The effect of convalescent plasma on the treatment of COVID-19 patients in Ardabil, Iran

Effat Iranijam¹, Hassan Ghobadi¹, Somaieh Matin¹, Shahram Habibzadeh², Hamed Zandian³, Jafar Mohammadshahi⁴, Shahnaz Fooladi⁴, Abdollah Dargahi⁵, Elham Safarzadeh⁶, Mohammad Negaresh², Javad Hosseinii⁸, Ali Hossein Samadi¹, Saeed Hoseininia¹, Hossein salehzadeh¹, Sharareh Dezhkam¹

ORIGINAL ARTICLE

Abstract:
BACKGROUND: Infection with COVID-19 has resulted in considerable mortality all around the world. This study aimed to investigate the effect of convalescent plasma on the treatment of hospitalized patients with COVID-19 in Imam Khomeini Hospital at Ardabil, Iran.

MATERIALS AND METHODS: In this quasi-experimental clinical trial, patients over 18 years of age with polymerase chain reaction-positive COVID-19 were admitted based on the clinical criteria of respiratory distress with hypoxia (O₂ saturation <90) and tachypnea (R Relative Risk (RR) >24) with moderate-to-severe lung involvement and in the 1st week of respiratory disease who were not intubated were nonrandomly assigned to two groups: convalescent plasma therapy (CPT) group (197 cases) and control group (200 cases). We used the Chi-square, t-test, Fisher’s exact test, and Pearson’s correlation coefficient for statistical analysis.

RESULTS: Analyses revealed that length of stay in hospital was significantly lower in the CPT group as compared to the control group (P = 0.001). Twenty-four cases (22.0%) in the CPT group and 85 cases (78.0%) in the control group needed intubation. Furthermore, mortality was 17 cases (18.3%) in the CPT group and 76 cases (81.7%) in the control group, the difference of which was also found to be statistically significant (P < 0.05).

CONCLUSIONS: It seems that CPT can be used as an alternative treatment at the early stages of COVID-19 to prevent the progress of the disease, reduce the need for intubation and consequently the length of stay in hospital, and finally, decrease mortality.

Keywords:
Convalescent, COVID-19, mortality, treatment

Introduction

The outbreak of severe acute respiratory syndrome (SARS) coronavirus-2, which began in Wuhan, China, has become a big concern all over the world.¹⁻³ COVID-19 is mainly characterized by symptoms such as fever, dry cough, and shortness of breath. Some symptoms such as nausea, vomiting, abdominal discomfort, and diarrhea have also been reported, but they are not very typical for this disease.⁴⁻⁷ There are only a few antiviral drugs that can be used for the treatment of COVID-19, and their effectiveness is unfortunately limited. Currently, there are no approved specific antiviral agents targeting the novel virus. However, there are some drugs which are still under investigation, including remdesivir and lopinavir/ritonavir.⁸⁻¹⁰ In general, convalescent plasma therapy (CPT) has been used for improving the survival rate of patients afflicted with a variety of viral epidemics, including SARS, Middle East respiratory syndrome, influenza, and

How to cite this article: Iranijam E, Ghobadi H, Matin S, Habibzadeh S, Zandian H, Mohammadshahi J, et al. The effect of convalescent plasma on the treatment of COVID-19 patients in Ardabil, Iran. J Edu Health Promot 2022;11:266.
Preliminary investigations have indicated the effectiveness of CPT in the treatment of COVID-19, especially when the applied plasma has high titers of neutralizing antibodies (NABs) and is administered in the early stages of the disease. Furthermore, it has been reported in a number of research articles that CPT seems to be one of the successful treatments for COVID-19. From the outbreak of coronavirus, this treatment has been considered by many researchers in various countries around the world, as well as in Iran. In a hospital in India, for instance, plasma therapy was performed on 333 patients, of whom 19 cases were admitted to intensive care unit (ICU). They observed that mortality reduced significantly in these patients. In another study, Ye et al. investigated the effectiveness of convalescent plasma in the treatment of COVID-19 patients in Wuhan, China. Their results showed that this type of treatment reduced COVID-19 disease. In this method of treatment, using an apheresis device, plasma is taken from recovered COVID-19 patients who have high levels of antibody in their blood and the result of their polymerase chain reaction (PCR) test is negative. Then, the obtained plasma is used for the treatment of afflicted patients. It seems that the use of convalescent plasma can reduce primary viremia and induce some level of passive immunity. However, the effect of convalescent plasma on the treatment of COVID-19 patients has not been investigated in northwestern Iran, especially in Ardabil Province. Therefore, this study aimed to explore the effect of convalescent plasma on the treatment of COVID-19 patients hospitalized in Imam Khomeini Hospital in Ardabil, Iran, during 2020.

