

The Use of Convalescent Plasma (CP) Transfusion Therapy in Moderate to Severe COVID-19 Patients: a Single Center Experience in Indonesia

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Coronavirus disease 2019 (COVID-19) was declared as a world pandemic since early 2020. There was no specific antiviral agent that appeared to be active against the virus, and antiviral agent such as remdesivir, favipiravir were in limited supply. We evaluated the use of convalescent plasma (CP) administered as adjunctive treatment to standard of care in moderate to severe COVID-19 patients. We conducted a series of 9 moderate to severe patients of COVID-19 older than 18 years received CP transfusion from 9 recovered donors at a single institution (Sulianti Saroso Infectious Disease Hospital, Jakarta, Indonesia) from January 2021 to June 2021. Out of 9 patients (age range 30-81 years, 6 males and 3 female), and all patients received at least 1 or 2 unit of 200 mL of CP from 9 recovered donors. There were 4 patients (age range 30-71 years, 4 male) that were not treated with antiviral therapy. Of the 9 patients, 2 severe cases were died, while all of moderate cases survived and they were discharged from the hospital (length of stay: 8-22 days). Our experience showed that CP transfusion in moderate COVID-19 patients might provide clinical benefit and it was well-tolerated. However, further development clinical trials with better designs and greater power is needed to evaluate the efficacy and safety of this treatment.

Keywords: Convalescent plasma transfusion; COVID-19; Clinical responses.

Coronavirus disease 2019 (COVID-19) was declared as a world pandemic on March 11, 2020.¹ The manifestation of illness are mild disease to severe respiratory failure that requiring intensive care unit admission.² As of September 24, 2021, it had caused a total of 230,418,451 cases of infection and resulted in 4,724,876 deaths globally.³ Dyspnea, comorbidities, elevated C-reactive protein levels, and desaturation predict mortality in moderate to severely ill COVID-19 patients.⁴

There was no antiviral agent that appeared to be active against the virus, and antiviral agent such as remdesivir, favipiravir were in limited supply.⁵ So far, the incomplete knowledge of COVID-19 is still the biggest challenge and resulting in a lack of effective drugs and adequate treatment strategies.⁶ Treatment guidelines are updated periodically.⁴

Previous studies showed that CP's efficacy was better if used at the early stages of infection,

and it was the most effective when administered before the patients produces a significant amount of Immunoglobulin G (IgG) antibodies.⁶ However the quality control of CP and variation of cases in patients in different studies make it rather difficult to evaluate the efficacy and risk of CP therapy, especially in our country.² Thus, in this study, we evaluated the use of CP administered in moderate to severe patients with COVID-19, such as variation of clinical outcomes, changes of laboratory parameters, the disappearance of SARS-CoV-2, and adverse events.

METHODS

A case series was conducted at sulianti saroso infectious disease hospital, Jakarta, from January 2021 to July 2021. This study was a part of a multicenter clinical trial of The National COVID-19 consortium that approved by the Ethics Committee of the Research and Development Agency, Ministry of Health, Indonesia (No.02.01/2/KE.351/2020) and each patient gave written informed consent.

Patients

This study evaluated 9 patients who were diagnosed with COVID-19 by RT-PCR; aged ≥ 18 years, had moderate to severe of COVID-19. Severe COVID-19 described by signs of severe respiratory such as any of oxygen saturation $< 93\%$ on room air and respiratory rate > 30 breaths/min. Moderate COVID-19 described by signs of pneumonia and as absence of any criteria for severe COVID-19. The 9 patient had signed informed consent form. The patients's serum was cross-checked for potential compatibility with the CP donor before the transfusion, and each patient received at least 1 or 2 unit of 200 ml CP (200 ml – 400 ml) according to the ABO blood types.

