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Analysis of the Factors Associated with Negative Conversion of Severe Acute Respiratory Syndrome Coronavirus 2 RNA of Coronavirus Disease 2019

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Abstract

AIM: To understand the factors associated with negative conversion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA, targeted surveillance and control measures can be taken to provide scientific basis for the treatment of the disease and to improve the prognosis of the disease.

METHODS: Using the method of retrospective cohort study, we collected the data of Coronavirus Disease 2019 (COVID-19) patients in Tongji Hospital of Wuhan, China from 10 January to 25 March, 2020. Among the data of 282 cases, 271 patients, according to whether the negative conversion happened, were divided into negative conversion group and control group. We made the quantitative variables into classification; Chi-square test single-factor and Cox regression were used in univariate analysis and extracted 30 meaningful variables, then through the collinearity diagnosis, excluded the existence of collinear variables. Finally, 22 variables were included in Cox regression analysis.

RESULTS: The gender distribution was statistically significant between two groups ($p < 0.05$). While in the negative conversion group, the patients of non-severe group occupied a large proportion ($p < 0.001$). The median time for the negative conversion group was 17 days, and at the end of the observation period, the virus duration in control group was 24 days ($p < 0.05$). A total of 55 variables were included in univariate analysis, among which 30 variables were statistically different between the two groups. After screening variables through collinearity diagnosis, 22 variables were included in the Cox regression analysis. Last, lactate dehydrogenase (LDH), age, fibrinogen (FIB), and disease severity were associated with negative conversion of SARS-CoV-2 RNA.

CONCLUSION: Our results suggest that in the treatment of COVID-19, focus on the age of more than 65 years old, severe, high level of LDH, FIB patients, and take some targeted treatment, such as controlling of inflammation, reducing organ damage, so as to provide good conditions for virus clearance in the body.

Introduction

At present, the coronavirus disease (COVID)-19 has been a global outbreak, which was first reported in Wuhan, the capital of Hubei, China. A novel CoV, named severe acute respiratory syndrome CoV 2 (SARS-CoV-2) was isolated and it is the seventh member of the family of CoVs that infect humans [1]. It is so highly contagious that most individuals are susceptible to infection. As for main sources, the wild animals and infected patients are of infectiousness [2]. COVID-19 has been spread to 216 countries, areas or territories [3]. According to the latest statistics of the World Health Organization, as of July 26, 2020, more than 15,785,641 cases of the disease have been confirmed with over 640,016 deaths, making COVID-19 a major health concern [4]. Current research on COVID-19 focuses on the epidemics, its clinical features, and treatment [5]. In this case, study the factors associated with negative conversion of viral RNA is of necessary to guide the isolation precautions and antiviral treatment.

This study aims to assess the risk factors associated with prolonged viral shedding to improve treatment and prognosis of COVID-19 by considering or adjusting relative factors.

Materials and Methods

Study design and data collection

This retrospective cohort study contains a total of 282 laboratory-confirmed COVID-19 patients

who were admitted to Tongji Hospital of Wuhan, China from 10 January to 25 March, 2020. All patients were collected throat swab samples and SARS-CoV-2 RNA was detected using real-time reverse transcription polymerase chain reaction. Data of demographic characteristics, comorbidities, symptoms, and laboratory values were collected using electronic medical records. A total of 271 patients were included in the study, excluding 11 cases whose results changed repeatedly and cannot judge the time of negative conversion. Ethical Committee of Tongji Hospital of Huazhong University of Science and Technology (No. TJ-IRB20200364) and China-Japan Union Hospital of Jilin University (No.2020032607) approved the study and waived the written informed consent for rapid emerging infectious.

