

Original Article

Serum triglyceride level and hypertension are highly associated with the recovery of COVID-19 patients

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Abstract: The coronavirus disease-19 (COVID-19) has been a global pandemic and caused thousands of deaths worldwide. So far, although some studies suggested some medications may be helpful, there is no effective treatment for COVID-19. It is critical to find important risk factors that affects the recovery or severity of COVID-19 and guide the treatment for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In this study, we recruited these discharged patients with COVID-19 from hospitals. We collected clinical data and analyzed the time from disease onset to the positive-to-negative transmission (TPNT) of nucleic acid tests and its related clinical variables. TPNT was considered as an important indicator for the recovery of COVID-19 patients from SARS-CoV-2 infection. COVID-19 patients were divided into short TPNT group and long TPNT group. There were significant differences on hypertension, abidol treatment, serum alanine aminotransferase (ALT), lymphocyte counts, and serum triglyceride (TG) between two groups ($P < 0.05$). Patients in low TPNT group had higher serum triglyceride and less proportion of hypertension. Further logistic regression analysis showed that TPNT was highly associated with serum TG level and hypertension that were related to the expression of ACE2, the targeting protein for the invasion of SARS-CoV-2. Therefore, our findings demonstrate that serum triglyceride level and hypertension were important influencing factors for the recovery from SARS-CoV-2 infection. Therefore, diet changes and antihypertensive medications can be translational to the treatment of COVID-19 and promote the recovery of COVID-19 patients.

Keywords: COVID-19, SARS-Cov-2, virus removal, triglyceride, hypertension

Introduction

The coronavirus disease-19 (COVID-19) has been a global pandemic and caused thousands of deaths worldwide. With a sudden outbreak of an unknown-pathogen pneumonia, Chinese scientists firstly reported a coronavirus as the pathogen and announced its RNA sequencing [1], which was officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of viruses on February 11, 2020 [2]. Later, this pneumonia was found to have a potential of person-to-person transmission and a high infectivity [3, 4]. Due to the publication of the virus RNA sequences, the detection of viral nucleic acid became the gold standard for the

diagnosis of COVID-19. The diagnosis of COVID-19 can be made on the basis of epidemiological data, respiratory system symptoms, and positive real-time fluorescent RT-PCR for samples from patients [5]. Currently, there is no specific drug for antiviral treatment of SARS-CoV-2 infection, although chloroquine and remdesivir were reported to show in some cases of COVID-19 [6, 7]. It seemed that COVID-19 is a self-limiting disease in mild-moderate patients [8]. More importantly, a large proportion of patients with COVID-19 were asymptomatic and become the source of disease transmission [9-12]. Therefore, it is critical to find the determinant factors that affects the recovery of COVID-19 or the viral clearance. Several studies have demonstrated that ageing, hypertension,

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high serum LDH level, serum d-dimer level, and obesity are risk factors that are highly associated with the mortality of severer COVID-19 patients [13-15]. However, the risk factors in the mild and moderate COVID-19 patients were not identified. Current clinical data showed that only about 20% of COVID-19 patients developed severe disease [16]. Considering the large proportion of asymptomatic, mild, and moderate patients, here, we performed a retrospective analysis in COVID-19 patients discharged from hospitals and analyzed the association between the time from disease onset to positive-to-negative transmission (TPNT) and clinical variables.

Materials and methods

Patients

Laboratory-confirmed COVID-19 patients in three cities (Xuzhou, Lianyungang, and Yangzhou) in Jiangsu Province, China from January to March, 2022 were included in this study. The diagnostic criteria of COVID-19 was according to the Guidelines for the Diagnosis and Treatment of Novel Coronavirus Infection by National Health Commission of the People's Republic of China (Trial Version 6). Types A and B of influenza virus were excluded from all the patients. For SARS-CoV-2-infected patients, before being discharged from hospitals, the disappears of symptoms and two consecutive negative results for viral nucleic acid tests were required. Patients without complete clinical data were removed from this study. This study was approved by the institutional review board from local hospitals. Informed consent was obtained from patients.

