

Successful Treatment of Convalescent Plasma Therapy in Three Patients With Severe SARS-CoV-2 Infection in Fuzhou, China

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Abstract

Background Up to now, there is no specific treatment for coronavirus disease 2019 (COVID-19) yet except for general supportive care. Hence, it will be critical to find a new strategy for COVID-19. The study is to explore whether convalescent plasma transfusion may be beneficial in the treatment of severe patients with COVID-19.

Methods This is a retrospective analysis of three severe patients with laboratory-confirmed COVID-19 and admitted in Fuzhou pulmonary hospital of Fujian province from February 18th, to May 15th, who met the following criteria: (1) within 3 weeks of symptom onset; laboratory confirmed cases or who had viremia conformed by clinical experts; (2) Severe patients with rapidly progress or the early stage of critically ill patients or who required plasma therapy were comprehensively evaluated by clinical experts. The data of clinical manifestations and the progresses of disease monitored by blood-gas analysis, biochemical tests, routine examine, radiological exam were abstracted and then analysis the changes before and after convalescent plasma transfusion.

Results All three patients (one male and two females; age range, 57-65years) were treated with convalescent plasma during the study. Two patients had underlying chronic diseases, including diabetes and hypertension. The most common symptoms were fever (three cases, 3/3) and cough (two cases, 2/3). All patients were treated with a combination of two antiviral drugs (lopinavir/ritonavir or arbidol combined with IFN- α), whereas none of the patients were given glucocorticoids. Following plasma transfusion, the symptoms of the whole group improved to some degree, mainly manifested as reducing in coughing and body temperature normalized. Several parameters tended to improve as compared to pre-transfusion, including increased lymphocyte counts ($0.97 \times 10^9/L$ vs. $1.08 \times 10^9/L$) and decreased IL-6 (41.34 pg/ml vs. 13.83 pg/ml). The density of bilateral infiltration on CT imaging showed varying degrees of absorption within 7days. Throat swab nucleic acid test of most patients became negative for the novel coronavirus within 3 days after the transfusion. No adverse effects and severe complications were observed.

Conclusions In this preliminary uncontrolled case series of 3 severe patients with COVID-19, convalescent plasma could be as a promising therapy for COVID-19 without corticosteroids and no serious adverse reactions associated with the transfusion of convalescent plasma were observed, which would improve the clinical outcomes following by improvement in their clinical status. Using the convalescent plasma at the early stage (less than 10 days) of disease could be more effective. Anticoagulation is necessary for severe patients with COVID-19 given the state of hypercoagulability. However, given the small sample size and limited study design, naturally these results should be taken with a grain of salt until replicated by other further investigation in larger well-controlled trials.

1. Introduction

Since late December 2019, an outbreak of severe acute respiratory syndrome coronavirus-2(SARS-CoV-2) infection which was named by World Health Organization (WHO) as coronavirus disease 2019(COVID-2019), was initially emerged in Wuhan, China[1-3].The epidemic spread rapidly worldwide and become an unprecedented global public health crisis[4, 5].As of May 16, 2020, COVID-19 had spread up to more than 200 countries and regions, that had been reported by WHO, with a total number of 4,425,485 cases, including 302,056 cases (6.83%)[6]. At the moment, there are still no specific therapies approved by the China Food and Drug Administration (CFDA) or U.S. Food and Drug Administration (FDA) for SARS-CoV-2, the virus that causes COVID-19, therapeutic strategy is being studied in addition to supportive care[7], while some drugs are still under investigation. Several agents are being used under clinical trial and compassionate use protocols based on *in vitro* activity (against SARS-CoV-2 or related viruses) and on limited clinical experience[8]. Efficacy has not been established for any drug therapy. Several agents seem to be clinically beneficial, but their efficacy is far from satisfactory[9].A recent trial showed lopinavir-ritonavir has no treatment benefit for severe illness caused by SARS-CoV-2[10].A randomized, double-blind, placebo-controlled, multicentre trial[11] revealed remdesivir was not associated with a difference in time to clinical improvement (hazard ratio 1.23 [95% CI 0.87–1.75]),which was not statistically significant. Although patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio 1.52 [0.95–2.43]).To the end, the effective vaccine and specific antiviral medicines are unavailable, therefore there are urgent needs to look for an COVID-19-specific treatment, especially among the severe patients. Previous reports[12] have shown treatment with convalescent plasma collated from recovered patients would have a shorter hospital stay and lower mortality than the comparator group(high-dose steroids pulse therapy), and no immediate adverse effect noted after plasma infusion. A meta-analysis involving 1703 influenza pneumonia patients who received influenza-convalescent human blood products, showed treatment with convalescent plasma could reduce virus load and pool absolute reduction of 21% in mortality[13]. However, the efficacy of convalescent plasma in critically ill patients with SARSCoV-2 infection remains unclear. Here, we performed this timely pilot study in three participating patients to describe whether it is also effective to use convalescent plasma therapy in the COVID-19 setting and discuss the preliminary experience of convalescent plasma transfusion administered to critically ill patients with COVID-19.

