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Laboratory indicators in COVID-19 and other pneumonias: Analysis for differential diagnosis and comparison of dynamic changes during 400-day follow-up

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ABSTRACT

Background: COVID-19 is spreading rapidly all over the world, the patients' symptoms can be easily confused with other pneumonia types. Therefore, it is valuable to seek a laboratory differential diagnostic protocol of COVID-19 and other pneumonia types on admission, and to compare the dynamic changes in laboratory indicators during follow-up.

Methods: A total of 143 COVID-19, 143 bacterial pneumonia and 145 conventional viral pneumonia patients were included. The model group consisted of 140 COVID-19, 80 bacterial pneumonia and 60 conventional viral pneumonia patients, who were age and sex matched. We established a differential diagnostic model based on the laboratory results of the model group on admission via a nomogram, which was validated in an external validation group. We also compared the 400-day dynamic changes of the laboratory indicators among groups.

Results: LASSO regression and multivariate logistic regression showed that eosinophils (Eos), total protein (TP), prealbumin (PA), potassium (K), high-density lipoprotein cholesterol (HDLC), and low-density lipoprotein cholesterol (LDLC) could differentiate COVID-19 from other pneumonia types. The C-index of the nomogram model was 0.922. Applying the nomogram to the external validation group showed an area under the curve (AUC) of 0.902. The 400-day change trends of the laboratory indexes varied among subgroups divided by sex, age, oxygenation index (OI), and pathogen.

Conclusion: The laboratory model was highly accurate at providing a new method to identify COVID-19 in pneumonia patients. The 400-day dynamic changes in laboratory indicators revealed that the recovery time of COVID-19 patients was not longer than that of other pneumonia types.

1. Introduction

The main manifestations of COVID-19 are fever, dry cough, and fatigue, with approximately 11.4% of patients having at least one gastrointestinal symptom [1]. Most severe cases of COVID-19 manifest with dyspnea after one week and rapidly progress to acute respiratory distress syndrome, septic shock, difficult-to-correct metabolic acidosis, coagulation dysfunction, and multiple-organ failure [2]. COVID-19 is highly infectious, and there were nearly 120 million confirmed cases by March 8, 2021, with a mortality of 2.2%. Among COVID-19 patients in intensive care units (ICUs), the mortality is up to 48.7% [3].

Pathogens of bacterial pneumonia mainly include *Streptococcus pneumoniae*, Staphylococcus, and *Klebsiella pneumoniae* [4], while for conventional viral pneumonia, they mainly include influenza A, B, C virus, and adenovirus [5,6]. Through a study of 836 COVID-19 patients, a low frequency of bacterial coinfection was found in the early COVID-19 hospital presentation, with no evidence of concomitant fungal infection, at least not in the early phase of COVID-19 [7]. Therefore, it can be inferred that coinfection is rare in the early stage of COVID-19. Because the clinical symptoms of COVID-19 are similar to those of bacterial pneumonia and conventional viral pneumonia, distinguishing COVID-19 patients from other pneumonia patients is of vital importance.

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At present, research on the differential diagnosis of COVID-19 and other pneumonia has mainly focused on imaging tools such as X-ray and CT [8]. A deep-learning convolutional neural network with the feature of transfer learning was built that could accurately differentiate COVID-19 on portable chest X-ray against normal ones. This approach could help radiologists and frontline physiologists provide timelier and more accurate diagnoses [9]. Li et al. found that a peripheral distribution, a lesion range >10 cm, the involvement of 5 lobes, the presence of hilar and mediastinal lymph node enlargement, and no pleural effusion were significantly associated with COVID-19 [10]. An AI system built by CT images can display parameters of the background, lung field, consolidation, ground-glass opacity (GGO), pulmonary fibrosis, interstitial thickening, and pleural effusion with an accuracy of approximately 91% [11]. However, imaging tools involve radiation and so are not suitable for pregnant women, and the image definition is related to the patient's breathing motion during the scan and the accuracy of the instrument [12]. It will be of great clinical significance to find other methods, such as laboratory indicators, to identify COVID-19 patients in the early stage of the disease.

In the laboratory, COVID-19 is mainly diagnosed by collecting nasal and pharyngeal swabs for viral nucleic acid detection by real-time reverse transcription-polymerase chain reaction (RT-PCR) [13]. The turnaround time (TAT) of the RT-PCR test is approximately 3–4 h, it has a false-negative rate of 15%–20% [14], and there may be a particular risk of contamination in the process of sample processing.

Research has shown that the differential diagnosis of pneumonia can also be assisted by common laboratory indicators. For example, patients with conventional viral pneumonia may have a lower white blood cell count (WBC) and lymphocyte count. In contrast, most bacterial pneumonia patients have a higher WBC count, and the neutrophil percentage increases. In addition, some infection indicators, such as CRP, SAA, and PCT, are helpful in the differential diagnosis of bacterial pneumonia and conventional viral pneumonia [15]. Previous studies have demonstrated that blood samples of COVID-19 patients are not infectious [16], and the TATs of conventional laboratory tests, such as routine blood tests, biochemistry, and blood coagulation, are 2 h or less, which is shorter than RT-PCR tests, and these tests are also available in African countries and primary hospitals [17,18]. Therefore, it is of great epidemiological value to distinguish COVID-19 from bacterial pneumonia and common viral pneumonia through common laboratory indicators with economical methods.

So far, some studies have explored the differences in some laboratory indicators between COVID-19 and non-COVID-19 patients. A study comparing COVID-19 and influenza pneumonia indicated that both cohorts showed reduced lymphocyte numbers, but the influenza cohort displayed higher white blood cell counts and PCT values [19]. Another study revealed that the white blood cell subset counts most closely correlated with COVID-19 risk were lower neutrophil and eosinophil counts [20]. Hu et al. found that laboratory indexes were different between nucleic acid-positive and nucleic acid-negative patients, and laboratory differences were also observed in COVID-19 patients and influenza patients [21]. In addition, a review showed that lymphopenia and an increased neutrophil/lymphocyte ratio (NLR) were the most consistent abnormal routine blood results and were associated with the disease course, especially in severe patients [22]. Although they compared the differences in laboratory indexes between COVID-19 and non-COVID-19 patients, they did not use laboratory indexes for modeling. Wang et al. established a differential diagnostic model for COVID-19 patients and influenza patients by using routine blood parameters through a nomogram. Although the model had a high area under the curve (AUC = 0.913), it lacked external verification, and the model could not distinguish COVID-19 patients and bacterial pneumonia patients [23].

Our study collected the results of standard laboratory indicators of bacterial pneumonia, conventional viral pneumonia, and COVID-19 patients on admission and during the 400-day follow-up, aiming to establish an early differential diagnostic model of COVID-19 and non-COVID-19 pneumonia patients through common laboratory indicators on admission, and to compare the recovery time and long-term dynamics of these laboratory indicators in different types of pneumonia patients.

2. Materials and methods

2.1. Cohort selection

From January 16, 2020, to April 1, 2020, a total of 144 patients with confirmed COVID-19 in Taizhou city were enrolled in the study. One patient missing more than 60% of the laboratory indicators was excluded, leaving 143 COVID-19 patients in the study. We also collected 191 cases of bacterial pneumonia and 234 cases of conventional viral pneumonia from January 16, 2020, to December 20, 2020 and recorded the symptom onset time and the results of all laboratory indicators at the time of admission. The exclusion criteria were as follows: (1) age under 18 years; (2) cancer, including leukemia; (3) more than 60% of the laboratory indicators missing at admission; and (4) interval between onset and admission longer than 30 days. The remaining 143 patients with bacterial pneumonia and 145 patients with conventional viral pneumonia were included.

