www.jcimcr.org

JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Research Article

Open Access, Volume 4

A 29-day clinical observational study at the beginning of the epidemic: Clinical characteristics of serious COVID-19 patients infected with early virus strains

Haisheng Hu[1,#]; Jiajia Wu[1,2#]; Mingshan Xue[1]; Xueqing Liang[1]; Ge Wu[1]; Mingxin Shi[1]; Huimin Huang[1]; Baoqing Sun[1]*; Ning Li [1]*

[1]Department of Allergy and Clinical Immunology, State Key Laboratory of Respiratory Disease, National Clinical Research Center of Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Medical University, Guangzhou 510120, Guangdong, China.

[2]Nanshan School, Guangzhou Medical University, Jingxiu Road, Panyu District, Guangzhou, 511436, China.

[#]Haisheng Hu, Jiajia Wu contributed equally to this work.

***Corresponding Author: Baoqing Sun**

State Key Laboratory of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiangxi Road, Guangzhou 510120, Guangdong, China.

Tel: +86 20 8306 2865 & +86-20-8306 2729;

Ning Li

State Key Laboratory of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiangxi Road, Guangzhou 510120, Guangdong, China.

Email: lining1971@139.com; sunbaoqing@vip.163.com

Received: Jul 03, 2023

Accepted: Jul 21, 2023

Published: Jul 28, 2023

Archived: www.jcimcr.org

DOI: www.doi.org/10.52768/2766-7820/2519

Abstract

Objective: Patients infected with different virus strains have different clinical characteristics. This study had observed the clinical indicators of COVID-19 patients infected with early virus strains, and the aim was to supplement the data of patients with early virus infection internationally, and reflect the thinking process of researchers and the strategy of clinical monitoring at the beginning of the epidemic.

Methods: The clinical indicators were detected in four of serious COVID-19 male patients (Case 1 [C1], Case 2 [C2], Case 3 [C3] and Case 4 [C4]) at 5 point of time: day 1 (1D), day 7 (7D), day 14 (14D), day 21 (21D) and day 28 (28D) of hospitalization, respectively.

Results: All of them presented different degrees of acute renal functional injury, and had combined myocardial injury except C2. With the intervention of clinical treatment, the number of CD3+CD4+T cells increased, while creatinine and creatine kinase decreased in all patients, and D-dimer gradually decreased after peaking at 7D in C2, C3 and C4, except C1 peaking at 14D. Interestingly, in C1 and C2, lactate dehydrogenase was also peaking at 7D, but in C3 and C4, lactate dehydrogenase was gradually decreased during the observation period.

Conclusions: Patients infected with early virus strains have different clinical characteristics. At the beginning of the epidemic, due to the lack of clinical monitoring strategies and emergency plans for sudden infectious diseases, COVID-19 patients have a long treatment cycle and unstable clinical indicators. It is very important to improve the research thinking of sudden infectious diseases in the future.

Keywords: 2019 novel coronavirus pneumonia (COVID-19); SARS-CoV-2; Early virus strains; Physiopathology biomarkers; Clinical monitoring.

Introduction

It has been nearly 2 years since the first reported of the 2019 novel coronavirus pneumonia (COVID-19) in Wuhan, China from December 2019 [1]. The pathogen of COVID-19 was SARS-CoV-2, a β-coronavirus like the SARS-CoV, which infects human cells through ACE2 receptor [2]. Previous studies have shown that SARS-CoV-2 can also invade the human nasal cavity [3], gastrointestinal tract [4], kidney [5], and nervous systems because the ACE2 receptor expressing cells also present in the above organs or tissue [6].

SARS-CoV-2 has many kinds of virus strains. The Alpha variant lineage emerged in September 2020 in South East England (Kent county, UK), and Gamma variant, initially identified in Manaus in late 2020 has rapidly spread throughout the Brazil. In addition, Delta variant was first detected in India in December 2020 and became the most commonly reported variant in the country starting in mid-April 2021. Patients infected with different virus strains have different clinical characteristic.