2. Methods

We did this timely descriptive study in 3 patients with COVID-19 in Fuzhou Pulmonary Hospital of Fujian province, which was the designated hospital in Fuzhou, China, from February 18th, to March 30th, 2020, and the final date of follow-up was April 30th, 2020. The study was reviewed and approved by the medical ethics committees of Fuzhou Pulmonary Hospital of Fujian province, and each participant gave written informed consent.

2.1 Patients

Patients with COVID-19 were laboratory confirmed by using throat swab SARS-CoV-2 real-time PCR (Detection Kit for 2019 Novel Coronavirus RNA PCR-Fluorescence Probing) (DAAN GENE Co, Ltd), who had been empirically treated with anti-viral drug arbidol or lopinavir-ritonavir, which are also recommended by the New Coronavirus Pneumonia Diagnosis and Treatment Program (6th edition) published by the National Health Commission of China^a

Patients, who were in accordance with the New Coronavirus Pneumonia Convalescent Plasma Therapy Guidance of China (2nd edition)^b, were given the convalescent plasma treatment if they fulfilled the following criteria: (1) within 3 weeks of symptom onset; laboratory confirmed cases or who had viremia confirmed by clinical experts; (2) Severe patients with rapidly progress or the early stage of critically ill patients or who required plasma therapy were comprehensively evaluated by clinical experts.

Exclusion criteria were^b: (1) patients allergic to plasma content or citrate; (2) The terminal stage of critical illness; (3) patients who developed multiple organ dysfunction syndrome; (4) patients who were comprehensive assessment by clinician unsuitable to use convalescent plasma.

2.2 Donors and convalescent plasma transfusion

2.21 Donors

The three donors of convalescent plasma were invited to donate their convalescent plasma after written informed consent was obtained. The convalescent plasma donors must fulfilled the following criteria^b: (1) at least 3 weeks following symptom onset; (2) comply with the latest version of the COVID-19 diagnosis and treatment protocol to remove isolation and discharge standards; (3) between the ages of 18 and 55 years; (4) No less than 50 kg for males and 45 kg for females; (5) No history of menstrual blood disease; (6) patients who were comprehensive assessment by clinician unsuitable to donate plasma.

2.22 Test items

All donors had been tested negative SARS-CoV-2, as well as for hepatitis B virus, hepatitis C virus, HIV, and syphilis at the time of blood donation. The novel coronavirus serum/plasma IgG antibody was found to be active and still positive after 160-fold dilution according to the reagent specification; or novel coronavirus serum/plasma total antibody was found to be reactive by qualitative test and was still positive after 320-fold dilution according to the reagent specification. Enzyme-linked immunosorbent assay (ELISA) should be used for the detection, and adequate evaluation or reference to the evaluation data shall be made to ensure the quality of the detection.

a. Available at

<http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2.shtml>

b. Available at

<http://www.nhc.gov.cn/zyygj/s7658/202003/61d608a7e8bf49fca418a6074c2bf5a2.shtml>

2.23 Convalescent plasma transfusion

According to the principle of cross compatibility, the eligible patients received the transfusion of ABO-compatible convalescent plasma. The first 15 minutes of infusion should be given at a slow speed, and the occurrence of adverse reactions to blood transfusion should be closely monitored. If there is no adverse reaction, the clinician will adjust the infusion speed according to the patient's condition. Infusion dose was 200ml for each cycle.