Detection of SARS-CoV-2

Samples were collected by using pharyngeal swabs every 1-2 days after admission and sent to the local Center for Disease Control and Prevention for the detection of SARS-CoV-2. The real-time polymerase chain reaction (RT-PCR) method was used to detect SARS-CoV-2 RNA.

The retrospective study designs and data collection

Clinical information was obtained from clinical records. In this study, TPNT was defined as the

time from disease onset to the date for the first negative viral RNA test after the diagnosis. According to the median of TPNT, patients were divided into two groups: low TPNT group and high TPNT group. In two groups, we collected the baseline demographic data (i.e. age, gender), clinical risk factors (i.e. hypertension, diabetes mellitus, onset time, TPNT, previous medical history, admission diagnosis, clinical classification, use of antiviral drugs, use of glucocorticoid, use of thymus, use of Aluvia, and use of Interferon). Laboratory examinations included lymphocyte count, neutrophil count, white blood cell (WBC) counts, fasting blood-glucose, serum aspartate aminotransferase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), albumin (Alb), C-reactive protein (CRP), ferritin, Interleukin-6 (IL-6), triglycerides (TG), total cholesterol (TC) were measured. NLR was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count on admission.

Statistical analysis

Continuous variables were expressed as mean \pm SD or median (interquartile range, IQR). The difference between two groups was compared by using student's t test or Mann-Whitney test as appropriate. The comparison between multiple groups was expressed by LSD-t test. Categorical variables were shown in percentages and compared by chi-squared test or Fisher's exact test. Univariate logistic regression analysis was performed to find variables that accounted for TPNT. To adjust for confounding factors with $P < 0.1$, multivariate logistic regression analysis was used to assess any independent factors. Data was presented as adjusted OR (aOR) and respective 95% CI. All the data were analyzed by SPSS 22.0 statistical software. The difference was statistically significant ($P < 0.05$).

Results

Total 67 patients (37 males and 30 females) with COVID-19 were included in this study. Most patients are mild-moderate clinical types and 6 cases were severe patients. The average age was 45.2 years old. The median TPNT was 16 days. According to the cut-off value 16 d of TPNT, patients were divided into two groups: short TPNT (≤ 16 d) group and long TPNT (> 16 d) group. The clinical data in two groups were

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Table 1. The relationship between TNPT and Clinical characteristics, treatment, and laboratory findings in patients with COVID-19

Clinical data	TNPT≤16	TNPT>16	t/U χ^2	P
Sex (M/F)	22/13	15/17	1.727	0.189
Age (y)	41.25±16.25	49.56±16.23	-2.014	0.920
Clinical types			3.807	0.237
Mild	14	7		
Moderate	18	22		
Severe	3	3		
Complications				
Diabetes	3	4	0.276	0.600
Hypertension	1	12	12.829	0.000*
Surgery history	1	1		
Hepatitis B infection	2	0	2.783	0.249
Treatment				
Abidol (Y/N)	16/19	23/9	4.703	0.03*
Aluvia (Y/N)	31/4	30/2	0.550	0.458
Interferon (Y/N)	29/6	29/3	0.867	0.352
Thymosin (Y/N)	8/28	8/23	1.108	0.575
Glucocorticoid (Y/N)	5/25	3/24	7.401	0.285
Laboratory findings				
AST (U/L)	28.24±10.52	29.28±21.17	-0.768	0.241
ALT (U/L)	29.58±19.29	45.86±34.46	-2.44	0.000*
LDH (U/L)	192 (111, 420)	194 (126, 460)	0.758	0.448
Alb (g/L)	43.78±4.47	43.27±6.08	0.408	0.283
Glu (mmol/L)	5.83 (4.41, 10.67)	6.24 (4.51, 8.72)	0.333	0.765
TC (mmol/L)	3.97 (3, 6)	3.7 (2, 7)	-0.124	0.901
TG (mmol/L)	1.25 (0.46, 5.22)	1.03 (0.57, 3.15)	-1.99	0.047*
WBC (10 ⁹ /L)	5.56±2.0	5.10±1.68	0.969	0.145
N (10 ⁹ /L)	1.28±0.63	3.69±1.26	0.071	0.944
L (10 ⁹ /L)	1.60±0.98	1.18±0.52	2.187	0.048*
NLR	2.81 (1.12, 22.15)	3.02 (1.45, 9.39)	0.073	0.789
CRP (mg/L)	6.45 (0, 142.4)	7.19 (0.2, 174.6)	0.288	0.773
IL-6 (pg/ml)	6.5 (2, 13)	10 (2, 62)	4.035	0.058
FER (ng/ml)	399.6 (72, 1848)	348.9 (39, 1247)	0.176	0.679

Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase; Alb, albumin; BMI, body mass index; CRP, C-reactive protein; Glu, Glucose; L, lymphocyte; LDH, lactate dehydrogenase; IL-6, interleukin-6; N, neutrophil; NLR, neutrophil to lymphocyte ratio; TC, total cholesterol; TG, triglyceride; WBC, white blood cells; *, P<0.05.

summarized in **Table 1**. We compared age, gender, clinical types, complications, treatments, and laboratory results in both groups. We found that there were significant differences on hypertension, abidol treatment, serum alanine aminotransferase (ALT), lymphocyte counts, and serum TG between the two groups (P<0.05, **Table 1**), but there were no differences on age, gender, clinical types, diabetes history, glucocorticoid treatment, serum LDH, serum IL-6 between the two groups (P>0.05,

Table 1). We further performed a multivariable logistic analysis to examine the factors that were associated with TPNT. Serum triglyceride level (B=-0.979, OR=0.376, 95.0% CI: 0.159-0.887, P=0.025) and hypertension (B=-2.783, OR=16.174, 95.0% CI: 1.168-161.661, P=0.018) was associated with TPNT.

Since serum TG level is negatively associated with TPNT. According to Chinese Guidelines for the Prevention and Treatment of Adult Dysli-

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Table 2. Clinical data of patients in high serum TG group and normal TG group

Clinical data	TG<2.3	TG≥2.3	t/U/χ ²	P
Sex (M/F)	34/25	3/5	1.154	0.283
Age (y)	45.3±17.6	44.4±11.9	0.139	0.890
TPNT	18.9±9.2	14.4±4.0	2.461	0.023*
Clinical types			1.830	0.608
Mild	20	1		
Moderate	34	6		
Severe	5	1		
Complications				
Bacterial infection	5/54	1/7	0.140	0.708
Diabetes	6/53	1/7	0.041	0.840
Hypertension	12/47	1/7	0.277	0.599
Treatment				
Abidol (Y/N)	35/24	4/4	0.252	0.616
Interferon (Y/N)	51/8	7/1	0.007	0.934
Thymosin (Y/N)	15/44	1/7	0.647	0.421
Glucocorticoid (Y/N)	14/45	4/4	2.475	0.116
Laboratory findings				
AST (U/L)	28.1±17.8	28.0±5.5	0.002	0.998
ALT (U/L)	38.2±30.1	40.3±21.7	-0.185	0.854
LDH (U/L)	215.0±79.7	209.1±30.1	0.687	0.492
Alb (g/L)	43.7±5.6	42.0±3.8	0.838	0.405
Glu (mmol/L)	6.4±1.7	7.5±2.0	-1.330	0.191
TC (mmol/L)	3.93 (2, 7)	3.93 (3, 4)	-0.276	0.789
TG (mmol/L)	1.05 (0.57, 2.25)	2.96 (2.41, 5.22)	4.556	-0.000*
WBC (10 ⁹ /L)	5.33±1.9	5.9±2.6	-0.766	0.446
N (10 ⁹ /L)	3.6±1.7	3.3±1.2	0.357	0.723
CRP (mg/L)	6.8 (0, 174.6)	9.2 (1.74, 63.8)	0.619	0.536
IL-6 (pg/ml)	9 (2, 62)	4.5 (2, 12)	-1.179	0.250
Ferritin (ng/ml)	396.3 (39, 1848)	422.1 (339, 578)	0.17	0.902
NLR	2.86 (1.12, 22.15)	2.85 (1.86, 6.69)	0.26	0.803

