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Research Article

A Case Series of COVID-19 Delta Variant in Anhui Province, China

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Abstract

Since the outbreak of coronavirus disease 2019 (COVID-19), it has caused serious casualties worldwide. In recent months, the virus has mutated into an increasingly infectious form (Delta variant) and spread rapidly. In the current study, we analyzed the clinical, epidemiological and viral genetic characteristics of the first four imported Delta cases in Anhui Province, China. These four patients developed lung inflammation, tissue damage and recovered after admission, and the serum high-sensitivity C-reactive protein (hs-CRP) and CRP levels showed a first increasing and then decreasing trend. The results showed that hs-CRP/CRP level showed the same trend as the degree of chest lesions in these patients, and serum neutralizing antibodies (Nab) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) level was also associated with the regression of chest lesions. The combination of genetic sequencing and epidemiological analysis suggested that the SARS-CoV-2 delta variant infection of these four patients may originate from Russia. Although the relatively smaller sample size of this study limited the extrapolation of the results, our study found a certain correlation between hs-CRP/CRP and Nab levels and the occurrence, development and outcome of COVID-19 delta variant, suggesting that monitoring hs-CRP/CRP and Nab levels of COVID-19 delta variant patients at hospital admission may be useful for understanding the severity of patients' current conditions.

Keywords: COVID-19, Delta variant, SARS-CoV-2

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1 INTRODUCTION

COVID-19, a severe, acute respiratory syndrome caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China in December 2019[1,2], and rapidly spread to the rest of the world within the next few months[3]. COVID-19 symptoms ranged from common cold-like symptoms to severe symptoms in multiple organs and, in some cases, death[4]. It has resulted in serious human casualties and has not been fully contained so far.

In early 2021, there is an emergence and rapid spread of SARS-CoV-2 variants (e.g., Delta) that were associated

with an increased transmissibility[5]. These variants have faster replication and transmission, higher pathogenicity and potential immune escape, which led to a rebound of the epidemic recently.

The delta variant has become the dominant strain causing COVID-19 in many countries[6]. Delta variant first emerged in India in June 2020, the global incidence of the Delta variant has made it a variant of concern (VOC)[7]. Compared with other variants, this VOC is characterized by a transmission advantage, an increased risk of hospitalization, and a higher virulence[8]. The Delta variant is 60% more infectious than the original Wuhan SARS-CoV-2 strain[9]. It is mainly seen in people who have not been vaccinated and incompletely vaccinated, as well as for symptomatic patients. In particular, due to the presence of L452R and P681R mutations in the receptor binding domain of the spike protein, the transmission of the B.1.617.2 variant is estimated to be twice as high as the previous circulating variant[7]. However, in countries with high vaccination coverage and experiencing delta variant infection waves, the hospitalization rate and mortality rate are lower than those of alpha variants[10].

The Delta variant of COVID-19 had never been found in Anhui Province before, but it was detected on June 21, 2021 from four entry personnel. In the current study, we analyzed the clinical, epidemiological, and viral genetic characteristics of these four cases, in order to provide scientific basis for preventive strategies of this variant epidemic. The better understanding of scientific basis of Delta variant and improvements of preventive strategies might be instructive for the disease control and prevention of novel SARS-CoV-2 variants.

2 MATERIALS AND METHODS

2.1 Patients

We recruited four imported cases, and they were asymptomatic travelers who arrived in Anhui province on a direct flight from Russia. All of them were tested positive for the SARS-Cov-2 Delta (B.1.617.2) variant. In addition, we conducted a clinical, epidemiological and virological analysis in the four imported cases. These four cases had worked in Irkutsk, Russia from September 2019 until they returned to China.

2.2 Data Source

Demographic information, epidemiological characteristics, clinical data and laboratory test results were obtained with standardized data collection forms through interviews of infected persons, relatives, close contacts, and health care workers. Investigators interviewed each COVID-19 patient and their relatives, where necessary, to determine exposure or close contact histories during the two weeks before the illness onset.

2.3 Isolation and Identification

Oropharyngeal swabs and sputum specimens were collected from cases with COVID-19 and filtered with 0.22μM membrane to remove impurity. The supernatants were inoculated onto Vero cells in a T25 culture flask. After 1h incubation at 37℃ with 5% carbon dioxide for binding, the inoculum was removed and replaced with fresh DMEM with 2% Fetal Bovine Serum (ThermoFisher, Gibco™, 10099141C). The cells were incubated at 37℃ with 5% carbon dioxide for 72 to 144h and monitoring daily to evaluate cytopathic effects. Finally, the supernatant was harvested and inactivated by treatment with beta-propiolactone. All of the above operations must be performed in the Biosafety Level-3 laboratory. Specific reverse transcription polymerase chain reaction (rRT-PCR) test was performed to identify gene open reading frames 1ab region (ORFs 1ab) and nucleocapsid protein (N) of SARS-CoV-2 using commercial kits (BioGerm, 20203400065) qualified by Chinese FDA. Once the results showed positive, the viral particles were collected from culture for next generation sequencing.

