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Early high-titer convalescent plasma therapy in patients with moderate and severe COVID-19

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ARTICLE INFO

Keywords:

COVID-19 serotherapy
SARS-CoV-2
Severity of illness index
Antibodies

ABSTRACT

Background and objectives: The use of COVID-19 convalescent plasma (CCP) has been approved by the FDA. We assessed the outcome of patients with moderate and severe COVID-19 following convalescent plasma therapy and the association with variables such as antibody titer in CCP units and transfusion time.

Materials and methods: In this prospective cohort study, 3097 patients with moderate and severe COVID-19 (according to WHO Progression Scale) had heterogeneous demographic and clinical characteristics received plasma with an unknown titer at the transfusion time. Firstly, information about age, sex, blood group, the time interval from hospitalization to CCP transfusion, underlying disease, and antibody titer with the outcome were investigated. Then, multivariate logistic regression and area under the curve (AUC) were performed for the association between disease severity and intubation variables with transfusion time and outcome.

Results: Patients with younger age receiving CCP in the first five days of hospitalization had lower mortality ($P < 0.0001$). Moreover, patients without the underlying disease had lower mortality ($P < 0.001$). The mortality rate also decreased in severe patients who were intubated receiving CCP for less than five days ($P < 0.001$). In patients with moderate severity (score less than 5) who received IgG antibody levels above 1:320 in less than five days had lower mortality ($P < 0.0001$).

Conclusion: Our findings suggested that COVID-19 patients with the moderate type of disease receiving CCP units with high antibody titers in the early stages of the disease experienced greater effectiveness of CCP therapy.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), as the causative virus of COVID-19 disease, was first recognized in Wuhan, China, in December 2019. The prevalence of the disease has become a significant global concern. Aside from supportive care, such as oxygenation, specific medications for the disease are still being researched [1]. However, no specific treatment has been shown to be so far effective for SARS-CoV-2 infection. Evidence suggests that convalescent plasma of patients who have recovered from viral infections can be used as a treatment without severe side effects [2]. Convalescent

plasma has been used to treat respiratory infectious diseases for more than a century [3,4].

Various studies have shown that the length of hospital stay in patients receiving COVID-19 convalescent plasma (CCP) was shorter than in non-recipients [5]. Preliminary clinical studies have shown different results of the effectiveness of this product [6–8]. The FDA issued an Emergency Use Authority (EUA) for CCP to treat patients admitted with COVID-19 on August 23rd, 2020 [9], so the administration of COVID-19 hyperimmune plasma was acknowledged. The reason for the effectiveness of CCP may be that antibodies derived from convalescent plasma may suppress viremia [2].

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<https://doi.org/10.1016/j.transci.2021.103321>

Received 28 August 2021; Received in revised form 6 November 2021; Accepted 13 November 2021

Available online 24 November 2021

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Previous studies have shown that plasma with higher antibody titers is likely to affect viral load significantly [10]. It has also been shown that the transfusion of CCP with high titers of antibodies at the early days of disease diagnosis has a better effect on reducing disease mortality [11].

Since the small sample size of studies and the need for further investigations have encouraged us to assess the effect of antibody titer in CCP units, the time interval between admission and CCP transfusion, and the severity of the disease on the patient's outcome.

2. Materials and methods

A prospective cohort study including a total of 3097 COVID-19 patients included in our cohort.

2.1. Participants

CCP unit was collected from recovered COVID-19 patients in 25 collection centers in Iran, and physicians authorized hospitals were eligible to apply for CCP from the Iranian Blood Transfusion Organization (IBTO). All patients who received CCP from November 21th, 2020, to March 20th, 2021 are incorporated in this analysis. Written informed consent was obtained from all patients. Ethical approval was obtained from High Institute for Education and Research in Transfusion Medicine (No: IR.TMI.REC.1399.029). Inclusion/exclusion criteria and indications for hospital referral are outlined in **supplement 1**. All CCP requests were reviewed and accepted based on these criteria. Patients could be given medications based on the guidance of the diagnosis and treatment of COVID-19 disease in the levels of outpatient and inpatient services published by Center for Disease Control and Prevention (CDC) of Iran's Ministry of Health and Medical Education (MOHME) [12]. The grading of COVID-19 disease severity in patients based on WHO rating [13] was defined as **supplement 2**.