A total of 140 COVID-19 patients above the age of 18 years were included in the model group. Eighty bacterial pneumonia patients and 60 conventional viral pneumonia patients, matched for age and sex with the COVID-19 group, were enrolled as the model group. Twenty bacterial pneumonia patients, 20 conventional viral pneumonia patients and 40 COVID-19 patients from Wenzhou Central Hospital were included as the external validation group (Fig. 1).

2.2. Diagnostic criteria

Diagnostic criteria included clinical manifestations, chest CT, and etiological examination. RT-PCR of nasopharyngeal swabs was used to diagnose patients with COVID-19 and conventional viral pneumonia. Patients with bacterial pneumonia were identified by sputum culture.

2.3. Biological detection

EDTA-K2 anticoagulant samples were measured by a Sysmex 2100D routine hematology analyzer (Sysmex, Japan), and ESR was performed by using the Italian Ali-fax Test 1 automatic ESR analyzer. Serum samples were centrifuged at 3500 rpm for 5 min, and both CRP and SAA were performed by using an AU5800 (OLYMPUS, Japan). PCT was carried out by adopting the Roche Cobas e411 electrochemiluminescence analyzer (Roche Diagnostics, Germany). Sodium citrate plasma samples were centrifuged at 3500 rpm for 5 min, and coagulation parameters were gathered using a Sysmex CS 5100i (Sysmex, Japan) automatic hemagglutination analyzer. Arterial blood gas analysis was performed by using the GEM Premier 3500.

2.4. Methods

First, we collected all the patients' laboratory indicators on admission, including blood routine, biochemical, hemagglutination,

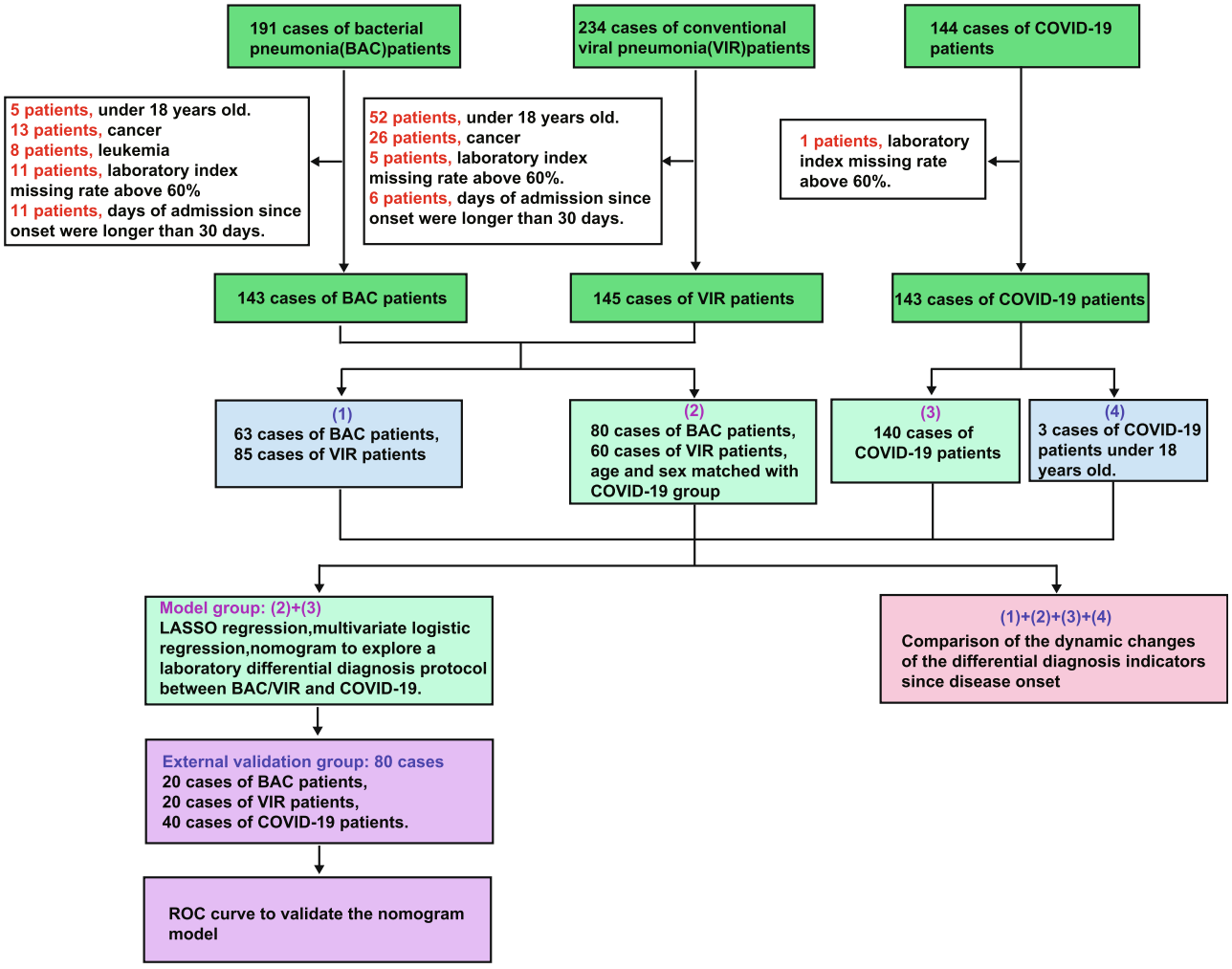

Fig. 1. The flow chart of the cohorts.

infectious, and blood gas indexes. We established a laboratory differential model of COVID-19 with bacterial pneumonia and conventional viral pneumonia by LASSO regression, multivariate logistic regression, and a nomogram. We also collected the laboratory indexes of all patients during up to 400 days of follow-up to compare the recovery time and long-term dynamics of the laboratory indicators in patients with different types of pneumonia.

2.5. Statistical analysis

All the graphs were drawn and the corresponding statistical analyses done in R (Version: 4.0.2). Continuous variables are expressed as median (P25-P75). The Mann-Whitney *U* test was used for comparisons between two groups. The Kruskal-Wallis H test was used to compare three groups. Categorical variables are expressed as number (percentage) and were compared between groups using chi-square test. LASSO regression and multivariate logistic regression analyses were used to screen laboratory indicators. Box plots and heat maps were used to compare laboratory indexes between groups. A nomogram was built to determine the role of each laboratory parameter in the differential diagnosis of COVID-19, bacterial pneumonia, and conventional viral pneumonia. A locally weighted scatterplot smoothing (LOWESS) plot was used to compare the dynamics of the laboratory indicators in different groups. $P \leq 0.05$ was considered to indicate statistical significance.

3. Results

3.1. Clinical information of study cohorts

The model group consisted of 80 cases of bacterial pneumonia (31 cases of gram-positive bacteria, 44 cases of gram-negative bacteria and 5 cases of multiple infection), 60 cases of conventional viral pneumonia (18 cases of influenza A and 42 cases of influenza B) and 140 cases of COVID-19. The prevalence of COPD, hypertension, thyroid nodules, cardiovascular disease, nervous system disease, hepatitis, urinary system disease and digestive system disease were the highest in conventional viral pneumonia patients. The proportions of tuberculosis and chronic bronchitis/bronchiectasis were the highest in bacterial pneumonia patients. There was no significant difference in the proportion of diabetes or cancer between groups. Basic information of all cohorts and the model group and the validation group are presented in Table 1 and Table S1. The first blood sampling times after admission following symptom onset in the model group and the validation group are displayed in Fig. S1.

3.2. Comparison of laboratory indexes between bacterial pneumonia, conventional viral pneumonia and COVID-19 patients

In the model group, among the routine blood and infection indicators, the WBC counts [especially eosinophils (Eos)] and

Table 1
Clinical information of the cohorts.

