Int J Clin Exp Med 2021;14(1):724-734
www.ijcem.com /ISSN:1940-5901/IJCEM0120858

Original Article

Analysis of clinical data and risk factors of long-term coronavirus positive nucleic acids in novel patients

Zhifeng Li[1], Jie Su[3], Weigan Xu[2], Kangyi Yang[2]

Departments of [1]Internal Medicine, [2]Emergency, The First People's Hospital of Foshan, Foshan, Guangdong Province, China; [3]Department of Respiratory, The Second People's Hospital of Foshan, Foshan, Guangdong Province, China

Received August 22, 2020; Accepted September 16, 2020; Epub January 15, 2021; Published January 30, 2021

Abstract: Objective: To analyze the clinical data and risk factors of long-term coronavirus positive nucleic acids in patients with coronavirus disease in 2019 (COVID-19), and provide clinical guidance for the management of such patients. Methods: The clinical data of 989 patients with COVID-19 were retrospectively analyzed, and patients were divided into three groups according to the duration of nucleic acid positivity. Patients with positive nucleic acids for coronavirus for a duration of 1-5 days were regarded as the short-term group, patients who were positive for coronavirus nucleic acids for 6-22 days were set as the mid-term group, and those who were positive for coronavirus nucleic acids for more than 23 days were set as the long-term group. We analyzed their clinical data including clinical features, laboratory tests, imaging features and treatment outcomes, and finally explored the risk factors for long-term nucleic acid positivity in COVID-19 patients. Results: There were significant differences among the three groups in terms of clinical features (such as age, diabetes and respiratory diseases), laboratory test results (such as neutrophil count, lymphocyte count and creatinine levels) and imaging features (such as reticular nodule shadow and involved lung lobes). Age, diabetes mellitus, reticular nodule shadow, involvement of lung lobes, abnormal creatinine level and lymphocyte counts were risk factors for long-term positive coronavirus nucleic acids in COVID-19 patients. Conclusion: age, diabetes, reticular nodule shadow, involvement of lung lobes, abnormal creatinine levels and lymphocyte counts can help doctors identify COVID-19 patients with higher risk factors.

Keywords: COVID-19, long-term coronavirus positive nucleic acids, clinical data, risk factors

Introduction

In the past two decades, coronaviruses have caused two epidemics, namely severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [1]. In December 2019, it was called 2019 coronavirus disease (COVID-19) by the World Health Organization, this version is spreading widely and rapidly [2]. Cases of COVID-19 have been found in many countries in the world [3, 4]. Mild cases present as self-limited respiratory disease, and severe cases may cause death due to progressive respiratory failure and multiple organ failure [5]. In previous case reports, most patients were aged 30-79 years old, with an overall case fatality rate of 2.3%. Among them, the case fatality rate of people aged 70-79 years old was 8.0%, while that of people over 80 years old was as high as 14.8% [6].

Qualitative detection of SARS-CoV-2 RNA in clinical practice is an important means to confirm coronavirus infection [7]. At present, isolation or hospitalization measures are mostly taken for patients with positive viral RNA test [8, 9]. In addition, patients who were negative for viral nucleic acid tests from respiratory tract samples for two consecutive times (the sampling interval was not less than 24 h) may be considered for release from hospital isolation and discharged from the hospital [10]. The persistence of the virus for a long time in an individual may spread it to other people or in the environment, both of which have a significant impact on health care [11]. Some studies suggest that the infectivity of COVID-19 patients depends on the presence of the virus in different body fluids, secretions and excreta, and the duration of being positive for coronavirus RNA nucleic acids may be related to the immunity of host cells

[12]. However, according to the available data, there has been no report on the clinical risk factors for COVID-19 patients who did not turn negative for a long time after nucleic acid test [13, 14].

To this end, we collected and analyzed the clinical data of 989 patients with COVID-19. The main objective was to analyze the risk factors of COVID-19 patients whose nucleic acid test did not turn negative for a long time, in order to provide guidance for the prevention and treatment of COVID-19.

Materials and methods

Research subject

A total of 989 COVID-19 patients confirmed in Wuhan No. 1 Hospital (Wuhan Hospital of Traditional Chinese & Western Medicine) from February 13 to March 30, 2020 were included in this retrospective analysis, and patients were diagnosed with COVID-19 according to the World Health Organization interim guidelines [15]. All the patients received chest imaging examination upon admission, and it was confirmed that the infected patients tested positive for SARS-CoV-2 virus in respiratory tract samples by real-time reverse transcription polymerase chain reaction (RT-PCR). All patients signed the informed consent, and this study was approved by the Ethics Committee of Wuhan No. 1 Hospital (Wuhan Hospital of Traditional Chinese & Western Medicine).

Exclusion criteria: Patients with incomplete clinical data; patients infected with other respiratory viruses, such as influenza virus, respiratory syncytial virus and adenovirus; patients with vasculitis, dermatomyositis and organized pneumonia; patients with survival time ≥23 days.

