Published online 2021 September 20 **Original Article**

# Impact of Time and Mechanical Ventilation on Convalescent Plasma in Severe/Critically Ill COVID-19 Patients

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**Received** 2021 February 16; **Revised** 2021 May 17; **Accepted** 2021 June 16.

**Abstract**

**Background:** Convalescent plasma (CP) transfusion is one of the suggested treatments for Coronavirus disease 2019 (COVID-19) especially in critically ill patients.

**Objectives:** This study aimed to investigate the efficacy and safety of CP transfusion were investigated in severe/critically ill COVID-19 patients.

**Methods:** This study was performed on 50 consecutive COVID-19 patients with severe/critically ill disease. Severe disease was defined as having at least one of the following symptoms: shortness of breath, respiratory frequency ≥ 20/min, blood oxygen saturation ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, lung infiltrates > 50% within the last 24-48 h. Critically ill disease was identified by intensive care unit admission, respiratory failure, septic shock, or multiple organ dysfunction or failure. Primary outcomes included the safety of CP transfusion, 14-day and 30-day survival rate, and change in lung computed tomography (CT) scan score. Several other clinical and laboratory features were evaluated as the secondary outcomes.

**Results:** Based on the results, 21 out of 50 consecutive patients were on mechanical ventilation at the time of CP transfusion. In total, 32 patients (64%) survived 30 days after CP transfusion. The survival rates were 74% and 44% in patients who received CP < 7 and ≥ 7 days after admission, respectively. While 92% of patients without mechanical ventilation survived, the survival rate of patients on mechanical ventilation was 29%. Moreover, the CT scan score and some other clinical features were improved in the group that received CP transfusion, and no adverse effects were observed.

**Conclusion:** The CP transfusion is a safe and effective treatment in severe/critically ill COVID-19 patients. The best outcome can be achieved in patients who are not on mechanical ventilation, especially early in the disease course.

*Keywords:* Convalescent plasma; COVID-19 patients; Critically Ill; Mechanical ventilation

## 1. Background

On 31 December 2019, pneumonia of unknown cause was reported in Wuhan, China. The pneumonia was found to have been triggered by the SARS-CoV-2 and was named Corona Virus Disease 2019 (COVID-19). Till April 28, 2020, the virus spread to 213 countries, infected nearly three million people, and resulted in 202,597 global deaths (1). Iran reported its first two cases on February 19, 2020, in the city of Qom and later in several other cities and the whole country (2,3). By the end of April 2020, more than 90,000 positive cases and nearly 6000 deaths were reported in Iran.

Global efforts have not yet resulted in any definitive treatment or vaccine for the disease. However, some reports have shown the efficacy of using convalescent plasma (CP) in the treatment of COVID-19 patients (4,5). This method is based on the theory that CP transfusion can neutralize the pathogen and eventually lead to its eradication from the blood circulation through administering

pathogen-specific antibodies (6). The Food and Drug Administration has approved the use of convalescent plasma to treat critically ill COVID-19 patients (7). World health organization also had previously recommended this method as an empirical treatment during the Ebola outbreak (8).

In 2006, a meta-analysis of 1703 patients concluded that convalescent human H5N1 plasma could be an effective treatment for patients with Spanish influenza pneumonia (9). Another meta-analysis has been performed on 32 studies exploring the effectiveness of convalescent plasma in the treatment of severe acute respiratory infections.

## 2. Objectives

In the aforementioned study, consistent evidence has also been found for the reduction of mortality in patients, especially when the transfusion is administrated shortly after the onset of the disease (10). Amidst the shortage of robust evidence regarding the use of this treatment in COVID-19 patients, the present study aimed to explore the efficacy of administrating convalescent plasma to 50 critically ill COVID-19 patients. To the best of our knowledge, this is the most comprehensive series reporting the use of CP in COVID-19 patients.

## 3. Methods

This study was conducted at Baqiyatallah Hospital, Tehran, Iran from March 14 to April 24, 2020, on 50 patients infected with COVID-19. This research was approved by the Ethics Committee of the Iranian Blood Transfusion Organization and registered in the Iranian Registry of Clinical Trials (ethics code: IRCT20200325046860N1).

