



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## High-density lipoprotein cholesterol as a factor affecting virus clearance in covid-19 patients

Xinmin Ding<sup>a,\*</sup>, Jie Zhang<sup>a,1</sup>, Lifei Liu<sup>b,1</sup>, Xiaodong Yuan<sup>a</sup>, Xuefeng Zang<sup>a</sup>, Feiping Lu<sup>a</sup>, Ping He<sup>c</sup>, Qian Wang<sup>c</sup>, Xiaomeng Zhang<sup>c</sup>, Yimin Xu<sup>a</sup>, Xiang Li<sup>a</sup>, Ying Liu<sup>a</sup>, Qun Li<sup>a</sup>, Xuebing Tan<sup>a</sup>, Yunhui Zheng<sup>a</sup>, Xue Lin<sup>a</sup>, Yuhang Liu<sup>a</sup>

<sup>a</sup> Beijing Shijitan Hospital Affiliated to Capital Medical University, China

<sup>b</sup> Beijing Hospital Management Center, China

<sup>c</sup> West District of Union Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology, China

### ARTICLE INFO

#### Keywords:

High-density lipoprotein cholesterol  
SARS-CoV-2  
COVID-19  
Virus clearance time  
Risk factors

### ABSTRACT

**Objective:** There were COVID-19 patients with SARS-CoV-2 nucleic acid long-term positive. This article aims to understand the relevant factors that affect SARS-CoV-2 clearance time.

**Methods:** The clinical data of 115 COVID-19 patients with SARS-CoV-2 nucleic acid positive time exceeding 14 days were collected retrospectively, and the relationship between clinical characteristics, chest CT scans, blood cells, biochemical indicators, and the time of viral nucleic acid turning negative were analyzed.

**Results:** The time from symptom onsets to nucleic acid turning negative was  $(32.5 \pm 8.7)$  days in this group of patients. The time of nucleic acid turning negative: no fever group was longer than fever group, diabetes group was longer than no comorbidity group, elevated levels of ALT (alanine aminotransferase), or GLU (fasting blood glucose) group, decreased levels of ALB (albumin) group or HDLC (high-density lipoprotein cholesterol) group was longer than its normal group separately ( $P < 0.05$ ). Cox multivariate regression analysis showed that ALT [odds ratio (OR): 2.164 (95% CI: 1.276–3.670),  $P = 0.004$ ], GLU [OR: 2.064 (95% CI: 1.195–3.566),  $P = 0.009$ ] and HDLC [OR: 0.527 (95% CI: 0.307–0.907),  $P = 0.021$ ] were independent factors which affected the time of nucleic acid turning negative.

**Conclusions:** ALT, GLU and HDLC were independent factors that influenced the time of nucleic acid turning negative. Although diabetes or hyperglycemia is a known risk factor, HDLC is the first to be identified, clinicians should be aware of dyslipidemia in covid-19 patients.

### 1. Introduction

Since December 2019, patients with pneumonia of unknown origin appeared in Wuhan, and it was confirmed subsequently that these patients had infected by 2019 novel coronavirus (2019 novel coronavirus, 2019-nCoV) [1]. On February 11, 2020, WHO named 2019-nCoV as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and disease infected by SARS-CoV-2 was named 2019 coronal Virus disease (Coronavirus disease 2019, COVID-19) [2]. SARS-CoV-2 is highly contagious. There are currently 209 countries and regions in the world that have been diagnosed with COVID-19. The cumulative number of confirmed cases has exceeded 2.2 million, and the number of deaths is

more than 150,000. Human life and health were threatened seriously [3]. Infected or asymptomatic carriers of SARS-CoV-2 are the source of infection, so removing viruses from the human body is one of the key factors for controlling COVID-19. Clinically, there are some patients with positive SARS-CoV-2 nucleic acid for a long time. This study retrospectively analyzed the clinical data of these patients in order to understand the relevant factors that affected virus clearance.

\* Corresponding author. Department of respiratory medicine, Beijing Shijitan Hospital Affiliated to Capital Medical University, NO.10 Tieyi Road, Haidian district, Beijing, 100038, China.

E-mail address: [dingfirst@sina.com](mailto:dingfirst@sina.com) (X. Ding).

<sup>1</sup> Ding Xinmin, Zhang Jie and Liu Lifei, Contributed equally to this article.

## 2. Methods

### 2.1. Inclusive and exclusive criteria

From January 29 to March 15, 2020, the clinic data managed by Beijing aid medical in Wuhan city were collected retrospectively on the west campus (single-center) of the Union Hospital of Tongji Medical College affiliated Huazhong University of Science and Technology. Inclusive criteria: (1), COVID-19 diagnosis and classification criteria refer to "Diagnosis and Treatment of Novel Coronavirus Infection Pneumonia (Trial Version 7)" [4]; (2), the time from symptom onsets to the last positive time of viral nucleic acid test (T1) was more than 14 days. Exclusive criteria: (1), monitor of nucleic acid was not timely (the time from the last positive nucleic acid to the first turning negative was more than 7 days); (2), the cases of death during hospitalization; (3), the cases of lacking important clinical data.

### 2.2. Methods of data collection

The age and gender of all patients were collected, whether there was a fever or not within one week from the onset to admission as well. They were divided into five groups according to their comorbidities: no comorbidity (None), with hypertension (Group I), with diabetes (Group II), with hypertension and diabetes (Group III), and with other comorbidities (Group IV). The following treatment data were collected: Antiviral Drugs [none, arbidol, lopinavir/ritonavir and others], Antibiotics [none, one kind, two kinds or more], whether or not to use glucocorticoids and Chinese traditional medicine. The following indicators were collected for the first examination on admission: White blood cell counts (WBC), absolute neutrophil counts (N), absolute lymphocyte counts (L), hemoglobin (Hb), alanine aminotransferase (ALT), Aspartate aminotransferase (AST), lactate dehydrogenase (LDH), albumin (ALB), albumin/globulin (A/G), prealbumin (PA), uric acid (Uric), fasting blood glucose (GLU), triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), blood homocysteine (HCY) and serum cystatin C (CysC) and C- Reactive protein (CRP).