Donors

This study recruited 9 the CP donors based on the following criteria: aged 18-60 years that had a history of hospitalization with a diagnosis of COVID-19 and asymptomatic for more than 14 days. The 9 donors were recruited to donate their convalescent plasma after they signed the informed consent form. All donors tested negative of SARS-CoV-2, hepatitis B virus, hepatitis C virus, HIV, and syphilis at the time of blood donation. We used the Abbott Sars-CoV-2 IgG test (Architect)

for detection of specific IgG levels against SARS-CoV-2 by the index (S/C) ≥ 4.5 of serum SARS-CoV-2 IgG.⁸ This immunoassay detected IgG antibodies in plasma and serum samples, which bind to SARS-CoV-2 recombinant antigen coated micro particles.⁷ The signal/cut off index (S/C) for this study was ≥ 4.5 as acceptable to be used for the purpose of qualifying high titer COVID-19 convalescent plasma.^{7,8} Following donation, 2 unit of CP (each unit being approximately 200 mL in volume) was obtained from each donor by aphaeresis.

Clinical Information

The 9 subjects were assessed on day 0 (before CP transfusion), day 1, day 3 and day 7 after CP transfusion such as clinical data, including body temperature, PAO2/FIO2, and Sequential Organ Failure Assessment (SOFA) score (range 0-11); laboratory data, including white blood cell count, blood gas analysis, cycle threshold value (Ct value), inflammatory factors C-reactive protein (CRP), procalcitonin, and interleukin-6; the various treatments; the data of chest X-ray; the clinical information of acute respiratory distress syndrome (ARDS). The other of clinical information such as demographic data, days of admission from symptom onset, any clinical symptom and also any comorbidity obtained from the medical record. We collected the all of data in tabular fashion.

Treatment outcome

We evaluated the use of CP administered in moderate to severe patients with COVID-19, such as variation of clinical outcomes, changes of laboratory parameters, the disappearance of SARS-CoV-2, and adverse events.

RESULTS

A total of 9 COVID-19 patients (age range 30-81 years, 6 males and 3 females) and none were smokers. Figure 1 showed the flowchart resuming of 9 patients. The most common comorbidity were Hypertension. The characteristics of patients who receiving CP transfusion as showed Table 1.

The majority patients were cough and shortness of breath. Radiological results showed the majority of subjects have infiltration. Range of Interval between symptom onset and admission or positive COVID-19 was 1 until 11 days, and interval between symptom onset and plasma

transfusion were 7 until 16 days (table 1).

Moderate and severe cases of COVID-19 were 6 and 3 cases, respectively. After the transfusion of convalescent plasma, two patient of severe cases required intensive ward and mechanical ventilation. Two patients were died, while all of moderate cases were survive and discharged from the hospital (length of stay: 8-22 days). All of 9 patients immediately received therapy standard at the hospital and also received CP transfusion. The range days of receiving CP transfusion on moderate cases and severe cases of COVID-19 were 7-16 days, 8-10 days, respectively. Meanwhile 2 patients of severe cases experienced Transfusion-related acute lung injury (TRALI). Majority patients received steroids therapy. Four patients received remdesivir, one patients received favipiravir, only 4 patients were not treated with antiviral therapy. They did not receive antiviral agents due to limited supply at the time. All of patients were treated with antibiotics, 2 patients got combination such as azithromycin and levofloxacinin. (Table 1)

Nine patients received at least 1 or 2 unit of 200 ml CP transfusion (200 ml – 400 ml) from 9 recovered donors. Table 2 showed Characteristic and antibody titer of convalescent plasma donors. The donors had recovered from SARS-Cov-2

infection and the majority of severities of Covid-19 were moderate to severe cases. Our study screened for the IgG test using an Abbott Sars-CoV-2 IgG test (Architect). Interval between moderate or severe symptom onset and IgG test were 39 – 180 days.

Figure 2 showed that the serial evaluation of overall SOFA scores decreased, except that SOFA scores of 2 patients increased. The range of SOFA Score was 0 until 11 that higher scores indicating more severe illness. The majority of SARS CoV-2 RT PCR cycle threshold (Ct) value after CP transfusion was not defined as undetectable (cut off index CT value in specimen negatif was > 31,5).