### *3.1. Donors*

The donors were selected from clinically- and laboratory-confirmed recovered patients of COVID-19 who were between 18 and 60 years old. Selected donors had negative quantitative real-time polymerase chain reaction (qRT-PCR) for COVID-19 and other standard virology tests at the time of donation while their test results had been previously positive by qRT-PCR for COVID-19. To prevent transfusion-related acute lung injury, female donors with a history of pregnancy were excluded; therefore, only male donors were included in the study. All donors had to lack any remaining symptoms for at least 14 days prior to donation. They were interviewed and examined by qualified physicians and were asked to fill out the related donation and consent forms.

Eligible donors were tested by the semi-quantitative enzyme-linked immunosorbent assay antibody identification test for COVID-19 (Sina Teb Co., Ltd) using a method similar to the protocol described by Duan et al. (5). Donors with antibody titer cut-off index higher than 1.1 were invited to donate 500 cc of plasma. The donated plasmas were sampled to perform routine screening tests for hepatitis B and C virus, human immunodeficiency virus, and syphilis spirochete. The donated plasmas that met the eligibility criteria for transfusion were sent to the hospital blood banks.

### *3.2. Recipients*

Recipients who met the inclusion criteria were selected by related physicians. After filling out the consent forms by recipients or authorized family members, the request of releasing CP was sent to the hospital blood bank. Plasma transfusion to the recipient was performed according to the available standards, such as conformity of blood groups. The first 500 cc (one unit) of plasma was administrated within 4 h, and if the patient did not show any sign of improvement after 24 h, another unit of plasma was administrated based on the decision of the responsible physician. All clinical and paraclinical data were recorded and transferred to the researcher. The follow-up of patients during hospitalization was performed by a monitoring table filled out every 12 h. Patients were also followed up weekly till one month after receiving CP.

### *3.3. Inclusion and exclusion criteria*

Patients with confirmed COVID-19 by qRT-PCR test, abnormal lung computed tomography (CT) scan, and severe or critically ill disease were included in the study. Severe disease was defined as having one or more of the following symptoms: shortness of breath (dyspnea), respiratory frequency of ≥ 20/min, blood oxygen saturation of ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio of < 300, and lung infiltrates of > 50% within the last 24-48 h. The patients were considered critically ill if they had at least one of the following symptoms: intensive care unit (ICU) admission, respiratory failure, septic shock, or multiple organ dysfunction or failure. Patients younger than 18 years old and patients with any suspicious history of allergy to plasma and ingredients were excluded from the study.

### *3.4. Outcome measures and definitions*

Primary outcomes included the safety of CP transfusion, 14-day and 30-day survival (from the date of receiving CP), and change in lung CT scan score. A lung CT scoring system was assigned to evaluate the lung involvement. The CT scan was assessed for ground-glass opacity, crazy paving, or consolidation in both lung fields. Each of the five lung lobes was scored from 0 to 5 based on the percentage of lobar involvement as follows: no involvement (0), <5% (1), 5-25% (2), 26%-49% (3), 50%-75% (4), >75% (5). The total CT score was calculated by adding five lobar scores and ranged from 0 (no involvement) to 25 (maximum involvement) (11). Secondary outcomes

included C-reactive protein (CRP), body temperature, lymphocyte count, sequential organ failure assessment (SOFA) score, systolic blood pressure (sBP), and diastolic blood pressure (dBP).

*3.5. Statistical analysis*

Continuous variables were reported as the mean and standard deviation or the median and interquartile range (IQR). The student's t-test was used to compare the variables, and the Kaplan-Meier survival curve was used to evaluate the survival rate of the patients. The analysis was performed in SPSS statistical software (version 24.0).

## 4. Results

*4.1. Baseline Features*

In total, 50 patients (36 males and 14 females) categorized as severe and/or critically ill were included in the study. The patients were between 25 and 85 years old (mean age: 51±13.4), and their blood groups were O (36%), B (32%), A (24%), and AB (8%). It should be mentioned that 42 patients received at least one type of anti-viral drugs, and eight patients received antibiotics. In this study, 32 patients (64%) had at least one co-morbidity, such as pregnancy, chemical injury, cancer, diabetes mellitus, hypertension, kidney transplantation, or asthma. Furthermore, 37 (74%) patients had tachypnea at the time of admission and 21 (42%) patients were on mechanical ventilation with mean SpO2 80.6±9.7 (53-92) prior to CP transfusion.

*4.2. Effects of convalescent plasma transfusion*

*4.2.1. Adverse effects of CP transfusion*

No adverse effect was observed in donors or recipients during the study.

