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SPECIAL REPORT

Quadruple therapy for asymptomatic COVID-19 infection patients

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ABSTRACT

Introduction: The novel coronavirus (COVID-19) is currently in epidemic stage. After large-scale interpersonal infection, asymptomatic patients appear. Whether asymptomatic patients are contagious or not and whether they need medication are the arguments among clinical experts.

Areas covered: This paper reports a special asymptomatic couple with COVID-19, of which the male patient is an intercity bus driver but has not induced confirmed infection of his 188 passengers. The patients were treated with four combinations of lopinavir/ritonavir tablets, arbidol tablets, Lianhuaqingwen granules, and recombinant human interferon-α2b (IFN-α2b) injection via aerosol. Their clinical characteristics and medication were summarized and analyzed.

Expert opinion: The two asymptomatic patients far away from Wuhan did not seem to be highly contagious. They improved obviously, after treatment with the quadruple therapy, but the effective drug is still unknown. It should be noted that lopinavir/ritonavir tablets have many drug interactions and are the most likely drugs to cause hyperlipidemia and hyperglycemia in these two patients. IFN-α2b is more effective in the early stage of virus infection. Arbidol instruction dose may not be sufficient to inhibit the novel coronavirus *in vivo*. The evidence-based medicine of Lianhuaqingwen granules for treating various viral infections is just based on Chinese patients.

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COVID-19; asymptomatic; adverse drug reaction; lopinavir; ritonavir; arbidol; IFN-α

1. Introduction

Since December 2019, the novel coronavirus (COVID-19) has been an epidemic. It is highly infectious and spreads rapidly. According to COVID-19 global cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU), more than 2 million cases have been diagnosed worldwide, and over 190 thousand patients have died. The World Health Organization (WHO) listed the outbreak caused by COVID-19 as 'public health emergencies of international concern (PHEIC).' This virus belongs to the same coronavirus as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus but has higher replication ability, stronger interpersonal transmission ability, and higher pathogenicity. The population is generally susceptible, and there are numerous severe patients. However, after large-scale interpersonal infection, it is surprising that 'asymptomatic persons' appeared with no clinical symptoms, but pathogen detection is positive.

The emergence of asymptomatic persons poses challenges to the prevention and treatment of the epidemic. Whether asymptomatic patients are contagious and whether they need treatment are controversial issues for clinical experts. On the one hand, in terms of the law of infectious diseases, asymptomatic persons are also capable of spreading the virus, but the viral load and transmission harm need to be investigated. On the other hand, the progress of asymptomatic patients and the effect of drug therapy are still unclear. Not long ago, a German asymptomatic patient was reported. The patient had chills, fever, and cough but recovered the next day and infected two colleagues in close contact with him in the latent period [1].

Here, we report two special asymptomatic patients, a couple, without definite contact history. Moreover, the male patient is an intercity bus driver; however, within 14 days after contact with him, no case of COVID-19 infection was confirmed in the 188 passengers he had carried. Only one passenger developed cough 6 days after taking the bus, whose COVID-19 nucleic acid tests have been negative for many times so far, and influenza B was once weakly positive, waiting to be excluded COVID-19 infection. This paper discussed the clinical characteristics of these two asymptomatic patients and summarized the pharmacological effects, clinical studies, and other precautions of the antiviral therapy on them, so as to provide a reference for the identification, diagnosis, and medication of asymptomatic patients in the epidemic prevention and control.

2. Case 1

2.1. Epidemiological history

The patient is a 54-year-old male, who is an intercity bus driver in Songxi County, Fujian Province, China, and has no definite contact history with Wuhan people.

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Article highlights

- Asymptomatic patients are controversial and concerning issues of COVID-19. The infectivity of some asymptomatic patients does not appear to be strong.
- Quadruple therapy, which is lopinavir/ritonavir tablets, arbidol tablets, Lianhuaqingwen granules, and recombinant human interferon-α2b (IFN-α2b) injection via aerosol, is a common regimen for patients with COVID-19 in China. The lung imaging of asymptomatic patients improved obviously after quadruple therapy, but which drug takes effect needs further studies.
- Lopinavir/ritonavir tablets cause high risks of drug interactions, hyperlipidemia, and hyperglycemia.
- Inhalation of IFN-α can raise its lung concentration. IFN-α2b is the most active type of IFN-α. 3.0–18 × 10^6 IU/day is the appropriate inhalation dose.
- Arbidol can effectively inhibit COVID-19 at a concentration of 10–30 μM (equal to 5.3–16.0 μg/mL) *in vitro*, but the peak arbidol concentration is only 0.41 μg/mL *in vivo*, indicating that the usual dose of arbidol may not be enough to suppress COVID-19 *in vivo*.
- The antiviral efficacy of Lianhuaqingwen granules still lacks evidence-based medicine.