### Materials and Methods

#### Study design and setting

In this quasi-experimental clinical trial, COVID-19 patients over 18 years of age were investigated after obtaining informed consent. The selected patients were hospitalized with positive PCR test results, respiratory distress, and moderate-to-severe pneumonia as revealed by computed tomography (CT) scan images and O2 saturation of lower than 90% equal to the World Health Organization Progression Scale of 4, 5, and 6. The patients were in the 1st week of the disease and were not under mechanical ventilation. The day of entrance to the study for the patients in the CPT group was the day of receiving plasma. For patients in the control group, on the other hand, it was the day that the treating physician nominated them for receiving plasma, but they either were not in the randomization, were not consented to receive plasma, or there was no plasma compatible with their blood group.

#### Study participants and sampling

To obtain plasma, patients recovered from COVID-19 who met the following requirements were invited to the blood transfusion center: having a history of COVID-19 verified by real-time PCR test at the time of being afflicted with the disease, being in the age range of 20–60 years, being discharged from a hospital or convalescent home due to having recovered in terms of clinical symptoms (not having fever, coughing, shortness of breath, and other related symptoms) and the relevant blood tests (complete blood count, C-reactive protein, erythrocyte sedimentation rate, and lactate dehydrogenase), having arterial blood oxygenation of equal to or higher than 95% without oxygen supplementation, and showing complete or considerable recovery in the lung as indicated by CT scan images. The invited recovered patients were first interviewed by a physician. After that, they filled out a donation form and signed informed consent. Then, the test for specific antibodies against coronavirus was conducted on each of them. Based on the results, individuals with antibody titer of higher than 1.1 were picked out and 500 cc of blood was taken from each of them. The donated plasma was analyzed with virology tests as per the national standards of blood transfusion in Iran. After verification of the analyses, the plasma was transferred to the hospital where the study was being conducted.

#### Data collection tool and technique

Patients were randomly assigned to CPT (consisting of 197 cases) and control (consisting of 200 cases) groups by the treating doctor based on the criteria considered for entering the study. Patients in both groups received routine treatments. In this study, the patients were selected via the use of convenience sampling method from among the patients who were hospitalized in Imam Khomeini Hospital. Randomization means an equal number of participants in equal time intervals for both intervention and control groups. For example, one type of treatment is given to the first block and another type is given to the second block. The sample size was determined using the ratio difference test of two communities (Equation 1). In this equation, \( \alpha \) is error of the first type, \( \beta \) is error of the second type, 1-\( \beta \) is test power, and \( P \) is the average ratio in the two groups.

\[
\alpha = 0.05 \\
\beta = 0.20 \\
\bar{p} = \frac{\bar{p}_1 + \bar{p}_2}{2} = \frac{0.1 + 0.2}{2} = 0.15 \\
2\times \left( z_{\frac{\alpha}{2}} + z_{\frac{\beta}{2}} \right)^2 \times \bar{p}(1-\bar{p}) \\
n = \frac{\left( \bar{p}_1 - \bar{p}_2 \right)^2}{2\times (1.96^2 + 0.84^2) \times (0.15 \times 0.85)} = 200
\]
After obtaining informed consent and confirming the compatibility of the blood group of the donor and receiver of plasma, patients in the CPT group also received 500 cc of plasma in the course of 4 h. Based on the treating doctor’s order, some patients who did not show any sign of improvement after the first round of plasma administration received a second dose 24 h after the first one. The vital signs of the patients were controlled and the possible side effects were checked carefully during the injection of plasma. The patients in the control group received only routine treatments and no plasma was used for them. The routine supportive cares were provided equally for both groups without interruption. The Consolidated Standards of Reporting Trials flowchart outlining participant flow from first contact to study completion is provided in Figure 1.