2.2. Convalescent plasma donors

IBTO encouraged general Iranian population via a public announcement through the traditional or social media to donate CCP. Donors were identified as an allogeneic donor, and these individuals were considered healthy if a physician who had examined the clinical history and confirmed them at the time of referral. Inclusion criteria for the CCP donation were considered with the following:

- Proven prior COVID-19 infection by real-time PCR
- Elapse of at least 28 days since full recovered

All donors expressed their informed consent to donate CCP. Also, they met the standard criteria for plasma donation, including a negative serological result for hepatitis B, C, HIV, HTLV, and syphilis. The study was approved by High Institute for Education and Research in Transfusion Medicine: IR.TMI.REC.1399.018. The maximum plasma volume was 500 cc, collected from apheresis equipment, MCS+ (HAEMONETICS, USA) and XJC2000 (NIGALE, China).

The prepared CCP was frozen within less than one hour after donation at a temperature of ≤ -30 °C by blast freezer. The titration tube was centrifuged; consequently, the prepared serum was stored in the freezer at -20 °C.

2.3. Determination of IgG level against S1 spike protein and its titration in the donated CCP

Measurement of anti-SARS-CoV-2 IgG antibody levels in CCP units was performed by enzyme-linked immunosorbent assay (ELISA) method via commercial kit (Euroimmun AG, Luebeck, Germany) according to the manufacturer's instruction. Patient samples were diluted at 1:101 in sample buffer for the evaluation of antibody titers. The ratios for this dilution are linearly interpolated based on the results obtained for 1:80

and 1:160. This assay applies a specific calibrator to report the ratio of specimen absorbance divided by calibrator absorbance. A ratio above the cutoff value (≥ 1.1) defines the final interpretation of positivity.

2.4. Treatment protocol

Frozen CCP units were transferred to the hospital and transfused to patients after thawing, according to standard procedure. IgG antibody titers were unknown at the time of CCP administration and were determined solely as these tests became available. CCP units were transfused 10 ml per kg body weight into patients, up to a maximum of 500 cc within 4 h.

2.5. Data collection tools

Data were collected prospectively using predetermined case report forms (**supplement 2**) from 25 collection centers in Iran. All data was meticulously reviewed by a committee consisting of several physicians and experts in IBTO headquarter.

2.6. Outcome measure

The primer outcome was considered as the rate of improvement in patients receiving CCP. Clinical improvement was determined according to one of the criteria mentioned in **supplement 3**. The second outcome assessed in the condition in which the mortality was at the lowest rate. Indeed, we examined the effect of various antibody levels at the several lengths of CCP transfusion time after admission in the recipients with different disease severity on the secondary outcome. Outcome measurements were performed until the patient was discharged or passed away.

2.7. Statistical analysis

The analysis was done using SPSS software version 25. Descriptive statistics [mean, median, standard deviation (SD) and interquartile range (IQR)] were used appropriately. We assessed the independent factors with clinical outcome using logistic regression. After that, Receiver operating characteristic (ROC) analysis was performed and Area under the curve (AUC) was calculated. The results presented as OR with a 95 % confidence interval (CI). We used the Chi-Square test to evaluate the relationship between antibody titer and rapid test results. The Mann-Whitney *U* test was used to execute analyses of continuous variables. The categorized data were appropriately compared using the Chi-Square test or Fisher's test. Significance was set at $p < 0.05$.

Role of funding source: The study received no funding and relied on IBTO's internal resources.

3. Results

3.1. Recipient characteristics

This study investigated information about COVID-19 patients receiving CCP (**Table 1**). Most of them were men (59.8 %). About 27 percent had comorbidity, including lung disease, heart disease, hypertension, hyperlipidemia, and diabetes. 1459 of 2626 patients (55.5 %) had the severe disease; 17.8 percent of whom were on mechanical ventilation at the time of transfusion.