Data collection

The data collected in the study were obtained by extracting demographic, clinical symptoms, laboratory indicators, and treatment methods from electronic medical records of 989 COVID-19 patients. The data sheet was based on the diagnosis and treatment protocols for COVID-19. The acquisition of original data and the quality assessment of methodology were discussed and determined by two researchers, independently.

Outcome measures

Outcome measures included age, gender, comorbidities (including cerebrovascular disease, hypertension, diabetes, heart disease, respiratory disease, etc.), signs and symptoms before/at admission (including cough, fever, fatigue, etc.), clinical classification (including mild, normal, severe, critical), clinical outcome (including survival, death), routine blood work (including white blood cell count, platelet count, lymphocyte, etc.), blood biochemistry (including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, etc.), blood coagulation function (including prothrombin time, active part thrombin time, D-dimer, etc.), chest X-ray or CT examination results at admission and treatment methods.

Grouping

According to the duration of SARS-CoV-2 RNA positivity, patients were divided into a short-term positive group (0-5 d, <25%), a middle-term positive group (6-22 d, 25-75%) and long-term positive group (≥23 d, 75-100%) based on the median and inter-quartile range (IQR) of the skewed distribution.

Statistical analysis

The data were analyzed by SPSS 20.0. The percentage was used to represent the categorical variables, and the median and IQR were used to represent the non-normally distributed data of continuous variables. The enumeration data were expressed as cases/percentage (n/%), and chi-square test was used for comparison between groups. The risk factors for long-term positive nucleic acids presence in COVID-19 patients were analyzed by a logistic multivariate regression model. The indicators with differences were analyzed by ROC curve, and the area under the ROC curve ≥0.7 was defined as a risk factor, and then it was converted to the categorical variables according to the cutoff value for logistic regression analysis. The test level was $\alpha=0.05$, and $P<0.05$ indicated that the difference was statistically significant.

Results

Clinical characteristics of patients with COVID-19

The clinical characteristics of 989 patients with COVID-19 were analyzed. As shown in **Table 1**,

Table 1. Presenting characteristics of patients with coronavirus disease 2019 (n, %)

Variable	Total (n=989)	Short-term group (1-5 d, n=236)	Middle-term group (6-22 d, n=494)	Long-term group (≥23 d, n=259)	P
Nucleic acid positive duration range (IQR)		12 (6, 23)	Min=1	Max=55	
Age (year)					0.01
Mean ($\bar{X}$ ± sd)	989	61.13±14.80	58.98±15.71	55.96±15.61	
0-18	10	1 (0.42)	6 (1.21)	3 (1.16)	
19-44	163	30 (12.71)	80 (16.19)	57 (22.01)	
45-64	434	94 (39.83)	209 (42.30)	121 (46.72)	
65-74	252	67 (28.39)	133 (26.92)	52 (20.08)	
≥75	136	44 (18.64)	66 (13.36)	26 (10.04)	
Sex					0.092
Female	570	130 (55.08)	278 (56.27)	162 (62.55)	
Male	419	106 (44.92)	216 (43.72)	97 (37.45)	
Comorbidities					
Hypertension	301	72 (30.51)	159 (32.18)	70 (27.03)	0.344
Diabetes mellitus	105	23 (9.75)	61 (12.34)	40 (15.40)	0.026
Heart disease	103	27 (11.44)	52 (10.52)	24 (9.27)	0.462
Respiratory system disease	57	21 (8.90)	28 (5.67)	8 (3.09)	0.007
Chronic kidney and liver system diseases	53	14 (5.93)	25 (5.06)	14 (5.41)	0.887
Cerebrovascular disease	41	14 (5.93)	17 (3.44)	10 (3.86)	0.277
Digestive system diseases	25	8 (3.39)	10 (2.02)	7 (2.70)	0.535
Unaccompanied disease	254	110 (46.61)	237 (47.98)	121 (46.72)	0.918
Signs and symptoms before/at admission					
Cough	570	99 (41.95)	302 (61.13)	169 (65.25)	0.009
Fever	568	145 (61.44)	276 (55.87)	135 (52.12)	0.038
Fatigue	439	115 (48.73)	201 (40.61)	123 (47.49)	0.062
Sore throat	432	14 (5.93)	26 (5.26)	24 (9.27)	0.098
Shortness of breath	219	52 (22.03)	128 (25.91)	44 (16.99)	0.082
Myalgia	190	47 (19.92)	94 (19.03)	49 (18.92)	0.951
Chill	180	43 (18.22)	88 (17.81)	49 (18.92)	0.933
Chest tightness	173	51 (21.61)	84 (17.00)	38 (14.67)	0.044
Sputum production	148	15 (6.36)	89 (18.02)	44 (16.99)	0.000
Diarrhea	64	13 (5.51)	20 (4.05)	10 (3.86)	0.441
Nausea	38	10 (4.24)	22 (4.45)	6 (2.32)	0.328
Runny nose	21	4 (1.69)	15 (3.04)	2 (0.77)	0.107
Blocked nose	15	2 (0.85)	10 (2.02)	3 (1.16)	0.519
Heart rate (IQR)	85 (78, 96)	86 (78, 99)	84 (78, 96)	86 (78, 95)	0.585
Respiration rate (IQR)	20 (18, 20)	20 (18, 20)	20 (18, 20)	19 (18, 20)	0.008
SpO_2 (IQR)	98 (97, 99)	98 (97, 99)	97.10 (97, 99)	97.06 (97, 99)	0.870
Clinical classification					0.550
Mild	60	14 (5.93)	31 (6.28)	15 (5.79)	
Common	753	176 (74.58)	382 (77.33)	195 (75.29)	
Severe	130	36 (15, 25)	54 (10.93)	40 (15.44)	
Critical	41	10 (4.24)	23 (4.66)	8 (3.09)	
Clinical outcome					0.192
Survival	840	229 (97.03)	484 (97.98)	257 (99.23)	
Died	19	7 (1.17)	10 (2.02)	2 (0.77)	

