Analysis of laboratory findings in recovered and non-recovered patients with COVID-19: a longitudinal observational study in Jilin Province of China

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Background: We aimed to describe the laboratory characteristics of patients with laboratory confirmed coronavirus disease 2019 (COVID-19), and to compare the laboratory data between recovered and non-recovered patients.

Methods: This is a multi-center study and 68 COVID-19 patients were recruited in Jilin Province, China, from January 21, 2020 to February 21, 2020. Laboratory tests were conducted at admission. Outcomes were followed up until February 21, 2020.

Results: Of the 68 patients, 63 were diagnosed as mild and 5 as moderate or severe. After follow-up, there are 28 and 40 patients in recovered and non-recovered group, respectively. Lymphocytes, including immature leukocyte subpopulation, were significantly increased after day 10 in recovered patients. Platelets and thrombocytocrit were significantly increased, while mean platelet volume was reduced markedly from day 6 in recovered patients. High-sensitivity C-reactive protein was elevated at onset and continued to decline at day 7 in recovered patients. Cardiac troponin I is always higher from onset to recovery in recovered patients, yet it is sharply declined below the upper limit of reference interval after day 10. Cholinesterase and alanine aminotransferase were higher during the recovery process in recovered patients than in non-recovered patients. Both eosinophil and age were identified as independent predictors for recovery.

Conclusions: Some markers had different change patterns between the recovered and non-recovered patients. Eosinophil may serve as an independent predictor for recovery in addition to age. The monitoring of the dynamic level of markers can give more effective clues for the judgment of the progress in COVID-19 patients.

Keywords: Severe acute respiratory syndrome coronavirus 2; coronavirus disease 2019 (COVID-19); eosinophil; large immature cells; high-sensitivity C-reactive protein

Introduction

Coronavirus disease 2019 (COVID-19) has caused an epidemic throughout the world since December, 2019. Although some researchers have established the clinical and/or epidemiologic features of the patients with COVID-19 (1,2), and a few researchers focus on the longitudinal observational study in T cell counts, cytokine levels and IgM, IgA and IgG SARS-CoV-2 antibodies in the patients with COVID-19 (3,4). The insightful clues have been confirmed to be revealed by longitudinal change patterns of laboratory tests on disease progression and recovery progression (5). Therefore, it is important to analyze and summarize longitudinal laboratory characteristics for monitoring and evaluating patients with COVID-19.

This research aimed to investigate epidemiological, the laboratory characteristics and outcomes of patients with COVID-19, including differences of laboratory data between recovered and non-recovered patients. We hope our study will provide useful prognostic factor from laboratory findings for accurate individualized assessment of COVID-19. We present the following article in accordance with the MDAR checklist (available at http://dx.doi.org/10.21037/aoe-20-72).

Methods

Patient selection and data sources

This study was a multi-center study focusing on the patients with a laboratory confirmed COVID-19, which included 68 patients in the First Hospital of Jilin University (n=4), Siping Infectious Disease Hospital (n=22) or Changchun Infectious Disease Hospital (n=42) in Jilin Province, China, from January 21, 2020 to February21, 2020. Epidemiological, demographic, date of illness onset, hospital admission date, laboratory findings, outcomes data, and severity of COVID-19 with data collection forms, were collected from electronic medical records system. Two researchers separately evaluated the record collection forms to ensure the accuracy of the record. The onset day was described as the date when any symptoms were observed by the patients. Severity of COVID-19 was described according to the diagnostic and treatment guideline for SARS-CoV-2 issued by Chinese National Health Committee (Version 3-5). Severe COVID-19 was confirmed if the patients had one of the following criteria: (I) respiratory distress with respiratory frequency ≥30/min;

(II) pulse oximeter oxygen saturation ≤93% at rest; (III) oxygenation index (artery partial pressure of oxygen (PaO2)/inspired oxygen fraction (FiO2) ≤300 mmHg. The clinical outcomes were continuously tracked until February 21, 2020. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of the First Hospital of Jilin University (No. 2020-313), the Ethics Committee of Changchun Infectious Disease Hospital (No. 2020-001), and the Ethics Committee of Siping Infectious Disease Hospital (No. 2020-001). Informed consent of all subjects was waived.

Laboratory tests

All the suspected patients with COVID-19 were taken sputum and throat swab specimens at admission and stored in virus transport medium, which were transported to local Center for Disease Control and Prevention (Changchun or Siping). Doubtful positive specimens were taken to determine again by Jilin Provincial Center for Disease Control and Prevention. Specimens were determined by real time reverse-transcription-polymerase-chain-reaction (RT-PCR) for SARS-Cov-2 RNA within three hours. Virus examination was repeated twice every 24 hours. The assay was carried out by SARS-CoV-2 nucleic acid detection kit based on the manufacturer's protocol (Shanghai bio-germ Medical Technology Co. Ltd, and Shanghai GeneoDx Biotech Co. Ltd). Patients with COVID-19 were rehabilitateed from hospital once the results of two RT-PCR tests at 24-hour intervals were negative for SARS-Cov-2. Laboratory tests, including haematological, biochemical, and immunological tests, were carried out at admission. All renewed results for laboratory data during hospitalization were collected as disease progressed. The laboratory findings for certain patients were missing because the absence of kinds of tests or delayed results. All reagents related to test were original from same manufacturer, which means that the reagent and analyzer are matched.

All clinicians, technicians, and nurses participating in the epidemic had been appropriately trained. In 2012, reference interval (RI) standards for common biochemical analyte and blood cell analysis in Chinese adults were published by the Ministry of Health of the People's Republic of China (6,7). The RIs of tests were all performed by these Standards in the three designated hospitals. The RI of troponin I was below the 99th percentile of healthy people.

Statistical analysis

The clinical characteristics such as age, recovery time, sex and the laboratory tests at the baseline line stratified by the recovery status are presented as median (IQR) for continuous variables and as n (%) for categorical variables.