3.2. Anti-SARS-CoV-2 IgG antibody titers in CCP units

The median antibody titers received in moderate and severe patients was 1:320, with IQR: 1:301.5–1:333.5 and 1:299.5–1:327.3, respectively. Antibody titers were above the threshold of 1:320 in 1673 (54 %) CCP units (**Table 2**). 509 of 1147 (44.4 %) patients with moderate disease and 638 of 1147 (55.6 %) patients with severe disease received CCP

Table 1
Demographics and clinical parameters of convalescent plasma recipients before transfusion.

Independent variable	Patients with mild disease	Patients with Severe disease	Total patients	P value
age (years) - median (IQR)	54(23)	58(22)	56(67)	P<0.0001
male – no. (%)	714 (45.6 %)	852 (54.4 %)	1566 (59.8 %)	P>0.05
Blood types – no. (%)				P>0.05
A	401(45.2 %)	486(54.8 %)	887(34.3 %)	
B	275(43.6 %)	356(56.4 %)	631(23.8 %)	
AB	102(42.9 %)	136(57.1 %)	238(9.0 %)	
O	388(44.9 %)	477(55.1 %)	865(32.9 %)	
Time between hospital admission and receiving CCP (days) - median (IQR)	3(4)	4(5)	4(6)	P<0.0001
Time between receiving CP and outcome (days) - median (IQR)	5(5)	6 (8)	5(9)	P<0.0001
Time between hospital admission and outcome (days) - median (IQR)	10 (11)	13(11)	11 (18)	P<0.0001
Underlying disease – Positive (%)	227(40.2 %)	338(59.8 %)	565(27.5 %)	P<0.0001
Titer				P>0.05
1:40	33(39.3 %)	51(60.7 %)	84(4.3 %)	
1:80	120(45.1 %)	146(54.9 %)	266(12.7 %)	
1:160	133(46.5 %)	153(53.5 %)	286(13.6 %)	
1:320	230(42.1 %)	316(57.9 %)	546(25.9 %)	
1:640	279(46.4 %)	322(53.6 %)	601(28.1 %)	
Negative	100(46.7 %)	114(53.3 %)	214(10.5 %)	
Borderline	40(37.4 %)	67(62.6 %)	107(4.8 %)	
Outcome				P<0.0001
Death	108(13.7 %)	680(86.3 %)	788(29.7 %)	
Discharged	1059(57.6 %)	779(42.4 %)	1838 (70.3 %)	

CCP: COVID-19 convalescent plasma.

units with antibody titers above the threshold of 1:320 (Fig. 1).

3.3. Clinical outcome

The composite outcome of discharge (improve)/death, outlined in **supplement 2**, was attained in all patients by the mean 24.7 days (Table 2). At this time, 1838 of 2626 (70.3 %) patients were discharged, 70.4 % of men and 71.1 % of women. The mean age of discharged and deceased patients was 53.8 and 60.9 years, respectively. Of 643 patients with comorbidity, (60.5 %) improved, while the recovery rate in patients without underlying disease was 73.6 %. Of 1459 patients (55.6 %) with severe disease at the time of CCP transfusion, 779 (53.4 %) patients improved. Among patients with severe disease (55.6 %), the rate of improvement was as follows: 951 (65.2 %) patients who received high-pressure oxygen/ non-invasive ventilation (without intubation), 467 (32.0 %) patients on mechanical ventilation, and 41 (2.8 %) patients required special procedures such as dialysis, vasopressor, hemoperfusion, and ECMO, as well as respiratory ventilation. In the group of patients with moderate disease, 1059(90.7 %) patients improved. Patients

Table 2
The relation between independent variables and outcome.