2.4 Serological Test

The sera were inactivated at 56℃ for 30min, the IgM (Immunoglobulin M) antibodies against SARS-CoV-2 were detected by using SARS-CoV-2 IgM chemiluminescent microparticle immunoassay (CMIA) (CMU0202, Autobio, Zhengzhou, China), the IgG (Immunoglobulin G) antibodies against SARS-CoV-2 were detected by using SARS-CoV-2 IgG CMIA (CMU0102, Autobio, Zhengzhou, China). the Neutralizing antibodies (Nab) against SARS-CoV-2 were detected by using SARS-CoV-2 Nab CMIA (CMU0602, Autobio, Zhengzhou, China). S/CO (Signal to Cutoff) of IgM or IgG≥1 indicated a positive result, and concentration of Nab≥30AU/mL suggested a positive result.

2.5 Whole Genome Capture and Sequencing

The nucleic acids of the virus inactivated products were extracted by GeneRotex Automatic Nucleic acid extractor (TIANLONG Technology CO. LTD, China). Commercial whole genome capture kit from Beijing MicroFuture Ltd. (ULSEN® Ultra-sensitive COVID-19 whole genome capture kit, V-090418) was used for amplification. An PCR enriched SARS-CoV-2 genome deep sequencing method was used to obtain the viral genome sequences according to previous report[11]. For library construction, we used the ATOPlex RNA Multiplex PCR-based Library Preparation Set V2.0 and MGIEasy Dual Barcode Circularization Kit according to the manufacturer's instructions. Sample Preparation System MGISP-100RS are required for the whole project. The library was amplified into DNA nanoball (DNB) which have more than 300 copies of one molecular. The DNBs were loaded into the patterned nanoarray and paired-end sequencing was performed on an MGISEQ-2000RS sequencing instrument, yielding about 200bp-sized sequencing reads.

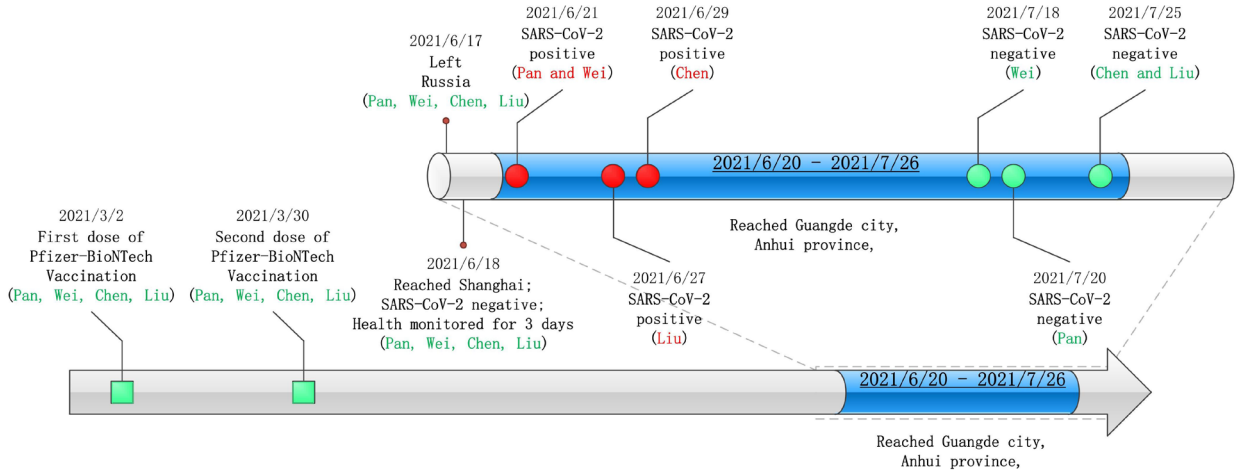

Figure 1. A timeline of imported iases from Guangde City, Anhui Province, China. Green marks mean negative nucleic acid test against SARS-CoV-2, red marks mean positive nucleic acid test against SARS-CoV-2, blue bars mean isolation period.

The obtained data were processed by using the Pathogen Fast Identification System, the reads number/ratio of SARS-CoV-2 and the corresponding virus sequence information were received. The full-length gene sequence of the virus was assembled by Microbial Genome Analysis Pipeline.