DISCUSSION

Our study explored the potential benefit of CP transfusion in 9 of COVID-19 patients consisting of 3 severe cases and 6 moderate cases of COVID-19. Six moderate cases of COVID-19 patients and 1 severe case with 8 – 22 days of length of stay received 1 or 2 unit of CP with a total of 200–400 ml. They were 7 of the survivor patients. The majority of survivor patients had one comorbid disease, meanwhile interval between symptom onset and CP therapy was 7-16 days.

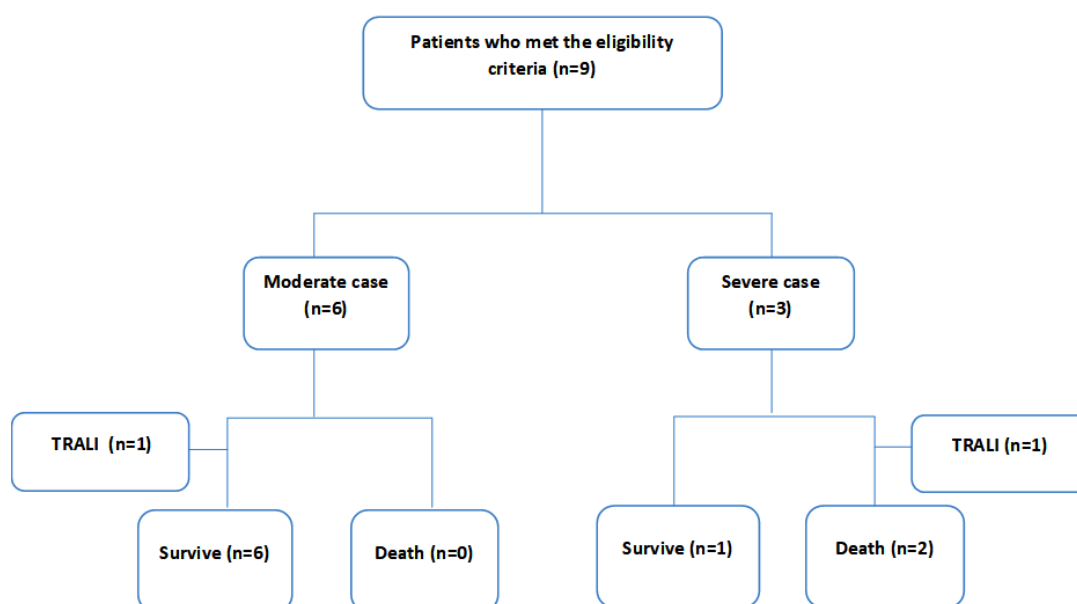


Fig. 1. Flowchart resumng of 9 patients

Table 1. Characteristics of Patients Who Receiving CP Transfusion

Subject	1	2	3	4	5	6	7	8	9
Sex	Female	Male	Male	Female	Female	Male	Male	Male	Male
Age (year)	51	55	81	50	74	42	30	69	71
Blood type	A	A	AB	B	O	B	B	B	A
Smoking	No	No	No	No	No	No	No	No	No
Comorbid number	1	1	2	0	3	1	0	2	3
Comorbidity	Cancer	Hypertension	Elderly, Hypertension	No	Elderly, DM, Hypertension	DM	No	Hypertension	DM, Hypertension
Symptoms	Cough, Shortness of Breath	Cough, Fever	Cough, Shortness of Breath, fever	Cough, Shortness of Breath	Cough, Nausea, vomiting	Cough, Shortness of Breath	Cough, Shortness of Breath, fever	Cough, Shortness of Breath, fever	Cough, Shortness of Breath, fever
Severity of Disease	Severe	Moderate	Severe	Moderate	Moderate	Severe	Moderate	Moderate	Moderate
Pneumonia, baseline	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ARDS, baseline	Yes	No	Yes	No	No	Yes	Yes	Yes	No
Interval between symptom onset and CP transfusion, days	8	8	14	16	12	10	10	14	7
Adverse event	TRALI	No	No	No	No	TRALI	No	No	No
Treatments	DXM	DXM	DXM	DXM	DXM	DXM	DXM	DXM	DXM
Steroid	MPM	AZT	LFX	LFX	AZTLFX	MPM	AZT	AZT	AZTLFX
Antibiotic	RMS	FPV	RMS	RMS	RMS	No	No	No	No
Interval between plasma transfusion and recovery	12	3	No	4	8	14	12	10	4
pneumonia (clinical & radiology), days	No	Yes	No	No	Yes	No	No	Yes	No
Negatif Sars-Cov-2 by per after transfusion	No	Yes	No	No	Yes	No	No	Yes	No
Required Intensive Ward	Yes	No	Yes	No	No	No	No	No	No