Here, the hospital day is divided into four periods: the first period on the day of admission, the second period ranges from the second day to the fifth day, the third period from the sixth day to the tenth day, and the fourth period after the tenth day. For the longitudinal laboratory measurement profiles, the Generalized Estimating Equation (GEE) models (8) were fit separately for each parameter to examine if there were different change patterns between the recovered group and the non-recovered group, with the hospital day indicators, the recovery status and their interaction terms as covariates and the correlation structure matrix as unstructured type. Upon those tests with either the absolute robust Z score of the recovery status indicator (meaning there is a difference between the two groups at the baseline) or those of at least one interaction term (meaning there might be a difference between the two groups during the hospitalized days) is larger than 1.96, and 1,000 bootstrapped replicates were made to construct the 95 % confidence intervals (CIs) of estimated values for individual period and recovery strata.

Lastly, a multiple logistic regression model with the recovery status as the response variable and patients' age, sex, severity type and laboratory tests that differed significantly at the baseline as covariates was fit, and a nomogram was diagramed. All analyses were performed by the R language, version 3.6.1 (www.r-project.org).

Results

Demographics and exposures

Of the 68 patients with COVID-19 in this study, 63 were diagnosed as mild and 5 as moderate or severe on admission. The median age of the patients was 41 years (range, 8–87 years), and 30.9% of them were more than 50 years old. Thirty-one (54.4%) of patients were male. The median intervals from the onset of symptoms to hospital admission for all patients were 4 days (IQR, 1–7 days). As of the termination day of this study, 28 subjects were rehabilitated (recovered group) and 40 patients were admitted still (non-recovered group). The median hospitalized time were 12.5 days (IQR, 10.0–16.0 days) for recovered patients and 13.0 days (IQR, 10.0–16.7 days) for non-recovered subjects.

The median age of the two groups was not statistically different, and the recovered group and the non-recovered group were 41 years old and 42.5 years old, respectively. None of the 68 patients had a history of Huanan seafood market exposure in Wuhan, 28 of them (41.2%) were imported cases. We define imported cases as patient who had been diagnosed as COVID-19 and had travel history in Hubei Province or contact history with COVID-19 patients outside Jilin Province within 14 days before the onset of symptoms. Here, 28 of them (41.2%) were primary cases, who stayed in Jilin Province without leaving but had a close exposure history with imported patients, and the other 12 (17.6%) patients were secondary cases, who had a close exposure history with primary contacts. The transmission route for COVID-19 patient is summarized in *Figure 1*. The baseline characteristics of recovered and non-recovered patients with COVID-19 is presented in *Table 1*.

For leukocyte parameters, white blood cell, neutrophils (NE), lymphocytes (LY), and eosinophils (EO) were below the lower reference limit (LRL) in 12.9%, 14.5%, 40.3%, and 51.6% patients, while basophils (BA) and monocytes were higher than upper reference limit (URL) in 4.8% and 14.5% patients at onset to hospital admission, respectively. The values of EO and BA in recovered patients were lower than non-recovered patients, respectively (P<0.05). For erythrocyte parameters, red blood cells (RBC), hemoglobin (HGB), and hematocrit (HCT) were below the LRL in 8.1%, 1.6%, and 4.8% patients, respectively. For Platelet parameters, decreased platelets count (PLT) was found in 12.9% patients. For coagulation parameters, activated partial thromboplastin time (APTT), prothrombin time (PT), and international Normalized Ratio were increased in 10.3%, 28.2% and 7.7% patients, respectively, while fibrinogen were decreased in 15.4% patients. For serum cardiac markers, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), creatinine kinase-muscle/brain activity (CK-MB), and cardiac troponin I (cTnI), are higher than the URL in 16.1%, 30.4%, 5.4%, 17.9%, and 13.3% patients, respectively. For liver function tests, increased alanine aminotransferase (ALT), γ-glutamyl transpeptidase, total bilirubin, direct bilirubin, and indirect bilirubin were found in 16.1%, 14.8%, 3.6%, 3.6% and 1.8% patients, while cholinesterase (CHE), total protein, albumin and globulin (GLB) were decreased in 4.7%, 20.0%, 7.3%, and 12.7% patients, respectively. For kidney function tests, blood urea nitrogen and creatinine were increased in 3.6%, and 5.4% patients, respectively. For electrolyte tests, potassium, sodium and chloride were
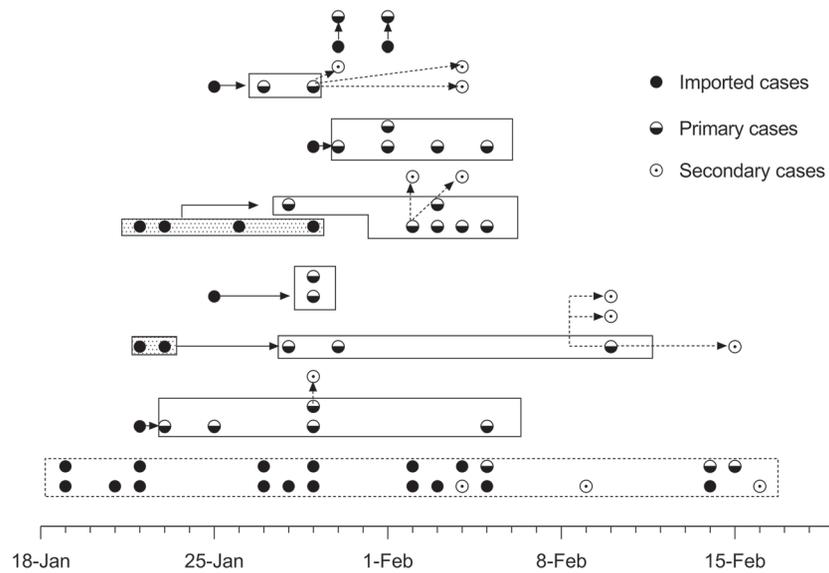
Figure 1 Transmission route for subjects with COVID-19 in Jilin province. Imported cases: subjects with travel history in Hubei Province or contact history with confirmed subjects outside Jilin Province within 14 days before the onset of symptoms; primary cases: subjects caused by imported cases; secondary cases: subjects caused by primary cases; dotted square: subjects who are not link to any specific individual. COVID-19, coronavirus disease 2019.

decreased in 5.3%, 28.1% and 22.8% patients, respectively. Laboratory data of patients with COVID-19 at onset to hospital admission are shown in *Table 2*.