Before the pandemic of COVID-19, we have been observing the clinical indicators of severe patients infected with early virus strains, and aim to exploring how to use these indicators to monitor the clinical status of patients with COVID-19. We found some interesting phenomena different from the current virus strains during the study, however, due to politics, treatment and affected by the epidemic, this part of the data has not been made public. At that time, we monitored more than 50 physiopathology biomarkers in four of severe COVID-19 patients infected with early virus strains on day 1, 7, 14, 21 and 28 of hospitalization respectively. The results of the study may not be novel, but it can reflect the thinking process of researchers at that time and the strategy of clinical monitoring in the initial stage of infectious diseases, meanwhile, supplement the clinical observation data of patients with early virus infection internationally, to provide more reference for the study of disease pathogenesis.

Materials and methods

Study design and objective

This was a 29-day-observational-study of four COVID-19 patients (case 1 [C1], case 2 [C2], case 3 [C3] and case 4 [C4]) from the Intensive Care Unit (ICU) of First Affiliated Hospital of Guangzhou Medical University during February 1 to 29, 2020 (Before the pandemic). The physiopathology biomarkers such as venous blood cells, C-reactive protein, coagulation function, biochemical indexes, myocardial function, lymphocyte count, cytokine, immune factors, urine chemistry and liver function were detected in the four patients at 5 time points: day 1 (1D), day 7 (7D), day 14 (14D), day 21 (21D) and day 28 (28D) of hospitalization, respectively. The selection of physiopathology biomarkers was base on the clinical monitoring strategy at that time in China. Details of the detection panels were shown in Support information. All the patients included in this study were male, considered as serious COVID-19, and complicated with acute respiratory distress syndrome.

Diagnostic criteria

COVID-19 diagnosis was according to "Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Seventh Edition from China)" in that time [7]: 1. Patient had a history of staying in high risk areas (such as Wuhan, Hubei Province), or a history of being contact with COVID-19 patients within 14 days before paroxysm; 2. Fever or respiratory symptoms; 3. COVID-19 imaging features (multiple patchy ground glass shadows in both lungs and we can see the thickened vascular shadow, which is shown as fine grid shadow, etc); 4. Positive result to the nucleic acid of SARS-CoV-2 test by real time RT-PCR. Serious COVID-19 was defined base on following symptoms: 1. respiratory failure requiring mechanical ventilation, 2. shock, identified by the use of vasopressor therapy and elevated lactate levels (>2 mmol/L) despite adequate fluid resuscitation, or 3. failure of other organs requiring admission to the ICU.

Clinical treatment and end point

Clinical treatment during the 29-day-observational-study: All of these patients were admitted to ICU. Patients were given supportive treatment after admission. Antiviral drugs (e.g., lopinavir/ritonavir, arbidol) were also used in them, and no adverse reactions. Corticosteroid was not used unless experts considered necessary. This was determined by people's understanding of the disease and the level of treatment at that time.

Endpoint of the study: 1. Meet the hospital discharge requirements (including symptoms relieved, all physical indicators return to normal and negative to the nucleic acid of SARS-CoV-2 test by real time RT-PCR in 2 continuously times). 2. Death or had adverse drug reactions. 3. Over 29 days in hospital. All the patients in this study were more than 29 days in hospital, and none of them died or meet the hospital discharge requirements during the study. This further indicates that COVID-19 need a long treatment period at that time, and the occupation of medical resources is difficult to estimate.

Statistical method

Normal distribution data were presented as mean ± standard error. Non-normally distributed data were presented as median (interquartile intervals 25%, 75%).