The patients’ demographic information including their age, gender, height, weight, clinical symptoms, comorbidities, use of drugs, and smoking was recorded. Then, other related variables such as length of stay in hospital, response to treatment, intubation rate, and mortality were recorded in the related checklist. The validity of this checklist was tested and the obtained value was 0.8. The reliability of this tool was also checked using Cronbach’s alpha and the obtained value was 0.86. The recovery criteria based on the treating doctor’s opinion were cessation of fever and coughing, improvement of lungs as indicated by CT scan images, and arterial blood saturation of equal to or higher than 95% without oxygen supplementation. The clinical and paraclinical data in both groups of patients were collected using the same methods of data collection, and all of the patients were followed up until they were either discharged from, or died in, the hospital. The collected data were analyzed using various statistical techniques.

**Ethical consideration**

This research project has been approved by the Research Ethics Committee of Ardabil University of Medical Sciences with the code of IR.ARUMS.REC.1399.052 and the IRCT code of IRCT20150808023559N21.

**Results**

The patients’ demographic and epidemiological characteristics were analyzed using descriptive statistics such as mean, standard deviation, and frequency percentage. From among inferential statistical techniques, t-test was used to compare two groups in terms of quantitative variables, one-way ANOVA as well as Chi-square or Fisher’s exact test were employed to compare three or more groups in terms of quantitative variables, and linear regression was used to predict the value of variables. The obtained results are reported in two subparts below: descriptive statistics and inferential statistics [Table 1]. The relationship between disease outcome and intubation rate in the two groups of patients is presented in Table 1. The relationship between length of hospitalization (days) before receiving plasma and disease outcome in the patients of the CPT group based on Fisher’s exact test is presented in Table 1.

Figure 2a and b show the relationship between disease outcome and intubation rate in the two groups of patients via the use of frequencies and percentages. Results of analysis with Chi-square indicated that the two groups of patients were significantly different in terms of mortality and discharge ($P = 0.001$). Results also revealed that a significant difference existed between the two groups as regards the intubation rate. In Figure 2c and d, the patients’ mean length of stay in hospital and age are compared. As can be seen, the two groups were significantly different in terms of the patients’ mean length of stay ($P<0.001$). However, as is evident in Figure 2c, the mean ages of the patients in the two groups were not significantly different. Based on the results obtained in this study, no significant difference was observed between disease outcome and the length of hospitalization before receiving plasma.

The relationship between length of stay in hospital and neutrophil-to-lymphocyte ratio has been investigated via the use of Pearson’s correlation coefficient. As can be seen, no significant correlation was observed between the two variables neither in the CPT group nor in the control group. In the CPT group, the correlation between these two variables was negative and decreasing, while in the control group, it was positive and increasing.

The analysis of the results indicated no significant correlation between the relationship between the two variables of length of stay in hospital and
Table 1: Distribution of demographic characteristics, relationship between disease outcome and intubation rate, and relationship between length of hospitalization (days) before receiving plasma and disease outcome in the two groups of patients

