OBSTETRICS

Immunity and coagulation and fibrinolytic processes may reduce the risk of severe illness in pregnant women with coronavirus disease 2019

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BACKGROUND: There are specific physiological features regarding the immunity and coagulation among pregnant women, which may play important roles in the development of coronavirus disease 2019.

OBJECTIVE: This study aimed to determine the key factors associated with the deterioration of patients with coronavirus disease 2019 and the differentiating clinical characteristics of pregnant women with coronavirus disease 2019 to interfere with the progression of coronavirus disease 2019.

STUDY DESIGN: A retrospective study of 539 Chinese Han adult patients with coronavirus disease 2019 was conducted, of which 36 cases were pregnant women. In addition, 36 pregnant women without coronavirus disease 2019 were recruited as the control. The characteristics of severe and critical illnesses, which were differentiated from mild and moderate illnesses in patients with coronavirus disease 2019, were analyzed using a machine learning algorithm. In addition, major differences between pregnant women with coronavirus disease 2019 and age-matched nonpregnant women with severe or critical coronavirus disease 2019, paired with pregnant women without coronavirus disease 2019, were explored to identify specific physiological features of pregnant women with coronavirus disease 2019.

RESULTS: For the total patient population, the lymphocyte, $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, and $CD16^+CD56^+$ cell counts were significantly lower, and white blood cell count, neutrophil count, and neutrophil-to-lymphocyte ratio were higher in those with severe or critical illness than those with mild or moderate illness ($P<.001$). The plasma levels of interleukin-6, interleukin-10, and interleukin-6—to—interleukin-10 ratio were significantly increased in patients with critical illness compared with patients with mild, moderate, and severe illnesses ($P<.001$). The above immunologic coclusters achieved an area under the receiver operating characteristic curve of 0.801 (95% confidence interval, 0.764—0.838), and its combined model with the coagulation and fibrinolysis indices (prothrombin time, D-dimer) achieved an area under the receiver operating characteristic curve of 0.815 (95% confidence interval, 0.779—0.851) using the random forest regression model to predict severe or critical illness. For pregnant women with coronavirus disease 2019, none had preexisting diseases. Compared with nonpregnant women with mild or moderate coronavirus disease 2019, pregnant women with coronavirus disease 2019 displayed increased white blood cell count, neutrophil count, neutrophil-to-lymphocyte ratio, and levels of D-dimer and fibrinogen, along with decreased lymphocyte and interleukin-4 levels ($P<.05$). Although they presented similar changes of immunologic markers of lymphocyte; white blood cell count; neutrophil-to-lymphocyte ratio; $CD3^+$, $CD4^+$, $CD8^+$, and $CD16^+CD56^+$ cell counts; and interleukin-6—to—interleukin-10 ratio, compared with nonpregnant women with severe or critical coronavirus disease 2019, none of the pregnant women with coronavirus disease 2019 deteriorated into severe or critical illness. There was no significant difference in white blood cell count, lymphocyte count, neutrophil count, neutrophil-to-lymphocyte ratio, immunologic markers, or coagulation and fibrinolysis markers between pregnant women with coronavirus disease 2019 and pregnant women without coronavirus disease 2019. As for the discrepancy of pathophysiological features between pregnant women with coronavirus disease 2019 and nonpregnant women with severe or critical coronavirus disease 2019, the immunologic markers achieved an area under the receiver operating characteristic curve of 0.875 (95% confidence interval, 0.773—0.977), and its combined model with coagulation and fibrinolysis indices achieved an area under the receiver operating characteristic curve of 0.931 (95% confidence interval, 0.850—1.000).

CONCLUSION: Immune dysregulation was identified as a crucial feature of patients with coronavirus disease 2019, which developed severe or critical illness, and pregnant women with coronavirus disease 2019 presented with similar immune responses but rarer incidences of severe or critical illness. Immune dysregulation is related to the risks of deterioration into severe or critical illness. The specific coagulation and fibrinolysis systems of pregnancy may reduce the risk of pregnant women with coronavirus disease 2019 without preexisting disease from developing severe illness.

Key words: coronavirus disease 2019, D-dimer, fibrinolysis, gestational physiology, illness development, immune dysregulation, severe acute respiratory syndrome coronavirus 2

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 33.2 million people in most of the countries worldwide, and as of September 29, 2020, 1 million and 40 people have died, as reported by the World Health Organization (WHO).[1] Despite tremendous efforts to combat this novel infectious disease globally, only a few medications have shown potentially curative effects. The coexistence of SARS-CoV-2 with human beings seems inevitable.[2] Finding a way to interfere with the development of illness to severe or critical stages and reducing

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AJOG at a Glance

Why was this study conducted?

This study aimed to determine the factors that predict the risk of severe or critical coronavirus disease 2019 (COVID-19) and reduce the risk of severe illness in pregnant women with COVID-19.

Key findings

Pregnant women with COVID-19 demonstrated similar immune response (increased interleukin-6 level and lymphocytopenia) with nonpregnant women with severe or critical COVID-19. No severe or critical COVID-19 cases occurred among pregnant women in the current study. The coagulation-fibrinolysis index (prothrombin time and D-dimer) showed remarkable differences between pregnant women with COVID-19 and nonpregnant women with severe or critical COVID-19.

What does this add to what is known?

Immune dysregulation is a crucial feature of patients with COVID-19 to develop severe or critical illness. The specific coagulation and fibrinolytic systems of pregnancy may reduce the risk of severe illness in pregnant women with COVID-19.

the mortality as much as possible may be another strategy.[3]

According to the current reports that provide information regarding pregnant patients, the illness severity of pregnant women with COVID-19 is similar with the common population or even lower.[4–10] In a study conducted in Wuhan city, China, only 9 of 118 pregnant patients (8%) were classified as severe cases, yet there were no maternal deaths.[9] The US COVID-NET Surveillance Team reported that half of the hospitalized pregnant women with COVID-19 (55% of 598 cases) were asymptomatic and only 1% of all cases were deceased owing to severe illness.[11] This phenomenon seems against the knowledge that pregnant women are more susceptible to respiratory pathogens and tend to develop severe illness after various infections, for example, germs, influenza, SARS, and Middle East respiratory syndrome.[12] It peaks our interest to find out the special pathologic feature of COVID-19 in pregnant women.

SARS-CoV-2 has been reported to trigger excessive inflammation. Increasing levels of inflammatory markers and overproduction of inflammatory cytokines[13–15] and lymphocytopenia along with an elevated neutrophil-to-lymphocyte ratio (NLR)[16] were reported to be associated with hospitalization rate, severity of illness or mortality. Furthermore, dysregulated coagulation and diffuse thrombosis have been observed in the lungs and extrapulmonary organs of patients with acute respiratory distress syndrome who died.[17–19]

However, during pregnancy, the neutrophil, NLR, and D-dimer also increase with the progression of gestational age. The microcirculation will undergo modifications during the course of pregnancy to aid adaptation to ensure adequate oxygen supply to the fetus.[20] We hypothesized that the specific immunity response and coagulation-fibrinolysis state among pregnant women with COVID-19 may play important roles in the progression of illness in COVID-19.

Herein, the clinical characteristics and laboratory indicators in 539 Chinese Han patients with COVID-19, including 36 pregnant women, were analyzed. Vital pathologic features distinguishing severe or critical illness from mild or moderate illness were identified via machine learning algorithms. The physiological features between pregnant women with COVID-19 and their counterpart controls were compared to determine the key factors that may hint the potential mechanism of development of COVID-19.

Materials and Methods

Population

This retrospective study was reviewed and approved by the Medical Ethical Committee of Renmin Hospital of Wuhan University (number WDRY2020-K087). The information of all patients diagnosed with COVID-19 from January 11, 2020, to Apr 1, 2020, were collected from the records of the inpatient department of Renmin Hospital of Wuhan University designated specially for patients with COVID-19. In total, 539 Chinese Han patients were included, among whom there were 36 pregnant women with COVID-19 aged 20 to 40 years old who were composed of the whole pregnant population admitted to the hospital. The diagnosis of COVID-19 was made on the basis of the WHO interim guidance and confirmed positive results for SARS-CoV-2 nucleic acid in respiratory samples via real-time reverse-transcription polymerase chain reaction (RT-PCR), based on the recommendation by the National Institute for Viral Disease Control and Prevention.[21] In addition, 36 age-matched pregnant women without COVID-19 who delivered in Renmin Hospital of Wuhan University from September 20, 2019, to October 30, 2019, were recruited as the control group compared with pregnant women with COVID-19, after excluding pregnant women with fever, respiratory symptoms and diseases, influenza A or B, and other systemic or obstetrical complications.

Data collection

The clinical, laboratory, and outcome data of patients with COVID-19 were obtained from the electronic medical records during the time of admission and discharge for mild illness; admission, improvement, and discharge for moderate illness; and admission, exacerbation, improvement, and discharge for severe or critical illness. In addition, laboratory data of pregnant women in

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the control group were collected on the date of admission. The data collection forms were independently reviewed by 2 researchers.

For laboratory assessments, blood samples were collected in the morning after fasting overnight to examine the following indexes: complete blood count (photoelectric colorimetry, XN-9000); coagulation and fibrinolysis indices (immunoturbidimetry, CS-5100); N-terminal probrain natriuretic peptide (NT-proBNP) (electrochemical laser method, E602); creatine kinase-MB (CK-MB), cardiac troponin I, or myoglobin (electrochemical luminescence, ADVIA Centaur); serum biochemical test (rate method, ADVIA-2400); cellular immune function and immunologic factors (flow cytometry analysis, antibodies used in flow cytometry were shown in Supplemental Table 1, BD FACSCalibur); humoral immune function (turbidimetry, Siemens BNII); and laboratory coronavirus nucleic acid (RT-PCR, LC480).

The definition of the severity of coronavirus disease 2019

The severity of the disease process is determined according to the *Diagnosis and treatment plan for novel coronavirus pneumonia cases (Provisional) (5th edition)*. Mild illness is defined as mild clinical symptoms with no evidence of pneumonia on imaging studies. Moderate illness is defined as fever, respiratory tract symptoms, and imaging displaying signs of pneumonia. Severe illness is defined as tachypnoea ($\geq$30 breaths/min), an oxygen saturation of $\leq$93% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of $\leq$300 mm Hg, or progression of lesions of >50% within 24 to 48 hours, as determined by pulmonary imaging. Critical illness is defined as respiratory failure requiring mechanical ventilation, shock, or organ failure requiring intensive care.

Statistical analysis

Data were presented as medians (interquartile ranges [IQRs]) or frequency (percentage). The differences between groups were compared using the Mann-Whitney *U* test or Kruskal-Wallis *H* test with post hoc Bonferroni correction for continuous variables and the Pearson chi-square test for categorical variables. The analyses were performed with IBM SPSS (Statistical Product and Service Solutions) Statistics software for Windows (version 22.0; SPSS Inc, Chicago, IL). A *P* value of $<.05$ was considered statistically significant. Violin plots were generated with GraphPad Prism program (version 8.0; GraphPad Software Inc, San Diego, CA).

For the methodology of grouping, first, a total of 539 patients with COVID-19 were divided into 4 subgroups: mild (n=22), moderate (n=297), severe (n=169), and critical (n=51), according to the severity of illness. Second, 36 pregnant women with COVID-19 and their counterparts of 82 nonpregnant women with COVID-19 aged 20 to 40 years old, which were age matched, were extracted from the total patients. The subgroups were categorized into pregnant women with COVID-19 (n=36), age-matched nonpregnant women with mild or moderate COVID-19 (n=72), and nonpregnant women with severe or critical COVID-19 (n=10) to analyze the biochemical characteristics. In addition, considering the multiple repeated times of blood investigations performed in this study, generalized mixed models and generalized estimating equation models were also used to assess the difference of laboratory characteristics among different subgroups.[22] These data were analyzed using Stata software (version 12.0; StataCorp LLC, College Station, TX). A random forest (RF) regression model was further used to evaluate the distinguishing abilities of clinical and laboratory markers. The data set was randomly split into a training set containing 80% of the samples and a validation set containing the remaining 20%. Variables used for distinguishing were selected on the basis of comprehensive consideration of ranking of importance (Supplemental Figure). The RF was implemented using R software (version 3.2.2; R Core Team 2014)[23] using the "random forest" package. The graphical receiver operating characteristic (ROC) curve was produced along with area under the ROC curve (AUC). Statistical significance was defined as $P<.05$.