Required Mechanical ventilation	Yes	No	Yes	No	No	No	No	No	No
Outcomes	Death	Survive	Death	Survive	Survive	Survive	Survive	Survive	Survive
Length of Stay, days	28	11	11	12	20	20	19	22	8

DM: diabetes mellitus; TRALI: Transfusion-related acute lung injury; DXM: Dexamethasone; MPM: Meropenem; AZT: azithromycin; LFX: levofloxacin; RMS: Remdesivir; FPV: Favipiravir

Table 2. Characteristic and IgG test of CP donors

Subject	1	2	3	4	5	6	7	8	9
Blood type	B	A	B	AB	B	O	B	A	A
Interval between symptom onset and IgG test, days	39	37	72	60	60	60	63	150	180
The history of severity of COVID-19	moderate	severe	moderate	severe	moderate	moderate	moderate	severe	Severe
IgG titer*	index (S/C) ≥ 4.5	index (S/C) ≥ 4.5	index (S/C) ≥ 4.5	index (S/C) ≥ 4.5	index (S/C) ≥ 4.5	index (S/C) ≥ 4.5	index (S/C) ≥ 4.5	index (S/C) ≥ 4.5	index (S/C) ≥ 4.5
Donated plasma volume, ml	400	400	400	400	400	200	400	400	400

*Sars-Cov-2 IgG (Architect) assay

Serial evaluation of overall SOFA scores decreased that it related to clinical improvement, from the beginning to 7 days after CP transfusion. From Dr. Kariadi Hospital, Semarang, Indonesia, a study of total 73 patients received CP transfusion and 38 did not received it. The study showed that CP significantly improved SOFA scores (median, min-max; 4, 4, 2-10 and 2.5, 0-9; < 0.001 , before and after CP transfusion).⁹

The treatment timing is an important factor of effectiveness of CP transfusion.² The passive immune therapy might present by the method of convalescent plasma. One possible mechanism for the efficacy of CP therapy is the high titer and high affinity IgG antibodies which may lead to the clearance of viremia.² Patients develop a primary immune response by days 10 -14, which is followed by virus clearance.² In fact, 4 of survivor patients were not treated with any antiviral agents such as remdesivir or favipiravir due to limited supply at the time. However, only 3 patients achieved Sars-cov-2 negative by PCR after therapy.