| Demographic variables | Case (n=197; 49.6%), n (%) | Control (n=200; 50.4%), n (%) | Total (n=397; 100.0%), n (%) | Significance | Test type |
|-----------------------|-----------------------------|-------------------------------|-----------------------------|--------------|-----------|
| Age group             |                             |                               |                             |              |           |
| >40                   | 18 (9.12)                   | 20 (10)                       | 38 (9.57)                   |              |           |
| 40-50                 | 36 (18.2)                   | 34 (17)                       | 70 (17.6)                   |              |           |
| 51-60                 | 50 (25.4)                   | 52 (26)                       | 102 (25.6)                  |              |           |
| 61-70                 | 70 (35.5)                   | 69 (34.5)                     | 139 (35)                    |              |           |
| 71-80                 | 16 (8.12)                   | 20 (10)                       | 36 (9)                      |              |           |
| <80                   | 7 (3.5)                     | 5 (2.5)                       | 12 (3)                      |              |           |
| Sum                   | 197 (100)                   | 200 (100)                     | 397 (100)                   |              |           |
| Gender                |                             |                               |                             |              |           |
| Male                  | 97 (49.2)                   | 98 (49)                       | 195 (49.1)                  |              |           |
| Female                | 100 (50.8)                  | 102 (51)                      | 202 (50.9)                  |              |           |
| Sum                   | 197 (100)                   | 200 (100)                     | 397 (100)                   |              |           |
| Occupation            |                             |                               |                             |              |           |
| Self employed         | 73 (37.1)                   | 76 (38)                       | 149 (37.5)                  |              |           |
| Employee              | 36 (18.3)                   | 34 (17)                       | 70 (17.6)                   |              |           |
| Housewife             | 62 (31.5)                   | 57 (28.5)                     | 119 (30)                    |              |           |
| Retired               | 26 (13.2)                   | 33 (16.5)                     | 59 (14.9)                   |              |           |
| Sum                   | 197 (100)                   | 200 (100)                     | 397 (100)                   |              |           |
| Education             |                             |                               |                             |              |           |
| Under diploma         | 101 (51.3)                  | 97 (48.5)                     | 198 (49.9)                  |              |           |
| Diploma               | 29 (14.7)                   | 41 (20.5)                     | 70 (17.6)                   |              |           |
| University degree     | 67 (34)                     | 62 (31)                       | 129 (32.5)                  |              |           |
| Sum                   | 197 (100)                   | 200 (100)                     | 397 (100)                   |              |           |
| Residence             |                             |                               |                             |              |           |
| Urban                 | 158 (80.2)                  | 167 (83.5)                    | 325 (81.9)                  |              |           |
| Rural                 | 39 (19.8)                   | 33 (16.5)                     | 72 (18.1)                   |              |           |
| Sum                   | 197 (100)                   | 200 (100)                     | 397 (100)                   |              |           |
| Smoke                 |                             |                               |                             |              |           |
| No                    | 181 (91.9)                  | 181 (90.5)                    | 362 (91.2)                  |              |           |
| Yes                   | 16 (8.1)                    | 19 (9.5)                      | 35 (8.9)                    |              |           |
| Sum                   | 197 (100)                   | 200 (100)                     | 397 (100)                   |              |           |
| Underlying disease    |                             |                               |                             |              |           |
| No                    | 64 (44)                     | 132 (66.3)                    | 196 (48.8)                  |              |           |
| Yes                   | 133 (66)                    | 68 (39.7)                     | 201 (51.2)                  |              |           |
| Sum                   | 197 (100)                   | 200 (100)                     | 397 (100)                   |              |           |
| Blood group           |                             |                               |                             |              |           |
| A                     | 80 (40.6)                   | 53 (26.5)                     | 133 (33.5)                  |              |           |
| B                     | 28 (14.2)                   | 21 (10.5)                     | 49 (12.3)                   |              |           |
| AB                    | 7 (3.6)                     | 2 (1)                         | 9 (2.3)                     |              |           |
| O                     | 82 (41.6)                   | 60 (30)                       | 142 (35.8)                  |              |           |
| Sum                   | 197 (100)                   | 136 (68)                      | 333 (83.9)                  |              |           |
| Disease outcome       |                             |                               |                             |              |           |
| Death                 | 17 (18.3)                   | 76 (81.7)                     | 93 (100.0)                  | 0.001        | χ²        |
| Release               | 180 (59.2)                  | 124 (40.8)                    | 304 (100.0)                 |              |           |
| Total                 | 197 (49.6)                  | 200 (50.4)                    | 397 (100.0)                 |              |           |
| Intubation rate       |                             |                               |                             |              |           |
| Yes                   | 24 (22.0)                   | 85 (78.0)                     | 109 (100.0)                 | 0.001        | χ²        |
| No                    | 173 (60.1)                  | 115 (39.9)                    | 288 (100.0)                 |              |           |
| Total                 | 197 (49.6)                  | 200 (50.4)                    | 397 (100.0)                 |              |           |
| Duration of hospitalization | 8.72 (2.58) | 13.21 (8.15) | 9.98 (6.87) | 0.001 | t-test |
| Age                   | 57.15 (12.14)               | 58.02 (12.82)                 | 5.57 (47.12)                | 0.487        | t-test |

Contd...


neutrophil-to-lymphocyte ratio neither in the CPT group nor in the control group. In the CPT group, the linear trend was decreasing, while in the control group, it was increasing.

Table 2 represents the results of applying independent t-test on variations of vital signs after plasma therapy. The two variables of mean respiratory rate and mean body temperature were found to be significantly lower in the CPT group as compared to the control group. Moreover, the mean heart rate, systolic blood pressure, and diastolic blood pressure turned out to be significantly higher in the control group as compared to the CPT group ($P < 0.001$).