2.2. Diagnosis and treatment

On 28 January 2020, the patient went to a hospital in Songxi County, Fujian Province, China, with 'soreness of loins' as the main complaint. The patient was in good health without previous medical history, medication history, and smoking or drinking habits. The physical examination showed the body temperature of 38°C, blood pressure of 138/80 mmHg, pulse rate of 92 beats per minute, respiratory rate of 22 breaths per minute, and oxygen saturation of 98% while the patient was breathing ambient air. Lung auscultation did not reveal rough breathing sounds, rhonchi, or pleural friction rub. Blood test results demonstrated his C-reactive protein (CRP) of 22.44 mg/L, procalcitonin of 0.12 ng/mL, glutamic oxaloacetic transaminase of 65 U/L, glutamic-pyruvic transaminase of 107 U/L, and glutamyl transpeptidase of 58 U/L, and other indicators were normal. Chest CT examination showed multiple ground-glass appearance (Figure 1). Since the patient works as a bus driver, COVID-19 pneumonia cannot be ruled out, although he claimed no known contact with anyone from Hubei. The hospital notified the local center for disease control and prevention (CDC) immediately and designated him as a 'suspected person.' The patient was isolated in the hospital. His throat swab specimen was obtained for COVID-19 nucleic acid detection. On the same day, the local CDC confirmed that the patient's COVID-19 test was negative.

On 29 January 2020, the patient did not have fever or any other discomforts, and the COVID-19 nucleic acid throat swab test was still negative. On 30 January, the patient had no discomfort. In order to exclude COVID-19 infection, double throat swab specimens of the patient were collected and sent to both local and provincial CDC for reexamination. On 31 January, the results showed positive.

With the coordination of the local health commission, the patient was sent to the isolation ward of Nanping First Hospital for treatment on 31 January 2020. On the first day of admission, the patient was suffered from soreness of waist, without cough, fever, shortness of breath, vomiting, or other discomforts. His vital signs appeared normal. The physical examination showed rough breathing sounds, and other monitored parameters were generally normal.

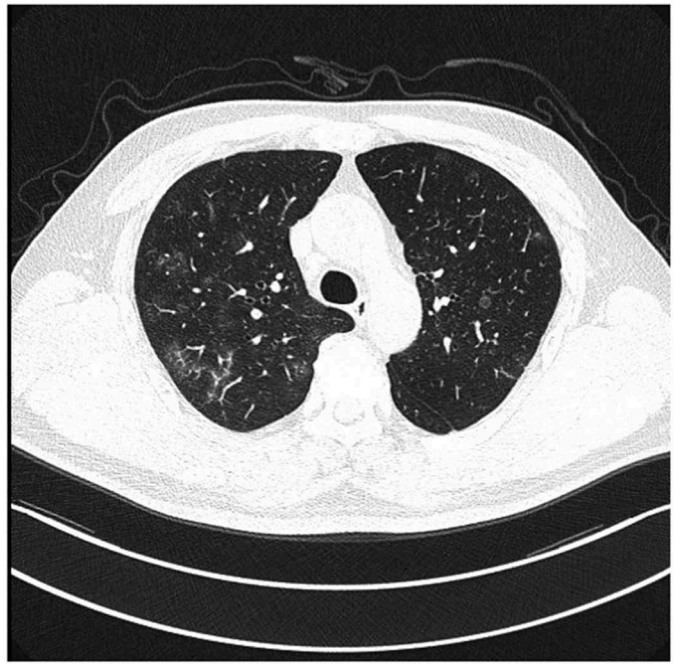

Figure 1. Chest CT of case 1, on 28 January 2020.

From 31 January 2020 to 10 February 2020, the patient was given quadruple therapy, including lopinavir/ritonavir tablets (400/100 mg every 12 h), arbidol tablets (0.2 g every 8 h), Lianhuaqingwen granules (a Chinese patent medicine, 6 g every 8 h) orally, and recombinant human interferon-α2b injection via aerosol (6.0 × 10^6 IU with 2 ml of sterilized water for injection every 12 h). The patient had stable vital signs and normal oxygen saturation, without any discomfort. His clinical laboratory indicators are shown in Table 1. The patient's white-cell count, absolute neutrophil count, absolute lymphocyte count, platelet count, and CRP were all in normal quantity. Fasting blood glucose and triglyceride continued going up to 15.45 and 6.69 mmol/L, respectively, significantly higher than normal values. Cholesterol rose to 5.47 mmol/L eventually. Alanine aminotransferase (54–76 IU/L) and glutamyl transpeptidase (46–50 IU/L) persisted a bit higher. Total bilirubin, fibrinogen, lactate dehydrogenase, and blood urate normalized after slightly exceeding the normal. On 10 February, compared with the previous chest CT result, the scattered patchy fuzzy shadows of both lungs slightly decreased. The patient was taken COVID-19 nucleic acid throat swab tests on 7 February 2020 and 10 February 2020, respectively, and the results were both negative. On 11 February 2020, the patient discharged without any discomfort and in good condition.

