



Clinical Outcomes of Convalescent Plasma Transfusion Therapy in Moderate to Critically Ill Covid-19 Patients: A Systematic Review and Meta-Analysis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Currently, Convalescent plasma (CP) is considered a favorable treatment option for moderate to critically ill Covid-19 patients. But there were very few systematic reviews focused on the effect of CP on clinical parameters. As a result, we undertook this systematic review to learn more about the safety and clinical benefits of convalescent plasma therapy over standard treatment (control).

Methodology: We searched Pub Med, Embase and other bibliographic databases to find relevant articles between December 2019 and February 2021 and identified 10 relevant articles which compared CP therapy taken in addition to standard medication with the Control group (who received standard medication). Two independent reviewers examined all full-text articles and extracted the required information into a predesigned proforma. Forest plots were drawn using RevMan v.5, a statistical tool offered by the Cochrane database to estimate the pooled effect.

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Results: The results of meta-analysis using a random effect model indicated a significant reduction in mortality rate in CP (about 27% risk reduction), a reduced length of hospital stay in about 2 days (Weighted Mean Difference: -2.53, 95% CI, -7.20 to -2.14, P<0.0001), less time to improve clinical symptoms in about 4 days (pooled mean; CP:10.82 days vs Control:15.14 days). C-Reactive Protein (CRP) concentration levels (mg/L) were well controlled with the control group than the CP group and significant changes in lymphocytes and D-dimer values were not observed after CP treatment. It was also found that no difference between CP transfusion and control was seen in improving the oxygen saturation levels.

Conclusion: CP transfusion can be considered safe and showed a significant reduction in mortality and possible benefits in clinical improvement. Patients on CP therapy had no significant benefits in improving inflammatory markers such as CRP, lymphocytes, D-dimer, or oxygen saturation levels over standard drug therapy, according to meta-analysis data.

Keywords: Convalescent plasma; covid-19; systematic review and meta-analysis.

ABBREVIATIONS

CP : Convalescent Plasma
 CRP : C-Reactive Protein
 FDA : Food and Drug Administration
 MD : Mean Difference
 MERS-CoV: Middle East Respiratory Syndrome
 NRCT : Non-Randomised Control Study
 PCR : Polymerase Chain Reaction
 PRISMA : Preferred Reporting Items for Systemic Review and Meta-Analysis
 RCT : Randomised Controlled Study
 SARI : Severe Acute Respiratory Infections
 WHO : World Health Organisation

1. INTRODUCTION

The current pandemic Covid-19 disease is caused by SARS-CoV-2, a virus first identified in pneumonia cases in Wuhan city, China, known to cause respiratory illnesses from the common cold to more rare and fatal diseases such as the Severe Acute Respiratory Syndrome (SARS) and the Middle East respiratory syndrome (MERS) [1, 2]. It has a low case fatality rate compared to SARS and MERS, but a higher basic reproduction number and transmission rates [3].

On June 3rd, 2021, 220 nations and territories afflicted by corona reported more than 17 crore cases, with India reporting 2,84,41,986 cases and 3,36,989 (1.19 percent) deaths, placing third in the death toll.[4] The most common immediate cause of death was septic shock and multi-organ failure, according to Elez Kurtaj S et al [5].

The available evidence suggests that genetic sequences of SARS-CoV-2 isolated from infected humans are similar to coronaviruses isolated from bat populations and probably transmitted from its ecological reservoir in bats

[6]. The World Health Organisation (WHO), however, calls for subsequent investigations to find the origin of the coronavirus. It can rapidly spread through respiratory droplets when an infected person coughs, sneezes, or talks. Infection also can occur if someone contacts a contaminated surface and subsequently touches their eyes, nose, or mouth [7].

Coronavirus was more common in adults between the ages of 35 and 55, as well as the elderly even a few cases in children and infants reported. Coronavirus, like influenza, targets the lungs and causes serious symptoms in people who already have diabetes, lung disease, or heart disease [8]. Vitamin D insufficiency and obesity were also identified as predisposing factors for Covid19, according to Abdollahi A et al [9].

Many Covid-19 cases in India are asymptomatic, which is concerning because there may be many asymptomatic persons who have yet to be diagnosed and are carrying the virus. The general symptoms include cough, fatigue, low-grade fever, and shortness of breath in severe cases [10]. Antigen and antibody testing can be used to detect Covid-19 disease. The polymerase chain reaction (PCR), a molecular test, detects viral RNA directly. Antigen testing, a swab test, can identify it on the spot, although it is not as accurate as a PCR test. Antibody tests can't detect active illness, but they can tell us how many people have been infected [11].