The relationship between the two variables of vital signs upon admission and mortality was investigated using linear regression, the results of which are given in Table 2. As can be observed, the results did not show any significant relationship between the two variables.
Discussion

Currently, there is no effective clinical treatment for COVID-19. The use of convalescent plasma seems to be one of the possible treatments.[21] The results of the present study indicated that length of stay in hospital, need for intubation, and mortality resulting from COVID-19 were significantly lower in the CPT group as compared to the control group. In a separate study, Abolghasemi et al. conducted a multicenter clinical trial on 189 patients afflicted with COVID-19 (115 patients in plasma therapy group and 74 patients in control group) with the aim of investigating the clinical effects of CPT on the infections induced by COVID-19. They found that mortality, length of stay in hospital, and the need for intubation were significantly lower in patients receiving plasma.[22] Therefore, their findings are all consistent with the findings of the current study.

In another study, Ahmad et al. investigated the effect of CPT on the treatment of patients afflicted with severe forms of COVID-19 and found that length of stay in ICU, mechanical ventilation support, vasopressor support, and mortality were lower in the CPT group as compared to the control group. Based on the results obtained, they concluded that CPT could be effective in the treatment of patients afflicted with severe forms of COVID-19.[25]

In the study conducted by Duan et al., 10 patients afflicted with severe forms of COVID-19 were investigated. The patients in their study received one dose of convalescent plasma (200 mL) with NAB titer of higher than 1.640 that was donated by people newly recovered from COVID-19. They observed that CPT was a bearable method of treatment for these patients. They also observed that it could improve clinical symptoms in patients afflicted with severe forms of COVID-19 via neutralizing viremia.[25] Their findings are also consistent with the findings of the present study.

In a randomized clinical trial, Gharbharan et al. compared the effects of CPT and standard medical care on patients hospitalized for COVID-19 in the Netherlands. In their study, no significant differences were observed between

| Variable          | Group     | n  | Mean (SD)   | Test statistics | Significance |
|-------------------|-----------|----|-------------|-----------------|--------------|
| Respiratory rate  | CPT       | 197| 19.35 (2.89) | -18.044         | <0.001       |
|                   | Control   | 200| 24.24 (2.48) |                 |              |
| Pulse rate        | CPT       | 197| 88.59 (11.09)| 10.56           | <0.001       |
|                   | Control   | 200| 78.13 (8.44) |                 |              |
| Body temperature  | CPT       | 197| 37.074 (0.56)| -13.34          | <0.001       |
|                   | Control   | 200| 37.69 (0.99) |                 |              |
| Systolic blood pressure | CPT    | 197| 128.68 (15.23)| 5.61           | <0.001       |
|                   | Control   | 200| 111.0 (11.87)|                 |              |
| Diastolic blood pressure | CPT     | 197| 72.84 (9.58) | 6.90           | <0.001       |
|                   | Control   | 200| 66.40 (8.99) |                 |              |

Table 2: Comparison of vital signs in the two groups after convalescent plasma therapy via the use of independent t-test and comparison of patients’ vital signs upon admission with mortality

SD=Standard deviation, SE=Standard error, CPT=Convalescent plasma therapy
the two types of treatment as regards mortality, length of stay in hospital, and severity of the disease on the 15th day after the onset of symptoms. Since NAB titer in most of the COVID-19 patients participating in this study was higher upon their hospitalization, the study was terminated ahead of schedule, and antibody screening was determined to be one of the key steps to be taken in recognizing the patients that might benefit from CPT.\[27\]

A systematic and meta-analytic investigation was also conducted on the findings related to the clinical effects of CPT on COVID-19. The results of global meta-analysis as well as the analysis of the data obtained from 28-day or 30-day standard follow-up of patients revealed that CPT was associated with lower mortality among COVID-19 patients. However, in two randomized controlled trials mentioned in this meta-analysis, CPT did not bring about any difference in mortality.\[23,28\] The findings of this meta-analysis suggest that CPT can be effective in the treatment of patients with COVID-19. Nonetheless, the mixed results of different studies regarding mortality make it impossible to arrive at a definitive conclusion on the improvement of survival rate as the result of CPT.\[29\]

In another study, Simonovich et al. investigated patients treated with CPT and those treated with placebo. Their results also did not show any significant differences between patients of the two groups as regards their clinical condition or mortality.\[29\] Bikdeli et al. investigated the effects of intermediate-dose versus standard-dose prophylactic anticoagulation on the treatment of COVID-19 patients admitted to the ICU. Their results showed that intermediate-dose compared with standard-dose prophylactic anticoagulation did not reduce a composite of death, treatment with ECMO, or venous or arterial thrombosis at 90-day follow-up.\[30\]