3. Case 2

3.1. Epidemiological history

The patient is a 55-year-old housewife and has close contact with her husband, the patient of case 1.

Table 1. Clinical laboratory results of case 1.

Measure	Reference range	1 February 2020	4 February 2020	7 February 2020	10 February 2020
White-cell count (/L)	$3.69–9.16 \times 10^9$	8.42	6.21	5.85	7.23
Red-cell count (/L)	$3.68–5.13 \times 10^{12}$	4.84	4.64	4.28	4.48
Absolute neutrophil count (/L)	$2.0–7.7 \times 10^9$	6.01	3.49	3.23	4.12
Absolute lymphocyte count (/L)	$0.8–4.0 \times 10^9$	1.82	3.12	2.12	2.51
Platelet count (/L)	$101–320 \times 10^9$	174	229	235	213
Hemoglobin (g/L)	113–151	154	147	135	143
Hematocrit (%)	33.5–45.0	43.7	41.5	38.2	40.4
Sodium (mmol/L)	135.0–148.0	135.95	135	136.74	137.13
Potassium (mmol/L)	3.50–5.30	3.52	2.5	3.23	3.79
Chloride(mmol/L)	98.0–108.0	102.70	98.78	100.40	98.60
Calcium (mmol/L)	2.1–2.7	2.13	2.12	2.30	2.26
Carbon dioxide (mmol/L)	21.0–29.0	22.44	28.22	25.48	29.00
Anion gap (mmol/L)	8.0–16.0	10.81	8.00	10.86	9.53
Fasting blood glucose (mmol/L)	3.9–6.1	10.23	10.15	13.72	15.45
Blood urea nitrogen (mmol/L)	2.1–7.8	5.99	6.11	6.80	4.73
Creatinine (μmol/L)	44.0–133.0	72.85	97.41	85.92	80.48
Total protein (g/L)	60.0–86.0	65.28	63.15	61.31	66.48
Albumin (g/L)	30.0–55.0	40.89	39.25	37.81	41.45
Total bilirubin (μmol/L)	5.1–19.0	23.20	20.10	12.60	12.20
Alanine aminotransferase (IU/L)	5–50	76	84	63	54
Aspartate aminotransferase (IU/L)	5–50	43	50	28	26
Alkaline phosphatase (IU/L)	34–114	95	95	97	108
Fibrinogen (g/L)	2–4	5.90	3.35	3.88	3.84
Lactate dehydrogenase (IU/L)	80–240	285	199	150	159
Prothrombin time (s)	9–13	11.90	12.40	12.00	11.30
International normalized ratio	0.8–1.2	1.05	1.10	1.06	1.00
Creatine kinase (IU/L)	24–183	103.0	63.1	57.8	77.7
Triglyceride (mmol/L)	0.2–1.7	2.36	3.83	6.10	6.69
Blood urate (μmol/L)	89–416	338.40	432.00	453.30	344.80
Glutamyl transpeptidase (IU/L)	7–40	50	43	40	46
Cholesterol (mmol/L)	2.00–5.17	4.46	4.68	4.75	5.47
C-reactive protein (mg/L)	0–10.0	9.69	3.11	2.00	1.44
Oxygen saturation (%)	95–99	98	98	99	99

3.2. Diagnosis and treatment

On 28 January 2020, the patient had no discomfort and accompanied her husband to a hospital in Songxi County, Fujian Province, China. As her husband was suspected to be infected with COVID-19, she was also hospitalized and isolated. The patient was in good health without previous medical history, medication history, and smoking or drinking habits. The physical examination showed her body temperature of 36.8°C, blood pressure of 118/72 mmHg, pulse rate of 78 beats per minute, respiratory rate of 20 breaths per minute, and oxygen saturation of 98% while the patient was breathing ambient air. Auscultation of both lungs was normal. Her clinical laboratory results were within normal range, except CRP of 22.44 mg/L (Table 2). On the same day, the local CDC confirmed that the patient's COVID-19 nucleic acid throat swab test was negative.