2.6 Phylogenetic Analysis and Mutation Identifications

A total of 53 SARS-CoV-2 genome sequences acquired from National Genomics Data Center database (http://bigd.big.ac.cn/ncov) and 4 sequences assembled by the current study were used for alignment. We aligned all the 57 genome sequences with MAFFT v7.220 with options -auto and -reorder. Then, we constructed the phylogenetic tree with options -nt and maximum-likelihood method using FastTree v2.1.8. At last, the phylogenetic tree was imported in iTOL (https://itol.embl.de/) to be visualized.

For mutation identification, we used MAFFT v7.220 to align the 4 sequence together with the reference NC_045512 first. And then, mutation sites were found by Python.

3 RESULTS

3.1 Epidemiological History of Patients

The age of the four patients were 49, 46, 55, and 41 years, respectively. All of these four cases worked in the same factory in Irkutsk, Russia before returning China. Each of the four patients had completed two doses of COVID-19 vaccination in Russia on March 2 and March 30, 2021. On June 17, they returned from Moscow, Russia by the same flight. They said they wore masks during the entire flight, and the nasopharyngeal swabs tested negative for the new coronavirus nucleic acid after landing. After three days of health observation in Shanghai, they were transferred from Shanghai to the centralized health observation point in Guangde, Anhui Provence by special vehicles on June 21. There was no activity outside the room during the isolation period (Figure 1).

3.2 Investigation and Management of Close Contacts

There were four staff on the transfer vehicle (2 drivers, 1 police officer, and 1 doctor), with secondary protection during the entire transfer period, and the vehicle-mounted staff were strictly separated from the transfer subjects. There were 14 health observation subjects who returned to Anhui in the same vehicle, all of whom reported wearing masks throughout the journey. As of June 29, the nucleic acid test results of all close contacts were negative, and no abnormalities were found in the health monitoring.

3.3 Laboratory Testing and Imaging Diagnosis

Among the four patients, there were one case of SARS-CoV-2 mild type and three cases of SARS-CoV-2 normal type. One case had a history of diabetes, and one case had anemia. The shortest experience from admission to discharge was 26 days, and the longest experience was 28 days, with an average of 27 days. Through the analysis of clinical test data, it was found that the absolute value of lymphocyte of the four patients decreased in the early stage after diagnosis (0.73×10^9/L to 1.01×10^9/L), and returned to normal levels within 3 to 9 days, and there was no abnormal increase in the absolute value of neutrophil (1.65×10^9/L to 5.80×10^9/L), the value of high-sensitivity C-reactive protein (hs-CRP) increased rapidly after diagnosis. The value of CRP in three patients began to increase rapidly from the 5th to 7th days, and the levels of CRP reached its peaks at 23.85mg/dL to 54.05mg/dL. Although the levels of CRP increased sharply, other types of examinations did not revealed that there was a bacterial infection. The absolute count of white blood cell (Liu) decreased to 2.65×10^9/L, and returned to normal levels on the 15th day. As the course of the disease progression, the four patients had transient lactic dehydrogenase elevation (253.9-372.1U/L) on the 1th to 6th days, of which two patients were accompanied with an elevation of α-HBDH (200-221U/L). In the four patients, the levels of D-dimer were increased from 0.53mg/L to 19.91mg/L on the 1st to

5th days, no changes of prothrombin time and activated partial thromboplastin time were found. Moreover, the normal platelet count and basically stable coagulation function were observed, indicating that there was no risk of disseminated intravascular coagulation.

Hs-CRP and CRP were used to evaluate the inflammation level of the body. We combined the chest CT to evaluate the progress of the patients. Due to the partial lack of Chen's data, we could not judge the specific change trend of the detection index while the remaining data of the other three patients were relatively complete. We observed four patients whose hs-CRP exceeded 5mg/dL for the first 3 to 5 days after admission. In addition to Chen, the value of CRP exceeded 10mg/dL for the first 4 to 7 days after admission, and multiple patchy shadows appeared for the first time on chest CT at 3 to 6 days, and the time differences between the first time multiple patchy shadows appeared on chest CT and the first time multiple patchy shadows appeared on hs-CRP at 5mg/dL was no more than 3 days, the time with CRP above 10mg/dL for the first time was not more than 1 day (Table 1).

Except for Chen, the levels of CRP of other three patients reached its peak at day 7, Liu's chest CT showed the increased number/size and density of lung lesions, Pan's and Wei's chest CT showed consolidations of lungs. In addition to Chen, the concentrations of hs-CRP were decreased (less than 5mg/dL) at 15 to 20 days, and the value of CRP also decreased to less than 10mg/dL, and the first-time chest CT showed lower lesions size and some lesions that showed partial absorption at 15-19 days. The differences between the first occurrence of lesions size decreased / partial absorption of some lesions and the change of hs-CRP/CRP was no more than 5 days (Table 1). Interestingly, we observed three patients other than Chen on day 17th (Table S1) with two reagents for at least single-target negative nucleic acid test results, this time was within two days of the first appearance of chest CT of lesions size decreased and partial absorption of some lesions (Figure 2).