	All cohorts				Model group			
	Bacterial pneumonia	Conventional viral pneumonia	COVID-19	P value	Bacterial pneumonia	Conventional viral pneumonia	COVID-19	P value
n	143	145	143		80	60	140	
Pathogen (%)				<0.001				<0.001
Bacteria	143 (100.0)	0 (0.0)	0 (0.0)		80(100.0)	0(0.0)	0(0.0)	
Gram positive bacteria	56 (39.2)	0 (0.0)	0 (0.0)		31(38.8)	0(0.0)	0(0.0)	
Gram negative bacteria	80 (55.9)	0 (0.0)	0 (0.0)		44(55.0)	0(0.0)	0(0.0)	
Multiple infection	7 (4.9)	0 (0.0)	0 (0.0)		5(6.2)	0(0.0)	0(0.0)	
Conventional virus	0 (0.0)	145 (100.0)	0 (0.0)		0(0.0)	60(100.0)	0(0.0)	
Influenza A virus	0 (0.0)	36 (24.8)	0 (0.0)		0(0.0)	18(30.0)	0(0.0)	
Influenza B virus	0 (0.0)	107 (73.8)	0 (0.0)		0(0.0)	42(70.0)	0(0.0)	
Adenovirus	0 (0.0)	1 (0.7)	0 (0.0)		0(0.0)	0(0.0)	0(0.0)	
Parainfluenza virus	0 (0.0)	1 (0.7)	0 (0.0)		0(0.0)	0(0.0)	0(0.0)	
SARS-COV-2	0 (0.0)	0 (0.0)	143 (100.0)		0(0.0)	0(0.0)	140(100.0)	
Age (years)	57.00(48.00–67.00)	65.00(54.00–75.00)	47.00(38.50–56.00)	<0.001	50.5(37.5–61.0)	52.0(44.0–58.0)	47.5(39.00–56.25)	0.592
Sex (%)				0.211				0.472
Male	70 (49.0)	86 (59.3)	77 (53.8)		36(45.0)	30(50.0)	75(53.6)	
Female	76(51.0)	59(40.7)	66(46.2)		44(55.0)	30(50.0)	65(46.4)	
Underlying diseases (%)								
COPD	9(6.3)	30(20.7)	0(0.0)	<0.001	4(5.0)	4(6.7)	0(0.0)	0.014
Hypertension	42(29.4)	55(37.9)	22(15.4)	<0.001	22(27.5)	18(30.0)	22(15.7)	0.033
Diabetes mellitus	15(10.5)	24(16.6)	14(9.8)	0.157	9(11.2)	7(11.7)	14(10.0)	0.925
Cardiovascular disease	22(15.4)	61(42.1)	3(2.1)	<0.001	9(11.2)	13(21.7)	3(2.1)	<0.001
Nervous system diseases	7(4.9)	36(24.8)	3(2.1)	<0.001	6(7.5)	10(16.7)	3(2.1)	0.001
Chronic bronchitis/ Bronchiectasis	44(30.8)	17(11.7)	4(2.8)	<0.001	22(27.5)	6(10.0)	4(2.9)	<0.001
Tuberculosis	13(9.1)	5(3.4)	4(2.8)	0.029	9(11.2)	1(1.7)	4(2.9)	0.009
Cancer	1(0.7)	0(0.0)	1(0.7)	0.601	0(0.0)	0(0.0)	2(1.4)	0.685
Thyroid nodule	9(6.3)	16(11.0)	5(3.5)	0.039	6(7.5)	10(16.7)	5(3.6)	0.006
Hepatitis	3(2.1)	8(5.5)	7(4.9)	0.304	0(0.0)	5(8.3)	7(5.0)	0.046
Urinary system diseases	29(20.3)	61(42.1)	2(1.4)	<0.001	18(22.5)	23(38.3)	2(1.4)	<0.001
Digestive system disease	40(28.0)	63(43.4)	7(4.9)	<0.001	21(26.2)	28(46.7)	7(5.0)	<0.001

Data was presented as number (percentage) or median (P25-P75).
P value of Age was obtained by Kruskal-Wallis H test; P values of the remaining indicators were obtained by chi-square test.

C-reactive protein (CRP) were lower in COVID-19 patients than other patients. Among liver function indicators, alanine aminotransferase (ALT), total protein (TP), globulin (Glb) and total bile acid (TBA) were the highest in COVID-19 patients. For the renal function indicators, COVID-19 patients had the highest creatinine (Cr) value and the lowest retinol binding protein (RBP), blood urea nitrogen (BUN) and estimated glomerular filtration rate (eGFR) levels. For serum electrolytes, the lowest potassium (K), sodium (Na) and chlorine (Cl) levels were found in COVID-19 patients. Among the blood lipid indexes, the highest triglyceride (TG) and low-density lipoprotein cholesterol (LDLC) and the lowest high-density lipoprotein cholesterol (HDLC) were found in COVID-19 patients. For coagulation-related indexes, the fibrin (Fib) and D-dimer (DD) levels in COVID-19 patients were the lowest. In addition, the highest levels of arterial oxygen saturation (SaO2) and oxygenation index (OI) were found in the COVID-19 group. Laboratory indicators of all cohorts and the model group on admission are displayed in Table 2.

3.3. Screening of modeling indicators

The laboratory indexes with significant differences among groups were included in the LASSO regression. The screened indicators, including Eos, HDLC, K, LDLC, TP, Na, WBC, DD, PA, Glu, Hb, ALP, Cl, OI, and CRP, were included in multivariate logistic regression. The indicators with a P value <0.01 were selected as modeling indicators: Eos, HDLC, K, LDLC, TP, PA and ALP. Heatmaps and box plots showed the differences in the above indexes among the groups (Fig. 2).

3.4. Laboratory differential diagnostic model between COVID-19 and non-COVID-19

We further established a nomogram model consisting of Eos, HDLC, K, LDLC, TP, PA and ALP. The model's C-index was 0.922. The calibration curve, clinical decision curve and clinical impact curve showed that the model had high differential diagnostic ability (Fig. 3A–D). Applying the nomogram to the validation group showed that the area under the curve (AUC) of the model was 0.902, with a sensitivity and specificity of 82.5% and 80.0%, respectively (Fig. 3E). The calibration curve of the validation group is displayed in Fig. 3F.

3.5. Comparison of dynamic changes in laboratory indicators during the 400-day follow-up

The level of Eos in COVID-19 patients stayed the lowest out of the 3 groups within 200 days after onset, and its dynamic changes were similar to those in conventional viral pneumonia patients, especially influenza B pneumonia patients. In COVID-19 patients, Eos stopped rising 25 days after onset, and patients with an oxygenation index <300 mmHg had a very low level of Eos for a long time after the onset of the disease. It recovered by 350 days after the onset of the disease. Eos in bacterial pneumonia patients showed a bimodal trend, with the second peak appearing 100 days after onset. In particular, among patients under 50 years of age with an oxygenation index >300 mmHg and gram-positive bacterial pneumonia, Eos exceeded the upper limit of the reference range at its second peak. In all 3 groups of patients, eosinophils

Table 2
Laboratory data of the cohorts.

