Safety and efficacy of convalescent plasma therapy for the management of COVID-19: A systematic review

Sitaram Khadka[1], Muhammad Saleem[2], Dhan Shrestha[3], and Pravash Budhathoki[4]

[1]Shree Birendra Hospital
[2]Government College University Faisalabad
[3]Mangalbare Hospital, Morang
[4]Dr Iwamura Memorial Hospital

June 3, 2020

Abstract

Aim: Till date, no proven treatment exists for coronavirus disease (COVID-19), though different types of treatment modalities are being practiced around the world. Small-scale convalescent plasma (CP) therapies from COVID-19 recovered donors have shown favorable results with fewer adverse consequences. In this systematic review, we aimed to determine the safety and efficacy of CP as a therapy for COVID-19. Methods: The English language databases of PubMed, Google Scholar, and ScienceDirect were searched upto 22 May 2020. Eligibility for inclusion, risk of bias assessment, and data extraction from the included studies was determined and a narrative synthesis was conducted. Results: A total of 12 studies were selected for review. The overall risks of bias was high. The results revealed that the initiation of CP therapy during the early stages of viremia was significant in a safety and efficacy viewpoint. The patients were also receiving concomitant drugs and other supportive therapies in 10 studies. Viral loads were documented to decrease and become negative in 8 studies within 3-26 days post-transfusion. The improvement in clinical symptoms following CP therapy was demonstrated in 9 studies. Most of the patients experienced very few adverse effects. There were a total of 622 mortalities out of 5079 patients in total studies. Conclusions: The rational practice of CP therapy based on a risk-benefit judgment can prove to be an efficacious therapeutic option until the approval of any therapeutic and/or prophylactic agent(s), though substantial randomized controlled trials (RCTs) are necessary to validate the effectiveness of such therapy.

Abstract

Aim : Till date, no proven treatment exists for coronavirus disease (COVID-19), though different types of treatment modalities are being practiced around the world. Small-scale convalescent plasma (CP) therapies from COVID-19 recovered donors have shown favorable results with fewer adverse consequences. In this systematic review, we aimed to determine the safety and efficacy of CP as a therapy for COVID-19.

Methods: The English language databases of PubMed, Google Scholar, and ScienceDirect were searched upto 22 May 2020. Eligibility for inclusion, risk of bias assessment, and data extraction from the included studies was determined and a narrative synthesis was conducted.

Results : A total of 12 studies were selected for review. The overall risks of bias was high. The results revealed that the initiation of CP therapy during the early stages of viremia was significant in a safety and efficacy viewpoint. The patients were also receiving concomitant drugs and other supportive therapies in 10 studies. Viral loads were documented to decrease and become negative in 8 studies within 3-26 days post-transfusion. The improvement in clinical symptoms following CP therapy was demonstrated in 9 studies. Most of the patients experienced very few adverse effects. There were a total of 622 mortalities out of 5079 patients in total studies.

Conclusions : The rational practice of CP therapy based on a risk-benefit judgment can prove to be an efficacious therapeutic option until the approval of any therapeutic and/or prophylactic agent(s), though substantial randomized controlled trials (RCTs) are necessary to validate the effectiveness of such therapy.

INTRODUCTION

COVID-19 is a respiratory tract infection caused by a new strain of coronavirus called severe acute respiratory syndrome conoravirus -2 (SARS-CoV-2) that spread so rapidly from its first outbreak in late December 2019 in Wuhan, Hubei province of China. There are altogether 5,267,419 confirmed cases with the death toll climbing at 341,155 worldwide as of 25 May 2020.[1] This infectious disease is associated with mild to severe symptoms such as fever, cough, fatigue, shortness of breath to acute respiratory disease syndrome (ARDS), sepsis, multi-organ failure including acute kidney injury and cardiac injury in a complicated status resulting in death[2]. Old age, immune-compromised cases, and comorbidities are the risk factors that lead to death in COVID-19.[2,3] A recent structural analysis indicated the probable origin of the virus as a bat, from where it has transmitted to humans after mutation in the spike glycoprotein and nucleocapsid protein.[4] Then human to human transmission started mainly through contact with an infected person as it gets airborne and by touching the face by hand after contact with an object containing the virus.[5] The world health organization (WHO) has already declared it as a pandemic on 11 March 2020 due to the over 118,000 reported cases from 110 countries around the world by that time with the sustained risk of further global spread.[6]