Novel coronavirus antibody IgM/IgG and Nab in patients were then tested to assess their humoral immune response. The results showed that IgM and IgG change from negative to positive in all 4 patients at 12-19 days after admission (Figure 3). Nab levels in four patients increased from admission to pre-discharge and exceeded 30 AU/mL at 12-19 days after admission (Figure 4).

3.4 Phylogenetic Tree Analysis of Four SARS-COV-2 Strains

Representative sequences of different lineages were selected from Global Initiative of Sharing All Influenza Data (GISAID) database and SARS-COV-2 genome sequences of four cases sequenced this time to construct maximum likelihood phylogenetic tree. Phylogenetic tree analysis showed that 4 cases of SARS-COV-2 in this study were in the Delta-B.1.617.2 lineage, with Bootstrap support values >95% (Figure 5).

3.5 Amino Acid Mutation Analysis

Compared with the Wuhan-HU-1 sequence, the four Anhui cases in this study had the same mutation sites, and 36 nucleotide mutation sites were found in all of them (Table 2), where 33 nucleotide mutation sites are located in the coding region, and the sequence of nucleotide mutation sites from more to less is: There are 12 regions of ORF1a, 7 regions of S, 4 regions of N, 4 regions of ORF1b, 3 regions of ORF7a, 2 regions of 5'UTR, 1 regions of M, 1 regions of ORF3a, 1 regions of ORF7b and 1 regions of 3' UTR. There are 6 nucleotide synonymous mutations (G210T, C241T, C3037T, C8986T, A11332G, G29742T) and 30 nucleotide missense mutations. There are 30 sites of amino acid variation and no insertion mutation was found. There are 9 proteins of ORF1a, 7 proteins of S, 4 proteins of N, 4 proteins of ORF1b, 3 proteins of ORF7a, 1 protein of M, 1 protein of ORF3a, and 1 protein of ORF7b.

At the same time, we compared 28 strains of delta-B.1.617.2 sequences uploaded from China and Russia from April to June, and found a total of 90 mutation sites, where there were only two mutation sites appeared in Anhui cases, nine mutation sites in cases of other provinces in China, and 44 mutation sites observed in Russia's cases. In addition, there were 11 mutations unique to Anhui cases and Russia cases, and had not been discovered in Chinese other provinces' input cases, one of the 11 mutations in the N gene, ten of them are on ORF genes. The other 18 mutations occurred simultaneously in the Anhui cases, the Russian cases and the other provinces of China, but there were no common mutations in the Anhui cases and the imported cases in other provinces of China (Figure 6). Therefore, the mutation characteristics of the Anhui cases and the Russian cases are more similar, and it is speculated that the Anhui cases may have been infected in Russia and then imported to Anhui province.

4 DISCUSSION

This study presented information on first four imported Delta cases in Anhui Province, China. We systematically analyzed the dynamics of clinical laboratory testing, imaging and serology, and preliminarily traced the source through epidemiological and pathogen genomic characteristics. Four patients experienced lung inflammation, tissue damage and recovery after admission, and the value of hs-CRP and CRP also experienced a period of first rise and then decline. In this study, the time of first occurrence of multiple patchy shadows on Case Pan's and Case Liu's chest CT (Computed Tomography) was within 3 days from the time of first occurrence of hs-CRP exceeding 5mg/dL and the first time that CRP exceeded 10mg/dL was less than 1 day except for Case Chen. For the first time, the difference between the time of showing partial absorption and the time of hs-CRP /CRP indicator change was less than 5 days. The level of hs-CRP/CRP showed the same trend as the level of chest

Table 1. The Dynamic Changes in Chest CT, Hs-CRP And CRP of the Four Patients from Admission to Discharge