In the present study, the mean respiratory rate and body temperature of the patients in the CPT group were reported to be lower than those of the control group, the reason for which might be the decrease of COVID-19 viremia in the blood and the improvement of symptoms. The mean heart rate, systolic blood pressure, and diastolic blood pressure were significantly higher in patients of the control group as compared to those in the CPT group, which might be due to fluid overload. In patients of the CPT group, there was a negative and decreasing correlation between length of stay in hospital and neutrophil-to-lymphocyte ratio, while in those of the control group, a positive and increasing correlation was observed between these two variables. These differences were not statistically significant.\[31,32\] Therefore, it can be assumed that CPT has improved this ratio and that improvement, in turn, has led to an improvement in the patients’ prognosis. The strengths of this study included the following: (1) relatively big sample size and comparison of patients with a control group, (2) studying patients in a certain phase of the disease (first week), and (3) using plasma therapy when antiviral therapies were not being used yet.

**Limitation and recommendation**

The limitations of the study include the impossibility of randomization and the lack of donated plasma compatible with blood group.

**Conclusions**

The findings of this clinical trial indicated the effectiveness of CPT in the treatment of COVID-19 patients suffering from severe respiratory symptoms at the early stages of the disease. According to the findings of the current study, CPT can decrease intubation rate, length of stay in hospital, and mortality via preventing the progress of the disease and improving the related symptoms, especially body temperature and respiratory rate. Therefore, the result of this study shows that CPT can be used in severe COVID-19 patients without significant adverse events. One of the limitations of this study was the impossibility of randomization due to the possible unwillingness of some patients to enter the study. Another limitation was lack of plasma compatible with some patients’ blood type to be administered at the time of need.

**Acknowledgments**

The authors hereby express their deepest gratitude to the patients participating in this project and all other individuals who cooperated in conducting this study. The grant code for this study was ARUMS-3766. The authors declare that they have no competing interests.

**Financial support and sponsorship**

This study was financially supported by Ardabil University of Medical Sciences (IR.ARUMS. REC.1399.052).

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Arefi MF, Babaei AP, Barzanouni S, Ebrahimi S, Salehi AR, Khajehnasiri F, Poursadeghian M. Risk Perception in the COVID-19 pandemic; a health promotion approach. J Edu Health Promot 2022;11:118.

2. Soltaninejad M, Babaei-Pouya A, Poursadeqiyam M, Feiz Arefi M. Ergonomics factors influencing school education during the COVID-19 pandemic: A literature review. Work. 2021;68 (1):69-75.

3. Khajehnasiri F, zaroushani v, poursadeqiyam m. Macroergonomics and health workers during Covid-19 pandemic. Work. 2021;69 (3):713-714.

4. Dargahi A, Jeddi F, Ghobadi H, Vosoughi M, Karami C, Sarailoo M,
et al. Evaluation of masks’ internal and external surfaces used by health care workers and patients in coronavirus-2 (SARS-CoV-2) wards. Environ Res 2021;196:110948.

5. Poursadeqyani M, Bazrafshan E, Arefi MF. Review of environmental challenges and pandemic epidemiology of Covid-19. J Edu Health Promot 2020;9:250.

6. Karami C, Normohammadi A, Dargahi A, Vosoughi M, Zandian H, Jeddi F, et al. Investigation of SARS-CoV-2 virus on nozzle surfaces of fuel supply stations in North West of Iran. Sci Total Environ 2021;780:146641.

7. Pourfarzi F, Rahim Pouran S, Dargahi A, Karami C, Fouladi N, Zandian H, Zahiri Moghadam T. The healthy behaviours and COVID-19 mortality among Iranian women: a case–control study. BMC Women’s Health. 2021;21 (1):1-8.

8. Zandian H, Sarailoo M, Dargahi S, Gholizadeh H, Vosoughi M, Dargahi A. Evaluation of knowledge and health behavior of university of medical sciences students about the prevention of COVID-19. Work. 2021,68 (3):543-549.

9. Erfanian N, Miri-Moghaddam E. Treatment of COVID-19 patients using plasma therapy. J Birjand Univ Med Sci 2021;28:84-7.

10. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends 2020;14:69-71.