Temporal trajectories of laboratory tests

LIC, an immature leukocyte subpopulation, was significantly increased after day 10 in recovered patients as well as increased trends in NE, LY, EO, BA and MO. Platelet parameters—PLT, plateletcrit (PCT) and mean platelet volume (MPV), indicators of platelet function *in vivo*, were in the range of RI in most cases and no difference before day 5 in recovered and non-recovered patients. Interestingly, PLT and PCT were significantly increased after day 6 in recovered patients, while MPV was reduced markedly from day 6 in recovered patients, even close to the LRL. For erythrocyte parameters—RBC, HGB, and HCT, no statistical differences before day 10 were found between recovered and non-recovered patients. All these three parameters were non-marginally higher after day 10 in recovered patients, while the parameters showed gradual decline, especially from day 6 below the LRL in non-recovered patients.

CRP, a marker of inflammation, was elevated at onset in both groups, and it declined to the URL at day 6 and remained constant afterwards in recovered patients, compared with always higher levels than the URL in non-recovered patients. Serum cardiac markers—AST, LDH, CK, CK-MB, and cTnI, are higher than the URL in 16.1%, 30.4%, 5.4%, 17.9%, and 13.3% patients at onset to hospital admission, respectively. Especially, cTnI that is a marker of myocardial injury was always higher from onset to recovery in recovered patients, yet it was sharply declined below the URL after day 10. CHE, an enzyme that reflects hepatic synthetic function, was always higher during the recovery process in recovered patients than in non-recovered patients. However, ALT, another enzyme in liver cells, was always slightly elevated over the URL in recovered patients than in non-recovered patients, indicating gently liver injury even disease recovery. Compared with non-recovered patients, GLB was lower at all time points, suggesting no strong immune response in these patients. Comparison of laboratory findings on the day of admission in recovered and non-recovered patients is shown in *Table 2* and their change trajectories over time are presented in *Figure 2*.

Predictors of recovery

According to the GEE analysis and the baseline comparison

Table 1 The baseline characteristics of recovered and non-recovered patients with COVID-19

Characteristic	Recovered group (n=28)	Non-recovered group (n=40)
Hospitalized time, median (P25–P75)	12.5 (10.0–16.0)	13.0 (10.0–16.7)
City, No. (%)		
Changchun	20 (71.4)	26 (65.0)
Siping	8 (28.6)	14 (35.0)
Age, median (P25–P75)		
Male	41 (32.0–49.0)	46 (29.0–72.0)
Female	38 (26.0–47.0)	41 (26.0–58.0)
Age groups, No. (%)		
<30 yr	8 (28.5)	13 (32.5)
30–49 yr	15 (53.6)	11 (27.5)
50–69 yr	4 (14.3)	9 (22.5)
≥70 yr	1 (3.6)	7 (17.5)
Sex-No. (%)		
Male	17 (60.7)	20 (50.0)
Female	11 (39.3)	20 (50.0)
Contact category, No. (%)		
Imported cases	17 (60.7)	11 (27.5)
Primary cases	8 (28.6)	20 (50.0)
Secondary cases	3 (10.7)	9 (22.5)
Signs and symptoms, No. (%)		
Fever	25 (89.3)	33 (82.5)
Cough	22 (78.6)	30 (75.0)
Nasal congestion	3 (10.7)	5 (12.5)
Sneezing	1 (3.6)	1 (2.5)
Haemoptysis	1 (3.6)	0 (0.0)
Sore throat	0 (0.0)	4 (10.0)
Pleuritic chest pain	1 (3.6)	2 (5.0)
Fatigue	12 (42.9)	13 (32.5)
Myalgia	6 (21.4)	6 (15.0)
Headache	3 (10.7)	3 (7.5)
Dyspnoea	2 (7.1)	7 (17.5)
Diarrhoea	6 (21.4)	3 (7.5)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Recovered group (n=28)	Non-recovered group (n=40)
Chronic basic diseases, No. (%)		
Endocrine system disease	1 (3.6)	5 (12.5)
Cardiovascular disease	4 (14.3)	6 (15.0)
Cerebrovascular disease	2 (7.1)	5 (12.5)
Respiratory system disease	0 (0.0)	4 (10.0)
Malignancy	2 (7.1)	0 (0.0)
Digestive system disease	0 (0.0)	1 (2.5)

COVID-19, coronavirus disease 2019.

(as shown in *Figure 2*), both EO and BA differed at the first measurement on the day of admission in recovered and non-recovered patients, and they had similar change trajectories over time. Since EO and BA are highly positively correlated at the baseline, BA was discarded from the downstream analysis to avoid the co-linearity issue, and a multiple logistic regression model was fit with EO level at the baseline, age, severity level and gender as predictors to estimate the possibility of recovery for the patients with COVID-19. Both age (P=0.041) and EO (P=0.025) were identified as independent predictors for recovery. The corresponding nomogram was made to elucidate graphically the association of these predictors with recovery (*Figure 3*). As shown in *Figure 3*, a young patient had a better chance to recover from the disease than an elderly patient. If a patient had a smaller EO value at the baseline, the probability of recovery was higher.