			All cohorts		Model group			
	Bacterial pneumonia	Conventional viral pneumonia	COVID-19	P value	Bacterial pneumonia	Conventional viral pneumonia	COVID-19	P value
n	143	145	143		80	60	140	
Blood routine test								
WBC ($\times10^9$/L)	6.82 (5.28–9.25)	7.20 (5.30–10.70)	5.24 (4.34–6.76)	<0.001	7.07(5.35–9.85)	6.35(4.35–9.48)	5.20(4.31–6.76)	<0.001
N ($\times10^9$/L)	4.90 (3.50–6.70)	5.50 (3.80–8.90)	3.40 (2.62–5.03)	<0.001	5.10(3.70–7.03)	4.60(3.05–7.68)	3.40(2.62–4.99)	<0.001
L ($\times10^9$/L)	1.50 (1.10–1.80)	0.90 (0.60–1.50)	1.18 (0.80–1.58)	<0.001	1.40(1.00–1.70)	0.90(0.60–1.50)	1.15(0.80–1.56)	0.002
M ($\times10^9$/L)	0.50 (0.40–0.70)	0.40 (0.30–0.60)	0.42 (0.31–0.54)	0.007	0.50(0.30–0.70)	0.35(0.27–0.60)	0.42(0.32–0.53)	0.01
E ($\times10^9$/L)	0.09 (0.05–0.18)	0.01 (0.00–0.08)	0.01 (0.00–0.04)	<0.001	0.09(0.05–0.17)	0.01(0.00–0.08)	0.01(0.00–0.04)	<0.001
B ($\times10^9$/L)	0.02 (0.01–0.03)	0.01 (0.01–0.02)	0.01 (0.01–0.02)	<0.001	0.02(0.01–0.03)	0.01(0.01–0.02)	0.01(0.01–0.02)	0.001
RBC ($\times10^{12}$/L)	4.27 (3.96–4.60)	4.13 (3.58–4.54)	4.50 (4.19–4.96)	<0.001	4.32(4.05–4.61)	4.23(3.78–4.60)	4.50(4.18–4.92)	<0.001
Hb (g/L)	128.00 (119.00–141.00)	124.00 (108.00–135.00)	135.00 (126.00–150.50)	<0.001	130.00(121.75–141.00)	126.00(109.00–136.25)	135.00(125.75–151.00)	<0.001
Hct	0.39 (0.36–0.41)	0.37 (0.32–0.41)	0.40 (0.38–0.44)	<0.001	0.39(0.36–0.42)	0.38(0.33–0.41)	0.40(0.38–0.44)	0.002
MCV (fL)	89.90 (87.40–93.10)	90.00 (87.20–93.00)	88.90 (86.50–91.15)	0.009	89.50(87.00–92.75)	89.05(86.40–92.05)	89.00(86.68–91.23)	0.416
MCH (pg)	30.30 (29.50–31.05)	29.90 (28.70–31.10)	30.20 (29.35–31.00)	0.107	30.30(29.48–31.00)	29.80(28.80–31.10)	30.25(29.40–31.00)	0.253
MCHC (g/L)	336.00 (327.00–344.00)	330.00 (323.00–340.00)	339.00 (334.00–345.00)	<0.001	336.00(327.75–344.00)	336.00(324.75–341.25)	339.00(334.00–345.00)	0.002
RDW (%)	13.00 (12.40–13.70)	12.70 (12.30–13.70)	12.50 (12.10–12.90)	<0.001	12.80(12.30–13.62)	12.60(12.20–13.43)	12.50(12.10–12.90)	0.005
PLT ($\times10^9$/L)	233.00 (190.50–292.50)	181.00 (145.00–240.00)	204.00 (165.50–247.50)	<0.001	228.50(185.25–295.00)	193.50(159.25–240.00)	203.00(164.25–247.00)	0.001
MPV (fL)	10.10 (9.50–11.00)	10.00 (9.10–10.70)	10.50 (10.00–10.90)	<0.001	10.15(9.60–11.00)	10.05(9.10–10.72)	10.50(10.00–10.90)	0.009
Pct	0.23 (0.20–0.29)	0.18 (0.15–0.22)	0.22 (0.18–0.26)	<0.001	0.24(0.19–0.29)	0.19(0.16–0.22)	0.22(0.18–0.25)	<0.001
ESR (mm/h)	39.00 (27.50–39.00)	29.00 (14.00–35.00)	34.50 (19.00–48.75)	<0.001	39.00(24.00–39.00)	29.00(14.00–29.00)	35.00(19.75–49.25)	<0.001
Infection index								
CRP (mg/L)	13.70 (2.06–32.22)	60.20 (19.50–99.20)	11.20 (3.95–25.50)	<0.001	14.80(2.42–32.22)	48.70(12.68–75.99)	11.95(4.07–26.00)	<0.001
Biochemistry								
Liver function								
ALT (U/L)	15.00 (10.00–24.50)	19.00 (13.00–32.00)	21.00 (14.00–34.00)	<0.001	17.00(10.00–25.00)	18.50(12.00–36.25)	21.00(14.00–34.00)	0.018
AST (U/L)	20.00 (17.00–26.00)	29.00 (20.00–50.00)	24.00 (19.00–30.00)	<0.001	20.50(16.00–26.25)	26.00(18.75–54.00)	24.00(19.00–30.00)	<0.001
ALP (U/L)	82.00 (68.00–98.00)	78.00 (66.00–95.00)	71.00 (60.50–82.00)	<0.001	82.00(63.00–94.25)	78.50(65.75–102.00)	71.00(60.00–81.25)	<0.001
GGT (U/L)	22.00 (15.50–37.00)	30.00 (17.00–58.00)	24.00 (17.00–37.00)	0.03	20.50(16.00–36.00)	29.00(16.75–54.25)	24.00(17.00–37.25)	0.189
TBIL (μmol/L)	13.10 (9.60–16.15)	11.20 (7.50–14.70)	12.60 (8.65–17.15)	0.006	14.30(9.57–18.60)	12.30(8.80–14.85)	12.65(8.85–17.08)	0.156
DBIL (μmol/L)	4.10 (3.10–5.80)	4.10 (2.70–5.60)	4.60 (2.85–6.30)	0.298	4.40(3.10–6.70)	4.20(2.90–5.43)	4.60(2.90–6.30)	0.695
TP (g/L)	65.80 (61.50–69.60)	61.70 (57.90–66.10)	68.90 (65.95–73.30)	<0.001	65.50(61.30–68.93)	63.25(59.27–68.00)	68.95(65.88–73.10)	<0.001
Alb (g/L)	39.10 (36.25–41.90)	34.20 (30.90–38.20)	39.60 (37.15–42.00)	<0.001	40.05(36.58–41.90)	37.00(32.68–39.30)	39.55(37.10–41.85)	<0.001
Glb (g/L)	26.50 (23.80–30.35)	27.00 (24.20–30.30)	29.40 (26.10–32.40)	<0.001	25.80(23.58–29.70)	26.75(23.38–29.35)	29.40(26.17–32.42)	<0.001
AG	1.50 (1.20–1.70)	1.30 (1.10–1.50)	1.30 (1.20–1.50)	<0.001	1.60(1.30–1.70)	1.40(1.20–1.60)	1.30(1.20–1.50)	0.001
TBA (μmol/L)	2.90 (1.70–4.80)	3.70 (2.10–6.70)	4.90 (2.90–7.25)	<0.001	2.85(1.70–4.65)	3.10(1.75–5.25)	4.90(2.85–7.23)	<0.001
PA (mg/dL)	21.60 (16.22–26.42)	15.00 (10.20–18.20)	16.90 (13.22–20.08)	<0.001	21.75 (20.80–21.80)	16.55 (12.38–21.25)	16.85 (13.10–20.00)	<0.001
Renal function								
RBP (mg/L)	39.45 (28.73–45.98)	31.30 (23.00–37.00)	31.35 (25.77–36.25)	<0.001	38.10 (28.98–41.80)	32.70 (25.90–40.50)	31.25 (25.48–36.15)	0.003
Cr (μmol/L)	68.00 (61.00–78.00)	74.00 (57.00–96.00)	75.00 (66.00–88.00)	0.004	68.00(59.00–78.25)	67.00(54.00–89.25)	75.00(66.00–88.00)	0.002
BUN (mmol/L)	4.45 (3.70–5.65)	6.03 (4.46–8.74)	4.08 (3.26–5.16)	<0.001	4.39(3.67–5.38)	5.11(4.07–7.03)	4.04(3.27–5.10)	<0.001
UA (μmol/L)	278.00 (219.00–354.00)	232.00 (186.00–344.00)	266.00 (217.50–335.50)	0.031	279.00(220.00–337.00)	261.00(208.25–356.25)	264.00(217.00–332.50)	0.736
eGFR (mL/min)	93.00 (84.00–104.00)	85.00 (65.00–101.00)	95.00 (83.00–105.00)	<0.001	95.50(88.75–112.00)	100.00(81.75–110.25)	95.00(83.00–104.00)	0.18
Electrolyte								
K (mmol/L)	3.90 (3.70–4.10)	3.97 (3.65–4.24)	3.74 (3.53–4.00)	<0.001	3.85(3.67–4.06)	3.95(3.60–4.23)	3.72(3.53–3.99)	0.003
Na (mmol/L)	139.90 (138.10–141.45)	140.00 (138.10–142.00)	137.90 (136.55–139.65)	<0.001	140.05(137.95–141.80)	140.00(138.05–142.10)	137.90(136.48–139.70)	<0.001
Cl (mmol/L)	104.40 (102.25–106.30)	104.20 (100.10–107.00)	102.50 (100.50–104.55)	<0.001	104.50(102.68–106.50)	105.20(102.17–107.15)	102.50(100.47–104.42)	<0.001
Ca (mmol/L)	2.21 (2.12–2.28)	2.10 (2.00–2.18)	2.19 (2.09–2.26)	<0.001	2.21(2.14–2.29)	2.12(2.05–2.20)	2.18(2.09–2.25)	<0.001
Mg (mmol/L)	0.87 (0.81–0.92)	0.88 (0.80–0.93)	0.86 (0.82–0.92)	0.911	0.86(0.81–0.92)	0.87(0.80–0.93)	0.86(0.82–0.93)	0.954
P (mmol/L)	1.03 (0.91–1.12)	0.98 (0.81–1.17)	0.99 (0.83–1.12)	0.276	1.04(0.90–1.15)	1.00(0.82–1.16)	0.98(0.82–1.11)	0.144

