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1.Title: Convalescent plasma a clutch at straws in COVID-19 management! A systematic review and meta-analysis

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11. Author's individual contribution:

Dr. Soumya Sarkar: Conceptualization**,** Search strategy**,** Study selection, Data extraction, Risk of bias assessment, and drafted the manuscript

Dr. Kapil Dev Soni*:* Study selection, Data extraction, Risk of bias assessment, Quality of the evidence assessment, Data synthesis, and editing

Dr. Puneet Khanna: Conceptualization, Search strategy, Study selection, Risk of bias assessment, Quality of the evidence assessment, and editing

12. **Summary statement**:

Impact of Convalescent plasma therapy in COVID-19 management:

- ↓ Mortality (OR 0.44, 95% CI 0.25 to 0.77)
- ↑ Viral clearance (OR 11.29,95% CI 4.9 to 25.9,)
- ↑ Clinical-improvement (OR 2.06, 95% CI 0.8 to 4.9)

Abstract:

Background: In absence of definitive therapy for coronavirus disease (COVID-19), convalescent plasma therapy (CPT) may be a critical therapeutic option. This review

was conducted to evaluate the impact of CPT in COVID-19 patients based on the publications reported to date.

Methods: A robust screening of electronic databases was conducted up to 10th July 2020. The randomized controlled trials (RCTs), cohort studies, and case series with control group evaluating the effectiveness and safety of CPT in patients with COVID-19 are included for the meta-analyses.

Results: Our search retrieved seven studies, including two RCTs and five cohort studies, with a total of 5,444 patients. In patients with COVID-19, the use of CPT reduces mortality [Odd's ratio (OR) 0.44, 95% CI 0.25 to 0.77], increases viral clearance [OR 11.29, 95% CI 4.9 to 25.9] and improves clinically [OR 2.06, 95% CI 0.8 to 4.9].However, the evidences are of low quality (mortality reduction, and viral clearance),and very low quality (clinical improvement).

Conclusions: CPT may be beneficial for reducing mortality, viral shedding. and improving clinical conditions in COVID-19 patients. However, further randomized control trials (RCT) are required to substantiate the safety margin, initiation, optimal dosage, titre and duration of CPT.

Key words: (COVID-19): coronavirus disease, (SARS-CoV-2): severe acute respiratory syndrome coronavirus-2, (CPT): convalescent plasma therapy

1.**Introduction:**

1.1 *Convalescent Plasma Transfusion* (CPT) has been traditionally tried during large-scale epidemics in patients with viral infections whose critical condition refractory to supportive care.[1] It is obtained from a recently recovered person from a viral illness,

which is prospected to have the maximum levels of polyclonal antibodies directed against the virus.[2]

Both passive immunity (reduction in viremia)[3] and active immunity (host immune response)[4]

have been postulated for providing an immediate promising treatment option during the evaluation of existing drugs and developing new definitive therapies.

The effectiveness of CPT has been tested since the Spanish Influenza pandemic in 1915-1917[5], severe acute respiratory syndrome (SARS) in 2003[6], influenza A (H1N1) in 2009[7], avian influenza A (H5N1)[8], and even in Ebola[2].

Recently, the US Food and Drug Administration has approved the use of CPT for the patients of coronavirus disease (COVID-19) under the emergency investigational new drug category and not for routine clinical use.[9]

1.2 *The* absence of a definitive therapeutic modality for COVID-19 has made CPT most relevant in the current grievous scenario. However, the clinical data for the studies involving COVID-19, are still scarce. Thus, the aim of our study is to systematically analyze the current evidence of the efficacy and safety of convalescent plasma therapy in COVID-19 patients, for decision-making to prevent and control this pandemic. This study is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines.

2.Methods

2.1. *Search strategy*

This systematic search was conducted in major electronic databases (PubMed and Medline), Google Scholar (https://scholar.google.com), and preprint platforms MedRxiv (https://www.medrxiv.org) from January 1st,2020 to July 10th ,2020,

independently by two researchers (SS & PK). The following terminologies: ("COVID-19") OR ("SARS-CoV-2") AND ("plasma" OR "convalescent plasma") were searched.

2.2. *Inclusion and exclusion criteria*

We included randomized controlled trials (RCT), controlled clinical trials, prospective and retrospective comparative cohort studies, case-control studies; cross-sectional studies, and case series with a control group on steroid therapy for COVID-19 patients.