Discussion

Most patients with COVID-19 were middle and elderly aged. SARS-CoV-2 infection was proved by RT-PCR in all patients. There are 28 patients in recovered group and 40 patients in non-recovered group in the current study, respectively. The median age of the two groups was not statistically different. Of the 68 patients, 41.2% were imported cases-patients, 41.2% were primary cases, and 17.6% were secondary cases. In this study, severe ill ones are all over 45 years old. We proposed that EO and age may

Table 2 Laboratory findings of patients with COVID-19 at onset to hospital admission

Laboratory parameters	Unit	Reference interval	All patients, n=68	Recovered group, n=28	Non-recovered group, n=40	P
White blood cell	10^9/L	3.50–9.50	5.15 (3.92–6.22)	5.10 (4.06–6.15)	5.24 (3.88–6.30)	0.860
Decrease			8/62 (12.9)	3/28 (10.7)	5/34 (14.7)	
Neutrophils	10^9/L	1.80–6.30	3.47 (2.58–4.38)	3.40 (2.70–4.75)	3.49 (2.13–4.14)	0.761
Increase			2/62 (3.2)	0/28 (0.0)	2/34 (5.9)	
Decrease			9/62 (14.5)	3/28 (10.7)	6/34 (17.6)	
Lymphocytes	10^9/L	1.10–3.20	1.20 (0.90–1.61)	1.20 (0.93–1.40)	1.30 (0.88–1.75)	0.453
Decrease			25/62 (40.3)	12/28 (42.9)	13/34 (38.2)	
Eosinophils	10^9/L	0.02–0.52	0.01 (0.00–0.04)	0.01 (0.00–0.03)	0.03 (0.01–0.06)	0.029
Decrease			32/62 (51.6)	16/28 (57.1)	16/34 (47.1)	
Basophils	10^9/L	0.00–0.06	0.02 (0.00–0.03)	0.00 (0.00–0.03)	0.02 (0.01–0.04)	0.013
Increase			3/62 (4.8)	1/28 (3.6)	2/34 (5.9)	
Monocytes	10^9/L	0.10–0.60	0.32 (0.26–0.52)	0.41 (0.23–0.58)	0.31 (0.26–0.46)	0.315
Increase			9/62 (14.5)	6/28 (21.4)	3/34 (8.8)	
Red blood cells	10^{12}/L	4.30–5.80 (M), 3.80–5.10 (F)	4.70 (4.29–5.05)	4.69 (4.39–5.02)	4.76 (4.16–5.11)	0.793
Increase			3/62 (4.8)	2/28 (7.1)	1/34 (2.9)	
Decrease			5/62 (8.1)	0/28 (0.0)	5/34 (14.7)	
Hemoglobin	g/L	130–175 (M), 115–150 (F)	146 (133–157)	147 (135–157)	142 (129–157)	0.581
Increase			3/62 (4.8)	1/28 (3.6)	2/34 (5.9)	
Decrease			1/62 (1.6)	0/28 (0.0)	1/34 (2.9)	
Hematocrit	L/L	0.40–0.50 (M), 0.35–0.45 (F)	0.42 (0.39–0.45)	0.43 (0.39–0.45)	0.42 (0.37–0.45)	0.724
Increase			8/62 (12.9)	7/28 (25.0)	1/34 (2.9)	
Decrease			3/62 (4.8)	0/28 (0.0)	3/34 (8.8)	
Mean corpuscular volume	fL	82.0–100.0	89.7 (87.2–92.6)	90.1 (87.3–92.5)	89.3 (86.4–92.8)	0.343
Increase			3/62 (4.8)	1/28 (3.6)	2/34 (5.9)	
Decrease			2/62 (3.2)	0/28 (0.0)	2/34 (5.9)	
Mean corpuscular hemoglobin concentration	g/L	316–354	345 (340–349)	347 (343–350)	344 (339–349)	0.190
Increase			4/62 (6.5)	1/28 (3.6)	3/34 (8.8)	
Mean corpuscular hemoglobin	pg	27.0–34.0	31.0 (30.0–31.9)	31.2 (30.0–31.9)	30.7 (29.7–31.9)	0.484
Increase			4/62 (6.5)	2/28 (7.1)	2/34 (5.9)	
Decrease			2/62 (3.2)	0/28 (0.0)	2/34 (5.9)	
Red blood cell distribution width	%	11.00–16.00	11.60 (11.30–12.00)	11.50 (11.20–11.90)	11.60 (11.30–12.10)	0.294

Table 2 (*continued*)

Table 2 (*continued*)

Laboratory parameters	Unit	Reference interval	All patients, n=68	Recovered group, n=28	Non-recovered group, n=40	P
Platelets count	10^9/L	125–350	202 (161–232)	197 (162–230)	202 (158–242)	0.966
Increase			3/62 (4.8)	1/28 (3.6)	2/34 (5.9)	
Decrease			8/62 (12.9)	4/28 (14.3)	4/34 (11.8)	
Mean platelet volume	fL	6.5–12.0	9.4 (8.5–10.0)	9.2 (8.4–9.7)	9.5 (8.6–10.7)	0.234
Increase			1/62 (1.6)	0/28 (0.0)	1/34 (2.9)	
Platelet distribution width	%	9.0–17.0	12.7 (10.7–14.6)	11.7 (10.5–13.4)	12.8 (11.0–15.2)	0.263
Increase			5/62 (8.1)	1/28 (3.6)	4/34 (11.8)	
Plateletcrit	%	0.108–0.282	0.180 (0.140–0.200)	0.170 (0.140–0.200)	0.180 (0.150–0.220)	0.458
Increase			5/62 (8.1)	2/28 (7.1)	3/34 (8.8)	
Decrease			3/62 (4.8)	3/28 (10.7)	0/34 (0.0)	
Thrombin time	s	14.0–20.0	15.6 (15.0–16.2)	16.2 (15.3–16.5)	15.5 (14.9–16.0)	0.115
Activated partial thromboplastin time	s	22.2–38.0	34.7 (31.8–36.3)	34.7 (31.5–36.4)	34.4 (31.7–36.2)	0.723
Increase			4/39 (10.3)	3/17 (17.6)	1/22 (4.5)	
Prothrombin time	s	11.0–13.0	12.0 (11.6–13.2)	12.4 (11.5–13.1)	12.0 (11.6–13.4)	0.989
Increase			11/39 (28.2)	4/17 (23.5)	7/22 (31.8)	
Decrease			3/39 (7.7)	1/17 (5.9)	2/22 (9.1)	
International normalized ratio	–	0.90–1.30	1.07 (1.00–1.20)	1.07 (1.00–1.14)	1.06 (1.00–1.20)	0.764
Increase			3/39 (7.7)	2/17 (11.8)	1/22 (4.5)	
Decrease			2/39 (5.1)	0/17 (0.0)	2/22 (9.1)	
Fibrinogen	g/L	2.00–4.00	2.20 (2.02–3.32)	2.02 (2.01–4.22)	2.20 (2.08–3.16)	0.820
Increase			6/39 (15.4)	4/17 (23.5)	2/22 (9.1)	
Decrease			6/39 (15.4)	3/17 (17.6)	3/22 (13.6)	
High-sensitivity C-reactive protein	mg/L	≤6.0	9.0 (2.4–32.5)	14.1 (4.3–38.9)	6.8 (2.1–30.8)	0.363
Increase			26/48 (54.2)	13/22 (59.1)	13/26 (50.0)	
Myoglobin	ng/ml	0.0–61.5	22.8 (19.3–26.0)	19.3 (17.8–24.0)	24.4 (20.6–27.9)	0.012
Cardiac troponin I	ng/ml	<1.50	1.30 (1.08–1.83)	1.40 (1.20–1.80)	1.30 (1.00–2.20)	0.829
Increase			4/30 (13.3)	4/11 (36.3)	0/19 (0.0)	
Creatine kinase	U/L	50–310 (M), 40–200 (F)	75 (55–126)	73 (55–113)	76 (54–129)	0.822
Increase			3/56 (5.4)	0/23 (0.0)	3/33 (9.1)	
Decrease			3/56 (5.4)	0/23 (0.0)	3/33 (9.1)	
Creatinine kinase-muscle/brain activity	U/L	0.0–24.0	15.0 (11.0–20.0)	13.0 (11.0–24.0)	15.0 (11.0–20.0)	0.777
Increase			10/56 (17.9)	5/23 (21.7)	5/33 (15.2)	