Note: SpO_2: oxygen saturation; IQR: interquartile range.

the patients were divided into three groups according to the duration of positive nucleic acid detection: 236 cases in the range of 1-5 days as the short-term group, 494 cases in

6-22 days as the middle-term group, and 259 cases in ≥23 days as the long-term group. The ages of each group were 61.13±14.80, 58.98±15.71 and 55.96±15.61 years old, respectively. We found that the age of patients in the long-term group was significantly younger than other groups (P<0.05), and the main age group was 19-64 years old (178 cases, 68.73%). In the analysis of chronic basic diseases, there were 40 (15.40%) diabetic patients in the long-term group, which was significantly more than the short-term and middle-term group (P<0.05). However, there were only 8 (3.09%) patients with respiratory system diseases in the long-term group, which was significantly less than the short-term and middle-term group (P<0.01). Observation of signs and symptoms before/at admission showed that cough was significantly more common (65.25%) in the long-term group than the short-term and middle-term group (P<0.05). The incidence of sputum production (16.99%) was significantly higher than that of the short-term group (P< 0.05), and the incidence of fever (52.12%), shortness of breath (16.99%) and chest tightness (14.67%) were significantly lower than those of the short-term and middle-term group (P<0.05).

Laboratory findings of patients with COVID-2019 upon admission

In routine blood tests, there were statistically significant differences in neutrophil count and lymphocyte count among the three groups (P<0.05). In the long-term group, there were 7 cases of abnormal reduction of neutrophil count (2.73%), which was lower than in the middle-term and short-term groups (3.72%, 50.64%). The proportion of abnormal increase in neutrophil count (4.69%) was also lower than in the middle-term and short-term groups (6.20%, 7.73%). An abnormal decrease of lymphocyte count occurred in 16 cases, and the proportion (6.53%) was lower than in the middle-term and short-term groups (12.61%, 21.89%). Besides, the proportion of abnormal increase in lymphocyte count (0.41%) was also lower than that in the middle-term and short-term groups (0.43%, 2.58%).

In blood biochemistry tests, there were statistically significant differences in levels of procalcitonin, albumin, hypersensitive troponin I, serum creatinine, blood urea nitrogen, interleukin-6 and C-reactive protein among the three groups (P<0.05). Observation of patients' serum procalcitonin showed that the percentage of increased serum procalcitonin level in the short-term group and the middle-term group was 43.50% and 24.11%, respectively; while the serum procalcitonin level in the long-term group was 80.37%, which was normal. In terms of albumin, 88.70% of the patients in the long-term group had no decrease, while the percentage of albumin decrease in the short-term and middle-term group was 22.94% and 15.80%, respectively. The serum levels of hypersensitive troponin I (98.34%), creatinine (97.57%), urea nitrogen (94.35%), interleukin-6 (90.59%) and C-reactive protein (91.83) in the long-term group were mostly in the normal range.

In the function of blood coagulation detection, there was a significant difference in D-dimer among the three groups (P<0.05). The normal rates of D-dimer in the three groups were 62.43%, 67.50% and 78.80%, respectively. The proportion of abnormal increase of D-dimer in the long-term group (21.20%) was lower than in the middle-term and short-term group (32.5%, 37.57%). See **Tables 2** and **3**.

Imaging characteristics and treatment methods of patients with COVID-19

The results of chest X-ray/CT examination upon admission showed that there were significant differences in reticular nodule shadow, lung consolidation, involvement of right upper lobe or right lower lobe and lesion range among the three groups (P<0.05). In the CT signs, the proportion of reticular nodule shadow in the long-term group (24.60%) was lower than in the middle-term and short-term groups (33.96%, 36.12%), and the proportion of lung consolidation (5.95%) was also lower than in the middle-term and short-term groups (6.88%, 11.45%). In terms of involvement of lung lobes, the proportion of involved right upper lobe in the long-term group (23.81%) was lower than in the middle-term and short-term groups (28.33% 33.92%), and the proportion of involved right lower lobe in the long-term group (65.87%) was also lower than in the middle-term and short-term groups (71.25%, 74.89%). As for the lesion range, the proportion of small lesion range in the long-term group (50.40%) was more than in the middle-term and short-term groups

Table 2. Laboratory findings of patients with coronavirus disease 2019 on admission (n, %)