Still, there is no proven treatment to cure the condition due to the lack of substantial evidence. The time constraint and pandemic outbreak are the major challenges to deal with COVID-19. Supportive care has been practiced as stated in the WHO interim guidance for COVID-19 management with a major focus on oxygenation, ventilation, symptomatic treatment, fluid management, and prevention of complications based on the clinical status of patients.[2] Different therapeutic agents are being used in clinical settings around the world, some of which are like a combination of azithromycin and hydroxychloroquine, antivirals like remdesivir, oseltamivir, ganciclovir, combination of lopinavir and ritonavir, and steroids.[7] Recently conducted RCT has shown a lower rate of seroconversion and more adverse effects with hydroxychloroquine among mild to moderate COVID-19 cases.[8] Other observational studies also showed no clinical efficacy with hydroxychloroquine.[9] As a ray of hope, the emergency use of remdesivir has been recently approved by the US-Food and Drug Administration (US-FDA) to be used in certain conditions[10], though its use has not led to significant benefit in RCT conducted by China.[11]

CP therapy is one of the approaches adopted following the guidance provided by the US-FDA to use CP as an investigational product during such a global health crisis.[12,13] The lack of effective intervention has made it necessary to explore and review CP therapy as a potential therapeutic modality for COVID-19. It is a classical adaptive immunotherapy where antibodies from the plasma samples of patients recovered from a virus are transfused with adequate neutralizing antibody titers to the patient affected by the same virus as a therapy or a prophylactic measure to patients exposed to the same virus.[14,15]

Figure 1: Convalescent plasma therapy process for COVID-19

METHODS

This review article was based on the PRISMA protocol.[16]

Search strategy

PubMed, Google Scholar, and Science Direct were searched for “COVID-19”, “Convalescent plasma therapy”, “COVID-19 plasma therapy”, “Plasma therapy coronavirus”, and “SARS-CoV-2 plasma therapy” for articles published till 25 May 2020. The search strategies used can be found in**supplementary data 2**.

Inclusion criteria

The original research articles including case reports, case series, observational studies, retrospective studies, randomized or controlled studies about CP therapy for the treatment of COVID-19 were reviewed and included.

Exclusion criteria

The exclusion criteria considered were articles about other viral pandemics without any discussion of COVID-19 and its management with CP therapy. Review articles, viewpoints, editorials, letters, perspectives, comments, and protocols were excluded along with non-English literature and articles with no full text.

Extraction of data

Data were extracted by two reviewers separately and a table was filled according to the data. Studies were selected by two reviewers (SK and PB) owing to the criteria and any differences between articles selections were resolved based on the review of a third person (DBS).

Assessment of bias

The overall bias for our study was determined to be high. All our studies were non-randomized. The sample size was small in most of the studies except Joyner's study (n = 5000), but it was a non-randomized trial. We found the selection bias to be high among all our studies. No blinding of treating physicians and patients was done in most of the cases. In a few studies, the lack of proper follow up of the patient's outcome was mentioned like Joyner's study. In most studies, other prognostic factors like chronic medical conditions were not taken into account. The detailed bias assessment is done in the**figure 2**.

Statistical analysis

It was not possible for a meta-analysis because of the inadequacy of research articles.

1. **RESULTS**
2. **Study selection**

A total of 1128 potentially eligible articles were retrieved from the initial database searches. After the exclusion of 132 duplicates, the abstracts of 996 articles were reviewed. 939 articles were excluded because of the unavailability of full texts, other languages, and being predominantly not related to plasma therapy and COVID 19. Full texts of 57 articles were extracted and among them, we selected 12 studies for review as depicted in **figure 3** .

Figure 3: Prisma flow diagram of the study process

Out of the 12 studies included; 6 studies were case-series, 3 case reports, and the rest of the 3 studies were a single-arm prospective intervention, retrospective observational study, and clinical trial. The extracted studies are mentioned in **table 1** , including their important particulars. Eight studies were conducted in China, three in the United States (US), and the rest in South Korea.

