence intervals; ECMO, extracorporeal membrane oxygenation; IPPV, invasive positive pressure ventilation.



Supplemental Figure 4. (A) Receiver operating characteristic curves showing the outcomes of patients with COVID-19 based on inflammatory biomarkers. (B) Multivariable logistic regression analysis of the relationship between critical outcomes, serum KL-6 levels, and other inflammatory biomarkers of COVID-19. The forest plot shows the adjusted odds ratios, 95% confidence intervals, and *P*-values of the parameters of the analysis. **Abbreviations:** AUC, area under the curve; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein.

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