As of now, there is no specific drug that acts against Covid-19. However, treatment options available are antiprotozoals (hydroxychloroquine), antiviral drugs ((ritonavir, lopinavir, remdesivir), blood thinners (Enoxaparin) antibiotics (azithromycin),

corticosteroids(dexamethasone) and monoclonal antibodies (casirivimab, imdevimab) [12].

Convalescent plasma (CP) which contains antibodies from the recovered Covid-19 patient has been approved by FDA (Food and Drug Administration) for emergency use in August 2020. When compared to patients who got the placebo, those who got early high titer convalescent plasma within three days of acquiring symptoms were 48% less likely to develop the severe covid-19 disease [13]. A meta-analysis that included 1060 patients from 4 Randomised Control Studies (RCTs), reported that CP therapy had not produced significant improvements in mortality rate and length of hospital stay compared to standard treatment and placebo [14]. Small clinical trials and a national access program indicated that convalescent plasma may help to reduce the severity of Covid-19 and shorten its duration [15].

Few systematic reviews look at the effectiveness of convalescent plasma therapy in Covid-19 patients. More research is needed to determine the clarity on the benefit of convalescent plasma therapy in Covid-19 patients. As a result, we undertook this systematic review to learn more about the safety and clinical benefits of convalescent plasma therapy over standard treatment.

2. METHODOLOGY

To increase the quality of evidence and minimize bias in reporting this systematic review and meta-analysis study, PRISMA (Preferred Reporting Items for Systemic Review and Meta-Analysis) criteria were followed. It also helps authors and peer reviewers for quality assessment and critical appraisal of various study designs included in the systematic review such as randomized clinical trials, cohort, case-control and cross-sectional studies [16].

2.1 Study Criteria

2.1.1 Inclusion criteria

Only RCTs, Non- Randomised Control Studies (NRCTs) and observational studies which compared CP therapy taken in addition to standard medication with the control group (who received standard medication) published between December 2019 and February 2021 were considered. Articles with full text that were available in English were included.

2.1.2 Exclusion criteria

Review articles, commentaries, notes to editors, animals or in-vitro studies were excluded. Articles that did not feature convalescent plasma therapy as a therapeutic option or compared with placebo were not eligible.

2.1.3 Sources of Information and search strategy

We searched PubMed, Embase, Google Scholar, Cochrane library, research gate, Lancet, Medline and other bibliographic databases to find relevant articles between December 2019 and February 2021 using keywords shown in Table 1. MeSH (Medical Subject Headings) terms were found by searching keywords in PubMed and then we developed a search term "(Outcomes AND critical* OR severe) AND (Corona OR Covid-19 OR SARS CoV-2) AND (Convalescent plasma) AND (Safe*) OR (Effic* OR effect*)". We, additionally, conducted a hand search on the bibliographies of selected articles to include studies that were not detectable during the search strategy.

Using relevant keywords and MeSH phrases, four separate reviewers found 51 articles in an electronic database and exported them to EndNote. Seven duplicates were deleted, and 44 records were assessed based on titles, abstracts, and intervention groups by two reviewers. Following the elimination of 31 papers (unrelated topics-10, meta-analysis-14 and insufficient data-7), a total of 10 papers with full text were considered for summarizing the results. Details of the search strategy were represented in Fig 1.

2.2 Data Extraction

Two independent reviewers examined all full-text articles and extracted the required information into a predesigned proforma. Data extracted were: authors, year of publication, study design, study location, treatment categories, CP dose, laboratory investigations before and after CP therapy, length of hospital stay, SpO₂ and mortality rate. Disagreements between reviewers were resolved by the third reviewer [17].

2.3 Quality Assessment of Studies

The quality of the included articles was assessed using the National Institute of Health (NIH) quality assessment tools. The NIH developed a

separate tool for assessing the quality of different study designs that can be rated as good, fair or poor. Questions were based on eligibility criteria, literature search strategy, quality of study review, publication bias, heterogeneity, etc [18].

2.4 Statistical Analysis

2.4.1 Forest plot

It summarizes the results of relevant studies focused on the same study issue and was created with RevMan v.5, a statistical tool offered by the Cochrane database. For mortality rate, we estimated the pooled effect of risk ratio as the data type was dichotomous. For C reactive protein (CRP), Length of Hospital stay, Lymphocyte count, D-dimer and SpO₂%, we calculated pooled effect of standard mean difference as the data type was continuous.

2.4.2 Testing for heterogeneity

Statistical heterogeneity describes the degree of variation in the effect estimates from a set of studies. Cochran’s Q test was used to measure the heterogeneity between studies with quantified I² statistics (P < 0.05 indicative of statistically significant heterogeneity). Heterogeneity was categorized as low, moderate, and high when the values were below 25%, between 25% and 75%, and above 75% [19].

2.4.3 Assessment of publication bias

Publication bias is a type of bias in published literature and can be assessed with the shape of the funnel plot. The symmetrical graph indicates no publication bias [20].