Results

Clinical features of the total patients with coronavirus disease 2019

The clinical and biochemical features of all 539 patients were first analyzed, as shown in Table 1. The median ages of the patients increased with disease severity of COVID-19, which were 31 (IQR, 27−52), 46 (IQR, 33−62), 64 (IQR, 51−74), and 68 (IQR, 60−80) years old, in mild, moderate, severe, and critical subgroups, respectively ($P<.001$). More patients in the critical subgroup had a history of smoking compared with those in the mild, moderate, and severe groups ($P<.001$). There were higher incidences of hypertension and cardiovascular disease in the severe and critical groups than in the mild and moderate group ($P<.001$); in addition, there were higher incidences of cerebrovascular disease and chronic kidney disease in the severe and critical groups than in the mild and moderate group ($P<.05$). The inhospital mortality rate of the mild group was 0.0% (0 of 22), moderate 0.34% (1 of 297), severe 20.1% (34 of 169), and critical 33.3% (17 of 51). These results indicated risk factors related to severe COVID-19, including older age, smoking history, cardiovascular disease, cerebrovascular disease, and nephropathy. The detailed laboratory characteristics are shown in Supplemental Table 2.

The immunologic and biochemical features of total patients with coronavirus disease 2019

On admission, lymphopenia was detected in 251 patients (46.6%) with COVID-19, as shown in Supplemental Table 2. The lymphocyte count and $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$ and $CD16^+CD56^+$ cell counts were significantly lower in patients with severe and critical illnesses than in patients with mild and moderate illnesses ($P<.001$). Serum white blood cell (WBC) count, neutrophil count, and NLR were significantly higher in patients with severe and critical illnesses than in patients with moderate illness ($P<.001$), as shown in Supplemental Table 2. Corresponding with the cellular immune dynamic in the aggravating severity of illness in patients

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TABLE 1
Comparison of demographics and clinical characteristics of patients with COVID-19 with different illness severity

Characteristics	Total (n=539)	Mild (n=22)	Moderate (n=297)	Severe (n=169)	Critical (n=51)	*P* value
Age (y)	56 (36.0–68.0)	31 (27.0–52.0)	46 (33.0–62.0)[a]	64 (51.0–74.0)[a,b]	68 (60.0–80.0)[a,b]	<.001
Respiratory rate of >24 breaths per min	61 (11.3)	0 (0.0)	6 (2.0)	38 (22.5)[a,b]	17 (33.3)[a,b]	<.001
Smoking history	180 (33.4)	4 (18.2)	79 (27.0)	65 (38.9)	32 (62.7)[a,b,c]	<.001
Period from onset to admission (d)	10 (7.0–15.0)	7 (1.0–11.0)	10 (7.0–14.5)	10 (7.0–15.0)[a]	10 (7.0–15.5)[a]	.045
Comorbidities						
Diabetes	67 (12.4)	0 (0.0)	32 (10.8)	28 (16.6)	7 (13.7)	.078
Hypertension	155 (28.8)	3 (13.6)	63 (21.2)	69 (40.8)[a,b]	20 (39.2)	<.001
Cardiovascular disease	48 (8.9)	1 (4.5)	13 (4.4)	27 (16.2)[b]	7 (13.7)	<.001
Cerebrovascular disease	11 (2.0)	0 (0.0)	2 (0.7)	6 (3.6)	3 (6.0)	.025
Chronic obstructive pulmonary disease	10 (1.9)	1 (4.5)	5 (1.7)	4 (2.4)	0 (0.0)	.441
Chronic kidney disease	10 (1.9)	0 (0.0)	1 (0.3)	6 (3.6)	3 (5.9)[b]	.007
Carcinoma	22 (4.2)	0 (0.0)	12 (4.1)	8 (4.8)	2 (4.0)	.936
Signs and symptoms						
Fever	403 (75.5)	7 (31.8)	217 (73.6)[a]	138 (83.1)[a]	41 (80.4)[a]	<.001
Highest temperature on admission						
<37.5°C	148 (29.6)	12 (63.2)	97 (35.9)	31 (19.1)[a,b]	8 (16.3)[a,b]	<.001
37.6°C–38.0°C	107 (21.4)	1 (5.3)	51 (18.9)	47 (29.0)	8 (16.3)	
38.1°C–39.0°C	176 (35.2)	5 (26.3)	92 (34.1)	58 (35.8)	21 (42.9)	
>39.0°C	69 (13.8)	1 (5.3)	30 (11.1)	26 (16.0)	12 (24.5)	
Cough	325 (60.3)	6 (27.3)	176 (59.3)[a]	113 (66.9)[a]	30 (58.8)	.005
Myalgia or fatigue	41 (7.6)	0 (0.0)	24 (8.1)	13 (7.7)	4 (7.8)	.710
Sputum production	153 (28.4)	0 (0.0)	81 (27.3)[a]	53 (31.4)[a]	19 (37.3)[a]	.003
Diarrhea	61 (11.3)	0 (0.0)	31 (10.4)	25 (14.8)	5 (9.8)	.164
Dyspnea	81 (15.0)	0 (0.0)	6 (2.0)	44 (26.0)[a,b]	31 (60.8)[a,b,c]	<.001
Inhospital mortality	52 (9.6)	0 (0.0)	1 (0.3)	34 (20.1)[a,b]	17 (33.3)[a,b,c]	<.001

All patients enrolled in this study are Chinese Han patients. Data are presented as number (percentage) or mean (interquartile range).

COVID-19, coronavirus disease 2019.

[a] Compared with the mild subgroup, $P<.05$; [b] Compared with the moderate subgroup, $P<.05$; [c] Compared with the severe subgroup, $P<.05$.

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with COVID-19, the plasma levels of interleukin (IL)-6, IL-10, and IL-6/10 were significantly increased in patients with critical illness than in patients with mild, moderate, and severe illnesses ($P<.001$), as shown in Supplemental Table 2. However, it is noteworthy that the incidence of more than triple the normal cutoff value of IL-6 (>60.0 pg/mL) was 34.6% (9 of 26) in patients with critical illness and 1.3% (1 of 78) in patients with severe illness. No significant difference was found in the serum levels of the other cytokine cocluster (ie, IL-2, IL-4, tumor necrosis factor [TNF]-α, and interferon [IFN]-γ) among the 4 subgroups.

For coagulation markers, the levels of prothrombin time (PT), fibrinogen (FIB), fibrinogen degradation product (FDP), and D-dimer were significantly increased in sequence with the progression of illness severity ($P<.001$). The analysis indicates that individuals with severe and critical COVID-19 displayed progressive immunologic disorder, which was featured by decreasing lymphocytes and its subpopulations, increasing neutrophil count and NLR, and increasing levels of inflammatory

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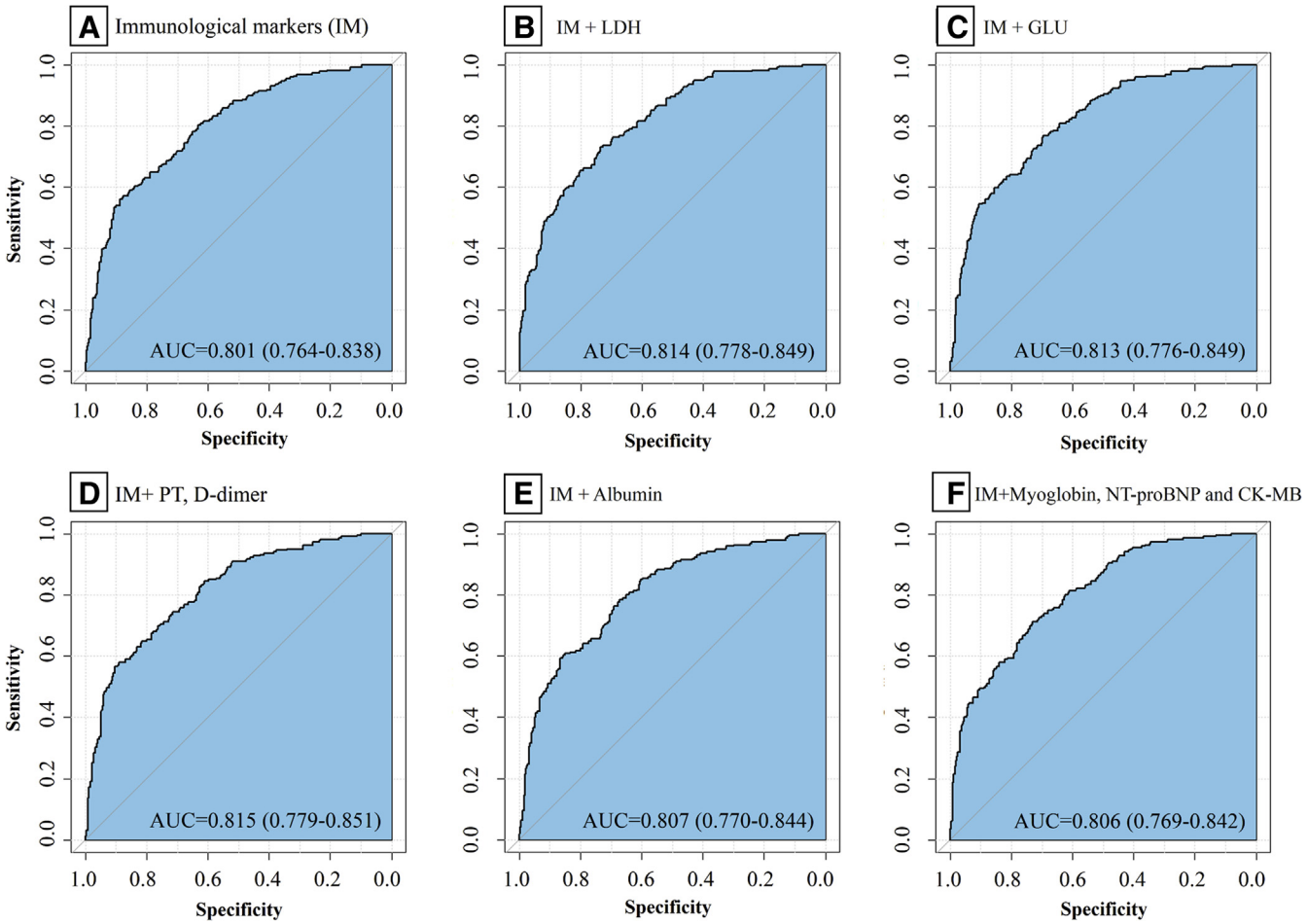
FIGURE 1
ROC curves for distinguishing severe and critical COVID-19 patients



For this analysis, 220 patients with severe or critical COVID-19 and 319 patients with mild or moderate COVID-19 were used. **A,** ROC curve for immunologic markers of NLR; $CD3^+$, $CD4^+$, $CD8^+$, and $CD16^+CD56^+$ cell counts; IL-6; IL-6/10; lymphocyte count; and WBC count. **B,** ROC curve for immunologic markers and LDH. **C,** ROC curve for immunologic markers and GLU. **D,** ROC curve for immunologic markers and PT and D-dimer. **E,** ROC curve for immunologic markers and albumin. **F,** ROC curve for immunologic markers and myoglobin, NT-proBNP, and CK-MB.

AUC, area under the ROC curve; *CK-MB*, creatine kinase-MB; *COVID-19*, coronavirus disease 2019; *GLU*, glucose; *IL-6*, interleukin-6; *IL-6/10*, interleukin-6—to—interleukin-10 ratio; *IM*, immunologic marker; *LDH*, lactate dehydrogenase; *NLR*, neutrophil-to-lymphocyte ratio; *NT-proBNP*, N-terminal probrain natriuretic peptide; *PT*, prothrombin time; *ROC*, receiver operating characteristic; *WBC*, white blood cell.

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cytokines, including IL-6, IL-10, and IL-6/10, in addition to coagulation dysfunction.

Prediction for severe and critical illnesses with immunologic and biochemical markers among total patients with coronavirus disease 2019

Furthermore, an RF regression model was performed to graft the dynamic change of the immunologic and biochemical markers and to identify the characteristics of severe and critical illnesses. The model based on immunologic markers (NLR, lymphocyte count, WBC count, $CD3^+$ cell count, $CD4^+$ cell count, $CD8^+$ cell count, $CD16^+CD56^+$ cell count, IL-6, and IL-6/10) achieved an AUC of 0.801 (95% CI, 0.764—0.838) (Figure 1 and Supplemental Table 3). In addition, the combined model with both immunologic markers and coagulation and fibrinolysis indices (PT, D-dimer) achieved the highest AUC of 0.815 (95% CI, 0.779—0.851) (Figure 1). These results illustrated that immunologic and coagulation and fibrinolysis indicators may predict the deterioration into severe COVID-19.