Definitions of basic concepts

To minimize the uncertainty of nucleic acid test, the time when a viral nucleic acid test was negative was defined as the time from the first onset of related symptoms to the time when two consecutive nucleic acid tests results were negative before discharge from the hospital, while for cases with the absence of the time of first symptom, the time of admission was replaced. If both were missing, the first sampling time was used instead. In the case of death, the time interval between the onset of symptoms and discharge was calculated without nucleic acid test data and was classified as non-negative group. Patients who returned to positive nucleic acid test after discharge and patients who were impossible to judge the time of negative conversion were excluded from the study.

General conditions and laboratory test indicators

We collected the patient's name, gender, disease severity, first symptom, basic diseases, urine routine, blood routine, erythrocyte sedimentation rate, glucose, biochemistry, coagulation, cytokines, and other indicators for the first admission test. Indicators with a missing value greater than 20% were not included in the analysis.

Statistical analysis

First, the indicators included in the analysis were analyzed by single factor analysis. According to the reference range of normal values, the quantitative variables were set as dichotomy or multiple categorization variables. Chi-square test and single-factor Cox regression were used to compare the negative conversion group and the control group. The test level was 0.05. To reduce the influence of the inclusion of variables on the stability of the model, the missing value of variables was filled, and the mean value method was used to fill. Then, the variables whose p values in the two single-factor test methods were both <0.05 were included in multivariate Cox regression analysis. The analysis software was IBM SPSS Statistics Version 24.0 and GraphPad Prism Version 8.2.1.

Results

The basic situation

It can be seen that the gender distribution was statistically significant between two groups ($p < 0.05$), while in the negative conversion group, the patients of non-severe disease occupied a large proportion (78.4%, $p < 0.001$). The median time for the negative conversion group was 17 days, and at the end of the observation period, the virus duration was 24 days ($p < 0.05$). The proportion of those older than 65 in the control group was larger ($p < 0.05$), as shown in Table 1.

Single factor analysis

Univariate analysis was performed for variables that were filled in missing values and converted into categorizing variables. A total of 55 variables were included, among which 30 variables were statistically different between the two groups, as shown in Table 1.

Then, to avoid collinearity among independent variables, which would affect the multi-factor analysis, collinearity diagnostics was made for quantitative variables with statistical significance, and the results are shown in Table 2.

As shown in Table 2, the VIF of calcium ion, HCO, interleukin (IL)-6, PCT, AST, and IL-8 were nearly or more than 10, which indicated the existence of collinearity. Since IL-6 and 8 had been widely reported in the previous studies [6], [7], [8], [9], [10], [11], [12], cytokine IL-10 was retained in this study to explore the influence of cytokine IL-10 on the negative transformation of COVID-19 virus. In addition, because we had enough variables, we deleted these variables as appropriate. After that, some variables were deleted because their VIF >4 and there were still variables of the same type. They were BU and eGFR.

After adjustment, there was no obvious collinearity between variables (Table 3). Although the VIF of TP is 3.132, we incorporated it into the analysis not to delete important variable. The screened variables were incorporated into Cox regression model for analysis. The analysis results were shown in Table 4.