Results

Baseline characteristic

Four patients with serious COVID-19 (C1, C2, C3 and C4) were included in this observational study, aging between 49-79 years old, and they were all positive to the IgG and IgM of SARS-CoV-2 in 1D, 7D, 14D, 21D and 28D. Among the patients, C4 had complicated with hypertension, coronary heart disease, chronic obstructive pulmonary disease and diabetes. Regarding clinical symptoms, only C3 had shortness of breath, while only C2 did not have fever. As the disease progressed, all patients had presented different degrees of acute renal function injury, and three of them were complicated with myocardial injury except C2. Analysis of venous blood cells showed that there were very high levels of neutrophil ratio in peripheral blood (ranging from 89.9% to 95.3%), D-dimer (ranging from 451.0 mg/L to 2643.0 mg/L) and creatinine (ranged from 132.5 umol/L to 322.2 umol/L) respectively in all patients. Surprisingly, C2 and C4 showed high levels of creatine kinase (9845.9 U/L and 1603.6 U/L), myoglobin (3997.0 ng/ml and 2390.6 ng/ml) and B-type natriuretic peptide precursor (4130.0 pg/ml and 710.1 pg/ml), respectively. In addition, among the cytokines detected

in this study, serum levels of IL-6 were the highest (ranging from 20.9 kU/L to 92.2 kU/L) in all patients. Urine chemistry showed that the level of red blood cell in C2 was 897.0 n/uL and gamma glutamyltranspeptidase in C3 was 224.7 U/L (Table 1).

Table 1: Baseline information.

Characteristic	C1	C2	C3	C4
Age (years old)	49	79	58	72
Past medical history				
Hypertension	√	√	√	×
Coronary heart disease	×	×	×	√
Chronic obstructive pulmonary disease	√	×	×	√
Diabetes	√	√	×	√
Clinical symptoms				
Fever	√	×	√	√
Cough	√	√	√	√
Shortness of breath	×	×	√	×
Fatigue	√	√	√	√
Complication				
Acute renal function injury	√	√	√	√
Myocardial injury	√	×	√	√
Abnormal coagulation	×	×	√	√
Hypoproteinemia	×	×	√	×
Bullae of lung	×	×	√	×
Hepatic cyst	×	×	√	×
Renal cyst	×	×	√	×
Multiple organ dysfunction syndrome	×	×	×	√
Diabetes	√	√	×	√
Coronary atherosclerotic heart disease	×	×	×	√
Chronic obstructive pulmonary disease	√	×	×	√
Hypertension	√	√	×	√
Emphysema mediastinum	√	×	×	×
Septic shock	√	×	×	×
Hyperuricemia	√	√	×	×
C-reactive protein (mg/dL)	6.2	11.3	14.8	11.7
Venous blood cells (%)				
Neutrophil	90.9	95.3	94.0	89.9
Lymphocyte	3.0	1.1	2.2	3.2
Monocyte	6.0	3.2	3.6	6.8
Eosinophil	0.1	0.0	0.0	0.0
Basophil	0.0	0.4	0.2	0.1
Nucleated erythrocytes	0.0	0.0	0.0	0.0
Coagulation function				
Prothrombin activity (%)	99.0	77.0	79.0	88.0
Fibrinogen (g/L)	6.1	6.3	6.2	6.2
Hemoglobin (g/L)	121.0	107.0	123.0	121.0
Platelet (10^9/L)	196.0	135.0	252.0	113.0
D-dimer (mg/L)	451.0	1318.0	1807.0	2643.0
Biochemical indexes				
Glucose (mmol/L)	11.2	16.0	7.1	17.4
Urea nitrogen (mmol/L)	13.4	34.0	17.6	17.3
Creatinine (μmol/L)	132.5	322.2	146.6	168.2
Potassium (mmol/L)	5.1	5.2	6.2	4.7
Sodium (mmol/L)	140.7	131.2	142.3	133.7
Chlorine (mmol/L)	106.1	102.5	115.7	105.8