Clinical features of pregnant women with coronavirus disease 2019

The median age of the 36 pregnant women with COVID-19 was 29.0 years old (IQR, 27.0—32.0). The gestational

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TABLE 2
Basic demographics and clinical characteristics of pregnant women

Characteristics	Pregnant women with COVID-19 (n=36)	Early pregnancy (n=6)	Middle pregnancy (n=5)	Late pregnancy (n=25)	Pregnant women without COVID-19 (n=36)
Age (y)	29.0 (27.0–32.0)	32.5 (27.8–36.3)	29.0 (25.5–33.5)	29.0 (27.0–32.0)	31.0 (28.8–34.0)
Gestational age at admission (wk)	36.3 (20.1–39.1)	8.2 (6.8–9.3)	18.4 (17.4–21.7)	38.5 (36.2–39.5)	39.0 (38.4–39.9)
Respiratory rate of >24 breaths per min	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	—
Smoking history	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	—
Period from onset to admission (d)	7.0 (3.0–11.8)	7.0 (5.0–10.5)	5.0 (2.5–11.0)	7.0 (0.0)	—
Comorbidities					
Diabetes	2 (5.6)	0 (0.0)	0 (0.0)	2 (8.0)	0 (0.0)
Hypertension	1 (2.8)	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)
Cardiovascular disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chronic kidney disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Signs and symptoms					
Fever	16 (44.4)	5 (83.3)	3 (60.0)	7 (29.2)	—
Highest temperature on admission					
<37.5°C	13 (61.9)	1 (16.7)	4 (80.0)	8 (88.9)	—
37.6°C–38.0°C	1 (4.8)	1 (16.7)	0 (0.0)	0 (0.0)	—
38.1°C–39.0°C	5 (23.8)	3 (50.0)	0 (0.0)	1 (11.1)	—
>39.0°C	2 (9.5)	1 (16.7)	1 (20.0)	0 (0.0)	—
Cough	12 (33.3)	3 (50.0)	2 (40.0)	6 (25.0)	—
Myalgia or fatigue	1 (2.8)	1 (16.7)	0 (0.0)	0 (0.0)	—
Sputum production	7 (19.4)	1 (16.7)	1 (16.7)	5 (20.0)	—
Diarrhea	1 (2.8)	0 (0.0)	0 (0.0)	1 (4.2)	—
Dyspnea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	—

Data are presented as number (percentage) or mean (interquartile range).

COVID-19, coronavirus disease 2019.

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age was from 5 weeks to 41 weeks, and 69.4% women were in the third trimester of pregnancy. Among the 36 patients, 7 (19.4%) had mild illness, 29 (80.6%) had moderate illness, and no patient had severe or critical illness. On admission, 16 (44.4%) had fever, 12 (33.3%) had cough, 7 (19.4%) had sputum production, 1 (2.8%) had myalgia or fatigue, and 1 (2.8%) had diarrhea. For comorbidities, 2 (5.6%) had gestational diabetes mellitus, and 1 (2.8%) had hypertension. For the 36 pregnant controls without COVID-19, the median age was 31.0 years (IQR, 28.8–34.0), and the mean gestational age was 39.0 weeks (IQR, 38.4–39.9). No individual in the control group had comorbidity (Table 2).

Compared with nonpregnant women with severe or critical COVID-19, pregnant women with COVID-19 displayed similar changes of immunologic markers of WBC; lymphocyte count; WBC count; NLR; $CD3^+$, $CD4^+$, $CD8^+$, and $CD16^+CD56^+$ cell counts, and IL-6/10 (Figure 2, A and B); furthermore, compared with nonpregnant women with mild or moderate COVID-19, pregnant women with COVID-19 had increased WBC count, neutrophil count, NLR, and levels of D-dimer and FIB and decreased lymphocyte count and IL-4 level ($P<.05$) (Table 3 and Supplemental Table 4).

The most dramatic changes between pregnant women with COVID-19 and nonpregnant women with severe or critical COVID-19 were the variation of

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FIGURE 2
Comparison of the immunity index and laboratory characteristics between groups

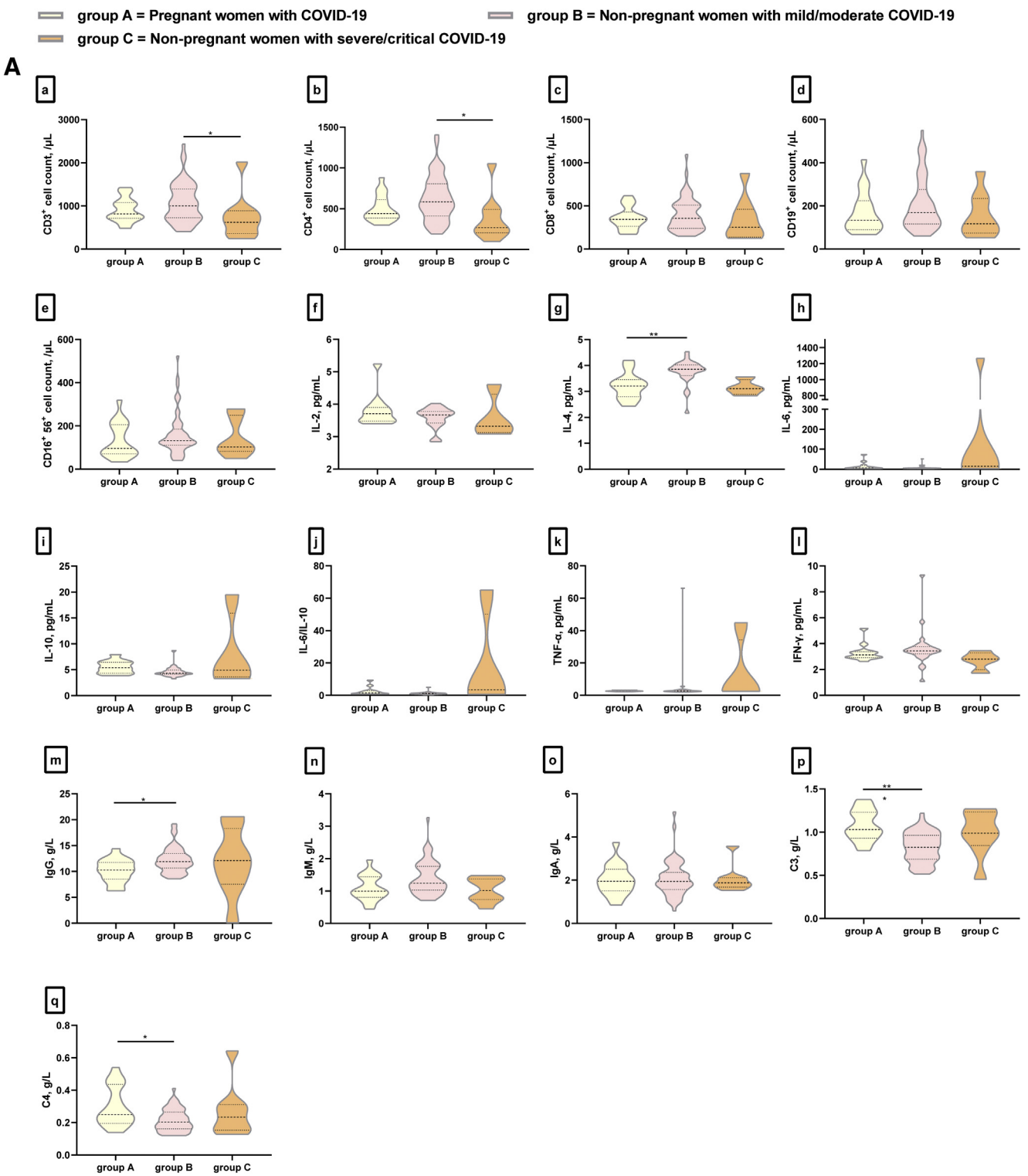

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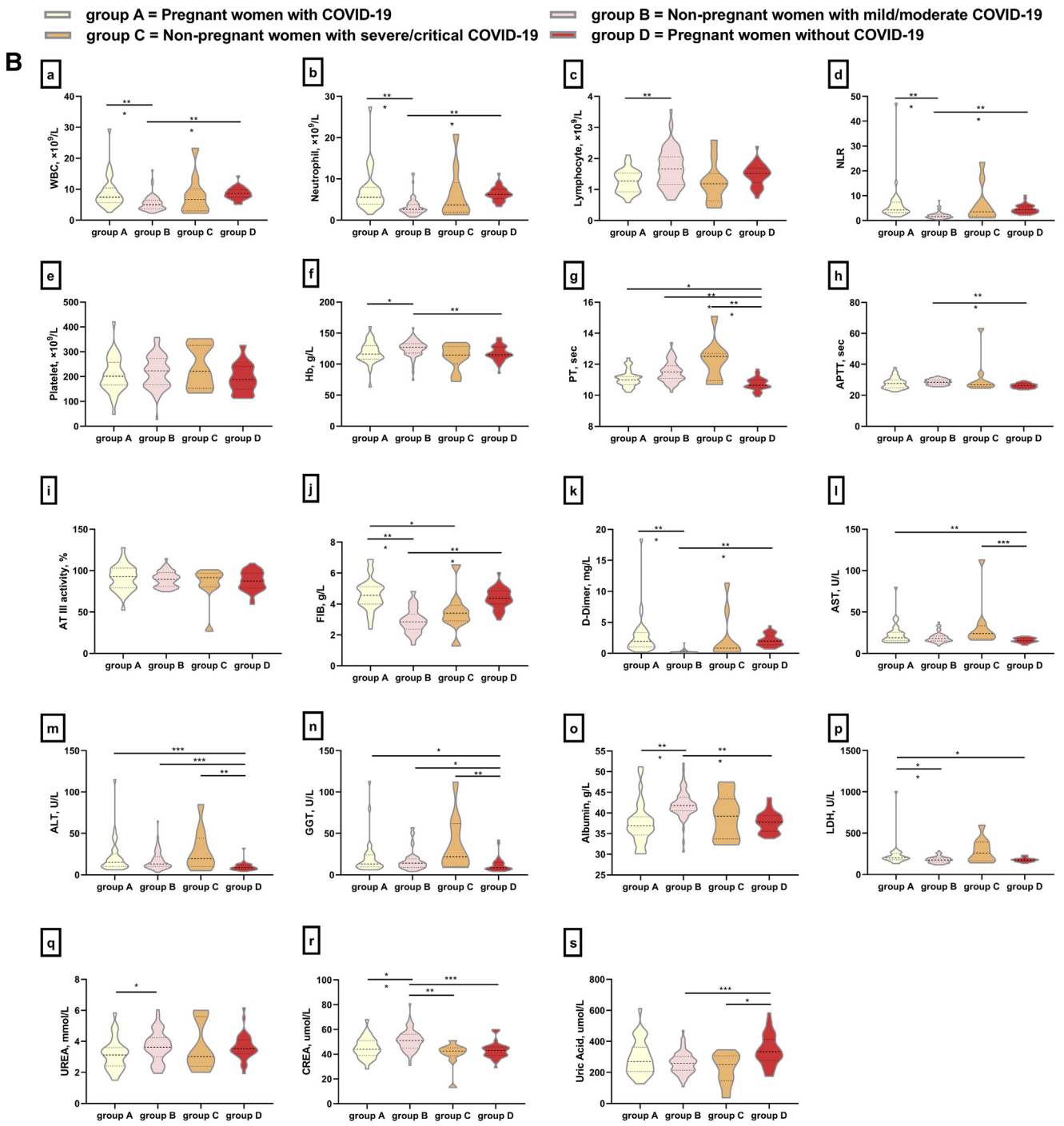
FIGURE 2
(*Continued*)



A, Cellular immune function ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16^+CD56^+$ cell count; **a**—**e**), cytokines (IL-2, IL-4, IL-6, IL-10, IL-6/10, TNF-α, IFN-γ; **f**—**l**), and humoral immune function (immunoglobulins, C3, C4; **m**—**q**) were shown. **B,** Complete blood count (WBC, neutrophil, lymphocyte, NLR, Hb; **a**—**f**), coagulation profile (PT, APTT, AT-III activity, FIB, D-dimer; **g**—**k**), liver function (AST, ALT, GGT; **l**—**n**), albumin (**o**), LDH (**p**), and kidney function (urea, CREA, uric acid; **q**—**s**) were shown. Group A, pregnant women with COVID-19 (n=36); Group B, nonpregnant women with mild or moderate COVID-19 (n=72); Group C, nonpregnant women with severe or critical COVID-19 (n=10); Group D, pregnant women without COVID-19 (n=36). Single asterisk indicates $P<.05$; double asterisk indicates $P<.01$; triple asterisk indicates $P<.001$

ALT, alanine aminotransferase; *APTT*, activated partial thromboplastin time; *AST*, aspartate aminotransferase; *AT-III activity*, antithrombin III activity; *C3*, complement 3; *C4*, complement 4; *COVID-19*, coronavirus disease 2019; *CREA*, creatinine; *FIB*, fibrinogen; *GGT*, γ-glutamyltranspeptidase; *Hb*, hemoglobin; *IFN-γ*, interferon-γ; *IgA*, immunoglobulin A; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M; *IL-2*, interleukin-2; *IL-4*, interleukin-4; *IL-6*, *interleukin-6*; *IL-10*, interleukin-10; *LDH*, lactate dehydrogenase; *NLR*, neutrophil-to-lymphocyte ratio; *PT*, prothrombin time; *ROC*, receiver operating characteristic; *WBC*, white blood cell.