Name	Date	hs-CRP (mg/dL)	CRP (mg/dL)	Chest CT
Liu	Day 2	2.11	<5.0	Revealed no abnormal
	Day 3	>5.0	8.91	Revealed multiple patchy ground-glass shadows in lung
	Day 4	>5.0	13.78	
	Day 6	>5.0	42.82	
	Day 7	>5.0	54.05	Lesions number and size increased, some lesions showed partial absorption
	Day 9	>5.0	15.73	
	Day 13			
	Day 15	3.28	<5.0	
	Day 19			Lesions showed partial absorption and decreased size
Pan	Day 1	4.99	<5.0	Revealed no abnormal
	Day 3	1.16	<5.0	Revealed no abnormal
	Day 4	>5.0	5.39	
	Day 5	>5.0	9.55	
	Day 6			Multiple patchy shadows in both lungs
	Day 7	>5.0	27.45	
	Day 8			Some consolidations were present
	Day 9	>5.0	10.23	
	Day 15			Lesions size and density decreased, some lesions showed partial absorption
	Day 20	2.2	<5.0	
Wei	Day 1	>5.0	9.2	Revealed no abnormal
	Day 3	3.41	<5.0	Revealed no abnormal
	Day 4	3.41	<5.0	
	Day 5	>5.0	6.74	
	Day 6	>5.0	16.93	Mmultiple patchy shadows, especially under the pleura
	Day 7	>5.0	23.85	
	Day 8			Some consolidations were present, left sided consolidation with pleural reaction
	Day 9	>5.0	20.3	
	Day 15			Lesions size and density decreased, some lesions showed partial absorption
	Day 20	0.57	<5.0	
Chen	Day 1			The density shadow of strip soft tissue in the right middle lobe of the lung, could be seen enhancement, with partial consolidation and blurred boundaries
	Day 2	1.39	<5.0	
	Day 3	>5.0	9.72	
	Day 4	>5.0	9.55	
	Day 5			Lesions size and density decreased, consolidation was observed in the middle lobe of right lung, some lesions showed partial absorption
	Day 6	>5.0	7.19	
	Day 13	0.92	<5.0	

lesions in patients. Hs-crp is CRP measured using a more sensitive method, and hypersensitive CRP is able to respond to very low concentrations of CRP changes compared to CRP measured by conventional methods[12]. In May 2020, Chen's team[13] found a correlation between CRP level and chest CT grading in patients with SARS-COV-2, with higher CRP level indicating more severe chest lesions. CRP returns to normal level as the disease subsides and the tissue, structure, and function recover. In addition, Nab levels in patients are also correlated with the regression of chest lesions. In August 2020, Zost et al.[14] showed that Nab reduced viral burden and inflammation levels in the lungs. In this study, the chest

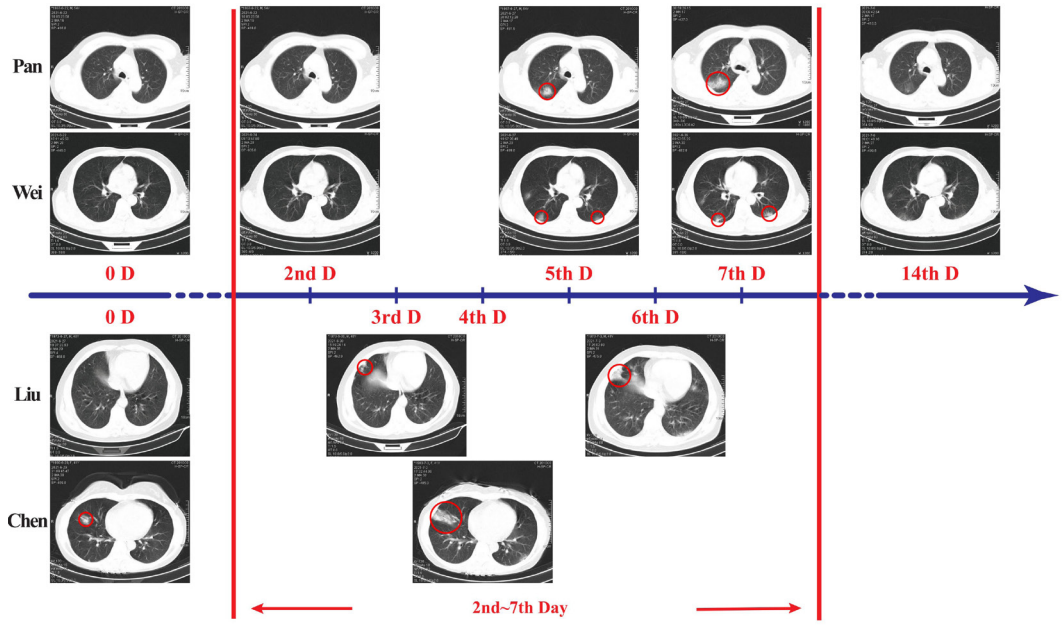

Figure 2. The dynamic changes in chest CT imaging of the four patients from admission to discharge.