Table 1: Results of single factor analysis

Variables	Group (%)		χ^2	p-value
	Control (n = 49)	Negative conversion (n = 222)		
Disease severity				
Non-severe	2 (4.1)	174 (78.4)	97.324	<0.001
Severe	47 (95.9)	48 (21.6)		
UPRO				
N	2 (4.1)	108 (48.6)	33.062	<0.001
P	47 (95.9)	114 (51.4)		
Gender				
Male	33 (67.3)	112 (50.5)	4.607	0.032
Female	16 (32.7)	110 (49.5)		
U-KET				
N	32 (65.3)	198 (89.2)	17.831	<0.001
P	17 (34.7)	24 (10.8)		
URO				
N	43 (87.8)	216 (97.3)	6.529	0.011
P	6 (12.2)	6 (2.7)		
WBC				
Normal	17 (34.7)	177 (79.7)	48.619	<0.001
Low	2 (4.1)	12 (5.4)		
High	30 (61.2)	33 (14.9)		
NEUT				
Normal	11 (22.4)	167 (75.2)	58.102	<0.001
Low	1 (2.0)	10 (4.5)		
High	37 (75.5)	45 (20.3)		
LC				
Normal	3 (6.1)	109 (49.1)	30.575	<0.001
Abnormal	46 (93.9)	113 (50.9)		
NT-PROBNP				
Normal	8 (16.3)	114 (51.4)	19.894	<0.001
High	41 (83.7)	108 (48.6)		
PCT				
Normal	1 (2.0)	91 (41.0)	27.158	<0.001
High	48 (98.0)	131 (59.0)		
Hypersensitive cardiac troponin				
Normal	17 (34.7)	170 (76.6)	32.921	<0.001
High	32 (65.3)	52 (23.4)		
AST				
Normal	16 (32.7)	162 (73.0)	28.950	<0.001
High	33 (67.3)	60 (27.0)		
TP				
Normal	24 (49.0)	183 (82.4)	24.902	<0.001
Abnormal	25 (51.0)	39 (17.6)		
Albumin				
Normal	7 (14.3)	105 (47.3)	18.040	<0.001
Low	42 (85.7)	117 (52.7)		
DBIL				
Normal	30 (61.2)	200 (90.1)	26.048	<0.001
Abnormal	19 (38.8)	22 (9.9)		
GGT				
Normal	30 (61.2)	172 (77.5)	5.587	0.018
Abnormal	19 (38.8)	50 (22.5)		
LDH				
Normal	0 (0.0)	60 (27.0)	17.009	<0.001
Abnormal	49 (100.0)	162 (73.0)		
Sodium				
Normal	26 (53.1)	183 (82.4)	29.732	<0.001
Low	9 (18.4)	28 (12.6)		
High	14 (28.6)	11 (5.0)		
Calcium ion				
Normal	7 (14.3)	95 (42.8)	13.898	<0.001
Abnormal	42 (85.7)	127 (57.2)		
BU				
Normal	24 (49.0)	145 (65.3)	41.100	<0.001
Low	1 (2.0)	51 (23.0)		
High	24 (49.0)	26 (11.7)		
HCO				
Normal	18 (36.7)	176 (79.3)	53.127	<0.001
Low	30 (61.2)	30 (13.5)		
High	1 (2.0)	16 (7.2)		
eGFR				
Normal	11 (22.4)	104 (46.8)	9.781	0.002
Abnormal	38 (77.6)	118 (53.2)		
PT				
Normal	12 (24.5)	170 (76.6)	49.376	<0.001
Abnormal	37 (75.5)	52 (23.4)		
INR				
Normal	24 (49.0)	194 (87.4)	37.638	<0.001
Abnormal	25 (51.0)	28 (12.6)		
Age (year)				
≤65	13 (26.5)	110 (49.5)	8.581	0.003
>65	36 (73.5)	112 (50.5)		
FIB				
Normal	18 (36.7)	67 (30.2)	14.199	0.001
Low	6 (12.2)	4 (1.8)		
High	25 (51.0)	151 (68.0)		
D-D dimer quantification				
Normal	1 (2.0)	59 (26.6)	14.018	<0.001
Abnormal	48 (98.0)	163 (73.4)		

(Contd...)

Table 1: *(Continued)*

Variables	Group (%)		χ^2	p-value
	Control (n = 49)	Negative conversion (n = 222)		
IL-2R				
Normal	4 (8.2)	111 (50.0)	35.554	<0.001
Low	1 (2.0)	16 (7.2)		
High	44 (89.8)	95 (42.8)		
IL-6				
Normal	2 (4.1)	106 (47.7)	31.930	<0.001
Abnormal	47 (95.9)	116 (52.3)		
IL-8				
Normal	35 (71.4)	216 (97.3)	35.604	<0.001
Abnormal	14 (28.6)	6 (2.7)		
IL-10				
Normal	19 (38.8)	177 (79.7)	33.636	<0.001
Abnormal	30 (61.2)	45 (20.3)		