Zeng H et al showed that Convalescent Plasma with high (Neutralizing antibody titer 50) NAT50 ($>1:640$) was better than low NAT50 value ($\leq 1:640$) of CP, including shorter negative conservation time of viral RNA, and higher increment of IgG level after CP transfusion, reduce repeated stimulation of the immune system by killer T cell, prevent cytokine storm, and prevent the progression of infection from mild to critical.^{2,6} Neutralizing antibody titer 50 is neutralizing antibody titer which was calculated with the highest dilution of plasma that resulted in a 50% reduction of virus infection.²

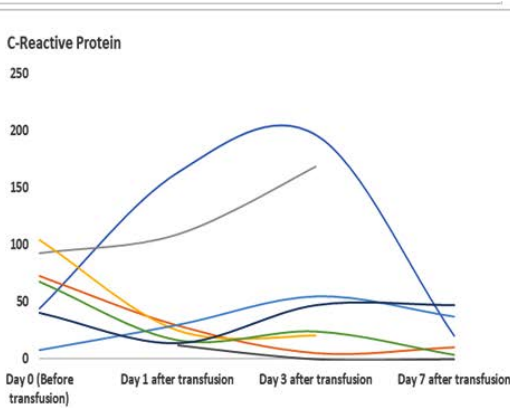
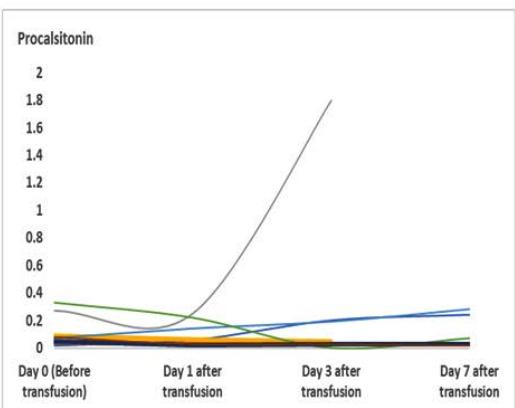
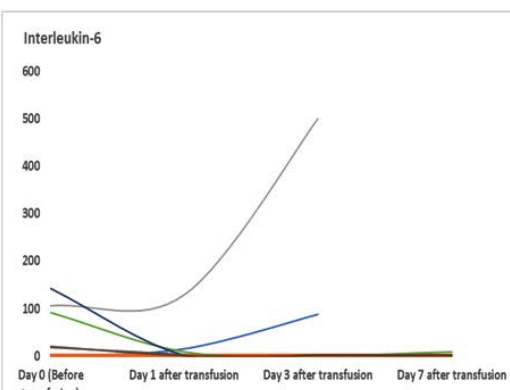
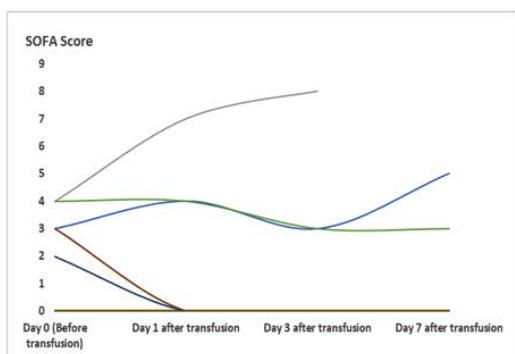
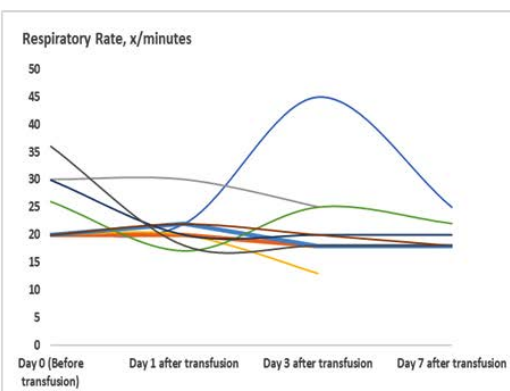
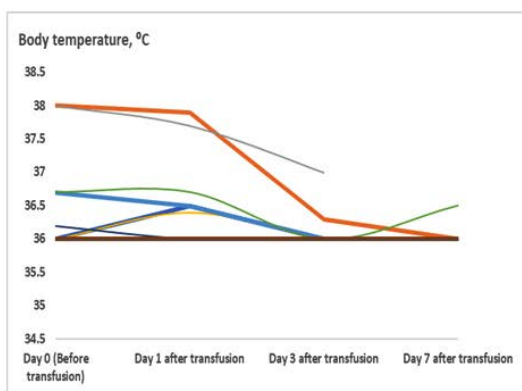
There is evidence that mild patients frequently had a lower level of Sars-CoV-2 specific antibodies than severe patients.² In fact, CP donors who usually recovered from mild infection may not generate adequate protective antibodies, and the minimum threshold of neutralizing antibody titers required to prevent Sars-CoV-2 re-infection are currently unestablished, more studies are needed.^{2,10,11}