2.3 Data sources and Statistical Analysis

Clinical information of the 3 cases was reviewed of the hospital compute system and included the following: epidemiological and demographic data, exposure history, clinical and laboratory examination, radiological characteristics and outcome disease. Continuous variables were presented as the median and IQR. Graphs were plotted using GraphPad Prism 7.0. Statistical software used included SPSS 22.0.

3. Results

A total number of three patients (one male and two females; age range, 57-65years) were treated with convalescent plasma during the study. Two of three had preexisting medical conditions. None of the patients was affected by cluster infection and exposure to Huanan Seafood Wholesale Market. General characteristics of patients in the study were listed in Table 1. The most common symptoms were fever (three cases, 3/3) and cough (two cases, 2/3). All the three patients were without dyspnea or hypoxemia. Two patients had underlying chronic diseases, including cerebrovascular diseases, diabetes and hypertension. All patients were treated with a combination of two antiviral drugs (lopinavir/ritonavir or arbidol combined with IFN- α), whereas none of the patients were given glucocorticoids (Table 2). Antibacterial treatment was used when bacterial infections had been confirmed, and then only one patient received ceftriaxone sodium (i.v.) (2.0g qd). Hydroxychloroquine or chloroquine had been administered to two patients. Throat swab nucleic acid test of most patients (2/3) became negative for the novel coronavirus within 3 days after the transfusion (Table 3).

Table 1. Clinical characteristics of patients receiving CP transfusion

Patient NO	1	2	3
Sex	F	M	F
Age ^y	65	57	59
Smoking	No	No	No
Blood type	A;Rh(D)-	B;Rh(D)+	B;Rh(D)+
Clinical classification	Severe	Severe	Severe
Day of admission from onset	8	5	3
Day of CP from symptom onset	10	7	10
Clustering infection	No	No	No
Coexisting chronic diseases	Hypertension, diabetes	Hypertension, cerebral infarction	Pulmonary nodules
Principal symptoms	Cough, fever	Cough, sputum production, fever	Cough, dry pharynx
Abbreviations CP=convalescent plasma			

Table2. Other treatments of patients receiving CP transfusion

Patient NO	1	2	3
Antiviral treatment	Arbidol 0.2 g q8h po. IFN- α 500MIU qd inh. Lopinavir/ritonavir two tablets po. bid	Arbidol 0.2 g q8h po. IFN- α 500MIU qd inh.	Arbidol 0.2 g q8h po. IFN- α 500MIU qd inh.
Antibiotic or antifungal treatment	None	None	Ceftriaxone sodium 2.0 qd i.v.
Corticosteroids treatment	None	None	None
Hydroxychloroquine or chloroquine	None	Chloroquine 0.5g bid po.	Hydroxychloroquine 0.2g bid po.
Oxygen support	Low-flow nasal cannula	Low-flow nasal cannula	Low-flow nasal cannula

Table 3. The results of throat swab SARS-CoV-2 real-time PCR before and after CP

Patient NO	1	2	3
On admission to hospital	positive	positive	positive
Just before plasma transfusion	positive	positive	positive
Day 1 post transfusion	positive	positive	positive
Day 3 post transfusion	negative	negative.	positive
Day 5post transfusion	negative	negative	positive
Day 6 post transfusion	none	negative	positive
Day 7post transfusion	none	none	negative
Day 9 post transfusion	none	none	negative

After the treatment, the values of Lymphocyte counts of all the cases, which was an important index for prognosis in COVID-19 tended to be improved after CP transfusion. The values of the inflammatory biomarkers CRP, IL-6 of all the patients decreased (Figure. 1). Several parameters tended to improve as compared to pre-transfusion, including increased lymphocyte counts ($0.97 \times 10^9/L$ vs. $1.08 \times 10^9/L$) and decreased IL-6 (41.34 pg/ml vs. 13.83 pg/ml). The level of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were slightly elevated in 2 patients. After the treatment of convalescent plasma, the myocardial zymogram-troponin T—which is the reliable marker of myocardial necrosis—was reduced greatly. All patients had differing degrees of increase in D-dimmer level.