3. RESULTS

To evaluate the safety and clinical outcomes of CP therapy, our systematic literature search identified and reported the relevant articles including confirmed the cases of moderate to critically ill covid-19. Ten studies proved eligible, including 7 RCTs, 1 NRCT, 1 Cohort Study and 1

Case-control study[21–30]. as indicated in Table 2. Studies were from different geographic regions including a total of 1981 covid-19 patients with a range from 21 to 694. The patients in our systematic review were at least 50 years old on average.

All studies consisted of two intervention groups, i.e., CP and Control. CP group was supplied with 200-400 ml of plasma therapy with a maximum of 600 ml in addition to standard medications while the control group was supplied with standard medications antiviral, antibiotics, or traditional medication like along with concomitant drugs such as steroids as recommended by standard care protocols. The NIH grading system was used to determine the quality of evidence, with 7 studies rated good and 3 receiving a fair rating (Table 3) and the summary of meta-analysis of safety and clinical outcomes with CP transfusion was represented in Table 4.

3.1 Mortality Rate

We extracted 10 sets of data to determine the mortality rate in Covid-19 patients. The results of meta-analysis using a random effect model indicated a significant reduction in mortality rate in the CP group compared to the control group (20.19% vs 28.27%, P = <0.0001). Each data set’s risk ratio was analyzed, and the pooled risk ratio was determined to be 0.73 (95% CI, 0.63-0.85), with low heterogeneity (I²=0) among studies included indicating that CP patients had a 27% lower risk of death than the control group(Fig. 2).

3.2 SpO₂

A meta-analysis of SpO₂ values was conducted with the data of 271 CP patients and 335 control group patients. Even though Improvement in oxygen saturation levels was better in the control group patients, it was not significant (P=0.51) and results obtained in both the groups were not satisfactory as SpO₂ readings do not exceed 90%(Fig 3).

Table1. keywords and MeSH terms used in search strategy

| SI no | Keywords | MeSH Terms |
|-------|-----------------------------|----------------------------------|
| 1 | Treatment outcome | Outcomes AND critical* OR severe |
| 2 | Corona | Corona OR Covid-19 OR SARS CoV-2 |
| 3 | Convalescent plasma therapy | Convalescent plasma |
| 4 | Safety | Safe* |
| 5 | Efficacy | Effic* OR effect* |

Table 2. Characteristics of included studies

| S NO | Author | Date of publication | Study Location | Study Design | Total covid patients | Patients with CP | Control | Cp dose | AGE (Mean± SD) |
|------|----------------------|----------------------------|----------------|--------------|----------------------|------------------|---------|------------|----------------|
| 1 | S. Alsharidah, et al | 26th Nov, 2020 | KUWAIT | NRCT | 368 | 135 | 233 | 200-400 ml | 50.33±49.62 |
| 2 | Ralph Rogers et al | 21st Aug, 2020 | USA | CS | 241 | 64 | 177 | 200-500 ml | 60.55±17.77 |
| 3 | S. Budhiraja et al | 11th Feb, 2021 | INDIA | CC | 694 | 333 | 361 | 200-400 ml | 59.5±12.95 |
| 4 | A. Allahyari et al | 2nd Dec, 2020 | IRAN | RCT | 64 | 32 | 32 | 600 ml | 56.69 ±14.32 |
| 5 | AlShehry et al | 26th Dec, 2020 | SAUDI ARABIA | RCT | 164 | 40 | 124 | 200-400 ml | 52.02±13.33 |
| 6 | A.M.Rasheed, et al. | 3rd Apr, 2020 | IRAQ | RCT | 49 | 21 | 28 | 400 ml | 51.74±16.59 |
| 7 | Abolghasemi, et al. | 6th July,2020 | IRAN | RCT | 189 | 115 | 74 | 200 ml | 55.62±14.34 |
| 8 | Hyun ah Yoon, et al | 21st Jan,2021 | USA | RCT | 146 | 73 | 73 | 200ml | 65.95±15.75 |
| 9 | Li, Ling, et al | 3rd June,2020 | CHINA | RCT | 45 | 23 | 22 | 200 ml | 69.99±11.47 |
| 10 | Qing-Lei zeng, et al | 16 th June 2020 | CHINA | RCT | 21 | 6 | 15 | 300 ml | 63.79±24.18 |

Note: CP = Convalescent Plasma, NRCT = Non-Randomized Controlled Trial, CS = Cohort Study, RCT = Randomized Controlled Trial, CC = Case Control study, SD = Standard Deviation