### 2.3. Grade of lung lesions on chest CT

All patients underwent chest CT scan within one week of admission. Two senior professional doctors took lung windows (window width 1250 Hu, window position -600 Hu) for image analysis and scoring. The modified Casarini method was used for scoring [5]: the left and right lungs are divided into six parts at the three levels of the aortic arch, right pulmonary artery trunk, and left and right ventricles; each part was scored according to the lesion area: 0 was no disease, 1 was  $\leq 25\%$  of the lesion area, 2 was from 26% to 50% of the lesion area, 3 was from 51% to 75% of the lesion area, 4 was  $\geq 75\%$  of the lesion area; the scores of the six parts are accumulated, and the integral range was 1–24 points. The lung lesions were graded into four levels: Grade I was 1–6 points, Grade II was 7–12 points, Grade III was 13–18 points, and Grade IV was 19–24 points.

### 2.4. Detection of nucleic acid and judgment of it's result

The SARS-CoV-2 nucleic acid was extracted from patients' oropharyngeal swabs, nasopharyngeal swabs, or deep sputum, and real-time fluorescent RT-PCR was used to detect the open reading frame 1 ab (open reading frame 1 ab, ORF1ab) and Nucleocapsid protein (N) genes. The criteria for nucleic acid positivity were as follows: (1) both targets of the ORF1ab and N gene were positive; (2) if the single target was positive, re-sampling/the other type of sample test was still single target positive. The criteria for nucleic acid turning negative were as follows: the patient's symptoms had basically disappear, CT examination showed that the lung lesions had been basically absorbed, and more than two

**Table 1**

Demographic characteristics of the 115 COVID-19 patients.

Variables	n (%)
Age cut-off mean (y)	48 (41.7)
<60	67 (58.3)
$\geq 60$	
Sex male	61 (53.0)
female	54 (47.0)
Fever (symptom) yes	93 (80.9)
no	22 (19.1)
Comorbidities hypertension (Group I)	23 (20.0)
diabetes (Group II)	22 (19.1)
hypertension + diabetes (Group III)	11 (9.6)
others (Group IV)	19 (16.5)
none	40 (34.8)
Severity of the disease common	6 (5.2)
severe	101 (87.8)
critical	8 (7.0)
Antiviral therapy arbidol	63 (54.8)
lopinavir/ritonavir	43 (37.4)
others	5 (4.3)
none	4 (3.5)
Antibiotic therapy one	59 (51.3)
two or more	16 (13.9)
none	40 (34.8)
Use Chinese patent medicine or herbal medicine yes	105 (91.3)
no	10 (8.7)
Corticosteroid therapy yes	14 (12.2)
no	101 (87.8)
Grades of lung lesions on chest CT	34 (29.6)
I	29 (25.2)
II	32 (27.8)
III	20 (17.4)
IV	

consecutive (intervals of more than 24 h) nucleic acid tests were negative [4]. The time from the symptom onsets to the last nucleic acid positive before the nucleic acid turning negative (T1) and the time from the symptom onsets to the first negative nucleic acid after the nucleic acid turning negative were calculated (T2).

### 2.5. Statistical methods

Data were processed by SPSS 19.0 software. The patient's age, T1 and T2 were tested for normal distribution by Kolmogorov-Smirnov method ( $P > 0.05$  was judged as the normal distribution). Normally distributed measurement data was represented by ( $\bar{X} \pm s$ ), non-normally distributed measurement data were described by the median, and count data was expressed as a percentage. Measurement data with a reference range of clinical normal values were grouped according to clinical significance according to the upper or lower limit of normal values. If there was no normal value range, the normally distributed measurement data was grouped by the mean value, and the non-normally distributed measurement data was grouped by the median. The independent-sample *t*-test was used to compare the two means, and the homogeneity of variance was tested by Levene's test ( $P > 0.05$  was judged as equal variance). One-way analysis of variance (One-Way ANOVA) was used for comparison of more than two means (homogeneity of variance analysis by LSD method,  $P > 0.05$  Judged as equal variance), and pairwise comparisons between groups were performed. If there was no difference between the two pairs, the *P*-value of the overall comparison was used. Firstly, the factors that affect the time for nucleic acid to turn negative were analyzed by univariate analysis (Log-rank test in Kaplan-Meier method), and then the factors with  $P < 0.15$  were included in the Cox model multi-factor stepwise regression analysis method (forward LR method).  $P < 0.05$  (both sides) indicates that the difference is statistically significant.