Study population

A total of 5079 patients were involved in 12 studies with 3197 males, 1856 females, and 23 other genders. The age range of the people was 19 – 97 across the 12 studies. Two pregnant patients were present in studies.[17,18] Comorbidities like chronic obstructive pulmonary disease (n = 2), hypertension (n = 17), and diabetes mellitus(DM) (n = 16) were present in the 7 studies.[14,17-23]

Dosage and neutralizing antibody titer

The dosage of CP therapy was varied from 200 – 2500 ml across 12 studies. The most frequently used dosage was 200 ml across 7 studies. Only 2 studies conducted by Shen et al and Duan et al mentioned the neutralizing antibody titer following CP therapy, which was found to be 1:80-1:480 and 1:640, respectively.[14,19]

Initiation of CP therapy

CP therapy was initiated 1-37 days after admission to the hospital or 4 – 31 days after onset of symptoms. Initiation of CP therapy during the early stages of viremia has generally been shown to be more beneficial in various studies.[18,23] The quickest initiation of CP therapy on the first day of admission was done in the study of Anderson et al.[18]

Intensive care unit (ICU) admission and mechanical ventilation

A total of 3391 patients were admitted to ICU in 12 studies. 49 patients were mechanically ventilated in 10 studies. In nine studies, nine patients received low oxygen flow therapy, while 17 patients received high flow oxygen therapy. According to Joyner et al, 72% (n=3600) patients had respiratory failure and most likely required ventilator support or other forms of oxygen therapy, but the modality has not been mentioned.[24] ARDS was diagnosed in 1750 cases across 10 studies except for Pei et al and Joyner et al.

Concomitant therapy

Antiviral, interferon, and steroids were widely used across all studies. Remdesvir was used in 2 studies done in the US by Andersen et al and Salazar et al.[18,23] Antibacterials like azithromycin, levofloxacin, and vancomycin were used along with antifungals. Hydroxychloroquine was used in 4 studies. Azithromycin, hydroxychloroquine, and remdesevir were used concomitantly in 2 studies done by Salazar et al and Andersen et al in the US.[18,23] The Chinese herbal medication was practiced in a study by Tan et al in China.[25]

Clinical benefit and discharge following CP therapy

The improvement in clinical symptoms following CP therapy has been mentioned in 9 studies. Studies conducted by Joyner et al and Pei et al did not properly mention such improvement.[24,26] About 75 patients in 9 studies required different forms of respiratory support at baseline. In Tan's study, the patient was clinically stable before CP therapy and remained stable until the end.[25]

Shen et al reported a normal temperature of patients within 3 days (n = 4).[19] An increase in PaO2/FiO2 was obtained within 12 days (Range: 172 – 276 before and 284 - 366 after) despite patients having severe ARDS before CP therapy. Neutralizing antibody titers increased (Range: 40 - 60 before and 80 - 320 on day 7) with the resolution of ARDS (n = 4) at 12 days and weaning of mechanical ventilation (n = 3) in 2 weeks. Three patients were discharged 32-35 days post CP therapy.

Zhang et al described extubation of 2 patients in 31 and 39 days of hospital stay, although all 4 patients had severe ARDS at baseline.[20] Three patients were discharged from 7 – 27 days post CP therapy. One patient got shifted to the ICU. Chest computed tomography (CT) showed a complete resolution in 1 case.

Ahn et al reported an increase in PaO2/ FiO2 to 230 and 300 on days 9 and 18 in 2 patients who had severe ARDS at baseline.[21] Weaning from ventilation and tracheostomy was done in 1 patient. Another patient was extubated and discharged at 18 days post CP therapy.

Duan et al mentioned improvement in clinical symptoms in 1-3 days following CP therapy and decreased respiratory support in 4 of the 10 patients.[14] The resolution of CT abnormalities was seen in 7 days. Normal lab findings and improvement in pulmonary functions reported after CP therapy. Then, 3 cases were discharged and 7 were prepared for discharge.

Ye et al reported improvement in clinical symptoms and resolution of CT scans in 4 patients requiring oxygen support following CP therapy.[17] Four patients were discharged 4 - 10 days post-transfusion.

Zeng et al described the discharge of 2 patients, one from treatment and another from the control group.[22] Nothing was mentioned about the clinical benefit following CP therapy with a primary focus on the clearance of viral load. All 21 patients were in ICU from both control and treatment groups at baseline.