All patients showed varying degrees of absorption in the density of bilateral infiltration on CT imaging after CP transfusion within 4 days—and showed remarkable absorption on image after CP transfusion within 12 days. The representative chest CT images of the three patients are shown on Fig 1-3.

4. Discussion

The study of the passive immunizations for the prevention and treatment of human infectious diseases began in the 20th century[14]. To date, there is no specific therapeutics for SARS-CoV-2 infection, and therefore administration of convalescent plasma can be still an important treatment[15]. Previous evidence has proven that the use of convalescent plasma transfusion in the treatment of various infectious, especially in coronavirus infectious[12, 16].

There were such three cases in our study—all of which were severe patients with COVID-19 and treated with convalescent plasma. Case One had many underlying diseases heavy, and the other two cases rapidly progressed after being admitted to hospital. Especially in case 3 that pulmonary lesion

progression exceeded 50% in a short period of time. However, after the treatment of convalescent plasma, the conditions of the 3 patients were well controlled in 3 days. The inflammatory indicators, including IL-6, CRP and blood routine examination were monitored regularly. Both clinical assessment and laboratory variables, the symptoms were significantly improved and lung lesions were significantly absorbed within 2 weeks.

However, to date, there are no proven options for prophylaxis for those who have been exposed to SARS-CoV-2, nor therapy for those who develop COVID-19[17]. Previous studies have reported the use of convalescent plasma transfusion as the treatment for COVID-19 Patients[18-22]. Similar to those, our study suggests that convalescent plasma from patients who have recovered from COVID-19 infection might be a promising treatment to treat patients without causing any severe adverse effects. The possible explanations for the efficacy of convalescent plasma therapy is that the antibodies from convalescent plasma might not only limited to free viral clearance and blocking new infection, but also included acceleration of infected cell clearance[23, 24]. The patient usually develops a primary immune response by days 10-14, so using the convalescent plasma at the early stage of disease could be more effective. The time from onset of illness to convalescent plasma transfusion was within 10 days, and this might be one of the contributions to the good prognosis.

The current guidelines emphasizes that systematic corticosteroids should not be given routinely for the treatment of COVID-19[25], however, whether to use the corticosteroids for COVID-19 patients remains a controversial topic[26]. The nonuse of corticosteroids is the major different from the current study[18-20, 22, 27].

Although it was reported that dexamethasone could cut deaths by one-third among patients critically ill with COVID-19[28], routinely use for the treatment of COVID-19 should need much more evidence. From our results, systematic corticosteroids for non-critical cases are not a must. Considering that we observed differing degrees of increase in D-dimer levels in all patients therefore anticoagulation is necessary for severe patients with COVID-19 given the state of hypercoagulability.

Conclusions

Convalescent plasma shows a promising therapeutic effect without corticosteroids and low risk in the treatment of severe COVID-19 patients. Using the convalescent plasma at the early stage of disease could be more effective. Anticoagulation is necessary for severe patients with COVID-19 given the state of hypercoagulability. However, given the small sample size and limited study design, naturally these results should be taken with a grain of salt until replicated by other further investigation in larger well-controlled trials.

Limitations

There are several limitations in this study. First, this was a retrospective analysis that had small case series and included no controls. Second, similar to most Chinese hospital, we lack the ability to detect the viral loads that may correlate with disease severity and progression. Third, in the current study, all patients received antiviral agents, including interferon and lopinavir/ritonavir, during and following convalescent plasma treatment, which also may have contributed to the viral clearance observed. Fifth, evidentially should need to further study in larger well-controlled trials.