*4.2.2. Clinical and paraclinical improvement*

The main clinical characteristics of patients at the time of admission and after CP transfusion are shown in Table 1. The mean length of ICU admission of patients till CP transfusion was 6.9±5.4 (range: 0-25) days. A significant improvement was found in the CT scan score which increased from 19.1±3.7 to 12.1±6.7 (P<0.0001) (Figure 1 and 2). The respiratory rate also increased from 23±5.7 to 18.6±2.6 (P=0.03).

**Table 1.** Features of COVID-19 patients at the time of admission and after the infusion of convalescent plasma. CP: convalescent plasma, CRP: C-reactive protein, IQR: interquartile range, sBP: systolic blood pressure, dBP: diastolic blood pressure

| Clinical or paraclinical parameter | On admission | Post-CP administration |
|---|---|---|
| **Mean body temperature (range) (C°)** | 36.9±0.6 (35.7-39.5) | 36.6±0.5 (35.4-37.2) |
| **Mean computerized tomography scan score (range) *** | 19.2±3.7 (8-25) | 12.1±6.7 (0-25) |
| **Mean lymphocyte count (range)** | 900.5±395.6 (116-2092) | 1009.2±683.8 (165-3104) |
| **Median CRP (IQR) (mg/L)** | 21.1 (13.8-31.9) | 11.6 (8.6-29.4) |
| **Median creatinine (IQR) (mg/dl)** | 1 (0.9-1.2) | 0.9 (0.7-1.2) |
| **Mean respiratory rate (range) *** | 23±5.7 (16-40) | 18.6±2.6 (11-24) |
| **Mean sBP (range) (mmHg)** | 126.1±19.2 (90-196) | 123.4±13.3 (100-135) |
| **Mean dBP (range) (mmHg)** | 75.4±10.7 (50-99) | 74.9±7.1 (68-91) |

*There was a statistically significant difference only in the computerized tomography scan score (P<0.0001) and respiratory rate (P=0.03).

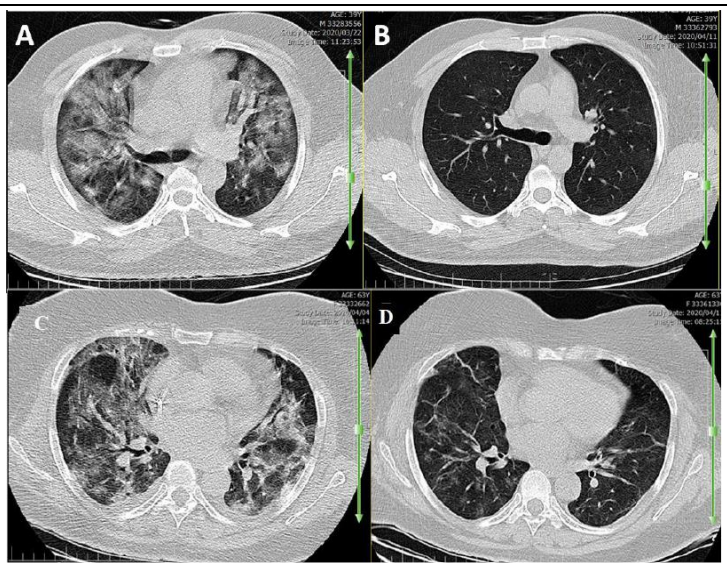


**Figure 1.** Axial lung computerized tomography scan without contrast of a 39-year-old male before plasma therapy shows diffuse ground glass and consolidative opacities in both lungs compatible with severe COVID-19 pneumonia (A) and a dramatic response and complete resolution of opacities 18 days after convalescent plasma transfusion (B). Axial lung computerized tomography scan without contrast in a 63-year-old female before plasma therapy shows diffuse ground glass and consolidative opacities and bilateral pleural effusion compatible with severe COVID-19 pneumonia (C) and a dramatic response to treatment with very faint residual ground opacities seven days after convalescent plasma transfusion (D).

