Convalescent Plasma in the Treatment of Severe COVID-19: A Systematic Review and Meta-Analysis

Xuanguo ZHANG¹, Li XI², Fang PANG³, Yan DU⁴, Qiuzhen YUAN⁵, Minjuan SHI⁵, Jiping LIU⁶, Hui MA⁷, *Bo LI⁵

¹Intensive Care Unit, Shaanxi Traditional Chinese Medicine Hospital, Xi'an, 710003, China
²Editorial Department of Shaanxi Journal of Traditional Chinese Medicine, Shaanxi Academy of Traditional Chinese Medicine, Xi'an, 710003, China
³College of Traditional Chinese Medicine, Chongqing Medical University, Chongqing, 400016, China
⁴Graduate School, Shaanxi University of Chinese Medicine, Xianyang, 712046, China
⁵Department of Pharmacy, Shaanxi Traditional Chinese Medicine Hospital, Xi'an, 710003, China
⁶Department of Pharmacology, Shaanxi University of Chinese Medicine, Xianyang, 712046, China
⁷Department of Healthcare-Associated Infection Control, Shaanxi Traditional Chinese Medicine Hospital, Xi'an, 710003, China

*Corresponding Author: Email: liboszy@sina.com
(Received 12 Aug 2020; accepted 19 Sep 2020)

Abstract

Background: COVID-19 is a public health emergency of international concern. Its incidence rates and mortality are very high; however, so far, an effective drug treatment remains unknown. Based on the role of convalescent plasma therapy in previously identified viral pneumonias, patients with severe COVID-19 have been given this therapy. This systematic review and meta-analysis aimed to summarize the clinical evidence regarding the efficacy and safety of convalescent plasma therapy in the treatment of severe COVID-19.

Methods: PubMed, Embase, Ovid, China Knowledge Network, China Biomedical, VIP Chinese Sci-tech Journal, Wanfang Database, and the International Clinical Trials Registry Platform were searched up to 21 June 2020, to identify clinical studies and registered trials on the use of convalescent plasma in the treatment of critically ill patients with COVID-19. Stata 13.0 was used to perform Meta-analysis. All records were screened as per the protocol eligibility criteria.

Results: Nineteen clinical reports regarding convalescent plasma in the treatment of severe COVID-19 were included. Through systematic analysis, convalescent plasma was found to yield some efficacy on severe COVID-19 and had almost no obvious adverse reactions.

Conclusion: Convalescent plasma therapy seems to yield some efficacy among patients with severe COVID-19 and almost no obvious adverse reactions were found. However, at present, the clinical evidence is insufficient, and there is an urgent need for support from high-quality clinical trial data.

Keywords: Coronavirus disease (COVID-19); SARS-CoV-2; Convalescent plasma; Pneumonia

Introduction

Coronavirus disease (COVID-19) is a public health emergency of international concern. According to the official website of WHO, as of 10 CEST of June 20, 2020, 8,525,042 people had been infected with COVID-19 and 456,973 related deaths had occurred worldwide. With the rap-
id increase in the number of confirmed cases worldwide, the number of deaths had increased at an even faster rate (1). Due to the high mortality rate of severe COVID-19, it is very important to institute effective treatment for critically ill patients. However, so far, there is no clear, effective, and proven drug treatment.

Convalescent plasma therapy has been used for more than 100 years and played a role during various viral infectious disease pandemics. A meta-analysis showed that the use of convalescent plasma, serum, or hyperimmune globulin may be effective in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe acute respiratory infection due to influenza viruses, it can reduce the associated mortality, and is safe (2). Convalescent plasma with antibody titer ≥1:80 was effective in the treatment of Middle East respiratory syndrome coronavirus (MERS-CoV) infection (3).

According to previous studies on viruses similar to SARS-CoV-2, including SARS and MERS viruses, convalescent plasma may be effective in the treatment of severe COVID-19. To seek evidence regarding convalescent plasma in the treatment of severe cases, the present paper systematically evaluated the evidence from a literature review.

Methods

Literature inclusion criteria
We assessed studies including randomized controlled trials, clinical controlled trials, cohort studies, case-control studies, case series studies, and case reports about the use of plasma therapy among convalescent COVID-19 patients. There was no restriction on language. The participants were critically ill patients diagnosed with COVID-19. The diagnostic methods could be based on the guidelines of COVID-19 published in various countries.