In this study, CP donors recovered from moderate to severe of Sars-CoV-2 infection that we assumed that had higher level of Sars-Cov-2 antibodies.¹² Patients met the eligibility criteria of CP donor that the signal/cut off index (S/C) for this

study was ≥ 4.5 . We used the Abbott Sars-CoV-2 qualitative test for detection of specific antibodies (IgG) levels against SARS-CoV-2.⁴ United State Food and Drug administration (FDA) reissued on August 23, 2020, letter of Authorization to add a test acceptable to be used in manufacture of COVID-19 convalescent plasma such as Abbott Sars-Cov-2 IgG test. Plasma donation

must be tested by registered or licensed blood establishments for anti-Sars-Cov-2 antibodies as manufacturing step to determine suitability before release.^{7,12,13}

In this study, one or two doses of CP with a total of 200–400 mL was well tolerated by 7 of survivor patients, while 1 out of 7 patients experienced adverse event such as TRALI, but



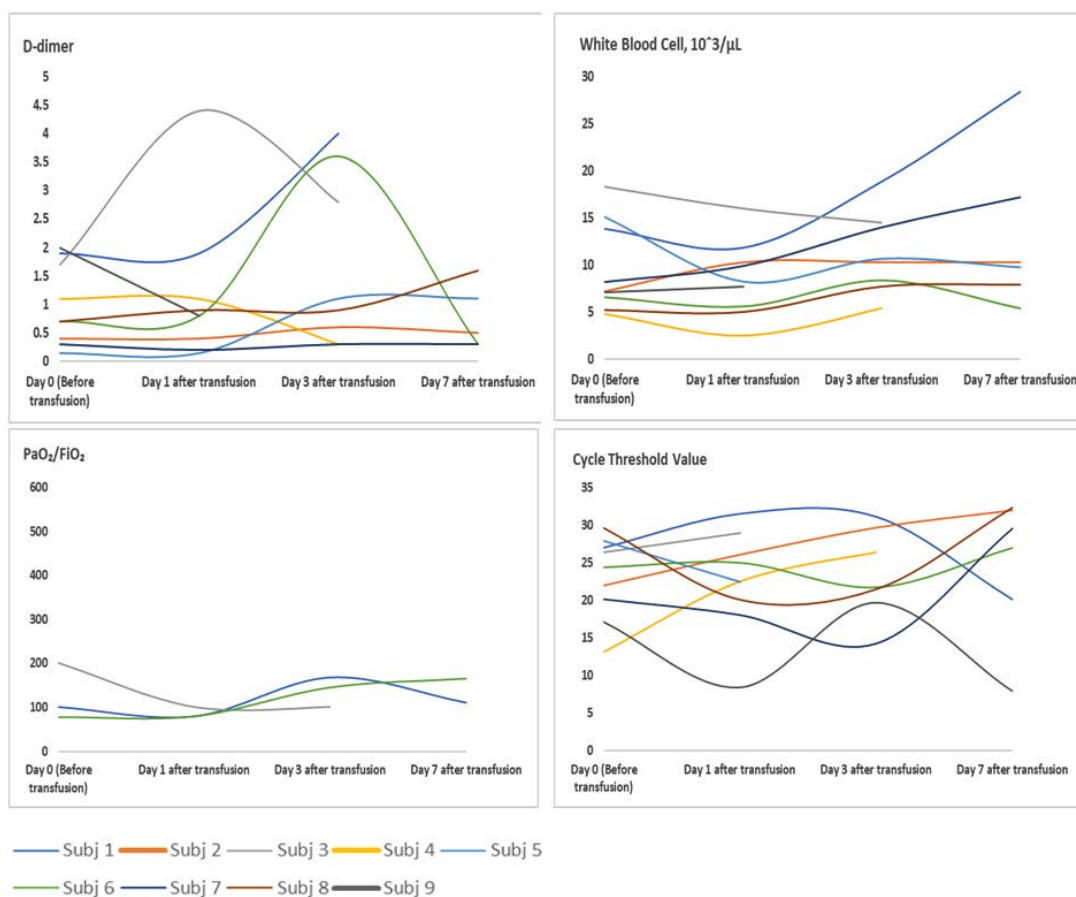


Fig. 2. Comparison of Clinical Characteristic and Laboratory of Patients during Before and After CP Transfusion

the patient recovered and survived. Previous study has reported the safety of convalescent plasma transfusion, meanwhile they could not conclude that a better improvement in patients with moderate cases were solely due to CP treatment.¹ A randomized control trial study mentioned that convalescent plasma seemed to improve resolution of shortness of breath and fatigue in patients with moderate COVID-19 and led to higher negative conversion of SARS-CoV-2 RNA on day 7 post transfusion, but CP was not associated with a reduction in progression to severe COVID-19 or all cause 28 days mortality.¹⁴

In this study, 2 severe cases of COVID-19 patients were died. One of severe case of COVID-19 patient had cancer as a comorbidity, while 1 elderly patient (81 years old) had hypertension. Interval between symptom onset and plasma transfusion

administration of those patients was 8 and 14 days. One patient experienced TRALI at the day after CP transfusion, but she recovered from TRALI, although after 20 days she was died. We assessed that the death could be explained by worsening COVID-19 and other the underlying disease or secondary infection.