(*continued on next page*)

Table 2 (*continued*)

	All cohorts				Model group			
	Bacterial pneumonia	Conventional viral pneumonia	COVID-19	P value	Bacterial pneumonia	Conventional viral pneumonia	COVID-19	P value
Blood glucose								
Glu (mmol/L)	5.03 (4.52–5.86)	5.99 (5.22–7.50)	6.57 (5.53–8.60)	<0.001	4.94(4.43–5.67)	5.96(5.12–7.49)	6.62(5.52–8.72)	<0.001
Blood lipids								
TG (mmol/L)	1.08 (0.78–1.54)	0.98 (0.71–1.41)	1.33 (0.98–2.08)	<0.001	1.11(0.84–1.62)	1.11(0.86–1.66)	1.33(0.99–2.10)	0.008
CH (mmol/L)	4.17 (3.44–4.69)	3.86 (3.12–4.54)	3.87 (3.49–4.49)	0.059	4.11(3.45–4.66)	4.08(3.60–4.74)	3.88(3.50–4.54)	0.324
HDLC (mmol/L)	1.17 (1.00–1.35)	1.16 (0.92–1.50)	1.04 (0.86–1.18)	<0.001	1.17(1.02–1.39)	1.20(0.96–1.50)	1.04(0.86–1.18)	<0.001
LDLC (mmol/L)	2.35 (1.79–2.73)	1.91 (1.35–2.46)	2.51 (2.14–3.07)	<0.001	2.23(1.79–2.72)	2.14(1.58–2.54)	2.52(2.17–3.09)	<0.001
Coagulation								
Fib (g/L)	3.41 (2.74–4.64)	4.45 (3.60–5.73)	3.36 (2.81–4.09)	<0.001	3.59(2.58–4.69)	4.19(3.27–4.72)	3.36(2.82–4.11)	0.001
DD (mg/L)	0.54 (0.27–0.94)	1.66 (0.56–2.48)	0.26 (0.19–0.49)	<0.001	0.59(0.24–0.94)	1.77(0.51–2.48)	0.26(0.19–0.50)	<0.001
Arterial blood gas								
pH (mmol/L)	7.43 (7.42–7.44)	7.42 (7.42–7.44)	7.42 (7.40–7.44)	0.01	7.43(7.41–7.44)	7.42(7.42–7.44)	7.42(7.40–7.44)	0.453
PO2 (mmHg)	92.00 (77.50–92.00)	91.00 (77.00–92.00)	91.50 (80.00–106.00)	0.157	92.00(79.50–92.00)	91.00(91.00–91.00)	90.50(80.00–106.00)	0.544
SaO2 (%)	96.00 (96.00–97.00)	95.00 (95.00–97.00)	97.00 (96.00–98.00)	<0.001	96.00(96.00–97.00)	95.00(95.00–97.00)	97.00(96.00–98.00)	<0.001
OI (mmHg)	388.00 (352.00–402.50)	309.00 (269.00–329.00)	420.00 (349.00–485.50)	<0.001	388.00(340.75–400.00)	309.00(309.00–310.00)	419.00(348.00–484.50)	<0.001

WBC: White blood cell; N: Neutrophils; L: Lymphocyte; M: Monocyte; E: Eosinophils; B: Basophil; RBC: Red blood cell; Hb: Hemoglobin; Hct: Hematocrit; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red blood cell distribution width; PLT: Platelet; MPV: Mean platelet volume; Pct: Platelet crit; ESR: Erythrocyte sedimentation rate; CRP:C-reactive protein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: γ-glutamine transferase; TBIL: Total bilirubin; DBIL: Direct bilirubin; TP: Total protein; Alb: Albumin; Glb:Globulin; AG: Albumin globulin ratio; TBA: Total bile acid; PA: Prealbumin; RBP: Retinol binding protein; Cr: Creatinine; BUN: Blood urea nitrogen; UA: Uric acid; eGFR: estimated Glomerular Filtration Rate; Cl: Chlorine; Ca: Calcium; Mg: Magnesium; P:Phosphorus; Glu: Glucose; TG: Triglyceride; CH: Total cholesterol; HDLC: High density lipoprotein cholesterol; LDLC: Low density lipoprotein cholesterol; PT: Prothrombin time; INR: International normalized ratio; APTT: Activated partial thromboplastin time; Fib: Fibrin; TT: Thrombin time; DD: D-Dimer; pH: Hydrogen ion concentration; PO2: Arterial partial pressure of oxygen; SaO2: Arterial oxygen saturation; OI: Oxygenation index. Data was presented as median (P25-P75), P value was obtained by Kruskal-Wallis H test.

peaked later in male patients, patients younger than 50 years of age and those with an oxygenation index >300 mmHg.

The ALP levels of COVID-19 patients stayed within the reference range throughout the 400-day follow-up, while obvious fluctuations were observed in bacterial pneumonia and conventional viral pneumonia patients during the follow-up period. The dynamic change trend of ALP was opposite between males and females. Different change trends were found between patients aged over 50 and under 50 and between patients with oxygenation indexes higher than 300 mmHg and lower than 300 mmHg. The change trends of influenza A pneumonia and influenza B pneumonia patients were similar, but those of gram-positive bacteria and gram-negative bacteria pneumonia patients were opposite after 50 days.