As intervention, the treatment group included convalescent plasma, and conventional therapy was unlimited. The treatment of the control group was unlimited. The outcome indicators included clinical efficacy, survival rate, mortality, viral load, antibody titer, and adverse reactions.

Exclusion criteria
We excluded other pieces of literature that did not meet the inclusion criteria, such as non-clinical reports, reviews, inconsistent research objectives, inconsistent intervention measures, and duplicate literature.

Data extraction
According to the pre-established data extraction table, the literature data were extracted and a unified data table was established using Excel 2013 (Microsoft Corp., Redmond, WA, USA), including author, year of publication, sample size, sex, age, underlying diseases, plasma therapy information, intervention measures, observation indicators, and clinical outcomes.

Data processing
The mortality and the negative rate of PCR data were analyzed by Meta-analysis using Stata 13.0.

Results

According to the inclusion and exclusion criteria, 19 clinical reports were retrieved.

Clinical report

Literature screening
According to the predetermined retrieval scheme, we searched the literature, and read the titles and abstracts. We initially excluded literature that did not meet the inclusion criteria, read the full text of the remaining literature, and excluded retrospective studies, duplicate studies, studies with inconsistent intervention measures, non-controlled studies, and other pieces of literature. Finally, 19 studies were included (Fig. 1).
Efficacy and safety of convalescent plasma in the treatment of COVID-19

Thus far, 19 clinical reports have been published on the use of convalescent plasma in the treatment of COVID-19(4-22), including those emanating from China, USA, South Korea and Turkey. Among the 146 patients who reported the clinical efficacy, the oldest was 100 years old and the youngest was 19 yr old. The most common complications of these patients were essential hypertension, cardio-cerebrovascular diseases, diabetes, and so on. The majority of patients received mechanical ventilation, while almost simultaneously else antiviral treatment including remdesivir, hydroxychloroquine, abidol, ribavirin or peramivir, and so on. According to the needs of the disease, they also received different anti-bacterial or antifungal treatments, hormone treatments, albumin, immunoglobulin, and other immune agent treatments. The clinical effect was evaluated after transfusion by assessing clinical symptoms, chest images or CT, nucleic acid detection, viral antibody level, blood leukocyte count, lymphocyte count, interleukin-6 (IL-6) levels, C-reactive protein (CRP) levels, disease prognosis, and so on. Most patients showed improvement in symptoms after transfusion; the inflammation had resolved on chest imaging or CT, viral nucleic acid test results returned negative, antibody titer increased, white blood cell and lymphocyte counts normalized, IL-6 and CRP levels decreased.

Some studies (5, 11, 15, 20) reported mortality. Baseline characteristics (age, gender, severity of the diseases, and so on) of patients between convalescent plasma treatment group and control group in these four studies showed no significant differences. The mortality rate of the treatment group was lower than control group, and the difference was significant (RR=0.59, 95% CI (0.37,0.94), P<0.05) (Fig. 2).
Zeng et al. (11) and Li et al. (15) reported the negative rate of PCR. Meta-analysis showed that the negative rate of the treatment group was higher than control group, and the difference was significant (RR=2.55, 95% CI (1.76,3.70), $P<0.05$) (Fig. 3).
In a study, the average time of plasma transfusion was 21.5 d after the onset of the disease in 5 patients who died (11), and the effect of transfusion within 14 d of disease onset of 3 patients were better than that observed more than 14 d after onset of 1 patient, suggesting that plasma transfusion should be carried out as early as possible among patients with severe disease (5).

In some studies, the specific requirements of plasma titer in convalescence were put forward (4-6,15,17,19,22). The titer of antibody was higher than 1:160-1:1000. In another studies, the age that requirements for blood donors were put forward was 18-67 yr old (5,6,8,10,14,15). Suggesting that the titer of plasma antibody should be as high as possible and the donors should be as young as possible.