On 29 January 2020, the patient had no discomfort, but her COVID-19 nucleic acid throat swab test was positive. On 30 January 2020, her throat swab was collected again and the result was also positive. Chest CT showed that her two lungs had diffuse patchy shadows and ground-glass appearance (Figure 2). She and her husband were sent to the isolation ward of Nanping First Hospital for treatment on 31 January 2020. On the first day of admission, the patient had no discomfort, and the vital signs were normal. The physical examination revealed rough breathing sounds, and other monitored parameters were generally normal.

From 31 January 2020 to 10 February 2020, the patient was treated with four drugs, which are oral administration of lopinavir/ritonavir tablets (400/100 mg every 12 h), arbidol tablets (0.2 g every 8 h), and Lianhuaqingwen granules (a Chinese patent medicine, 6 g every 8 h) and atomization inhalation of recombinant human interferon-α2b injection (6.0×10^6 IU with 2 ml of sterilized water for injection every 12 h). The patient's vital signs were stable, and oxygen saturation was normal. There were no discomfort and any abnormal quantity of white-cell count, absolute neutrophil count, or absolute lymphocyte count. Fasting blood glucose (6.48–-8.4 mmol/L) and triglyceride (2.42–5.2 mmol/L) remained relatively high. CRP and fibrinogen dropped back to normal from 29.15 mg/L and 4.72 g/L, respectively. Platelet count increased slightly to 313×10^9/L finally. On 7 February, from chest CT, it can be seen that the ground-glass shadow in her lungs has narrowed. The patient's COVID-19 nucleic acid throat swab tests became negative on 15 February 2020 and thus discharged from the hospital without any discomfort.

4. Discussion

COVID-19 infection presents a cluster attack. Most patients were male, with an average age of 55.5 years [2]. Fifty-one percent of patients were suffered from chronic diseases, including cardiovascular and cerebrovascular diseases, endocrine system diseases, digestive system diseases, respiratory system diseases, malignant tumors, and nervous system diseases. Elderly men with complications are more likely to be infected and may lead to serious or even fatal respiratory diseases [2]. Although the two patients in this paper were

Table 2. Clinical laboratory results of case 2.

Measure	Reference range	1 February 2020	4 February 2020	7 February 2020	10 February 2020
White-cell count (/L)	$3.69–9.16 \times 10^9$	6.08	5.70	5.39	5.47
Red-cell count (/L)	$3.68–5.13 \times 10^{12}$	4.37	4.39	4.04	3.96
Absolute neutrophil count (/L)	$2.0–7.7 \times 10^9$	3.53	3.50	2.96	3.26
Absolute lymphocyte count (/L)	$0.8–4.0 \times 10^9$	1.95	1.72	1.96	1.77
Platelet count (/L)	$101–320 \times 10^9$	231	244	322	313
Hemoglobin (g/L)	113–151	135	132	128	123
Hematocrit (%)	33.5–45.0	38.6	38.8	35.8	34.9
Sodium (mmol/L)	135.0–148.0	136.15	138	138.13	136.54
Potassium (mmol/L)	3.50–5.30	3.1	3.78	3.92	3.6
Chloride (mmol/L)	98.0–108.0	100.8	101	99.4	100.2
Calcium (mmol/L)	2.1–2.7	2.1	2.15	2.39	2.29
Carbon dioxide (mmol/L)	21.0–29.0	26.12	29	29	27.5
Anion gap (mmol/L)	8.0–16.0	9.23	8	9.73	8.84
Fasting blood glucose (mmol/L)	3.9–6.1	6.48	8.18	7.68	8.4
Blood urea nitrogen (mmol/L)	2.1–7.8	4.96	3.99	5.19	4.09
Creatinine (μmol/L)	44.0–133.0	48.35	54.29	57.94	53.25
Total protein (g/L)	60.0–86.0	63.67	67.74	68.17	63.13
Albumin (g/L)	30.0–55.0	39.55	40.77	40.89	38.5
Total bilirubin (μmol/L)	5.1–19.0	14.8	16.7	12.9	11.9
Alanine aminotransferase (IU/L)	5–50	21	17	18	21
Aspartate aminotransferase (IU/L)	5–50	19	15	16	18
Alkaline phosphatase (IU/L)	34–114	68	71	71	67
Fibrinogen (g/L)	2–4	4.72	3.57	3.84	3.62
Lactate dehydrogenase (IU/L)	80–240	203	198	195	186
Prothrombin time (s)	9–13	12.9	11.7	11.1	10.9
International normalized ratio	0.8–1.2	1.14	1.04	0.98	0.96
Creatine kinase (IU/L)	24–183	57.2	56.8	63.9	73.6
Triglyceride (mmol/L)	0.2–1.7	2.42	3.61	4.35	5.2
Blood urate (μmol/L)	89–416	237.5	221.9	242.6	237.3
Glutamyl transpeptidase (IU/L)	7–40	12	13	13	13
Cholesterol (mmol/L)	2.00–5.17	3.33	3.65	4.2	4.5
C-reactive protein (mg/L)	0–10.0	20.96	29.15	3.88	1.12
Oxygen saturation (%)	95–99	98	99	99	99