Pei et al described 2 successful cases of CP therapy who were discharged on 7 and 14 days post-transfusion. The patient who had anaphylaxis to such therapy was discharged later than successful cases on 23 days post failed transfusion.[26]

Salazar et al described changes in clinical status on day 7 and day 14 using a 6 point WHO ordinal scale.[23] All 25 patients were in critical condition and admitted to ICU at baseline. At day 7 post-transfusion, 9 patients got improvement, while 13 remained static and 3 deteriorated. At day 14 post-transfusion, 19 patients got clinically better, while 3 were unchanged, 3 deteriorated, and 1 died. At days 7 and 14, the discharged cases

were 7 and 11, respectively. This was a prospective study that demonstrated clinical benefit following CP therapy.

Anderson et al described a patient who required high flow oxygen on the day of CP therapy and was intubated a day post CP transfusion.[18] She was extubated after 9 days, oxygen support was withdrawn after 10 days, and discharged after 13 days post-transfusion. The patient was continued on remdesivir which affects the certainty of evidence regarding the benefit being solely due to CP therapy.

Yang et al described a patient who required non-invasive positive pressure ventilation at baseline. Upon 4 doses of CP therapy, the clinical and radiological improvement was demonstrated after 3 days of the fourth plasma transfusion.[27]

Mortality

Out of 5079 patients across 12 studies, the mortality reached 622. No mortalities were there in 9 studies (n=33). Among the rest 3 studies; 1 mortality in Salazar's study, 19 in Zeng's study where 5 in treatment and 14 in the control group, and 602 mortality in 7 days after CP therapy in Joyner's study were demonstrated.[22-24]

Viral load after CP therapy

Viral loads were documented to decrease and become negative in 8 studies.[14,17,19-22,25] The time frame for negative viral load post CP therapy varied from 3-26 days. Zeng et al performed a retrospective observational study in which viral clearance was 100 % in the treatment group (n = 6) and only 21.4% in control group, which supports the evidence of quicker viral clearance with CP therapy.[22] Similarly, a study conducted by Tan et al demonstrated a negative viral load a day after transfusion.[25]

3.10 Adverse effects

Most of the patients experienced very few adverse effects. The incidence of adverse effects and mortality rate were < 1 % and 0.3%, respectively, as stated by Joyner et al. Transfusion-associated circulatory overload (TACO) (n = 7), transfusion-related lung injury (TRALI) (n = 11) , and severe allergic reactions (n = 3) were reported.[24] This is the largest study done and was focused especially on the safety of CP therapy. Besides, a study done by Pei et al. showed anaphylaxis as a severe side effect of CP therapy, but the number of study subjects was small.[26] Some abnormal skin reactions like red spots or morbilliform rash have been explained in only one patient each in the study done by Duan and Salazar et al.[14,23] Fever was seen in a study done by Tan et al following CP therapy.[25]

Table 1**:**Studies on CP therapy for COVID-19 treatment

Currently, 75 clinical trials are being done all around the world[28](Supplementary data 3 – **Clinical trials/ Table 2**). With most of the 30 trials in the US, followed by other trials in Colombia-5 trials, Mexico-5 trials, Italy- 4 trials, and Egypt-3 trials. Switzerland, Chile, France, Canada, Sweden, Spain, and India are conducting 2 trials each. While countries like North Macedonia, Russian Federation, Saudi Arabia, Pakistan, Netherlands, Bahrain, China, Hungary, Indonesia, Argentina, Iran, and Denmark are also conducting 1 trial each. No location is being provided in the case of 2 trials. A total of 40 trials are recruiting participants while 24 trials have not yet begun recruiting. There are 2 active and not recruiting trials, 3 trials are enrolled by invitation, and 6 trials are in available status. A total of 2 trials are observational and 6 available trials are of expanded excess type, while the rest of the trials are RCTs. The smallest trial enrollment is 10 while the largest trial enrollment is 2000.[28]

DISCUSSION

The review was primarily done to focus on the therapeutic efficacy and safety of CP therapy among COVID 19 patients. For this purpose, we included 12 different studies ranging from case series, case reports, case trials, observational cohort study, retrospective study, and single-arm intervention study.