Analyzed some key safety metrics after transfusion of ABO compatible human COVID-19 convalescent plasma in 5,000 hospitalized adults with severe or life-threatening COVID-19, the incidence of all serious adverse events (SAEs) in the first four hours after transfusion was <1%, including mortality rate (0.3%)[1]. Of the 36 reported SAEs, there were 25 reported incidences of related SAEs, including mortality (n=4), transfusion-associated circulatory overload (n=7), transfusion-related acute lung injury (n=11), and severe allergic transfusion reactions (n=3). However, only 2 (of 36) SAEs were judged as definitely related to the convalescent plasma transfusion by the treating physician. These early indicators suggest that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19.

The use of convalescent plasma in the treatment of patients with severe COVID-19 seemed to yield some efficacy and almost no serious adverse reactions were found. However, these results were limited by the use of antiviral, hormone, and other treatments; and the low level of clinical evidence. (Table 1 and 2).

### Table 1: Summary of general information of patients in clinical reports

| Author and time of publication | Country/region | Sample size | Sex | Age or Median Age (yr) | Underlying diseases |
|-------------------------------|----------------|-------------|-----|------------------------|---------------------|
| Li et al., April 2020         | China, Qingdao | 1           | Female | 79                     | Epilepsy            |
| Duan et al., March 2020       | China, Wuhan   | 10          | 4 females, 6 males | 52.5                | 4 patients had cardio-cerebrovascular disease and essential hypertension |
| Shen et al., March 2020       | China, Shenzhen | 5           | 3 males, 2 females | 36-73                | 1 patient with hypertension complicated with mitral regurgitation |
| Zhang et al., March 2020      | China, Dongguan, Xiangtan, Zhongshan | 4 | 2 males, 2 females | 31-73                | 1 patient with hypertension |
| Ahn et al., April 2020        | Korea          | 2           | 1 female, 1 male  | 67-71                | 1 pregnant woman    |
| Ye et al., April 2020         | China, Wuhan   | 6           | 3 males, 3 females | 28-75                | 1 patient with Sjogren’s syndrome |
| Zhang et al., April 2020      | China, Nanjing | 1           | Female                      | 64                   | Hypertension and diabetes |
| Zeng et al., April 2020       | China, Zhengzhou | 6           | 5 males, 1 female          | 61.5                | 1 patient with diabetes |
| Dai et al., March 2020        | China, Qinghai | 3           | 3 males                      | Young and middle-aged | 1 patient with hypertension |
| Li et al., June 2020          | China, Wuhan   | 52          | 27 males, 25 females        | 70                  | 1 patient with cardiovascular disease, 29 patients with hypertension |
| Jonathon Anderson et al., May 2020 | USA, Nashville, Tennessee | 1           | 1 female                     | 35                  | 14 patients with Cardiovascular disease, 11 patients with Cerebrovascular disease |
|                               |                |             |                               |                     | 8 patients with hepatopathy, 3 patients with cancer |
|                               |                |             |                               |                     | 2 patients with nephropathy, Pregnant, diabetes, asthma, obesity |
Table 2: Summary of Efficacy and Adverse Reactions of Convalescent Plasma Therapy in Clinical Reports

| Author and time of publication | Use of convalescent plasma therapy | Prognosis | Adverse reactions | Remarks |
|-------------------------------|-----------------------------------|-----------|------------------|---------|
| Li et al., April 2020         | 200ml                             | Improvement | None                  | /       |
| Duan et al., March 2020       | 200ml                             | Improvement | One patient had fleeting facial erythema | cohort study |
| Shen et al., March 2020       | 400ml, Continuous transfusion     | Improvement | Not described       | antibody titer >1:1000 |
| Zhang et al., March 2020      | 200–300ml each time, a total amount of 200–2400ml | Improvement | No serious adverse reactions | Pregnant woman experienced a stillbirth |
| Ahn et al., April 2020        | Plasma was transfused twice at intervals of 12 hours | Improvement | None | No evaluation of antibody titer in convalescent plasma |
| Ye et al., April 2020         | 200ml, 1–3 times                  | Improvement | None | 1 case was negative of pharyngeal swab test |
| Ma et al., April 2020         | 200 ml                            | Improvement | None                  | /       |
| Zeng et al., April 2020       | 200–600 ml                        | Improvement | No further issues after discharge | continuing antenatal care |
| Dai et al., March 2020        | 50 ml, very two days, 100 ml in total | 1 patient was cured | Not described | antibody titer was undetectable, RCT |
| Li et al., June 2020          | 4 to 13 mL/kg, 200–300 mL         | Improvement | 1 patient developed chills and rashes, no further issues after discharge | continuing antenatal care |
| Jonathon Anderson et al., May 2020 | 1 unit                          | Improvement | 1 patient presented with shortness of breath, cyanosis, and severe dyspnea | |
| Eric Salazar et al., May 2020 | 300ml, 1 patient received a second transfusion | Improvement | 1 patient developed a morbilliform rash | / |
| Ma et al., April 2020         | 400ml                             | Improvement | Not described       | /       |