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TABLE 3
Clinical laboratory indices between pregnant and nonpregnant patients with COVID-19 considering repeated tests by using the generalized estimating equation

Variable	Coefficient	SE	*t*	*P* value	95% CI	
WBC, $\times 10^9$/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−3.48	0.58	−6.01	<.001	−4.62	−2.35
Nonpregnant women with severe or critical COVID-19 (n=10)	−1.21	0.94	−1.29	.197	−3.05	0.63
Pregnant women without COVID-19 (n=36)	−0.13	0.70	−0.18	.858	−1.49	1.24
Neutrophil count, $\times 10^9$/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−3.83	0.52	−7.39	<.001	−4.85	−2.82
Nonpregnant women with severe or critical COVID-19 (n=10)	−1.28	0.83	−1.54	.123	−2.91	0.35
Pregnant women without COVID-19 (n=36)	−0.44	0.63	−0.70	.485	−1.67	0.80
Lymphocyte count, $\times 10^9$/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	0.41	0.12	3.43	.001	0.18	0.65
Nonpregnant women with severe or critical COVID-19 (n=10)	0.10	0.21	0.48	.630	−0.30	0.50
Pregnant women without COVID-19 (n=36)	0.17	0.14	1.21	.227	−0.11	0.44
NLR						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−4.08	0.67	−6.12	<.001	−5.38	−2.77
Nonpregnant women with severe or critical COVID-19 (n=10)	−0.44	1.04	−0.42	.671	−2.47	1.59
Pregnant women without COVID-19 (n=36)	−1.35	0.82	−1.64	.102	−2.96	0.27
$CD3^+$ cell count, cells/μL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	169.31	120.16	1.41	.159	−66.20	404.82
Nonpregnant women with severe or critical COVID-19 (n=10)	−28.65	173.96	−0.17	.869	−369.59	312.30
$CD4^+$ cell count, cells/μL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	122.63	75.06	1.63	.102	−24.49	269.75
Nonpregnant women with severe or critical COVID-19 (n=10)	−18.48	107.43	−0.17	.863	−229.04	192.07
$CD8^+$ cell count, cells/μL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	43.35	50.81	0.85	.394	−56.24	142.93
Nonpregnant women with severe or critical COVID-19 (n=10)	20.15	74.36	0.27	.786	−125.60	165.89
$CD19^+$ cell count, cells/μL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	34.22	33.63	1.02	.309	−31.70	100.14
Nonpregnant women with severe or critical COVID-19 (n=10)	47.41	46.58	1.02	.309	−43.90	138.71

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(continued)

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TABLE 3
Clinical laboratory indices between pregnant and nonpregnant patients with COVID-19 considering repeated tests by using the generalized estimating equation *(continued)*

Variable	Coefficient	SE	*t*	*P* value	95% CI	
$CD16^{+}CD56^{+}$ cell count, cells/μL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	28.24	23.93	1.18	.238	−18.67	75.14
Nonpregnant women with severe or critical COVID-19 (n=10)	5.72	33.68	0.17	.865	−60.28	71.73
IL-2, pg/mL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−0.14	0.13	−1.10	.273	−0.38	0.11
Nonpregnant women with severe or critical COVID-19 (n=10)	−0.29	0.18	−1.58	.114	−0.64	0.07
IL-4, pg/mL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	0.76	0.16	4.91	<.001	0.46	1.07
Nonpregnant women with severe or critical COVID-19 (n=10)	−0.46	0.22	−2.10	.036	−0.90	−0.03
IL-6, pg/mL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−8.42	49.56	−0.17	.865	−105.56	88.72
Nonpregnant women with severe or critical COVID-19 (n=10)	128.82	65.10	1.98	.048	1.24	256.41
IL-10, pg/mL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−0.74	0.78	−0.94	.345	−2.27	0.80
Nonpregnant women with severe or critical COVID-19 (n=10)	4.90	1.14	4.29	<.001	2.66	7.14
TNF-α, pg/mL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	3.29	3.36	0.98	.328	−3.31	9.88
Nonpregnant women with severe or critical COVID-19 (n=10)	7.00	5.30	1.32	.187	−3.40	17.39
IFN-γ, pg/mL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	0.28	0.33	0.87	.384	−0.35	0.92
Nonpregnant women with severe or critical COVID-19 (n=10)	−0.75	0.50	−1.49	.135	−1.73	0.23
PT, s						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	0.30	0.17	1.77	.077	−0.03	0.64
Nonpregnant women with severe or critical COVID-19 (n=10)	1.03	0.21	4.92	<.001	0.62	1.44
Pregnant women without COVID-19 (n=36)	−0.40	0.20	−1.99	.046	−0.80	−0.01
PTA, %						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−10.64	2.46	−4.33	<.001	−15.45	−5.83
Nonpregnant women with severe or critical COVID-19 (n=10)	−10.95	3.35	−3.26	.001	−17.52	−4.37

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TABLE 3
Clinical laboratory indices between pregnant and nonpregnant patients with COVID-19 considering repeated tests by using the generalized estimating equation *(continued)*

Variable	Coefficient	SE	*t*	*P* value	95% CI	
APTT, s						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	1.08	1.08	1.00	.319	−1.04	3.20
Nonpregnant women with severe or critical COVID-19 (n=10)	3.22	1.74	1.86	.063	−0.18	6.63
Pregnant women without COVID-19 (n=36)	−1.09	1.16	−0.93	.351	−3.37	1.20
FIB, g/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−1.60	0.18	−8.96	<.001	−1.95	−1.25
Nonpregnant women with severe or critical COVID-19 (n=10)	−0.88	0.26	−3.37	.001	−1.39	−0.37
Pregnant women without COVID-19 (n=36)	−0.12	0.20	−0.61	.541	−0.51	0.27
D-dimer, mg/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−2.33	0.57	−4.12	<.001	−3.45	−1.22
Nonpregnant women with severe or critical COVID-19 (n=10)	0.48	0.70	0.68	.494	−0.89	1.85
Pregnant women without COVID-19 (n=36)	−0.35	0.67	−0.52	.606	−1.66	0.97
FDP, mg/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−6.67	1.87	−3.57	<.001	−10.33	−3.01
Nonpregnant women with severe or critical COVID-19 (n=10)	2.26	2.29	0.99	.323	−2.22	6.74
AT-III activity, %						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−0.47	2.51	−0.19	.852	−5.38	4.44
Nonpregnant women with severe or critical COVID-19 (n=10)	−1.87	3.61	−0.52	.604	−8.96	5.21
Pregnant women without COVID-19 (n=36)	−2.62	2.80	−0.94	.349	−8.11	2.87

APTT, activated partial thromboplastin time; *AT-III activity*, antithrombin III activity; *CI*, confidence interval; *COVID-19*, coronavirus disease 2019; *FDP*, fibrinogen degradation product; *FIB*, fibrinogen; *IFN-γ*, interferon-γ; *IL-2*, interleukin-2; *IL-4*, interleukin-4; *IL-6*, interleukin-6; *IL-10*, interleukin-10; *NLR*, neutrophil-to-lymphocyte ratio; *PT*, prothrombin time; *PTA*, prothrombin activity; *Ref*, referent; *TNF-α*, tumor necrosis factor-α; *WBC*, white blood cell.

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the coagulation and fibrinolysis indicators, where the levels of FIB and D-dimer were significantly higher, with lower PT and activated partial thromboplastin time (APTT) values in pregnant women with COVID-19 ($P<.05$). To determine whether pregnancy itself caused these changes, the difference between pregnant women with COVID-19 and pregnant women without COVID-19 was further investigated. There was no significant difference in terms of WBC count, lymphocyte count, neutrophil count, NLR for immunologic markers, and coagulation and fibrinolysis markers (Figure 2, A and B). In our study, no pregnant woman with COVID-19 developed severe or critical illness. Compared with nonpregnant women with severe or critical COVID-19, there are significant differences in immunologic and coagulation and fibrinolysis indicators.

Laboratory markers to distinguish pregnant women with coronavirus disease 2019 from nonpregnant women with coronavirus disease 2019

In addition, the RF regression model was used to distinguish between 36 pregnant women with COVID-19 and 82 nonpregnant women with COVID-19. The model based on immunologic markers achieved an AUC of 0.898 (95% CI, 0.834−0.961) (Supplemental Table 5). More strikingly, for this grouping analysis, the model based on coagulation and fibrinolysis indices achieved an AUC of 0.949 (95% CI, 0.885−1.000). Meanwhile, the combined model with both immunologic markers and coagulation and fibrinolysis indices achieved the highest AUC of 0.942 (95% CI, 0.892−0.992). As for the difference between 36 pregnant women with COVID-19 and 10 nonpregnant women with severe or

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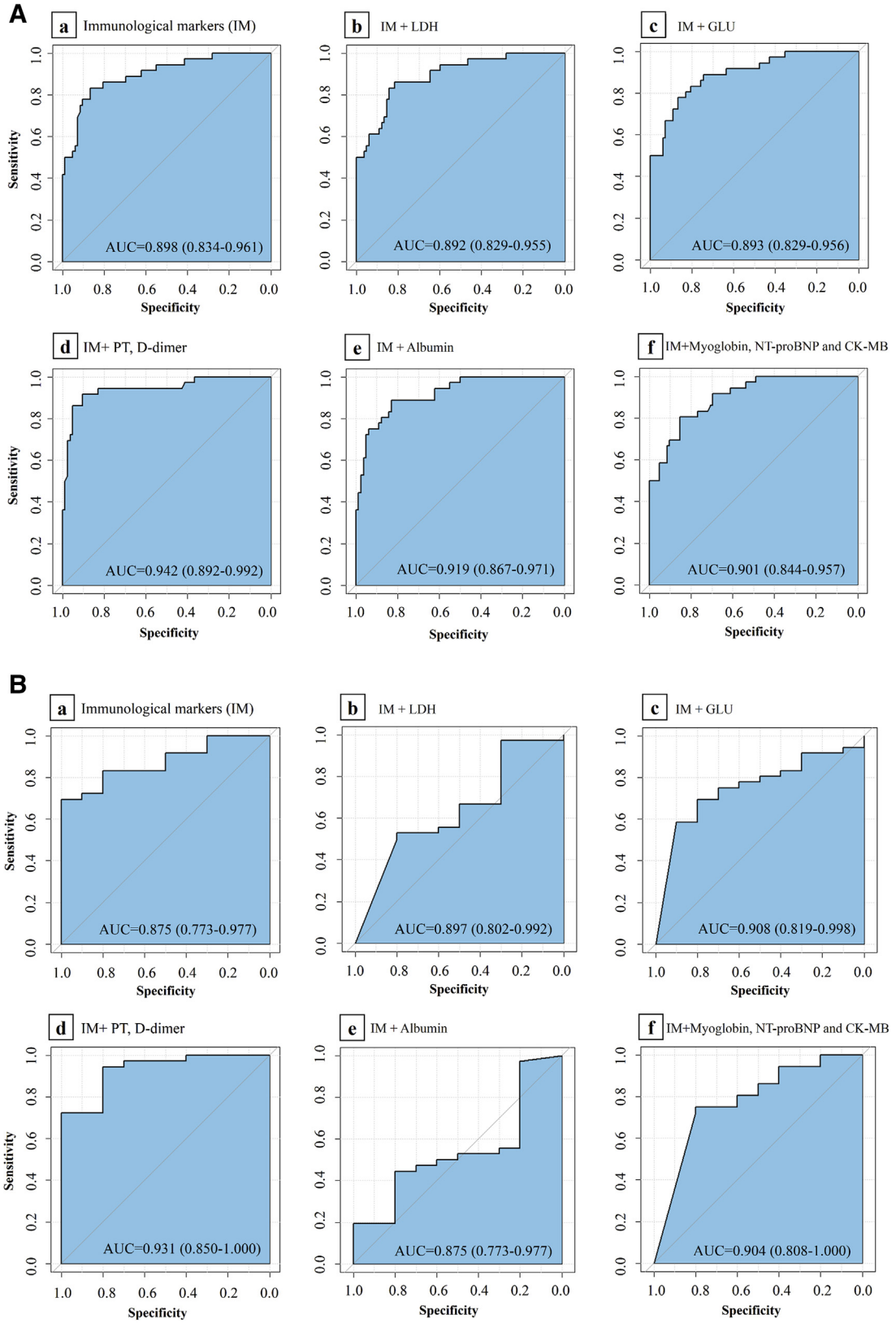
FIGURE 3
ROC curves for distinguishing between the pregnancy and non-pregnancy



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critical COVID-19, the model achieved an AUC of 0.875 (95% CI, 0.773−0.977) and 0.897 (95% CI, 0.766−1.000) based on immunologic and coagulation and fibrinolysis markers, respectively (Supplemental Table 4). The combined model with both immunologic markers and the coagulation and fibrinolysis indices (PT, D-dimer) also achieved the highest AUC of 0.931 (95% CI, 0.850−1.000) (Figure 3). The coagulation and fibrinolysis indices were demonstrated as the important indicator to distinguish pregnant women with COVID-19 from nonpregnant women with COVID-19.