Table 3. Quality of studies based on NIH ranking

| S. No | Author | Date of publication | Nih ranking |
|-------|------------------------|----------------------------|-------------|
| 1 | S. Alsharidah, et al | 26 th Nov 2020 | Good |
| 2 | Ralph Rogers et al | 21 st Aug 2020 | Good |
| 3 | S. Budhiraja et al. | 11 th Feb 2021 | Good |
| 4 | A. Allahyari et al | 2 nd Dec 2020 | Good |
| 5 | AlShehry et al | 26 th Dec 2020 | Good |
| 6 | A.M. Rasheed, et al. | 3 rd Apr 2020 | Poor |
| 7 | H. Abolghasemi, et al. | 6 th July 2020 | Fair |
| 8 | Hyun ah Yoon, et al | 21 st Jan2021 | Fair |
| 9 | Li, Ling, et al | 3 rd June 2020 | Good |
| 10 | Qing-Lei Zeng, et al | 16 th June 2020 | Fair |

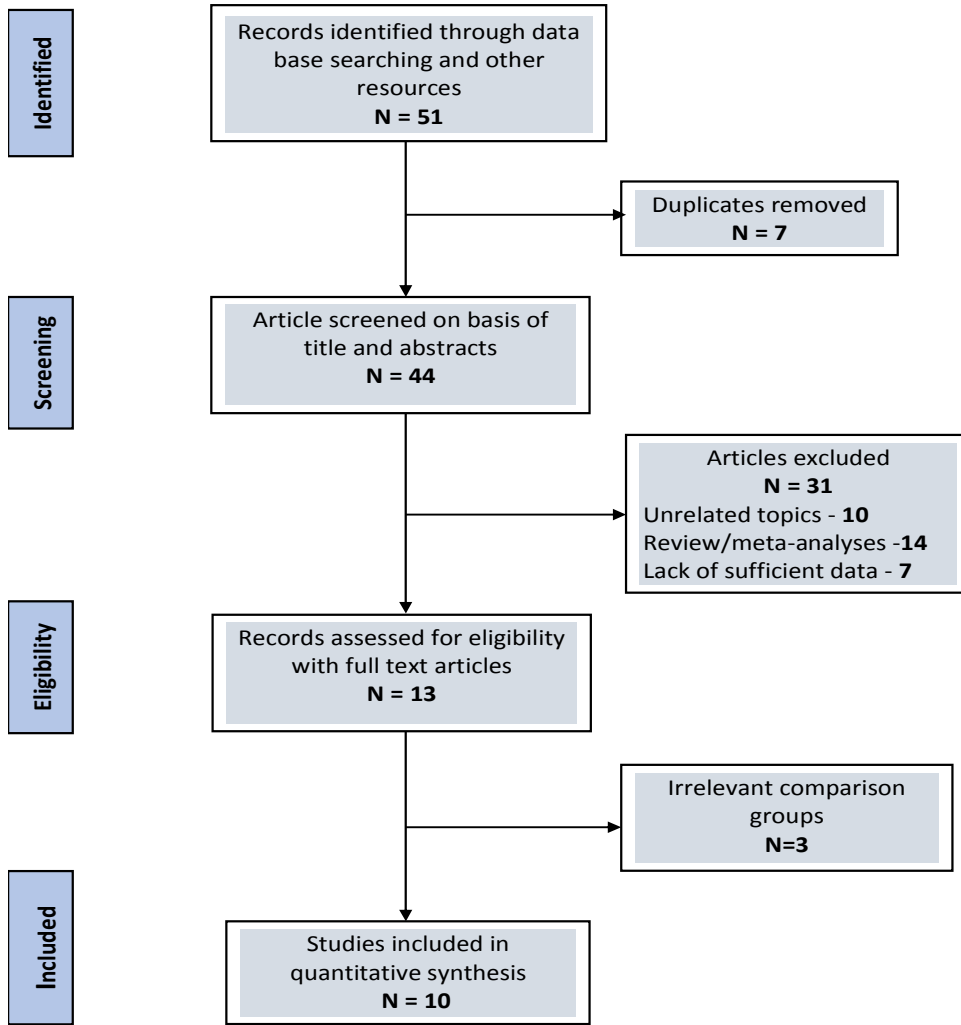


Fig. 1. PRISMA flow chart

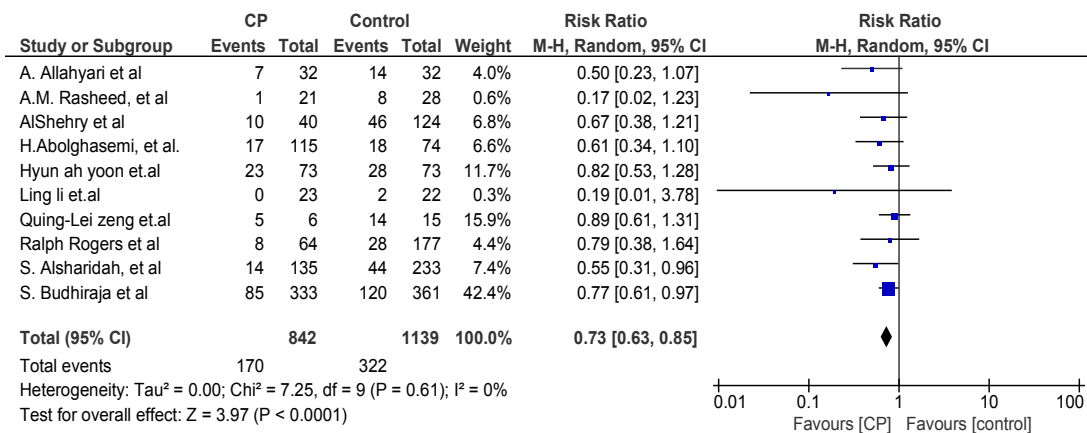


Fig. 2. Forest plot of risk ratio for mortality in Covid 19 patients

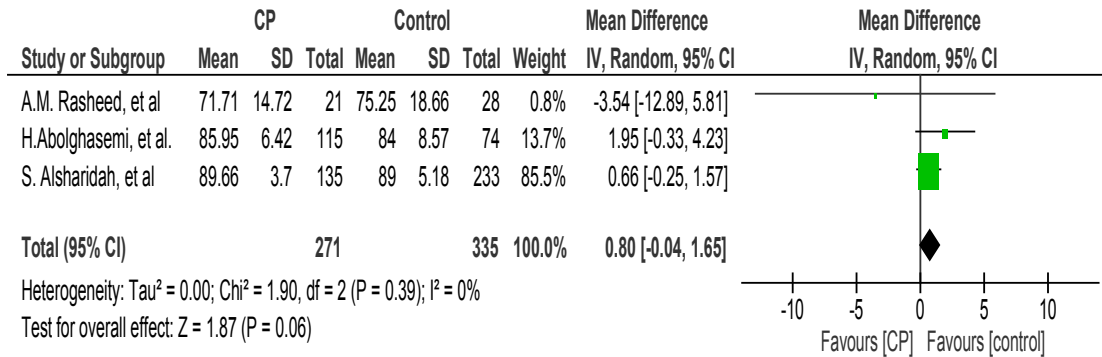


Fig. 3. Forest plot of SpO₂- CP vs control

3.3 Length of Hospital Stay

The length of hospital stay in Covid-19 patients was reported in four research studies. In comparison to the control group, CP patients had a reduced length of hospital stay in about 2 days (Weighted Mean Difference (MD): -2.53, 95% CI, -7.20 to -2.14, P<0.0001). However, significant heterogeneity of 92% showed that the evidence was of poor quality (Fig 4).

3.4 Time to Improve Clinical Symptoms

Patients who received CP had taken less time to improve clinical symptoms in about 4 days (pooled mean; CP:10.82 vs Control:15.14). As shown in Fig 5, there was a significant difference in time to see the clinical improvement between patients on CP and patients on standard medication (Weighted MD: -3.71, 95% CI, - 7.10 to -0.32, P=0.03).

3.5 C Reactive Protein (mg/dl)