Available at: [http://ijph.tums.ac.ir](http://ijph.tums.ac.ir)
Discussion

Convalescent plasma therapy yields some efficacy among patients with severe COVID-19 and almost no obvious adverse reactions were found. However, the clinical evidence is insufficient and there is an urgent need for support from high-quality clinical trial data. In addition, special attention should be paid to the indications, contraindications, selection criteria of donors, and storage and transfusion procedures for plasma therapy. At present, under the condition that there is no effective treatment for patients with severe COVID-19, some countries have put forward some guidelines based on the clinical experience regarding convalescent plasma therapy in the treatment of SARS, MERS, and severe avian influenza.

Epstein Jay et al. (23) compiled a document approved by the Global Blood Safety Working Group of the International Society of Blood Transfusion and reported that as a possible treatment for COVID-19, factors such as prescreening and pre-donation testing of donors, qualification criteria of whole blood or plasma donors and collection standards should be taken into account when preparing and transfusing COVID-19 convalescent plasma. From January 27th to Apr 1st, 2020, China has successively issued guidelines for the diagnosis and treatment of COVID-19 (the trial version and the fourth to seventh editions)(24-27), "COVID-19 Convalescent Plasma Clinical Treatment Plan (trial first and second editions)"(28), "Further strengthening COVID-19 convalescent plasma treatment work plan"(29), and "Severe COVID-19: A series of guidelines for the diagnosis and treatment of critical and severe cases (trial second edition)"(30). The scope of application of plasma therapy for COVID-19 in the convalescent stage has been revised continuously. Convalescent plasma therapy should be considered for severe cases and critically ill patients under certain conditions, for patients with rapid disease progression, and convalescent plasma containing novel coronavirus antibody should be used in the treatment of early COVID-19. It can be considered as a choice for specific treatment. The titer of protective antibody in convalescent plasma should be measurable. The recommended dosage of transfusion in two stages is 200–500 ml (4–5 ml/kg body weight) and clear requirements have been put forward in three aspects: target task, work measures, and work requirements. On March 24, 2020, the United States Federal Drug Administration approved a clinical study of convalescent plasma in the treatment of COVID-19 (31). The guidelines for the diagnosis and treatment of COVID-19 issued by the National Institutes of Health (32) on Apr 21, 2020 point out that there are not enough data to recommend the use of recovered plasma or hyperimmune globulin for the treatment of COVID-19 (level of evidence: IIIA). Despite a good historical record, few controlled trials had assessed the efficacy of convalescent plasma, largely due to its emergent use during epidemics (33). Data on the use of convalescent plasma therapy be collected and mined from ongoing clinical studies. Based on the severity of the situation in Italy, convalescent plasma therapy would be regarded as "empirical". A donor diagnosed with COVID-19, based on virology, should fully recover within at least 14 d, and a titer of at least 1:320 is recommended (34).
Conclusion

In the clinical trials conducted under the guidance of normative documents in various countries or regions, the existing reported clinical data show that convalescent plasma therapy seems to yield some efficacy among patients with severe COVID-19 and almost no obvious adverse reactions were found. However, the level of clinical evidence is low due to the small sample size, as well as the influence of antiviral, hormonal, and other treatments. Therefore, this clinical treatment modality should be used cautiously in patients with severe COVID-19 when there is a lack of high-quality clinical trial data. The principle of early treatment should be followed when using it. The correlation between the plasma dose and therapeutic effect of plasma therapy in the treatment of COVID-19 cannot be confirmed. Follow-up clinical trials of plasma therapy for COVID-19 should pay attention to the differences in implementation of treatment (dose, frequency, timing, etc.) and the influence of donor plasma standards, and adopt randomized controlled studies as far as possible to arrive at conclusions that are more accurate.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

This work was supported by the Emergency launch of science and technology program during epidemic prevention and control in Shaanxi Province (grant number 2020LCZX-02).