Discussion

Principal findings

In this retrospective study with the clinical outcomes of patients with COVID-19, the immune dysregulation was identified as a vital feature of patients with COVID-19 who developed severe or critical illness, and pregnant women with COVID-19 presented similar immune response with nonpregnant women with severe or critical COVID-19 but rare incidence of severe or critical illness. Digging deeper into the discrepancy between pregnant women with COVID-19 and nonpregnant women with severe or critical COVID-19, the coagulation and fibrinolysis indices (PT, D-dimer) showed remarkable differences. However, for pregnancy itself, pregnant women without COVID-19 also demonstrated similar changes of immunologic markers, consisting of WBC, lymphocyte, neutrophil, and NLR, as the pregnant women with COVID-19.

Clinical implications

In our study, pregnant women with COVID-19 presented with milder symptoms and mild illness compared with nonpregnant women with COVID-19 of reproductive age. The result is partly consistent with a meta-analysis, including 13118 pregnant and 83486 nonpregnant women with COVID-19, which demonstrated that pregnant women with COVID-19 had milder symptoms. Although the meta-analysis indicated that pregnant women with COVID-19 were more likely to require admission to an intensive care unit (ICU) (1.62; 95% CI, 1.33−1.96; I^2=0%) at first glance, it was further elucidated that severe COVID-19 or requirement of admission to an ICU were actually associated with older age, obesity, and preexisting maternal comorbidities, such as hypertension and diabetes.[24] Our data also indicated that risks of severe and critical COVID-19 were associated with the above factors, in accordance with these reports. Most pregnant patients in our study had no comorbidities or complications, which may partly explain their mild to moderate illness. The maternal immune system is unique during normal pregnancy. However, to date, most of the published studies enrolling pregnant women with COVID-19 focused on maternal clinical manifestations and birth outcomes.[4,5,10,25] It is an urgent need to draw a clear picture of immunologic features in pregnant women with COVID-19.

In general, normal maternal immune system is actively modulated at different gestational stages. The first trimester of pregnancy is a proinflammatory state in favor of embryo implantation; the second trimester of pregnancy is bias toward T helper 2 (Th2)-type immune environment, which is actually an anti-inflammatory state benefiting fetal growth; and the third trimester of pregnancy changes to a second proinflammatory state featured by a Th1-type immune environment necessary for labor. Viral invasion switches the immune environment from the Th2 type to Th1 type and activates inflammation by overproduction of cytokines, including IL-6.[10] The pregnant women with COVID-19 in the third trimester of pregnancy were composed nearly 70% of the whole pregnant population in our study. This may explain why the immunologic files are similar between pregnant women with COVID-19 and pregnant women without COVID-19.

Our data indicated that for the general women population with COVID-19, the immune dysregulation mainly manifesting as increased IL-6, IL-10, and IL-6/10 levels and a decreased lymphocyte count and its subsets, along with increased NLR, is related to the risks of severe and critical illnesses. Pregnant women with COVID-19 demonstrated similar immune changes, but no severe illness occurred. The most dramatic discrepancy between pregnant women with COVID-19 and nonpregnant women with COVID-19 was the coagulation and fibrinolysis index variances.

The significant increase of IL-6 (proinflammatory cytokine), IL-10 (an anti-inflammatory cytokine) and IL-6/10 in severe or critical illness indicated that the host immune system switches to a predominantly proinflammatory state. It was reported that infection with SARS-CoV-2 triggers a proinflammatory response characterized by the production of IL-6, C-X-C motif chemokine 10, and type 1 interferons, which attract macrophages, monocytes, and T lymphocytes to infection sites.[26] However, in our study, there was no significant difference in terms of serum IL-2, IL-4, TNF-α, and IFN-γ levels within

The 36 pregnant women with COVID-19 and 82 nonpregnant women with COVID-19 (**A**) or 10 nonpregnant women with severe or critical COVID-19 (**B**) were extracted for this analysis. ROC curves for immunologic markers of NLR; $CD3^+$, $CD4^+$, $CD8^+$, and $CD16^+CD56^+$ cell counts; IL-6; IL-6/10; lymphocyte count; and WBC count (**a**); immunologic markers and LDH (**b**); immunologic markers and GLU (**d**); immunologic markers and PT and D-dimer (**d**); immunologic markers and albumin (**e**); immunologic markers and myoglobin, NT-proBNP, and CK-MB (**f**) were shown.

AUC, area under the ROC curve; *CK-MB*, creatine kinase-MB; *COVID-19*, coronavirus disease 2019; *GLU*, glucose; *IL-6*, interleukin-6; *IL-6/10*, interleukin-6—to—interleukin-10 ratio; *LDH*, lactate dehydrogenase; *IM*, immunologic marker; *NLR*, neutrophil-to-lymphocyte ratio; *NT-pro BNP*, N-terminal probrain natriuretic peptide; *PT*, prothrombin time; *ROC*, receiver operating characteristic; *WBC*, white blood cell.

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comparisons among defined subgroups. It demonstrates the heterogeneity of the host immune response to SARS-CoV-2.

It is notable that proinflammatory cytokines (mainly IL-6) are common triggers to induce the expression of tissue factor (TF) on both mononuclear cells and vascular endothelial cells. TF activates the transformation of prothrombin into thrombin, converts circulating FIB into fibrin and D-dimer, and results in thrombin generation and vascular endothelialitis in the extrinsic pathway.[27] In a normal and healthy pregnancy, increasing levels of plasminogen, D-dimer, and fibrin degradation products and decreasing levels of α-2 plasmin inhibitor and antiplasmin indicate activation of the fibrinolytic system. The expression and activity of TF secreted by monocytes are low in favor of preventing pregnant women from contracting venous thromboembolism, achieving a delicate balance between coagulation and anticoagulation.[28]

Another noteworthy result in our study is that coagulation dysfunction could be used as a marker to distinguish pregnant women with COVID-19 from nonpregnant women with COVID-19. Autopsy findings demonstrated diffuse endothelialitis and thrombosis in venous and arterial systems.[29,30] Ramlall et al[31] also found that a history of macular degeneration and history of coagulation disorders were risk factors for SARS-CoV-2—associated morbidity and mortality, supporting our results. The crucial delicate balance between coagulation and anticoagulation during pregnancy may ameliorate the adverse outcomes of SARS-CoV-2 infection.

Therefore, lymphopenia as a factor related to severe COVID-19 has been reported.[32−34] Our data indicated that the absolute counts of total lymphocyte and its subsets were decreased and sustained in severe and critical patients, along with increased NLR, predicting the risks for severe or critical COVID-19, in accordance with Qin's study[35] that lymphopenia, especially reduction of $CD4^+$ and $CD8^+$ T cells, was related with the deterioration and signs of poor prognosis.[36,37] In addition, neutrophil extracellular traps (NETs) released by neutrophils recruited at the infection sites could trigger thrombotic events by the intrinsic pathway.[38] Zuo et al[39] found significantly increased serum levels of cell-free DNA, a specific makers for NET in individuals with COVID-19, highlighting the role of neutrophils in the pathogenesis of immunothrombosis associated with COVID-19. Therefore, immunity disorders mainly consisting of increased IL-6, neutrophil, and NLR may trigger thrombotic events by extrinsic and intrinsic pathways simultaneously, promoting the pathologic process to severe COVID-19.

Research implications

The main finding of our study is the association between excessive immune response, coagulation-fibrinolysis dysregulation, and severity of the disease in both general population and pregnant subgroup. Given the unique immune state in pregnancy, as described before, a deeper investigation needs to be performed to figure out the exact mechanism between SARS-CoV-2—induced inflammation and coagulopathy. In addition, in a series of 11 autopsy cases of patients with severe COVID-19 from Australia, all cases found pulmonary arterial obstruction using thrombotic materials at both the macroscopic and microscopic levels. Interestingly, 10 of these cases received pharmacologic venous thrombus embolism (VTE) prophylaxis, and VTE was not clinically suspected in any cases before autopsy as a contributor of death.[18] A method to evaluate microcirculation disorders and identify early alert biomarkers is needed. Early anticoagulant therapy is implicated according to our study. However, the treatment timing, dose, indications, and drug combination need further clinical research.[40,41]

During pregnancy, a 28-amino acid pleiotropic polypeptide, called vasoactive intestinal peptide, could be synthesized by trophoblast cells, which possesses vasodilating, prosecretory, and anti-inflammatory effects, which might be assumed to be potential protective mechanisms against the physiological process of COVID-19 and need to be further investigated. Furthermore, the presence of pregnancy may lead to adaptive changes in maternal immunity to accept the existence of the fetus as a semialien. Likewise, it is also possible that there is an unknown mechanism temporarily in mater compromising the invasion of SARS-CoV-2. Therefore, long-term follow-up of pregnant women with COVID-19 and their offspring is necessary. Therefore, we are also concerned about microcirculatory impairments related to endothelialitis and microangiopathy, because some adverse pregnant outcomes, for example, preeclampsia and hemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome), are caused by this physiological change.[42]

Strengths and limitations

The strengths of the study include using machine learning algorithm to clinical data sets for the purpose of developing robust risk models of COVID-19 and comparing pregnant women with COVID-19 and age-matched nonpregnant women with severe or critical COVID-19 to indicate the factors that may reduce pregnant women with COVID-19 from deteriorating into severe illness. The limitations of our study include a single-center retrospective design and a small sample size of age-matched nonpregnant women with severe or critical COVID-19. Further research is needed to elucidate the mechanisms of pregnancy dealing with COVID-19.

Conclusion

Immune dysregulation is a crucial feature of the development of severe or critical illness in patients with COVID-19. The activation and balance of the coagulation and fibrinolysis systems during pregnancy may reduce the risk of women with COVID-19 from developing severe illness. ■

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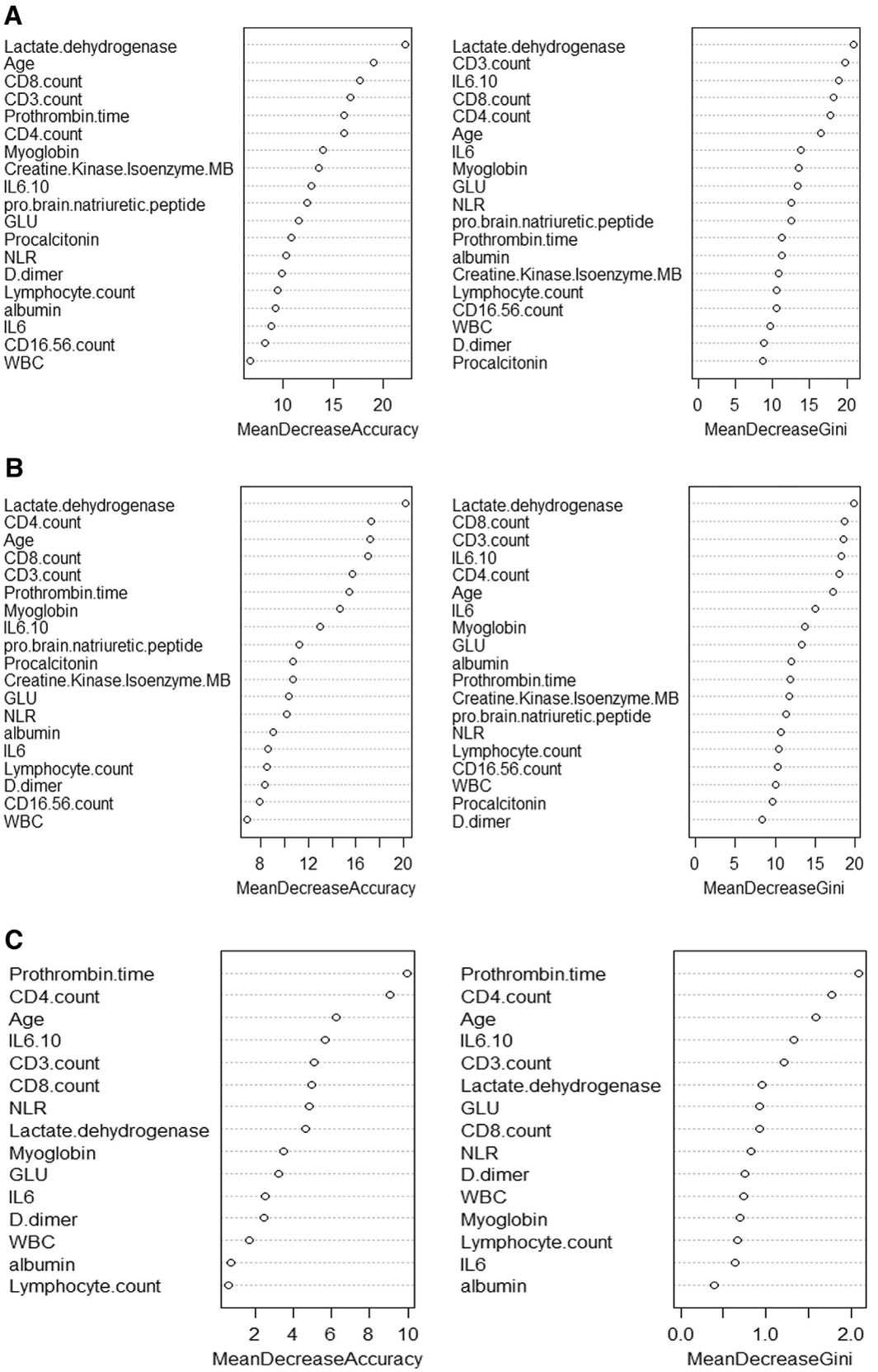
SUPPLEMENTAL FIGURE
Scaled relative variable importance for the full predictive mode