The levels of total protein (TP) and prealbumin (PA) in the 3 groups were significantly different; COVID-19 patients had the highest TP level, and conventional viral pneumonia patients had the lowest TP level. TP and PA in the COVID-19 patients were low up to 20 days after onset and then quickly recovered and stayed in the normal range. TP and PA in female patients, patients aged >50 years and patients with an oxygenation index <300 mmHg were lower. In particular, in patients with an oxygenation index <300 mmHg, although the TP level was normal, the PA level was below the lower limit of the reference range, and the change trend of PA in influenza B patients was similar to that in COVID-19 patients whose oxygenation index was lower than 300 mmHg.

The trends of serum potassium level in COVID-19 patients and conventional viral pneumonia patients were basically the same: low at onset and then recovering and stabilizing in the normal range. In bacterial pneumonia patients, there was a downward trend 100 days after the onset, and it was even below the lower limit of the reference range at 180 days. A rise in the serum potassium levels of patients under 50 years old and with an oxygenation index below 300 mmHg was observed after an obvious downward trend.

High-density lipoprotein cholesterol (HDLC) and low-density lipoprotein cholesterol (LDLC) levels in bacterial pneumonia patients were relatively stable during the follow-up period, but the trends of change between gram-positive and gram-negative bacterial pneumonia were different. HDLC and LDLC levels were different between COVID-19 and conventional viral pneumonia patients, but the trends were similar. The LDLC levels of COVID-19 patients were the highest throughout the follow-up period. The HDLC and LDLC of patients of different sexes, ages and oxygenation index groups were similar during the follow-up period, showing a slight decrease at first, followed by an increase, before finally stabilizing within the normal range. HDLC and LDLC in patients with oxygenation index below 300 mmHg had a peak approximately 120 days after onset, and HDLC significantly exceeded the upper limit of the reference range, then returned to the reference range 400 days after onset. The change trends of HDLC and LDLC in conventional viral pneumonia patients in different age and oxygenation index groups were different: They peaked in patients under 50 years of age and patients with an oxygenation index lower than 300 mmHg at 120–150 days after onset at levels far above the upper limits of the reference ranges (Fig. 4).

4. Discussion

In this study, a differential diagnostic model was established in the form of a nomogram based on the laboratory test results on admission of patients with COVID-19, bacterial pneumonia, and conventional viral pneumonia. It is suitable for patients whose visit time is within 30 days of onset. A nomogram is a graphical representation of complex mathematical formulas. It describes a statistical prediction model graphically by using clinical and laboratory indicators. The model provides probabilities of the occurrence of specific clinical events, such as disease recurrence and death. The nomogram is displayed graphically, each variable is listed separately and can be scored independently, and then the probability

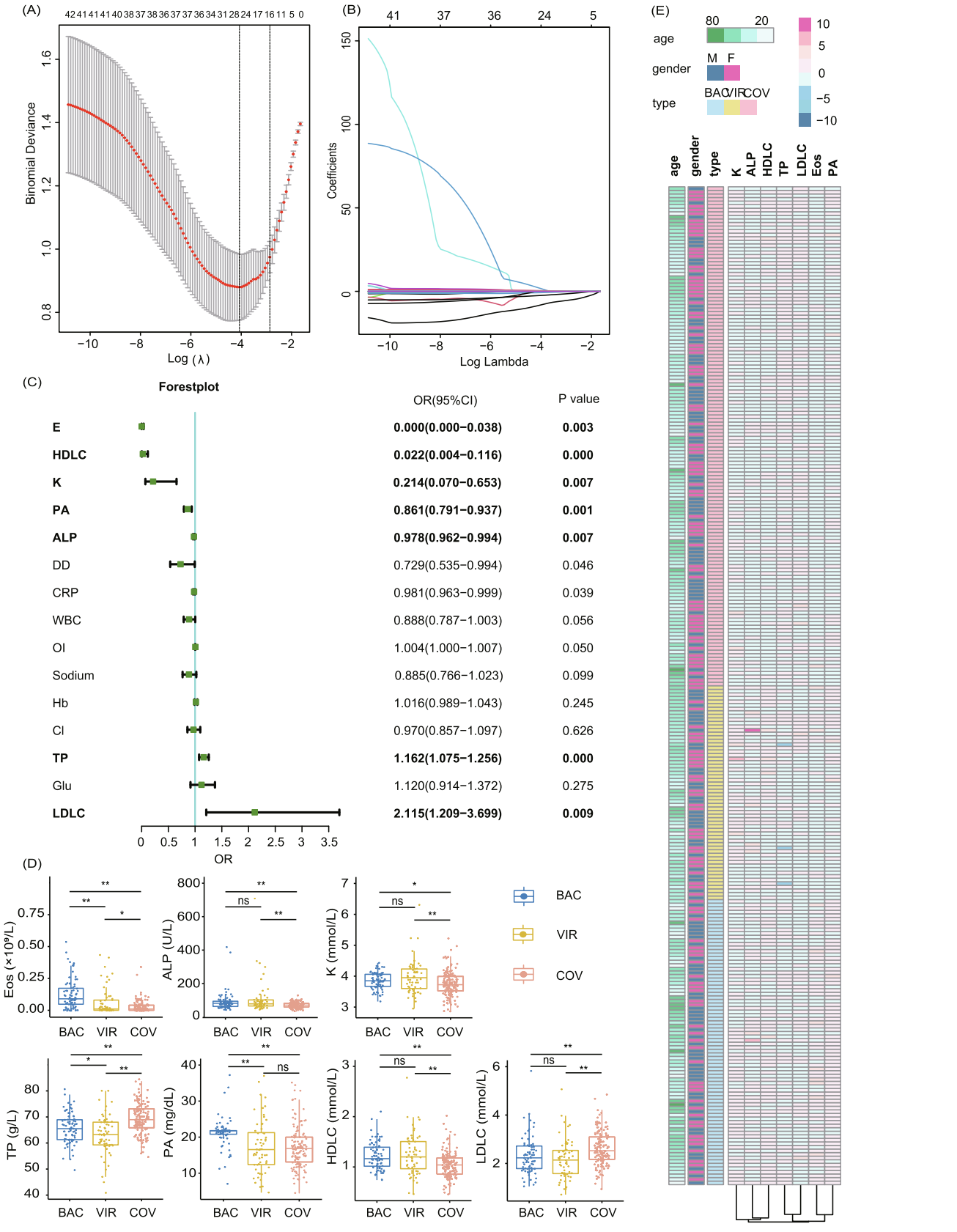

Fig. 2. Comparison of laboratory indexes between COVID-19, bacterial pneumonia and conventional viral pneumonia patients (A) The plot of partial likelihood deviance of LASSO logistic regression; (B) Plot of LASSO coefficient profiles; (C) Forest map of multivariate logistic regression; (D) Boxplots of eosinophils (Eos), potassium (K), alkaline phosphatase (ALP), total protein (TP), prealbumin (PA), high-density lipoprotein cholesterol (HDLC) and low-density lipoprotein cholesterol (LDLC) between COVID-19, bacterial pneumonia and conventional viral pneumonia patients; (E) Heatmap of eosinophils (Eos), potassium (K), alkaline phosphatase (ALP), total protein (TP), prealbumin (PA), high-density lipoprotein cholesterol (HDLC) and low-density lipoprotein cholesterol (LDLC) between COVID-19, bacterial pneumonia and conventional viral pneumonia patients.