Table 2 (*continued*)

Table 2 (*continued*)

Laboratory parameters	Unit	Reference interval	All patients, n=68	Recovered group, n=28	Non-recovered group, n=40	P
Lactate dehydrogenase	L	120–250	211 (185–266)	242 (185–274)	207 (184–237)	0.279
Increase			17/56 (30.4)	11/23 (47.8)	6/33 (18.2)	
Aspartate aminotransferase	U/L	15.0–40.0 (M), 13.0–35.0 (F)	25.0 (20.0–30.0)	26.0 (19.0–31.0)	22.0 (20.0–30.0)	0.835
Increase			9/56 (16.1)	4/23 (17.4)	5/33 (15.2)	
Decrease			2/56 (3.6)	1/23 (4.3)	1/33 (3.0)	
Alanine aminotransferase	U/L	9.0–50.0 (M), 7.0–40.0 (F)	25.0 (16.0–43.0)	25.0 (19.0–40.0)	24.0 (16.0–46.0)	0.771
Increase			9/56 (16.1)	3/23 (13.0)	6/33 (18.2)	
γ-glutamyl transpeptidase	U/L	10.0–60.0 (M), 7.0–45.0 (F)	24.0 (15.0–38.5)	24.0 (17.3–37.0)	26.0 (15.0–43.3)	0.839
Increase			8/54 (14.8)	2/22 (9.1)	6/32 (18.8)	
Decrease			1/54 (1.9)	0/22 (0.0)	1/32 (3.1)	
Cholinesterase	U/L	5,000–12,000	8171 (6638–9045)	8661 (6885–9110)	7898 (6196–8952)	0.328
Decrease			2/43 (4.7)	0/19 (0.0)	2/24 (8.3)	
Total protein	g/L	65.0–85.0	67.9 (65.1–72.7)	67.6 (65.0–72.0)	68.8 (65.6–73.2)	0.597
Decrease			11/55 (20.0)	5/23 (21.7)	6/32 (18.8)	
Albumin	g/L	40.0–55.0	43.7 (42.2–45.9)	43.6 (41.8–44.8)	44.2 (42.2–46.5)	0.361
Decrease			4/55 (7.3)	1/23 (4.3)	3/32 (9.4)	
Globulin	g/L	20.0–40.0	24.0 (21.8–27.9)	24.0 (20.7–28.5)	24.7 (21.9–27.6)	0.714
Decrease			7/55 (12.7)	3/23 (13.0)	4/32 (12.5)	
Total bilirubin	µmol/L	≤23.0	8.8 (7.1–13.5)	8.8 (6.8–13.5)	8.4 (7.1–13.7)	0.946
Increase			2/55 (3.6)	0/23 (0.0)	2/32 (6.3)	
Direct bilirubin	µmol/L	≤8.0	3.9 (3.2–5.1)	4.4 (3.1–5.1)	3.8 (3.2–5.3)	0.858
Increase			2/55 (3.6)	0/23 (0.0)	2/32 (6.3)	
Indirect bilirubin	µmol/L	5.10–21.40	4.90 (3.50–8.10)	5.10 (3.20–9.10)	4.75 (3.53–7.93)	0.811
Increase			1/55 (1.8)	0/23 (0.0)	1/32 (3.1)	
Decrease			19/55 (34.5)	11/23 (47.8)	8/32 (25.0)	
Blood urea nitrogen	mmol/L	3.10–8.00 (M), 2.60–7.50 (F)	3.67 (2.92–4.73)	3.28 (2.95–4.87)	3.80 (2.77–4.70)	0.987
Increase			2/56 (3.6)	1/23 (4.3)	1/33 (3.0)	
Creatinine	µmol/L	57.0–97.0 (M), 41.0–73.0 (F)	67.4 (57.5–76.8)	75.7 (56.9–85.6)	66.5 (58.9–72.2)	0.360
Increase			3/56 (5.4)	1/23 (4.3)	2/33 (6.1)	
Carbon dioxide combining power	mmol/L	22.0–29.0	21.3 (18.9–23.1)	21.5 (19.4–22.6)	20.9 (18.5–24.0)	0.771
Increase			1/56 (1.8)	1/23 (4.3)	0/33 (0.0)	
Decrease			34/56 (60.7)	14/23 (60.9)	20/33 (60.6)	