Calcium (mmol/L)	2.2	1.7	1.9	1.9
Carbon dioxide (mmHg)	24.8	13.3	20.7	20.7
Myocardial function				
Glutamic oxaloacetylase (U/L)	25.3	279.0	72.7	44.7
Creatine kinase (U/L)	501.6	9845.9	66.5	1603.6
Lactate dehydrogenase (U/L)	386.6	476.6	811.7	529.6
Troponin I (μg/L)	0.0	0.1	0.0	0.1
Myoglobin (ng/ml)	327.4	3997.0	40.9	2390.6
B-type natriuretic peptide precursor (pg/ml)	220.9	4130.0	241.1	710.1
Lymphocyte count (n/μL)				
CD3+ CD45+ T cell	169.0	50.0	174.0	355.0
CD3+ CD4+ Th cell	101.0	27.0	116.0	320.0
CD3+ CD8+ Tr cell	63.0	26.0	56.0	33.0
CD3- CD19+ B cell	48.0	81.0	86.0	110.0
CD3- CD16+ CD56+ NK cell	32.0	5.0	35.0	4.0
CD3+ CD56+ CD16+ NK T cell	14.0	6.0	17.0	1.0
Cytokine				
IL-2 (kU/L)	2.0	0.7	1.2	1.6
IL-4 (kU/L)	2.7	1.8	1.6	1.1
IL-6 (kU/L)	20.9	52.9	26.9	92.2
IL-10 (kU/L)	3.1	28.4	7.9	55.6
TNF-α (mol/ml)	1.7	1.3	1.9	1.7
IFN-γ (μg/L)	1.2	1.2	1.2	11.7
Immune factors				
IgG (g/L)	12.9	14.6	17.6	13.4
IgA (g/L)	1.6	0.9	1.6	2.3
IgM (g/L)	0.8	0.5	2.0	0.4
C3 (g/L)	1.2	0.7	0.9	1.0
C4 (g/L)	0.3	0.2	0.2	0.3
CH50 (g/L)	79.0	70.4	61.9	49.4
β_2-microglobulin (mg/L)	2.5	8.4	2.8	5.7
Ceruloplasmin (g/L)	0.4	0.2	0.3	0.3
C-reactive protein (mg/L)	6.2	11.3	14.8	11.7
Urine dry chemistry				
Urine glucose (mg/dL)	56.0	11.0	5.5	28.0
Urine protein	+	+	+	+
Ascorbic acid	+	-	++	-
White blood cell (n/uL)	0.0	69.0	9.0	9.0
Red blood cell (n/uL)	19.0	897.0	69.0	6.0
Liver function				
Alanine aminotransferase (U/L)	20.1	23.7	70.2	26.8
Total protein (g/L)	71.4	60.9	65.0	60.2
Albumin (g/L)	42.4	32.7	32.6	30.2
Gamma glutamyltranspeptidase (U/L)	71.4	50.9	224.7	56.9
Total bile acid (μmol/L)	3.6	5.7	6.3	2.5
α - L-Fucosidase (u/g)	32.5	48.2	24.9	21.4
Total bilirubin (μmol/L)	36.1	9.3	15.1	11.2
Direct bilirubin (μmol/L)	21.4	4.3	5.7	4.2

√: Had; ×: Hadn`t; +: Positive; -: Negative; Baseline characteristic of four patients with serious COVID-19 (C1, C2, C3 and C4) were show in table.