about 55 years old, they had good health and no basic medical history, which may be one reason why they had no obvious clinical symptoms of COVID-19 pneumonia. However, whether there are other possibilities need to be discussed and confirmed. For example, the male patient of the first case, saying no contact with Wuhan people, might be infected unconsciously by other people who got in touch with Wuhan people. After repeated reproduction and transmission, the virus is getting weak. Or, the viral load entering the body is relatively low; thus, under the condition of a good immune system, it will not emerge that large and rapid virus proliferation and migration *in vivo* lead to serious damage to lungs and even other organs. All these conjectures need further investigation.

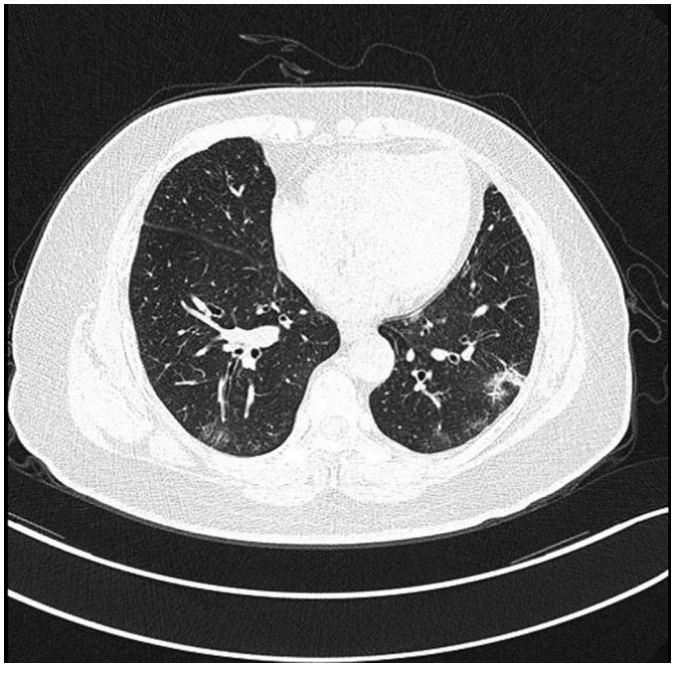

Figure 2. Chest CT of case 2, on 30 January 2020.

Asymptomatic cases are easy to miss diagnosis or misdiagnose, due to the lack of specific COVID-19 pneumonia manifestations and normal inflammatory indexes such as white blood cells, lymphocytes, and CRP. At present, there have been some asymptomatic cases in China, which should be paid attention to. It is worth noting that the first male patient in this paper, complaining of soreness of loins, is similar to the atypical COVID-19 pneumonia German patient with myalgias as a complaint [1]. The male patient of case 1 also showed transient elevation of serum lactate dehydrogenase. With respect to muscle pain, there are similarities between asymptomatic infection of COVID-19 and influenza to some extent, and sometimes, the rise of serum creatine kinase, lactate dehydrogenase, and myoglobin can be seen. At present, the guidelines of COVID-19 pneumonia in various countries do not list muscle pain as one of the clinical manifestations, which may lead to the omission of some patients, especially the mild patients.

What should be taken seriously is not only that asymptomatic patients did not have typical COVID-19 infection symptoms but also that the COVID-19 nucleic acid throat swab tests showed false negative in these patients, delaying the

diagnosis of COVID-19 infection. This may be caused by two reasons, one is that asymptomatic patients may have a low viral load, and the other is that the detection rate of nucleic acid throat swab may be not high enough. For mild cases of COVID-19 infection, the use of lung imaging as a supplement or even an alternative to throat swab detection may also be an effective means to reduce the omission diagnostic rate. Under certain circumstances, lower respiratory tract specimens such as tracheal aspirates, bronchoalveolar lavage, and sputum, with higher viral load, can be tested to raise the detection rate. On the other hand, interpretation of positive results is equally important. At present, in China, two consecutive negative results of COVID-19 nucleic acid throat swab test are the necessary standard for patients to leave the hospital. In this paper, the female patient has no symptoms all the time, but the duration of positive nucleic acid test results is longer than that of the male patient, so she cannot be discharged from the hospital for a longer time. That provokes questions that how long the course of antiviral treatment should be and whether the sign of stopping antiviral treatment should be the clinical manifestation or nucleic acid turning negative. What is worth thinking about is whether it is a better choice for asymptomatic patients to rest at home instead of medication at hospital in order to prevent adverse drug reactions, such as the increase of triglyceride in cases 1 and 2 as described below.