**Table 2**  
Laboratory findings of the 115 COVID-19 patients.

Variables (Normal reference range)	n (%)
WBC [(3.5–9.5) × 10 <sup>9</sup> /L]	11 (9.6)
<3.5 × 10 <sup>9</sup> /L (3.5–9.5) × 10 <sup>9</sup> /L	101 (87.8)
>9.5 × 10 <sup>9</sup> /L	3 (2.6)
N [(1.8–6.3) × 10 <sup>9</sup> /L]	6 (5.2)
<1.8 × 10 <sup>9</sup> /L (1.8–6.3) × 10 <sup>9</sup> /L	93 (80.9)
>6.3 × 10 <sup>9</sup> /L	16 (13.9)
L [(1.1–3.2) × 10 <sup>9</sup> /L]	50 (43.5)
<1.1 × 10 <sup>9</sup> /L (1.1–3.2) × 10 <sup>9</sup> /L	64 (55.7)
>3.2 × 10 <sup>9</sup> /L	1 (0.9)
Hb(130–175 g/L)	67 (58.3)
<130 g/L	46 (40.0)
130–175 g/L	2 (1.7)
>175 g/L	
AST (8–40 U/L)	0 (0.0)
<8 U/L	90 (77.4)
8–40 U/L	25 (21.7)
>40 U/L	
ALT (5–40 U/L)	0 (0.0)
<5 U/L	66 (57.4)
5–40 U/L	49 (42.6)
>40 U/L	
LDH (109–245 U/L)	0 (0.0)
<109 U/L	72 (62.6)
109–245 U/L	43 (37.4)
>245 U/L	
PA (150–400 mg/L)	47 (40.9)
<150 mg/L	63 (54.8)
150–400 mg/L	5 (4.3)
>400 mg/L	
ALB (33–55 g/L)	72 (62.6)
<33 g/L	43 (37.4)
33–55 g/L	0 (0.0)
>55 g/L	
ALB/GLB (1.5–2.5)	91 (79.1)
<1.5	23 (20.0)
1.5–2.5	1 (0.9)
>2.5	
Uric acid (208–428 μmol/L)	26 (22.6)
<208 μmol/L	78 (67.8)
208–428 μmol/L	11 (9.6)
>428 μmol/L	
GLU (3.9–6.1 mmol/L)	0 (0.0)
<3.9 mmol/L	47 (40.9)
3.9–6.1 mmol/L	68 (59.1)
>6.1 mmol/L	
TG (0–1.7 mmol/L)	76 (66.1)
0–1.7 mmol/L	39 (33.9)
>1.7 mmol/L	
HDLC (1.04–1.66 mmol/L)	75 (65.2)
<1.04 mmol/L	36 (31.3)
1.04–1.66 mmol/L	4 (3.5)
>1.66 mmol/L	
LDLC (0–3.12 mmol/L)	84 (73.0)
0–3.12 mmol/L	31 (27.0)
>3.12 mmol/L	
CRP (0–8 mg/L) <sup>a</sup>	54 (48.6)
0–8 mg/L	57 (51.4)
>8 mg/L	
HCY (0–20 μmol/L) <sup>b</sup>	88 (95.7)
0–20 μmol/L	4 (4.3)
>20 μmol/L	
CycC (0.55–1.05 mg/L) <sup>c</sup>	1 (0.9)
<0.55 mg/L	92 (83.6)
0.55–1.05 mg/L	17 (15.5)
>1.05 mg/L	

<sup>a</sup> Data missing in 4 cases, <sup>b</sup> Data missing in 23 cases, <sup>c</sup>Data missing in 5 cases.

**Table 3**  
Effects of demographic characteristics on T1 or T2 of the 115 COVID-19 patients.

Variables	n (%)	T1(d)		T2(d)	
		Mean ± SD	P	Mean ± SD	P
Age cut-off mean (y)	48	28.0 ±	0.718	32.4 ±	0.869
<60	(41.7)	8.2		8.3	
≥60	67	28.7 ±		32.6 ±	
	(58.3)	8.8		9.1	
Sex male	61	30.1 ±	0.022	34.5 ±	0.010
female	(53.0)	7.7		7.7	
	54	26.5 ±		30.3 ±	
	(47.0)	9.1		9.2	
Fever yes	93	27.0 ±	0.000	31.1 ±	0.000
No	(80.9)	8.3		8.5	
	22	34.5 ±		38.5 ±	
	(19.1)	7.0		7.3	
Comorbidities none	42	26.9 ±	0.516 <sup>a</sup>	30.9 ±	0.480 <sup>a</sup>
Group I	(36.5)	7.3	0.124 <sup>a</sup>	7.2	0.080 <sup>a</sup>
Group II	23	28.5 ±	0.055 <sup>a</sup>	32.7 ±	0.049 <sup>a</sup>
Group III	(20.0)	10.5	0.739 <sup>a</sup>	10.6	0.809 <sup>a</sup>
Group VI	22	30.0 ±	0.188 <sup>a</sup>	34.5 ±	0.169 <sup>a</sup>
Group I+Group III	(19.1)	7.6	0.040 <sup>a</sup>	8.4	0.028 <sup>a</sup>
Group II+Group III	11	32.2 ±		36.3 ±	
	(9.6)	10.0		10.2	
	17	27.6 ±		31.4 ±	
	(14.8)	8.5		8.7	
	34	29.7 ±		33.8 ±	
	(30.0)	10.3		10.4	
	33	30.7 ±		35.1 ±	
	(28.7)	8.4		8.9	
Severity of the disease	6 (5.2)	28.8 ±	0.040 <sup>a</sup>	33.2 ±	0.054 <sup>a</sup>
common	101	10.6		10.6	
severe	(87.8)	28.7 ±		32.9 ±	
critical	8 (7.0)	8.7		8.8	
		20.5 ±		25.0 ±	
		7.5		6.8	
Antiviral therapy arbidol	63	26.9 ±	0.008 <sup>b</sup>	31.0 ±	0.013 <sup>b</sup>
lopinavir/ritonavir	(54.8)	6.9		6.9	
others	43	31.3 ±		35.3 ±	
none	(37.4)	9.5		9.9	
	5 (4.3)	29.0 ±		33.2 ±	
	4 (3.5)	23.2		13.4	
		20.8 ±		25.3 ±	
		7.3		7.6	
Antibiotic therapy one	59	28.7 ±	0.598 <sup>a</sup>	32.9 ±	0.693 <sup>a</sup>
two or more	(51.3)	8.8		9.0	
none	16	29.9 ±		33.4 ±	
	(13.9)	10.0		10.6	
	40	27.5 ±		31.5 ±	
	(34.8)	7.5		7.5	
Use Chinese patent medicine or herbal medicine	105	29.0 ±	0.000	26.7 ±	0.000
yes	(91.3)	8.6		3.8	
No	10	22.2 ±		33.1 ±	
	(8.7)	3.9		8.9	
Corticosteroid therapy yes	14	24.3 ±	0.053	27.9 ±	0.035
No	(12.2)	6.5		6.4	
	101	29.0 ±		33.1 ±	
	(87.8)	8.7		8.8	
Grades of lung lesions on chest CT	34	27.2 ±	0.586 <sup>a</sup>	31.4 ±	0.681 <sup>a</sup>
I	(29.6)	9.4		9.4	
II	(25.2)	8.7		9.0	
III	32	28.1 ±		32.4 ±	
IV	(27.8)	8.5		8.9	
	20	28.4 ±		32.3 ±	
	(17.4)	8.5		7.0	