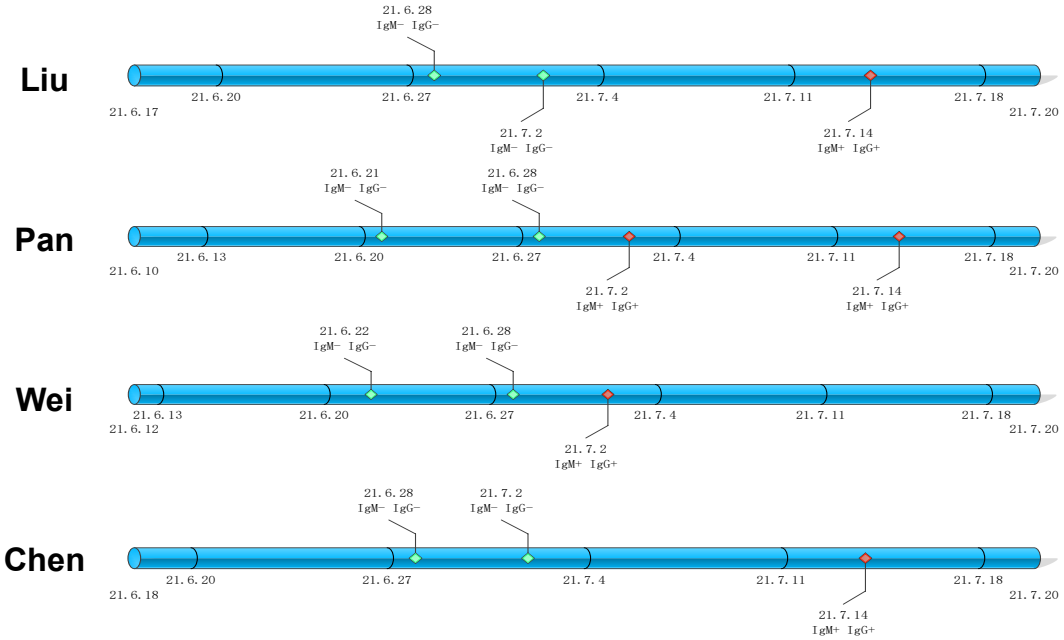

Figure 3. The dynamic variations of serum IgG/IgM antibodies against SARS-CoV-2 among the four patients from admission to discharge. Green mark means negative results, red mark means positive results.

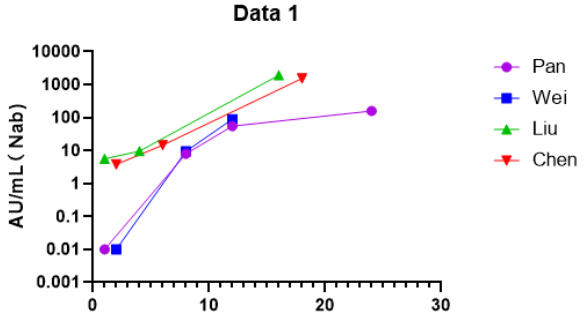

Figure 4. The dynamic changes in serum levels of neutralizing antibodies (nab) against SARS-Cov-2 of the four patients from admission to discharge, when nab levels exceeded 30AU/Ml prompts a positive outcome.

lesions also began to dissipate after the patients' Nab levels changed from negative to positive.

According to the second-generation sequencing results, all 4 patients belonged to the B.1.617.2 lineage, and had 36 amino acid mutation sites identical to the sequence of Wuhan reference strain NC_045512. Among them, 29 mutation sites (29/36, 80.56%) appeared simultaneously in the Russian cases, and 18 mutation sites (18/36, 50%) concurrent occurrence in other regions of China, except for Anhui. The 4 patients had 11 mutated loci that were not found in the cases in other regions of China except for Anhui, but were carried in the Russian cases. Combined with epidemiological analysis,