UPRO: Urine protein; P: positive; N: Negative; U-KET: urine ket; URO: Urobilinogen; WBC: white blood cell count (normal: 3.50–9.50 low: <3.50 high: >9.50, 10^9/L); NEUT: neutrophil count (normal: 1.80–6.30 low: <1.80 high: >6.30, 10^9/L); LC: lymphocyte count (normal: 1.10–3.20 abnormal: <1.10 or >3.20,10^9/L); NT-PROBNP: amino-terminal pro-brain natriuretic peptide (normal: <241/285 (male/female) high: ≥241/285 (male/female), pg/mL); PCT: Procalcitonin (normal: 0.02–0.05 high: ≥0.05, ng/mL); Hypersensitive cardiac troponin (normal: ≤34.2/15.6 (male/female) high: >34.2/15.6 (male/female), pg/mL); AST: Glutamic oxalacetic transaminase (normal: ≤40/32 (male/female) high: >40/32 (male/female) U/L); TP: Total protein (normal: 64–83 abnormal: <64 or >83, g/L); Albumin (normal: 35–52 low: <35, g/L); DBIL: Direct bilirubin (normal: ≤8.0 abnormal: >8.0, μmol/L); GGT: Gamma-glutamyl transpeptidase (normal: 10/6–71/42 (male/female) abnormal: <10/6 or >71/42 (male/female), U/L); LDH: Lactic dehydrogenase (normal: 135–225/214 (male/female) abnormal: <135 or >225/214 (male/female), U/L); Sodium (normal: 136–145 low: <136 high: >145, mmol/L); Calcium ion (normal: 2.20–2.55 abnormal: <2.20 or >2.55, mmol/L); BU: Blood urea (normal: 3.6/3.1–9.5/8.8 (male/female) low: <3.6/3.1 (male/female) high: >9.5/8.8 (male/female), mmol/L); HCO: Bicarbonate radical (normal: 22.0–29.0 low: <22.0 high: >29.0, mmol/L); eGFR: Epidermal growth factor receptor (normal: >90 abnormal: ≤90, mL/min/1.73m^2); PT: Prothrombin time (normal: 11.5–14.5 abnormal: <11.5 or >14.5,s); INR: International normalized ratio (normal: 0.80–1.20 abnormal: >1.20); FIB: Fibrinogen (normal: 2.00–4.00 low: <2.00 high: >4.00, g/L); D-D dimer quantification (normal:<0.5 abnormal: ≥0.5,μg/mL FEU); IL-2R: Interleukin-2 receptor (normal: 223–710 low: <223 high: >710, U/mL); IL-6: Interleukin 6 (normal: <7.0 abnormal: ≥7.0, pg/mL); IL-8: Interleukin 8 (normal: <62 abnormal: ≥62, pg/mL); IL-10: Interleukin 10 (normal: <9.1 abnormal: ≥9.1, pg/mL).

Table 2: Collinearity diagnostics results

Model	Collinearity statistics	
	Tolerance	VIF
Age	0.492	2.032
WBC	0.567	1.765
LC	0.523	1.911
NT-PROBNP	0.483	2.070
Hypersensitive cardiac troponin	0.540	1.851
TP	0.244	4.105
DBIL	0.617	1.621
GGT	0.826	1.211
LDH	0.169	5.903
Sodium	0.159	6.270
Calcium ion	0.026	38.389
HCO	0.037	27.243
PT	0.528	1.893
INR	0.954	1.048
FIB	0.608	1.644
D-D dimer quantification	0.513	1.948
IL-2R	0.374	2.676
IL-6	0.028	35.273
NEUT	0.444	2.252
PCT	0.045	22.313
AST	0.096	10.420
Albumin	0.319	3.139
BU	0.205	4.879
eGFR	0.236	4.234
IL-8	0.030	33.805
IL-10	0.109	9.157