Conflicts of interest

The authors declare no conflict of interest.

References

1. Helmy YA, Fawzy M, Elaswad A, et al (2020). The COVID-19 Pandemic: A Comprehensive Review of Taxonomy, Genetics, Epidemiology, Diagnosis, Treatment, and Control. J Clin Med, 9(4):1225.
2. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al (2015). The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis, 211(1):80-90.
3. Ko JH, Seok H, Cho SY, et al (2018). Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: A single centre experience. Antivir Ther, 23(7):617-622.
4. Ying Li, Shuchao Zhang, Shaoqiang Zhang, et al (2020). Treatment with convalescent plasma for one covid-19 patient. Journal of Clinical Transfusion and Laboratory Medicine. Available from: http://kns.cnki.net/kcms/detail/34.1239.R.20200415.1851.002.html
5. Kai Duan, Bende Liu, Cesheng Li, et al (2020). Effectiveness of convalescent plasma therapy in severe covid-19 patients. Proc Natl Acad Sci U S A, 117(17):9490-96.
6. Chenguang Shen, Zhaoqin Wang, Fang Zhao, et al (2020). Treatment of 5 critically ill patients with covid-19 with convalescent plasma. JAMA, 323(16):1582-1589.
7. Bin Zhaing, Shuyi Liu, Tan Tan, et al (2020). Treatment with convalescent plasma for critically ill patients with severe acute respiratory syndrome coronavirus 2 infection. Chest, 158(1): e9-e13
8. Ahn JY, Sohn Y, Lee SH, et al (2020). Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. J Korean Med Sci, 35(14): e149.
9. Mingshiang Ye, Dian Fu, Yi Ren, et al (2020). Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol, 10.1002/jmv.25882.
10. Libo Zhang, Rongrong Pang, Xiang Xue, et al (2020). Anti-SARS-CoV-2 virus antibody levels in convalescent plasma of six donors who have recovered from COVID-19. *Aging (Albany NY)*, 12(8):6536–6542.

11. Qinglei Zeng, Zuijiang Yu, Jianjun Gou, et al (2020). Effect of convalescent plasma therapy on viral shedding and survival in patients with coronavirus disease 2019. *J Infect Dis*, 222(1):38–43.

12. Jingtao Dai, Ma Zhuo, Aiqi Xi, et al (2020). Treatment experience of three covid-19 cases in the fourth people’s hospital of qinghai province. *Chinese High Altitude Medicine and Biology*, 41:19–21.

13. Anderson J, Schauer J, Bryant S, et al (2020). The use of convalescent plasma therapy and remdesivir in the successful management of a critically ill obstetric patient with novel coronavirus 2019 infection: A case report. *Case Rep Womens Health*, 27: e00221.

14. Salazar E, Perez KK, Ashraf M, et al (2020). Treatment of coronavirus disease 2019 (COVID-19) patients with convalescent plasma. *Am J Pathol*, 190(8):1680–1690.

15. Ling Li, Wei Zhang, Yu Hu, et al (2020). Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening covid-19. *JAMA*, 324(5): 460–470.

16. Yinglong Ma, Zhenggui Yang, Qiang Ye, et al (2020). Effect of plasma treatment novel coronavirus pneumonia in critically ill patients in ningxia designated hospital. *Ningsxia Medical Journal*, 42(4):356–357.

17. Yujie Kong, Chen Cai, Li Ling, et al (2020). Successful treatment of a centenarian with coronavirus disease 2019 (COVID-19) using convalescent plasma. *Transfus Apher Sci*, 102820. Available from: https://doi.org/10.1016/j.transci.2020.102820

18. Joyner M, Wright RS, Fairweather D, et al (2020). Early safety indicators of covid-19 convalescent plasma in 5,000 patients. Preprint. medRxiv, doi: 10.1101/2020.05.12.20099879.