Independent variable	Death	Discharged	P-Value
Number	907 (29.3 %)	2190(70.7 %)	P<0.001
Gender– no. (%)			P>0.05
Male	545 (29.6 %)	1298(70.4 %)	P>0.05
Female	362 (28.9 %)	892(71.1 %)	
Age- median (IQR)	61.5 (72)	54.0(65)	P<0.001
Comorbidity			P<0.001
Positive (%)	254 (39.5 %)	389(60.5 %)	
Negative (%)	235 (26.4 %)	656(73.6 %)	
Not clear (%)	226 (26.5 %)	628(73.5 %)	
Blood types – no. (%)			P>0.05
A	295 (27.6 %)	773(72.4 %)	
B	227 (30.9 %)	508(69.1 %)	
AB	92(33.0 %)	187(67.0 %)	
O	288 (28.6 %)	719(71.4 %)	
The time interval from hospital admission to CCP transfusion less and equal 5 Day– no. (%)	393 (28.3 %)	997(71.7 %)	P<0.001
Intubation- Positive (%)	409 (81.8 %)	91(18.2 %)	P<0.001
Disease severity– no. (%)			P<0.001
Moderate	108 (13.7 %)	1059(57.6 %)	
Severe	680 (86.3 %)	779(42.4 %)	

CCP: COVID-19 convalescent plasma.

with A blood group had the highest discharge rate (72.4 %) and the lowest mortality rate (27.6 %) among other blood groups (Table 2).

3.4. Anti-SARS-CoV-2 IgG antibody titers, CCP transfusion time, and disease severity related to clinical outcome

Although there was no significant relationship between antibody titers and outcome alone (Fig. 1), there was an association between patients' discharge and antibody levels related to the time elapsed from hospital admission and disease severity (Fig. 2). In patients receiving CCP transfusion five days or less after admission, 373 of 529 improved (70.5 %) in the group with low antibody titers versus 452 of 621 (72.8 %) in the group that received high titer CCP, OR 2.251 (95 % CI 1.663_3.047), P < 0.0001. In patients receiving CCP more than five days after diagnosis, 133 of 218 (61.0 %) improved in the group with low antibody titers versus 139 of 256 (54.3 %) in the group that received high titer CCP, OR 1.528 (95 % CI 1.098_2.126), P < 0.001.

3.5. Logistic regression for disease severity, the time interval from hospitalization to CCP transfusion in association with clinical outcome

Logistic regression model calculated by the two-state outcome as a dependent variable and intubation and the time interval from hospitalization to CCP transfusion (less and more than 5 days) as independent predictors (AUC: 0.76, 95 %CI: 0.74–0.79) (Table 3).

Logistic regression model calculated by the two-state outcome variable as a dependent variable and the variables severe type of disease and the time interval between hospitalization time and plasma transfusion of more and less than 5 days as independent variables (AUC: 76 %, 95 %CI: 74–78) (Table 4).