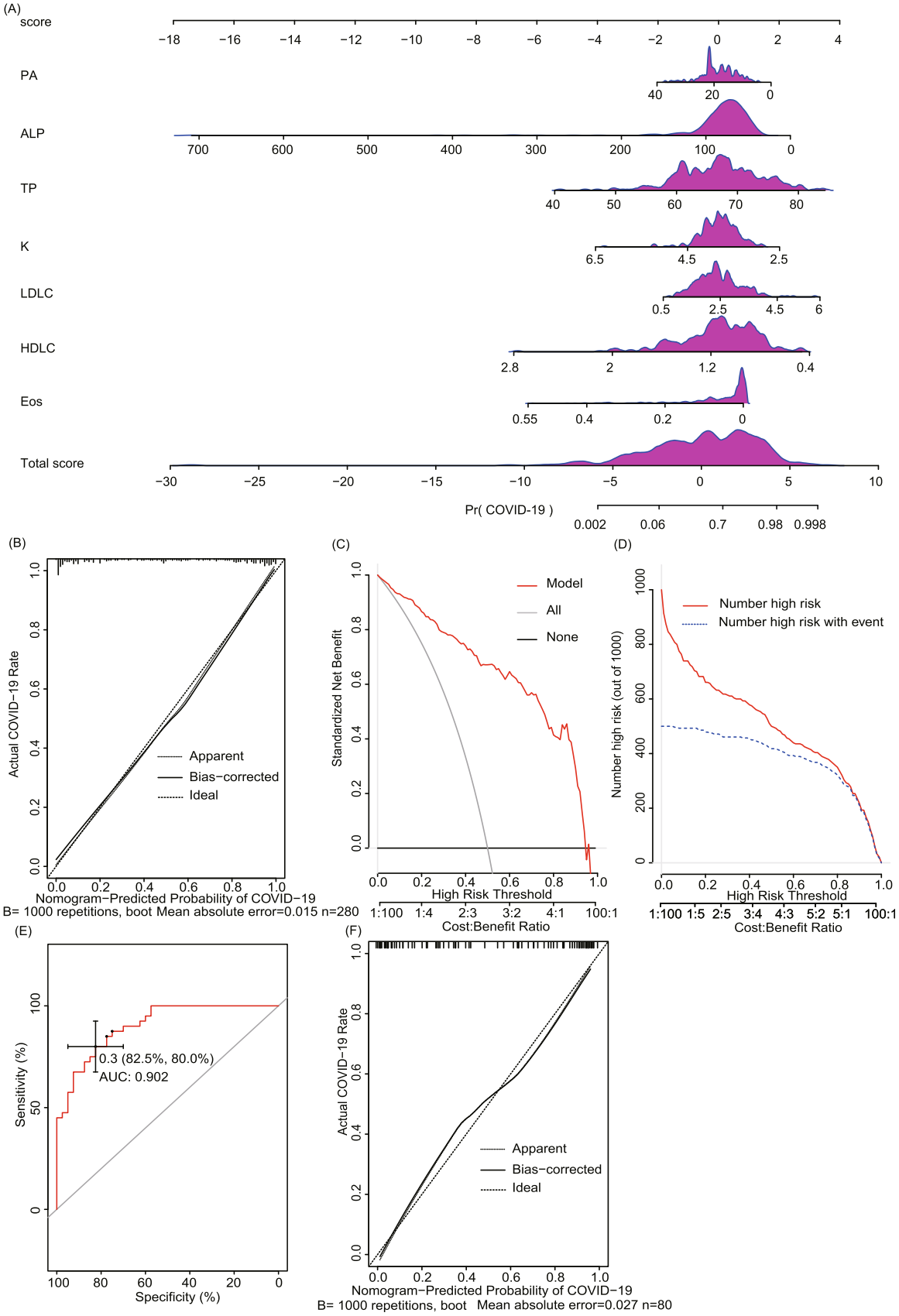

Fig. 3. Laboratory differential diagnostic model of COVID-19, bacterial pneumonia and conventional viral pneumonia (A) Nomogram model for the differential diagnosis of COVID-19, bacterial pneumonia and conventional viral pneumonia; (B) calibration curve; (C) clinical decision curve; (D) clinical impact curve; (E) ROC curve of the validation group; (F) calibration curve of the validation group.

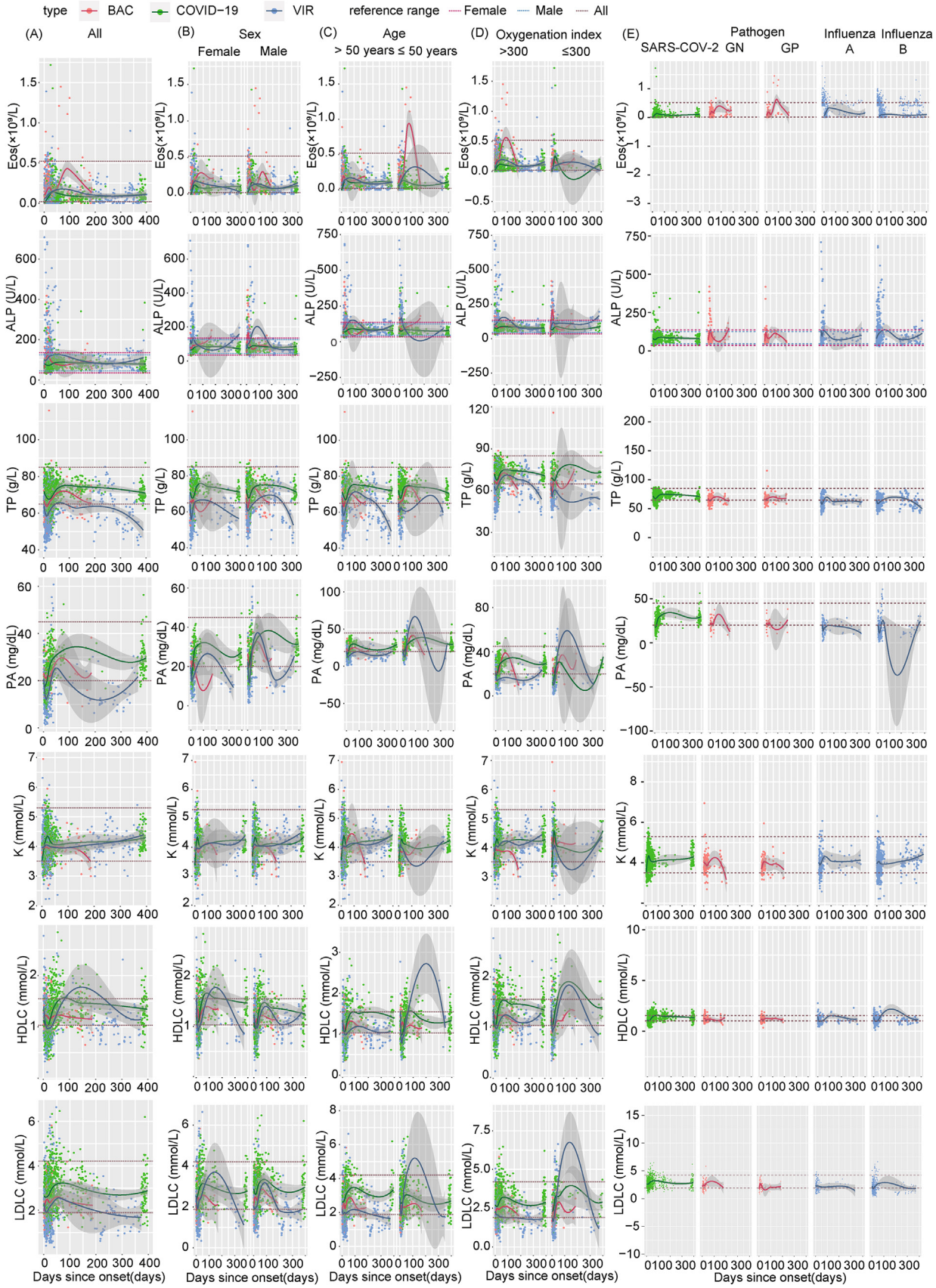

Fig. 4. Comparison of the dynamic changes in eosinophils (Eos), potassium (K), alkaline phosphatase (ALP), total protein (TP), prealbumin (PA), high-density lipoprotein cholesterol (HDLC) and low-density lipoprotein cholesterol (LDLC) in COVID-19, bacterial pneumonia and conventional viral pneumonia patients. (A) All patients; (B) Female vs. male; (C) Age >50 years vs. age ≤50 years; (D) Oxygenation index >300 mmHg vs. oxygenation index ≤300 mmHg; (E) Different pathogens.

of clinical events can be obtained according to the cumulative score of all variables [24].