19. Çınar, O. E, Sayınalp B, Aladağ Karakulak, E, et al (2020). Convalescent (immune) plasma treatment in a myelodysplastic COVID-19 patient with disseminated tuberculosis. *Transfus Apher Sci*. Available from: https://doi.org/10.1016/j.transci.2020.102821

20. Hegerova L, Gooley TA, Sweerus KA, et al (2020). Use of convalescent plasma in hospitalized patients with COVID-19: case series. *Blood*, 136(6): 759–762.

21. Tianmin Xu, Bin Lin, Cong Chen, et al (2020). Non-optimal effectiveness of convalescent plasma transfusion and hydroxychloroquine in treating COVID-19: a case report. *Virus J*, 17: 80.

22. Kun Xiao, Yang Lin, Zhifang Fan, et al (2020). Effect of transfusion convalescent recovery plasma in patients with coronavirus disease 2019. *Zhong Nan Da Xue Xue Ban Yi Xue Ban*, 45(5):565-570.

23. Epstein J, Burnouf T (2020). Points to consider in the preparation and transfusion of COVID-19 convalescent plasma. *Vox Sang*, Available from: https://doi.org/10.1111/vox.12939

24. National Health Commission of China (2020). COVID-19 diagnosis and treatment plan (trial fourth edition) (EB/OL) (2020-01-27) (2020-05-06). National Health Commission. http://www.nhc.gov.cn/yzwj/s7653p/202001/4294563ed35b43209b317396d7085e67/ files/7a9309111267475a99d430692e8bf78.pdf

25. National Health Commission of China (2020). COVID-19 diagnosis and treatment plan (trial fifth edition) (EB/OL) (2020-02-05) (2020-05-06). National Health Commission. http://www.nhc.gov.cn/zywjg/s7653p/202002/3b09b894ae9b4204a79db3b8912d4440/files/7260301a393845ec87ff6dec5d2965e7.pdf

26. National Health Commission of China (2020). COVID-19 diagnosis and treatment plan (trial sixth edition) (EB/OL) (2020-02-19) (2020-05-06). National Health Commission. http://www.nhc.gov.cn/zywjg/s7653p/202002/8334a8326d94d329df51d7da8ae6c2/files/b218cfeb1bce54639a227f922b6b817.pdf

27. National Health Commission of China (2020). COVID-19 diagnosis and treatment plan (trial seventh edition) (EB/OL) (2020-03-04) (2020-05-06). National Health Commission. http://www.nhc.gov.cn/zywjg/s7653p/2020...
03/46c9294a7dfe4cef80d7f5912eb1989/files/3e3e6945832a438aeae41535088e6964.pdf
28. National Health Commission of China (2020). COVID-19 convalescent plasma clinical treatment plan (trial second edition). National Health Commission. http://www.nhc.gov.cn/yzygj/s7653p/202004/c083f2b0e7eb4036a59be419374ea89a/files/0f4be6a0f4f0419caecab666ef7ceed.pdf
29. National Health Commission of China (2020). Further strengthen the work plan for plasma treatment of convalescent covid-19 patients (EB/OL). (2020-02-28 ) (2020-05-06). National Health Commission Web; Available from: http://www.nhc.gov.cn/yzygj/s7658/202002/9c53edf84f1f480e9d6d5f5f5c6a5f.shtml
30. National Health Commission of China (2020). COVID-19’s diagnosis and treatment plan for severe and critical cases (trial second edition). (2020-03-04) (2020-05-06). National Health Commission. http://www.nhc.gov.cn/yzygj/s7658/202002/6d608a7e8bf49eca418a6074e2bf5a2/files/a5e0023491544c6867a3e6b7c111b7.pdf
31. Food and Drug Administration (2020). Coronavirus (COVID-19) update: Daily roundup. (2020-03-24) (2020-05-06). Food and drug administration. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-march-24-2020
32. National Institutes of Health (2020). COVID -19 is an emerging, rapidly evolving situation. National Institutes of Health. Available from: https://www.covid19treatmentguidelines.nih.gov/critical-care/pharmacologic-interventions/
33. Bloch EM, Shoham S, Casadevall A, et al (2020). Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest, 130(6): 2757–2765.
34. Franchini M, Marano G, Velati C, et al (2020). Operational protocol for donation of anti-COVID-19 convalescent plasma in Italy. Vox Sang. Advance online publication. https://doi.org/10.1111/vox.12940

Available at: http://ijph.tums.ac.ir