Our primary outcome of interest was mortality, and secondary outcomes included improvement in clinical conditions and clearance of viral shedding.

We excluded articles written in languages other than English, absence of essential data, and without retrievable full text (PRISMA flow diagram).[10-11].

2.3. *Study selection*

The available literature was screened independently after the removal of duplications by two researchers (SS and KDS). We screened all the abstracts primarily to exclude irrelevant articles. Finally, full-texts of the potentially eligible studies were screened for inclusion. Disagreements were consulted with a third researcher (PK).

2.4. *Data extraction*

Two researchers (SS and KDS) extracted the data independently from all included studies with the use of pre-conceived data extraction sheet. The Extracted information contained details of the intervention and control groups, mortality, clinical improvement, and viral clearance. The number of events along with the total number

of patients per group was extracted for dichotomous data. Studies with missing or unusable data are reported in findings descriptively.

2.5. *Risk of bias assessment:*

Two researchers (SS & PK) assessed the potential bias in each selected study independently. The third researcher (KDs)was consulted for resolving any difference of opinion.

The RoB 2.0 tool [12], was used for RCTs, which includes five domains: "randomization process", "deviations from intended interventions", "missing outcome data", "measurement of the outcome", and "selection of the reported result". We used the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I)[13] tool for assessing the risk of bias in non-randomized studies. It comprises of seven domains: "bias due to confounding", "selection of participants, classification of interventions", "deviations from intended interventions", "missing data", "measurement of outcomes", and "selection of the reported result". Each domain is graded as "Low", "Moderate", "Serious", and "Critical".

2.6. *Quality of the evidence:*

Two experienced researchers (PK & KDS) evaluated the quality of evidence by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.[14-15] It has five downgrading factors (study limitations, consistency of effect, imprecision, indirectness, and publication bias) and three upgrading factors (large magnitude of the effect, dose-response relation, and plausible confounders or biases). The quality of evidence of each outcome is classified as "High", "Moderate", "Low" or "Very low".[16-22]

2.7. *Data synthesis:*

Review manager version 5.4 was used for conducting the meta-analysis. The Odd's ratio (OR) with 95% confidence intervals (CIs) was assessed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [23]. Statistical heterogeneity was assessed with the I^2 statistic, >50% indicating substantial heterogeneity. Funnel plot was used to assess publication bias.

The present study was not registered for rapid decision making in the context of the ongoing public health emergency.

3. Results

3.1. *Basic characteristics*

We included seven studies (two RCTs and five cohort studies) out of 679 identified publications in this rapid review, after satisfying the inclusion criteria. (Figure 1) (Table 1). The risk of bias was low in one of the included RCTs and the other one had some concerns. (Figure 2a). Out of the rest five studies, four studies have been associated with a moderate degree of bias. (Figure 2b)

3.2. *Meta-analysis*

Mortality was assessed in seven articles (two RCTs and five cohort studies) with a total of 5,444 patients. The use of CPT reduced the risk of mortality almost by half in COVID-19 (OR =0.44, 95% CI 0.25 to 0.77, I^2=0), which is statistically significant (Figure 3)

Five studies with a total of 259 patients assessed the clinical improvement in COVID-19. The majority of the COVID-19 patients who received CPT showed clinical

improvement than in patients who received no CPT (OR 2.06, 95% CI 0.8 to 4.9, I^2=44%;), (Figure 4a). However, the finding is not statistically significant.

The incidence of viral clearance was assessed in two studies with a total of 144 patients. It is found that the use of CPT helps in viral clearance (OR 11.29, 95% CI 4.9 to 25.9, I^2=0%;) significantly. (Figures 4b).

Apert form mild heterogeneity among studies on assessing clinical improvement (I^2=44), the overall findings are homogenous. In view of the high homogeneity, the overall effect seems to be conclusive.

3.3. *Quality of evidence*

The quality of evidence on the impact of CPT on mortality and viral clearance in COVID-19 is of low quality, and clinical improvement is of very low quality (Table 2).

3.4. *Publication bias*

We assessed publication bias for the studies on COVID-19 mortality. The Funnel plot indicates a publication bias is likely in view of smaller studies with large effect. (Supplemental Figure 1)

4. **Discussion:**

4.1. We have identified low-quality evidence with variability that the convalescent plasma therapy is associated with around 44% reduction in the mortality in COVID-19 patients.