Only one CT has been done so far, which has primarily focused on the early safety of CP therapy.[24] Based on the trial, there has been preliminary evidence of CP therapy being a safe treatment with < 1 % mortality. Due to the lack of studies focusing on the therapeutic efficacy of CP therapy alone, a query remains to comprehend whether the results of the studies were due to natural disease progression, CP therapy, or other concomitant treatments. Major outcomes are discussed below:

Mortality following CP therapy

There were a total of 622 mortalities out of 5079 patients across the 12 studies. The majority of mortalities were found in the clinical trials with a total of 602 mortalities in Joyner's study, but this trial is in the early phase and more reporting is still to be done as only 5000/8932 trial reports are mentioned in this study.[24] Zeng's study has 19 mortalities out of 21 patients which can be considered high, but CP therapy was given at a median of 21.5 days after infection, and there is theoretical evidence that such therapy is only most effective when given early in the disease course.[22]Salazar's study had just 1 mortality out of 25 patients as CP therapy was given early with a median of 10 days from the onset of symptoms.[23] Therefore, early initiation of CP therapy might have a positive impact on mortality. However, in 10 studies except for Joyner's and Pie's study, the patients received concomitant drug therapy, which puts a query in the determination of the exact effect of CP therapy even though the CP therapy was initiated earlier.

Improvement of clinical symptoms

Clinical improvements were seen in 9 studies following CP therapy, though most of the patients required respiratory support at baseline. Finally, most patients were weaned from ventilator support and other forms of oxygen therapy.

ICU Admission and discharge

The range for the discharge of patients was from 4 - 35 days following CP therapy across 9 studies. The total number of patients discharged was 49 out of 79 across 11 studies except for the study conducted by Joyner et al. Among the studies reviewed, a total of 3391 patients were admitted to ICU. Most of the patients did not need ICU at the end and some got discharged in 10 studies. The studies conducted by Joyner et al and Pei et al did not mention the patients' status at the end.[24,26]

Viral load and antibody titer

Viral loads were negative following CP therapy in 8 studies and antibody titers following such therapy were measured only in 2 studies.[14,19]. It is important to conduct trials on known antibody titers following CP therapy as it is important to determine the protective titer that is necessary for safeguarding against COVID-19. US-FDA has recommended the titer of 1:160 for the donation of blood for plasma.[13] The protective titer of the antibody for Middle East respiratory syndrome was found to be 1:80 in a study conducted by Ko et al.[29] Two of the reviewed studies found the antibody titer following CP therapy to be 1:80-1:480 and 1:640.[14,19] In Zhang's study, the IgG antibody titer after 29-46 days of 6 patients who recovered from COVID-19 without the use of CP therapy was found to be more than 1:320 among 5 of the 6 donors.[30] It is not clear whether the antibody titers mentioned in the 2 studies were due to CP therapy alone or as an innate immune response to the infection like in Zhang's study.

Adverse effects

Because of the large clinical trials done in the US where the results of 5000 people are out, it is remarkable that CP therapy is a safe treatment option for COVID-19 as only $< 1\%$ adverse events have been observed with 0.3% mortality.[24] However, the trial was not randomized and early reporting of 5000 cases may have led to selection bias in the studies. Based on multiple studies, the adverse events found were severe allergic reactions including anaphylaxis, TACO, TRALI, transient red macular spots, morbilliform rash, and fever.[14,23-26]

LIMITATIONS OF THE STUDY

Most of the included studies were case reports and case series. Only one clinical trial was included which

focused solely on side effects and was non-randomized and had early reporting. Because of incomplete clinical trials focusing on the therapeutic efficacy of CP therapy so far, we could not include these in our study. Most of our studies lacked a control group except for the one conducted by Zeng et al. There was a moderate to high risk of biases in our studies.

CONCLUSION

Based on data from the reviewed studies; CP therapy, in addition to concomitant drug therapy and other supportive therapies, has shown superior evidence in clinical improvement, viral clearance, safety, and survival rate. The perplexities remain for getting a conclusion about the possible favorable outcome is due to CP therapy alone based on given evidence and not due to natural disease progression or additional therapies. This question can only be answered after the ongoing RCTs focusing on therapeutic efficacy in terms of mortality rates, requirements of respiratory support, changes in viral load, and antibody titers following therapy are completed. In the end, it is noteworthy to tackle the global pandemic by CP therapy as a last resort along with additional therapies accompanied by risk-benefit judgment until the availability of therapeutic and/or prophylactic agent(s) for use.