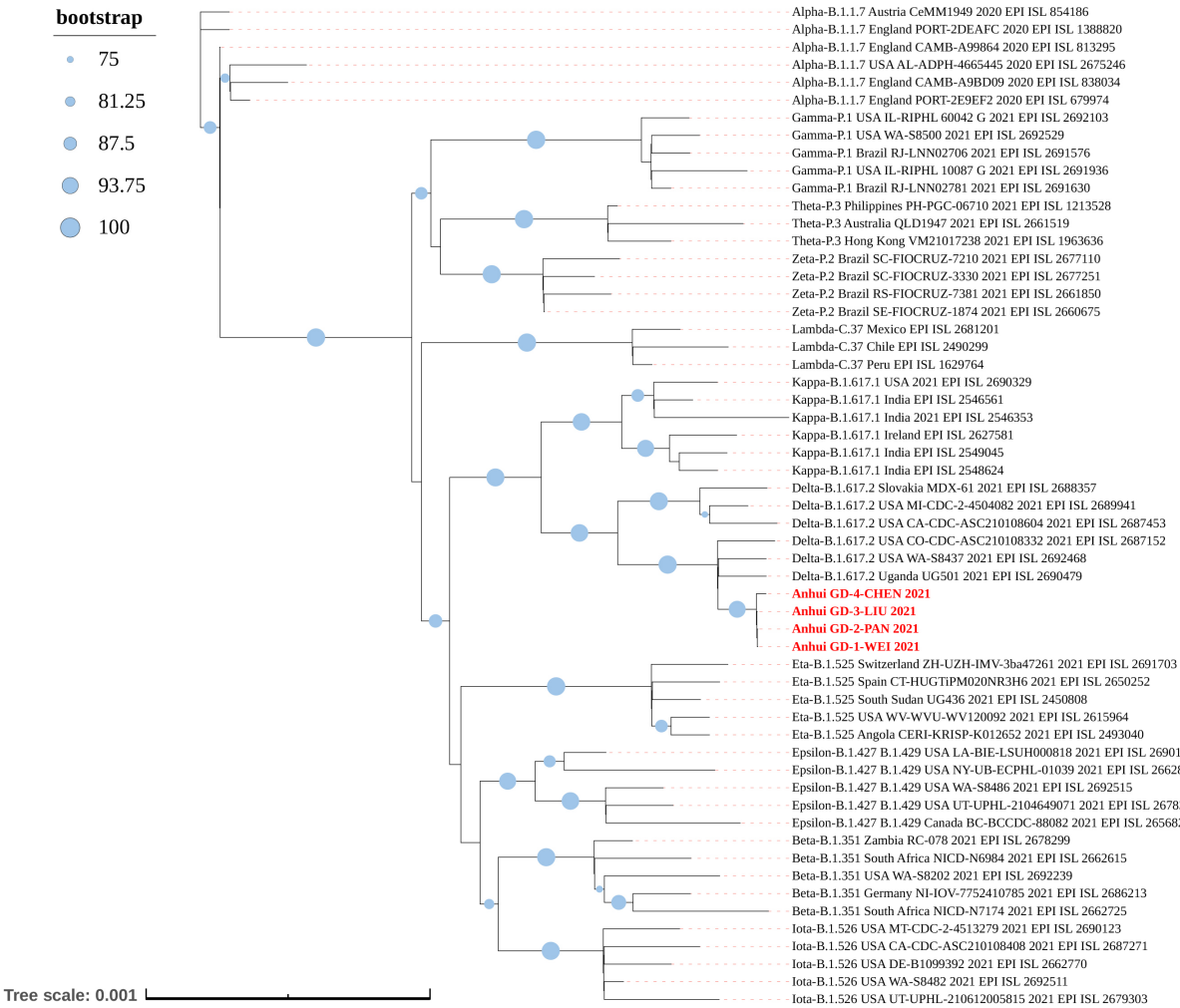

Figure 5. Phylogenetic tree was constructed based on whole genome nucleotide sequence. Red words indicate the strains in this study.

Table 2. Comparisons of Nucleotide and Amino Acid Substitutions between the Four Viruses Sequenced in This Study and the Wuhan Strain (NC_045512.2)

Gene	Nucleotide mutation	AA mutation	Gene	Nucleotide mutation	AA mutation
5′UTR	G210T	/		A11332G	/
	C241T	/	ORF1b	C14408T	P314L
M	T26767C	I82T		G15451A	G662S
N	A28461G	D63G		C16466T	P1000L
	G28881T	R203M		C19220T	A1918V
	G28916T	G215C	ORF3a	C25469T	S26L
	G29402T	D377Y	ORF7a	C27527T	P45L
ORF1a	G1048T	K261N		T27638C	V82A
	C1824T	A520V		C27752T	T120I
	C3037T	/	ORF7b	C27874T	T40I
	G4181T	A1306S	S	C21618G	T19R
	C6402T	P2046L		G21987A	G142D
	C7124T	P2287S		T22917G	L452R
	A7190G	I2309V		C22995A	T478K
	C8986T	/		A23403G	D614G
	G9053T	V2930L		C23604G	P681R
	C10029T	T3255I		G24410A	D950N
	A11201G	T3646A	3′UTR	G29742T	

Notes: UTR: untranslated region; ORF: open reading frame.