Similar systematic review and meta-analysis on severe acute respiratory syndrome (SARS), reported that the CPT is beneficial for reducing the (OR, 0.25; 95% confidence interval, .14–.45; I^2 = 0%) in comparison to placebo or no therapy.[31]

Another recent systematic review on CPT in COVID-19 patients reported about a potential reduction in mortality but unable to provide any opinion regarding the efficacy of CPT in COVID-19 due to paucity in quantitative synthesis [32]

The present study has identified a very low-quality evidence regarding improvement in clinical conditions and a low-quality evidence for viral clearance, are associated with CPT.

A recent systematic review on the efficacy of CPT for the management of COVID-19 also reported a significant decrease in Viral loads and improvement in clinical symptoms within 3-26 days post-transfusion.[33] Rajendran k et al [32] also reported similar findings in their Systematic review.

Another meta-analysis on efficacy and safety of convalescent plasma have found uninformative results regarding complete recovery(OR 1.04, 95% CI 0.69 to1.64), length of stay (mean difference–1.62, 95% CI –3.82 to 0.58,)and reduction in viral load on day 3 (RR 1.07, 95% CI 0.58 to 1.8),&, day 7 (RR1.32, 95% CI 0.97 to 1.81,). However, the quality of evidence was very low due to the presence of high level of indirectness.[34]

Salazar et al reported out of 25 critically ill patients, who received CPT on 7th post-transfusion day 9 patients got improvement, while 13 remained static, and 3 deteriorated, and on 14th post-transfusion day 19 patients had better clinical status, as per 6 points WHO ordinal scale.[35]

The studies have shown significant variation regarding the timing of initiation, dosage and neutralizing antibody titer, and concomitant therapy.

However, the dilemma for getting a concrete conclusion exist about the favorable outcome is due to CP therapy alone based on given evidence and not due to natural disease progression or concomitant therapies.

4.2. ***Adverse events:***

The overall incidence of serious adverse events was very low. None of the patients, who received CPT of two studies Gharbharan et al (n=43)[26] and Zeng et al (n=6)[30] had shown any adverse event. Joyner et al [27]reported the incidence of serious adverse events after CPT was low (<1%) in 5,000 patients. They reported about Transfusion-associated circulatory overload (TACO) (n = 7), transfusion-related lung injury (TRALI) (n = 11) and severe allergic reactions (n =3). Dua et al[25] reported about rashes in one patient out of 10 patients, who received CPT. Another study reported about TRALI in one patient and rashes in one patient out of 52 patients.[28]

4.3. ***Strengths and limitations***

Our study is one of the first comprehensive and systematic review of the effectiveness and safety of convalescent plasma therapy for patients with COVID-19 using data from the COVID-19 studies and may be considered at the moment as the best evidence for decision-making.

Although in the current scenario, CPT is an effective therapeutic option in addition to current antiviral, antimicrobial agents. A wide range of variation regarding selection of the donor, clinical stage of the recipient, initiation time, antibody titer, volume, dose and duration of CPT is noted across the available studies so far. We could not conduct subgroup analyses due to lack of data. We also acknowledge the procedure is yet to be standardized and information in this regard is still evolving.

5. Conclusion:

CPT may be an effective therapeutic option, until the availability of therapeutic and/or prophylactic agents for COVID-19, with some early promising evidence on safety, viral clearance, and reduction in mortality. However, large multi-center clinical trials are the need of the hour for establishing stronger quality of evidence along with the optimal doses, titer, and initiation time point for the CPT for effective use.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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doi:https://doi.org/10.1101/2020.05.08.20095471

Legends:

Table 1: Characteristics of included studies

SN	Studies, Year	Type of Study, centre	No of Patients	Patient Condition	Time of administration	Dosage of CPT	Antibody titer	Concomitant therapy	Author's conclusion
1	Chen et	Retrospect	29	Severel	19 days	200–500	>1:160	Not specified	Significa

	al,[24] 2020	ive Observational, MC		y ill	(IQR14 - 20)	ml (4–5 ml/kg)			nt improvement in clinical outcomes in comparison to the untreated cases.
2	Duan et al,[25] 2020	Pilot prospective cohort with a historical control group, SC	20	Severely ill	16.5 days (IQR 11-19)	200 ml.	>1:640	antiviral therapy, steroids and supportive care as appropriate.	CPT shows a potential therapeutic effect and low risk in the treatment of severe COVID-19 patients.
3	Gharbha	Open-	86	Mild –	9 days	300	1:640	Chloroquine,	No