A total of 453 patient data on C-reactive protein (CP-166, Control-287) from four studies was analyzed, and the pooled mean difference was determined to be 1.37 (95% CI, 0.49 to 2.24) which favors the control group (Fig 6).

3.6 Lymphocytes (10⁹/L)

This meta-analysis included 580 patients (237 CP patients and 343 control patients) data from four studies showed that the control group had better improvement in lymphocyte count than patients on CP therapy with low heterogeneity (Weighted MD:0.08, 95%, CI, - 0.03 to 0.19, P=0.16) but it was not significant (Fig 7).

3.7 D – Dimer(mg/dl)

We used 580 patient's data from 4 studies to assess the changes in D-dimer readings. A meta-analysis showed in Fig. 8 estimated that the weighted MD was 0.01 (95% CI, -0.04-0.06) which indicated that there was no difference between CP and standard treatment in improvement of D-dimer readings. However, studies focused on the D-dimer test reported great variations in D-dimer test results from patient to patient.

4. DISCUSSION

Since there is no specific antiviral drug available to treat Covid-19, CP therapy, a practice of transfusion of antibodies collected from people who have recovered from Covid-19 to boost the immunity of critically ill patients. CP could be a valid option in Covid-19 patients to reduce mortality and quick recovery [31]. But there is limited data on safety and efficacy in Covid-19 patients though CP therapy proved its potential benefits in the Middle East Respiratory Syndrome coronavirus (MERS-CoV), Ebola, and Severe Acute Respiratory Infections (SARI) viruses. Therefore, the current study aimed at the assessment of safety and efficacy of CP in Covid-19 patients and also traced the laboratory results include CRP, Lymphocyte count, D-dimer and SpO₂.