Variable	Total (n=989)	Short-term group (1-5 d, n=236)	Middle-term group (6-22 d, n=494)	Long-term group (≥23 d, n=259)	P
White blood cell count (/L, normal range, *10^9)					0.412
Decrease	44	9 (3.86)	23 (4.83)	12 (4.63)	
Normal	893	214 (91.83)	443 (93.07)	236 (91.12)	
Increase	31	10 (4.29)	10 (2.10)	11 (4.25)	
Platelet count (/L, normal range: 125-350) *10^9					0.287
No increase	917	220 (94.42)	464 (95.87)	233 (93.20)	
Increase	50	13 (5.58)	20 (4.13)	17 (6.80)	
Neutrophil count (/L, normal range: 1.8-6.3) *10^9					0.000
Decrease	143	118 (50.64)	18 (3.72)	7 (2.73)	
Normal	770	97 (41.63)	436 (90.08)	237 (92.58)	
Increase	60	18 (7.73)	30 (6.20)	12 (4.69)	
Lymphocyte (/L, normal range: 1.1-3.2) *10^9					0.000
Decrease	126	51 (21.89)	59 (12.61)	16 (6.53)	
Normal	811	176 (75.54)	407 (86.97)	228 (93.06)	
Increase	9	6 (2.58)	2 (0.43)	1 (0.41)	
Monocyte count (/L, normal range: 0.1-0.6) *10^9					0.213
Normal	920	220 (94.42)	457 (94.42)	243 (97.20)	
Increase	47	13 (5.58)	27 (5.58)	7 (2.80)	
ESR (mm/L, normal range: 0-15)					0.360
Normal	140	30 (28.85)	61 (30.81)	48 (36.92)	
Increase	293	74 (71.15)	137 (69.19)	82 (63.08)	
Alanine aminotransferase (U/L, normal range: 0-55)					0.752
Normal	867	205 (89.13)	429 (90.89)	233 (89.96)	
Increase	94	25 (10.87)	43 (9.11)	26 (10.04)	
Aspartate aminotransferase (U/L, normal range: 5-34)					0.265
Normal	882	211 (91.34)	430 (90.72)	241 (94.14)	
Increase	79	20 (8.66)	44 (9.28)	15 (5.86)	
Alkaline phosphatase (U/L, normal range: 40-150)					0.501
No increase	953	229 (99.13)	472 (99.58)	252 (98.82)	
Increase	7	2 (0.97)	2 (0.42)	3 (1.18)	
Procalcitonin (ng/m, normal range: 0-0.051)					0.000
Normal	549	100 (56.50)	277 (75.89)	172 (80.37)	
High	207	77 (43.50)	88 (24.11)	42 (19.63)	
Albumin (g/L, normal range: 35-52)					0.001
Decrease	157	53 (22.94)	75 (15.8)	29 (11.3)	
No Decrease	806	178 (77.06)	401 (84.2)	227 (88.7)	
Total bilirubin (umol/L, normal range: 3.4-20.5)					0.762
No increase	902	219 (95.22)	448 (94.12)	239 (93.73)	
Increase	55	11 (4.78)	28 (5.88)	16 (6.27)	
Direct bilirubin (umol/L, normal range: 0-8.6)					0.228
Normal	898	218 (96.46)	445 (94.08)	235 (92.89)	
Increase	54	8 (3.54)	28 (5.92)	18 (7.11)	
Creatine kinase-MB, (U/L, normal range: 0-3.1)					0.142
Normal	590	149 (96.75)	265 (93.31)	176 (96.70)	
Increase	30	5 (3.25)	19 (6.69)	6 (3.30)	
Creatine kinase (U/L, normal range: <190)					0.287
No increase	485	112 (99.12)	209 (98.12)	164 (97.04)	
Increase	10	1 (0.88)	4 (1.88)	5 (2.96)	
Hypersensitive troponin I, (pg/mL, normal range: 0-34.2)					0.049
Normal	575	141 (94.00)	256 (93.43)	178 (98.34)	
Increase	30	9 (6.00)	18 (6.57)	3 (1.66)	
Serum creatinine (mmol/L, normal range: 64-10)					0.003
No increase	886	205 (91.52)	440 (95.44)	241 (97.57)	

Increase	46	19 (8.48)	21 (4.56)	6 (2.43)	
Blood urea nitrogen (mmol/L, normal range: 3.2-7.4)					0.048
No increase	852	200 (89.29)	418 (90.67)	234 (94.35.)	
Increase	81	24 (10.71)	43 (9.33)	14 (5.65)	
Lactate (mmol/L, normal range: 0.5-1.6)					0.398
No increase	23	9 (16.98)	6 (10.71)	8 (20.51)	
Increase	124	43 (83.02)	50 (89.29)	31 (79.49)	
Interleukin-6, (pg/mL, normal range: 0-10)					0.004
No increase	523	115 (79.31)	254 (89.44)	154 (90.59)	
Increase	76	30 (20.69)	30 (10.56)	16 (9.41)	
C-reactive protein, (mg/L, normal range: 0-10)					0.007
No increase	847	191 (83.77)	420 (87.32)	236 (91.83)	
Increase	119	37 (16.23)	61 (12.68)	21 (8.17)	

Note: ESR: erythrocyte sedimentation rate.