<sup>a</sup> Among groups.

<sup>a</sup> vs none.

<sup>b</sup> arbidol vs lopinavir/ritonavir.

### 3. Results

#### 3.1. Demographic and clinical characteristics of patients

A total of 115 patients with COVID-19 were included, and their ages

were in a normal distribution, average age was (60.5 ± 12.2) y (Kolmogorov-Smirnov method normal distribution test, *P* = 0.200). There were 61 males (53.0%) and 54 females (47.0%). 93 cases (80.9%) with fever and 22 cases (19.1%) without fever. Comorbidities: 40 cases (34.8%) without comorbidities, 75 cases (65.2%) with comorbidities,

**Table 4**  
Effects of laboratory findings on T1 or T2 of the 115 COVID-19 patients.

Variables (Normal reference range)*	n (%)	T1(d)		T2(d)	
		Mean ± SD	P	Mean ± SD	P
WBC [(3.5–9.5) × 10 <sup>9</sup> /L]	11 (9.6)	32.5 ± 9.8	0.225 <sup>Δ</sup>	34.5 ± 9.8	0.043 <sup>Δ</sup>
<3.5 × 10 <sup>9</sup> /L	(87.8)	27.9 ± 8.2		32.1 ± 8.5	
(3.5–9.5) × 10 <sup>9</sup> /L	3 (2.6)	30.0 ± 13.2		35.0 ± 13.7	
>9.5 × 10 <sup>9</sup> /L					
N [(1.8–6.3) × 10 <sup>9</sup> /L]	6 (5.2)	32.8 ± 9.7	0.349 <sup>Δ</sup>	35.8 ± 9.1	0.551 <sup>Δ</sup>
<1.8 × 10 <sup>9</sup> /L	93	28.4 ± 8.6		32.5 ± 8.8	
(1.8–6.3) × 10 <sup>9</sup> /L	(80.9)	26.9 ± 7.6		31.3 ± 8.2	
>6.3 × 10 <sup>9</sup> /L	16	28.9 ± 7.9	0.666	32.9 ± 7.7	0.735
>1.1 × 10 <sup>9</sup> /L	(43.5)	28.2 ± 9.1		32.3 ± 9.5	
Hb (130–175 g/L)	50	27.7 ± 8.5	0.265	31.5 ± 8.6	0.133
<130 g/L	(58.3)	29.5 ± 8.6		34.0 ± 8.7	
≥130 g/L	48	28.0 ± 8.5	0.366	32.2 ± 8.6	0.406
AST (8–40 U/L)	90	29.8 ± 8.8		33.8 ± 9.2	
≤40 U/L	(78.3)	26.1 ± 9.3	0.017	30.8 ± 7.6	0.012
>40 U/L	25	30.8 ± 7.6		34.9 ± 9.6	
ALT (5–40 U/L)	66	28.7 ± 8.9	0.681	32.7 ± 8.9	0.757
≤245 U/L	(62.6)	28.0 ± 8.0		32.1 ± 8.5	
>245 U/L	43	27.0 ± 7.0	0.067	31.0 ± 7.1	0.069
PA (150–400 mg/L)	47	29.8 ± 9.4		33.9 ± 9.5	
<150 mg/L	(40.9)	29.8 ± 8.0	0.022	34.0 ± 8.2	0.020
≥150 mg/L	68	26.1 ± 9.0		30.1 ± 9.1	
ALB (33–55 g/L)	72	28.0 ± 8.3	0.353	32.1 ± 8.3	0.350
<33 g/L	(62.6)	29.9 ± 9.4		29.9 ± 9.4	
≥33 g/L	43	28.5 ± 8.8	0.721	32.5 ± 9.0	0.981
ALB/GLB (1.5–2.5)	91	27.5 ± 6.3		32.4 ± 6.2	
<1.5	(79.1)	26.0 ± 8.5	0.011	29.9 ± 8.2	0.007
≥1.5	24	30.1 ± 8.2		34.3 ± 8.7	
Uric acid (208–428 μmol/L)	104	29.0 ± 8.8	0.351	33.1 ± 8.9	0.356
≤428 μmol/L	(90.4)	29.9 ± 8.0		34.0 ± 8.5	
>428 μmol/L	11 (9.6)	28.1 ± 8.3	0.011	34.0 ± 8.5	0.009
GLU (3.9–6.1 mmol/L)	47	25.7 ± 8.5		29.7 ± 8.6	
3.9–6.1 mmol/L	(40.9)	28.1 ± 8.4	0.528	32.1 ± 8.5	0.516
>6.1 mmol/L	68	29.3 ± 8.9		33.4 ± 9.3	
TG (0–1.7 mmol/L)	76	29.1 ± 9.9	0.435	33.1 ± 10.1	0.559
0–1.7 mmol/L	(66.1)	27.8 ± 7.3		32.1 ± 7.4	
>1.7 mmol/L	39	28.8 ± 8.7	0.645	32.8 ± 8.9	0.814
HDLC (1.04–1.66 mmol/L)	75	26.7 ± 4.9		31.8 ± 3.6	
<1.04 mmol/L	(65.2)				
≥1.04 mmol/L	40				
LDLC (0–3.12 mmol/L)	84				
0–3.12 mmol/L	(73.0)				
>3.12 mmol/L	31				
CRP (0–8 mg/L) <sup>a</sup>	54				
0–8 mg/L	(48.6)				
>8 mg/L	57				
HCY (0–20 μmol/L) <sup>b</sup>	88				
0–20 μmol/L	(95.7)				
>20 μmol/L	4 (4.3)				