*, P<0.05.

pidemia (2016 Version), high serum TG was defined as TG≥2.3 mmol/L [17]. Patients was divided into high TG group and normal TG group. The clinical data were listed in **Table 2**. As shown in **Table 2**, patients in high TG group had shorter TPNT compared with normal TG group (14.4±4.0 versus 18.9±9.2, P<0.05).

In addition, hypertension is also an important factor that influencing the recovery after SARS-CoV-2 infection. In this study, hypertension was also highly associated with TPNT. We examined TPNT level in patients with hypertension or patients without hypertension. The clinical data were summarized in **Table 3** in two groups. There were significant differences on age, TP-

NT, complicated bacterial infection, abidol treatment, serum AST, and serum Alb between the two groups (P<0.05, **Table 1**), but there were no differences on gender, clinical types, serum LDH, serum TC, and TG between the two groups. Multivariable Logistic multivariate analysis showed that hypertension was associated with age (B=0.097, OR=1.102, 95.0% CI: 1.027-1.183, P=0.007), TPNT (B=0.094, OR=1.099, 95.0% CI: 1.102-1.193, P=0.024), complicated bacterial infection (B=2.288, OR=17.95, 95.0% CI: 1.314-245.125, P=0.030), but not associated with abidol treatment, serum AST, and serum Alb (P>0.05). To further demonstrate the relationship between hypertension and TPNT, cumulative number of pati-

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Table 3. Clinical data of patients in hypertension group and non-hypertension group

Clinical data	HT group	Non-HT group	t/U/ χ^2	P
Sex (M/F)	9/4	28/26	1.28	0.258
Age (y)	61.9±11	41.1±15.7	-4.505	0.000*
TPNT	25.5±9.5	16.7±7.9	-3.473	0.001*
Clinical types			2.301	0.317
Mild	2	19		
Moderate	9	31		
Severe	2	4		
Complications				
Bacterial infection	4/9	2/52	9.414	0.002*
Diabetes	3/10	4/50	2.75	0.097
Treatment				
AbidoI (Y/N)	11/2	28/26	4.623	0.032*
Interferon (Y/N)	12/1	46/8	0.457	0.499
Thymosin (Y/N)	5/8	11/43	1.886	0.17
Glucocorticoid (Y/N)	4/9	14/40	0.125	0.724
Laboratory findings				
AST (U/L)	36.9±32.4	25.9±9.5	-2.174	0.033*
ALT (U/L)	51.1±41.3	35.4±24.9	-1.77	0.081
LDH (U/L)	247.6±99.7	206.3±67	-1.804	0.076
Alb (g/L)	40.3±8.2	44.3±4.2	2.497	0.015*
Glu (mmol/L)	7.1±1.7	6.4±1.7	-1.141	0.261
TC (mmol/L)	3.69 (2, 7)	3.97 (3, 7)	-0.035	0.927
TG (mmol/L)	1.36 (0.85, 3.15)	1.14 (0.57, 5.22)	0.048	0.962
WBC ($10^9/L$)	5.7±1.7	5.3±2.1	-0.603	0.548
N ($10^9/L$)	4.1±1.5	3.4±1.7	-1.098	0.279
L ($10^9/L$)	1.1±0.5	1.5±0.9	1.474	0.145
CRP (mg/L)	16 (0.2, 174.6)	6.8 (0, 142.4)	1.237	0.216
IL-6 (pg/ml)	11.5 (3, 62)	7 (2, 29)	0.14	0.155
Ferritin (ng/ml)	678.7 (151, 1247)	346.8 (39, 1848)	0.338	0.367
NLR	3.02 (1.45, 9.39)	2.81 (1.12, 22.15)	0.464	0.475

*, P<0.05.

ents with positive tests was recorded in **Figure 1**. We found that cumulative patients with positive tests reduced quickly in non-hypertension group (**Figure 1**).