Table 3. Coagulopathy findings of patients with coronavirus disease 2019 on admission (n, %)

Variable	Total (n=989)	Short-term group (1-5 d, n=236)	Middle-term group (6-22 d, n=494)	Long-term group (≥23 d, n=259)	P
Prothrombin time (s, normal range: 9.2-15)					0.314
No increase	747	180 (97.83)	362 (98.64)	205 (99.51)	
Increase	10	4 (2.17)	5 (1.36)	1 (0.49)	
Active part thrombin time (s, normal range: 21-37)					0.160
No increase	689	163 (88.59)	335 (90.79)	191 (92.72)	
Increase	70	21 (11.41)	34 (9.21)	15 (7.28)	
International Normalized Ratio (s, normal range: 0.8-1.25)					0.284
No increase	735	177 (95.68)	357 (97.28)	201 (97.57)	
Increase	23	8 (3.8)	10 (2.72)	5 (2.43)	
D-dimer (mg/L, normal range: 0-0.55)					0.001
Normal	492	108 (62.43)	228 (67.5)	156 (78.8)	
High	217	65 (37.57)	110 (32.5)	42 (21.2)	

(43.96%, 39.65%), and the proportion of scattered lesions (3.17%) was lower than inthe middle-term and short-term groups (6.67%, 8.37%). See **Table 4**.

In terms of treatment methods, there were no significant differences in oxygen therapy, noninvasive mechanical ventilation and invasive mechanical ventilation among the three groups (P>0.05). The proportion of patients who received oxygen therapy in the long-term group (72.97%) was higher than in the middle-term and short-term groups (67.61%, 68.22%), while the proportion of patients who received invasive mechanical ventilation (1.16%) was lower than in the middle-term and short-term groups (1.42%, 4.48%). See **Table 5**.

Risk factors of long-term nucleic acid positivity in patients with COVID-19

To further analyze the risk factors of long-term nucleic acid positivity in patients with COVID-19, taking the long-term group as the dependent variable, the statistically significant clinical characteristics of COVID-19 patients were included in the logistic multivariate regression model. After correcting the confounding factors, the results showed that age, diabetes mellitus, reticular nodule shadow, involvement of lung lobes, abnormal creatinine and lymphocyte count were the risk factors of long-term nucleic acid positivity in COVID-19 patients. See **Table 6**.

Discussion

COVID-19 is a new infectious disease discovered in 2019, and is now spreading rapidly in many countries [16]. At present, the short-term and long-term harm caused by long-term positive nucleic acid in COVID-19 patients is not yet clear, while analyzing the clinical characteristics and risk factors of long-term positive nucleic acid in COVID-19 patients is of great significance for improving medical awareness and

Table 4. CT findings of patients with coronavirus disease 2019 on admission (n, %)

Admission chest X-ray/CT findings	Total (n=989)	Short-term group (1-5 d, n=236)	Middle-term group (6-22 d, n=494)	Long-term group (≥23 d, n=259)	P
Lung involvement					0.894
Unilateral	111	25 (11.01)	60 (12.50)	26 (10.32)	
Bilateral	787	188 (82.82)	388 (80.83)	211 (83.73)	
No abnormal	61	14 (6.17)	32 (6.67)	15 (5.95)	
Predominantly CT pattern					
Reticular nodule shadow	307	82 (36.12)	163 (33.96)	62 (24.60)	0.006
Ground-glass opacities	873	207 (91.19)	433 (90.21)	233 (92.46)	0.596
Pleural effusion	16	6 (2.64)	5 (1.04)	7 (2.78)	0.141
Peribronchial wall thickening	10	1 (0.44)	7 (1.46)	2 (0.79)	0.594
Lung consolidation	74	26 (11.45)	33 (6.88)	15 (5.95)	0.027
Pulmonary oedema		0	1 (0.21)	0	1
Venous congestion		0	0	0	1
Atelectasis	6	2 (0.88)	2 (0.42)	2 (0.79)	0.648
Normal	59	13 (5.73)	31 (6.46)	15 (5.95)	0.920
Clearance displacement	6	2 (0.88)	3 (0.62)	1 (0.40)	0.759
Adjacent pleural thickening	14	4 (1.76)	8 (1.67)	2 (0.79)	0.605
Pulmonary fibrosis	100	28 (12.33)	52 (10.83)	20 (7.94)	0.113
Involved lung lobes					
No	60	14 (6.17)	31 (6.46)	15 (5.95)	0.963
Right upper lobe	273	77 (33.92)	136 (28.33)	60 (23.81)	0.015
Right middle lobe	559	137 (60.35)	276 (57.50)	146 (57.94)	0.766
Right low lobe	678	170 (74.89)	342 (71.25)	166 (65.87)	0.030
Upper left lobe	543	137 (60.35)	264 (55.00)	142 (56.35)	0.405
Left low lobe	610	149 (65.64)	309 (64.38)	152 (60.32)	0.220
Involved lung segments	4 (3, 10)	6 (3, 12)	5 (3, 10)	4 (3, 9)	0.077
Lesion range					0.012
No abnormal	60	14 (6.17)	31 (6.46)	15 (5.95)	
Rarely	428	90 (39.65)	211 (43.96)	127 (50.40)	
More	238	51 (22.47)	120 (25.00)	67 (26.59)	
A lot of	174	53 (23.35)	86 (17.92)	35 (13.89)	
Diffuse	59	19 (8.37)	32 (6.67)	8 (3.17)	
Distribution location					0.927
Peripheral subpleura	474	109 (48.02)	243 (50.63)	122 (48.41)	
Central by the hilum	2	0 (0.00)	2 (0.42)	0 (0.00)	
Both peripheral and center	422	104 (45.81)	203 (42.29)	115 (45.63)	
No	61	14 (6.17)	32 (6.67)	15 (5.95)	
Old lesions					0.535
YES	62	14 (6.17)	28 (5.83)	20 (7.94)	
No	897	213 (93.83)	452 (94.17)	232 (92.06)	