**Table 4 (continued)**

Variables (Normal reference range)*	n (%)	T1(d)		T2(d)	
		Mean ± SD	P	Mean ± SD	P
CycC (0.55–1.05 mg/L) <sup>c</sup>	93	28.4 ± 8.8	0.772	32.5 ± 9.0	0.856
≤1.05 mg/L	(84.5)				
>1.05 mg/L	17	27.8 ± 7.8		32.0 ± 7.8	

<sup>Δ</sup>Among Groups.

<sup>a</sup> Data missing in 4 cases.

<sup>b</sup> Data missing in 23 cases.

<sup>c</sup> Data missing in 5 cases.

including 23 cases of hypertension (20%), 22 cases of diabetes (19.1%), and 11 cases of hypertension and diabetes (9.6%), other comorbidities was 19 cases (16.5%). The grades lung lesions severity of chest CT: 34 cases (29.6%) of grade I, 29 cases (25.2%) of grade II, 32 cases (27.8%) of grade III, 20 cases (17.4%) of grade IV. Grades of clinical severity: 6 cases of common type (5.2%), 101 cases of severe type (87.8%), and 8 cases of critical type (7.0%). Antiviral drugs: 4 cases (3.5%) were not used, 63 cases (54.8%) of arbidol, 43 cases (37.4%) of lopinavir/ritonavir, 5 cases (4.3%) of others. Antibiotics: 40 cases (34.8%) were not used, 59 cases (51.3%) used one antibiotic, and 16 cases (13.9%) used two or more antibiotics. Glucocorticoid: 101 cases (87.8%) were not used, 14 cases (12.2%) were used. Chinese traditional medicine: 10 cases (8.7%) were not used, 105 cases (91.3%) were used (Table 1).

### 3.2. Analysis of patients' blood cells and biochemical findings

More than 50% of patients have abnormal indicators: 67 cases (58.3%) with hypohaemoglobinemia (<130 g/L), 72 cases (62.6%) with hypoproteinemia (<33 g/L), 68 cases (59.1%) with elevated levels of GLU (>6.1 mmol/L), 75 cases (65.2%) with decreased levels of HDLC (<1.04 mmol/L), 57 cases (51.4%) with elevated levels of CRP (>8 mg/L) (Table 2).

### 3.3. The time of the nucleic acid turning negative

The time from the symptom onsets to the last nucleic acid positive before the nucleic acid turning negative (T1) was (28.4 ± 8.5) days (normal distribution, P = 0.056) (the range:14–52 days); the time from the symptom onsets to the first negative nucleic acid after the nucleic acid turning negative (T2) was (32.5 ± 8.7) days (normal distribution, P = 0.200)(the rang: 16–59 days).

### 3.4. The impact of clinical characteristics and laboratory findings on the time of nucleic acid turning negative

Statistics found that T1 and T2 in the female group were shorter than the male group, the fever group was shorter than the non-fever group, and no comorbidity group was shorter than Group II plus group III (P < 0.05). The grade of lung lesions on chest CT had no correlation with T1 and T2. T1 and T2, in the elevated levels of ALT group or GLU group, and decreased levels of ALB group or HDLC group, were longer than it's normal group (P < 0.05). (Table 3, Table 4).

### 3.5. Analysis of the influencing factors of nucleic acid turning negative time

Single-factor analysis showed gender, fever, diabetes, severity of the disease, ALT, ALB, GLU and HDLC were influencing factors of T1 or T2 (P < 0.15). Then the above factors were included in the Cox model, and the forward LR method was used for multi-factor regression analysis. The results showed that ALT, GLU, and HDLC were independent factors of T1 or T2 (Table 5).

**Table 5**  
Cox proportional hazards model analysis of risk factors for the duration of viral positivity in the 115 patients with COVID19.