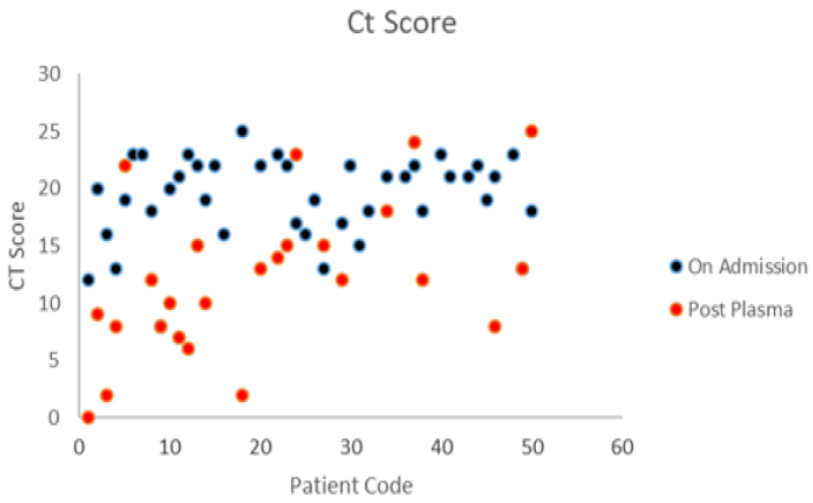


**Figure 2.** Scatter plot of lung computerized tomography score before and after convalescent plasma transfusion shows decreased lung computerized tomography score after treatment

Median SOFA score was 3 (IQR, 2-4) and 2.5 (IQR, 1-8) before and after CP transfusion, respectively. The laboratory indexes also improved after CP transfusion, particularly CRP and lymphocyte count.

*4.2.3. Survival, treatment time, and mechanical ventilation*

In total, 36 (72%) and 32 (64%) patients survived 14 and 30 days after CP transfusion, respectively. The survival rate was further investigated by categorization of the patients based on the time of CP transfusion and mechanical ventilation (Table 2). Figure 3 shows the Kaplan-Meier survival curve comparing the survival of patients with and without mechanical ventilation (Figure 3a), and also patients receiving CP before or after seven days of admission (Figure 3b).

**Table 2.** Survival rate of patients in the whole group and four subgroups

| Survival | Survived patients 14 days after CP transfusion No. (%) | Survived patients 30 days after CP transfusion No. (%) |
|---|---|---|
| **Whole group** | 36 (72%) | 32 (64%) |
| **CP transfusion<7 days after admission (n=34)** | 28 (82%) | 25 (74%) |
| **CP transfusion≥7 days after admission (n=16)** | 8 (50%) | 7 (44%) |
| **Patients on mechanical ventilation (n=21)** | 11 (52%) | 6 (29%) |
| **Patients without mechanical ventilation (n=39)** | 36 (92%) | 36 (92%) |

CP: convalescent plasma

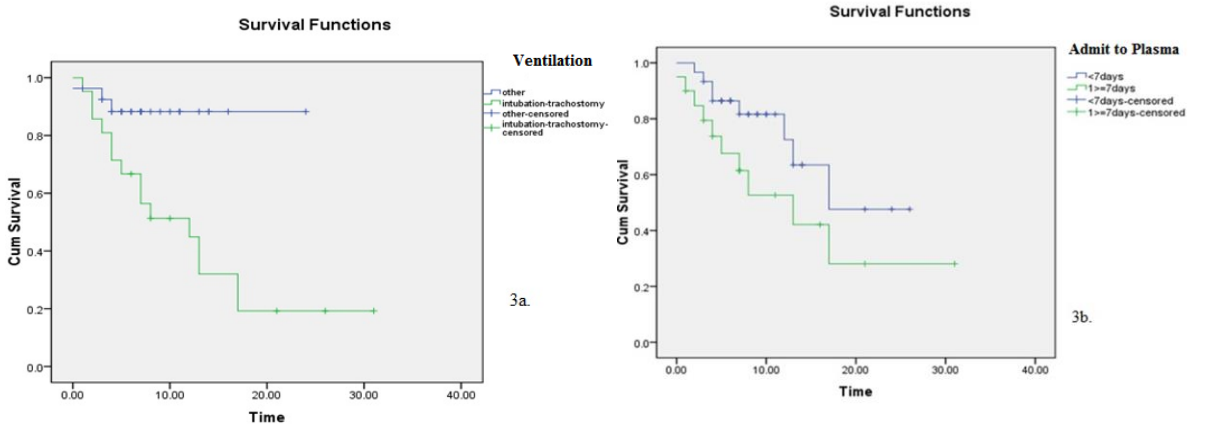


**Figure 3.** Kaplan-Meier survival curve comparing survival of patients with and without mechanical ventilation (Figure 3a) and patients receiving convalescent plasma before or after seven days of admission (Figure 3b)

## 5. Discussion

In this study, it was found that administration of CP to COVID-19 critically ill patients resulted in the improvement of their clinical symptoms and lung CT scan score, no adverse effects, and a high survival

rate. These results were especially observed when the transfusion was performed before the seventh day of their hospitalization on patients who were not on mechanical ventilation. Decreased C-reactive protein and improved lung CT scan score following CP transfusion to the participants indicated the reduction of inflammation and pulmonary tissue injury following the transfusion.