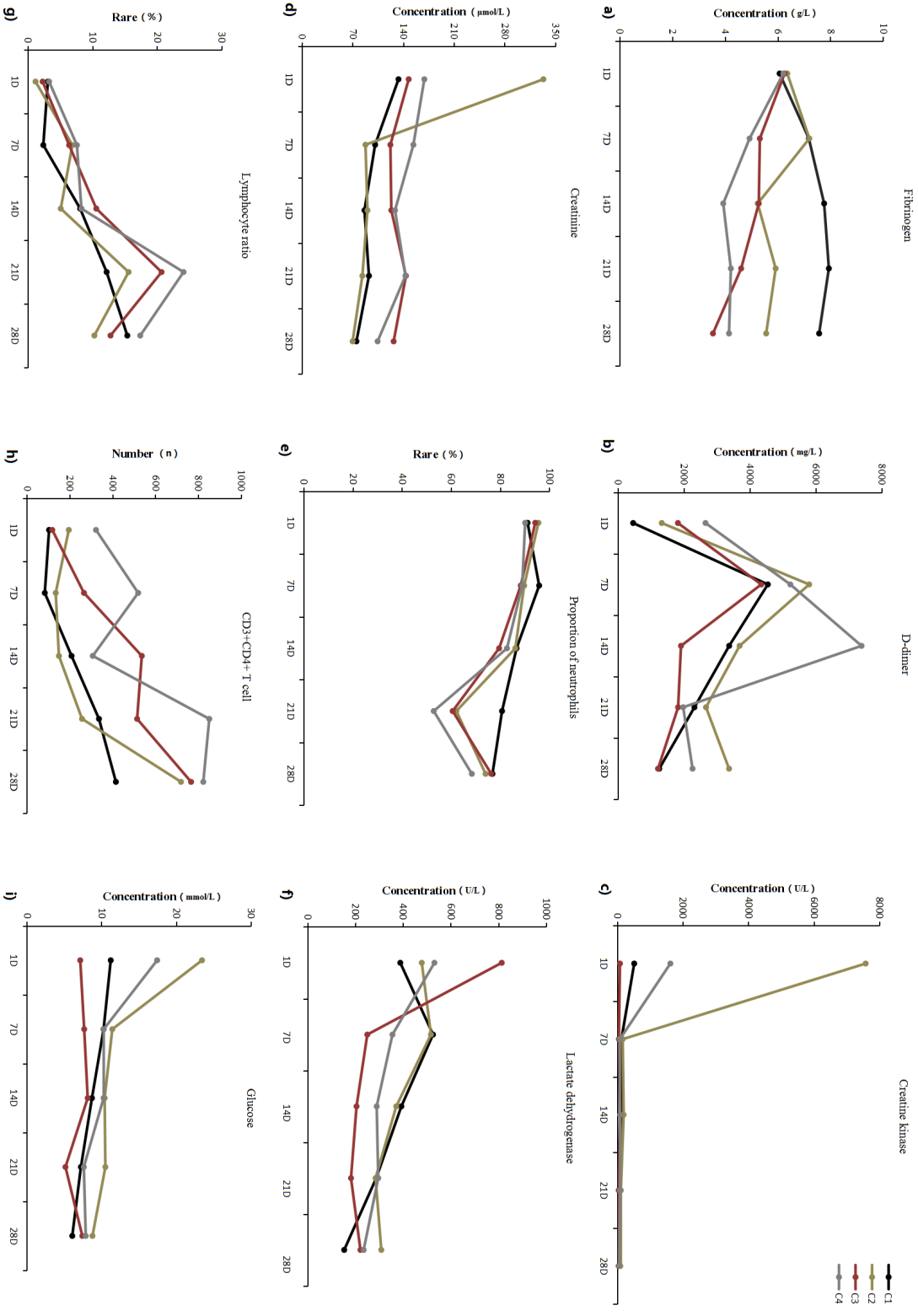

Figure 1: The changes of physiopathology biomarkers in 4 of COVID-19 patients at different point of time.

The changes of physiopathology biomarkers

With the intervention of clinical treatment, in C1, the level of C- reactive protein, fibrinogen concentration, lymphocyte ratio in peripheral blood and number of CD3+CD4+T cells were increased, while creatinine, glucose, proportion of neutrophils in peripheral blood and creatine kinase were decreased. Meanwhile, D-dimer and lactate dehydrogenase was gradually decreased after peaking at 7D.