Table 2 (*continued*)

Table 2 (*continued*)

Laboratory parameters	Unit	Reference interval	All patients, n=68	Recovered group, n=28	Non-recovered group, n=40	P
Glucose	mol/L	3.89–6.11	6.12 (5.54–7.31)	6.04 (5.53–7.35)	6.26 (5.46–6.85)	0.960
Increase			28/56 (50.0)	10/23 (43.5)	18/33 (54.5)	
Potassium	mmol/L	3.50–5.30	4.10 (3.90–4.50)	4.10 (3.70–4.40)	4.20 (3.90–4.50)	0.199
Increase			1/57 (1.8)	1/23 (4.3)	0/34 (0.0)	
Decrease			3/57 (5.3)	2/23 (8.7)	1/34 (2.9)	
Sodium	mmol/L	137–147	138 (137–140)	138 (136–141)	138 (137–140)	0.317
Increase			1/57 (1.8)	0/23 (0.0)	1/34 (2.9)	
Decrease			16/57 (28.1)	9/23 (39.1)	7/34 (20.6)	
Chloride	mmol/L	99–110	100 (98–102)	98 (95–102)	101 (99–102)	0.122
Decrease			13/57 (22.8)	12/23 (52.2)	1/34 (2.9)	

Continuous variables are displayed as median (P25-P75), and others are displayed as n (%); P: comparing recovered group and non-recovered group were from Mann-Whitney U test. COVID-19, coronavirus disease 2019.

be a potential predictor.

Haematological tests

In this study, eosinopenia was found in 51.6% patients at onset to hospital admission, consistent with other recent report (9). The recovered patients had significantly lower EO levels than the non-recovered patients at onset. However, EO level was significantly increased after day 10 in recovered patients as well as BA. Therefore, the trend of EO may be used as a recovery indicator for COVID-19. Eosinopenia may be a crucial diagnostic clue in the patients with typical symptoms and radiological changes with and without lymphopenia. In those confirmed patients with COVID-19, continuously increased EO and BA level after treatment may be a sign for beginning recovery. The pathophysiology for eosinopenia in COVID-19 remains uncertain but is likely associated with multiple factors, involving inhibition of EO egress from the bone marrow, blockade of eosinophilopoiesis, decreased expression of chemokine receptors/adhesion factors and/or direct EO cell death induced by type 1 interferons released during the acute infection (10).

The absolute value of LY in 40.3% patients was decreased at onset to hospital admission in this study, between 35% and 75.4% in previous studies (9,11). Lymphopenia indicates that SARS-CoV-2 might primarily work on LY, as does SARS-CoV. LY, including immature leukocyte subpopulation, were significantly increased after day 10 in recovered patients, predicting increased leukocyte release and improved immune response after effective treatment in recovered patients.

PLT were below the LRL in 12.9% patients at onset to hospital admission, consistent with the report of 12% patients (n=99) in certain hospital (11), and lower than the study of 36.2% patients (n=1,099) in 552 hospitals, China (12). The abnormalities of these laboratory indexes are more obvious in critically ill cases. In our previous research (13), the possible mechanisms of thrombocytopenia in the patients with COVID-19 are as following: (I) The virus directly infects bone marrow stromal cells, inducing cell apoptosis and growth inhibition. (II) Platelets are damaged by the immune system. (III) Platelets aggregates and forms microthrombus, resulting in increased consumption in lung. In this study, PLT and PCT are significantly increased and MPV is decreased sharply in most cases within the range of RI after day 6 in recovered patients. The changes of these parameters suggested platelet parameters are probably indicative indexes for recovered patients.