In this paper, two patients were treated with quadruple therapy combining Chinese and western medicines. COVID-19, SARS, and MERS belong to the same coronavirus, and their protein structures have many similarities. The antivirus drugs used in this paper have been proved to have an inhibitory effect on SARS/MERS *in vitro* or *in vivo*, but their adverse reactions and efficacy/safety in special populations such as liver and renal insufficiency still need to be paid attention to by clinicians.

Lopinavir/ritonavir is recommended by the National Health Commission of China for the treatment of COVID-19 at present [3]. Lopinavir is used to prevent the HIV gag-pol polyprotein from splitting. The action site of ritonavir is aspartyl protease of the virus, blocking the precursor of HIV gag-pol polyprotein. The two components work together, resulting in immature virus particles without regeneration capability. Moreover, ritonavir is also an enhancer of lopinavir, which can inhibit the CYP3A-mediated degradation of lopinavir in the liver [4]. Two SARS-based clinical studies [5,6] and a MERS-based clinical case report [7] suggested that lopinavir/ritonavir has an anticoronavirus effect. In addition, lopinavir/ritonavir was listed as a candidate therapeutic drug in an anti-MERS guideline written by clinical experts in South Korea [8]. These studies are of great significance for the treatment of COVID-19 with lopinavir/ritonavir. However, the clinical studies on SARS published by Chan and Chu both pointed out that lopinavir/ritonavir as the initial treatment can remarkably improve the total mortality rate, oxygen saturation reduction rate, intubation rate, or glucocorticoid usage. But for treating the terminal stages, there was no obvious curative effect [5,6]. This may be because lopinavir/ritonavir mainly acts by inhibiting the formation of new virus and cannot prevent the virus from entering cells, but numerous viruses have entered cells in the end-stage patients, causing organ damage and poor outcome.

In terms of adverse reactions, lopinavir/ritonavir induces diarrhea, hyperglycemia, hyperlipidemia, arrhythmia, liver dysfunction, etc. Its serious adverse reactions also include fatal diseases such as pancreatitis [4]. In this paper, the triglyceride and fasting blood glucose levels of the two patients exhibited a huge rise far above normal after treatment. According to Naranjo's adverse drug reaction probability scale score, 5 points were obtained, indicating that lopinavir/ritonavir probably caused adverse reactions of hyperlipidemia and hyperglycemia in both the patients. The adverse drug reactions may be common in patients because these two patients, as good representatives, had normal basic monitoring indexes and good liver/kidney function and physical condition and took lopinavir/ritonavir in a short time, thus metabolized and excreted lopinavir/ritonavir efficiently. For severe patients with liver function injury, risk of the adverse drug reactions may become higher, possibly leading to serious consequences, including fat overload syndrome, pancreatitis, other pathogen infection, and even prolonged hospitalization or death for reasons other than COVID-19 infection. Besides, lopinavir and ritonavir, both inhibitors of CYP3A, may increase the plasma concentration of drugs metabolized mainly by CYP3A, such as amiodarone, fentanyl, and midazolam, commonly used in severe patients. The drug action time will prolong and the occurrence of adverse drug reactions may increase. Lopinavir and ritonavir also have certain inhibition effects on ATP-binding cassette subfamily B member 1 (ABCB1), but the effects of ABCB1 were only detectable in the presence of CYP3A, suggesting that the simultaneous use of ABCB1 substrates should also be cautious [9].

The severe pneumonia incidence of COVID-19 infection is relatively high, especially in the elderly. For severe patients with hepatic or renal insufficiency, it should be noted that blood drug concentration of lopinavir showed a rapid increase in the patients with liver dysfunction [10], suggesting the necessity of therapeutic drug monitoring of lopinavir. Therapeutic concentration of lopinavir was 3–8 mg/L, and toxic concentration was above 8 mg/L [11]. However, patients with renal insufficiency can continue to take lopinavir/ritonavir at the conventional dosage because the renal clearance rate of lopinavir and ritonavir is extremely low. Moreover, both lopinavir and ritonavir have strong protein-binding capacity, so hemodialysis will not affect their clearance greatly [12]. But lopinavir/ritonavir was reported to be strongly related to kidney impairment, so its potential nephrotoxicity should be concerned [13,14]. There are few reports of old people treated with lopinavir/ritonavir, yet the lopinavir plasma level in the elderly seems to be higher than the recommended value [15].