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SUPPLEMENTAL TABLE 1
Antibodies used in flow cytometry

Protein	Company	Product code
Cytokine (Th1 or Th2 subgroup: IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ)	CellGene Biotech Co, Ltd, Hang Zhou, China	0032
Lymphocyte subpopulation (CD3, CD4, CD8, CD19, CD16, CD56)	Becton, Dickinson and Company, United States	65241

C3, complement 3; *C4*, complement 4; *IFN-γ*, interferon-γ; *IgA*, immunoglobulin A; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M; *IL-2*, interleukin-2; *IL-4*, interleukin-4; *IL-6*, interleukin-6; *IL-10*, interleukin-10; *TNF-α*, tumor necrosis factor-α.

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SUPPLEMENTAL TABLE 2
Comparison of laboratory characteristics of patients with COVID-19 with different illness severity on admission

Variable	Mild (n=22)	Moderate (n=297)	Severe (n=169)	Critical (n=51)	*P* value
WBC, $\times 10^9$/L	6.3 (5.0–7.6)	5.4 (4.0–6.6)	5.7 (4.3–8.2)	8.9 (6.1–12.6)[b,c]	<.001
<4.0	2/22 (9.1)	69/292 (23.6)	36/169 (21.3)	4/49 (8.2)	
>10.0	3/22 (13.6)	19/292 (6.5)	24/169 (14.2)	18/49 (36.7)	
Neutrophil count, $\times 10^9$/L	3.1 (2.5–5.7)	3.3 (2.3–4.4)	4.1 (2.6–6.3)[b]	7.3 (4.7–11.0)[a,b,c]	<.001
<1.8	1/22 (4.5)	41/292 (14.0)	11/169 (6.5)	3/49 (6.1)	
>6.3	5/22 (22.7)	32/292 (11.0)	42/169 (24.9)	31/49 (63.3)	
Lymphocyte count, $\times 10^9$/L	1.8 (1.4–2.3)	1.3 (0.9–1.7)[a]	0.9 (0.7–1.3)[a,b]	0.7 (0.5–0.9)[a,b,c]	<.001
<0.8	1/22 (4.5)	42/292 (14.4)	57/169 (33.7)	34/49 (69.4)	
NLR	2.1 (1.3–3.8)	2.4 (1.6–3.8)	4.0 (2.5–8.8)[a,b]	12.4 (5.5–17.2)[a,b,c]	<.001
Platelet count, $\times 10^9$/L	233.0 (166.0–275.8)	210.0 (154.3–267.8)	208.0 (152.5–271.0)	188.0 (133.0–229.5)	.103
<100	1/22 (4.5)	7/292 (2.4)	13/169 (7.7)	6/49 (12.2)	
Hb, g/L	129.0 (110.5–132.5)	126.0 (116.0–137.0)	123.0 (111.0–136.0)	129.5 (111.5–141.5)	.154
Male <120 g/L	1/4 (25.0)	16/114 (14.0)	15/84 (17.9)	8/34 (23.5)	
Female <110 g/L	4/18 (22.2)	24/177 (13.6)	27/85 (31.8)	8/16 (50.0)	
$CD3^+$ cell count, cells/μL	1173.5 (925.5–1415.8)	810.0 (616.0–1138.5)	538.0 (364.0–841.0)[a,b]	331.0 (218.0–576.0)[a,b,c]	<.001
<723	3/18 (16.7)	89/237 (37.6)	103/155 (66.5)	38/43 (88.4)	
$CD4^+$ cell count, cells/μL	685.5 (521.5–889.0)	488.0 (338.0–662.0)	316.0 (209.0–511.0)[a,b]	195.0 (139.0–320.0)[a,b,c]	<.001
<404	3/18 (16.7)	79/237 (33.3)	98/155 (63.2)	37/43 (86.0)	
$CD8^+$ cell count, cells/μL	455.5 (326.8–646.3)	290.0 (198.0–400.5)	194.0 (108.0–307.0)[a,b]	120.0 (64.0–206.0)[a,b]	<.001
<220	3/18 (16.7)	75/237 (31.6)	91/155 (58.7)	33/43 (76.7)	
$CD19^+$ cell count, cells/μL	201.5 (136.0–354.3)	146.0 (98.0–229.0)	138.0 (79.0–208.0)[a]	95.0 (60.0–147.0)[a,b]	<.001
<80	0/18 (0.0)	32/237 (13.5)	40/155 (25.8)	16/43 (37.2)	
$CD16^+CD56^+$ cell count, cells/μL	205 (155.0–327.8)	129.0 (84.5–194.5)[a]	108.0 (70.0–165.0)[a]	86.0 (43.0–154.0)[a,b]	<.001

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A, Scaled relative variable importance for the full predictive model of distinguishing severe and critical illnesses among patients with COVID-19. **B,** Scaled relative variable importance for the full predictive model of distinguishing between pregnant women with COVID-19 and nonpregnant women with COVID-19. **C,** Scaled relative variable importance for the full predictive model of distinguishing between pregnant women with COVID-19 and nonpregnant women with severe or critical COVID-19.

CK-MB, creatine kinase-MB; *GLU*, glucose; *IL-6/10*, interleukin-6—to—interleukin-10 ratio; *LDH*, lactate dehydrogenase; *NLR*, neutrophil-to-lymphocyte ratio; *NT-proBNP*, N-terminal probrain natriuretic peptide; *PCT*, procalcitonin; *PT*, prothrombin time; *RF*, random forest; *WBC*, white blood cell.

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SUPPLEMENTAL TABLE 2

Comparison of laboratory characteristics of patients with COVID-19 with different illness severity on admission

(continued)

Variable	Mild (n=22)	Moderate (n=297)	Severe (n=169)	Critical (n=51)	*P* value
<84	0/18 (0.0)	57/237 (24.1)	54/155 (34.8)	21/43 (48.8)	
IL-2, pg/mL	3.5 (3.3–3.9)	3.7 (3.4–4.0)	3.6 (3.2–4.1)	3.6 (3.2–4.1)	.591
IL-4, pg/mL	3.5 (3.1–3.9)	3.8 (3.0–4.1)	3.2 (2.9–3.7)	3.3 (3.0–3.6)	.063
IL-6, pg/mL	4.4 (3.6–5.9)	5.7 (4.7–8.6)	6.2 (4.3–10.6)	43.2 (16.4–102.8)[a,b,c]	<.001
>20.0	0/13 (0.0)	10/87 (11.5)	11/78 (14.1)	18/26 (69.2)	
>60.0	0/13 (0.0)	3/87 (3.4)	1/78 (1.3)	9/26 (34.6)	
IL-10, pg/mL	4.4 (4–5.6)	5.3 (4.6–6.4)	5.5 (4.7–6.6)	8.5 (6.7–14.4)[a,b,c]	<.001
>5.9	2/13 (15.4)	26/77 (33.8)	21/53 (39.6)	23/26 (88.5)	
>17.7	0/13 (0.0)	0/77 (0.0)	0/53 (0.0)	6/26 (23.1)	
IL-6/10	0.9 (0.8–1.7)	1.1 (0.9–1.5)	1.3 (1.0–1.9)	4.2 (2.3–8.7)[a,b,c]	<.001
TNF-α, pg/mL	2.9 (2.2–3.2)	2.9 (2.6–3.9)	3.3 (2.8–3.9)	3.0 (2.7–3.5)	.125
>5.5	0/13 (0.0)	9/77 (11.7)	9/53 (17.0)	2/26 (7.7)	
>16.3	0/13 (0.0)	3/77 (3.9)	3/53 (5.7)	0/26 (0.0)	
IFN-γ, pg/mL	3.3 (2.9–3.4)	3.4 (3.0–4.0)	3.2 (2.8–4.1)	3.5 (3.1–4.1)	.285
>18	0/13 (0.0)	2/77 (2.6)	3/53 (5.7)	0/26 (0.0)	
>54	0/13 (0.0)	2/77 (2.6)	1/53 (1.9)	0/26 (0.0)	
hs CRP>5 mg/L	4/17 (23.5)	129/214 (60.3)[a]	105/134 (78.4)[a,b]	41/42 (97.6)[a,b]	<.001
PCT>0.1 ng/mL	1/16 (6.3)	29/233 (12.4)	56/163 (34.4)[b]	35/48 (72.9)[a,b,c]	<.001
IgG, g/L	11.6 (9.5–13.6)	11.8 (10.0–13.8)	11.9 (10.0–14.6)	13.1 (10.9–15.3)	.271
<7	0/18 (0.0)	3/228 (1.3)	3/151 (2.0)	0/40 (0.0)	
>16	0/18 (0.0)	29/228 (12.7)	26/151 (17.2)	7/40 (17.5)	
IgM, g/L	1.2 (0.8–1.9)	1.0 (0.7–1.3)	0.9 (0.6–1.2)	0.9 (0.7–1.3)	.035
<0.4	1/18 (5.6)	4/228 (1.8)	5/151 (3.3)	3/40 (7.5)	
>2.3	2/18 (11.1)	4/228 (1.8)	3/151 (2.0)	1/40 (2.5)	
IgA, g/L	2.1 (1.8–2.5)	2.2 (1.6–2.8)	2.5 (1.9–3.2)[b]	3.0 (1.8–3.8)[b]	<.001
<0.7	1/18 (5.6)	4/228 (1.8)	1/151 (0.7)	0/40 (0.0)	
>4.0	1/18 (5.6)	11/228 (4.8)	18/151 (11.9)	8/40 (20.0)	
IgE>100 IU/mL	6/18 (33.3)	158/228 (25.4)	44/151 (29.1)	12/40 (30.0)	.772
C3, g/L	0.9 (0.7–1.0)	1.0 (0.8–1.1)	1.0 (0.9–1.2)	1.0 (0.8–1.2)	.022
<0.9	9/18 (50.0)	80/228 (35.1)	44/151 (29.1)	12/40 (30.0)	
>1.8	0/18 (0.0)	1/228 (0.4)	0/151 (0.0)	1/40 (2.5)	
C4, g/L	0.2 (0.1–0.3)	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.3 (0.2–0.3)	.493
<0.1	0/18 (0.0)	6/228 (2.6)	10/151 (6.6)	0/40 (0.0)	
>0.4	2/18 (11.1)	19/228 (8.3)	10/151 (6.6)	4/40 (10.0)	
PT, s	11 (10.7–11.8)	11.6 (11.1–12.2)	12.2 (11.5–13.0)[a,b]	12.2 (11.7–13.4)[a,b]	<.001
≥16	0/19 (0.0)	0/252 (0.0)	2/161 (1.2)	2/46 (4.3)	
PTA,	93.0 (85.5–102.9)	89.7 (81.7–98.8)	80.2 (71.9–93.2)[a,b]	82.9 (67.8–90.4)[a,b]	<.001
APTT, s	26.8 (24.9–29.9)	27.7 (25.7–29.9)	27.7 (25.9–30.5)	29.1 (26.8–31.2)	.098