WBC: White blood cell count; LC: Lymphocyte count; NT-PROBNP: Amino-terminal pro-brain natriuretic peptide; TP: Total protein; DBIL: Direct bilirubin; GGT: Gamma-glutamyl transpeptidase; LDH: Lactic dehydrogenase; HCO: Bicarbonate radical; PT: Prothrombin time; INR: International normalized ratio; FIB: Fibrinogen; IL-2R: Interleukin-2 receptor 2; IL-6: Interleukin 6; NEUT: Neutrophil count; PCT: procalcitonin; AST: Glutamic oxalacetic transaminase; BU: Blood urea;; eGFR: Epidermal growth factor receptor; IL-8: Interleukin 8; IL-10: Interleukin 10.

Table 3: Collinearity diagnostics after adjusting variables

Model	Collinearity statistics	
	Tolerance	VIF
Age	0.712	1.404
WBT	0.599	1.670
LC	0.542	1.845
NT-PROBNP	0.789	1.267
Hypersensitive cardiac troponin	0.620	1.614
TP	0.319	3.132
DBIL	0.689	1.450
GGT	0.921	1.086
LDH	0.356	2.808
Sodium	0.428	2.336
PT	0.549	1.823
INR	0.970	1.031
FIB	0.710	1.409
D-D dimer quantification	0.555	1.801
IL-2R	0.474	2.109
NEUT	0.467	2.140
Albumin	0.358	2.793
IL-10	0.643	1.556

WBC: White blood cell count; LC: Lymphocyte count; NT-PROBNP: Amino-terminal pro-brain natriuretic peptide; TP: Total protein; DBIL: Direct bilirubin; GGT: Gamma-glutamyl transpeptidase; LDH: Lactic dehydrogenase; PT: Prothrombin time; INR: International normalized ratio; FIB: Fibrinogen; IL-2R: Interleukin-receptor 2; NEUT: Neutrophil count; IL-10: Interleukin 10.

Multivariate analysis results

The variables whose p < 0.05 in a single factor analysis and whose missing values were filled were included in Cox regression analysis, the method was forward: LR, with inclusion criteria of 0.05 and exclusion criteria of 0.10. We found that lactic dehydrogenase (LDH), age, fibrinogen (FIB), and disease severity were associated with delayed clearance of viral RNA in patients, as shown in Table 4. Then, drew the Kaplan and Meier curves and performed Log Rank test, as shown in Figures 1-4.

Table 4: Multivariate analysis results

Variables	B	SE	Wald	df	p-value	HR	95.0% CI for HR
Age	−0.302	0.137	4.824	1	0.028	0.739	(0.565,0.968)
Disease severity	−1.111	0.172	41.540	1	0.000	0.329	(0.235,0.462)
FIB normal			19.555	2	0.000		
Low	−0.657	0.530	1.537	1	0.215	0.519	(0.184,1.465)
High	−0.715	0.162	19.406	1	0.000	0.489	(0.356,0.672)
LDH	−0.532	0.161	10.952	1	0.001	0.587	(0.428,0.805)

FIB: Fibrinogen (normal: 2.00–4.00 low: <2.00 high: >4.00, g/L); LDH: Lactic dehydrogenase.

Discussion

We found that on the whole, men were less likely than women to undergo negative conversion of SARS-CoV-2 RNA (p < 0.05), which was consist with some other studies to some extent [13], [14], [15]. However, in our study, univariate Cox regression showed that gender was not related factor, so we did not include it. By the end of observation, the median duration of virus in the control group was 24 days that in the negative conversion group was 17 days; the difference was statistically significant (p < 0.05). It is very important to study the factors related to the negative transformation of the virus to shorten the duration of the virus and eliminate the virus in the body as soon as possible.