strengthening epidemic prevention management [17].

In this study, we divided COVID-19 patients into three groups according to the duration of coronavirus nucleic acid positivity, namely the short-term group (1-5 d), the middle-term group (6-22 d) and the long-term group (≥23 d). Based on the analysis of patients' clinical data, we concluded that diabetes mellitus, reticular nodule shadow, involvement of lung lobes, abnormal creatinine and lymphocyte count were

Table 5. Complications and treatment methods of patients with coronavirus disease 2019 (n, %)

Treatment	Total (n=989)	Short-term group (1-5 d, n=236)	Middle-term group (6-22 d, n=494)	Long-term group (≥23 d, n=259)	P
Oxygen treatment					
Oxygen	684	161 (68.22)	334 (67.61)	189 (72.97)	0.231
Non-invasive mechanical ventilation	12	4 (1.69)	5 (1.012)	3 (1.16)	0.362
Invasive mechanical ventilation	12	2 (4.478)	7 (1.42)	3 (1.16)	0.760

Table 6. Risk factors for long-term nucleic acid positivity in COVID-19 patients

Indicators	Standardized β	OR	95% CI	P
Diabetes Mellitus	0.768	2.156	1.442-3.224	<0.001
Reticular nodule shadow	0.470	0.625	0.433-901	0.012
Involved lung lobe	0.474	0.623	0.409-0.948	0.027
High creatinine level	0.474	0.623	0.452-0.858	0.004
Abnormal lymphocyte count	0.740	2.096	1.204-3.650	0.004
Age	0.705	2.024	1.115-3.674	0.020

Note: OR: odds ratio; CI: confidence interval.

risk factors of being positive long-term for coronavirus nucleic acids in COVID-19 patients. It has been reported that the severity of COVID-19 could be aggravated by age, weakness and combination of underlying diseases (such as kidney disease, heart disease) [18]. In this study, we found that the patients in the long-term group were younger than the short-term and middle-term group. Multivariate analysis showed that an age of 19-44 years old was a risk factor for the long-term persistence of SARS-CoV-2 virus. It is generally believed that older COVID-19 patients, especially those with poor health conditions, have a more severe state of illness than younger people, and are at higher risk of death [19]. Chen reported that although most COVID-19 patients were mildly ill, 80% of adults aged more than 60 years old died, and only 0.1% of people younger than 19 years old died [20]. Thus, elderly COVID-19 patients tend to have worse outcomes. It is worth noting that the existence time of SARS-CoV-2 virus in our study showed an opposite effect with age.

In this study, we found that at least half of the patients had some comorbidities, such as hypertension, diabetes, respiratory systemic diseases and so on. In addition, 15.40% of patients with diabetes mellitus in the long-term group had replication of SARS-CoV-2 virus for a long time, which was significantly higher than that in the middle-term and short-term groups. It was reported that people with diabetes had an increased risk of contracting influenza and pneumonia, and this risk may be reduced through good blood sugar control, although it cannot be completely eliminated [21, 22]. Some studies have suggested that patients with diabetes have a significantly increased risk of COVID-19 infection, and some treatment measures for COVID-19 patients with diabetes may require more frequent monitoring of blood glucose and drug adjustment [23]. Controlling the condition of patients with diabetes may also be a direction for inhibiting SARS-CoV-2 RNA virus, but it is still necessary to further study the relationship between diabetes mellitus and long-term replication of SARS-CoV-2 virus [24].