Variables	n (%)	T1				T2			
		Log Rank		Multivariate analysis		Log Rank		Multivariate analysis	
		$\chi^2$	p value	HR (95% CI)	p value	$\chi^2$	p value	HR (95% CI)	p value
Age cut-off mean (y)		0.337	0.561			0.140	0.708		
<60y	48 (41.7)								
≥60y	67 (58.3)								
Sex male		2.45	0.117		0.903	3.741	0.053		0.924
female	61 (53.0)								
	54 (47.0)								
Fever (symptom) yes		9.081	0.003		0.286	9.151	0.002		0.297
no	93 (80.9)								
	22 (19.1)								
Comorbidities none		4.136	0.042		0.311	4.925	0.026		0.259
diabetes	42 (36.5)								
	33 (28.7)								
Severity of the disease common		6.464	0.039		0.132	7.363	0.025		0.228
severe	6 (5.2)								
critical	101 (87.8)								
	8 (7.0)								
Grades of lung lesions on chest CT		0.060	0.807			0.129	0.720		
I	34 (29.6)								
II	29 (25.2)								
III	32 (27.8)								
IV	20 (17.4)								
WBC [(3.5–9.5) × 10 <sup>9</sup> /L]		1.515	0.218			0.774	0.379		
<3.5 × 10 <sup>9</sup> /L (3.5–9.5) × 10 <sup>9</sup> /L	11 (9.6)								
>9.5 × 10 <sup>9</sup> /L	101 (87.8)								
	3 (2.6)								
N [(1.8–6.3) × 10 <sup>9</sup> /L]		1.921	0.166			1.280	0.258		
<1.8 × 10 <sup>9</sup> /L (1.8–6.3) × 10 <sup>9</sup> /L	6 (5.2)								
>6.3 × 10 <sup>9</sup> /L	93 (80.9)								
	16 (13.9)								
L [(1.1–3.2) × 10 <sup>9</sup> /L]		0.001	0.971			0.008	0.931		
<1.1 × 10 <sup>9</sup> /L	50 (43.5)								
≥1.1 × 10 <sup>9</sup> /L	65 (56.5)								
Hb (130–175 g/L)		0.840	0.359			2.095	0.148		0.907
<130 g/L	67 (58.3)								
≥130 g/L	48 (41.7)								
AST (8–40 U/L)		0.566	0.444			0.434	0.510		
≤40 U/L	90 (78.3)								
>40 U/L	25 (21.7)								
ALT (5–40 U/L)		6.390	0.011	1.957 (1.159–3.303)	0.012	7.339	0.007	2.164 (1.276–3.670)	0.004
≤40 U/L	66 (57.4)								
>40 U/L	49 (42.6)								
LDH (109–245 U/L)		0.465	0.495			0.465	0.495		
≤245 U/L	72 (62.6)								
>245 U/L	43 (37.4)								
PA (150–400 mg/L)		0.453	0.501			0.472	0.492		
<150 mg/L	47 (40.9)								
≥150 mg/L	68 (59.1)								
ALB (33–55 g/L)		2.849	0.091		0.396	2.744	0.098		0.423
<33 g/L	72 (62.6)								
≥33 g/L	43 (37.4)								
ALB/GLB (1.5–2.5)		0.960	0.327			1.274	0.259		
<1.5	91 (79.1)								
≥1.5	24 (20.9)								
Uric acid (208–428 μmol/L)		0.536	0.464			0.223	0.637		
≤428 μmol/L	104 (90.4)								
>428 μmol/L	11 (9.6)								
GLU (3.9–6.1 mmol/L)		4.071	0.044	1.731 (1.018–2.945)	0.043	5.780	0.016	2.064 (1.195–3.566)	0.009
3.9–6.1 mmol/L	47 (40.9)								
>6.1 mmol/L	68 (59.1)								
TG (0–1.7 mmol/L)		1.405	0.236			1.179	0.278		
0–1.7 mmol/L	76 (66.1)								
>1.7 mmol/L	39 (33.9)								
HDLc (1.04–1.66 mmol/L)		4.728	0.030	0.526 (0.307–0.904)	0.020	5.419	0.020	0.527 (0.307–0.907)	0.021
<1.04 mmol/L	75 (65.2)								
≥1.04 mmol/L	40 (34.8)								
LDLc (0–3.12 mmol/L)		0.381	0.537			0.466	0.495		
0–3.12 mmol/L	84 (73.0)								
>3.12 mmol/L	31 (27.0)								
CRP (0–8 mg/L) <sup>a</sup>		2.037	0.154			1.844	0.174		
0–8 mg/L	54 (48.6)								
>8 mg/L	57 (51.4)								

(continued on next page)

Table 5 (continued)

Variables	n (%)	T1				T2			
		Log Rank		Multivariate analysis		Log Rank		Multivariate analysis	
		$\chi^2$	p value	HR (95% CI)	p value	$\chi^2$	p value	HR (95% CI)	p value
HCY (0–20 $\mu\text{mol/L}$ ) <sup>b</sup>									
0–20 $\mu\text{mol/L}$	88 (95.7)								
>20 $\mu\text{mol/L}$	4 (4.3)								
CycC (0.55–1.05 mg/L) <sup>c</sup>									
≤1.05 mg/L	93 (84.5)	0.243	0.622			0.236	0.624		
>1.05 mg/L	17 (15.5)								

<sup>a</sup> Data missing in 4 cases.

<sup>b</sup> Data missing in 23 cases.

<sup>c</sup> Data missing in 5 cases.

#### 4. Discussion

The clearance of SARS-CoV-2 in the human body is one of the important indicators for the recovery of COVID-19 patients. Some studies have found that the average time from the beginning of symptom onsets to the first negative test of throat swab SARS-CoV-2 was 9.5–11 days [6,7], the virus-negative rate was 94.5% by the fifteenth day [8]. The above research suggests that the SARS-CoV-2 in the most patients was cleared within two weeks, but we also found some COVID-19 patients with SARS-CoV-2 nucleic acid positive exceed two weeks. The 115 patients enrolled in this study, from the symptom onsets to the first nucleic acid negative time after the nucleic acid turning negative (T2) was 32.5 days (16–59 days). Because this study was a retrospective analysis, in order to rule out the prolonged turning negative time due to untimely nucleic acid detection, this study also calculated the last nucleic acid positive time from symptom onsets to virus turning negative (T1). The average time of T1 was 28.4 days (14–52 days). This result suggests that the SARS-CoV-2 virus clearance time in this group was far more than two weeks.