Atomization inhalation of interferon-α (IFN-α) is also recommended by the National Health Commission of China as medication for COVID-19. IFN-α is bound to receptors on the cell surface to induce the production of various antiviral proteins, thereby inhibiting the replication of viruses in cells. IFN-α has a broad antivirus spectrum. In addition, it can enhance the specific cytotoxic effect of macrophages and lymphocytes by regulating immune function and thereby stop the invasion and infection of the virus effectively. At present, there are three types of IFN-α subtypes approved for clinical use, namely IFN-α2b, IFN-α2a, and IFN-α1b. It is found that IFN-

α2b used in this paper tends to have a relatively higher activity [16]. IFN-α is mainly administered subcutaneously and intramuscularly, which is easy to cause influenza-like symptoms, myelosuppression, mental abnormalities, and other adverse reactions. Inhalation will not inactivate IFN-α and can raise the lung concentration [17]. 3.0×10^6 IU/day is the minimum inhalation dose of IFN-α that can induce biological effects without side effects [18]. Below the dose of 18×10^6 IU/day, IFN-α hardly enters the systemic circulation through inhalation [19].

As for the treatment of IFN-α on coronavirus, early therapy of IFN-α inhalation combined with antiviral drugs has been shown to be associated with better outcomes [20,21]. While the clinical research of Omrani et al. demonstrated that the combination therapy of ribavirin and IFN-α2a inhalation can improve the early and intermediate survival rate of severe MERS patients significantly, it was useless for the late survival rate [22]. However, the sample sizes of the above investigations were small, and the effectiveness of IFN-α inhalation on coronavirus still lacks sufficient evidence-based medical evidence.

Inhalation of IFN-α may induce bronchospasm reaction and decrease the peak expiratory flow rate [19,23] but few systemic adverse reactions such as influenza-like symptoms [19]. There are no data about the application of IFN-α inhalation on the elderly and patients with liver or renal insufficiency. However, the usage of IFN-α injection for inhalation is off-label, so the patient-informed consents are required. Besides, attention should be paid to the possibility of allergy caused by IFN-α and auxiliary materials.

The two patients in this paper also used hemagglutinin inhibitor, arbidol, which is not recommended by the National Health Commission of China for COVID-19. Arbidol can specifically inhibit the contact, adhesion, and fusion of virus lipid membrane and host cell membrane and block virus gene from penetrating into nucleus, by activating 2,5-oligoadenylate synthetase (antiviral protein) [24,25]. At present, there is no clinical report of arbidol on coronavirus pneumonia, but it has a good inhibition effect on SARS, even Ebola virus (EBOV) and Lassa virus (LASV) *in vitro* [26–28]. An arbidol concentration of 20 μg/mL was required to achieve a 50% reduction in virus proliferation and hemagglutinin levels [29]. According to China News, cell experiments *in vitro* showed that arbidol can effectively inhibit COVID-19 up to 60 times at the concentration of 10–30 μM and significantly suppress the pathological effect of the virus on cells [30]. However, the concentration of 10–30 μM is equivalent to 5.3–16.0 μg/mL of arbidol, which is far above the peak concentration (0.41 μg/mL) that can be achieved *in vivo* by oral administration of single- and multiple-dose arbidol [31,32]. Therefore, whether to apply a higher dose of arbidol for COVID-19 pneumonia needs to be concerned and studied.

Liver and intestine are the main metabolic organs of arbidol in the human body, and CYP3A4 is the major isoform enyzme, indicating possible drug interactions between arbidol and CYP3A4 substrates [33]. Additionally, the adverse event rate of arbidol is approximately 6.2%, mainly manifested as nausea, diarrhea, dizziness, and increased serum transaminase [34], which is similar to the adverse reactions of the digestive system in COVID-19-infected patients, probably increasing difficulties in differential diagnosis. In the bioequivalence experiment of arbidol preparation conducted in China, 3 h after taking the medicine, some healthy subjects had bradycardia (heart rate less than 60 beats/min and reduced 2–24 beats per minute). But the subjects had no adverse symptoms and the correlation with arbidol was unclear.

Arbidol can be used for the elderly patients and improve their cellular immunity [35]. For patients with hepatic or renal insufficiency, the safety of arbidol is not clear. In view of the fact that arbidol is mainly removed by feces, accounting for 32.4% of the dose, and its glucuronide and sulfuric acid metabolites are excreted in urine, accounting for 6.3% of the dose, therefore, patients with severe liver dysfunction need to use arbidol with caution or reduction, while patients with renal insufficiency may consider the original dose [33].