Discussion

COVID-19 is an emerging infectious disease caused by SARS-CoV-2. COVID-19 mainly has the symptoms of the respiratory system such as fever, cough, shortness of breath, and breathing difficulty, but also involves other systemic symptoms including the nervous system and the digestive system [1, 5, 18]. SARS-CoV-2 belongs to the β genus of the family of coronavirus and its RNA sequence is closely related to

and SARS-CoV and middle east respiratory syndrome coronavirus (MERS-CoV) [1, 19]. The understanding of the structure and invasion of SARS-CoV-2 mostly comes from the knowledge of SARS-CoV and MERS-CoV [20]. The lessons from SARS-CoV and MERS-CoV may help the treatment for SARS-CoV-2 infection [21-23]. In 2003, SARS disappeared as the temperature increased. Dose COVID-19 disappear in this summer with increasing temperature? What is the natural course of COVID-19? What factors affect virus positive-to-negative transformation? These issues are still unresolved so far. Although some studies found factors to be highly associated with the mortality of COVID-19 patients [13-15], in this study, we examined

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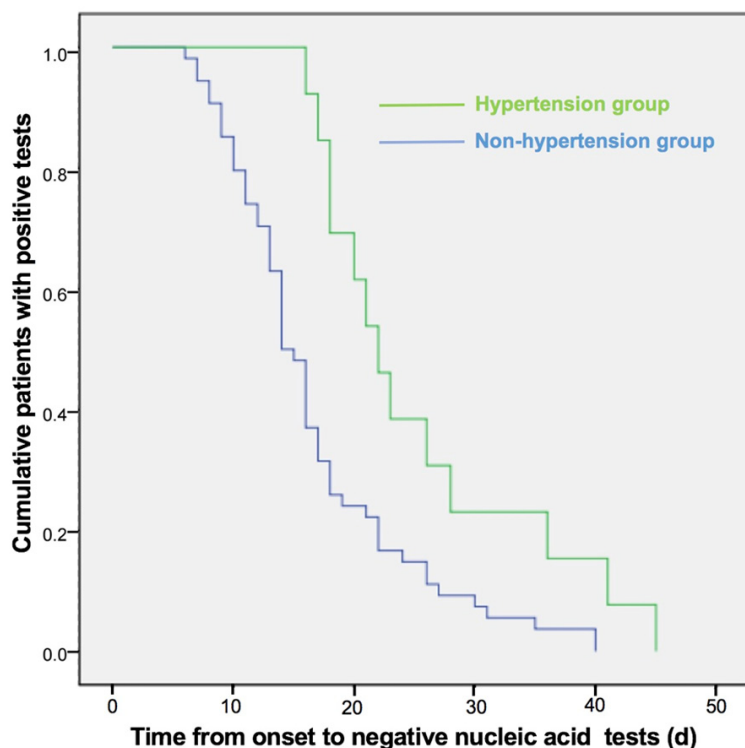


Figure 1. The curve of cumulative COVID-19 patients with positive nucleic acid tests in different groups. COVID-19 patients were divided into two groups: hypertension group and non-hypertension group. The curve of cumulative COVID-19 patients with positive test results was made in two groups.

the clinical factors that might affect the recovery from the SARS-CoV-2 infection. Our finding showed that serum TG and hypertension were two important factors that were related to TPNT in COVID-19 patients with mild and moderate clinical subtypes, indicating the association of two factors with the viral clearance in non-severe patients.