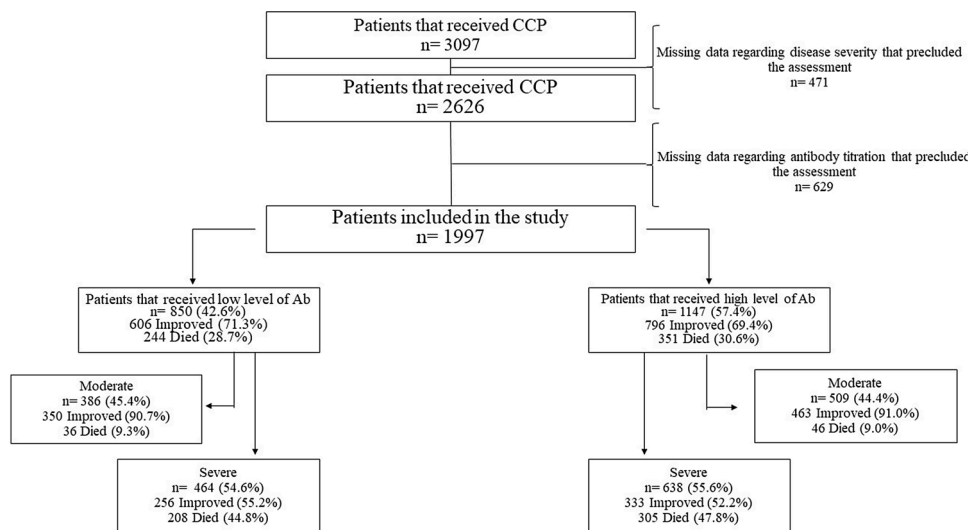


Fig. 1. Outcome in patients according to disease severity and Anti-SARS-CoV-2 IgG antibody titers (>1:320 or <1:320) in CCP units. Patients were divided according to the mean antibody (Ab) titers they received (>1:320 or <1:320). Clinical improvement was determined according to one of the criteria mentioned in **supplement 3**. CCP: COVID-19 convalescent plasma.

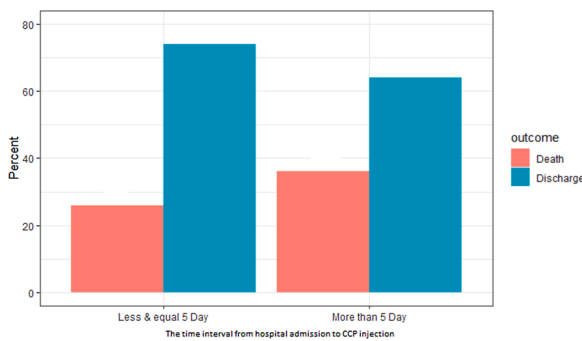


Fig. 2. Relationship between time interval from admission to CCP transfusion and outcome.

4. Discussion

CCP for many infectious diseases has been applied. Recently, it has been used to treat Ebola patients and eventually led to the identification of specific antibodies with high neutralizing activity against the virus, producing synthetic monoclonal antibodies to treat Ebola [14]. The use of CCP to treat patients with COVID-19 began in May 2020 in Iran. Here, we conducted a prospective analysis of a large cohort of 3097 COVID-19 hospitalized patients receiving CCP within the health care system of MOHME. Finally, we measured the effect of transfusion of CCP with varied titration to patients with moderate and severe COVID-19 undertaken within different days of hospitalization on reducing mortality. Our finding similar to another study [15] revealed that disease

prevalence, severity and mortality rate were higher in the male gender while difference related to gender and blood type in our study was not significant.

Patients with A blood group had the highest discharge rate (72.4 %) and the lowest mortality rate (27.6 %) among other blood groups, similar results reported by El-Shitany et al. [16].

In line with our findings, another study demonstrated that older patients [17] are more likely to experience more severe types of COVID-19 infections and deaths. Also, consistent with our results, another study of 3082 patients conducted by Joyner et al. [18] in which antibody titers in CCP received were compared, resulting in patients with higher antibody titers had lower mortality rates. Some studies [8, 19] revealed that there was no significant difference in clinical status or overall mortality between patients treated with convalescent plasma and those treated with placebo; however, some studies have also been performed to increase the effectiveness of CCPs. The study in 49 patients with COVID-19 by Maor et al. showed that patients who received CCP with high antibody levels had a lower mortality rate versus those receiving CCP with low levels of antibody [10]. In our study, about 54 % of CCPs had antibody levels below 1:320. In previous similar studies [20, 21], 15 % of CCPs were lower than the cut-off. Thus, it is critical to assess antibody levels in plasma, ideally before donation, or prior transfusion, to assure therapeutic efficacy and provide the required time for antibody testing before transfusing the units. At the time of plasma transfusion, we did not know the titer of the transfused antibody. This factor caused the plasma to be transfused randomly between patients with different conditions and made it possible to study and analyze more accurately.

The time interval between hospitalization and transfusion was longer in the group of patients who passed away; indeed, patients who received

Table 3
Multivariate Logistic regression for association between outcome with intubation and time interval.