Acknowledgment

We are highly thankful to Ms. Pragya Pandey, Kathmandu, and Muhammad Abdul Jabar Adnan, Lecturer Department of Sports Science and Physical Education, University of the Punjab, Lahore, for their help in the finalization of this manuscript.

Conflict of interest

We have no conflict of interest for writing this review

Authors' contributions

SK and MS conceived the idea. MS reviewed the manuscript and guided in a systematic analysis. SK, DBS, and PB contributed to the literature search and systematic analysis and drafted the manuscript.

All the co-authors read and approved the final manuscript.

Funding statement

We have not received any funding for this work.

REFERENCES

1. Coronavirus (COVID-19). WHO. https://who.sprinklr.com/. Published 2020. Accessed May 25, 2020.

2. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. WHO. file:///C:/Users/Admin/Downloads/WHO-2019-nCoV-clinical-2020.4-eng.pdf. Published 2020. Accessed May 21, 2020.

3. CDC. Coronavirus Disease. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Published 2020. Accessed May 25, 2020.

4. Benvenuto, D., Giovanetti, M., Ciccozzi, A., Spoto, S., Angeletti, S., & Ciccozzi M. The 2019-new coronavirus epidemic: evidence for virus evolution. *J Med Virol* . 2020;92(4):455-459.

5. Shereen, M. A., Khan, S., Kazmi, A., Bashir, N., & Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *J Adv Res* . 2020;24:91-98. doi:https://doi.org/10.1016/j.jare.2020.03.005

6. World Health Organization Declares COVID-19 a "Pandemic." Here's What That Means. *Time* . March 2020. https://time.com/5791661/who-coronavirus-pandemic-declaration/.

7. Cunningham, A. C., Goh, H. P., & Koh D. Treatment of COVID-19: old tricks for new challenges. *Crit Care* . 2020;24(91). doi:https://doi.org/10.1186/s13054-020-2818-6

8. Tang, W., Cao, Z., Han, M., Wang, Z., Chen, J., Sun, W., ... & Chen W. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* . 2020;369:m1849. doi:https://doi.org/10.1136/bmj.m1849

9. Mahévas, M., Tran, V. T., Roumier, M., Chabrol, A., Paule, R., Guillaud, C., ... & Schlemmer F. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ* . 2020;369:m1844. doi:https://doi.org/10.1136/bmj.m1844

10. Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment. US-FDA. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment. Published 2020. Accessed May 21, 2020.

11. Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., ... & Hu Y. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* . 2020. doi:https://doi.org/10.1016/S0140-6736(20)31022-9

12. 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.

13. Recommendations for Investigational COVID-19 Convalescent Plasma. US-FDA. https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma. Published 2020. Accessed May 25, 2020.

14. Duan, K., Liu, B., Li, C., Zhang, H., Yu, T., Qu, J., ... & Peng C. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci* . 2020;117(17):9490-9496. doi:https://doi.org/10.1073/pnas.2004168117

15. Casadevall, A., & Pirofski LA. The convalescent sera option for containing COVID-19. *J Clin Invest* . 2020;130(4).

16. Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., ... & Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* . 2009;151(4):W-65.

17. Ye, Mingxiang., Fu, Dian., Ren, Yi., Wang, Faxiang., Wang, Dong., Fang, Zhang., Xia, Xinyi., & Lv T. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol* . 2020. doi:https://doi.org/10.1002/jmv.25882

18. Anderson, J., Schauer, J., Bryant, S., & Graves CR. 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 Reports Women's Heal* . 2020;27:e00221. doi:https://doi.org/10.1016/j.crwh.2020.e00221

19. Shen, C., Wang, Z., Zhao, F., Yang, Y., Li, J., Yuan, J., ... & Wei J. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *Jama* . 2020;323(16):1582-1589. doi:10.1001/jama.2020.4783

20. Zhang, B., Liu, S., Tan, T., Huang, W., Dong, Y., Chen, L., ... & Zou Y. Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. *Chest* . 2020. doi:https://doi.org/10.1016/j.chest.2020.03.039