Abbreviations

COVID-19:coronavirus disease 2019

SARS-CoV-2:severe acute respiratory syndrome coronavirus-2

WHO :World Health Organization

CFDA :China Food and Drug Administration

FDA :U.S. Food and Drug Administration

ALT :alanine aminotransferase

AST : aspartate aminotransferase

Declarations

Availability of data and materials

The datasets used or analyzed in the study are available from the corresponding author on reasonable request.

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Author contributions

BSX and GXL and LZC conceived and designed the study. DW, XLZ and SJS and FHL took care of the patient and contributed to the acquisition of data. BSX and GXL and LZC contributed to analysis and interpretation of data. DW, XLZ and SJS and FHL wrote this paper. DW, XLZ and SJS and FHL contributed equally to this work.

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Ethics declarations

Ethical Approval and Consent to participate

The study was reviewed and approved by the medical ethics committees of Fuzhou Pulmonary Hospital of Fujian province, and each participant gave written informed consent.

Consent for publication

Not applicable.

Conflict of interests

We declare no competing interests.

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Figures

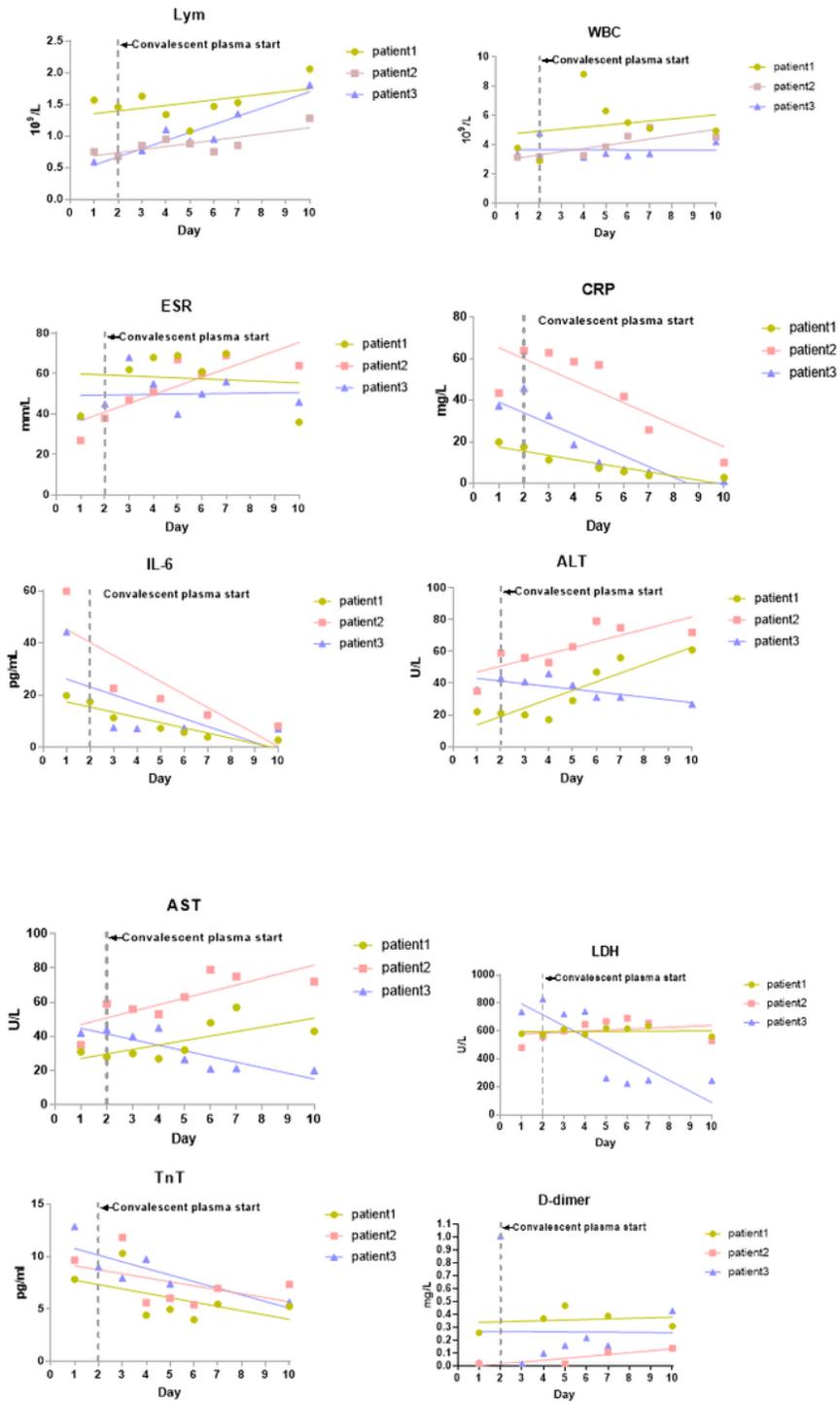


Figure 1

Changes of laboratory parameters in patients receiving Convalescent Plasma.

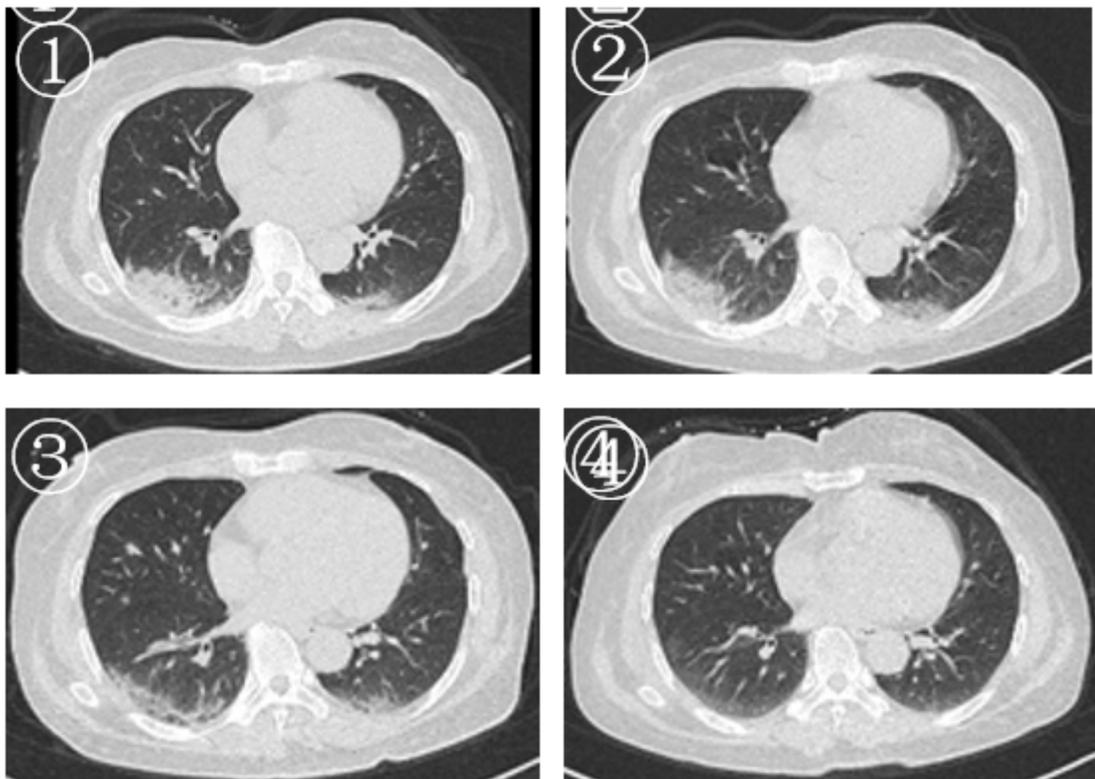


Figure 2

Chest CTs of NO.1 patient. ① Chest CT obtained on March 21 before CP transfusion showed ground-glass opacity with uneven density involving the multi-lobar segments of both lungs. The lesion was close to the pleura. ②-④ Chest CT Image taken on March 25 (Day 4 post transfusion), March 31 (Day 10 post transfusion), April 30 (Day 40 post transfusion), respectively, which showed the absorption of bilateral ground-glass opacity after CP transfusion. Only a few lesions left.