	Time interval	outcome	N	Percent	P-value*	P-value†
Not Intubated	Less & equal 5 Day	Discharge (Ref.)	1047	85.3	Ref.	
		Death	181	14.7		
	More than 5 Day	Discharge (Ref.)	685	76.9	<0.001	
		Death	206	23.1	(1.44, 3.4)	
Intubated	Less & equal 5 Day	Discharge (Ref.)	51	19.9	Ref.	
		Death	205	80.1		
	More than 5 Day	Discharge (Ref.)	40	16.4	<0.001	
		Death	204	83.6	(1.44, 3.4)	<0.001 (15.75, 26.2)

* Relationship between time interval from admission to CCP transfusion and outcome adjusted for intubation.

† Relationship between intubation and outcome adjusted for time interval. AUC: 0.76, 95 %CI: 0.74, 0.79. Omnibus chi-square test: P-value<0.001.

Table 4

Multivariate Logistic regression for association between outcome with disease severity and time interval from admission to CCP transfusion.

Disease severity	Time interval	outcome	N	Percent	P-value * OR (95% CI)	P-value† OR (95%CI)
Moderate	Less & equal 5 Day	Discharge (Ref.)	705	93.1	Ref.	Ref.
		Death	52	6.9		
	More than 5 Day	Discharge (Ref.)	414	87.7		
		Death	58	12.3		
Severe	Less & equal 5 Day	Discharge (Ref.)	393	54.1	-	<0.001
		Death	334	45.9		
	More than 5 Day	Discharge (Ref.)	311	46.9		
		Death	352	53.1		

* Relationship between time interval from admission to CCP transfusion and outcome adjusted for disease severity.

† Relationship between disease severity and outcome adjusted for time interval from admission to CCP transfusion. AUC: 76 %, 95 %CI: 74–78. Omnibus chi-square test: P-value<0.001.

CCP with high antibody titers in the first five days of hospitalization had lower mortality rates than patients with elapsed time from admission until CCP transfusion more than five days. Similar to our findings, a study on 35,000 COVID-19 patients receiving CCP showed that the mortality rate would reduce plasma transfused within the first three days of diagnosis [11]. Also, a cohort study conducted by Salazar et al. on 351 vaccinated patients found that the best time for CCP transfusion and patient recovery was in the first 44 h of hospitalization. The period between hospital admission and transfusion was investigated in this research similar to ours and their reports confirm our results.

In patients whose disease severity was more than five based on WHO classification, mortality was about 4.5-fold.

We followed patients until the results were obtained, and this is our advantage over similar studies [10] where solely follow-ups were performed at specific intervals.

On the other hand, one of our study's limitations is the lack of a control group that limits the evaluation of CCP effectiveness. Also, although patients received standard treatments based on a single protocol, this treatment may interfere with evaluating the impact of antibody titers on clinical outcomes.

5. Conclusions

Our findings explicated that COVID-19 patients with the moderate type of disease receiving CCP units with high antibody titers in the early stages of the disease experienced greater effectiveness of CCP therapy. Therefore, the approaches of CCP transfusion that have been used and the quality of transfused CCP are among critical criteria to convalescent plasma-mediated resolution of COVID-19.

CRedit authorship contribution statement

Saeed Mohammadi: Conceptualization. **Alieh Fazeli, Fatemeh Behdad:** Methodology. **Alieh Fazeli, Nooshin Jelveh, Shamsi Okati, Gilda Esmailifar:** Formal analysis. **Alieh Fazeli, Gilda Esmailifar, Nooshin Jelveh:** Investigation. **Saeed Mohammadi, Shahin Sharifi:** Resources. **Peyman Eshghi, Shamsi Okati, Saeed Mohammadi:** Data curation. **Alieh Fazeli, Fatemeh Behdad, Shahin Sharifi:** Writing—original draft preparation. **Alieh Fazeli, Fatemeh Behdad, Shahin Sharifi:** Writing—review and editing. **Peyman Eshghi, Saeed Mohammadi, Shahin Sharifi:** Supervision. **Peyman Eshghi:** Project

administration. **Peyman Eshghi:** Funding acquisition.

Funding

None.

Declaration of Competing Interest

The authors declare no competing interests.