	ran et al,[26] 2020	label RCT, MC		moderately ill	(IQR 7 – 13)	ml	(IQR 1:320 - 1:1280)	azithromycin, lopinavir/ritonavir, tocilizumab, anakinra as appropriate.	statistically significant differences in mortality (OR 0.95, CI 0.20 – 4.67, p=0.95) or improvement in the day-15 disease severity (OR 1.30, CI 0.52 - 3.32, p=0.58) was observed

									when the study was suspended.
4	Joyner et al,[27] 2020	Observational CT, MC	5000	Critically ill	Not specified	200 – 500 ml	Not specified	Not specified	Seven-day mortality rate = 14.9%
5	Li et al[28]., 2020	Open label RCT, MC	103	Critically ill	27 days (IQR 22-39)	4 to 13 mL/kg 200 ml (IQR 200-300),	>1:640	antivirals, steroids, immunoglobulin, antibiotics and Chinese herbal medicines, as appropriate	In severe or life-threatening COVID-19 patients, in addition to standard treatment, CPT did

									not result in a statistically significant improvement in time to clinical improvement within 28 days. Interpretation is limited by early termination of the trial
6	Liu et al[29],	Case controlled	185	Moderate-Criticall	4 days (IQR 1-7)	2 units. Each	>1:320	antivirals, anti-biotics,	Plasma recipients also

	2020	study, SC		y ill		unit of 250 ml		steroid and immunoglobulins as appropriate	demonstrated improved survival, compared to control patients
7	Zeng et al[30]. 2020	Retrospective observational study, MC	21	Critically ill	21.5 days (IQR17.8–23)	300 ml (IQR 200-600)	Not specified	antivirals, steroid and immunoglobulins as appropriate.	CPT can discontinue the viral shedding and contribute longer survival duration in COVID-19 patients with respiratory failure,

									although it cannot reduce the mortality in critically end-stage patients.

CPT: Convalescent plasma transfusion, MC: Multi center, SC: Single center, IQR: Inter quartile range,

RCT: Randomized controlled trial, OR: Odds ratio

Table 2: GRADE evidence profile of COVID-19 studies

Outcome	No. of participants			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence (Grade)	Relative effect
	Total no.	Intervention	Control							
Mortality	5444	5169	285	Yes	No	No	No	None	Low ⊕⊕⊖⊖	OR 0.44 (95

										% CI 0.25 to 0.77)
Clinical improvement	259	130	129	Yes	No	No	Yes	None	Very low ⨁⊖⊖⊖	OR 2.06 (95 % CI 0.8 to 4.9)
Viral Clearance	144	68	76	Yes	No	No	No	None	Low ⨁⨁⊖⊖	OR 11.29 (95 % CI 4.9 to

										25.9)

CI = confidence interval; COVID-19 = coronavirus disease 2019; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; MD =mean difference; OR = odds ratio;

Figure 1: PRISMA-2009-Flow-Diagram-

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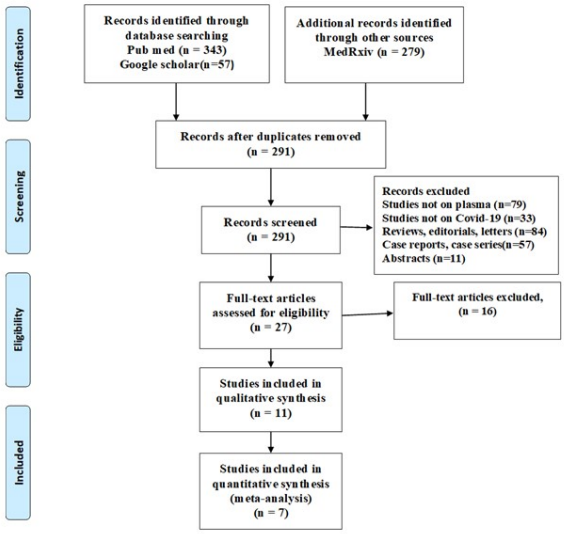

Figure 2a: ROB2 tool assessment for the included RCTs

Figure2b: ROBINS-I assessment for the included non-randomized cohort studies

Figure 2: Risk of bias assessment in RCTs(ROB2), & non-randomized cohort studies (ROBINS-I)