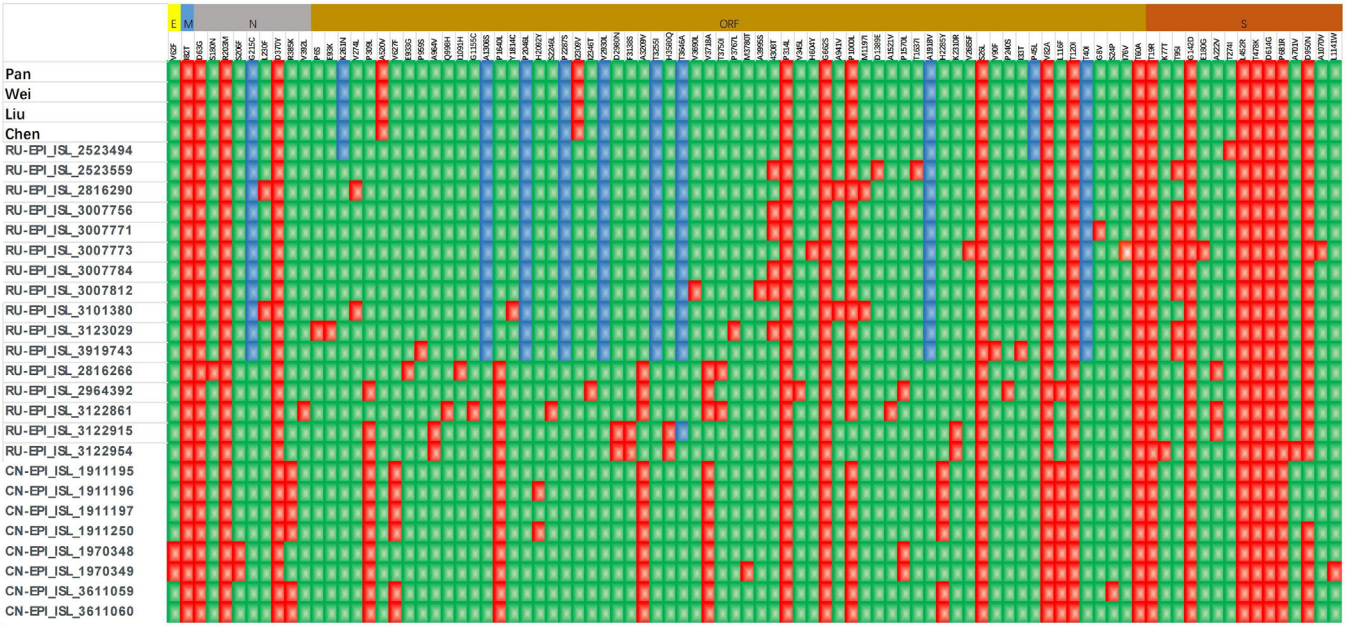

Figure 6. Amino acid mutations of the strains in this study. The sequences of strains isolated in China and Russia from April to June were downloaded from GISAID database. The green square indicated that the strain does not have the mutations; The red square indicated that the mutations appear in the strains isolated from China and Russia, including our strains; The blue square indicated that the mutations appear both in our strains in this study and the strains from Russia.

it is more likely that the source of the novel coronavirus infections in the four patients came from an area inside Russia.

Due to the good implementation of COVID-19 prevention and control measures in China, more imported cases did not cause local transmission, so the number of patients in Anhui in this study was only four. Due to the small number of patients, and infrequent sample collection and relevant laboratory testing of patients, some experimental data were missing, the application of extrapolation of the analysis results in this study is limited. However, this study found a certain correlation between hs-CRP/CRP and Nab levels and the occurrence, development and outcome of the disease in patients. During admission, monitoring hs-CRP/CRP and Nab levels of patients has certain guiding significance for understanding the current disease severity of patients, it would be of great help for physicians to provides medically appropriate care for these patients. Furthermore, when facing the pandemic risk of novel SARS-CoV-2 variant Omicron, previous experiences regarding the methods of disease diagnosis and prevention and control measures against Delta variant would also be instructive for monitoring the spread of the SARS-CoV-2 Omicron variant.

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Ethics Approval

This study was approved by the Ethical Committee of Anhui Provincial Center for Disease Control and Prevention (Hefei, Anhui, China). All the study subjects provided informed consent to participate in this study.

Availability of Data and Materials

Data available on request from the authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Author Contribution

He J, Wu X, Hou S, Feng Y, and Chen X were responsible for conceptualization, methodology, investigation, and writing the original draft. Gong L, Wang W, Chen Q, Yu J, and Li W contributed to methodology, formal analysis, and writing through review and editing. He L, Zhang Z, Wang P, Zhou X, Zhou J, Luo W, Yuan Y, and Sun Y provided validation, resources, and visualization. Wu J, Wang P, and Su B oversaw supervision, project administration, and also contributed to writing through review and editing.

Abbreviation List

COVID-19, Coronavirus disease 2019
CRP, C-reactive protein
CT, Computed tomography
GISAID, Global initiative of sharing all influenza data
hs-CRP, High-sensitivity C-reactive protein
IgG, Immunoglobulin G
IgM, Immunoglobulin M
Nab, Neutralizing antibodies
ORFs 1ab, Open reading frames 1ab region

rRT-PCR, Reverse transcription polymerase chain reaction
SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2

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