For the viral clearance from patients, antiviral medication may be important factors. Interferon nebulization therapy was recommended in Chinese guidelines and a potential efficacy of human type I Interferon in suppressing SARS-CoV-2 infection was reported in an *in vitro* study [24], but this study found that interferon nebulization therapy has no effect on the time for viral removal of SARS-CoV-2 from patients' throat swab samples. Another broad-spectrum antiviral drug, arbidol, is a non-nucleoside broad-spectrum antiviral drug, which has been approved for the treatment of influenza virus and other viral infections and has also shown good efficacy in the treatment for influenza

[25]. In addition, it also showed a significant inhibition on Zika virus *in vitro* [26]. Although this study found high ratio of arbidol use in low TNPT group, there was no difference of arbidol treatment on TPNT between patients taking arbidol and those not taking arbidol after adjusting the confounder factors. Since antiviral therapy has no specific effect, the modulation on the immune function may be helpful for virus clearance. In this study, we observed that there was no significant difference in virus clearance between patients with and without thymosin.

The application of glucocorticoids has been controversial in SARS patients and a large dose of glucocorticoid may delay the clearance of coronavirus due to its immunosuppression [27], the use of glucocorticoids is unclear for COVID-19 patients. Small doses of glucocorticoids were recommended for COVID-19 patients with severe pneumonia by Chinese guidelines for COVID-19 [28]; however, some clinical evidence was against the use of glucocorticoids for COVID-19 [29]. In this study, there was no difference on TNPT between the group with small dose of glucocorticoid (3-7 days) and the group without glucocorticoid. This also suggests that the short-term application of glucocorticoids has no effect on virus clearance.

Angiotensin-converting enzyme 2 (ACE2) protein of host cells is considered as the targeting protein for the invasion of SARS-CoV-2 and is verified as a potential therapeutic target for antiviral treatment [30]. Therefore, ACE2 expression or its activity is close related to the invasion or removal of SARS-CoV-2. Studies have shown that ACE2 deficiency was associated with increased cellular content of triglyceride while ACE2 activation by diminazene increases serum triglyceride in mice [31, 32]. Interestingly, in our patients, the TPNT was highly associated with serum triglyceride. Although no evidence demonstrated that high

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serum triglyceride might decrease cellular ACE2 protein, our data suggest that the reduced TPNT in high triglyceride group may be related to the reduction of ACE2 activation or expression in human body, which provides a critical clue to how to remove virus in human body. Patients with COVID-19 could be suggested to have high-fat diets to increase serum triglyceride and decrease the TPNT. In addition, hypertension is also associated with the TPNT. On the contrary, previously study indicated that ACE2 levels is up-regulated in patients with cardiovascular diseases including hypertension [33]. In this study, 12 individuals among 13 patients with hypertension had longer TPNT, indicating that hypertension is related to increased TPNT probably by the increase of ACE2 in patients. Paradoxically, because ACE inhibitors (ACEI) are regarded to increase ACE2 level [34], all the patients with hypertension were suggested to replace ACE inhibitors with calcium channel blocker. Based on this evidence, patients with hypertension should continue ACEI anti-hypertensives and may benefit from the use of ACEI as recent recommendations [35]. Therefore, the effect of ACEI therapy on SARS-CoV-2 virus removal awaits more investigations.

In this study, we only found that serum TG and hypertension were highly associated with TPNT in mild and moderate COVID-19 patients, which need to be verified in large populations and to address the limitation of small size of the COVID-19 patients in this study. Through a large population study, more risk factors related to TPNT may be found.

In conclusion, although SARS-CoV-2, SARS-CoV, and MERS-CoV are coronavirus, the pathogenicity, infectivity and clinical characteristics of SARS-CoV-2 infection are different from SARS and MERS. SARS disappears with increasing temperature; MERS has a low infectivity and high mortality, but lasts for several years [36]. The outcome of SARS-CoV-2 infection cannot be predicted as like SARS or MERS. Probably, like MERS-CoV, SARS-CoV-2 may coexist with human kinds for a long time. Therefore, before finding the vaccine for SARS-CoV-2, the risk factors related to the prevention and treatment for SARS-CoV-2 should be further investigated.

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Disclosure of conflict of interest

None.

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