The C-index of the nomogram model was 0.922, and in the external validation group, which had 20 bacterial pneumonia patients, 20 conventional viral pneumonia patients and 40 COVID-19 patients, the AUC was 0.902, meaning it was highly accurate. This result indicated that the model established in this study could distinguish COVID-19 from other pneumonia types. The selected indicators could represent the differences in the nature and pathogenesis of COVID-19 and non-COVID-19 pneumonias. It was noteworthy that we followed up the cohorts' laboratory indicators for more than 400 days, and patients were grouped by age, sex, disease severity and pathogen to compare the dynamic changes in laboratory indicators of different pneumonias among the subgroups, in order to speculate on the role of laboratory indicators in reflecting the patient's disease condition and prognosis.

The bacterial pneumonia and conventional viral pneumonia patients we enrolled were older than the COVID-19 patients. Some studies have shown that older patients are more susceptible to COVID-19 [25], so we selected bacterial pneumonia and conventional viral pneumonia patients who matched the age and sex of COVID-19 patients as the model group. Nevertheless, among the 3 cohorts in this study, COVID-19 patients had the fewest underlying diseases, while conventional viral pneumonia patients had the most underlying diseases. This may be related to the fact that approximately 75% of the 140 COVID-19 patients in this study had mild pneumonia, and most of them had a history of exposure or contact with infectious sources in Wuhan and had a certain tendency to aggregate. Therefore, we speculated that not only elderly patients and patients with more underlying diseases but also younger patients and those with fewer underlying diseases are susceptible to COVID-19. The most important COVID-19 risk factor is a contact history with infection sources.

We collected all patients' laboratory results on admission for modeling. Because there were more laboratory indicators than members of each cohort, we first used LASSO regression to screen the indicators. LASSO regression was characterized by variable selection and regulation while fitting the generalized linear model. Therefore, whether the response variable is continuous, binary or multivariate discrete can be modeled and predicted by LASSO regression. In clinical applications, if the independent variables have multicollinearity or the number of variables is much larger than the sample size, LASSO regression should be done [26].

According to the LASSO regression results, we further included the selected indicators in multivariate logistic regression, and we selected 7 indicators with $P < 0.01$, including Eos, HDLC, K, LDLC, TP, PA and ALP, to establish the differential diagnostic model. Boxplots and heatmaps showed that LDLC and TP were higher in the COVID-19 group, and Eos, HDLC, K, PA and ALP were lower. During the follow-up of 400 days, it was found that there were significant differences in the dynamic changes between COVID-19 patients and other pneumonia patients.

Previous studies have found that eosinophils in COVID-19 patients are significantly low on admission, especially in critically ill patients, and the recovery of eosinophils could be used as a predictor of recovery [27]. In our study, eosinophil counts were always the lowest in COVID-19 patients on admission and during follow-up. Moreover, eosinophils stopped rising after 25 days of onset, as the median duration of COVID-19 was approximately 20 days [28], indicating that eosinophils were sensitive indicators of the recovery of COVID-19 patients. In addition, eosinophils of COVID-19 patients with OI < 300 mmHg were very low for a long time after the onset of the disease but recovered by 350 days after the onset of the disease. Because OI < 300 mmHg was an index for the diagnosis of severe COVID-19 patients, our findings indicate that the recovery time of severe COVID-19 patients was approximately 1 year, while that of non-severe patients was 50 days or less.

In this study, we found that the total protein level of COVID-19 patients was higher than that of bacterial pneumonia and conventional viral pneumonia patients, but prealbumin was lower. Prealbumin is a specific indicator reflecting the synthetic function of the liver that is more sensitive and accurate than albumin [29], and a previous study revealed lower prealbumin levels in COVID-19 patients than in non-COVID-19 patients [30], which was consistent with our study. Therefore, we can infer that acute liver injury may arise in the early stage of COVID-19.

A study showed that the ALP in COVID-19 patients was significantly lower than that in patients with influenza virus infection [31] and community-acquired pneumonia (CAP) [32]. In this study, we also found that the ALP levels of COVID-19 patients were lower than those of bacterial pneumonia and conventional viral pneumonia patients on admission. Our study also found that sex and age influenced the changes in ALP in bacterial pneumonia and conventional viral pneumonia patients during follow-up, but no significant difference was observed in COVID-19 patients between subgroups, suggesting that ALP was not a sensitive indicator of the disease course of COVID-19 patients, which might be related to the mild degree of liver injury in COVID-19 patients.

It has been revealed that hypokalemia is the second most common complication in emergency patients with community-acquired pneumonia, which was related to the prolonged hospital stay, but it has nothing to do with pneumonia recurrence [33]. Our data showed that the serum potassium level of COVID-19 patients was the lowest at the onset of the disease, but it remained stable during the following 400 days of follow-up. The serum potassium concentration of bacterial pneumonia patients fluctuated greatly during the follow-up period, and they were more prone to hypokalemia. The serum potassium level of patients under 50 years of age and patients with severe conventional viral pneumonia showed a rapid decreasing trend within 150 days after onset, indicating that the dynamic change in the serum potassium level could reflect the severity of pneumonia.

HDLC is a kind of plasma lipoprotein that can resist atherosclerosis [34], while LDLC has the opposite effect [35]. At the time of onset, HDLC was the lowest and LDLC was the highest in COVID-19 patients. During the follow-up, the changes in HDLC and LDLC in the 3 groups were similar. Among them, LDLC and HDLC in severe COVID-19 patients had a rising trend within 150 days after the onset, especially the HDLC level, which even exceeded the upper limit of the reference range, which might be related to the influence of virus clearance on lipid metabolism and the change in diet. Conventional viral pneumonia patients also had a rising trend similar to that of COVID-19 patients.

There are some limitations to this study. First, due to the small number of confirmed COVID-19 patients in the Taizhou area, the sample size of the cohort was comparatively small. Second, according to our inclusion and exclusion criteria, the proportions of gram-positive bacteria and gram-negative bacteria in bacterial pneumonia and the proportions of influenza A and influenza B in conventional viral pneumonia patients were imbalanced, which may have biased the results.

5. Conclusions

In conclusion, the differential diagnostic model established by laboratory indicators on admission in this study is highly accurate when it is used to distinguish COVID-19 from bacterial pneumonia and conventional viral pneumonia. It can provide a new method for clinicians to identify COVID-19 patients, although a larger sample

and prospective studies are still needed for further validation. More importantly, we compared the 400-day dynamic changes in laboratory parameters between groups and revealed that the recovery time of COVID-19 patients was not longer than that of bacterial pneumonia and conventional viral pneumonia patients.

Ethics approval and consent to participate

Medical Ethics Committee of Taizhou Hospital of Zhejiang Province. (Identification code: K20200211, date: 28 February 2020).

Consent for publication

All the authors have accepted responsibility for this submitted manuscript's entire content and approved submission.

CRediT authorship contribution statement

Jing Wang: Methodology, Software, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration, Funding acquisition. **Yufen Zheng:** Methodology, Investigation, Resources, Data curation. **Yijun Chen:** Formal analysis, Data curation. **Xingzhong Hu:** Validation. **Minfei Peng:** Writing - review & editing. **Yicheng Fang:** Writing - review & editing. **Bo Shen:** Methodology, Resources, Data curation, Supervision, Project administration. **Guoguang Lu:** Methodology, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.csbj.2021.04.063.

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