In C2, the level of C- reactive protein and the number of CD3+CD4+T cells was increased continuously. However, creatinine, glucose and creatine kinase was decreased continuously. In addition, D-dimer and lactate dehydrogenase were also decreased gradually after peaking at 7D, but lymphocyte ratio in peripheral blood peaked at 21 days.

In C3, the number of CD3+CD4+T cells was increased, but C- reactive protein, fibrinogen and lactate dehydrogenase was decreased. Meanwhile, D-dimer peaking at 7 days and lympho-

cyte ratio in peripheral blood peaked at 21 days.

In C4, the level of C- reactive protein, fibrinogen, creatinine, creatine kinase and proortion of neutrophils were declining, D-dimer peaking at 14D and lymphocyte ratio in peripheral blood peaking at 21D (Figure 1).

The detection results of a) fibrinogen; b) D-dimer; c) creatine kinase; d) creatinine; e) proportion of neutrophils; f) lactate dehydrogenase; g) lymphocyte ratio; h) CD3+CD4+T cell; and i) glucose in four COVID-19 patients (C1, C2, C3 and C4) at 5 point of time were show in figure.

Discussion

The changes of clinical indicators during the treatment of four serious COVID-19 patients with early virus infection in 29 days were observed in this study, and the purpose at that time was to provide the practical experience for clinical monitoring. Due to the sudden outbreak of SARS-CoV-2, we have no time to formulate a detailed research plan, such as which type of indicators should be monitored and which type of patients should be selected. We can only use routine clinical indicators to evaluate the patient's condition, which is also our research thinking at the beginning of the epidemic.

In this study, we found that all the patients had acute renal function injury, and myocardial injury occurred in C1, C2 and C3, meanwhile, C2 and C3 had high levels of creatine kinase, myoglobin and B-type natriuretic peptide precursor, could be possibly related to their previous medical history of coronary heart diseases and diabetes [2]. Recent reports show that the viral load of individuals infected with Delta variant was 1260 times higher than that of those infected with early virus strain, and the above clinical indicators was higher.

We also found that the lymphocyte ratio and number of CD3+CD4+T cells in all of patients was increasing during the treatment. In the early stage of COVID-19, patient's body failed to produce an effective immune response to SARS-CoV-2 because of the lower number of CD3+CD4+ T cells. With the treatment, the number of leukocyte increased and these cells could effectively fight against SARS-CoV-2 in COVID-19 patients, but in the process of fighting the virus, leukcyte will also die [8]. So we had deduced that maintaining the balance of immune cells is the key to fighting the virus.

Then, our study also showed that all patients had a high level of D-dimer at 7D or 14D. D-dimer was the simplest fibrin degradation product, and elevated D-dimer level indicated hypercoagulability and secondary hyperfibrinolysis in vivo [9-20]. This clinical observation showed that severe patients often develop dyspnea or hypoxemia, as well as multiple organ damage after one week of hospitalization, and the time point of aggravation overlapped with the peak of D-dimer level. The formation and dissolution balance of fibrin is an important index to monitor the state of patients.

Although the results of this study may not be novel, this was a 29-day clinical observational study at the beginning of the epidemic, and explained the clinical characteristics of serious COVID-19 patients infected with early virus strains in China. In terms of research strategy, we have been passive because we have never encountered a virus with rapid transmission and long incubation period like SARS-CoV-2 before. Therefore, the establishment of biological resource banks, such as antibody bank and virus bank, can make researchers respond to sudden infectious diseases faster, improve the efficiency of clinical diagnosis and treatment.

Conclusions

Patients infected with early virus strains have different clinical characteristics, using the clinical indicators to monitor the clinical status of patients with COVID-19 is necessary. At the beginning of the epidemic, due to the lack of clinical monitoring strategies and emergency plans for sudden infectious diseases, COVID-19 patients have a long treatment cycle and unstable clinical indicators. It is very important to improve the research thinking of sudden infectious diseases in the future.