In the guideline for COVID-19 pneumonia of China, traditional Chinese medicine has equal status with western medicine. Lianhuaqingwen preparation has broad antiviral spectrum, antipyretic effect, and anti-inflammatory effect and is even superior to oseltamivir in improving the symptoms of influenza infection [36,37]. Lianhuaqingwen preparation has been recommended by the National Health Commission of China repeatedly in a series of infectious public health events such as SARS, MERS, H1N1, avian influenza, and hand–foot–mouth disease, for more than 10 years, and plays an important role in prevention and treatment. Lianhuaqingwen preparation can obviously inhibit the replication of SARS virus with IC50 of 0.11 mg/mL and therapeutic index of 40.3 [38]. Lianhuaqingwen preparation has 61 compounds or more, in which 12 high-content compounds are salidroside, chlorogenic acid, forsythoside E, cryptochlorogenic acid, amygdalin, sweroside, hyperin, rutin, forsythoside A, phillyrin, rhein, and glycyrrhizic acid [39]. The common adverse reactions of Lianhuaqingwen preparation were mostly related to digestive system, mainly manifested as nausea, diarrhea, vomiting, and abdominal pain. Skin allergy reaction and clinical laboratory results are rare and can be relieved after drug withdrawal. The treatment of Lianhuaqingwen preparation on COVID-19 pneumonia has yet to be proved by clinical trials.

The best medication for COVID-19 infection has not yet been confirmed. In this paper, two patients were treated with quadruple therapy combined with Chinese and western medicines. The symptoms and chest X-rays of both patients have been greatly improved. It can be said that quadruple therapy has a certain curative effect, but the possibility of spontaneous improvement cannot be ruled out, and it is impossible to tell whether one or more drugs work. The reason why the two patients were selected is that they were the only asymptomatic patients in Northern Fujian Province of China, and their medication was analyzed by the authors, who often discuss difficult cases in the form of multidisciplinary team. The treatment of two patients met the guideline for COVID-19 pneumonia of China and got the ethical approval of relevant hospitals. This paper has limitations. It is a report of individual cases, and we have not quantified the viral load, leaving the virus dynamics unclear. More clinical data are

needed for asymptomatic patients as well as this combination medication.

5. Expert opinion

Asymptomatic patients have no fever or respiratory tract symptoms, but pneumonia can still be seen on imaging. For asymptomatic patients, pharmaceutical care should be strengthened while virus detection and antiviral treatment are carried out, including the discovery, solution, and prevention of potential or actual drug problems, so as to ameliorate the safety, effectiveness, and economy of medication and achieve the ideal goal of improving the quality of life for patients with COVID-19.

The lack of effective drugs directly targeting COVID-19 is the major challenge to doctors and the treatment of patients. Whether the western medicine lopinavir/ritonavir, remdesivir, arbidol, and chloroquine or traditional Chinese medicine with antiviral activity has caused the public to expect the control of COVID-19 but lacks 'effectiveness' and 'safety' from multicenter, randomized, double-blind, controlled studies. In fact, it takes quite a long way from *in vitro* experiments to actual clinical use. In the design of clinical trials for COVID-19, the trial efficiency is of great importance; thus, Phase I trials with extended cohorts, trials based on pattern recognition, machine learning, and other technologies should be utilized.

Further study of COVID-19 is not limited to antiviral drugs. Anti-inflammatory (anti-IL-6, anti-TNF-α, etc.) treatment should be actively carried out to quickly neutralize the cytokine storm *in vivo* and reduce the mortality of critical patients. Adoptive reinfusion of cured patients' serum and the immune regulation of mesenchymal stem cells may also show a certain effect. With the help of multidisciplinary cross-analysis, to control symptoms quickly and reduce mortality effectively is the main task at present.

A reasonable analysis of existing clinical data to make treatment decisions is the only choice in the absence of effective COVID-19 antiviral drugs. The efficient utilization of clinical data needs the establishment of big data and the promotion of scientific, networked, and shared data collection and management modes. Specifically, many complicated clinical data are cleaned and integrated, and the terminology is unified. The outliers or small-sample data are eliminated. Repeated researches are conducted in clinical manifestations, laboratory test results, lung imaging, combined basic diseases, drug therapy and clinical outcomes, etc., via statistical analysis to find out characteristic data, helping physicians to realize accurate differential diagnosis and treatment of COVID-19.

In the future, the following aspects should be emphasized for the control of COVID-19: (1) Strengthen epidemiological research, especially the prevention and control of asymptomatic and mild cases as infection sources; (2) Carry out in-depth research on structures and functions of various virus proteins and then conduct drug prediction and high-throughput screening; and (3) Enhance international cooperation. For example, traditional Chinese medicine has played a positive role in preventing and treating COVID-19, but further discussion is needed on how to standardize the use, how to reasonably evaluate the curative effect, and how to integrate with western medicine.

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