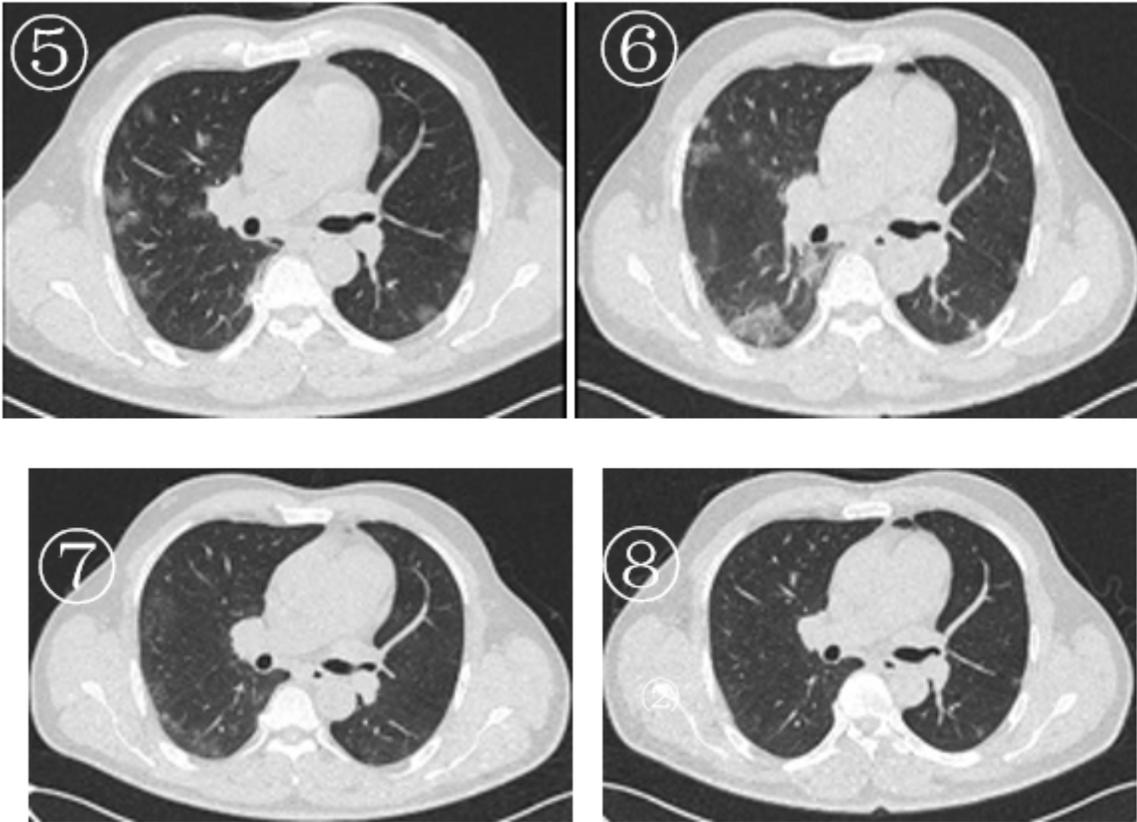


Figure 3

Chest CTs of NO.2 patient. ☒Chest CT obtained on March 21 before CP transfusion showed ground-glass opacity with uneven density involving the multi-lobal segments of both lungs,which was rapidly progress. ☒☒Chest CT Image taken on March 25(Day 4 post transfusion), April 06 (Day 12 post transfusion), April 20(Day 26 post transfusion) , respectively, which showed the absorption of bilateral ground-glass opacity after CP transfusion. Almost complete absorption.