The occurrence and progression of COVID-19 depends on the interaction between the virus and the body's immune system [25]. Lymphocytes play a vital role in stabilizing immune homeostasis and inflammatory response [26]. It is understood that controlling lymphocyte levels in the blood may be a useful therapeutic strategy for the future treatment of COVID-19 [27]. In our study, compared with the short-term and middle-term groups, the blood lymphocytes in the long-term group were mostly in the normal range, and the reduction of lymphocyte was a risk factor for patients with long-term positive nucleic acid. In the report of Zhang et al., compared with SARS-CoV-2 negative patients with suspected symptoms, patients infected with SARS-CoV-2 showed a de-

crease in white blood cell and lymphocyte [28]. It has also been suggested that COVID-19 virus may directly infect lymphocytes and lead to cell death, while the persistent disorder of inflammatory cytokines may also lead to lymphocyte apoptosis. Observation of other laboratory indicators showed the elevated levels of inflammatory markers in the long-term group, such as neutrophils, procalcitonin, hypersensitive troponin I, creatinine, interleukin-6, and C-reactive protein, and abnormal creatinine were also risk factors for long-term nucleic acid positivity in COVID-19 patients. This may because the long-term existence of SARS-CoV-2 will stimulate the immune system and inflammatory response of the body, and reduce the immune response ability, which is not conducive to the shedding of the virus [29]. In addition, imaging examinations have been very helpful for the early detection and diagnosis of COVID-19 [30]. The opaque and ground-glass opacities in the periphery of the lungs are the main features of chest CT in patients with COVID-19 [31]. It is believed that about 75% of COVID-19 patients have bilateral pneumonia [32]. Our data showed that the proportion of reticular nodule shadow, involvement of the right upper lobe and right lower lobe in the long-term group were lower than those in the short-term and middle-term group, and reticular nodule shadow and involvement of lung lobe were also risk factors for long-term positive nucleic acid in patients. The above results may be related to the fact that the ventilation of the right lung is better than the left lung, and the virus is easier to enter the right lung, resulting in more infection in the right lung lobe than in the left lung lobe [33].

Although our study confirmed that age, diabetes mellitus, reticular nodule shadow, involvement of lung lobe, abnormal creatinine and lymphocyte count were risk factors for long-term positive coronavirus nucleic acids in COVID-19 patients, there was still room for improvement. First of all, we can supplement the analysis of short-term and long-term prognosis in patients with long-term positive COVID-19 patients. Secondly, we can increase the research on the basic mechanism of long-term nucleic acid positivity in COVID-19 patients to find out the underlying principle. We will gradually improve the research based on the above two points in the future.

In summary, age, diabetes, reticular nodule shadow, involvement of lung lobe, abnormal creatinine and lymphocyte count could help doctors identify COVID-19 patients with long-term positive coronavirus nucleic acids, which are conducive to auxiliary medical decision-making.

Disclosure of conflict of interest

None.

Address correspondence to: Zhifeng Li, Department of Internal Medicine, The First People's Hospital of Foshan, No. 81 Lingnan Avenue, Chancheng District, Foshan 528000, Guangdong Province, China. Tel: +86-13827748878; E-mail: lizhifeng-52fs@163.com

References

[1] Abdirizak F, Lewis R and Chowell G. Evaluating the potential impact of targeted vaccination strategies against severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks in the healthcare setting. Theor Biol Med Model 2019; 16: 16.

[2] Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, Iosifidis C and Agha R. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). Int J Surg 2020; 76: 71-76.

[3] Dey SK, Rahman MM, Siddiqi UR and Howlader A. Analyzing the epidemiological outbreak of COVID-19: a visual exploratory data analysis approach. J Med Virol 2020; 92: 632-638.

[4] Ivanov D. Predicting the impacts of epidemic outbreaks on global supply chains: a simulation-based analysis on the coronavirus outbreak (COVID-19/SARS-CoV-2) case. Transp Res E Logist Transp Rev 2020; 136: 101922.

[5] Hussain A, Bhowmik B and do Vale Moreira NC. COVID-19 and diabetes: knowledge in progress. Diabetes Res Clin Pract 2020; 162: 108142.

[6] The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)-China, 2020. China CDC Wkly 2020; 2: 113-122.

[7] Zheng SF, Fan J, Yu F, Feng BH, Lou B, Zou QD, Xie GL, Lin S, Wang RN, Yang XZ, Chen WZ, Wang Q, Zhang D, Liu YC, Gong RJ, Ma ZH, Lu SM, Xiao YY, Gu YX, Zhang JM, Yao HP, Xu KJ, Lu XY, Wei GQ, Zhou JY, Fang Q, Cai HL, Qiu YQ, Sheng JF, Chen Y and Liang TB. Viral load dynamics and disease severity in patients infect-