11. Marano G, Vaglio S, Pupella S, Faccio G, Catalano L, Liunbuno GM, et al. Convalescent plasma: New evidence for an old therapeutic tool? Blood Transfus 2016;14:152-7.

12. Salazar E, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA, et al. Treatment of coronavirus disease 2019 (COVID-19) patients with convalescent plasma. Am J Pathol 2020;190:1680-90.

13. Sarailoo M, Matin S, Vosoughi M, Dargahi A, Gholizadeh H, Rajabi Damavandi M, Abbasi-Ghahramanloo A, Kamran A. Investigating the relationship between occupation and SARS-CoV-2. Work. 2021, 68 (1): 27–32.

14. Focosi D, Anderson AO, Tang JW, Tuorri M. Convalescent plasma therapy for COVID-19: State of the art. Clin Microbiol Rev 2020;33:e00072-20.

15. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis 2020;20:398-400.

16. Budhiraja S, Dewan A, Aggarwal R, Singh O, Junesa D, Patakh S, et al. Effectiveness of convalescent plasma in Indian patients with COVID-19. Blood Cells Mol Dis 2021;88:102548.

17. 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;92:1890-901.

18. Zahirian Moghadam T, Pourfarzi F, Karami C, Rahimpouran S, Zandian H, Dargahi A. The Effect of Working-based Individual Protective Behaviors (WIPB) on COVID-19 Mortality in North-West of Iran: A Case-Control Study. JOHE. 2021; 10 (3):158-168.

19. Sahr F, Ansumana R, Massaquoli TA, Idriss BR, Sesay FR, Lamir JM, et al. Evaluation of convalescent whole blood for treating Ebola virus disease in Freetown, Sierra Leone. J Infect 2017;74:302-9.

20. Van Griensven J, Edwards T, de Lammallerie X, Semple MG, Gallian P, Balize S, et al. Evaluation of convalescent plasma for Ebola virus disease in Guinea. N Engl J Med 2016;374:33-42.

21. Zhao Q, He Y. Challenges of convalescent plasma therapy on COVID-19. J Clin Virol 2020;127:104358.

22. Abolghasemi H, Esghi P, Cheraghal AM, Imani Fooladi AA, Bolouki Moghaddam F, Imamzadeh S, et al. Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: Results of a multicenter clinical study. Transfus Apher Sci 2020;59:102875.

23. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P, et al. Convalescent plasma in the management of moderate COVID-19 in adults in India: Open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ 2020;371:m3939.

24. Alsharidah S, Ayed M, Ameen RM, Alhuraish F, Rouheldeed NA, Alshammari FR, et al. COVID-19 convalescent plasma treatment of moderate and severe cases of SARS-CoV-2 infection: A multicenter interventional study. Int J Infect Dis 2021;103:439-46.

25. Ahmad A, Salsabili M, Oliver T. Mortality rates in matched cohort, pseudo-randomised and randomised trials of convalescent plasma given to COVID-19 patients.medRxiv 2020,3:102955.

26. 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 U S A 2020;117:9490-6.

27. Gharbharan A, Jordans CC, GeurtsvanKessel C, den Hollander JG, Karim F, Millema FP, et al. Convalescent plasma for COVID-19. A randomized clinical trial. medRxiv 2020;4 (3):1-10.

28. Vegivinti CT, Pederson JM, Saravu K, Gupta N, Evanson KW, Kamrowski S, et al. Efficacy of convalescent plasma therapy for COVID-19: A systematic review and meta-analysis. J Clin Apher 2021;36:470-82.

29. Simonovich VA, Burgos Pratts 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;384:619-29.

30. Bikdeli B, Talasaz AH, Rashidi F, Bakhshandeh H, Rafiee F, Rezaeifar P, et al. Intermediate-dose versus standard-dose prophylactic anticoagulation in patients with COVID-19 admitted to the intensive care unit: 90-day results from the INSPIRATION Randomized Trial. Thromb Haemost 2021;1485-2372.

31. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol 2020;84:106504.

32. Alshammari FR, Alsharidah S, Karami C, Normohammadi A, Pourfarzi F, Rahim Pouran S, Dargahi A, Karami C, Normohammadi A, et al. Increased age, neutrophil-to-lymphocyte ratio (NLR) and white blood cells count are associated with higher COVID-19 mortality. Am J Emerg Med 2021;40:11-4.