21. Ahn JY, Sohn Y, Lee SH et al. Use of Convalescent Plasma Therapy in Two COVID-19 Patients with Acute Respiratory Distress Syndrome in Korea. *J Korean Med Sci* . 2020;35(14). doi:10.3346/JKMS.2020.35.E149

22. Zeng, Q. L., Yu, Z. J., Gou, J. J., Li, G. M., Ma, S. H., Zhang, G. F., ... & Li C. Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. *J Infect Dis* . 2020. doi:https://doi.org/10.1093/infdis/jiaa228

23. Salazar, E., Perez, K. K., Ashraf, M., Chen, J., Castillo, B., Christensen, P. A., ... & Subedi S. Treatment of COVID-19 Patients with Convalescent Plasma in Houston, Texas. *medRxiv* . 2020. doi:https://doi.org/10.1101/2020.05.08.20095471

24. Joyner, M., Wright, R. S., Fairweather, D., Senefeld, J., Bruno, K., Klassen, S., ... & Rea R. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients. *medRxiv* . 2020. doi:https://doi.org/10.1101/2020.05.12.20099879

25. Tan, L., Kang, X., Zhang, B., Zheng, S., Liu, B., Yu, T., ... & Miao H. A special case of COVID-19 with long duration of viral shedding for 49 days. *medRxiv* . 2020. doi:https://doi.org/10.1101/2020.03.22.20040071

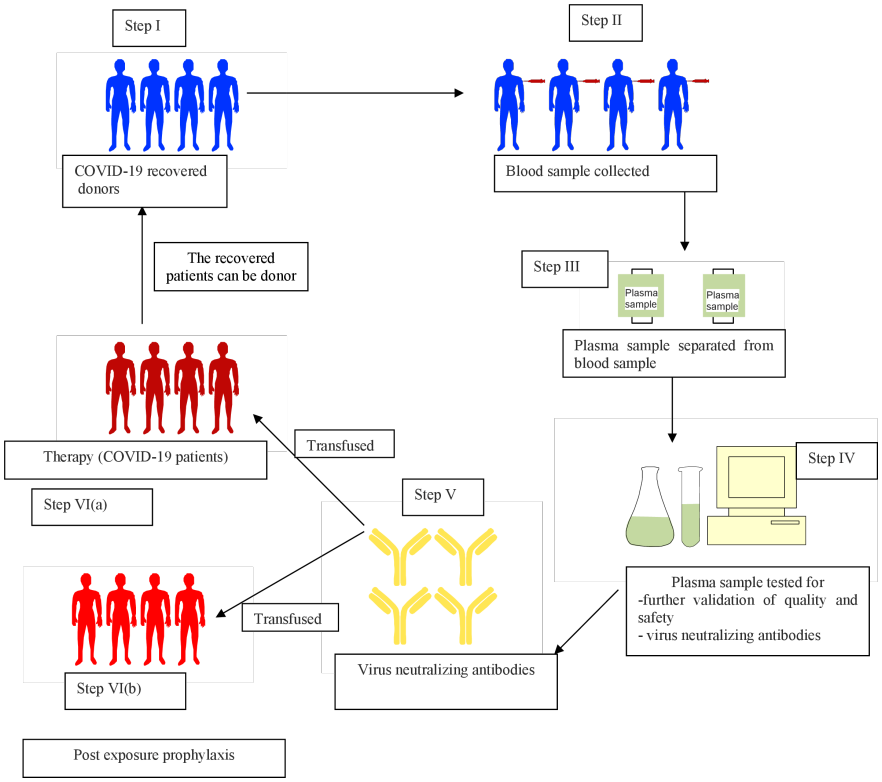
26. Pei, S., Yuan, X., Zhang, Z. Z., Yao, R. R., Xie, Y., Shen, M. M., ... & Yin M. Convalescent plasma to treat covid-19: Chinese strategy and experiences. *medRxiv* . 2020. doi:https://doi.org/10.1101/2020.04.07.20056440

27. Yang, X., Sui, Y., Liu, F., Kang, Z., Wu, S., Zhao, J., ... & Zhang Y. Clinical Characteristics and Convalescent Plasma Therapy in Severe and Critically Ill COVID-19 Patients. *Prepr with LANCET* . 2020. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3576894.