^{15,16,17} Laboratory data of 2 severe cases showed an increase of CRP, IL-6, WBC, procalcitonin level and Sofa Score on day 3 after CP transfusion. It can be assumed that CP transfusion and other treatment has not been used successfully to treat late stages of infection.^{9,17} According to Eastern Virginia Medical School (EVMS) Critical Care COVID-19 Management Protocol, the course of COVID-19 consists of 4 phases: incubation, symptomatic, early pulmonary phase, and late pulmonary phase.¹⁹

However, we present 2 out of 9 patients

who received standard of care and convalescent plasma and required intensive care and mechanical ventilation. More evidence of the efficacy and safety of CP transfusion are needed.^{11,21,22} Transfusion-Related Acute Lung Injury might be caused by the result of patient and blood component factors which lead to neutrophil activation and endothelial cell damage and capillary leak in the lung causing pulmonary edema and hypo perfusion.²³ A cases of TRALI have been reported after administration of convalescent plasma in patients with COVID-19.²³

There is evidence that dyspnea, the presence of any co morbid disease, elevated CRP levels, and low pulse O₂ saturation levels predict mortality in moderate to severely ill COVID-19 patients.^{4,21} The patients who meet these criteria should be treated and monitored closely and also be aware of the possibility of TRALI.^{4,23}

Our study has several limitations. We present 9 patients that might be difficult to draw scientifically conclusions about beneficial of CP transfusion. Meanwhile, variable of cases and antiviral therapy could have caused a difference in the outcomes. In this study that CP transfusion was administered 7 to 16 days after symptom onset that we should be confirmed about the different timing of CP administration which might be related to different outcomes. Furthermore, randomized control trial with large number of samples and better selection of severity cases is needed to better results.

CONCLUSION

Our experience showed that CP transfusion in moderate COVID-19 patients might provide clinical benefit and it was well-tolerated. However, further development clinical trials with better designs and greater power is needed to evaluate the efficacy and safety of this treatment.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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