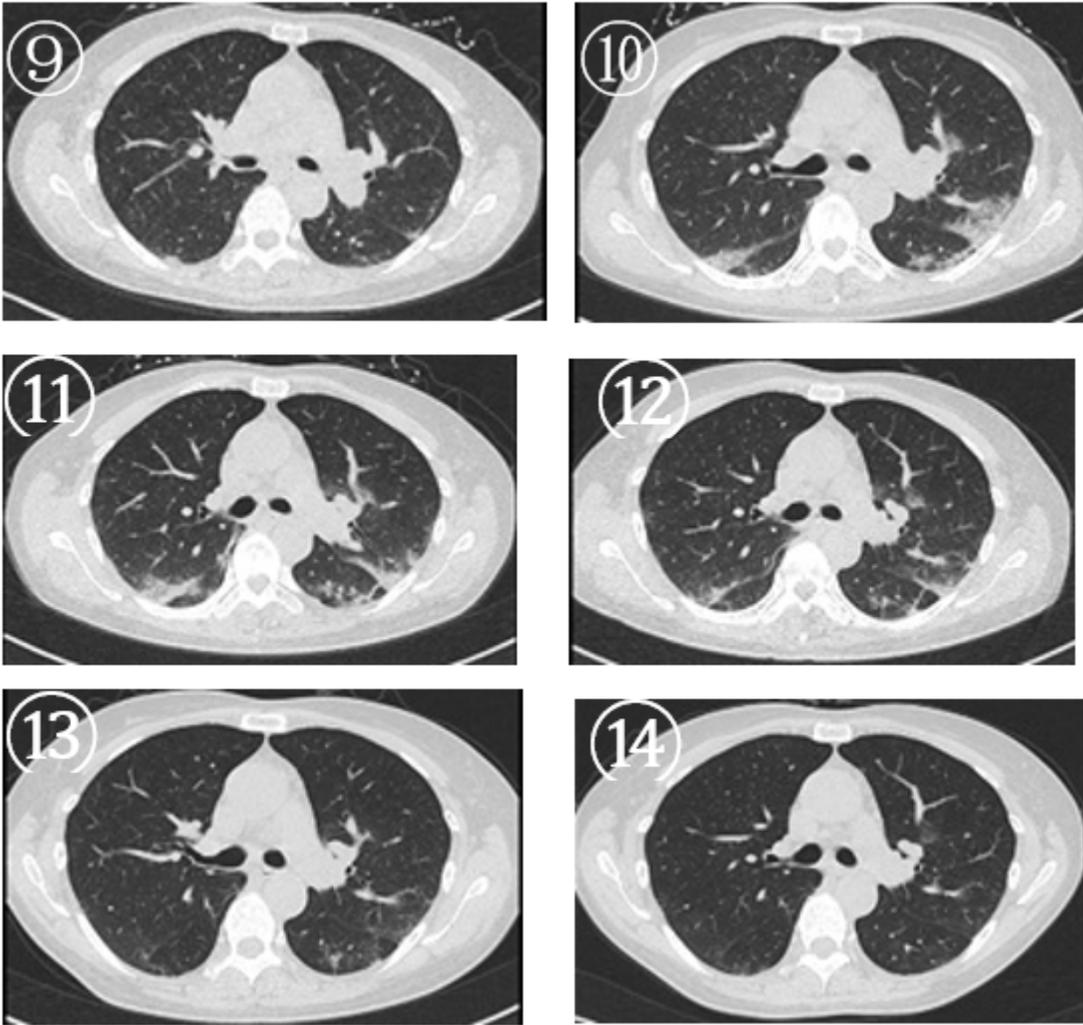


Figure 4

Chest CTs of NO.3 patient. ☒-☒Chest CT Image taken on March 22, March 25, March 28 , respectively, which showed the consolidation lesions rapidly progressed. The NO.3 patient received the convalescence plasma treatment on March 28. ☒-☒Chest CT Image taken on March 31(Day 4 post transfusion), April 06 (Day 10 post transfusion), April 19 (Day 23 post transfusion), respectively, this was showing the absorption of bilateral consolidation opacity after CP transfusion. Almost complete absorption on April19.