Our study assessed that CP therapy was associated with a statistically significant reduction in mortality rate. Current data aggregated from RCTs and matched control studies revealed that CP patients had a 27% reduction in mortality rate than patients on standard treatment [32]. A subgroup analysis of

Table 4. Summary of meta-analysis of safety and clinical outcomes with CP transfusion

| S. No | Variable | CP patients (n) | Control group (n) | Risk ratio / std mean difference | P-value | Summary |
|-------|------------------------------|-----------------|-------------------|----------------------------------|---------|---|
| 1 | Mortality | 842 | 1139 | 0.73(0.63-0.85) | 0.0001 | Significant reduction in mortality with CP transfusion |
| 2 | Length of hospital stay | 242 | 397 | -2.53(-7.20 to 2.14) | 0.29 | CP patients were benefited from reduced length of the hospital in about 2 days (but high heterogeneity among studies) |
| 3 | C-reactive protein | 166 | 287 | 1.37(0.49-2.24) | 0.002 | CRP concentration levels(mg/L) were well controlled with the control group than CP group |
| 4 | Lymphocytes | 237 | 343 | 0.08(-0.03 to 0.19) | 0.16 | transfusion with CP had no benefit over control group |
| 5 | D-dimer | 237 | 343 | 0.01(-0.04 to 0.06) | 0.65 | There was no benefit of taking CP therapy in addition to standard treatments |
| 6 | Sp _o ₂ | 271 | 335 | 0.80 (-0.04 to 1.65) | 0.06 | No difference between CP transfusion and control in improving the oxygen saturation levels |
| 7 | Clinical improvement | 219 | 407 | -3.17 (-7.10 to 0.32) | 0.03 | CP therapy showed possible benefit in clinical improvement |