Declarations

Ethics approval and consent to participate: Approval was obtained from the ethic committee of The First Affiliated Hospital of Guangzhou Medical University (Reference number: GYFYY-2020-16). All patients sign informed consent and this study did not interfere with clinical treatment.

Competing interests: The authors declare that they have no competing interests.

Funding: This study was funded by the Guangzhou Institute of Respiratory Health Open

Project (Funds provided by China Evergrande Group) (Project No: 2020GIRHHMS04) and Guangzhou Science and Technology Foundation (Project No.: 201804020043).

Author's contributions: Conceived and designed the experiments: BQS. Performed the experiments: XQL, HMH, GW, MXS, and MSX. Analyzed the data: HSH and NL. Wrote the paper: HSH and JJW. All authors read and approved the final manuscript.

Acknowledgements: We thank everyone involved in the collection, detection, and date management of the serum samples.

References

1. Zu ZY, et al. Coronavirus Disease 2019 (COVID-19): A Perspective from China. Radiology. 2020; 296: E15-25.

2. Guo YR, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020; 7: 11.

3. Hamming I, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004; 203: 631-7.

4. Gu J, Han B, Wang J. COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology. 2020; 158: 1518-9.

5. Rismanbaf A, Zarei S. Liver and Kidney Injuries in COVID-19 and Their Effects on Drug Therapy; a Letter to Editor. Arch Acad Emerg Med. 2020; 8: e17.

6. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19patients. J Med Virol. 2020; 92: 552-5.

7. Bischof E, Chen G, Ferretti MT.Understanding COVID-19 new diagnostic guidelines - a message of reassurance from an internal medicine doctor in Shanghai. Swiss Med Wkly. 2020; 150: w20216.

8. Nguyen-Thi-Dieu T, Le-Thi-Thu H, Duong-Quy S. The profile of leucocytes, CD3+, CD4+, and CD8+ T cells, and cytokine concentrations in peripheral blood of children with acute asthma exac-

erbation. J Int Med Res. 2017; 45: 1658-69.

9. Linkins LA, Takach Lapner S. Review of D-dimer testing: Good, Bad, and Ugly. Int J Lab Hematol. 2017; 39: 98-103.

10. Liu Q, et al. Gross examination report of a COVID-19 death autopsy. Fa Yi Xue Za Zhi. Chinese. 2020; 36: 21-3.

11. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: Management and challenges. Lancet Gastroenterol Hepatol. 2020; 5: 428-30.

12. Wang W, et al. Heterozygote loss of ACE2 is sufficient to increase the susceptibility to heart disease. J Mol Med (Berl). 2014; 92: 847-58.

13. Ramos JM, et al. Interleukin (IL) -1 β, IL-6 and tumor necrosis factor in patients with seasonal flu. Rev Esp Quimioter. 2018; 31: 542-5.

14. Chen J, et al. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect. 2020; 80: e1-6.

15. Jialal I, Sokoll LJ. Clinical utility of lactate dehydrogenase: A historical perspective. Am J Clin Pathol. 2015; 143: 158-9.

16. Ndrepepa G, Kastrati A. Creatine kinase myocardial band - a biomarker to assess prognostically relevant periprocedural myocardial infarction. Int J Cardiol. 2018; 270: 118-9.

17. Lebreton A, Casini A. Diagnosis of congenital fibrinogen disorders. Ann Biol Clin (Paris). 2016; 74: 405-12.

18. Lake MA. What we know so far: COVID-19 current clinical knowledge and research. Clin Med (Lond). 2020; 20: 124-7.

19. Li N, et al. Value of immune factors for monitoring risk of lung cancer in patients with interstitial lung disease. J Int Med Res. 2019; 47: 3344-53.

20. Yuen KS, et al. SARS-CoV-2 and COVID-19: The most important research questions. Cell Biosci. 2020; 10: 40.