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SUPPLEMENTAL TABLE 2

Comparison of laboratory characteristics of patients with COVID-19 with different illness severity on admission

(continued)

Variable	Mild (n=22)	Moderate (n=297)	Severe (n=169)	Critical (n=51)	*P* value
>31.3	0/19 (0.0)	43/250 (17.2)	32/160 (20.0)	11/46 (23.9)	
FIB, g/L	2.7 (1.9–4.1)	3.5 (2.8–4.7)	4.3 (3.2–5.7)[a,b]	5.0 (3.3–5.9)[a,b]	<.001
>5	5/19 (26.3)	94/250 (37.6)	88/160 (55.0)	30/47 (63.8)	
D-dimer, mg/L	0.3 (0.2–1.8)	0.5 (0.3–1.5)	0.8 (0.4–2.3)[a,b]	2.8 (1.2–8.8)[a,b,c]	<.001
>0.55	7/19 (36.8)	120/250 (48.0)	99/160 (61.9)	44/47 (93.6)	
FDP, mg/L	0.6 (0.3–6.5)	1.6 (0.6–5.2)	3.0 (1.1–9.4)[a,b]	10.3 (4.6–30.9)[a,b,c]	<.001
>5	5/19 (26.3)	67/250 (26.8)	57/160 (35.6)	32/47 (68.1)	
AT-III activity,	84.6 (78.8–95.5)	90.9 (82.4–97.6)	84.6 (78.2–93.2)[b]	83.4 (72.6–89.6)[b]	<.001
>120	0/19 (0.0)	4/250 (1.6)	0/160 (0.0)	0/47 (0.0)	
AST, U/L	17.0 (15.0–22.0)	23.0 (18.0–32.0)	30.0 (21.0–43.0)[a,b]	37.5 (24.3–56.0)[a,b]	<.001
>40	1/21 (4.8)	32/283 (11.3)	45/168 (26.8)	19/48 (39.6)	
ALT, U/L	13.0 (8.0–28.0)	21.0 (13.0–34.0)	27.0 (17.3–45.0)[a,b]	28.5 (16.3–45.8)[a]	<.001
>50	2/21 (9.5)	36/283 (12.7)	36/168 (21.4)	10/48 (20.8)	
GGT, U/L	14.0 (10.0–29.0)	23.0 (14.0–44.0)	33.0 (17.5–60.5)[a,b]	43.0 (18.0–120.3)[a,b]	<.001
>60	1/21 (4.8)	43/281 (15.3)	41/165 (24.8)	16/48 (33.3)	
Albumin, g/L	42.0 (39.1–43.3)	39.1 (36.1–42.0)	36.0 (32.9–38.8)[a,b]	34.2 (31.1–37.5)[a,b]	<.001
<40	8/21 (38.1)	157/282 (55.7)	134/163 (82.2)	43/48 (89.6)	
LDH, U/L	165.0 (146.5–195.3)	209.0 (177.0–269.3)[a]	291.5 (217.3–412.0)[a,b]	458.0 (276.0–641.0)[a,b,c]	<.001
>250	1/20 (5.0)	86/270 (31.9)	96/160 (60.0)	40/47 (85.1)	
Urea, mmol/L	4.2 (3.3–4.9)	4.0 (3.3–5.2)	5.0 (3.8–7.4)[b]	6.5 (5.1–10.9)[a,b,c]	<.001
>8.0	0/21 (0.0)	12/282 (4.3)	33/167 (19.8)	18/47 (38.3)	
CREA, μmol/L	50.0 (45.5–57)	56.0 (49.0–69.0)	63.0 (48.0–75.0)	66.0 (52.0–81.3)[a,b]	.002
>97	0/21 (0.0)	8/282 (2.8)	18/167 (10.8)	7/48 (14.6)	
eGFR, mL/min	125.5 (103.5–130.5)	107.5 (95.5–120.6)[a]	96.7 (87.9–109.1)[a,b]	92.1 (78.2–104.1)[a,b]	<.001
<90	2/21 (9.5)	41/281 (14.6)	51/167 (30.5)	21/48 (43.8)	
CK-MB, ng/mL	0.7 (0.4–1.2)	0.8 (0.6–1.1)	1.1 (0.7–2.3)[b]	1.6 (0.8–3.5)[a,b]	<.001
>10	0/11 (0.0)	1/182 (0.5)	6/155 (3.9)	2/45 (4.4)	
Myoglobin, μg/L	25.9 (18.8–37.3)	32.2 (22.7–44.7)	44.2 (28.1–87.7)[a,b]	65.7 (31.6–127.1)[a,b]	<.001
>200	0/11 (0.0)	1/182 (0.5)	23/155 (14.8)	9/45 (20.0)	
CTnI, >0.08 ng/mL	0/11 (0.0)	2/182 (1.1)	15/155 (9.7)	8/45 (17.8)	<.001
NT-proBNP, pg/mL	48.2 (24.7–78.6)	51.4 (21.8–160.7)	211.1 (58.0–475.6)[a,b]	580.4 (167.8–1147.0)[a,b,c]	<.001
>900	0/10 (0.0)	8/143 (5.6)	18/142 (12.7)	15/44 (34.1)	
GLU, mmol/L	4.6 (4.2–5.2)	5.1 (4.6–6.1)	6.0 (5.3–7.4)[a,b]	6.9 (5.4–8.7)[a,b]	<.001
≥5.6	1/21 (4.8)	98/282 (34.8)	106/167 (63.5)	34/49 (69.4)	
Serum calcium, mmol/L	2.3 (2.2–2.3)	2.2 (2.1–2.3)[a]	2.1 (2.0–2.2)[a,b]	2.0 (2.0–2.2)[a,b]	<.001
<2.1	1/21 (4.8)	78/283 (27.6)	88/167 (52.7)	29/48 (60.4)	
Uric acid, μmol/L	277.0 (213.0–313.0)	268.5 (218.3–328.3)	262.0 (194.0–341.0)	219.5 (156.8–344.3)	.277
>428	0/21 (0.0)	24/282 (8.5)	14/167 (8.4)	9/48 (18.8)	

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(continued)

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SUPPLEMENTAL TABLE 2
Comparison of laboratory characteristics of patients with COVID-19 with different illness severity on admission
(continued)

Variable	Mild (n=22)	Moderate (n=297)	Severe (n=169)	Critical (n=51)	*P* value
Serum potassium, mmol/L	4.1 (3.9–4.2)	4.0 (3.7–4.3)	4.0 (3.5–4.4)	3.9 (3.6–4.6)	.633
<3.5	0/21 (0.0)	37/285 (13.0)	38/165 (23.0)	10/48 (20.8)	
>5.3	0/21 (0.0)	7/285 (2.5)	7/165 (4.2)	5/48 (10.4)	
Serum natrium, mmol/L	140.0 (139.0–144.5)	141.0 (139.0–144.0)	141.0 (137.0–144.0)	141.0 (137.0–144.0)	.820
<137	2/21 (9.5)	23/284 (8.1)	32/167 (19.2)	11/49 (22.4)	
Serum chloride, mmol/L	106.0 (104.8–108.4)	105.5 (103.5–107.6)	106.0 (103.0–108.4)	104.0 (100.3–107.8)	.066
<99	1/21 (4.8)	6/283 (2.1)	11/167 (6.6)	9/48 (18.8)	
Serum magnesium, mmol/L	0.8 (0.7–0.9)	0.8 (0.8–0.9)	0.8 (0.8–0.9)	0.9 (0.8–0.9)[b]	.005
<0.75	5/21 (23.8)	55/284 (19.4)	19/166 (11.4)	6/48 (12.5)	
Anion gap, mmol/L	13.5 (11.2–17.1)	14.2 (11.6–16.5)	14.2 (11.5–17.1)	15.3 (12.1–18.0)	.394
<12	6/21 (28.6)	79/281 (28.1)	52/167 (31.1)	11/47 (23.4)	
>20	2/21 (9.5)	10/281 (3.6)	12/167 (7.2)	9/47 (19.1)	
Osmotic pressure, mosm/L	289.6 (275.7–295.6)	284.6 (279.0–292.9)	283.8 (276.9–291.9)	284.8 (278.3–294.9)	.625
<280	8/21 (38.1)	86/281 (30.6)	59/167 (35.3)	15/47 (31.9)	
>310	0/21 (0.0)	1/281 (0.4)	7/167 (4.2)	4/47 (8.5)	

Data are presented as number (percentage) or median (interquartile range).

ALT, alanine aminotransferase; *APTT*, activated partial thromboplastin time; *AST*, aspartate aminotransferase; *AT-III activity*, antithrombin III activity; *C3*, complement 3; *C4*, complement 4; *CK-MB*, creatine kinase-MB; *COVID-19*, coronavirus disease 2019; *CREA*, creatinine; *CTnI*, cardiac troponin I; *eGFR*, estimate glomerular filtration rate; *FDP*, fibrinogen degradation product; *FIB*, fibrinogen; *GGT*, γ-glutamyl transpeptidase; *GLU*, glucose; *Hb*, hemoglobin; *hs CRP*, hypersensitive c-reactive protein; *IFN-γ*, interferon-γ; *IgA*, immunoglobulin A; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M; *IL-2*, interleukin-2; *IL-4*, interleukin-4; *IL-6*, interleukin-6; *IL-10*, interleukin-10; *IL-6/10*, interleukin-6—to—interleukin-10 ratio; *LDH*, lactate dehydrogenase; *NLR*, neutrophil-to-lymphocyte ratio; *NT-proBNP*, N-terminal probrain natriuretic peptide; *PCT*, procalcitonin; *PT*, prothrombin time; *PTA*, prothrombin activity; *SE*, standard error; *TNF-α*, tumor necrosis factor-α; *WBC*, white blood cell.

[a] Compared with the mild subgroup, $P<.05$; [b] Compared with the moderate subgroup, $P<.05$; [c] Compared with the severe subgroup, $P<.05$.

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SUPPLEMENTAL TABLE 3
The power of different models to distinguish severe and critical illnesses among the total patients with COVID-19

Different models with relative variables		AUC (95% CI)
1	LC, WBC, NLR, CD3, CD4, CD8, CD16/56, IL-6/10, and IL-6	0.801 (0.764–0.838)
2	LDH	0.690 (0.645–0.736)
3	GLU	0.606 (0.557–0.655)
4	Prothrombin time and D-dimer	0.670 (0.624–0.716)
5	Albumin	0.628 (0.581–0.675)
6	Myoglobin, NT-proBNP, and CK-MB	0.755 (0.715–0.796)
7	Age	0.688 (0.643–0.733)
8	The full predictive model	0.839 (0.807–0.872)

The 220 cases of severe or critical illness with COVID-19 and 319 cases of mild or moderate illness with COVID-19 were used for this analysis. AUCs of 9 models with relative variables were calculated. Model 1 was also calculated in 3 subgroups. From model 2 to model 8, each separate AUC and cumulated combined AUC based on model 1 was calculated.

AUC, area under the ROC curve; *CD3*, $CD3^+$ cell count; *CD4*, $CD4^+$ cell count; *CD8*, $CD8^+$ cell count; *CD16/56*, $CD16^+CD56^+$ cell count; *CI*, confidence interval; *CK-MB*, creatine kinase-MB; *COVID-19*, coronavirus disease 2019; *IL-6*, interleukin-6; *IL-6/10*, interleukin-6—to—interleukin-10 ratio; *LC*, lymphocyte count; *LDH*, lactate dehydrogenase; *NLR*, neutrophil-to-lymphocyte ratio; *NT-proBNP*, N-terminal probrain natriuretic peptide; *ROC*, receiver operating characteristic; *WBC*, white blood cell.