RBC, HGB, and HCT were mostly in the range of RI in the whole course of disease and were non-marginally higher after day 10 in recovered patients. However, the three parameters showed gradual decline, especially from day 6 below the LRL in non-recovered patients. A recent study showed the ORF8 and surface glycoprotein may respectively bind to the porphyrin, while orf1ab, ORF10 and ORF3a
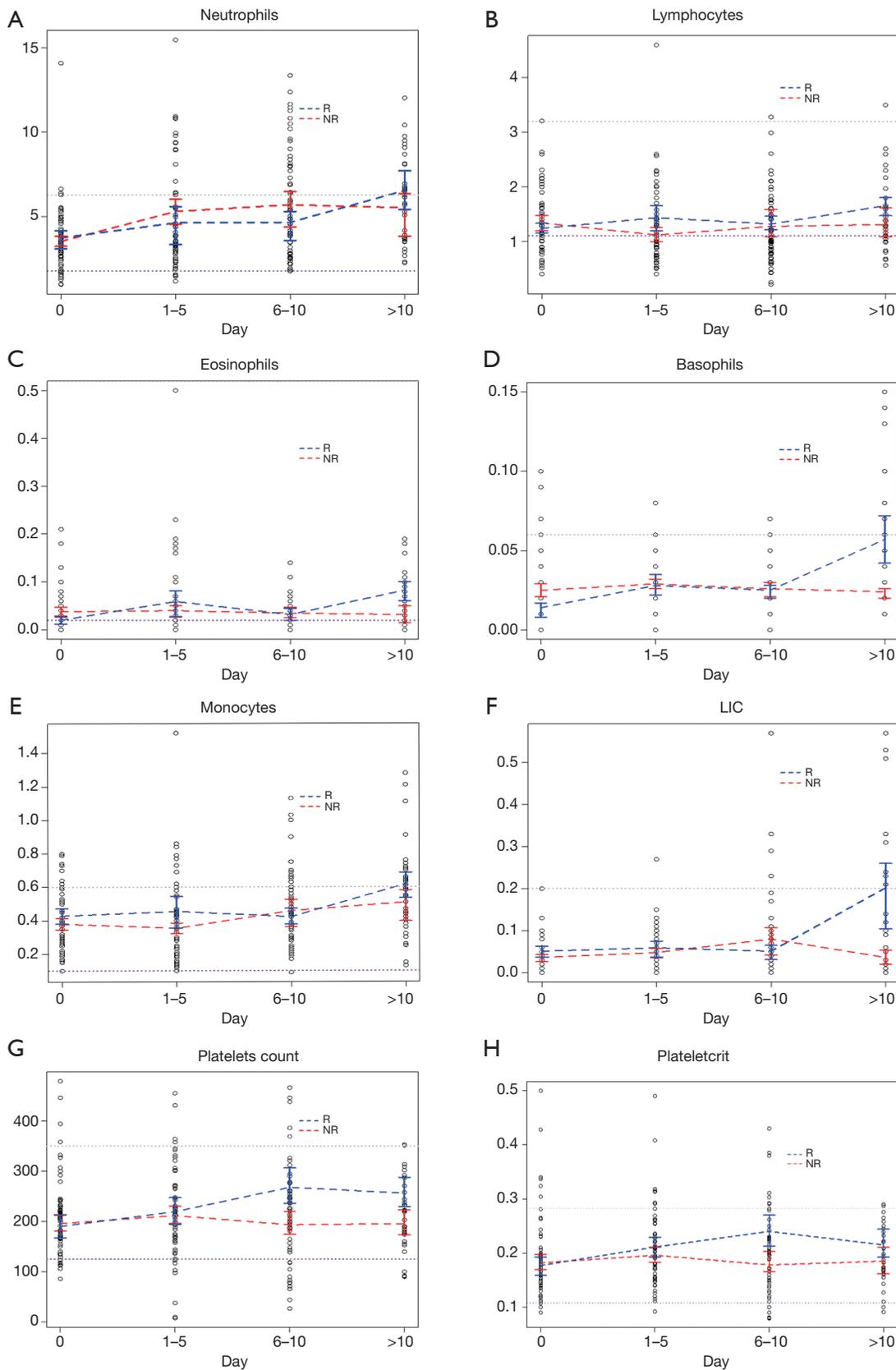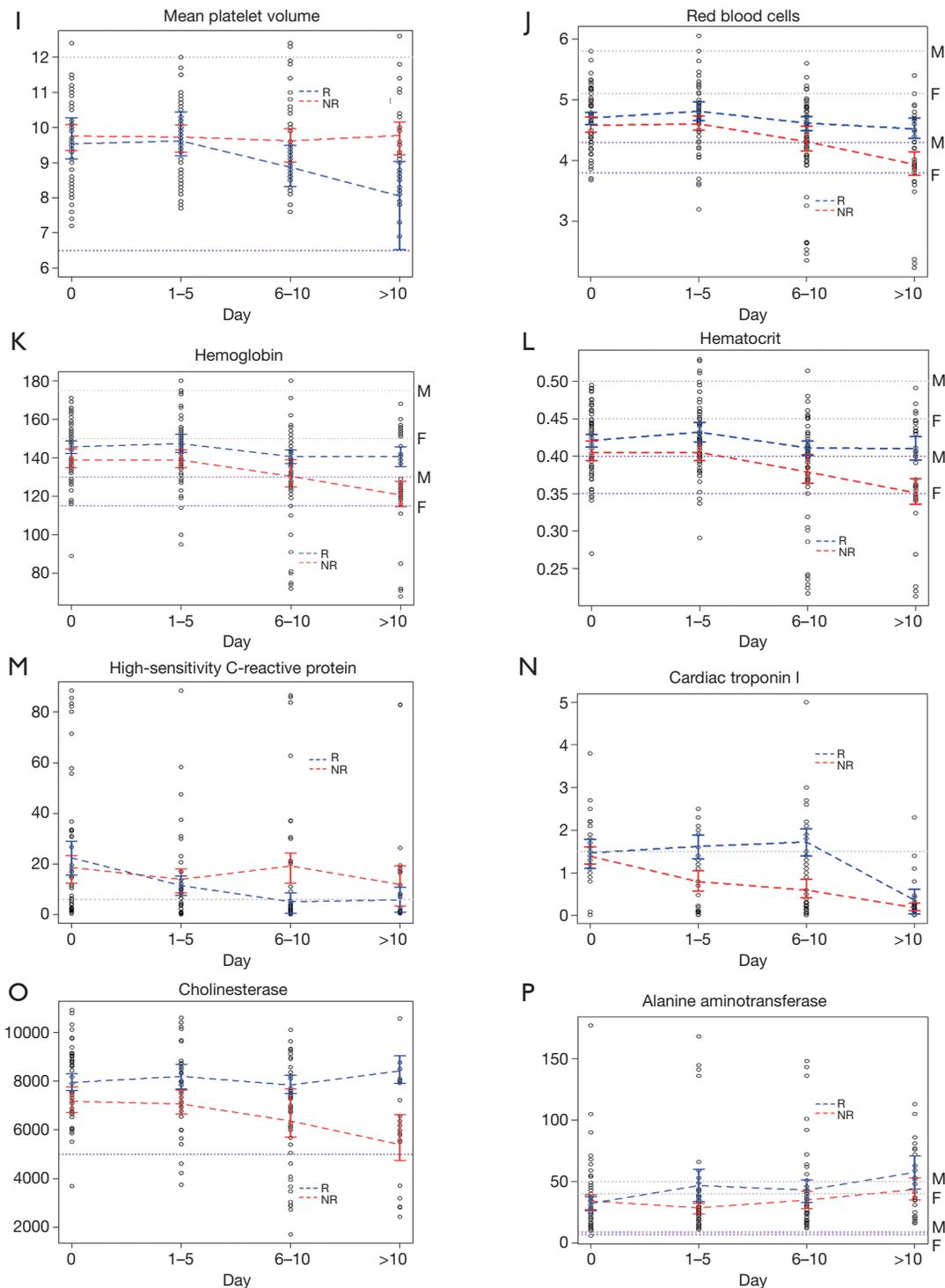
Figure 2 Temporal trajectories of laboratory tests. (A) Neutrophils. (B) Lymphocytes. (C) Eosinophils. (D) Basophils. (E) Monocytes. (F) LIC. (G) Platelets count (H) Plateletcrit. (I) Mean platelet volume. (J) Red blood cells. (K) Hemoglobin. (L) Hematocrit. (M) High-sensitivity C-reactive protein. (N) Cardiac troponin I. (O) Cholinesterase. (P) Alanine aminotransferase. Here, only the parameters that differed over time between the recovered group and the non-recovered group were presented. The gray dotted line represents the upper bound of RI whereas the purple dotted line represents the lower bound. R: the recovered group (n=28); NR: the non-recovered group (n=40). F: the RIs for females; M: RIs for males.
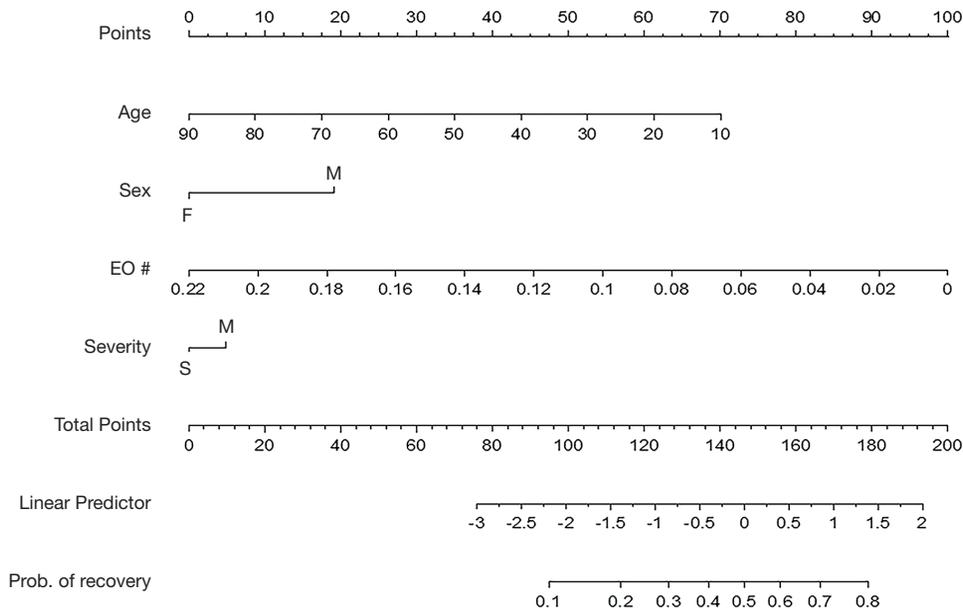
Figure 3 Nomogram to illustrate how age, gender, severity level and EO at the day of admission to hospitals are related to recovery. EO, eosinophils.