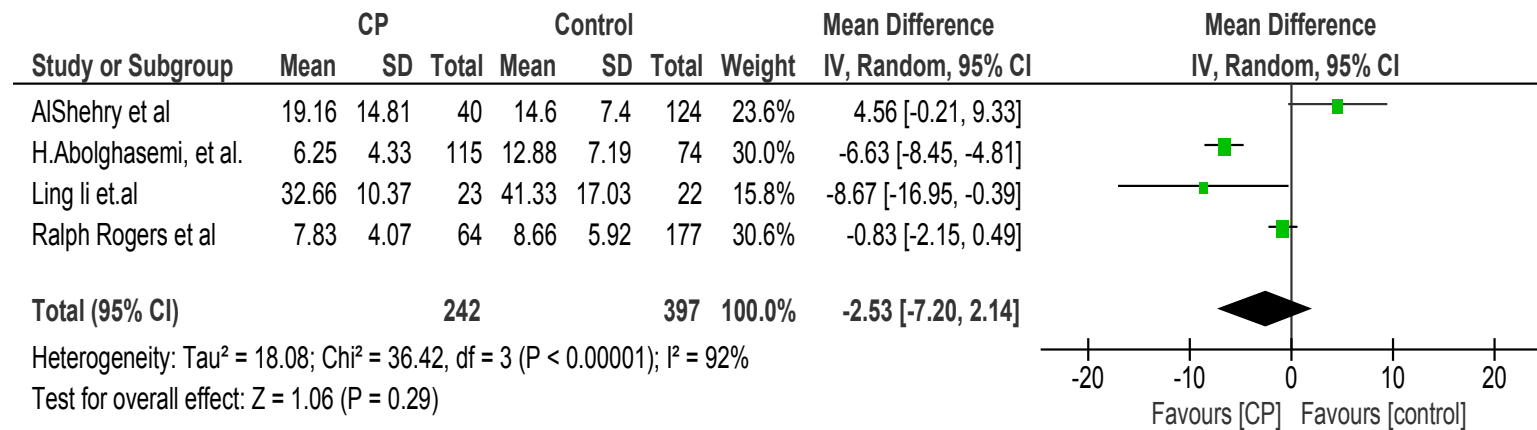


Fig. 4. Forest plot of length of hospital stay CP vs control

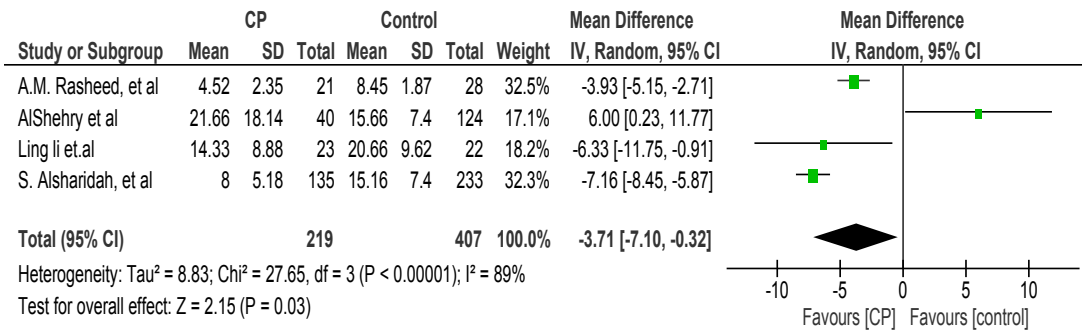


Fig. 5. Forest plot of clinical improvement- CP vs control

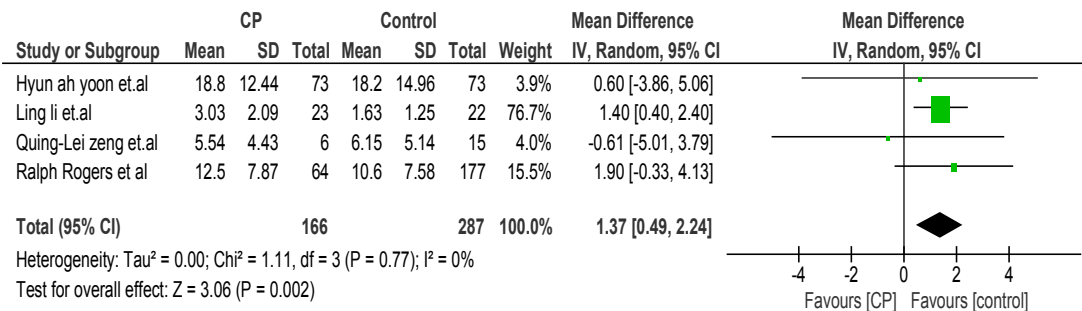


Fig. 6. Forest plot of C reactive protein (mg/dl)-CP vs control

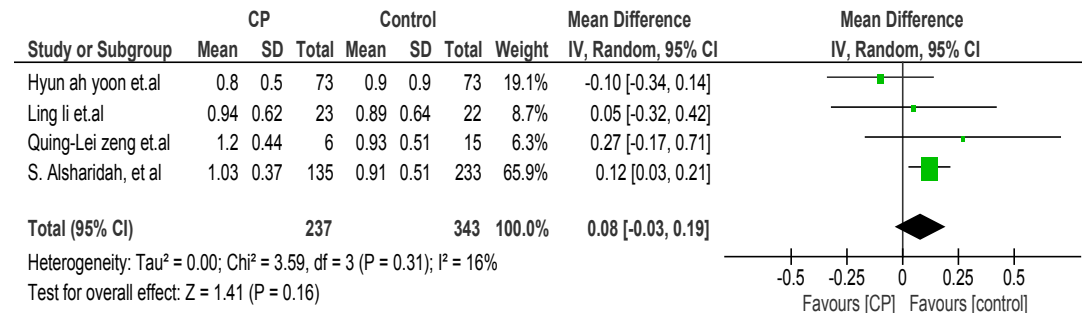


Fig. 7. Forest plot of lymphocyte count- CP vs control

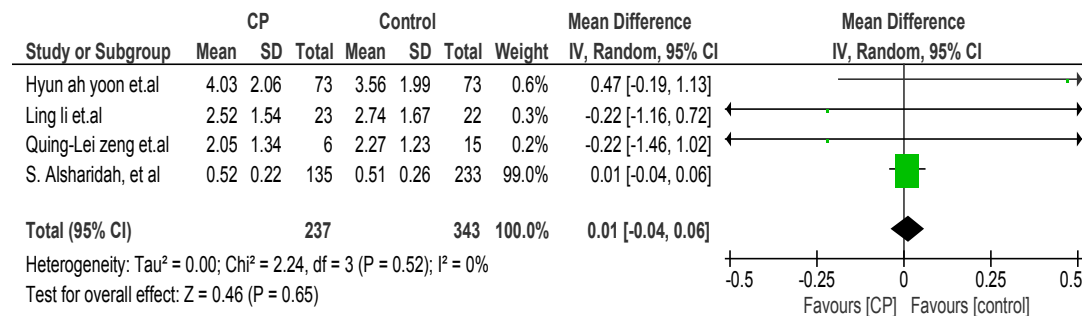


Fig. 8. Forest plot of D-dimer- CP vs control

RCTs indicated that there was no association between CP transfusion and mortality rate [33]. Moreover, CP transfusion has been widely used as it reduces the viral load and improves clinical symptoms [34].

The reported side effects were associated with transfusion. The common symptoms were chills, fever, dyspnea, itching, mild skin redness, shortness of breath and cyanosis. The percentage of patients affected with Adverse Drug Reactions (ADRs) were range from 0.86-8.69%. No severe ADRs were seen with CP transfusion and it was considered safe and this was supported by several other studies [35, 36].