In our study, multivariate Cox regression showed that age was a relevant factor for viral nucleic

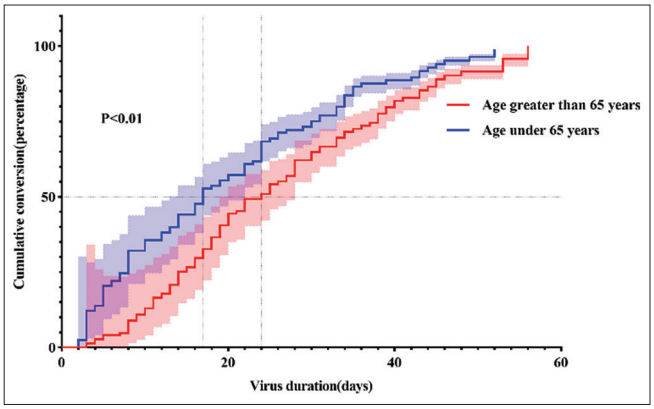

Figure 1: Negative conversion curves in coronavirus disease-19 patients according to age

acid negative transformation, and those younger than 65 years were more likely to have negative conversion than those older than 65 years (HR = 0.739, p < 0.05).

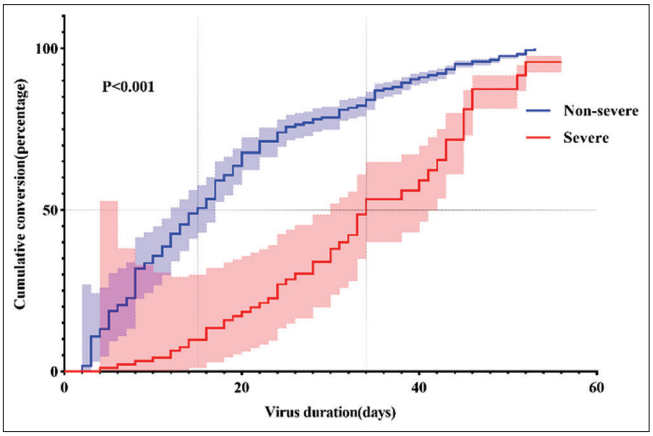

Figure 2: Negative conversion curves in coronavirus disease-19 patients according to disease severity

When the cutoff for age was set at 45 years as a related study did [16], we did not find this difference between the two age groups.

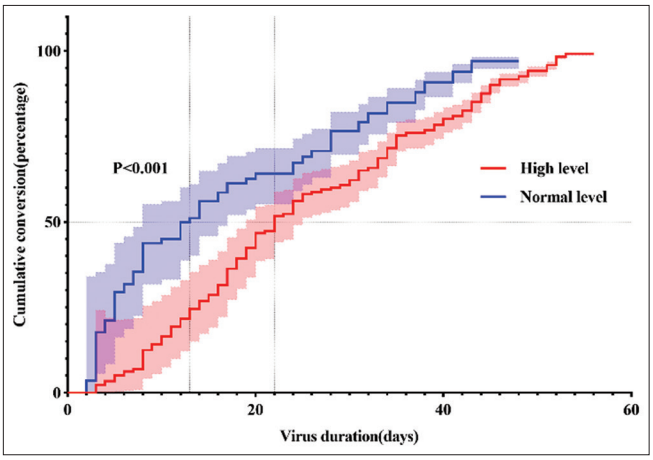

Figure 3: Negative conversion curves in coronavirus disease-19 patients according to fibrinogen

So we set the cutoff at 65 years as another research did [17] and found age > 65 years was a factor associated with viral negative conversion. First, older patients have a poorer prognosis as some studies showed [18], [19], [20]. Then, elderly patients are prone to systemic complications that may affect the clearance of SARS-CoV-2 [21]. In addition, it is generally believed that with age, immune system becomes weaker. Therefore, the risk of infection increases and the virus is difficult to remove from the body [22], [23].