Acknowledgment

Special thanks for Farmed Behin Azma Company for providing free Rapid kit tests for IBTO.

References

- [1] Zhang L, Liu Y. Potential interventions for novel coronavirus in China: a systematic review. *J Med Virol* 2020;92(5):479–90.
- [2] Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect Dis* 2020;20(4):398–400.
- [3] Luke TC, Casadevall A, Watowich SJ, Hoffman SL, Beigel JH, Burgess TH. Hark back: passive immunotherapy for influenza and other serious infections. *Crit Care Med* 2010;38:e66–73.
- [4] Casadevall A, Scharff MD. Return to the past: the case for antibody-based therapies in infectious diseases. *Clin Infect Dis* 1995;21(1):150–61.
- [5] Dong Y, Shamsuddin A, Campbell H, Theodoratou E. Current COVID-19 treatments: rapid review of the literature. *J Glob Health* 2021;11.
- [6] Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci* 2020;117(17):9490–6.
- [7] Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol* 2020;92(10):1890–901.
- [8] Simonovich VA, Burgos Pratz LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med* 2021;384(7):619–29.
- [9] https://www.google.com/search?client=safari&rls=en&q=gov/vaccines-blood-biologics/investigational-new-drug-id-or-device+exemption-process-cber/investigational-covid-19-convalescent-plasma-emergency-indcs&spell=1&sa=X&ved=2ahUKEwiG-NX1id_xAhVQHMQKHyt2BrEQBSgAegQIAhAw.
- [10] Maor Y, Cohen D, Paran N, Israely T, Ezra V, Axelrod O, et al. Compassionate use of convalescent plasma for treatment of moderate and severe pneumonia in COVID-19 patients and association with IgG antibody levels in donated plasma. *EclinicalMedicine* 2020;26:100525.
- [11] Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. *N Engl J Med* 2021;384(11):1015–27.
- [12] Education IMoHaM. The guidance of the diagnosis and treatment of COVID-19 disease in the levels of outpatient and inpatient services; 9th edition. <https://web.ssu.ac.ir/Dorsapax/userfiles/Sub28/09.pdf>.
- [13] Clinical Management of Covid-19—Interim Guidance. [Internet]. Available from: <https://www.who.int/publications/i/item/clinical-management-of-covid-19>.
- [14] Corti D, Misasi J, Mulangu S, Stanley DA, Kanekiyo M, Wollen S, et al. Protective monotherapy against lethal Ebola virus infection by a potentially neutralizing antibody. *Science* 2016;351(6279):1339–42.
- [15] Nikpouraghdam M, Farahani AJ, Alishiri G, Heydari S, Ebrahimnia M, Samadinia H, et al. Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: a single center study. *J Clin Virol* 2020;127:104378.
- [16] El-Shitany NA, El-Hamamsy M, Alahmadi AA, Eid BG, Neamatallah T, Almkadi HS, et al. The impact of ABO blood grouping on COVID-19 vulnerability and seriousness: a retrospective cross-sectional controlled study among the Arab community. *Int J Environ Res Public Health* 2021;18(1):276.
- [17] Pimenoff VN, Elfstrom M, Dillner J. A systematic review of convalescent plasma treatment for COVID19. *medRxiv* 2020.
- [18] Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, et al. Convalescent plasma antibody levels and the risk of death from covid-19. *N Engl J Med* 2021.
- [19] Janiaud P, Axfors C, Schmitt AM, Gloy V, Ebrahimi F, Hepprich M, et al. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. *Jama* 2021;325(12):1185–95.
- [20] Salazar E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, et al. Significantly decreased mortality in a large cohort of coronavirus disease 2019 (COVID-19) patients transfused early with convalescent plasma containing high-titer anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein IgG. *Am J Pathol* 2021;191(1):90–107.
- [21] Rojas M, Rodríguez Y, Monsalve DM, Acosta-Ampudia Y, Camacho B, Gallo JE, et al. Convalescent plasma in Covid-19: possible mechanisms of action. *Autoimmun Rev* 2020;102554.