From the data of 606 patients from 2 RCTs and 1 NRCT studies, it was assessed that CP treatment did not improve the oxygen saturation. The evidence was dominated by one NRCT which accounted for 85.5% of the weight in the meta-analysis. However, some studies reported that CP treatment was significantly associated with improved oxygen saturation during the first 72 hours in critically ill patients[15, 37].

This meta-analysis included three RCTs and one Cross-sectional study demonstrated that CP patients were benefited from reduced length of hospital in about 2 days. The certainty of the evidence was low due to the summarized sample size was considerably small, high heterogeneity among studies and there was also no significant association of CP therapy with benefits on a reduced length of hospital stay. Systematic reviews and meta-analyses focused on the length of hospital stay reported contrast results on a reduced length of hospital stay. For example, JaniaudP et al[14] which included 10 RCTs (comparing CP with standard treatment) demonstrated there was no significant association between CP therapy and reduction in length of hospital stay whereas Mair-Jenkins, J[38] which included 27 studies having moderate to high risk of bias reported that CP therapy was significantly increased proportion of Covid-19 patients within 22 days of admission.

According to our meta-analysis study, the time to show clinical improvement is 4 days on average after transfusion with CP. The time frame for clinical improvement in studies includes for meta-analysis range from 4.52 ± 2.35 days to 21.66 ± 18.14 days. The pooled results were inconclusive due to high heterogeneity and inconsistent definitions for clinical improvements and insufficient reports from published literature.

However, there was a signal of possible benefit of CP therapy showing improvement in clinical symptoms.

CRP is one of the mandatory tests recommended in all hospitalized Covid-19 patients. The high CRP level indicates the level of inflammation which can be caused by various infections due to cancers or inflammation in the arteries of the heart and it further worsen symptoms of Covid-19. The mean CRP concentration was found to be an increase on average of 20 to 50 mg/L in moderate to severe Covid-19 patients [39]. There was a significant reduction in CRP levels before and after CP transfusion but the mean CRP concentration levels(mg/L) were well controlled with the control group than CP group in 14 to 28 days of recovery time as corticosteroids in standard treatment substantially reduce CRP levels within 72 hours [40].

A high level of CRP in the blood is a marker of inflammation. It can be caused by a wide variety of conditions, from infection to cancer. High CRP levels can also indicate that there's inflammation in the arteries of the heart, which can mean a higher risk of heart attack.

Lymphocytopenia ($<1 \times 10^9/L$) is one of the key inflammatory markers and is more frequently observed in hospitalized Covid-19 patients [41]. Administration of hyperimmune CP passively transfers antibodies and clears the viral load that leads to an increased recovery rate in lymphocyte count [42]. Within 14 days, the lymphocyte count increased to reach $1 \times 10^9/L$ ($1-4 \times 10^9/L$) after transfusion with CP but there was no benefit over the control group.

D-dimer test is highly essential in severe forms of Covid-19 patients who are prone to develop blood clots and also a useful biomarker for mortality. High D-dimer levels in Covid-19 indicate its severity [43]. In this meta-analysis, D-dimer data aggregated from 580 patients indicated that there was no benefit of taking CP therapy in addition to standard treatments in the change of D-dimer values. Apart from this, studies aimed to investigate the association between CP transfusion and D-dimer readings concluded that post CP therapy patients having D-dimer values higher than 5 mg/L were at high risk of mortality [44]. This finding raises the possibility that CP therapy in Covid-19 could exacerbate the increased thrombotic risk [45].

5. CONCLUSION

CP transfusion can be considered safe and showed a significant reduction in mortality and possible benefits in clinical improvement. Patients on CP therapy have no significant benefits in improving inflammatory markers such as CRP, lymphocytes, D-dimer, or oxygen saturation levels over standard drugs, according to meta-analysis data. Further, more randomized clinical trials with a large study sample are required to conduct to provide the data on the effect of CP administration on improvement in clinical symptoms, mechanical ventilation and clinical parameters for estimating the best-pooled effect.

6. STUDY LIMITATIONS

To the best of our knowledge, this is the first systematic review pooling the effects of CP on clinical parameters such as CRP, lymphocyte count and D-dimer readings. This study has several limitations. First, studies included for meta-analysis have inconsistency in giving the definitions for critically ill or moderate to severely ill Covid-19 patients. Second, very few articles only provided data on the effect of CP transfusion on oxygen saturation, D-dimer, CRP and lymphocyte count. Third, high heterogeneity among studies will result in inconclusive reports.

CONSENT

It is not required.

ETHICS APPROVAL

Ethical approval is not required because this study is a systematic review and meta-analysis.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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