ed with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. BMJ 2020; 369: m1443.
[8] Yang Y, Peng F, Wang R, Yange M, Guan K, Jiang T, Xu G, Sun J and Chang C. The deadly coronaviruses: the 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. J Autoimmun 2020; 109: 102434.
[9] Heffernan DS, Evans HL, Huston JM, Claridge JA, Blake DP, May AK, Beilman GS, Barie PS and Kaplan LJ. Surgical infection society guidance for operative and peri-operative care of adult patients infected by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Surg Infect (Larchmt) 2020; 21: 301-308.
[10] Zhang JF, Yan K, Ye HH, Lin J, Zheng JJ and Cai T. SARS-CoV-2 turned positive in a discharged patient with COVID-19 arouses concern regarding the present standards for discharge. Int J Infect Dis 2020; 97: 212-214.
[11] Carrasco G. Reflections on the quality of health care after the SARS-CoV-2 pandemic. J Healthc Qual Res 2020; 35: 61-63.
[12] Ling Y, Xu SB, Lin YX, Tian D, Zhu ZQ, Dai FH, Wu F, Song ZG, Huang W, Chen J, Hu BJ, Wang S, Mao EQ, Zhu L, Zhang WH and Lu HZ. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J (Engl) 2020; 133: 1039-1043.
[13] Zhou YL, Zhang ZC, Tian J and Xiong SY. Risk factors associated with disease progression in a cohort of patients infected with the 2019 novel coronavirus. Ann Palliat Med 2020; 9: 428-436.
[14] Liu R, Han H, Liu F, Lv ZH, Wu KL, Liu YL, Feng Y and Zhu CL. Positive rate of RT-PCR detection of SARS-CoV-2 infection in 4880 cases from one hospital in Wuhan, China, from Jan to Feb 2020. Clin Chim Acta 2020; 505: 172-175.
[15] Patel A and Jernigan DB; 2019-nCoV CDC Response Team. Initial public health response and interim clinical guidance for the 2019 novel coronavirus outbreak - United States, December 31, 2019-February 4, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 140-146.
[16] Lai CC, Shih TP, Ko WC, Tang HJ and Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agent 2020; 55: 105924.
[17] Yan Y, Shin WI, Pang YX, Meng Y, Lai J, You C, Zhao H, Lester E, Wu T and Pang CH. The first 75 days of novel coronavirus (SARS-CoV-2) outbreak: recent advances, prevention, and treatment. Int J Environ Res Public Health 2020; 17: 2323.
[18] Wu J, Li W, Shi X, Chen Z, Jiang B, Liu J, Wang D, Liu C, Meng Y, Cui L, Yu J, Cao H and Li L. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19). J Intern Med 2020; 288: 128-138.
[19] CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 343-346.
[20] Chen LK. Older adults and COVID-19 pandemic: resilience matters. Arch Gerontol Geriatr 2020; 89: 104124.
[21] Luzi L and Radaelli MG. Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic. Acta Diabetol 2020; 57: 759-764.
[22] Muniyappa R and Gubbi S. COVID-19 pandemic, corona viruses, and diabetes mellitus. AJP Endocrinol Metabol 2020.
[23] Rico-Mesa JS, White A and Anderson AS. Outcomes in patients with COVID-19 infection taking ACEI/ARB. Curr Cardiol Rep 2020; 22: 31.
[24] Singh AK, Singh A, Shaikh A, Singh R and Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: a systematic search and a narrative review with a special reference to India and other developing countries. Diabetes Metab Syndr 2020; 14: 241-246.
[25] Kattan J, Kattan C and Assi T. Do checkpoint inhibitors compromise the cancer patients' immunity and increase the vulnerability to COVID-19 infection? Immunotherapy 2020; 12: 351-354.
[26] Montalban-Arques A, Chaparro M, Gisbert JP and Bernardo D. The innate immune system in the gastrointestinal tract: role of intraepithelial lymphocytes and lamina propria innate lymphoid cells in intestinal inflammation. Inflamm Bowel Dis 2018; 24: 1649-1659.
[27] Tan L, Wang Q, Zhang DY, Ding JY, Huang QC, Tang YQ, Wang QS and Miao HM. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther 2020; 5: 33.
[28] Zhang C, Zhang LJ, Chen X, Zhang H and Fei Y. Decreased "WBC*LYM" was observed in SARS-CoV-2-infected patients from a fever clinic in Wuhan. Clin Chem Lab Med 2020; 58: 1152-1155.
[29] Conti P, Gallenga CE, Tetè G, Caraffa A, Ronconi G, Younes A, Toniato E, Ross R and Kritas SK. How to reduce the likelihood of coronavirus-19 (CoV-19 or SARS-CoV-2) infection and lung inflammation mediated by IL-1. J Biol Regul Homeost Agents 2020; 34: 333-338.

[30] Huang ZX, Zhao S, Xu L, Chen JX, Lin W, Zeng HJ, Chen ZX, Du L, Shi YJ, Zhang N and Song B. Imaging features and mechanisms of novel coronavirus pneumonia (COVID-19): Study Protocol Clinical Trial (SPIRIT Compliant). Medicine (Baltimore) 2020; 99: e19900.

[31] Yang WJ, Sirajuddin A, Zhang XC, Liu GS, Teng ZZ, Zhao SH and Lu MJ. The role of imaging in 2019 novel coronavirus pneumonia (COVID-19). Eur Radiol 2020; 1-9.

[32] Chen NS, Zhou M, Dong X, Qu JM, Gong FY, Han Y, Qiu Y, Wang JL, Liu Y, Wei Y, Xia JA, Yu T, Zhang XX and Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-513.

[33] Chu JJ, Yang N, Wei YQ, Yue HH, Zhang FQ, Zhao JP, He L, Sheng GH, Chen P, Li G, Wu SS, Zhang B, Zhang S, Wang CY, Miao XP, Li J, Liu WH and Zhang HL. Clinical characteristics of 54 medical staff with COVID-19: a retrospective study in a single center in Wuhan, China. J Med Virol 2020; 92: 807-813.