proteins could coordinately attack heme to dissociate the iron to form the porphyrin (14). The mechanism heavily disturbed with the normal heme anabolic pathway of the human body. Moreover, chloroquine could prevent orf1ab, ORF3a and ORF10 to attack the heme to form the porphyrin, and inhibit the binding of ORF8 and surface glycoproteins to porphyrins to some extent. In the present study, the changes of these parameters indicate that enough RBC and HGB can improve the recovery of recovered patients.

Biochemical and immunological tests

A study reported COVID-19 patients had a great deal of proinflammatory cytokines including IL1B, IFNγ, IP10, and MCP1, probably leading to activated T-helper-1 (Th1) cell responses (15). In this study, marker of inflammation-CRP was elevated at onset to hospital admission in both groups as well as serum ferritin (4 cases in the First Hospital of Jilin University, data not show), serum procalcitonin (1 case in Siping Infectious Disease Hospital, data not show), and erythrocyte sedimentation rate (8 cases in Siping Infectious Disease Hospital, data not show). Moreover, CRP continued to decline to the LRL at day 7 in recovered patients, compared with always higher levels than the URL in non-recovered patients. This study suggested that the cytokine storm was related to recovery process.

A study confirmed that about 12% patients with COVID-19 subjected acute cardiac injury (15). Subjects with cardiac disease had a higher fatality rate. In this study, serum cardiac markers—AST, LDH, CK, CK-MB, and cTnI, were higher than the URL in 5.4% to 30.4% patients at onset to hospital admission, respectively. Moreover, cTnI is always higher from onset to recovery in recovered patients, yet it is sharply declined below the URL after day 10. Therefore, the serum cardiac markers of in patients with COVID-19 are important to evaluate heart function.

Hepatic injury has been observed patients among COVID-19 (16). In this study, CHE is always higher during the process in recovered patients than in non-recovered patients. However, ALT is always slightly elevated over the URL in recovered patients than in non-recovered patients, indicating gently liver injury in the process of disease recovery. In contrast with non-recovered patients, GLB is lower at all time points, suggesting no strong immune response in recovered patients.

Limitations of this study

There were some limitations in the study. First, 68 patients were enrolled in this study and the number of samples was limited by region. Second, for the main objective in

the present study was to discuss the temporal trajectories of laboratory results, the data of clinical manifestation of patients with COVID-19 was absent.

Conclusions

By evaluating the temporal trajectories of laboratory markers, we found that many had different change patterns between the recovered and non-recovered patients. Especially, EO may serve as an independent predictor for recovery in addition to age. The monitoring of the dynamic level of markers can give more effective clues for the judgment of the progress in COVID-19 patients. Since COVID-19 is a new type of infectious disease, people know little about it so far. This study can help decipher the disease and pinpoint effective treatment regimen from the view of laboratory tests which are more inexpensive and routine compared to nucleic acid testing and CT. It will be necessary to confirm this data in larger samples, without excluding the need for RT-PCR.

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Footnote

Reporting Checklist: The authors have completed the MDAR checklist. Available at http://dx.doi.org/10.21037/jphe-20-82

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jphe-20-82). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Hospital of Jilin University (No.: 2020-313), the Ethics Committee of Changchun Infectious Disease Hospital (No.: 2020-001), and the Ethics Committee of Siping Infectious Disease Hospital (No.: 2020-001) and individual consent for this retrospective analysis was waived.

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