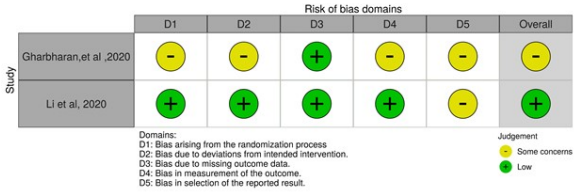

Fig: 2a

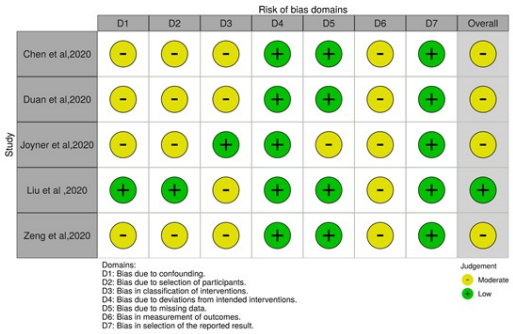

Fig: 2b

Figure 3: The efficacy of convalescent plasma therapy on mortality in COVID-19 patients

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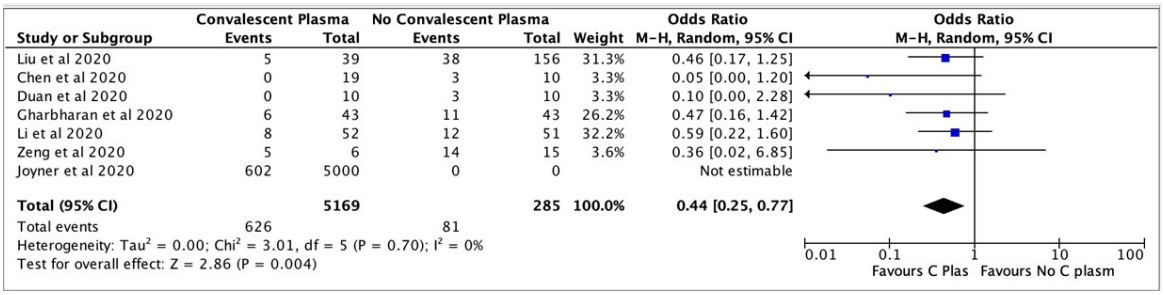

Figure 4a: The impact of convalescent plasma therapy on clinical improvement in COVID-19 patients

Figure 4b: The effect of convalescent plasma therapy on viral clearance in COVID-19 patients

Figure 4: The effect of convalescent plasma therapy on clinical improvement, & viral clearance in COVID-19 patients

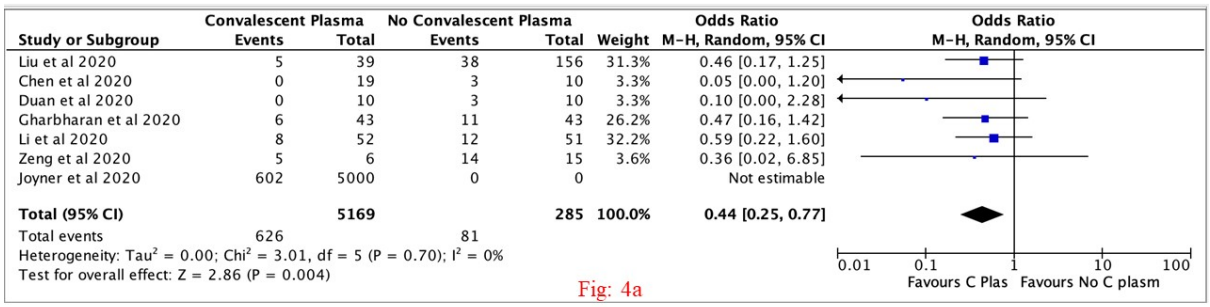

Fig: 4a

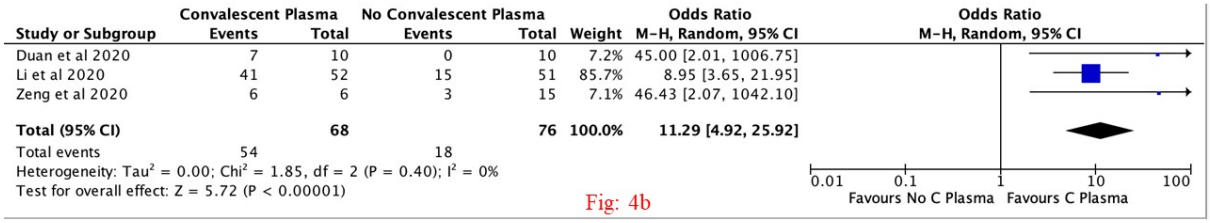

Fig: 4b