Based on the findings, CP transfusion is a safe treatment without any significant adverse effects. Moreover, the results are consistent with those of two other studies conducted in China exploring the efficacy of the use of CP in COVID-19 patients. In both studies, the patients experienced improved clinical symptoms and laboratory and radiological parameters after CP transfusion [3, 4]. Moreover, CP therapy in two COVID-19 patients with acute respiratory distress syndrome resulted in subsidization of fever and oxygen demand (12). Possible mechanisms of action of CP transfusion in COVID-19 include direct neutralization of the virus, control of an overactive immune system, and immunomodulation of a hypercoagulable state (13).

While the 30-day survival rate was 64% in the whole group, the results showed that the earlier CP transfusion would result in better survival. In other words, late transfusion would reduce its efficacy. This finding is consistent with those of previous studies which indicated that patients who received CP transfusion earlier had a better outcome, compared to those who received plasma later. In a study conducted in 2004 on 80 SARS patients who received CP, a higher rate of discharge on day 22 was observed in patients treated before day 14 of illness, compared to others (14).

A meta-analysis of 32 studies on CP treatment in SARS patients also confirmed the consistent evidence of reduced mortality, especially when CP was administered early after symptom onset (9). Moreover, the survival rate was much higher in patients who were not on mechanical ventilation prior to CP transfusion. Accordingly, 15 out of 18 patients who died during the study were on ventilation prior to CP transfusion. One month after CP transfusion, 92% and 28% of patients with and without mechanical ventilation survived, respectively.

In their study, Yang et al. described the clinical course and outcome of critically ill patients with COVID-19 (15). They found that 38.5% of critically ill patients survived till day 28. More precisely, 7 out of 37 (18.9%) patients on mechanical ventilation and 13 out of 15 (86.7%) patients without mechanical ventilation survived till day 28. Their results showed a much worse prognosis in patients on mechanical ventilation, compared to that of the present study. On the other hand, critically ill patients who received CP transfusion in the present study had a better survival rate in the whole group, and also in both patients with and without mechanical ventilation.

In this study, no significant improvement was found in the temperatures and SOFA scores of the participants. The main reason might be related to having a low SOFA score and surprisingly normal mean body temperature prior to CP transfusion. Furthermore, the SOFA score might not be a precise indicator in COVID-19 patients. Tang et al. compared acute respiratory distress syndrome patients infected with COVID-19 or H1N1 (16). They found that 31.5% and 13.3% of COVID-19 and H1N1 patients had sepsis at the time of admission, respectively. Nevertheless, COVID-19 patients had a significantly lower median SOFA score compared to H1N1 patients (2 vs. 5). It might be assumed that COVID-19 patients have severe pulmonary involvement at the time of admission, while other systems are still not affected or just mildly involved. Hence, the SOFA score should be used and interpreted in COVID-19 patients more cautiously.

One of the limitations of the present study was that it was not a randomized clinical trial, and the outcomes were not compared to a control group. Given the difficult situation of COVID-19 patients, it might not be ethically possible to easily run a clinical trial in critically ill patients. Another limitation was the use of various treatment regimens before CP transfusion, which was inevitable. The strength of this study was reporting the most comprehensive series of critically ill COVID-19 patients which enabled us to evaluate the survival rate of different subgroups based on the time of CP transfusion and mechanical ventilation.

## 6. Conclusion

The results indicated that CP treatment can be considered a safe and effective therapy for COVID-19 patients with critically ill/severe disease. Based on our findings, the time of CP administration is a key factor determining the efficacy of CP transfusion, the earlier CP transfusion is applied, the better outcomes will be achieved. Moreover, the need for mechanical ventilation prior to CP transfusion is an important prognostic factor impacting the final outcome.

## Acknowledgments

The authors would like to acknowledge all healthcare workers involved in the diagnosis and treatment of patients in Baqiyatallah Hospital affiliated with Baqiyatallah University of Medical Sciences, Tehran, Iran.

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