28. ClinicalTrials.gov. NIH U.S. National Library of Medicine. https://clinicaltrials.gov/ct2/results?term=covid+19+convalescent+plasma&Search=Search. Published 2020. Accessed May 25, 2020.

29. Ko, J. H., Seok, H., Cho, S. Y., Ha, Y. E., Baek, J. Y., Kim, S. H., ... & Cho D. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. *Antivir Ther* . 2018;23(7):617-622. doi:10.3851/imp3243

30. Zhang, L., Pang, R., Xue, X., Bao, J., Ye, S., Dai, Y., ... & Yi Y. Anti-SARS-CoV-2 virus antibody levels in convalescent plasma of six donors who have recovered from COVID-19. *Aging (Albany NY)* . 2020;12(8):6536-6542. doi:10.18632/aging.103102



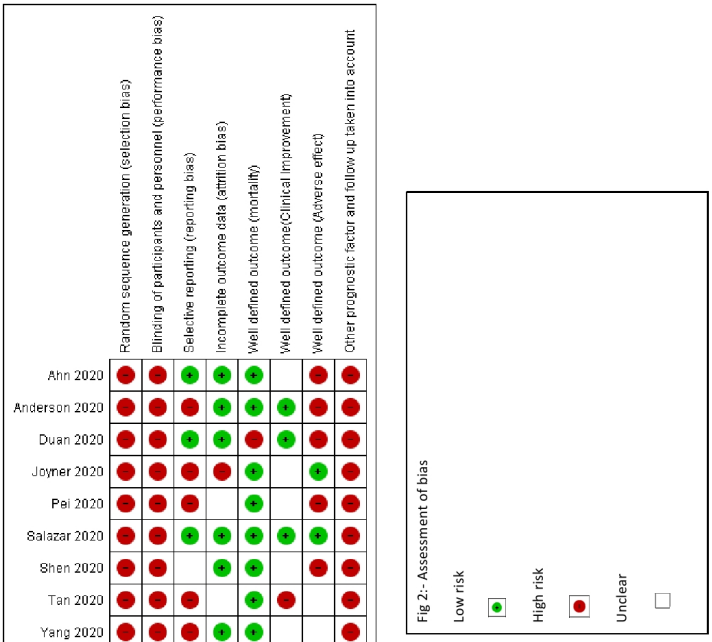
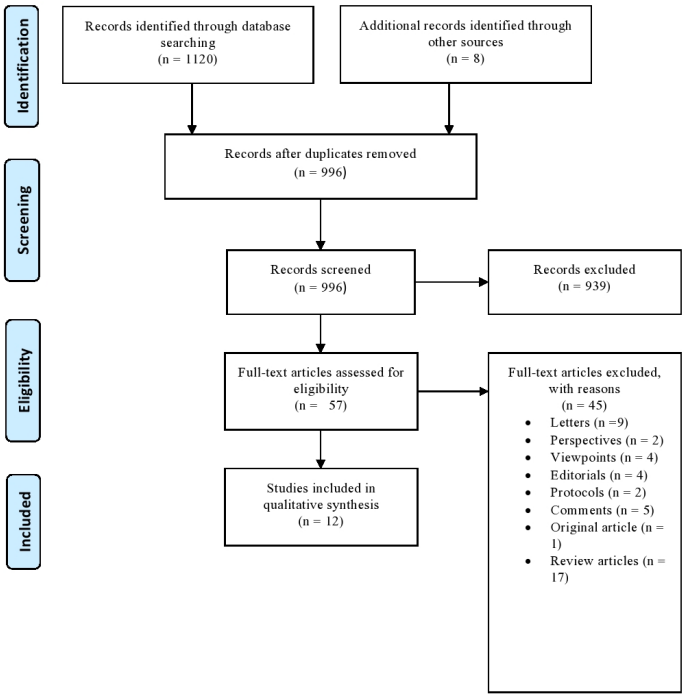


Fig 2:- Assessment of bias



Hosted file

Table 1 (Studies Reviewed).docx available at https://authorea.com/users/329335/articles/456329-safety-and-efficacy-of-convalescent-plasma-therapy-for-the-management-of-covid-19-a-systematic-review