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SUPPLEMENTAL TABLE 4

Supplemental clinical laboratory indices between pregnant and nonpregnant patients with COVID-19 considering repeated tests by using generalized estimating equation

Variable	Coefficient	SE	*t*	*P* value	95% CI	
AST, U/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−0.90	3.18	−0.28	.776	−7.14	5.34
Nonpregnant women with severe or critical COVID-19 (n=10)	12.88	4.03	3.20	.001	4.98	20.78
Pregnant women without COVID-19 (n=36)	−6.60	4.00	−1.65	.099	−14.44	1.24
ALT, U/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−2.01	5.42	−0.37	.710	−12.63	8.60
Nonpregnant women with severe or critical COVID-19 (n=10)	3.58	8.66	0.41	.680	−13.39	20.54
Pregnant women without COVID-19 (n=36)	−11.00	6.27	−1.75	.079	−23.29	1.29
GGT, U/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−1.58	4.10	−0.39	.699	−9.61	6.45
Nonpregnant women with severe or critical COVID-19 (n=10)	23.68	6.19	3.83	<.001	11.56	35.80
Pregnant women without COVID-19 (n=36)	−8.85	4.80	−1.85	.065	−18.26	0.55
Albumin, g/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	4.82	0.87	5.51	<.001	3.11	6.53
Nonpregnant women with severe or critical COVID-19 (n=10)	0.97	1.37	0.71	.479	−1.72	3.66
Pregnant women without COVID-19 (n=36)	0.79	1.02	0.78	.438	−1.20	2.78
LDH, U/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−56.89	17.79	−3.20	.001	−91.76	−22.03
Non or pregnant women with severe or critical COVID-19 (n=10)	43.10	26.02	1.66	.098	−7.90	94.10
Pregnant women without COVID-19 (n=36)	−56.13	20.90	−2.69	.007	−97.08	−15.17
Urea, mmol/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	0.50	0.20	2.45	.014	0.10	0.90
Nonpregnant women with severe or critical COVID-19 (n=10)	0.36	0.32	1.14	.254	−0.26	0.98
Pregnant women without COVID-19 (n=36)	0.46	0.24	1.95	.052	0.00	0.93
CREA, μmol/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	5.53	1.64	3.38	.001	2.33	8.73
Nonpregnant women with severe or critical COVID-19 (n=10)	−6.01	2.62	−2.30	.022	−11.14	−0.88
Pregnant women without COVID-19 (n=36)	−2.08	1.90	−1.10	.272	−5.80	1.63
eGFR, mL/min						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−6.12	2.23	−2.74	.006	−10.49	−1.74
Nonpregnant women with severe or critical COVID-19 (n=10)	6.91	3.26	2.12	.034	0.53	13.30
Pregnant women without COVID-19 (n=36)	2.41	2.64	0.91	.362	−2.77	7.59

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SUPPLEMENTAL TABLE 4

Supplemental clinical laboratory indices between pregnant and nonpregnant patients with COVID-19 considering repeated tests by using generalized estimating equation *(continued)*

Variable	Coefficient	SE	*t*	*P* value	95% CI	
CK-MB, ng/mL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−0.09	0.14	−0.69	.492	−0.36	0.17
Nonpregnant women with severe or critical COVID-19 (n=10)	−0.03	0.17	−0.15	.884	−0.36	0.31
Myoglobin, μg/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	2.19	3.87	0.57	.571	−5.40	9.78
Nonpregnant women with severe or critical COVID-19 (n=10)	6.01	4.84	1.24	.214	−3.48	15.50
CTnI, ng/mL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	0.00	0.00	−1.19	.233	0.00	0.00
Nonpregnant women with severe or critical COVID-19 (n=10)	0.00	0.00	0.32	.749	0.00	0.00
NT-proBNP, pg/mL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−179.06	80.63	−2.22	.026	−337.09	−21.02
Nonpregnant women with severe or critical COVID-19 (n=10)	−132.58	98.06	−1.35	.176	−324.77	59.61
GLU, mmol/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	0.34	0.29	1.17	.241	−0.23	0.90
Nonpregnant women with severe or critical COVID-19 (n=10)	1.45	0.41	3.55	<.001	0.65	2.25
Pregnant women without COVID-19 (n=36)	−0.32	0.12	−2.68	.007	−0.55	−0.09
Serum calcium, mmol/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−0.01	0.02	−0.37	.709	−0.06	0.04
Nonpregnant women with severe or critical COVID-19 (n=10)	−0.05	0.04	−1.30	.195	−0.12	0.02
Pregnant women without COVID-19 (n=36)	−0.05	0.03	1.79	.073	−0.01	0.10
Uric acid, μmol/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−33.29	17.48	−1.91	.057	−67.55	0.97
Nonpregnant women with severe or critical COVID-19 (n=10)	−75.15	27.17	−2.77	.006	−128.41	−21.90
Pregnant women without COVID-19 (n=36)	49.97	20.48	2.44	.015	9.83	90.12
Serum potassium, mmol/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	0.18	0.09	1.92	.055	0.00	0.36
Nonpregnant women with severe or critical COVID-19 (n=10)	−0.04	0.13	−0.30	.767	−0.30	0.22
Pregnant women without COVID-19 (n=36)	0.10	0.11	0.87	.386	−0.12.	0.32

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SUPPLEMENTAL TABLE 4

Supplemental clinical laboratory indices between pregnant and nonpregnant patients with COVID-19 considering repeated tests by using generalized estimating equation *(continued)*

Variable	Coefficient	SE	*t*	*P* value	95% CI	
Serum natrium, mmol/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−064	0.72	−0.89	.376	−2.06	0.78
Nonpregnant women with severe or critical COVID-19 (n=10)	−0.33	1.00	−0.33	.740	−2.29	1.63
Pregnant women without COVID-19 (n=36)	−1.26	0.90	−1.40	.161	−3.03	0.50
Serum chloride, mmol/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−0.62	1.19	−0.52	.603	−2.95.	1.72
Nonpregnant women with severe or critical COVID-19 (n=10)	−1.13	1.67	−0.68	.499	−4.40	2.14
Pregnant women without COVID-19 (n=36)	−1.15	1.48	−0.78	.436	−4.04	1.74
Serum magnesium, mmol/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	0.05	0.02	3.14	.002	0.02	0.08
Nonpregnant women with severe or critical COVID-19 (n=10)	0.03	0.02	1.26	.207	−0.02	0.08
Pregnant women without COVID-19 (n=36)	−0.01	0.02	−0.47	.641	−0.05	0.03
Anion gap, mmol/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−2.98	0.59	−5.08	<.001	−4.13	−1.83
Nonpregnant women with severe or critical COVID-19 (n=10)	−3.69	0.84	−4.38	<.001	−5.34	−2.04
Pregnant women without COVID-19 (n=36)	−2.22	0.72	−3.10	.002	−3.62	−0.82
Osmotic pressure, mosm/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	9.41	1.57	5.99	<.001	6.33	12.49
Nonpregnant women with severe or critical COVID-19 (n=10)	−0.30	2.32	−0.13	.896	−4.84	4.23
Pregnant women without COVID-19 (n=36)	−2.80	1.89	−1.48	.139	−6.50	0.91
Platelet count, $\times 10^9$/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	6.39	12.17	0.53	.600	−17.46	30.23
Nonpregnant women with severe or critical COVID-19 (n=10)	−7.01	19.62	−0.36	.721	−45.46	31.43
Pregnant women without COVID-19 (n=36)	−21.23	14.69	−1.45	.148	−50.03	7.57
Hb, g/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	9.20	2.84	3.24	.001	3.64	14.77
Nonpregnant women with severe or critical COVID-19 (n=10)	−2.39	4.83	−0.50	.620	−11.86	7.08
Pregnant women without COVID-19 (n=36)	−0.19	3.31	−0.06	.955	−6.68	6.31

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SUPPLEMENTAL TABLE 4

Supplemental clinical laboratory indices between pregnant and nonpregnant patients with COVID-19 considering repeated tests by using generalized estimating equation *(continued)*

Variable	Coefficient	SE	*t*	*P* value	95% CI	
hs CRP>5 mg/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−1.75	0.79	−2.22	.026	−3.30	−0.21
Nonpregnant women with severe or critical COVID-19 (n=10)	−0.76	1.06	−0.71	.477	−2.84	1.33
PCT>0.1 ng/mL						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−0.08	0.03	−3.26	.001	−0.13	−0.03
Nonpregnant women with severe or critical COVID-19 (n=10)	0.02	0.03	0.49	.625	−0.05	0.08
IgG, g/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	1.80	0.85	2.12	.034	0.13	3.47
Nonpregnant women with severe or critical COVID-19 (n=10)	4.23	1.12	3.79	<.001	2.04	6.42
IgM, g/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	0.30	0.12	2.44	.014	0.06	0.54
Nonpregnant women with severe or critical COVID-19 (n=10)	0.00	0.18	−0.02	.985	−0.36	0.35
IgA, g/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	0.05	0.20	0.23	.817	−0.35	0.44
Nonpregnant women with severe or critical COVID-19 (n=10)	0.04	0.32	0.12	.907	−0.58	0.65
IgE, g/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	2.55	49.73	0.05	.959	−94.91	100.02
Nonpregnant women with severe or critical COVID-19 (n=10)	−37.09	78.30	−0.47	.636	−190.55	116.36
C3, g/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−0.25	0.05	−5.20	<.001	−0.34	−0.16
Nonpregnant women with severe or critical COVID-19 (n=10)	−0.11	0.07	−1.52	.128	−0.26	0.03
C4, g/L						
Pregnant women with COVID-19 (n=36)	Ref					
Nonpregnant women with mild or moderate COVID-19 (n=72)	−0.09	0.03	−3.38	.001	−0.13	−0.04
Nonpregnant women with severe or critical COVID-19 (n=10)	−0.04	0.04	−1.09	.277	−0.12	0.03

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *C3*, complement 3, *C4*, complement 4; *CI*, confidence interval; *CK-MB*, creatine kinase-MB; *COVID-19*, coronavirus 2019; *CREA*, creatinine; *eGFR*, estimate glomerular filtration rate; *GGT*, γ-glutamyltranspeptidase; *GLU*, glucose; *Hb*, hemoglobin; *hs CRP*, hypersensitive c-reactive protein; *IgA*, immune globulin A; *IgG*, immune globulin G; *IgM*, immune globulin M; *LDH*, lactate dehydrogenase; *PCT*, procalcitonin; *Ref*, referent.

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SUPPLEMENTAL TABLE 5
The power of different models to distinguish between pregnant women with COVID-19 and nonpregnant women with COVID-19 controls

Different models with relative variables		AUC (95% CI)
1	LC, WBC, NLR, CD3, CD4, CD8, CD16/56, IL-6/10, and IL-6	0.898 (0.834—0.961)
2	LDH	0.532 (0.411—0.653)
3	GLU	0.495 (0.374—0.617)
4	Prothrombin time and D-dimer	0.949 (0.885—1.000)
5	Albumin	0.761 (0.668—0.853)
6	Myoglobin, NT-proBNP, and CK-MB	0.867 (0.803—0.931)
7	Age	0.557 (0.445—0.670)
8	The full predictive model	0.953 (0.914—0.993)

The 36 pregnant women with COVID-19 and 82 nonpregnant women with COVID-19 controls were extracted for this analysis. AUCs of 9 models with relative variables were calculated. Model 1 was also calculated in 3 subgroups. From model 2 to model 8, each separate AUC and cumulated combined AUC based on model 1 was calculated.

AUC, area under the ROC curve; *CD3*, $CD3^+$ cell count; *CD4*, $CD4^+$ cell count; *CD8*, $CD8^+$ cell count; *CD16/56*, $CD16^+CD56^+$ cell count; *CI*, confidence interval; *CK-MB*, creatine kinase-MB; *COVID-19*, coronavirus disease 2019; *IL-6*, interleukin-6; *IL-6/10*, interleukin-6—to—interleukin-10 ratio; *LC*, lymphocyte count; *LDH*, lactate dehydrogenase; *NLR*, neutrophil-to-lymphocyte ratio; *NT-proBNP*, N-terminal probrain natriuretic peptide; *ROC*, receiver operating characteristic; *WBC*, white blood cell.

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SUPPLEMENTAL TABLE 6
The power of different models to distinguish between pregnant women with COVID-19 and nonpregnant women with severe or critical COVID-19

Different models with relative variables		AUC (95% CI)
1	LC, WBC, NLR, CD3, CD4, CD8, IL-6/10, and IL-6	0.875 (0.773—0.977)
2	LDH	0.639 (0.447—0.831)
3	GLU	0.742 (0.581—0.902)
4	Prothrombin time and D-dimer	0.897 (0.766—1.000)
5	Albumin	0.508 (0.311—0.706)
6	Myoglobin	0.733 (0.547—0.919)
7	Age	0.742 (0.556—0.927)
8	The full predictive model	0.939 (0.853—1.000)

The 36 pregnant women with COVID-19 and 10 nonpregnant women with severe or critical COVID-19 were extracted for this analysis. AUCs of 9 models with relative variables were calculated. Model 1 was also calculated in 3 subgroups. From model 2 to model 8, each separate AUC and cumulated combined AUC based on model 1 was calculated.

AUC, area under the ROC curve; *CD3*, $CD3^+$ cell count; *CD4*, $CD4^+$ cell count; *CD8*, $CD8^+$ cell count; *CI*, confidence interval; *COVID-19*, coronavirus disease 2019; *IL-6*, interleukin-6; *IL-6/10*, interleukin-6 to interleukin-10 ratio; *LC*, lymphocyte count; *LDH*, lactate dehydrogenase; *NLR*, neutrophil-to-lymphocyte ratio; *ROC*, receiver operating characteristic; *WBC*, white blood cell.

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