There are many factors that affect the removal of viruses in the human body, such as with or not a comorbidity, nutritional status, treatment options, etc. Common cases only 5.2% included in this study, which may be related to the fact that more than 85% of the covid-19 patients in our department were severe or critical. Therefore, we cannot understand as that the prolonged the time of virus clearance was mainly due to severe patients. In addition, antiviral therapy were mainly used with abidor or lopinavir-ritonavir in our department, so the cases enrolled in this study also used the above two antiviral drugs. In this study, it was found that the time of virus turning negative in the abidor group was shorter than that in the lopinavir-ritonavir group, and the difference between the two groups was statistically significant. However, whether abidor and lopinavir-ritonavir have antiviral effects on SARS-CoV-2 is still controversial [9–11], so antiviral treatment was not be analyzed as a risk factor in this study. Because glucocorticoids were considered to have side effects on prolonging the time of virus clearance [12,13], the use of glucocorticoids was strictly limited in clinical practice, and the number of cases treated with glucocorticoids were significantly less in this group. However, it was found that the time of virus turning negative in the glucocorticoid treatment group was shorter than without glucocorticoid group. Studies by other authors have also found that the application of low-dose glucocorticoids does not prolong the virus clearance time [14,15]. Therefore, it is still controversial whether glucocorticoids will affect the time of the virus turning negative, and this study did not analyze glucocorticoids as a risk factor.

This study found that the time of virus turning negative in the female group or fever group were shorter than that in their control group. And in the group of increased alanine aminotransferase or fasting blood glucose, and the group of decreased albumin or high-density lipoprotein cholesterol, the time of virus turning negative were longer than that in their control group. The amino acid aminotransferase, fasting blood glucose, and high-density lipoprotein cholesterol were independent risk

factors for the prolongation of virus turning negative by Cox multi-factor regression analysis. Of note, the grades lung lesions on chest CT had no effect on the time of viral turning negative, which suggests that lung lesions are not only directly caused by a viral infection, there may also be secondary factors, such as inflammatory response [16,17].

Many studies have found that glycemic control was related to the prognosis of COVID-19 patients. Increased fasting blood glucose was a risk factor of poor prognosis [18–21]. 28.7% of the patients in this study had diabetes, which was higher than the 19% reported earlier [22]. The time of SARS-CoV-2 nucleic acid turning negative with diabetes was significantly longer than without comorbidities, and the increased fasting blood glucose was an independent risk factor for the time of nucleic acid turning negative. Therefore, clinicians should pay more attention to the control of blood glucose in these patients. In addition, the increased alanine aminotransferase was also an independent risk factor for the time of nucleic acid turning negative. Alanine aminotransferase is a sensitive indicator of acute liver cell injury. A meta-analysis showed that severe COVID-19 patients with severe liver injury were significantly more than mild cases [23], especially the increased alanine aminotransferase was closely related to the risk of death [24]. Therefore, in order to shorten nucleic acid turning negative time and improve the prognosis, we need to protect the liver function of COVID-19 patients.

This study also found that 65.2% of patients with HDLC decreased, viral nucleic acid turning negative time in decreased HDLC group was longer than the normal group. Cox multivariate regression analysis showed that HDLC reduction was an independent risk factor of the prolonged nucleic acid turning negative time. There is no literature on whether HDLC affects virus clearance in the human body. The decrease of HDLC was observed in HIV patients [25,26]. Whether SARS-CoV-2 has similar characteristics of HIV remains to be studied. Antiviral drugs can also cause abnormal fat metabolism, causing a drop in HDLC [27]. In addition, HDLC is mainly synthesized by the liver. Due to the impaired liver function of the enrolled patients, we can't rule out that the decreased high-density lipoprotein cholesterol due to secondary damage of liver cells. Because this was a retrospective study, the reason for the decreased HDLC could not be further analyzed, but the decreased HDL cholesterol was an independent influencing factor that prolonged nucleic acid turning negative time.

The limitations of our study were as follows: As West District of Union Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology, was a designated hospital for severe or critical COVID-19 patients, so more than 85% of the covid-19 patients in our department were severe or critical. Therefore, we cannot understand as that the prolonged the time of virus clearance was mainly due to severe patients. In addition, as a retrospective study, the reason for the decreased HDLC could not be further analyzed.

In conclusion, alanine aminotransferase, fasting blood glucose, and high-density lipoprotein cholesterol were independent risk factors that affect the time of nucleic acid turning negative. In order to shorten the time of SARS-CoV-2 clearance in COVID-19 patients, clinicians should

pay more attention to protection of liver function, maintain normal fasting blood glucose and normal lipid metabolism. Although diabetes or hyperglycemia is a known risk factor, HDLC is the first to be identified, clinicians should be aware of dyslipidemia in covid-19 patients.

## Funding

This work was not grant-funded.

## Credit author statement

Study design : Ding Xinmin, Zhang Jie, Liu Lifei.

Data collecting : Ding Xinmin, Yuan Xiaodong, Zang Xuefeng, Lu Feiping, He Ping, Wang Qian , Zhang xiaomeng, Xu Yimin, Li Xiang, Liu Ying, Li Qun, Tan Xuebing, Zheng Yunhui, Lin Xue, Liu Yuhang.

Statistical analysis: Ding Xinmin, Zhang Jie, Liu Lifei, Read critically the manuscript: Ding Xinmin, Zhang Jie, Liu Lifei.

## Declaration of competing interest

The authors do not have any financial or personal relationships with people or organizations that may have inappropriately influenced their work in the present article.

## Acknowledgments

We thank all patients involved in the study and all the front-line medical staffs of Beijing aid medical team in Wuhan city. We thank Dr. chen xiaolan of department of respiratory medicine, Beijing Shijitan Hospital Affiliated to Capital Medical University for his help in correcting grammatical errors.