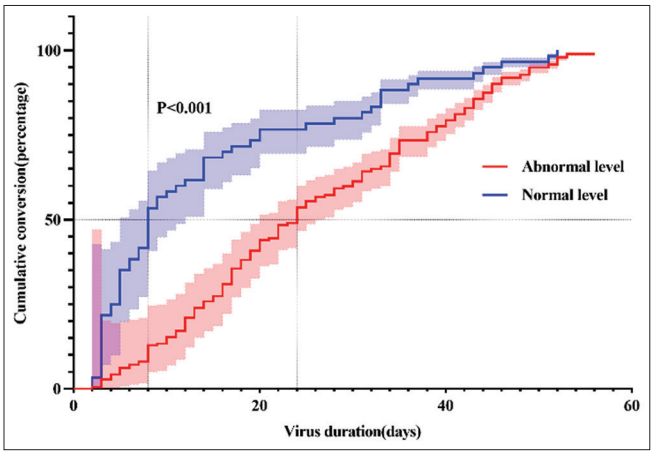

Figure 4: Negative conversion curves in coronavirus disease-19 patients according to lactic dehydrogenase

We found that the clearance of SARS-CoV-2 was associated with disease severity. It will be less conducive to virus removal if the illness at the time of admission is more serious. Ding Shi and other researchers have proved the same result [17]. The consensus view is that having severe COVID-19 symptoms affects the prognosis. As we all know, the more serious the disease is, the more critical complications may happen, which may affect the clearance of the virus in the body [24], [25].

Early studies have suggested that COVID-19 patients were easy to present with coagulopathy, disseminated intravascular coagulation, and other complications [26], [27], [28]. Based on this finding, our study has demonstrated that high levels of FIB were related to the delayed virus clearance. Although few studies have been consistent with our results, some researchers have confirmed that FIB seems to increase early in COVID-19 patients or severe patients and may be used as a risk stratification marker [29], [30]. As for the mechanism of clotting disorder, according to relative research, the endothelial glycocalyx is one of the important targets in the pathogenesis of virus-induced coagulopathy, while it still remains to be clarified whether similar mechanisms exist in COVID-19 or not. Besides, in a severer viral infection, both direct virus-induced cytotoxic effect and indirect injury may damage the host, pro-inflammatory cytokines and chemokines reported in COVID-19 were examples [31], [32]. For coagulation disorders, the corresponding treatment may indirectly help the virus to turn negative so as to improve the prognosis.

Meta-analysis showed that the laboratory indicator abnormality that COVID-19 patients were more likely to occur was the elevated LDH level and it had stronger correlations with COVID-19 mortality [20], [33]. In other studies, patients were divided into the severe group with diabetes and the group without diabetes, the

cardiovascular disease group and the non-cardiovascular disease group. The results showed that the level of LDH in the former group was higher than that in the control group, which indicates the increase of LDH may be associated with cooccurring chronic diseases. These patients were more likely to suffer from multiple organ dysfunction syndrome [6], [34]. It has been reported that the cause of elevated LDH may be that the virus damages muscles and myocardial [35]. Increased LDH may cause the decrease of cytosolic pH and exacerbate muscle soreness [36]. Therefore, it is necessary to detect the LDH concentration in time and to determine the degree of damage to important organs in the body.

We studied the related factors from the perspective of virus negative conversion. It has been rarely studied in the previous research. In addition, variables with missing values greater than 20% were eliminated and other missing values were filled to ensure the stability of multi-factor analysis results. However, this study still has some shortcomings. Factors that may affect the lab indicators, such as comorbidities, were not included in the analysis because of the excessive lack of data and the causal relationship between laboratory findings and disease severity could not be determined.

Conclusion

Our study found that age older than 65 years, more severe disease; the elevated levels of LDH and FIB were not conducive to the negative conversion of SARS-CoV-2 RNA. Under the same conditions, the elevated group would prolong the virus clearance time. Therefore, in the treatment of COVID-19, attention should be paid to people over 65 years old and in critical condition and monitor these indicators, so as to control the inflammation and organ damage caused by viral infection, and help to improve the prognosis of patients.

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