## References

- [1] N. Zhu, D. Zhang, W. Wang, et al., A novel coronavirus from patients with pneumonia in China, 2019 [J], *N. Engl. J. Med.* 382 (8) (2020) 727–733.
- [2] [https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-\(covid-2019\)-and-the-virus-that-causes-it](https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it).
- [3] <https://covid19.who.int/>.
- [4] <http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989/files/ce3e6945832a438eaae415350a8ce964.pdf>.
- [5] M. Casarini, F. Ameglio, L. Alemanno, et al., Cytokine levels correlate with a radiologic score in active pulmonary tuberculosis, *Am. J. Respir. Crit. Care Med.* 159 (1) (1999) 143–148.
- [6] Y. Ling, S.B. Xu, Y.X. Lin, et al., Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients, *Chin. Med. J.* 133 (9) (2020) 1039–1043.
- [7] J. Chen, T. Qi, L. Liu, et al., Clinical progression of patients with COVID-19 in Shanghai, China, *J. Infect.* 80 (5) (2020) e1–e6.
- [8] J. Yuan, R. Zou, L. Zeng, et al., The correlation between viral clearance and biochemical outcomes of 94 COVID-19 infected discharged patients, *Inflamm. Res.* 69 (6) (2020) 599–606.
- [9] Z. Zhu, Z. Lu, T. Xu, et al., Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19, *J. Infect.* S0163–4453 (20) (2020) 30188–30192, <https://doi.org/10.1016/j.jinf.2020.03.060> [Epub ahead of print].
- [10] L. Deng, C. Li, Q. Zeng, et al., Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: a retrospective cohort study, *J. Infect.* S0163–4453 (20) (2020) 30113–30114, <https://doi.org/10.1016/j.jinf.2020.03.002> [Epub ahead of print].
- [11] N. Lian, S. Xie H1 Lin, et al., Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study, *Clin. Microbiol. Infect.* (20) (2020) 30234–30242, <https://doi.org/10.1016/j.cmi.2020.04.026> [Epub ahead of print], S1198–743X.
- [12] C. Zhang, S. Huang, F. Zheng, et al., Controversial treatments: an updated understanding of the coronavirus disease 2019, *J. Med. Virol.* (2020), <https://doi.org/10.1002/jmv.25788> [Epub ahead of print].
- [13] H. Li, C. Chen, F. Hu, et al., Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis, *Leukemia* (2020), <https://doi.org/10.1038/s41375-020-0848-3> [Epub ahead of print].
- [14] X. Fang, Q. Mei, T. Yang, et al., Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19, *J. Infect.* S0163–4453 (20) (2020) 30168–30177, <https://doi.org/10.1016/j.jinf.2020.03.039> [Epub ahead of print].
- [15] C. Zheng, J. Wang, H. Guo, et al., Risk-adapted treatment strategy for COVID-19 patients, *Int. J. Infect. Dis.* 94 (2020) 74–77, <https://doi.org/10.1016/j.ijid.2020.03.047> [Epub ahead of print].
- [16] J. Zhifeng, A. Feng, T. Li, Consistency analysis of COVID-19 nucleic acid tests and the changes of lung CT, *J. Clin. Virol.* 127 (2020) 104359, <https://doi.org/10.1016/j.jcv.2020.104359> [Epub ahead of print].
- [17] Kim H, Hong H and Yoon SH. Diagnostic performance of CT and reverse transcriptase-polymerase chain reaction for coronavirus disease 2019: a meta-analysis. *Radiology*, 2020, 201343. doi: 10.1148/radiol.2020201343. [Epub ahead of print].
- [18] L. Zhu, Z.G. She, X. Cheng, et al., Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes, *Cell Metabol.* S1550–4131 (20) (2020) 30238–30242, <https://doi.org/10.1016/j.cmet.2020.04.021> [Epub ahead of print].
- [19] Y. Yan, Y. Yang, F. Wang, et al., Clinical characteristics and outcomes of patients with severe covid-19 with diabetes, *BMJ Open Diabetes Res Care* 8 (1) (2020), e001343, <https://doi.org/10.1136/bmjdr-2020-001343>. pii.
- [20] I. Huang, M.A. Lim, R. Pranata, Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia-A systematic review, meta-analysis, and meta-regression, *Diabetes Metab Syndr* 14 (4) (2020) 395–403.
- [21] A.K. Singh, R. Gupta, A. Ghosh, et al., Diabetes in COVID-19: prevalence, pathophysiology, prognosis and practical considerations, *Diabetes Metab Syndr* 14 (4) (2020) 303–310.
- [22] F. Zhou, T. Yu, R. Du, et al., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, *Lancet* 395 (10229) (2020) 1054–1062.
- [23] M. Parohan, S. Yaghoubi, A. Seraj, Liver injury is associated with severe Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of retrospective studies, *Hepatol. Res.* (2020 May 9), <https://doi.org/10.1111/hepr.13510> [Epub ahead of print].
- [24] F. Lei, Y.M. Liu, F. Zhou, et al., Longitudinal association between markers of liver injury and mortality in COVID-19 in China, *Hepatology* (2020), <https://doi.org/10.1002/hep.31301> [Epub ahead of print].
- [25] M. Calvo, E. Martinez, Update on metabolic issues in HIV patients, *Curr. Opin. HIV AIDS* 9 (4) (2014) 332–339.
- [26] B.T. Tadesse, B.A. Foster, A. Chala, et al., HIV and cART-associated dyslipidemia among HIV-infected children, *J. Clin. Med.* 8 (4) (2019) E430.
- [27] M. van der Valk, P. Reiss, Lipid profiles associated with antiretroviral drug choices, *Curr. Opin. Infect. Dis.* 16 (1) (2003) 19–23.